DNA methylation clocks are altered in persons with undetectable HIV and correlate with brain aging

Kalen J. Petersen[1], Sarah Cooley[1], Brittany Nelson[1], Mauricio Caocci[2], Tricia H. Burdo[2], Beau M. Ances1

[1]Neurology, Washington University, St. Louis MO; [2]Rutgers Institute of Translational Medicine and Science, Rutgers, The State University of New Jersey, New Brunswick.

611

BACKGROUND

- DNA methylation (**DNAm**) clocks are quantitative markers of biological aging.
- HIV and its neuropsychiatric complications have been linked with **accelerated** biological aging using several DNAm clocks.
  - **First-generation** clocks (e.g., Horvath, Hannum) track chronological age closely.
  - **Second-generation** clocks (e.g., GrimAge, PhenoAge) track morbidity, mortality.
  - The **third-generation** clock DunedinPACE is specialized to predict longitudinal rate-of-change in epigenetic age.
- Relevance of DNAm clocks in **virally suppressed** persons with HIV (PWH), relationship with brain health remain unclear.

HYPOTHESIS

- Second-generation DNAm clocks will be **accelerated** in virally suppressed PWH compared to persons without HIV (PWoH) and associated with **brain aging**.

METHODS

- Participants recruited from St. Louis metropolitan area
  - **PWH** (n=61; sex=39/22 M/F; 34/27 Afr. Amer./White; age=51.7±11.1 yr.).
  - **PWoH** (n=50; 22/28 M/F; 28/20/2 A.A./W/other; age=51.3±13.9 yr.).
- Structural magnetic resonance imaging (**MRI**) to quantify brain health (1-mm uniform resolution).
  - **DeepBrainNet** neural network model used to estimate brain-age acceleration (BAA).
- DNA extracted from peripheral blood mononuclear cells (**PBMCs**) for all participants
  - DNA methylation profiling using Illumina methylation **microarrays** (EPICv2, 930K CpGs).
  - Multiple first-, second-, and third-generation DNAm clocks tested for HIV effects, associations with brain-predicted age.
- Statistical methods: multiple linear regression, with age, sex at birth, and blood cell proportions as covariates.

HIV is associated with increased epigenetic age even with viral suppression. Moreover, the degree of epigenetic aging is correlated with brain aging metrics derived from neuroimaging.

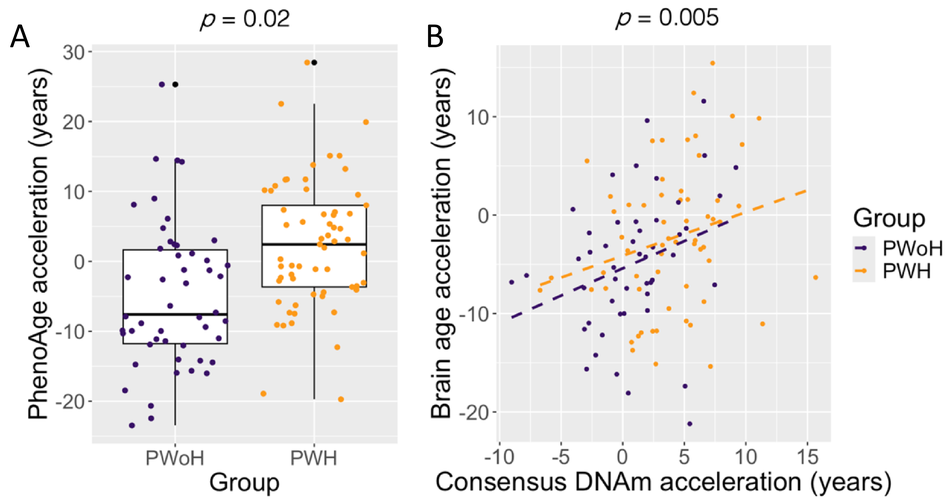


Fig. 1. (A) HIV-positive serostatus is linked with a 4.8-year mean increase in epigenetic age according to the second-generation PhenoAge clock. (B) The consensus of all epigenetic clocks examined shows a significant correlation with brain age acceleration, derived from structural MRI.

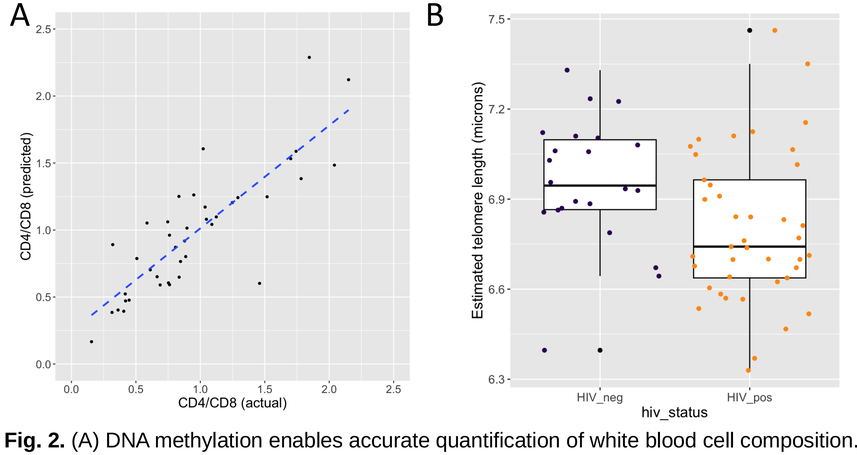


Fig. 2. (A) DNA methylation enables accurate quantification of white blood cell composition. CD4/CD8 ratio from flow cytometry is highly correlated with DNAm-derived values. (B) Estimated telomere length derived from DNAm is significantly shorter for virally suppressed PWH than PWoH.

RESULTS

- **First-generation** Horvath and Hannum clocks were not significantly different by serostatus (p=0.51, p=0.053).
- **Second-generation** PhenoAge showed a +4.8-year effect of HIV-positive serostatus (p=0.02, **Fig. 1A**), but GrimAge did not associate with HIV (p=0.16*).*
- **Third-generation** DunedinPACE was not significantly increased in PWH vs. PWoH (p=0.82*),* indicating that rate-of-change for epigenetic change does not differ by serostatus.
- A **consensus** clock averaging all models shoed a significant 1.9-year increase in epigenetic age (p=0.02) in PWH.
- **Brain age acceleration** was significantly associated with the Hannum (p=0.002), PhenoAge (p=0.008), and consensus (p=0.005) clocks across serostatus (**Fig. 1B**).
- DNAm accurately predicted PBMC **cell type** composition, including CD4 / CD8 lymphocyte ratio (**Fig. 2A**), enabling disentanglement of cell type from epigenetic effects.
- Predicted **telomere length** from DNAm was shorter for virally suppressed PWH than for PWoH (p=0.02) **(Fig. 2B).**

CONCLUSIONS

- Biological clocks reflecting the epigenetic age of immune cells may represent **sensitive biomarkers** reflecting brain health in virally suppressed PWH.
- Relationships between other morbidity- and mortality-tuned epigenetic clocks (e.g., GrimAge, PhenoAge) and **cognitive** and **neuropsychiatric** phenotypes merit future study.

CITATIONS

- Bashyam, V., et al. "MRI signatures of brain age and disease over the lifespan based on a deep brain network and 14 468 individuals worldwide." *Brain* 143.7 (2020): 2312-2324.
- Horvath, S. "DNA methylation age of human tissues and cell types." *Genome biology* 14 (2013): 1-20.
- Lu, Ake T., et al. "DNA methylation-based estimator of telomere length." Aging. 11.16 (2019): 5895.
- Houseman, E. Andres, et al. "DNA methylation in whole blood: uses and challenges." Current env. health rep. (2015): 145-154.

ACKNOWLEDGMENTS

We are grateful to the study participants. *Funding:* NIMH F32MH129151, K01MH136862, amfAR Krim Fellowship, R01DA054009, R01MH118031.