Characterizing the Role of Monocytes in HIV Neuropathogenesis

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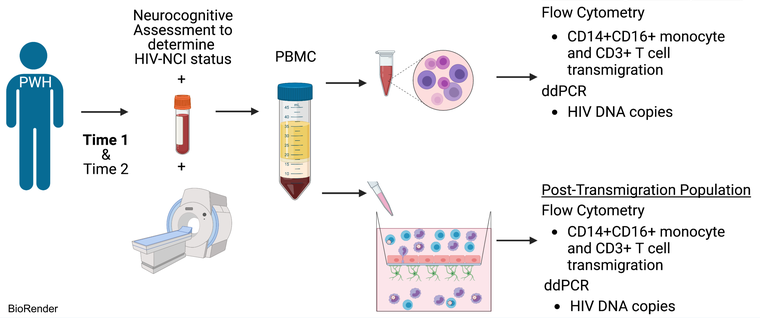
Background

15-40% of people with HIV (PWH) develop HIV associated Neurocognitive Impairment (HIV-NCI) despite viral suppression with ART. HIV-NCI is mediated, in part, by transmigration of infected CD14+CD16+ monocytes across the blood brain barrier (BBB), establishing a CNS viral reservoir, resulting in neuroinflammation and neuronal damage. We showed PWH have higher transmigration of CD14+CD16+ monocytes across a BBB model to CCL2, elevated in the CNS of PWH. It unknown if cells that harbor viral DNA (HIV⁺) contribute to HIV-NCI more than cells that do not. This study characterizes CCL2-mediated transmigration of CD14+CD16+ monocytes across the BBB of PWH on ART with and without HIV-NCI. It also evaluates associations between HIV-NCI and neurometabolites using neuroimaging.

Methods



Cohort Study: Manhattan HIV Brain Bank	
Inclusion Criteria	• Adults with HIV • ART for at least 3 months (tenofovir-emtricitabine backbone) • HIV plasma RNA levels below 1000 copies/mL • English fluency
Exclusion Criteria	• Active Substance Use Disorder • Hepatitis C

Table 1: Cohort Characteristics at Study Entry

Cohort Characteristics mean (SD), median [IQR], or n(%)	Overall (N=52)	Normal Cognition (n=23)	HIV-NCI (n=29)	P value
Age (yr)	54.8 (5.8)	53.3 (5.1)	56.1 (6.0)	0.08
Sex				
Female	27 (51.9%)	14 (60.9%)	13 (44.8%)	0.28
Male	25 (48.1%)	9 (39.1%)	16 (55.2%)	
Race				
Black	32 (61.5%)	15 (65.2%)	17 (58.6%)	
White	13 (25.0%)	6 (26.1%)	7 (24.2%)	0.67
Other/More than one race	7 (13.5%)	2 (8.7%)	5 (17.2%)	
Ethnicity				
Identify as Hispanic	15 (28.9%)	6 (26.1%)	9 (31.0%)	0.69
HIV-NCI	29 (55.8%)			
Nadir CD4	211 [126-384]	200 [127-376]	270 [124-387]	0.77
CD4 T cell count	636 [543-807]	685 [559-992]	619 [495-760]	0.29
Education	14 [12-16]	13 [12-16]	14 [12-16]	0.63
Plasma HIV RNA level				
Undetectable	28 (53.9%)	12 (52.2%)	16 (55.2%)	
Less than 20	8 (15.4%)	3 (13.0%)	5 (17.2%)	0.86
Above 20	16 (30.8%)	8 (34.8%)	8 (27.6%)	

Pairwise comparison performed by two-tailed t test, Mann-Whitney test, or Fisher's exact test

Figure 1: CD14+CD16+ monocytes are enriched after PBMC transmigration across the BBB to CCL2

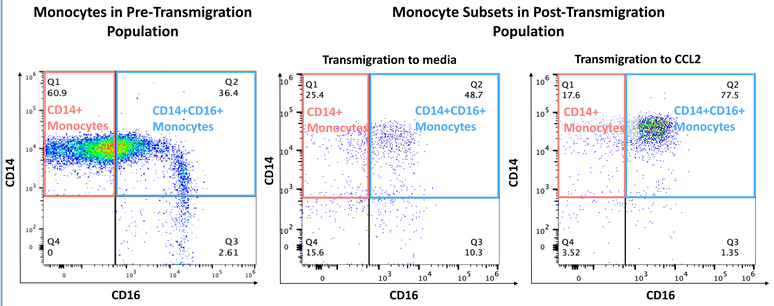


Figure 1: Flow cytometry plots illustrate that CD14+CD16+ monocytes represent the majority of transmigrated monocytes. Transmigration across the BBB to media alone is used as baseline control for each participant.

Figure 2: PWH on ART with HIV-NCI have higher transmigration of CD14+CD16+ monocytes to CCL2 than PWH on ART with normal cognition at Time 1

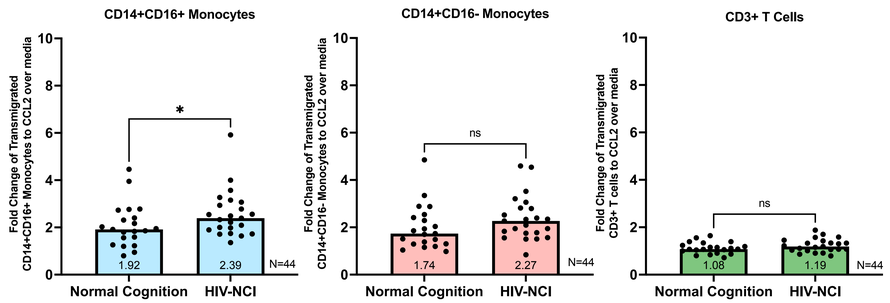


Figure 2. Fold change in transmigration of each cell type to CCL2 was calculated by setting percent of cells transmigrating across the BBB to media alone as a baseline of 1. Fold change in transmigration of each cell type was compared between those with HIV-NCI and those with normal cognition. CD14+CD16+ monocytes transmigrated more in those with HIV-NCI (Median=2.39) than those without (median=1.92). There was no difference in fold change of transmigration to CCL2 of CD14+CD16- monocytes and of CD3+ T cells between those with and without HIV-NCI. *p<0.05, Mann-Whitney Rank Sum Test.

Figure 3: PWH on ART with impairments in the domains of Speed Information Processing and Working Memory have higher transmigration of CD14+CD16+ Monocytes to CCL2 at Time 1

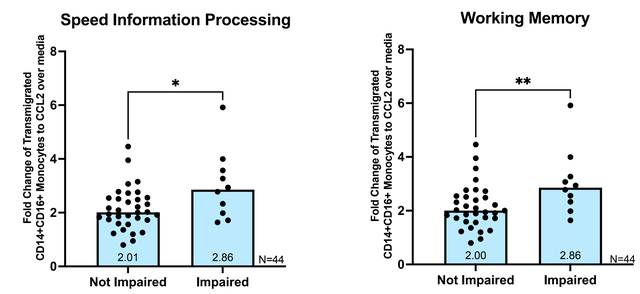


Figure 3. Fold change in transmigration of CD14+CD16+ monocytes across the BBB to CCL2 is higher in PWH on ART with impairments in the domains of Speed Information Processing (SIP) and Working Memory (WM), domains impacted by HIV-NCI. Participants were assigned normalized T scores for several cognitive domains. Impairment was classified as having a T score less than 40. Median fold changes for those with normal SIP= 2.01, impaired SIP=2.86, normal WM=2.00, impaired WM=2.86. P<0.05, Mann-Whitney Test.

Figure 4: CD14+CD16+ monocytes are enriched after PBMC transmigration across the BBB

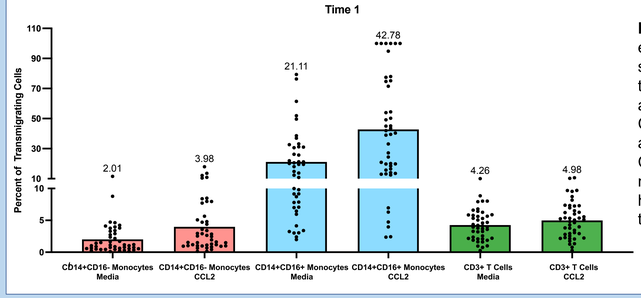


Figure 4: Percent of each immune cell subset that transmigrates across the BBB to CCL2 or media alone is shown. CD14+CD16+ monocytes are highly enriched after transmigration.

Figure 5: Preliminary analysis shows linear association between neurometabolite ratios in left caudate with cognitive domains at Time 1

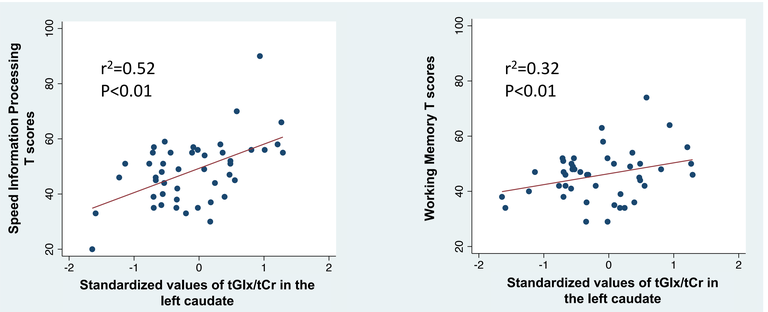


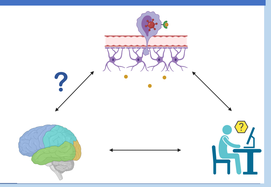
Figure 5. Neurometabolite ratios in the left caudate were standardized into z scores and correlated with cognitive domain T scores. Significant linear associations were found between SIP T scores and standardized values of total glutamate and glutamine over total creatine (tGlx/tCr) (r^2=0.53, p<0.01), and between WM T scores and tGlx/tCr (r^2= 0.32, p<0.1). Pearson Correlation test.

Future Directions

- Complete longitudinal arm of the study
- Perform statistical modeling to determine associations between peripheral immune cells, cognitive function, and neurometabolite indicators of neuronal health to characterize further HIV-NCI pathogenesis in the context of viral suppression

Significance

CD14+CD16+ monocyte transmigration across the BBB to CCL2 contributes to HIV-NCI in PWH with viral suppression



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