Heterogeneity of PD-1 expression in PLHIV and its relationship with host and viral-related factors

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BACKGROUND

Anti-PD-1 immunotherapy (API) can potentially reverse T-cell exhaustion, reinvigorate HIV-specific T-cell responses, and reduce the HIV reservoir in people living with HIV (PLHIV). API responsiveness is not directly associated with PD-1 expression on T-cells. Therefore, we aimed to assess 1. the variability of PD-1 expression on subsets of T-cells, 2. which host factors relate to PD-1 heterogeneity, 3. correlate PD-1 expression with PBMC functionality.

METHODS

High-dimensional flow cytometric PD-1 measurements from viral suppressed PLHIV using ART of the 2000HIV cohort (NCT03994835) were analyzed, separated into discovery cohort (n=1147) and validation cohort (n=225). We assessed percentages and MFI of PD1 in 21 T-cell subsets (Tc). Participants were categorized into high, intermediate, and low consistent PD-1 expression groups when >75% of Tc had PD-1 values in one of the following tertiles of PD-1 distribution, T3, T2 and T1 respectively. We explored the relationship of PD-1 expression with clinical and HIV-related factors as well as ex-vivo PBMC cytokine production capacity after stimulation using Spearman-rank correlation analysis.

PD1 expression on T cells is heterogeneous and related to clinical factors!
Important for anti-PD1 responses?

RESULTS

1. Effector memory T cells are the subsets with the highest proportion and expression of PD-1

2. Less than 40% of the participants had a consistent PD1 expression across all T cell subsets evaluated

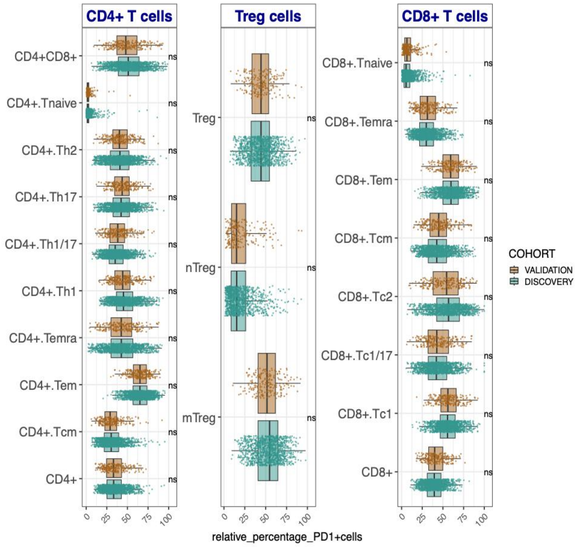


Figure 1. Comparison of PD1+ Immune Cell Proportions in the 2000 HIV study. Boxplots show the proportions of PD1+ immune cells in the discovery cohort (n = 1147) and validation cohort (n = 225). The center line represents the median, and the box extends from the first to the third quartile (interquartile range). Statistical significance was determined using the Wilcoxon rank-sum test with adjusted p-values (< 0.001 ***, < 0.01 **, < 0.05 *).

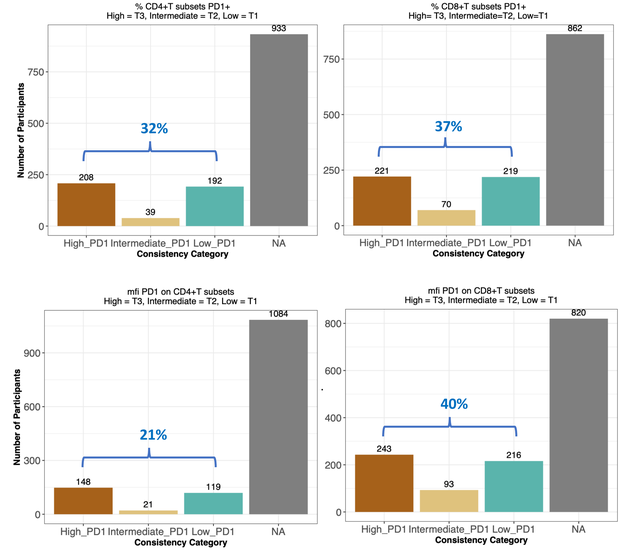


Figure 2. Classification of Participants Based on PD-1 Expression Across 21 T Cell Subsets. Participants were categorized into high (T3), intermediate (T2), and low (T1) PD-1 expression groups. Classification was based on tertiles, with individuals assigned to a group if more than 75% of their T cells exhibited PD-1 expression levels within the corresponding tertile. The analysis included CD4+ T cells, CD8+ T cells, and regulatory T cells (Tregs).

3. PD-1-expressing cells are associated with host- and viral- factors in PLHIV.

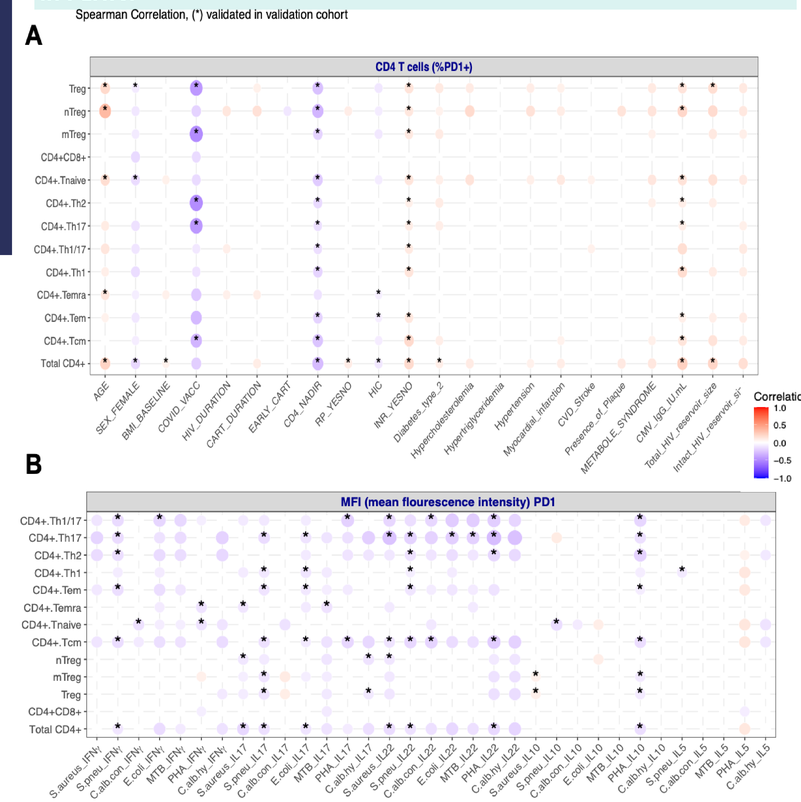


Figure 3. Spearman-Rank correlation analysis showing the correlation of: A. host and viral-related factors with proportions of CD4Tc expressing PD-1 B. PD-1 expression on CD4Tc with ex-vivo cytokines secretion upon stimulation with microbial stimuli.

CONCLUSIONS

- PLHIV exhibited a heterogeneous PD-1 expression across all Tc subsets, which negatively impacted cytokines production, indicating immune exhaustion.
- PLHIV with higher CMV reactivity, higher HIV reservoir size, males and immunological non-responders show highest PD-1 expression and may react differently to API than other groups.

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www.2000HIV.com