Host Glycomic Determinants of Coronary Atherosclerosis During Treated HIV Infection

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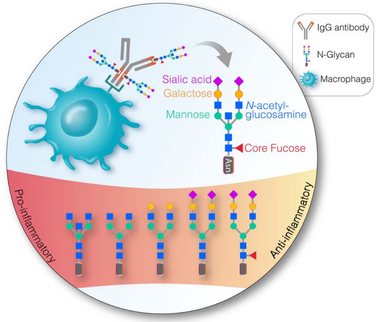
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BACKGROUND

- HIV-induced inflammation is associated with accelerated atherosclerosis, even with effective ART. Host glycomic alterations, in particular, loss of galactose and sialic acid on circulating glycoproteins (including IgG) drive inflammation and are associated with premature aging.
- Whether glycomic alterations are associated with coronary atherosclerosis in persons living with HIV (PLWH) remains unknown.



METHODS

HIV⁻ Control: 22 HIV-negative, No coronary plaque
HIV⁻ Cases: 22 HIV-negative, Coronary stenosis ≥50%
HIV⁺ Controls: 34 HIV+ ART-treated, No coronary plaque
HIV⁺ Cases: 34 HIV+ ART-treated, Coronary stenosis ≥50%

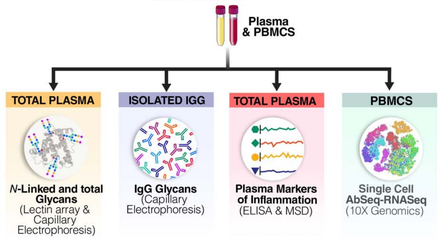
Baseline characteristics of the study participants

		HIV- controls (n=22)	HIV- cases (n=22)	P value (HIV-, cases vs controls)	HIV+ controls (n=34)	HIV+ cases (n=34)	P value (HIV+, cases vs controls)
Age (years)		57.4 (48-71)	57.9 (49-65)	ns	51.4 (43-63)	51.8 (44-62)	ns
Race (%)	White, non-Hispanic	82%	82%	-	62%	62%	-
	White, Hispanic	5%	5%		3%	3%	
	Black, non-Hispanic	14%	14%		21%	21%	
	Black, Hispanic	0%	0%		9%	0%	
	Other	0%	0%		3%	0%	
	Other Hispanic	0%	0%		3%	15%	
BMI		25.5 (20-33)	28.7 (21-38)	ns	26 (18-34)	24.9 (17-34)	ns
Systolic Blood Pressure (mm Hg)		123.8 (103-148)	130.7 (110-151)	ns	126.4 (108-164)	124.1 (100-148)	ns
Diastolic Blood Pressure (mm Hg)		75.9 (62-95)	82 (66-108)	0.041	79.6 (65-91)	76.5 (61-101)	ns
Fasting glucose (mg/dL)		93.5 (68-133)	113 (72-247)	0.021	104.6 (78-277)	106.9 (80-252)	ns
Total cholesterol (mg/dL)		185.9 (138-259)	202.3 (133-320)	ns	190.2 (115-294)	186.6 (127-269)	ns
High Density Lipoprotein (mg/dL)		56 (39-91)	49.4 (29-73.7)	ns	49.8 (23-101)	45.2 (25-83)	ns
Triglycerides (mg/dL)		88.8 (23-199)	168.8 (45-344)	<0.0001	143.6 (43-425)	141.4 (47-304)	ns
Low Density Lipoprotein (mg/dL)		112.2 (56-166)	119.1 (52-210)	ns	113.9 (22-218)	113.7 (65-202)	ns
Statin use (%)	Yes	32%	55%	ns	38%	38%	ns
Aspirin use (%)	Yes	73%	73%	ns	41%	41%	ns
Diabetes status (%)	Yes	5%	23%	ns	18%	21%	ns
Smoking Status At Visit (%)	Current smoker	5%	18%	ns	18%	24%	ns
ACC/AHA risk estimate		0.08 (0.03-0.23)	0.12 (0.03-0.22)	0.014	0.07 (0.01-0.29)	0.08 (0.01-0.34)	ns
CD4 count (cells/mm³)		-	-	-	592 (103-1228)	624 (205-1255)	ns
Nadir CD4 (cells/mm³)		-	-	-	282.9 (8-733)	227.6 (0-560)	ns
Cumulative years of ART use		-	-	-	7.9 (0-15.4)	9.3 (0.05-14.3)	ns
Viral suppression (%)	Supressed	-	-	-	91%	82%	ns
Diagnosed with AIDS (%)	AIDS Dx	-	-	-	15%	18%	ns

ns = $P > 0.05$ — Mean (range) are displayed

Case-control study within the Multicenter AIDS Cohort Study (MACS)

A nearest neighbor algorithm was used to match for age, gender, ethinicity, &HIV status



RESULTS

Figure 1. Plasma markers of inflammation and microbial translocation are elevated in HIV+ cases.

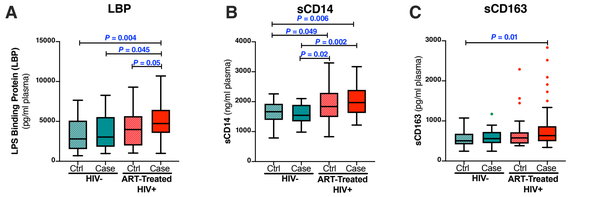


Figure 2. LPS binding protein levels are associated with the presence of coronary plaque in HIV+ cases compared to HIV+ controls, but not between HIV- cases and controls.

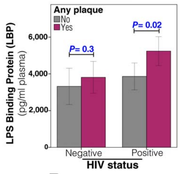
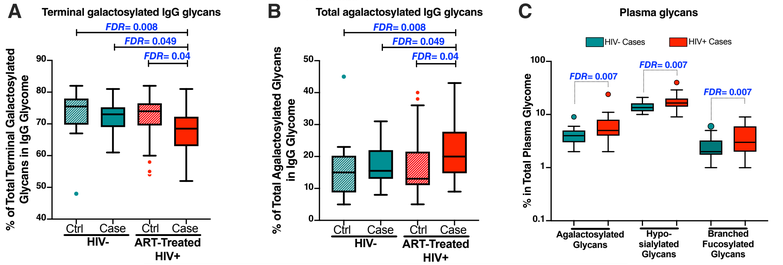


Table 2. Plasma markers of inflammation and microbial translocation.

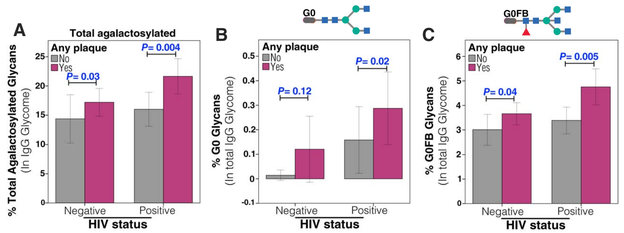
	HIV- controls (n=22)	HIV- cases (n=22)	HIV+ controls (n=34)	HIV+ cases (n=34)
	Mean (SD) pg/ml	Mean (SD) pg/ml	Mean (SD) pg/ml	Mean (SD) pg/ml
LBP	3375.4 (2106.9)	3820.8 (2214.9)	4018.6 (2195.1)	5165 (2317.4)
sCD163	548 (188.9)	600.3 (213.7)	683.3 (391.7)	883.9 (630.3)
sCD14	1633137 (367471)	1580028 (348586)	1900147 (549256)	2011467 (470251)
Fractalkine	5929.8 (1559.5)	5374.9 (1025.3)	6811.5 (2388.3)	6273.8 (1758.3)
IL10	0.25 (0.24)	0.53 (0.89)	0.33 (0.35)	0.43 (0.57)
IL1β	0.81 (2)	0.29 (0.53)	0.2 (0.15)	0.24 (0.39)
IL6	0.76 (0.33)	1.1 (0.95)	1.27 (1.941)	1.59 (2.67)
MCP2	21.04 (7.38)	22.86 (5.96)	28.09 (13.27)	30.43 (21.94)
MIP1α	18 (10.31)	17.89 (6.343)	18.37 (10.38)	46.08 (133.72)
SDF1α	734.5 (415.4)	846.1 (545.8)	761.5 (443.1)	839.1 (254.2)
TNFα	1.7 (1.6)	1.53 (0.79)	1.73 (1.3)	2.68 (3.63)
TGFβ1	7397.7 (6398.9)	6691.3 (6832.1)	7299.5 (8438.1)	9173.2 (10822.5)
TGFβ2	36.84 (25.2)	37.51 (29.7)	45.27 (54.9)	66.64 (82.3)
TGFβ3	2.73 (1.47)	2.86 (1.55)	3.06 (2.56)	3.092 (2.35)

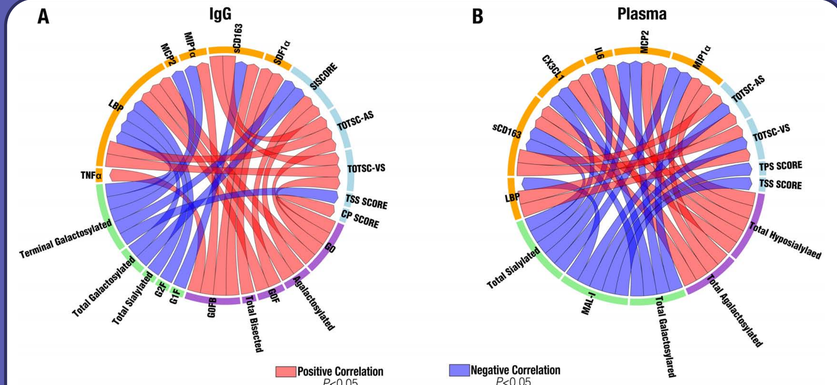


Multivariate model adjusting for CVD risk factors (ACC/AHA score) & aspirin use

Figure 3. Premature-aging-associated glycomic dysregulation, in particular, agalactosylation and hyposialylation, are more evident among HIV+ cases. (A) Anti-inflammatory galactosylated glycans were lower in the IgG of HIV+ cases compared to HIV+ controls. **(B)** Pro-premature-aging agalactosylated glycans were higher in HIV+ cases compared to HIV+ controls. These differences were not observed between HIV- cases, and HIV- controls. **(C)** pro-inflammatory hypo-sialylated and agalactosylated glycans were higher in the plasma of HIV+ cases compared to HIV- cases.

Figure 4. Premature-aging-associated glycomic traits are associated with the presence of coronary plaque in HIV+ cases compared to HIV+ controls.





‡**G1** = mono-galactosylated; **G2** = di-galactosylated; **G0** = agalactosylated; **F**= fucosylated; **B** = bisected GlcNac; **MAL-1** = Siaα2-3Gal (β-1,4) GlcNAc

***SISCORE** = Segment involvement score; **TOTSC-AS** = Total Agatson Score. **TOTSC-VS** = Total Volumetric Score; **TSS SCORE** = Total Segment Stenosis Score; **TPS SCORE** = Total Plaque severity score; **CP SCORE**= Calcified plaque score

Multivariate model adjusting for CVD risk factors (ACC/AHA score) & aspirin use (data from HIV⁺ ART-treated only)

Figure 5. Circos plots highlighting the interactions between the circulating glycome, inflammatory markers, and cardiovascular disease (CVD) severity scores. (A) IgG glycome, **(B)** plasma glycome. Levels of galactosylated and sialylated IgG and plasma glycans associated with lower CVD scores, whereas levels of agalactosylated and hypo-sialylated glycans associated with higher scores.

CONCLUSIONS

- Premature-aging-associated glycomic dysregulation, in particular, agalactosylation and hyposialyation, are more evident among HIV+ ART+ individuals (compared to all other groups) and are associated with the prevalence and degree of subclinical atherosclerosis.
- Potential HIV-promoted glycomic pathways fostering CVD warrant further investigation to examine their prognostic and functional significance.

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