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Statin Therapy decreases NT-proBNP in HIV: Randomized Placebo-Controlled Trial

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Abstract

Objective—HIV-infected participants are at a higher risk of cardiovascular disease (CVD). N-terminal pro-B-type natriuretic peptide (NT-proBNP) is a significant predictor of CVD in the general population and is associated with mortality in HIV.

Design and Methods—The 96-week Stopping Atherosclerosis and Treating Unhealthy Bone with Rosuvastatin in HIV (SATURN-HIV) trial randomized 147 patients on stable antiretroviral therapy (ART) with LDL-cholesterol <130mg/dL and without overt heart failure to 10 mg daily rosuvastatin or placebo. We measured NT-proBNP levels by ELISA. Baseline and changes in NT-proBNP were compared between groups. Spearman correlation was used to explore relationships between baseline NT-proBNP, inflammation and CVD risk markers. Multivariable analyses were conducted to assess associations with NT-proBNP levels.

Results—Median age was 46 years, 80% were men, 69% were African American and 46% were on protease inhibitors. At baseline, median (Q1, Q3) NT-proBNP was higher in the rosuvastatin group than placebo [41(20,66.5) vs. 25 pg/mL (11, 56); p=0.012)]. Baseline NT-proBNP correlated with bulb and common carotid artery intima media thickness, coronary calcium score, IL-6 and cystatin C. After 96 weeks, median NT-proBNP decreased significantly in the rosuvastatin group versus placebo (-1.50 vs. +4.50 pg/mL, p=0.041). Within the rosuvastatin group, changes in NT-proBNP were negatively correlated with changes in insulin resistance and total limb fat.

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Author Contributions:

GM designed the study and obtained funding. SD and Y.J. provided statistical support. All authors contributed to data analysis and writing of the manuscript.

Conclusions—Rosuvastatin reduces plasma NT-proBNP in HIV-infected participants on ART. NT-proBNP correlated with several measures of CVD risk, independent of inflammation markers.

Keywords

inflammation; cardiovascular disease; statin therapy; NT-proBNP

Introduction

B-type natriuretic peptide (BNP) is a 32-amino acid polypeptide secreted by ventricular myocytes during periods of increased ventricular stretch and wall tension. BNP plays an important role in the regulation of volume, osmosis, pressure regulation and sodium balance[1]. After secretion, the BNP precursor is split into the biologically active peptide and the more stable N-terminal fragment (NT-proBNP). Circulating levels of BNP or NT-proBNP are predictive of left-ventricular dysfunction[2-4] and adverse clinical outcomes in patients with acute coronary syndromes[5]. Because these peptides are directly released from cardiomyocytes during ischemia, it is believed that their levels are also relevant to the vascular events [6].

Many prospective studies have investigated the relationship of lower levels of BNP to CVD events in community-based studies of subjects without overt heart failure. A meta-analysis of 40 long term prospective cohort studies reported on the predictive role of BNP and NT-proBNP on CVD[7]. Overall, there was an almost 3 fold increase in risk of CVD (any fatal or nonfatal myocardial infarction, stroke, transient ischemic attack or heart failure) for participants with the highest baseline BNP or NT-proBNP.

Data on NT-proBNP in patients with HIV are limited. In the Strategies for Management of Anti-Retroviral Therapy Study (SMART) higher NT-proBNP was associated with greater risk of CVD independently of traditional CVD risk factors and inflammatory markers[8]. In the Women's Interagency HIV Study (WIHS), women with HIV had higher BNP levels than uninfected controls[9], and BNP was independently associated with greater mortality[10]. HIV-infected patients have been shown to have a higher prevalence of diastolic dysfunction and higher left ventricular mass index when compared to uninfected controls and higher plasma BNP was associated with higher left ventricular mass index but not with diastolic dysfunction[11].

In the HIV population, antiretroviral therapy (ART) has significantly decreased morbidity and mortality for patients with HIV[12]; however when compared to the general population, they remain at a higher risk of cardiovascular disease (CVD) [13-16] The causes are multi-factorial and could include specific antiretroviral agents, HIV viral replication, and enhanced chronic inflammation and immune activation. As the HIV population ages, it is imperative to identify effective therapies to attenuate CVD risk. Beyond their effect of cholesterol lowering, statins, or 3 hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors can reduce inflammation and reactive oxygen species and can improve endothelial function[17,18]. Data on the effect of statins on BNP levels in the HIV-uninfected populations is sparse and focuses on the therapeutic use in established heart failure. In the setting of heart failure, several studies have shown that plasma NT-proBNP levels are lower in

patients who are taking statins[19,20]. To our knowledge, there are no data on the effect of statins on NT-proBNP levels in HIV infected participants or if NT-proBNP levels are associated with enhanced immune activation and inflammation in this population. In SATURN-HIV, a 96-week statin study in HIV-infected participants on stable ART, we have shown that after 24 weeks of rosuvastatin there was a significant decrease in markers of inflammation, monocyte activation and cystatin C[21-23] in HIV-infected participants on antiretroviral therapy. Here, we present the results of an analysis of the statin therapy on NT-proBNP, and the relationship between NT-proBNP, inflammation, and CVD risk measures in HIV-infected adults on stable ART.

Materials and Methods

Study Design

SATURN-HIV is a 96-week randomized, double-blind, placebo controlled study designed to measure the effect of rosuvastatin on markers of cardiovascular risk, skeletal health, and immune activation in HIV disease[22]. The study was reviewed and approved by the Institutional Review Board of University Hospitals Case Medical Center, Cleveland, Ohio. Written informed consent was provided by all participants. The study is registered on clinicaltrials.gov (NCT01218802). Participants were randomized 1:1 to rosuvastatin 10 mg daily vs. matching placebo. All participants were ≥18 years of age, with HIV-1 infection on stable ART for at least 3 months with cumulative ART duration of at least 6 months, HIV-1 RNA <1000 copies/mL, fasting LDL-cholesterol (LDL-C) ≤130 mg/dL and triglyceride ≤500 mg/dL. Additionally, participants were required to have evidence of either heightened T-cell activation, identified as the proportion of CD8+ T cells that expressed CD8+CD38+HLA-DR+ ≥19%, or levels of high-sensitivity C-reactive protein (hs-CRP) ≥2 mg/L. Participants were excluded if they had a history of coronary disease or diabetes, were pregnant or lactating, or had an active infectious or inflammatory condition,

STUDY EVALUATIONS

At entry, week 48 and 96, fasting (> 12 hours) blood draws were obtained for real time measurements of renal and lipid profiles, glucose and insulin levels. Additionally, blood was processed and plasma, serum and peripheral blood mononuclear cells were stored for measurement of NT-proBNP, soluble and cellular markers of immune activation and markers of systemic inflammation and coagulation. HIV-1 RNA levels and CD4+ cell counts were drawn as part of clinical care and measures closest to study visits were used for analysis. The homeostatic model assessment of insulin resistance (HOMA-IR) was calculated as described[24]. Glomerular filtration rate was estimated using the 2009 Chronic Kidney Disease Collaboration creatinine-based equation (eGRFcr)[25]. NT-proBNP was measured by quantitative sandwich ELISAs (Siemens Healthcare, Newark, New Jersey, USA), coefficient of variation 3-4.4%.

Inflammation and soluble immune activation markers—Soluble plasma biomarkers of monocyte activation (soluble CD14 and soluble CD 163), systemic inflammation [hs-CRP, IL-6, tumor necrosis factor-alpha receptor I (sTNFR-1)], cystatin C and coagulation (D-dimer) were measured as previously described[21,22].

Cellular markers of monocyte and T-cell activation—Monocyte and T-cells were phenotyped by flow cytometry as previously described[21].

Body composition and cardiovascular measures—Body composition measures, including lean mass, trunk and limb fat were derived from a whole body DEXA scan (Lunar Prodigy Advance (GE Healthcare). Ten-year Framingham risk score was determined using a published risk calculator[26].

At entry and week 96, coronary artery calcium score was measured by a non contrast CT scan, as described previously[27]. B mode ultrasound scan of the carotid arteries was performed using a Philips iU22 ultrasound system with an L9-3 MHz linear array transducer. Mean-mean and mean-max common carotid artery intima media thickness (CCA-IMT) were measured as described previously[28]. Flow-mediated dilation (FMD) of the brachial artery was calculated as the percentage change in brachial artery diameter from baseline to 60 s post reactive hyperemia[28].

Statistical Analysis

The major objectives of this study were to compare changes from baseline to 96 weeks (primary outcome) and baseline to 48 weeks in pro-BNP levels between groups. Secondary objectives were to evaluated changes in pro-BNP within groups over both 48 and 96 weeks, to examine associations between pro-BNP and markers of systemic inflammation, immune activation, coagulation as well as measures of cardiovascular risk and to explore predictors of change in pro-BNP.

Demographics, clinical indices and HIV-related factors are presented overall and by group at baseline. Median and interquartile range (IQR) are reported for continuous variables and frequency and percent for nominal variables. Absolute and percent or relative changes from baseline to week 48 and from baseline to week 96 in pro-BNP levels were determined. All baseline variables as well as endpoints were compared between groups using unpaired t-tests or Wilcoxon Rank Sum tests as warranted by distribution for continuous variables and by Chi-Square tests, Fisher's Exact tests, or Pearson Exact Chi-Square tests as appropriate for categorical variables. Within-group changes were tested using paired t-tests or Wilcoxon Signed Rank tests as appropriate for the distribution.

Spearman correlation analysis was utilized to assess the relationships between baseline and relative change over 96 weeks in pro-BNP , markers of inflammation, immune activation, coagulation and cardiovascular risk as well as clinically relevant demographic and HIV-related factors (continuous variables only). Next, multivariable linear regression was employed to answer three questions (1) what baseline variables are independently associated with pro-BNP; (2) what variables independently predict relative change in pro-BNP over 96 weeks; (3) does pro-BNP independently predict CIMT after adjustment for clinically relevant variables, as well as, markers of inflammation, immune activation and coagulation. For each of these questions, separate multivariable models were constructed. For the first model, baseline pro-BNP was the outcome and all those variables with $p<0.1$ in the correlation analysis were considered for inclusion. Stepwise selection was utilized to construct the final model keeping only those variables with $p<0.05$. For the second model

where relative change over 96 weeks in pro-BNP was the outcome, randomization group, all those variables with $p<0.1$ in the correlation analysis and clinically relevant variables regardless of statistical significance were included in the final model. For the final question, we constructed a series of models where baseline CIMT was the outcome. Each model included pro-BNP level and the following clinically relevant variables: age, gender, total lean body mass (g), $eGFR_{cr}$ (ml/min/1.73m^2), framingham score and ARV duration (per month). To this model each marker of inflammation and immune activation marker was added in turn to assess whether these variables were independently associated with the outcome or if the parameter estimate for pro-BNP changed or was no longer significant.

All analyses were initially performed using intent-to-treat principles based on randomized treatment assignment which used all available data. Modifications to randomized treatment and missing values were ignored. As-treated analyses did not differ from intent-to-treat analyses; therefore, only the former data are presented. All statistical tests were two-sided and considered significant with $p<0.05$. Analyses were performed with SAS version 9.3 (SAS Institute, Cary, NC).

RESULTS

Baseline characteristics

Overall, 123 out of the 147 SATURN population had stored plasma samples available for BNP measurements and were included in the present analysis. Demographic information and baseline characteristics of the 123 participants are displayed in Table 1; except for prevalence of hepatitis C and HOMA-IR levels which were higher in the placebo arms, all other indices were similar between groups ($p>0.05$). Overall, the median age of the participants was 46 years; 80% were men, 67% were African American and BMI was 27. Tenofovir and protease inhibitors were used in 87% and 48% of participants, respectively. At baseline, NT-proBNP levels were higher in the statin group [median (Q1, Q3) NT-proBNP level in placebo group was 25 pg/mL (11, 56) and in the statin group was 41pg/mL (20, 66.50) ($p= 0.012$)].

Baseline Associations with NT-proBNP levels

At baseline, baseline NT-proBNP was associated with several demographics and clinical parameters including age, total lean mass, Framingham risk score and creatinine clearance. NT-proBNP was also positively with some markers of systemic inflammation including IL-6 and cystatin C (table 2). HIV-related factors were not associated with NT-proBNP. In multivariate analysis, after adjustment for clinically-relevant variables, factors independently associated with higher baseline NT-proBNP level were lower total lean mass, higher sTNF-RII and higher CD8 activation (% CD8+CD38+HLA-DR+) (table 2).

Relationship between NT-proBNP and markers of cardiovascular disease

At baseline, NT-proBNP levels were positively correlated with markers of cardiovascular, both markers of vascular disease (bulb and CCA-IMT) and atherogenesis (coronary artery calcium score). . After adjustment for factors known to affect CVD risk and markers of

immune activation, higher NT-proBNP remained independently associated with larger CCA-IMT (see table 3 for a representative model).

Changes in NT-proBNP after statin

In the rosuvastatin group, NT-proBNP decreased significantly over the 96 weeks of the study. The median (Q1, Q3) percent change in NT-proBNP was -6% (-41%, +37%);p=0.15 after 48 weeks and -6% (-53%, +71%), p=0.04 after 96 weeks], whereas an increase was seen in the placebo group [+32 (-13, +78)%, p=0.006 after 48 weeks; and +30 (-20, +135) %; p=0.005 after 96 weeks]. Further, the changes in NT-proBNP after 48 and 96 weeks were different between the treatment groups (p=0.01 and 0.04, respectively) (Figure 1).

Predictors of change of NT-proBNP levels on study

After adjusting for demographics, renal function, body composition variables (lean, and peripheral and central fat depots), randomization to rosuvastatin remained independently associated with a decrease in NT-proBNP levels. In addition, relative change from baseline to 96 weeks in HOMA-IR and total limb fat were independently associated with relative change of NT-proBNP at week 96 (see table 4).

Discussion

For the first time in HIV infected participants, we investigated the effects of 96 weeks of statin therapy on NT-proBNP levels. This study provides the first evidence that 10 mg of daily rosuvastatin effectively decreases plasma NT-proBNP in treated HIV infection, and that plasma NT-proBNP is associated with carotid IMT.

In HIV-uninfected populations, NT-proBNP is a powerful predictor of many cardiovascular outcomes; however, there is little data on NT-proBNP in HIV. In our study, participants had NT-proBNP levels that are consistent with what is reported in participants without overt heart failure[3] where natriuretic peptide concentrations are determined by the balance of low level production (chronic ischemia, left ventricular hypertrophy, and subclinical myocardial dysfunction) and varying levels of clearance (renal disease and adiposity). Additionally, inflammation plays a significant role in the development of cardiovascular complications with HIV infection and this is supported by our finding that NT-proBNP levels are associated with sTNF-RII and CD8+ activation [CD8+CD38+HLADR+].

Statins have been shown to reduce NT-proBNP[29] and risk of cardiovascular events in patients with heart failure[19,23] and particularly in those who have lower baseline plasma NT-proBNP levels [20,30] . In the CORONA[30] (Controlled Rosuvastatin Multinational Trial in Heart Failure) trial, there was no significant differences in primary end- point (cardiovascular mortality, nonfatal myocardial infarction or nonfatal stroke) between patients taking 10 mg of rosuvastatin when compared to placebo, however when restricted to those patients with the lowest tertile of NT-proBNP the hazard ratio favored the patients assigned to rosuvastatin for the primary outcome (hazard ratio 0.65, p=0.005). This effect was seen despite similar effects of statin on lipid profile and hsCRP in each tertile of NT-proBNP. In addition, in the rosuvastatin group, there was a reduction in hospitalizations for cardiovascular reasons and for worsening heart failure in patients with the lowest tertile of

NT-proBNP. However, in the Heart Protection Study[31], statin therapy reduced the risk of major vascular events regardless of NT-proBNP levels.

In this study, changes in NT-proBNP levels inversely correlated with changes in insulin resistance and limb fat. It has been shown that obese patients have lower levels of NT-proBNP than lean persons[32-34]. This is despite the fact that obese individuals have higher prevalence of conditions associated with elevated natriuretic peptides such as hypertension and left ventricular hypertrophy[32]. This is believed to be secondary to a "natriuretic handicap" with a reduced response to cardiac wall stress[35] impairing blood pressure regulation and one of the potential links between hypertension and obesity[36]. Weight loss in obese patients is associated with an increase and sustained response in NT-proBNP without increase in systolic blood pressure or left ventricular pressure [37] suggesting that obesity directly causes lower levels of NT-proBNP through adipocyte receptor mediated clearance[32]. This is likely largely mediated by insulin resistance as NT-proBNP in the lower range (<120pg/mL) is inversely and independently associated with insulin resistance[36,38,39]. Although, statins are known to cause insulin resistance, the statin effect on NT-proBNP persisted in our model even after adjustment for changes in HOMA-IR.

NT-proBNP undergoes renal clearance and so a lower GFR is expected to be associated with a higher NT-proBNP; therefore, the use of NT-proBNP as a marker of CVD in patients with poor renal function has been debated[40]. In the PREVEND (Prevention of Renal and Vascular End-stage Disease) study, NT-proBNP remained associated with cardiovascular events after adjusting for eGFR, albuminuria, age and gender. In our study, baseline eGFR was associated with baseline NT-proBNP levels, but this was no longer true when markers of inflammation were added to the models. Thus, non-GFR determinants such as inflammation may play a larger role in influencing NT-proBNP, as suggested in studies outside of HIV[41,42]. Our findings that circulating marker of generalized inflammation (sTNF-RII) and marker of T-cell activation (%CD8+CD38+HLADR+ T-cells) were independently associated with baseline NT-proBNP further support this hypothesis. In addition, inflammation itself may be linked to renal function and glomerular filtration [43].

Subjects included in this study were excluded if they had a history of coronary disease or diabetes but not if they were on antihypertensive medications as 25% of the subjects were on antihypertensive medications. At baseline, there was no statistical difference between the statin and placebo groups for hypertensive medications (p=0.4). When comparing patients on hypertensive medications compared to no medications, NT-proBNP values differed between the groups at baseline (p=0.013). However, by week 96 the percent change in NT-proBNP between these groups were similar (13% vs 15% respectively, p=0.9).

NT-proBNP is associated with co-morbidities[9] but there is little data on how it relates to markers of cardiovascular disease in HIV. Data recently presented on the WIHS[44] study examined the relationship of NT-proBNP with mortality during two different time periods (1994-1997 and 2008) in HIV-infected women. During both time periods, an elevated NT-proBNP level was associated with worse overall survival in with an adjusted hazard ratio of 1.78 and 2.81 during early and late periods respectively. This relationship was not seen in HIV uninfected persons. The causes of deaths were not described but many are likely due to

cardiopulmonary disease. In our present study, NT-proBNP levels were associated with multiple measures of subclinical vascular disease. Further, even after adjustment for markers of general inflammation, and monocyte and T-cell activation, NT-proBNP remained independently associated with CCA IMT. Therefore, this study enhances the understanding of NT-proBNP as a predictor of cardiovascular risk in patients with treated HIV infection.

Our study has several strengths, including the double-blind, placebo controlled randomized trial design, and the comprehensive evaluations of inflammation, immune activation and cardiovascular disease risk. For the cross-sectional analyses, we cannot prove causal relationships or exclude the possibility of residual confounding. In addition, the lack of echocardiograms precludes us from making any observations regarding the structural heart indices and their relationship to NT-proBNP levels. Finally, we investigated a specific population of interest-HIV-infected persons with heightened inflammation but normal LDL cholesterol level. Our population was also mostly men and blacks, so our findings may not be applicable to other HIV-infected populations.

In conclusion, we show that when compared to placebo, rosuvastatin 10 mg daily reduces NT-proBNP, a marker correlated with several measures of CVD risk, in HIV-infected patients on ART. Vascular disease and myocardial dysfunction are prominent in patients with HIV. HIV infected subjects on ART with elevated levels of inflammation but overall low levels of NT-proBNP may gain a protective cardiovascular benefit from statins. The effect of statins in HIV-infected subjects with higher levels of proBNP, underlying CVD, and/or myocardial injury deserves further investigations.

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Conflicts of Interest and Sources of Funding:

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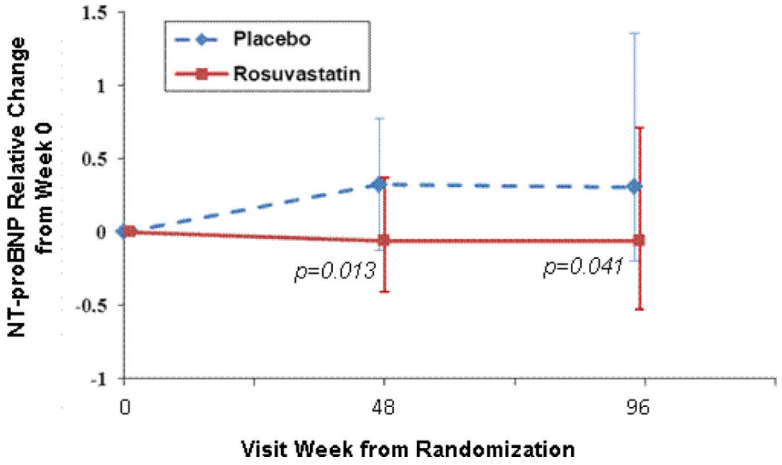

Figure 1. NT-proBNP relative change from 0, 48 and 96 weeks

Values shown are percent change in NT-proBNP from baseline to 48 and 96 weeks. Error bars shown represent the interquartile ranges. P-values shown are for between group comparisons at each timepoint.

Table 1

Baseline Characteristics

	Rosuvastatin	**Placebo**
	N=64	**N=59**
Demographics		
Age (years)	46 (41, 51)	46 (37, 52)
Male sex	53 (83.00%)	45 (76.00%)
African American	44 (69%)	38 (64%)
HIV parameters		
HIV duration (months)	122 (69, 195)	121 (70, 216)
Current CD4+ count (cells/mm^3)	595 (426, 792)	627 (400, 832)
Nadir CD4+ count (cells/mm^3)	177 (85, 314)	206 (92.5, 292)
HIV-1 RNA < 50 copies/ml	52 (81%)	49 (83%)
ART duration (months)	56 (30, 115)	62 (39, 109)
Current protease inhibitor use	26 (48%)	26 (44%)
Current tenofovir use	56 (87%)	54 (91%)
Metabolic and cardiovascular risk factors		
Body mass index (kg/m^2)	27(23, 30)	27 (23, 30)
Total limb fat (kg)	8852 (5418, 12546)	7863 (4870, 14449)
Active Hepatitis B	3 (5%)	4 (7%)
Active Hepatitis C	**3 (5%)**	**6 (10%)**
Systolic blood pressure (mmHg)	121 (112, 130)	120 (112, 132)
Current anti-hypertensive medication	17 (27%)	13 (22%)
HDL cholesterol (mg/dL)	48	48
LDL cholesterol (mg/dL)	94 (75, 105)	97 (78.5, 119)
HOMA-IR ≥2.5	**20 (31%)**	**28 (48%)**
Current smoking	37 (58%)	41 (69%)
Framingham risk score	3 (1, 7)	4 (1, 7)
Measure of subclinical vascular disease		
Mean-Max common carotid artery IMT (mm)	0.84 (0.73, 0.93)	0.84 (0.75, 0.95)
Carotid bulb IMT (mm)	0.82 (0.73, 0.93)	0.83 (0.69, 0.98)
FMD (%)	3.9 (2.1, 6.2)	3.3 (1.6, 5.1)
Coronary artery calcium score	20	50
Inflammation and Immune activation		
hsCRP (μg/mL)	1.67 (0.77,4.89)	2.00 (0.72,5.50)
D-dimer (μg/mL)	0.20 (0.13,0.33)	0.16 (0.09,0.28)
Interleukin 6 (pg/mL)	3 (2, 4.6)	2.6 (1.9, 5.3)
NT-proBNP (pg/mL)	41 (20, 66)	25 (11, 55)
TNFα- receptor I (pg/mL)	1619 (1331, 2198)	1456 (1206, 2418)

	Rosuvastatin	**Placebo**
	N=64	**N=59**
TNFα- receptor II (pg/mL)	2477 (1815, 3052)	2142 (1605, 2582)
CD4+CD38+HLADR+ T-cells (%)	5.34 (3.67,6.84)	4.60 (3.48,6.13)
CD8+CD38+HLADR+ T-cells (%)	13.30 (8.96,19.10)	11.35 (8.48,15.66)
CD14+CD16+ monocytes (%)	23.11 (18.20, 33.60)	22.34 (17.53, 33.93)
sCD14 (ng/mL)	2114 (1787, 2495)	2195 (1684, 2467)
sCD163 (ng/mL)	645 (533, 804)	655 (504, 906)
Kidney Function		
eGFRcr (ml/min/1.73m^2)	98	103
Cystatin C (mg/L)	0.85 (0.76, 1)	0.81 (0.71, 0.95)

Data presented as median (Q1,Q3) for continuous variables and by frequency (column percent) for nominal variables.

P > 0.05 between-groups for all variables listed except for hepatitis C (p= 0.01) and HOMA-IR (p=0.02)

Table 2

Univariate and Multivariable relationship of baseline NT- proBNP level

	Spearman r	p- value	Multivariable Analysis estimate	p-value
Demographics and clinical parameter				
Age (per decade)	0.317	**0.0004**	0.057	0.88
Male sex	−0.128	0.16	−7.486	0.31
Total lean mass (kg)	−0.209	**0.02**	−0.0005	**0.04**
Framingham score	0.191	**0.03**	−0.400	0.62
$eGFR_{cr}$ (ml/min/1.73m^2)	−0.302	**0.0007**	−0.260	0.084
Hemoglobin (g/dL)	−0.253	**0.0048**		
Current anti-hypertensive Medication	0.225	**0.01**		
HIV-specific factors and co-infections				
Nadir CD4 (per 100cells/m^3)	−0.094	0.29		
HIV duration (per month)	0.090	0.32		
ART duration (per month)	0.160	0.09	0.092	0.052
Hepatitis C co-infection	0.121	0.18		
Inflammation and Immune activation				
Interleukin 6 (pg/mL)	0.178	**0.049**		
Cystatin C (mg/L)	0.323	**<0.0001**		
IP 10	0.175	0.05		
TNFα- receptor I (pg/mL)	0.154	0.09		
TNFα- receptor II (pg/mL)	0.109	0.44	0.006	**0.048**
CD4+CD38+HLADR+ T-cells (%)	0.149	0.11		
CD8+CD38+HLADR+ T-cells (%)	0.172	0.06	0.591	**0.049**
CD14+CD16+ monocytes (%)	0.169	0.07		
Cardiovascular measures				
Carotid bulb IMT (mm)	0.232	**0.0137**		
Mean-Max CCA IMT (mm)	0.265	**0.0030**		
Coronary artery calcium score	0.253	**0.0047**		

Only variables with p <0.1 included; variables tested in Spearman analysis but not included: Demographics and clinical parameters (male sex, Caucasian, African American BMI, trunk fat, HOMA IR, metabolic syndrome and score, HDL, LDL, smoking status, hemoglobin); HIV specific factors (nadir CD4, current CD4, viral load, protease inhibitors, HIV duration, ARV duration); inflammation and immune activation (IP10, CRP, sCD14, sCD163, D-dimer, CD8+CD38+HLADR+ T-cells, CD14+CD16+ monocytes, CD14dimCD16+ monocytes); cardiovascular measures (systolic and diastolic blood pressures, FMD, plaque, hypertension medications)

Table 3

Multivariable analyses of the relationship between baseline CCA-IMT and baseline NT-proBNP and markers of inflammation and immune activation

	Multivariable analysis estimate	**p-value**
NT-proBNP	0.0004	**0.0209**
Age	0.0043	**0.0012**
Male sex (vs female)	−0.0190	0.4646
Total lean body mass (g)	0.000	0.1490
$eGFR_{cr}$ (ml/min/1.73m^2)	0.0002	0.7349
Framingham score	0.0080	**0.0076**
ARV duration (per month)	−0.0003	**0.0457**
CD4+CD3 8+HLADR+ T-cells (%)	0.0040	0.1607

Table 4

Multivariable analyses of the relationship between relative change of NT-proBNP at week 96 and statin

	Multivariable analysis estimate	p-value
Randomization to statin (vs placebo)	−0.3992	**0.0168**
Age	0.0248	**0.0492**
Male sex (vs female)	0.1439	0.5537
African American (?vs other)	0.2409	0.1928
Total lean body mass (g)	0	0.5280
Relative change HOMA IR over 96 weeks (%)	−0.1184	**0.0103**
Relative change total limb fat over 96 weeks (%)	−1.0488	**0.0010**
ARV duration (per month)	−0.0018	0.2019
$eGFR_{cr}$ (ml/min/1.73m^2)	−0.0026	0.6009
Framingham score	−0.0331	0.1865