REVIEW PAPER

Evidence of vitamin D deficiency in mediating disease progression among people living with human immunodeficiency virus: a narrative review

Jan Racky Masa

Institute of Tourism and Hotel Management, Far Eastern University, Manila, Philippines
Institute of Human Nutrition and Food, University of the Philippines Los Baños, Laguna, Philippines

Abstract

Advances in human immunodeficiency virus (HIV) diagnosis and management have increased life expectancy of HIV-infected individuals. However, despite rising quality of life among HIV patients, maintaining nutritional health and depending on antiretroviral regimen are key factors in the management of disease progression. Scientific articles published between January 2011 and December 2021 were examined. The study and compounding evidence from the literature revealed that poor nutrition and delayed adherence to HIV antiretroviral treatment contribute to micro-nutrient deficiency and HIV pathogenesis. Prevalence of micro-nutrient deficiencies were highly evidenced among HIV patients, particularly in countries with food insecurity and limited access to a variety of food. The use of antiretroviral drugs has the potential to lower vitamin D levels, consequently leading to disease progression by increasing oxidative stress, deterioration of CD4+ count level, and development of metabolic complications. Furthermore, vitamin D supplementation intervention study provided contradictory results, implying that more research is needed. In general, corroborated findings established protection and potency of supplementation of vitamin D among people with HIV receiving antiretroviral therapy. Therefore, according to this review, vitamin D supplementation may be a potential protective therapy for HIV-infected individuals with prior deficiencies.

HIV AIDS Rev 2025; 24, 2: 85-93
DOI: https://doi.org/10.5114/hivar/153413

Key words: vitamin D, oxidative stress, CD4+, HIV, antiretroviral therapy.

Introduction

Human immunodeficiency virus (HIV)/acquired immune deficiency syndrome (AIDS) remains a global health concern that greatly impacts countries with poor healthcare system and food insecurity, especially in low-income and developing nations. Provision of food security is critical for HIV-infected patients to maintain their physical health [1]. As the number of HIV cases increases in developing countries, delayed and inconsistent antiretroviral therapy (ART) adherence has been associated with inadequate viral suppression and disease progression. Additionally, the literature suggests that HIV-positive patients have been subjected to the burden of malnutrition before initiation and during ART. Weight loss and wasting were observed among young HIV-infected individuals, and the trend of obesity was observed among adults. The persistent incidence of malnutrition in HIV-positive people contributes to the immune system's progressive deterioration and increased suscep-

Address for correspondence: Jan Racky Masa, Far Eastern University, Manila, Philippines, e-mail: masajanracky@gmail.com

Article history:
Received: 31.05.2022
Revised: 24.08.2022
Accepted: 01.09.2022
Available online: 05.05.2025

tibility to opportunistic infections. Thus, micro-nutrient deficiency raises the incidence of developing into advanced stage of HIV infection as a result of malabsorption, altered metabolism, altered gut microbiota, and delayed adherence to ART. This is supported by a study that found that female adults in Zimbabwe face a double burden of malnutrition, i.e., under-nutrition in the young population and overweight/obesity in adults, both of which were linked to an elevated incidence of lifestyle-related comorbidities and mortality [2]. A study found that an increased consumption of cholesterol, saturated and trans fats, sodium, and simple carbohydrates, was associated with increased consumption of fast food, low fiber intake, and a decrease in CD4+ T lymphocyte count. As a result, HIV patients in Sao Paolo, Brazil, exhibited weight gain and an increase in body mass index (BMI) [3]. Furthermore, a study observed predominant changes in body fat composition and weight gain among HIV-infected patients [4]. Malnutrition was shown to have a negative impact on the immune system in every way. Negative effects on immunity can also be seen from a lack of essential micro-nutrients, such iron, folic acid, zinc, selenium, and vitamins A, C, and D [5]. Limited access to healthcare and diets lacking essential vitamins and minerals, influence malnutrition-related immunosuppression, which is a contributing factor in the advancement of disease and impaired health outcomes among HIV patients. Even with the converging evidence suggesting that achieving good nutrition and promoting antioxidants intake, particularly vitamin D, may benefit both healthy and HIV-infected individuals by the reduction of inflammation and oxidative stress, the efficacy and safety of vitamin D supplementation among HIV patients remains to be undetermined. Despite the increase in life expectancy due to the use of ART, the literature shows that metabolic problems and micro-nutrient deficiencies are becoming increasingly prevalent among HIV-positive patients. This coincides with the transition from acute to chronic disease management.

Therefore, in this study, the evidence of vitamin D deficiency and its effect on health-related outcomes among HIV-positive patients were investigated. This review presented various epidemiological and experimental evidence of hypovitaminosis D and its relationship to adverse health outcomes, such as the development of metabolic complications, oxidative stress, and effect on CD4+ count of HIV patients. Additionally, this study elucidated the potential mechanism of action and interventional strategies for the improvement of health-related outcomes of vitamin D supplementation in HIV-infected patients.

Material and methods

This study utilized a comprehensive narrative review to synthesize the existing literature evidence on vitamin D deficiency among HIV patients, by conducting a rigorous search through electronic databases, including PubMed, ProQuest, and Google Scholar search engine, to gain insight into the current state of the literature. A total of 287 scholarly articles published from January 2011 to December 2020 were included for screening. To meet the inclusion criteria, the papers were peer-reviewed and written in the English language. Prospective and experimental studies on human cases were considered the most important articles for this review. The search for reputable publications focused on deficiency of vitamin D among HIV-infected individuals, with no restrictions in age, ethnic origin, gender, clinical status, or other characteristics. The study employed a valid research and statistical design to address the research objectives. Papers including more than 10 patients were considered as a factor for inclusion. Title, authors, duration, and characteristics of sample, with baseline vitamin D status, cut-off of vitamin D deficiency, 25(OH)D = 20 ng/ml; vitamin D deficiency or insufficiency, 25(OH)D = 30 ng/ml; exposure and outcome variables, limitations, and conclusion of the study were all extracted. Furthermore, articles from various epidemiologic and experimental studies were considered to present connection of malnutrition, evidence of vitamin D deficiency, and associated impacts on disease progression, oxidative stress, and CD4+ status in HIV-infected patients under ART. After selecting articles for the review based on inclusion criteria, fifteen ($n = 15$) scientific articles, including 9 observational ($n = 9$) and 6 experimental studies ($n = 6$), were reviewed and examined to interpret the strength of relationship.

Results and discussion

Metabolic disturbances in PLHIV under antiretroviral therapy

Over the years, the access to ART has become increasingly available. Adherence to ART showed huge reductions in rates of death and infections when the treatment was provided in early stages of the disease. However, studies have shown that people living in HIV or even before receiving ART, suffer from malnutrition. Undernutrition exists in mother-to-child transmission, and continues to affect children and adolescents in low-income countries [6], while overnutrition has been increasingly observed in adults on ART in Ethiopia [7]. HIV infection and malnutrition are strongly related. Thus, nutritional health is critical for HIV/AIDS patient's immune system, as adequate amounts of macro- and micro-nutrients are required for normal functioning. Nutrition intervention as well as the provision of proper nutrition and food security, are all part of the regimen for ensuring positive health outcomes in HIV-infected patients.

The increase in life expectancy has been attributed to the adherence to antiretroviral medications among HIV patients. Despite improvement in health-related outcomes, metabolic disturbances and complication have been reported in HIV patients using ART. HIV medications, including nucleoside reverse transcriptase inhibitors (NRTIs), such as zidovudine and tenofovir, non-nucleoside reverse transcriptase inhibitors (NNRTIs), such as nevirapine and efavirenz as well as protease inhibitors (PIs), such as lopinavir and ritonavir, were specifically investigated in the association

of nutritional health and metabolic disturbances. Converging evidence from the review supports the shift of condition from mortality-related infection to chronic disease, with respect to the use of ART and milieu factors, which were similarly observed in general population. Metabolic alterations in the use of antiretroviral drugs were common in HIV-infected patients, and exacerbated the risk of obesity and oxidative stress, which consequently may contribute to a variety of morbidities, including insulin resistance and type 2 diabetes mellitus [8]. In HIV patients under ART, an increased level of LDL and pro-atherogenic compounds were observed, considered as precursors in the incidence of heart diseases, most notably atherosclerosis and cardiovascular complications [9]. In line with this previous findings, a study among HIV patients who were not on antiretroviral drugs, showed that metabolic disorders were associated with HIV infection and lifestyle-related factors, such as inadequate physical activity, cigarette smoking, and poor nutrient consumption. This recent study also revealed that patient's introduction into ART can enhance dyslipidemia and increase the risk of cardiovascular disease [10]. In several clinical trials, changes in lipid concentrations were reported in HIV patients who initiated ART. Findings suggested that, in comparison with people with normal lipid levels, HIV-infected patients on ART presented lower levels of HDL and modified lipoproteins, which were ascribed to systemic inflammation of the disease and initiation of antiretroviral medication [11]. Significant impairment of normal lipolytic activity may result in low HDL plasma concentrations and increased LDL level in the blood. Therefore, prolonged exposure to this condition may lead to progression of the disease and cardiovascular disorders among HIV-positive patient receiving ART [12, 13].

The presence of insulin resistance in HIV patients under ARV was attributed to various factors, including lipodystrophy, oxidative stress, pre-existing inflammation, and other predisposing features, such genetics, age, BMI, and gender. Studies also revealed that ART causes insulin resistance by inhibiting the insulin signaling pathway, and the effect of increased mitochondrial dysfunction in adipocytes and muscles was observed in different epidemiological studies. Protease inhibitor inhibits GLUT4 transporter that leads to decrease of glucose uptake in the muscles and adipocyte tissue. Furthermore, alteration of adipogenic proteins, such as the sterol regulatory element binding protein-1, with the use of protease inhibitor present in antiretroviral drugs, inhibits normal cell morphology [14]. Adipocyte differentiation and adipokine secretion are known to modulate insulin sensitivity, which is necessary for normal blood glucose control for both healthy and HIV-infected individuals.

In HIV-infected patients, the initiation of lopinavir-ritonavir therapy showed an increasing incidence of metabolic abnormalities, especially hypertriglyceridemia. Moreover, an increased circulating level of total serum cholesterol and elevated level of LDL were found after the initiation of PI therapy and the use of ART in HIV cohort [15, 16]. Among NNRTIs, it has been well-established that efavirenz exposure increases triglyceride and LDL cholesterol levels. A study conducted in Thailand among HIV-positive adolescent individuals corroborates the previous literature. Additionally, the same study discovered that prolonged exposure to tenofovir decreases the associated risk [17].

Vitamin D deficiency in PLHIV receiving antiretroviral therapy

Deficiency in vitamin D level has been associated with a variety of pathologic infections and immune disorders in HIV-infected individuals. Vitamin D deficiency has been strongly connected to oxidative stress and mitochondrial dysfunction in HIV patients on and not on ART [18, 19]. Epidemiological studies conducted worldwide demonstrated high incidence of inadequate levels of vitamin D across all age groups. The 2013 National Nutrition Survey confirms prior research, indicating an increased number of cases with vitamin D deficiency recorded in a Filipino cohort. Moreover, the study discovered that gender, age, and geographic location were strongly associated with an increased prevalence of vitamin D deficiency [20].

The interaction of oxidative stress and systemic inflammation have been shown to accelerate the development of HIV disease into AIDS. While ART decreases viral load and slows the progression of opportunistic infections, vitamin D's critical role in immunity was recognized as a cornerstone of pro-hormone activity, and a precursor in activating innate and adaptive immune pathways, which enhance the immune response to the virus. Calcitriol or 1.25 dihydroxy vitamin D's interaction with intra-cellular receptors has an effect on gene transcription and activation of vitamin D receptors, resulting in the initiation of multiple second messenger systems. As a result, it is unsurprising that vitamin D deficiency elevates the risk and pathogenesis of a number of age-related metabolic complications associated with oxidative stress [21]. As previously stated, HIV, pre-existing micro-nutrient deficiency (particularly hypovitaminosis D), and ART, all increase the risk of lifestyle-mediated metabolic complications, especially lipodystrophy, obesity, type 2 diabetes, and cardiovascular disease.

Oxidative stress may be involved in multiple stages of the viral life cycle, including viral replication and its associated effects, such as pro-inflammatory response and reduced immune cell proliferation. HIV-infected individuals receiving antiretroviral medication produce more free radical species than antiretroviral-naive HIV patients as well as healthy subjects [22]. Additionally, a clinical study revealed that hypovitaminosis D was linked to the increase in inflammatory markers (TNF-α) and adiponectin in HIV patients receiving ART [23]. Subsequently, an increase in lipid peroxidation in response to high molecular weight aldehyde (MDA) and an elevated level of reactive oxygen species in HIV-positive patients, indicated a decline in total antioxidant capacity (TAC) [24]. This is equally related to the findings of a study, in which HIV infection increased oxidative stress. This was further exacerbated by the use of ART, as

demonstrated by the increase in MDA and antioxidant profile between HIV-positive individuals undergoing ART. ART-naive HIV individuals and healthy children cohorts were compared with baseline and end-line trends [25]. The presence of chronic inflammation and oxidative stress impaired the progression of HIV disease.

Vitamin D deficiency has been strongly correlated with late CD4+ recovery following ART initiation in HIV-infected patients. Vitamin D deficiency was identified as a common occurrence in HIV patients receiving ART [26]. Vitamin D deficiency/insufficiency was associated with the use of efavirenz, nevirapine, tenofovir, and protease inhibitors [27]. Additionally, patients receiving efavirenz had an increased risk of opportunistic infection [28]. Increasing number of studies confirmed that the advancement of HIV infection into AIDS, along with the occurrence of chronic inflammation and impaired immune response, contribute to drastic decline of vitamin D levels. People with deficiency and insufficiency of vitamin D demonstrate high susceptibility of cancer mortality [29]. HIV infection and exposure to certain antiretroviral medications may both affect vitamin D status. In addition, insufficient levels of vitamin D contributed to advanced cell aging, and may influence CD4+ count [30] (Tables 1 and 2).

Intervention studies on vitamin D supplementation in HIV-positive patients under ART

A systematic review on micro-nutrient supplementation among HIV cohort discovered that combining multiple micro-nutrient supplements, containing multivitamins and minerals with ART, had no plausible result in reducing HIV-related morbidity [31]. Daily supplementation has little-to-no effect on the level of CD4+ cells and viral load, which are common measures to assess progressive deterioration of health in HIV individuals even under ART. Similar findings were reported in studies on single or dual micro-nutrients. Despite a paucity of moderate evidence, vitamin A, D, zinc, and selenium supplementations may help HIV-infected patients in their existing micro-nutrient deficiency. In children with HIV infection, vitamin A supplementation showed protective effects and efficacy in reducing mortality attributed to improvement of immune response and paucity of evidence in reduction of diarrhea [32]. Zinc appeared to have the same anti-diarrheal properties in HIV-positive children as it does in HIV-negative children. In HIV-infected malnourished children, multiple micro-nutrient supplements exhibited some clinical benefits. An observational study conducted in Italy revealed that both oral and intra-muscular vitamin D supplementation significantly increased vitamin D levels in HIV patients with hypovitaminosis D. The literature confirms this finding, demonstrating that 12 weeks of oral vitamin D supplementation was effective in increasing vitamin D levels in study participants. As supported by a research with 24 weeks of intervention protocol using vitamin D supplementation, resulting in an increased 25 (OH) D levels in HIV patients with vitamin D deficiency. This study showed a strong correlation and association between increasing vitamin D level and CD4+ T lymphocyte status [33]. A randomized control trial conducted in Canada found that after six months of vitamin D supplementation, HIV-infected patients enrolled in ART failed to increase CD4+ count levels. However, the study suggested to induce vitamin D level using 1,000-2,000 IU as compared with 800 IU and 1,600 IU single-dose weekly supplementation for six months used in the study [34].

An experimental intervention study in Botswana revealed repleting vitamin D levels in the blood using 12-week induced dosage of endogenous vitamin D supplementation, demonstrating safety and efficacy. In addition, the study showed associated improvements in weight gain and BMI regulation in children and adolescents, and an increase in BMI in adults [35]. Another study demonstrated safety and efficacy of a 12-month long-term daily high-dose vitamin D_3 supplementation as adjunct therapy in HIV-infected adults and children [36]. Additionally, supplementation with vitamin D provided evidence for the improvement and normalizing of vitamin D level, increasing CD4+ count, and decreasing viral load. As demonstrated in a clinical intervention study, increased CD4+ levels in HIV patients with improved and optimum vitamin D levels over time, indicated strong connection with vitamin D innate and adaptive immune response as well as plausible link with CD4+ restoration and proliferation in HIV patients [37]. However, some research provided inconsistent correlation in improving effect in CD4+ count and viral load level in vitamin D intervention, due to advance stages of disease. Lack of association in improving CD4+ status was reported in a clinical experiment among HIV patients, who were enrolled in antiretroviral regimen [12]. Successful repletion of vitamin D levels in the blood did not correlate with increased level of CD4+ among control groups adhering to vitamin D supplementation and ART [38]. A systematic review and meta-analysis concluded that ten months of adherence to ART and vitamin D supplementation in the early stage of the disease, effectively increased CD4+ count level [39]. Additionally, safety and efficacy of vitamin D supplementation among HIV-infected patients with hypovitaminosis D demonstrated a promising result in normalizing vitamin D status, with no adverse effects. Therefore, supplementation can be considered as an adjunct therapy in HIV patients receiving ART.

Mechanism of vitamin D action in oxidative stress and immune regulation in HIV disease

Chronic inflammation and oxidative stress are common in HIV-positive patients due to impaired immune response to infection. As HIV infection rely on constant adherence to ART, the role of endogenous supplementation of nutrients and minerals through dietary consumption and supplementation are primary considerations to alleviate the burden of micro-nutrient deficiency and malnutrition among

Table 1. Observational studies on the incidence of vitamin D deficiency among HIV-positive patients

Authors (year of publication) [Ref.], participants	Findings of the study	Type of the study and limitations
Aziz *et al.* (2012) [26], *n* = 204 HIV-infected women who completed 6-12 months observation: WIHS study in HAART intervention	89% patients had vitamin D deficiency (169 out of 204 study cases). Late CD4+ recovery after ART initiation in women with advanced disease was associated with vitamin D deficiency.	Cohort study
Allavena *et al.* (2012) [28], *n* = 2,994 HIV-positive patients followed in five French centers: Dat' AIDS cohort study	86.7% patients had vitamin D deficiency out of 2994 patients (55.6% vitamin D insufficiency, 31.1% vitamin D deficiency). An increased incidence of the prevalence of vitamin D deficiency was higher among patients taking antiretroviral therapy compared with general population. Increased risk was observed among patients on efavirenz.	Prospective cohort study
Hoffman *et al.* (2016) [23], *n* = 106 HIV-positive patients with 12-24 months follow-up visits: CARE vitamin D cohort	*n* = 66 vitamin D insufficient vs. *n* = 40 vitamin D sufficient subjects. The study suggests an association between vitamin D deficiency and markers of increased level of inflammation (TNF-α) and adiponectin	Cohort study
Theodorou *et al.* (2014) [44], *n* = 2,044 HIV-positive patients, with follow-up from December 2005 to March 2011	89.2% had 25(OH)D < 30 ng/ml. 32.4% had 25(OH)D < 10 ng/ml. Vitamin D deficiency was positively associated with progression of HIV disease into AIDS.	Retrospective analysis
Ezeamama *et al.* (2015) [46], *n* = 398 HIV-positive adults, clinical nutrition	23% of vitamin D sufficiency, 60% of vitamin D insufficiency, and 17% of vitamin D deficiency. CD4+ T cell recovery in HIV-positive patients on antiretroviral therapy was reduced in those with vitamin D deficiency. Supplementing with vitamin D may raise serum vitamin D levels and, consequently, CD4+ cell count.	Cross-sectional
Kanwal and Rehman (2023) [47], *n* = 398 HIV-positive patients, *n* = 232 HIV-negative individuals	15% of vitamin D deficiency and 39% of vitamin D insufficiency. According to the findings, HIV patients with vitamin D deficiency or insufficiency were more likely to contract an opportunistic infection. Vitamin D deficiency is significantly related to increased HIV viral load and CD4 count.	Cross-sectional
Antony *et al.* (2018) [30], *n* = 94 HIV-positive patients	37 patients had vitamin D deficiency. Vitamin D deficiency is more common as people get older. The study found that age may potentially influence CD4+ count.	Cross-sectional
Deshwal and Arora (2018) [27], *n* = 475 HIV-positive adults	92.63% of patients had vitamin D deficiency; 65.68% males were vitamin D deficient. Vitamin D deficiency was high in HIV patients on antiretroviral regimens. Efavirenz, nevirapine, tenofovir, and protease inhibitors were associated with high levels of vitamin D deficiency/insufficiency.	Cohort study
Poiana *et al.* (2019) [45], *n* = 118 HIV-positive patients (72 males, 46 females) from Romania	The study found that hypovitaminosis D was present in 84.04% of HIV-infected patients, but there was no correlation between serum 25(OH)D concentration and any specific HIV-related factor. There is a need for clinical guidelines for HIV patients regarding vitamin D status and supplementation.	Cohort study

HIV-infected individuals. The role of antioxidants warrants protective and adjunct therapy in regulating and supporting immunity in HIV pathogenesis. Hypovitaminosis D promotes the expression of pro-inflammatory response and altered gene expression. Subsequently, antiretroviral medication are shown to decrease vitamin D utilization and absorption, resulting in deficiency of this and other micro-nutrients, such as antioxidants. As a result, antioxidant enzymes are induced to combat reactive oxygen species. Intuitively, increasing the antioxidant level in the cell may imply a protective and maintenance effect against oxidative stress and further mitochondrial dysfunction.

As a pro-hormone, vitamin D can be obtained in a variety of ways, the most common of which is through sunlight-

Table 2. Interventional studies on vitamin D supplementation among people living with HIV receiving antiretroviral therapy

Reference	Study design, location, and population	Intervention	Primary outcomes	Findings and conclusions
Falasca *et al.* (2014) [38]	Prospective cohort study in Italy, with 182 HIV-positive participants (*n* = 153 vitamin D deficient).	Vitamin D supplementation groups: Group 1: Oral supplementation; Group 2: Intra-muscular supplementation; Group 3: Control group. 10 months of follow-up.	Fasting glucose, insulin resistance, triglycerides, cholesterol (HDL, LDL), C-reactive protein, Na, K, phosphorus, and calcium serum levels were investigated. CD4+ and CD8+ T cell counts were also measured.	Oral and intra-muscular 10-month vitamin D supplementation improved 25(OH)D vitamin D level. In terms of CD4+ count, the study reported no significancy in the way of vitamin D supplementation.
Lake *et al.* (2015) [12]	Prospective, non-randomized, open-label without placebo control study in Los Angeles, California. 122 study participants were enrolled (40 cases with sufficient vitamin D level and 82 vitamin D deficient). HIV-positive individuals and HIV-uninfected with low bone mineral density.	Oral vitamin D supplementation was administered to vitamin D deficient patients with 50,000 IU, twice a day, for 5 weeks, followed by 2,000 IU daily for 12 weeks; the same regimen followed by 1,400 IU daily for 12 weeks was administered to subjects with sufficient vitamin D level.	Success rate in 25(OH)D level repletion after 12 weeks of vitamin D supplementation.	Oral vitamin D supplementation was efficacious in repleting vitamin D levels in both treatment groups. There was no association in the improvement of HIV status based on CD4+ count while under supplementation and antiretroviral treatment.
Coelho *et al.* (2015) [33]	Non-randomized, case control study in Rio De Janeiro, Brazil. 97 HIV-positive participants enrolled (*n* = 34 vitamin D sufficient; *n* = 63 vitamin D-deficient).	No intervention group: vitamin D-sufficient. Experimental group: HIV patients: 50,000 IU twice weekly for 5 weeks, followed by 8,000 IU twice weekly for 24 weeks.	Triglycerides, glucose, cholesterol (HDL, LDL), C-reactive protein, CD4+ T lymphocyte were measured.	In HIV patients with vitamin D deficiency, standardized vitamin D supplementation was effective after 24 weeks in raising of 25(OH)D level. Increases in CD4+ T lymphocyte counts were found to be strongly correlated with rising levels of active vitamin D.
Randomized control trial				
Kakalia *et al.* (2011) [34]	Randomized, non-blinded, controlled clinical trial in Canada. 53 HIV-positive patients completed the study, and were randomized into 3 study arms.	Vitamin D supplementation group 1: Group 2 (placebo): 5,600 IU (800 IU/ day). Group 3: 11,200 IU (1,600 IU/day, single-dose supplementation weekly for 6 months).	CD4+ count, viral load, serum calcium, phosphate, alkaline phosphatase, urine calcium, and creatinine were assessed.	CD4+ level did not increase after six months of supplementation with vitamin D in the treatment groups. At least, 1,000-2,000 IU of vitamin D may be necessary.
Steenhoff *et al.* (2015) [35]	Double-blind, randomized controlled trial in Botswana. Study participants were 60 HIV-positive children and adults with hypovitaminosis D.	Vitamin D supplementation randomized into 5 age groups, each receiving 4,000 or 7,000 IU per day of vitamin D_3 for 12 weeks.	Safety and efficacy measures as efficacy, serum 25-hydroxy vitamin D $\geq$ 32 ng/ml safety, as no simultaneous elevation of serum calcium and 25 D improvement in HAZ, WAZ, and BMIZ scores as well as CD4+ count and viral load.	Supplementation with a high-dose vitamin D_3 for 12 weeks was safe and effective in replenishing vitamin D levels, which was associated with an increase in BMI in adults as well as an improvement in HIV status.
Stallings *et al.* (2015) [36]	Clinical intervention trial in Philadelphia. HIV-positive African American and Hispanic participants (*n* = 58).	Oral vitamin D_3 supplementation, 7,000 IU/day and placebo, for 12-month follow-up.	Safety and efficacy outcomes, and CD4+ status, viral load, and vitamin D-related and metabolic variables.	12-month, long-term daily high-dose vitamin D_3 application demonstrated safety and efficacy in HIV-infected children and young adults. Vitamin D supplementation improved vitamin D status, including increase of CD4+ count and decrease of viral load.

induced skin synthesis. Calcidiol or 25-dihydroxyvitamin D and their active hormonal forms, calcitriol or 1.25-dihydroxyvitamin D, are both required for physiological functions in humans, including inflammation regulation and excessive intra-cellular oxidative stress, which are effective determinants of vitamin D status. A dysfunctional redox system in HIV patients is associated with a depletion of protective enzymes (i.e., glutathione peroxidase; superoxide dismutase; vitamins A, C, D, and E; and selenium, etc.), activation of immune signaling molecules (cytokines and chemokines), and an increase in free radical production (superoxide anion, hydrogen peroxide, and hydroxyl radicals). The immunological and biological consequences of this condition include lymphocyte and phagocyte activation, chronic inflammation, increased polyunsaturated fatty acid concentration, and lipoperoxidation. The effects of various pathological agents, whether direct or indirect, were also discussed. As the search for a functional cure of HIV intensifies, the oxidative stress status of natural HIV infection controllers continues to be a critical success factor for disease cure and management [40]. A number of antioxidant enzymes, such as superoxide dismutase (SOD), catalase, and glutathione peroxidase as well as numerous endogenous and dietary antioxidant compounds, were found in the body's natural antioxidant system, which react with and inactivate ROS to protect functional and structural molecules from ROS-mediated tissue damage.

Vitamin D's mechanism of action helps innate and adaptive immunity to overcome inflammation, reduce oxidative stress, control aging process, and reduce inter-cellular toxicity. Vitamin D is required in modulation of systemic inflammation, reduction of oxidative stress, mitochondrial function, and aging. On the other hand, vitamin D deficiency exacerbates systemic inflammation, increases mitochondrial dysfunction, and amplifies the production of reactive oxygen species. ART was linked to increased mitochondrial toxicity, because it inhibits a mitochondrial DNA polymerase. According to a review, this manifests as the onset of lactic acidosis, neuropathy, myopathy, and hepatic failure in HIV patients [41]. Moreover, intra-cellular nuclear factor erythroid-2 (Nfr2) protects cells from oxidative stress, and is modulated by vitamin D. Calcitriol, a type of vitamin D, helps to adjust and maintain normal cell signaling pathways, in addition to regulating ROS levels in the mitochondria through anti-inflammatory and anti-oxidant expression. As a result, tissues are shielded against toxins, mitochondrial dysfunction, and other harms. Systemic inflammation was found exacerbated by both hypovitaminosis D and mitochondrial dysfunction. As a result, adequate serum vitamin D levels in HIV-positive patients were critical for immune maintenance and HIV pathogenesis reduction [42].

The role of vitamin D, antioxidants, and optimal nutrition can subdue oxidative stress and chronic inflammation and maintain mitochondrial respiration. The adherence to antiretroviral medication and the impact of HIV infection were shown to consequently contribute to the elevation of reactive oxygen species (ROS) in turn action of antioxidant enzyme levels and functions of glutathione peroxidase (catalase), glutathione reductase (catalase), and superoxide dismutase (SOD), which were inhibited by HIV infection and antiretroviral medications, respectively [22]. Vitamin D influences the functions of monocytes, macrophages, and dendrite cells, which are all involved in the body's response to inflammation [43]. Because of its direct effect on T cells, vitamin D can induce an anti-inflammatory response. Therefore, the presence of vitamin D deficiency in HIV-infected patients demonstrate strong correlation with the progression of the disease by adversely modulating both the innate and adaptive immune responses to HIV infection.

Study limitations and drawbacks

The study has certain limitations and mainly relied on open-access literature related to the search topic. The number of participants in some of the studies reviewed was limited due to restricted availability of sample cases and missing data on follow-ups, as reported in the inclusion criteria of observation and experimental studies.

Conclusions

Compounding evidence from the review of epidemiologic and experimental studies revealed that people living with HIV have increased susceptibility of micro-nutrient deficiency. Thus, nutritional health plays a role in the onset of opportunistic infections, increased oxidative stress, decreased CD4+ count, and mediates viral load suppression. Most specifically in this review, induced vitamin D deficiency was observed in HIV-infected individuals receiving ART. Subsequently, hypovitaminosis D exacerbates oxidative stress and chronic inflammation, and was demonstrated to be involved in the development of HIV into AIDS, and elevated risk of metabolic complications, such as cardiovascular disease and diabetes. Low level of vitamin D inhibits the innate and adaptive immunity response. Hence, instinctively, vitamin D supplementation can potentially be used as adjunct therapy to reduce chronic inflammation, control oxidative stress, and improve mitochondrial function and immunity.

Supplementation strategy demonstrated to be efficacious and safe in vitamin D repletion while under ART. The role of supplementation as adjunct therapy can be potentially useful in regulating immune response and protection of HIV-related comorbidities and infection. Future research in vitamin D supplementation and status should examine the level of oxidative stress and other health parameters in HIV-infected patients under ART, in order to understand other factors, such as drug and supplement interaction. Furthermore, the current study provides new insights for physicians, nutritionists, and dietitians to investigate, particularly the role of supplementation in managing metabolic complications in people with HIV under antiretroviral medication as well as in developing guidelines for nutritional counseling of people living with HIV and with pre-existing nutrient deficiencies.

Disclosures

1. Institutional review board statement: Not applicable.
2. Assistance with the article: None.
3. Financial support and sponsorship: None.
4. Conflicts of interest: None.

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