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Baseline vitamin D deficiency decreases the effectiveness of statins in HIV-infected adults on antiretroviral therapy

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Abstract

Objective—Vitamin D deficiency is common in HIV. Statins may increase vitamin D and it is unknown whether vitamin D modifies the effect of statins on cardiovascular disease.

Design—SATURN-HIV was a 96-week, randomized, placebo-controlled trial designed to evaluate the effect of rosuvastatin on immune activation and subclinical vascular disease in HIV-infected adults on antiretroviral therapy. This analysis focuses on the pre-specified secondary endpoint 25-hydroxyvitamin D [25(OH)D] concentrations.

Methods—Mixed effects linear modeling and ANOVA were used to assess the rosuvastatin effect on plasma 25(OH)D concentrations over time and to determine whether baseline vitamin D modifies the rosuvastatin effect on changes in outcomes over the trial.

Results—147 adults were randomized (72 to rosuvastatin, 75 to placebo); 78% were men, 68% African American, with mean age of 45 years. Baseline 25(OH)D concentrations were similar (overall mean 18 ng/ml) with 65% of participants below 20 ng/ml. Changes in 25(OH)D at 96 weeks were small and not significant within- or between-rosuvastatin and placebo groups. There were significant group by vitamin D status interactions for changes in LDL-cholesterol, proportion of patrolling monocytes expressing tissue factor (CD14dimCD16+TF+), lipoprotein-associated phospholipase A2 and common carotid artery intima media thickness at most time points. For each of these outcomes, the beneficial effects of rosuvastatin were either not apparent or attenuated in participants with 25(OH)D <20 ng/ml.

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Conclusion—While 25(OH)D did not change with rosuvastatin, baseline vitamin D deficiency decreased the effectiveness of rosuvastatin. Vitamin D supplementation may be warranted for deficient patients initiating statin therapy.

Keywords

Vitamin D; rosuvastatin; cardiovascular disease; inflammation; HIV infection

Introduction

Chronic HIV infection leads to accelerated atherosclerosis and higher risk of myocardial infarction compared to the general population^{1–3}. The recognition of this association is establishing HIV infection as risk factor for cardiovascular disease (CVD). Prevention efforts that have targeted this high risk group include administration of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors or statins which play an important role in CVD prevention in the general population even with normal low density lipoprotein (LDL)⁴. The immunomodulatory effects of statins make them an attractive strategy for disease prevention in HIV infection, a disease state characterized by chronic activation of the immune system. Indeed, we and others have shown that in HIV-infected adults on antiretroviral therapy without clinically apparent atherosclerotic heart disease, statins halt progression of common carotid artery intima media thickness (CCA IMT)⁵, reduce non-calcified coronary plaque volume and number of high risk coronary plaques⁶ and improve immune activation^{7,8} and vascular inflammation⁹. Although the improvement in subclinical vascular disease is likely due to the improvement in lipids and immune activation, a potential mediator of this outcome is the effect of statins on vitamin D levels. Rosuvastatin and other statins have been shown to increase vitamin D in HIV-uninfected populations^{10–16}. 7-dehydrocholesterol (7-DHC) is the direct precursor of both cholesterol and vitamin D, and it is thus possible that statins exert an effect on both cholesterol and vitamin D metabolism¹⁷.

Sufficient levels of vitamin D may be cardioprotective. Proposed mechanisms include the anti-inflammatory effects of vitamin D^{18–22} and effects on vasculature through modulation of myocardial and vascular smooth muscle cell growth^{23,24}. Clinically, vitamin D supplementation in adults with type 2 diabetes and in healthy controls increased flow mediated dilation (FMD) of the brachial artery, an established measure of endothelial function^{25,26}. Further, while the best-characterized sequelae of vitamin D deficiency involves the musculoskeletal system, a growing body of evidence suggests that low levels of vitamin D may adversely affect the cardiovascular system as well²⁷. Clinical studies have reported cross-sectional associations between lower vitamin D levels and hypertension^{28–30}, low HDL-cholesterol²⁸, coronary artery calcification^{31,32}, prevalent CVD^{33–36}, as well as, all-cause and cardiovascular mortality³³. In HIV-infected adults, we have previously shown that low vitamin D levels were associated with worse vascular disease³⁷.

Importantly, if statins increase vitamin D levels, this could provide immunomodulatory benefits that could improve CVD risk. On the other hand, low vitamin D levels could decrease the effectiveness of statins. In this study, we aimed to evaluate the effect of

rosuvastatin on 25-hydroxyvitamin D [25(OH)D] concentrations over time and whether vitamin D status alters the effect of rosuvastatin on select outcome measures that differed between groups in the SATURN-HIV study, a 96-week, randomized, placebo-controlled trial to evaluate the effect of rosuvastatin 10 mg daily on immune activation and subclinical vascular disease in HIV-infected adults on stable ART with LDL 130 mg/dL. Our hypotheses were that 25(OH)D concentrations would improve on rosuvastatin and that the beneficial effects of rosuvastatin would be greater in those with sufficient 25(OH)D concentrations at baseline.

Methods

Full eligibility criteria for SATURN-HIV may be found on clinicaltrials.gov (NCT01218802). In brief, participants were 18 years old with HIV-1 infection and on stable ART for at least three months with HIV-1 RNA <1000 copies/mL and fasting LDL 130 mg/dL. Additional entry criteria included proportion of CD8+ T-cells that express CD38 and HLA-DR 19% or high sensitivity C-reactive protein (hsCRP) 2 mg/L. Known coronary artery disease or diabetes mellitus or inflammatory conditions besides HIV were exclusionary. Randomization was to rosuvastatin 10 mg daily or matching placebo in a 1 to 1 ratio. This analysis focuses on a pre-specified secondary endpoint, 25(OH)D concentration, and two aims were assessed. First, we evaluated the impact of rosuvastatin on 25(OH)D concentrations over the 96-week study. Second, in a post hoc analysis, we determined if vitamin D status at baseline modified the effect of rosuvastatin on changes in the markers of subclinical vascular disease, immune activation, inflammation, lipids and insulin resistance that differed between groups over the study. In this trial, we have previously reported that compared to placebo rosuvastatin halted CCA IMT progression, improved LDL and oxidized LDL, improved markers of systemic and vascular inflammation including cystatin C, interferon γ inducible protein-10 (IP-10) and lipoprotein-associated phospholipase A2 (Lp-PLA2) and improved markers of immune activation including soluble CD14 (sCD14), proportion of tissue factor expressing patrolling monocytes and proportion of activated CD4+ and CD8+ T-cells^{5,8,38–40}. Insulin resistance measured by HOMA-IR worsened in the rosuvastatin group⁴¹. The protocol and written informed consent were approved by the Institutional Review Board of the University Hospitals Case Medical Center, Cleveland, Ohio, and registered on clinicaltrials.gov (NCT01218802).

Study evaluations

All participants underwent high resolution ultrasound scanning of the carotid arteries at 0, 48 and 96 weeks using a Philips iU22 with L9-3 MHz linear array transducer (Philips Healthcare; Andover, MA, USA) following the consensus protocol of the American Society of Echocardiography⁴² and CCA IMT was measured as previously described⁴³.

Additionally, a 12-hour fasting blood draw was performed at 0, 24, 48 and 96 weeks. Plasma samples (drawn in tubes with spray EDTA) were cryopreserved at -80°C until analysis. Plasma 25(OH)D concentrations were determined using the IDS-iSYS automated platform using the chemiluminescent technique (Immunodiagnostic Systems, Inc., Fountain Hills, AZ). The laboratory participates in the DEQAS quality assessment scheme and the

NIST/NIH Vitamin D Quality Assurance Program (VitDQAP) to ensure external quality control. Assessment of total vitamin D status is best determined by measuring 25(OH)D concentrations as the serum half-life is long, i.e. three weeks, and production in the liver is primarily dependent on substrate concentration⁴⁴. Cellular markers of immune activation were phenotyped from PBMCs by flow cytometry as previously described⁸. CD4+ and CD8+ T-cells expressing CD38 and HLA-DR (activated) were quantified as a percentage of the overall CD4+ and CD8+ lymphocyte population, respectively. Monocyte subsets including CD14+CD16+ (inflammatory) and CD14dimCD16+ (patrolling) were quantified as a percentage of the overall monocyte population. Monocyte subset expression of tissue factor (TF) was also quantified. Soluble markers of monocyte activation (sCD14), systemic (IP-10) and vascular inflammation (Lp-PLA2) and oxLDL were measured by ELISA (R&D Systems, Minneapolis, MN, USA for all except diaDexus, Inc., CA, USA for Lp-PLA2 and Mercodia, Uppsala, Sweden for oxLDL). Cystatin C was measured by particle enhanced immunonephelometric assay on a BNII nephelometer (Siemens, Munich, Germany). Homeostasis model of insulin resistance (HOMA-IR) was calculated using the following formula: $\text{HOMA-IR} = \text{fasting glucose (mg/dl)} \times \text{fasting insulin } (\mu\text{U/ml}) / 405^{45}$.

Statistical analysis

Baseline characteristics are described overall by mean $\pm$ standard deviation (SD) for continuous variables and by frequency and percent for categorical variables. Differences between rosuvastatin and placebo groups were tested using unpaired t-tests or Wilcoxon Rank Sum tests as appropriate for continuous variables and by Chi-Square tests, Fisher's Exact tests or Pearson Exact Chi-Square tests as appropriate for categorical variables.

For the initial aim of this analysis, the primary outcome was absolute change in 25(OH)D concentrations over 96 weeks. Changes over 24 and 48 weeks were tested as well. Paired t-tests or Wilcoxon signed rank tests and unpaired t-tests or Wilcoxon rank sum tests as appropriate were used for within-and between-rosuvastatin and placebo group comparisons, respectively. Next, to measure the effect of rosuvastatin on repeated measurements of 25(OH)D concentrations over time and for controlling the effects of confounding factors, we used linear mixed effects models with random intercept and random slope. We used unstructured variance-covariance matrix for the two random effects and estimated the model parameters using restricted maximum likelihood (REML) method. Because the distribution of the dependent variable, 25(OH)D, was skewed, this variable was transformed by taking the natural logarithm prior to analysis. To test if randomization group had an effect on 25(OH)D concentration over time, we looked at the significance of the randomization group by time interaction term. Age, sex, race, nadir CD4+ cell count, HIV-1 RNA level at baseline, efavirenz status, protease inhibitor status and month of enrollment (to account for the effect of season) were adjusted for in the multivariable model.

The second aim of this analysis was to evaluate if vitamin D status at baseline modified the effect of rosuvastatin on outcomes that differed between the rosuvastatin and placebo groups in the SATURN-HIV study. ANOVA was used to model absolute change in each outcome over 24 (if available), 48 and 96 (if available) weeks. Independent variables included in each model were randomization group, vitamin D status at baseline [baseline 25(OH)D <20 ng/ml

= 1; baseline 25(OH)D level = 20 ng/ml = 0] and a group by vitamin D status interaction. Stratum specific estimates for mean change in the outcome are provided where the interaction was significant. Because most outcome variables were skewed, each was transformed by taking the natural logarithm prior to analyses.

For all above analyses, participants were analyzed in the group to which they were randomized. Analyses of follow-up data were restricted to participants with full outcome information at each time point. All statistical tests were two-sided and considered significant if $p < 0.05$. Analyses were performed using SAS v. 9.4 (The SAS Institute, Cary, North Carolina, USA).

Results

Overall, 147 adults were enrolled and randomized (72 to rosuvastatin, 75 to placebo) in the SATURN-HIV study. Participant flow through 96 weeks has been previously published⁵. Twenty-eight participants (9 on rosuvastatin, 19 on placebo) withdrew or were lost to follow-up prior to week 96; none due to study drug-related adverse events.

Baseline characteristics

Demographics and other clinical characteristics were similar between randomization groups at baseline. Of the 147 participants at baseline, 78% were men, 68% were African American and 29% were Caucasian. Mean $\pm$ SD age was 45.4 years $\pm$ 9.9 years and body mass index (BMI) was 28.1 $\pm$ 6.5 mm/kg². Mean Framingham risk score at baseline was low at 5 $\pm$ 5% 10-year risk and LDL, HDL and triglyceride levels were 94.4 $\pm$ 24.9, 48.6 $\pm$ 15.9 and 151.4 $\pm$ 109.9 mg/dl, respectively. Eight percent had chronic hepatitis C, 63% of participants were current smokers and an additional 16% were smokers in the past. Mean current and nadir CD4⁺ cell counts were 640 $\pm$ 300 and 200 $\pm$ 146 cells/mm³, respectively, and known duration of HIV infection was 12.2 $\pm$ 6.9 years. All participants were on ART by design (51% on protease inhibitor- and 49% on efavirenz-containing regimens) with a mean ART duration of 7.1 $\pm$ 5.2 years. Seventy-six percent had HIV-1 RNA level <48 (range 20–600) copies/ml.

Baseline plasma 25(OH)D concentrations were similar at baseline. Overall, mean $\pm$ standard deviation and median (interquartile range) plasma 25(OH)D concentrations were 18 $\pm$ 8.3 ng/ml and 16.1 (11.7, 22.2), respectively, with 88.9% of participants below 30 ng/ml (23.1% had 25(OH)D <30, but = 20 ng/ml, ie were vitamin D insufficient, 53.1% had 25(OH)D <20, but = 10 ng/ml, ie were vitamin D deficient, and 13.6% had 25(OH)D <10 ng/ml, ie were severely vitamin D deficient). The minimum and maximum 25(OH)D concentrations were 6 and 48.2 ng/ml, respectively. Table 1 shows baseline demographics for rosuvastatin and placebo groups by vitamin D status.

Changes in 25(OH)D

Over the 96-week study 25(OH)D remained consistently low in both the rosuvastatin and placebo groups (Figure 1). There was a small, but statistically significant decrease in 25(OH)D level from baseline to week 48 in the rosuvastatin group (mean absolute change in 25(OH)D -2.6 $\pm$ 8.2 ng/ml; $p < 0.01$) that was different from placebo (+1.0 $\pm$ 8.5 ng/ml;

$p=0.51$) ($p=0.02$ between groups). Using longitudinal mixed modeling, there was a trend toward significance for the effect of randomization group on 25(OH)D level over 96 weeks ($p=0.07$ for group by time interaction) although the changes in 25(OH)D concentrations over time were small in both the rosuvastatin and placebo groups. Results remained similar when adjusting for baseline age, sex, race, nadir CD4+ cell count, HIV-1 RNA level, efavirenz use, protease inhibitor use and month of enrollment ($p=0.06$ for group by time interaction in adjusted model).

Effect of baseline vitamin D deficiency on rosuvastatin effectiveness

There were significant randomization group by vitamin D status interaction terms for 0–24 ($p=0.02$), 0–48 ($p<0.01$) and 0–96 ($p=0.02$) week changes in LDL. Table 2 shows the mean changes in each outcome for the rosuvastatin and placebo groups by vitamin D status where the interaction term was significant. Stratum specific estimates for changes in LDL reveal that at each time point, those participants with 25(OH)D concentrations ≥ 20 ng/ml at baseline sustained a greater decrease in LDL cholesterol with rosuvastatin than those who were vitamin D deficient.

Similarly, the interaction was significant for 0–24 ($p<0.01$) and 0–96 ($p=0.04$) week change in proportion of patrolling monocytes expressing tissue factor (CD14dimCD16+TF+ monocytes) and trended towards significance for 0–48 week ($p<0.1$) change. The improvement in proportion of CD14dimCD16+TF+ monocytes with rosuvastatin was greater and significantly different from placebo only for those with 25(OH)D concentration ≥ 20 ng/ml at baseline. Other significant randomization group by vitamin D status interactions were apparent for 0–48 ($p=0.02$) and 0–96 ($p=0.02$) week changes in Lp-PLA2. Lp-PLA2 improved with rosuvastatin regardless of vitamin D status, but the mean differences between rosuvastatin and placebo were greater in those with 25(OH)D concentrations ≥ 20 ng/ml.

Last, and importantly, the interaction was significant for 0–96 ($p<0.01$) week change in CCA CIMT and trended towards significance for 0–48 ($p=0.07$) week change. The stratum specific estimates reveal that the improvement in CCA CIMT with rosuvastatin was significant only for those with 25(OH)D concentrations ≥ 20 ng/ml. Figure 2 shows the differences in means between the rosuvastatin and placebo groups by vitamin D status where the interaction term was significant. No effect modification by vitamin D status was apparent for changes in the selected markers of systemic inflammation (sTNF-RII, IP-10, cystatin C), the soluble marker of monocyte activation, sCD14, the proportion of activated CD4+ or CD8+ T cells (CD38+HLADR+ T cells), oxidized LDL or HOMA-IR.

Discussion

In this 96-week randomized, placebo-controlled trial of HIV-infected adults on ART, we have shown that 25(OH)D concentrations did not improve with rosuvastatin. However, baseline vitamin D deficiency in this patient group did modify the effect of rosuvastatin on several of the outcomes that differed between groups in this study including changes in LDL, proportion of tissue factor expressing patrolling monocytes, Lp-PLA2 and CCA IMT. The beneficial effects of rosuvastatin on these outcomes were not apparent or were

attenuated in vitamin D deficient participants. To our knowledge, this is the first study to report potentially clinically significant interactions between vitamin D status and rosuvastatin on outcomes other than the cholesterol-lowering effect in HIV.

7-dehydrocholesterol (7-DHC) is the direct precursor of both cholesterol and vitamin D¹⁷. It is possible that metabolism of vitamin D and cholesterol are related as epidemiologic studies have found that low vitamin D levels are significantly associated with increased LDL⁴⁶, increased triglycerides and decreased HDL^{28,47}. 3-hydroxy-3 methylglutaryl coenzyme A (HMG-CoA) reductase catalyzes HMG-CoA to mevalonate which is a direct precursor to 7-DHC⁴⁸. Inhibition of this enzyme by HMG-CoA reductase inhibitors or statins may alter the synthesis of vitamin D₃. While studies are mixed, several statins, including rosuvastatin, have been shown to paradoxically increase vitamin D levels in different populations^{10–16}. In a prospective cohort study of 91 hyperlipidemic adults not previously treated with lipid-lowering agents, 8 weeks of rosuvastatin increased mean 25(OH)D from 14 to 36 ng/ml ($p<0.001$)¹³. Further, in a small study by Wilczek et al, there appeared to be a dose-response effect, ie a higher dose of simvastatin lead to a greater increase in vitamin D than the lower dose comparator¹⁵. Although, most studies showing an improvement in vitamin D status with statins were small, single arm or active-control studies, ie comparing two different statins without a placebo control. In our study, 25(OH)D concentrations did not improve in the rosuvastatin group and, in fact, decreased a little over the 96-week study. Other studies have shown similar results^{49–54}. In the Atherosclerosis Prevention in Pediatric Lupus Erythematosus (APPLE) trial, a 3-year randomized, placebo controlled trial of atorvastatin in over 200 children and young adults with systemic lupus erythematosus (SLE), 25(OH)D concentrations did not change appreciably and were similar to the placebo group over the course of the study⁵⁴. It is possible that higher dose statin treatment is required to see this effect or that vitamin D levels remain low due to an alternative mechanism, eg chronic inflammation or immune activation in disease states such as HIV and SLE.

While statins may not improve vitamin D status, interestingly, sufficient vitamin D levels may work synergistically to modulate the effects of statins on their pleiotropic effects. In a small study (N=69), hyperlipidemic adults on stable doses of statins were randomized to vitamin D supplementation or placebo for 6 months. Reductions in total cholesterol, triglyceride levels and LDL were significantly greater in the vitamin D group⁵⁵, results that were consistent with prior research⁵⁶. In vitro, vitamin D₃ and its metabolites inhibit cholesterol synthesis by inhibition of HMG-CoA reductase activity in an effect that is concentration dependent⁵⁷. Consistent with this, in our study, participants with 25(OH)D concentrations ≥ 20 ng/ml sustained a greater decrease in LDL cholesterol with rosuvastatin than those who were vitamin D deficient.

There is biologic rationale for why vitamin D may work synergistically with statins to lower inflammation as well. There is mounting evidence that vitamin D plays an important role in the modulation of the immune system and that vitamin D has a potent anti-inflammatory effect. In healthy women, 25(OH)D concentrations have been found to be inversely related to tumor necrosis factor-alpha (TNF- α) concentrations, even after controlling for body fat mass, menopausal status, age and hormonal contraceptive use⁵⁸. In vitro, vitamin D receptors are expressed constitutively or after immune stimulation on most immune cells,

including antigen presenting cells, such as dendritic cells, and T and B lymphocytes⁵⁹. Vitamin D maintains equilibrium between T helper 1 and 2 cells by inhibiting production of interleukin-12, a cytokine that plays an important role in activation and differentiation of T helper 1 cells, perhaps by down-regulation of nuclear factor-kappa B activation^{18,19}. The active form of vitamin D, 1,25(OH)₂D, also inhibits interleukin-2 and interferon-gamma production from T lymphocytes at the transcription level²², interleukin-6, -2 and -1 production from antigen presenting cells²¹, TNF-induced adhesion molecule and e-selectin expression in endothelial cells^{20,60} and TNF-induced tissue factor expression on monocytes⁶¹. Congruent with this, the improvement in proportion of patrolling monocytes expressing tissue factor (CD14dimCD16+TF+ monocytes) with rosuvastatin was greater and significantly different from placebo only for those with 25(OH)D concentrations ≥ 20 ng/ml at baseline in our study. On the other hand, there was no effect modification by vitamin D status in the inflammatory marker changes in this trial. However, given above, it is possible that with vitamin D supplementation and statin therapy, there could be an additive anti-inflammatory effect and this should be studied.

Last, it is possible that vitamin D may act synergistically with statins to improve CVD risk as well. Cardioprotective effects of vitamin D include: inhibition of vascular smooth muscle proliferation, modulation of the immune system by up and down-regulation of cytokines as described above and inhibition of the renin-angiotensin system. Vascular smooth muscle and endothelial cells express receptors for vitamin D and have the ability to convert circulating 25(OH)D to 1,25(OH)₂D⁶². Subsequently, 1,25(OH)₂D regulates the growth and proliferation of vascular smooth muscle cells and cardiomyocytes²⁴. Additionally, 1,25(OH)₂D directly suppresses renin gene expression^{63,64}. Studies in knockout mice confirm that the absence of vitamin D receptor activation leads to tonic up regulation of the renin-angiotensin system with the development of hypertension and left ventricular hypertrophy^{65,66}. While vitamin D supplementation studies have failed to show a benefit in terms of myocardial infarction and stroke risk^{67–69}, in our study, changes in both Lp-PLA2, an important marker of vascular inflammation and CVD risk independent of other factors^{70,71}, and CCA IMT, an established measure of subclinical vascular disease⁷², with rosuvastatin, differed depending on vitamin D status. Similar results were shown in the APPLE trial referenced above regarding effect modification by vitamin D status on IMT changes with atorvastatin⁵⁴. Again, this suggest that in diseases with heightened inflammation such as HIV and SLE, this strategy may be more beneficial than in the general population.

Strengths of this study include the randomized, placebo-controlled study design, large number of outcomes evaluated and clinically relevant patient population, i.e. HIV-infected adults on ART. However, because this study was not designed to test for effect modification, we may not have detected all relevant interactions due to limited power. We did look at stratum specific estimates for all outcomes to see if the rosuvastatin effect was different and this was not apparent. Further, only patients with fasting LDL ≥ 130 mg/dL and with evidence of heightened inflammation were included. As a result, the findings may not be generalizable to all HIV-infected individuals.

In conclusion, vitamin D status modifies the effect of rosuvastatin on several outcomes that differed between groups in the SATURN-HIV study including changes in LDL, proportion of patrolling monocytes expressing tissue factor, Lp-PLA2 and CCA IMT such that the beneficial effects of rosuvastatin on these outcomes were not apparent or were attenuated in vitamin D deficient participants. Because vitamin D deficiency is common in HIV^{73,74}, further study is needed to see if vitamin D supplementation concurrent with statin administration improves outcomes in this subgroup.

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	Entry (N=147)	Week 24 (N=136)	Week 48 (N=128)	Week 96 (N=119)
Rosuvastatin	19.6 ± 9.5	18.7 ± 10.7	17.3 ± 9.4	18.6 ± 9.3
Placebo	16.5 ± 6.8	17.7 ± 8.8	17.7 ± 9.8	18.9 ± 8.1

Figure 1. 25-hydroxyvitamin D levels over time by group

Circle and square symbols and values in the table show the mean 25(OH)D levels in ng/ml for each group at each time point. Error bars in the figure represent the 95% confidence intervals around the means. The standard deviation of each mean is show in the table.

Figure 2. Difference between means for outcomes that differed by vitamin D status

The symbols represent the mean difference in change in the outcome listed over the time period listed between rosuvastatin and placebo groups. The error bars show the 95% confidence interval around the means. A mean difference less than zero favors the rosuvastatin group.

Figure 3.
Possible mechanisms for the interaction between vitamin D status and statins

Table 1

Baseline demographics in rosuvastatin and placebo group by vitamin D status

	Rosuvastatin		Placebo	
	Vitamin D n=29	20 Vitamin D <20 n=43	Vitamin D n=20	20 Vitamin D <20 n=55
Male	25 (86)	33 (77)	17 (85)	40 (73)
African American	15 (52)	35 (81)	9 (45)	41 (74)
Caucasian	12 (41)	8 (19)	11 (55)	12 (22)
Other	2 (7)	0 (0)	0 (0)	2 (4)
Age, years	47.7 ± 9.4	43.8 ± 8.7	50.3 ± 8.8	43.6 ± 10.8
BMI, mm/kg ³	26.7 ± 5.7	29 ± 6.7	26.2 ± 4.4	28.8 ± 7.2
Framingham score, %	5.7 ± 5	4.6 ± 4.7	6.3 ± 4.5	4.4 ± 4.2
LDL, mg/dl	91.3 ± 23.3	92.7 ± 25	92.6 ± 28.2	97.9 ± 24.7
HDL, mg/dl	48.2 ± 15.3	48.8 ± 17.4	48.8 ± 13.1	48.7 ± 16.3
Triglycerides, mg/dl	198.4 ± 164.2	126.5 ± 89.9	143.7 ± 64.7	149 ± 96
Hepatitis C	4 (14)	1 (2)	3 (15)	4 (7)
Current smokers	16 (55)	27 (63)	10 (50)	40 (73)
Current CD4+, cells/mm ³	680 ± 244	619 ± 313	657 ± 322	628 ± 314
Nadir CD4+, cells/mm ³	198 ± 164	207 ± 160	152 ± 109	206 ± 145
Duration of HIV, years	13.8 ± 6.1	10.3 ± 6.6	15.8 ± 6.4	11.6 ± 7.2
ART duration, years	8.2 ± 5.3	6.2 ± 5.2	9 ± 5.4	6.6 ± 5
HIV-1 RNA < 48 cp/ml	22 (76)	33 (77)	18 (90)	39 (71)
On efavirenz	9 (31)	21 (49)	8 (40)	27 (49)
25(OH)D, ng/ml	29 ± 7.2	13.3 ± 3.8	25.4 ± 5.3	13.2 ± 3.5

Values shown are mean ± standard deviation for continuous variables and frequency (percent) for categorical variables.

BMI, body mass index; LDL, low density lipoprotein; HDL, high density lipoprotein; ART, antiretroviral therapy; 25(OH)D, 25-hydroxyvitamin D

Table 2
Mean change in outcomes that differed by vitamin D status for rosuvastatin and placebo groups

	Rosuvastatin ¹	Placebo ¹	Mean difference between groups	P-value between groups	P-value for Interaction
LDL					
<i>0–24 wk change</i>					
Vitamin D <20	–0.2595	0.0183	–0.2777	<0.01	0.02
Vitamin D ≥20	–0.4792	0.0748	–0.5541	<0.01	
<i>0–48 wk change</i>					
Vitamin D <20	–0.2183	0.0223	–0.2406	<0.01	<0.01
Vitamin D ≥20	–0.4864	0.0862	–0.5726	<0.01	
<i>0–96 wk change</i>					
Vitamin D <20	–0.1859	–0.0425	–0.1434	0.06	0.02
Vitamin D ≥20	–0.4866	–0.0063	–0.4803	<0.01	
%CD14dimCD16+TF+					
<i>0–24 wk change</i>					
Vitamin D <20	–0.2217	–0.2227	0.0009	0.99	<0.01
Vitamin D ≥20	–0.6044	–0.0195	–0.5848	<0.01	
<i>0–48 wk change</i>					
Vitamin D <20	–0.3921	–0.1853	–0.2069	0.09	0.1
Vitamin D ≥20	–0.7335	–0.1579	–0.5757	<0.01	
<i>0–96 wk change</i>					
Vitamin D <20	–0.3218	–0.4372	0.1154	0.41	0.04
Vitamin D ≥20	–0.6427	–0.2481	–0.3946	0.05	
Lp-PLA2					
<i>0–24 wk change</i>					
Vitamin D <20	–0.1162	–0.0224	–0.0938	0.01	0.14
Vitamin D ≥20	–0.1186	0.0683	–0.1869	<0.01	
<i>0–48 wk change</i>					
Vitamin D <20	–0.1797	–0.0859	–0.0938	0.02	0.02
Vitamin D ≥20	–0.1589	0.1037	–0.2627	<0.01	
<i>0–96 wk change</i>					
					0.02

	Rosuvastatin ¹	Placebo ¹	Mean difference between groups	P-value between groups	P-value for Interaction
Vitamin D <20	-0.2473	-0.1572	-0.0901	0.01	
Vitamin D ≥ 20	-0.2947	-0.0236	-0.2711	<0.01	
CIMT					
<i>0-48 wk change</i>					
Vitamin D <20	0.016	0.0243	-0.0083	0.57	0.07
Vitamin D ≥ 20	-0.0304	0.0243	-0.0547	0.01	
<i>0-96 wk change</i>					
Vitamin D <20	0.0293	0.027	0.0023	0.89	<0.01
Vitamin D ≥ 20	-0.0192	0.0641	-0.0833	<0.01	

¹Values shown are mean absolute change from baseline in log-transformed outcome.