# HIV DNA and activation differ for long-lived CD4 T cells in lymph nodes and PBMC on ART

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## BACKGROUND

Understanding the mechanisms underlying the establishment, persistence, and location of the HIV latent reservoir is a key step for developing cure interventions. T-cell activation and HIV reservoir size are higher in rectal tissue and lymph nodes (LN) compared with peripheral blood mononuclear cells (PBMC). However, the relative contribution of CD4 T cell subsets to this anatomic difference is unknown and could identify critical targets for interventions.

## OBJECTIVE

**To identify the relationship between PBMC and LN HIV DNA content and activation markers on key T cell subsets: naïve, central memory (CM), transitional memory (TM) and effector memory (EM) in participants taking antiretroviral therapy (ART) and identify differences between immune responders and immune suboptimal responders.**

## METHODS

- Included a total of 32 people with HIV on ART
- All participants underwent large volume blood draw and 11 of those also underwent LN biopsy, which were included in a paired analysis:
  - 5 virologically suppressed immunologic responders (IR, achieved a CD4 T cell count >500 cells/μL in the first two years after ART initiation)
  - 6 virologically suppressed immunologic suboptimal responders (ISR, did not achieve a CD4 T cell count >500 cells/μL in the first two years after ART initiation)
- Measured total HIV DNA, PD-1, TIGIT and CD38+HLA-DR+expression on CD4 T cell subsets.

- **Cohort characteristics:**
  - 29 cisgender men (91%) and 3 cisgender women (9%)
  - Mean age 50 ±11
  - 23 African American (72%), 5 white (16%), 4 Hispanic (13%).
  - CD4 mean nadir, cells/mm3: 182 ± 145
  - Mean duration of ART, years: 4 ± 2
  - Mean plasma HIV viral load, 92 ± 95

## RESULTS

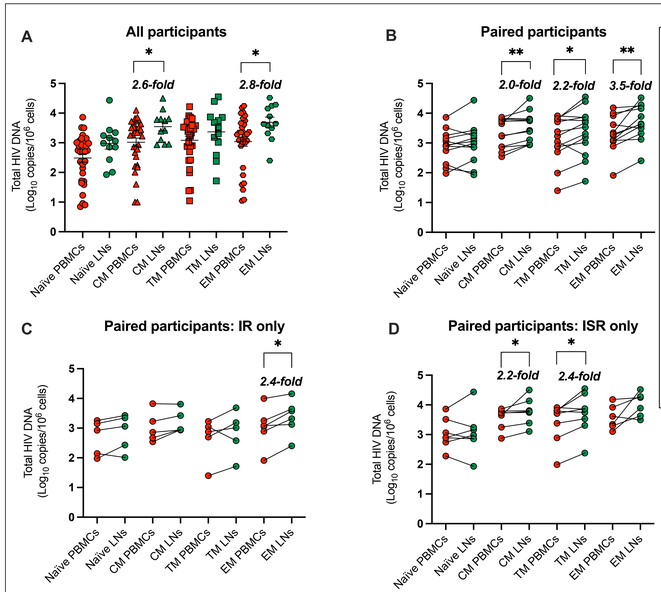



**Figure 1. Total HIV DNA was significantly higher in central memory (CM) and effector memory (EM) CD4 T cells from lymph nodes (LNs) compared to those from peripheral blood mononuclear cells (PBMCs) in all participants (A).** In our paired analysis for participants who had both PBMCs and LNs this difference also became significant in the transition memory CD4 T cells *(B).* The difference in EMs remained significant in the immune responder subgroup (IR) *(C)* while immune suboptimal responders (ISR) had significant differences in CMs and TMs *(D).*

**Key:** PBMCs: peripheral blood mononuclear cells; LNs: lymph nodes; IR: immune responders; ISR: immune suboptimal responders. PD-1: Programmed cell death protein 1; TIGIT: T cell immunoreceptor with Ig and ITIM domains

Mann-Whitney test performed for unpaired analyses. Wilcoxon test performed for paired analyses. Statistical significance: *p ≤ 0.05**p≤0.01;***p ≤0.001;****p ≤0.0001.

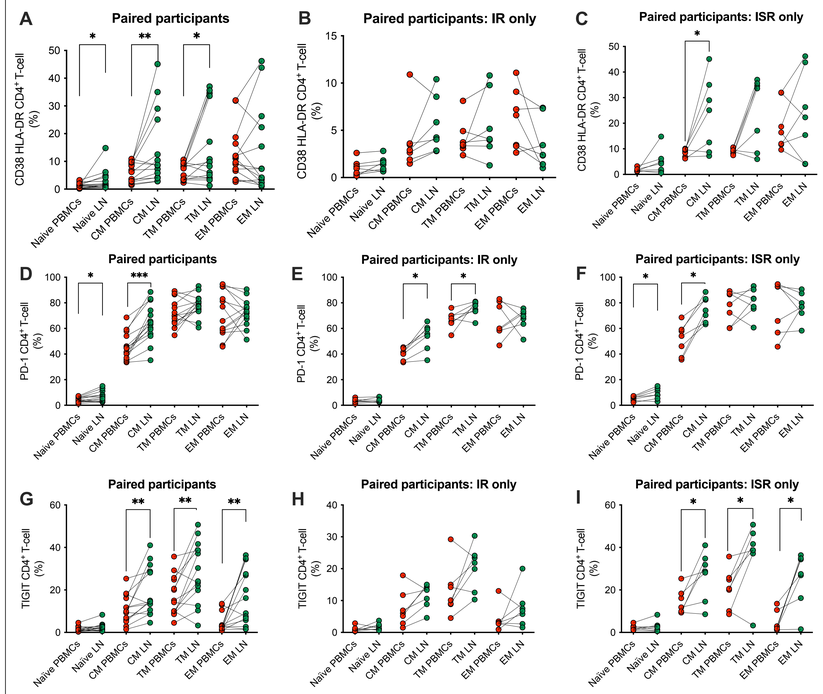



**Figure 2. CD38+HLA-DR+** was significantly higher in naïve, CM and TM CD4 T cells from LNs compared with PBMCs *(A).* This difference was maintained in CM CD4 T cells from ISR participants *(C).* **PD-1 expression** was significantly higher in naïve and CM CD4 T cells from LNs compared with PBMCs *(D).* This difference was maintained in ISR *(F),* while IR had significantly higher LN levels of PD1 expression on CM and TM subsets *(E).* **TIGIT expression** was significantly higher in CM, TM and EM from LNs compared with PBMCs (G). This difference was mainly driven by ISR participants (I).

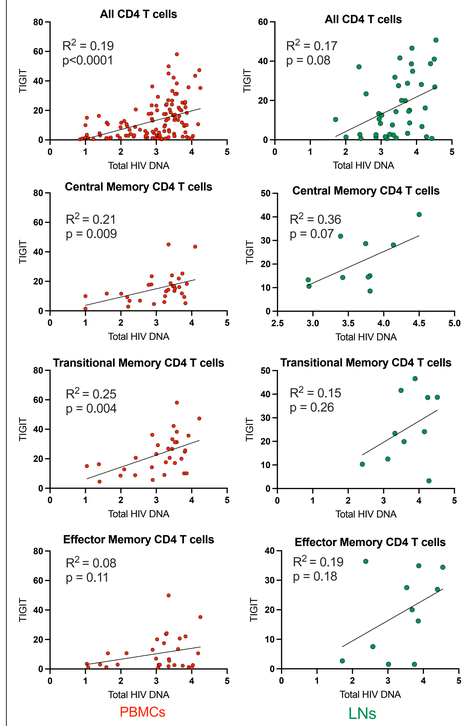



**Figure 3. Total HIV DNA correlated with TIGIT in all T cell subtypes from PBMCs, except EM CD4 T cells.** There was a trend towards positive correlation in CMs and TMs from lymph nodes but this did not reach statistical significance.

There was no significant correlation between total HIV DNA and Activated CD38+HLA-DR+ CD4+ T cells or PD-1 (data not shown).

## CONCLUSIONS

- **HIV-DNA content, T cell immune activation, TIGIT and PD-1 expression are higher in LN than PBMCs, particularly for long-lived CD4 T-cell subsets.**
- **Differences in HIV-DNA content, T cell immune activation and TIGIT between LNs and PBMCs are further pronounced in or specific for ISR, thus highlighting increased residual disease in LN as a critical feature of and a potential mechanism for individuals with poor CD4 T cell reconstitution during ART.**

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