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

Karl Goodkin, Eric N Miller, Christopher Cox, Sandra Reynolds, James T Becker, Eileen Martin, Ola A Selnes, David G Ostrow, Ned C Sacktor, for the Multicenter AIDS Cohort Study

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 ($p<0·0001$), 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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Department of Psychiatry and Behavioral Sciences, James H Quillen College of Medicine, East Tennessee State University, Johnson City, TN, USA (Prof K Goodkin MD); **University of California, Los Angeles, Los Angeles, CA, USA** (Prof E N Miller PhD); **Johns Hopkins School of Public Health, Baltimore, MD, USA** (Prof C Cox PhD, S Reynolds MA); **University of Pittsburgh, Pittsburgh, PA, USA** (Prof J T Becker PhD); **Rush University, Chicago, IL, USA** (Prof E Martin PhD); **Johns Hopkins School of Medicine, Baltimore, MD, USA** (Prof O A Selnes PhD, Prof N C Sacktor MD); **and David G Ostrow & Associates Consulting, Chicago, IL, USA** (D G Ostrow MD)

Correspondence to:
Dr Karl Goodkin, Department of Psychiatry and Behavioral Sciences, James H Quillen College of Medicine, East Tennessee State University, PO Box 70567, Johnson City, TN 37614, USA
goodkin@etsu.edu

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).[4,5] During the transitional period to effective ART, Hardy and colleagues[6] 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 coauthors[7] used data adapted from Hardy and colleagues' study[6] 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

Research in context

Evidence before this study

We searched PubMed with the terms "aging", "HIV", and "cognition disorders" as medical subject heading terms for human studies published in any language between Jan 1, 1985 (soon after the initiation of the Multicenter AIDS Cohort Study), and March 22, 2017 (the date of our final search). In place of "cognition disorders", we also used ["cognition" (all fields) and "disorders" (all fields)] or ["cognitive" (all fields) and "impairment" (all fields)] or ["cognitive impairment" (all fields)]. We included studies of participants aged 65 or older and those of participants aged 45–64 years, because "older age" in HIV infection has been generally defined as age 50 years or older. This designation is partly because of the epidemiological rationale of the US Centers for Disease Control and Prevention. Notably, most older individuals living with HIV are aged 50–64 years. The biological rationale that age 50 years is typically when age-associated neurocognitive deficits and immunological deficits are first noted in the general population also plays a part. We identified reports of ageing and HIV infection affecting neurocognitive function beginning in 1994. Results of studies identified by our strategy varied widely, with some showing no significant effect of ageing, others showing an additive effect of ageing and HIV infection, and others showing a truly synergistic, interactive effect of ageing and HIV infection on the designated neurocognitive outcomes. We also identified studies of outcomes associated with neurocognitive deficits, such as cerebrospinal fluid parameters of CNS injury, structural and functional neuroimaging findings, magnetic resonance spectroscopic findings of brain tissue metabolites by brain region, and neuropathological outcomes. Weaknesses in published research include a lack of control for both medical and psychiatric comorbidities and other factors that might affect cognition. Additionally, almost no studies in which duration of infection (eg, as length of HIV-positive serostatus) was separately assessed have been reported, partly because this variable is generally acknowledged to be difficult to ascertain.

Added value of this study

To our knowledge no other studies in this area have been active for as long as the Multicenter AIDS Cohort Study, and the breadth of data allowed us to explore the effects of ageing in HIV more fully longitudinally. Our study also adds to the methodological rigour of published work through its controls for medical and psychiatric comorbidities and other factors that can affect cognition. Furthermore, this study shows the importance of controlling for duration of HIV infection, which had significant effects that accounted for otherwise apparently anomalous statistical interactions between ageing and HIV infection on cognition.

Implications of all the available evidence

Our results show that future studies of ageing and HIV infection should include controls that account for the recognised effects of medical and psychiatric comorbidities and other factors that affect cognition. Attempts to control for duration of HIV infection might be required to separate the effect of ageing from that of the longevity of the infectious process, irrespective of age. An overall, categorical differentiation of an additive but independent pattern versus a synergistic, interactive pattern of results of ageing and HIV infection on cognition might be an oversimplification. These relationships might vary by the specific domains of neurocognitive function analysed. Episodic memory and motor function, which have been prominent among the areas of cognitive function affected by HIV infection, show a pattern of synergistic, interactive effects. Older individuals with HIV should be regularly screened for HIV-associated neurocognitive disorder with tests aimed at the episodic memory and motor function domains.

in late-stage systemic disease. Furthermore, as in Hardy and colleagues' study,[6] 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,[8] 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).[9]

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.