



Quantitating HIV-1 RNA in brain tissue:

Prediction by antemortem cerebrospinal fluid (CSF) versus plasma viral load

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Abstract

Although numerous investigations have employed cerebrospinal fluid (CSF) HIV RNA levels as a surrogate measure of the magnitude of viral replication in brain parenchyma, direct comparisons of viral load in CSF and brain tissue have been reported previously for only 22 patients. In 26 subjects who had undergone both ante-mortem (A-M) clinical and post-mortem (P-M) neuropathological assessments, we measured HIV RNA by RT-PCR in A-M CSF and plasma as well as P-M frontal cortex (FC) and subcortical white matter (SCWM). The median interval between A-M and P-M evaluations was 15 weeks (interquartile range 9, 28). As a predictor of viral load in P-M FC, A-M CSF viral load; was better than plasma. Parallel analyses for viral load in P-M SCWM yielded similar results. In stepwise regressions predicting brain viral load from A-M plasma and CSF viral load, A-M CSF entered the model first; adding A-M plasma to the model provided no additional predictive power. As a predictor of HIV replication in brain tissue, viral load in CSF is better than in plasma. These findings are consistent with compartmentalization of HIV infection in the CNS, and support the utility of CSF viral load as a surrogate for brain tissue viral replication, at least near the end of life.

Background

- The principal target cells for HIV infection in the brain (macrophages, microglia) differ from those in the periphery (lymphocytes)
- Because HIV replication cannot be measured directly in brain during life, CSF and plasma viral loads have been studied as surrogates
- Direct comparisons of viral load in CSF and brain tissue have been reported previously for 22 patients (McArthur et al. Ann Neurol. 1997; 42: 689).

Objective

To compare viral load (HIV RNA) in plasma and CSF as surrogates for brain tissue viral load.

Methods

- SUBJECTS:** 26 HIV-infected individuals underwent ante-mortem (A-M) clinical and post-mortem (P-M) neuropathological assessments. Median interval between A-M and P-M evaluations was 15 weeks (interquartile range 9, 28).
- BRAIN HIV RNA EXTRACTION:** see Figure 3
- VIRAL LOAD DETERMINATION:** HIV RNA by RT-PCR (Roche Amplicor®)
 - A-M CSF - ultra-sensitive (sensitivity 50 copies/mL)
 - A-M plasma standard version 1, sensitivity 400 copies/mL)
 - P-M frontal cortex (FC), subcortical white matter (SCWM) - ultra-sensitive
- ANTIRETROVIRAL THERAPY (ART):** Regimens at last A-M visit classified as highly active (HAART - 3 or more ARVs) or non-HAART (no ARVs, monotherapy or dual therapy)
- STATISTICAL ANALYSIS:** Viral loads log₁₀ transformed; non-parametric analyses used
 - Correlation of A-M and P-M viral load evaluated by linear regression.
 - Stepwise regression to evaluate CSF vs plasma as predictors of brain viral load

Figure 1. Relationship of Brain Viral Load to A-M Viral Load

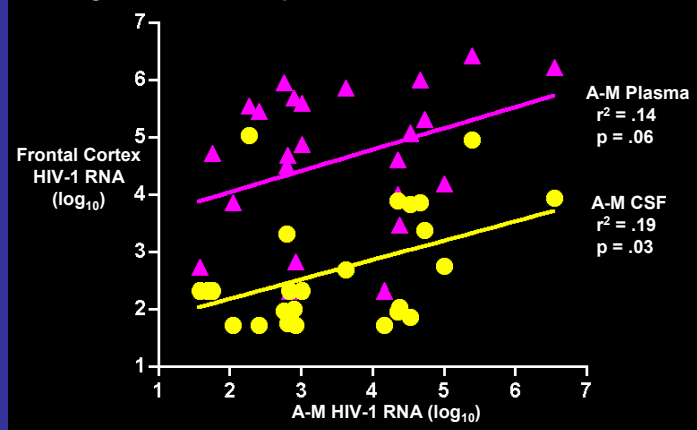
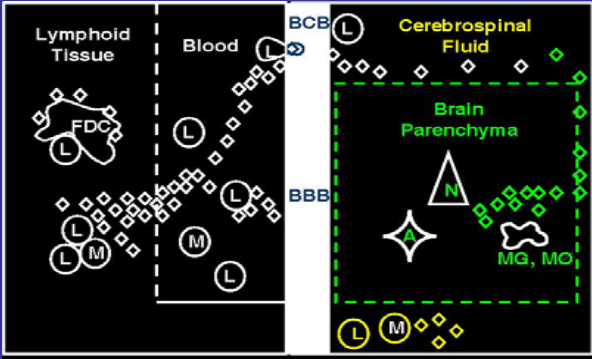


Table 1. Subject characteristics.

Demographics		Clinical Characteristics	
Age, yrs*	42.1 (34.8 - 48.4)	CD4 Count*	59 (8 - 178)
Education, yrs*	13 (12 - 14)	PL RNA (log ₁₀)*	4.8 (3.7 - 5.6)
Ethnicity:		CSF RNA (log ₁₀)*	2.3 (1.9 - 3.5)
White	18 (69%)	On HAART	11/20 (61%)
Black	3 (12%)	AIDS	25 (96%)
Other	5 (19%)	AM-PM Interval (wks)*	15(9-28)
Male	21 (81%)	CSF WBC* ¹	1 (0 - 2)

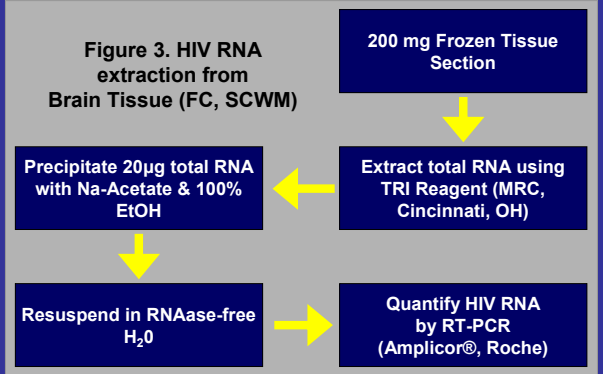
*Median (IQR), ¹n=20

Figure 3. Schematic of CSF - brain and blood - lymphoid tissue relationships.



BCB blood-CSF barrier
 BBB blood-brain barrier
 FDC follicular dendritic cell
 L, M lymphocyte, monocyte
 N neuron
 A astrocyte
 MG microglial cell
 MO macrophage

Figure 3. HIV RNA extraction from Brain Tissue (FC, SCWM)



Results

- As a predictor of viral load in P-M FC, A-M CSF viral load; was better than plasma.
- Parallel analyses for viral load in P-M SCWM yielded similar results.
- In stepwise regressions predicting brain viral load from A-M plasma and CSF viral load, A-M CSF entered the model first; adding A-M plasma to the model provided no additional predictive power (Table 2).

Table 2. Predictors of frontal cortex HIV viral load.

Predictors	F	R ²	Δ R ²	P
CSF HIV RNA	5.5	0.19	--	0.03
Plasma HIV RNA	3.8	0.14	--	0.06
CSF + Plasma HIV RNA	3.3	0.23	0.04	0.05

Summary

- Antemortem plasma and CSF viral loads both significantly predicted post-mortem brain tissue viral load
- CSF was somewhat (non-significantly) better than plasma as a predictor of brain viral load
- Stepwise multiple regression supported the conclusion that CSF viral load was more closely related to brain viral load
- Even after accounting for antemortem viral loads in plasma and CSF, there remained substantial unexplained variability in brain viral load

Conclusions

- Findings support the utility of CSF viral load as a surrogate for brain tissue viral replication near the end of life
- Results are consistent with compartmentalization of HIV infection in the CNS

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