Non-Classical Monocytes Correlate Negatively With HIV-Associated Cognitive Performance

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Background: Excessive platelet activation during HIV infection leads to formation of transient platelet-monocyte complexes (PMCs) in circulation. It has been shown through *in vitro* studies that such monocytes exhibit increased propensity to extravasate through the blood brain barrier (BBB) and contribute to neuroinflammation. Despite anti-retroviral treatment (cART), people living with HIV (PLWH) are more susceptible to CSVD and VCI, highlighting the need to understand the role of platelet monocyte interaction and its effect on monocyte activation in these co-morbidities.

Methods

- PLWH, on cART (n=101) and equal numbers of age, sex matched healthy individuals, not infected with HIV (n=102) were enrolled.
- Platelet-monocyte interaction, monocyte activation and soluble markers of monocyte and endothelial activation were measured in whole blood by flow cytometry.
- Neuropsychological testing and brain MRI imaging was performed.
- Mann Whitney U test or Kruskal Wallis test followed by Dunn's multiple comparisons and Spearman Correlation were used for data analysis as appropriate (GraphPad Prism V 9.4.1).

Results

Demographics: RRS- Reynold's risk score; Ethnicity /race- Hispanic :Not Hispanic :Not Reported; W:B:O- White :Black :Other/Not Reported; CSVD WMH Fazekas score- DWMH: deep white mater hyperintensities; PVWMH: periventricular white matter hyperintensities represented as 0:>0. Units; Clinical comorbidities- present :not present.

Category	Variable	HIV+	HIV–	P-value
Basic	N	101	102	0.944
	Age (years)	53.20 (10.90)	50.33 (16.72)	0.389
	RRS	6.60 (6.38)	5.98 (6.24)	0.088
	Sex (Female : Male)	28:73	32:69	< 0.001
Ethnicity/ Race	Hispanic	12:88:1	7:94:1	< 0.001
	W:B:O	52:35:14	83:11:8	< 0.001
CSVD	DWMH	31:70	43:58	< 0.001
	PVWMH	63:38	79:22	< 0.001
HIV	CD4+ Counts/mL	672 (318)	–	–
	Viral Load (Count/μL)	8.75 (17.7)	–	–
Clinical	Diabetes Type II	9:92	0:102	< 0.001
	Hepatitis C	11:90	1:101	< 0.001
	Hypertension	32:69	23:79	< 0.001

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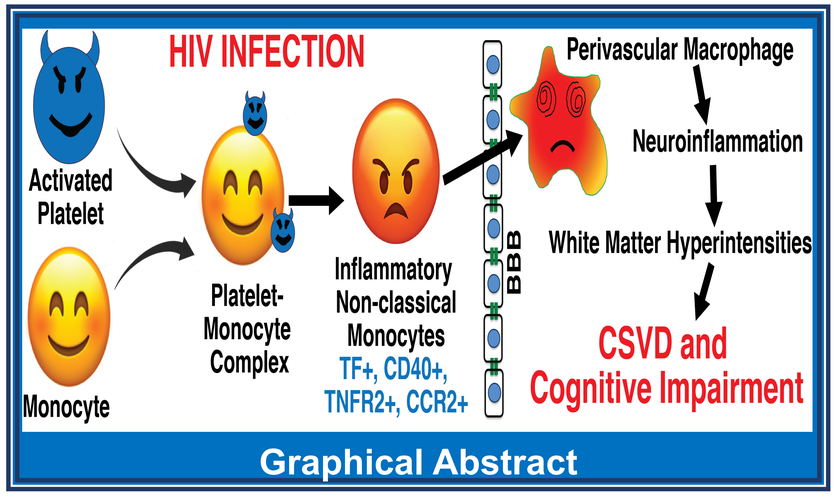
References: 1) Murray et al, Frontiers in Neurology, 2020. 2) Singh et al, J. Immunology, 2014. 3) Murray et al NeuroImage Clinical, 2021

- Levels of non-classical monocytes exhibited inverse correlation with cognitive z scores in PLWH as compared to age-, sex-at-birth- and RRS-matched cohort of persons not infected with HIV, with **strongest correlation in HIV+CSVD+ study group (r = -0.3579)**.
- Aberrant interaction with platelets inculcates an inflammatory, promigratory, non-classical phenotype in monocytes, which could upon extravasation across BBB, contribute to progression of Cerebral small vessel disease (CSVD) and vascular cognitive impairment (VCI).



Graphical Abstract

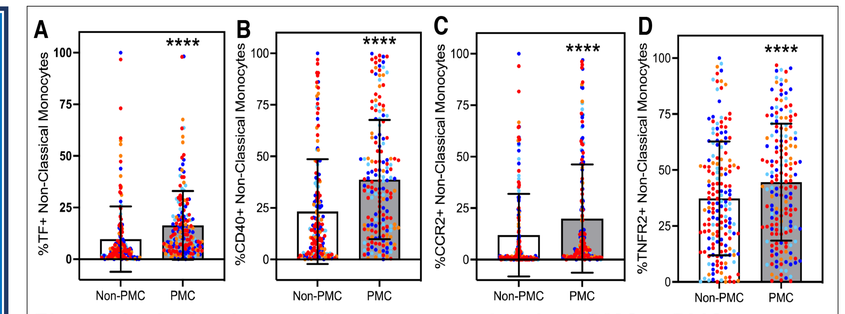


Figure 2: Activation markers on non-classical PMCs. PMCs express higher levels of **(A)** tissue factor, **(B)** CD40, **(C)** CCR2, **(D)** TNFR2 as compared to non-complexed monocytes irrespective of HIV status. **** P<0.0001

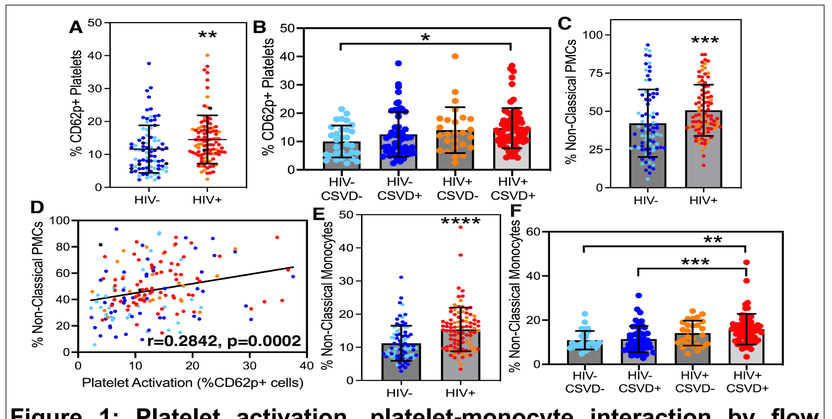


Figure 1: Platelet activation, platelet-monocyte interaction by flow cytometry. Platelet activation (%CD62p+ cells) categorized by **(A)** HIV, **(B)** HIV and CSVD status. **(C)** Percentages of platelet-monocyte complexes (PMCs) among non-classical monocytes. **(D)** Correlation analysis between platelet activation and non-classical PMCs. Percentages of non-classical monocytes categorized by **(E)** HIV, **(F)** HIV and CSVD status. * p<0.05, ** p<0.01, *** p<0.001, **** P<0.0001

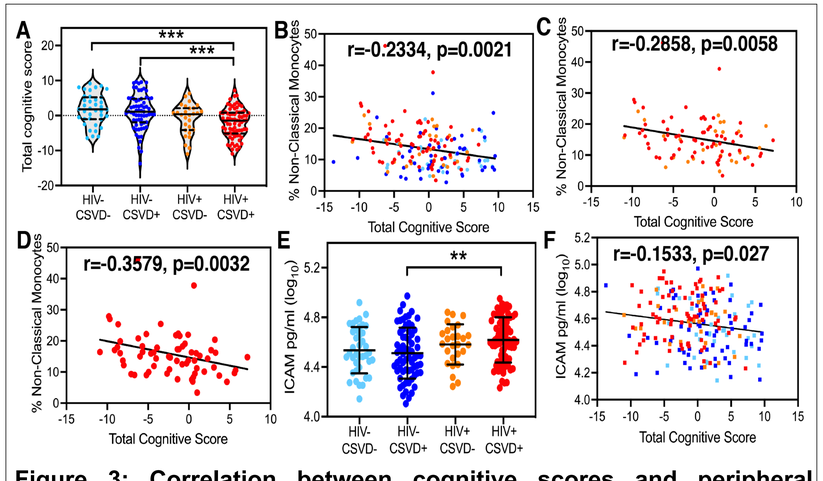


Figure 3: Correlation between cognitive scores and peripheral markers. (A) Total cognitive scores categorized by HIV and CSVD status. Lower scores represent poor cognitive performance. Correlation between cognitive scores and non-classical monocyte percentages for **(B)** all study participants, **(C)** for PLWH and **(D)** for PLWH with CSVD. **(E)** Plasma soluble ICAM levels by ELISA **(F)** Correlation between cognitive scores and ICAM for all study participants ** p<0.01, *** P<0.001