# Single Cell Transcriptomics Reveals Depletion of TB-specific Th1 and Th17 Cells After HIV Infection

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## BACKGROUND

- **People with HIV have >20-fold higher risk of active tuberculosis (TB) in the absence of anti-retroviral therapy (ART).**
- **Despite ART and immune reconstitution, people with HIV maintain a >4-fold higher risk of active TB.**
- **Although CD4 T cells are necessary for control of *Mycobacterium tuberculosis* (Mtb), the exact mechanisms underlying the loss of Mtb control in PWH have not been clearly defined.**

## COHORT DESCRIPTION

- PBMCs were collected from adults before and after HIV and before and after ART in Mombasa, Kenya.
- People with HIV starting ART early started treatment within 6 months following HIV infection.
- People with HIV starting ART later started ART within 1-4 years following HIV infection.

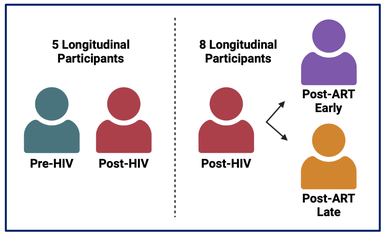



**Figure 1.** Study participant groups.

## METHODS

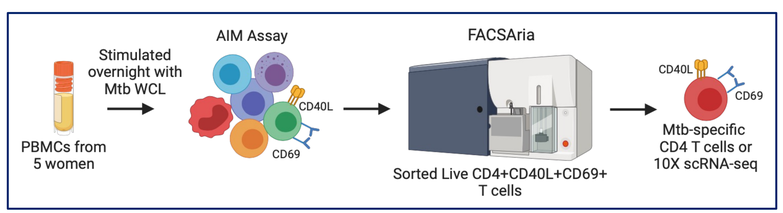



**Figure 2. Experimental Approach.** PBMCs were incubated with Mtb whole cell lysate (WCL) overnight in an activation-induced marker (AIM) assay. CD40L+CD69+ TB-specific CD4 T cells were sorted and used in 10X single cell RNA sequencing (scRNA-seq).

TB-specific Th1 and Th17 cells are depleted within the first year after acquisition of HIV.

## RESULTS

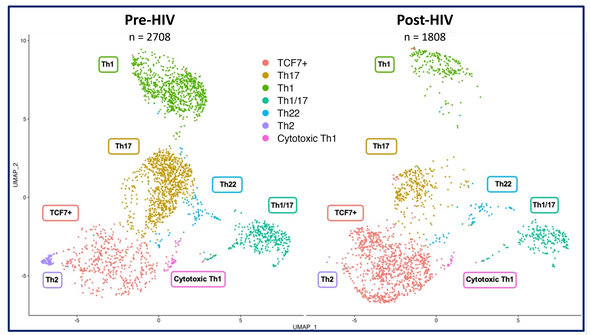



**Figure 3. TH1 and TH17 clusters of TB-specific CD4 T cells are diminished within 1 year after HIV infection.** UMAP of scRNA-seq expression profiles of TB-specific CD4 T cells from five individuals before and after HIV infection.

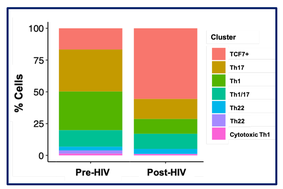



**Figure 4. Proportions of TB-specific Th1 and Th17 clusters are diminished after HIV infection.** Frequency of TB-specific CD4 T cell clusters before and after HIV infection.

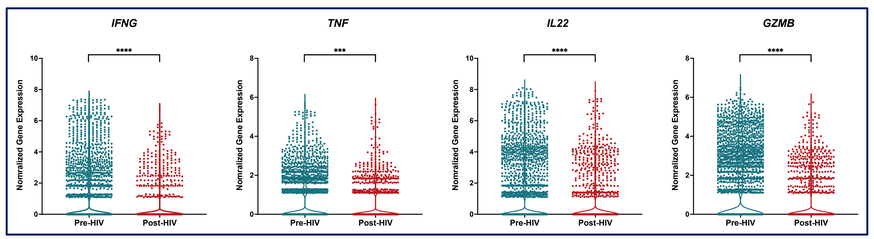



**Figure 5. Cytokine genes in TB-specific CD4 T cells are downregulated after HIV infection.** Normalized gene expression of select genes in TB-specific CD4 T cells (*** $p \leq 0.0001$, **** $p \leq 0.00001$).

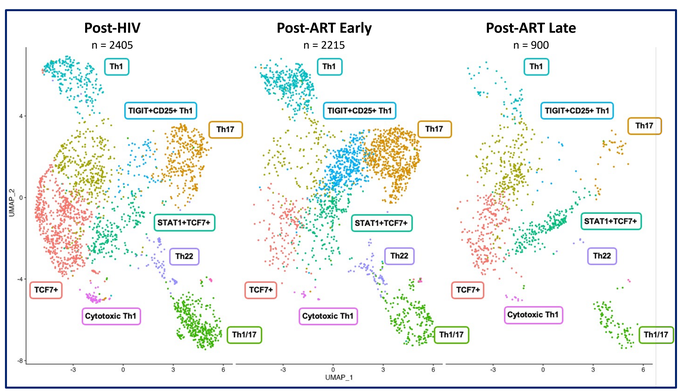



**Figure 6. TH1 and TH17 clusters of TB-specific CD4 T cells expand after initiation of ART within 1 year of HIV infection.** UMAP of scRNA-seq expression profiles from eight individuals before and after HIV infection.

## RESULTS

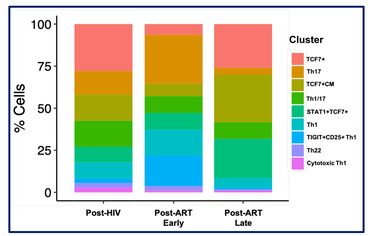



**Figure 7. Proportions of TB-specific Th1 and Th17 clusters are expanded after early start of ART and diminished after later start of ART.** Frequency of TB-specific CD4 T cell clusters before and after ART with some individuals starting ART within 1 year (early) and some starting ART 1-4 years (ART) after HIV infection.

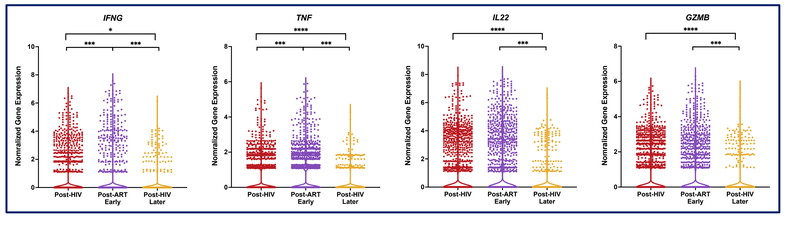



**Figure 8. Cytokine genes in TB-specific CD4 T cells are upregulated after ART initiation within 1 year after HIV infection.** Normalized gene expression of select genes in TB-specific CD4 T cells (* $p \leq 0.01$ *** $p \leq 0.0001$, **** $p \leq 0.00001$).

## CONCLUSIONS

- **TB-specific Th1 and Th17 cells are depleted and the expression of key cytokine genes are diminished within the first year after HIV infection.**
- **Initiating ART within 1 year following HIV infection may preserve key TB-specific CD4 T cell populations and their function.**
- **Impairment and depletion of TB-specific CD4 T cells may contribute to compromised control of Mtb in people with HIV, leading to higher risk of TB.**

## ACKNOWLEDGEMENTS

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