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Distinct Innate Immune-Driven TNFa Pathway Is Linked With Durable ART-Free Aviremia in Pediatric HIV

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Background

The search for sustained combination anti-retroviral therapy (cART)-free remission continues to elude us. Owing to the tolerogenic state of the pediatric immune environment, it is thought that early cART-treated children possess higher potential to achieve cART free remission. We focus our efforts on a cohort of mother-to-child transmission HIV-positive pediatric individuals (Ucwaningo Lwabantwana)[1]. Previously, our group report a subset of children maintained aviremia despite unscheduled complete discontinuation of cART, referred to as "putative cures". Characterization of viruses within these individuals suggested that poor viral replicative capacity (VRC) may contribute to the observed phenotype[2]. However, the host-pathogen interplay that confers "putative cure" remains to be understood.

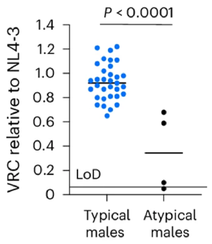


Figure adapted from Bengu et al. demonstrating differential VRC within putative cures compared to typical individuals

Methods


Dried Blood Spot


Digital Droplet PCR (ddPCR)

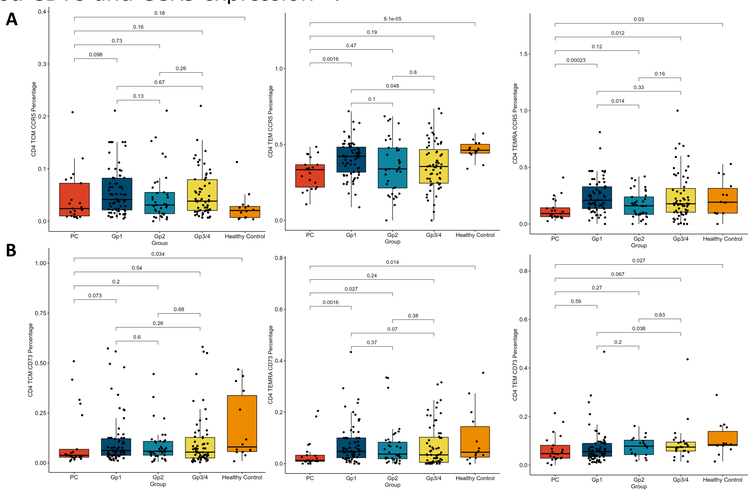

Gene Xpert


Plasma+ WB PCR

5 independent tests to diagnose HIV infection or putative cure phenotype. **105 individuals** were then split into 5 groups, putative cures, HIV infected (no viral blips (Group 1), 2 or fewer (Gp 2), more than 2 (Gp 3/4)) and healthy controls. We then conducted **scRNA-seq** and **T-cell immune phenotyping** of participants.

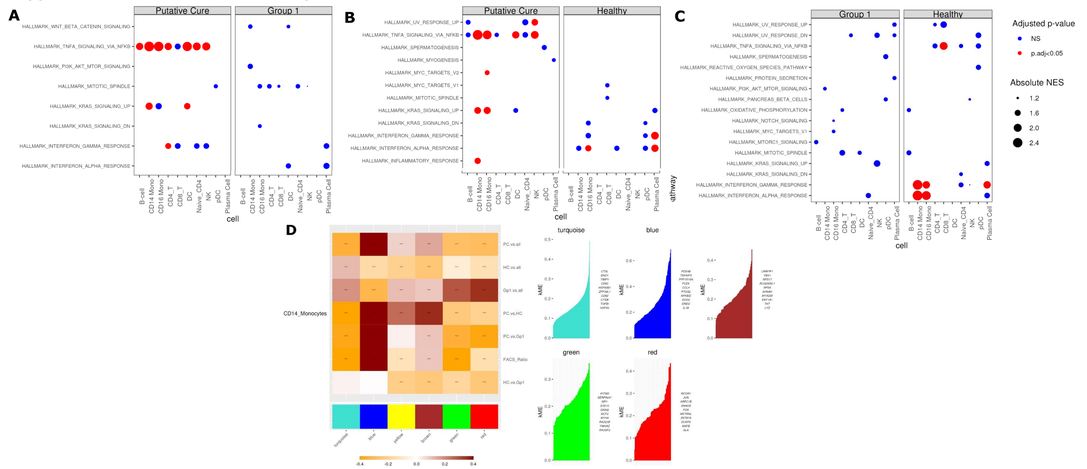
Putative Cures are characterized by decreased CCR5 and CD73 expression on major CD4 T-cell memory subsets

A. Elevated CCR5 has been associated with increased viral entry and viral load[3,4]. **B.** Elevated CD73 expression in CD4 T-cells has been attributed to increased HIV latency and larger proviral reservoir[5,6]. Notably, increased TNFα has been associated with decreased CD73 and CCR5 expression[7,8].



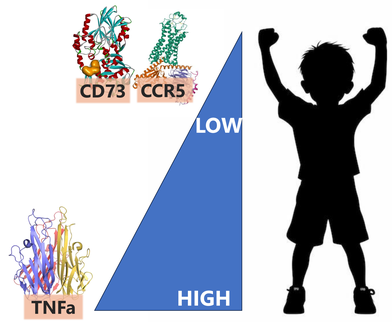
Putative cures upregulate TNFα pro-inflammatory pathways whilst maintaining lower type-I IFN response.

A-C. Geneset enrichment analysis (GSEA) calculated from pre-ranked differentially expressed genes demonstrates upregulated pathways compared between putative cures, Group 1s. **D.** Weighted gene correlation network analysis (WGCNA) of CD14+ monocytes reveal unsupervised construction of TNFα based inflammatory module within putative cures, and type-I IFN modules in Group 1s.



Takeaways

Cure Potential



- Increased TNFα drives lower CCR5/CD73 associated with viral entry and latent reservoir size
- Lower VRC and inflammatory response that circumvents type-I IFN resistance of HIV
- Perfect combination of these factors drive the putative cure phenotype

Conclusion

The potential for TNF-based therapeutics in HIV is not a novel avenue on its standalone in the quest for a cure. Our data invites further investigation into the benefits of a multi-faceted approach to sustained remission. However, further validation of differential inflammatory responses to TNFa between putative cures and progressors/ART-suppressed individuals is required.

References

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