HIV-1 Clade C Reservoir Traits in Blood and Lymph Node Tissue in Acute and Chronic Treated Infection

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Background

- HIV-1 latently infected cells that persist in tissues during antiretroviral therapy (ART) are a barrier to HIV-1 cure.
- These reservoirs are hard to reach and therefore poorly characterized.
- In this study we performed a comparative cross-sectional analysis of HIV-1 reservoir characteristics in paired blood and excised lymph node (LN) tissue.
- We studied 12 individuals from South Africa identified with acute infection by virtue of being HIV-RNA positive and antibody negative with subsequent seroconversion.

Methods

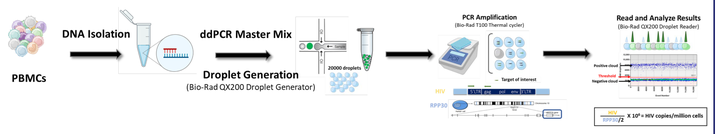


Figure 1: HIV reservoir quantification by droplet digital PCR (ddPCR)

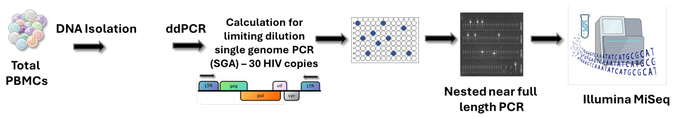


Figure 2: HIV Sequencing by FLIP-seq

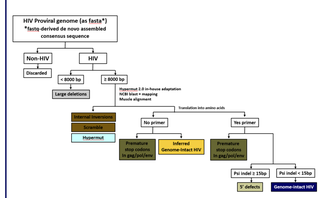


Figure 3: Bioinformatics Workflow

Table 1: Study Participants

PID	Treatment Status at Sampling	Treatment initiation days after diagnosis	PBMC days after treatment	LN excision days after treatment	ddPCR	FLIP-Seq
683	Early Treated	1	495	428	✓	×
1210	Early Treated	1	160	120	✓	×
442	Early Treated	3	913	926	✓	✓
1012	Early Treated	0	833	760	✓	✓
1442	Early Treated	1	13	8	✓	✓
3830	Late treated	unknown	1989	2068	✓	×
37	Late treated	538	548	554	✓	×
93	Late treated	310	1114	1065	✓	✓
83	Late treated	779	235	256	✓	✓
95	Late treated	84	935	899	✓	✓
79	Untreated	1587	-73	-269	✓	✓
108	Untreated	unknown	-	-	✓	✓

- ❖ **HIV DNA genome profiles in peripheral blood may not reflect those in tissue and viral compartmentalization persists during suppressive ART.**
- ❖ **Design of HIV curative strategies should target all relevant organ systems.**

Results

Table 2: Sample Characteristics

Sample ID	Treatment Status	Tissue	Days Post Treatment	Number of cells sampled	Viral Load (copies/ml)
79	Untreated	PBMC	-73	1 556	18 000
		LN	-269	3 728	22 000
108	Untreated	PBMC	unknown	8 018	14 000
		LN	unknown	7 857	14 000
93	Late Tx	PBMC	1114	12 143	<20
		LN	1065	13 139	<20
95	Late Tx	PBMC	935	78 733	<20
		LN	899	81 900	<20
83	Late Tx	PBMC	235	140 625	<20
		LN	256	163 849	<20
442	Early Tx	PBMC	913	86 600	<20
		LN	926	475 500	<20
1012	Early Tx	PBMC	832	59 400	<20
		LN	758	79 280	<20
1442	Early Tx	PBMC	13	68 561	870
		LN	8	75 513	55 000

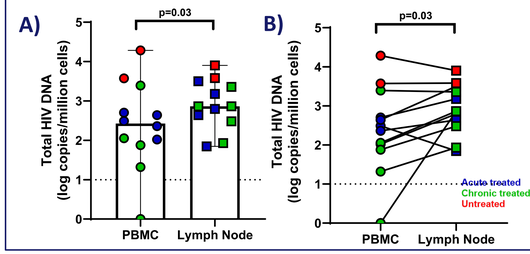


Figure 4: Total HIV DNA levels are higher in lymph nodes compared to matched PBMCs (A) from the same participant (B).

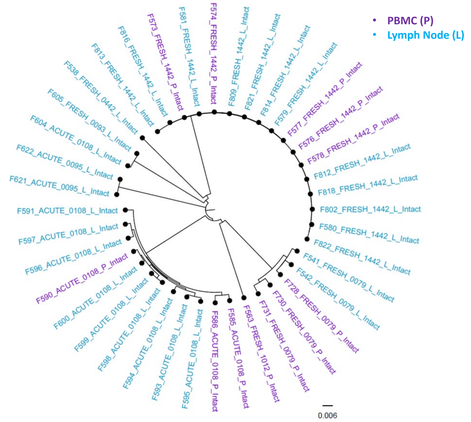


Figure 5: Approximately-maximum-likelihood phylogenetic tree of intact HIV-1 DNA genomes constructed using FastTree2. Sequences from LN and PBMC are differentiated by colour.

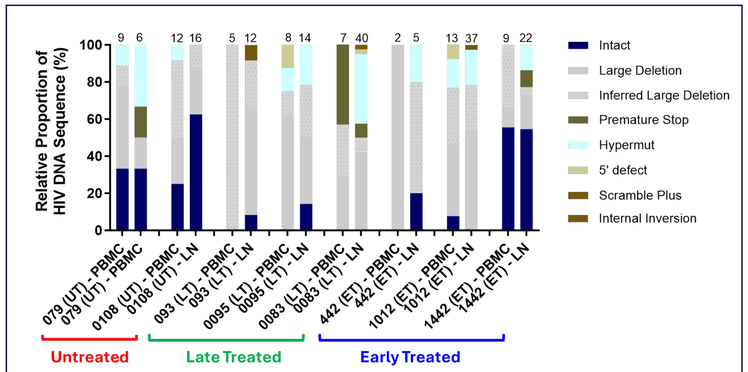


Figure 6: Differences in the proviral landscape in PBMCs and lymph nodes.

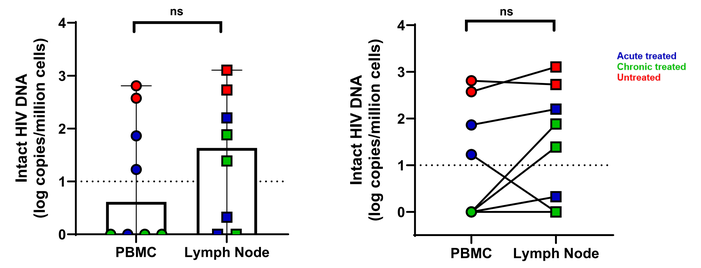


Figure 7: A) Genome-intact viruses are present at a higher frequency in lymph nodes compared to matched PBMCs (5/8) from the same participant (B)

Summary

- We obtained 65 single genome sequences from PBMCs and 159 from LN samples.
- Around 50% of participants well-suppressed on ART for > 2 years had detectable intact HIV-1 DNA in LN but not in PBMC.
- LN had higher proportions of intact viral genomes in both CT and UT individuals (CT: 5% vs 0% intact, sampling depth 66 and 20 genomes from 258 888 and 231 501 cells; UT: 54% vs 29% intact, sampling depth 22 and 21 genomes from 11 585 and 12 686 cells, in LN and PBMC respectively).
- In AT, proportions of intact HIV-DNA were similar between compartments: LN and PBMC was 20% vs 25% intact respectively (sampling depth 64 and 24 genomes from 630 293 and 214 561 cells).

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