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Review

Effects of sunlight exposure and vitamin D supplementation on HIV patients

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ABSTRACT

Unlike many vitamins derived predominantly from food sources, vitamin D is produced endogenously in the skin upon exposure to sunlight. Ethnicity, skin pigmentation, socioeconomic status, geographic location, climate and sunscreen; all of these factors contribute to the amount of insolation for any given individual. Insufficient insolation creates the prerequisites for vitamin D deficiency. This is particularly true in HIV-infected individuals, who are highly vulnerable to vitamin D insufficiency/deficiency, as it plays a huge role in the musculoskeletal and cardiovascular systems. Antiretroviral therapy may also be a factor in vitamin D deficiency. Today, as the issues of preventing common skeletal and non-skeletal diseases with HIV-infected people are becoming highly relevant, the maintenance of vitamin D levels through exposure to sunlight or supplementation appears to be an effective and safe solution. This review focuses on studies concerning the potential role of vitamin D supplementation through adequate sunlight exposure or dietary intake in HIV-infected people. The biology and epidemiology of HIV infection, as well as the issues related to vitamin D deficiency, its status on immune function, the effect of vitamin D against HIV disease progression and other health aspects of this vitamin, are briefly explained.

1. Biology and pathogenesis of HIV

The human immunodeficiency virus (HIV) is classified in the *Retroviridae* family of retroviruses, and more specifically belongs to the *Lentivirus* genus. Two types of HIV have been intensively studied: HIV-1 and HIV-2 [1,2]. HIV-1, formally known as human T-lymphotropic virus 3/lymphadenopathy associated virus, HTLV-III/LAV, which is the most common and pathogenic type of HIV, initially described in 1983 [3,4]. The global HIV emergence is mainly due to the epidemic spread of HIV-1. In the overwhelming majority of cases, unless otherwise specified, HIV implies HIV-1. The type of HIV-1 is categorized into the main group M, which is responsible for most HIV-1 infections in the global AIDS pandemic and several subgroups: N, O, and P. It is believed that these lineages were formed as a result of independent cross-species transmission, and subsequent mutations [5]. HIV-2 was identified in 1986 [6], with greater genetic similarity to the simian immunodeficiency virus (SIVsmm) of mangabey monkey. The genomes of HIV-1 and HIV-2 have about 60 % homology in the conserved genes as *gag* (group-specific antigen) and *pol* (polymerase) genes, and up to 45 % homology in the *env* (envelope) genes [7].

The virion of HIV, shown in Fig. 1, consists of a genome containing two copies of positive-sense single-stranded RNA and enzymes, such as reverse transcriptase, integrase, and protease. The cylindrical capsid is composed and made up of 2000 copies of the viral protein p24 [8]. The outer membrane of the capsid is represented by a lipid bilayer, the viral envelope, which contains trimeric spikes of the virus-encoded external glycoproteins gp120 and transmembrane gp41 glycoproteins [9]. The penetration of HIV-1 into host cells is initiated by interaction between envelope glycoprotein gp120 and chemokine receptors CXCR4 and CCR5. Molecule-specific recognition of CXCR4 or CCR5 is mediated through the V3 loop of the HIV-1 glycoprotein gp120. The binding of the V3 loop to CXCR4 or CCR5 determines the cellular tropism of HIV-1 and represents a purposeful step toward the entry of HIV-1 into $CD4^+$ T cells [10].

The schematic depiction of the HIV-1 life cycle and its potential steps is demonstrated in Fig. 2. The main target cells of HIV-1 are $CD4^+$ T lymphocytes and macrophages. Once the virus is integrated into the host genome, HIV is called a provirus (DNA copy), on the matrix of which viral RNA is synthesized by the virus's reverse transcriptase [11]. In addition to $CD4^+$ T lymphocytes and macrophages, dendritic cells of the bone marrow, skin, mucous membranes, lymph nodes, and microglial cells serve as a virus reservoir [12]. In the lymph nodes, the proportion of lymph node mononuclear cells (LNMC) containing proviral DNA is higher than in peripheral blood mononuclear cells (PBMC) [13],

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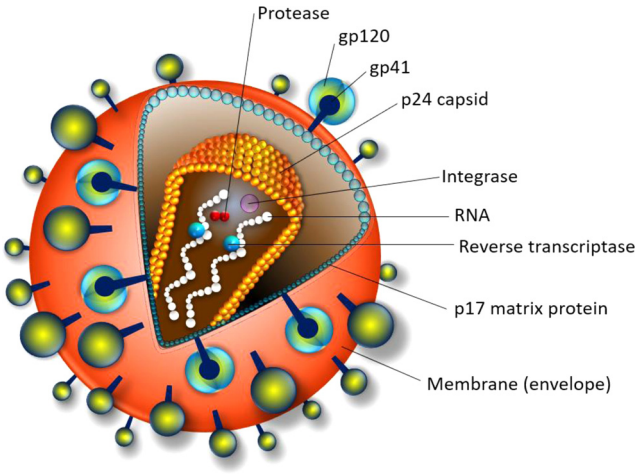

Fig. 1. Virion structure and genome of HIV-1.
Family: RETROVIRIDAE
Genome: Positive-stranded linear dimeric RNA
Capsid: Enveloped
Hosts: Human, vertebrates
Reference strain: HIV-1 (human immunodeficiency virus)
Retrovirus structure: Virions are enveloped, spherical to pleomorphic in shape, 80 – 100 nm in diameter.

and HIV replication in the lymphoid tissue is higher than in PBMC [14]. Detection of HIV proviral DNA can serve as an early marker of infection in patients with undetectable HIV serum RNA, such as in newborn or early needle stick situations [15]. HIV-infected $CD4^+$ T lymphocytes lose their ability to recognize and destroy bacteria, viruses, fungi, protozoa, and tumor cells. Opportunistic infections such as tuberculosis might appear, while the risk of virus-related malignant diseases, such as Kaposi's sarcoma and non-Hodgkin's lymphoma, increase [16].

In the environment, HIV can be inactivated by boiling, autoclaving [17], and using various chemicals such as formaldehyde, glutaraldehyde, and hypochlorite; however, HIV can remain viable in blood for up to four weeks at room temperature in a used syringe [18]. HIV is resistant to UV irradiation [19], but fast-inactivated by chemicals and disinfectants [20,21]. Transmission of HIV-1, like other retroviruses, can occur via sexual, parenteral, or vertical donor-recipient routes of infection [22,23]. The source of infection can be an infected person without clinical signs. HIV epidemiology is similar to those of hepatitis B and C-positive patients. In most cases, HIV is spread from an infected person to an uninfected person through bodily fluids [24].

According to the Joint United Nations Programme on HIV/AIDS (UNAIDS) 2018 report, 36.9 million people globally were living with HIV in 2017, including 35.1 million adults and 1.8 million children (< 15 years) [Report on the global AIDS epidemic joint program of the United Nations Geneva: United Nations; 2018; http://www.unaids.org/en/resources/fact-sheet]. According to this report only 75 % of all people living with HIV knew their HIV status in 2017, while about 9.4 million people were unaware that they were living with HIV.

2. Vitamin D

Scientific understanding of the significance of vitamin D has expanded notably beyond the fact that it is necessary for proper assimilation of calcium and phosphorus for the formation and maintenance of healthy bones and teeth [25], particularly among aging adults [26]. In addition to the regulation of bone homeostasis, vitamin D plays important physiological roles in many non-skeletal processes, including regulation of the normal functions of the thyroid gland, blood clotting, providing muscle strength and flexibility, enhancing the production of endogenous antibiotics, preventing the development of autoimmune and allergic diseases, confronting infectious diseases and preventing tumor growth [27–34].

The daily intake of vitamin D for adults is 15 μg (600 IU), under the age of 70. Everyone over 70 should get 20 μg daily (800 IU), which is the recommended dietary allowances (RDAs), according to the National Institutes of Health (NIH) [Institute of Medicine, Food and Nutrition Board. Dietary Reference Intakes for Calcium and Vitamin D. Washington, DC: National Academy Press, 2010; https://www.ncbi.nlm.nih.gov/books/NBK56056/]. This need is fulfilled by the formation of vitamin D_3 (cholecalciferol) in the skin under exposure to UVB light, and the supplementation of provitamin D_2 (ergocalciferol) with food. D_3 is prevailing: 20 – 30 min daily sunlight exposure to bare skin fills the daily need for vitamin D [35]. However, the ability of the skin to produce vitamin D_3 decreases with age [36]. The presence of provitamin D_2 in food products is of paramount importance for people living in areas with insufficient insolation or spending abundant time indoors [37].

The synthesis of vitamin D begins with the conversion of its endogenous precursor 7-DHC (7-dehydrocholesterol) contained in the epidermis, illustrated in Fig. 3. The highest concentrations of 7-DHC are found in the stratum basale and stratum spinosum [38]. This zoosterol is also a precursor for cholesterol. Under natural solar or artificial UV irradiation, the 7-DHC is converted into vitamin D_3. Vitamin D-binding protein transports 7-DHC from the epidermis into the bloodstream, then in the liver, it is hydroxylated to 25(OH)D_3 (25-hydroxycholecalciferol, calciferol), adding a hydroxyl group at position 25 via 25-hydroxylase enzymes (either the 57 microsomal (CYP2R1) or the mitochondrial (CYP24A1) P450 enzymes) [39]. Finally, another hydroxyl group is located at position 1 by a single activation enzyme, the mitochondrial 1α-hydroxylase (CYP27B1). The process occurs not only in the cells of the proximal tubule of the kidney [40], but also in many other cells (large intestine, bronchial wall, prostate, pancreas, immune system), primarily in monocytes, dendritic cells, osteoblasts and keratinocytes [41,42]. As a result, the active form of vitamin D_3 (1,25-dihydroxycholecalciferol [1,25$(OH)_2D_3$]), also known as calcitriol, is formed.

Another source for the synthesis of vitamin D can serve as ergocalciferol and ergosterol, the steroids that come from food. Ergocalciferol is found in fish liver, seafood, dairy products, some cheeses, vegetable, butter, and raw yolks. Despite common misconceptions, there is not much vitamin D contained in milk. Moreover, the absorption of vitamin D in the intestine is hampered by the phosphorus present in the milk. Ergosterol is found in yeast, cereals, potatoes, and parsley. Vitamin D_2 is formed and activated from these precursors, in the same way as D_3 from cutaneous 7-DHC [43]. As a result, depending on the source, either D_3 (a half-life of about 15 h) or D_2 (a half-life of about 15 days) are produced, which are biological analogs [44]. Since the formation of vitamin D occurs endogenously, it is also referred to as hormones [45]. Vitamin D belongs to the category of fat-soluble vitamins and is deposited mainly in adipose tissue, where it can last up to 6 months [46].

The synthesis of vitamin D is controlled by hormones regulating the mineral composition of bone tissue, as well as mediators of the immune system. A decrease in the level of ionized calcium in the extracellular fluid leads to the release of parathyroid hormone (PTH) into the blood. It increases the activity of 1-hydroxylase in the kidneys, apparently, indirectly changing transmembrane fluxes of phosphate ions in the cells of the renal tubules. The secretion of PTH is turned off when the level of vitamin D in the blood reaches approximately 40 – 60 ng/mL [47]. In the immune system, 1-hydroxylase activity is regulated by several mediators, including interferon-γ (IFNγ) and Toll-like receptors (TLRs), which recognize lipopolysaccharides, lipoproteins and other molecular components of the microbial surfaces [48,49].

The vitamin D receptor (VDR) belongs to the ligand-activated nuclear receptors for transcription factors. It is a phosphoprotein with a molecular weight of 50 kDa, in a structure resembling steroid, thyroid and retinoid receptors. VDR contains a specific ligand for vitamin D and a DNA binding motifs [50]. VDR can be found in cell membranes,

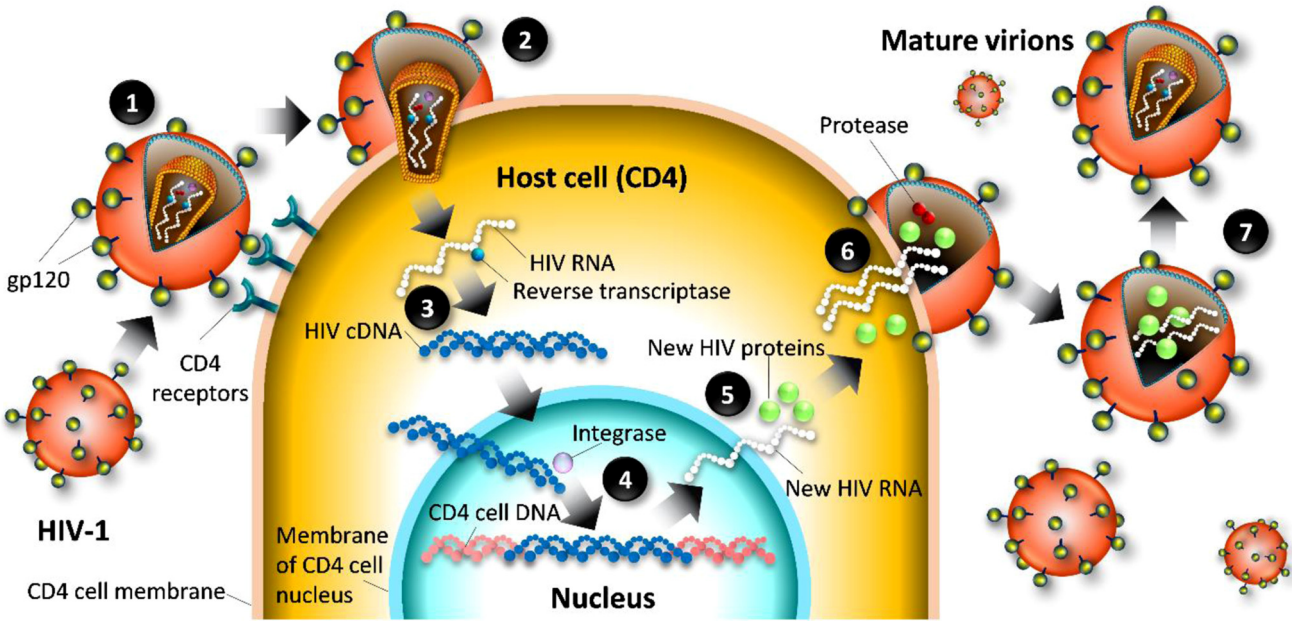

Fig. 2. The HIV-1 life cycle.
1 - attachment (binding)
2 - fusion
3 - reverse transcription
4 - integration
5 - replication
6 - assembly
7 - budding and maturation

cytoplasm, perinuclear zone, and mitochondria. VDR is present in a wide variety of tissues and is involved in the regulation of intracellular calcium metabolism, cell growth, and differentiation (see Table 1). In particular, VDR is found in most types of immune cells. The serum $25(OH)D_3$ is the most important indicator of the status of vitamin D. There are a variety of assays used to measure $25(OH)D_3$ concentration [51]. Unlike $25(OH)D_3$, the active form of vitamin D [i.e.,$1,25(OH)_2D_3$] is usually not suitable to assess vitamin D status, since it has a short half-life of ~15 h [52].

3. Vitamin D and immune response

Vitamin D has a crucial regulatory effect on innate and adaptive immune responses. $1,25(OH)_2D_3$ directly modulates the proliferation of T-lymphocytes, inhibits the development of Th17 cells, controls the differentiation of B cell precursors into plasma cells, prevents the production of Th1-associated cytokines and costimulatory molecules (CD40, CD80, and CD86), and stimulates the production of Th2 -associated cytokines. In particular, vitamin D supports antibacterial and antiviral immunity. In cases of vitamin D deficiency, the levels of proinflammatory cytokines increase, which significantly reduces the effectiveness of the immune response to infection [53]. This is illustrated in Fig. 4

The relationship between vitamin D and tuberculosis is a widely studied example of the anti-infective effects of this vitamin. Fundamental studies have shown the key role of the active metabolite of vitamin D to enhance the immune response to mycobacteria [54]. Macrophages are the main type of cells exposed to *Mycobacterium tuberculosis*. They are regulated by vitamin D with the participation of interleukin-1-beta (IL-1β), which significantly increases the survival of infected macrophages and reduces the burden of mycobacteria [55]. Alveolar macrophages recognize molecules associated with *M. tuberculosis* (for example, mycobacterial lipoprotein LpqH) by Toll-like receptors (TLR) 2/1 and co-receptor CD14. The interaction of these receptors activates the AMPK-p38 MAPK signaling pathway, which leads to increased expression of Cyp27b1 hydroxylase and enhancement of $25(OH)D_3$ biotransformation into the active form of vitamin $1,25(OH)D_3$ [56]. It binds to VDR receptors and as part of the vitamin-receptor complex is transferred to the nucleus, where it activates immune defense genes containing DNA fragments, called "VD response elements" (VDRE). As a result, the biosynthesis of antimicrobial peptides LL-37 (cathelicidin) and β-defensin-2 (BD-2) is enhanced. The antimicrobial peptide cathelicidin stimulates the elimination of mycobacteria by promoting the fusion of mycobacteria-containing autophagosomes with lysosomes. The combination of *M. tuberculosis* infection and high levels of $1,25(OH)_2D_3$ stimulates the expression of the IL-1b gene, resulting in increased biosynthesis of interleukin-1β, which stimulates the expression of β-defensin-2 in alveolar epithelial cells. The release of BD-2 contributes to the accelerated destruction of mycobacteria in macrophages, illustrated in Fig. 5 [57].

Autophagy is important for adaptive immunity because of its role in histocompatibility complex class I and II antigen presentation. Viruses such as cytomegalovirus, HIV-1, herpes simplex virus I, influenza A virus, and dengue virus, as well as bacteria, including *Yersinia, Listeria, Shigella, Salmonella, and E. coli* are the microorganisms under the control of autophagy [58]. Many HIV proteins, such as Env (gp120 and gp41), Tat, Nef, and Vpu can trigger autophagy via various pathways. This is illustrated in Fig. 6. The role of viral proteins in cell autophagy of HIV-1 target cells, illustrated in Fig. 7, is well discussed by Leymarie et al. [59].

4. HIV and Vitamin D

Vitamin D has been a focus for researchers pursuing an HIV cure in recent decades. In particular, a considerable amount of literature is available regarding the ability of vitamin D to influence the course of cardiovascular disease (CVD) under HIV [60,61], the virologic response in co-infection HIV/HCV [62,63], and formulated recommendations for

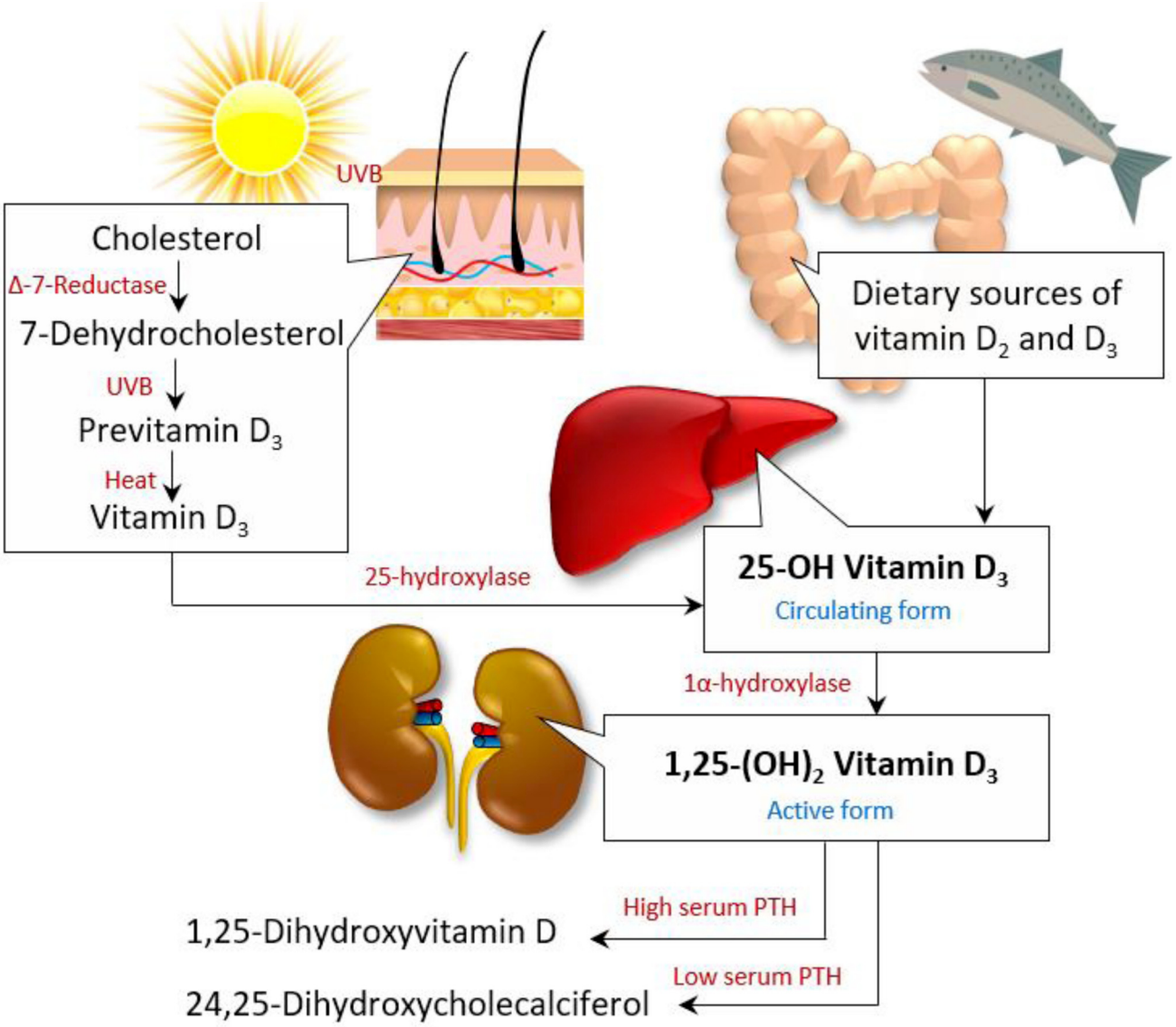

Fig. 3. The major metabolic pathways of vitamin D.
Vitamin D_2 can only be originated from plant-plant based diets (yeast, bread, mushrooms, some vegetables). Vitamin D_3 can also come from food, mainly of animal origin (fish oil, butter, eggs, milk). However, food products are not able to compensate for the physiological need for this vitamin, so the main source of vitamin D_3 is sunlight. The ultraviolet B (UVB) radiation between 290 – 315 nm stimulates the synthesis of vitamin D_3 from 7-dehydrocholesterol (provitamin D) in the epidermis of the skin. Then D_3 enters the blood circulation and is transported to the liver, where its first hydroxylation occurs with the formation of 25(OH)D_3, a circulating form of vitamin D_3. In the kidneys, under the influence of hydroxylase, 1,25(OH)$_2$D is formed, the active form of vitamin D_3 [99,100].

Table 1
Localization of vitamin D receptor (VDR).

System/organ/tissue	Cell types	Function	Pathology
Intestine (small and large)	Epithelium	Mineral (Ca) absorption	Calcium malabsorption
Bone (osteoblasts and chondrocytes)	Osteoblasts and chondrocytes	Osseogenesis and mineralization	Osteoporosis, osteomalacia, osteodystrophia
Skin	Keratinocytes	Keratinocyte differentiation, hair growth and repair	Hair loss (alopecia)
Reproductive system (testis, prostate and mammary glands)	Germ cells and epithelium	Ovarian/testicular function	Infertility
Immune system (thymus, parathyroid, pituitary gland)	Epithelium	Immune monitoring	Autoimmune diseases
Brain (cerebrum, cerebellum, spinal cord)		Mental function	Schizophrenia
Kidney (distal and proximal tubules, glomerular podocytes)	Epithelium and podocytes	Regulating Ca re-absorption	Chronic kidney disease

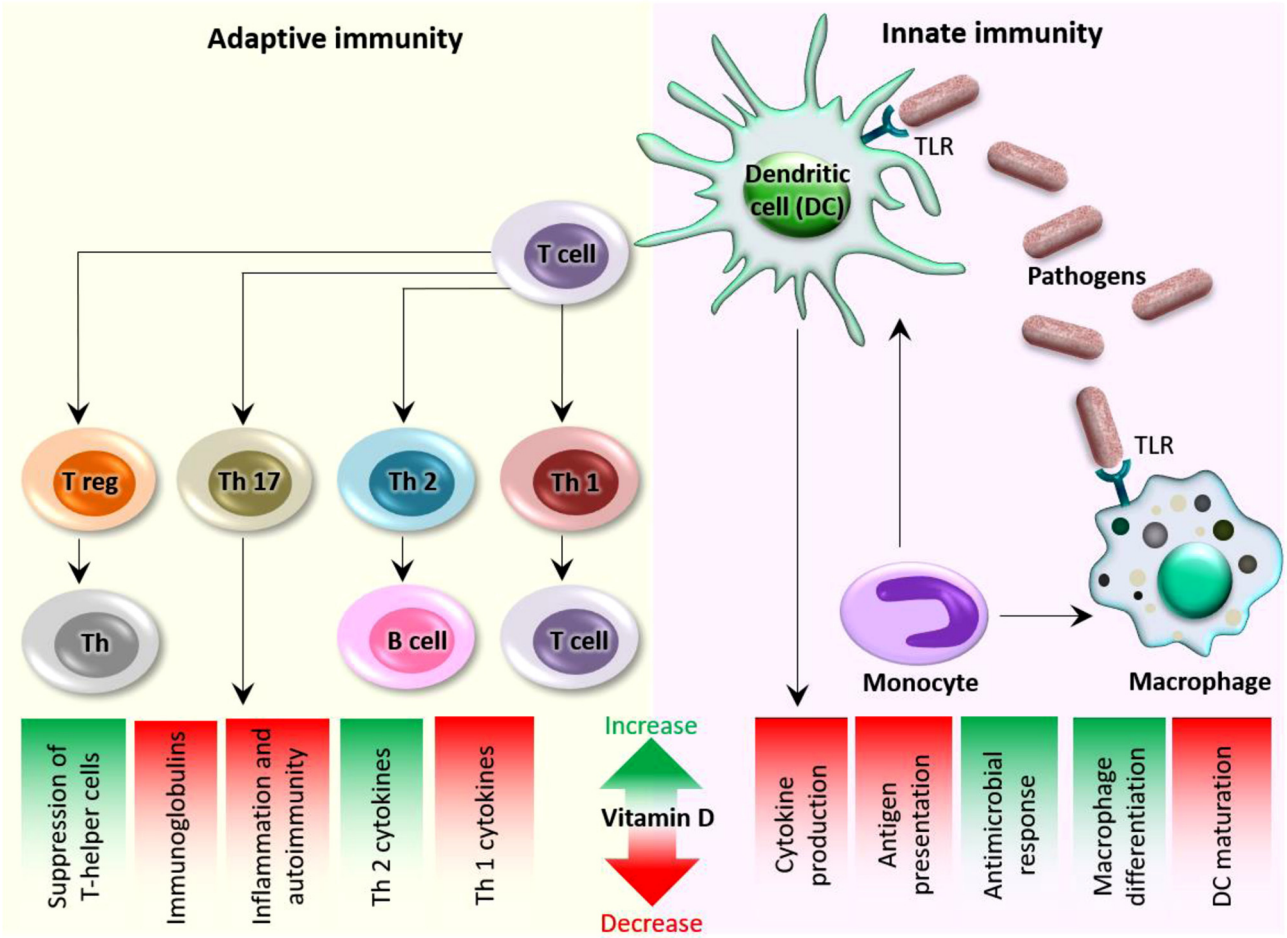

Fig. 4. The possible immune effects of vitamin D.
Vitamin D regulates both innate and adaptive immune responses. In innate immunity, vitamin D stimulates the production of endogenous antibodies, such as cathelicidin and defensin, which have antiviral and antibacterial effects. Also, it plays a crucial role in aiding and killing of pathogens by macrophages. In adaptive immunity, vitamin D has an anti-inflammatory effect by reducing the number of Th1 and T-helper 17 cells and stimulating the production of Th2 cells. It also prevents autoimmune diseases.

the diagnosis, prevention, and treatment of vitamin D deficiency in HIV-positive patients. Here, we review the results of these various studies to examine the association between HIV and vitamin D.

A clinical guide [64] for doctors on the diagnosis, therapy, and prevention of vitamin D deficiency, with an emphasis on groups that have risks of vitamin D deficiency was published in 2011. Clinical guidelines recommend a daily intake of at least 600 IU vitamin D for healthy HIV-negative adults, and 600–800 IU/d for adults over age 50 yrs. Ideally, vitamin D intake should be between 1500 and 2000 IU/d. For adults with HIV, daily intake of vitamin D in the range of 6,000–10,000 IU is recommended. The guide also formulates diagnostic approaches. A wide routine testing of $25(OH)D_3$ levels in risk groups for vitamin D deficiency, including HIV-infected, is suggested. Blood concentrations of $25(OH)D_3$ below 20 ng/mL (50 nmol/L) are considered as an indication for the treatment of vitamin D deficiency.

A study conducted by Havers et al. [65] determined the role of vitamin D as a factor influencing the virologic response during anti-retroviral therapy (ART). Through retrospective analysis of the large amount of data obtained through the Prospective Evaluation of Antiretorvirals in Resource Limited Settings (PEARLS) study, a more refined understanding of the aspects related to vitamin D has been reached. From 2005 to 2007, the study examined HIV patients from Brazil, Haiti, India, Malawi, Peru, South Africa, Thailand, USA and Zimbabwe, 49 % of whom had a low baseline $25(OH)D_3$ level. The prevalence of vitamin D deficiency varied significantly by country, ranging from 27 % in Brazil, to 78 % in Thailand. Low $25(OH)D_3$ was associated with more than 2-fold hazard of virologic failure with antiretroviral therapy (HR = 2.13, 95 % CI, 1.81-3.50). Evidence suggests that vitamin D deficiency may result in slow development or impaired immune status in the treatment of HIV infection [66,67].

Choi et al. [60] showed a significant relationship between vitamin D levels and the risks of cardiovascular diseases in HIV-infected patients. The study involved 139 patients (75 % of those receiving ART), and in 52 % of cases a low level of vitamin D [< 30 ng/mL $25(OH)D_3$] was detected. The carotid intima-media thickness (cIMT) is known to be a subclinical event of atherosclerosis and an early predictor of cardiovascular risk. HIV-infected patients with vitamin D insufficiency in this study revealed a statistically significant thickening cIMT. The study demonstrated that the management of vitamin D levels in HIV-infected people reduces the risk of cardiovascular diseases by almost a third (RR = 0.70; 95 % CI, 0.52–0.95).

In addition to the risks of cardiovascular diseases, vitamin D deficiency is also associated with the risks of developing depressive disorders [68]. Up to 60 % of HIV-infected people are subject to depressive disorders, which makes this problem extremely urgent. A study published in 2015 [69] concluded that the effectiveness of a treatment depends on the level of vitamin D. The study involved 398 HIV-infected patients receiving highly active antiretroviral therapy (HAART) for 18 months. Data included vitamin D levels and CD4 + T-cell count at baseline and on months 3, 6, 12, and 18. Researchers observed how

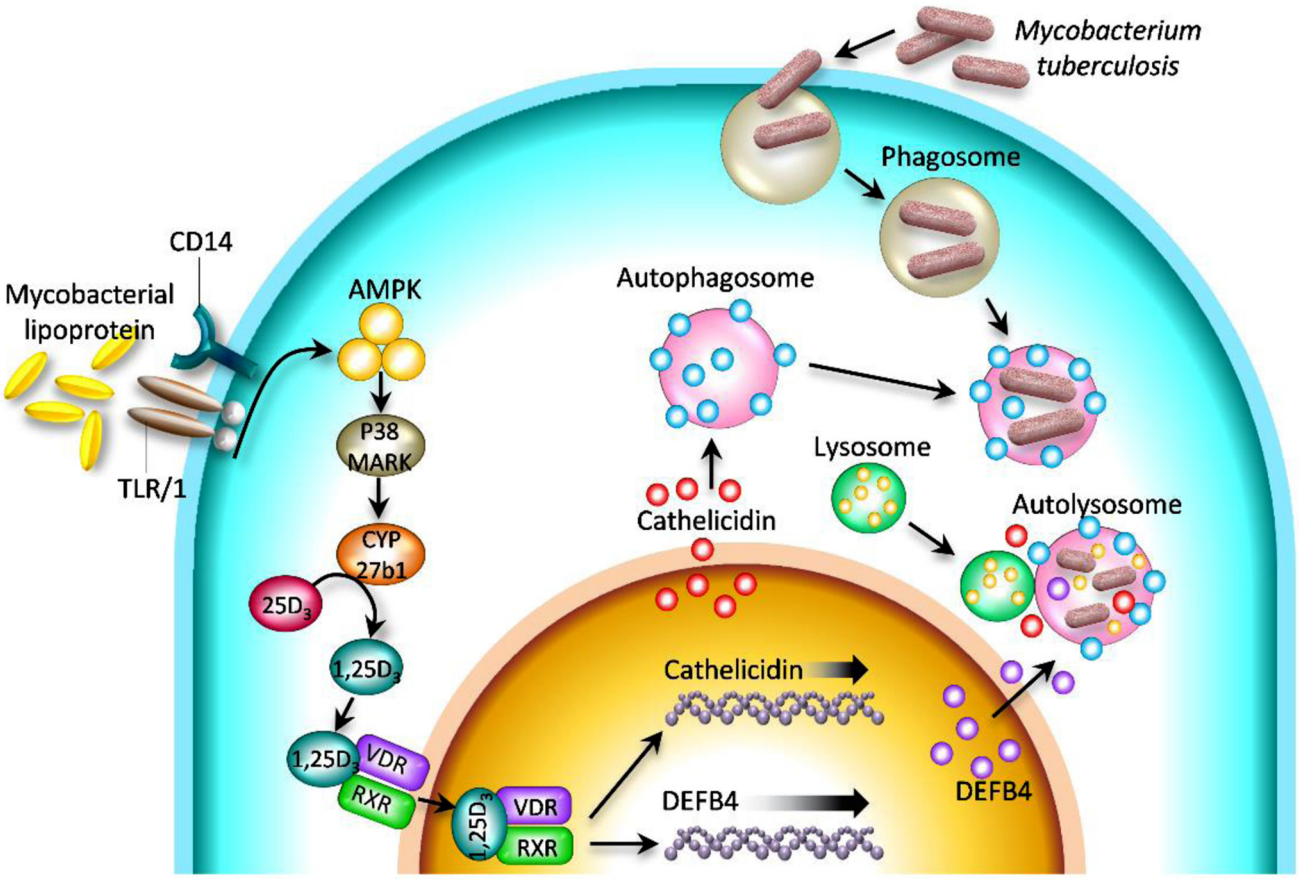

Fig. 5. Vitamin D and immune response against *M. tuberculosis.*
Pathogens and lipopolysaccharides (LPS) stimulate TLR of macrophages, causing transcription of VDR and increase activity of CYP27B in mitochondria. This leads to the formation of $1,25(OH)_2D$, which stimulates the synthesis of cathelicidin, an antimicrobial peptide active against *M. tuberculosis*.

changes in the number of CD4 + T-cells are associated with vitamin D levels. They found that participants with a sufficient level of vitamin D recovered their immune system faster than participants with vitamin D deficiency. And this effect was more prominent among young participants.

5. Effects of vitamin D supplementation on HIV-infected individuals

In 2015, the journal Clinical Infectious Diseases [70] published guidance for evaluation and management of bone disease in patients with HIV, as well as prevention following a fragility fracture. 34 HIV experts from 16 countries took part in this project, issuing recommendations based upon research findings. These experts were convinced that densitometry after 40 years should be a routine part of monitoring HIV-positive patients. The primary trigger for increased attention to bone mineral density (BMD) in HIV was the fact that a number of studies [71–75] revealed higher risk of major fractures in HIV-infected patients than the general population. At that time, it was not fully clear what causes loss of bone minerals during HIV infection, but either way, during the first two years of therapy BMD decreases by 2–6 %. Indicators suggest that boosted protease inhibitors (PIs) and tenofovir disoproxil fumarate (TDF) cause a greater loss of BMD than other antiretroviral drugs. Persons over the age of 40 can undergo a fracture risk assessment using the Fracture Risk Assessment Tool (FRAX) every three years without bone densitometry. X-ray absorptiometry (DXA) can be provided under the condition that the risk of major osteoporotic fracture over the next 10 years is > 10 % when assessed by FRAX. The recommendations include DXA for postmenopausal females and males > 50 years of age. The expert group, as a preventive measure, encourages supplementation of vitamin D at a level sufficient to maintain the concentration of $25(OH)D_3$ approximately 30 ng/mL. Males aged 50–70 years should receive at least 1000 mg of dietary calcium per day, while females over 50 and males over 70 years old should receive 1300 mg of calcium per day. On those occasions, if desired rates of vitamin D are achieved and the amount of calcium is sufficient, but there is no sufficient dynamics of BMD, the intake of bisphosphonates is well recommended; namely, alendronate in a dose of 70 mg once weekly, and in case of inefficiency, intravenous zoledronic acid 5 mg annually.

Zoledronate, a type of bisphosphonate, has been successfully used to increase BMD and suppress bone turnover in postmenopausal women [76]. The annual administration of 4 mg zoledronate, together with a supplement of 400 mg/d elemental calcium and 1.25 mg/month vitamin D_3, is a potent and effective treatment for osteopenia and osteoporosis in HIV positive men [77]. In another study, Huang et al. [78] also confirmed that annual dosing of 5 mg zoledronate, following 12 months daily 1 g calcium and 50,000 IU vitamin D supplements treat bone loss in HIV-infected individuals. A randomized study lead by Negredo et al. [79] compared the impact of a single dose of zoledronate in 2 years with that of annual administration in HIV-infected individuals with low BMD. Diet counseling was provided to assure appropriate vitamin D (800 mg/day) and calcium (1200 − 1500 mg/day) intake. Zoledronate (5 mg) was administered as an intravenous infusion. The results suggest that the use of zoledronate every 2 years to prevent toxicity and reduce costs can be helpful.

Alendronate, another type of bisphosphonates, has been shown to potently inhibit bone resorption and is effective against osteoporosis.

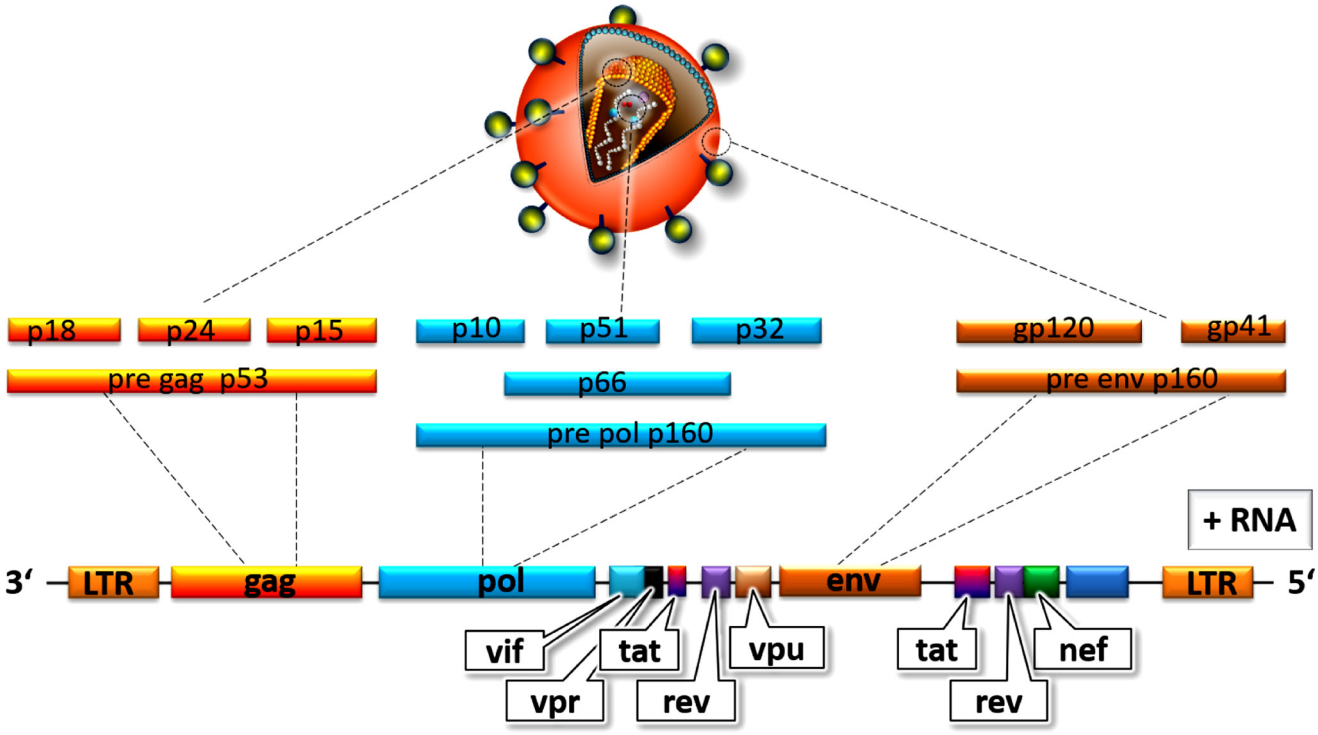

Fig. 6. Genome organization and gene expression of HIV-1.
The DNA genome converted from the RNA genome of HIV-1 contains nine ORFs:
gag - group specific antigen gene, encodes viral nucleopcapsid proteins: p24, a nucleoid shell protein, MW = 24,000; several internal proteins, p15, p55 and others. **pol** - polymerase gene; encodes the viral enzyme, protease (p10), reverse transcriptase (p51/66; alpha and beta subunits) and integrase (p32). **env** - envelope gene; encodes the viral envelope glycocproteins gp120 (extracellular glycoprotein, MW = 120 000) and gp41 (transmembrane glycoprotein, MW = 41,000).
tat - encodes trans-activator protein **rev** - encodes a regulator of expression of viral protein **vif** - associated with viral infectivity **vpu** - encodes viral protein U **vpr** - encodes viral protein R **nef** - encodes a 'so-called' negative regulator protein
LTR - long terminal repeats; repetitive sequence of bases Notably, Env, Tat, Nef and Vpu proteins are able to modulate autophagy pathway by various strategy at the initiation and maturation steps.

McComsey et al. [80] studied the effectiveness of calcium and vitamin D (as calcium carbonate 500 mg/ vitamin D 200 IU tablet twice a day) supplementation with or without once-weekly alendronate (70 mg) in improving BMD in HIV-infected subjects receiving ART. They concluded that alendronate increases lumbar spine and hip BMD beyond that achieve with calcium and vitamin D alone, and is well tolerated without gastrointestinal or major adverse events. In a seperate study [81], HIV-infected subjects with bone loss received 70 mg of alendronate weekly, 1 g calcium carbonate, and 400 IU vitamin D daily. Overall, the supplementation was safe and useful in the treatment of lumbar spine BMD. Rozenberg et al. [82] shows that alendronate 70 mg weekly for 96 weeks improves BMD in ART HIV-infected patients with t-scores $\leq$ 2.5, with effects similar to those observed in non-infected individuals.

Overton et al. [83] reported a study on the effect of vitamin D_3 on bone mineral density. The trials included 165 patients with HIV (90 % men), who were randomly assigned to receive 4000IU of vitamin D_3 and 1000 mg of calcium daily (n = 79) and placebo (n = 86) from September 2011 to February 2012. In the vitamin D_3 and calcium groups, the bone density drop was mitigated by about 50 % compared with the placebo group. The study involved only patients receiving efavirenz /emtricitabine /tenofovir regimen; however, the effects of other regimens were not studied.

Hileman et al. [84] analyzed the main results of a study focused on the relationship between vitamin D deficiency and the effectiveness of statins in HIV-infected patients. In those HIV infection, the patients were evaluated in a 96-week, randomized, placebo-controlled SATURN-HIV study (n = 147), which explored the effect of rosuvastatin on the vascular aspects of chronic immune inflammation. A total of 13.6 % of SATURN-HIV participants had a severe vitamin D deficiency. While 23.1 % were vitamin D insufficient, 53.1 % were vitamin D deficient. A greater decrease in LDL cholesterol while taking rosuvastatin was detected when the concentration of the 25(OH)D_3 was $\geq$20 ng/mL. An optimal vitamin D level was found to be associated with a decrease in inflammatory immune markers, such as cystatin C, interferon γ inducible protein-10 (IP-10) and lipoprotein-associated phospholipase A2 (Lp-PLA2).

Calza et al. [85] published a retrospective cohort study on vitamin D deficiency and statin-related symptomatic myalgia. In the study, 545 patients received atorvastatin (55.8 %) or rosuvastatin (44.2 %), with a mean duration of statin therapy of 29 months, 7.7 % of participants showed isolated symptomatic myalgia, and in 4.6 % myalgia associated with increased levels of total creatine kinase (CK). Analysis of the data showed that there is a statistically significant relationship between vitamin D deficiency and the occurrence of symptomatic myalgia in patients with statins (p = 0.009), and this connection was also found with an increase in CK levels accompanied by myalgia (p = 0.046). These findings mentioned above make it possible to recommend monitoring the level of 25(OH)D_3 in HIV patients, who are prescribed statins, and the correction of the level of vitamin D.

Effects of the combined delivery of vitamin D with different compounds may be variable. In a recently published study, Ashenafi et al. [86] investigated the effect of daily nutritional supplementation with vitamin D_3 (5000 IU) and phenylbutyrate (PBA, 2 × 500 mg) in treatment-naïve HIV patients in Ethiopia. The results revealed a total improvement of vitamin D_3 status within 10 weeks. However, clinical adverse events were similar in both observed vitamin D_3 + PBA and placebo groups. Also, the study has shown that D_3 supplementation

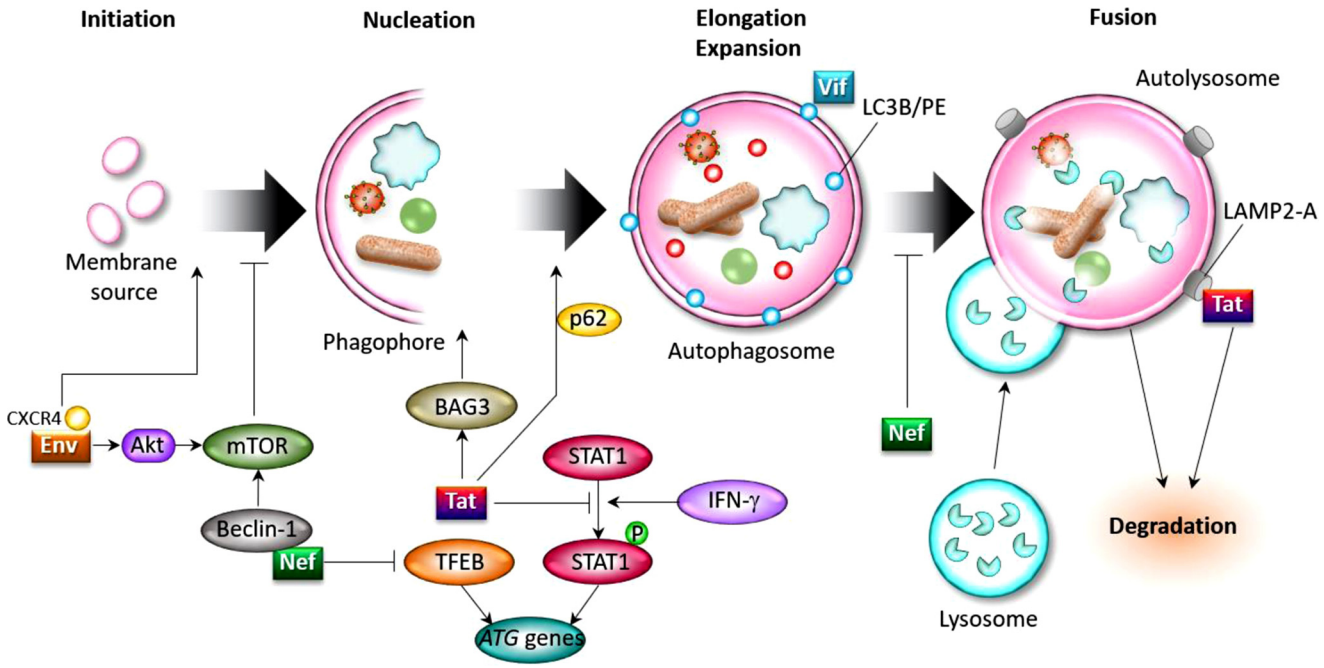

Fig. 7. Interaction of HIV-1 proteins with the autophagy pathway [Adapted and modified from [101]].
1. HIV-1 Tat induces autophagy by upregulating BAG3. On the other side, Tat perturbs interferon IFN-γ signaling through the suppression of transcription 1 (STAT1) phosphorylation and consequently inhibits major autophagy genes including microtubule-associated protein 1 light chain 3B (LC3B). The interaction of Tat with lysosomal-associated membrane protein 2A (LAMP2A) suggests its role in lysosomal fusion in neurons.
2. HIV-1 Nef is an anti-autophagic maturation factor which binds Beclin-1 resulting in mammalian target of rapamycin (mTOR) activation, transcription factor EB (TFEB) phosphorylation and cytosolic sequestration, as a result, the biosynthesis of ATG proteins are decreased.
3. Binding of HIV-1 Env to C-X-C chemokine receptor type 4 (CXCR4) activates cellular autophagy.
4. On the surface of autophagosomes, HIV-1 Vif interacts directly with LC3B and blocks autophagic flux.

(60,000 (medium) or 120,000 (high) IU/month) effectively raises serum 25(OH)D_3 in the majority of 8–25 years old HIV-infected youth, regardless of efavirenz (EFV), a drug used as a part of ART [87].

In a study conducted by the same research group [88] the high-dose vitamin D supplementation (120,000 IU/month) given over 12 months decreased bone turnover markers in HIV-infected youth 8–25 years old (25(OH)D_3 < 30 ng/mL). Lerma-Chippirraz et al. [89] proposed a practical scheme for vitamin D supplementation in HIV-infected patients. Subjects were supplemented with 16.000 IU (0.266 mg) vitamin D_3 weekly in case of its deficiency (25(OH)D_3 < 10 ng/mL) or fortnightly, in case of its insufficiency or high parathyroid hormone levels (25(OH)D_3 < 20 ng/mL). They demonstrated that the vitamin D supplementation is effective, safe and valid for correcting vitamin D abnormalities and to improve raised PTH levels, but not enough for normalizing them, especially in individuals exposed to tenofovir or protease inhibitors.

In a study conducted by Lake et al. [90], HIV-infected patients with vitamin D insufficiency (25(OH)D_3 < 30 ng/mL) received 50 000 IU oral vitamin D_3 twice weekly for 5 weeks, which effectively replete calcifediol levels to ≥ 30 ng/mL in 81 % of participants on suppressive antiretroviral therapy, and efficacy was similar to that observed among HIV-uninfected historical controls. Supplementation with high-dose vitamin D (7000 IU/day) for 12-months among HIV-infected children and young adults leads a positive impact to neuromuscular motor skill proficiency and an increased concentration of serum calcifediol [91].

A study [92] found that supplementation with an oral monthly dose of 16,000 IU 25(OH)D_3 is safe and effective, improving serum calcifediol levels and the decreasing prevalence of secondary hyperparathyroidism (SHP), a known cause of lower bone mineral density (BMD). In a separate study, researchers [93] reported that monthly high-dose vitamin D_3 (50,000 IU) supplementation significantly increases lumbar spine BMD (LSBMD) over 48 weeks in HIV-infected individuals aged 16–24 years on stable tenofovir disoproxil fumarate (TDF) containing combination antiretroviral therapy, regardless of baseline vitamin D status. However, a study performed by Rovner et al. [94] found that despite high-dose vitamin D_3 supplementation (7000 IU/day) for 12-month did not bring any changes in body composition, or bone health in 5.0–24.9 years old patients with HIV infection.

6. Effect of sunlight exposure on HIV-infected individuals

Numerous studies provide evidence indicating that insufficient presence of vitamin D is characteristic of the majority of the population living in the temperate zone [95,96]. Between November and February, the entire area of the world above 42 °N is at risk for vitamin D insufficiency/deficiency. In many countries, vitamin D deficiency is registered in 30–50 % of both children and adults [97]. The lack of sufficient solar exposure significantly increases the risk of several diseases, including HIV/AIDS. However, the population with high eumelanin content is more prone to vitamin D deficiency, and also needs greater UVB exposure to make previtamin D_3 [98].

A study performed by Jablonski et al. [98] questions the intake of vitamin D_3 in winter and its effect on immunity parameters among HIV-infected patients. In particular, the research team investigated seasonal fluctuations in vitamin D_3 metabolites and their influence on the immune status of indigenous and mixed origin residents in South Africa. In the winter period, all participants (n = 100) received cholecalciferol at a dose of 50,000UI weekly for 6 weeks. A severe deficiency of 25(OH) D_3 (less than 30 nmol/L) was detected in winter for 18 % of participants from indigenous people and 12 % of participants of mixed origin. Overall, females had higher levels of decreased 25(OH)D_3. Correlations have been found between the levels of D_3 and HIV replication. Winter vitamin D supplementation increased peripheral WBC count ($p = 0.0016$) and in particular lymphocyte count ($p = 0.023$).

7. Conclusion

Vitamin D is a group of biologically active substances, which play a role in controlling many pathways within the complex pathophysiology. While lack of this vitamin is a common problem among adults, for HIV-positive individuals, vitamin D insufficiency and deficiency lead to many health-related conditions, such as impaired calcium metabolism, cardiovascular diseases, insulin resistance, type II diabetes, oncopathology, dyslipidemia, decrease in cognitive functions, and decrease in immunity. Vitamin D deficiency is becoming more common among HIV/AIDS patients, due in part to increasing urbanization and decreasing amounts of time spent in the sun by adults in general. HIV infection itself is a risk factor for the premature development of many diseases, where vitamin D deficiency can be a catalyst for these pathological processes. Results of systematic reviews and meta-analyses suggest that vitamin D is fundamentally necessary for HIV-infected individuals to maintain the normal physiological functioning of the immune system, including activation of antibacterial and antiviral protection, and reduction of excessive inflammation.

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