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PCSK9 Levels in Relation to Immune Activation and Subclinical Coronary Plaque in HIV

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Background

- Proprotein convertase subtilisin /kexin 9 (PCSK9) modulates homeostasis of low density lipoprotein cholesterol (LDL-c), but it may also be involved in immune activation and atherogenesis.
- A pro-inflammatory milieu stimulates diverse cell types to secrete PCSK9 into the circulation. Conversely, PCSK9 may elicit pro-inflammatory responses in monocytes/macrophages, with relevance to immune-modulated atherogenesis.
- In the general population, PCSK9 levels relate to major adverse cardiovascular events, even after controlling for LDL-c levels.

Objectives

- Individuals with HIV display high-level systemic immune activation and an increased subclinical coronary atherosclerotic plaque burden.
- We therefore hypothesized that PCSK9 levels would be elevated among asymptomatic individuals with HIV (vs. without HIV).
- Further, we hypothesized that among individuals with HIV, PCSK9 would relate to levels of systemic monocyte activation markers and/or to subclinical coronary atherosclerotic plaque parameters.

Methods

- PCSK9 levels among asymptomatic individuals with and without HIV were assessed using ELISA.
- Levels of systemic monocyte activation markers were measured using ELISA, and subclinical coronary atherosclerotic plaque parameters were assessed using coronary computed tomography angiography.
- It was further determined whether PCSK9 levels related to levels of systemic monocyte markers and/or to plaque within each group.

Results

Parameter	Non-HIV-infected (N=69)	HIV-infected (N=149)	P value	P value adjusted*
Demographics and Traditional CVD Risk Parameters				
Race/Ethnicity				
Asian	4% (3/69)	1% (1/149)		
White	49% (34/69)	52% (77/149)		
Black/African American	35% (24/69)	34% (51/149)	0.47	--
American Indian/Alaskan Native	3% (2/69)	3% (4/149)		
More than One Race	3% (2/69)	1% (2/149)		
Hispanic	6% (4/69)	9% (14/149)		
Sex (male)	59% (41/69)	65% (97/149)	0.42	0.52
Age (years)	47 (43, 51)	48 (43, 52)	0.33	0.23
Current statin use	4% (3/67)	14% (20/146)	**0.03**	--
Current HTN	17% (12/69)	22% (33/147)	0.39	0.53
Current DM	7% (5/69)	9% (14/148)	0.59	0.67
Current smoking	38% (26/69)	42% (62/148)	0.56	0.46
Total cholesterol (mg/dL)	178 (159, 208)	178 (156, 205)	0.98	0.78
LDL-c (mg/dL)	107 ± 31	103 ± 33	0.36	0.31
HDL-c (mg/dL)	49 (42, 63)	49 (40, 60)	0.64	0.93
Triglycerides (mg/dL)	84 (63, 126)	96 (77, 174)	**0.002**	**0.03**
BMI (kg/m^2)	26.9 (23.9, 30.2)	26.4 (23.5, 29.8)	0.27	0.16
WHR	0.9 ± 0.1	0.9 ± 0.1	0.31	0.41
HCV infection	9% (6/69)	25% (37/149)	**0.003**	**0.004**
Total Framingham Point Score	9 (5, 11)	9 (7, 12)	0.20	0.26
HIV-specific Parameters				
Duration since HIV diagnosis (years)	--	14 (10, 19)	--	--
Currently on ART	--	99% (148/149)	--	--
Currently on NRTIs	--	95% (141/149)		
Currently on NNRTIs	--	38% (57/149)		
Currently on PIs	--	56% (83/149)		
Currently on Integrase Inhibitors	--	14% (20/146)		
Total duration of ART (years)	--	8 (4, 11)	--	--
CD4 count (cells/mm^3)	--	484 (347, 741)	--	--
Nadir CD4 (cells/mm^3)	--	180 (53, 263)	--	--
VL (copies/mL)	--	<50 (<50, <50)	--	--
Immune Parameters				
sCD14 (ng/mL)	326.5 (163.9, 1316.6)	431.1 (223.3, 1755.7)	**0.047**	0.08
sCD163 (ng/mL)	831.5 (607.9, 1134.3)	1224.9 (806.4, 1787.0)	**<0.0001**	**0.001**
MCP-1 (pg/mL)	223.5 (170.8, 273.0)	252.0 (179.0, 358.0)	**0.03**	**0.045**
Lp-PLA$_2$ (nmol/min/ml)	174.2 (147.0, 218.7)	188.9 (155.3, 234.2)	0.10	0.10
Oxidized LDL (U/L)	44.4 (36.3, 56.5)	43.9 (35.2, 53.5)	0.52	0.51
CRP (mg/L)	1.3 (0.5, 3.6)	1.4 (0.5, 4.1)	0.60	0.13
hsIL-6 (pg/mL)	1.0 (0.6, 1.8)	1.1 (0.7, 1.9)	0.31	0.77
Cardiac CT Parameters*				
Total # of plaque segments	0.0 (0.0, 3.0)	1.0 (0.0, 3.0)	0.09	0.38
# of non-calcified plaque segments	0.0 (0.0, 0.0)	0.0 (0.0, 1.8)	**0.003**	**0.03**
Miscellaneous				
PCSK9 (ng/mL)	304 (257, 375)	332 (272, 412)	**0.047**	**0.02**

Table 1. Baseline Characteristics Among HIV-infected and Non-HIV-infected Subjects
Abbreviations: ART, antiretroviral therapy; BMI, body mass index; CRP, C-reactive protein; CT, computed tomography; DM, diabetes mellitus; HCV, hepatitis C virus; HDL-c, high density lipoprotein cholesterol; HIV, human immunodeficiency virus; hsIL-6, high sensitivity interleukin-6; HTN, hypertension; LDL-c, low density lipoprotein cholesterol; Lp-PLA2, lipoprotein-associated phospholipase A2; MCP-1, monocyte chemoattractant protein-1; NNRTIs, Non-Nucleoside Reverse Transcriptase Inhibitors; NRTIs, Nucleoside Reverse Transcriptase Inhibitors; PCSK9, proprotein convertase subtilisin / kexin 9; PIs, Protease Inhibitors; sCD14, soluble CD14; sCD163, soluble CD163; VL, viral load; WHR, waist-to-hip ratio.
Normally distributed variables are presented as mean ± standard deviation; non-normally distributed data are presented as median (interquartile range).
*P values are adjusted for current statin use.
**Based on data from 206 participants who completed CT procedures.

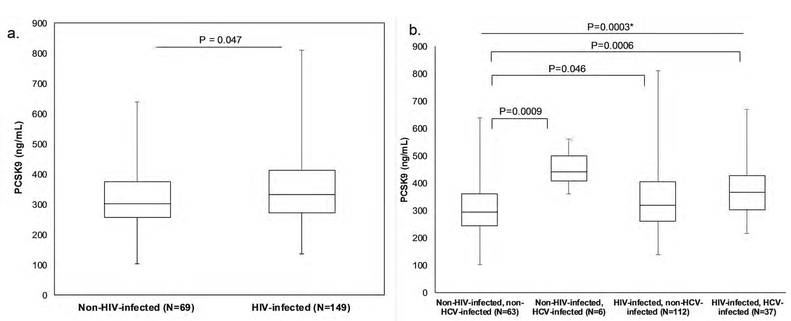


Figure 1. (A) PCSK9 levels among HIV-infected and non-HIV-infected subjects. HIV-infected subjects (n = 149) exhibited higher PCSK9 levels relative to non-HIV-infected subjects (n = 69); 332 [272, 412] ng/mL vs 304 [257, 375] ng/mL; P = .047. **(B) PCSK9 Levels by HIV and HCV Status.** There was a significant difference in PCSK9 levels across groups (* overall P value). Significant between-group differences in PCSK9 levels were noted when the following comparisons were made: (1) non-HIV-infected, non-HCV-infected vs non-HIV-infected, HCV-infected subjects (294 [244, 360] ng/mL vs 441 [408, 499] ng/mL; P = .0009); (2) non-HIV-infected, non-HCV-infected vs HIV-infected, non-HCV-infected subjects (294 [244, 360] ng/mL vs 318 [262, 404] ng/mL; P = .046); and (3) non-HIV-infected, non-HCV-infected vs HIV-infected, HCV-infected subjects (294 [244, 360] ng/mL vs 366 [301, 427] ng/mL; P = .0006).
Results are displayed as medians (horizontal lines) and interquartile ranges (upper and lower edges of boxes), and the error bars stretch from the quartiles to the maximum and minimum.

Results Continued

	Non-HIV-infected		HIV-infected	
	Spearman's Rho	P value	Spearman's Rho	P value
Demographics and Traditional CVD Risk Parameters				
Age (years)	0.35	**0.003**	0.002	0.98
Total cholesterol (mg/dL)	0.13	0.31	0.28	**0.0005**
LDL-c (mg/dL)	0.07	0.58	0.16	**0.05**
HDL-c (mg/dL)	0.14	0.26	0.16	**0.04**
Triglycerides (mg/dL)	0.22	0.07	0.02	0.77
BMI (kg/m^2)	0.15	0.21	0.02	0.77
WHR	0.05	0.69	-0.13	0.14
Total Framingham Point Score	0.51	**<0.0001**	0.33	**<0.0001**
HIV-specific Parameters				
Duration since HIV diagnosis (years)	--	--	0.007	0.93
Total duration of ART (years)	--	--	-0.07	0.50
CD4 count (cells/mm^3)	--	--	0.02	0.80
Nadir CD4 (cells/mm^3)	--	--	0.10	0.30
LogVL	--	--	-0.12	0.19
Immune Parameters				
sCD14 (ng/mL)	0.02	0.90	0.22	**0.009**
sCD163 (ng/mL)	-0.05	0.67	0.23	**0.006**
MCP-1 (pg/mL)	0.17	0.18	0.02	0.78
Lp-PLA2 (U/L)	-0.02	0.89	0.01	0.86
Oxidized LDL (U/L)	0.14	0.25	0.10	0.24
CRP (mg/L)	-0.21	0.09	0.04	0.64
hsIL-6 (pg/mL)	-0.05	0.72	0.16	0.07
Cardiac CT Parameters				
Total # of plaque segments	-0.11	0.37	-0.009	0.92
# of non-calcified plaque segments	-0.11	0.37	0.001	0.99

Table 2. Associations Between PCSK9 Levels and Cardiometabolic Risk Parameters among Individuals with and without HIV.

Conclusions

- Among asymptomatic individuals with HIV, PCSK9 levels are elevated relative to those without HIV.
- Within the HIV group, PCSK9 related to systemic markers of monocyte activation but not to coronary plaque.
- Additional research is necessary to determine effects of PCSK9 on immune activation and atherogenesis in HIV.
- Given that PCSK9 inhibition leads to a significant reduction in the risk of cardiovascular events among individuals in the general population, additional studies are needed to assess whether PCSK9 inhibition may reduce immune activation and coronary plaque burden in the HIV population.

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