Effect of Tuberculosis Preventative Therapy on *Mtb*-Specific T Cell Profile in the A5279/BRIEF TB Trial

Pablo C. Alarcon,[1] Xinyu Du,[2] Manuel G. Feria,[1] Ashley McKhann,[2] Michelle A. Kendall,[2] Michael L. Freeman,[3] Susan Swindells,[4] Amita Gupta,[5] Gavin Churchyard,[6] Richard E. Chaisson,[5] Cheryl L. Day,[7] Moises A. Huaman[1]

[1] Department of Internal Medicine, University of Cincinnati College of Medicine, Cincinnati, Ohio, USA; [2] Center for Biostatistics in AIDS Research, Harvard T.H. Chan School of Public Health, Harvard University, Boston, USA; [3] Department of Medicine, Case Western Reserve University School of Medicine, Cleveland, Ohio, USA; [4] Division of Infectious Diseases, Department of Medicine, University of Nebraska Medical Center, Omaha, Nebraska, USA; [5] Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA; [6] The Aurum Institute, Johannesburg, South Africa; [7] Department of Microbiology and Immunology, Emory University School of Medicine, Atlanta, Georgia, USA

BACKGROUND

- People with HIV (PWH) have abrogated *Mycobacterium tuberculosis* (*Mtb)*-specific T cell responses.
- Whether TB preventative therapy (TPT) impacts the *Mtb*-specific T cell response in PWH is unknown.
- We analyzed samples from the ACTG A5279 clinical trial, a phase III trial of PWH comparing 9 months of daily isoniazid (9H) to 4 weeks of daily isoniazid/rifapentine (1HP).
- Study Objective: Assess the magnitude and quality of antigen-specific T cell responses to *Mtb* antigens in PWH with latent TB infection (LTBI) pre- and post-TPT.

METHODS

- Peripheral Blood Mononuclear Cells (PBMC) were obtained and cryopreserved pre-TPT (week 0) and post-TPT (week 48) from participants in the A5279/BRIEF TB trial.
- End-point analysis inclusion criteria
  - Positive Tuberculin Skin Test (TST) or Interferon-Gamma Release assay (IGRA) at study entry
  - Stable antiretroviral therapy (HIV viral load <200 copies/mL and CD4⁺ T cell count >100 cells/mm³)
  - Median CD4⁺ count (Q1, Q3) : 640 cells/mm³ (468, 816)
  - Median time on ART (Q1, Q3): 5.3 years (3.2, 6.8)
- Statistical analyses
  - Primary comparisons: **pre-TPT** vs **post-TPT** *Mtb*-specific T cell phenotypes and cytokine responses calculated as absolute change (week 48-week 0)
  - Exploratory comparisons: **1HP** vs **9H** treatment arms of the absolute changes in *Mtb*-specific T cell phenotypes and cytokine responses
  - Statistical Tests: Wilcoxon signed-ranked test (primary) and Wilcoxon rank-sum test (exploratory), with no adjustment for multiple comparisons.

Table: Baseline Demographics [Median (Q1-Q3) or N (%)]

	Total (n=27)	9H (n=15)	1HP (n=12)
Age (years)	38 (35, 48)	36 (33, 50)	41 (36, 47)
Male sex at birth	20 (74%)	11 (73%)	9 (75%)
Country of Enrollment			
Brazil	1 (4%)	1 (7%)	0 (0%)
Kenya	1 (4%)	0 (0%)	1 (8%)
Thailand	6 (22%)	4 (27%)	2 (17%)
USA	19 (70%)	10 (67%)	9 (75%)

TB preventative therapy has a **minimal impact** on T cell responses to *Mtb* antigens in people with HIV with latent TB co-infection

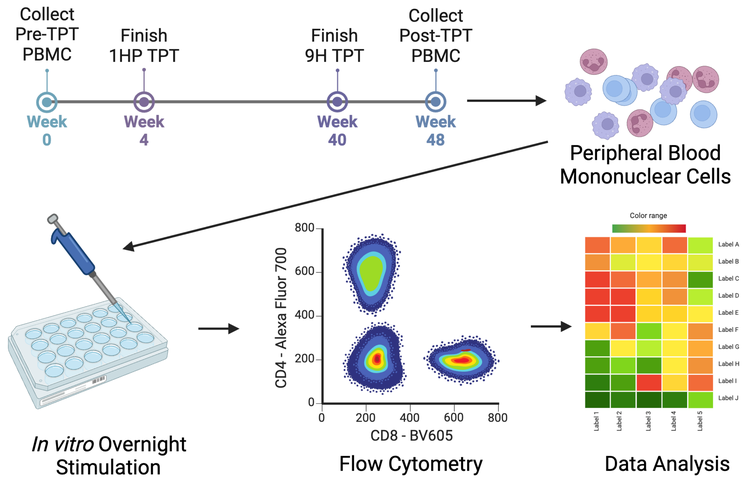


Figure 1: Experimental Design Cryopreserved PBMCs obtained at week 0 and week 48 from patients without progression to active TB disease were thawed and stimulated (*Mtb* ESAT-6/CFP-10 peptide pool or whole cell *Mtb* lysate (WCTBL)). Using flow cytometry, T cells were identified using CD3, CD4, and CD8. Markers of T cell activation and differentiation were used to phenotype the cells and cytokine production was measured.

RESULTS

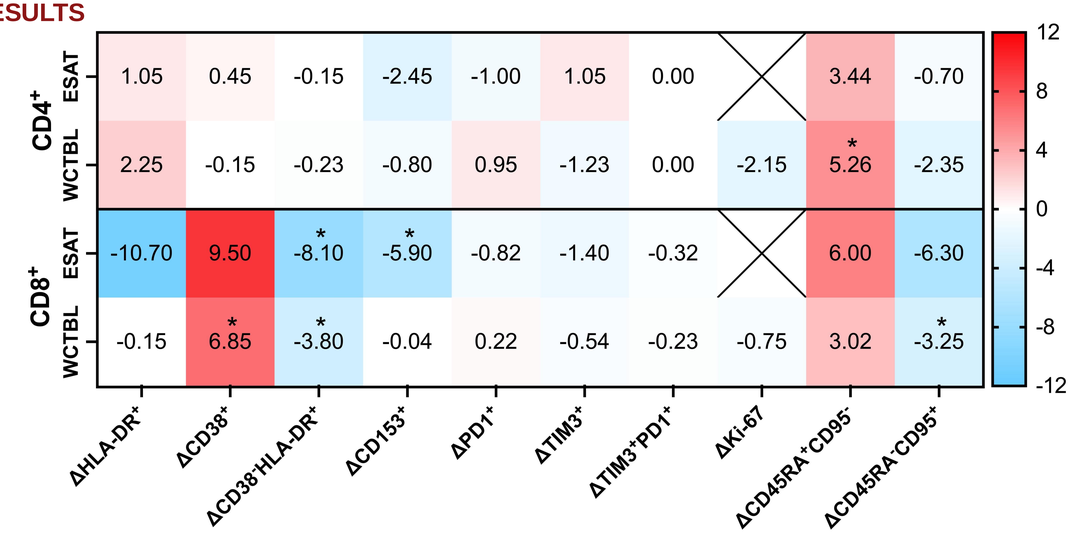


Figure 2: Comparisons of the pre- vs post-TPT percentages of CD4⁺ and CD8⁺ T cell activation and differentiation markers (ESAT or WCTBL stimulation) summarized as median absolute change. For CD4⁺, ESAT n=12, WCTBL n=10. For CD8⁺, ESAT n=9, WCTBL n=16. Data not available for ΔKi-67 for ESAT-stimulated CD4⁺ and CD8⁺ T cells. * = P<0.05

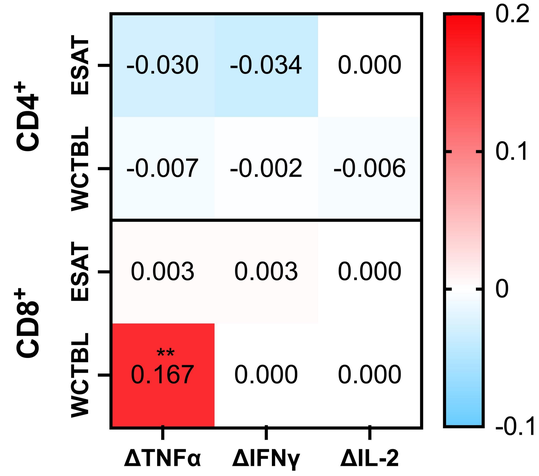


Figure 3: Comparisons of pre- vs post-TPT percentages of CD4⁺ and CD8⁺ T cell TNFα, IFN*γ*, and IL-2 cytokine production (ESAT or WCTBL stimulation) summarized as median absolute change. n=27 for all comparisons. ** = P<0.01

CONCLUSIONS

- Our findings suggest that *Mtb*-specific CD4⁺ and CD8⁺ T cell phenotype, differentiation, and functional attributes are **similar pre- and post-TPT.**
  - However, modest changes were observed in **CD8 T cell TNF-α production** post-TPT.
- Our findings suggest that the minimal impact of TPT on TB-specific T cell responses in PWH and LTBI is **similar between both treatment arms (data not shown).**

ACKNOWLEDGEMENTS

We thank the participants and study team of ACTG A5279 /BRIEF TB trial. This work was in part supported by a University of Cincinnati Office of Research (awarded to MAH), NHLBI (R01HL156779 to MAH) and NIAID (UM1 AI068634, UM1 AI068636, UM1 AI106701 to ACTG). Figures created in GraphPad Prism or BioRender.

Correspondence: Moises A Huaman, MD MSc
Email: moises.huaman@uc.edu

ACTG Advancing Clinical Therapeutics Globally for HIV/AIDS and Other Infections

University of CINCINNATI