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DNA Methylation-Based Telomere Length Is Associated with HIV Infection and Cancer in Relation to HIV Frailty and All-Cause Mortality

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BACKGROUND

- Telomere length (TL) is an indicator of cellular aging and health.
- TL is influenced by various factors, including chronic stress, inflammation, unhealthy lifestyles, and certain medical conditions.
- Shorter TL is associated with several aging-related diseases.
- Studies have suggested that DNA methylation (DNAm) and TL are interconnected and may influence each other in complex ways.
- Measuring TL based on DNAm (TLDNAmAge) is one approach that has been used to overcome some of the technical difficulties associated with direct measurement.

METHODS

Phenotypes of Interest

- TLDNAmAge: We estimated the TLDNAmAge using a method established by Lu et al. (2019), which involves a weighted average of 140 CpG sites [1].
- HIV frailty: The VACS Index 2.0 (VACS Index) was used as a measure of HIV physiologic frailty. Individuals with a high VACS Index tend to have poorer HIV outcomes and higher VACS Index scores are linked to an increased risk of mortality.
- Cancer: A cancer case refers to participants who have been diagnosed with cancer of any type.

Statistical Analysis

- Our analysis utilized data from the Veterans Aging Cohort Study (VACS)-HIV Biomarker cohort, which comprised 1,147 people with HIV (PWH) and 104 people without HIV (PWoH).
- Epigenome-wide DNAm levels from VACS whole blood samples were assessed using Illumina HumanMethylation450 BeadChip.
- To adjust for significant global confounding factors, race, BMI, smoking status, alcohol consumption (lnPEth), and six cell type proportions (CD4+ T, CD8+ T, NK, B cell, Monocyte, Granulocyte) were included as covariates in each model.
- Epigenetic Age Acceleration (EAA) Telomere Length is defined as the residual of regressing TLDNAmAge on chronological age.
- We used multivariable linear regression to estimate the association between TLDNAmAge and cancer, and VACS Index.
- We utilized Cox proportional hazards models to evaluate the relationship between TLDNAmAge and the survival time, representing the risk of all-cause mortality.

References

1. Lu AT, Seeboth A, Tsai PC, Sun D, Quach A, Reiner AP, et al. DNA methylation-based estimator of telomere length. *Aging* (Albany NY). 2019;11(16):5895-923.

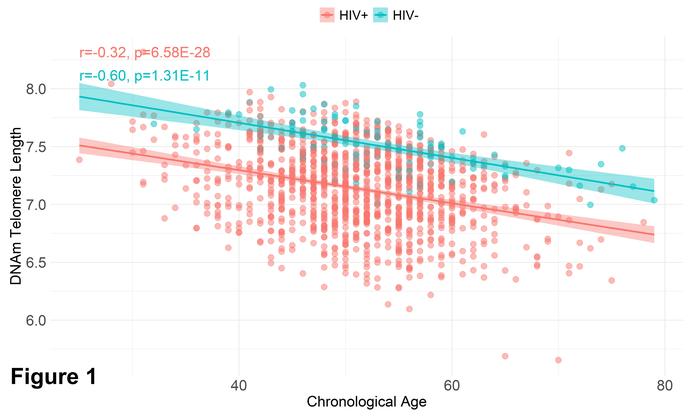


Figure 1

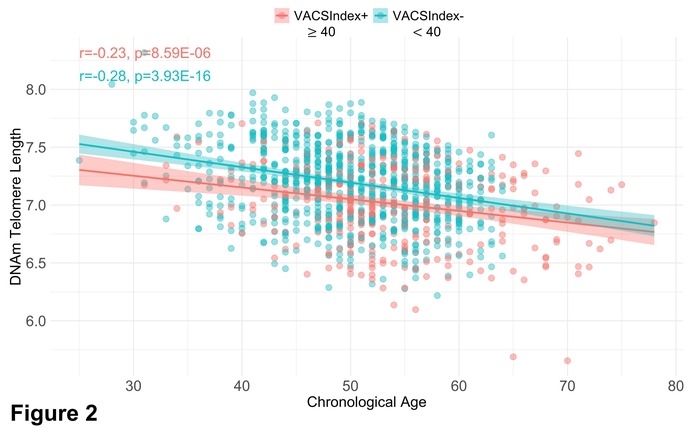


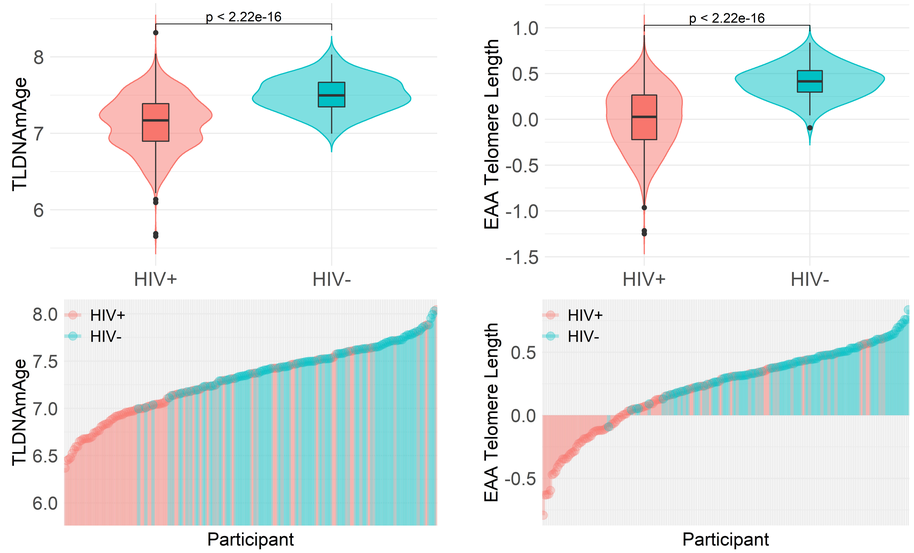
Figure 2

Table 1. Result of Cox proportional hazards regression analysis.

phenotype	HR	95% CI
cancer+	1.39	(1.12, 1.72)
TLDNAmAge	0.60	(0.44, 0.82)
age	1.04	(1.03, 1.06)
race (AA)	1.04	(0.82, 1.32)
smoking	1.57	(1.27, 1.96)
lnPEth	1.02	(0.97, 1.08)

RESULTS

- HIV and VACS Index were associated with shortened TLDNAmAge [HIV: beta=-0.33, p=1.36E-17 (Figure 1); VACS Index: beta=-0.0026, p=2.56E-05 (Figure 2)].
- One unit decrease in TLDNAmAge was associated with a 40% increase in mortality risk [Hazard Ratio: 0.60 (0.44,0.82), p=1.42E-03] (Table 1).



CONCLUSIONS

- Our findings suggest a potential association between TLDNAmAge and HIV infection, TLDNAmAge and HIV frailty, as well as TLDNAmAge and cancer.
- While TLDNAmAge serves as a proxy for TL and the VACS Index serves as a proxy for HIV physiologic frailty, further research is needed to validate this association and explore its underlying mechanisms.

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