

# 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<sup>1</sup>
- Specific patterns of DNA methylation have been associated with an epigenetic frailty score<sup>2</sup>

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

## METHODS

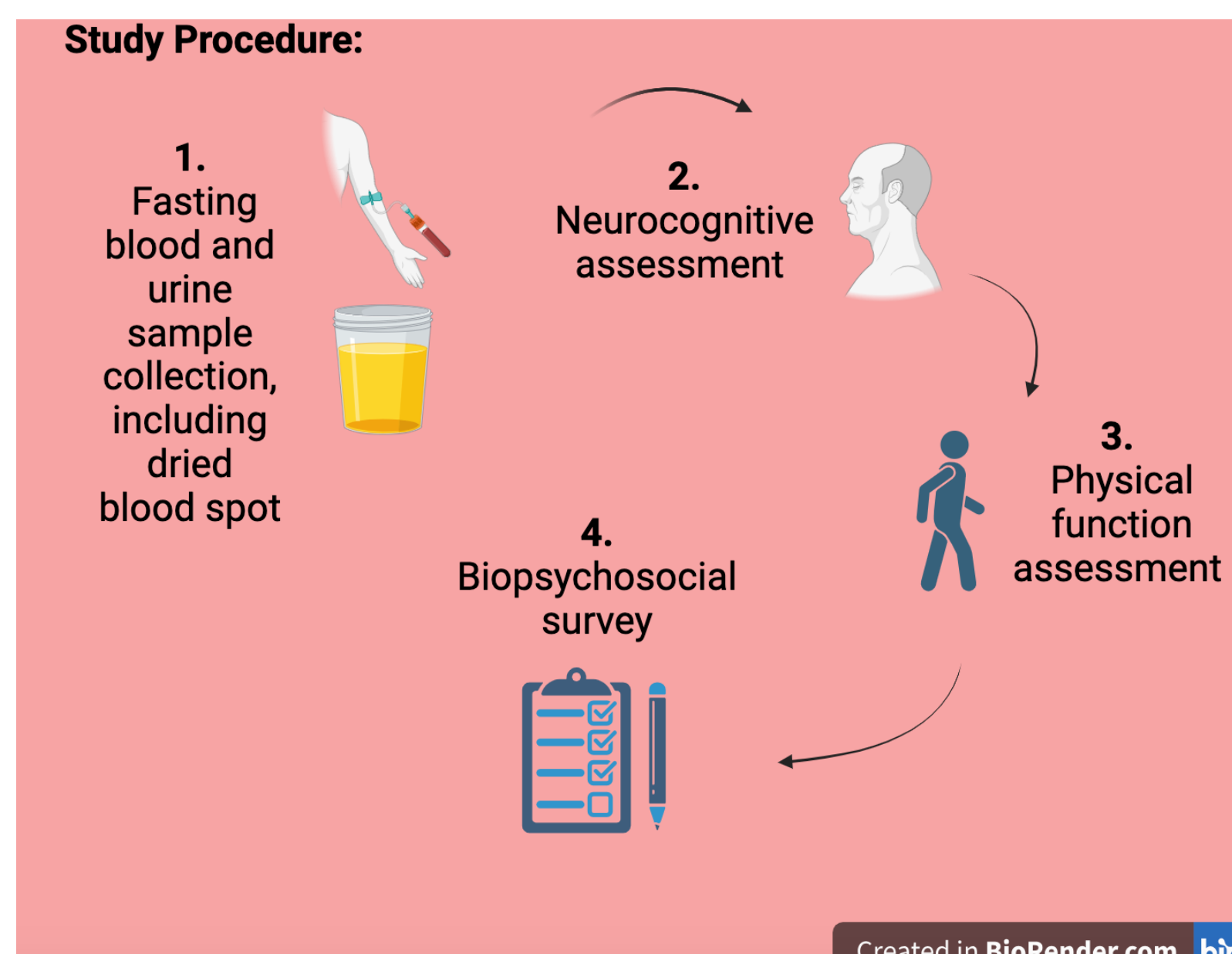
### Recruitment:

- 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<sup>2</sup>.

### 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 <sup>†</sup>            | 5.4 (SD 6.6)         |
| eFRS Frailty Score                                 | 0.09 (0.06-0.12)     |
| Fried Frailty Category <sup>‡</sup>                |                      |
| - Nonfrail   | 49 (33%)             |
| - Prefrail   | 84 (56%)             |
| - Frail  | 16 (11%)             |

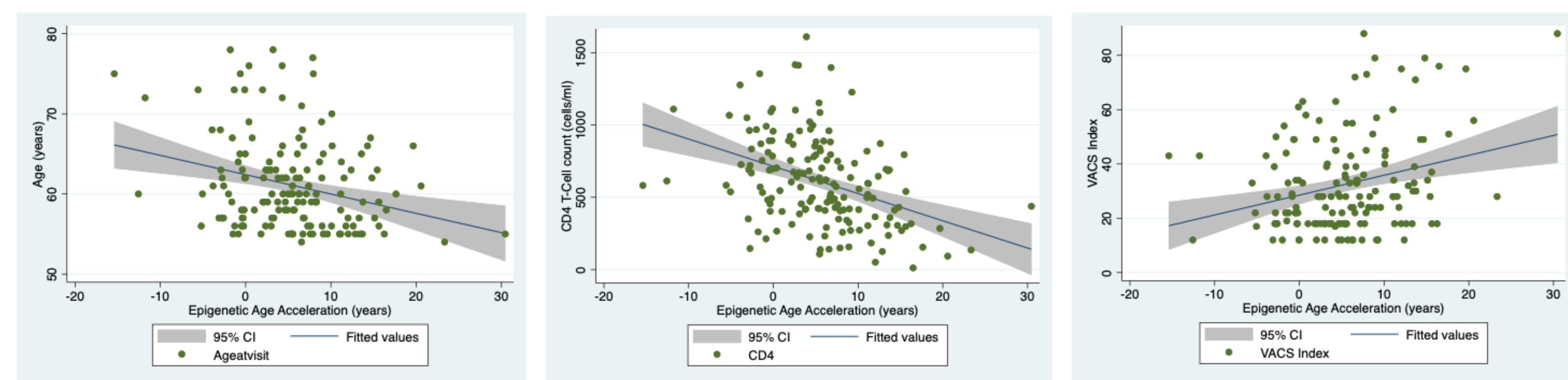
<sup>\*</sup>Veterans Aging Cohort Study (VACS) Index of 28 correlates to a 10.8% risk of all-cause 5 year mortality.

<sup>†</sup>Epigenetic Age Advancement defined as PhenoAge - Chronologic Age

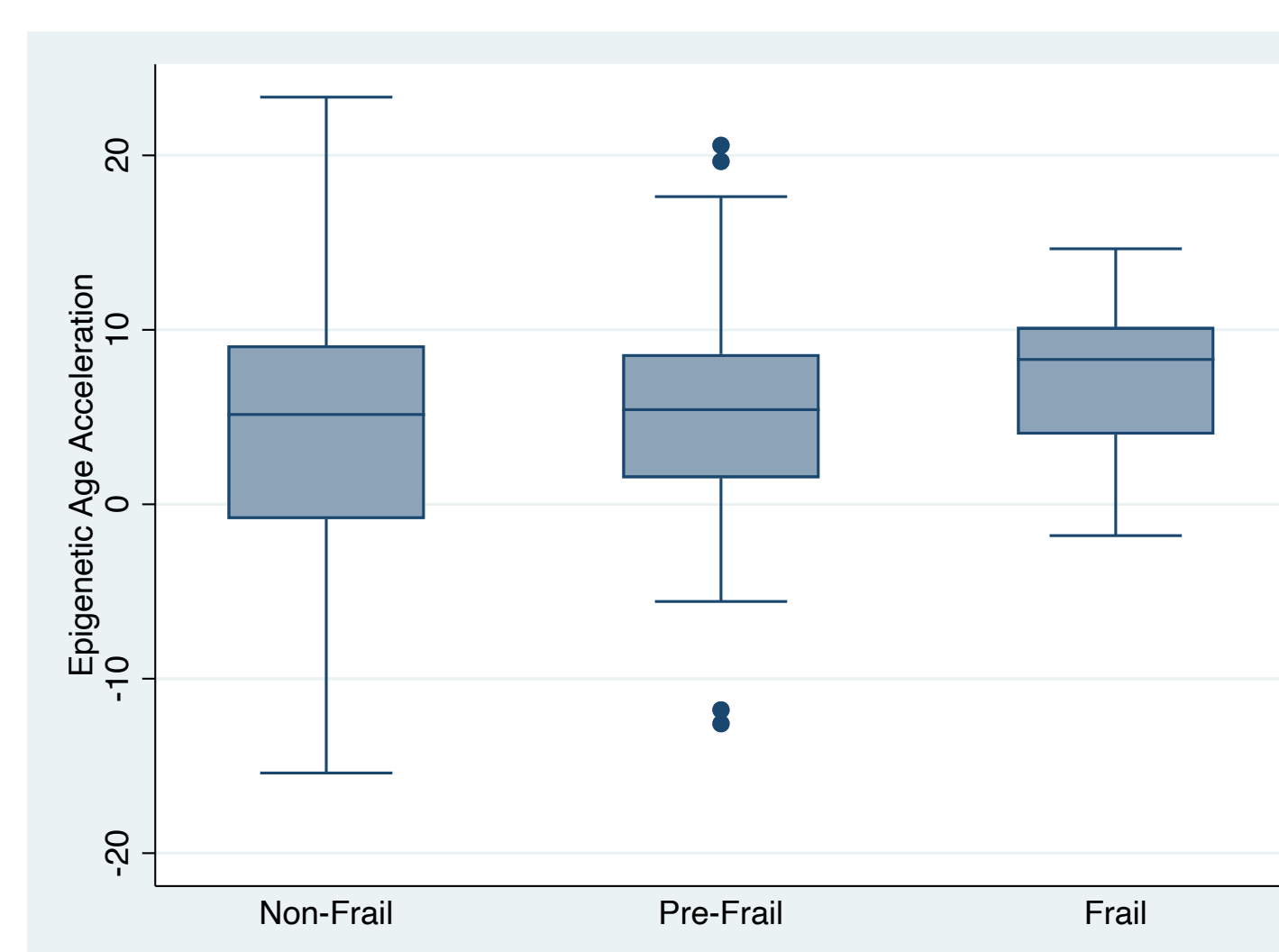
<sup>‡</sup>Frailty data missing/incomplete for 8 participants.

## 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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2. Li, Xiangwei, et al. *Nature Communications* 13.1 (2022): 5269.