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Sex-based Differences in HIV-1 DNA in Brain and Neurocognition

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Background

- HIV persists in the brain.
- The clinical and biological factors that influence HIV in brain tissue are unknown.

Objective

To measure the size and distribution of the HIV reservoirs in post-mortem brain tissue from suppressed HIV-infected women and men, and its association with neurocognitive (NC) functioning.

Methods

- 63 cases selected from the National NeuroAids Tissue Consortium (1999-2014): 12 women and 51 men.
- Suppressed HIV-infected participants dying on ART without evidence of CNS opportunistic disease.
- Neurocognitive (NC) functioning was measured by Clinical Rating based on 7 neuropsychological abilities, measured at last visit (median 3 months before death).
- Paired post-mortem [i] frontal (FC) and [ii] occipital (OCC) cortex, [iii] basal ganglia (BG) and [iv] peripheral lymphoid tissues (lymph node and spleen) had HIV DNA levels measured by droplet digital (dd)PCR (HIV Gag), normalized for cellular input (human RPP30 gene).
- Bayesian hierarchical regression model was used to evaluate the relationship between brain regions, sex, and NC functioning. The model used a zero-inflated negative-binomial family with a logit link function. Significance was assessed with the Bayesian p-value: $2*p(\theta>0|X)$.

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Results

- HIV DNA was detected in 62.5% of brain samples and 100% of lymphoid tissues (table).
- HIV DNA copies ranged 2.3 to 2,968 /10^6 cells in brain and 9.3 to 3,741 /10^6 cells in lymphoid tissues.
- Lymphoid tissue had higher levels of HIV DNA than brain ($p<0.001$) (table).
- No significant association between HIV DNA in lymphoid and brain tissues ($p=0.7$).
- Among brain tissues, BG had the highest levels of HIV DNA, followed by the FC ($p=0.018$) and OCC ($p=0.005$) (table).

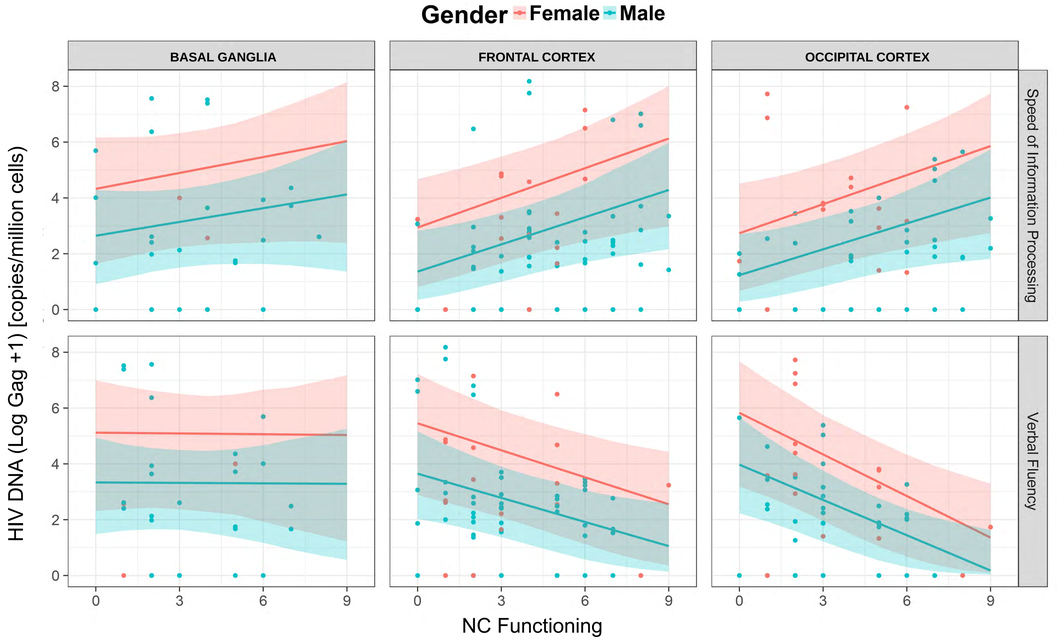
Table. Demographic and Reservoir characteristics between Female and Male.

Parameters	All (n=63)	Female (N= 12, 19%)	Male (N= 51, 81%)
Demographics			
Age[a]	55 [48.5, 61]	56 [49.5, 62.3]	54 [48, 61]
Caucasian %	60.3	25	68.6
Current CD4[a]	164 [80, 390]	330 [126, 453]	155 [77, 285]
EDI (years)[a]	14 [10, 19]	17 [15.5, 19]	13 [8.8, 18.3]
Estimated exposure LT ART (years)[a]	5.6 [2.4, 9.4]	6.2 [4.1, 9.5]	5.3 [2, 9.4]
Global Clinical Rating (CR)	6 [4, 7]	5.5 [4, 6]	6 [4, 7]
HIV DNA [% detectable (n)][b]			
Frontal Cortex	65.6 (61)	75 (12)	63.3 (49)
Occipital cortex	56.6 (60)	66.6 (12)	47.6 (42)
Basal Ganglia	67.8 (31)	100 (2)	65.6 (29)
Lymphoid Tissue	100 (37)	100 (6)	100 (31)
HIV DNA [cps/million cells][c]			
Frontal Cortex	13 [5.7 – 28.2]	30.1 [24.5, 106.7]	10.8[5.5, 21.2]
Occipital cortex	9.3 [5.2, 36.9]	26.4 [4.2, 51.6]	7.6 [5.4, 26.4]
Basal Ganglia	20.3 [7.4, 53.6]	29.8 [18, 41.7]	20.3 [8.7, 75.3]
Lymphoid Tissue	85.6 [72, 174.8]	102.8 [56.2, 648.2]	83.3 [51, 187]

ART=antiretroviral therapy; LT=lifetime. EDI: estimated duration of infection.
[a]Data shown as median [interquartile range]
[b]Data shown as % (n= number of processed samples)

- Female sex and younger age were associated with higher HIV DNA in brain ($p=0.026$, $p=0.06$, respectively) but not in lymphoid tissues ($p=0.31$). (Figure)
- None of the tested covariates (EDI, time on ART, CD4) were associated with HIV DNA in brain (all $p>0.2$).
- Overall, NC functioning ranged from mild to moderate impaired and it was not associated with HIV DNA ($p=0.5$).
- When evaluating NC sub-domains (Figure):
  - Higher HIV DNA (any brain region) was associated with slower speed of information processing ($p=0.012$).
  - Higher HIV DNA in FC and OCC (but not BG) was associated with better verbal fluency ($p<0.05$).
  - No sex-differences in NC functioning was observed.

Figure: HIV DNA Levels in Brain tissues of women and men and NC functioning.



Conclusions

- HIV DNA was detected in the majority of brain samples despite documented virologic suppression in blood plasma.
- HIV DNA levels in peripheral lymph tissue did not predict brain HIV DNA levels.
- Women had significantly higher levels of HIV DNA in brain than men but not in the lymph tissues. Also, younger age was associated with higher brain HIV DNA levels.
- Higher levels of HIV DNA in brain tissue affected the speed of information processing in both sexes.
- The association of higher HIV DNA levels with better verbal fluency requires more investigation.