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Vitamin D and the anti-viral state

Jeremy A. Beard^b, Allison Bearden^{a,b}, and Rob Striker^{a,b,*}

^aW. S. Middleton Memorial Veterans Administration Hospital, 53705, USA

^bUniversity of Wisconsin-Madison, Department of Medicine, 53706, USA

Abstract

Vitamin D has long been recognized as essential to the skeletal system. Newer evidence suggests that it also plays a major role regulating the immune system, perhaps including immune responses to viral infection. Interventional and observational epidemiological studies provide evidence that vitamin D deficiency may confer increased risk of influenza and respiratory tract infection. Vitamin D deficiency is also prevalent among patients with HIV infection. Cell culture experiments support the thesis that vitamin D has direct anti-viral effects particularly against enveloped viruses. Though vitamin D's anti-viral mechanism has not been fully established, it may be linked to vitamin D's ability to up-regulate the anti-microbial peptides LL-37 and human beta defensin 2. Additional studies are necessary to fully elucidate the efficacy and mechanism of vitamin D as an anti-viral agent.

Keywords

Vitamin D; LL-37; Anti-viral; Human beta defensin 2; RTIs

1. Introduction and general physiology

Vitamin D is known for its traditional role in bone mineralization and calcium homeostasis. It is an essential part of the human diet. The body can handle doses as high as 10,000 IU (250 µg) per day for several months.¹ Mounting evidence suggests that it plays a major role in mediating the immune system's response to infection.² Therefore, vitamin D represents a potentially useful intervention for combating viral infection. Further study may aid in understanding the role of vitamin D in viral pathogenesis. The vast literature on vitamin D includes reviews on many topics including its effects on innate immunity,³ cardiovascular health,⁴ and cancer.⁵ This review focuses on vitamin D's putative role in establishing a preventative and therapeutic anti-viral state.

Vitamin D exists in several forms including 25-hydroxyvitamin D [25(OH)D], the primary circulating form, and 1,25-dihydroxyvitamin D [1,25(OH)₂D], the active form.¹ Vitamin D is obtained by skin exposure to sunlight (thereby converting 7-dehydrocholesterol to cholecalciferol, vitamin D₃), from foods, or through supplements. It can be ingested in the form of vitamin D₃ or vitamin D₂ (ergocalciferol). Vitamin D₂ is derived from irradiation of the fungal steroid ergosterol.⁶ After digestion, vitamin D is processed by 25-hydroxylases present in the liver and other tissues to generate 25-hydroxyvitamin D [25(OH)D].^{7–9}

*Corresponding author at: University of Wisconsin-Madison, Department of Medicine, 1550 Linden Dr., 53706 Madison, WI, USA. Tel.: +1 608 262 2994; fax: +1 608 262 8418. rtstriker@wisc.edu (R. Striker).

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Subsequently, 25-hydroxyvitamin D is converted to 1,25-dihydroxyvitamin D by the enzyme 25-hydroxyvitamin D-1- α -hydroxylase, CYP27B1.^{10,11}

Serum 25(OH)D correlates with overall vitamin D stores and is the most commonly used biomarker for assessing vitamin D deficiency.¹⁰⁻¹⁴ Deficiency is often defined by circulating 25(OH)D levels below 20 ng/ml (50 nmol/l).^{11,15,16} but 30 ng/ml (75 nmol/l)^{17,18} and even 40 ng/ml (100 nmol/l) are sometimes advocated for specific patients.¹⁹⁻²¹

1,25-Dihydroxyvitamin D [1,25(OH)₂D] is primarily generated in the kidneys by a 1- α -hydroxylase, CYP27B1.^{10,11} CYP27B1 is also present in a variety of extra-renal tissues including immune cells, and unlike the renal form of the enzyme, is not regulated by calcium metabolism signaling.²²⁻²⁴ CYP27B1 in keratinocytes is up-regulated in response to injury, and toll-like receptor (TLR) activation by microbial products.^{25,26} In addition, activated macrophages, dendritic cells, T lymphocytes, and B lymphocytes express CYP27B1.²⁷⁻³⁰ Catabolism of vitamin D is accomplished by 24-hydroxylases including CYP24A1. A negative feedback loop exists as catabolic enzymes are induced by 1,25(OH)₂D.¹⁰

Given that 1,25(OH)₂D is the active form of vitamin D, it is tempting to use this for diagnosis and monitoring of vitamin D status. Such an approach can be problematic. Due to its increased biological half-life and other factors, 25(OH)D is normally present in higher concentrations than its active metabolite. However, vitamin D deficiency results in increased parathyroid hormone, inducing renal hydroxylation of 25(OH)D via renal CYP27B1.¹⁴ This additional regulation of vitamin D by calcium and parathyroid hormone can result in normal or elevated 1,25(OH)₂D levels despite systemic vitamin D deficiency.^{14,22,23}

2. Vitamin D molecular mechanisms and immune modulation

The effects of 1,25(OH)₂D are mediated by it binding to the vitamin D receptor (VDR). VDR is a nuclear receptor and once it binds its ligand, VDR dimerizes with an isoform of the retinoid X receptor. These VDR-RXR heterodimers bind to vitamin D response elements present on target genes.³¹⁻³³ In addition to transcriptional activation, the heterodimers can displace the nuclear factors of activated T cells resulting in repression of cytokine related genes.³⁴

1,25(OH)₂D suppresses Th-1 cell proliferation leading to lowered production of interferon gamma and interleukin-2.^{27,35,36} Lower levels of circulating cytokines leads to less antigen presentation by dendritic cells, in addition to less T lymphocyte recruitment and proliferation.³⁶ Expression of Th-2 associated cytokines, including interleukin-4 are increased by 1,25(OH).³⁷ Overall, vitamin D polarizes the adaptive immune system away from Th-1 and toward Th-2 responses.

Vitamin D also plays a role in innate immune response modulation. The toll-like receptors (TLRs) in macrophages, polymorphonuclear cells, monocytes, and epithelial cells are central to the innate immune response.^{38,39} TLRs recognize pathogen associated molecular patterns associated with infectious agents.³⁹ For example, TLR2 recognizes the lipopolysaccharides of bacteria. TLRs have also been shown to recognize viral proteins and nucleic acids.⁴⁰ Upon recognition, activated TLRs release cytokines that induce expression of antimicrobial peptides and reactive oxygen species.

Several TLRs both affect and are affected by VDR stimulation. Expression of CD-14, the co-receptor for TLR4, is induced by 1,25(OH)₂D in monocytes and epidermal keratinocytes.^{26,41} Stimulation of TLR2 in macrophages by anti-microbial peptides leads to increased local expression of CYP27B1, resulting in the conversion of vitamin D to its

active form.²⁵ Some anti-microbial peptides associated with TLRs have demonstrated anti-viral effects, and their expression is affected by vitamin D levels.⁴² Human beta defensin 2 is modestly up-regulated by 1,25(OH)₂D and may contribute to anti-viral effects as a chemoattractant for neutrophils and monocytes.^{38,43} Conversely, in monocytes activation by 1,25(OH)₂D alone is insufficient for induction of gene expression.⁴⁴ Human cathelicidin is an antimicrobial peptide induced by TLR1/2 activation. Cathelicidin is strongly up-regulated by 1,25(OH)₂D due to the its VDR response element.⁴⁴⁻⁴⁶

Cathelicidins are a family of proteins with a C-terminal cationic anti-microbial domain activated by cleavage from the N-terminal cathelin domain.⁴⁶ In humans, the active antimicrobial cathelicidin peptide LL-37 is cleaved from the propeptide, hCAP18.⁴⁷ Although the majority of cathelicidin is stored in neutrophil granules for release at sites of infection, several other types of immune cells including monocytes, NK cells, and B cells express hCAP18.⁴⁸ It is secreted into the blood and by the epithelia of the conjunctiva, cornea, respiratory tract, digestive tract, epithelial tract, intestines, urinary tract, and skin.⁴⁹⁻⁵² At the cellular level, expression of CYP27B1 in macrophages and keratinocytes induces cathelicidin expression.^{14,25} If there is no 25(OH)D, VDR, or CYP27B1 present, the ability of these cell types to induce cathelicidin is significantly impaired.^{25,26}

In addition to anti-bacterial effects including membrane disruption^{25,51-53}, cathelicidin in the peptide form LL-37, has demonstrated anti-viral effects including inhibition of herpes simplex virus type one (HSV-1), vaccinia virus replication, retroviral replication, and replication of some adenovirus serotypes at certain peptide concentrations.^{50,54-56}

3. Evidence for role of vitamin D in viral respiratory infections

Recent work highlights vitamin D's potential role in fighting viral respiratory infections. Lung epithelial cells express high basal levels of CYP27B1 and low levels of CYP24A1, favoring conversion of vitamin D to its active form.⁵⁷ When treated with vitamin D, these cells increase the levels of the TLR co-receptor CD-14 and cathelicidin.⁵⁷ In airway epithelial cells, treatment with vitamin D induces IκBα, an NF-κB inhibitor resulting in a decrease of viral induction of inflammatory genes.⁵⁸

Studies have identified possible links between vitamin D and respiratory infections by examining VDR polymorphisms. Single nucleotide polymorphisms in VDR and related genes are associated with severe outcomes in respiratory syncytial virus (RSV) related bronchiolitis and acute lower respiratory tract infection (RTI) likely due to VDR association with innate immunity.^{59,60}

Controlled trials examining the effect of vitamin D supplementation on reducing RTIs have had mixed results. A 1994 study done in India showed a reduction in respiratory infections of 27 children treated for six weeks with vitamin D.⁶¹ These children had a previous history of RTIs and vitamin D deficiency. A British study of 1740 elderly patients administered 800 IU over a two year period showed no significant reduction in infections compared to controls.⁶² A New York study involving a mostly Caucasian population showed daily administration of 2000 IU of vitamin D₃ had no significant effect on decreasing the incidence or severity of respiratory tract infections during winter.⁶³

In the New York study, the serum mean of 25(OH)D was above deficiency levels. In addition, the subjects did not begin vitamin D supplementation prior to the wintertime. As the authors note, given that it can take up to three months for 25(OH)D levels to reach a steady state with supplementation, this may have influenced the study result.^{64,65} These results suggest the effect is most pronounced or only present in vitamin D deficient patients. Differences between the trials might result from patient underreporting of RTIs. Many relied

on patient questionnaires and not clinical diagnosis. The results of the controlled trials are summarized in Table 1.

Observational studies evaluating the relationship between serum 25(OH)D concentrations and respiratory infections also have had mixed results. A Finnish study found an association between serum 25(OH)D concentrations less than 16 ng/ml (40 nmol/l) and an increased incidence of acute respiratory tract infections.⁶⁶ A two month study of Bangladeshi children found a significant correlation between increased numbers of RTIs and significantly lower mean levels of 25(OH)D of 11.7 ng/ml (29.1 nmol/l) versus 15.7 ng/ml for controls (39.1 nmol/l).⁶⁷ Similar results were found in studies of Indian and Turkish children.^{68,69} Two Canadian studies of children showed no significant difference in mean 25(OH)D levels between RTI patients and controls.^{70,71} A retrospective analysis of the Third National Health and Nutrition Examination Survey of 18,883 patients showed that 25(OH)D levels less than 30 ng/ml (75 nmol/l) were associated with an increased risk of upper respiratory tract infection.⁷² Patients with levels less than 10 ng/ml had a 55% risk of infection when compared to controls. Again, this suggests that if a patient is not vitamin D deficient, there is limited anti-viral benefit gained from supplementation. The results of the observational studies are summarized in Table 2.

While researchers have suggested a link between seasonal variation in vitamin D levels and influenza,⁷³ a Japanese supplementation trial during the winter and early spring showed only a mild reduction in influenza A infections in children taking vitamin D₃ supplements. However, the study used only outpatients and did not measure serum concentrations of 25(OH)D or serum antibody concentrations to influenza A. It is possible that the milder forms of disease and the extreme forms requiring hospitalization were not recorded.⁷⁴

The Japanese study's homogeneous population means the correlation between mild reduction of influenza A and vitamin D supplementation cannot easily be generalized as skin pigmentation impacts vitamin D production.^{73,75} Therefore, darker skin individuals may gain more benefit from supplementation. For example, in a three-year study of post-menopausal African-American women receiving vitamin D supplementation, researchers found a reduction in reported cold and influenza.⁷⁶

4. Evidence for vitamin D influence on HIV infection

Observational studies have reported lower levels of vitamin D in HIV populations. In a German study, 25(OH)D levels of less than 20 ng/ml (50 nmol/l) were found in 47.6% of the subjects with AIDS.⁷⁷ Another study of 50 women with HIV found significantly lower 1,25(OH)₂D levels in the patients compared to healthy female controls.⁷⁸ In a study of HIV-infected adults from the United States, serum levels of 25(OH)D were below normal values in only 17% of subjects and the 1,25(OH)₂D serum levels were low in 11% of subjects though the differences were of only borderline statistical significance.⁷⁹ A Norwegian study of 53 patients also found significantly lower 1,25(OH)₂D serum levels than controls.⁸⁰ Interestingly, in this Norwegian study the serum concentrations of 25(OH)D were not significantly lower than that of the controls. Even when patients being treated with drugs known to inhibit CYP27B1 were excluded, the deficiency in the cohort persisted.⁸⁰ This suggests a novel mechanism.

Although the studies (summarized in Table 3) show an association between lower vitamin D levels and HIV infection, they do not clarify the nature of that relationship. As the active form of vitamin D, 1,25(OH)₂D is typically more reduced than 25(OH)D, it is unlikely this is solely because of diet and sunlight exposure. However, in some patients, pre-infection vitamin D levels were low because of such factors.⁸¹ One possible mechanism put forth to explain the vitamin D deficiencies is that over activation of TNF- α in HIV patients might

lead to a blocking of the stimulatory effect of parathyroid hormone on renal 1- α -hydroxylase.⁸²

As some anti-retroviral drugs, including protease inhibitors, have been shown to interfere with vitamin metabolism *in vitro*,⁸³ several studies have examined the potential impact of HAART regimens on vitamin D levels in HIV patients. These studies have found associations between low vitamin D levels and the use of non-nucleoside reverse transcriptase inhibitors and protease inhibitors.⁸⁴⁻⁸⁸ However, at least one study supported the idea that though protease inhibitors are associated with lower 1,25(OH)₂D levels, they were not the cause of vitamin D deficiency.⁸⁹

Due to the different effects of anti-virals on vitamin D metabolism and cohort effects, the clinical implication of low vitamin D levels in HIV patients is not clear. Observational studies of humans have found positive correlations between vitamin D and CD4⁺ levels.^{78,80,82,90,91} At least one study has found a correlation between higher vitamin D levels and increased survival times of HIV-infected patients.⁸⁰ However, a 2004 study by Madeddu et al. of 152 adult patients on HAART, found no correlation between vitamin D and CD4⁺ T cell levels.⁸⁹ A 2001 study of 19 perinatally infected female children also found no correlation between vitamin D and CD4⁺ T cell levels.⁹²

5. Evidence for vitamin D influence on Epstein Barr virus

Studies have suggested a link between multiple sclerosis (MS) and Epstein-Barr virus (EBV), thus vitamin D levels may play a role in the development of MS.^{93,94} This topic was reviewed by Trygve Holmoy in *Medical Hypotheses*.⁹⁵ Holmoy notes that MS risk is associated with low vitamin D status and EBV infection. He proposes that vitamin D modulates the immune response to EBV and suppresses activation of auto-reactive T cells that may contribute to MS pathology.

6. Other evidence for vitamin D influence on enveloped viruses

Although few studies have examined the effects of vitamin D on Hepatitis B infection, a study of 2015 Gambian tuberculosis patients identified a silent T to C base change polymorphism in codon 352 of the VDR that was correlated with significantly lowered rates of persistent Hepatitis B infection and tuberculosis, but not malaria.⁹⁶ This polymorphism affects vitamin D levels, VDR mRNA stability, and VDR mRNA levels.⁹⁷⁻¹⁰⁰ The anti-Hepatitis B response in these patients may be cathelicidin mediated, much like the cathelicidin-mediated anti-tuberculosis response recently described.²⁵

In a Vietnamese dengue study, the same polymorphism was associated with resistance to severe dengue.¹⁰¹ At least one study has demonstrated administration of oral vitamin D₃ reduces the severity and length of dengue fever, but the small sample size ($n = 5$) makes it difficult to draw any robust conclusions.¹⁰²

A study conducted by Bitetto et al. showed that in immune competent patients 25(OH)D levels of less than 10 ng/ml (25 nmol/l) are significantly associated with poorer response to the standard antiviral hepatitis C therapy of ribavirin and pegylated interferon.¹⁰³ An earlier study by Petta et al. revealed an association between lower vitamin D levels and failure to clear virus during treatment in chronic hepatitis C patients.¹⁰⁴ The same study showed that low vitamin D levels were also associated with liver fibrosis. Therefore, this makes it difficult to determine whether lower vitamin D levels correlate with lower viral clearance or are just a consequence of damaged livers.

7. Potential mechanisms of anti-viral effects

The anti-viral effects of vitamin D could be explained by cathelicidin (in the form of LL-37), human beta defensin 2, and perhaps through the release of reactive oxygen species. A recent study showed hepatitis C replicon replication reduction in human hepatoma cells may be mediated by vitamin D induced oxidative stress.¹⁰⁵ Given vitamin D's pleiotropic effects, other mechanisms are possible.

LL-37's anti-bacterial effect is linked to its ability to disrupt bacterial membranes through electrostatic interactions.⁵³ Similar interactions may occur with the lipid envelopes of viruses. LL-37 may also block viral entry in a similar manner to what is seen with other anti-microbial peptides.¹⁰⁶ The epidemiologic evidence describing a positive vitamin D related immune effect includes many studies which feature enveloped viruses. This supports the notion that LL-37's anti-viral effects may be partially mediated by envelope disruption.

8. Experimental investigation of the anti-viral effects of vitamin D

Vitamin D induction of antimicrobial peptides may have antiviral effects.⁴³ Direct incubation of LL-37 with HSV-1 showed a significant dose dependent reduction of HSV-1 titer when compared to controls.⁵⁰ The same researchers also demonstrated a less pronounced but still significant reduction of adenovirus serotype Ad19 titer when exposed to higher LL-37 concentrations, but no significant titer reduction of the other adenovirus serotypes tested (Ad8, Ad5 and Ad3). Human papilloma virus appears sensitive to LL-37 inactivation or entry inhibition at physiological concentrations of LL-37, but some retroviruses are also sensitive to LL-37 mediated titer reduction at concentrations that may not be physiologically relevant.^{54,56,107} Methodological differences may affect these comparisons.

While mouse models do not perfectly parallel vitamin D's effects on human anti-microbial peptides, they provide evidence that anti-microbial peptides may have an effect against viruses. Studies involving incubation of LL-37 or CRAMP, a murine homolog, with vaccinia showed an almost complete inhibition, as measured by titer, of the virus at a concentration of 50 micromolar.⁵⁴ The vaccinia experiments also showed that in CRAMP knockout mice inoculated with skin pricks of vaccinia, four of six knockout animals developed vaccinia pox compared to only one of fifteen controls. While beta defensin 2 was unable to reduce vaccinia titer,⁵⁴ it is capable of inhibiting RSV in lung epithelial cell culture. Transmission electron microscopy showed the degradation of the RSV membrane after incubation with human defensin beta 2.¹⁰⁸ Mice infected with RSV expressed increased levels of murine beta defensin 4, a murine analog of human beta defensin 2, suggesting the cell culture results have *in vivo* relevance.

9. Conclusions

These results support the hypothesis that vitamin D induced LL-37, and to a lesser extent human beta defensin 2, may play a major role in the inhibition of viruses. However, these experiments do not completely model the complex effects of vitamin D and may not accurately represent its systemic influence. Further experiments are necessary to fully elucidate the mechanisms of vitamin D induced peptides and vitamin D itself.

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Abbreviations

25(OH)D	25-hydroxyvitamin D
1, 25(OH)₂ D	1,25-dihydroxyvitamin D
VDR	vitamin D receptor
TLR	toll-like receptor
HSV-1	herpes simplex virus type one
RSV	respiratory syncytial virus
RTI	respiratory tract infection
CRAMP	cathelicidin related anti-microbial peptide
HAART	highly active anti-retroviral therapy

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Table 1

Controlled studies of vitamin D based treatment for prevention of respiratory tract infections and influenza.

Study	Length	Trial type	Test group criteria	Test population	Control population	Vitamin D dosage and type	RTI/influenza evaluation method	Significant reduction in RTI or influenza	P-value	95% CI
Rehman ⁶¹	6 weeks	NRCT	>6 respiratory infections in previous 6 months	27 (children, both sexes, ages 3–12)	20 (children, age and sex matched)	60,000 IU weekly, oral	Clinical diagnosis	Y	<0.005*	N/A
Avenell et al. ⁶²	2 years	RCT	Ambulatory, age > 70 years	1740 (age 70+, 85% female)	1704 (age 70+, 85% female)	800 IU daily, oral D ₃	Self-reporting on questionnaire 18 (median) months after randomization	N	0.06	0.64–1.01
Li-Ng et al. ⁶³	12 weeks	RCT	Ambulatory, age 18–80	78 (78.2% female, median age 59.3)	70 (81.4% female, median age 58.1)	2000 IU daily, oral D ₃	Self-reporting on bi-weekly questionnaire	N	0.56	-2.4 to 3.4
Urashima et al. ⁷⁴	4 months	RCT	School children, age 6–15	167 (43% female, median age 10.0)	167 (45% female, median age 10.4)	1200 IU daily, oral D ₃	Nasopharyngeal swab by clinician	Y	0.04*	0.34–0.99
Aloia and Li-Ng ⁷⁶	3 years	RCT	Post-menopausal African-American women	104 (100% female, median age 61.2)	104 (100% female, median age 59.9)	2000 IU daily	Self-reporting during clinician visit every 6 months	Y	<0.002*	N/A

NRCT = Non-Randomized Controlled Trial, RCT = Randomized Controlled Trial.

* P-values of less than 0.05 considered significant.

Table 2

Observational studies correlating vitamin D deficiencies with respiratory tract infection and influenza.

Study	Length	Study type	Study population	Control population	Average 25(OH)D level associated with increased RTI/ influenza ng/ml (nmol/l)	Average 25(OH)D level in controls ng/ml (nmol/l)	P-value	95% confidence interval
Laaksi et al. ⁶⁶	6 months	Prospective cohort	24 (100% male, age 18–29)	628 (100% male, age 18–29)	<16.0 (40.0)	32.1 (80.2)	0.004*	1.15–2.24
Roth et al. ⁶⁷	2 months	Case-control (ALRI)	25 (20% female, median age 4.2 months)	25 (20% female, median age 4.2 months)	11.7 (29.1)	15.7 (39.1)	0.0146*	0.30–0.96
Wayse et al. ⁶⁸	4 months	Case-control (ALRI)	80 (36.3% female, median age 23.9 months)	70 (45.7% female, median age 23.9 months)	9.12 (22.8)	15.4 (38.4)	0.001*	0.03–0.24
Karatekin et al. ⁶⁹	4 months	Case-control (ALRI)	25 (36% female, 10.9 days)	15 (60% female, 5.6 days)	<10.0 (25)	16.3 (40.8)	0.041*	1.058–17.070
McNally et al. ⁷⁰	7 months	Case-control (ALRI)	105 (41% female, median age, 13.8 months)	92 (42% female, median age, 13.4 months)	32.5 (81)	33.3 (83.0)	0.71	N/A
Roth et al. ⁷¹	3 months	Case-control (ALRI)	64 (36% female, median age 8.4 months)	65 (25% female, median age 13.3 months)	30.8 (77)	30.9 (77.2)	0.960	0.998–1.002
<i>a</i> Ginde et al. ⁷²	4 years	Retrospective Cohort	3588 (47.3% female)	15,295 (52% female, median age 38)	10 (25.0), 28 (69.9)	29.0 (72.4)	<05* <.0001*	1.18–2.05 1.11–1.47

ALRI = Acute Lower Respiratory Tract Infection.

Values in nmol/l given in parentheses.

* P-values of less than 0.05 considered significant.

a Categories separated by severe (<10 ng/ml) vitamin D deficiency and rest of patient population.

Table 3

Observational studies examining vitamin D deficiencies and HIV infection.

Study	Study type	Study population	Control population	Average 25(OH)D level of patients ng/ml (nmol/l)	Average 25(OH)D of controls ng/ml (nmol/l)	P-value	1,25(OH) ₂ D levels of patients (pg/ml)	1,25(OH) ₂ D levels of controls (pg/ml)	P-value
Kuehn et al. ⁷⁷	Case-control	828 HIV+ (14% female, median age 37.5)	549 (54% male, median age 48.5)	<20 (<50)	N/A	N/A	N/A	N/A	N/A
Teichmann et al. ⁷⁸	Case-Control	50 HIV+ (100% female, median age 37.4)	50 (100% female, median age 35.1)	37.3 (93.1)	61.5 (153.5)	<0.01*	19.4	47.3	<0.01*
Coodley et al. ⁷⁹	Prospective cohort	47 HIV+ (4% female)	N/A	17% of patients deficient	N/A	0.07	11% of patients deficient	N/A	0.72
Haug et al. ⁸⁰	Case-control	53 HIV+	28	End stage: 26.8 (66.9) Asymptomatic: 53.0 (132.3)	50.6 (126)	>0.05	All: 42 Symptomatic: 33	49	<0.01*

N/A: Non-applicable or not given in study.

Value in nmol/l given in parentheses.

* P-values of less than .05 considered significant.