Low Vitamin D among HIV-Infected Adults: Prevalence of and Risk Factors for Low Vitamin D Levels in a Cohort of HIV-Infected Adults and Comparison to Prevalence among Adults in the US General Population

Christine N. Dao,[1] Pragna Patel,[1] E. Turner Overton,[2] Frank Rhame,[3] Sherri L. Pals,[1] Christopher Johnson,[1] Timothy Bush,[1] John T. Brooks,[1] and the Study to Understand the Natural History of HIV and AIDS in the Era of Effective Therapy (SUN) Investigators

[1]Division of HIV/AIDS Prevention, Centers for Disease Control and Prevention, Atlanta, GA; [2]Washington University School of Medicine, Department of Infectious Diseases, St Louis, MO; [3]Abbott-Northwestern Hospital, Department of Infectious Diseases, Minneapolis, Minnesota

(See the editorial commentary by Yin and Stein, on pages 406–408.)

Background. We explored serum 25-hydroxyvitamin D (25[OH]D) levels and associated factors for insufficiency or deficiency in an adult human immunodeficiency virus (HIV) cohort and compared 25(OH)D levels with those in the general US population.

Methods. Using baseline data from the Study to Understand the Natural History of HIV and AIDS in the Era of Effective Therapy (SUN), a prospective, observational cohort study of HIV-infected adults enrolled at 7 HIV specialty clinics in 4 US cities from March 2004 to June 2006, we estimated the prevalence of vitamin D insufficiency or deficiency (defined as 25(OH)D levels <30 ng/mL), standardized by age, race, and sex. Using multiple logistic regression, we examined risk factors for vitamin D insufficiency or deficiency.

Results. Among 672 SUN participants with baseline serum 25(OH)D determinations who were not receiving vitamin D supplements, 70.3% (95% confidence interval [CI], 68.1%–74.9%) were vitamin D insufficient or deficient, compared with 79.1% (95% CI, 76.7–81.3) of US adults. Factors associated with vitamin D insufficiency or deficiency included black race (adjusted odds ratio [aOR], 4.51; 95% CI, 2.59–7.85), Hispanic ethnicity (aOR, 2.78; 95% CI, 1.31–5.90), higher body mass index (aOR, 1.04; 95% CI, 1.00–1.09), hypertension (aOR, 1.88; 95% CI, 1.10–3.22), lack of exercise (aOR, 3.14; 95% CI, 1.80–5.47), exposure to efavirenz (aOR, 1.98; 95% CI, 1.18–3.34), higher exposure to ultraviolet light (aOR, .78; 95% CI, .71–.86), renal insufficiency (aOR, .55; 95% CI, .36–.83), and exposure to ritonavir (aOR, .56; 95% CI, .35–0.89).

Conclusions. Similar to findings in US adults generally, vitamin D insufficiency or deficiency is highly prevalent among HIV-infected adults and is associated with known risk factors. Observed associations of vitamin D levels with renal insufficiency and with use of ritonavir- and efavirenz-containing regimens are consistent with both HIV-related and therapy-mediated alterations in vitamin D metabolism. Clinicians should consider screening all patients for vitamin D insufficiency or deficiency.

Vitamin D is essential for calcium homeostasis and bone metabolism [1]. Vitamin D deficiency is associated with a number of comorbidities, including hypertension, cardiovascular disease, insulin resistance, diabetes, dyslipidemia, impaired immune function, decreased neurocognitive function, and malignancies [2–6]. The primary determinant of vitamin D status is exposure to sunlight. With increasing urbanization and sunscreen use, vitamin D deficiency has become highly prevalent among the general population [7, 8].

Currently, serum concentration of 25-hydroxyvitamin D (25[OH]D) is considered the best indicator of vitamin D status, because it represents cumulative

Received 15 July 2010; accepted 18 November 2010.

Presented in part: 17th Conference on Retroviruses and Opportunistic Infections, San Francisco, California, 16–29 February 2010.

Correspondence: Pragna Patel, MD, MPH, Division of HIV/AIDS Prevention, Centers for Disease Control and Prevention, 1600 Clifton Rd, MS E-45, Atlanta, GA 30333 (plp3@cdc.gov).

Clinical Infectious Diseases 2011;52(3):396–405
Published by Oxford University Press on behalf of the Infectious Diseases Society of America 2011.
1058-4838/2011/523-0001$37.00
DOI: 10.1093/cid/ciq158

exposure to sunlight and dietary intake of vitamin D [8]. There is growing consensus that the necessary vitamin D level for calcium homeostasis and healthy bone metabolism is at least 30–32 ng/mL; below this level, secondary hyperparathyroidism develops to compensate for decreased absorption of calcium [9, 10]. A 25(OH)D level of >30 ng/mL indicates sufficient vitamin D, and levels of 21–29 ng/mL indicate an insufficiency [1, 8, 11, 12]. Using these definitions, it is estimated that 1 billion persons worldwide have vitamin D insufficiency or deficiency and that levels of vitamin D vary by sex, race, and age [1–3]. Low vitamin D levels can be caused by decreased cutaneous production of vitamin D3, decreased absorption of vitamin D in the intestine, increased hydroxylation of 25(OH)D to its active form, 1,25-dihydroxyvitamin D ($1,25[OH]_2D$), or increased catabolism of both 25(OH)D and $1,25(OH)_2D$ into biologically inactive calcitronic acid [8].

Middle-aged persons with human immunodeficiency virus (HIV) infection are at risk for numerous comorbidities typically seen in older aging populations, including frailty, metabolic syndrome, osteoporosis and fragility fractures, insulin resistance, diabetes, cardiovascular disease, and cognitive impairment [13–17], many of which have also been associated with vitamin D deficiency [5, 18–20]. Recently, low vitamin D levels have been associated with HIV disease progression and HIV-related complications [21]. Therefore, the role of vitamin D in preventing or mitigating these complications of HIV is of particular interest. Low vitamin D levels among HIV-infected persons have been described; however, these reports were either case series or studies from small cohorts of HIV-infected persons [22–28]. HIV infection and exposure to certain antiretrovirals might contribute to altered levels of 25(OH)D [25–30].

We assessed vitamin D status among HIV-positive adults in the Study to Understand the Natural History of HIV and AIDS in the Era of Effective Therapy (SUN). We compared the prevalence of vitamin D insufficiency or deficiency among HIV-infected adults with that in adults in the general US population. Finally, we examined potential risk factors for vitamin D insufficiency or deficiency among SUN participants.

METHODS

SUN Participants

The SUN is a prospective cohort study of 700 HIV-infected persons enrolled in 4 US cities (Denver, CO; Minneapolis, MN; Providence, RI; and St Louis, MO) from March 2004 to June 2006. The study design and methods have been described elsewhere [31]. Participants were generally healthy HIV-infected adults who were naive to antiretroviral therapy (ART) or had been exposed only to combination ART (cART) and were receiving routine HIV care at one of the study clinics. Demographic data, diagnoses, treatments (including dosage and duration), and laboratory data from all clinical visits were abstracted from medical records and entered into electronic databases. All enrolled participants provided written informed consent. The study protocol was approved and has been annually renewed by the institutional review boards of the Centers for Disease Control and Prevention (CDC) and each participating institution.

We reviewed behavioral, clinical, and laboratory data, including bone mineral density (BMD) and 25(OH)D levels, collected at study enrollment (baseline). SUN participants who had no documented vitamin D supplementation and baseline 25(OH)D assessments were included in the analysis. Serum vitamin D levels were measured using the 25(OH)D iodine 125 radioimmunoassay (Diasorin). Baseline comorbidities were defined as medical conditions clinically diagnosed and present at the baseline visit. Medications that participants were taking at enrollment and continued taking for at least 1 month thereafter were considered baseline concomitant medications. We estimated ultraviolet light (UV) exposure using data from National Weather Service for 2004–2006, calculating a 3-year average monthly UV exposure for the month at the location where the blood specimen was collected [32]. Participants were defined as chronically hepatitis B virus (HBV) infected if they had had a positive test for serum HBV surface antigen and as hepatitis C virus (HCV) infected if they had had a positive HCV serologic result or a detectable HCV plasma viral load, at or anytime before baseline in both cases.

National Health and Nutrition Examination Survey. The National Health and Nutrition Examination Survey (NHANES) has been conducted annually by the National Center for Health Statistics at CDC since 1999. Each year, NHANES surveys a nationally representative sample of ~5000 persons from 15 counties across the United States. Each person is interviewed to collect data on demographics, socioeconomic status, dietary habits including dietary supplement use, and health-related topics. Examinations are conducted on each participant to obtain medical and laboratory measures, including serum 25(OH)D level, which is measured using the 25(OH)D iodine 125 radioimmunoassay. NHANES data is released in 2-year cycles [33]. For this analysis, we used NHANES 2003–2004 and 2005–2006 data to describe levels of vitamin D in the general US population for comparison with SUN participants. The investigation followed the guidelines of the US Department of Health and Human Services regarding protection of human subjects. The study protocol was approved and renewed annually by each participating institution's ethical review board, and all study participants provided written informed consent.

Statistical Analysis. We calculated the age, race/ethnicity, and sex-adjusted prevalence of vitamin D deficiency (defined as serum 25[OH]D levels <20 ng/mL), and vitamin D insufficiency or deficiency (defined as levels <30 ng/mL) among SUN participants, using estimates for the US adult population

obtained from NHANES 2003–2006 data. We estimated the overall prevalence of vitamin D deficiency and insufficiency or deficiency in the US adult population using sample design variables and sample weights to account for the complex sampling scheme used for NHANES 2003–2006 [34]. We did not adjust the prevalence of vitamin D insufficiency or deficiency for UV index, because city- and state-level data on NHANES participants were unavailable.

We used univariate logistic regression to identify potential risk factors for vitamin D insufficiency or deficiency among SUN participants. Variables included (1) demographic and behavioral variables, including age, sex, race/ethnicity, exercise, HIV transmission category (men who have sex with men, injection drug users, heterosexual); (2) HIV-related variables including baseline CD4 T cell count, nadir CD4 T cell count, plasma HIV-1 viral load, ART exposure and duration of antiretroviral use; (3) environmental variables, including clinic site, UV exposure, and month of specimen collection; and (4) clinical variables including body mass index (BMI), BMD of the lumbar spine, neck, and hip measured using dual-energy x-ray absorptiometry, comorbidities, concomitant treatments, and select laboratory measures (eg, estimated glomerular filtration rates [GFRs]) (Table 2). Variables with a P value of $<.25$ in univariate analysis were included in the multiple logistic regression model [35]. In our primary logistic regression model, we only included antiretroviral exposure variables along with all other variables identified from univariate analysis. We constructed a second multiple logistic regression model with the same variables as the primary model but included variables for duration (in months) of antiretroviral use instead of antiretroviral exposure variables. Associations were assessed using adjusted odds ratios (aORs) and corresponding 95% confidence intervals (CIs). We fit a multiple linear regression model that included the same independent variables, with vitamin D as a continuous dependent variable.

RESULTS

The 672 SUN participants included in this analysis were predominantly male (76%), non-Hispanic white (58%), and men who have sex with men (55%) and had a median age of 41 years (interquartile range [IQR]: 35–47 years). They had a median CD4 T cell count of 471 cells/mm^3 (IQR, 334–681 cells/mm^3), 74% were virologically suppressed (HIV viral load, <400 copies/mL), and 79% were currently receiving cART (Table 1). Persons surveyed for the 2003–2006 NHANES represented nearly 170 million US adults, of whom 51% were male and 70% were non-Hispanic white, with a median age of 43 years (IQR, 31–56 years).

The age-, race-, and sex-adjusted prevalence of vitamin D deficiency (25[OH]D, <20 ng/mL) among SUN participants

Table 1. Baseline Characteristics of SUN Participants (n = 672), 2004–2006

Characteristic	No. (%) of Participants[a]
Sex	
Male	513 (76.1)
Female	161 (23.9)
Age, years	
Median (IQR)	41 (35–47)
20–29	74 (11.0)
30–39	209 (31.1)
40–49	273 (40.6)
≥50	116 (17.3)
Race/ethnicity	
White, non-Hispanic	390 (57.9)
Black, non-Hispanic	203 (30.1)
Hispanic	66 (9.8)
Other	15 (2.2)
HIV transmission risk category	
Men who have sex with men (MSM)	370 (54.9)
Intravenous drug user (IDU)	47 (7.0)
MSM-IDU	43 (6.4)
High-risk heterosexual	82 (12.2)
No identified risk	132 (19.6)
Site of clinic	
Denver, Colo	86 (12.8)
Minneapolis, Minn	227 (33.7)
Providence, RI	191 (28.3)
St Louis, Mo	170 (25.2)
BMI	
Median (IQR), kg/m^2	25.5 (22.8–28.7)
≤25 kg/m^2	307 (45.6)
25.1–29.9 kg/m^2	232 (34.4)
≥30 kg/m^2	135 (20.0)
Baseline CD4 T cell count	
Median (IQR), cells/mm^3	471 (334–681)
>350 cells/mm^3	471 (70.2)
200–350 cells/mm^3	153 (22.8)
<200 cells/mm^3	47 (7.0)
Nadir CD4 T cell count	
>350 cells/mm^3	131 (19.8)
200–350 cells/mm^3	204 (30.8)
<200 cells/mm^3	327 (49.4)
Viral load, copies/mL	
Median (IQR), copies/mL	<400 (<400 to 456)
<400 copies/mL	499 (74.3)
≥400 copies/mL	173 (25.7)
cART exposure	
Naive	75 (11.1)
Exposed but not current	64 (9.5)
Current exposure	533 (79.4)

Abbreviations: BMI, body mass index; cART, combination antiretroviral therapy; HIV, human immunodeficiency virus; IQR, interquartile range; SUN, Study to Understand the Natural History of HIV and AIDS in the Era of Effective Therapy.

[a] Values represent numbers (percentages) of patients, except where otherwise indicated.

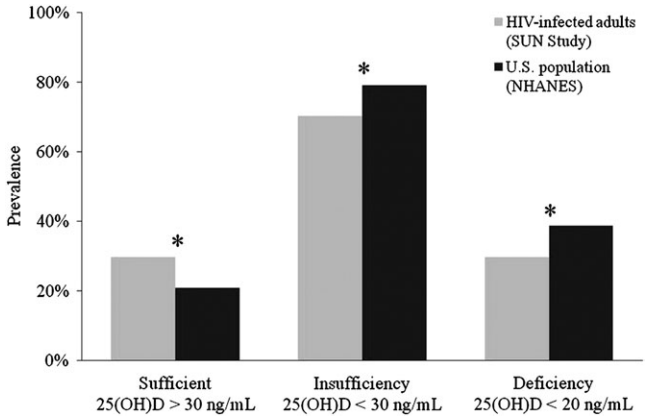

Figure 1. Prevalence of vitamin D insufficiency and deficiency among human immunodeficiency virus (HIV)–infected adults in the Study to Understand the Natural History of HIV and AIDS in the Era of Effective Therapy (SUN) 2004–2006 ($n = 672$), compared with adults in the general US adult population surveyed by the National Health and Nutrition Examination Survey (NHANES) (2003–2004 and 2005–2006 cycles; standardized by age, sex, and race/ethnicity). 25(OH)D, 25-hydroxyvitamin D. *Statistically significant differences (95% confidence intervals do not overlap, $p<0.05$).

included in this analysis was 29.7% (95% CI, 26.3%–33.2%), compared with 38.8% (95% CI, 34.6%–43.1%) for US adults (Figure 1). The age-, race-, and sex-adjusted prevalence of vitamin D insufficiency or deficiency (25[OH]D, <30 ng/mL) among SUN participants was 70.3% (95% CI, 68.1%–74.9%), compared with 79.1% (95% CI, 76.7%–81.3%) for US adults (Figure 1). Among SUN participants and US adults, vitamin D insufficiency or deficiency was more prevalent among non-Hispanic blacks, Hispanics, and persons with lower UV exposure (Figure 2). Among US adults, the prevalence of vitamin D insufficiency or deficiency was equal among men and women (79% for both sexes); however, 80% of women in SUN were vitamin D insufficient or deficient, versus 69% of men ($P = .01$) (Figure 2). Vitamin D levels typically decrease with increasing age, as observed among US adults, but 82% of SUN participants 20–29 years of age were vitamin D insufficient or deficient, compared with 71% of those 30–39 years of age, 67% of those 40–49 years of age, and 76% of those ⩾50 years of age ($P = .04$) (Figure 2) [2]. The difference in prevalence of vitamin D insufficiency or deficiency by age is explained by the overrepresentation of men and young, non-Hispanic black subjects among the SUN participants (45% participants aged 20–29 years were non-Hispanic black).

In univariate analysis, factors significantly associated ($P < .25$) with higher odds of vitamin D insufficiency or deficiency included female sex, older age, both non-Hispanic black and Hispanic race/ethnicity, lower UV exposure, higher BMI, chronic HBV coinfection, HCV coinfection, GFR ⩾90 mL/min/1.73 m^2, hypertension, exercise <3 times per week, and exposure to efavirenz (Table 2). The odds of vitamin D insufficiency or deficiency differed by the geographic location of the clinic and by season of specimen collection. Persons who had any cART exposure at baseline had a higher odds of vitamin D insufficiency or deficiency than those who were ART naive. Tenofovir and ritonavir (low- or standard-dose) exposure were associated with lower odds of vitamin D insufficiency or deficiency (Table 2). The duration of efavirenz and tenofovir exposure were associated with vitamin D insufficiency or deficiency ($P = .003$ and .08, respectively), but not duration of nevirapine or ritonavir exposure ($P = .92$ and .94, respectively). Immune parameters, such as nadir CD4 T cell count and AIDS diagnosis, were not significantly associated with vitamin D insufficiency or deficiency.

In multiple logistic regression, non-Hispanic black race/ethnicity, Hispanic ethnicity, higher BMI, hypertension, lack of exercise, and efavirenz use were independently associated with significantly higher odds of vitamin D insufficiency or deficiency (Table 2). Higher UV exposure, GFR <90 mL/min/1.73 m^2, and use of ritonavir were independently associated with significantly lower odds of vitamin D insufficiency or deficiency (Table 2). We did not observe significant associations between vitamin D insufficiency or deficiency and age or sex. In the model that included duration of antiretroviral use, we observed the same associations as in our primary multiple logistic regression model (data not shown), with the exception that only duration of efavirenz exposure was associated with vitamin D insufficiency or deficiency (aOR, 1.02; 95% CI, 1.01–1.03), and duration of tenofovir exposure was not (aOR, .91; 95% CI, .73–1.12).

When we fit a multiple linear regression model with the same independent variables as our primary logistic regression model, we did not observe significant associations between serum 25(OH)D concentrations and hypertension ($P = .17$) or exposure to ritonavir ($P = .07$) (Table 3). However, exposure to tenofovir and higher BMI were independently associated with higher levels of 25(OH)D (Table 3). All other variables that were significant in our primary multiple logistic regression model remained independently associated with serum 25(OH)D concentrations (Table 3). When we included variables for duration

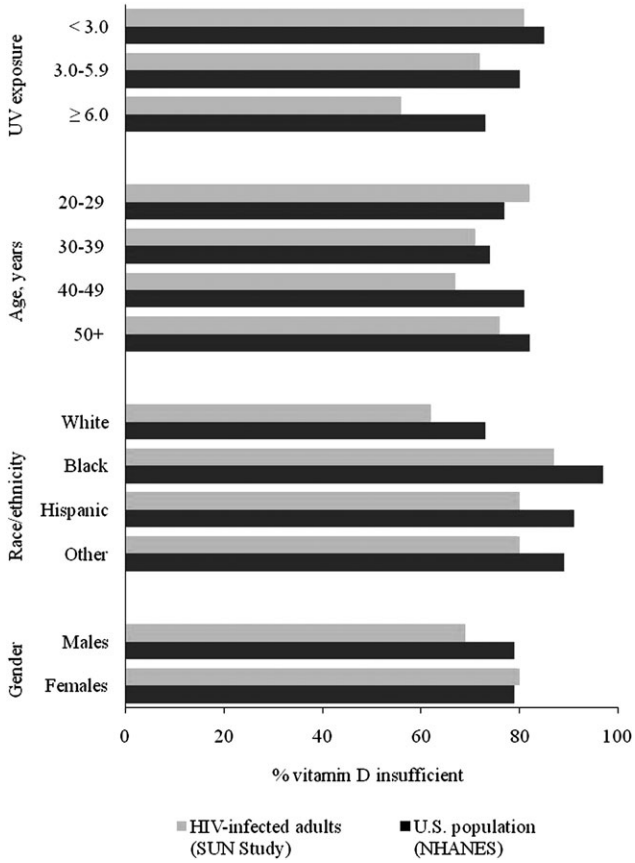

Figure 2. Prevalence of vitamin D insufficiency or deficiency among human immunodeficiency virus (HIV)–infected adults in the Study to Understand the Natural History of HIV and AIDS in the Era of Effective Therapy (SUN) 2004–2006 ($n = 672$), compared with adults in the general US adult population surveyed by the National Health and Nutrition Examination Survey (NHANES) (2003–2004 and 2005–2006 cycles), by demographic characteristics. See Table 2 for an explanation of how ultraviolet light (UV) exposure was calculated.

of specific antiretroviral use in the multiple linear regression model, only the duration of efavirenz use was independently associated with lower levels of 25(OH)D ($P < .0001$).

DISCUSSION

Vitamin D deficiency and insufficiency or deficiency was highly prevalent among HIV-infected SUN participants but was less prevalent than among adults in the general US population. Similar to previous reports of vitamin D status in the general population, we observed higher odds of vitamin D insufficiency or deficiency among HIV-infected persons who were of non-Hispanic black or Hispanic race/ethnicity, had higher BMI, exercised less, or had hypertension [1, 6]. However, we did not observe associations between vitamin D insufficiency or deficiency and some other established predictors of 25(OH)D levels, including age and sex. Although we could not assess the association between levels of 25(OH)D and HIV infection, we did explore the associations between vitamin D insufficiency or deficiency and specific antiretroviral drugs [36].

Previous small cohort studies focused on vitamin D deficiency defined as 25(OH)D levels ranging between <10 ng/mL and <20 ng/mL [24, 26, 30]. We defined deficiency as 25(OH)D levels <20 ng/mL to identify both patients with severe and those with moderate deficiency. Our definition of vitamin D insufficiency or deficiency as levels <30 ng/mL was similar to that in previous NHANES assessments of vitamin D insufficiency or deficiency in the general US population and other reviews of the optimal 25(OH)D level for preventing several skeletal and nonskeletal health outcomes [2, 11, 37]. Based on these definitions, our findings corroborate other estimates of vitamin D levels among HIV-infected adults [24, 26, 30]. By focusing our analysis on vitamin D insufficiency or deficiency, we were able to explore risk factors among HIV-infected patients who were potentially at risk for bone disease, as well as other comorbidities associated with vitamin D status.

Previous small cohorts studies have reported associations between vitamin D deficiency and nonnucleoside reverse transcriptase inhibitors, and case studies have described low vitamin D levels among HIV-infected persons receiving

Table 2. Baseline Demographic and Clinical Factors Associated with Vitamin D Insufficiency or Deficiency in the SUN Cohort ($n = 672$), 2004–2006

Characteristic	Vitamin D Status		Odd Ratio (95% CI)	
	Vitamin D Insufficient or Deficient (<30 ng/mL[a]) ($n = 481$)	Vitamin D Sufficient (≥30 ng/mL) ($n = 191$)	Unadjusted	Adjusted[b]
Sex				
Male	353 (68.9)	159 (31.1)	Referent	Referent
Female	128 (80.0)	32 (20.0)	1.80 (1.17–2.77)	.96 (.56–1.66)
Median age, years (IQR)	41 (35–48)	41 (36–47)	.99 (.97–1.01)	.99 (.97–1.02)
Race/ethnicity				
White, non-Hispanic	239 (61.6)	149 (38.4)	Referent	Referent
Black, non-Hispanic	177 (88.5)	23 (11.5)	4.24 (2.68–6.72)	4.51 (2.59–7.85)
Hispanic	53 (80.3)	13 (19.7)	2.54 (1.34–4.82)	2.78 (1.31–5.90)
Other	12 (80.0)	3 (20.0)	2.49 (.69–8.98)	3.23 (.78–13.4)
Site of clinic				
Denver, CO	50 (58.8)	35 (41.2)	Referent	–
Minneapolis, MN	162 (71.4)	65 (28.6)	1.75 (1.04–2.93)	–
Providence, RI	135 (71.1)	55 (28.9)	1.72 (1.01–2.93)	–
St Louis, MO	134 (78.8)	36 (21.2)	2.61 (1.48–4.60)	–
Monthly average UV exposure, median (IQR)[c]	3.3 (1.8–5.5)	4.6 (2.6–6.4)	.82 (.76–.88)	.78 (.71–.86)
Body mass index, median (IQR), kg/m^2	25.9 (22.9–29.4)	24.7 (22.8–27.0)	1.06 (1.02–1.10)	1.04 (1.00–1.09)
Duration since HIV diagnosis, median (IQR), years	5.3 (2.6–8.1)	3.9 (1.5–7.7)	1.00 (.99–1.01)	–
AIDS diagnosis				
No	186 (72.1)	72 (27.9)	Referent	–
Yes	295 (71.0)	119 (29.0)	.96 (.68–1.36)	–
Baseline CD4 T cell count, cells/mm^3				
>350	341 (72.7)	128 (27.3)	Referent	
200–350	107 (79.9)	46 (30.1)	.87 (.59–1.30)	–
<200	30 (63.8)	17 (36.2)	.66 (.35–1.24)	–
Nadir CD4 T cell count, cells/mm^3				
>350	97 (74.0)	34 (26.0)	Referent	–
200–350	148 (72.9)	55 (27.1)	.94 (.57–1.55)	–
<200	226 (69.3)	100 (30.7)	.79 (.50–1.25)	–
Prescribed glucocorticoids				
No	473 (71.8)	186 (28.2)	Referent	–
Yes	8 (61.5)	5 (38.5)	.63 (.20–1.95)	–
Prescribed anticonvulsants				
No	475 (71.8)	187 (28.2)	Referent	–
Yes	6 (60.0)	4 (40.0)	.59 (.17–2.12)	–
Chronic hepatitis B virus coinfection				
No	333 (72.1)	129 (27.9)	Referent	Referent
Yes	148 (70.5)	62 (29.5)	.93 (.65–1.33)	1.10 (.72–1.68)
Hepatitis C virus coinfection				
No	412 (70.4)	173 (29.6)	Referent	Referent
Yes	69 (79.3)	18 (20.7)	1.61 (.93–2.78)	1.24 (.65–2.35)
ALT (SGPT) level				
Normal (<56 U/L)	429 (72.0)	167 (28.0)	Referent	–
Elevated (≥56 U/L)	48 (68.6)	22 (31.4)	.85 (.50–1.45)	–
AST (SGOT) level				
Normal (<40 U/L)	399 (71.8)	157 (28.2)	Referent	–
Elevated (≥40 U/L)	77 (71.3)	31 (28.7)	.98 (.65–1.54)	–
Other chronic liver disease[d]				
No	472 (71.6)	187 (28.4)	Referent	–
Yes	9 (69.2)	4 (30.8)	.89 (.27–2.93)	–

Table 2. (*Continued*)

Characteristic	Vitamin D Status		Odd Ratio (95% CI)	
	Vitamin D Insufficient or Deficient (<30 ng/mL[a]) (n = 481)	Vitamin D Sufficient (≥30 ng/mL) (n = 191)	Unadjusted	Adjusted[b]
GFR, mL/min/1.73m^2				
≥90	313 (78.1)	88 (21.9)	Referent	Referent
<90	164 (61.9)	101 (38.1)	.45 (.32–.64)	.55 (.36–.83)
Hypertension				
No	360 (68.7)	164 (31.3)	Referent	Referent
Yes	121 (81.8)	27 (18.2)	2.04 (1.30–3.22)	1.88 (1.10–3.22)
Diabetes				
No	455 (71.1)	185 (28.9)	Referent	–
Yes	26 (81.3)	6 (18.8)	1.76 (.71–4.35)	–
High-density lipoprotein, mg/dL				
<40	209 (71.6)	83 (28.4)	Referent	–
≥40	249 (71.8)	98 (28.2)	1.01 (.71–1.43)	–
Tobacco smoking status				
Nonsmoker	159 (74.3)	55 (25.7)	Referent	–
Previous smoker	106 (69.7)	46 (30.3)	.80 (.54–1.19)	–
Current smoker	202 (69.9)	87 (30.1)	.80 (.50–1.27)	–
Exercise				
≥3 days/week	198 (63.9)	112 (36.1)	Referent	Referent
1–2 days/week	130 (73.4)	47 (26.6)	1.57 (1.04–2.35)	1.50 (.94–2.37)
None	127 (83.0)	26 (17.0)	2.77 (1.71–4.47)	3.14 (1.80–5.47)
Bone mineral density				
Normal (t score > −1)	180 (70.6)	75 (29.4)	Referent	–
Low (t score ≤ −1)	279 (71.5)	111 (28.5)	1.05 (.74–1.48)	–
cART exposure				
Naive	36 (48.0)	39 (52.0)	Referent	–
Exposure but not current	44 (68.8)	20 (31.3)	1.46 (.90–2.37)	–
Current exposure	306 (57.4)	227 (42.6)	2.38 (1.19–4.78)	–
NRTI-containing regimen				
No	78 (56.5)	60 (43.5)	Referent	–
Yes	308 (57.7)	226 (43.3)	.99 (.65–1.50)	–
Efavirenz-containing regimen				
No	263 (53.1)	232 (46.9)	Referent	Referent
Yes	123 (69.5)	54 (30.5)	1.95 (1.29–2.97)	1.98 (1.18–3.34)
Nevirapine-containing regimen				
No	341 (58.2)	245 (41.8)	Referent	–
Yes	45 (52.3)	41 (47.7)	.79 (.50–1.24)	–
Tenofovir-containing regimen				
No	308 (75.3)	101 (24.7)	Referent	Referent
Yes	173 (65.8)	90 (34.2)	.63 (.45–.89)	.69 (.46–1.04)
Ritonavir-containing regimen (low or regular dose)				
No	354 (76.6)	108 (23.4)	Referent	Referent
Yes	127 (60.5)	83 (39.5)	.47 (.33–.66)	.56 (.35–.89)

NOTE. Data are presented as no. (%) unless otherwise indicated.

Abbreviations: ALT (SGPT), alanine aminotransferase (serum glutamic-pyruvic transaminase); AST (SGOT), aspartate aminotransferase (serum glutamic-oxaloacetic transaminase); cART, combination antiretroviral therapy; CI, confidence interval; GFR, glomerular filtration rate; HIV, human immunodeficiency virus; IQR, interquartile range; NRTI, nucleoside reverse transcriptase inhibitor; SUN, Study to Understand the Natural History of HIV and AIDS in the Era of Effective Therapy; UV, ultraviolet light.

[a] The conversion factor for converting nanograms per milliliter to nanomoles per liter is 2.496.

[b] The final logistic regression model included sex, age, race/ethnicity, monthly average UV exposure, body mass index, hepatitis B virus coinfection, hepatitis C virus coinfection, GFR, hypertension, exercise, and exposure to efavirenz, tenofovir, and ritonavir-containing regimens.

[c] UV exposure is measured using the UV index, an estimate of the strength of UV radiation that reaches the earth's surface. The UV index is calculated by dividing the clear sky UV dose rate (in milliwattsper square meter), which accounts for elevation, cloud cover, air pollution, and haze, by the standard of 25 mW/m^2, resulting in a unitless value. UV index values range from 0 to ~15.

[d] Liver disease other than chronic hepatitis B or hepatitis C virus infection, including liver failure, cirrhosis of liver, hepatic encephalopathy, and hepatitis steatosis.

Table 3. Multiple Linear Regression Analysis of Correlates of 25-Hyroxyvitamin D Concentrations, SUN, 2004–2006 ($n = 672$)

Correlate	Coefficient	Standard Error	*P*
Female vs male sex	−1.29	1.10	.24
Age (years)	.10	.05	.05
Race/ethnicity			
Non-Hispanic white	Referent	–	–
Non-Hispanic black	−8.26	1.03	<.0001
Hispanic	−5.32	1.45	.0003
Other	−4.69	2.78	.09
Monthly average UV exposure	1.17	.19	<.0001
BMI (kg/m^2)	−.21	.08	.01
Chronic hepatitis B virus infection	.80	.91	.38
Hepatitis C virus infection	−.85	1.25	.50
GFR <90 mL/min/1.73m^2	2.20	.90	.02
Hypertension	−1.36	1.07	.20
Exercise			
None	−4.17	1.06	<.0001
1–2 days/week	−3.31	1.00	.001
Efavirenz-containing regimen	−2.89	1.04	.006
Tenofovir-containing regimen	2.37	.90	.01
Ritonavir-containing regimen (low or regular dose)	1.78	1.04	.09

Abbreviations: BMI, body mass index; GFR, glomerular filtration rate; SUN, Study to Understand the Natural History of HIV and AIDS in the Era of Effective Therapy; UV, ultraviolet light.

efavirenz [24–30, 38–40]. In our analysis, we did not observe any significant association between nevirapine use and vitamin D insufficiency or deficiency, a finding consistent with those of one small longitudinal study [41]. The association we observed between efavirenz exposure and higher odds of vitamin D insufficiency or deficiency has been reported in 2 case studies that described the potential role of efavirenz in altering the metabolism of 25(OH)D and 1,25$(OH)_2$D, leading to increased risk of vitamin D deficiency (25[OH]D, <10 ng/mL) [27, 38–40]. Similar to some antiepileptic agents and alcohol, efavirenz probably reduces levels of circulating 25(OH)D by inducing 24-hydroxylase, a cytochrome P450 enzyme, which hydrolyzes 25(OH)D to its inactivate form, 24,25$(OH)_2$D [27, 28, 42].

Our findings suggest that there is an association between ritonavir exposure and lower odds of vitamin D insufficiency or deficiency, which might reflect the underlying action of ritonavir on vitamin D metabolism. Another study found higher levels of 25(OH)D in white HIV-infected persons exposed to protease inhibitors, compared with those exposed to nonnucleoside reverse transcriptase inhibitors or naive persons, but that study did not specifically explore associations with ritonavir exposure [30]. Ritonavir, a potent inhibitor of cytochrome P450 enzymes, has previously been shown in vitro to block the action of the 1α-hydroxylase that is responsible for the conversion of 25(OH)D to 1,25$(OH)_2$D in the kidney [43]. Consequently, patients prescribed ritonavir might appear to have adequate levels of 25(OH)D but low levels of 1,25$(OH)_2$D.

The association of tenofovir exposure with higher levels of 25(OH)D has biological plausibility. Tenofovir causes proximal tubule injury, inducing renal dysfunction, as measured by declines in GFR and increases in urine protein-creatinine ratio [44–46]. Given that the conversion of 25(OH)D to 1,25$(OH)_2$D by 1α-hydroxylase occurs primarily in the proximal tubule, tenofovir-induced proximal tubule dysfunction might also reduce hydroxylation of 25(OH)D to 1,25$(OH)_2$D, causing accumulation of 25(OH)D and leading to surreptitiously normal 25(OH)D levels despite low levels of 1,25$(OH)_2$D [25, 47]. A recent study observed significantly higher levels of 1,25$(OH)_2$D with tenofovir use but no association with 25(OH)D levels, highlighting the need for future studies to elucidate the effect of antiretrovirals on vitamin D metabolism [26].

Although HIV-infected persons are at higher risk for osteoporosis and fragility fractures [14, 16], we did not observe an association between BMD and vitamin D insufficiency or deficiency. However, in addition to 25(OH)D, BMD is determined by other key regulators of bone homeostasis, including parathyroid hormone, which regulates serum calcium levels through bone resorption and stimulation of 1α-hydroxylase activity to increase production of 1,25(OH)D and, therefore, increase absorption of calcium from the intestine. A study of 36 HIV-infected men showed elevated levels of parathyroid hormone among those who were prescribed tenofovir; among these persons, parathyroid hormone levels were much higher among men who were vitamin D insufficient than among vitamin D–sufficient men [48]. We did not measure serum concentrations of

parathyroid hormone and therefore could not assess these levels among SUN participants receiving tenofovir. Future studies among HIV-infected persons are needed to assess the contributions of vitamin D status, parathyroid hormone, calcium, phosphorus, $1,25(OH)_2D$, and certain antiretroviral drugs, such as tenofovir, to low BMD.

Our study was subject to several limitations. SUN is only conducted in only 4 US cities; therefore, data presented here may not be generalizable to all HIV-infected persons in the United States. Moreover, this analysis was cross-sectional; thus, causal relationships cannot be determined. To assess potential alterations in vitamin D metabolism requires cohort and case-control studies that are sufficiently powered to evaluate serum concentrations of 25(OH)D and $1,25(OH)_2D$ at the time HIV infection is diagnosed and throughout treatment with various ART regimens.

In summary, our study compares the prevalence of vitamin D insufficiency or deficiency among a large, diverse, contemporary cohort of HIV-infected adults with that in adults in the general US population. Although the modestly lower prevalence of vitamin D insufficiency or deficiency among SUN participants was significant after adjustment for age, race, and sex, vitamin D insufficiency or deficiency remained highly prevalent, affecting >70% of HIV-infected persons, and was associated with exposures to certain antiretrovirals. The associations between low levels of 25(OH)D and many chronic conditions that are prevalent among HIV-infected persons highlight the need for routine screening for vitamin D insufficiency or deficiency. Future studies are needed to verify potential alterations in vitamin D metabolism caused by the exposure to antiretrovirals and their duration of use. Although one study has shown increases in 25(OH)D with vitamin D supplementation, larger studies are necessary to assess the impact of vitamin D supplementation on prevention of comorbidities among HIV-infected adults, such as osteoporosis or osteopenia and cardiovascular disease [49].

Acknowledgments

The findings and conclusions from this review are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention.

Financial support. This work was supported by the CDC (contract numbers 200-2002-00610, 200-2002-00611, 200-2002-00612, 200-2002-00613, 200-2007-23633, 200-2007-23634, 200-2007-23635, and 200-2007-23636).

Potential conflicts of interest. E.T.O. has served as a consultant or on an advisory board for Gilead, Bristol Myers Squibb, Glaxo-Smith-Kline, Tibotec, Merck, and Monogram Sciences. Frank Rhane has served as a consultant or study investigator or on an advisory board for Boehringer Ingelheim, Tibotec, GSK/ViiV, Merck, and Gilead. All other authors report no conflicts of interest.

SUN Investigators. John T. Brooks, Pragna Patel, Lois Conley, and Tim Bush, Division of HIV/AIDS Prevention, National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention, CDC, Atlanta, Georgia; Kathleen Wood, Rose Baker, and Cheryl Akridge, Cerner Corporation, Vienna, Virginia; John Hammer, Tara Kennedy, Barbara Widick, and Billie Thomas, Denver Infectious Disease Consultants, Denver, Colorado; Ken Lichtenstein and Cheryl Stewart, National Jewish Medical and Research Center, Denver; Keith Henry, Jason Baker, Edie Gunderson, Miki Olson, and John Hall, Hennepin County Medical Center, Minneapolis, Minnesota; Frank Rhame, Mark Olson, and Eve Austad, Abbott-Northwestern Hospital, Minneapolis; Hal Martin, Meaghan Morton, and Cheri Murch, Park-Nicollet Institute, Minneapolis; Charles Carpenter, Susan Cu-Uvin, Kenneth Mayer, Erna Milunka Kojic, Lynn Taylor, Jennifer Florczyk, Sara Metzler, and Patricia D'Aiello, Miriam Hospital, Providence, Rhode Island; E. Turner Overton, Lisa Kessels, Mariea Snell, Dorothea Dedeaux-Turner, Sara Hubert, Don Connor, Mike Klebert, Sara Hubert, Dave Coughlan, and Kenneth Griffie, Washington University School of Medicine, St Louis, Missouri; Stephanie Robinson and Peter Meyer, Research Data Center, National Center for Health Statistics (CDC).

References

1. Holick MF. Vitamin D deficiency. N Engl J Med **2007**; 357:266–81.
2. Ginde AA, Liu MC, Camargo CA. Demographic differences and trends of vitamin D insufficiency in the US population, 1988–2004. Arch Intern Med **2009**; 169:626–32.
3. Looker AC, Dawson-Hughes B, Calvo MS, Gunter EW, Sahyoun NR. Serum 25-hydroxyvitamin D status of the US population: 1988–1994 compared with 2000–2004. Am J Clin Nutr **2008**; 88:1519–27.
4. Giovannucci E. The epidemiology of vitamin D and cancer incidence and mortality: a review (United States). Cancer Causes Control **2005**; 16:83–95.
5. Martins D, Wolf M, Pan D, et al. Prevalence of cardiovascular risk factors and the serum levels of 25-hydroxyvitamin D in the United States. Arch Intern Med **2007**; 167:1159–65.
6. Forman J, Giovannucci E, Holmes M, et al. Plasma 25-hydroxyvitamin D levels and risk of incident hypertension. Hypertension **2007**; 49:1063–9.
7. Bouillon R. Vitamin D: from photosynthesis, metabolism, and action to clinical applications. In: DeGroot LJ, Jameson JL eds: Endocrinology, 4th ed. Vol 2. Philadelphia, PA: WB Saunders, **2001**: 1009–28.
8. Food and Nutrition Board IoM. 1997 dietary reference intakes for calcium, magnesium, phosphorus, vitamin D, and fluoride. Washington, DC: National Academy Press, **2009**.
9. Chapuy M-C, Preziosi P, Maamer M, et al. Prevalence of vitamin D insufficiency in an adult normal population. Osteoporos Int **1997**; 7:439–43.
10. Heaney R, Dowell M, Hale C, Bendich A. Calcium absorption varies within the reference range for serum 25-hydroxyvitamin D. J Am Coll Nutr **2003**; 22:142–6.
11. Dawson-Hughes B, Heaney RP, Holick MF, Lips P, Meunier PJ, Vieth R. Estimates of optimal vitamin D status. Osteoporos Int **2005**; 16:713–6.
12. Office of Dietary Supplements NIoH. Dietary supplement fact sheet: vitamin D. Available at: http://ods.od.nih.gov/factsheets/vitamind.asp. Accessed 10 December 2009.
13. Palella F, Delaney K, Moorman A, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. N Engl J Med **1998**; 338:853–60.
14. Onen N, Agbebi A, Shacham E, Stamm K, Onen A, Overton E. Frailty among HIV-infected persons in an urban outpatient care setting. J Infect **2009**; 59:346–52.
15. Goulet J, Fultz S, Rimland D, et al. Do patterns of comorbidity vary by HIV status, age, and HIV severity? Clin Infect Dis **2007**; 45:1593–601.
16. Brown T, Qaqish R. Antiretroviral therapy and the prevalence of osteopenia and osteoporosis: a meta-analytic review. AIDS **2006**; 20:2165–74.
17. Triant V, Lee H, Hadigan C, Grinspoon S. Increased acute myocardial infarction rates and cardiovascular risk factors among patients with human immunodeficiency virus diseases. J Clin Endocrinol Metab **2007**; 92:2506–12.

18. Shardell M, Hicks G, Miller R, et al. Association of low vitamin D levels with the frailty syndrome in men and women. J Gerontol A Biol Sci Med Sci **2009**; 64:69–75.
19. Chiu K, Chu A, Go V, Saad M. Hypovitaminosis D is associated with insulin resistance and B dysfunction. Am J Clin Nutr **2004**; 79:820–5.
20. Llewellyn D, Langa K, Lang I. Serum 25-hydroxyvitamin D concentration and cognitive impairment. J Geriatr Psychiatry Neurol **2009**; 22:188–95.
21. Mehta S, Spiegelman D, Magusi F, Giovannucci E, Msmanga G, Fawzi W. Vitamin D HIV-related complications and HIV disease progression women in Tanzania. In: Program and abstracts of the 17th Conference on Retroviruses and Opportunistic infections (San Francisco, CA). **2010**.
22. Bolland MJ, Grey A, Horne AM, Thomas MG. Osteomalacia in an HIV-infected man receiving rifabutin, a cytochrome P450 enzyme induce: a case report. Ann Clin Microbiol Antimicrobials **2008**; 7:3.
23. Haug C, Muller F, Aukrust P, Froland SS. Subnormal serum concentration of 1,25-vitamin D in human immunodeficiency virus infection: correlation with degree of immune deficiency and survival. J Infect Dis **1997**; 169:889–93.
24. Rodriguez M, Daniels B, Gunawardene S, Robbins GK. High frequency of vitamin D deficiency in ambulatory HIV-positive patients. AIDS Res Hum Retroviruses **2009**; 25:9–14.
25. Madeddu G, Spanu A, Solinas P, et al. Bone mass loss and vitamin D metabolism impairment in HIV patients receiving highly active antiretroviral therapy. Q J Nucl Med Mol Imaging **2004**; 48:39–48.
26. Mueller N, Fux C, Ledergerber B, et al. High prevalence of severe vitamin D deficiency in combined antiretroviral therapy-naive and successfully treated Swiss HIV patients. AIDS **2010**; 24:1127–34.
27. Gyllensten K, Josephson F, Lidman K, Saaf M. Severe vitamin D deficiency diagnosed after introduction of antiretroviral therapy including efavirenz in a patient living at latitude 59N. AIDS **2006**; 20:1906–7.
28. Fabbriciani G, De Socio GV. Efavirenz and bone health. AIDS **2009**; 23:1181.
29. Villamor E. A potential role for vitamin D on HIV infection? Nutr Rev **2006**; 64:226–33.
30. Van Den Bout-Van Den Beukel CJP, Fievez L, Michels M, et al. Vitamin D deficiency among HIV Type 1-infected individuals in the Netherlands: effects of antiretroviral therapy. AIDS Res Hum Retroviruses **2008**; 24:1375–82.
31. Vellozzi C, Brooks JT, Bush TJ, et al. The study to understand the natural history of HIV and AIDS in the era of effective therapy (SUN study). Am J Epidemiol **2009**; 169:642–52.
32. NOAA, National Weather Service Climate Prediction Center. UV index: annual time series. Available at: http://www.cpc.ncep.noaa.gov/products/stratosphere/uv_index/uv_annual.shtml. Accessed 9 October 2009.
33. National Center for Health Statistics, Centers for Disease Control and Prevention. National health and nutrition examination survey. Available at: http://www.cdc.gov/nchs/nhanes/about_nhanes.htm. Accessed 17 February 2009.
34. National Center for Health Statistics, Centers for Disease Control and Prevention. NHANES analytic guidelines. Available at: http://www.cdc.gov/nchs/data/nhanes/nhanes_general_guidelines_june_04.pdf. Accessed 17 February 2009.
35. Hosmer D, Lemeshow S. Applied logistic regression. 2nd ed. New York: Wiley, 2000.
36. Stephensen CB, Marquis GS, Kruzich LA, Douglas SD, Aldrovandi GM, Wilson CM. Vitamin D status in adolescents and young adults with HIV infection. Am J Clin Nutr **2006**; 83:1135–41.
37. Bischoff-Ferrari H, Giovannucci E, Willett W, Dietrick T, Dawson-Hughes B. Estimation of optimal serum concentrations of 25-hydroxyvitamin D for multiple health outcomes. Am J Clin Nutr **2006**; 84:18–28.
38. Herzmann C, Arasteh K. Efavirenz-induced osteomalacia. AIDS **2009**; 23:274–5.
39. Welz T, Childs K, Ibrahim F, Poulton M, Post F. Efavirenz use is associated with severe vitamin D deficiency in a large, ethnically diverse urban UK HIV cohort. In: Program abstracts of the 5th International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention (Cape Town, South Africa). 2009.
40. Brown T, McComsey G. Association between initiation of antiretroviral therapy with efavirenz and decreases in 25-hydroxyvitamin D. Antivir Ther **2009**; 14(Suppl 2):A15.
41. Lattuada E, Lanzafame M, Zoppini G, Concia E, Vento S. No influence of nevirapine on vitamin D deficiency in HIV-infected patients. AIDS Res Hum Retroviruses **2009**; 25:849–50.
42. Valsamis HA, Surender KA, Labban B, McFarlane SI. Antiepileptic drugs and bone metabolism. Nutr Metab **2006**; 3:36.
43. Cozzolino M, Vidal M, Vittoria Arcidiacono M, Tebas P, Yarasheski KE, Dusso AS. HIV-protease inhibitors impair vitamin D bioactivation to 1,25-dihydroxyvitamin D. AIDS **2003**; 17:513–20.
44. Woodward C, Hall A, William I, et al. Tenofovir-associated renal and bone toxicity. HIV Med **2009**; 10:482–7.
45. Peyriere H, Reynes J, Rouanet I, et al. Renal tubular dysfunction associated with tenofovir therapy. J Acquir Immune Defic Syndr **2004**; 35:269–73.
46. Horberg M, Tang B, Towner W, et al. Impact of tenofovir on renal function in HIV-infected, antiretroviral-naive patients. J Acquir Immune Defic Syndr **2010**; 53:62–9.
47. Haug C, Muller F, Aukrust P, Froland SS. Subnormal serum concentration of 1,25-vitamin D in human immunodeficiency virus infection: correlation with degree of immune deficiency and survival. J Infect Dis **1994**; 169:889–93.
48. Childs K, Fishman S, Bateman K, et al. Should vitamin D be prescribed with tenofovir/FTC? In: Program and abstracts of the 48th Annual Interscience Conference on Antimicrobial Agents and Chenotherapy/Infectious Disease Society of America 46th Annual Meeting (Washington, DC). **2008**.
49. Childs K, Fishman S, Factor S, Dieterich D, Mullen M, Branch A. First report of dose/response data of HIV-infected men treated with vitamin D3 supplements. In: Program and abstracts of the 16th Conference on Retroviruses and Opportunistic Infections (Montreal, Canada). 2009.