

No Benefit of Standard Vitamin D/Calcium Supplementation in HIV-infected Individuals

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Background

The prevalence of vitamin D deficiency (25-hydroxyvitamin D (25[OH] D) in HIV infected individuals ranges from 60 to 90% and is associated with female gender, black ethnicity and antiretroviral use [1-2]. Specifically, non-nucleoside reverse transcriptase inhibitors (NNRTI) and protease inhibitors (PI) interrupt normal 25OHD synthesis and metabolism via modulation of the cytochrome P450 system(s) that control hydroxylation of vitamin D and its metabolites [3-8].

The management of vitamin D deficiency is unclear and this is reflected in variations between guidelines. In the general population, the American Institute of Medicine recommends vitamin D 600 IU/day [9] whereas the US Endocrine Society recommends 1500-2000 IU/day [10]. For HIV infected individuals, the doses required are unknown [1]. We report week 48 data of a prospective, randomized, open-label trial investigating whether standard dose vitamin D supplementation increases 25[OH]D levels to within normal range and/or improves bone mineral density (BMD) in a cohort of HIV infected individuals stable on antiretroviral therapy with vitamin D deficiency.

Methods

Study design and study population

HIV-1 infected individuals aged between 18-65, stable on antiretroviral therapy with confirmed vitamin D deficiency (25 [OH] D <40 nmol/L or 16 ng/ml) were recruited. All subjects provided written informed consent. The study was approved by the National Research Ethics Service.

Intervention

Patients were randomised 1:1 to receive daily vitamin D3/Calcium carbonate supplementation (800 IU/3000 mg) [9], or no supplementation (control arm) for 48 weeks. Calcium, Phosphate, ALP, vitamin D binding protein, CD4 and CD38 cells were assessed at baseline, week 12, 24 and 48. At screening and week 48, dual energy X-ray absorptiometry (DXA) measurements were obtained using the Hologic and GE Healthcare Lunar iDXA bone densitometers with operators for both machines following a standardised protocol. Bone mineral density (expressed in g/cm²) of the lumbar spine (L1-L4 composite), the non-dominant total hip and the non-dominant neck of femur (NOF) were included in analysis. In addition, individuals completed a survey of dietary vitamin D intake and a pill count was carried out at baseline, week 24 and 48. Patients with confirmed

osteopenia or osteoporosis requiring replacement therapy were excluded.

The primary outcome was change in 25(OH) D at week 48.

Statistical analysis

Data management and analyses used Stata (version 14.0, StataCorp, College Station, TX). Baseline characteristics were summarised by randomised group. Linear regression was used to analyse the change from baseline to week 48 in primary and secondary outcomes between treatment arms. Final multivariate model included baseline measurement, season of recruitment, age, ethnicity and gender. All analyses were based on an intention-to-treat basis, statistical tests were two-tailed, p-values and confidence intervals were presented as appropriate.

Results

Study participants

30 individuals were randomised between October 2011 and December 2013 and one patient was lost to follow up. The mean age (SD) of participants was 44 years, 80% were male, 72 % white, 45% were receiving a PI based regimen, 48% a NNRTI and 7% an integrase inhibitor. The groups had similar clinical and demographic at baseline. Vitamin D adherence in the supplementation arm, assessed by pill count was 80% at week 48. Both groups had similar vitamin D levels at screening but at baseline the control group had lower vitamin D values (20.55 vs 10.5 ug/L). The mean change from baseline to week 48 was -5.02 ug/L in the intervention arm and 0.2 ug/L in the control arm (p=0.85). The adjusted mean percentage change between the arms in bone mineral density from baseline to week 48 was -0.01 (-0.16, 0.14) p=0.907 at the hip, and 0.01 (-0.22, 0.25) p=0.902 at the spine for supplementation arm compared to control arm (Table 1). There was no significant difference between the arms from baseline to week 48 in hip bone mineral density (p=0.907), spine bone mineral density (p=0.902), Calcium (p=0.36), phosphate (p=0.95), ALP (p=0.12), vitamin D binding protein (p=0.99) or immunological markers including CD4 (p=0.80), CD8:CD38 (p=0.77). No statistical association with efavirenz use and response to vitamin D supplementation was observed (p=0.50).

Adverse events

Twenty-nine adverse events were reported in 15 individuals on supplementation and 14 controls; and none were associated with

vitamin D replacement therapy and there was no difference between the groups (fisher's exact test p=0.215).

Primary outcome	Vitamin D supplement arm N=15		No-vitamin D arm N=14		Adjusted β coefficient (95% CI) between arms from baseline to week 48*	P-value
	Baseline [SD] or median [IQR]	Week 48 (mean or median)	Baseline (SD)	Week 48 (SD)		
25(OH)D ug/L	20.55 (10.37)	15.53 (9.83)	10.5 (5.55)	10.70 (6.34)	0.74 (-7.60, 9.08)	0.85
Bone mineral density (BMD) (g/cm ²)						
Hip TSC	-0.01 (0.88)	-0.01 (0.85)	-0.28 (0.79)	-0.28 (0.84)	-0.01 (-0.16, 0.14)	0.9
Hip ZCS	-0.06 (0.65)	-0.04 (0.66)	-0.20 (0.56)	-0.16 (0.59)	-0.04 (-0.12, 0.04)	0.32
Spine TSC	-0.17 (1.41)	-0.12 (1.49)	-0.68 (1.18)	-0.62 (1.13)	0.01 (-0.22, 0.25)	0.9
Spine ZCS	-0.26 (1.40)	-0.37 (1.46)	-0.51 (1.17)	-0.46 (1.06)	-0.13 (-0.60, 0.34)	0.56

SD: Standard Deviation; 25(OH)D: 25-hydroxy vitamin D; *Multivariate model comparing mean difference between arms adjusted for age, ethnicity, gender, season and baseline

Table 1: Multivariate linear regression for primary and secondary outcomes.

Discussion

Despite high rates of vitamin D insufficiency in HIV infected patients, the management remains unclear. In this cohort of HIV-infected adults on suppressive ART, a supplementation regimen of vitamin D3/Calcium carbonate (800 IU/3000 mg) once daily for 48 weeks did not achieve higher vitamin D levels than controls and failed to improve bone markers or bone mineral density.

The most effective dose of vitamin D/Calcium supplementation in HIV infected people observed to date is using 50,000 IU of vitamin D3 twice weekly for 5 weeks, then 8000 IU twice weekly to complete 24 weeks [11]. But with studies using smaller doses showing inconsistent benefit [12-14]. European AIDS Clinical Society guidelines recommend a vitamin D loading dose of 10,000 IU/day for 8-10 weeks followed by a maintenance dose of 800-2000 IU/day [15].

We did not observe any association between specific antiretroviral agents and response to vitamin D supplementation, although analysis is limited by small sample size [16].

A supplementation with a higher Vitamin D dose initiated in individuals starting an antiretroviral combination has been shown to

attenuate bone loss [17]. We did not observe any benefit in bone mineral density using vitamin D3/Calcium carbonate (800 IU/3000 mg). This may suggest that significant clinical benefits may need higher doses of supplementation and/or longer follow up.

Overall, we show that a standard vitamin D dose (with no loading dose) does not increase plasma 25 (OH) Vit D levels and should not be recommended. Further research to inform guidelines to manage vitamin D deficiency in HIV infected individuals is required.

Transparency Declarations

The authors declare that they have no conflict of interest.

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