Genetic Diversification and Tissue-Resident Reservoir Persistence During ART Suppression

392

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Background

Antiretroviral therapy (ART) suppresses HIV-1 replication but does not eliminate replication-competent viral reservoirs, which drive rapid viral rebound following treatment interruption. While circulating memory T cells have long been considered the dominant reservoir, increasing evidence suggests that tissue-resident reservoirs play a critical role in rebound initiation.

Methods

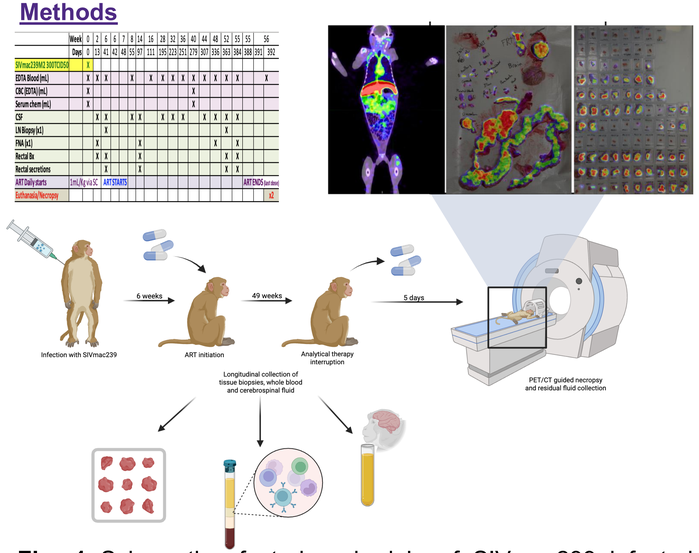


Fig. 1 Schematic of study schedule of SIVmac239 infected macaques for the interrogation of SIV reservoir establishment and rebound.

Genomic Analysis Pipeline

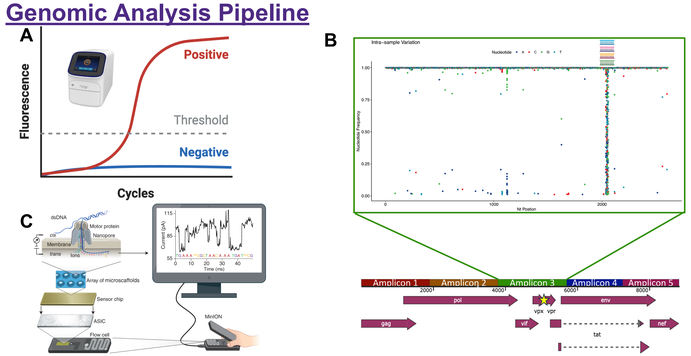
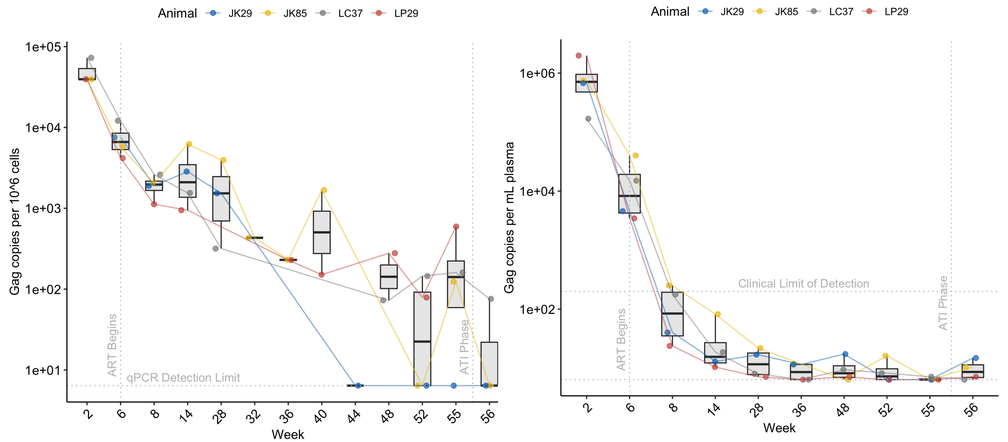


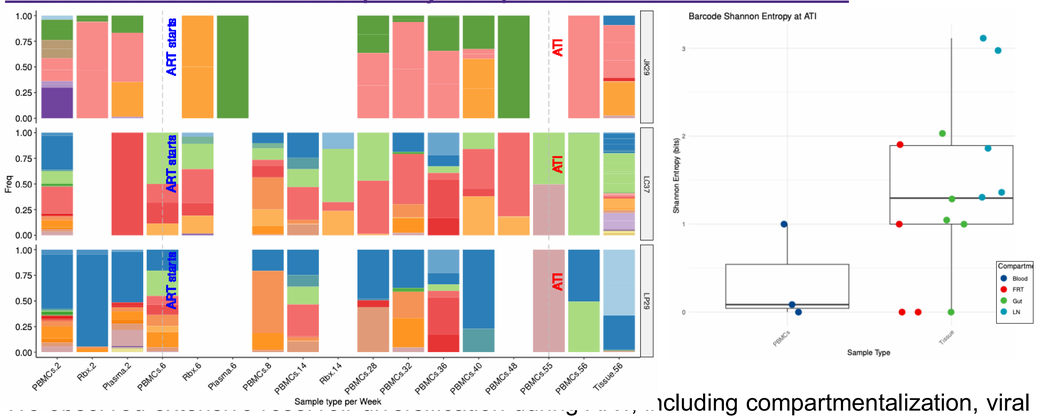
Fig. 2 Schematic of genomic analysis methods. **A.** Quantitative PCR (qPCR) quantification of extracted viral nucleic acid. **B.** PCR amplification of whole SIV genome or desired fragment of interest. **C.** Whole genome sequencing using of amplicons using nanopore technologies.

Persistent, highly diverse SIV reservoirs in gut tissues seed the earliest stages of viral rebound after ART interruption, highlighting critical non-blood targets for cure strategies.

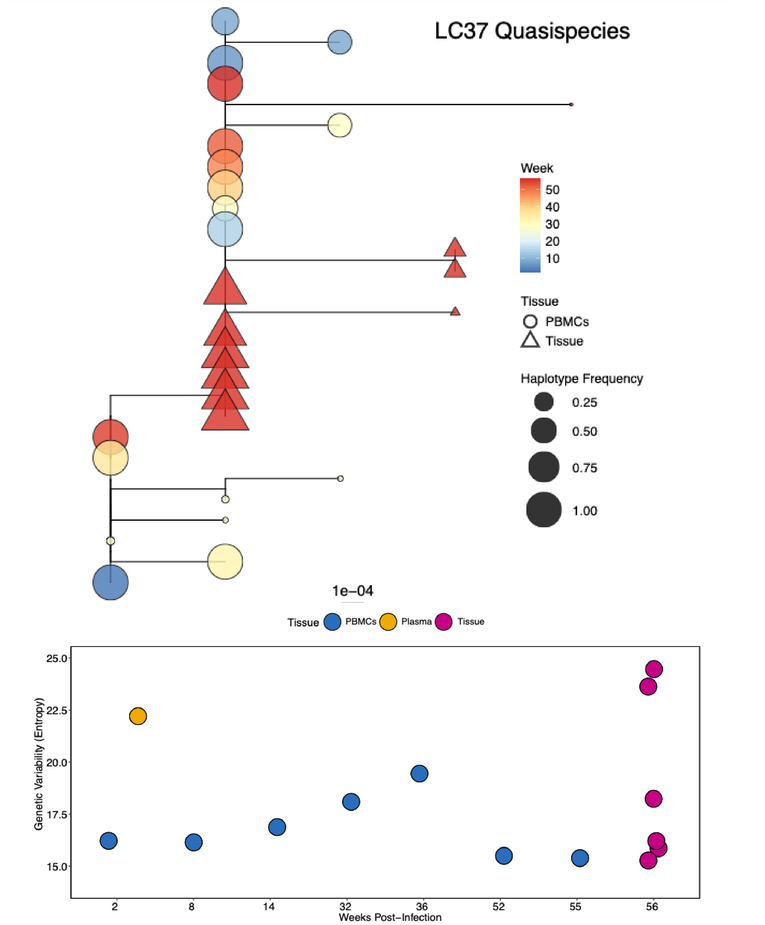
SIV RNA and Cell Associated Proviral DNA Dynamics from Longitudinal Blood Samples Reveal Residual Viremia



Viral Barcode Distribution Grouped by Timepoint and Anatomical Location



SIV Population Dynamics in PBMC and Necropsy Tissues LC37



Longitudinal sampling revealed declining proviral diversity in blood but sustained diversity in tissue reservoirs, including compartmentalization, viral lineage turnover, and convergent evolution. Tissue-derived viral populations, particularly from gut-associated tissues, exhibited greater genetic diversity than parallel PBMC-derived sequences. Barcode analyses revealed declining proviral diversity in blood but sustained diversity in tissue reservoirs, indicating that non-blood reservoirs preserve viral diversity, seeding early rebound.

PLAIN LANGUAGE SUMMARY

HIV exists in cells all around the body which makes it hard to know where the virus is hiding. New scanning methods can find these cells in animal models to help us understand what viruses are doing in different areas of the body during therapy.

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