Tissue resident T Cell Receptor (TCR) Repertoires linked to HIV Persistence.

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BACKGROUND

Latently-infected CD4⁺ T cells are a barrier to cure an HIV. Clonal expansion of CD4⁺ T cells is a crucial mechanism of HIV persistence, and this expansion can be driven by homeostatic, integration site-driven, and antigen-driven proliferation.

STUDY GOAL

Our study set out to characterize the composition and diversity of TCR repertoires across tissues and blood of people with HIV (PWH) from the Last Gift cohort, and their interaction with measures of HIV persistence (size, activity, diversity, integration sites).

METHODS

Cohort: The Last Gift Program enrolls altruistic PWH to participate in end-of-life research in San Diego. Blood and tissues were collected by rapid research autopsy. **Table 1.**

Bulk TCR sequencing was performed across four systems in 178 unique samples included in this study. **Figure 1.**

- **GI Tract**: duodenum, jejunum, ileum, colon, rectum.
- **CNS:** frontal, occipital and parietal cortex, basal ganglia, spinal cord, hippocampus.
- **Lymphoid:** spleen, lymph nodes.
- **Vascular:** heart, peripheral blood.

Reservoir measures:

- HIV reservoir size (total HIV DNA) and activity (cellular HIV RNA) by ddPCR.
- HIV molecular diversity (Shannon Entropy) from HIV *env* single genome sequencing.
- Proviral integration site sequencing for one participant from 4 selected tissues.

Analysis:

- TCR data were analyzed using mixcr bioinformatic platform (PMID: 25924071)
- VDJdb and McPASTCR databases used to predict TCR specificities (PMID 31588507, 28481982)
- Repertoire overlap were assessed by computing Morisita's overlap index (immunarch R package).
- Generalized mixed effects models were used to examine the association between HIV reservoir measures as predictors (size, activity, diversity) and TCR measures as outcomes (proportion of hyperexpanded clones, TCR diversity)

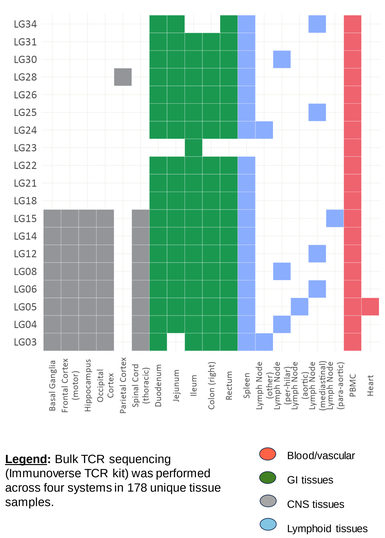
Our study unveils the expansion and cross-tissue migration of clonal T cells, which are linked to measures of HIV persistence.

Table 1. Participants Characteristics

Characteristic	N = 19[†]
Sex	–
Female	2 (11%)
Male	16 (84%)
Transgender Female	1 (5.3%)
Age group	–
≤50 yrs	2 (11%)
50-60 yrs	5 (26%)
60-70 yrs	5 (26%)
70-80 yrs	6 (32%)
>80 yrs	1 (5.3%)
Race/ethnicity	–
Asian/Pacific Islander/Non-Hispanic	1 (5.3%)
Black/African American/Non-Hispanic	2 (11%)
Caucasian/Hispanic	2 (11%)
Caucasian/Non-Hispanic	14 (74%)
Year of HIV diagnosis	1996 (1987, 2005)
Missing/Unknown	1
Last CD4 count	224 (142, 347)
Detectable last HIV RNA	–
Virally suppressed	16 (84%)
Viremic	3 (16%)
Solid tumor	–
No	9 (47%)
Yes	10 (53%)

[†] n (%); Median (IQR)

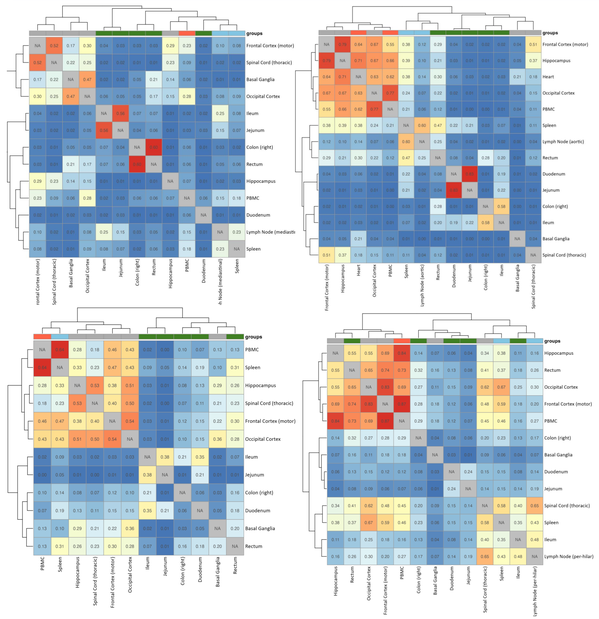
Figure 1. Sampling Overview



Legend: Bulk TCR sequencing (Immunoverse TCR kit) was performed across four systems in 178 unique tissue samples.

Figure 2. TCR Landscape across Tissues Systems

We identified **shared clonotypes** in all tissues suggesting T cell migration across tissue sites.

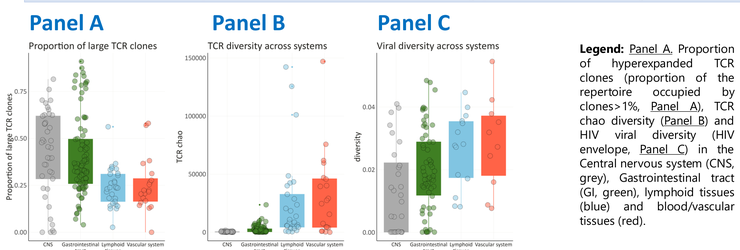


Legend: TCR repertoire overlap between samples within four selected participants was assessed by computing Morisita's overlap index (immunarch R package).

Colored boxes represent degree of overlap, red: high overlap, blue: low overlap.
Top: Tissue colored by groups.

Figure 3. TCR Expansion within Tissue Systems

We identified **expansions of TCR clonotypes** within all systems.



Legend: Panel A. Proportion of hyperexpanded TCR clones (proportion of the repertoire occupied by clones>1%, Panel A), TCR chao diversity (Panel B) and HIV viral diversity (HIV envelope, Panel C) in the Central nervous system (CNS, grey), Gastrointestinal tract (GI, green), lymphoid tissues (blue) and blood/vascular tissues (red).

- The CNS had more hyperexpanded TCR clones (45% [34-61]), compared to the GI tract (18% [34-61], p=0.004), lymphoid (13% [8-23], p=0.001) and vascular (24% [16-38], p=0.24).
- The CNS exhibited significantly lower TCR Chao and HIV DNA diversity compared to other systems.

Table 2. Associations between HIV Reservoir and TCR Measures.

Higher transcriptional activity (cellular HIV RNA) was associated with lower proportion of hyperexpanded clones (p=0.004).

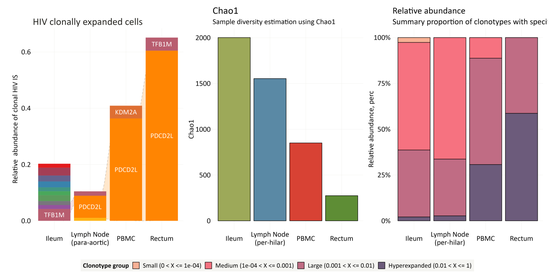
	HIV RESERVOIR MEASURES		
	Total HIV DNA	Cellular HIV RNA)	Diversity
TCR Chao diversity	0.341	0.108	0.200
Proportion of hyperexpanded TCR clones	0.211	**0.004**	0.615

Legend: P-values shown. Green indicates positive association, red indicates negative.

We did not find any evidence for TCR expansions driven by cytomegalovirus or other common pathogens.

Figure 4. TCR and Proviral Integration Site Expansion

In selected tissues from one participant, proviral integration site sequencing confirmed that proportion of HIV-infected clonally expanded cells was negatively associated with TCR diversity and positively with the proportion of expanded TCR clones.



Legend: In 4 samples from one participant, the proportion of clonally expanded HIV infected cells evaluated by integration site (IS) sequencing is shown on the left, TCR chao diversity and the proportion of hyperexpanded clonotypes across the same tissues are shown on the middle and right panel. TFB1M: transcription factor B1, PCD2L: Programmed cell death 2 like, KDM2: Lysine demethylase 2A, TFB1M: Dimethyladenosine transferase 1

CONCLUSIONS

- This is the first comprehensive analysis of the TCR repertoire landscape across the tissues of PWH.
- Our findings unveil the expansion and cross-tissue migration of clonal T cells, which might be linked to the dynamics of the HIV reservoir.
- This work sheds light on the interplay between HIV persistence and T cell immunity.

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NIH National Institute of Allergy and Infectious Diseases

CFAR San Diego | Center for AIDS Research