Vitamin D Supplementation Does Not Affect Metabolic Changes Seen with ART Initiation

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Background

- Metabolic abnormalities, including insulin resistance and dyslipidemia, are common among HIV-infected persons and may worsen with initiation of antiretroviral therapy (ART).
- ART initiation with efavirenz (EFV) has been associated with less favorable changes in lipid concentrations compared to other non-nucleoside reverse transcriptase inhibitors (NNRTIs) and a greater increase in fasting glycemia compared to atazanavir/ritonavir in ACTG 5224s
- ART initiation with EFV also decreases 25-OH Vitamin D concentrations which may contribute to the high prevalence of vitamin D deficiency observed in HIV-infected populations.
- In the general population and in HIV-infected patients, vitamin D deficiency has been associated with dyslipidemia and insulin resistance. It is unclear whether the relationship is causal.
- Vitamin D supplementation trials examining glucose and lipid outcomes have had mixed results in the general population.
- Randomized trial data investigating the effect of vitamin D supplementation in HIV-infected persons on metabolic outcomes are limited and no study, to our knowledge, has examined the period of ART initiation.
- We have previously shown in a randomized, placebo controlled trial (ACTG A5280) that daily supplementation with vitamin D/calcium (4000 IU/1000 mg) given to HIV-infected individuals initiating ART with tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC)/EFV attenuated the loss in bone mineral density by approximately 50% over 48 weeks
- Here, we report the effect of vitamin D/calcium on metabolic outcomes in ACTG A5280

Objective

- To determine the effect of vitamin D/calcium supplementation on insulin resistance and lipids in HIV-infected persons initiating TDF/FTC/EFV

Methods

Study Design and Participants

- Randomized, double-blind, placebo-controlled, 48 week study to determine effects of vitamin D plus calcium supplementation in HIV-infected persons initiating TDF/FTC/EFV
- Randomization stratified by screening 25-OH vitamin D level (10-20 vs. 21-75 ng/mL)
- ART-naïve, HIV-infected adults with baseline 25 -OH Vitamin D between 10-75 ng/mL were eligible to enroll. Persons with a history of bisphosphonate use, fragility fracture, nephrolithiasis, hypercalcemia, recent steroid use, or serious intercurrent illness were excluded.

Intervention

- Vitamin D3 4000 IU/Ca++ 1000 mg or matching placebo

Metabolic Assessments (Baseline, 24 w, 48 w):

- Insulin Resistance: Homeostatic Model Assessment (HOMA-IR): [(fasting glucose (mg/dL) x fasting insulin (mU/L)/405
- Fasting Lipid Profile (Total Cholesterol, High Density Lipoprotein-cholesterol (HDL-c), Low Density Lipoprotein-cholesterol (LDL-c), Triglycerides)
- Waist Circumference (cm)
- Presence of Metabolic Syndrome (≥ 3 of the following: 1) Central obesity: Waist circumference ≥ 102 cm (male), ≥ 88 cm (female); 2) High triglyceride: ≥ 150 mg/dL ;3) Low HDL-c: HDL –c level< 40 mg/dL (male), < 50 mg/dL (female) ; 4) High blood pressure: Systolic ≥ 130 mmHg or diastolic ≥ 85 mmHg; 5) High fasting glucose: ≥ 110 mg/dL)

Data Analysis

•ITT approach limited to subjects with available data regardless of treatment change/discontinuation.

•Continuous Variables:
- •Stratified Wilcoxon rank sum tests for differences between treatment groups, stratified by screening 25-OH vitamin D
- •Wilcoxon signed-rank test for within treatment group change

•Categorical Variable: Stratified normal score tests for differences between treatment groups, stratified by screening 25 -OH vitamin D

• All tests are 2-sided at 5% significance level without adjusting for multiple comparisons

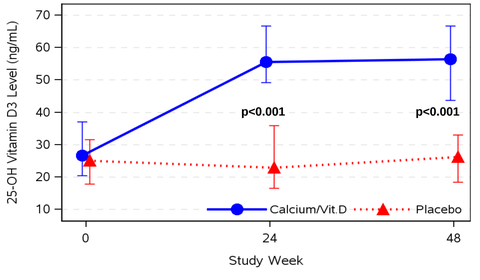
•Plots display median, Q1, Q3

Results

Table 1. Subject Characteristics at Baseline (N=165)

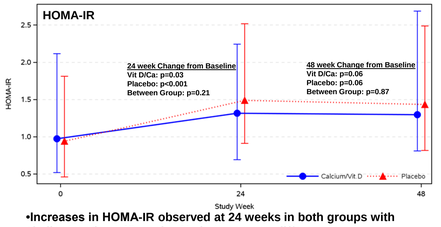
Parameter [Median (Q1, Q3)]	Vitamin D + Calcium (n=79)	Placebo (n=86)
Age in years*	36 (28, 47)	31 (25, 44)
Race/ethnicity White non-Hispanic Black non-Hispanic Hispanic Other	 28 (35%) 24 (30%) 23 (29%) 4 (6%)	 33 (38%) 30 (35%) 18 (21%) 5 (6%)
Male sex	72 (91%)	77 (90%)
BMI (kg/m^2)*	25.0 (22.5, 28.2)	24.0 (21.7, 27.2)
Plasma HIV RNA (log_{10} cp/mL)*	4.5 (4.1, 5.1)	4.5 (4.0, 5.1)
CD4 cell count (cells/mm^3)* < 200 cells/mm^3	339 (230, 500) 17 (22%)	342 (232, 454) 15 (17%)
Estimated daily Ca intake (mg)	813 (492, 1303)	811 (365, 1227)
Estimated daily Vit D intake (IU)	120 (62, 215)	137 (59, 279)

Figure 1. 25 OH Vitamin D over 48 Weeks



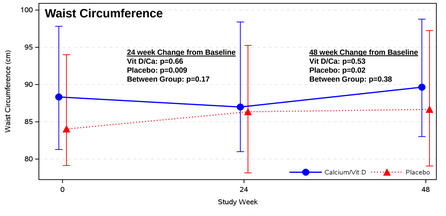
•Significant increases in the Vit D/ Calcium Arm at 24 and 48 weeks (p<0.001)
• Significant between-arm differences in changes in 25-OH Vitamin D levels from baseline to both weeks 24 and 48 (p<0.001).

Figure 2. Glucose Metabolism over 48 Weeks



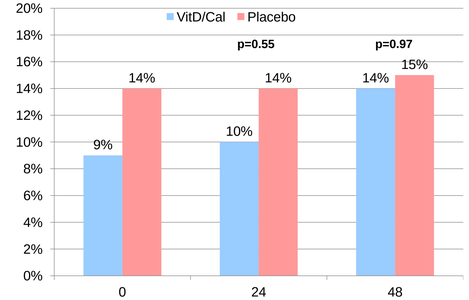
•Increases in HOMA-IR observed at 24 weeks in both groups with similar trends at 48 weeks. No between arm differences
•Similar results observed for insulin and glucose concentrations (data not shown)

Figure 3. Body Composition over 48 Weeks



•Increases in waist circumference in the Placebo group at 24 and 48 weeks
•No change in waist circumference was detected in the Vit D/Ca group
•No between group differences at either timepoint
•No changes in BMI in either group (data not shown)

Figure 4.Metabolic Syndrome Prevalence over 48 Weeks



•Compared to previous ACTG trials, the prevalence of metabolic syndrome prior to ART initiation was low.
(20% in 2247 HIV-infected persons at ART initiation: Krishnan, JAIDS, 2012)

•No significant between-group differences in metabolic syndrome prevalence at 24 and 48 weeks.

Table 2. Changes in Lipid Profile over 48 Weeks

Parameter	Baseline Values			Week 24 Values			Week 48 Values		
	n	VitD/Cal	Placebo	n	VitD/Cal	Placebo	n	VitD/Cal	Placebo
Total Chol (mg/dL)	162	161 (138,182)	156 (135,184)	154	**167* (151,192)**	**174* (154,201)**	141	**167* (151,191)**	**170* (152,192)**
HDL-c (mg/dL)	155	43 (34,50)	42 (33,49)	145	**47* (41,59)**	**49* (39, 61)**	134	**49* (40,58)**	**50* (39,60)**
LDL-c (mg/dL)	154	95 (80,112)	89 (72,115)	142	97 (78,115)	99 (79,124)	132	99 (84,115)	98 (79,116)
Triglycerides (mg/dL)	160	99 (65,127)	96 (73,116)	152	96 (72,140)	93 (73,140)	139	101 (77,147)	97 (68,142)

All values given as median (Q1,Q3), *significant change in parameter from baseline (P<0.01).

• Increases in total cholesterol and HDL-c were observed in both groups
• No changes in LDL-c or triglycerides were detected in either group
• There were no significant differences between groups in changes from baseline at weeks 24 and 48 (p≥0.17 for all)

Conclusions

- ART initiation with TDF/ FTC/EFV was associated with modest increases in fasting glucose, insulin resistance, and waist circumference in this metabolically healthy population of HIV-infected persons initiating ART.
- Although 25 OH vitamin D concentrations increased significantly with the vitamin D/calcium intervention, we observed no evidence that vitamin D supplementation impacts the metabolic changes observed with initiation of TDF/FTC/EFV over 48 weeks.
- Whether vitamin D supplementation would have different effects with other ART regimens or in patients with a higher prevalence of baseline metabolic abnormalities should be examined.

Acknowledgements

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