Single-Cell Multiomics Reveals Systemic Immune Aging Acceleration in People Living with HIV

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Rainer Knoll[1], Martina van Uelft[1,2], Lisa Holsten[1,2], SysMed group[1], Jéssica dos Santos[3], Vasiliki Matzaraki[3], Maartje CP Jacobs-Cleophas[3], Nadira Vadaq[3], Adriana Navas[3], Marc Beyer[1,4], Elena DeDomenico[2,4], Lorenzo Bonaguro[1], Andre JAM van der Ven[3], Mihai G Netea[3,6], Joachim L. Schultze[1,2,4], Anna C. Aschenbrenner[1]

1 Systems Medicine, German Center for Neurodegenerative Diseases (DZNE), Bonn, Germany 2 Genomics & Immunoregulation, Life & Medical Sciences Institute, University of Bonn, Bonn, Germany 3 Department of Internal Medicine and Infectious Diseases, Radboud University Medical Center, Nijmegen, The Netherlands 4 PRECISE Platform for Single Cell Genomics and Epigenomics, DZNE and University of Bonn, Germany

BACKGROUND

Chronic HIV infection is associated with immune dysfunction and premature aging, but the cellular and molecular mechanisms remain incompletely defined.

We hypothesized that HIV accelerates immune aging through alterations in immune cell composition, function, and molecular signatures despite antiretroviral therapy (ART).

METHODS

We studied people living with HIV (PLHIV, n=290) from the 2000HIV cohort (NCT03994835) and people without HIV (PWoH, n=108) across age groups. Immune subsets were quantified by flow cytometry. Cytokine production was assessed *ex vivo* by ELISA. Serum proteomics was performed using OLINK. Single-cell transcriptomic data (1.1 million cells) were generated with BD Rhapsody and analyzed with Seurat to define transcriptional patterns across immune subsets. Aging analyses included spearman correlations with chronological age and enrichment testing with gene set variation analysis (GSVA) across groups. Statistical significance was assessed using Wilcoxon tests.

ADDITIONAL INFORMATION

correspondance: rainer.knoll@dzne.de

Despite viral suppression, HIV accelerates immune aging and defines a senescence-high phenotype linked to clinical vulnerability

RESULTS

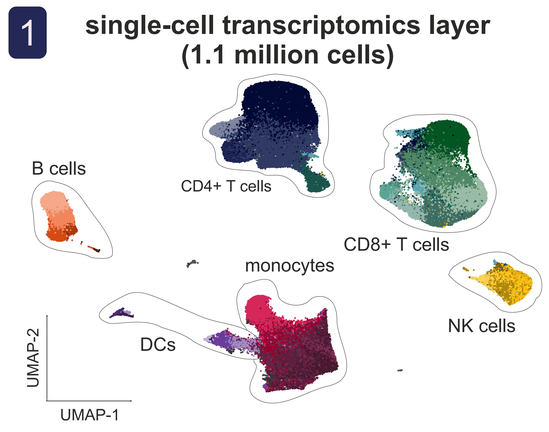


Figure 1:
High-resolution UMAP of 1.1 million circulating immune cells, annotated for major immune cell types.

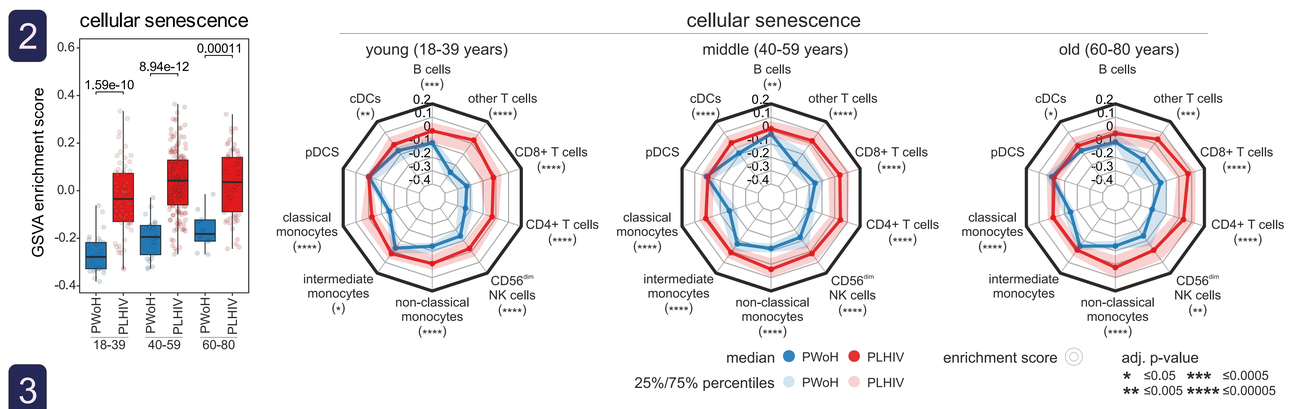


Figure 2:
Enrichment of cellular senescence gene signatures across all circulating immune cells (left) and within each major cell type (right), stratified by age and disease status (PLHIV in red, PWoH in blue). Significance assessed by Wilcoxon rank-sum test.

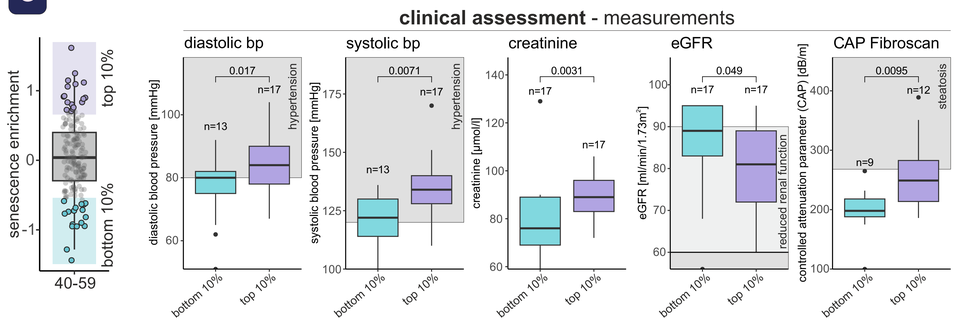
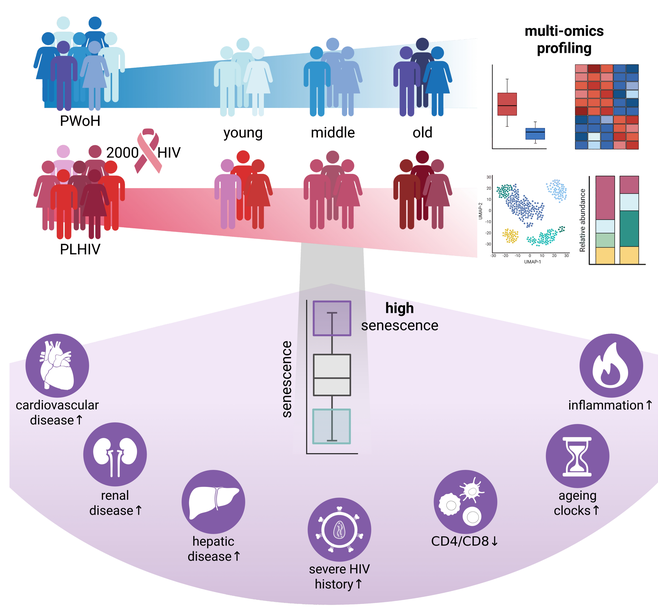


Figure 3:
Stratification of PLHIV (age 40-59) by senescence (left) and assessment of clinical measurements between high- and low-senescence groups.

CONCLUSIONS

Chronic HIV infection under ART is associated with immune aging characterized by altered T cell composition, reduced cytokine responses and sustained molecular signatures of senescence. These findings provide a comprehensive single-cell view of immune aging in PLHIV and identify potential targets for interventions to mitigate aging-related complications.

GRAPHICAL SUMMARY



PLAIN LANGUAGE SUMMARY

Even when HIV is well controlled with therapy, the immune system shows signs of aging earlier than expected. We found that this accelerated immune aging is linked to higher risk for age-related health problems, suggesting it could help identify people who may benefit from closer monitoring.

The 2000HIV study is supported by ViiV Healthcare