# Epigenetic Age Advancement is Associated with Lower CD4 T-cell Count, Increased Mortality Risk, and Frailty in Older Adults with HIV

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## BACKGROUND

With advancements in antiretroviral therapy, people with HIV (PWH) are living longer lives and often aging into geriatric care. PWH are more likely to experience medical co-morbidities and geriatric syndromes including frailty as they age.

- Epigenetic changes to DNA by different patterns of methylation have been associated with aging
- People with HIV have been demonstrated to have advancement of epigenetic-based age calculation compared to chronologic age[1]
- Specific patterns of DNA methylation have been associated with an epigenetic frailty score[2]

**We aimed to investigate the association between epigenetic aging and phenotypic measures of frailty, as well as epigenetic methylation signatures associated with frailty, in older PWH.**

## METHODS

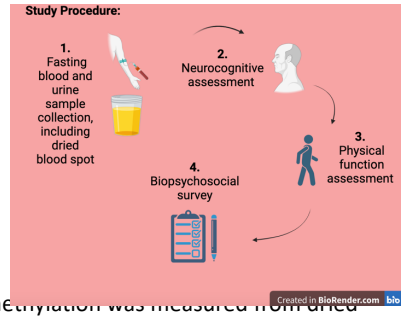
Recruitment:

- Older adults (55 years and older) with HIV were recruited from the outpatient HIV clinical practice at NYPH-WCM using an age-stratified random selection strategy.

Procedures:

Study Participants (N=164) Completed a study visit in the CTSC

Of those, 158 provided a blood spot for epigenetic analysis




Analysis:

- Genome-wide DNA methylation was measured from dried blood spots using the Illumina MethylationEPIC platform and analyzed using 6 established epigenetic age algorithms including DNAm PhenoAge.
- The epigenetic frailty risk score (eFRS) was calculated based on characteristic methylation loci[2].

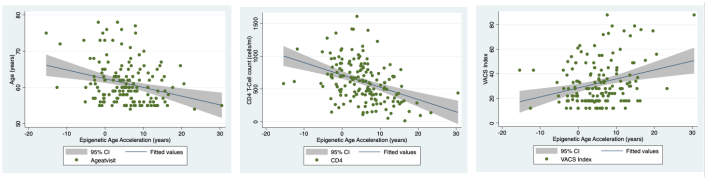
Study Population:

| Characteristic | N(%) or Median (IQR) |
|---|---|
| Age (years) | 60 (56-64) |
| Female sex | 52 (33%) |
| Self-Identified Race | |
| - Black | 76 (50%) |
| - White | 47 (31%) |
| - Other | 30 (19%) |
| CD4 T-cell Count (cells/ml) | 588 (323-811) |
| Veterans Aging Cohort Study (VACS) Mortality Index | 28 (18-43) |
| PhenoAge | 66 (62-71) |
| Epigenetic Age Advancement[γ] | 5.4 (SD 6.6) |
| eFRS Frailty Score | 0.09 (0.06-0.12) |
| Fried Frailty Category[ϕ] | |
| - Nonfrail | 49 (33%) |
| - Prefrail | 84 (56%) |
| - Frail | 16 (11%) |

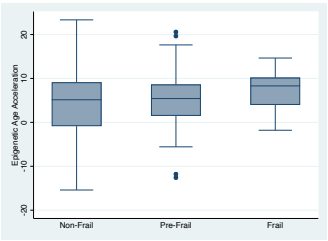
*Veterans Aging Cohort Study (VACS) Index of 28 correlates to a 10.8% risk of all-cause 5 year mortality.
[γ] Epigenetic Age Advancement defined as PhenoAge – Chronologic Age
[ϕ] Frailty data missing/incomplete for 8 participants.

## RESULTS:

***Epigenetic Age Advancement is associated with younger age, lower CD4 T-Cell Count and higher VACS Index in Older Adults with HIV***




***Epigenetic Age Advancement Related to Frailty Status***




| Ordinal Logistic Regression Model for Non-Frail, Pre-Frail, and Frail Phenotype | | | |
|---|---|---|---|
| Variable | Odds Ratio | 95% CI | P-Value |
| Epigenetic Age Advancement (yr) | 1.06 | (1.00, 1.12) | 0.04 |
| Age (yr) | 1.12 | (1.05, 1.19) | <0.01 |
| Female Sex | 1.19 | (0.57, 2.50) | 0.65 |
| Race | 1.24 | (0.79, 1.93) | 0.35 |

- Epigenetic age advancement was related to epigenetic frailty risk score in a univariate logistic regression model (B coefficient 57.6 [95%CI: 34.9-80.2])

## CONCLUSIONS

- In this study of older adults with HIV, the average epigenetic age advancement (EAA) was 5.4 years, as calculated by PhenoAge.
- EAA was associated with lower CD4 T-cell counts and higher VACS indices.
- In a model that included age, sex and race, EAA was also associated with an epigenetic frailty risk score and frailty phenotype

**These results suggest epigenetic clocks are a valuable biomarker of aging-related pathologies including frailty and mortality risk, and warrant further study.**

## ADDITIONAL INFORMATION

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## REFERENCES

1. Horvath, S. and Levine, A.J., 2015. The Journal of infectious diseases, 212(10), pp.1563-1573.
2. Li, Xiangwei, et al. *Nature Communications* 13.1 (2022): 5269.