Effect of ageing on neurocognitive function by stage of HIV infection: evidence from the Multicenter AIDS Cohort Study

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Summary

Background The demographics of the HIV epidemic in the USA have shifted towards older age. We aimed to establish the relationship between the processes of ageing and HIV infection in neurocognitive impairment.

Methods With longitudinal data from the Multicenter AIDS Cohort Study, a long-term prospective cohort study of the natural and treated history of HIV infection among men who have sex with men in the USA, we examined the effect of ageing, HIV infection (by disease stage), and their interaction on five neurocognitive domains: information processing speed, executive function, episodic memory, working memory, and motor function. We controlled for duration of serostatus in a subanalysis, as well as comorbidities and other factors that affect cognition. Analyses were by linear mixed models for longitudinal data.

Findings 5086 participants (47 886 visits) were included in the analytic sample (2278 HIV-seropositive participants contributed 20 477 visits and 2808 HIV-seronegative control participants contributed 27 409 visits). In an a-priori multivariate analysis with control variables including comorbidities and time since seroconversion, significant, direct negative effects of ageing were noted on all neurocognitive domains (p<0·0001 for all). Similar effects were noted for late-stage HIV disease progression on information processing speed (p=0·002), executive function (p=0·0001), motor function (p=0·001), and working memory (p=0·001). Deleterious interaction effects were also noted in the domains of episodic memory (p=0·03) and motor function (p=0·02).

Interpretation A greater than expected effect of ageing on episodic memory and motor function with advanced stages of HIV infection suggests that these two domains are most susceptible to the progression of neurocognitive impairment caused by ageing in individuals with HIV. This deficit pattern suggests differential damage to the hippocampus and basal ganglia (specifically nigrostriatal pathways). Older individuals with HIV infection should be targeted for regular screening for HIV-associate neurocognitive disorder, particularly with tests referable to the episodic memory and motor domains.

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Introduction Until the advent of effective antiretroviral therapy (ART) in the mid-1990s, the prevalence of older adults (ie, aged 50 years or older) living with HIV was low. By 2010, however, older adults accounted for more than 50% of AIDS cases in San Francisco (CA, USA), a pattern expected to be seen nationwide by 2020. Older age continues to be predictive of excess mortality, despite suggestions that increasing age might be associated with higher antiretroviral adherence,1 and despite adjustment for natural ageing, which accounts for more than 50% of mortality in individuals aged 45 years or older with HIV.2 The prevalence of HIV-associated neurocognitive disorders seems to have increased too, primarily as a function of increased survival and ageing in the ART era, although the number of newly infected older adults is also increasing.3 Studies of neurocognitive dysfunction among older individuals with HIV have increased in number in the past 15 years, but results have been inconsistent. Neurocognitive dysfunction and HIV-associated neurocognitive disorders in older individuals with HIV have been focused upon as high priorities in the field, and thus systematic attempts to identify and resolve the sources of these inconsistencies are needed.

A substantial body of evidence shows that older age is associated with an increased likelihood of HIV-associated neurocognitive disorders, particularly of HIV-associated dementia and, less so, of mild neurocognitive disorder and HIV-associated neurocognitive impairment generally (across systemic HIV disease stages).55 During the transitional period to effective ART, Hardy and colleagues5 reported that, in a sample of 257 men with HIV, older men (aged 37 years or older; mean age 44·5 years) showed lower performance than younger men (aged 36 years or younger; mean age 31·5 years) on several neuropsychological tests. As expected, men in the late symptomatic stage of HIV (ie, AIDS) showed lower performance than those with earlier-stage disease. Subsequently, Hinkin and coauthors6 used data adapted from Hardy and colleagues’ study7 to investigate the interaction between age (<40 years, 40–49 years, ≥50 years) and HIV disease category (HIV seronegative, HIV seropositive [non-AIDS], and HIV seropositive [AIDS]), and showed that age was a significant risk factor for HIV-associated neurocognitive impairment.
in late-stage systemic disease. Furthermore, as in Hardy and colleagues’ study, neurocognitive impairment was more common in individuals aged 50 years or older who had progressed to AIDS than in those in younger groups with and without AIDS. In a subsequent study by Hardy and colleagues, HIV-associated neurocognitive impairment was not consistently more frequent with age across domains, and a large inter-individual variation in neuropsychological performance was noted among older individuals with HIV. Longer follow-up and increased use of control variables for neuropsychological performance, particularly for medical comorbidities, depressed mood, and alcohol or substance use, could help to decrease inter-individual variation in older individuals and improve the consistency of results. Another influence of concern that has been noted but not generally assessed as a specific type of control is the duration of HIV infection (as opposed to the effect of ageing itself). In summary, limitations of the work published so far include the truncation of the oldest age range and the incomplete use of controls for other possible influences on neurocognitive function beyond education, ethnicity, and stage of HIV disease. The need to control for additional factors, such as medical comorbidities common in the general population that affect cognition (eg, diabetes, hypertension, coronary artery disease, cerebrovascular disease, thyroid disease), has been increasingly acknowledged. Furthermore, controls for depressed mood, use of alcohol, psychoactive substances, or psychotropic drugs, history of hepatitis C virus infection, pain, and fatigue also need to be considered routinely. Thus, we aimed to examine the hypothesis that ageing interacts with the effect of HIV infection on neurocognitive impairment and simultaneously to address the limitations of published work by using the Multicenter AIDS Cohort Study (MACS) dataset.
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