Immunological Non-Responders have CD4+ Immunosenescence and Impaired Lymphocyte Cytokine production

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BACKGROUND

Immunological non-responders (INR) are people living with HIV (PLHIV) that fail to restore CD4+ T-cell counts despite adequate viral suppression under combination antiretroviral therapy (cART). INR are at increased risk for non-AIDS morbidity and mortality. Previous research has shown that a IL-2 induced CD4+ T-cell count increase did not change clinical endpoints. This indicates a persistent immunological qualitative defect.

METHODS

Design and participants INR were identified in the cross sectional 2000HIV study (clinicaltrials NTC03994835) of 1895 PLHIV in the Netherlands. In line with literature, INR were defined as CD4<350 after at least two years of adequate cART. INR were compared to immunological responders (IR) who did show CD4+ restoration under cART, and were defined as CD4>500. An independent discovery cohort (62 INR, 1224 IR) and validation cohort (26 INR, 243 IR) were included

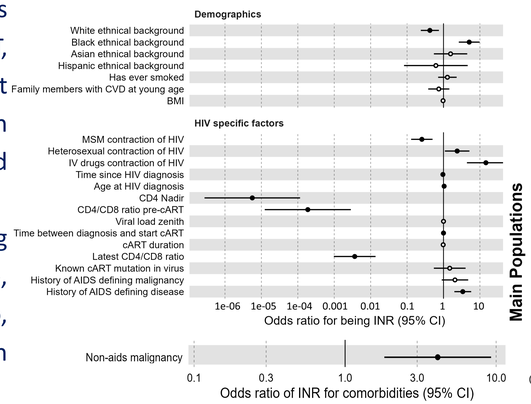
Methods Extensive Immunophenotyping using flow cytometry panels for monocytes, DC-, NK-, B-, CD4+ T- and CD8+ T- cells was performed. Also, monocyte and lymphocyte cytokine production in response to multiple stimuli was measured.

Statistical analyses Logistic and rank based regression were used to compare INR to IR. Analyses were corrected for sex at birth and age (all), seasonality (immunophenotyping), and current monocyte/lymphocyte ratio (cytokine production).

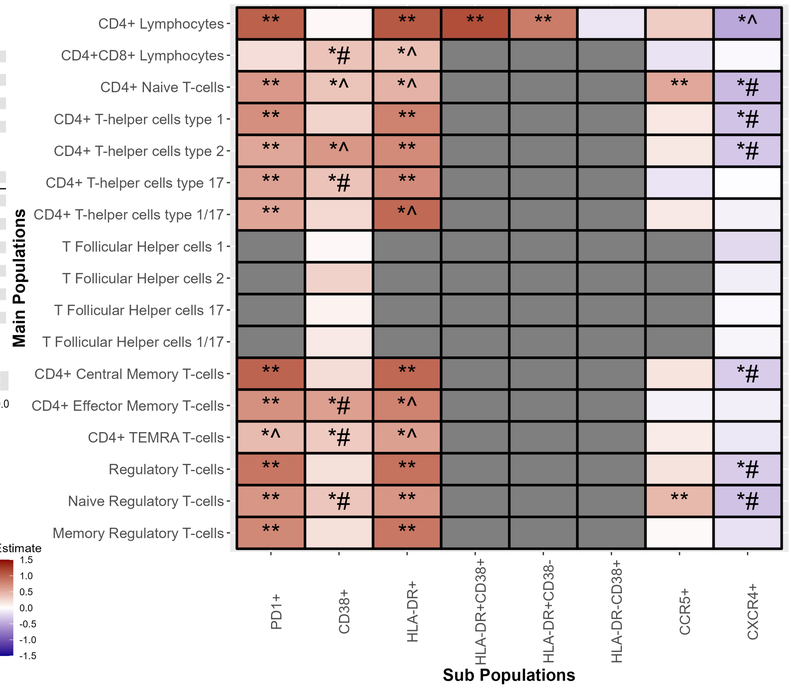
- Immune defects of immunological non-responders (INR) go beyond low CD4+ T-cell counts
- CD4+ T-cells of INR show more activation and increased immunosenescence
- Stimulated lymphocytes of INR produce less cytokines
- PD1 checkpoint inhibitors could theoretically be beneficial for INR

RESULTS

Demographic and clinical associations



Immunophenotyping (percentage populations)

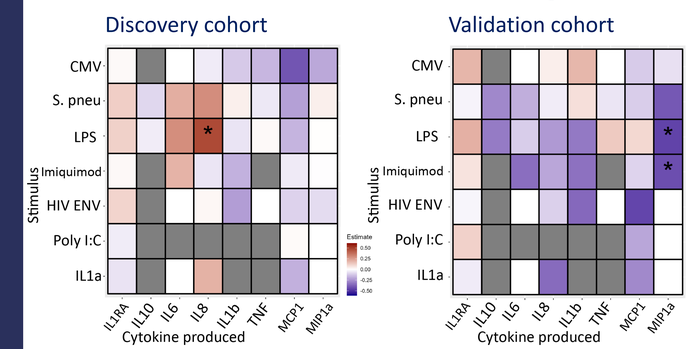


** Significant in discovery & validation cohort
*^ Significant in discovery cohort and equal directionality in validation cohort
*# Significant in validation cohort with different directionality in validation cohort

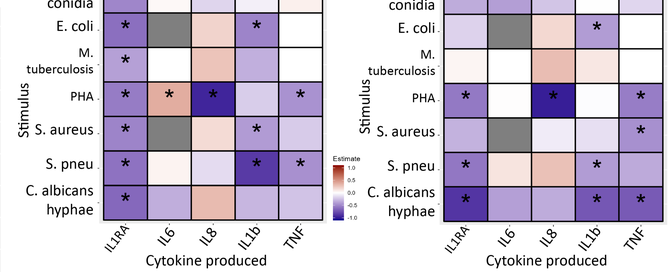
Estimate 1.5 1.0 0.5 0.0 -0.5 -1.0 -1.5

Monocyte production capacity

* Significant



Lymphocyte production capacity



CONCLUSIONS

- Immunological non-responders (INR) more often had a medical history of non-AIDS cancer
- INR CD4+ have a higher percentage of PD1+ and HLA-DR+ subpopulations
- INR lymphocyte cytokine production is decreased, whereas monocyte cytokine production is unchanged

ADDITIONAL INFORMATION

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The 2000HIV study is supported by ViiV Healthcare
www.2000HIV.com