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IL-6 and CD8 Senescence Independently Associate with Atherosclerosis in Treated HIV

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Background:

- Cardiovascular disease (CVD) is a major cause of mortality in patients with treated HIV infection.
- Persistent immune activation contributes to the elevated CVD risk in patients on anti-retroviral therapy (ART).
- Carotid intima media thickness (CIMT) measurement can quantitate atherosclerotic burden and predict future CVD risk.
- We explored the correlations between markers of immune activation and CIMT in patients on ART with virologic suppression.

Methods:

- HIV-infected patients on ART with suppressed viral load (<75 copies/mL) were identified from the SCOPE study, a longitudinal observational study with >1500 HIV-infected and uninfected persons.
- CIMT was measured using high resolution ultrasound in a total of 12 segments (near and far walls of the common carotid, bifurcation, and internal carotid region) according to standardized protocol.
- Mean CIMT was calculated as the average of the 12 segments.
- Plaque was defined as a focal region of CIMT >1.5mm.
- Cryopreserved peripheral blood mononuclear cells were stained with fluorescent conjugated antibodies in order to evaluate markers of: T-cell (% of HLA-DR$^+$CD38$^+$, CD28$^-$CD57$^+$ and CX3CR1$^+$ cells in CD4$^+$ and CD8$^+$ T cells) and monocyte activation (% of CD14^{++}CD16$^-$, CD14$^+$CD16$^+$, CD14^{dim}CD16$^+$, CCR2$^+$, CX3CR1$^+$ and Tissue factor (TF)$^+$ monocytes and intensity of CCR5 expression) by flow cytometry.
- Soluble markers of inflammation (IL-6, C-Reactive Protein (CRP), soluble (s)CD14 and sCD163) and coagulopathy (d-dimer and soluble tissue factor) were assessed by a multiplex electrochemiluminescence assay.
- Associations between CIMT (at the bifurcation region, internal carotid, common carotid, and mean IMT) and immunologic markers were assessed by bivariable Spearman's rank correlation and partial correlation adjusting for traditional CV risk factors and CD4 count.
- Associations between the presence of plaque and immunologic markers were evaluated by Wilcoxon test.

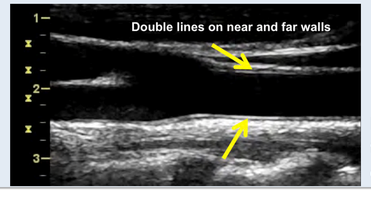
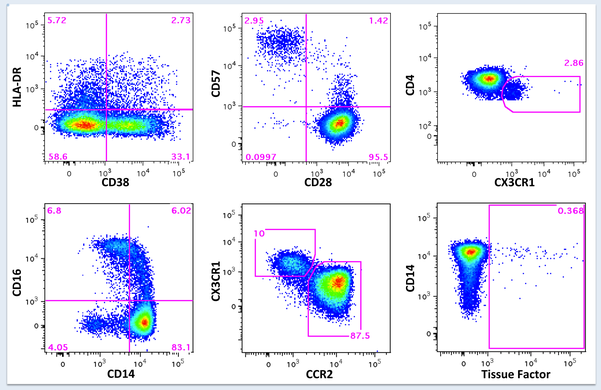


Fig 1. Longitudinal view of the common carotid artery on high resolution US

Fig 2. Representative plots of markers of T cell and monocyte activation



Results:

Table 1: Patient characteristics

Patients (n)	149
Age (yrs)	48.5 (44.0-54.4)
Male (%)	138 (92.6)
Race	
White (%)	100 (67.1)
Black (%)	30 (20.1)
Latino (%)	9 (6)
Other (%)	10 (6.7)
Current Smoking (%)	38 (25.5)
CVD (%)	9 (6)
Diabetes (%)	10 (6.7)
Hypertension (%)	51 (34.2)
Anti-hypertensive drugs (%)	46 (30.9)
LDL (mg/dL)	110 (90-134)
Triglyceride (mg/dL)	142.5 (95.5-242)
Cholesterol lowering drugs (%)	58 (39.2%)
BMI	24.7 (22.6-27.9)
Duration of HIV infection (yrs)	15.2 (10.9-18.6)
Duration of ART (yrs)	8.1 (4.7-11.4)
Nadir CD4 count (cells/μL)	140 (32-250)
CD4 count at CIMT measurement (cells/μL)	522 (325-726)

Data are presented as median (IQR) or numbers (percent)

Results (Cont):

Table 2: Median (IQR) CIMT measurements at different regions

Common CIMT (mm)	Internal CIMT (mm)	Bifurcation CIMT (mm)	Mean CIMT (mm)	Presence of Plaque (%)
0.8 (0.7-1.0)	0.9 (0.7-1.1)	1.2 (1.0-1.6)	1.0 (0.8-1.2)	80 (53.7)

Table 3: Factors correlated with common and mean CIMT

	Bivariable correlation				Partial correlation *			
	Common CIMT		Mean CIMT		Common CIMT		Mean CIMT	
	Rho	P value	Rho	P value	Rho	P value	Rho	P value
CD4 T cells								
% of HLA-DR$^+$CD38$^+$	-0.06	N.S	-0.12	N.S	0.03	N.S	0.01	N.S
% of CD28$^-$CD57$^+$	0.10	N.S	0.12	N.S	0.02	N.S	-0.01	N.S
% of CD57$^+$ within CD28$^-$ cells	-0.13	N.S	-0.11	N.S	-0.04	N.S	0.02	N.S
% of CX3CR1$^+$ cells	0.07	N.S	0.06	N.S	0.03	N.S	-0.02	N.S
CD8 T cells								
% of HLA-DR$^+$CD38$^+$	0.07	N.S	-0.01	N.S	0.18	N.S	0.09	N.S
% of CD28$^-$CD57$^+$	0.10	N.S	0.14	N.S	-0.04	N.S	0.01	N.S
% of CD57$^+$ within CD28$^-$ cells	-0.11	N.S	-0.17	0.041	0.02	N.S	-0.11	N.S
% of CX3CR1$^+$ cells	0.04	N.S	0.05	N.S	0.01	N.S	-0.03	N.S
Monocytes								
% of CD14^{++}CD16$^-$ cells	-0.01	N.S	0.05	N.S	0.06	N.S	0.16	N.S
% of CD14$^+$CD16$^+$ cells	0.01	N.S	-0.07	N.S	0.04	N.S	-0.07	N.S
% of CD14^{dim}CD16$^+$ cells	0.05	N.S	-0.02	N.S	-0.12	N.S	-0.22	N.S
% of CX3CR1$^+$ cells	0.02	N.S	-0.04	N.S	-0.08	N.S	-0.19	N.S
% of CCR2$^+$cells	-0.04	N.S	0.02	N.S	0.04	N.S	0.15	N.S
% of Tissue Factor$^+$ cells	-0.05	N.S	-0.08	N.S	0.03	N.S	-0.05	N.S
CCR5 Expression	0.26	0.002	0.07	N.S	0.20	0.041	0.06	N.S
Soluble Markers								
D-Dimer	0.11	N.S	0.12	N.S	-0.04	N.S	0.01	N.S
CRP	0.05	N.S	0.01	N.S	0.04	N.S	0.02	N.S
sCD14	-0.10	N.S	-0.02	N.S	-0.10	N.S	-0.01	N.S
IL-6	0.22	0.008	0.20	0.013	0.24	0.011	0.22	0.021
sCD163	-0.02	N.S	0.03	N.S	0.08	N.S	0.12	N.S
Tissue Factor	0.07	N.S	0.08	N.S	-0.07	N.S	-0.03	N.S

* Adjusted for age, gender, race, history of cardiovascular disease, diabetes, hypertension and smoking, LDL and triglyceride levels and CD4 count

Results (Cont):

- Plasma IL-6 was also significantly associated with CIMT at the bifurcation region and remained significant in the adjusted model (rho= 0.2, P=0.036).
- None of the factors were significantly associated with internal CIMT or the presence of plaque after adjusting for traditional CV risk factors and CD4 count.

Conclusions:

- In patients on ART with virologic suppression, higher levels of plasma IL-6 and greater CCR5 expression on monocytes were independently associated with thicker common CIMT after adjusting for CVD risk factors and CD4 count.
- Higher levels of plasma IL-6 was the only factor found to be independently associated with CIMT at the bifurcation region and mean CIMT (average measurement of 12 segments of the right and left carotid arteries) after adjusting for CVD risk factors and CD4 count.
- Dysfunction of innate immune cells likely contribute to atherosclerosis in the setting of treated HIV infection.

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