The GrimAge clock corresponds to accelerated brain aging and executive dysfunction in people with HIV

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BACKGROUND

- DNA methylation (**DNAm**) **clocks** are quantitative, reproducible markers of biological aging.
- HIV alters DNAm including from early infection (Corley *et al*.) and chronically (Horvath *et al*.).
- Role of DNAm changes in **neurological health** and **cognitive function** are poorly understood.
- Machine learning models using deep neural networks can estimate biological **brain aging** from magnetic resonance imaging (**MRI**), which correlates with cognitive function.
- **GrimAge** is an epigenetic proxy of both healthspan and lifespan (Lu *et al*.).

HYPOTHESES

- The GrimAge clock is **accelerated** in virally suppressed PWH compared to persons without HIV (PWoH), consistent with existing literature.
- GrimAge acceleration is negatively correlated with overall and domain-specific **cognitive impairment**.
- GrimAge acceleration is negatively associated with brain integrity from **MRI** including brain-age gap (**BAG**).
- **Social determinants of health** including education and socioeconomic status are associated with resilient or poor epigenetic aging outcomes (Woods *et al*.).

METHODS

- Participants comprised two groups: virally suppressed PWH and PWoH (**Table 1**).
- DNA extraction from peripheral blood mononuclear cells (**PBMCs**).
- **Cognitive testing** included five domains (learning, recall, executive, psychomotor, language).
- DNA methylation profiling using Illumina MethylationEPIC **microarrays**.
- T_1-weighted **structural MRI** with 1-mm spatial resolution.
- **DeepBrainNet** used to calculate BAG, i.e., brain-predicted age minus chronological age.
- **Statistics**: multiple linear regression, with age, race, birth sex, and cell proportions as covariates.

Virally suppressed HIV remains associated with accelerated aging across multiple epigenetic clocks. Social determinants of health may contribute to the measured impact on cognition and brain integrity.

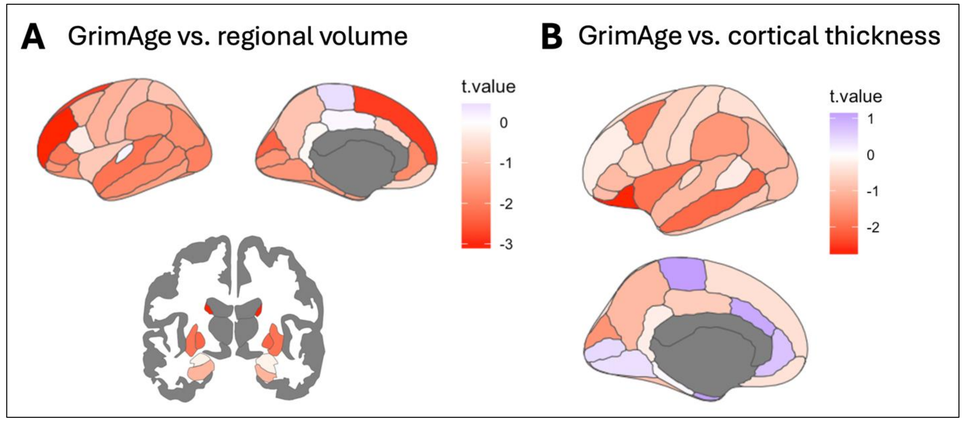


Fig. 1: Relationship between structural MRI and GrimAge clock. *(A) Higher GrimAge is associated with reduced cortical and subcortical volume. (B) GrimAge is associated with reduced cortical gray matter thickness across all brain lobes.*

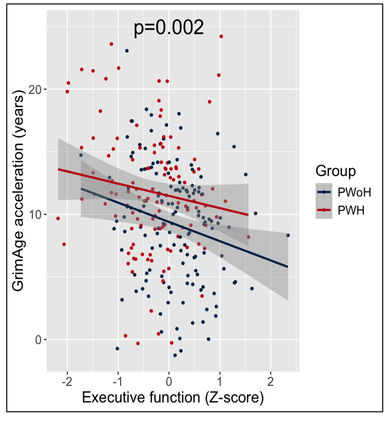


Fig. 2: Relationship between GrimAge and cognition. *GrimAge acceleration was associated with poorer executive function across both participant groups.*

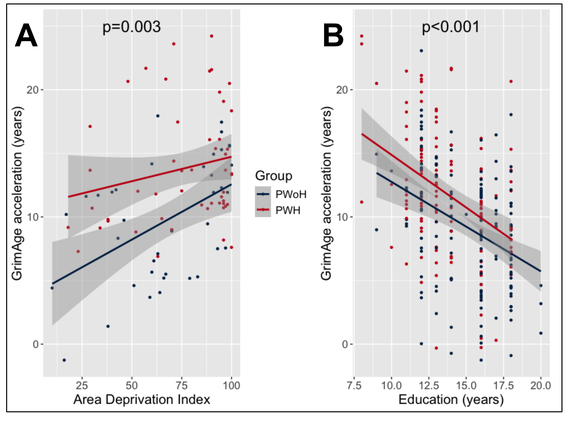


Fig. 3: Relationship between GrimAge and social risk or resilience factors. *(A) Increased Area Deprivation Index (ADI) was associated with greater GrimAge acceleration across both participant groups. (B) Increasing education was associated with lower GrimAge.*

Table 1: Demographics	**PWoH**	**PWH**
Number	174	156
Sex (M/F)	91 / 83	113 / 43
Age (mean ± SD)	46.8 ± 16.2	51.1 ± 13.1
Race (W / AA / Other)	99 / 61 / 14	59 / 91 / 6
Education (mean ± SD)	15.2 ± 2.5	13.7 ± 2.5

RESULTS

- Consistent with prior work, PWH with viral suppression had higher GrimAge (p=0.01).
- Accelerated GrimAge was associated with reduced regional brain volumes and cortical thickness (**Fig. 1**), greater impairment in executive function **(Fig. 2**) and psychomotor speed (both p=0.03), and with greater brain-age gap (p=0.02).
- Increased Area Deprivation Index (ADI), lower education, and poorer reading ability were associated with greater GrimAge acceleration across both groups (**Fig. 3**).

CONCLUSIONS

- Epigenetic clocks remain increased in virally suppressed PWH.
- This acceleration effect is significantly related to both cognitive function and structural brain health.
- Hower, social determinants of health likely contribute to these group differences, possibly more so than direct effects of HIV.

CITATIONS

- Corley M, *et al*. "Abrupt and altered cell-type specific DNA methylation profiles in blood during acute HIV infection persists despite prompt initiation of ART." *PLOS Pathogens* (2021).
- Horvath S, *et al*. "HIV, pathology and epigenetic age acceleration in different human tissues." *GeroScience* (2022).
- Lu A, *et al.* "DNA methylation GrimAge strongly predicts lifespan and healthspan." *Aging* (2019).
- Woods SP, *et al.* "Accelerated epigenetic aging in older adults with HIV disease." *GeroScience* (2023).

ACKNOWLEDGMENTS

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