BRAIN
SCIENTIFIC COMMENTARY

Is neurocognitive ageing accelerated in virally suppressed people with HIV and multimorbidity?

This scientific commentary refers to 'Twelve-year neurocognitive decline in HIV is associated with comorbidities, not age: a CHARTER study' by Heaton *et al.* (https://doi.org/10.1093/brain/awac465).

In this issue of *Brain*, Heaton and co-workers[1] present the latest findings from one of the largest and longest North American NeuroHIV observational studies, CHARTER (CNS HIV ART Effects Research).

The authors followed up 402 people with HIV from among the original 1597 participants for a 12-year assessment (in 2015 or 2020). The study documented antiretroviral therapy (ART) use, plasma and CSF viral load, as well as a comprehensive range of medical, age-related and psychiatric comorbidities. Neuropsychological assessment was performed using the current gold standard in the field, with changes over time shown as evidence-based change scores. The 12-year assessment included all baseline measures as well as some new evaluations (the Fried Frailty Index, the Framingham Cardiovascular Risk and 10-year Stroke Risk Indices, plus additional information about non-ART medication use). Enrolment was balanced across the six CHARTER sites and across the two age groups enrolled (<60 years and ≥60 years). This resulted in a majority male group (76.4%), with a mean age of 43 years, mean education of 13 years, and in which 46% of participants were African American, 41.5% White and 10.7% Hispanic. Just over 60% of participants had an AIDS diagnosis at baseline, while participants had a median HIV duration of almost 10 years, and a median current CD4 count of slightly less than 500 cells/μl. Importantly, at baseline almost 74% of participants were on ART, with 45.8% having an undetectable viral load in plasma and 70.3% an undetectable viral load in CSF. Overall, the subgroup of 402 people with HIV was representative of the original sample; however, the subgroup had slightly more education, fewer neuropsychiatric comorbidities, and higher rates of hypertension and hyperlipidaemia.

When Heaton and colleagues[1] assessed cognitive performance at 12 years, they found that both the younger and older age groups showed neurocognitive decline, beyond what would be expected in typical ageing, but the magnitude of this decline did not differ between the two age groups. In other words, there was no chronological age effect beyond the normative age correction for the older group versus the younger, arguing against accelerated neurocognitive ageing in people with HIV. More worryingly, in the 12-year sample as a whole, individuals who were impaired at baseline showed significant further deterioration, demonstrating the importance of baseline impairment as a predictor of future neurocognitive ability.[2] The absence of an age effect on the cross-sectional impairment rate is the most unexpected finding, as chronological age is one of the strongest predictors of cognitive impairment in patients with or at risk of neurological conditions,[3] as also described by some previous NeuroHIV studies.[4] The reasons for the lack of evidence of accelerated ageing here are likely to be complex.

The primary baseline factors that predicted neurocognitive decline were hypertension, chronic pulmonary disease, depression, lifetime cannabis use disorder, higher serum hepatic aspartate transaminase, and lower serum protein. At 12-year follow-up, the primary factors associated with neurocognitive decline were diabetes, chronic pulmonary disease, lower haematocrit, depression, the combination of prefrailty and frailty, and a lifetime history of cannabis use disorder. None of the HIV disease measures were associated with the neurocognitive decline, despite some of them providing evidence of disease progression. The authors are to be commended for acknowledging the limitations of their analysis, including the absence of data on survivor bias, on the timing of comorbidities, and on treatment efficacy; the lack of dedicated biomarkers of biological ageing[5]; the lack of a control group without HIV; and the fact that there were no data on social determinants of cognition, which may limit the generalizability of the findings beyond the USA.

Focusing on biological ageing, we note that the younger CHARTER participants appeared to show abnormally high levels of biological ageing, as assessed by their comorbidity burden (i.e. the deficit model of biological ageing[6]), which increased further at follow-up. Notably, the under and over 60's did not differ at either baseline or 12-year follow-up in age-related comorbidities including diabetes, chronic pulmonary disease, metabolic syndrome and frailty. There was also evidence that many people with HIV in the study were not treated for their comorbidities, although it is not clear if this differed by age. The significant burden of comorbidities is further underlined by the lack of correlation between neurocognitive decline and the nadir CD4-T cell count (a relationship that has been found in prior studies): the impact of comorbidities on cognitive decline is masking the effect of the nadir CD4-T cell count. Put simply, with respect to biological ageing, was the younger group really that young? Hence, was it the right comparator for the older group?

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The second point is that the data may indeed be mostly relevant to the USA and countries with similar people with HIV profiles. In our multisite observational study in Australia with $n = 457$ individuals,[7] we did detect an abnormal chronological ageing effect (while accounting for comorbidities and various health factors including social determinants of health) and observed a much lower level of meaningful cognitive decline. In fact, cognitive decline was not different from what would be expected with typical ageing. But this Australian cohort had been virally suppressed for years and there was no evidence of HIV disease progression. Notably, we did not have a control group without HIV showing that the effect of chronological age can be accounted for very well using normative data.

Nonetheless, the Heaton *et al.*[1] study did find a signal for accelerated cognitive ageing limited to those who were not virally suppressed. However, the degree of non-suppression is not clear: was it between 50 and 200 HIV-1 copies/ml (so called 'blips' that are not thought to be clinically important) or was it significantly higher? This would have an impact on clinical management.

But should we be concerned about the additional impact of chronological age when there is such a high rate of neurocognitive impairment (40–45%) in American people with HIV despite treatment and viral suppression? Should we worry about chronological age when there is evidence of serious neurocognitive worsening in so many, old and young (up to 81% in those worst affected)? Should we care about the effects of ageing when neurocognitive improvement is already the exception?

From a pathophysiological and hence treatment perspective, the answer is yes. If HIV-related premature, accentuated or accelerated ageing[4] is being masked in these older Americans with treated HIV disease by their high levels of multimorbidity, then this means that the risk of dementia is becoming very real and will be greater than what would be expected in the general population; HIV disease may reach a tipping point. Evidence for this potential tipping point can be seen in findings from HIV basic science, including HIV-associated mechanisms driving multimorbidity via immune senescence, immune activation and inflammation,[8] as well as signs of continued HIV transcriptional activity despite years of viral suppression.[9] The clear trajectory of decline in this CHARTER sample is worrying and should sound an alarm bell to clinicians and the community. In this context, calls to action like the recent 'Glasgow Manifesto' by the International Coalition of Older People with HIV (iCOPe HIV)[10] ought to be heeded.

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Competing interests

The authors report no competing interests.

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