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ORIGINAL ARTICLE

# Factors Affecting Vitamin D Level in Antiretroviral Treatment Naive Persons Living with HIV

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## Abstract

**Introduction:** In this study, it was aimed to investigate the factors affecting vitamin D levels in antiretroviral treatment naive persons living with HIV.

**Methods:** This retrospective study, which included 100 patients, was performed in the Department of Infectious Diseases and Clinical Microbiology, Haydarpasa Numune Training and Research Hospital. The relationship between patients' 25(OH)D vitamin levels and demographic characteristics, underlying diseases, coinfection or malignancy, possible transmission time of HIV infection, substance use, smoking and alcohol use, CD4+ T lymphocyte counts, HIV RNA levels, and laboratory values were investigated.

**Results:** Of the 100 patients included in the study, 90 (90%) were male, and the mean age was 36.7±11.5. At the time of admission, 84 patients (84%) had either vitamin D deficiency or insufficiency. For between-group differences, the patients were divided into two groups based on a 25(OH)D level of <30 ng/ml and ≥30 ng/ml. The two groups were similar with respect to age, body mass index, comorbidities, sex, smoking status, alcohol use, and possible transmission time of HIV infection ($p>0.05$). Except for the ALT level ($p<0.05$), the two groups were similar with respect to all laboratory variables.

**Discussion and Conclusion:** This study found that antiretroviral treatment naive persons living with HIV, with and without vitamin D deficiency, showed similar characteristics with respect to some traditional risk factors such as age, gender, and obesity. However, only significant correlations were found between ALT and vitamin D levels. More studies are needed to show the relationship between ALT and vitamin D levels.

**Keywords:** HIV; risk factors; vitamin D level.

Vitamin D is crucial to calcium homeostasis and bone metabolism[1]. Vitamin D deficiency is a global public health problem and has been associated with a wide variety of conditions, including osteoporosis, hypertension, insulin resistance, cardiovascular disease, diabetes, metabolic syndrome, dyslipidemia, immune system disorder, malignancy, and impaired neurocognitive function[1-3].

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Serum 25-hydroxyvitamin D (25[OH]D) level is the best indicator to determine vitamin D status. There is a consensus that the 25(OH)D levels required for calcium homeostasis and healthy bone metabolism should at least be 30-32 ng/mL[1]. Vitamin D deficiency is associated with having dark skin, decreased exposure to sunlight, hepatic failure, obesity, advanced age, adverse drug effects, and a diet poor in vitamin D[2,3]. Vitamin D deficiency is commonly identified in both the overall population and people infected with human immunodeficiency virus (HIV) [4]. The rate of vitamin D deficiency among HIV-infected patients varies from 12% to 100%[5]. Middle-aged patients infected with HIV are at risk for many comorbidities that are typically similar to those observed in the elderly, including osteoporosis, diabetes, fragility fractures, cardiovascular disease, and cognitive impairment, many of which are accompanied by vitamin D deficiency. Low levels of 25(OH) D have been associated with HIV-related complications and the progression of HIV[1].

Vitamin D deficiency among HIV-infected patients is attributed to defects in renal hydroxylation and excessive metabolic use of vitamin D[6]. This study aimed to determine vitamin D status among newly diagnosed HIV-infected patients in whom antiretroviral therapy had not been initiated and to investigate the factors affecting 25(OH)D levels.

## Materials and Methods

This retrospective study was conducted in the Infectious Diseases and Clinical Microbiology Clinic of a Training and Research Hospital, between January 1, 2015 and October 1, 2016. Data were retrieved from follow-up files and hospital records. The study included 100 HIV-infected patients aged 18 years or older who were followed up by the outpatient clinic. Patients who had not received antiretroviral therapy or vitamin D replacement therapy before and whose vitamin D level was checked at the time of admission were included in the study. The study was approved by the institutional Clinical Research Ethics Committee (HNEAH KAEK 2016/KK/100). The study protocol complies with the ethical criteria of the 1964 Declaration of Helsinki.

Demographic characteristics, underlying diseases, substance abuse, possible transmission time of HIV infection, predicted risk factors for vitamin D deficiency, and signs and symptoms related to vitamin D deficiency were examined. In addition, the baseline hemogram and biochemical values, CD4+ T lymphocyte counts (cell/mm$^3$), HIV RNA levels (IU/ml), and 25(OH)D levels (ng/ml) were evaluated. 25(OH)D was measured using the CMIA (Chemiluminescent Microparticle Immunoassay) technology with flexible test protocols called Chemiflex (Architect-Aeroset-Abbott Diagnostics, IL, USA).

Cut-off values of 25(OH)D for vitamin D deficiency and insufficiency were <20 ng/ml and 20 to 29 ng/ml, respectively. Higher levels (≥30 ng/ml) were considered sufficient[7,8,9]. The staging of HIV infection was made according to the CDC criteria[10,11]. Body mass index (BMI) was classified according to the World Health Organization (0-18.4 kg/m$^2$ underweight, 18.5-24.9 kg/m$^2$ normal weight, 25.0-29.9 kg/m$^2$ overweight, 30.0-34.9 kg/m$^2$ class I obesity, 35.0-39.9 kg/m$^2$ class II obesity, and 40.0 kg/m$^2$ and above class III obesity)[12].

### Statistical Analysis

Data were processed using the MedCalc Statistical Software version 12.7.7 (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2013). Descriptive statistics were used to express continuous variables (mean, standard deviation, minimum, median, maximum). Comparison of normally distributed continuous variables was made with the Student's t-test and the Mann-Whitney U test was used for comparison of variables that were not normally distributed. Categorical variables were compared using the chi-squared test or Fisher's Exact test where appropriate. A p value of less than 0.05 was considered statistically significant.

## Results

Of 100 patients, 90 (90%) were males. The mean age was 36.7±11.5 years (min-max: 18-72). Based on BMI measurements, four patients (4%) were underweight, 61 (61%) had normal weight, 31 (31%) were overweight, three (3%) had class I obesity, and one (1%) had class II obesity.

The mean 25(OH)D level was 19.9±11.6 ng/ml (min-max: 3.9-83.7). The majority of patients (n=60; 60%) had a 25(OH) D level of ≤20 ng/ml; 24 (24%) had a 25(OH)D level of 21-29 ng/ml; and 16 (16%) had a 25(OH)D level of ≥30 ng/ml. Overall, 84 patients (84%) had either vitamin D deficiency or insufficiency.

For between-group differences, the patients were divided into two groups based on a 25(OH)D level of <30 ng/ml and ≥30 ng/ml. The two groups were similar with respect to age, BMI, comorbidities, sex, smoking status, alcohol use, and possible transmission time of HIV infection (p>0.05)

**Table 1.** Distribution of age and BMI based on 25(OH)D levels

| | 25(OH)D levels (ng/ml) | N | Mean | SD | Min | Max | p* |
|---|---|---|---|---|---|---|---|
| Age | | | | | | | |
| | ≥30 | 16 | 40.38 | 12.654 | 24 | 69 | 0.158 |
| | <30 | 84 | 36.04 | 11.211 | 18 | 72 | |
| BMI | | | | | | | |
| | ≥30 | 16 | 24.27 | 2.03 | 21.6 | 27.78 | 0.142 |
| | <30 | 84 | 23.46 | 3.71 | 15.62 | 35.38 | |

BMI: Body mass index; *Mann-Whitney U.

(Tables 1, 2). All the patients, except one patient who was from Iran, were Turkish citizens.

At presentation, 52 patients (52%) had symptoms and signs that might be related to vitamin D deficiency, including fatigue in 33 (33%), headache in 19 (19%), constipation or diarrhea in 15 (15%), joint pain in 14 (14%), depression in 14 (14%), muscle cramps in 11 (11%), bone pain in 9 (9%), weight gain in seven (7%), and hypertension in five (5%).

Laboratory findings are summarized in Table 3. Except for the ALT level ($p<0.05$), the two groups were similar with respect to all laboratory variables. According to CD4+ T lymphocyte counts, 37 patients (37%) had >500 cells/mm$^3$, 41 (41%) had 200-500 cells/mm$^3$, and 22 (22%) had <200 cells/mm$^3$. Patients with a 25(OH)D level of <30 ng/ml and ≥30 ng/ml did not differ significantly with respect to both CD4+ T lymphocyte count and HIV RNA level ($p>0.05$) (Table 4).

Separate analysis of CD4+ lymphocyte counts (≥200 and <200) and HIV RNA levels (<100,000 copies/ml and ≥100,000 copies/ml) also showed no significant differences between the two patient groups ($p>0.05$) (Table 5).

Thirty patients (30%) had co-infections or malignancies, including three (3%) tuberculosis infections (two lung, one miliary tuberculosis); two (2%) cytomegalovirus (CMV) infections, causing colitis and retinitis, respectively; 11 (11%) syphilis, of which, one PCP and one neurosyphilis; seven (7%) oral candidiasis; five (5%) candida esophagitis; two (2%) acute HBV infections; one molluscum contagiosum in association with a penile intraepithelial neoplasia; one disseminated Mycobacterium avium complex infection; one progressive multifocal leukoencephalopathy; one cryptococcal meningitis in association with molluscum contagiosum; one herpes zoster infection. The two patient groups were similar with respect to the incidence of co-infections or malignancies ($p>0.05$) (Table 6).

**Table 2.** Distribution of comorbidities, risk factors based on 25(OH) D levels

| | 25(OH)D levels (ng/ml) | | p* |
|---|---|---|---|
| | <30, n (%) | ≥30, n (%) | |
| Diabetes mellitus | | | |
| No | 80 (95.2) | 16 (100) | 0.492 |
| Yes | 4 (4.8) | 0 (0) | |
| Hypertension | | | |
| No | 77 (91.7) | 15 (93.8) | 0.624 |
| Yes | 7 (8.3) | 1 (6.2) | |
| Kidney disease | | | |
| No | 82 (97.6) | 16 (100) | 0.704 |
| Yes | 2 (2.4) | 0 (0) | |
| Chronic HBV infection | | | |
| No | 82 (97.6) | 14 (87.5) | 0.119 |
| Yes | 2 (2.4) | 2 (12.5) | |
| Chronic HCV infection | | | |
| No | 83 (98.8) | 16 (100) | 0.840 |
| Yes | 1 (1.2) | 0 (0) | |
| Psychiatric disease | | | |
| No | 77 (91.7) | 15 (93.8) | 0.624 |
| Yes | 7 (8.3) | 1 (6.2) | |
| Substance abuse | | | |
| No | 80 (95.2) | 16 (100) | 0.492 |
| Yes | 4 (4.8) | 0 (0) | |
| Cardiovascular disease | | | |
| No | 79 (94) | 16 (100) | 0.410 |
| Yes | 5 (6) | 0 (0) | |
| Others | | | |
| No | 83 (98.8) | 15 (93.8) | 0.296 |
| Yes | 1 (1.2) | 1 (6.2) | |
| Sex | | | |
| Male | 74 (88.1) | 16 (100) | 0.160 |
| Female | 10 (11.9) | 0 (0) | |
| Smoking status | | | |
| Non-smoker | 44 (52.4) | 11 (68.8) | 0.176 |
| Current smoker | 40 (47.6) | 5 (31.3) | |
| Alcohol use | | | |
| Does not drink | 51 (60.7) | 8 (50) | 0.299 |
| Drinks | 33 (39.3) | 8 (50) | |
| HIV transmission time | | | |
| <24 months | 36 (50.7) | 8 (61.5) | 0.340 |
| ≥24 months | 35 (49.3) | 5 (38.5) | |

Others: Asthma, benign prostatic hypertrophy; *Fisher's Exact.

**Table 3.** Distribution of laboratory findings based on 25(OH)D levels

| | 25(OH)D levels (ng/ml) | N | Mean | SD | Min | Max | p* |
|---|---|---|---|---|---|---|---|
| Hb (gr/dL) | ≥30 | 16 | 14.22 | 2.01 | 8.5 | 16.7 | 0.199 |
| | <30 | 84 | 13.7 | 2.01 | 7 | 16.4 | |
| Plt (K/uL) | ≥30 | 16 | 218.6 | 68.7 | 129 | 384 | 0.836 |
| | <30 | 84 | 203.5 | 62.3 | 15 | 342 | |
| WBC (K/uL) | ≥30 | 16 | 312.6 | 1223.3 | 2.85 | 4900 | 0.452 |
| | <30 | 84 | 758.6 | 2298.6 | 1.42 | 10000 | |
| CRP (mg/dL) | ≥30 | 6 | 1.91 | 2.95 | 0.1 | 7.8 | 0.115 |
| | <30 | 57 | 0.487 | 0.79 | 0.1 | 4.8 | |
| Protein (g/dL) | ≥30 | 13 | 7.61 | 0.535 | 6.8 | 8.6 | 0.276 |
| | <30 | 79 | 7.79 | 0.779 | 5 | 10 | |
| Albumin (g/dL) | ≥30 | 16 | 4.21 | 0.574 | 2.6 | 5 | 0.557 |
| | <30 | 80 | 4.29 | 0.54 | 2.7 | 5.3 | |
| AST (IU/L) | ≥30 | 16 | 32.8 | 27.6 | 14 | 130 | 0.275 |
| | <30 | 84 | 27.4 | 18.6 | 9 | 118 | |
| ALT (IU/L) | ≥30 | 16 | 45.89 | 39.6 | 18 | 177 | 0.014 |
| | <30 | 84 | 37.68 | 91.032 | 6 | 847 | |
| LDH (IU/L) | ≥30 | 9 | 273.2 | 101.48 | 156 | 460 | 0.200 |
| | <30 | 61 | 231.6 | 72.62 | 138 | 497 | |
| Ca (mg/dL) | ≥30 | 7 | 9.1 | 0.766 | 7.6 | 10 | 0.545 |
| | <30 | 59 | 9.31 | 0.588 | 8 | 10.6 | |
| P (mg/dL) | ≥30 | 12 | 3.23 | 0.4887 | 2.4 | 4.1 | 0.206 |
| | <30 | 71 | 3.51 | 0.6485 | 2.4 | 5.8 | |
| ALP (IU/L) | ≥30 | 12 | 110.67 | 108.7 | 42 | 447 | 0.100 |
| | <30 | 64 | 70.53 | 25.31 | 4.1 | 169 | |
| GGT (IU/L) | ≥30 | 15 | 90.27 | 135.495 | 11 | 432 | 0.143 |
| | <30 | 70 | 41.77 | 87.679 | 9 | 721 | |
| BUN (mg/dL) | ≥30 | 15 | 11.53 | 2.67 | 8 | 17 | 0.517 |
| | <30 | 82 | 12.07 | 3.48 | 5 | 31 | |
| Creatinine (mg/dL) | ≥30 | 16 | 0.82 | 0.085 | 0.7 | 1 | 0.830 |
| | <30 | 83 | 0.85 | 0.233 | 0.58 | 2.6 | |

WBC: Leukocyte count; CRP: C-reactive protein; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; LDH: Lactate dehydrogenase; Ca: Calcium; P: Phosphorus; ALP: Alkaline phosphatase; GGT: Gamma glutamyl transferase; BUN: Blood urea nitrogen; *Mann-Whitney-U.

**Table 4.** Comparison of CD4 + T lymphocyte counts and HIV RNA levels based on 25(OH)D levels

| | 25(OH)D levels (ng/ml) | N | Mean | SD | Min | Max | p* |
|---|---|---|---|---|---|---|---|
| HIV RNA levels (IU/ml) | ≥30 | 16 | 14424960.9 | 33540784.7 | 1793 | 10000000 | 0.579 |
| | <30 | 84 | 2850075.5 | 11403231.9 | 6746 | 10000000 | |
| CD4 counts ($mm^3$) | ≥30 | 16 | 437.1 | 319.1 | 58 | 1083 | 0.948 |
| | <30 | 84 | 434.8 | 272.6 | 5 | 1190 | |

*Mann-Whitney U.

**Table 5.** Comparison of those with CD4+ T lymphocyte counts ≥200 and <200 ($mm^3$) according to 25(OH)D levels

| | 25(OH)D levels (ng/ml) | | p* |
|---|---|---|---|
| | <30 | ≥30 | |
| CD4 + T lymphocyte counts ($mm^3$) | | | |
| ≥200 | 67 (79.8) | 11 (68.8) | 0.252 |
| <200 | 17 (20.2) | 5 (31.3) | |

*Fisher's Exact.

**Table 6.** Distribution of patients with co-infections or malignancy based on 25(OH)D levels

| | 25(OH)D levels (ng/ml) | | p* |
|---|---|---|---|
| | <30 | ≥30 | |
| Coinfection/malignancy | | | |
| No | 58 (69) | 12 (75) | 0.454 |
| Yes | 26 (31) | 4 (25) | |

*Fisher's Exact.

## Discussion

Being not only a global public health problem, vitamin D deficiency has also been shown to be common among HIV-infected patients[5,13]. Vitamin D deficiency among HIV-infected patients has been reported to arise from multiple factors, and apart from the traditional risk factors, pharmacological effects of antiretroviral therapy as well as metabolic complications accompanying HIV infection raise the risk for vitamin D deficiency[14]. Bearden et al.[15] reported that, of 112 HIV-infected patients, 73% had a 25(OH)D level of less than 30 ng/ml. Another study found that, of 672 HIV-positive patients, 70.3% had 25(OH)D levels of less than 30 ng/ml[1]. A study of 96 HIV-positive patients from Istanbul found a higher rate of 83.4%[16]. In the current study, a similar rate of 84% was found among HIV-infected patients.

Obesity is a risk factor for vitamin D deficiency in HIV-infected patients. The 25(OH)D level is considered to decrease in obese patients due to its sequestration in adipose tissue. In addition, decreased outdoor activity and exposure to sunlight also reduce 25(OH)D levels in obese people[17]. In a study of 1268 HIV-positive women, only 13% were found to have normal vitamin D status (25(OH)D >30 ng/ml). Interestingly, the rates of vitamin D deficiency/insufficiency were 54% in underweight-normal women, 62% in overweight women, and 71% in obese women; hence, the higher BMI, the more likely vitamin D deficiency[17]. The same trend was also reported in HIV-positive patients in whom a high BMI was associated with low levels of 25(OH)D[18]. In our study, 31% of the patients were overweight and 4% were obese, and there was no significant difference in BMI between patients having a 25(OH)D level of <30 ng/ml and ≥30 ng/ml.

Smoking has a negative effect on vitamin D metabolism, decreasing 25(OH)D levels[19, 20]. A study of 334 antiretroviral-treated naive patients reported low 25(OH)D levels (<30 ng/ml) in 82.3%, of whom 41.3% were current smokers, showing that smoking was associated with vitamin D deficiency[20]. In this study, nearly half of the patients (45%) were smokers, but there was no significant difference in smoking status between patients having a 25(OH)D level of <30 ng/ml and ≥30 ng/ml.

Vitamin D is known to have a significant role in immune function[21]. Vitamin D-deficient subjects are more likely to develop inflammation, immune activation, and to have low peripheral CD4+ T cell counts[13]. A study of 2044 HIV-positive patients found a significant relationship between CD4+ T cell count and 25(OH)D levels. Patients with a CD4+ T cell count of <200/μl had significantly decreased 25(OH)D levels compared to those with a CD4+ T cell count of ≥200/μl (median 11.5 ng/dl vs. 14.1 ng/dl) [22]. In contrast, Kim et al.[23] found no relationship between CD4+ T lymphocyte counts and 25(OH)D levels. We also found no significant difference in CD4+ T lymphocyte counts between patients having a 25(OH)D level of <30 ng/ml and ≥30 ng/ml.

Vitamin D is considered to contribute to the inhibition of HIV-1 infection in T cells by increasing antiviral gene expression, decreasing viral coreceptor CCR5 on CD4+ T cells, and promoting HIV-1-restrictive CD38+ HLA-DR+ immunophenotype[13]. Low 25(OH)D levels were found to be associated with high HIV RNA in plasma and rapid AIDS progression[13]. Kim et al.[23] reported a significant association between HIV viral load above 50 copies/ml and vitamin D deficiency. In contrast, Nugmanova et al.[24] found no association between 25(OH)D and HIV RNA among 564 HIV-infected patients. We also found similar HIV RNA levels in patients having a 25(OH)D level of <30 ng/ml and ≥30 ng/ml.

Vitamin D is known to have an immunomodulatory effect on both natural and adaptive immune responses and to reduce the incidence and severity of opportunistic infections[25-27]. Sudfeld et al.[25] showed a strong association between vitamin D deficiency and the development of pulmonary tuberculosis and oral candidiasis among 1103 HIV-positive patients. Canuto et al.[28] reported higher 25(OH)D levels among patients with previous opportunistic infections. Our study found no significant difference in the incidence of opportunistic infections in patients having a 25(OH)D level of <30 ng/ml and ≥30 ng/ml.

Of the laboratory findings analyzed in the current study, only the ALT level showed a significant difference between the two patient groups based on 25(OH)D level. Patients with a 25(OH)D level of ≥30 ng/ml had a higher ALT level. Dao et al.[1] found no significant differences in ALT and AST levels between patients with and without vitamin D deficiency. Contrary to our finding, elevated liver enzyme levels in serum, including ALT, were found in a significant proportion (42.8%) of patients with vitamin D deficiency who had not received antiretroviral therapy[27]. Elevated liver enzyme levels were attributed to vitamin D hydroxylation associated with HIV-induced liver damage[29]. In a study by Gurbuz et al.[30] on 50 pediatric patients with chronic liver disease, a significant improvement was observed in AST and ALT levels after vitamin D replacement. Skaaby et al.[31] evaluated 2649 people from the general population. The

risk of having a high level of ALT, AST, or GGT tended to be higher for lower vitamin D levels, although not statistically significant.

A main limitation to this study is the small number of patients. We examined a number of parameters in HIV-positive adults in relation to 25(OH)D levels. Unlike previous studies, we found the two patient groups similar – except for ALT – as classified by the 25(OH)D level. The small patient size may have affected our findings.

## Conclusion

In conclusion, vitamin D deficiency is common among HIV-infected persons, which may be associated with the disease itself or the accompanying pathologies. This study found that HIV-infected persons with and without vitamin D deficiency showed similar characteristics with respect to some traditional risk factors such as age, gender, and obesity. Increased ALT levels accompanying a normal vitamin D status (25(OH)D level of ≥30 ng/ml) need to be verified by further studies enrolling a large number of patients.

**Ethics Committee Approval:** Approval was granted by the Ethics Committee of Haydarpasa Training and Research Hospital in Istanbul, Türkiye.

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