

11TH EDITION

DECEMBER 10-13, 2024

HIV PERSISTENCE DURING THERAPY

Reservoirs & Eradication Strategies Workshop



Dual-tropic SHIV.D model of systemic and CNS persistence on ART

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No conflicts of interest.

Key Question:

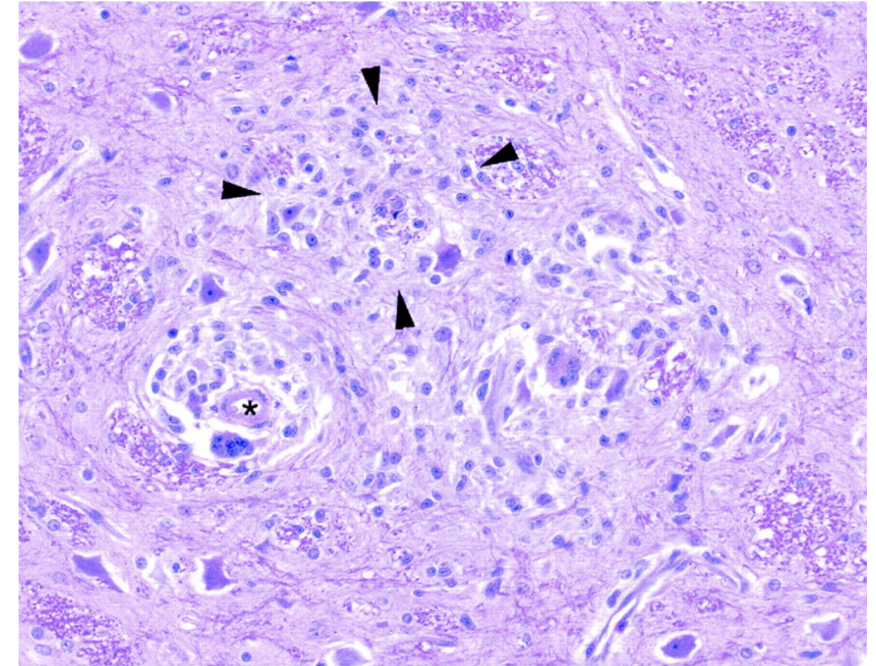
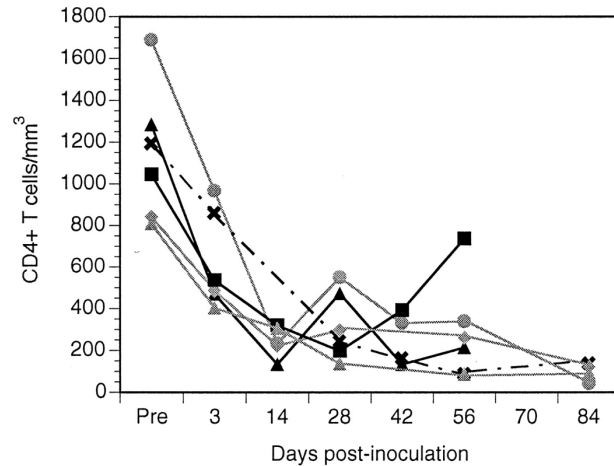
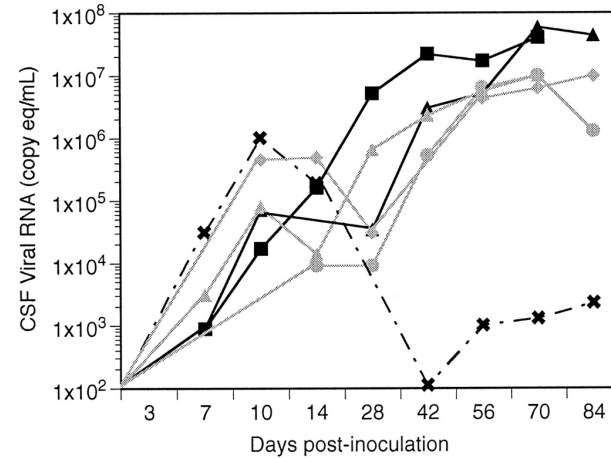
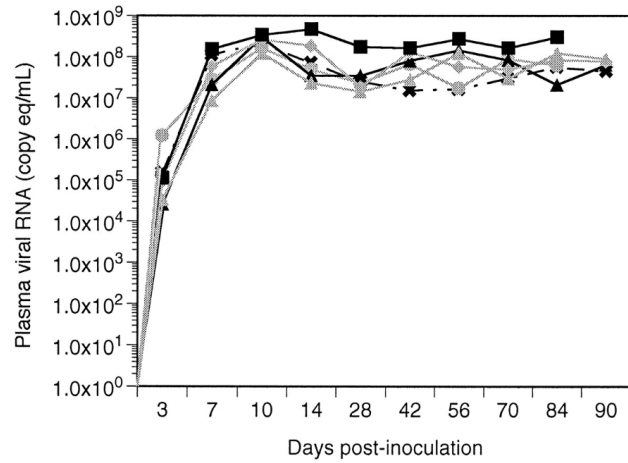
Can we validate a SHIV-NHP model of HIV-1 persistence across brain and systemic tissues, and within CD4 T cells and Macrophages

Key Findings:

In SHIV.D infected Rhesus Macaques that started ART at 10 weeks of viremia and maintained suppression over 9 to 20 months, we found:

- Virus persisted through ART in CD4 T cells and Myeloid cells, within brain and systemic reservoirs
 - Across tissues, reservoir levels were 1-2 logs lower in Macrophage vs. CD4 T cells
 - Brain reservoirs persisted over 9-20 months, detectable by virus barcode quantification and tissue staining

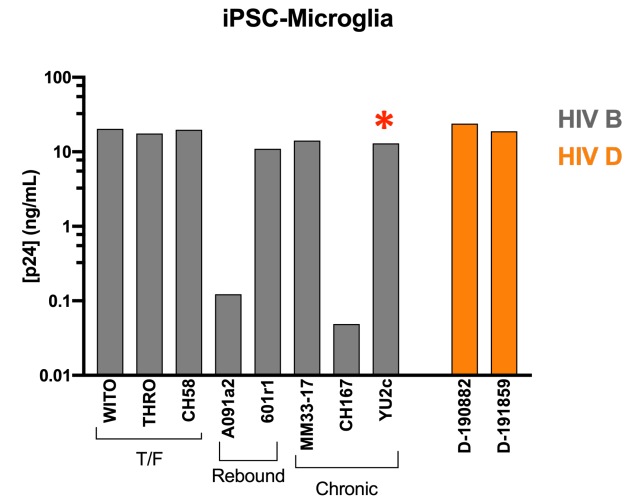
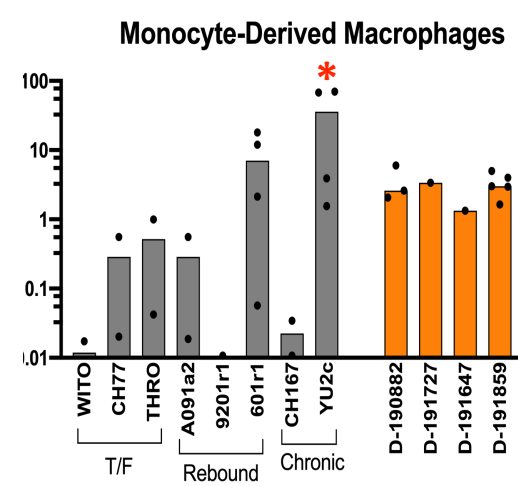
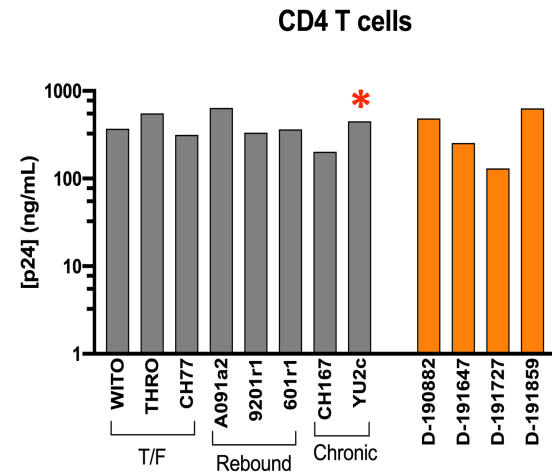
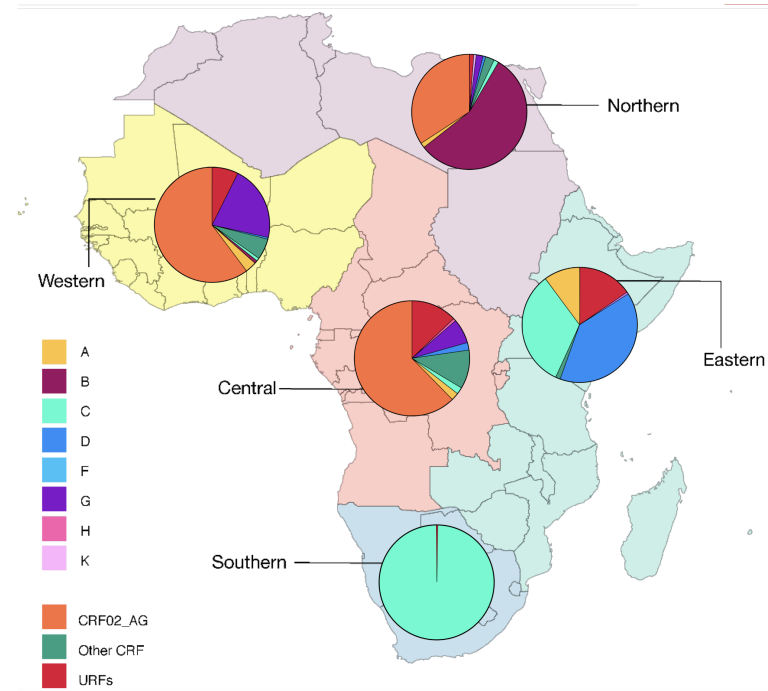
Classic SIV-NHP models of encephalitis



- Mixed pathogenic + neurotropic SIV infection of Pigtailed macaques: SIV/deltaB670 + SIV/17E-Fr
- High VL in plasma ($>10^8$) and CSF; rapid CD4 depletion; frank SIV encephalitis by histology

Zink MC *et al.* J Virol. 1999

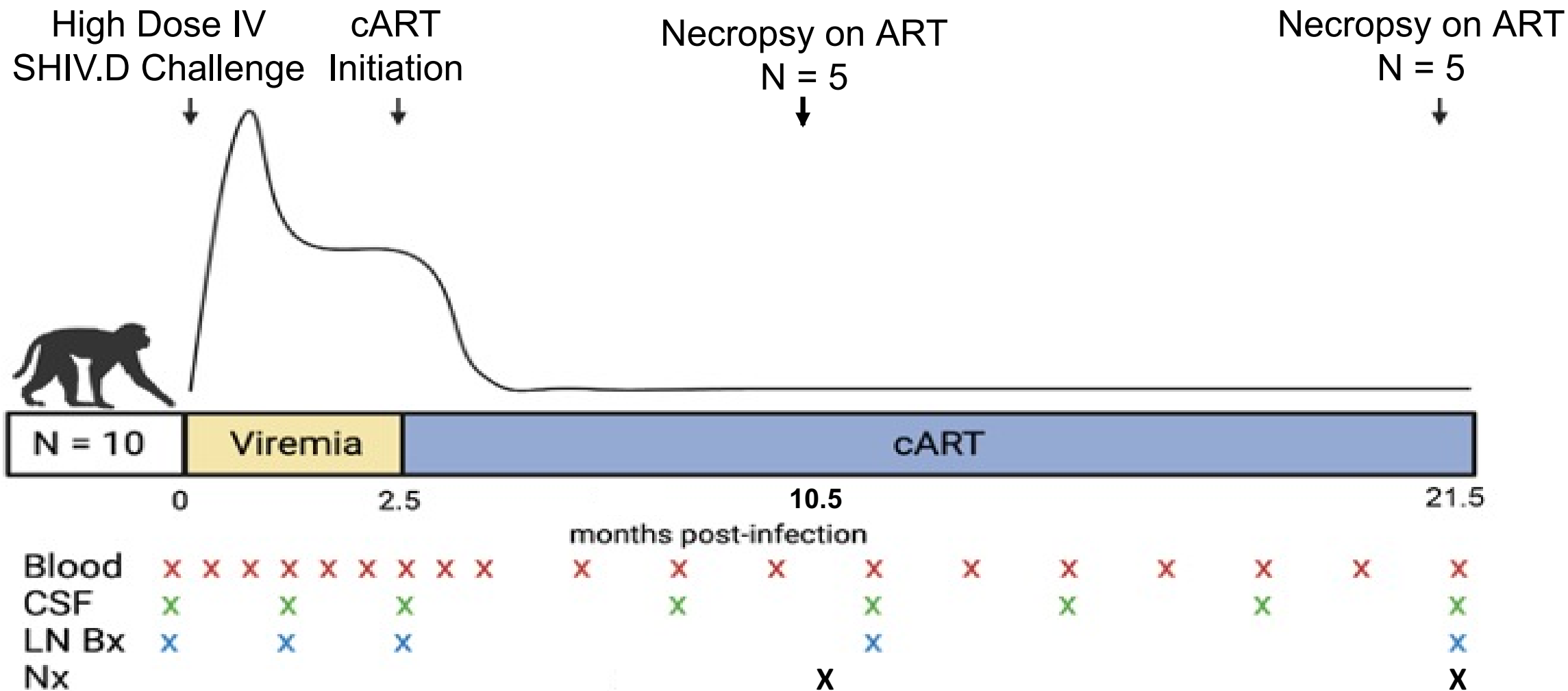
Clade D HIV: CD4 T cell & Macrophage tropism *in vitro*



Clade D is prevalent in East Africa
Associated with rapid progression and neuropathogenesis

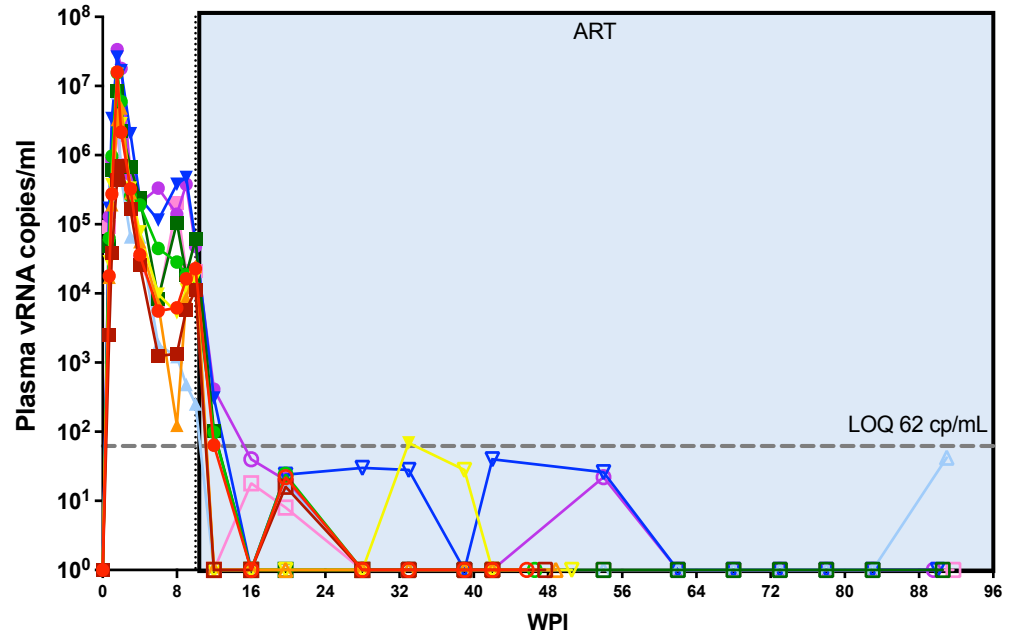
Clade D HIV replication in CD4 T cells and macrophage-lineage cells
Clade B vs. Clade D HIV-1 Primary Isolates

NHP Study Schema

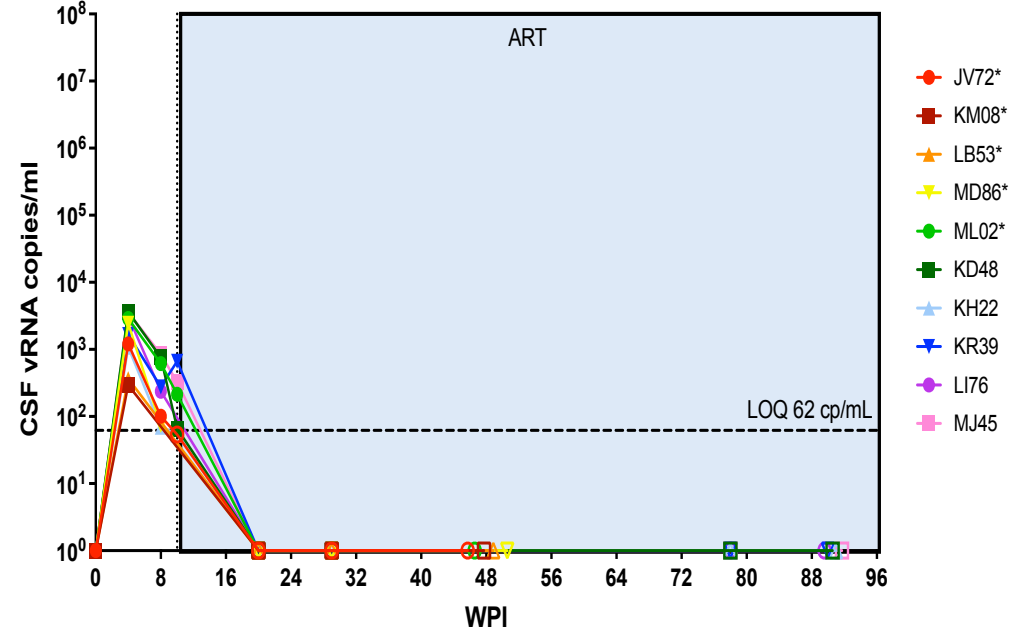


Viral Kinetics

Plasma VL



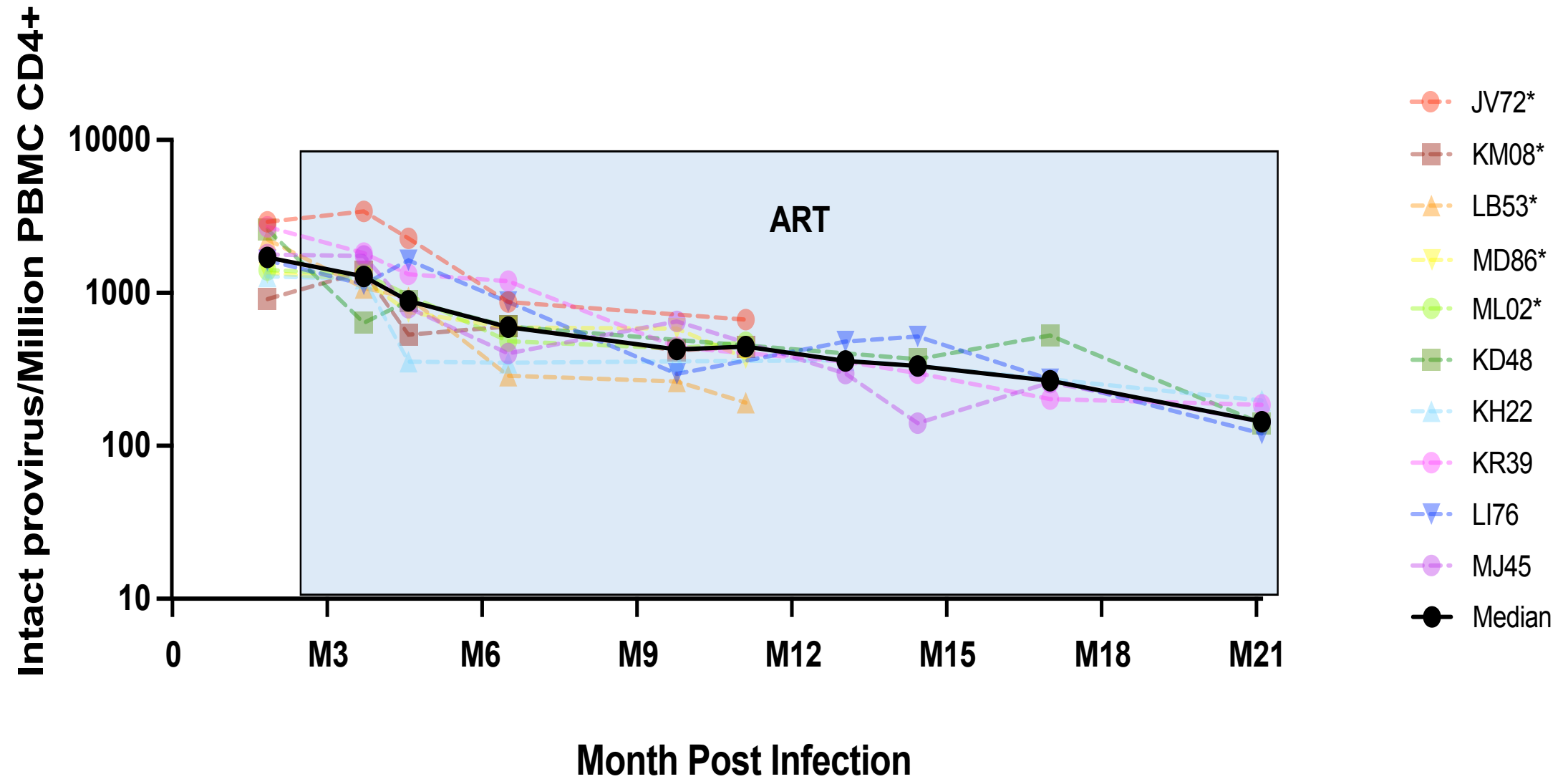
CSF VL



Viral kinetics pre- and post- ART
 are similar to HIV-1 in humans

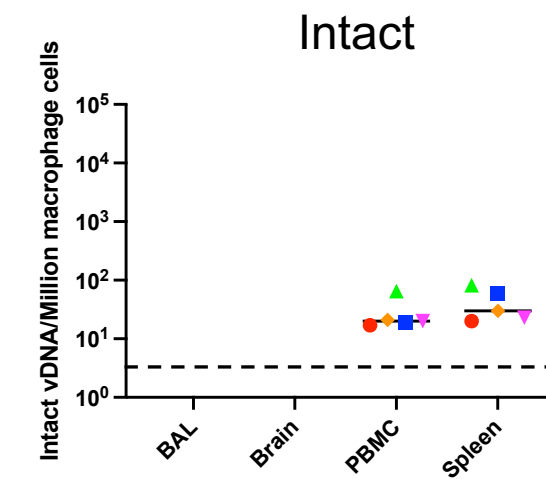
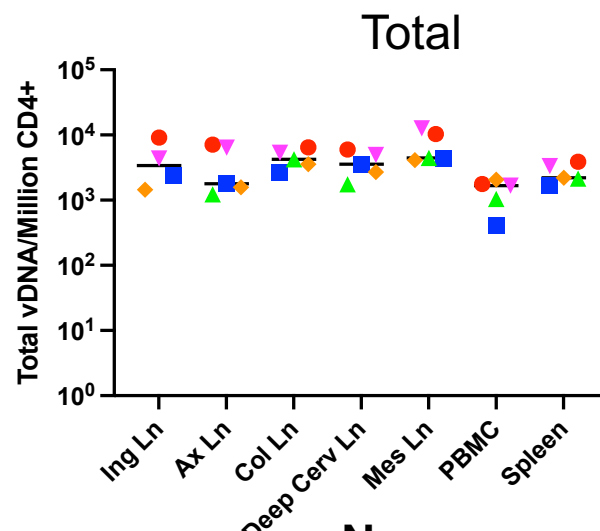
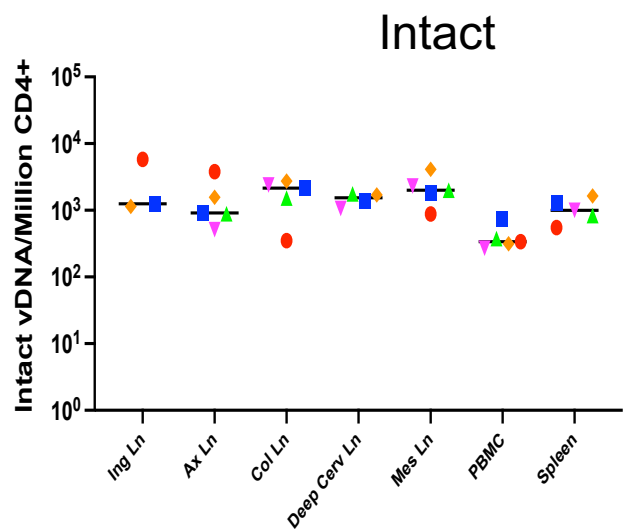
CSF VL ~ 2 log below
 plasma viremia

Reservoir quantification in peripheral CD4+ T cells: IPDA

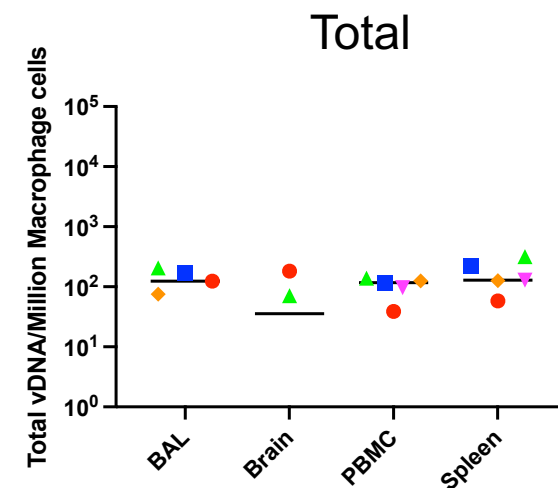


Reservoir quantification at 9 and 20 months ART

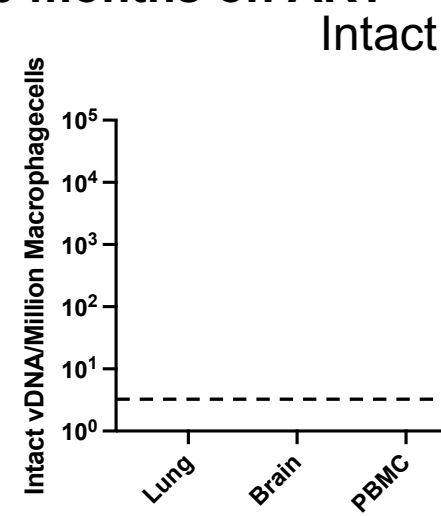
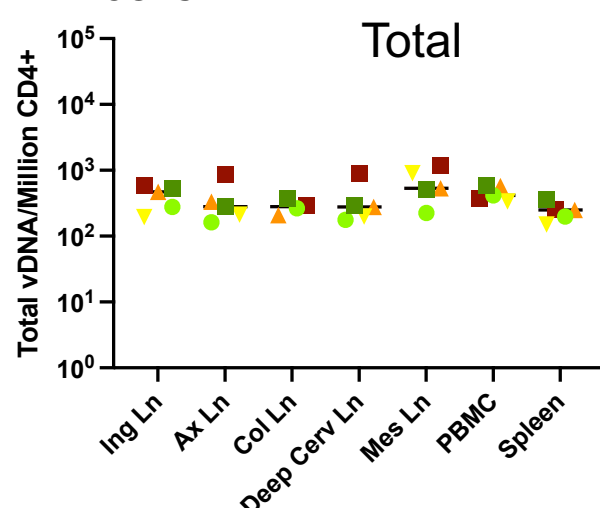
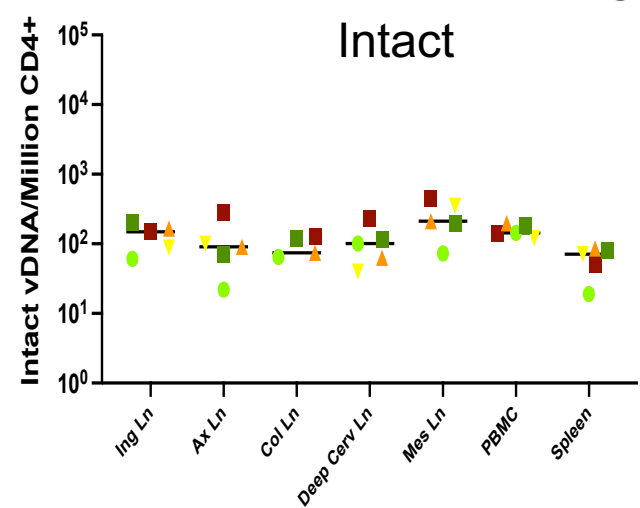
CD4+ T cells Necropsy - 9 months on ART



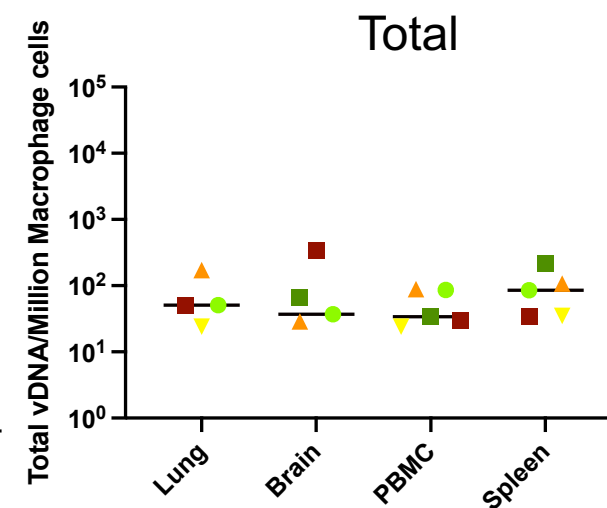
MΦ cells



CD4+ T cells Necropsy - 20 months on ART



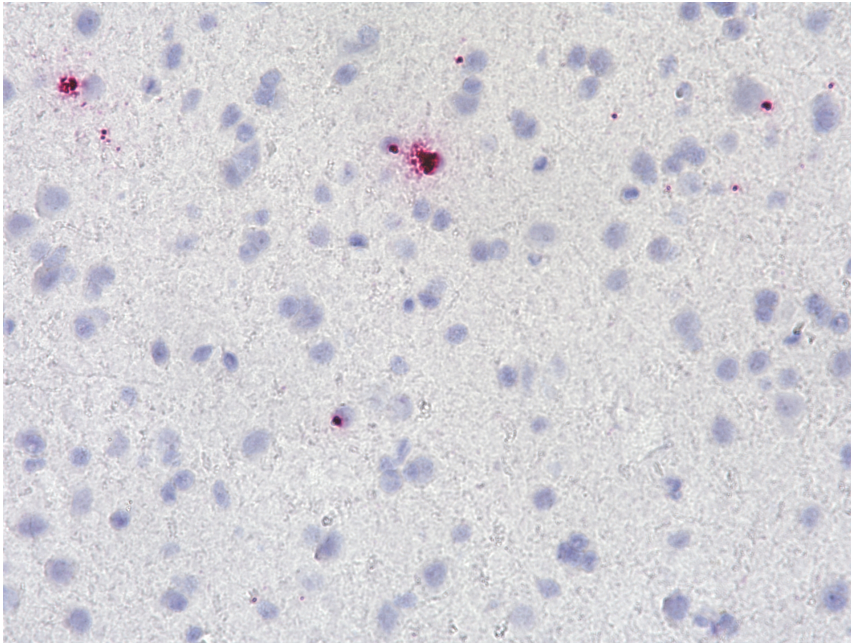
MΦ cells



Reservoir quantification: DNAscope in CNS at m9 necropsy

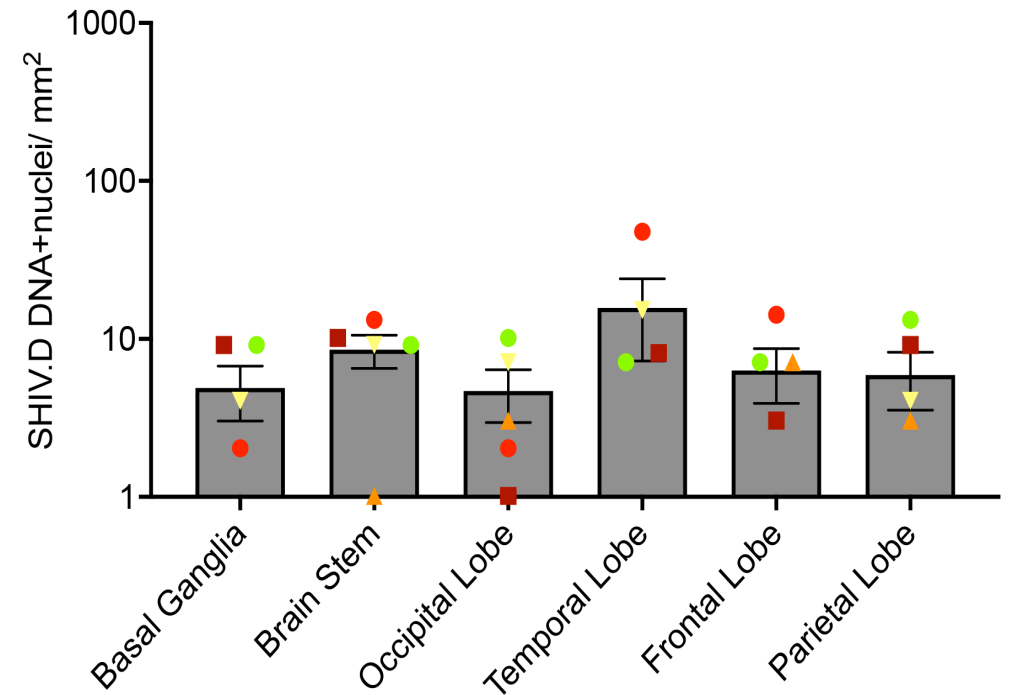
Necropsy - 9 months on ART

DNAscope



KM08 Parietal Lobe (20X)

DNAscope

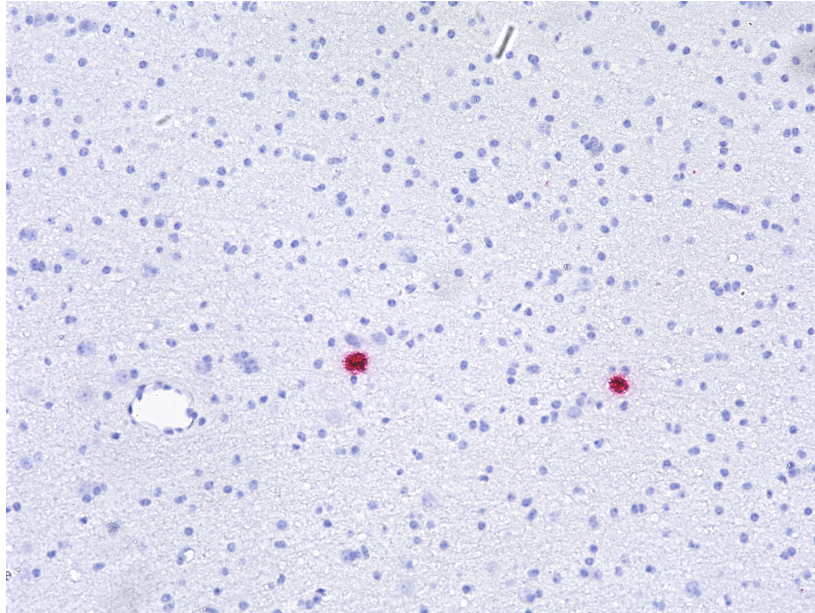


● JV72 ■ KM08 ▲ LB53 ▼ MD86 ● ML02

Reservoir quantification: RNAscope in CNS at m9 necropsy

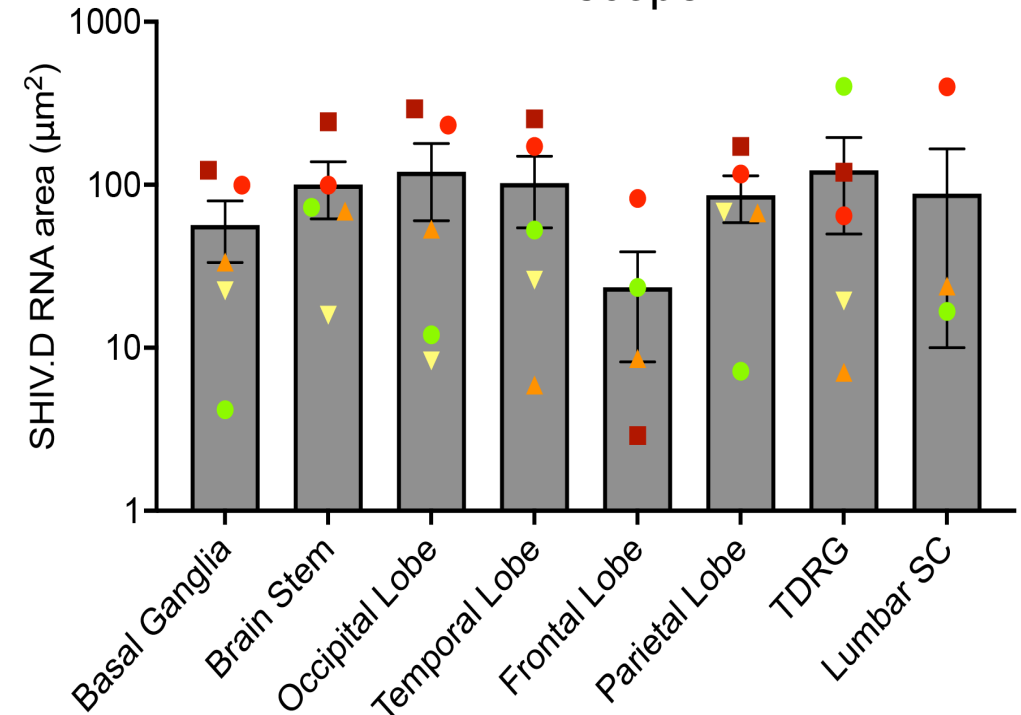
Necropsy - 9 months on ART

RNAscope



KM08 Parietal Lobe (20X)

RNAscope

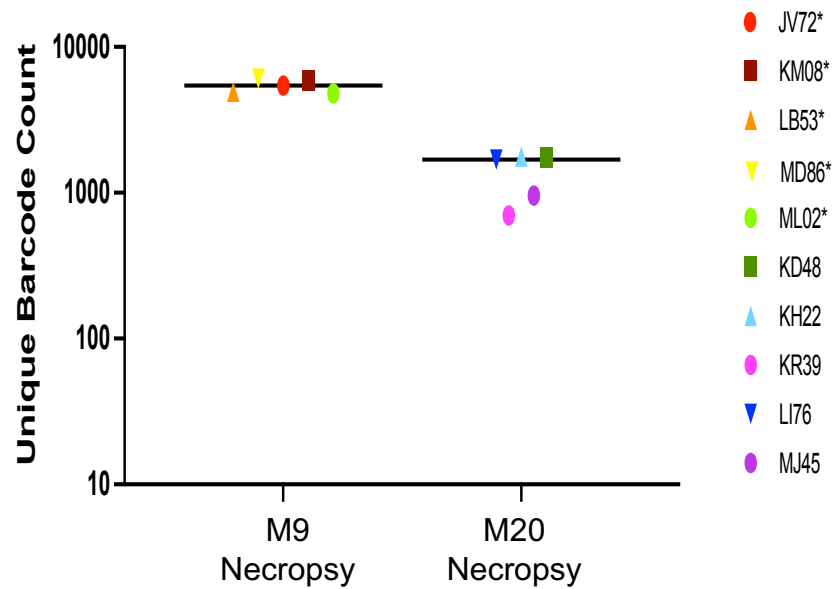


● JV72 ■ KM08 ▲ LB53 ▼ MD86 ● ML02

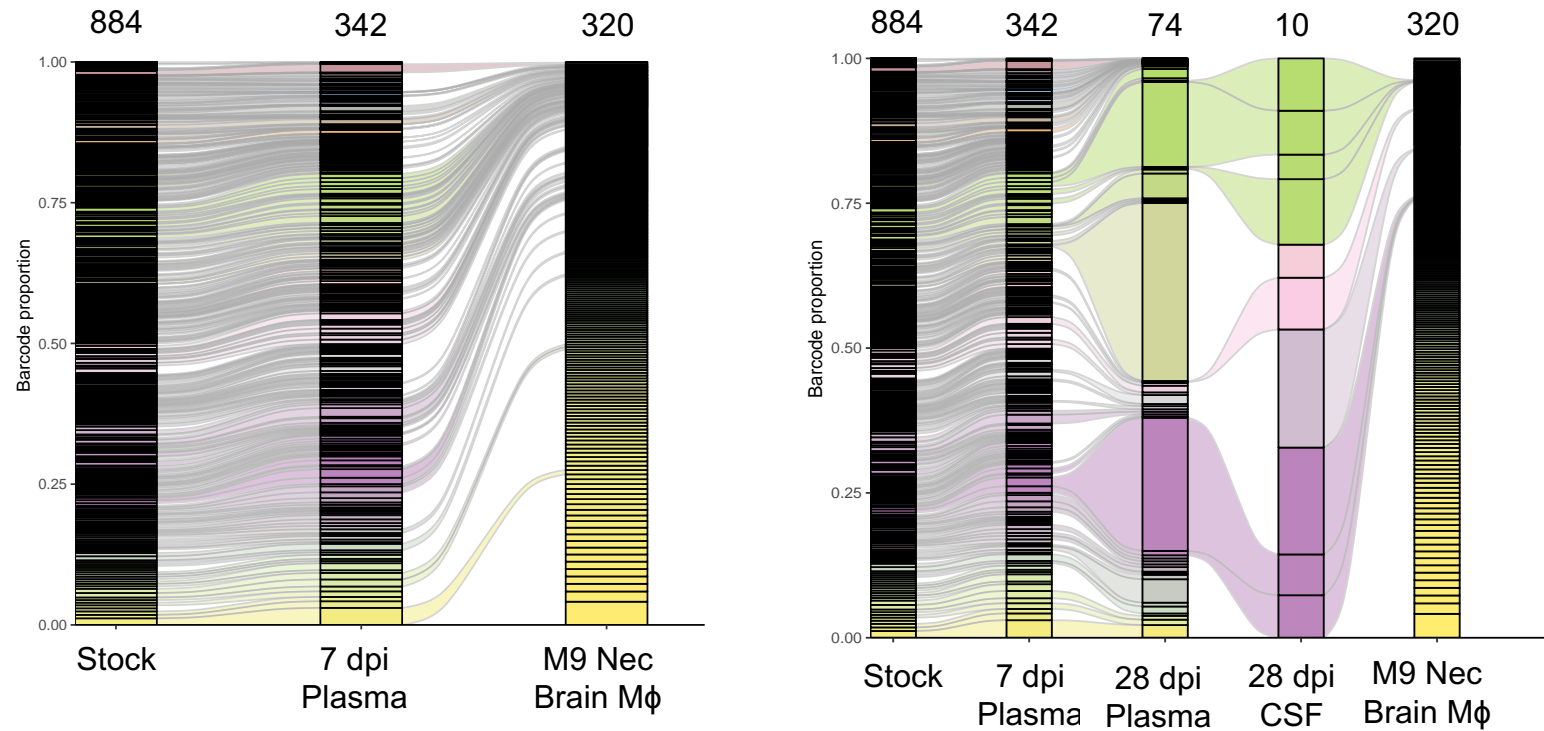
20X frame area = 393,880 μm^2

SHIV D barcode distribution in brain and systemic reservoir

Barcode count in 9-month and 20-month Necropsy Tissues



Barcode proportion and count in 9-month Necropsy Tissues

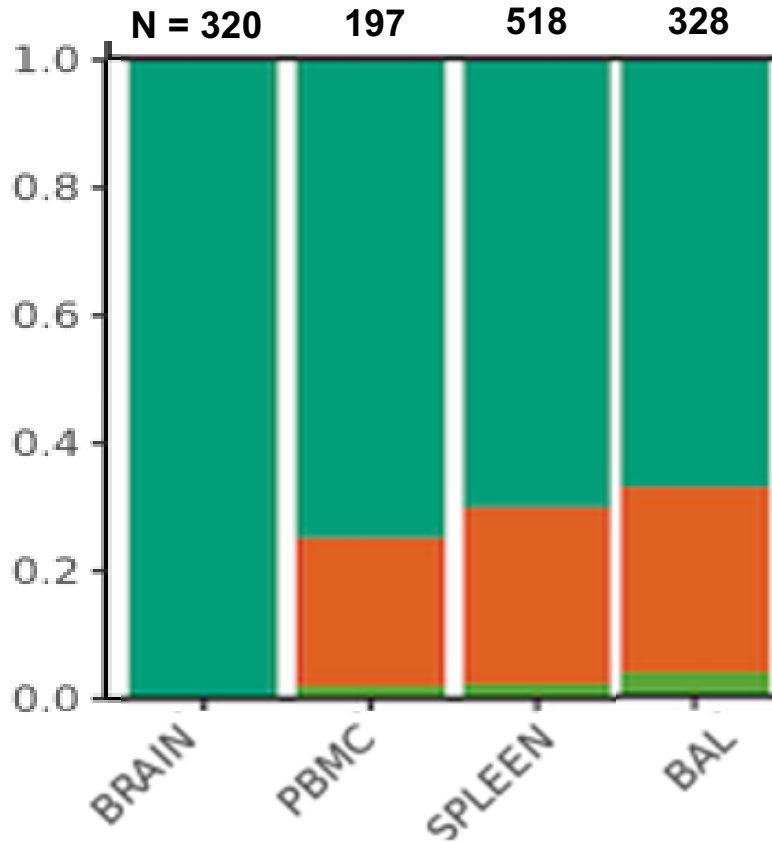


Alluvial plot showing relatedness of barcodes across samples

SHIV D barcode distribution in reservoir at m9 ART: RM ML02

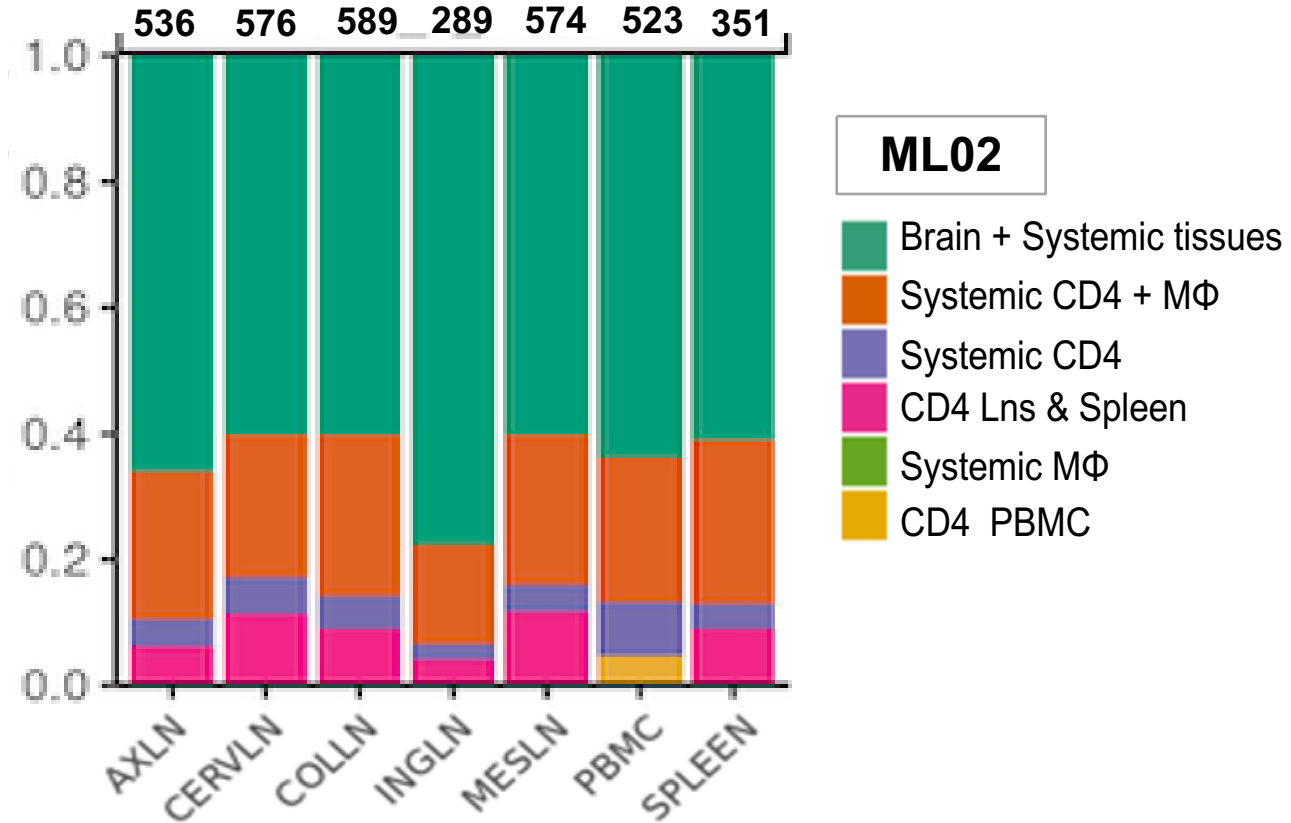
Brain Barcode Clonotypes

Proportion Detected in Other **Tissue Macrophages**



Brain Barcode Clonotypes

Proportion Detected in Other **Tissue CD4+ T cells**



Barcodes overlap in Brain + Systemic reservoirs; CD4 T cell and Macrophage reservoirs

Summary

SHIV.D-infected RM recapitulate key features of HIV-1 persistence. Early ART initiation maintained over 9 to 20 months demonstrated:

- Virus persisted in **CD4 T** and **Myeloid** cells, within **Brain** and **Systemic** reservoirs
 - In blood and systemic tissues, intact provirus declined substantially over first 6-9 months of ART, then less more gradually. *Modeling of reservoir decline is ongoing.*
 - Across timepoints, intact and total DNA levels were found in both myeloid and CD4 T cells and were consistently **~1-2 logs lower in myeloid cells.**
 - **Brain reservoirs persisted over 9-20 months**, detectable by virus barcode quantification and RNA and DNAscope. IPDA fell below the limit of detection. *Full analyses of m20 are ongoing.*
 - For this **dual-tropic virus** with only 10 weeks of viremia pre-ART, barcode analyses show **no evidence of virus compartmentalization** between brain and body, or CD4 T cells and myeloid cells.
- **Results support use of SHIV.D infection as a model of CNS and systemic HIV-1 persistence. Ongoing studies are testing cure interventions.**

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