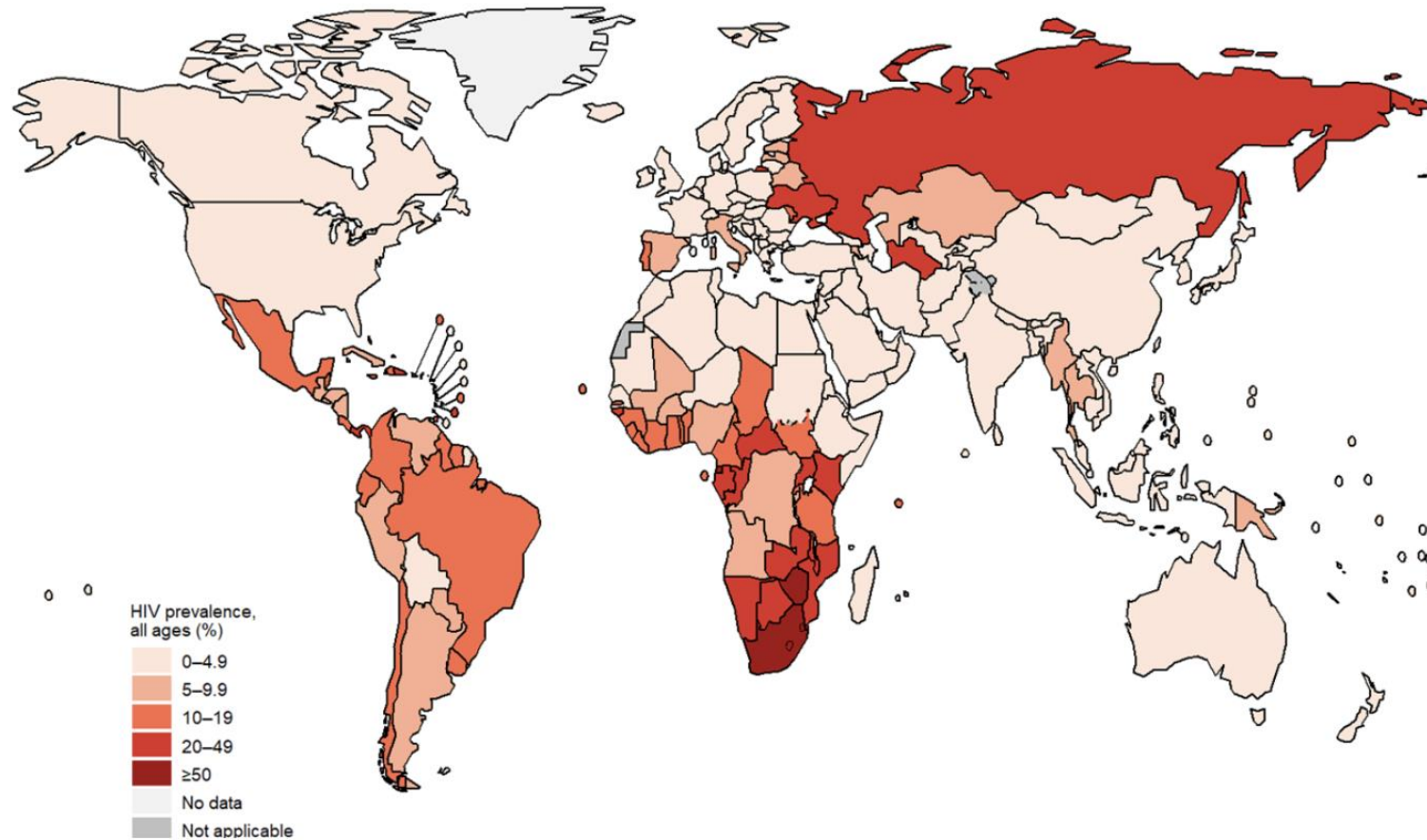




T helper cell subsets and integrin $\alpha_4\beta_1$ and $\alpha_4\beta_7$ expression in TB/HIV co-infection

Dr. Thando Maseko

HIV prevalence in people with a new/relapse episode of TB



Role of T cells in TB

- CD4⁺ T cells are crucial for Mtb control with Th1 and Th17 cells being key effector cells
- Rapid trafficking of antigen-specific T cells plays an important role in the control in the control of Mtb replication and was shown to be mediated by integrin $\alpha_4\beta_1$
- The depletion of Mtb of Mtb specific CD4⁺ T cells results in increased risk of TB infection, and TB dissemination
- HIV mediated changes in T helper cell distribution and cell surface integrin expression could have important consequences on T cell trafficking into the lungs and subsequent TB control

Study Design

Aims

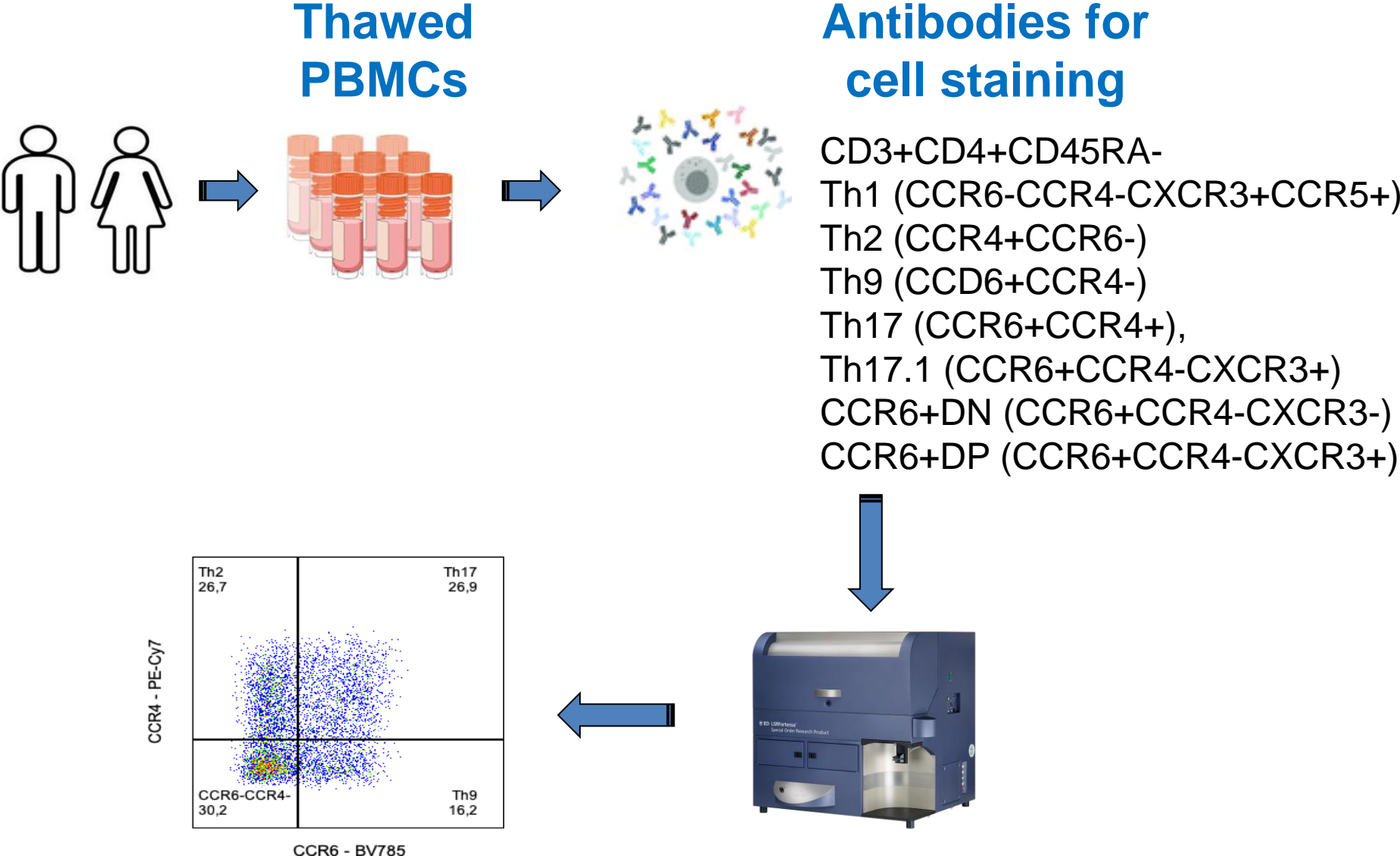
- To assess the differences in memory CD4⁺ T cell phenotypes between TB and TB/HIV co-infected participants of the CAPRISA 011 Improving Retreatment Success (IMPRESS) Trial as well as the effect of treatment on changes in CD4⁺ T cell memory phenotypes
- To assess the associations between systemic memory CD4⁺ T cell subsets and time to culture conversion and cavitory disease.

Study cohort

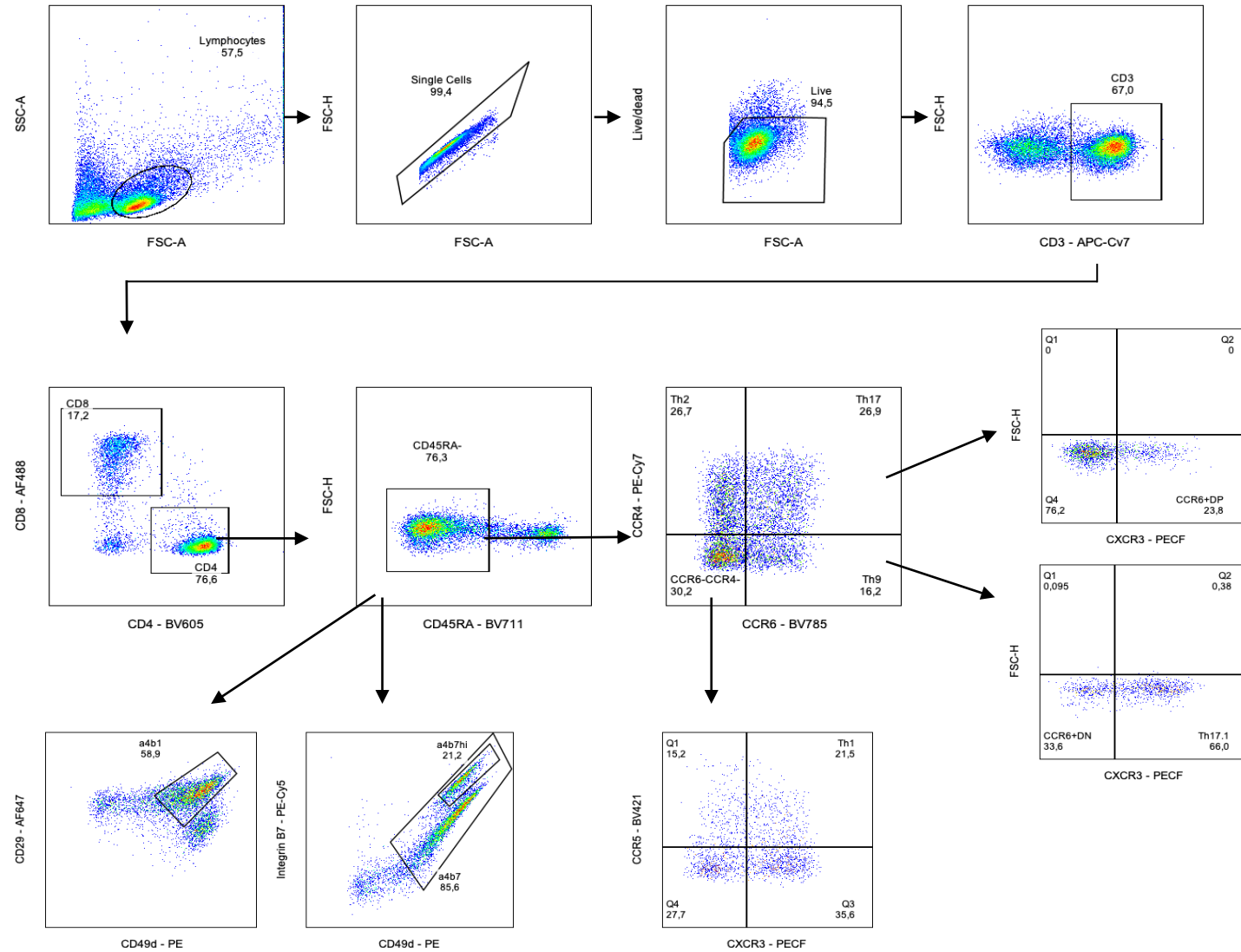
- CAPRISA 011 (IMPRESS) n=45: HIV infected/uninfected participants diagnosed with active TB and followed up for 18 months (Perumal *et al.*, 2020) and 13 healthy controls from KwaZulu-Natal, South Africa.



Methodology



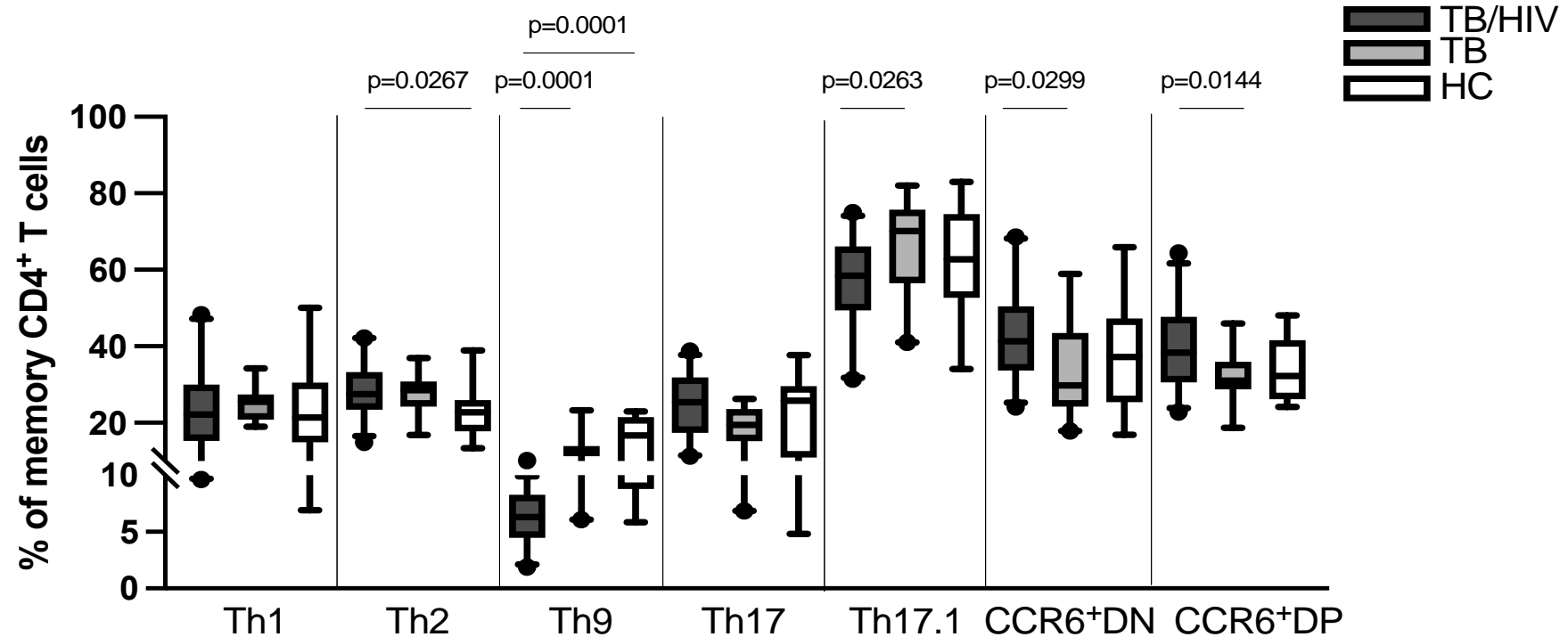
Gating Strategy



Results

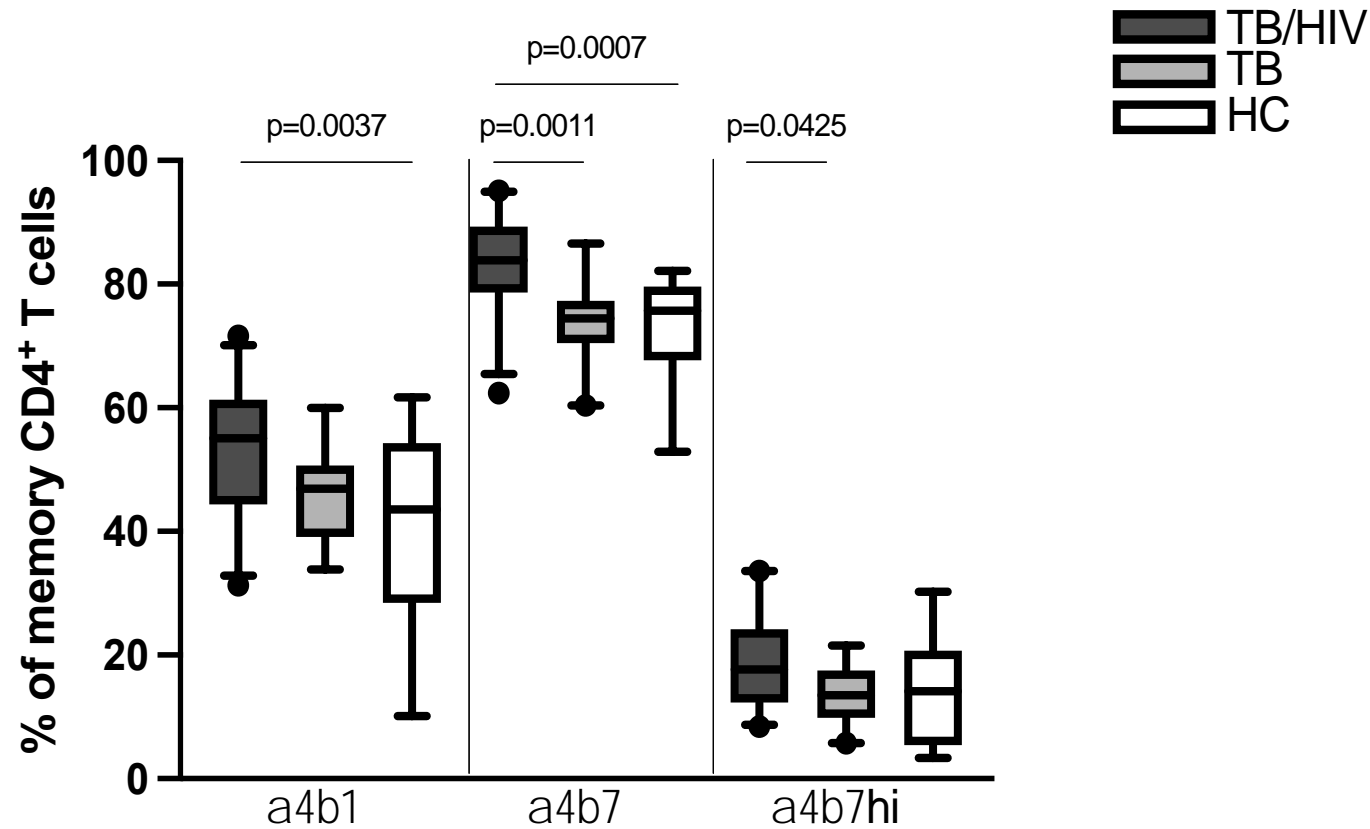
Variables	Total cohort n = 45	HIV positive n = 26	HIV negative n = 19
Randomization arm n (%)			
HRZE - Control	18 (40.0)	9 (34.6)	9 (47.4)
HRZM - Active	27 (60.0)	17 (65.4)	10 (52.6)
Gender, n (%)			
Male	30 (66.7)	14 (53.8)	16 (84.2)
Age (y), median (IQR)	33 (27 – 43)	33.5 (30.8 – 41.5)	29 (23 - 52)
Body mass index (kg/m²), median (IQR)	20.4 (18.6 – 23.4)	20.8 (18.9 – 23.9)	20.0 (18.5 – 21.8)
HIV Viral load (copies/ml), median (IQR)	-	26,520 (940 – 668236)	-
CD4 cell count (cells/mm³), median (IQR)	-	285.5 (127.5 – 382)	-
ARV status^a, n (%)			
Receiving ART	-	13 (50.0)	-
Lung Cavities^b, n (%)			
None	11 (24.4)	7 (26.9)	4 (21.1)
Unilateral	15 (33.3)	9 (34.6)	6 (31.6)
Bilateral	13 (28.9)	8 (30.8)	5 (26.3)
Alcohol Use in the past 3 months n (%)			
Yes	8 (17.8)	7 (26.9)	1 (5.3)
Smoking in past 3months n (%)			
Yes	15 (33.3)	7 (26.9)	8 (42.1)

Effect of HIV co-infection on % of memory CD4⁺ T cell subsets in patients with TB

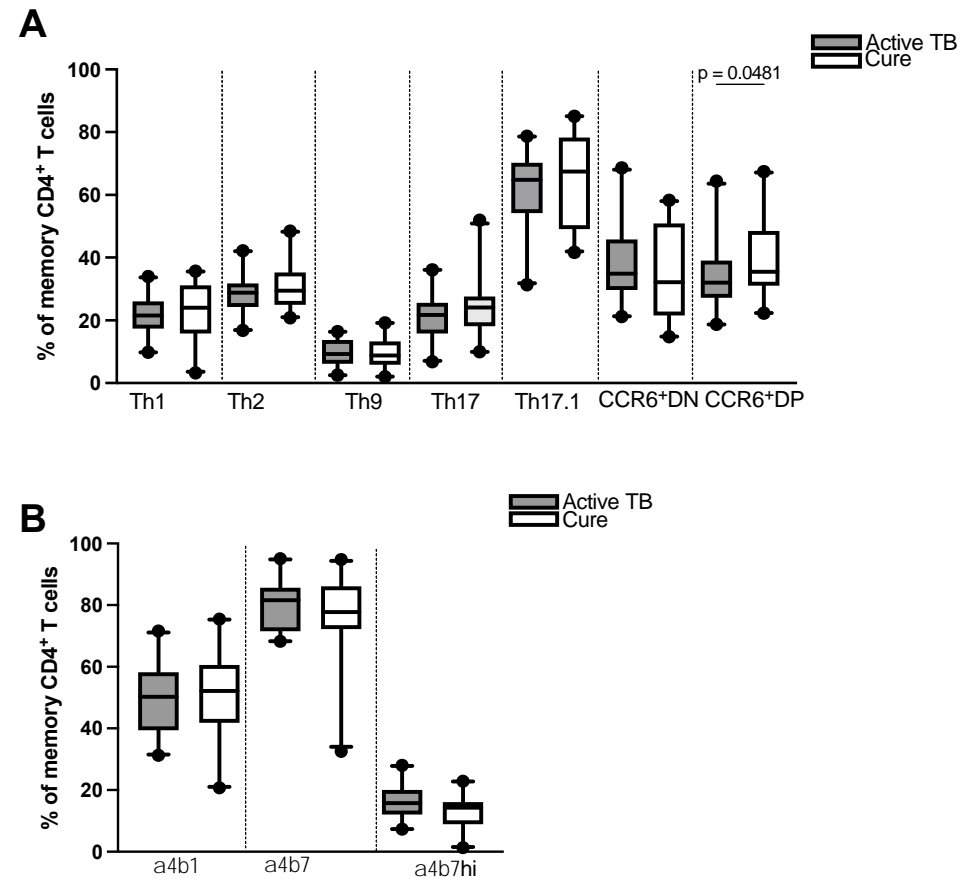


↓ Th9, Th17.1 ↑ Th2, CCR6⁺DN, CCR6⁺DP in TB/HIV co-infection

Higher % of $\alpha_4\beta_1$, $\alpha_4\beta_7$ integrins in TB/HIV co-infection



Effect of TB treatment on memory CD4⁺ T cell subsets in TB and TB/HIV co-infection



↑ CCR6⁺DP cells post TB treatment

Associations between memory CD4⁺ T cell subsets and time to culture conversion

Marker	Bivariable			Multivariable		
	HR	95% CI	p-value	aHR	95% CI	p-value
Th1	0.973	0.927 – 1.022	0.276	0.973	0.931 – 1.018	0.235
Th2	1.035	0.981 – 1.091	0.214	1.018	0.959 – 1.081	0.559
Th9	0.974	0.893 – 1.062	0.550	0.931	0.792 – 1.094	0.384
Th17	0.989	0.943 – 1.037	0.651	0.971	0.921 – 1.024	0.282
Th17.1	0.991	0.962 – 1.022	0.584	0.983	0.950 – 1.017	0.332
CCR6 ⁺ DP	1.002	0.968 – 1.037	0.915	0.995	0.956 – 1.036	0.822
CCR6 ⁺ DN	1.008	0.978 – 1.040	0.596	1.017	0.983 – 1.052	0.339
α 4 β 1	0.992	0.958 – 1.028	0.671	0.992	0.956 – 1.029	0.664
α 4 β 7	1.012	0.973 – 1.053	0.553	1.003	0.962 – 1.046	0.875
α 4 β 7 ^{hi}	1.016	0.964 – 1.071	0.551	0.999	0.943 – 1.060	0.986

Associations between memory CD4⁺ T cell subsets and cavitory disease

Marker	Bivariable			Multivariable		
	OR	95% CI	p-value	OR	95% CI	p-value
Th1	1.003	0.923 – 1.089	0.951	1.003	0.925 – 1.088	0.938
Th2	0.933	0.836 – 1.041	0.216	0.924	0.822 – 1.039	0.187
Th9	1.070	0.895 – 1.279	0.458	1.150	0.861 – 1.536	0.344
Th17	1.002	0.917 – 1.096	0.960	1.004	0.910 – 1.108	0.934
Th17.1	0.997	0.941 – 1.057	0.928	0.994	0.936 – 1.057	0.855
CCR6 ⁺ DP	1.007	0.940 – 1.078	0.848	1.013	0.941 – 1.091	0.730
CCR6 ⁺ DN	1.004	0.947 – 1.063	0.903	1.007	0.947 – 1.070	0.829
α 4 β 1	1.043	0.972 – 1.120	0.240	1.061	0.980 – 1.149	0.143
α 4 β 7	1.040	0.957 – 1.131	0.354	1.058	0.961 – 1.165	0.252
α 4 β 7 ^{hi}	0.963	0.874 – 1.062	0.451	0.946	0.846 – 1.058	0.331

Summary

- The TB and HIV syndemic remains a public health challenge. CD4⁺ T cell responses are crucial for host defense against *Mtb*.
- We observed higher % of Th2 and lower % of Th9 cells in TB/HIV co-infected participants compared to healthy controls and lower % of Th17.1 cells in TB/HIV co-infected participants compared to TB participants.
- We observed higher % CCR6⁺DN and CCR6⁺DP cells in TB/HIV co-infected participants compared to TB-infected participants. Peripheral CCR4⁺CCR6⁺ and CXCR3⁺CCR6⁺ T cells were shown to be highly permissive to HIV infection due to co-expression of CCR5 while CCR6⁺ DN cells have been implicated in HIV persistence during ART.
- We observed an increase in both $\alpha_4\beta_1$, and $\alpha_4\beta_7$ in TB/HIV co-infected participants compared to healthy controls. Additionally, we observed increased expression of $\alpha_4\beta_7$ and $\alpha_4\beta_7^{\text{hi}}$ in TB/HIV co-infection compared to active TB alone.
- During active TB, HIV induces changes in CD4⁺ T cell subset distribution and lymphocyte trafficking marker expression that may have detrimental effects on *Mtb* control

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