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Vitamin D Status and Kidney Function Decline in HIV-Infected Men: A Longitudinal Study in the Multicenter AIDS Cohort Study

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Abstract

Vitamin D may play an important role in a range of disease processes. In the general population, lower vitamin D levels have been associated with kidney dysfunction. HIV-infected populations have a higher risk of chronic kidney disease. Few studies have examined the link between lower vitamin D levels and kidney function decline among HIV-infected persons. We investigated the associations of serum 25-hydroxyvitamin D [25(OH)D] and 1,25-dihydroxyvitamin D [1,25$(OH)_2$D] with kidney function decline in a cohort of HIV-infected white and black men under highly active antiretroviral therapy treatment in the vitamin D ancillary study of the Multicenter AIDS Cohort Study. The associations of 25(OH)D and 1,25$(OH)_2$D with annual change in estimated glomerular filtration rate (eGFR) were evaluated using linear mixed effects models. This study included 187 whites and 86 blacks with vitamin D measures and eGFR ≥60 ml/min/1.73 m^2 at baseline. Over a median follow-up of 8.0 years, lower 25(OH)D levels were significantly associated with faster eGFR decline in whites (adjusted annual change in eGFR, tertile 1: −2.06 ml/min/1.73 m^2 vs. tertile 3: −1.23 ml/min/1.73 m^2, p trend .03), while no significant association was detected in blacks. Lower 1,25$(OH)_2$D was associated with faster kidney function decline in both whites and blacks, although the estimates were not statistically significant. In conclusion, lower 25(OH)D levels were significantly associated with faster eGFR decline in a cohort of HIV-infected white men, but not in those with black ancestry. Further research is warranted to investigate the association of 25(OH)D and 1,25$(OH)_2$D with kidney function decline in larger and ethnically diverse populations.

Keywords: 25(OH)D, 1,25$(OH)_2$D, glomerular filtration rate, kidney function decline, vitamin D

Introduction

Approximately 40% of U.S. adults and 30% of persons with HIV infection have been estimated to be vitamin D deficient based on the commonly used threshold of serum 25-hydroxyvitamin D [25(OH)D] levels ≤20 ng/ml.[1,2] Recent evidence suggests that vitamin D may play an important role in a range of physiologic functions and disease processes beyond its traditional role in bone metabolism.[3,4] In HIV-uninfected populations, lower levels of 25(OH)D have been associated with kidney function decline or increased albuminuria, a marker of kidney damage.[5–7] In HIV-infected persons, highly active antiretroviral therapy (HAART), particularly nonnucleoside reverse transcriptase inhibitors (NNRTIs), is known to increase the risk of low 25(OH)D.[8] HIV-infected persons also have a fourfold higher risk of kidney disease and a threefold higher risk of end-stage renal disease compared to HIV-uninfected persons.[9,10] Thus the link between vitamin D and kidney function may be more relevant in HIV-infected compared to HIV-uninfected populations. Regardless of HIV serostatus, black Americans have higher risk for chronic kidney disease (CKD) and experience faster

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CKD progression than white Americans.[11–13] The additional risk factor of HIV seropositivity has been noted to markedly increase the CKD risk in black Americans.[14]

Few studies have examined the association between 25(OH)D and kidney function decline in HIV-infected persons. Studies on the association between $1,25(OH)_2D$, the active form of vitamin D, and kidney function decline in the general population and HIV-infected population are even more limited.[7] Given the higher risk for CKD among HIV infected, we measured the levels of 25(OH)D and $1,25(OH)_2D$ and evaluated their associations with kidney function decline among white and black participants with preserved kidney function [estimated glomerular filtration rate (eGFR) ≥ 60 ml/min/1.73 m^2] in the Multicenter AIDS Cohort Study (MACS). We hypothesized that lower 25(OH)D and $1,25(OH)_2D$ levels would be associated with faster kidney function decline, and these associations would be particularly notable among self-reported blacks.

Methods

Study population

The MACS is an ongoing prospective study of HIV-infected and -uninfected homosexual and bisexual men conducted in four study sites: Baltimore, MD; Chicago, IL; Los Angeles, CA; and Pittsburgh, PA. A total of 6,972 men were enrolled in 1984–1985, 1987–1990, and 2001–2003. Details of the study design have been reported previously.[15] In semiannual visits, participants received standardized questionnaires and physical examination and contributed biospecimens for analysis.

Vitamin D levels, 25(OH)D and $1,25(OH)_2D$, were measured in an ancillary study that evaluates the impact of HAART initiation on vitamin D metabolism[16] and available in 640 HIV-infected participants following HAART initiation. The visit at which vitamin D levels were measured occurred between 1997 and 2013 and was used as the baseline visit. Participants were followed from baseline until September 30, 2014. Among the participants with measures of vitamin D following HAART initiation, 391 had measures of eGFR at the same visit. The kidney has a key role in converting 25(OH)D to $1,25(OH)_2D$, its active form.[17] To avoid a potential bidirectional relationship between $1,25(OH)_2D$ and kidney function, participants with eGFR <60 ml/min/1.73 m^2 ($n = 16$) at baseline were excluded. Of the remaining 375 participants, 325 had values for all covariates (187 whites, 86 black Americans, 52 Hispanics of white, black, or other ancestries). The sample size of Hispanics of white, black, or other ancestries ($n = 52$) was too small to analyze separately. Thus, this study included a total of 273 participants (187 whites and 86 black Americans). The details of the rationale for race-stratified analysis are presented in the Statistical Analysis section. We compared the levels of 25(OH)D and $1,25(OH)_2D$ between men included and excluded from this study using *t*-tests.

Measurement of vitamin D and eGFR

Serum 25(OH)D, the sum of $25(OH)D_2$ and $25(OH)D_3$, and $1,25(OH)_2D$, the sum of $1,25(OH)_2D_2$ and $1,25(OH)_2D_3$, were measured using immunoaffinity purification and liquid chromatography–tandem mass spectrometry.[18] The median time between HAART initiation and the measurement of vitamin D metabolites was 2.1 years (25th and 75th percentiles: 1.7, 2.3). Serum creatinine was measured at each site using the modified Jaffe method.[19] eGFR was calculated based on serum creatinine using the Chronic Kidney Disease–Epidemiology Collaboration (CKD-EPI) equation.[20]

Measurement of covariates

Race, education levels, and household income were self-reported. The binary variable, cohort, was used to account for potential demographic and behavioral differences between participants enrolled before and during the Third Enrollment (2001–2003) in the post-HAART era. Diabetes mellitus was defined as a fasting serum glucose ≥ 126 mg/dl or self-reported history of diabetes and the use of diabetes medications. Hypertension was defined as systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, or self-reported history of hypertension and the use of antihypertensive medications. Plasma HIV-1 RNA levels were measured by the Roche assays (Hoffmann-La Roche, Nutley, NJ). $CD4^+$ lymphocyte counts were measured using standardized flow cytometry. The definition of HAART was guided by the DHHS/Kaiser Panel[21] guidelines and defined as three or more antiretroviral drugs consisting of one or more protease inhibitors or one NNRTI or NRTI: abacavir or tenofovir disoproxil fumarate, or an integrase strand transfer inhibitor or an entry inhibitor.

Statistical analysis

Serum 25(OH)D levels vary by season.[22] The methods for adjusting out seasonal variation have been reported previously.[16] Briefly, a linear regression analysis was conducted using 25(OH)D as the dependent variable and the season of blood collection as a categorical independent variable (January to March, April to June, July to September, and October to December). The seasonally adjusted 25(OH)D values were estimated by adjusting out the seasonal variation (adding the residuals of the model to the model intercept). These adjusted levels of 25(OH)D were used in all subsequent analyses. The Spearman correlation between levels of 25(OH)D and $1,25(OH)_2D$ before and after seasonal adjustment was calculated to assess the results of the adjustment.

The levels of 25(OH)D were modeled by tertiles in the two race groups separately. Analysis by tertiles avoids making assumptions on a clinically relevant threshold for vitamin D levels for kidney function since the nonskeletal effects of 25(OH)D are still under investigation.[23] The tertiles were determined in the two race groups separately because 25(OH)D levels differ substantially by race and the bioavailability of 25(OH)D may differ by genetic background.[24–26] Levels of $1,25(OH)_2D$ were also analyzed by tertiles to avoid making assumptions on the relevant thresholds. Few studies have compared levels of $1,25(OH)_2D$ by race. Given that the levels of $1,25(OH)_2D$ did not differ significantly between the two race groups in our data (*t*-test *p*: .24), tertiles of $1,25(OH)_2D$ were determined based on all measures combining the two race groups.

Levels of 25(OH)D and $1,25(OH)_2D$ were compared by race using *t*-tests. The baseline characteristics of participants were compared by tertiles of 25(OH)D and $1,25(OH)_2D$ using *t*-tests, Kruskal–Wallis tests, Fisher exacts, or Chi-square tests as appropriate.

The associations of 25(OH)D or $1,25(OH)_2D$ with eGFR decline were evaluated using linear mixed effects models with random effect terms to account for within-individual correlation and individual differences in eGFR patterns. The random intercept accounted for individual differences in baseline eGFR, and the random slope terms accounted for individual differences in eGFR change patterns.

Model 1 covariates included age, center, cohort, and follow-up time in years. Model 2, in addition, included baseline education levels, household income, and clinical variables (baseline eGFR and longitudinal values of diabetes, hypertension, $CD4^+$ lymphocyte count, and viral load). $CD4^+$ lymphocyte count and viral load values were obtained at the same visit as eGFR. Diabetes and hypertension statuses during follow-up were considered as absorbent state from previous visits and updated from new values from follow-up visits when available. For $1,25(OH)_2D$, in addition to the race-stratified analysis, overall analyses combining the two race groups were performed for Models 1 and 2 since the tertiles of $1,25(OH)_2D$ were based on overall $1,25(OH)_2D$ levels, and the associations between $1,25(OH)_2D$ and eGFR decline were in the same direction in the two race groups. Race was included as a covariate in the overall analysis. Model 3 was constructed for 25(OH)D by adding $1,25(OH)_2D$ as a covariate to Model 2 to evaluate whether the association between 25(OH)D and kidney function decline may be mediated by $1,25(OH)_2D$. The *p*-values for the difference in annual change in eGFR by tertiles of 25(OH)D or $1,25(OH)_2D$ were obtained using an interaction term of follow-up year and tertiles as an ordinal variable.

Prior research has reported evidence of nephrotoxicity related to tenofovir and atazanavir.[27,28] The associations of tenofovir or atazanavir use with baseline eGFR and annual decline in eGFR were evaluated, including the covariates in Model 2.

The analysis of baseline characteristics was conducted using R 3.2.1, and the analysis of linear mixed effects models was conducted using SAS 9.3. This study is approved by the Institutional Review Board at Johns Hopkins University and conducted according to the Declaration of Helsinki. All participants provided written informed consent.

Results

Seasonal adjustment of 25(OH)D increased the Spearman correlation between 25(OH)D and $1,25(OH)_2D$ from 0.12 to 0.14 after adjustment. Between participants included and excluded from this study, the vitamin D levels did not differ significantly: 25(OH)D *p*: .65; $1,25(OH)_2D$ *p*: .18. Among participants included in the study, the difference in 25(OH)D levels between white and black participants was highly significant [season-adjusted mean (SD) in ng/ml, white participants: 23.8 (10.0); black participants: 15.0 (9.2), *p*: <.0001], and the difference in $1,25(OH)_2D$ levels was not significant [mean (SD) in pg/ml, white participants: 46.0 (14.1); black participants: 48.2 (14.1); *p*: .24].

At baseline, the mean age was 48 in whites and 43 in blacks. The mean eGFR was 96 ml/min/1.73 m^2 in whites and 106 ml/min/1.73 m^2 in blacks. The median CD4 lymphocyte count was 539 per ml in whites and 450 per ml in blacks. The proportion of participants with detectable HIV viral load was 21% in whites and 40% in blacks. By tertiles of 25(OH)D levels, among white participants, those with lower serum 25(OH)D levels had significantly higher baseline eGFR, whereas in black participants, there were no significant differences in baseline eGFR by 25(OH)D levels (Table 1). Efavirenz use, which has been associated with lower 25(OH)D levels,[29] did not differ significantly by 25(OH)D levels. By tertiles of $1,25(OH)_2D$ levels, among white participants, those with lower serum $1,25(OH)_2D$ levels had fewer atazanavir users compared to those with higher serum $1,25(OH)_2D$ levels. However, the total number of atazanavir users is small ($n = 18$). Among black participants, no significant differences were observed in the baseline characteristics (Table 2). The median follow-up time was 8.3 years (IQR: 7.0) for whites and 7.4 years (IQR: 5.2) for blacks. The proportion of participants with a decline of eGFR to a level <60 ml/min/1.73 m^2 was 26% ($n = 48$) in whites and 19% ($n = 16$) in blacks.

Lower 25(OH)D levels in white participants were associated with faster eGFR decline in a dose-dependent manner in all three models (*p*: .03). The addition of $1,25(OH)_2D$ as a covariate in Model 3 resulted in similar associations as in Model 2. In the fully adjusted model (Model 3), white participants in tertile 1 had an annual change in eGFR of −2.06 ml/min/1.73 m^2 per year [95% confidence interval (CI): −2.58 to −1.53] versus −1.34 (95% CI: −1.84 to −0.84) and −1.23 (95% CI: −1.77 to −0.68) in tertiles 2 and 3, respectively (Table 3). In black participants, 25(OH)D levels were not significantly associated with eGFR decline.

Lower $1,25(OH)_2D$ levels were associated with faster eGFR decline in both race groups, although the differences were not statistically significant. Among white participants, the fully adjusted eGFR change in tertile 1 was −1.72 ml/min/1.73 m^2 (95% CI: −2.24 to −1.20) vs. −1.49 ml/min/1.73 m^2 (95% CI: −2.05 to −0.93) in tertile 3 (*p*: .59) (Model 2 in Table 4). Among black participants, the annual change in eGFR was −2.71 ml/min/1.73 m^2 (95% CI: −3.96 to −1.47) in tertile 1, which was twice the annual rate in tertile 3 (−1.35 ml/min/1.73 m^2, 95% CI: −2.38 to −0.33, *p*: .09). In the fully adjusted model combining both race groups (Model 2), the annual change in eGFR was −1.76 ml/min/1.73 m^2 in tertile 1 (95% CI: −2.21 to −1.32) and −1.26 ml/min/1.73 m^2 in tertile 3 (95% CI: −1.68 to −0.84, *p*: .18).

Tenofovir use was significantly associated with lower baseline eGFR in white participants in adjusted analysis (whites: −4.57 ml/min/1.73 m^2, 95% CI: −7.46 to −1.67; blacks: −3.05 ml/min/1.73 m^2, 95% CI: −7.30 to 1.20, Table 5). However, tenofovir use was not significantly associated with subsequent eGFR decline. Atazanavir use had no significant association with baseline eGFR or annual change in eGFR in adjusted analysis (Table 5).

Discussion

In a cohort of HIV-infected men, lower 25(OH)D levels were significantly associated with faster eGFR decline in white, but not in black men on HAART. Men with lower $1,25(OH)_2D$ appeared to have faster eGFR decline in both race groups, although this association was not statistically significant.

Our findings of an association between lower 25(OH)D levels and faster kidney function decline in HIV-infected white men extend previous findings in HIV-uninfected populations.[5] A study in white and black HIV-uninfected older

Table 1. Participant Characteristics by Tertiles of Baseline Serum 25(OH)D (N=273)

	White participants				*Black participants*			
Range (ng/ml)	*Tertile 1 1.5–18.5*	*Tertile 2 18.6–27.5*	*Tertile 3 27.6–53.9*	p	*Tertile 1 1.0–10.2*	*Tertile 2 10.5–16.6*	*Tertile 3 16.7–48.0*	p
N	62	63	62		29	28	29	
Age, mean (SD)	47.5 (8.4)	47.5 (7.9)	49.0 (9.0)	.33	45.2 (9.2)	41.1 (7.8)	42.6 (8.2)	.25
No college education, % (*n*)	12.9 (8)	11.1 (7)	11.3 (7)	.94	27.6 (8)	50 (14)	55.2 (16)	.08
Annual income <$20,000, % (*n*)	25.8 (16)	30.2 (19)	24.2 (15)	.73	44.8 (13)	75 (21)	82.8 (24)	.01
BMI, mean (SD)[a]	26.0 (4.4)	24.8 (3.6)	25.3 (3.7)	.38	27.2 (6.1)	27.8 (6.3)	24.7 (5.3)	.13
Prevalent diabetes, % (*n*)[a]	7.5 (3)	5.3 (2)	5.4 (2)	.90	13 (3)	5 (1)	8.7 (2)	.66
Prevalent hypertension, % (*n*)[a]	36.1 (22)	31.0 (18)	29.3 (17)	.71	29.6 (8)	33.3 (9)	31 (9)	.96
eGFR, mean (SD)	94.9 (14.4)	91.6 (14.1)	89.2 (15.2)	.03	103.0 (17.5)	111.5 (20.4)	102.5 (23.0)	.92
$CD4^+$ lymphocyte count/ml median (1st, 3rd quartile)	530 (346, 671)	520 (370, 662)	552 (396, 724)	.53	393 (325, 617)	503 (369, 747.5)	461 (332, 644)	.23
Viral load >50 copies/ml, % (*n*)	21.0 (13)	25.4 (16)	16.7 (10)	.49	46.4 (13)	44.4 (12)	31.0 (9)	.44
Tenofovir use, % (*n*)	8.1 (5)	3.2 (2)	12.9 (8)	.13	20.7 (6)	10.7 (3)	10.3 (3)	.58
Atazanavir use, % (*n*)	8.1 (5)	9.5 (6)	11.3 (7)	.83	13.8 (4)	14.8 (4)	10.3 (3)	.92
Efavirenz use, % (*n*)	19.7 (12)	25.8 (16)	12.9 (8)	.19	31 (9)	21.4 (6)	20.7 (6)	.67
Enrolled during the Third Enrollment (2001–2003)	33.9 (21)	27 (17)	33.9 (21)	.63	65.5 (19)	78.6 (22)	89.7 (26)	.09
Center,% (*n*)				.46				.14
Baltimore	35.5 (22)	28.6 (18)	27.4 (17)		37.9 (11)	28.6 (8)	20.7 (6)	
Chicago	19.4 (12)	15.9 (10)	14.5 (9)		48.3 (14)	25 (7)	37.9 (11)	
Pittsburgh	40.3 (25)	39.7 (25)	48.4 (30)		6.9 (2)	17.9 (5)	10.3 (3)	
Los Angeles	4.8 (3)	15.9 (10)	9.7 (6)		6.9 (2)	28.6 (8)	31.0 (9)	
Number of eGFR measures, median (1st, 3rd quartile)	12.5 (7, 20)	16 (9, 20)	12.5 (8, 17)	.44	12 (8, 16)	14 (7.5, 19)	11 (7, 18)	.68

Serum 25(OH)D ranges were based on seasonally adjusted values.

[a]Sample sizes for BMI were 173 in white participants and 80 in black participants, prevalent diabetes 115 in white participants and 66 in black participants, prevalent hypertension 177 in white participants and 83 in black participants, $CD4^+$ cell count 184 in white participants and 85 in black participants, and viral load 185 in white participants and 84 in black participants.

BMI, body mass index; eGFR, estimated glomerular filtration rate.

TABLE 2. PARTICIPANT CHARACTERISTICS BY TERTILES OF BASELINE SERUM $1,25(OH)_2D$ ($N=273$)

	White participants				*Black participants*			
Range (pg/ml)	*Tertile 1 5.9–40.2*	*Tertile 2 40.3–51.3*	*Tertile 3 51.4–96.9*	p	*Tertile 1 5.9–40.2*	*Tertile 2 40.3–51.3*	*Tertile 3 51.4–96.9*	p
N	66	61	60		24	32	30	
Age, mean (SD)	46.9 (8.6)	49.1 (8.47)	48.1 (8.19)	.39	41.5 (8.41)	43.59 (8.66)	43.57 (8.51)	.40
No college education, % (*n*)	15.2 (10)	13.1 (8)	6.7 (4)	.31	29.2 (7)	50 (16)	50 (15)	.22
Annual income <$20,000, % (*n*)	30.3 (20)	31.1 (19)	18.3 (11)	.20	58.3 (14)	65.6 (21)	76.7 (23)	.35
BMI, mean (SD)[a]	25.1 (4.31)	25.0 (3.3)	26.2 (4.02)	.15	26.17 (5.07)	25.36 (3.66)	28.16 (8.2)	.22
Prevalent diabetes, % (*n*)[a]	5.9 (2)	8.1 (3)	4.5 (2)	.80	22.2 (4)	4 (1)	4.3 (1)	.08
Prevalent hypertension, % (*n*)[a]	29.5 (18)	27.6 (16)	39.7 (23)	.33	16.7 (4)	36.7 (11)	37.9 (11)	.18
eGFR, mean (SD)	92.2 (14.5)	92.7 (14.2)	90.7 (15.6)	.58	106.57 (20.99)	107.74 (19.49)	102.53 (21.68)	.45
$CD4^+$ lymphocyte count/ml median (1st, 3rd quartile)	537 (344, 651)	513 (373, 787)	569 (428, 707)	.58	393 (241, 556)	415 (334, 647)	511 (363, 757)	.26
Viral load >50 copies/ml, % (*n*)	24.6 (16)	18.3 (11)	20 (12)	.67	43.5 (10)	37.5 (12)	41.4 (12)	.90
Tenofovir use, % (*n*)	4.5 (3)	6.6 (4)	13.3 (8)	.19	12.5 (3)	18.8 (6)	10 (3)	.63
Atazanavir use, % (*n*)	3 (2)	9.8 (6)	16.7 (10)	.03	12.5 (3)	15.6 (5)	10.3 (3)	.92
Efavirenz use, % (*n*)	19.7 (13)	21.7 (13)	16.9 (10)	.81	29.2 (7)	28.1 (9)	16.7 (5)	.47
Enrolled during the Third Enrollment (2001–2003)	31.8 (21)	26.2 (16)	36.7 (22)	.47	75 (18)	71.9 (23)	86.7 (26)	.34
Center, % (*n*)				.67				.19
Baltimore	27.3 (18)	29.5 (18)	35 (21)		37.5 (9)	15.6 (5)	36.7 (11)	
Chicago	18.2 (12)	14.8 (9)	16.7 (10)		41.7 (10)	43.8 (14)	26.7 (8)	
Pittsburgh	48.5 (32)	44.3 (27)	35 (21)		12.5 (3)	15.6 (5)	6.7 (2)	
Los Angeles	6.1 (4)	11.5 (7)	13.3 (8)		8.3 (2)	25 (8)	30 (9)	
Number of eGFR measures, median (1st, 3rd quartile)	12.5 (7, 20)	15 (9, 20)	12 (8.5, 19)	.80	11.5 (6, 16.5)	13 (9, 18)	13.5 (7, 19)	.44

[a]Sample sizes for BMI were 173 in white participants and 80 in black participants, prevalent diabetes 115 in white participants and 66 in black participants, prevalent hypertension 177 in white participants and 83 in black participants, $CD4^+$ cell count 184 in white participants and 85 in black participants, and viral load 185 in white participants and 84 in black participants.

TABLE 3. ANNUAL CHANGE IN eGFR (ML/MIN/1.73 M^2) BY TERTILES OF 25(OH)D ($N=273$)

	White participants				*Black participants*			
25(OH)D range (ng/ml)	*Tertile 1 1.5–18.5*	*Tertile 2 18.6–27.5*	*Tertile 3 27.6–53.9*	p	*Tertile 1 1.0–10.2*	*Tertile 2 10.5–16.6*	*Tertile 3 16.7–48.0*	p
Model 1	−0.79 (−1.51, −0.07)	−0.13 (−0.83, 0.58)	Reference	.03	0.35 (−1.21, 1.92)	0.34 (−1.23, 1.92)	Reference	.66
Model 2	−0.80 (−1.54, −0.06)	−0.08 (−0.81, 0.64)	Reference	.03	0.59 (−0.96, 2.14)	0.20 (−1.36, 1.77)	Reference	.44
Model 3	−0.82 (−1.56, −0.08)	−0.09 (−0.82, 0.64)	Reference	.03	0.60 (−0.96, 2.15)	0.21 (−1.36, 1.78)	Reference	.46
Annual change in eGFR estimated from Model 3	−2.06 (−2.58, −1.53)	−1.34 (−1.84, −0.84)	−1.23 (−1.77, −0.68)		−1.64 (−2.70, −0.57)	−1.96 (−3.05, −0.87)	−2.24 (−3.37, −1.11)	

Model 1 covariates: age, center, cohort, and follow-up time. Model 2 covariates: Model 1 + baseline education below college, baseline income less than $20,000, longitudinal values of diabetes and hypertension status, and log transformed CD4 count and viral load. Model 3 covariates: Model 2 + baseline $1,25(OH)_2D$. Random effects: random intercept, which accounted for difference in baseline eGFR, and random slope, which accounts for individual differences in eGFR change patterns. *p*-Value was obtained using an interaction term between follow-up time in years and the tertile of 25(OH)D as an ordinal variable. Sample sizes were 187 for white participants and 86 for black participants in all models. Serum 25(OH)D ranges were based on seasonally adjusted values.

adults, including a substantial number of participants with advanced CKD (baseline eGFR <60 ml/min/1.73 m^2), detected a significant association between lower 25(OH)D levels and eGFR decline.[5] However, studies among HIV-uninfected white persons excluding participants with eGFR <60 ml/min/1.73 m^2 detected significant associations of lower 25(OH)D levels with increased albuminuria, a marker of kidney damage, but not with eGFR decline.[6,7] Our study excluded participants with eGFR <60 ml/min/1.73 m^2 and detected a significant association between lower 25(OH)D levels and eGFR decline in white participants. This association might be an early manifestation of end-organ disease associated with accelerated aging in HIV-infected persons on HAART.[30] This result suggests the need for further investigation on whether lower 25(OH)D levels may be a more salient risk factor for kidney function decline among white HIV-infected persons than in HIV-uninfected persons.

In contrast, in HIV-infected black men, the association between 25(OH)D levels and faster kidney function decline was not statistically significant. The younger age and higher eGFR in black participants are potential reasons for the different results in whites and blacks. The differential association of 25(OH)D levels with eGFR decline in whites and blacks in our study is consistent with the findings in other studies of 25(OH)D and chronic disease in the general population. Lower 25(OH)D levels have been associated with lower bone mineral density and higher risk of heart failure, coronary heart disease, and diabetes in whites and not in

TABLE 4. ANNUAL CHANGE IN eGFR (ML/MIN/1.73 M^2) BY TERTILES OF $1,25(OH)_2D$ ($N=273$)

Range (pg/ml)	*Tertile 1 5.9–40.2*	*Tertile 2 40.3–51.3*	*Tertile 3 51.4–96.9*	p
Difference in annual change in eGFR using tertile 3 as the reference				
White participants				
Model 1	−0.22 (−0.95, 0.51)	0.16 (−0.60, 0.89)	Reference	.51
Model 2	−0.20 (−0.95, 0.55)	0.09 (−0.67, 0.85)	Reference	.56
Black participants				
Model 1	−1.17 (−2.80, 0.46)	−0.55 (−1.98, 0.88)	Reference	.15
Model 2	−1.39 (−2.99, 0.21)	−0.57 (−1.97, 0.84)	Reference	.09
Overall				
Model 1	−0.39 (−1.09, 0.30)	−0.22 (−0.90, 0.46)	Reference	.29
Model 2	−0.50 (−1.11, 0.10)	−0.31 (−0.89, 0.28)	Reference	.18
Annual change in eGFR estimated from Model 2				
White	−1.72 (−2.24, −1.20)	−1.43 (−1.96, −0.90)	−1.49 (−2.05, −0.93)	
Black	−2.71 (−3.96, −1.47)	−1.95 (−2.92, −0.97)	−1.35 (−2.38, −0.33)	
Overall	−1.76 (−2.21, −1.32)	−1.57 (−1.98, −1.16)	−1.26 (−1.68, −0.84)	

Model 1 covariates: baseline age, center, cohort, and follow-up time. Model 2 covariates: Model 1+baseline education below college, baseline income less than $20,000, longitudinal values of diabetes and hypertension status, and log transformed CD4 count and viral load. Race was a covariate in the overall analysis combining whites and blacks. Random effects: random intercept, which accounted for difference in baseline eGFR, and random slope, which accounts for individual differences in eGFR change patterns. *p*-Value was obtained using an interaction term between follow-up time in years and the tertiles of 25(OH)D as an ordinal variable. Sample sizes were 187 for white participants and 86 for black participants in all models.

Table 5. Association of Tenofovir and Atazanavir Use with Baseline eGFR and Annual Change in eGFR ($N=273$)

	Estimate (95% confidence interval)	
	White participants	*Black participants*
Tenofovir use		
Baseline eGFR, ml/min/1.73 m^2	−4.57 (−7.46, −1.67)	−3.05 (−7.30, 1.20)
Annual change in eGFR	0.22 (−0.30, 0.74)	−0.21 (−1.30, 0.88)
Atazanavir use		
Baseline eGFR, ml/min/1.73 m^2	−3.37 (−7.17, 0.43)	2.59 (−2.60, 7.79)
Annual change in eGFR	−0.32 (−1.41, 0.76)	0.67 (−2.68, 1.33)

Covariates for baseline eGFR: age, center, cohort, education below college, income less than $20,000, diabetes and hypertension status, CD4 count and viral load, and season-adjusted 25(OH)D and $1,25(OH)_2D$. Covariates for annual change in eGFR: baseline age, center, cohort, and follow-up time, baseline education below college, baseline income less than $20,000, longitudinal values of diabetes and hypertension status, log transformed CD4 count and viral load, and baseline season-adjusted 25(OH)D and $1,25(OH)_2D$. The annual change in eGFR was estimated using linear mixed effects models with the random intercept term accounting for difference in baseline eGFR and the random slope term accounting for individual differences in eGFR change patterns. Sample sizes were 187 for white participants and 86 for black participants.

blacks.[24,31–36] Further studies are warranted to evaluate the applicability of serum 25(OH)D as a marker of vitamin D status across racial groups.

When serum $1,25(OH)_2D$ levels were examined, the direction of association was consistent across HIV-infected white and black men. It is worth noting that $1,25(OH)_2D$ is the active form of vitamin D, while 25(OH)D is a biomarker of vitamin D status with vastly different levels between whites and blacks and its bioavailability may depend on genetic background.[25,26] Given the availability of good quality assay for $1,25(OH)_2D$,[18] our results suggest the potential for further investigation on the relationship between $1,25(OH)_2D$ and eGFR change in larger studies.

Our findings are consistent with the potential renoprotective function of vitamin D. Both 25(OH)D and $1,25(OH)_2D$ can bind to the vitamin D receptor, a transcription factor that regulates gene expression, with $1,25(OH)_2D$ having substantially higher affinity.[37] Both animal and *in vivo* studies have shown that $1,25(OH)_2D$ can inhibit the expression of renin and, thus, regulate the renin-angiotensin-aldosterone system.[38–40] Animal studies have also shown that $1,25(OH)_2D$ can reduce renal fibrosis through the suppression of the transforming growth factor beta 1 signaling pathway.[41,42] In HIV-uninfected populations, observational studies have shown that higher 25(OH)D levels are associated with lower risk of kidney function decline or albuminuria,[5,6,43] and randomized control trials have demonstrated that the supplementation of $1,25(OH)_2D$ or its analog could reduce albuminuria in patients with CKD.[44] However, whether the reduction in albuminuria would prevent kidney function decline is uncertain.

This study is the first longitudinal study evaluating the association of both 25(OH)D and $1,25(OH)_2D$ with kidney function in an HIV-infected population that included both white and black Americans. Kidney function was estimated at frequent intervals (every 6 months) with a median follow-up time of 8 years. Some limitations warrant mentioning. First, important correlates of vitamin D metabolism, such as measures of vitamin D binding protein and parathyroid hormone, were not available. Second, measures of albuminuria, a marker of kidney damage and an important predictor of kidney function decline, were not available. Therefore, whether the association between vitamin D and kidney function decline was independent of albuminuria was not evaluated. Third, one-time measures of 25(OH)D and $1,25(OH)_2D$ were used as predictors. While 25(OH)D has longer half-life and relatively stable concentration, $1,25(OH)_2D$ has short half-life and may be less stable.[45] Finally, our sample size is moderate, particularly in HIV-infected black men. Further research is warranted to investigate the association of 25(OH)D and $1,25(OH)_2D$ with kidney function decline in larger and ethnically diverse populations.

In summary, lower 25(OH)D levels were associated with faster kidney function decline in a cohort of HIV-infected white men but not in those with black ancestry. Further research is warranted to investigate appropriate markers of vitamin D status across ethnic groups and whether vitamin D supplementation might have therapeutic value for the prevention of kidney function decline.

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