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Effect of rosuvastatin on plasma coenzyme Q10 in HIV-infected individuals on antiretroviral therapy

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Abstract

BACKGROUND—Coenzyme Q10 (CoQ10) deficiency has been associated with statin-induced myopathy, and supplementation with CoQ10 may reduce inflammation markers. The effects of statins on CoQ10 and its anti-inflammatory properties have not been investigated in HIV-positive patients.

OBJECTIVE—The objectives of this study were to examine the effect of rosuvastatin on CoQ10 and CoQ10/LDL ratio over 24 weeks SATURN-HIV trial, explore the associations between CoQ10 levels and markers of vascular disease, inflammation, and immune activation, and assess whether changes in CoQ10 affected the anti-inflammatory effects of statin therapy or were associated with myalgia symptoms.

METHODS—This was a secondary analysis of the SATURN-HIV trial, a 96-week randomized clinical trial of 10mg daily rosuvastatin vs. placebo in HIV-infected patients on antiretroviral therapy. We assessed the statin treatment effect on CoQ10 levels and CoQ10/LDL ratios and whether changes in these markers were related to myalgias. Relationships between CoQ10, subclinical vascular disease, and biomarkers of inflammation and immune activation were explored using Spearman correlations and multivariable regression models.

RESULTS—Overall, 147 patients were included. Median age was 46 years; 78% were male, 68% African American. At baseline, CoQ10 levels and CoQ10/LDL ratio were modestly correlated with markers of HIV disease, immune activation, and carotid distensibility. After 24 weeks of statin therapy, CoQ10 levels decreased ($p=0.002$ for between group difference) and CoQ10/LDL ratio increased ($p=0.036$). In the statin treatment arm, we did not find evidence of a relationship between changes in CoQ10 or CoQ10/LDL ratio and changes in markers of inflammation or immune activation. There was a borderline statistically significant association between changes in CoQ10 and myalgia symptoms [OR 4.0 per 0.1mg/L decrease in CoQ10, $p=0.07$].

CONCLUSION—Twenty-four weeks of 10mg daily rosuvastatin decreases CoQ10 concentration and increases CoQ10/LDL ratio in HIV-infected patients on antiretroviral therapy.

Keywords

Coenzyme Q10; rosuvastatin; HIV; inflammation; myalgias

INTRODUCTION

Statins—3-Hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors—are widely used to lower serum cholesterol and reduce cardiovascular mortality in both primary and secondary prevention^{1,2}. It is also well-established that statins lower plasma Coenzyme Q10 (CoQ10) levels^{3–10}. CoQ10 is a naturally occurring quinolone that is an integral part of the electron transport chain and oxidative phosphorylation in the mitochondria¹¹. CoQ10, in its reduced form, acts as an antioxidant providing protection for cell membranes¹². Because of evidence that CoQ10 deficiency can cause peripheral myopathy^{10, 13–14}, there has been a longstanding concern that statin-induced myopathy may be mediated in part by CoQ10 deficiency. Although pre-statin CoQ10 levels predict the risk of myalgias, clinical trials of oral CoQ10 supplementation have had mixed results^{10, 14–18}.

Interestingly, studies have also demonstrated that CoQ10 lowers inflammatory markers when orally supplemented, including tumor necrosis factor- α (TNF- α), interleukin-6 (IL-6), oxidized low-density lipoprotein (LDL) and high-sensitivity C-reactive protein (hs-CRP)^{19–22}. A CoQ10-mediated increase in inflammation may explain the lack of statin benefit in patient with heart failure²³, though the observational studies linking CoQ10 levels to heart failure outcomes are conflicting^{24–25}. There is also limited evidence that CoQ10 supplementation may improve endothelial function in healthy volunteers²⁶.

Chronic HIV infection is characterized by residual inflammation, immune activation, profound endothelial dysfunction, and high cardiovascular risk despite effective antiretroviral therapy (ART)²⁷, yet little is known about the relationships between CoQ10, inflammation, and vascular disease in HIV. Small, single-center studies have been published describing conflicting results about the effect of CoQ10 in HIV-infected individuals^{28–30}. One study conducted before effective ART showed no statistically significant difference in CoQ10 levels between HIV-infected patients and uninfected controls²⁸. More recently, there is evidence that CoQ10 supplementation may ameliorate the neurotoxicity and endothelial dysfunction associated with the use of mitochondrial toxic ART^{31–32}. No study has examined CoQ10 changes in response to statin therapy in chronic HIV infection.

To this end, the primary objective of this study was to examine the effect of rosuvastatin on CoQ10 and CoQ10/LDL ratio over 24 weeks in the Stopping Atherosclerosis and Treating Unhealthy Bone with Rosuvastatin in HIV (SATURN-HIV) trial³³. Second, we explored associations between CoQ10 levels and markers of vascular disease, inflammation, and immune activation at baseline. Third, we assessed whether changes in CoQ10 affected the anti-inflammatory effects of statin therapy or were associated with myalgia symptoms.

METHODS

Study Design

This study was a secondary analysis of the recently completed SATURN-HIV trial. SATURN-HIV was a randomized, double-blind placebo-controlled trial designed to measure the effect of rosuvastatin on markers of cardiovascular risk and skeletal bone health in patients with well-treated HIV infection. All subjects were 18 years of age, on stable ART for 3 months, with HIV-1 RNA level 1000 copies/ml. Additional entry criteria included LDL cholesterol <130mg/dL and evidence of heightened inflammation and/or T-cell activation (high sensitivity C-reactive protein (hsCRP) >2.0mg/dL and/or CD8+CD38+HLA-DR+ T-cells 19%). Full inclusion/exclusion criteria can be found at clinicaltrials.gov (NCT01218802). Randomization was conducted by the primary investigational pharmacist at 1:1 to active rosuvastatin 10 mg daily vs. matching placebo. Randomization was stratified by protease inhibitor use and by the presence or absence of coronary artery calcification and osteopenia at baseline. The study was approved by the Institutional Review Board of University Hospitals Case Medical Center (Cleveland, OH), and all subjects signed a written consent before enrollment.

Demographics, medical history, and clinical variables were obtained at the baseline visit. HIV-1 RNA and CD4+ T-cell count were obtained as part of routine clinical care. Venous blood was drawn after a 12-hour fast at baseline and 24 weeks. Lipoproteins, insulin, glucose, and creatinine were measured at the University Hospitals clinical laboratories. Insulin resistance was calculated from fasting glucose and insulin using the homeostatic model assessment of insulin resistance (HOMA-IR). Peripheral blood mononuclear cells (PBMCs) were separated by centrifugation with Ficoll-Hypaque and were cryopreserved until analyzed by flow cytometry in batch. Frozen plasma samples were stored at -80°C and analyzed in batch.

CoQ10, Inflammation, and Immune Activation

CoQ10 concentrations were measured from frozen plasma using high performance liquid chromatography (Quest Diagnostics; Madison, NJ, USA). HsCRP was measured by particle enhanced immunonephelometric assay on a BNII nephelometer (Siemens; Munich, Germany). Other soluble biomarkers of inflammation [IL-6 and TNF- α receptors I and II (sTNFR-I and II)] and monocyte activation [soluble CD14 and CD163] were measured by enzyme-linked immunosorbent assay (R&D Systems, Minneapolis, Minnesota). Interassay coefficients of variation ranged from 0.4 to 18%.

Monocytes and T-cells were phenotyped by flow cytometry as previously described²⁸. Three monocyte subsets: (1) CD14+CD16+, (2) CD14dimCD16+, and (3) CD14+CD16- were each quantified as a percentage of the overall monocyte population. T-cell activation was quantified as the percentage of CD4+ or CD8+ cells that expressed both CD38 and HLA-DR. PD1 expression on CD4+ and CD8+ cells was measured as a marker of T-cell exhaustion.

Ultrasound Measurement of Subclinical Vascular Disease

Common carotid artery intima-media thickness (CCA-IMT) and brachial artery endothelial function (flow-mediated dilation [FMD] and hyperemic velocity-time integral [VTI]) were measured by ultrasound using semiautomated edge detection software (Medical Imaging Applications LLC, Coralville, Iowa) as previously described³⁴. Carotid distensibility was measured with semiautomated edge detection software from 10-beat ultrasound cine loops. The diameter of the distal 1 cm of the right carotid artery was measured in systole (Ds) and diastole (Dd). Blood pressure was obtained at the time of carotid ultrasound to determine the pulse pressure (PP). Carotid distensibility was calculated using the same formula $[(2 \times (Ds - Dd) / Dd) / PP]$ used in the Women's Interagency Health Study and the Multicenter AIDS Cohort Study and is reported in units of $10^{-6} \times N-1 m^2$ ³⁵⁻³⁶.

Statistics

This was a secondary analysis of a clinical trial using data from the baseline and week 24 study visits. The analyses of treatment effect were performed using intent-to-treat principles based on randomized treatment assignments. Baseline characteristics of the study participants were described using median and interquartile ranges for continuous variables of frequency and percent for categorical variables.

Comparisons of baseline characteristics by group were made using unpaired t tests, Wilcoxon rank-sum tests, or Fisher exact tests as appropriate. Zero to 24 week changes in CoQ10 and CoQ10/LDL among those assigned to statin versus placebo were compared using t tests with assumption of unequal variances. The relationship between changes in CoQ10 levels and odds of developing myalgia symptoms was assessed with logistic regression. Separately for baseline CoQ10 levels and CoQ10/LDL ratio, we used Spearman correlation coefficients to test associations with traditional cardiovascular risk factors, HIV disease characteristics, markers of inflammation and immune activation, and ultrasound markers of subclinical vascular disease. We constructed scatter plots and used linear regression to explore the associations of 24 week changes in CoQ10 level and CoQ10/LDL ratio with 24 week changes in inflammation and immune activation markers. Two biomarkers of interest (IL-6 and hs-CRP) were strongly associated with CoQ10 changes in univariate analyses, but appeared to be driven primarily by a small number of outliers. For comparison, we therefore repeated the regression models after excluding these outliers.

All statistical tests were two-sided and considered significant at a level of $p < 0.05$. Analyses were performed using SAS version 9.2 (SAS Institute, Cary, North Carolina).

RESULTS

Of the 202 subjects screened for the SATURN-HIV study between March 2011 and August 2012, 147 were enrolled: 72 were randomized to the rosuvastatin (10 mg) arm and 75 to the placebo arm. The characteristics of the 55 patients who screened out and the 11 (5 statin; 6 placebo) patients who were lost to follow-up in the first 24 weeks of the study have been described previously³⁷⁻³⁸.

Baseline characteristics of study participants are described in Table 1. There were no baseline differences between the treatment and placebo arm ($p < 0.05$). Briefly, the overall median age was 46 (IQR 40–53) years, 78% of patients were male, and 68% were African-American. Participants had low risk lipid profiles and calculated 10-year Framingham scores.

CoQ10 and markers of CVD risk and inflammation

Table 2 shows the correlations of CoQ10 concentrations and CoQ10/LDL ratio with traditional CVD risk factors, HIV-specific factors, biomarkers of inflammation and immune activation, and subclinical vascular disease. As expected, CoQ10 concentrations were modestly positively correlated with LDL cholesterol levels ($r = 0.208$, $p = 0.012$) and there was a stronger, negative correlation between CoQ10/LDL ratio and LDL levels ($r = -0.441$, $p < 0.0001$). Interestingly, both CoQ10 concentration and CoQ10/LDL ratio were negatively correlated with Caucasian race but were not correlated with age, gender or smoking status.

CoQ10 and CoQ10/LDL were positively correlated with HIV disease duration and undetectable HIV-1 viremia, and negatively correlated with CD4+ T-cell count. Despite modest positive correlations with activated T-cells and proinflammatory monocyte phenotypes [T-cell activation (CD38+HLA-DR+ on CD4+ and CD8+), T-cell exhaustion (PD1+CD38+HLA-DR+), and “patrolling” monocytes (CD14dimCD16+)], there were no baseline correlations with soluble markers of systemic inflammation or immune activation. Finally, carotid distensibility was negatively correlated with both CoQ10 concentrations and CoQ10/LDL ratio; but no correlation was seen with carotid IMT or brachial FMD.

CoQ10 Changes on Statin

At baseline, median (IQR) CoQ10 concentration was borderline statistically higher in the placebo group [0.77(0.60–1.04) vs. 0.89(0.67–1.12) mg/L, statin vs. placebo; $p = 0.06$] but CoQ10/LDL ratio was similar [0.008(0.006–0.012) vs. 0.009(0.007–0.012); $p = 0.27$]. Twenty-four week changes in CoQ10 and CoQ10/LDL ratio are displayed in Figures 1A and 1B, with the treatment effects analysis displayed below the graphs. As hypothesized, absolute CoQ10 levels declined after 24 weeks of statin therapy. Because of a relatively larger reduction in LDL cholesterol (–28% vs. +3.8%; statin vs. placebo, $p < 0.01$), the CoQ10/LDL ratio increased slightly. Overall, there was a statistically significant correlation between changes in CoQ10 and changes in LDL ($r = 0.341$, $p < 0.001$) which was borderline significant when the statin treatment arm was analyzed separately ($r = 0.228$, $p = 0.06$).

CoQ10 and Changes in Biomarkers of Inflammation

Among those assigned to statin therapy, 0–24 week changes in IL-6 and hs-CRP were associated with CoQ10/LDL changes in univariate linear regression models ($p < 0.001$); other biomarkers shown in Table 2 were not associated (all $p > 0.05$). In further analyses, however, these associations were driven primarily by a small number of outliers ($n = 2$ with IL-6 change > -20 pg/mL and $n = 4$ with hs-CRP change > -20 µg/mL). When outliers were excluded, there was no evidence of an association ($p = 0.86$ for IL-6 and $p = 0.79$ for hs-CRP).

CoQ10 and Muscle Symptoms

Four participants in the statin arm (5.6%) experienced low-grade myalgia symptoms (Grade 1 or 2) within the first 24 weeks of the study. Only one of these four developed clinically significant myalgias (Grade 3) with mild elevation of creatinine kinase at week 5 requiring cessation of study drug. His symptoms quickly resolved and he continued to be followed on study but off study drug. Baseline CoQ10 concentration was not associated with higher odds of developing myalgia symptoms during the study ($p=0.42$); however, there was a borderline statistically significant inverse association between changes in CoQ10 and myalgia symptoms [OR 4.0 per 0.1mg/L decrease in CoQ10, $p=0.07$]. Twenty-four week changes in CoQ10 were unrelated to changes in creatinine kinase or aspartate transaminase (AST) concentrations ($p > 0.4$).

DISCUSSION

In this study, we present the first evidence that statin therapy is associated with reductions in plasma CoQ10 and increases in CoQ10/LDL ratio in the HIV-infected population. Despite modest correlations between CoQ10 and biomarkers of inflammation and immune activation, we did not find any evidence of an association between changes in CoQ10 on statin therapy and changes in inflammation markers. These findings may be relevant for the management of cardiovascular disease in patients with HIV-infection or other chronic inflammatory conditions.

We used both CoQ10 and CoQ10/LDL ratio in this study. Approximately 60% of CoQ10 is transported via the LDL molecule; therefore, large reductions in LDL may significantly affect the concentrations of free CoQ10 in the blood³⁹. This can be corrected by using the CoQ10/LDL ratio. Studies are conflicting regarding the effect of statins on CoQ10/LDL ratio, though some have demonstrated an increase in the ratio^{3, 6–7,39}.

The changes in CoQ10 and CoQ10/LDL in our study are consistent with those seen in studies of HIV-negative individuals. A study in heart failure patients using the same dose of rosuvastatin showed a 27–51% change at 12 weeks in CoQ10.⁴⁴ A smaller study of the general population using rosuvastatin 3 mg demonstrated only a 2% decrease of CoQ10 at 20 weeks.⁴⁵ Our study conducted over a 24 week period demonstrated a 24% change. Although this is the first study on HIV patients, our study did not have an HIV-uninfected control group, and thus we cannot definitively say whether HIV-infection is associated with any more or less change in CoQ10 compared to the general population.

The decrease of CoQ10 is mediated by the inhibition of the conversion of HMG-CoA to mevalonic acid in the sterol biosynthesis pathway. This sterol precursor is shared by both cholesterol and ubiquinone. As reported previously, the 25% reduction in LDL cholesterol over 24 weeks in SATURN-HIV was somewhat lower than the ~45% reduction that would be expected for rosuvastatin 10mg in the general population^{38,40}. Despite this modest reduction in LDL, the CoQ10/LDL ratio still increased in our study.

To our knowledge, no prior study has evaluated the effect of statin therapy on CoQ10 levels in the context of any chronic inflammatory disorder. Yet, prior studies have suggested that

both statins and CoQ10 supplementation may reduce inflammation. The anti-inflammatory properties of statins have been extensively studied and have been reviewed previously⁴¹. The anti-inflammatory effects of CoQ10 are relatively less well-studied^{19–22,42–43}, and even fewer clinical studies have been performed. In one clinical study, Lee et al demonstrated that high dose CoQ10 supplementation appears to raise CoQ10 and reduce plasma IL-6 concentrations in subjects with coronary artery disease; however, there was no correlation between changes in CoQ10 and changes in IL-6 in their study¹⁹. Similarly, in subjects with multiple sclerosis CoQ10 supplementation reduced plasma IL-6 and TNF- α ²².

In the SATURN-HIV trial, 10mg of daily rosuvastatin led to early and sustained reductions in several biomarkers of immune activation such as soluble CD14 (a marker of monocyte activation), proportion of non-classical “patrolling” monocytes expressing tissue factor, and cell-surface markers of T-cell activation and exhaustion; yet the effect on circulating inflammatory cytokines and acute phase reactants was less consistent^{37, 38}. We hypothesized that adverse effects on CoQ10 or the CoQ10/LDL ratio may underlie the blunted statin effect on these markers of inflammation, relative to cellular markers of immune activation. Although, we did observe an inverse relationship between changes in CoQ10/LDL and changes in IL-6 and hs-CRP in initial analyses, this was driven primarily by a small number of outliers. When these outliers were excluded, there was no evidence of any relationship. It is unknown whether co-supplementation with oral CoQ10 in an HIV-infected population might augment the anti-inflammatory effect of statin therapy; however, our results suggest that the effect is likely to be very small.

The incidence of myalgias over 24 weeks in the statin group was 5.6%. This rate of myalgia symptoms is comparable to other rosuvastatin trials such as JUPITER or CORONA^{23,44}. There was no relationship between baseline CoQ10 and odds of developing muscle symptoms, although there was a borderline statistically significant association with changes in CoQ10 level over 24 weeks. Because of a small number of myalgia events, our study had limited power to detect a significant relationship.

CoQ10 levels and CoQ10/LDL were both inversely associated with carotid distensibility at baseline, but there were no other significant relationships with measures of subclinical vascular disease. The clinical significance of the relationship with carotid stiffness is unclear but should be investigated in future studies.

A major strength of our study is the randomized clinical trial design and extensive phenotyping of study participants in terms of inflammation, immune activation, and subclinical vascular disease. Although SATURN-HIV is the largest placebo controlled trial of statin therapy conducted in treated HIV infection to date, we may have lacked power to detect clinically significant relationships between CoQ10 and myalgia symptoms. The majority of our population had suppressed HIV-1 viremia on ART and was predominately African American and male, which may affect the generalizability of our results.

In conclusion, 24 weeks of rosuvastatin 10 mg daily reduces CoQ10 concentrations but modestly raises CoQ10/LDL ratio in a population of HIV-infected subjects on ART. In this study, changes in CoQ10 and CoQ10/LDL ratio on statin were not associated with

changes in inflammation or immune activation. The relationships between CoQ10, statins, and inflammation could be further explored in larger clinical studies of patients with treated HIV-infection or other chronic inflammatory conditions.

Abbreviations

CoQ10	Coenzyme Q10
HIV	Human Immunodeficiency Virus
LDL	Low Density Lipoprotein
TNF-α	Tumor necrosis factor- α
IL-6	Interleukin-6
hs-CRP	High-sensitivity C-reactive protein
ART	Antiretroviral therapy
CCA-IMT	Common carotid artery intima-media thickness
FMD	flow-mediated dilation
VTI	Hyperemic velocity-time integral

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Figure 1. Absolute Change of (A) CoQ10 and (B) CoQ10/LDL Ratio from Baseline to 24 Weeks. Values in figure represent median values and error bars represent interquartile range.

Table 1

Baseline characteristics of study participants by treatment group.

	Rosuvastatin (n = 72)	Placebo (n = 75)
Demographics and Traditional CVD Risk Factors		
Age, y	45 (41–51)	47 (39–53)
Male sex	81%	76%
African American Race	69%	67%
Body Mass Index, kg/m ²	27 (23–30)	27 (23–30)
HDL cholesterol, mg/dL	47 (38–58)	46 (37–57)
LDL cholesterol, mg/dL	96 (76–107)	97 (77–121)
Current Smoking	60%	67%
Framingham risk score, % 10-year risk	3 (1–7)	4 (1–7)
HIV Parameters		
HIV Duration, y	11 (6–17)	12 (6–19)
Current CD4+ Count, cells/uL	608 (440–948)	627 (398–853)
Nadir CD4+ count, cells/uL	173 (84–312)	190 (89–281)
Undetectable viral load, <50 copies/mL	78%	77%
Total ART Duration, y	5.2 (3.1–9.9)	5.9 (3.3–9.6)
Current PI use	50%	48%
PI duration, y	3.9 (1.1 – 8.8)	3.3 (0.2 – 6.7)
Current AZT/D4T use	5.6%	5.3%
AZT/D4T Duration, m	40.5 (5.5 – 82.3)	25.0 (0 – 64.5)
Subclinical Vascular Disease		
Mean-mean CCA-IMT, um	664 (624, 772)	670 (602, 752)
Carotid Distensibility, 10-6 x N-1 x m ²	24 (19–32)	23 (19–30)
FMD, %	3.9 (2.1–6.2)	4.0 (2.0–6.0)
Hyperemic VTI (cm)	80 (60, 94)	76 (67, 95)

Data presented as a median (interquartile range) or percentage. There were no statistically significant differences between groups ($p > 0.05$). PI = protease inhibitor; AZT = zidovudine; D4T = stavudine; TNF- α RII = tumor necrosis factor alpha receptors I/II; CCA-IMT = common carotid artery intima-media thickness; FMD = flow-mediated dilation of the brachial artery; VTI, velocity time integral.

Table 2

Correlations of baseline CoQ10 and CoQ10/LDL with traditional risk factors, HIV parameters, markers of inflammation and immune activation, and subclinical vascular disease.

	CoQ10		CoQ10/LDL	
	Spearman r	p value	Spearman r	p value
Demographics and Traditional CVD Risk Factors				
Age	0.122	0.141	0.021	0.804
Male Gender	−0.001	0.989	0.108	0.195
Caucasian Race	−0.217	0.008 *	−0.285	0.0005 *
Body Mass Index	0.089	0.284	0.005	0.950
LDL	0.208	0.012 *	−0.441	<0.0001 *
HDL	0.468	0.445	0.092	0.270
Current smoker	−0.070	0.402	0.021	0.798
HIV Parameters				
HIV duration	0.204	0.013 *	0.172	0.037 *
Absolute CD4 count	−0.181	0.028 *	−0.146	0.078
Nadir CD4 count	−0.059	0.477	−0.068	0.412
Viral load <50 copies/mL	0.159	0.055	0.189	0.022 *
PI duration	0.108	0.247	0.104	0.265
AZT/D4T duration	−0.063	0.546	−0.052	0.621
Inflammation and Immune Activation				
IL-6	−0.042	0.616	0.034	0.680
hsCRP	0.042	0.610	−0.007	0.937
TNF- α RI	−0.140	0.090	−0.105	0.207
TNF- α RII	0.013	0.872	0.077	0.353
Oxidized LDL	−0.141	0.093	−0.163	0.051
sCD163	0.085	0.306	0.123	0.138
sCD14	−0.038	0.648	0.032	0.700
CD8+DR+38+ T-cells	0.142	0.090	0.168	0.045 *
CD4+DR+38+ T-cells	0.187	0.025 *	0.161	0.054 *
CD8+PD1+DR+38+ T-cells	0.133	0.113	0.196	0.019 *
CD4+PD1+DR+38+ T-cells	0.195	0.020 *	0.209	0.012 *
CD14+CD16+ monocytes	−0.104	0.219	−0.059	0.488
CD14+CD16- monocytes	0.003	0.968	−0.028	0.739
CD14dimCD16+ monocytes	0.207	0.013 *	0.178	0.034 *
Subclinical Vascular Disease				
Mean-mean CCA-IMT	−0.001	0.988	−0.071	0.394
Carotid Distensibility	−0.276	0.0007 *	−0.178	0.031 *

	CoQ10		CoQ10/LDL	
	Spearman r	p value	Spearman r	p value
FMD	0.063	0.446	-0.056	0.503
Hyperemic VTI	-0.006	0.942	-0.010	0.909

*
p < 0.05.

PI = protease inhibitor; AZT = zidovudine; D4T=stavudine; TNF- α RII = tumor necrosis factor alpha receptors I/II; CCA-IMT= common carotid artery intima-media thickness; FMD= flow-mediated dilation of the brachial artery; VTI, velocity time integral.