Effect of ART Treatment on Macrophage Accumulation in the CNS with SIV.

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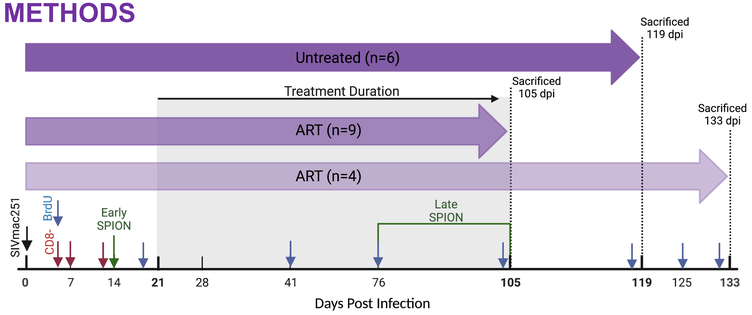
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BACKGROUND

Perivascular macrophage (PVM) are a major target for HIV and SIV and a viral reservoir in the CNS. Few studies have been done on PVM and other CNS macrophages in SIV infected monkeys or HIV infected humans on ART or following ART interruption. We used i.c. injections of SPIONs—that are selectively taken up by CNS PVM—and assessed the number of SPION labeled PVM in the CNS, CNS meningeal macrophages, and traffic of SPION labeled cells in peripheral tissues including cervical dorsal root ganglia (DRG), cervical draining lymph node, and spleen.

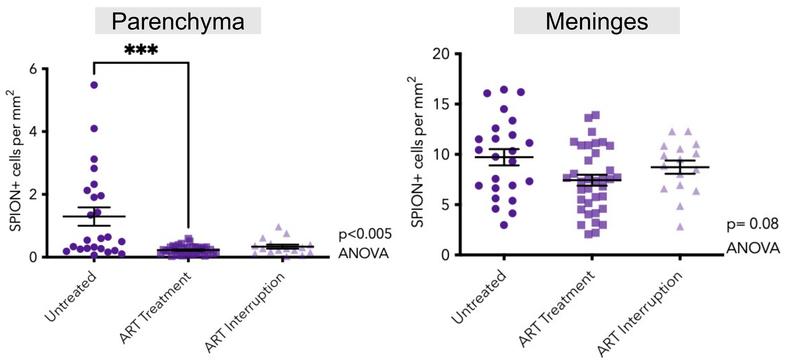
METHODS



Nineteen SIV-infected, CD8-depleted rhesus macaques received I.C. SPION injection at early and late infection time-points. 5-bromo-2′-deoxyuridine (BrdU) was administered by i.v. longitudinally and flow cytometry was quantified to detect recently emigrated monocytes. Plasma sCD163 was measured by ELISA and plasma viral load was quantified throughout infection. SPION containing macrophage (Prussian Blue) and CD163+ PVM (DAB:Brown) accumulation was assessed in cortical CNS regions, peripheral lymphoid tissue, and DRGs. SIV-RNA was detected by RNAscope using probes for SIVmac239. Cell counts are expressed as cells/mm^2. Statical analysis was done using Prism: Mann-Whitney t-test, Kruskal-Wallis test, and Spearman's rank test. ⋆Peripheral tissue was only available and analyzed for 3 ART treated macaques.

RESULTS

Figure 1. ART reduced the number of SPION labeled PVM in the CNS parenchyma, but not in the meninges.



[Right] Triple label IHC: Prussian blue SPION+ cells are CD163+ PVM (brown) adjacent to GLUT-1+ CNS endothelial cells (red).

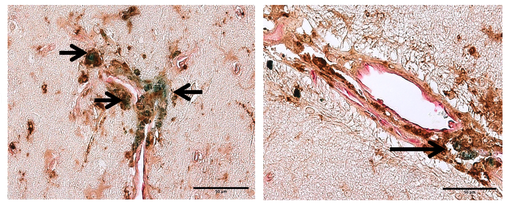


Figure 2. Plasma virus, BrdU+ monocytes, and sCD163 correlates with the number of SPION+ PVM in the brain parenchyma, but less in the meninges.

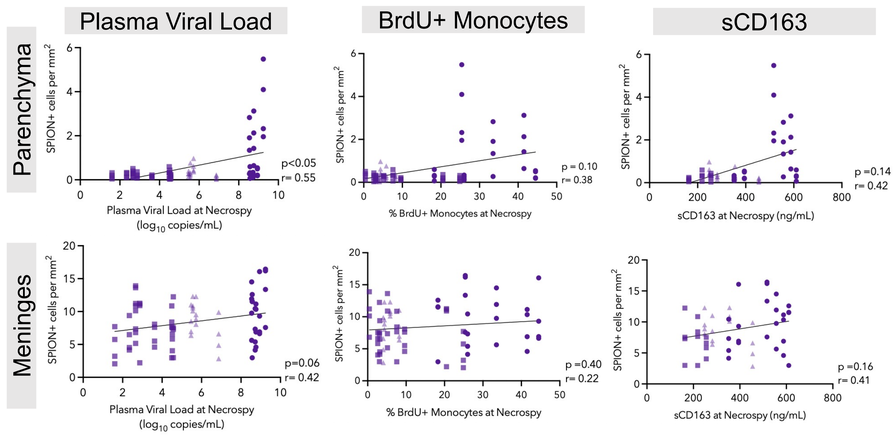
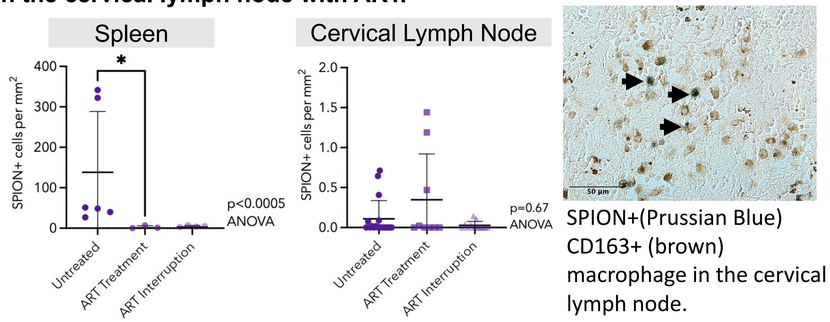
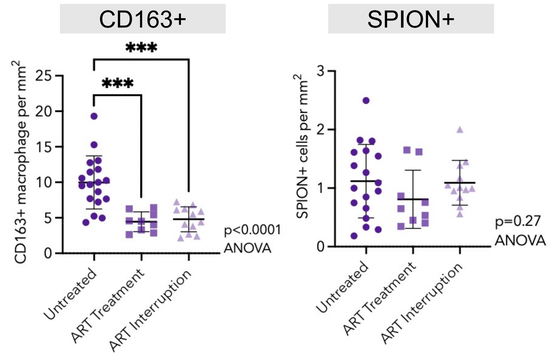


Figure 3. There are decreased numbers of SPION+ cells in the spleen but not in the cervical lymph node with ART.



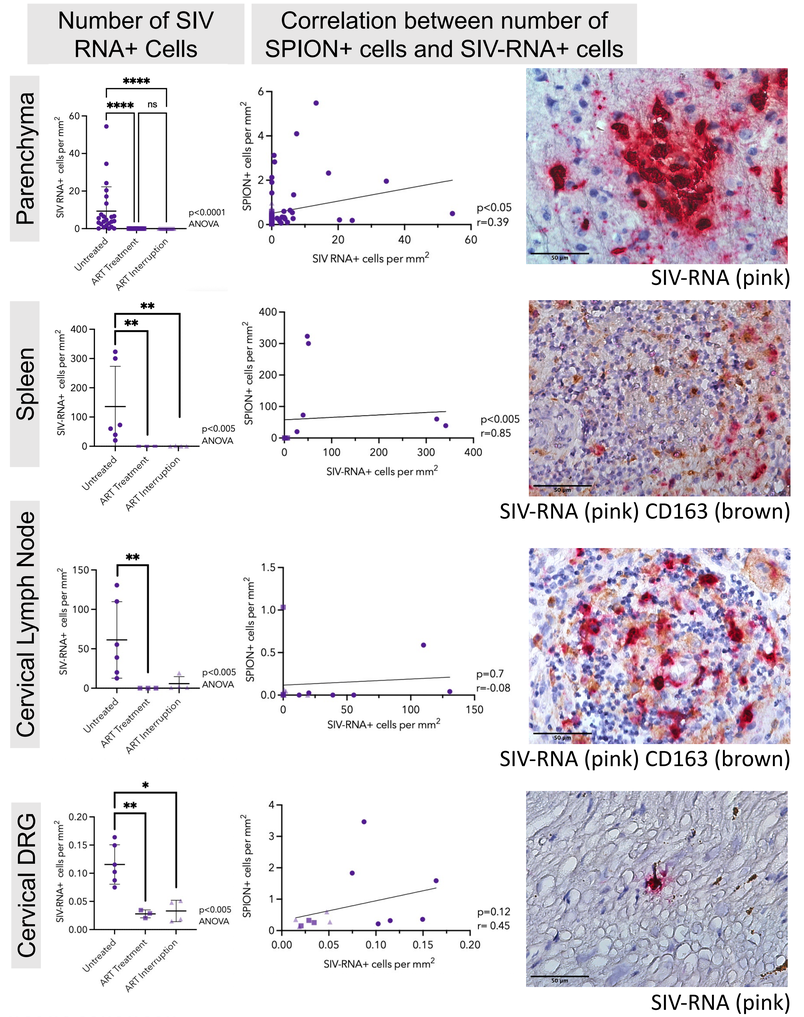
SPION+(Prussian Blue) CD163+ (brown) macrophage in the cervical lymph node.

Figure 4. There is a significance decrease in the number of CD163+ PVM with ART and no difference in the number of SPION+ cells in the cervical DRG.



Unlabeled SPION containing cells (amber) and CD163+ (brown) macrophage in the DRG. Inset: magnification of SPION+ clusters (amber/black).

Figure 5. The number of SIV-RNA+ cells in the CNS, peripheral lymphoid tissue, and DRGs correlates with an increase in the number of SPION+ cells.



CONCLUSIONS

- SPION labeled PVM are found in the CNS parenchyma and in the meninges of SIV infected animals.
- With ART, there is a reduced number of SPION labeled PVM in the parenchyma but a stable, non-changing number of SPION labeled macrophages in the meninges, underscoring differential traffic and retention.
- We found SPION labeled macrophages in the DRG's, cervical lymph node, and spleen with SIV infection that was reduced with ART in the spleen but not in the cervical lymph node and DRG's.

These results are consistent with differential trafficking and retention of PVM in the CNS with SIV infection that is reduced with ART. The kinetics of macrophage traffic in the meninges is consistent with blood, and differential traffic of CNS PVM out of the CNS to the DRG's, cervical lymph node, and the spleen that are reduced with ART.