Monocyte Activation in People with HIV and Latent Tuberculosis Co-Infection in the ACTG A5279/BRIEF TB trial (ACTG NWCS 476)

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BACKGROUND

- Latent Tuberculosis infection (LTBI) has been linked to increased immune activation and cardiovascular risk
- In ACTG NWCS 476, we investigated the activation profile of monocytes from people with HIV (PWH) who participated in the ACTG A5279 trial, a phase III trial of 4 weeks of daily rifapentine (RFP) / isoniazid (INH) versus 9 months of daily INH as TB prevention therapy (TPT)
- Hypothesis: PWH and evidence of LTBI will have higher levels of monocyte activation compared to PWH without evidence of LTBI

METHODS

- We analyzed cryopreserved PBMCs from PWH who participated in the A5279 trial. PBMCs were obtained at baseline (pre-TPT) and at week 48 (post-TPT)
- Inclusion criteria for this analysis: A5279 participants on antiretroviral therapy, with HIV viral load ≤200 copies/mL, tuberculin skin test (TST) or interferon-gamma release assay (IGRA) result at entry
- PBMCs were stained with markers of monocyte subsets (CD14, CD16), activation (HLA-DR, CD64, CD80, CD86), chemotaxis (CX3CR1, CCR2), and scavenger receptors (CD36, CD163)
- *In vitro* stimulation with lipopolysaccharide (LPS) was performed to evaluate monocyte markers, and IL-6 and TNF-alpha expression
- Samples were examined with multiparameter flow cytometry

Statistical analyses:

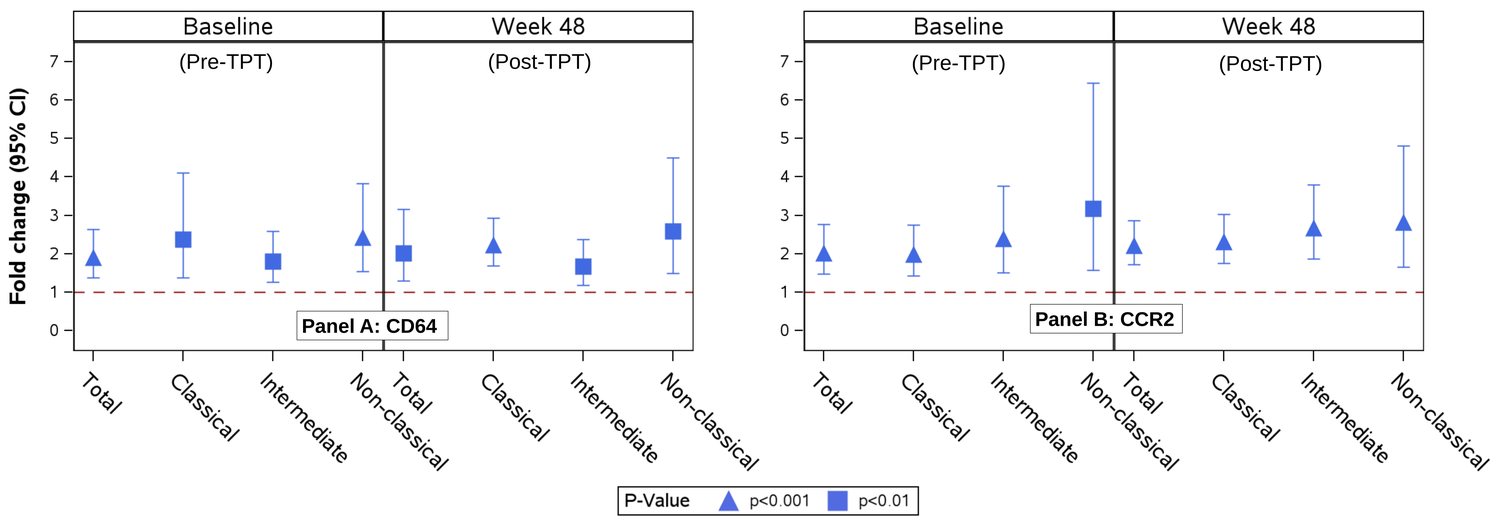
- Primary comparisons were between TST/IGRA-positive (evidence of LTBI) and TST/IGRA-negative groups
- Multivariable linear regression of $\log_{10}$-transformed markers adjusted for age, sex at birth, country, and CD4 count

People with HIV with evidence of latent TB co-infection exhibited monocyte alterations indicative of persistent activation and tissue migration before and after TB preventive therapy

Table. Baseline demographics [median (Q1-Q3) or N (%)]

	TST/IGRA positive (N=31)	TST/IGRA negative (N=27)	Total (N=58)
Age (years)	38 (35–48)	37 (33–46)	38 (34–47)
Female sex at birth	8 (26%)	17 (63%)	25 (43%)
Race/ethnicity			
White Non-Hispanic	1 (3%)	0 (0%)	1 (2%)
Black Non-Hispanic	10 (32%)	9 (33%)	19 (33%)
Hispanic (regardless of race)	13 (42%)	0 (0%)	13 (22%)
Asian, Pacific Islander	7 (23%)	18 (67%)	25 (43%)
Country of enrollment			
Brazil	2 (6%)	0 (0%)	2 (4%)
Kenya	2 (6%)	9 (33%)	11 (19%)
Thailand	6 (19%)	18 (67%)	24 (41%)
USA	21 (68%)	0 (0%)	21 (36%)
History of comorbidity at entry	11 (35%)	8 (30%)	19 (33%)
CD4 count (cells/mm³)	630 (452–816)	395 (319–461)	463 (347–650)

Figure. Fold change comparisons of monocyte MFI of CD64 (Panel A) and CCR2 (Panel B) using multivariate linear models between TST/IGRA-positive (evidence of LTBI) and TST/IGRA-negative groups (Anti-logged linear regression results adjusted for age, sex at birth, country, and CD4 count are presented with 95% confidence intervals)



RESULTS

- 58 participants from 4 countries were included. Median age was 38 years (IQR, 34 – 47). 33 (57%) men and 25 (43%) women; see **Table.** None of the participants developed active TB during the trial follow-up period
- At baseline (pre-TPT), compared to TST/IGRA-negative group, those with LTBI exhibited higher percentage and/or median fluorescence intensity (MFI) of CD64 and CCR2 on their total and classical monocytes
- At week 48 (post-TPT), compared to TST/IGRA-negative group, participants with LTBI had higher percentage and/or MFI of CD64 on total and all monocyte subsets, as well as differential expression of CD80, CD163, and CX3CR1 across some monocyte subsets
- Upon LPS stimulation, there were no differences in IL-6 or TNF-alpha production by TST/IGRA status; however, LTBI was associated with higher MFI of CD36 and CCR2, and lower MFI of CX3CR1 on total monocytes and subsets
- In multivariate analysis, LTBI was consistently associated with increased MFI of CD64 (unstimulated) and CCR2 (post-LPS) at baseline and week 48 across monocyte subsets; see **Figure**

CONCLUSIONS

- Compared to PWH with negative TST/IGRA at baseline, PWH with evidence of LTBI exhibited monocyte alterations indicative of persistent activation and tissue migration at baseline (pre-TPT) and week 48 (post-TPT)
- Our findings suggest that PWH and LTBI co-infection may have persistent monocyte activation despite TB preventive therapy, which could contribute to the development of inflammation-driven comorbidities. Longitudinal changes will be evaluated in future studies

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