Single-Cell Multiomics Reveals ART-Induced Naïve CD8⁺ T Cell Remodeling Predicts Delayed HIV-1 Rebound

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Background

Antiretroviral therapy (ART) suppresses HIV-1 replication and prevents disease progression in people living with HIV (PLWH). However, the latent reservoir allows viral rebound after analytical treatment interruption (ATI), with wide variation in rebound timing. We hypothesize that immune cell states influence rebound kinetics. The RV254 Thai cohort of PLWH who initiated ART during acute HIV-1 infection (AHI) and subsequently underwent ATI provided a unique opportunity for us to use multiomic profiling and machine learning (ML) with explainable AI to identify signatures that could predict viral rebound following ATI.

Methods

Peripheral blood mononuclear cells (PBMC) were obtained from PLWH from ATI studies in Thailand without additional intervention. Participants were diagnosed during AHI and were on ART for a median of 3 years. Longitudinal single-cell multiomics profiling, including single-cell transcriptomics, chromatin accessibility, and surface protein expression, was performed at AHI (week 0), 60 weeks post-ART (ART), and before ATI (PreATI). Statistical analyses included t-tests, ANOVA and multi-variable regression with cross-validation.

Figure 1. Study design and longitudinal single-cell multiomics

Results

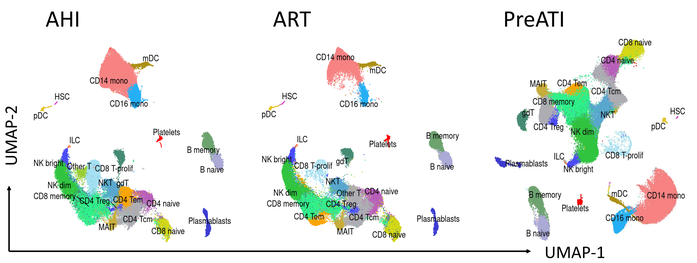

Figure 2. scCITE-seq identifies major PBMC populations

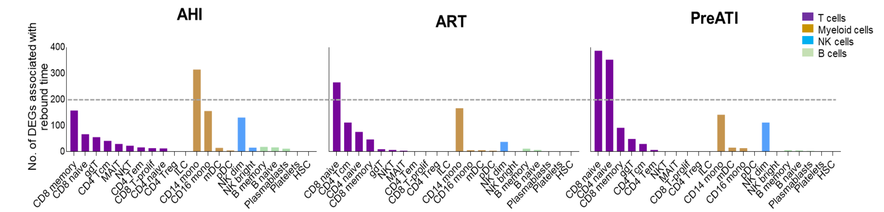

Figure 3. Gene expression changes across immune cell types associated with time to viral rebound

Figure 4. Enriched signaling pathways in naïve CD8⁺ T cells during ART and pre-ATI that are associated with delayed viral rebound

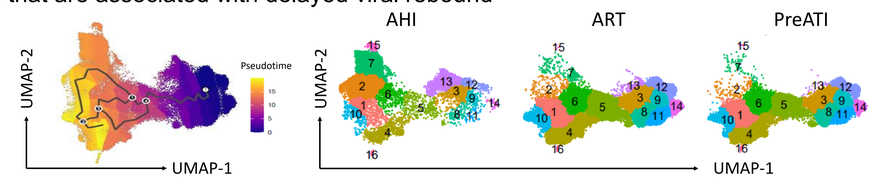

Figure 5. CD8⁺ T cell differentiation trajectories are reshaped by ART

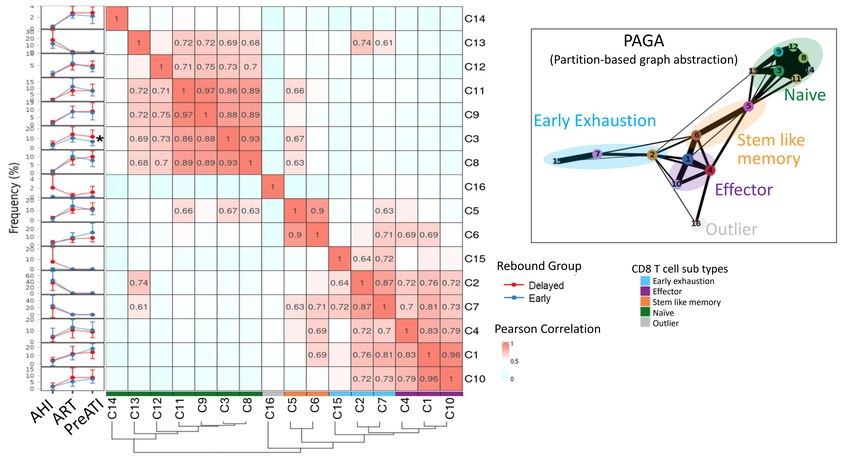

Figure 6. Emergence of a reprogrammed naïve CD8⁺ T cell subset (C3) poised for stem like memory differentiation during ART and associated with delayed rebound

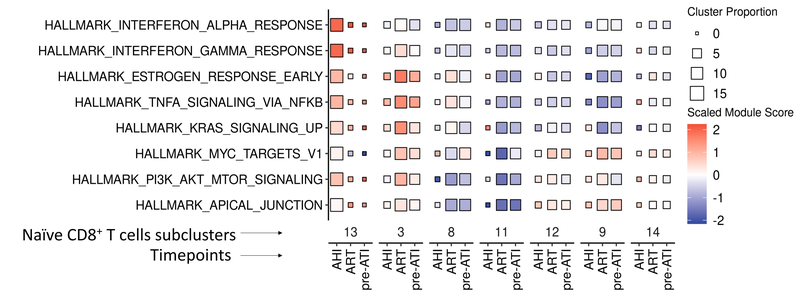

Figure 7. C3 drives survival-oriented programs linked to delayed rebound

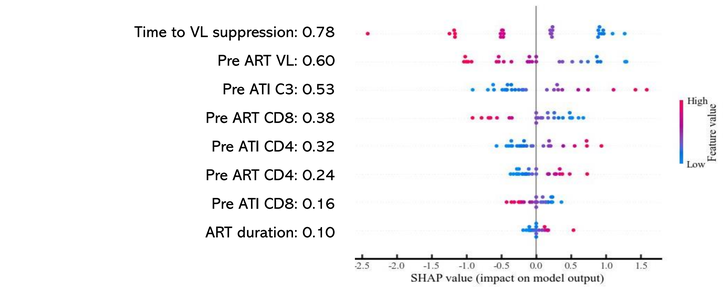

Figure 8. C3 identified as a top predictor of delayed viral rebound by SHAP-based SVR modeling

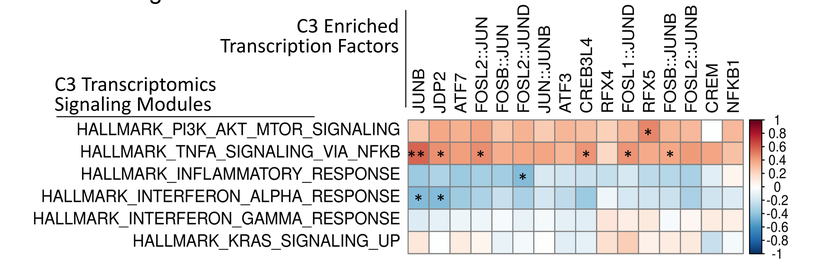

Figure 9. C3 is functionally primed through AP-1 transcription factor activity

Conclusion

ART drives the remodeling of naïve CD8⁺ T cells into a primed subset whose abundance predicts delayed viral rebound, highlighting naïve CD8⁺ states as key determinants of rebound timing and potential targets for HIV cure strategies.

Acknowledgements

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