Does HIV prematurely age the brain?

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In an Article in *The Lancet HIV*,[1] Karl Goodkin and colleagues answer the controversial question of whether chronic HIV infection leads to premature ageing in the combination antiretroviral therapy (ART) era: it does.

With the success of ART leading to durable viral suppression, the average age of patients with HIV has increased, and in some countries most patients are older than 50 years. Life expectancy in people with HIV is nearly the same as that in the general population, except for in some important minority groups (eg, African Americans).[2] Counterbalanced against this momentous step forward is the fact that chronic HIV infection, even in people with long-lasting viral suppression, is still characterised by chronic inflammation, albeit at a lower level than that in those who are not virally suppressed.[3] Such chronic inflammation is linked, probably at least partly in a causal manner, to several diseases associated with advancing age and with ageing itself.[3,4]

It is therefore unsurprising that researchers have tried to address the issue of whether chronic HIV infection leads to premature ageing of the brain. The results of these efforts have, however, not been definitive. The reasons are numerous: small sample size, inclusion of young patients (ie, younger than 50 years), inclusion of patients with varying degrees of infection severity (something we have termed as the age–stage effect), cross-sectional rather than prospective design, inclusion of confounding factors such as substance use, the lack of appropriate controls (especially for age-related comorbidities), and lack of accounting for what has been termed the age–duration effect. The age–duration effect is supported by increasing evidence that duration of HIV infection is important in establishing the effect of advancing age, although this hypothesis is not universally accepted.[5] For example, if in a study of 60-year-old people with HIV, some participants were infected aged 20 years but others were infected at ages 40 or 50 years, results will probably be conflicting if all patients are analysed together.

By using data from the Multicenter AIDS Cohort Study, Goodkin and colleagues have largely overcome these issues. Their study included the largest sample so far: 5086 participants (2278 of whom had HIV) and 47 886 visits (20 477 of which were contributed by people with HIV). The sample size ensured an adequate proportion of participants aged older than 50 years and even beyond 65 years. They also excluded people with major neurological and psychiatric disorders, including current, severe alcohol or substance use disorders. More minority participants were in the HIV-seropositive group than in the seronegative group. Older age was significantly associated with lower performance in all five neuropsychological domains tested (working memory, episodic memory, motor function, executive function, and information processing speed; $p<0{\cdot}0001$ for all comparisons). Furthermore, the effects were related to the degree of advancement of HIV disease as assessed by US Centers for Disease Control and Prevention clinical disease staging, and duration of HIV infection was significantly associated with worse performance on information processing speed, working memory, and executive function.

As noted by the authors, their study had several limitations, chief among which is the fact that the cohort was entirely male. However, these limitations do not detract from the results, which will hopefully be extended (particularly to women) and better understood by further studies. The design of the study did not allow for analyses of HIV-specific variables such as CD4 cell count nadir, plasma HIV load, treatment adherence, or ART central nervous system penetration effectiveness scores. Furthermore, Goodkin and colleagues did not test for complex effects such as interactions between age, education, and ethnicity interactions. Finally, data for cholesterol and triglyceride concentration, renal and hepatic function, and indices of general nutritional status were insufficient. But diabetes, hypertension, body-mass index, and total bodyweight were associated with poor neuropsychological performance.

Goodkin and colleagues' results have important implications for future work. First, age–stage and age–duration variables should be incorporated into prospective large cohort studies to ensure meaningful results. Second, large studies are needed to address whether ageing people with HIV are at increased risk of age-associated neurodegenerative disorders, such as vascular cognitive impairment[6,7] and perhaps Alzheimer's disease in people who are genetically predisposed.[4,8] Third, investigators will need to establish whether the same findings of accelerated ageing apply to patients

who have been chronically virally suppressed and have no history of advanced HIV disease. In other words, will early adoption of ART negate premature ageing or will it contribute to ageing through potential toxic effects? Finally, and most importantly, Goodkin and colleagues' results should spur the development of geriatric medicine into an integrated multidisciplinary model of care for ageing patients with HIV.

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I declare no competing interests.

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