Lymph Node Tfh Cells Form a Clonally Expanded, Epigenetically Active HIV Reservoir During ART

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BACKGROUND

HIV persists in distinct anatomical reservoirs despite effective antiretroviral therapy (ART). Clonal expansion of HIV-infected cells has been reported in peripheral blood mononuclear cells (PBMCs) and lymph node (LN)-derived follicular helper (Tfh) cells during viremia. In contrast, during ART clonal expansion has been observed mainly in PBMCs, but has not yet been reported in LN-derived Tfh cells. We analyzed HIV integration sites (IS) and clonal dynamics in blood and LN to define tissue-specific reservoir features as shown in *Figure 1*, aiming at targeted HIV cure strategies.

METHODS

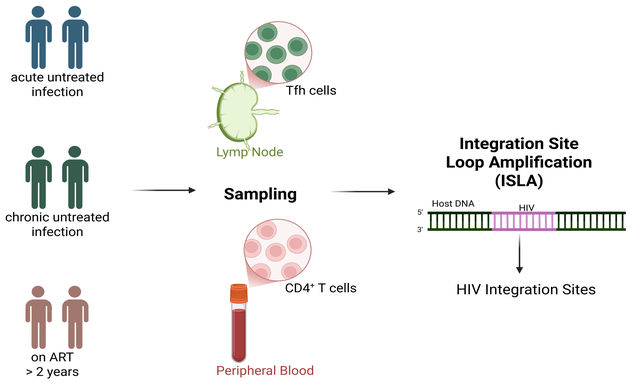


Figure 1: Overview of the experimental workflow.

Hi-C compartment annotation: from human B-lymphoblastoid sub compartment (NCBI GEO: GSE63525)

Histone marks: ROADMAP ChIP-seq data from PB

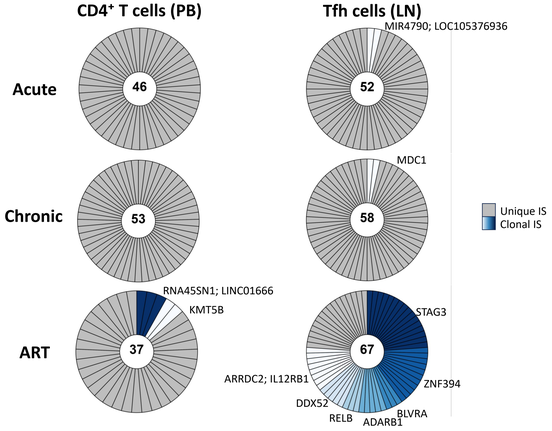


Figure 2: PB- and LN-derived HIV integration sites across infection stages, with clonal expansion indicated by color.

RESULTS

Across all samples, 136 and 177 HIV IS were identified in CD4⁺ T cells from PBMC and Tfh cells from lymph nodes. Notably, we provide the first evidence that LN-derived Tfh cells undergo clonal expansion during ART and harbor substantially larger clonal reservoirs than CD4⁺ T cells from blood (*Figure 2*). Overall, a higher proportion of HIV IS in Tfh cells were in transcriptionally active compartments compared to CD4⁺ T cells (72% vs. 59%, p=0.103). This difference was most pronounced in ART-treated individuals, where the majority of Tfh IS, particularly those derived from clones, were found in active compartments (87% vs. 60%, p=0.094; *Figure 3*).

In ART-treated individuals, HIV IS in Tfh cells were predicted to be surrounded by a significantly higher density of both active and repressive histone marks (±5 kb) compared with PBMC-derived CD4⁺ T cells, driven mainly by clonally expanded integration (*Figure 4*).

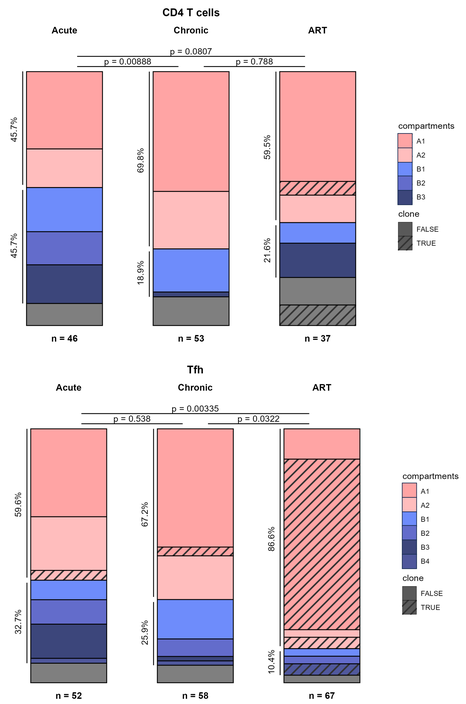


Figure 3: Distribution of HIV integration in active (pink) versus repressive (blue) compartments across infection stages in CD4⁺ T cells (top) and Tfh cells (bottom).

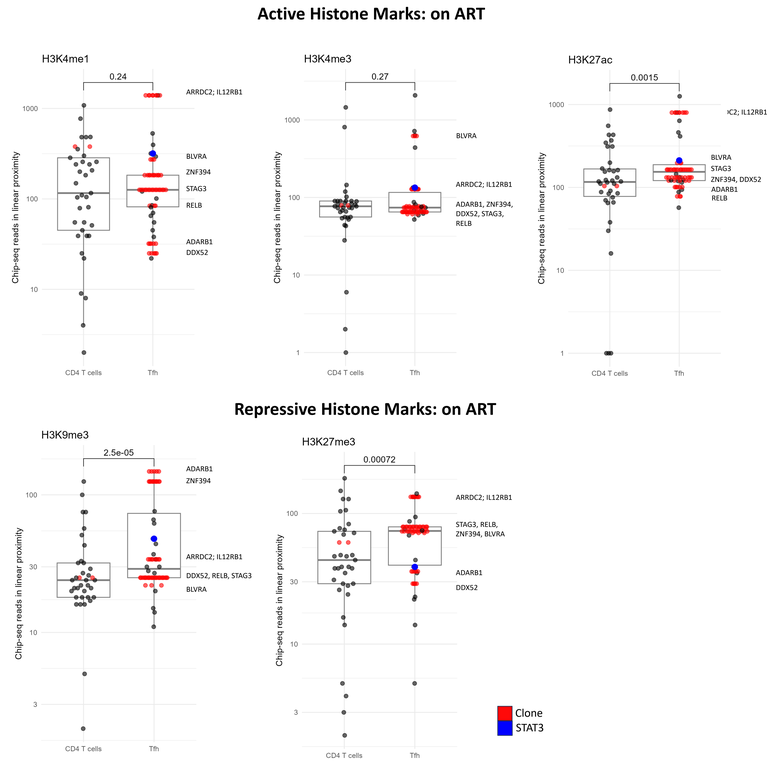


Figure 4: Active (top) and repressive (bottom) histone marks ±5 kb around HIV integration sites on ART in CD4⁺ T cells and Tfh cells, with clonally expanded integrations shown in red.

Lymph node Tfh cells harbor larger clonally expanded HIV reservoirs during ART with a distinct, transcriptionally active integration landscape compared to peripheral blood-derived CD4⁺ T cells.

CONCLUSIONS

This study demonstrates that LN-derived Tfh cells harbor substantially more HIV infected clonal expanded cell populations during ART than peripheral blood-derived CD4⁺ T cells and exhibit a distinct integration landscape enriched in epigenetically active regions. Despite integration into transcriptionally permissive chromatin, these reservoirs persist through clonal expansion, highlighting fundamental biological differences between tissue and blood HIV reservoirs and emphasizing the importance for tissue-targeted HIV cure strategies.

PLAIN LANGUAGE SUMMARY

Even with effective HIV treatment, the virus continues to clonally expand in immune cells inside lymph nodes in ways that are not detected by blood test, highlighting a major challenge for cure efforts.

ACKNOWLEDGEMENT

We thank the study participants and the clinical nursing teams for their essential contributions to this research.

CONTACT INFORMATION

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