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The Effect of Rosuvastatin on Vascular Disease Differs by Smoking Status

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BACKGROUND:

- Smoking is an important contributor to cardiovascular disease (CVD) risk[1] and is highly prevalent in the HIV-infected population[2]
- We have shown that rosuvastatin improves markers of inflammation [soluble tumor necrosis factor alpha receptor-II (sTNF-RII), interferon γ inducible protein 10 (IP-10) and lipoprotein associated phospholipase A2 (LpPLA2)], immune activation [soluble CD14 (sCD14), proportion of tissue factor positive patrolling (CD14dimCD16+) monocytes and proportion of activated CD4+ and CD8+ T cells (HLA-DR+CD38+)], oxidized LDL (oxLDL) and arrests common carotid artery intima media thickness (CCA IMT) progression in HIV-infected adults[3-7]
- Whether smoking status modifies these effects of rosuvastatin is unknown

METHODS:

The SATURN-HIV study is a randomized placebo-controlled trial to evaluate the effect of rosuvastatin on immune activation and subclinical vascular disease in HIV-infected adults on stable antiretroviral therapy (ART) with LDL ≤130 mg/dL. Here we assessed whether smoking status modifies the effect of rosuvastatin on select outcome measures that differed between groups over the study.

INCLUSION CRITERIA:
- HIV-1 infection
- 18 years or older
- Stable ART for 12 weeks with cumulative ART of at least 24 weeks
- HIV-1 RNA <1000 copies/mL in last 24 weeks
- Fasting LDL ≤130 mg/dL and triglycerides ≤500 mg/dL
- HLA-DR+CD38+ ≥19% or high sensitivity C-reactive protein ≥2 µg/mL

EXCLUSION CRITERIA:
- Known coronary artery disease or diabetes mellitus
- Any active infectious or inflammatory condition
- Use of any immunomodulating agents or lipid-lowering medication
- Pregnant or breastfeeding
- Creatinine clearance <50 mL/min

Rosuvastatin

Placebo

Stratified by:
- **PI vs not**
- **Osteopenia vs not**
- **CAC vs not**

ENDPOINTS (*included in this analysis*):
- **Cardiovascular**
  - **Carotid IMT (*CCA IMT*)**
  - **Coronary artery calcium score**
- **Systemic and vascular inflammation (*sTNF-RII, IP-10, LpPLA2*)**
- **Lymphocyte and monocyte activation (*sCD14, %CD14dimCD16+TF+, %CD4+HLA-DR+CD38+, %CD8+HLA-DR+CD38+*)**
- **Lipids (*oxLDL*)**
- **Insulin resistance**

Week 0 → Week 48 → Week 96

STATISTICAL ANALYSIS:
- Unadjusted between group comparisons were done using Chi Square tests, Fisher's Exact tests or Pearson Exact Chi Square tests for categorical variables and using t tests and Wilcoxon rank sum tests for continuous variables as appropriate.
- ANCOVA was used to model each outcome including a group by smoking status interaction.
  - Stratum specific results are provided where the interaction was significant.

RESULTS:

TABLE 1: Baseline Demographic, CVD and HIV Related Factors by Group

N=147	Rosuvastatin n=72	Placebo n=75
Age, years	45±9	45±11
Men	58 (81)	57 (76)
Race		
White	20 (28)	23 (31)
Black	50 (69)	50 (67)
Other	2 (3)	2 (3)
BMI, kg/m²	28±6	28±7
Smoking status		
Never	18 (25)	12 (16)
Past	11 (15)	13 (17)
Current	43 (60)	50 (67)
LDL, mg/dL	92±24	96±26
HDL, mg/dL	49±16	49±15
Triglycerides, mg/dL	155±129	148±88
Systolic BP, mmHg	125±18	121±15
Diastolic BP, mmHg	80±9	78±10
Chronic hepatitis C	7 (10)	10 (13)
Current CD4+, cells/ mm³	644±287	636±314
Nadir CD4+, cells/mm³	210±155	192±137
HIV-1 RNA <50 copies/mL	56 (78)	58 (77)
HIV duration, years	12±7	13±7
ART duration, years	7±5	7±5

Continuous variables are reported as mean ± standard deviation and categorical variables as frequency (percent). The groups were similar with regard to each of these baseline variables (p<0.05).

TABLE 2: Group by Smoking Status Interaction Terms from ANCOVA

Outcome	Parameter estimate (standard error)	p-value
sTNF-RII		
0-48 week change	-0.019 (0.083)	0.82
IP-10		
0-48 week change	0.204 (0.189)	0.28
LpPLA2		
0-24 week change	0.028 (0.057)	0.62
0-48 week change	0.074 (0.072)	0.3
0-96 week change	0.078 (0.077)	0.31
sCD14		
0-24 week change	-0.127 (0.083)	0.13
0-48 week change	-0.092 (0.111)	0.41
%CD14dimCD16+TF+		
0-24 week change	-0.138 (0.18)	0.45
0-48 week change	-0.152 (0.182)	0.4
%CD4+HLA-DR+CD38+		
0-24 week change	-0.258 (0.099)	0.01
0-48 week change	-0.466 (0.155)	<0.01
%CD8+HLA-DR+CD38+		
0-48 week change	-0.321 (0.174)	0.07
oxLDL		
0-24 week change	0.011 (0.139)	0.94
CCA IMT		
0-48 week change	0.074 (0.024)	<0.01
0-96 week change	0.058 (0.03)	0.06

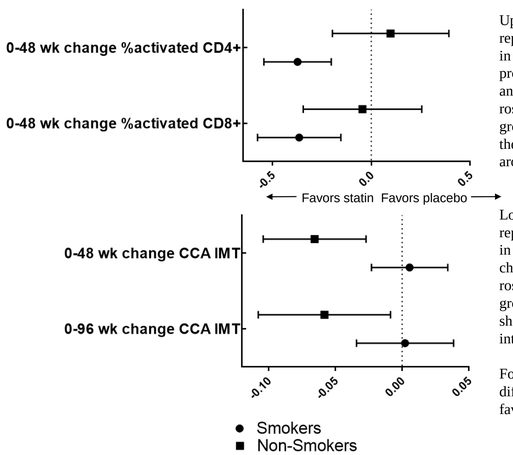
ANCOVA was used to model each outcome above. Independent variables included in each model were baseline value for the outcome measure, group, smoking status and a group by smoking status interaction. Parameter estimates and p-values shown are for the group by smoking status interaction terms.

TABLE 3: Mean Change in T-cell Activation and CCA IMT for Rosuvastatin and Placebo Groups by Smoking Status

	Rosuvastatin	Placebo	p-value
Activated CD4+ T-Cells			
0-48 wk change			
Smokers	-0.511	-0.138	<0.01
Non-smokers	-0.365	-0.463	0.51
Activated CD8+ T-Cells			
0-48 wk change			
Smokers	-0.613	-0.248	<0.01
Non-smokers	-0.506	-0.462	0.77
CCA IMT			
0-48 wk change			
Smokers	0.018	0.012	0.7
Non-smokers	-0.024	0.042	<0.01
0-96 wk change			
Smokers	0.018	0.016	0.9
Non-smokers	0.008	0.066	0.02

Values shown are mean absolute change from baseline in log-transformed outcome adjusted for the log-transformed baseline value of that outcome. P-values are for between group t tests.

FIGURE: Difference Between Means for Outcomes that Differed by Smoking Status



Upper – The symbols represent the mean difference in 0-48 week change in proportion of activated CD8+ and CD4+ T-cells between rosuvastatin and placebo groups. The error bars show the 95% confidence interval around the means.

Lower – The symbols represent the mean difference in 0-48 week and 0-96 week change in CCA IMT between rosuvastatin and placebo groups. The error bars again show the 95% confidence interval around the means.

For both figures, a mean difference less than zero favors the rosuvastatin group.

RESULTS SUMMARY:

1. There were significant randomization group by smoking status interactions terms for:
   - 0-24 (p=0.01) and 0-48 (p<0.01) week changes in proportion of activated CD4+ T-cells and a trend towards significance for 0-48 week change in activated CD8+ T-cells (p=0.07)
   - 0-48 week change in CCA IMT (p<0.01) and a trend towards significance for 0-96 week change in CCA IMT (p=0.06)

2. The stratum specific estimates reveal:
   - the improvement in CD4+ and CD8+ T-cell activation with rosuvastatin is significant for the smoking group only
   - the beneficial effect of rosuvastatin on CCA IMT was significant for the non-smoking group only

3. No effect modification by smoking was detected for changes in markers of monocyte activation (sCD14 and proportion of CD14dimCD16+TF+ monocytes), markers of systemic and vascular inflammation (sTNF-RII, IP-10 and Lp-PLA2) or oxLDL

LIMITATIONS:

- Because this study was not designed to test effect modification, we may not have detected all relevant interactions due to limited power.
- Only participants with fasting LDL ≤130 mg/dL were included in this study. As a result, the findings may not be generalizable to all HIV-infected individuals.

CONCLUSIONS:

- In SATURN-HIV, active smoking modified the effect of rosuvastatin on CCA IMT and T-cell activation.
- The beneficial effect of rosuvastatin on CCA IMT was not apparent in smokers.
- However, T-cell activation appears to improve more in smokers.

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