Association of CSF Viral Compartmentalization and Macrophage Tropism with Neurosymptomatic HIV

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Background

HIV-1 can be detected in CSF throughout untreated infection but it is unknown how often this is due to local replication in the CNS versus infected T cells entering the CNS from the blood. Local replication can generate genetically distinct viral populations in the CNS (compartmentalized) that can include the unique ability to efficiently infect myeloid lineage cells (macrophage- or M-tropic). Little is known about the frequency of compartmentalized and/or M-tropic HIV-1 in the CNS of people with HIV-1 (PWH) who are neurosymptomatic (including HIV-associated dementia/HAD) or who have less severe symptoms.

Methods

Partial HIV-1 *env* genes (V1-V3) were sequenced from viral RNA in plasma and CSF samples collected from a cross-sectional cohort of ART-naïve PWH (N=109). For a subset of PWH (N=45), full-length *env* genes were also generated and analyzed for the ability to efficiently enter cells expressing low surface CD4 density (M tropism); distinguishing them from T-tropic HIV-1 which requires a high CD4 density for efficient entry. Phylogenetic analyses and modified Slatkin-Maddison tests identified compartmentalized viral populations in CSF, and Inflammatory biomarkers were measured in plasma and CSF. Standardized questionnaires or clinical diagnosis were used to determine if PWH were neurosymptomatic (NS) or neuroasymptomatic.

Cohort

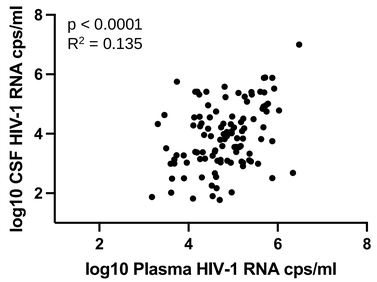
	All (N = 109)	Symptomatic (N = 55)	Asymptomatic (N = 49)
Plasma HIV-1 RNA (log_{10}copies/ml), median (IQR)	4.8 (4.3 - 5.2)	4.8 (4.3 - 5.4)	4.8 (4.3 - 5.2)
CSF HIV-1 RNA (log_{10} copies/ml), median (IQR)	3.9 (3.1 - 4.6)	4.3 (3.4 - 5.2)	3.5 (3.0 - 4.0)
CSF:Plasma HIV-1 RNA $log_{10}\Delta$, median (IQR)	-0.91 (-1.58 - -0.23)	-0.59 (-1.18 - 0.10)	-1 (-1.92 - -0.79)
Blood CD4 (cells/ul), median (IQR)	173 (70 - 281)	139 (56 - 238)	239 (85 - 331)
Nadir Blood CD4 (cells/ul), median (IQR)	167 (54 - 282)	177 (46 - 261)	167 (53 - 302)
CSF WBC (cells/ul), median (IQR)	5 (1 - 10)	5 (1 - 13)	6 (2 - 9)
Compartmentalization, %	34	49	20

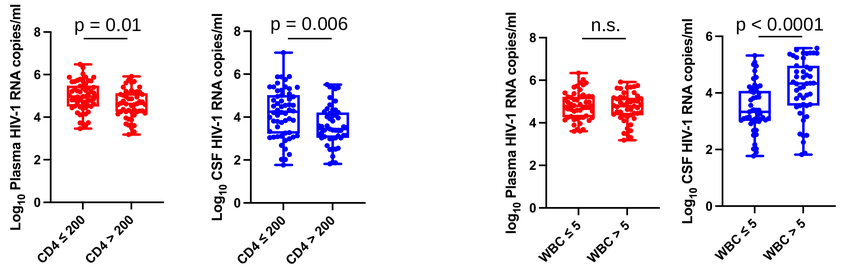
• 109 untreated PWH with paired blood and CSF samples

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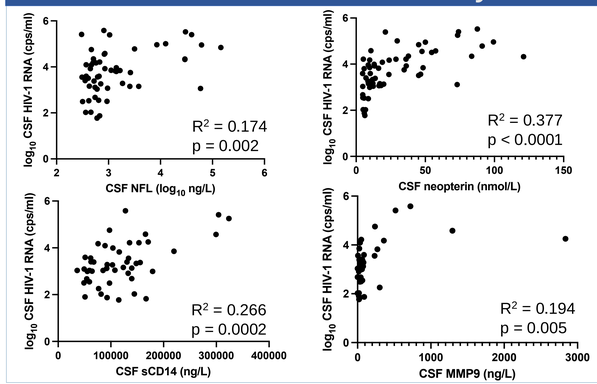
HIV-1 RNA in the CSF, but not blood, is associated with elevated CSF white blood cell count





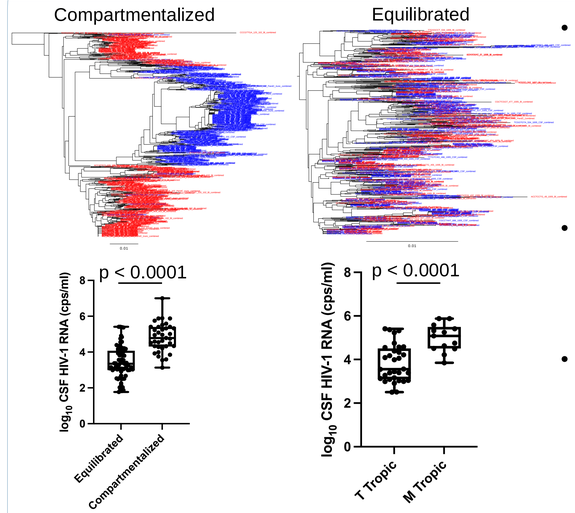
- Plasma HIV-1 RNA and CSF HIV-1 RNA are correlated although not very tightly
- Plasma and CSF HIV-1 RNA are associated with blood CD4+ T cell count
- CSF HIV-1 RNA , but not plasma HIV-1 RNA, is associated with elevated CSF WBC count

Levels of CSF HIV-1 RNA are correlated with some inflammatory biomarkers



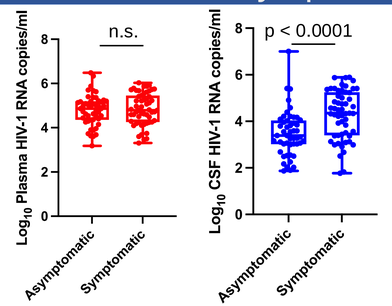
CSF NFL, neopterin, IP10, sCD14, sCD163, MMP9 and TNFa are correlated with levels of CSF HIV-1 RNA

Levels of CSF HIV-1 RNA are associated with compartmentalization and macrophage tropism



- A phylogenetic tree was generated for each participant, representative examples shown here
- 34% of participants have compartmentalized virus in the CSF
- CSF HIV-1 RNA is higher with CSF compartmentalization and when macrophage-tropic virus is present

Level of CSF HIV-1 RNA is higher in neurosymptomatic participants



- CSF HIV-1 RNA, but not plasma HIV-1 RNA, is associated with neurologic symptoms
- Higher CSF HIV-1 RNA is associated with M-tropism in PWH with symptoms but not T-tropism

	Median CSF HIV-1 RNA (copies/ml)	
	Neurosymptomatic	Asymptomatic
Compartmentalized M tropic (N = 13)	117,187	11,854
Compartmentalized T tropic (N = 8)	21,380	20,958
Compartmentalized unknown tropism (N = 16)	102,000	7,040
Not compartmentalized (N = 72)	2,974	1,833

Conclusions

- Higher HIV-1 RNA in the CSF is associated with:
  - Biomarkers for greater CNS inflammation (neopterin, IP10, MMP9, CSF WBC) and monocyte/macrophage activation (sCD14)
  - Replication in the CNS (CSF compartmentalization)
  - Adaptation to infect myeloid cells (macrophage tropism)
  - The presence of neurologic symptoms
  - More neuronal damage (NFL)