Epigenetic Age Acceleration and Mortality among Persons who Inject Drugs with Poorly Controlled HIV

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Introduction

- HIV infection and substance use are linked to accelerated epigenetic aging, with studies showing that active drug injection influences methylation patterns and biological aging.
- Limited data exist on the long-term health implications of epigenetic aging in persons who inject drugs (PWID) with HIV, particularly regarding immune dysfunction, viral suppression, and mortality risk.
- This study examines the longitudinal association between HIV severity (viral suppression, immune dysfunction) and epigenetic age acceleration, as well as the relationship between HIV, epigenetic aging, and all-cause mortality in PWID.

Methods

Study Population and Data Collection

- We included participants from the AIDS Linked to the Intravenous Experience (ALIVE) study, a prospective cohort of PWID in Baltimore, MD.
- Participants included in the analysis have available buffy coat blood samples (all collected after 2005) who had visits discordant for active injection drug use of any heroin or any cocaine, or abstinence from all recreational drugs.

Measurements

- **DNA Methylation**: DNA was isolated from buffy coat samples and treated with bisulfite before being analyzed using the Illumina MethylationEPIC BeadChip
- **Epigenetic Age**: Biological aging was estimated using four established DNA methylation clocks—PhenoAge, Horvath Age, Hannum Age, and GrimAge.
- **HIV Status**: HIV infection was confirmed through ELISA and PCR, with participants classified based on viral load (detectable vs. undetectable), CD4+ T-cell count, and CD4:CD8 ratio to capture immune function.
- **Mortality**: All participants were annually linked to the National Death Index-Plus (NDI-Plus), with vital status and causes of death from 1988 to present.

Statistical Analyses

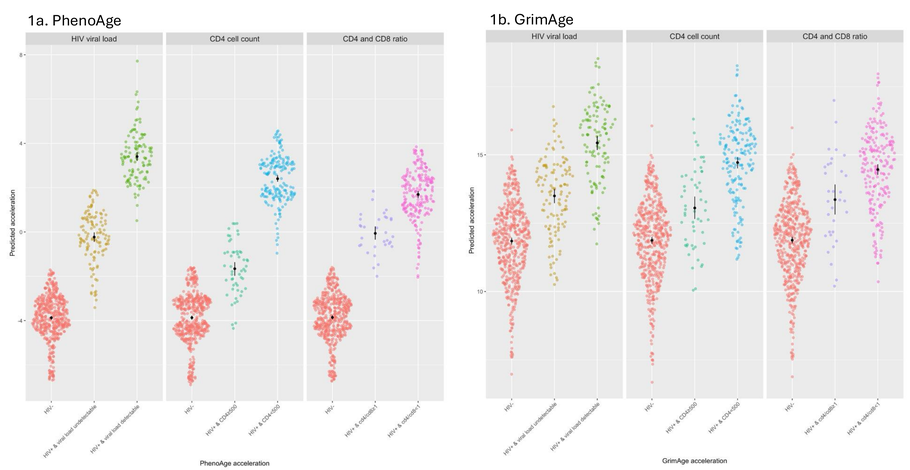
- We used linear mixed-effects regression models to evaluate trajectories of epigenetic age acceleration over time. Cox proportional hazards regression was used to estimate the hazard of all-cause mortality based on epigenetic age and HIV status.
- All models controlled for demographics, current injection drug use, and current smoking.

People with HIV who have low CD4 counts and a detectable viral load experience faster epigenetic age acceleration. Epigenetic age acceleration is associated with increased mortality risk among people with HIV.

Results

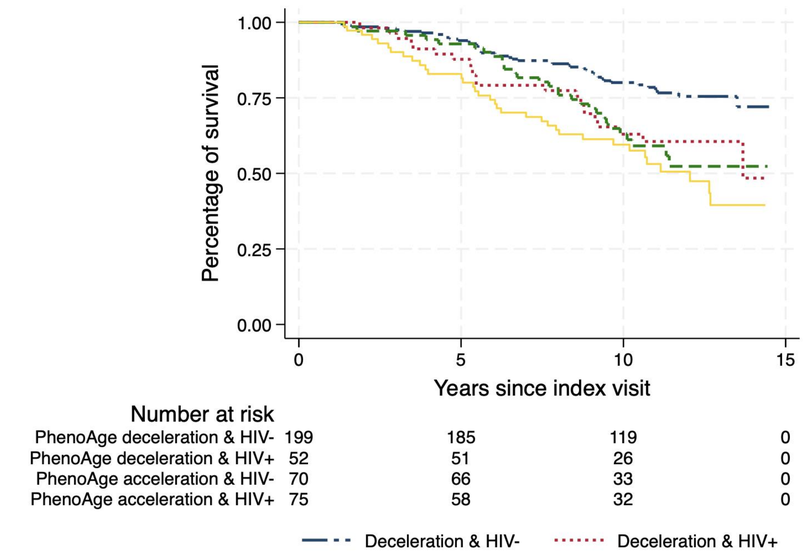
- Total N = 396 with 127 PWH
- At baseline, the median age at baseline was 48.5 years (IQR43.4, 53.1). Of these, the majority were Black (89%) and male (69%).
- Compared to people without HIV (PWoH), PWH exhibited age acceleration based on multiple epigenetic clocks. This acceleration was further exacerbated by poorly controlled HIV viral load.
- PhenoAge acceleration with or without HIV was associated with a 3.28 (95% CI: 2.06, 5.02) and 2.12 (95% CI: 1.32, 3.41) times higher hazard of all-cause mortality, respectively.

Figure 1. Associations of epigenetic age acceleration by HIV status and biomarkers



Results (cont.)

Figure 2. Survival Probability by HIV serostatus and PhenoAge in the ALIVE cohort, 2005-2020.



Conclusions

- PWH exhibited significant epigenetic age acceleration compared to people without HIV (PWoH), particularly in GrimAge and PhenoAge clocks.
- PWH with a detectable viral load experienced the greatest acceleration in aging, with PhenoAge showing nearly 7 additional years of biological aging compared to PWoH.
- Age acceleration and HIV infection independently and jointly increase mortality risk among persons who inject drugs. These findings highlight the importance of addressing molecular aging to reduce mortality burden among PWID

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