Statin Effects on oxLDL in Relationship to Plaque and Arterial Inflammation in HIV

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Background

- In non-HIV, circulating oxidized LDL (oxLDL) is a marker of CVD risk[1] and decreases with statin therapy[2].
- In HIV, oxLDL may contribute to monocyte activation[3], a potential risk factor for CVD.
- In HIV, statins reduce coronary plaque on coronary computed tomography angiography (CCTA)[4] but relationship with oxLDL and markers of immune activation are unknown.
- Leveraging CT data obtained from a 12-month, placebo-controlled trial, the aim of the study was to investigate the effects of atorvastatin on oxLDL, markers of monocyte activation, and coronary atherosclerosis.

Methods

- 12-month, randomized, double-blind, placebo-controlled trial of atorvastatin in 40 men and women with HIV on stable ART, no prior history of CVD, LDL-cholesterol between 70-130 mg/dL ,and evidence of subclinical coronary atherosclerosis on CCTA
- Measured at baseline + 12 mos:
  - Calcified and non-calcified plaque volume and high-risk morphology features on CCTA.
  - Lipids: Serum oxLDL (ELISA, Mercodia, Uppsala, Sweden), direct LDL, HDL, TG, TC
  - Monocyte and vascular activation markers: sCD163, sCD14, Lp-PLA2
  - HIV factors: HIV viral load, CD4+ T-cell count
- **Statistical Analysis**
  - Between group comparison with t-test or Wilcoxon as appropriate.
  - Pearson's or Spearman's correlation analysis as appropriate
  - Multiple regression analysis between oxLDL and non-calcified plaque volume with variables of interest
  - Partial correlation coefficient analysis for oxLDL, direct LDL, and non-calcified plaque volume

Table 1. Baseline Demographics and Characteristics

Characteristics	Placebo (n=21)	Atorvastatin (n=19)
Age (years)	50.0 (5.6)	52.2 (3.8)
Male	17 (81%)	15 (79%)
Race or ethnic group		
White	13 (68%)	13 (68%)
Black	3 (16%)	3 (16%)
Hispanic	1 (5%)	1 (5%)
Framingham Risk (%)	5.4 (4.4)	6.9 (4.1)
Systolic BP (mmHg)	119 (16)	117 (13)
Diastolic BP (mmHg)	76 (10)	73 (8)
Fasting glucose (mg/dL)	88.6 (6.9)	85.8 (11.8)
Hemoglobin A1c (%)	5.5 (0.3)	5.6 (0.4)
Current Smoker	6 (29%)	5 (26%)
CD4 T-cell count (cells/uL)	590 (289)	522 (263)
HIV Viral Load (copies/mL)	<48 (<48-48)	<48 (<48-<48)
HIV Duration (years)	15.0 (6.9)	16.8 (5.1)
Duration of ART (years)	11.4 (5.8)	12.4 (3.7)
Current PI treatment	8 (38%)	11 (58%)

Data presented as mean (SD), median (IQR), or n (%).

Table 3: Spearman Correlations Between Change in Plaque Characteristics and Change in Lipids and Inflammatory Markers

	Δ Non-calcified Plaque Vol (mm3)	Δ Total Plaque Vol (mm3)	Δ Pos. Remodeled Plaque (# segs)	Δ Low Attenuation Plaque (# segs)
Δ oxLDL (U/L)	**ρ= 0.50; p= 0.002**	**ρ= 0.34; p= 0.04**	**ρ= 0.34; p= 0.047**	**ρ= 0.41; p= 0.02**
Δ Lp-PLA$_2$ (ng/mL)	**ρ= 0.44; p= 0.007**	**ρ= 0.34; p= 0.04**	**ρ= 0.34; p= 0.04**	**ρ= 0.36; p= 0.03**
Δ Direct LDL (mg/dL)	ρ= 0.26; p= 0.12	ρ= 0.27; p= 0.11	ρ= 0.17; p= 0.31	ρ= 0.14; p= 0.41
Δ Total Chol (mg/dL)	ρ= 0.16; p= 0.34	ρ= 0.14; p= 0.43	ρ= 0.09; p= 0.59	ρ= 0.29; p= 0.09
Δ HDL Chol (mg/dL)	**ρ= -0.32; p= 0.05**	ρ=-0.20 ; p= 0.23	ρ= -0.20; p= 0.24	ρ= -0.30; p= 0.07
Δ Triglycerides (mg/dL)	ρ= 0.23; p= 0.16	ρ= 0.06; p= 0.71	ρ= -0.16; p= 0.35	ρ= 0.29; p= 0.09

Data are Spearman's rank correlation coefficients. Significant p-values are shown in bold.

Table 4. Effects of oxLDL on Non-Calcified Plaque Volume

A	Δ Non-calc. Plaque Volume (mm3)	
	β estimate	p value
Δ in oxLDL (U/L)	2.2	**0.02**
Framingham Risk	-0.6	0.78
CD4 count (cells/uL)	0.0	0.91
Log Viral Load (copies/mL)	-25.4	0.57
Δ LDL (mg/dL)	-0.3	0.38

Significant p-values are shown in bold.

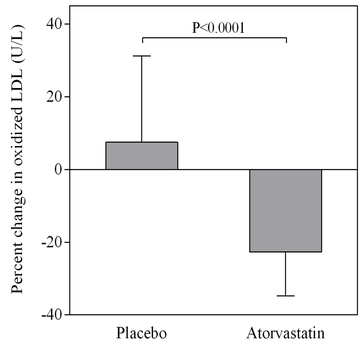


Figure 1. Mean percent change in oxidized LDL over 12-months between study groups. Mean (bar) and SD (error bar).

Table 2: Baseline and Between Group Changes in Lipids, Inflammatory Markers, and Plaque Characteristics on cCTA

Variable	Baseline Placebo (n=21)	Baseline Atorvastatin (n=19)	Between group p-value	Change in Placebo (n=20)	Change in Atorvastatin (n=17)	Between group p-value
oxLDL (U/L)	63.5 (13.1)	62.2 (15.9)	0.78	4.2 [-3.0 to 11.3]	-14.9 [-20.0 to -9.9]	**<0.0001**
Lp-PLA$_2$ (ng/mL)	272.5 (73.7)	285.6 (75.0)	0.58	-13.3 [-32.8 to 6.2]	-52.2 [-70.4 to -34.0]	**0.005**
Direct LDL (mg/dL)	124.5 (32.1)	123.6 (36.8)	0.93	11.4 [1.5 to 21.3]	-38.5 [-53.3 to -23.7]	**<0.0001**
Total Cholesterol (mg/dL)	191.7 (27.1)	198.6 (37.7)	0.52	5.9 [-3.4 to 15.1]	-46.2 [-57.4 to -35.0]	**<0.0001**
HDL (mg/dL)	50.8 (14.9)	51.9 (19.4)	0.84	-1.0 [-5.9 to 4.0]	0.9 [-3.9 to 5.7]	0.58
Triglycerides (mg/dL)	113 (92 to 136)	120 (97 to 204)	0.39	8.0 (-36.0 to 32.0)	-10.0 (-39.5 to 38.3)	0.55
sCD14 (ng/mL)	1953 (350 to 2400)	2100 (1088 to 2552)	0.48	125 (-238 to 495)	-162 (-780 to 201)	0.15
sCD163 (ng/mL)	2440 (1080 to 3476)	2503 (980 to 3778)	0.94	417 (-834 to 1342)	-51 (-829 to 165)	0.29
Non-calcified Plaque Volume (mm3)	66.1 (14.8 to 94.8)	33.7 (19.6 to 83.5)	0.72	6.7 (-6.5 to 29.8)	-8.2 (-18.3 to 3.5)	**0.03**
Total Plaque Volume (mm3)	81.1 (30.6 to 134.9)	55.2 (23.0 to 153.6)	0.63	12.0 (0.8 to 100.4)	-0.8 (-16.8 to 14.2)	**0.02**
Positively Remodeled (# segments)	2.1 (1.8)	2.0 (2.4)	0.59	0.4 (-0.1 to 0.8)	-0.2 (-0.4 to 0.1)	**0.04**
Low Attenuation (# segments)	0.4 (0.6)	0.8 (1.0)	0.14	0.4 (0.0 to 0.7)	-0.2 (-0.6 to 0.2)	**0.03**

Data are mean (SD) and median (IQR) for baseline values and mean [95% CI] for change columns. Significant p-values are shown in bold.

Conclusions

- Over 12 months, oxLDL decreases with statin treatment.
- Reductions in serum oxLDL are associated with changes in non-calcified plaque volume, total plaque volume, positively remodeled plaque, and low attenuation plaque.
- The relationship between oxLDL and non-calcified plaque volume is independent of baseline 10-year estimated Framingham Risk, HIV viral load, CD4+ T-cell count, and change in direct LDL.
- Changes in serum oxLDL had a stronger relationship with non-calcified plaque volume than change in direct LDL by partial correlation coefficient analysis (r=0.40, p=0.02 versus r= -0.16, p=0.38, respectively).

Limitations

- Due to limitations in sample size, we were not able to adequately determine relationships between changes in monocyte/macrophage activation and changes in oxLDL.

Future Directions

- Future studies needed to investigation whether reductions in oxLDL predict lower CVD event rates.

References

1. Koenig W, Karakas M, Zierer A, Herder C, Baumert J, Meisinger C, *et al.* Oxidized LDL and the risk of coronary heart disease: results from the MONICA/KORA Augsburg Study. *Clin Chem* 2011,**57**:1196-1200.
2. Singh U, Devaraj S, Jialal I, Siegel D. Comparison effect of atorvastatin (10 versus 80 mg) on biomarkers of inflammation and oxidative stress in subjects with metabolic syndrome. *Am J Cardiol* 2008,**102**:321-325.
3. Zidar DA, Juchnowski S, Ferrari B, Clagett B, Pilch-Cooper HA, Rose S, *et al.* Oxidized LDL levels are increased in HIV infection and may drive monocyte activation. *J Acquir Immune Defic Syndr* 2015.
4. Lo J, Lu MT, Ihenachor EJ, Wei J, Looby SE, Fitch KV, *et al.* Effects of statin therapy on coronary artery plaque volume and high-risk plaque morphology in HIV-infected patients with subclinical atherosclerosis: a randomised, double-blind, placebo-controlled trial. *The Lancet HIV* 2015,**2**:e52-e63.

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