



Revisión

Effect of vitamin D₃ supplementation on HIV-infected adults: a systematic review

Efecto de la suplementación con vitamina D₃ en adultos infectados por el VIH: una revisión sistemática

Nayra do Socorro Caldas Carvalho de Almeida Teixeira¹, Beatriz de Mello Pereira¹, Iara Katrynne Fonsêca Oliveira¹, Carlos Henrique Ribeiro Lima¹, Cecília Maria Resende Gonçalves de Carvalho², Ivone Freires de Oliveira Costa Nunes¹, Dorcas Lamounier Costa³ and Adriana de Azevedo Paiva²

¹Graduate Program in Food and Nutrition. Universidade Federal do Piauí. Brazil. ²Nutrition Department. Universidade Federal do Piauí. Brazil. ³Mother and Child Health Department. Universidade Federal do Piauí. Brazil

Abstract

Introduction: much evidence confirms that vitamin D may be associated with an improvement in CD4 cell counts in HIV-infected individuals, where antiretroviral therapy (ART) is used and associated with decreased 25(OH)D levels.

Objective: to carry out a systematic review on the effect of vitamin D supplementation on HIV-infected adult patients.

Methods: the research was conducted in the databases Science Direct, PubMed, BVS, Scielo Cochrane and Periods, from February to April 2018, with publication limit from 2000 to 2018, without restriction of gender, ethnicity and involving individuals with age older than 18 years. To evaluate the quality of the studies, we used the protocol Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and the Jadad scale.

Results: the search initially resulted in 198 articles. After the selection process 5 articles were identified as eligible, where they highlight that vitamin D supplementation may be an associated and effective intervention to reduce hypovitaminosis. ART reduces vitamin D₃ levels and changes its metabolism, being associated with the risk of mortality. However, adequate levels of 25(OH)D are positively associated with the number of CD4 + cells and the reduction of infection levels.

Conclusion: vitamin D supplementation promotes immune recovery. However, the cases analysed were few, insufficient to fully confirm the benefits and recommend supplementation. Therefore, intervention studies are needed to elucidate the role of vitamin D in human protection against HIV infections.

Key words:

Vitamin D.
Supplementation. HIV.

Resumen

Introducción: muchas evidencias ratifican que la vitamina D puede estar asociada con la mejora de los niveles de células CD4 en individuos infectados por el VIH, tratados con terapia antirretroviral (ART) que se asocia a la disminución de los niveles de 25(OH)D.

Objetivo: realizar una revisión sistemática sobre el efecto de la suplementación de vitamina D en pacientes adultos infectados con VIH.

Métodos: la investigación fue realizada en las bases de datos Science Direct, PubMed, BVS, Scielo Cochrane y periódicos, de febrero a abril de 2018, con límite de publicación de 2000 a 2018, sin restricción de género, etnicidad y que involucra a individuos con edad mayores de 18 años. Para la evaluación de la calidad de los estudios, se utilizó el protocolo Preferred Reporting Items for Systematic Reviews y Meta-Analyses (PRISMA) y la escala de Jadad.

Resultados: la encuesta inicialmente resultó en 198 artículos. Después del proceso de selección, 5 artículos fueron identificados como elegibles, donde ponen de manifiesto que la suplementación con vitamina D puede ser una intervención asociada y eficaz para reducir la hipovitaminosis. La ART reduce niveles de la vitamina D₃ y altera su metabolismo, estando asociada al riesgo de mortalidad. Sin embargo, los niveles adecuados de 25(OH)D están asociados positivamente al número de células CD4 + y la reducción de los niveles de infecciones.

Conclusión: la suplementación de vitamina D promueve la recuperación inmunológica. Sin embargo, los casos analizados fueron pocos, insuficientes para confirmar totalmente los beneficios y recomendar la suplementación. Por lo tanto, estudios de intervención son necesarios para elucidar la actuación de la vitamina D en la protección humana contra las infecciones por el VIH.

Palabras clave:

Vitamina D.
Suplementación. VIH.

Received: 29/04/2019 • Accepted: 08/06/2019

Teixeira NSCCA, Pereira BM, Oliveira IKF, Lima CHR, Carvalho CMRG, Nunes IFPC, Costa DL, Paiva AA. Effect of vitamin D₃ supplementation on HIV-infected adults: a systematic review. *Nutr Hosp* 2019;36(5):1205-1212

DOI: <http://dx.doi.org/10.20960/nh.02647>

Correspondence:

Carlos Henrique Ribeiro Lima. Graduate Program in Food and Nutrition. Universidade Federal do Piauí. Brazil
e-mail: carlosnutri@hotmail.com.br

INTRODUCTION

Vitamin D is attributed to calcium and phosphate metabolism (1-3). At the same time, it is also involved in cell differentiation, proliferation and immunomodulation (4). Its requirement for the organism is basically supplied by endogenous synthesis (90-95%). However, endogenous synthesis is profoundly affected by several factors, such as the degree of skin pigmentation, the time of the day of exposure to the sun, season, weather conditions, air pollution, clothing and the use of sunscreen (3).

Vitamin D deficiency is characterized by serum levels below 20 ng/mL; insufficiency, between 21 and 29 ng/mL; and adequacy, serum levels greater than 30 ng/mL (5,6). Deficiency and insufficiency are associated with several pathological conditions such as lack of exposure to UVB, inadequate dietary intake, malabsorption, multiple risk factors for CNCD (7).

The relationship between chronic viral infections and hypovitaminosis D is well known. A high prevalence of vitamin D deficiency was specifically described in the study by Villamor (8) in the seropositive population, with high rates of 83%, corroborating with the EuroSIDA study (9). Several studies have focused on the parameters that influence hypovitaminosis D in HIV-positive patients (10).

However, the results of the analyzes of many studies around the world remain discordant, especially regarding the modalities of treatment. In fact, several studies have shown that vitamin D concentrations are related to antiretroviral therapy (ART) and to the use of specific antiretroviral class.

The concentration of vitamin D may be specifically lower in patients treated with non-nucleoside reverse transcriptase inhibitors (NNRTIs) than in those treated with protease inhibitors (PIs), in particular efavirenz, but there are still discrepancies on the deleterious role of NNRTI regarding levels of vitamin D (11). About the severity of the disease, vitamin D deficiency is associated with a low TCD4 cell count and a viral load higher than 50 copies/mL (12). In addition, vitamin D deficiency is more common in HIV-infected patients with advanced pathology progression (13). Thus, there is an increased risk of morbidity and mortality in HIV-infected patients with low levels of vitamin D (14).

Scientific evidence involving vitamin D supplementation in people with human immunodeficiency virus is very few and inconclusive, so the aim of this study was to conduct a systematic review of the available clinical trials on this subject, in order to lead researchers to this promising theme in the field of nutrition.

METHODS

SEARCH STRATEGY

A systematic review (RS) of clinical trials about vitamin D supplementation in HIV patients was performed. In the elaboration of the guiding question of the present study the PICO strategy was used, which represents the acronym for problem or population (P), intervention (I), comparison (C) and outcome (O).

The PICO strategy culminated in the delimitation of the following guiding question: does vitamin D supplementation lead to improvements in the clinical picture of HIV patients? Each PICO dimension was equivalent to the following elements: (P) HIV patients, (I) vitamin D supplementation, (C) placebo, and (O) clinical improvement of HIV patients.

The virtual search was performed in the PubMed, Scopus, Science Direct, Scielo, LILACS and Cochrane Library databases, from February to April 2018, by two authors. The researched clinical trials had publication limits between 2000 and 2018, without gender, ethnicity restrictions, and published in the English language, involving individuals aged over 18 years. The "and" connective was used in the combination of the Medical Subject Headings Terms (MeSH terms): vitamin D, supplementation and HIV.

SELECTION OF PAPERS

The titles and abstracts of the selected articles were analyzed to evaluate whether they met the inclusion criteria: to have a controlled clinical trial design and to be available in full. The evaluation of the eligibility criteria was done independently by two authors, and in case of divergence a third researcher was consulted.

QUALITY ASSESSMENT OF STUDIES

In order to assure the quality of the SR, the protocol Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) was used (15). The Jadad scale (16) was employed independently and blinded by two researchers for qualitative classification. Scores were assigned to the studies (from zero to five), based on the criteria: randomization method (sequences and criteria for randomization of participants), use of masking (for patients and researchers) and description of the proportion of loss to follow-up. The risk of bias in the trials included in this study was identified by the Cochrane Collaboration Tool (17) (Fig. 1).

RESULTS

The bibliographic research, according to the pre-established strategy, initially resulted in 198 articles. Of these, 143 from Science direct, 37 studies from the PubMed database, 13 from the VHL, 05 from Scielo and no articles from Periods and the Cochrane Library. After the process of selection and removal of 19 articles, that were duplicated and that were not clinical trials, 05 original articles from randomized controlled trials (RCTs) dealing with vitamin D supplementation in adults living with HIV were identified as eligible for this systematic review. Figure 1 shows the flowchart of the result of the search in the sources of information, of the selection and inclusion of the original articles in the Systematic Review, according to the protocol PRISMA statement.

Clinical trials showed homogeneous methodological quality based on bias risk assessment by the Cochrane tool (Table I).

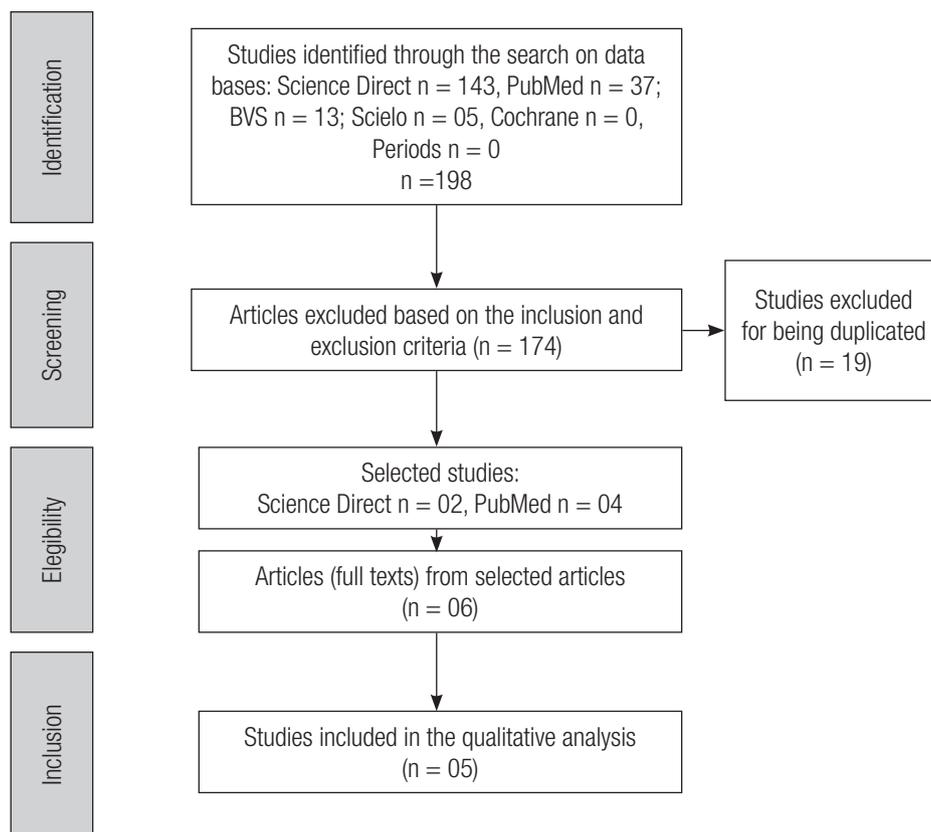


Figure 1.
Flow diagram.

Table I. Analysis of the methodological quality and risk of bias proposed by the Cochrane Collaboration. Teresina-PI. Brazil, 2018

Variables	Longenecker CT, et al. (2104)	Havens PL, et al. (2014)	Coelho L, et al. (2015)	Lake JE, et al. (2016)	Sudfeld C. R, et al. (2017)
Random sequence generation	Uncertain	Low risk	Uncertain	Uncertain	Low risk
Allocation concealment	Low risk	Low risk	Low risk	Low risk	Low risk
Blinding of participants and professionals	Low risk	Low risk	Low risk	High risk	Low risk
Blinding of outcome assessors	Uncertain	Low risk	Low risk	High risk	Low risk
Incomplete outcomes	Low risk	Uncertain	Low risk	Low risk	Uncertain
Report of selective outcome	Low risk	Low risk	Low risk	Low risk	Low risk
Other sources of bias	Low risk	Low risk	Low risk	Low risk	Low risk

Random sequence generation was adequately reported in 40% (2/5) low risk and 60% (3/5) uncertainty studies, allocation concealment with 100% (5/5) low risk, blinding of participants and professionals 100% (5/5) low-risk, blinding of outcome assessors with 20% (1/5) of uncertain and 80% (4/5) of low risk for incomplete outcomes were 40 (2/5) of uncertain 60% (3/5) of low risk, in the report of selective outcome we had 100% (5/5) of low risk and other sources of bias presented 100% (5/5) of low risk.

Table II shows the results of the quality evaluation of articles analyzed according to the Jadad scale. In relation to the items evaluated, all articles adequately described the aspects evaluated in that scale.

The data presented in table II combine the results of the reviewed articles including authors, year of publication, place of study, study sample size, dose, duration of supplementation and main outcomes. It was observed that the five trials included in this review were conducted with persons over eighteen years of age of both sexes, in different countries. Doses of vitamin D supplementation ranged from 2,000 IU to 50,000 IU per week, and the duration of interventions ranged from 12 weeks to 3 years.

The main variables investigated were: 25(OH)D, socio-demographic data, age, BMI, CD4 lymphocytes, but some studies went further and included biochemical tests and immunological data.

The results of the five clinical trials demonstrated that vitamin D supplementation increased serum levels of the vitamin. In addition, they demonstrated a positive effect of supplementation on CD4 lymphocytes count supporting the vitamin D benefit in immunological recovery, which is particularly relevant for the HIV-infected population and effective for a variety of antiretroviral suppressive regimens (ART).

DISCUSSION

Antiretroviral therapy coverage is rapidly expanding worldwide and treatment programs need interventions in order to prolong and improve the quality of life of HIV-infected individuals in resource-limited contexts (18). Supplementation of vitamin D₃ may be an associated and effective intervention since vitamin D₃ deficiency is common among HIV-infected individuals, ART may reduce even more vitamin D levels by altering their metabolism. Multiple cohort studies have determined that low levels of vitamin D are associated with increased risk of mortality, tuberculosis and disease progression among individuals and supplementation is known to be effective and safe in improving their condition (8,19,20).

About the extra skeletal functions of vitamin D, the presence of a nuclear vitamin D receptor in many human tissues has been described, corroborating with its current definition of hormone (21). The deficiency of this substance is being increasingly described in the world population and attributed to this, its association with the development of immunological, neoplastic, endocrine-metabolic diseases, among others. However, there is a great discussion as to the serum levels of vitamin D considered insufficient or deficient, hindering the conduct of supplemental therapy.

Table II. Characteristics of studies according to authors, country and year of publication, sample, analyzed variables, intervention and outcome in people living with HIV supplemented with vitamin D. Teresina-PI. Brazil, 2018

Authors/ year/ country	Sample	Analyzed variables	Intervention	Outcomes	Jadad
Longenecker et al., 2014 Cleveland, OH, USA	n = 45	Relevant demographic data, medical history, medication, physical examination. Glucose, insulin and lipoproteins, serum concentrations of 25(OH)D and PTH. Soluble VCAM-1 (sVCAM-1), soluble ICAM-1 (sICAM-1), C-reactive protein of high sensitivity (hs-CRP), IL-6, soluble receptors of TNF- α (sTNFR-1 and sTNFR-II), D-dimer and fibrinogen. CD4 cell count + concentrations of RNA – HIV-1. Complete blood count, uric acid in the blood, creatinine, electrolytes, calcium and a panel of liver function	4,000 IU of cholecalciferol (vitamin D ₃ , 2 x 2,000 mg capsules) or two corresponding placebo capsules. Daily. Duration: 12 weeks.	The results showed that in HIV-infected individuals with vitamin D deficiency, supplementation with 4,000 IU of vitamin D ₃ per day for 12 weeks modestly improved vitamin D and cholesterol status, but it aggravated insulin resistance without change in endothelial function. The mechanisms of resistance to standard doses of vitamin D and the complex role of vitamin D in glucose, the metabolism in this population requires more research	07
Havens et al., 2014 Washington, DC	n = 203	FGF23 and VDBP, 1, free 25-OH (2) D were measured	VITD (50,000 IU every four weeks) or placebo (PL). In the beginning and at week 12, they compared the changes through TDF treatment and through the randomized group with VITD. Duration: 12 weeks	The results suggested that the cAefarT containing TDF may alter the response of FGF23 to vitamin D supplementation in HIV-infected youngsters	03

(Continúa en la página siguiente)

Table II (Cont.). Characteristics of studies according to authors, country and year of publication, sample, analyzed variables, intervention and outcome in people living with HIV supplemented with vitamin D. Teresina-PI. Brazil, 2018

Authors/ year/ country	Sample	Analyzed variables	Intervention	Outcomes	Jadad
Coelho et al., 2015 Rio de Janeiro, Brazil	n = 100	Levels of 25(OH)D, sex, age, race, CD4+T lymphocytes, times (ART, TDF, AZT, EFV, PI), dexa (normal, osteopenia, osteoporosis), BMI, C-reactive protein, glucose, HbA1c, triglycerides, total cholesterol, HDL and LDL.	50,000 IU (twice a week) for 5 weeks; 8,000 IU (twice a week) for 19 weeks. Duration: 24 weeks	Effective to restore 25(OH)D levels after 24 weeks. The time with efavirenz was positively associated with post-repletion levels of 25(OH) D, while no other antiretroviral associations were observed. Strong correlation and association between increases in the levels of 25(OH) D and CD4 + T lymphocyte counts support a benefit of vitamin D on immunological recovery	03
Lake J.E., et al., 2016 California, Los Angeles	n = 122	Levels of 25(OH)D, gender, race, smoking, age, BMI, CD4+T lymphocytes, ART, entry and integrase inhibitor, NNRTI, PI, abacavir, lamivudine, emtricitabine, tenofovir, DM, HAS, hyperlipidemia, cardiovascular diseases, hepatitis C and B	50,000 IU (twice a week) for 5 weeks; 2,000 IU (once a day) for 12 weeks. Duration: 17 weeks.	Effectively replete 25(OH)D levels to ≥ 30 ng/mL in 81% of the participants. In this cohort of HIV-infected individuals on ART, and efficacy was similar to the one observed among uninfected HIV patients. Maintenance therapy with 2,000 IU D ₃ daily maintained levels of 25(OH) D at ≥ 30 ng/mL for most participants, and no adverse events occurred. The regimen was considered safe and effective for recovering and maintenance of 25(OH)D levels in infected patients and positive for suppressive ART regimens	02
Sudfeld et al., 2017 sub-Saharan Africa	n = 4000	Vitamin D ₃ , pulmonary tuberculosis (TB), incident hypercalcemia, TCD4 cells, non TB related comorbidity incidence, gender, age BMI, hemoglobin concentration, WHO stage of the HIV disease, TB, receiving isoniazid preventive therapy, ART regimen and compliance with the test regimen	50,000 IU of vitamin D ₃ once a week, during 3 weeks (four doses) followed by daily oral supplements of 2,000 IU. Duration: 3 years	The protocol (ToV4) provided causal evidence on the effect of vitamin D ₃ supplementation on the incidence of pulmonary tuberculosis and mortality among HIV-infected Tanzanian adults initiating HAART. The results will also give an idea whether vitamin D ₃ supplementation trials for the prevention of pulmonary TB should be performed in non-HIV infected populations	04

Despite the high rates of vitamin D insufficiency in patients on antiretroviral therapy, few studies have been carried out regarding the supplementation of this vitamin in this population, here in Brazil. In other countries this topic is growing among the researches, with important associations with the anthropometric, biochemical and immunological parameters in this population. The included articles resulted in a population of 4,470 people living with HIV. Regarding the gender, two articles had a majority of males, and in regard to ethnicity the majority of white people. As for the age group, the selected studies had similar average ages of 45 (22) and 49 years (23).

Therefore, the studied population with an age group of young adults falls within the growing risk group among HIV-positive individuals, being a group at risk for having or acquiring vitamin D deficiency and cardiovascular diseases (24), which makes the analysis of these variables with vitamin D deficiency an important study to understand metabolic changes that may occur in this public. This study has a limitation regarding the sample that would be small to fully evaluate the relations between the level changes of 25(OH)D and specific clinical and demographic factors. But Sudfeld et al. (25) brings a very high number of participants, confirming that vitamin D deficiency among HIV-infected individuals has listed mortality or morbidity outcomes.

The research by Coelho et al. (23) was carried out in Rio de Janeiro, during 2 years and throughout all seasons, similar to the one by Lake et al. (22) that carried out in Los Angeles, United States, for 11 months, as well as the other studies that took seasons into consideration.

In North America the seasons are well defined, differently of what happens in South America and Africa, which can influence on the results. It is important to consider the seasons in the studies with vitamin D, considering that the concentrations of this vitamin can be altered according to the solar exposure and radiation to which each person will be exposed, possibly being a variable of confusion (24).

Body composition is of extreme importance for assessing the prognosis of HIV/AIDS, as well as the nutritional status, which interferes in a directly proportional way in vitamin D concentrations (26). Among the articles analyzed, all of them presented a population that was mostly eutrophic according to the body mass index (BMI), however this index alone is not a very effective method for analyzing body composition. It is important that their values correlate with other independent measures that determine the composition in terms of body fat and lean mass (27). Therefore, the assessment of body composition is recommended to have BMI, waist circumference, skin folds, being quite effective.

CD4 + or T-helper cells are leukocytes that organize the immune system response to some microorganisms, including viruses. The CD4 + cell count in a healthy, non-HIV-infected individual may range from 500 to 1,200 cells/mm³. This quantification assesses the state of the immunological system and the risk of debilitating complications and infections. It is known that the human immunodeficiency virus infects CD4+ cells and decreases their available amount in the human body. A low concentration of these cells, from 200 to 250 cells/mm³, increases the risk of opportunistic diseases (28).

In the study by Lake et al. (22) 67% of the participants were in the range of 200 to 499 cells/mm³, while in the one by Coelho et al. (23) 72% were in the range > 500 cells/mm³, such as on the studies by Legeai et al. (29) and by Sheperd et al. (30) who demonstrated that there is an association between vitamin D levels and the number of CD4 + cells, and that these decreased levels would be related to inflammation in untreated HIV patients, which has led to researches with vitamin D supplementation, aiming to reduce the level of infections of these individuals.

In HIV treatment programs in Tanzania and sub-Saharan Africa they are moving towards the smaller use of TCD4 cells from 350 to 500 with μ L limit for initiation of antiretroviral (ART) based on WHO guidelines (31).

As Wagner et al. (32) reported, there is no consensus on the exact values of normal concentrations of vitamin D, and there is no standardization of methodologies to assess its deficiency, insufficiency and sufficiency, so the comparison between studies that used different cut-off points for this vitamin should take into account the different measurement parameters (33).

Although calcidiol is recognized as an ideal parameter for evaluating body vitamin D, there is no agreement between the organizations or authors regarding the ideal cut-off point for characterizing vitamin D deficiency, as it was observed in the results of this article, in which the authors used different cut-off points to classify sufficiency and insufficiency. The authors Lake et al. (22) and Coelho et al. (23) classified vitamin D sufficiency and deficiency in which the 25(OH)D levels were \geq 30 ng/mL and < 30 ng/mL. In the study by Sudfeld et al. (25) the restriction of the studied population for subjects was less than 30 ng/mL of 25(OH)D that also assists in translating the findings as HIV Programs in similar environments that may estimate the potential impact of implementation of vitamin D₃ supplementation based on the local prevalence of 25(OH)D < 30 ng/mL.

Several HIV related risk factors, as well as non-HIV related factors, have been associated with vitamin D deficiency (34). Some risk factors such as winter, increased age, low daily vitamin D intake, and elevated skin pigmentation are common to the general population. In addition to the risk factors observed in the general population, several studies have demonstrated an association with highly active antiretroviral therapy (HAART), especially with the use of efavirenz, a NNRTI, with increased risk of vitamin D deficiency (35,36).

Participants in the selected studies in this review were using (HAART). In the study by Coelho et al. (23), the levels of 25(OH)D were decreased within 24 weeks after initiation of efavirenz with lamivudine/zidovudine or emtricitabine/tenofovir, but they stabilized thereafter (36). With an average time of five-year therapy, the authors were not able to assess changes in the 25(OH)D levels related to the initiation of HAART, however, vitamin D insufficiency was associated with current use of efavirenz and nevirapine regardless of the duration of the treatment.

At the study by Lake et al. (22) no association was observed between specific antiretroviral agents and basal levels of 25(OH)D, as there was no association between antiretroviral agents and the success or failure to reach levels higher than 30 ng/mL of

25(OH)D after 12 weeks, which may be justified according to the authors by the small sample size that may have prevented the detection of association between therapy and depletion rates. The authors reported that efavirenz therapy was associated with increased prevalence of vitamin D insufficiency (11). Patients taking efavirenz require higher doses of vitamin D compared to other antiretroviral drugs, since it increases the catabolism of 25(OH)D. However, the precise dose has not yet been defined. A study of HIV-infected patients with HAART (37) demonstrated an increase in bone biomarkers following supplementation with 300,000 IU of vitamin D.

In Longenecker et al. (38) inflammatory biomarkers were not altered by vitamin D supplementation. The statistically significant difference was in the change in IL-6 between groups, with an increase in the probability of the placebo group rather than a decrease in concentrations of IL-6 among those taking vitamin D. However, the authors recommend that further studies are needed to discover the relative importance of inflammatory biomarkers in pathophysiology for the risk of comorbidities in people living with HIV.

Regarding the duration of the intervention, the study by Coelho et al. (23) lasted 24 weeks, in which vitamin D was measured by chemiluminescent assay, and the participants with insufficient vitamin D levels were prescribed a regimen of vitamin D₃ supplementation of 50,000 IU, orally, twice weekly for five weeks, followed by another phase with supplementation of 8,000 IU twice a week, for 19 weeks, a regimen that was in agreement with the Society of Endocrinology (33).

The study by Lake et al. (39) was from June 2010 to April 2011, in which vitamin D was also measured by chemiluminescence, and the project participants were divided into two groups: participants with vitamin D insufficiency initiated an oral vitamin D₃ supplementation regimen of 50,000 IU twice a week, for five weeks, and then 2,000 IU per day until the end of 12 weeks; and the other group was made up of non-HIV infected people, with low bone mineral density, who underwent a supplementation regimen of 50,000 IU per week, for five weeks, followed by maintenance therapy with 1,400 IU daily.

The five studies aimed to evaluate the effect of cholecalciferol supplementation on vitamin D blood levels and all of them found positive results, in which vitamin D levels were increased after weeks of supplementation, proving the efficiency of supplementation, similar to other studies such as the one by Sheperd et al. (40) and the European AIDS Clinical Society guidelines of 2014, that recommend supplementation in patients with 25(OH)D levels < 10 ng/mL.

Vitamin D supplementation may, therefore, decrease the progression of HIV and prevent the development of tuberculosis and other opportunistic diseases, which makes it more important to carry out clinical studies such as those chosen in this review that help to prove the efficacy of vitamin D supplementation in the prevention of infectious diseases and the very progression of HIV. In patients with vitamin D deficiency, this may be a cost-effective and non-toxic therapeutic option. As vitamin toxicity, characterized by hypercalcemia, is observed very rarely and Hathcock et al. (41)

evaluated several studies and did not find any case of intoxication in individuals with daily doses up to 10,000 IU of cholecalciferol.

The protocol of this review was designed considering the recommendations for systematic review and was published allowing the reproducibility of the research and reducing the potential bias of selection of the studies. However, there was a choice of the Portuguese and English languages for the search of the studies and with publication limit of 10 years, which nevertheless ensures a broad scope of the research.

However, this review does not have the limitations, the studies analyzed presented only small samples, not influencing the ability to evaluate the association between changes in 25(OH)D levels and clinical and demographic factors, such as the use of antiretroviral therapy; the majority of the studies do not have national representativeness, and the findings cannot be generalized for women and people of non-white ethnicity; the lack of standardization in the supplementation regime (dose, duration), mainly in the maintenance phase, can influence the final result.

However, the gap remains in the knowledge about the effects of vitamin D supplementation on biochemical markers in people with HIV, which reinforces the need for future research to elucidate these issues. In the meantime, we encourage the adoption of an adequate diet associated with other healthy practices, at the individual level, obviously seeking to find an alternative for the improvement of the vitamin D status of the HIV patient.

CONCLUSION

The results of this systematic review provide evidence that vitamin D supplementation in HIV-positive patients on antiretroviral therapy increased serum levels of 25(OH)D. The five studies reviewed here showed a positive effect of supplementation on lymphocyte counts supporting the vitamin D benefit in immunological recovery, which is particularly relevant for the population living with HIV and effective for a variety of suppressive ART regimens. However, given the scarcity of results, new studies of supplementation with this vitamin in this public are needed to add to the protocol of treatment of the antiretroviral therapy.

REFERENCES

1. Premaor MO, Furlanetto TW. Hipovitaminose D em adultos: entendendo melhor a apresentação de uma velha doença. *Brazilian Archives of Endocrinology and Metabolism* 2006;50(1):25-37.
2. Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP et al. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2006;96:7.
3. Peters BSE, Martini LA. Funções Plenamente Reconhecidas de Nutrientes-Vitamina D. Brasil: International Life Sciences Institute Brasil (ILSI); 2014.
4. Etminani-Esfahani M, Khalili H, Jafari S, Abdollahi A, Dashti-Khavidaki S. Effects of vitamin D supplementation on the bone specific biomarkers in HIV infected individuals under treatment with efavirenz. *BMC Res Notes*, 2012;5:1.
5. Rodrigues AD, Weirich E, Duarte EZ. Determinação de valores próprios de referência para vitamina D, hormônio paratireoideo e cálcio em um laboratório de análises clínicas. *Scientia Medica* 2018;28:4.

6. Holick MF. Vitamin D deficiency. *N Engl J Med* 2007;357:3.
7. Bischoff-Ferrari HA, Giovannucci E, Willett WC, Dietrich T, Dawson-Hughes B. Estimativa das concentrações séricas ótimas de 25-hidroxivitamina D para múltiplos desfechos em saúde. *A Revista Americana de Nutrição Clínica* 2006;84(1):18-28.
8. Villamor E. Um papel potencial para a vitamina D na infecção pelo HIV? *Revisões Nutricionais* 2006;64(5):226-33.
9. Viard JP, Souberbielle JC, Kirk O, Reekie J, Knysz B, Losso M. Vitamin D and clinical disease progression in HIV infection: results from the EuroSIDA study. *Aids* 2011;25(10):1305-15.
10. Van den Bout-Van Beukel DCJ, Fievez L, Michels M, Varredura FC, Hermus AR, Bosch ME, et al. Deficiência de vitamina D entre indivíduos infectados pelo HIV tipo 1 na Holanda: efeitos da terapia anti-retroviral. *Pesquisa sobre a AIDS e Retrovírus Humanos* 2008;24(11):1375-82.
11. Brown TT, Mccomsey GA. Association between initiation of antiretroviral therapy with efavirenz and decreases in 25-hydroxyvitamin D. *Antivir Ther* 2010;15:3.
12. Kim JH, Gandhi V, Psevotos GJ, Espinoza F, Parque J, Sharp V. Avaliação dos níveis de vitamina D entre pacientes infectados pelo HIV na cidade de Nova York. *Pesquisa sobre a AIDS e Retrovírus Humanos* 2012;28(3):235-41.
13. Ezeamama AE, Guwatudde D, Wang M, Bagenda D, Kyeyune R, Sudfeld C, et al. Vitamin-D deficiency impairs CD4+ T-cell count recovery rate in HIV-positive adults on highly active antiretroviral therapy: A longitudinal study. *Clinical Nutrition, Oxford*, 2016;35:5.
14. Rehman AM, Woodd SL, Heimbürger DC, Koethe JR, Friis H, Praygod G, et al. Changes in serum phosphate and potassium and their effects on mortality in malnourished African HIV-infected adults starting antiretroviral therapy and given vitamins and minerals in lipid-based nutritional supplements: secondary analysis from the Nutritional Support for African Adults Starting Antiretroviral Therapy (NUSTART) trial. *Br J Nutr* 2017;117(6):814-21.
15. Moher D, Liberati A, Tetzlaff J, Altman DG. PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med* 2009;151:4.
16. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJM, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary?. *Control Clin Trials* 1996;17:1.
17. de Carvalho APV, Silva V, Grande AJ. Avaliação do risco de viés de ensaios clínicos randomizados pela ferramenta da colaboração Cochrane. *Rev Diagn Tratamento* 2013;18:1.
18. Brinkhof MW, Boule A, Weigel R, Messou E, Mathers C, Orrell C. Mortalidade de HIV- pacientes infectados que iniciam a terapia anti-retroviral na África Subsaariana: comparação com mortalidade não relacionada ao HIV. *PLoS Medicine* 2009;6:4.
19. Haverkort ME, van der Spek BW, Lips P, Slieker WA, Ter Heine R., Huitema AD, et al. Síndrome de Fanconi induzida por tenofovir e osteomalácia em dois pacientes infectados pelo HIV: papel dos níveis intracelulares de difosfato de tenofovir e revisão da literatura. *Revista Escandinava de Doenças Infecciosas* 2011;43(10): 821-6.
20. Sudfeld CR, Mugusi F, Aboud S, Nagu TJ, Wang M, Fawzi WW. Efficacy of vitamin D₃ supplementation in reducing incidence of pulmonary tuberculosis and mortality among HIV-infected Tanzanian adults initiating antiretroviral therapy: study protocol for a randomized controlled trial. *Trials* 2017;18:5.
21. Klassen K, Martineau AR, Wilkinson RJ, Cooke G, Courtney AP, Hickson M. O efeito do tenofovir no metabolismo da vitamina D em adultos infectados pelo HIV depende do sexo e da etnia. *PLoS One* 2012;7:9.
22. Lake JE, Hoffman RM, Tseng CH, Wilhalme HM, Adams JS, Currier JS. Success of Standard Dose Vitamin D Supplementation in Treated Human Immunodeficiency Virus Infection. *Open Forum Infectious Diseases* 2016;2:2.
23. Coelho L, Cardoso SW, Luz PM, Hoffman RM, Mendonça L, Veloso VG, et al. Vitamin D3 supplementation in HIV infection: effectiveness and associations with antiretroviral therapy. *Nutrition Journal* 2015;14:81.
24. Canuto JMP, Canuto VMP, Lima MHA, Omena ALCS, Morais TML, Paiva AM, et al. Fatores de risco associados à hipovitaminose D em indivíduos adultos infectados pelo HIV/aids. *Arq Bras Endocrinol Metab* 2015;59:1.
25. Sudfeld CR, Mugusi F, Aboud S, Nagu TJ, Wang M, Fawzi WW. Efficacy of vitamin D3 supplementation in reducing incidence of pulmonary tuberculosis and mortality among HIV-infected Tanzanian adults initiating antiretroviral therapy: study protocol for a randomized controlled trial. *Trials* 2017;18:5.
26. Conrado T, Miranda-Filho DB, Ximenes RAA, Albuquerque MF, Lacerda HR, Ramos RCF, et al. Vitamin D Deficiency in HIV-Infected Women on Antiretroviral Therapy Living in the Tropics. *J Int Assoc Physicians AIDS Care* 2011;10:4.
27. Cervi A, Francheschini SCC, Priore SE. Critical analysis of the use of the body mass index for the elderly. *Rev Nutr* 2015;18:6.
28. Shafie H, Wang S, Inci F, Toy M, Henrich TJ, Kuritzkes DR, et al. Emerging Technologies for Point of Care Management of HIV Infection. *Annu Rev Med* 2015;66:1.
29. Legeai C, Vigouroux C, Souberbielle JC, Bouchaud O, Boufassa F, Bastard JP, et al. Associations between 25-Hydroxyvitamin D and Immunologic, Metabolic, Inflammatory Markers in HIV-Infected Persons. *J Infect Dis* 2014;210:2.
30. Shepherd L, Souberbielle JC, Bastard JP, Fellahi S, Capeau J, Reekie J, et al. Prognostic Value of Vitamin D Level for All-cause Mortality, and Association With Inflammatory Markers, in HIV-Infected Persons. *J Infect Dis* 2014;210:2.
31. WHO, Organização Mundial da Saúde, et al. Atualização global sobre o tratamento do HIV 2013: resultados, impacto e oportunidades; 2013.
32. Wagner D. Ensaio clínico aleatório de doses de vitamina D3 nos níveis de metabólitos prostáticos de vitamina D e rotulagem ki67 em pacientes com câncer de próstata. *J Clin Endocrinol Metab* 2013;98:4.
33. Holick MF. Vitamin D deficiency. *N Engl J Med* 2007;357:3.
34. Allavena C, Delpierre C, Cuzin L, Rey D, Viget N, Bernard J, et al. High frequency of vitamin D deficiency in HIV-infected patients: effects of HIV-related factors and antiretroviral drugs. *J Antimicrob Chemother* 2012;67:9.
35. Dao CN, Patel P, Overton ET, Rhame F, Pals SL, Johnson C, et al. Low Vitamin D among HIV-Infected Adults: Prevalence of and Risk Factors for Low Vitamin D Levels in a Cohort of HIV-Infected Adults and Comparison to Prevalence among Adults in the US General Population. *Clin Infect Dis* 2011;52:3.
36. Havers FP, Detrick B, Cardoso SW, Berendes S, Lama JR, Sugandhavesa P, et al. Change in Vitamin D Levels Occurs Early after Antiretroviral Therapy Initiation and Depends on Treatment Regimen in Resource-Limited Settings. *PLoS ONE* 2014;9:4.
37. Etmnani-Esfahani M, Khalili H, Jafari S, Abdollahi A, Dashti-Khavidaki S. Effects of vitamin D supplementation on the bone specific biomarkers in HIV infected individuals under treatment with efavirenz. *BMC Res Notes* 2012;5:1.
38. Longenecker CT, Hileman CO, Carman TL, Ross AC, Seydalkan S, Brown TT, et al. Vitamin D supplementation and endothelial function in vitamin D deficient HIV-infected patients: a randomized placebo-controlled trial. *Antivir Ther* 2014;17:4.
39. Lake JE, Hoffman RM, Tseng CH, Wilhalme HM, Adams JS, Currier JS. Success of Standard Dose Vitamin D Supplementation in Treated Human Immunodeficiency Virus Infection. *Open Forum Infect Dis* 2015;2:2.
40. Hathcock JN, Shao A, Vieth R, Heaney R. Risk assessment for vitamin D. *Am J Clin Nutr* 2007;85:1.