Perturbations in the myeloid cell compartment persist in early-treated people living with HIV.

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Jozefien De Clercq[1,2,a], Sofie Rutsaert[1,a], Jolien Vermeire[1], Linos Vandekerckhove[1,2,b], **Sarah Gerlo**[1,b]
[1]Ghent University, Ghent, Belgium; [2] Ghent University Hospital, Ghent, Belgium; [a]shared first authors; [b]shared senior authors

BACKGROUND

Despite antiretroviral therapy (ART) initiation during acute HIV infection (AHI), persistent immune alterations remain. To better understand the deviation from immune homeostasis, we performed longitudinal phenotypic and transcriptional profiling of peripheral blood mononuclear cells (PBMCs) from early-treated people living with HIV (PLWH) using HIV-negative controls as reference population.

Even with ART initiation during AHI, CD14 monocyte activation remains aberrant in virally suppressed people living with HIV. These findings highlight monocytes as a potential driver of residual immune dysfunction and suggest they may represent a therapeutic target to mitigate long-term immune activation.

METHODS

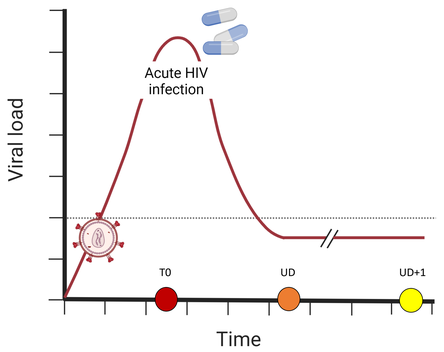


Figure 1. Matched **PBMC** samples (n = 39) were analyzed during **AHI (T0)**, at **viral suppression (UD)** and after **one year of stable viral suppression (UD+1)**. PBMC from HIV-negative individuals (HCs) were included as controls. **Flow cytometry** (26-color) data were clustered using FlowSOM. **Cellular indexing of transcriptomes and epitopes (CITE-seq)** was performed for T0 UD+1 and HCs (n=7). Cells were clustered with unsupervised weighted-nearest neighbor (WNN) analysis integrating RNA and protein features to define immune cell states. Differential gene expression, pathway analysis and MultiNicheNet analysis were performed on the different cellular clusters.

PLAIN TEXT SUMMARY
Starting HIV treatment very early helps the immune system recover. Even after a year of successful treatment, however, certain immune cells remain unusually activated and keep the immune system in a state of ongoing inflammation.

RESULTS (flow cytometry)

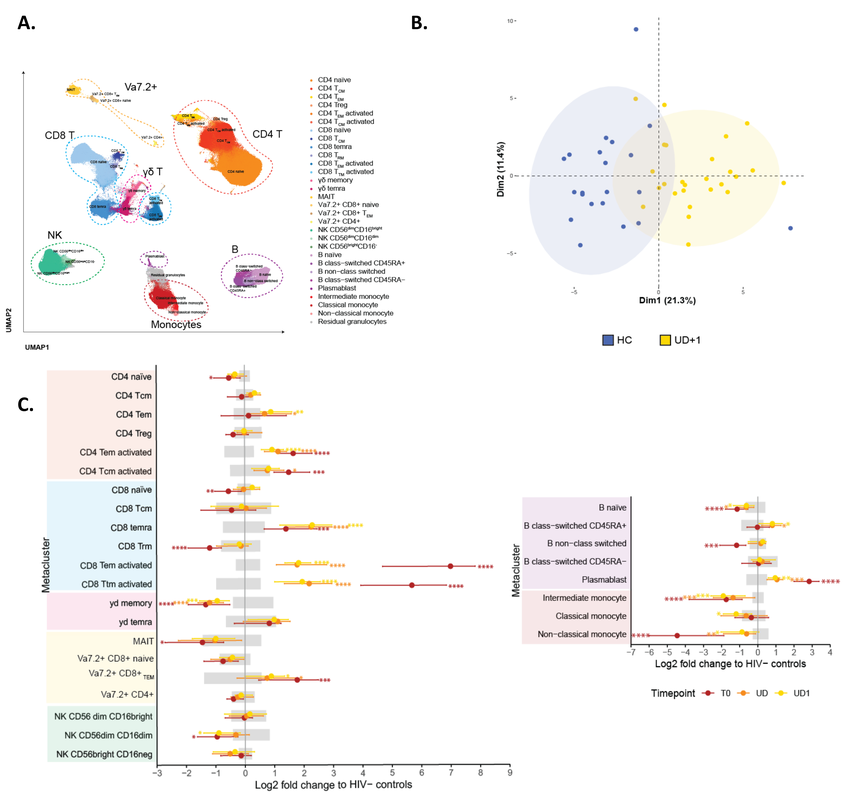


Figure 2. A. Flow cytometry identifies 30 metaclusters of CD4 and CD8 T cells, γδ T cells, MAIT cells, NK cells, B cells, and monocytes. **B.** PCA analysis of relative proportions of metaclusters distinguishes stably suppressed PLWH from HC. **C.** AHI is associated with marked shifts in cellular composition and activation that largely normalize after one year of ART. Clusters defined by (terminal) effector memory phenotypes and immune cell activation, however, differentiate PLWT at UD+1 from HC. CD8 TEMRA cells remain elevated despite viral suppression. In addition, monocyte frequencies are reduced during AHI and fail to normalize with ART.

ADDITIONAL KEY INFORMATION

Author Contact Information: Sarah.Gerlo@ugent.be; Linos.Vandekerckhove@ugent.be
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RESULTS (CITE-seq)

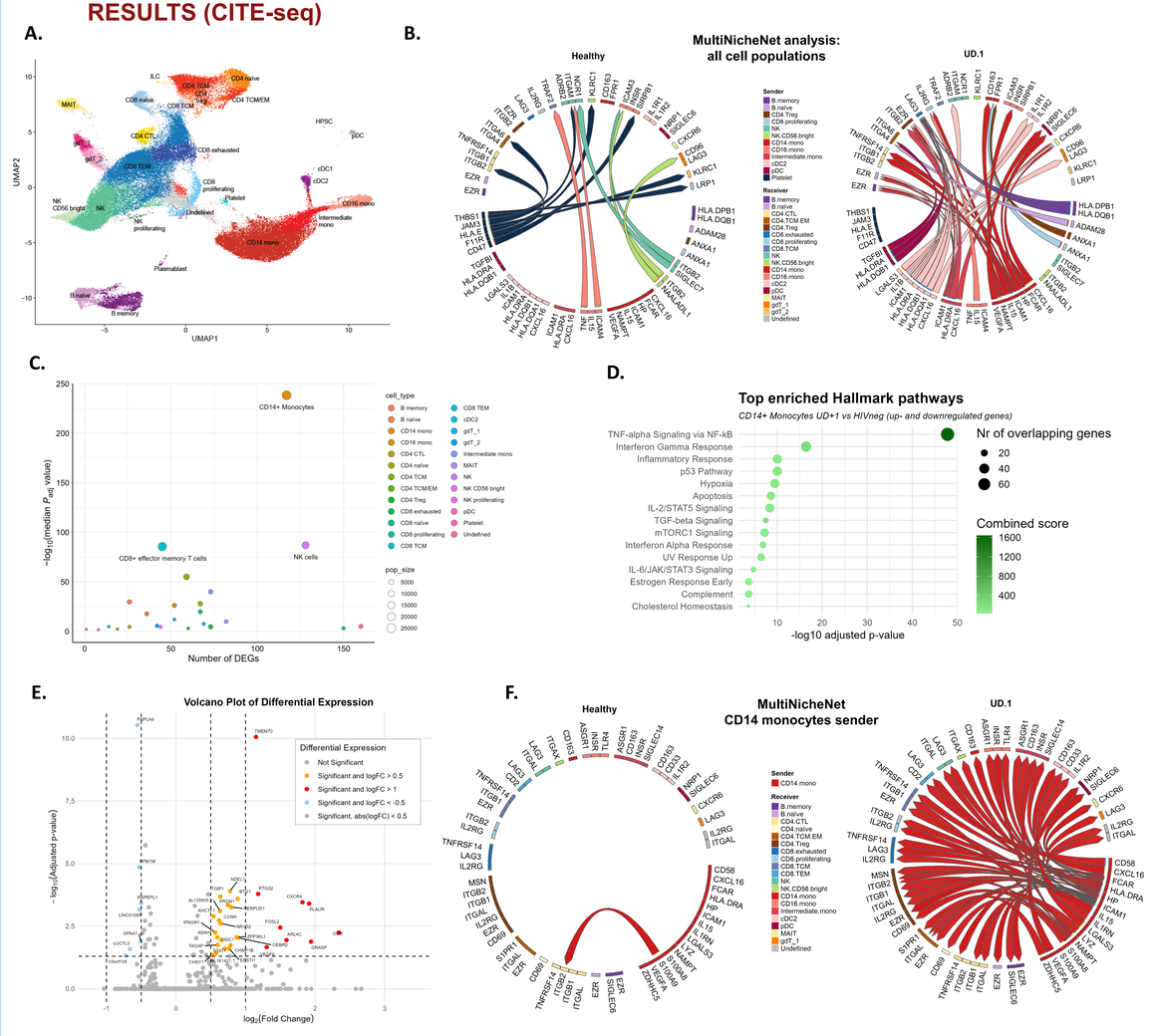


Figure 3. A. CITE-seq analysis identifies 28 distinct cellular clusters. **B.** MultiNicheNet analysis shows intensified cell-cell communication in PLWH at UD+1 versus HC, with prominent contribution of myeloid cells in the signaling network. **C**. Classical CD14 monocytes of PLWH at UD+1 are transcriptionally the most divergent from HC. **D.** Pathway analysis and **E.** differential gene expression reveal enrichment of NF-κB- and IFNγ-driven programs in CD14+ monocytes
F. CD14 monocytes of PLWH exhibit increased “sender” activity in the cell-communication network when compared to those of HC.