Success of Standard Dose Vitamin D Supplementation in Treated Human Immunodeficiency Virus Infection

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Background. Vitamin D insufficiency is prevalent in human immunodeficiency virus-positive (HIV+) persons. Human immunodeficiency virus and antiretroviral therapy (ART) may create unique risk factors, and the optimal vitamin D repletion and maintenance regimen in HIV+ persons remains unclear.

Methods. Human immunodeficiency virus-positive adults on suppressive ART underwent routine serum 25-hydroxyvitamin D (25OHD) screening. Persons with vitamin D insufficiency (25OHD <30 ng/mL) received open-label, oral vitamin D_3 50 000 international units (IU) twice weekly for 5 weeks, then 2000 IU daily to complete 12 weeks. We predicted 70% (95% confidence interval, 60%–80%) repletion to 25OHD ≥30 ng/mL compared with 85% among historical HIV-negative controls. Eighty participants provided 91% power to detect this difference. Ability to maintain 25OHD ≥30 ng/mL after 24 weeks was also assessed.

Results. Baseline characteristics were similar between the 82 vitamin D insufficient and 40 sufficient persons enrolled: 95% male, 60% white, 88% nonsmokers, median age 49 years, body mass index 26 kg/m^2, and CD4$^+$ T lymphocyte count 520 cells/mm^3. After 12 weeks, 81% (66 of 82) of insufficient persons achieved 25OHD ≥30 ng/mL (P = .32 vs historical controls), with only older age (odds ratio [OR] = 1.06; P = .06), higher baseline 25OHD (OR = 1.14; P < .01), white race (OR = 3.39; P = .04), and current smoking (OR = 0.25; P = .06) associated with successful repletion. After 24 weeks, 73% (48 of 66) maintained 25OHD ≥30 ng/mL, with tenofovir (OR = 5.00; P = .01) and abacavir use (OR = 0.23; P = .02) associated with success and failure, respectively, to maintain 25OHD levels.

Conclusions. The 25OHD repletion rates were comparable between HIV+ adults on suppressive ART and historical HIV-negative controls, indicating that successful oral repletion can be achieved in this population.

Keywords. antiretroviral therapy; HIV; vitamin D.

Low serum 25-hydroxyvitamin D levels (25OHD <30 ng/mL) are highly prevalent in both human immunodeficiency virus (HIV)-infected persons and the general population [1–5], and these levels have been associated with cardiovascular disease, insulin resistance, progression to acquired immune deficiency syndrome, and increased mortality [3, 6–11]. Human immunodeficiency virus infection and antiretroviral therapy (ART) may create unique risk factors for vitamin D insufficiency. For example, increased tumor necrosis factor-alpha levels have been associated with both HIV infection and vitamin D insufficiency [12] and the protease inhibitor (PI), and nonnucleoside reverse transcriptase inhibitor (NNRTI) classes of antiretroviral agents may interrupt normal 25OHD synthesis and metabolism via modulation of the cytochrome P450 system(s) that control hydroxylation of vitamin D and its metabolites [2, 12–15].

In HIV-uninfected adults, the safety of vitamin D supplementation has been demonstrated at a wide range of doses [16, 17], and the efficacy of oral supplementation in repleting 25OHD levels is generally high. In HIV-infected persons, the safety of vitamin D supplementation at a wide range of doses has also been

described, but repletion success rates have been less consistent, even at doses of 2000–4000 international units (IU) daily [4, 18].

The Institute of Medicine recommends 600 IU of vitamin D daily for most adults, with 4000 IU recommended as the upper limit of supplementation [19]. The Endocrine Society also recommends 600–800 IU for most adults, but it specifically recommends at least 2 to 3 times this amount for HIV-infected persons on ART [20]. The US Preventive Services Task Force released a statement in November 2014 against screening for vitamin D insufficiency in nonpregnant, asymptomatic community-dwelling adults; however, this recommendation did not apply to populations at increased risk for vitamin D insufficiency or for whom benefits of repletion therapy have been established [21]. Given the complex inflammatory physiology associated with HIV infection, the prevalence of metabolic bone disease, and the potential for ART to alter the efficacy of vitamin D replacement strategies, vitamin D supplementation at the higher end of recommended values is likely prudent in HIV-infected persons. However, the optimal oral vitamin D repletion and maintenance regimen for HIV-infected adults on ART remains unknown. To help answer this question, we conducted an open-label trial of standardized vitamin D supplementation in HIV-infected men and women on suppressive ART.

MATERIALS AND METHODS

Study Design

At the time of routine 25OHD level screening by their primary care provider, patients were offered participation in a 24-week, observational study of standardized vitamin D repletion. After provision of informed consent, eligibility was determined. Inclusion criteria required participants to be ≥18 years of age and have HIV-1 RNA <200 copies/mL on ART. Potential participants were excluded if they did not meet inclusion criteria, were using vitamin D supplementation >400 IU daily (the amount in a standard multivitamin) at screening, and/or were not willing to have their 25OHD results monitored by the study team.

Medical record review was performed for collection of demographic and clinical information including age, race, sex, ART regimen, past medical history, concomitant medications, CD4^{+} T lymphocyte counts (absolute and percentage), HIV-1 RNA, 25OHD levels, substance use history (including tobacco), and the presence of hepatitis B or C virus coinfection. Vitamin D hormone, 1,25-dihydroxyvitamin D $(1,25(OH)_2 D)$, calcium, and parathyroid hormone levels were not routinely available for collection.

Participants with baseline 25OHD >30 ng/mL (vitamin D sufficient) completed study participation after the baseline assessment. Participants with 25OHD levels <30 ng/mL (vitamin D insufficient) were offered vitamin D supplementation according to the standardized protocol outlined below. For vitamin D insufficient participants, supplements were provided at no cost

to ensure uniformity of supplement type and dosing schedule across providers.

After 12 weeks, serum 25OHD measurement was repeated, as consistent with local standard of care. Participants who achieved 25OHD >30 ng/mL were encouraged to continue maintenance therapy. For participants with persistent 25OHD levels <30 ng/mL, decisions regarding further vitamin D supplementation were deferred to their primary care provider. After 24 weeks, 25OHD levels were again obtained via routine care. Interim chart review was repeated at 12 and 24 weeks post-initiation of vitamin D supplementation. All participants were encouraged to continue vitamin D supplementation at maintenance doses after study cessation (if approved by their primary provider), but no additional supplements were provided to participants after the 24-week study period.

Due to the observational nature of the study, adverse events reported to the study team or primary provider were handled at the discretion of the primary provider irrespective of relatedness to study product.

Vitamin D Supplementation Regimen

Vitamin D insufficient participants initiated an open-label, oral vitamin D_3 supplementation regimen of 50 000 IU twice weekly for 5 weeks, followed by 2000 IU daily to complete 12 weeks. In HIV-uninfected persons with low bone mineral density, a similar induction regimen of 50 000 IU twice weekly for 5 weeks (500 000 IU total) followed by maintenance therapy with 1400 IU daily achieved 25OHD levels ≥30 ng/mL in 85% of subjects after 12 weeks with an excellent safety profile [1, 22, 23].

Supplementation with Carlson's Ddrops (2000 IU of emulsified vitamin D_3 per drop) was chosen for quality and consistency in addition to lack of pill burden (J. R. Carlson Laboratories, Inc., Arlington Heights, IL). Drops were kept in a humidity-controlled, locked, storage cabinet before dispensation to participants by study personnel. Participants were instructed to take 25 drops twice weekly for 5 weeks followed by 1 drop daily. Medication accountability was assessed by patient report to the primary physician and study coordinator, but droplet counts could not be performed for feasibility reasons.

25-Hydroxyvitamin D Level Measurement

Serum 25OHD was measured via DiaSorin Liaison direct competitive chemiluminescence immunoassay at The University of California, Los Angeles Clinical Laboratories. This assay has a lower limit of detection of 4 ng/mL and within- and between-assay coefficients of variation of <7.7% and <12.6%, respectively (DiaSorin, Stillwater, MN).

Sample Size and Power

The primary endpoint was mean change in 25OHD level after 12 weeks of vitamin D supplementation for insufficient participants, which was dichotomized to success or failure to achieve a

week 12 25OHD level ≥30 ng/mL. We predicted that HIV-infected participants would have a 70% 12-week repletion success rate (95% confidence interval [CI], 60%–80%) compared with 85% among HIV-uninfected historical controls [1, 22, 23], and that a variance of more than 10% from the control success rate was clinically significant. Eighty participants provided 91% power to detect a 12-week repletion rate statistically different than 85%.

Analytic Techniques

Chart review was performed for sociodemographic and medical characteristics at baseline and after 12 and 24 weeks. Descriptive statistics (mean, standard deviation, median, interquartile range, and frequency distribution) were generated for baseline demographic information and clinical characteristics, as well as 12- and 24-week outcomes. All participants who initiated vitamin D supplementation were included in the analysis, irrespective of adherence. Participants who stopped ART or experienced virologic failure were excluded from analysis given the multiple metabolic and inflammatory changes associated with those states. The exact binomial test was used to compare the observed 12-week repletion success rate with the historical rate of 85%. For other endpoints, the Wilcoxon rank-sum and Fisher's exact tests were used to compare continuous and categorical variables, respectively, among (1) participants who were vitamin D sufficient and insufficient at baseline, (2) participants who did and did not successfully replete to 25OHD ≥30 ng/mL after supplementation, and (3) participants who did and did not maintain 25OHD ≥30 ng/mL after successful repletion. Factors associated with successful repletion and maintenance were evaluated with bivariate logistic regression. Significance was defined at a nominal value of 0.05 for the primary outcome and 0.10 for secondary endpoints. Because this was a pilot study, analyses were exploratory and did not adjust for multiple testing. In addition, we did not adjust for season, because the primary endpoint was after a 12-week follow-up period, which was within the same season for most participants.

Ethics Statement

This study was conducted in accordance with the Declaration of Helsinki and national and institutional standards. The University of California, Los Angeles Institutional Review Board (IRB) approved the study protocol and all study documents before study commencement (IRB no. 10-000031). In addition, all participants provided informed consent before initiation of study procedures. This trial is registered at ClinicalTrials.gov (NCT01250899).

RESULTS

Study Population

One hundred twenty-two participants were screened and enrolled between June 2010 and April 2011. Forty participants
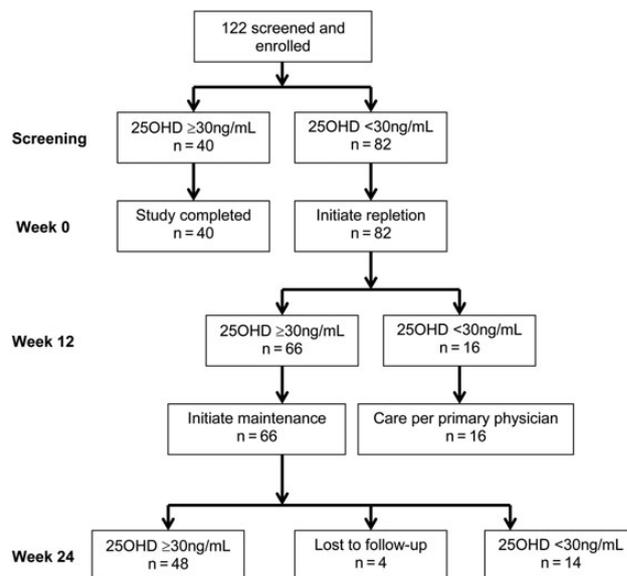

Figure 1. The graphic illustrates disposition and enrollment. Abbreviation: 25OHD, 25-hydroxyvitamin D.

had serum 25OHD ≥30 ng/mL at baseline, and 82 participants were vitamin D insufficient. All insufficient participants initiated repletion therapy. Four participants were lost to follow-up (Figure 1).

Complete baseline demographic and clinical characteristics stratified by 25OHD status are presented in Table 1. Overall, median age was 49 years, 25OHD 26 ng/mL, body mass index (BMI) 26 kg/m^2, CD4$^+$ T lymphocyte count 520 cells/mm^3; 95% of participants were male, 60% self-identified as white, and 12% were current smokers. Baseline ART included 58% NNRTI, 34% PI, 17% raltegravir, 80% tenofovir, and 29% abacavir. The most common NNRTI was efavirenz (36%), and the most common PI was atazanavir (16%). The insufficient and sufficient groups differed at baseline only by median 25OHD level (insufficient median 20 ng/mL; sufficient 36 ng/mL; $P < .0001$). In addition, baseline 25OHD level was not associated with age, gender, race, current smoking status, BMI, or current ART use.

Week 12 Repletion Rates

After 12 weeks, 81% of participants (n = 66) achieved 25OHD ≥30 ng/mL (95% CI, 70%–88%). Our observed repletion success rate of 81% was not statistically different from the HIV-uninfected historical control rate of 85% ($P = .32$). Ten participants (8%) self-reported difficulty with adherence, but 7 (70%) of those participants still achieved week 12 25OHD ≥30 ng/mL. Thirteen participants reported adherence but failed to successfully replete. Mean baseline and week 12 25OHD values for participants with repletion success were 21 and 47 ng/mL (Figure 2), respectively, compared with 16 and 24 ng/mL for participants failing to replete. No adverse events or toxicities

Table 1. Baseline Clinical and Demographic Characteristics[a]

Variable	25OHD <30 ng/mL (n = 82)	25OHD ≥30 ng/mL (n = 40)	P Value
25OHD (ng/mL)	20 (15, 26)	36 (33, 42)	<.0001
Sex			
Female	5%	5%	.99
Male	95%	95%	
Race			
White	55%	70%	.11
Non-white	45%	30%	
Current smoker	11%	15%	.53
Age (years)	49 (41, 55)	49 (43, 56)	.85
BMI (kg/m²)	27 (25, 30)	26 (24, 29)	.38
CD4+ T lymphocyte count (cells/mm³)	485 (390, 681)	548 (403, 603)	.90
Current ART			
Entry inhibitor	4%	0%	.55
Integrase inhibitor	13%	23%	.20
NNRTI	59%	55%	.71
PI	35%	30%	.56
Abacavir	28%	30%	.82
Lamivudine	26%	30%	.61
Emtricitabine	65%	70%	.56
Tenofovir	77%	88%	.16
Comorbidities[b]			
Diabetes	5%	0%	.30
Hypertension	44%	38%	.50
Hyperlipidemia	33%	25%	.50
Cardiovascular disease	2%	0%	.99
Hypogonadism	18%	20%	.82
Hepatitis C	6%	0%	.17
Hepatitis B	7%	5%	.99
Bone disease	5%	5%	.97

Abbreviations: ART, antiretroviral therapy; BMI, body mass index; 25OHD, 25-hydroxyvitamin D; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

[a] Median and interquartile range or percentage.

[b] Determined by chart review.

were reported. No participant changed ART during the 12-week repletion phase.

Factors associated with week 12 25OHD level in bivariate analysis (P < .10) were as follows: older age (odds ratio [OR; per 10 years] = 1.78; 95% CI, .97–3.32; P = .06), higher baseline 25OHD level (OR = 1.14; 95% CI, 1.03–1.2; P = .009), white race (OR = 3.39; 95% CI, 1.05–10.87; P = .04), and current smoking status (OR = 0.25; 95% CI, .06–1.05; P = .06) (Table 2). No individual antiretroviral agents or classes were associated with success or failure of repletion.

Week 24 Maintenance Rates

All 66 participants with 25OHD ≥30 ng/mL at week 12 continued maintenance therapy with 2000 IU of vitamin D₃ daily. At week 24, 48 participants (73%; 95% CI, 65%–87%) maintained 25OHD ≥30 ng/mL. Fourteen participants (22%) had declines in 25OHD to <30 ng/mL. Seven participants reported difficulty with regimen adherence between weeks 12 and 24, 6 of whom still maintained 25OHD ≥30 ng/mL. Four participants (6%) were lost to follow-up. No adverse events were reported. No participant changed ART during the maintenance phase.

Median 25OHD levels for participants maintaining and failing to maintain 25OHD ≥30 ng/mL at week 24 were 42 and 26 ng/mL, respectively. In bivariate analysis (Table 2), the only factor associated with maintaining 25OHD ≥30 ng/mL at week 24 was tenofovir use (OR = 5.00; 95% CI, 1.37–18.23; P = .01). In contrast, abacavir use (OR = 0.23; 95% CI, .07–.82; P = .02) was associated with failure to maintain 25OHD levels at week 24. No other significant associations between ART use and 25OHD levels at week 24 were observed, including efavirenz use.

DISCUSSION

In this cohort of HIV-infected adults on suppressive ART, a standardized regimen of 50 000 IU D₃ twice weekly for 5 weeks followed by 2000 IU daily achieved statistically similar repletion rates compared with HIV-uninfected adults receiving similar vitamin D repletion for low bone mineral density [1]. Although the historical control groups were older and more likely to be female [22, 23], our data suggest that higher-dose repletion regimens may not be necessary for most HIV-infected persons. The efficacy of this regimen is further supported by our use of a conservative threshold for vitamin D sufficiency (25OHD >30 ng/mL), which could bias findings toward a null result compared with lower thresholds such as 20 ng/mL. Despite this conservative threshold, excellent repletion efficacy was achieved.

We did not observe associations between specific antiretroviral agents and baseline 25OHD levels in this analysis. Likewise, we did not observe associations between specific antiretroviral agents and success or failure to achieve 25OHD ≥30 ng/mL after 12 weeks, although our small sample size may have precluded our ability to detect associations between specific ART combinations and repletion rates. Efavirenz initiation has been associated with increased prevalence of vitamin D insufficiency [24]; however, switch from efavirenz to raltegravir was not associated with an improvement in 25OHD levels in participants remaining on tenofovir/emtricitabine [25]. Therefore, it is possible that traditional risk factors for vitamin D insufficiency are stronger determinants of baseline and postrepletion 25OHD levels than ART regimen. In addition, HIV-specific risk factors such as chronic inflammation and/or ongoing HIV replication may contribute more to vitamin D insufficiency than specific antiretrovirals [26], although assessing those mechanisms was beyond the scope of this study.

In the maintenance phase, most participants were able to maintain 25OHD ≥30 ng/mL for up to 24 weeks on 2000 IU daily, suggesting that this regimen may be sufficient for most

Table 2. Odds Ratios for Clinical and Demographic Factors Associated With Normalization of 25OHD Levels at Weeks 12 and 24

Variable	Week 12 OR (95% CI)	P Value	Week 24 OR (95% CI)	P Value
Age (per 10 years)	**1.78 (.97, 3.32)**	**.06**	0.73 (.36, 1.48)	.38
Male sex[a]	<0.01 (.00, ∞)	.98	<0.01 (.00, ∞)	.98
White race	**3.39 (1.05, 10.87)**	**.04**	0.78 (.23, 2.67)	.69
Current smoker	**0.25 (.06, 1.05)**	**.06**	0.85 (.09, 8.25)	.89
Baseline 25OHD per (ng/mL)	**1.14 (1.03, 1.25)**	**.009**	1.10 (.99, 1.23)	.06
BMI (per 10 kg/m^2)	1.19 (.45, 3.11)	.72	0.80 (.37, 1.71)	.56
CD4$^+$ T lymphocyte count (per 100 cells/mm^3)	0.98 (.77, 1.24)	.85	1.05 (.81, 1.36)	.70
Entry inhibitor	<0.01 (.00, ∞)	.98	0.57 (.05, 6.74)	.65
Integrase inhibitor	1.11 (.21, 5.70)	.90	2.60 (.30, 22.79)	.39
NNRTI	0.81 (.27, 2.50)	.72	0.66 (.19, 2.25)	.50
PI	1.26 (.39, 4.05)	.70	0.99 (.29, 3.42)	.98
Abacavir	1.21 (.35, 4.24)	.76	**0.23 (.07, .82)**	**.02**
Tenofovir	0.41 (.09, 2.00)	.27	**5.00 (1.37, 18.23)**	**.01**
Efavirenz	0.61 (.20, 1.83)	.38	1.64 (.45, 5.98)	.46

Abbreviations: 25OHD, 25-hydroxyvitamin D; BMI, body mass index; CI, confidence interval; NNRTI, nonnucleoside reverse transcriptase inhibitor; OR, odds ratio; PI, protease inhibitor.

[a] An exact point estimate cannot be computed due to low sample size for female participants.

Results in bold are statistically significant (P < .01).

HIV-infected adults on suppressive ART, particularly after receiving aggressive vitamin D repletion. We observed associations between both tenofovir use and successful 25OHD level maintenance and abacavir use and failure of 25OHD level maintenance in participants receiving 2000 IU D₃ daily. These specific associations have not previously been reported, and they may be confounded by other factors such as underreporting of adherence or chronic inflammation. However, factors specifically associated with maintenance of 25OHD levels after successful repletion are not well described, and these findings warrant further investigation.
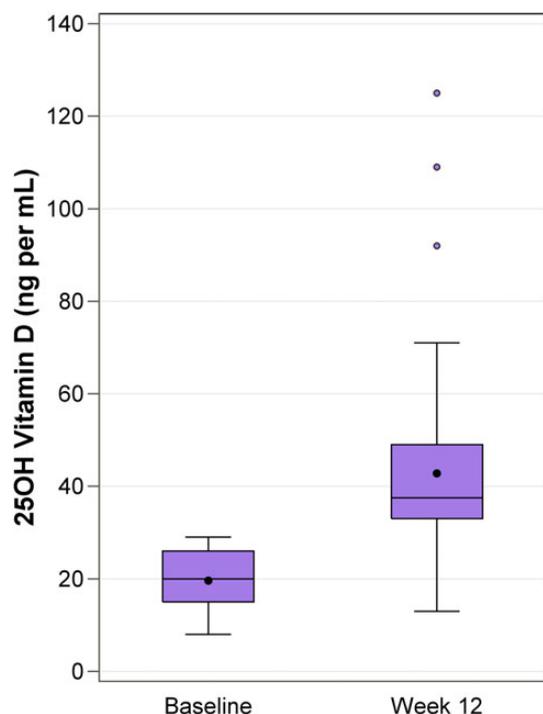
Limitations

This trial was prospective but open label and not randomized. However, given the high rates of vitamin D insufficiency in HIV-infected persons [3, 5], the documented associations between vitamin D insufficiency and both comorbid disease and mortality [3, 10, 11, 27], and the recommendation to screen for and treat vitamin D insufficiency in high-risk populations [20], randomization to placebo would not have been clinically appropriate. An additional limitation is that we did not require participants to keep adherence logs and could not collect droplet counts for feasibility reasons. However, participants were asked about adherence, and most participants were believed to be adherent, as evidenced by our repletion success rate. Study participants were also largely male and self-identified as white, and results may not be generalizable to women and those of non-white race. Finally, although our repletion regimen was identical to that of historical controls (50 000 IU twice weekly for 5 weeks), our maintenance regimen was slightly higher (2000 IU daily vs 1400 IU daily). The primary endpoint was to compare the repletion phase with historical controls and experts in the field suggested the maintenance doses were likely comparable (Adams, personal communication); however, we cannot exclude the possibility that differences in maintenance phase dosing slightly biased our results towards similar repletion rates.

Figure 2. Shown are the serum 25OHD levels before and after vitamin D repletion. Abbreviation: 25OHD, 25-hydroxyvitamin D.

CONCLUSIONS

An oral regimen of vitamin D_3 50 000 IU twice weekly for 5 weeks effectively repleted 25OHD levels to ≥30 ng/mL in 81% of participants in this cohort of HIV-infected subjects on suppressive ART, and efficacy was similar to that observed among HIV-uninfected historical controls. In addition, maintenance therapy with 2000 IU D_3 daily maintained 25OHD levels at ≥30 ng/mL for the majority of participants, and no adverse events occurred. Therefore, this regimen should be considered safe and effective for the repletion and maintenance of 25OHD levels in HIV-infected adults on a variety of suppressive ART regimens.

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