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Vitamin D deficiency in HIV-infected and un-infected women in the US

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Abstract

Background—Vitamin D deficiency is of increasing concern in HIV-infected persons, because of its reported association with a number of negative health outcomes that are common in HIV. We undertook this study to determine the prevalence and predictors of vitamin D deficiency among a nationally representative cohort of middle-aged, ethnically diverse HIV-infected and uninfected women enrolled in the Women's Interagency HIV study (WIHS).

Methods—Vitamin D testing was performed by Quest Diagnostics on frozen sera using the liquid chromatography/mass spectroscopy (LC-MS) method. Vitamin D deficiency was defined as 25 (OH) D < 20 ng/ml. Comparisons of continuous and categorical characteristics among HIV-infected and HIV-uninfected women were made by Wilcoxon tests and Pearson chi-squared tests, respectively.

Results—1778 women (1268 HIV+) were studied. 63% had vitamin D deficiency (60% HIV+ vs. 72% HIV−; $p < 0.001$). Multivariable predictors of Vitamin D Deficiency were being African American (AOR 3.02), Hispanic (AOR 1.40), Body mass index (AOR 1.43), Age (AOR 0.84), HIV+ (AOR 0.76), Glomerular filtration rate < 90/ml/min (AOR 0.94) and WIHS site; Los Angeles (AOR 0.66), Chicago (AOR 0.63). In the HIV+ women multivariate predictors were; undetectable HIVRNA (AOR 0.69), CD4 50–200 cells/mm³ (AOR 1.60), CD4 < 50 cells/mm³ (AOR 1.94) and recent Protease Inhibitor use (AOR 0.67).

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Conclusions—In this study of over 1700 women in the US, most women with or without HIV infection had low vitamin D levels and African American women had the highest rates of Vitamin D deficiency. An understanding of the role that vitamin D deficiency plays in non-AIDS related morbidities is planned for investigation in WIHS.

Keywords

Vitamin D; Vitamin D Deficiency; HIV infected; HIV uninfected

Introduction

Vitamin D deficiency is of increasing concern in HIV-infected persons, because of its reported association with a number of negative health outcomes that are common in HIV. In addition to its known association with osteoporosis, low serum levels of 25-hydroxyvitamin D [25 (OH) D] in studies in the general population have been linked to hypertension, diabetes, metabolic syndrome, cardiovascular disease [1–7], and certain solid organ malignancies [8–9]. Low serum levels of 25 (OH) D may also partly explain racial differences in disease outcomes. A recent US study found that the higher risk of cardiovascular mortality observed in blacks versus whites was attenuated by adjusting for serum 25 (OH) D levels [10].

While the evidence supporting the role of vitamin D on a variety of health outcomes continues to emerge, vitamin D deficiency remains common in the US population [11, 12]. In the most recent NHANES study report, only 23% of the adult US population had sufficient vitamin D levels [11]. Vitamin D deficiency can be caused by several factors, including decrease in skin synthesis of pre-vitamin D with skin pigmentation and aging, low sunlight exposure, obesity, and insufficient vitamin D intake. In HIV-infected persons, certain antiretroviral medications may be associated with vitamin D deficiency due to their potential effect on vitamin D metabolism [13–15]. The reported prevalence of vitamin D deficiency among HIV-infected adolescents and adults has varied widely, ranging from 45% to 87% in studies conducted in Europe, Australia, and the US [16–22]. To date, studies on Vitamin D in HIV-infected individuals have included primarily white men, [16–21], or have focused on young adults [22].

We undertook this study to determine the prevalence and predictors of vitamin D deficiency among a nationally representative cohort of middle-aged, ethnically diverse HIV-infected and uninfected women enrolled in the Women's Interagency HIV study (WIHS).

Methods

Patient selection

The WIHS is an ongoing prospective cohort study of HIV-infected and uninfected at-risk women enrolled at six sites: Chicago, San Francisco Bay Area (SF), Brooklyn and Bronx/Manhattan, New York, Washington, DC (DC) and Los Angeles (LA). The WIHS cohort was designed to reflect the demographics of the HIV epidemic among women in the United States. Details of cohort recruitment, retention and demographics are published elsewhere [23, 24]. Briefly, participants undergo semiannual visits that include an interviewer-administered questionnaire, a physical exam and collection of blood and genital specimens. The current, cross-sectional study includes 1778 WIHS participants (1268 HIV-infected and 510 HIV-uninfected) who had stored sera collected from visit 27 (October 1, 2007–March 30, 2008). 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.

Vitamin D testing

Between October 2009 and January 2010, vitamin D testing was performed 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 and equally specific for both forms of 25(OH) D. The average inter-assay coefficient of variation (CV) % across the analytical range of the assay is 7%. Results were obtained for total 25[OH] D, 25 [OH] D3 and 25 [OH] D (reportable range 4–512 ng/mL). 25 (OH)D status is primarily based on 25(OH) D3 levels as it is the main circulating vitamin D metabolite with a half-life of 2–3 weeks and represents vitamin D from dietary intake and UVB exposure. 25 [OH] D represents vitamin D from exogenous supplements. For the rest of the paper Vitamin D refers to both vitamin D2 and vitamin D3, the 2 major forms of vitamin D. Sufficient vitamin D was defined as >30 ng/ml and vitamin D insufficiency as >20 and <30 ng/ml. Vitamin D deficiency was defined as 25 (OH) D <20 ng/ml and severe deficiency as <10 ng/ml.

Statistical analysis

Comparisons of continuous and categorical characteristics among HIV-infected and HIV-uninfected women were made by Wilcoxon tests and Pearson chi-squared tests, respectively. Logistic regression models were used to quantify associations with vitamin D deficiency. Variables which have been reported to impact vitamin D status were considered [18–22]. These included demographic (age, race, income, education, employment status, WIHS site), clinical and behavioral factors [body mass index (BMI), estimated glomerular filtration rates (GFRs), Hepatitis C Virus (HCV) antibody status, Center for Epidemiologic Studies Depression Scale (CES-D)[25] and current smoking status. In analysis including only HIV-infected participants, we also examined CD4 cell count, HIV viral load, recent (since the last visit) use of Protease inhibitor (PI) or non-nucleoside reverse transcriptase inhibitor (NNRTI) and recent efavirenz use (since efavirenz has been associated with vitamin D deficiency in prior studies [13–15,21]. Variables with a p value <0.1 were included in the multivariate models. A restricted cubic spline with four knots was used to model CD4 cell count in multivariable models. Multiple imputation using the `aregImpute` function in the Regression Modeling Strategies 'rms'. R package version 2.1-0. <http://CRAN.R-project.org/package=rms> 0.2 to four percent of observations had missing values; CES-D 2%, BMI 4%. All other variables had $<1\%$ missing observations. R package was used to impute missing values for multivariable analyses. All analyses were performed in R (R Development Core Team (2009). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. ISBN 3-900051-07-0, URL <http://www.R-project.org>).

Results

Table 1 shows the demographic and clinical characteristics of the 1778 women included in the analysis by HIV status. HIV-infected women were older, more likely to be HCV sero positive, and less likely to be current smokers or currently employed compared with HIV-uninfected women ($p<0.001$). Median vitamin D levels were higher in HIV-infected (16, interquartile range 10–25) than HIV-uninfected women (14, IQR 9–20), both in the Vitamin D deficient (25 (OH) D <20 ng/ml) range. The proportion of women with Vitamin D deficiency was also lower in HIV-infected than uninfected women (60% vs. 72%; $p<0.001$). Overall, 63% of women had vitamin D deficiency and 22% had severe vitamin D deficiency [25 (OH) D <10 ng/ml]. Only 13% of the entire cohort had sufficient vitamin D levels (>30 ng/ml). There were 128 (7%) women with detectable 25 (OH) D levels (implying measurable levels from oral supplementation) and this did not differ significantly across sites (data not shown). HIV-infected women were more likely to have detectable vitamin D2

levels OR of 1.57 (95% confidence interval: 1.03–2.46). Older age was associated with detectable vitamin D2 levels, with an unadjusted OR of 1.96 (95% confidence interval: 1.53–2.51) comparing the 75th age percentile 50 years of age to the 25th age percentile 37 years of age. We also observed a correlation between age and vitamin D2 level ($r = 0.07$, $p = .005$).

Predictors of vitamin D deficiency

In univariate analysis including the entire cohort, non-white race, younger age, HIV-uninfected status, HCV-uninfected status, current smoking, a higher BMI, normal renal function, being employed and WIHS site were associated with vitamin D deficiency (Table 2). In multivariable analysis, being of black or Hispanic race (compared to white race) was associated with higher odds of vitamin D deficiency, as was a greater BMI and normal renal function. On the other hand, HIV infection, older age and being from the LA or Chicago WIHS site (compared to the Bronx site) were associated with lower odds of vitamin D deficiency. When Vitamin D was studied continuously in the entire cohort, we found similar associations, although the association of HIV infection with higher vitamin D levels did not reach significance (+0.06 log Vitamin D increase; 95% CI: -0.01, +0.13).

Treatment related factors among HIV-infected women

We studied the HIV-related factors associated with vitamin D deficiency in HIV-infected participants only in a model that controlled for all the variables presented in table 2. Undetectable HIVRNA was associated with a lower odds of vitamin D deficiency and lower CD4 count was associated with a higher odds of Vitamin D deficiency after adjustment for demographic and clinical factors (table 3). Compared to no ART use, recent PI use was associated with lower odds of vitamin D deficiency, while recent NNRTI use was associated with higher odds of vitamin D deficiency, although the association did not reach statistical significance. Because efavirenz has been linked to low vitamin D levels [13–15, 21] we conducted a separate analysis of efavirenz and vitamin D status. When compared with participants not on antiretroviral therapy, the lowest risk of Vitamin D deficiency was in women on non-efavirenz containing regimens; efavirenz-/tenofovir-; OR 0.49 (0.35–0.68) $p < 0.001$, and efavirenz-/tenofovir+; OR 0.42 (0.31–0.57).

Discussion

In the largest study to date of vitamin D levels in HIV-infected persons in the US, vitamin D deficiency was highly prevalent among HIV-infected women but was less prevalent than among the HIV-uninfected women. Overall, 66% of the cohort had vitamin D deficiency and 22% had severe deficiency. African American race was the strongest independent predictor of vitamin D deficiency. Similar to the recently published SUN study [21], HIV-infected women in our study were less likely to have vitamin D deficiency than HIV-uninfected women. HIV infected women in the WIHS may be more engaged in primary care (and thus have a greater knowledge regarding vitamin D; a higher proportion had detectable 25 (OH) D levels and had a lower prevalence of risk factors associated with vitamin D deficiency than their HIV-uninfected counterparts, who were enrolled based upon having similar risk behaviors as HIV-infected women. However, it is important to note that only 15% and 8% of HIV-infected and HIV-uninfected women, respectively, in our cohort had sufficient vitamin D levels compared with 23% of the adult US population [11].

Our prevalence of 60% with vitamin D deficiency in HIV-infected women is consistent with the 45%–87% range of vitamin D deficiency reported in other studies conducted in HIV-infected individuals [16–22]. The wide range of reported deficiency rates likely reflects differences in chosen cut-points for deficiency; (<10 ng/ml, <15 ng/ml, <20 ng/ml to <30

ng/ml) and differences in geographic location, season of the year and demographics of the participants. Our definition of vitamin D deficiency as levels <20 ng/ml was similar to that in previous NHANES studies of vitamin D and other studies in the literature. Our finding of an association of non-white race with lower vitamin D levels is consistent with other studies [16, 17–21], as is our finding of an association of greater BMI with lower vitamin D levels [19, 21, 66–30]. The association of non-White race likely reflects the increased skin melanin content which interferes with the UV-B required conversion of pre-vitamin D3 to vitamin D3 in the skin. African-American and Hispanic women are at particularly high risk of vitamin D deficiency, and this may be associated with high BMI values. In agreement with this notion, visceral adiposity was associated with lower vitamin D levels in a recently published study of African American diabetic patients [27, 28]. Obesity and central fat deposition is thought to lead to lower vitamin D levels due to sequestration of vitamin D in fat cells, leaving lower levels of circulating vitamin D available for hydroxylation to active forms [1, 28]. Another possible reason may be decreased outdoor activity and thus sun-exposure in obese individuals [30]. The interplay between these factors and race is likely synergistic, particularly in the WIHS and needs study.

We found an association between increasing age and higher vitamin D levels, which is contrary to what is known in the general population, where the elderly have lower vitamin D levels [11, 12]. A possible reason may be that the vast majority of older women in WIHS were below the age categorized as elderly in the general population. In our study, the median age of the >50 years group was 55.6 years, a decade lower than the >65 years definition of elderly in the general population. In the NHANES study, while there was a trend toward lower vitamin D levels with increasing age for non-Hispanic whites and Mexican Americans, this inverse association between age and vitamin D levels was not seen in non-Hispanic blacks [12], who are the majority of our study participants. We also found an association between increasing age and detectable 25(OH) levels which could indicate higher rates of Vitamin D supplementation in older WIHS women due to the perceived increased risk for bone disease.

Our multicenter study also allowed us to examine geographical differences in vitamin D levels. In temperate latitudes near sea level, cutaneous production of vitamin D almost ceases in winter. In the REACH study [22], latitude in the US was an independent predictor of vitamin D levels. We found a significant association between US city of residence and vitamin D levels, with Chicago and LA women having the highest mean vitamin D levels and lowest rates of deficiency. Surprisingly, we found that women in San Francisco had lower levels of vitamin D, whereas women in Los Angeles had higher levels compared to the Bronx site after controlling for other factors. San Francisco is in the northern part of the state and thus may have lower UV-B rays year round. A variety of unmeasured factors including varying degrees of sun exposure, use of sun-block, use of artificial light and tanning beds, dietary differences in consumption of vitamin D rich foods and supplemental vitamin D intake could explain differences in vitamin D levels across sites.

In our study, we found that renal insufficiency was associated with higher vitamin D levels. This is contrary to many reports that in chronic kidney disease, vitamin D levels are decreased [31–33], but consistent with findings from the large SUN study [21]. We did not measure levels of 1, 25 (OH) D, the active form of vitamin D, so we do not speculate on the clinical significance of this finding.

Among the HIV-infected women, control of HIV viremia and higher CD4 counts were associated with higher vitamin D levels after controlling for other demographic and clinical factors. We found that women currently on a PI-based regimen were significantly less likely to have low vitamin D levels compared to treatment naïve women and women on NNRTI

based regimens. While women on efavirenz had a higher risk of vitamin D deficiency, it did not reach statistical significance. The mechanism by which efavirenz, a non-nucleoside reverse transcriptase inhibitor (NNRTI) lowers vitamin D levels is through induction of 24-hydroxylase, a CYP450 enzyme, which causes increased catabolism of 25(OH)D3 into the inactive form 24, 25 (OH)2D [34]. Further exploration of individual antiretrovirals especially efavirenz, ritonavir and tenofovir on vitamin D status is planned within the WIHS.

The limitations of the current study need to be addressed. First, vitamin D testing was performed on stored samples. However, this has been done routinely in many, large epidemiologic studies of vitamin D and results are valid if samples are stored at -70°C until testing as was done here. Second, we did not have data from all sites on some of the most prominent factors in determining vitamin D level, including sun exposure, sunscreen use and dietary vitamin D intake, and could not factor these into our analysis. Third, the samples tested were collected over a 6-month period when women came in for visits, however they were all fall/winter samples, representing the same season in all the women. The strengths of our study include the large sample size of HIV-infected women across the US, an HIV-uninfected control group and the analysis of vitamin D during the same time period in all women. Finally, while women in this study do not represent the US population, they are reflective of the epidemiology of HIV in women in the US, the largest growing demographic group of the current USHIV epidemic.

In conclusion, in this study of over 1700 women in the US, we found that most women with and without HIV infection had low vitamin D levels, and African American women had the highest rates of Vitamin D deficiency. While there are no formal guidelines on testing for and supplementation of vitamin D in HIV-infected women, it will be important to explore the response to vitamin D supplementation in these women and the impact on a myriad of health outcomes including insulin resistance, cardiovascular disease, bone health and a variety of mental health outcomes. An understanding of the role that vitamin D deficiency plays in non-AIDS related morbidities reported in excess among HIV infected individuals is planned for investigation in WIHS.

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Summary

Among 1778(1268 HIV+) women in the US, 63% had vitamin D deficiency. African American women had the highest rates of Vitamin D deficiency and HIV infection was not associated with higher rates of vitamin D deficiency.

Figure 1.
Vitamin D strata by HIV status

Table 1

Demographic and clinical characteristics of 1778 WIHS women by HIV status

Characteristic	HIV+ (n = 1268)	HIV- (n = 510)	p
Vitamin D <20 ng/ml n (%)	758 (60)	366 (72)	<.001
Age median (IQR), y	44 (39–51)	41 (34–49)	<.001
Race n (%)			.040
White	300 (24)	96 (19)	
African-American	740 (58)	328 (64)	
Hispanic	189 (15)	65 (13)	
Other	39 (3)	21 (4)	
HCV Antibody + n (%)	356 (28)	97 (19)	<.001
BMI Median (IQR)	28 (24–33)	30 (26–36)	<.001
Income n (%)			.130
< \$12,000	600 (48)	217 (43)	
\$12,000–24,000	288 (23)	129 (25)	
> \$24,000	363 (29)	163 (32)	
Education n (%)			.540
Less than HS	497 (39)	188 (37)	
HS Grad	365 (29)	159 (31)	
More than HS	404 (32)	161 (32)	
Employed n (%)	477 (38)	245 (48)	<.001
Smoking n (%)	479 (38)	266 (52)	<.001
GFR median (IQR)	95 (78–113)	95 (83–111)	.122
CES-D median (IQR)	11 (4–21)	10 (4–20)	.350
Site n (%)			.040
Bronx	229 (18)	125 (25)	
Brooklyn	256 (20)	103 (20)	
DC	186 (15)	68 (13)	
LA	248 (20)	84 (17)	
SF	173 (14)	72 (14)	
Chicago	176 (14)	58 (11)	
CD4 Count/ml3 median (IQR)	460 (298–663)		
ART n (%)			
None	359 (28)		
ARV, no PI/NNRTI	52 (4)		
PI, no NNRTI	518 (41)		
NNRTI, no PI	304 (24)		
NNRTI and PI	34 (3)		
Median log10 HIVRNA	1.5 (ud-2.58)		
Undetectable HIVRNA (%)	695 (56)		

Table 2

Factors associated with Vitamin D deficiency among 1778 WIHS women.

Characteristics	Deficient n (%)	Univariate Model		Multivariate Model	
		OR (95% CI)	p	OR (95% CI)	p
Serostatus					
HIV−	366 (72)				
HIV+	758 (60)	0.59 (0.47–0.73)	<.001	0.76 (0.60–0.98)	.031
Age, y					
< 40	435 (70)			0.84 (0.73–0.96) ¹	.009
40–50	433 (62)	0.69 (0.55–0.87)	.002		
50	256 (56)	0.55 (0.43–0.71)	<.001		
Race					
White	174 (44)				
Black	782 (73)	3.48 (2.74–4.44)	<.001	3.02 (2.30–3.97)	<.001
Hispanic	132 (52)	1.38 (1.01–1.89)	.046	1.40 (0.99–1.96)	.055
Other	36 (60)	1.91 (1.10–3.36)	.021	1.41 (0.79–2.54)	.248
HCV					
No	858 (65)				
Yes	261 (58)	0.73 (0.58–0.91)	.004	0.84 (0.65–1.09)	.189
BMI					
Thin-Normal	280 (54)			1.43 (1.23–1.66) ¹	<.001
Overweight	301 (62)	1.34 (1.04–1.73)	.020		
Obese	503 (71)	2.08 (0.64–2.64)	.000		
Smoking					
No	613 (60)				
Yes	496 (67)	1.31 (1.08–1.60)	.007	1.25 (0.99–1.58)	.060
GFR					
> 90	703 (70)			0.94 (0.90–0.98) ²	.004
60–90	360 (55)	0.52 (0.42–0.64)	<.001		
< 60	57 (49)	0.40 (0.27–0.59)	<.001		
CES-D Score					

Characteristics	Deficient n (%)	Univariate Model		Multivariate Model	
		OR (95% CI)	p	OR (95% CI)	p
< 16	698 (63)			1.03 (0.94–1.12) ¹	.521
16–23	147 (58)	0.82 (0.62–1.08)	.155		
> 23	254 (65)	1.08 (0.85–1.38)	.528		
Employment					
No	639 (61)				
Yes	475 (66)	1.22 (1.00–1.49)	.047	1.29 (0.99–1.68)	.063
Education					
Less than HS	427 (62)				
HS Grad	349 (67)	1.20 (0.95–1.53)	.126	0.97 (0.75–1.27)	.847
More than HS	344 (61)	0.94 (0.75–1.18)	.600	0.90 (0.69–1.19)	.469
Income					
< \$12,000	504 (62)				
\$12,000–24,000	273 (66)	1.18 (0.92–1.51)	.194	1.11 (0.84–1.47)	.464
> \$24,000	334 (64)	1.08 (0.86–1.36)	.505	0.95 (0.69–1.30)	.735
Site					
Bronx	232 (66)				
Brooklyn	254 (71)	1.27 (0.93–1.75)	.136	0.92 (0.65–1.30)	.636
DC	177 (70)	1.21 (0.86–1.71)	.284	1.04 (0.71–1.53)	.833
LA	160 (48)	0.49 (0.36–0.66)	<.001	0.66 (0.47–0.93)	.018
SF	169 (69)	1.17 (0.83–1.66)	.381	1.34 (0.91–1.96)	.137
Chicago	132 (56)	0.68 (0.48–0.96)	.027	0.63 (0.43–0.91)	.013

¹For 10-unit increase

²For 10-unit decrease

Table 3

Factors associated with Vitamin D deficiency among 1268 HIV+ WIHS women*

Characteristics	Deficient n (%)	Univariate Model		Multivariate Model	
		OR (95% CI)	p	OR (95% CI)	p
HIV Viral Load					
Detectable	382 (69)				
Undetectable	374 (53)	0.51 (0.41–0.65)	<.001	0.69 (0.50–0.95)	.024
CD4 Count					
>500	312 (55)				
350–500	172 (61)	1.27 (0.95–1.70)	.109	1.14 (0.86–1.51) [/]	.363
200–350	151 (61)	1.25 (0.92–1.70)	.148	1.33 (0.94–1.88) [/]	.106
50–200	87 (67)	1.66 (1.15–2.51)	.012	1.66 (1.11–2.48) [/]	.014
<50	28(78)	2.77 (1.29–6.68)	.008	1.95 (1.12–3.41) [/]	.019
ART					
None	254 (71)				
ARV no PI/no NNRTI	28 (54)	0.48 (0.27–0.88)	.018	0.89 (0.45–1.74)	.725
PI, no NNRTI	271 (52)	0.45 (0.34–0.60)	<.001	0.67 (0.48–0.95)	.025
NNRTI, no PI	189 (62)	0.68 (0.49–0.94)	.020	1.15 (0.77–1.74)	.493
NNRTI and PI	15 (44)	0.33 (0.16–0.67)	.002	0.61 (0.27–1.41)	.251

[/] Estimated with restricted cubic spline function of CD4 Count, using midpoint of range

* adjusted for Age, Race, HCV, BMI, Smoking, GFR, CES-D, Employment, Education, Income, and Site.