Epigenetic Age Acceleration is not mirrored by cognitive performance in people with and without HIV

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Background: Antiretroviral therapy has extended survival among people with HIV (PWH), shifting attention toward accelerated biological aging. Immune dysregulation drives both aging and cognitive decline. Whether epigenetic age acceleration (EAA) is mirrored by cognitive performance in PWH remains unclear. We examined whether cognition tracks with HIV serostatus, immune markers, or EAA, and whether serostatus modifies the aging–cognition link.

Methods: In this cross-sectional study of 84 adults (53 PWH, 31 without HIV [PWoH]; mean age 47.7 years, 68% male, 71% Black), whole-blood DNAm yielded five clocks (Horvath, Hannum, PhenoAge, GrimAge, DunedinPACE). Cognition (BRACE battery) was reduced by factor analysis to four domains; per Frascati criteria, impairment was performance below the normative mean on at least two domains. Cognition was regressed on serostatus, on CD4 and CD4:CD8 within PWH, and on EAA (with an HIV × EAA interaction); correlates were screened univariably (FDR-corrected) and in a multivariable model, adjusting for age and sex.

Results: HIV serostatus tracked with faster molecular aging: PWH were epigenetically 7.7 years older than expected on PhenoAge ($p<0.001$), with smaller acceleration on Horvath ($p=0.007$) and Hannum ($p=0.04$); lower CD4 showed a non-significant trend toward greater PhenoAge acceleration ($\beta=-0.37$ years/100 cells, $p=0.14$). This aging signal did not extend to cognition. PWH and PWoH performed comparably across the four cognitive domains (standardized β: motor speed +0.15, $p=0.51$; speeded executive control −0.20, $p=0.36$; attention/executive +0.10, $p=0.68$; fine-motor psychomotor −0.09, $p=0.72$), and impairment was equally common (at least two domains: 13% vs 16%, $p=0.96$). Within PWH, cognition was unrelated to CD4 or CD4:CD8 ($\beta\leq0.04$, all $p\geq0.24$). No epigenetic clock was associated with cognition (β −0.12 to +0.12, all $p\geq0.14$), and this did not differ by HIV status (interaction $p=0.38$–0.87). Across demographic, immune, oral-health, and epigenetic factors, only older age predicted cognition ($\beta=-0.05$/year, $p<0.001$).

Conclusions: In this diverse, largely suppressed cohort, cognition was comparable across HIV serostatus and, apart from chronological age, was not associated with immune status, epigenetic aging, or oral health, despite clear links between HIV, immune markers, and faster molecular aging. Given the modest sample and cross-sectional design, larger longitudinal cohorts are needed to test whether EAA predicts later cognitive decline.