

# ART Exposure and Accelerated Aging in PLHIV: Insights from Proteomic and Methylation Clocks

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## BACKGROUND

People living with HIV (PLHIV) using antiretroviral therapy (ART) are exposed to persistent low grade of inflammation, which may accelerate aging. However, the impact of various ART regimens on residual inflammation and accelerated aging remains largely unclear. This study investigates the relationship between cumulative ART exposure and age acceleration in virally suppressed PLHIV on ART.

## METHODS

Data from the 2000HIV cohort (NCT03994835) (n=1875):

Cumulative ART exposure by duration (in years) and regimen type and drug class. Detailed treatment data available for each participant

### Age Acceleration Assessment (biological clocks):

- Proteomic clock (based on Olink Proteomics 3072 data)
- Epigenetic/methylation clocks (Horvath, Hannum, PhenoAge, GrimAge) using genome-wide methylation data measured by Illumina MethylationEPIC array

### Analyses Conducted:

- Examined the relationship between cumulative ART exposure and age acceleration score using five biological clocks
- Differential expression analyses (DEA) and pathway enrichment analyses of proteomic data to explore underlying mechanisms

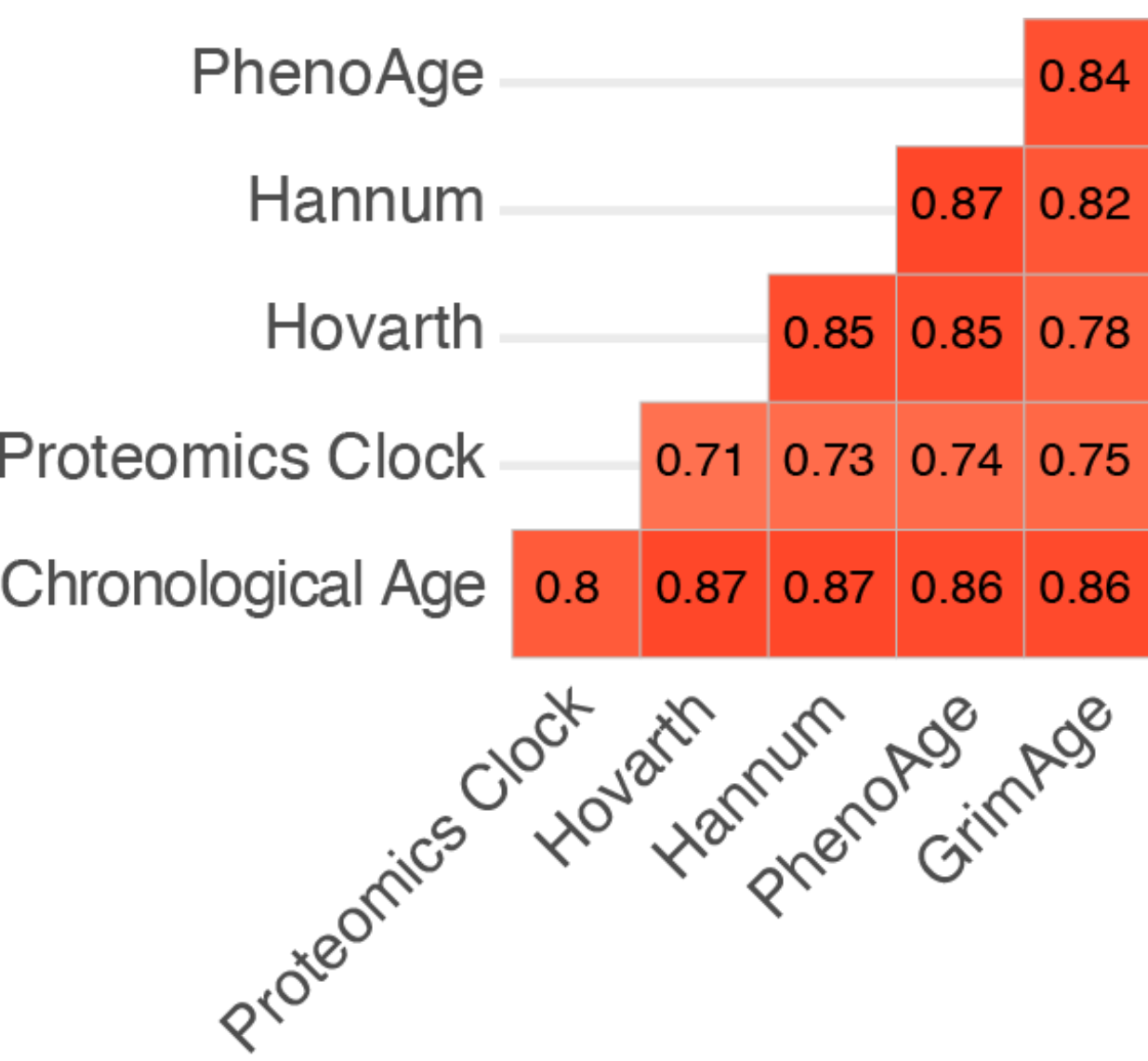
## ADDITIONAL KEY INFORMATION

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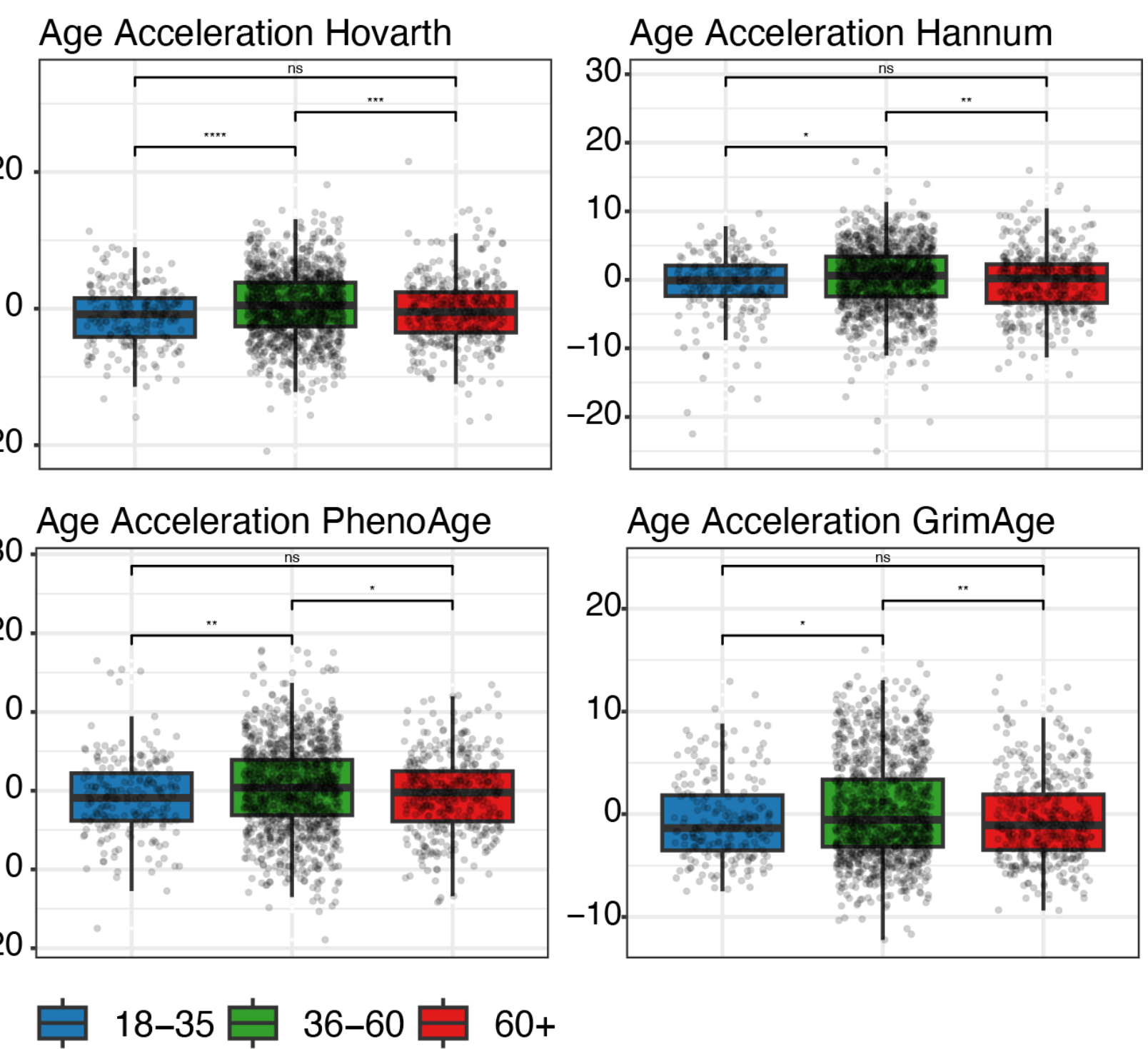
Cumulative ART exposure correlates with age acceleration in PLHIV, with some drugs (e.g., DTG, RPV) linked to slower aging and others (e.g., TDF, FTC, DRV, ATV) to faster aging. These effects are mediated by changes in innate immune pathways.

## RESULTS

### A. Correlation between biological clocks

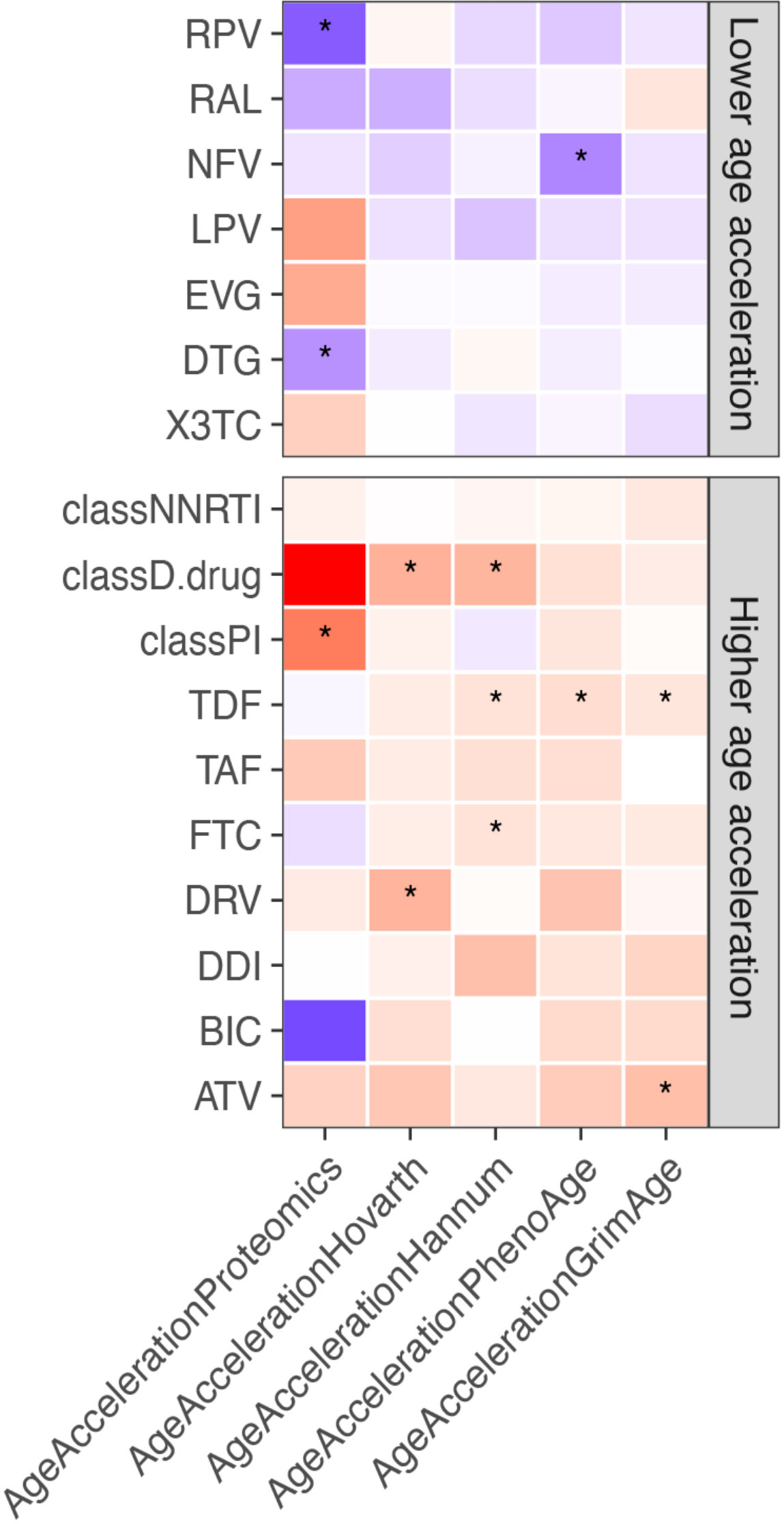


### B. Age acceleration based on age categories



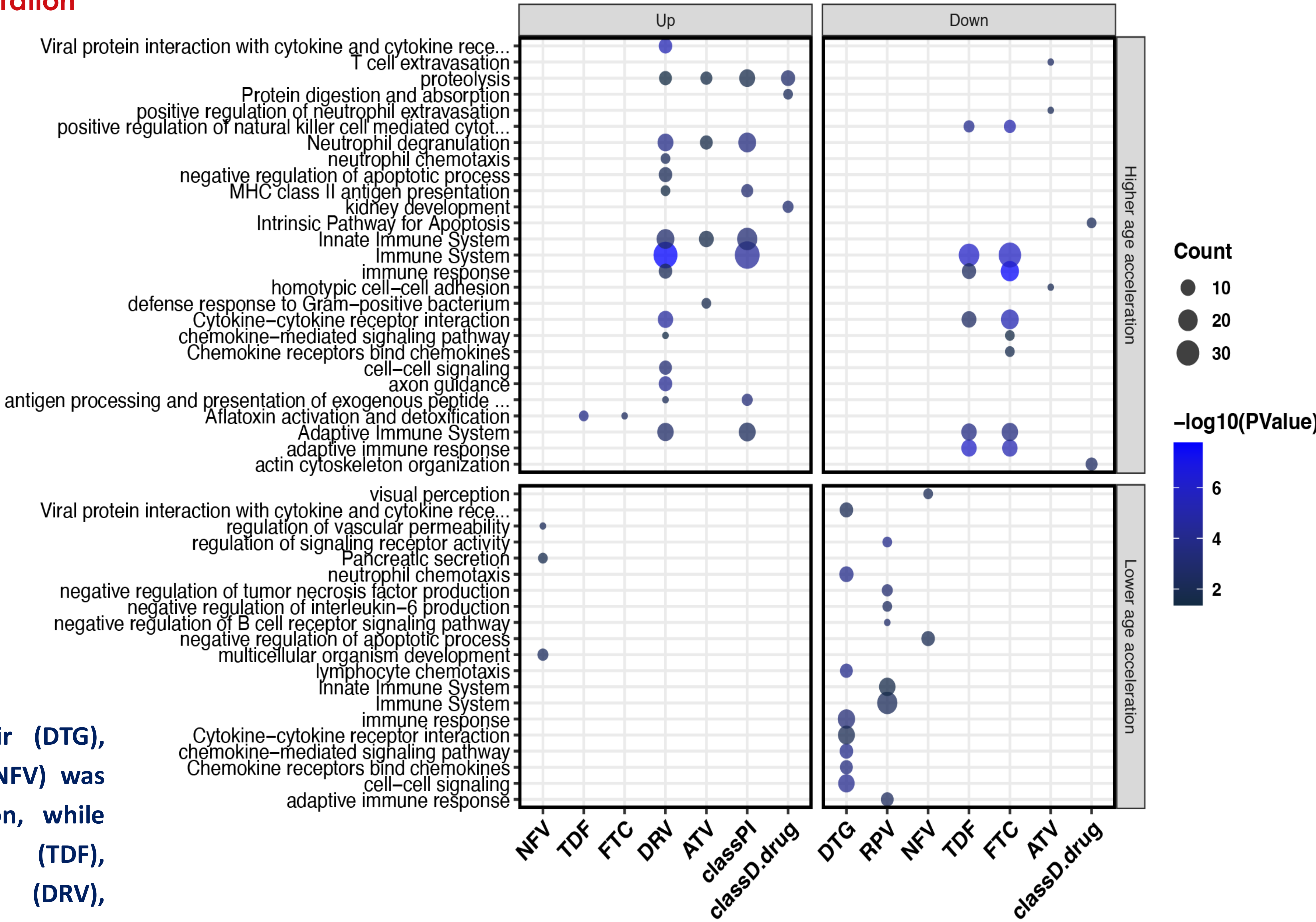
- Participants aged 36–60 showed faster epigenetics age acceleration compared to both younger and older participants.

### C. Cumulative ART exposure associated with higher and lower age acceleration



- Longer exposure to dolutegravir (DTG), rilpivirine (RPV) and nelfinavir (NFV) was linked to lower age acceleration, while tenofovir disoproxil fumarate (TDF), emtricitabine (FTC), darunavir (DRV), atazanavir (ATV), and dideoxynucleoside analogues (d-drugs) were associated with higher age acceleration.

### D. Proteomic pathways linked with higher and lower age acceleration



- DTG and RPV exposure correlated with downregulated innate immune pathways, while DRV and ATV linked to their upregulation.