BRAIN INJURY CORRELATES WITH CSF CELL-ASSOCIATED HIV-1 RNA TRANSCRIPTS WHICH ARE LINKED TO CD4+ T CELLS, NOT MONOCYTES.

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Background:
Despite suppressive ART, mild to moderate neurochemical injury remains prevalent in people with HIV-1 (PWH). Previously we found that high levels of cell-associated (CA) HIV-1 RNA transcripts in CSF cells correlated with current neuronal and axonal dysfunction. We hypothesized, following the current model, that inflammatory monocytes (Mø) trafficking from blood to the CNS would be the chief source of transcripts in CSF cells.

Methods:
For 16 PWH on fully suppressive ART, DNA and RNA were extracted from: (i) pelleted CSF cells; (ii) paired PBMC; and (iii) Mø highly purified from PBMC using magnetic beads (median 0.3% contaminating CD4 T-cells). CA HIV-1 RNA was quantified by the Double-R πCode MicroDiscs assay, as copies/10^6 cells. CSF cells and PBMC were analyzed by 18-colour flow cytometry. ^{1}H MR spectroscopy was used to assess in vivo neuronal and axonal injury.

Results:
CA HIV-1 RNA transcripts were detected in 14/16 CSF cell samples with a median 9,226 copies/10^6 CD4 T-cells, compared to 185 copies/10^6 CD4 T-cells from PBMC. Higher levels of CSF CA HIV-1 RNA transcripts were associated with greater axonal injury (Std β=-0.73; $p<0.01$). CA HIV-1 RNA levels in CSF cells were strongly correlated with PBMC levels ($r=0.83$; $p=0.003$). CSF cells contained median 3,605 CD4 T-cells (enriched in memory CXCR3+CD49d+CCR5+ cells), but only 378 Mø (>90% intermediate CD14+CD16+ phenotype). 10/16 highly purified Mø isolations (containing >10^5 cells) from PBMC samples were undetectable for CA HIV-1 RNA transcripts, while 6 Mø isolations were detectable with median 9 copies/10^6 Mø compared with 306 copies/10^6 CD4 T-cells.

Conclusion:
With suppressive ART, the contribution of Mø CA HIV-1 RNA transcripts to PBMC was vanishingly small, strongly suggesting a novel neuropathogenesis model where residual HIV-infected memory CXCR3+CD49d+CCR5+ CD4 T-cells in blood, rather than Mø, seed the brain through trafficking, with subsequent involvement of longer-lived resident brain macrophage lineage cells.

Disclosure of Interest Statement:

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All other authors report no conflicts of interest.