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Brief Original Article

Relationship between vitamin D and human immunodeficiency virus (HIV) viral load among HIV-infected patients in Kazakhstan

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Abstract

Introduction: Human immunodeficiency virus (HIV) is associated with inflammation. An association between vitamin D deficiency and inflammation also exists. Our study attempts to examine whether there may be a relationship between vitamin D and HIV viral load (HIV RNA) by: 1) characterizing the distribution of 25-hydroxyvitamin D (25-OHD), and 2) determining if 25-OHD is independently associated with HIV RNA.

Methodology: A cross-sectional study among HIV-infected adults was conducted. Demographics, clinical / social / HIV characteristics and data on antiretroviral therapy were collected by questionnaire, medical records and laboratory testing. All patients provided blood samples. Bivariate and multivariate analyses were conducted to quantify the relationship between vitamin D and HIV RNA.

Results: Among the 564 patients, the median (interquartile range, IQR) 25-OHD value was 24.42 (16.22 – 34.10) ng/mL. The mean (standard deviation, SD) log-HIV RNA was 3.51 (1.11) copies/mL. There were 304 patients (53.9%) with an undetectable HIV RNA (< 500 copies/mL). In the bivariate analyses, no differences were observed between patients with and without an undetectable HIV RNA in mean (SD) 25-OHD, 25-OHD insufficiency (< 30 ng/mL), or 25-OHD deciles. In the log-binomial regression analyses, there was no association between 25-OHD and an undetectable HIV RNA (prevalence ratio: 1.00, 95% confidence interval: 0.99 – 1.01, p = 0.67).

Conclusions: No relationship was observed between 25-OHD and HIV RNA among HIV-infected patients in Kazakhstan.

Key words: HIV; vitamin D; viral load.

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Introduction

Patients with human immunodeficiency virus (HIV) infection are vulnerable to the effects of chronic inflammation, immune dysregulation and early immunosenescence [1]. Poor outcomes associated with persistent inflammation among HIV-infected individuals include an increased risk of cardiovascular disease, opportunistic infections, disease progression and death [2,3]; high HIV viral loads hasten disease progression as well [4].

The availability of antiretroviral therapy (ART) has led to significant reductions in HIV RNA replication and improved outcomes [5]. However, inflammation and accelerated immunosenescence persist [6]. Over the last decade, interest has grown in identifying biomarkers of inflammation, like vitamin D, as an early marker of immunosenescence among individuals with HIV [7-10]. However, the precise relationship between vitamin D and HIV RNA is unclear. Understanding this relationship may help us better predict the onset of immunosenescence.

This study evaluated the relationship between vitamin D and HIV RNA among HIV-infected patients receiving care in Kazakhstan. The study objectives were to: 1) characterize the distribution of vitamin D, and 2) determine if 25-hydroxyvitamin D is independently associated with HIV-RNA levels.

Methodology

A cross-sectional study was performed among adult HIV-infected patients living in Kazakhstan. Blood samples were collected and questionnaires were completed between April 2013 and July 2013. The study was approved by the Research Ethics Committee

at the Kazakh National Medical University. All patients signed a written informed consent.

Study Population

Patients receiving care at the Almaty AIDS Centre (Almaty, Kazakhstan) were eligible for inclusion if: 1) age ≥ 18 years; 2) had documented laboratory-confirmed HIV infection; and 3) spoke Kazakh or Russian. Patients recently (≤ 3 months) linked to HIV-related care were not included.

Study Data

Three sources were used to obtain data: 1) a comprehensive questionnaire completed by patients; 2) abstracted medical records; and 3) blood samples for laboratory testing.

The questionnaire included demographics (age, sex, ethnicity, marital status and education), self-perceived health status, [11] comorbidities, and social behaviours (such as recreational drug use).

The patient's history of HIV infection was abstracted from the medical records, including: year of diagnosis, mode of transmission, and risk behaviours. The most recent list of antiretroviral medications was collected. The laboratory values extracted from the patients' medical records were: all CD4 values in the preceding year, hepatitis C (HCV) status, HIV RNA and CD4 count at the time of diagnosis, and all HIV RNA values in the preceding year.

Laboratory data

The following laboratory tests were performed upon vitamin D sampling: HIV RNA, absolute CD4 count, serum creatinine, glucose, complete blood count, and liver function panel.

Blood samples were collected to determine 25-hydroxyvitamin D3 levels (25-OHD). *In vitro* quantification of 25-OHD was performed using the Elecsys Vitamin D3 assay (Roche Diagnostics GmbH, Mannheim, Germany). Patients provided two blood samples (5 mL each); one sample was reserved for a validation study (data not reported). Blood samples were collected in standard blood collection tubes for obtaining serum. Within 1 hour of collection, samples were centrifuged at room temperature at 3000 – 4000 rpm for 15 minutes. The serum was withdrawn, split into 2 aliquots, and transferred into separate polypropylene cryogenic storage tubes. Within 1 hour of separating the serum, the samples were stored at -20°C until assayed in November of 2013.

Outcomes

The outcome of interest in this study was the HIV RNA. First, HIV RNA was evaluated as a dichotomous variable and patients were classified as having an undetectable vs. detectable HIV RNA. The lower limit of detection was 500 copies/mL (AmpliSens HIV monitor-FRT, Moscow, Russia per instructions of the Central Research Centre of Epidemiology, Moscow, Russia; Real-time PCR – IQ-5, Bio-Rad, Hercules, USA), and an undetectable HIV RNA was defined as a HIV RNA < 500 copies/mL. Second, HIV RNA was assessed as a continuous variable after log-transformation to approximate a more normal distribution.

Data Analysis Plan

Descriptive statistics were used to characterize the distribution of 25-OHD values. Bivariate analyses described the association between all of the clinical covariates and undetectable HIV-RNA. Categorical variables were compared using the Chi-square test for independence or Fisher's exact test. Continuous variables were evaluated using the Student's t or Mann-Whitney U test. A series of stratified analyses were performed by comparing stratum-specific estimates using the Breslow-Day test. Because of the low sensitivity of this test, a cut-off of $p < 0.2$ was used to denote statistical significance for these analyses only. All variables associated with the outcomes of interest in the bivariate analysis ($p < 0.2$) were considered for inclusion in the explanatory multivariate regression models.

To assess the relationship between 25-OHD and HIV RNA, two sets of multivariate analyses were performed: 1) among all patients, and 2) among patients not receiving ART. We performed log-binomial regression because it is well-suited for outcomes with a proportion > 10% [12]. Potential confounders were retained in the final model if removing them resulted in a > 10% change in the prevalence ratio or beta coefficient for the relationship between 25-OHD and HIV RNA. A backwards stepwise approach was used to derive the most parsimonious model.

All calculations were computed using SPSS version 11.5 (SPSS Inc., Chicago, IL) and SAS version 9.2 (Cary, NC).

Table 1. Relationship between clinical/demographic characteristics and undetectable HIV RNA

Covariate	N	Detectable HIVRNA (n = 260)	Undetectable HIVRNA (n = 304)	P-value
25-hydroxyvitamin D				
25-hydroxyvitamin D, mean (SD), ng/mL	564	26.4 (11.4)	25.9 (13.2)	.61
Vitamin D insufficiency (25-OHD level < 30 ng/mL)	564	169 (65.0)	198 (65.1)	.97
Distribution of vitamin D deciles	564			.15
< 10.00		15 (5.8)	24 (7.9)	
10.00 – 19.99		67 (25.8)	96 (31.6)	
20.00 – 29.99		87 (33.5)	78 (25.7)	
30.00 – 39.99		59 (22.7)	61 (20.1)	
40.00 – 49.99		23 (8.8)	26 (8.6)	
≥ 50.00		9 (3.5)	19 (6.3)	
Demographic and social characteristics				
Sex, male	564	143 (55.0)	168 (55.3)	1.00
Ethnicity	554			.39
Kazakh		82 (31.9)	79 (26.6)	
Russian		135 (52.5)	163 (54.9)	
Turkish		1 (0.4)	0 (0)	
Korean		5 (1.9)	3 (1.0)	
Uigur		13 (5.1)	22 (7.4)	
Other		21 (8.2)	30 (10.1)	
Age in years, mean (SD)	556	35.9 (8.7)	38.2 (9.0)	.003
Education	556			.61
None		1 (0.4)	2 (0.7)	
Primary		3 (1.2)	6 (2.0)	
High school		223 (86.8)	248 (82.9)	
Higher education (University)		30 (11.7)	43 (14.4)	
Marital status	561			.05
Single		53 (20.6)	51 (16.8)	
Married or cohabitating		181 (70.4)	215 (70.7)	
Divorced		20 (7.8)	22 (7.2)	
Widow		3 (1.2)	16 (5.3)	
Does not engage in IV drug use	498	129 (54.7)	135 (51.5)	.48
Comorbidities and underlying health status				
Hepatitis C infection	564	119 (45.8)	144 (47.4)	.70
Duration since diagnosis of HCV infection, median (IQR), years	245	3.3 (2.7)	4.4 (3.2)	.008
Heart disease	396	10 (5.6)	9 (4.1)	.51
Liver disease	483	134 (60.4)	176 (67.4)	.11
Chronic Kidney Disease	397	15 (8.3)	25 (11.5)	.49
Other diseases	402	37 (14.2)	42 (13.8)	.79
Health status	553			.78
Very bad		2 (0.8)	2 (0.7)	
Bad		14 (5.5)	16 (5.4)	
Neither bad nor good		92 (36.2)	94 (31.4)	
Good		144 (56.7)	186 (62.2)	
Very good		2 (0.8)	1 (0.3)	

Table 1 (continued). Relationship between clinical/demographic characteristics and undetectable HIV RNA

Covariate	N	Detectable HIVRNA (n = 260)	Undetectable HIVRNA (n = 304)	P-value
History of HIV infection				
Mode of Transmission	535			.09
Sexual		140 (57.4)	151 (51.9)	
Parenteral		99 (40.6)	138 (47.4)	
Blood transfusion		0 (0)	1 (0.3)	
Other		5 (2.0)	1 (0.3)	
Risk Behaviour	528			.64
Intravenous drug use		111 (46.6)	151 (52.1)	
Men who have sex with men		5 (2.1)	3 (1.0)	
Perinatal		1 (0.4)	0 (0)	
Healthcare-acquired		8 (3.4)	9 (3.1)	
Heterosexual		111 (46.6)	125 (43.1)	
Other		2 (0.8)	2 (0.7)	
Duration since diagnosis HIV infection, median (IQR), years	564	3.7 (2.8)	4.4 (3.1)	.002
CD4 count, mean (standard deviation, SD)	545	313 (183)	353 (184)	.01
CD4 categories	545			<.001
< 200		71 (28.9)	45 (15.1)	
200 – 349		84 (34.1)	119 (39.8)	
≥ 350		91 (37.0)	135 (45.2)	
Antiretroviral therapy				
Use of antiretroviral therapy	564	97 (37.3)	236 (77.6)	<.001
Number of antiretroviral agents, median (IQR)	564	0 (0 – 3)	3 (2 – 3)	<.001
Zidovudine	564	70 (26.9)	211 (69.4)	<.001
Lamivudine	564	88 (33.8)	228 (75.0)	<.001
Abacavir	564	5 (1.9)	6 (2.0)	1.00
Emtricitabine	564	3 (1.2)	7 (2.3)	.35
Tenofovir	564	20 (7.7)	26 (8.6)	.71
Stavudine	564	8 (3.1)	7 (2.3)	.61
Didanosine	564	0 (0)	3 (1.0)	.25
Nevirapine	564	16 (6.2)	55 (18.1)	<.001
Efavirenz	564	60 (23.1)	136 (44.7)	<.001
Lopinavir	564	9 (3.5)	19 (6.3)	.13

All data presented as n (%), mean (standard deviation, SD), or median (interquartile range), unless indicated otherwise. Covariates observed in < 5% of study population and non-significant ($p > 0.05$) were: diabetes, hypertension, dyslipidemia, asthma, thyroid disease and cancer.

Results

There were 564 patients in these analyses; the majority were male (55.1%) and identified as either Russian (52.8%) or Kazakh (28.5%). The mean (standard deviation, SD) age was 38.0 (11.5) years. The median (interquartile range, IQR) duration since HIV diagnosis was 4 (2–6) years. The majority were receiving antiretroviral therapy (59.0%) and 43.5% of patients had CD4 values above 350 cells/mm^3. Hepatitis C coinfection was the most common infectious comorbidity, present in 263 patients (46.6%). The mean (SD) log-HIV RNA was 3.51 (1.11) copies/mL. There were 304 patients (53.9%) with an undetectable HIV RNA (< 500 copies/mL).

Distribution of 25-hydroxyvitamin D

The mean (SD) and median (IQR) 25-OHD values were 26.11 (12.41) ng/mL and 24.42 (16.22 – 34.10) ng/mL. There were 39 (6.9%) patients with severe hypovitaminosis D (25-OHD < 10 ng/mL). The decile distribution of 25-OHD values was as follows: 10-19.99 (28.9%), 20-29.99 (29.3%), 30-39.99 (21.35%), 40-49.99 (8.7%) and > 50 ng/mL (5.0%).

Relationship between 25-hydroxyvitamin D and HIV RNA

The bivariate analyses of clinical/demographic characteristics associated with an undetectable HIV RNA are displayed in Table 1. The variables significantly associated with an undetectable HIV RNA were age, marital status, duration since HIV diagnosis, CD4 count and use of ART. In the bivariate analyses, there were no observable differences between patients with and without an undetectable HIV RNA in mean (SD) 25-OHD, 25-OHD insufficiency (< 30 ng/mL), and 25-OHD deciles.

The results of the stratified analyses assessing the relationships between 25-OHD insufficiency (< 30 ng/mL), 25-OHD deficiency (< 20 ng/mL) and undetectable HIV RNA, stratified by HCV status,

Table 2. Bivariate relationship between vitamin D insufficiency (25-hydroxyvitamin D < 30 ng/mL) and HIV RNA, stratified by hepatitis C status, use of antiretroviral therapy and CD4 category

Covariate	Detectable HIV RNA	Undetectable HIV RNA	Prevalence Ratio	95% Confidence Interval	P-value
OVERALL					
Vitamin D insufficiency	169 (65.0)	198 (65.1)	1.00	0.83 – 1.21	.97
Vitamin D deficiency	82 (31.5)	120 (39.5)	1.21	1.00 – 1.48	.06
Hepatitis C coinfection present (n = 263)					
Vitamin D insufficiency	76 (63.9)	91 (63.2)	0.98	0.75 – 1.30	.91
Vitamin D deficiency	33 (27.7)	51 (35.4)	1.22	0.90 – 1.67	.18
Hepatitis C absent (n = 301)					
Vitamin D insufficiency	93 (66.0)	107 (66.9)	1.02	0.79 – 1.32	.87
Vitamin D deficiency	49 (34.8)	69 (43.1)	1.21	0.94 – 1.57	.14
Use of antiretroviral therapy (n = 333)					
Vitamin D insufficiency	63 (65.0)	152 (64.4)	0.98	0.69 – 1.40	.93
Vitamin D deficiency	36 (37.1)	95 (40.3)	1.01	0.78 – 1.56	.59
No use of antiretroviral therapy (n = 231)					
Vitamin D insufficiency	106 (65.0)	46 (67.7)	1.03	0.87 – 1.23	.70
Vitamin D deficiency	46 (28.2)	25 (36.8)	1.13	0.93 – 1.37	.20
CD4 count < 200 (n = 116)					
Vitamin D insufficiency	38 (53.5)	29 (64.4)	1.19	0.89 – 1.58	.25
Vitamin D deficiency	22 (31.0)	18 (40.0)	1.17	0.85 – 1.62	.32
CD4 count 200 – 350 (n = 203)					
Vitamin D insufficiency	56 (66.7)	77 (64.7)	0.95	0.67 – 1.35	.77
Vitamin D deficiency	30 (35.7)	51 (42.9)	1.20	0.85 – 1.69	.31
CD4 count > 350 (n = 226)					
Vitamin D insufficiency	63 (69.2)	90 (66.7)	0.93	0.66 – 1.32	.69
Vitamin D deficiency	22 (24.2)	50 (37.0)	1.47	1.00 – 2.17	.04
Spring season (n = 334)					
Vitamin D insufficiency	97 (69.3)	141 (72.7)	1.01	0.84 – 1.44	.50
Vitamin D deficiency	52 (37.1)	92 (47.4)	1.28	0.98 – 1.67	.06
Summer season (n = 230)					
Vitamin D insufficiency	72 (60.0)	57 (51.8)	0.85	0.66 – 1.10	.21
Vitamin D deficiency	30 (25.0)	28 (25.5)	1.01	0.76 – 1.35	.94

ART use, CD4 categories and season are displayed in Table 2. Within each of the strata, there were no statistically significant relationships observed between 25-OHD insufficiency/deficiency and undetectable HIV RNA. The only exception to this was within the strata of patients with CD4 > 350 cells/mm^3: 25-OHD deficiency was observed more frequently among patients with an undetectable HIV RNA. There was no heterogeneity among the prevalence ratios observed in any of the stratified analyses (Breslow-Day p-values > 0.2).

The log-binomial regression analysis found no significant independent association between 25-OHD and an undetectable HIV RNA (prevalence ratio, PR: 1.00, 95% CI: 0.99 – 1.01, p = 0.67). The only variable to be significantly and independently associated with an undetectable HIV RNA was the use of ART (PR: 2.41, 95% CI: 1.95 – 2.98, p < 0.001). In a separate model, the use of ART was replaced with the individual medications. Again, there was no association between 25-OHD (PR: 1.00, 95% CI: 0.99 – 1.01, p = 0.96) and an undetectable HIV RNA after adjustment for zidovudine, tenofovir and nevirapine.

Given the known and strong effect of ART on HIV RNA, a second set of regression analyses was performed and restricted to patients who were not on ART. In the log-binomial regression analysis, there was no significant association between 25-OHD and an undetectable HIV RNA (PR: 1.00, 95% CI: 0.98 – 1.02, p = 0.95) and the only other variable to remain in the model was the CD4 category (PR: 1.83, 95% CI: 1.19 – 2.81, p = 0.006). None of the interaction terms demonstrated the presence of effect modification in any of the log-binomial regression models.

Discussion

This is not the first study unable to tie 25-OHD to a specific clinical/laboratory outcome [13]. Because viral load contributes to immunosenescence, identification of inflammatory biomarkers that may alter HIV RNA replication are of significant interest to the HIV community in understanding mechanisms of immunosenescence. In our study, no association was found between 25-OHD and HIV RNA using a comprehensive set of analyses. Thus, we recommend that the focus remain on ensuring optimal ART adherence.

A small, yet interesting, finding to note was in the stratified analyses examining the relationship between 25-OHD deficiency and undetectable HIV RNA (Table 2). Within the strata for CD4 cell count, the measure of association appeared to increase in a monotonic fashion as the CD4 count category increased. This may indicate that mechanisms of vitamin-D-mediated immunosenescence in HIV-infected patients may be more strongly influenced by CD4 count than HIV RNA. Future studies should explore the role of CD4 count and immunosenescence.

Unlike previous studies that have demonstrated efavirenz and tenofovir as variables that are associated with diminished vitamin D levels, we did not observe any difference in 25-OHD between efavirenz/tenofovir recipients and non-recipients. As a result, receipt of either of these medications did not modify the relationship between 25-OHD and virologic outcomes.

As with all studies, limitations exist. First, we studied HIV-infected individuals at a single site in Kazakhstan and our results may not be generalizable. For instance, the median (IQR) duration since HIV diagnosis was 4 (2–6) years and use of ART was only observed in 59% of patients. The low frequency of self-reported comorbidities may have been a function of poor health literacy. While population-based differences may limit the external validity of these findings, we intentionally studied this population because the likelihood of patients taking multivitamins and vitamin D supplements was low. Vitamin D supplements have only recently been commercially licensed in Kazakhstan; they are not widely used by the general population, minimizing the opportunity for information bias. Also, because of the high frequency of HIV/HCV coinfection, moderate ART use and wide distribution of CD4 cell counts, we were able to assess the relationship between 25-OHD and HIV RNA among these important subgroups of patients. Unbound vitamin D might be a better marker of vitamin D status. Patients with HIV and HCV infections often have lower protein and this may have impacted our results. Future studies should assess the contributory effects of protein binding.

Second, a 25-OHD test result is affected by a number of factors like diet, exposure to sunlight, and genetic polymorphisms. We did not collect these variables. However, our sampling occurred during a short window in the spring/summer months when sunlight is most prevalent. Upon stratification by spring/summer, we observed no heterogeneity. While we did not collect information about dietary consumption of foods rich in vitamin D, this is not likely an issue since the Kazakh diet consists primarily of meat and grains.

Third, the assay used to determine HIV RNA values in Kazakhstan constrained by its higher limit of detection (500 copies/mL); newer tests are more

sensitive (20 copies/mL). Fewer patients might have been classified as having an undetectable HIV RNA if a more specific assay had been utilized.

In summary, a significant relationship between 25-OHD and HIV RNA among HIV-infected patients receiving care in Kazakhstan was not observed. These data should be interpreted cautiously as 25-OHD may affect other markers of HIV infection and inflammation. Additional research should examine the interactive relationship between vitamin D and other immunologic and inflammatory markers, as well as among subgroups of HIV-infected patients at greatest risk for poor outcomes associated with inflammation and immunosenescence.

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Author Contributions

Z. Nugmanova and L.A. McNutt collaborated on the study design, data analysis and edited the manuscript. N. Patel developed the study design, conducted the data analysis and drafted the manuscript. G. Akhmetova, G. Kurmangalieva, and M. Abdumananova collected data, helped conduct interviews and provided clinical care for study participants; N. Kovtunenko collected blood samples and coordinated Vitamin D assessment. A. Akanov provided overall coordination of the research project and study sites. All authors assisted in the interpretation of the results and have approved the final version of the manuscript.

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