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## **DNA Methylation-Based Telomere Length Is Associated With HIV Frailty and All-Cause Mortality**

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Telomere length (TL), which is an important indicator of cellular aging and health, is influenced by various factors, including chronic stress, inflammation, unhealthy lifestyles, and certain medical conditions. Shorter TL is associated with several aging-related diseases. However, due to the technical difficulties, measuring TL remains a challenging aspect of telomere biology research. Studies have suggested that DNA methylation (DNAm) and TL are closely interconnected and may influence each other in complex ways. In contrast to the classical approaches to measuring TL, measuring TL based on DNAm (DNAmTL) is one approach that has been used to overcome some of the technical difficulties associated with direct measurement. In this study, we used DNAmTL as a novel approach to investigate the role of HIV in the aging process. The Veterans Aging Cohort Study Index (VACSIndex) was used as a measure of physiologic frailty. The associations of DNAmTL with HIV, HIV physiologic frailty, and all-cause mortality, which was assessed over ten years, were examined among 1,144 participants. After adjusting for demographic and clinical variables, HIV and VACSIndex were associated with shortened DNAmTL (HIV:  $\beta = -0.33$ ,  $p = 1.36E-17$ , VACSIndex:  $\beta = -0.0026$ ,  $p = 2.56E-05$ ). Furthermore, using a Cox proportional hazards model among people living with HIV (PLWH), the risk of mortality increased by 2.13 for each unit decrease in the DNAmTL (HR: 0.47,  $p = 4.24E-05$ ). In conclusion, HIV-infection and VACSIndex shorten DNAmTL that is associated with an increased mortality risk among PLWH.