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Vitamin D insufficiency may impair CD4 recovery among Women's Interagency HIV Study participants with advanced disease on HAART

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Abstract

Background—Recent studies in HIV-infected men report an association between low vitamin D (25OH-D) and CD4 recovery on HAART. We sought to test this relationship in the Women's Interagency HIV Study (WIHS).

Methods—We examined 204 HIV-infected women with advanced disease, who started HAART after enrollment in the WIHS. We measured vitamin D (25OH-D) levels about 6 months prior to HAART initiation. The relationship between CD4 recovery (defined as increases of ≥50, 100, and 200 cells at 6, 12, and 24 months) and exposure variables was examined using logistic regression models at 6, 12 and 24 months post-HAART initiation in unadjusted and adjusted analyses, and using multivariable longitudinal Generalized Estimating Equations (GEE). Vitamin D insufficiency was defined as 25OH-D levels at least 30 ng/ml.

Results—The majority were non-Hispanic black (60%) and had insufficient vitamin D levels (89%). In adjusted analyses, at 24 months after HAART, insufficient vitamin D level (OR 0.20, 95% CI 0.05–0.83) was associated with decreased odds of CD4 recovery. The undetectable viral load (OR 11.38, 95% CI 4.31–30.05) was associated with CD4 recovery. The multivariable GEE model found that average immune reconstitution attenuated significantly (P <0.01) over time

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Conflicts of interest

There are no conflicts of interest.

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among those with insufficient vitamin D levels compared with those with sufficient vitamin D levels.

Conclusion—Vitamin D insufficiency is associated with diminished late CD4 recovery after HAART initiation among US women living with advanced HIV. The mechanism of this association on late CD4 recovery may be late vitamin D-associated production of naive CD4 cells during immune reconstitution.

Keywords

antiretroviral therapy; HIV; immune reconstitution; vitamin D; women

Introduction

Vitamin D plays a role in overall health, and vitamin D deficiency has been linked to cellular immunity, cardiovascular disease, autoimmune disease, insulin resistance, depression, and impaired control of infections, such as tuberculosis [1–4]. The active form of vitamin D, 1,25-$(OH)_2$D, has anti-inflammatory activity [5] and there are numerous studies describing its role in the regulation of human T-cell and antigen-presenting cell (APC) functions [6].

Cross-sectional studies in HIV-infected patients have reported high rates of vitamin D insufficiency and deficiency [7–11] and we found that 60% of participants in the Women's Interagency HIV Study (WIHS) had vitamin D deficiency with African American race being a strong predictor for this deficiency [11]. In two small cross-sectional studies, vitamin D-deficient HIV patients had significantly lower CD4 counts [12,13]. In one study in HIV and Mycobacterium Avium Complex coinfected patients [12], there was a strong inverse correlation between TNF-α and 1,25$(OH)_2$D and the authors concluded that this might further impair immune response and represent an important feature of the pathogenesis of HIV-related immunodeficiency. A proportion of individuals who start HAART fail to achieve adequate CD4 cell reconstitution despite sustained viral suppression, a recent study in HIV patients showed a correlation between vitamin D levels and CD4 T-cell recovery [14] but did not assess for associations over time. In our study, we aimed to determine the association of vitamin D insufficiency with immune recovery over time after HAART initiation in HIV-infected women.

Methods

The WIHS is a prospective cohort study of HIV-infected and uninfected at-risk women from six sites. Women are seen semi-annually for an interview and a physical exam with collection of blood and genital specimens. Informed consent was obtained from all participants in accordance with the US Department of Health and Human Services guidelines and the institutional review boards of participating institutions. The cohort was designed to reflect the demographics of the HIV epidemic among women in the United States [15].

Of the 1357 HIV-infected women who started HAART during the WIHS study, we found that 460 of these women had CD4 less than 200 at last pre-HAART visit. We examined HIV-infected women who started HAART during the WIHS study and who had CD4 data 6 and 12 months after HAART initiation (n = 348). The patients were then excluded if there was no available data for 6 and 12 month visits (n = 10) as well as if there were no vitamin D test results from last pre-HAART visit (n = 79). Women with the last preantiretroviral therapy (pre-ART) visit occurring prior to May 1, 1996 were excluded to ensure a cohort treated after the advent of HAART (n = 55). Patients who were started on any antiretroviral

therapy after this date were included, even if it was not HAART therapy. A total of 204 HIV-infected women were included in the analysis. The primary outcome was CD4 count obtained at 6, 12 and 24 months after HAART initiation.

Vitamin D (25OH-D) testing was performed on stored sera from their last pre-HAART visit by Quest Diagnostics on frozen sera stored at −70°C using the liquid chromatography/mass spectroscopy/tandem spectroscopy (LC/MS/TS) method. The LC/MS/TS method is sensitive with the average inter-assay coefficient of variation percentage across the analytical range of 7%. Sufficient vitamin D was defined as more than 30 ng/ml and vitamin D insufficiency as less than or equal to 30 ng/ml [2].

Statistical analyses

In univariate analysis, differences in categorical variables were assessed using the Pearson's chi-square tests, or their nonparametric equivalent, and differences in continuous variables were assessed with the nonparametric Kruskal–Wallis test. The relationship between CD4 recovery and vitamin D was examined at 6, 12 and 24 months post-HAART initiation. The relationship between CD4 recovery and exposure variables was examined using logistic regression models at 6, 12 and 24 months post-HAART initiation in unadjusted and adjusted analyses, and with longitudinal Generalized Estimating Equations (GEE). In the logistic regression models, CD4 recovery was defined as an increase of 50 cells or less at 6 months, 100 cells or less at 12 months, and 200 cells or less at 24 months based on previous studies defining suboptimal recovery of CD4 count in HIV-infected patients [16–20]. CD4 count over time was measured as a continuous variable in the GEE analysis. Both analyses were adjusted for the following covariates in addition to vitamin D status: age, race/ethnicity, BMI, any history of previous antiretroviral use, baseline viral load, viral load at each time point and WIHS site location. A *P*-value less than 0.05 was considered significant. Statistical analyses were conducted using SAS version 9.2 and IBM SPSS Statistics 19.

Results

Table 1 shows the characteristics of the 204 HIV-infected women included in the study. The majority of women were non-Hispanic black (60%) and had pre-HAART vitamin D levels 30 ng/ml or less] (89%). Vitamin D2 levels were available for 169 of 204 patients, and were detectable (levels >3) in 29 of 169 (17%), whereas 10 (6%) had levels above 10. Women with vitamin D levels 30 ng/ml or less were more likely to be older than 38 years of age (94 vs. 85%) and be either overweight or obese (98 vs. 82%) compared with women with sufficient vitamin D levels. However, these groups did not differ in hepatitis C status, CD4 nadir, use of any antiretroviral therapy for any length of time prior to HAART, viral load at the visit prior to HAART initiation, or having an undetectable viral load 24 months after HAART initiation.

In the adjusted logistic regression analyses at 6 months, having an undetectable viral load 6 months post-HAART initiation was the only characteristic significantly associated with CD4 recovery more than 50 cells in the adjusted analysis [OR 8.89, 95% confidence interval (CI): 3.72–21.23]. At 12 months, being naive to any antiretroviral use (not just HAART) prior to HAART initiation (OR 2.56, 95% CI: 1.16–5.69) and having an undetectable viral load 12 months post-HAART initiation (OR 7.68, 95% CI: 3.46–17.03) were positively associated with CD4 recovery more than 100 cells in the adjusted analyses. At 24 months, vitamin D levels 30 ng/ml or less (OR 0.20, 95% CI 0.05–0.83) were associated with decreased odds of achieving a CD4 increase of more than 200 cells/μl, while having an undetectable viral load 24 months post-HAART initiation (OR 11.38, 95% CI 4.31–30.05) remained associated with an increased odds of achieving a CD4 increase of more than 200 cells/μl in the adjusted analysis at 24 months (Table 2). The mean change in CD4 from the pre-HAART visit until

24 months was +188 in the sufficient vitamin D group and +134 for the insufficient group. We also examined a subset of women with vitamin D levels less than 20 and found that their odds of achieving a CD4 increase of more than 200 cells/μl at 24 months was 0.21 (95% CI 0.05–0.91, $P = 0.04$) compared with women with sufficient vitamin D levels after adjusting for all other covariates in the model.

In the GEE model controlling for age, race/ethnicity, BMI, antiretroviral therapy history, viral load over time and WIHS site there was a significant and positive main effect of linear time on CD4 reconstitution ($P < .01$). There was no significant difference in CD4 count at baseline by vitamin D status. The difference in immune reconstitution between vitamin D groups was modeled by a quadratic time trend, which found a modest but significant ($P < 0.01$) attenuation from the average positive curvilinear trend among those with vitamin D levels 30 ng/ml or less compared with those with sufficient vitamin D levels (Fig. 1).

Discussion

Vitamin D homeostasis plays an essential role in overall health [2,21]. Vitamin D receptors (VDR) have a broad distribution that includes activated T and B lymphocytes. Although the most well known and studied effects of low vitamin D levels have been on the musculoskeletal system, recent investigations show that vitamin D is linked to cellular immunity, cardiovascular disease, autoimmune disease, insulin resistance, and in the control of infections, such as tuberculosis [22–28].

Our study found that vitamin D insufficiency is associated with late CD4 recovery after HAART initiation. Our results extend the findings of Ross *et al.* [14], which reported that among 149 HIV-infected patients, greater vitamin D level was associated with greater CD4 T-cell restoration after HAART initiation ($P < 0.01$). This analysis examined change in CD4 count (defined as current CD4 T-cell count at time of evaluation minus nadir CD4 T cell count) and did not perform longitudinal analysis controlling for time varying covariates. The GEE model is a much more robust way to control for the effect of time on immune reconstitution. Although vitamin D has been reported to have seasonal variations, a study by our group in 108 HIV infected women which looked at two separate time periods 3 years apart suggests that in the absence of active pharmacologic interventions, vitamin D deficiency will persist among the majority of them (O.A., unpublished data).

There may be biological mechanisms, which explain the effect of vitamin D insufficiency on late CD4 cell recovery after HAART initiation. During CD4 cell recovery, a rapid increase in the number of memory T cells within 1–2 weeks of starting HAART and continuing over the first 3 months to a year occurs due to expansion of preexisting clones, redistribution of T cells sequestered in lymphoid tissues, or reduction in apoptotic cell death. A slower second stage occurs in naive T cells, which may be due to de-novo T-cell synthesis from the thymus or redistribution of T cells from tissue to blood [11–14]. This results in the long-term rise in CD4 count. This long-term rise is related to the level of virologic control in each patient. Our study findings suggest that vitamin D insufficiency could be related to production of naive T cells.

In addition, recent studies have shown that vitamin D is crucial for the activation of immune defenses [29,30]. Vitamin D is closely involved in the functioning of T and B lymphocytes in the adaptive immune system by regulating the activation of lymphocytes directly and by effects on APC. Vitamin D also has well known effects on the innate immune system [31]. One particular study described the requirement for vitamin D binding to the VDR in order to activate the gene for phospholipase C-γ1, which in turn is required for T-cell activation by the classical T-cell antigen receptor (TCR) signaling pathway [29]. An alternative pathway

used by naive T cells due to their low expression of VDR involves signaling through the mitogen-activated protein kinase 38, which results in VDR upregulation and subsequent signaling through the classical pathway. Thus, this study indicated vitamin D requirement for activation of both naive and memory T cells [25] and the difference in activation between memory and naive T cells. Late immune reconstitution that is dependent on de-novo synthesis of naive T cells from the thymus may therefore be affected by vitamin D deficiency.

Limitations of our study include that we were under-powered to examine more detailed associations due to the low representation of some of the baseline demographic characteristics and the small percentage of vitamin D-sufficient patients. Although dichotomous representations of these variables were adjusted for in the multivariable model, future studies should recruit larger samples of women with sufficient vitamin D levels. In addition, our criteria for immune reconstitution at each of the time points, while chosen from data in the literature [16–20], may have been too restrictive. However, our additional analysis of CD4 recovery over time continued to show an effect of pre-HAART vitamin D levels on CD4 recovery.

Finally, we did not have vitamin D levels at each of the time points and instead used pre-HAART vitamin D levels. Although we have only pre-HAART vitamin D levels, other large epidemiologic studies have used baseline vitamin D to assess outcomes up to 10 years later [32–34]. In a separate WIHS analysis, we found that vitamin D levels did not differ significantly over a 3-year period in the absence of interventions (OA, unpublished data). Future studies on this issue should measure vitamin D levels at multiple time points.

Conclusion

Vitamin D insufficiency is associated with impaired late CD4 recovery on HAART in the WIHS cohort. The mechanism of this association CD4 recovery may be impaired late vitamin D-associated production of naive CD4 cells during immune reconstitution, however this merits further exploration.

Acknowledgments

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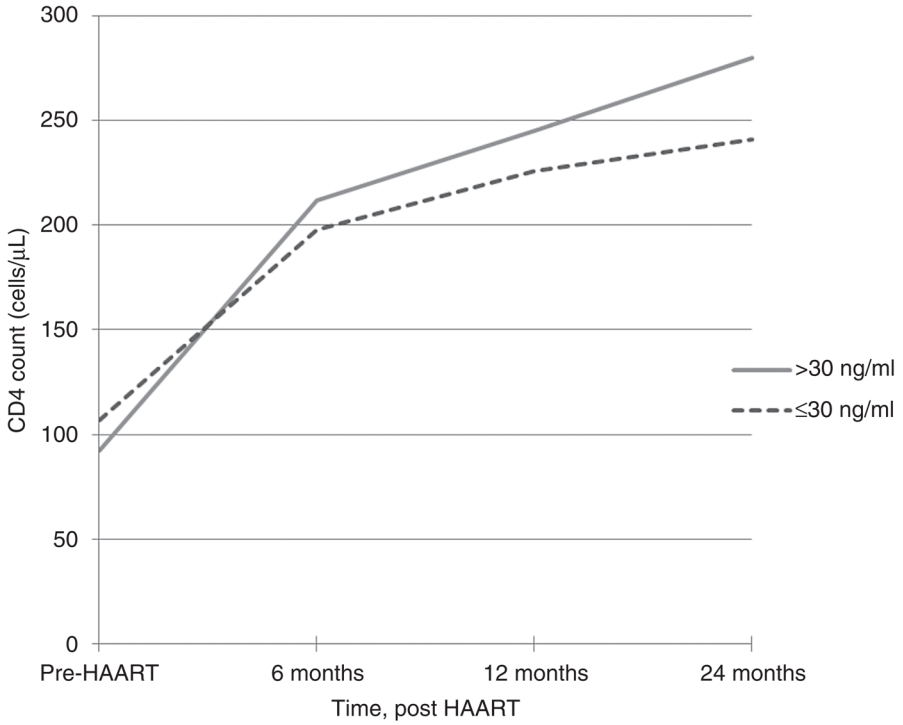

Fig. 1. Mean CD4 count (cells/μl) among women with normal (>30 ng/ml) and insufficient or deficient vitamin D (≤ 30 ng/ml), before HAART initiation and 6, 12, and 24 months post-HAART initiation

In univariate analysis of variance (ANOVA), difference in mean CD4 by vitamin D status is nonsignificant ($F = 0.639$, $P = 0.424$); difference in mean CD4 by time point is significant (ANOVA $F = 14.92$, $P < 0.001$), and vitamin D by time interaction is nonsignificant ($F = 0.358$, $P = 0.783$).

Table 1

Participant demographic and clinical characteristics by vitamin D status, *n* = 204.

	Vitamin D status		
	>30 ng/ml	**≤30 ng/ml**	***P*-value**
Total, *n* (%)	22 (11)	182 (89)	
Age, *n* (%)			
38 years or younger	16 (15)	89 (85)	0.04
Over 38 years	6 (6)	93 (94)	
Race/ethnicity[a], *n* (%)			
Non-Hispanic white	8 (38)	13 (62)	<0.0001
Hispanic	7 (17)	35 (83)	
Non-Hispanic black	4 (3)	119 (97)	
Other	3 (17)	15 (83)	
Median BMI (kg/m^3) (IQR)	22.2 (21.2–22.9)	25.3 (21.6–30.4)	0.002
Hepatitis C antibody status, *n* (%)			
Negative	17 (13)	119 (87)	0.26
Positive	5 (7)	63 (93)	
CD4 nadir, *n* (%)			
50 cells/μl or more	13 (10)	123 (90)	0.42
Less than 50 cells/μl	9 (13)	59 (87)	
Antiretroviral naive[a], *n* (%)			
No	19 (13)	130 (87)	0.20
Yes	3 (5)	52 (95)	
Viral load last pre-HAART[a], *n* (%)			
<100 000, cells/ul	15 (11)	116 (89)	0.32
100 000+, cells/ul	4 (6)	58 (94)	
Undetectable viral load 24 months post-HAART visit, *n* (%)			
No	13 (11)	108 (89)	0.94
Yes	7 (11)	56 (89)	

Chi-square tests were utilized to examine the relationship between vitamin D status and categorical variables. The nonparametric Kruskal–Wallis test was used to examine the difference in median BMI by vitamin D status. Due to missing values, not all rows add up to *n* = 204.

[a]Fisher's exact test used where expected cell size was less than 5.

Table 2

Multivariate analysis of factors associated with an increase in CD4 cell count of 200 cells/μl or greater at 24-months post-HAART visit, $n = 167$[a].

	Odds ratio (95% CI)
Age	
38 years or younger	Ref
Over 38 years	0.84 (0.35–2.00)
Race/ethnicity	
Non-Hispanic white	Ref
Hispanic	0.23 (0.05–1.10)
Non-Hispanic black	0.88 (0.24–3.20)
Other	2.05 (0.41–10.34)
Vitamin D (250H-D) status	
>30 ng/ml	Ref
≤30 ng/ml	0.20 (0.05–0.83)
BMI (kg/m^3) status	
Underweight/normal weight (<25 kg/m^3)	Ref
Overweight/obese(≥25 kg/m^3)	0.93 (0.38–2.24)
Antiretroviral naive	
No	Ref
Yes	1.28 (0.50–3.27)
Viral load last pre-HAART	
<100 000, cells/ul	Ref
100 000+, cells/ul	0.73 (0.27–1.95)
Undetectable viral load 24 months post-HAART visit	
No	Ref
Yes	11.38 (4.31–30.05)

The model is adjusted for all variables presented. CI, confidence interval; Ref, Reference category.

[a]Women with missing data were excluded from the multivariate analysis.