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 ($p<0·0001$), 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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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.

Methods

Study design and participants

The MACS is an ongoing, long-term prospective cohort study of the natural and treated history of HIV infection among men who have sex with men in the USA. Men were enrolled at four study sites: Baltimore (MD) and Washington, DC, Chicago (IL), Los Angeles (CA), and Pittsburgh (PA). 6972 men have been enrolled since the study's inception: 4954 between April 2, 1984, and April 8, 1985; 668 between April 1, 1987, and March 16, 1995; and 1350 between Oct 4, 2001, and Aug 20, 2003. Participants return every 6 months for an interview, physical examination, and collection of blood for laboratory testing. The assessments cover physical health, medical treatments, sexual behaviours, and psychoactive substance use. The dataset has long-term longitudinal data for participants examined biannually over many years, allowing the use of several selected controls of importance for other effects on neurocognitive functioning.

In the original MACS cohort from the mid-1980s, eligible participants were homosexual or bisexual men aged 18 years or older with no active malignancy or immunosuppression as a result of a medical condition or prescribed therapy. For the 2001–03 cohort, first use of ART, a plasma HIV load, and a CD4 cell count had to have been documented within the 6 months before initiation. This study received institutional review board approval from Northwestern University (Evanston, IL), University of California, Los Angeles (Los Angeles, CA), the University of Pittsburgh (Pittsburgh, PA), and the Johns Hopkins Bloomberg School of Public Health (Baltimore, MD). Participants had to be able to give informed consent, and had to sign a written informed consent form in the English language. Strict privacy and limited access to individual identifiers was assured through a Certificate of Confidentiality issued by the US National Institutes of Health.

For the purposes of our study, we applied additional exclusion criteria: history of CNS opportunistic infections or tumours; treatment with chemotherapy; major psychiatric disorder (eg, psychosis); history of or current non-HIV-associated neurological disease; current severe alcohol or substance-use disorder; collagen vascular disease; thyroid disease; chronic obstructive pulmonary disease; emphysema; congestive heart failure; angina pectoris; myocardial infarction within the previous 6 months; hepatic failure; renal failure; daily use of systemic steroids (catabolic or anabolic), narcotic or opioid analgesics, or immunostimulant or immunosuppressive drugs; and participation in blinded trials of antiretrovirals that were not approved by the US Food and Drug Administration. Individuals with a history of intravenous drug use were few and were not excluded.

Procedures

Age and HIV disease stage were the independent variables. Age was determined by proof of date of birth. HIV clinical disease stage was used as an index of disease progression and based on the revised US Centers for Disease Control and Prevention staging system for HIV infection, in which there are three stages: (A) asymptomatic, (B) early symptomatic, and (C) late symptomatic or clinically defined AIDS. We added a fourth group, 0, to include HIV-seronegative participants at each visit. We developed an algorithm specifically for use on the MACS database for this purpose.

Scores on neuropsychological tests were the dependent variables. Testing was administered in accordance with the standardised MACS neuropsychological test protocol. Neuropsychological outcomes were captured by five domain scores: information processing speed, episodic memory, executive function, motor function, and working memory. Information processing speed was measured by the Symbol-Digit Substitution Test, measuring visuoperceptual and motor processes, and the Simple and Choice Reaction Time from the California Computerized Assessment Package (CalCAP), a computerised neuropsychological test program. Episodic memory was examined with verbal and visual memory tasks of summed recall from trials 1–5 of the Rey Auditory Verbal Learning Test (RAVLT), delayed recall of the RAVLT, and the copy and delayed recall measures on the Rey-Osterreith Complex Figure. Executive function was measured with the Trail Making Test (TMT) part B and the interference trial from the Stroop. Measurement of motor function comprised the Grooved Pegboard Task, yielding time to place small metal pegs with keys along one side into slotted holes as quickly as possible with the non-dominant hand. Working memory was measured with a one-back procedure from the foregoing CalCAP reaction time test.

We used control variables to optimise control for extraneous sources of variance in neuropsychological outcomes. Educational level[10] (<8th grade, 9–11th grade, high school graduation, some university or university degree, or some graduate school or graduate degree), race and ethnicity[11] (white, non-Hispanic *vs* all other race categories), and income (concurrent annual income category at each visit <$20 000, $20 000–40 000, or >$40 000) were self-reported by participants. Other control variables were time since seroconversion (months at each visit [in a subsample analysis] by actual date of seroconversion [or date of study entry as a proxy]; HIV-seronegative participants were coded as 0), ART era (before and after Jan 1, 1996, which was defined as the beginning of the era of effective ART), medical comorbidities (diabetes diagnosis,[12] which was defined by self-report on at least two consecutive visits or by a fasting glucose concentration of more than 6·9 mmol/L on at least two consecutive visits [with a consecutive visit defined as the next available visit within 2 years]; hypertension diagnosis,[13] which was defined by self-report on at least two consecutive visits or blood pressure higher than 140 mm Hg systolic and 90 mm Hg diastolic on at least two consecutive visits; and history of exposure to hepatitis[14] B virus [metabolic effects] or C virus [metabolic

For information about **MACS, including the data collection instrument** see http://www.statepi.jhsph.edu/macs/macs.html

	HIV seropositive		HIV seronegative		Overall	p value
	Age 50 years or older	Age younger than 50 years	Age 50 years or older	Age younger than 50 years		
n (baseline)	115	2163	267	2541	5086	..
n (last visit)	471	1962	890	1763	5086	..
Cohort subsample						
Baseline	47 (41%)	1376 (64%)	209 (78%)	1856 (73%)	3488 (69%)	<0·0001
1987	15 (13%)	250 (12%)	11 (4%)	157 (6%)	433 (9%)	..
2001	53 (46%)	537 (25%)	47 (18%)	528 (21%)	1165 (23%)	..
Visits	3125	17 352	6832	20 577	47 886	..
Cohort subsample, by visits						
Baseline	2223 (71%)	11 459 (66%)	6148 (90%)	16 283 (79%)	36 113 (75%)	<0·0001
1987	315 (10%)	2142 (12%)	215 (3%)	1160 (6%)	3832 (8%)	..
2001	587 (19%)	3751 (22%)	469 (7%)	3134 (15%)	7941 (17%)	..
Age at baseline, years	54·0 (4·1)	35·3 (6·3)	55·3 (5·2)	36·2 (7·0)	37·2 (8·3)	<0·0001
Age by visits, years	54·5 (4·1)	38·6 (6·2)	56·4 (5·7)	39·1 (6·5)	42·4 (9·2)	<0·0001
Education at baseline						
Less than high school	6 (5%)	133 (6%)	11 (4%)	113 (4%)	263/5086 (5%)	<0·0001
High school	18 (16%)	327 (15%)	29 (11%)	284 (11%)	658/5086 (13%)	..
Some university	35 (30%)	714 (33%)	50 (19%)	665 (26%)	1464/5086 (29%)	..
University degree	13 (11%)	464 (21%)	31 (12%)	641 (25%)	1149/5086 (23%)	..
Post-university degree education	42 (37%)	521 (24%)	146 (55%)	825 (32%)	1534/5086 (30%)	..
Missing	1 (1%)	4 (<1%)	..	13 (1%)	18/5086 (<1%)	..
Race and ethnicity						
White, non-Hispanic	75 (65%)	1456 (67%)	223 (84%)	1918 (75%)	3672 (72%)	<0·0001
Other	40 (35%)	707 (33%)	44 (16%)	621 (24%)	1412 (28%)	..
Missing	..	..	..	2 (<1%)	2 (<1%)	..
Annual income at baseline (US$)						
<20 000	31 (27%)	477 (22%)	39 (15%)	488 (19%)	1035 (20%)	<0·0001
20 000–39 999	21 (18%)	276 (13%)	68 (25%)	488 (19%)	853 (17%)	..
≥40 000	27 (23%)	201 (9%)	98 (37%)	463 (18%)	789 (16%)	..
Refused to answer	3 (3%)	36 (2%)	10 (4%)	52 (2%)	101 (2%)	..
Missing	33 (29%)	1173 (54%)	52 (19%)	1050 (41%)	2308 (45%)	..
Months from enrolment for seroprevalent participants	23·3 (30·8)	26·1 (28·4)	..	..	25·9 (28·5)	0·027
Time from seroconversion, months	65·3 (68·4)	33·4 (29·0)	..	..	35·3 (33·2)	0·012
Time to known or imputed seroconversion, months	71·1 (44·8)	50·4 (30·3)	..	..	51·2 (31·1)	<0·0001
Antiretroviral therapy era, by visits						
Before Jan 1, 1996	641 (21%)	9800 (56%)	2231 (33%)	14 062 (68%)	26 734 (56%)	<0·0001
On or after Jan 1, 1996	2484 (79%)	7552 (44%)	4601 (67%)	6515 (32%)	21 152 (44%)	..
HIV clinical disease stage						
A (asymptomatic)	44 (38%)	1051 (49%)	..	..	1095 (48%)	0·031
B (symptomatic)	61 (53%)	1011 (47%)	..	..	1072 (47%)	..
C (AIDS)	10 (9%)	101 (5%)	..	..	111 (5%)	..
CD4 cell nadir by visits (cells per μL)	435·2 (241·7)	404·2 (237·1)	..	..	409·0 (238·1)	<0·0001
CD4 cell count by visits (cells per μL)	530·2 (283·4)	492·1 (286·5)	..	..	497·9 (286·3)	<0·0001
Plasma HIV RNA, by visits						
No	1587 (51%)	6892 (40%)	..	..	8479 (41%)	<0·0001
Yes	1365 (44%)	7623 (44%)	..	..	8988 (44%)	..
Missing	173 (6%)	2837 (16%)	..	..	3010 (15%)	..

(Table 1 continues on next page)

	HIV seropositive		HIV seronegative		Overall	p value
	Age 50 years or older	Age younger than 50 years	Age 50 years or older	Age younger than 50 years		
(Continued from previous page)						
Diagnosis of diabetes, by visits						
No	2904 (93%)	16 787 (97%)	6590 (96%)	20 014 (97%)	46 295 (97%)	<0·0001
Yes	179 (6%)	171 (1%)	169 (2%)	135 (1%)	654 (1%)	..
Missing	42 (1%)	394 (2%)	73 (1%)	428 (2%)	937 (2%)	..
Diagnosis of hypertension, by visits						
No	1453 (46%)	10 998 (63%)	3135 (46%)	12 790 (62%)	28 376 (59%)	<0·0001
Yes	1614 (52%)	4083 (24%)	3587 (53%)	5523 (27%)	14 807 (31%)	..
Missing	58 (2%)	2271 (13%)	110 (2%)	2264 (11%)	4703 (10%)	..
Psychotropic drug use, by visits						
No	2572 (82%)	15 190 (88%)	5809 (85%)	18 115 (88%)	41 686 (87%)	<0·0001
Yes	553 (18%)	2161 (12%)	1023 (15%)	2462 (12%)	6199 (13%)	..
Missing	..	1 (<1%)	..	..	1 (<1%)	..
History of hepatitis B virus infection, by visits						
No	2806 (90%)	15 973 (92%)	6575 (96%)	19 860 (97%)	45 214 (94%)	<0·0001
Yes	319 (10%)	1379 (8%)	257 (4%)	717 (3%)	2672 (6%)	..
History of hepatitis C virus infection, by visits						
No	2681 (86%)	15 671 (90%)	6482 (95%)	19 853 (96%)	44 687 (93%)	<0·0001
Yes	444 (14%)	1681 (10%)	350 (5%)	724 (4%)	3199 (7%)	..
Pain (present or absent), by visits						
No	2404 (77%)	14 889 (86%)	5542 (81%)	18 725 (91%)	41 560 (87%)	<0·0001
Yes	721 (23%)	2463 (14%)	1290 (19%)	1852 (9%)	6326 (13%)	..
Fatigue (present or absent), by visits						
No	2715 (87%)	15 323 (88%)	6451 (94%)	19 722 (96%)	44 211 (92%)	<0·0001
Yes	399 (13%)	2001 (12%)	371 (5%)	843 (4%)	3614 (8%)	..
Missing	11 (<1%)	28 (<1%)	10 (<1%)	12 (<1%)	61 (<1%)	..
Alcohol use frequency, by visits						
None or occasional	1090 (35%)	5385 (31%)	1881 (28%)	4876 (24%)	13 232 (28%)	<0·0001
Used	2005 (64%)	11 893 (69%)	4899 (72%)	15 627 (76%)	34 424 (72%)	..
Missing	30 (1%)	74 (<1%)	52 (<1%)	74 (<1%)	230 (<1%)	..
Cannabis use frequency, by visits						
None or occasional	2383 (76%)	12 291 (71%)	5928 (87%)	16 365 (80%)	36 967 (77%)	<0·0001
Used	670 (21%)	4605 (27%)	834 (12%)	3932 (19%)	10 041 (21%)	..
Missing	72 (2%)	456 (3%)	70 (1%)	280 (1%)	878 (2%)	..
Nitrite inhalant use frequency, by visits						
None or occasional	2443 (78%)	13 890 (80%)	5846 (86%)	17 403 (85%)	39 582 (83%)	<0·0001
Used	604 (19%)	2906 (17%)	902 (13%)	2720 (13%)	7132 (15%)	..
Missing	78 (2%)	556 (3%)	84 (1%)	454 (2%)	1172 (2%)	..

Categorical variables are presented as n or n (%); continuous variables are presented as mean (SD). Percentages are based on n at baseline or number of visits, as indicated. We used χ^2 analysis to compare categorical variables, and ANOVA tests to compare continuous variables.

***Table 1*: Sociodemographics and clinical characteristics of the sample**

effects and direct CNS effects], which was defined as lifetime positivity for hepatitis B virus surface antigen status or hepatitis C virus antibody), global nutritional status[15] (relative change in total bodyweight from the previous visit and body-mass index [BMI], which were obtained by weighing participants: underweight [<18·5], average [18·5–24·9], overweight [25·0–29·9], and obese [>30·0]), depressed mood level (per the Centers for Epidemiology-Depression [CES-D] Scale[16]), fatigue level[17] (self-reported fatigue in the previous 2 weeks), and pain[18] (self-report by number of types present [head, joint, abdominal, muscle, or urinary]—0=0–1 types, 1=2–3 types, and 2=4–5 types present). Alcohol and psychoactive substances requiring control were reduced to self-report of alcohol use[19] (categorical variable based on frequency of use by a MACS-derived algorithm), cigarette smoking[20] (MACS-derived algorithm generating total pack-years), and frequency of use (none *vs* any) of cannabis[21] and

	Overall	HIV seronegative	HIV seropositive				p value (HIV seropositive vs seronegative)	p value (HIV seropositive by clinical disease stage and seronegative group)
			All	A (asymptomatic)	B (early symptomatic)	C (late symptomatic or AIDS)		
Information processing speed	47·4 (9·2)	47·9 (9·1)	46·8 (9·4)	48·5 (9·4)	46·0 (9·1)	42·4 (9·0)	0·0005	<0·0001
Episodic memory	47·3 (9·2)	47·4 (9·3)	47·1 (9·1)	47·9 (9·0)	46·5 (9·1)	45·5 (8·8)	0·42	0·04
Executive function	47·7 (10·3)	48·4 (10·2)	46·9 (10·5)	47·7 (10·2)	46·5 (10·6)	43·3 (10·6)	<0·0001	0·0002
Motor function	46·5 (12·0)	46·8 (11·9)	46·4 (12·0)	48·0 (11·1)	45·4 (12·4)	40·9 (13·7)	0·62	0·0001
Working memory	48·3 (10·6)	48·3 (10·6)	48·4 (10·5)	50·0 (11·0)	47·7 (10·2)	44·3 (10·2)	0·92	0·02

Data are neurocognitive domains scores adjusted to T scores (with mean of 50 and SD of 10). We also shifted the valence such that higher scores always reflected higher performance. Tests for significance between HIV-seropositive vs HIV-seronegative subsamples and tests among the HIV seropositive subsamples by clinical disease stage (including the HIV seronegative subsample) were done with Kruskal-Wallis ANOVAs.

***Table 2*: Baseline status of neurocognitive function by domain**

nitrite inhalants (ie, poppers).[22] Psychotropic drug use[23] was controlled by use at assessment derived from self-report based on relevant drugs listed across psychotropic categories. HIV-specific control variables (eg, CD4 cell count nadir, plasma HIV load, antiretroviral adherence, and CNS-penetration scores) were not used because these variables cannot be properly defined for HIV-seronegative participants. Insufficient data were available to allow us to control for cholesterol and triglyceride concentrations, renal and hepatic function, and laboratory measures of general nutritional status.

Statistical analysis

Analyses were done with visit-based (rather than participant-based) sets of linear mixed models for longitudinal data.[24] Age was used as a continuous measure, and HIV disease stage was characterised as an ordinal variable at three levels: A (1), B (2), and C (3). We added a fourth group, 0, to include seronegative participants at each visit. Each model included a random participant effect to account for repeated measurements in the same participant. We used analysis of residuals to check the required assumptions of normally distributed errors with constant variance; if necessary, we log-transformed outcome variables to stabilise the variance or produce a more normal error distribution. Neuropsychological outcome measures were not adjusted for age or ethnicity. Neuropsychological outcomes were assessed on the basis of the age and HIV disease-stage variables to examine main effects, and on the basis of the interaction of these two variables to examine evidence for the hypothesised, deleterious synergistic effect. All qualifying visits were included from the beginning of neuropsychological testing in the MACS. We analysed four separate sets of models. The full model on the entire sample (model 1) included independent variable predictors for age, HIV disease stage, the age-by-HIV-disease-stage interaction term, and all control variables. The reduced model on the entire sample (model 2) was a confirmatory model, in which we eliminated all non-significant control variable predictors from model 1. The full model adding time since seroconversion (model 3) added this single control to the set in a subsample with data available to estimate this crucial parameter. The full model without time since seroconversion on the seroconversion subsample (model 4) was another confirmatory model to identify any possible factors in the outcome that might have been related to the subsample composition.

Role of the funding source

The study funders had no role in study design; data collection, analysis, or interpretation; or writing of the Article. The corresponding author had full access to all study data and had final responsibility for the decision to submit for publication.

Results

Our sample comprised 5086 participants, 2278 of whom were HIV seropositive and 2808 of whom were HIV seronegative (table 1). We analysed 47 886 visits, 20 477 of which were by HIV-seropositive individuals and 27 409 by HIV-seronegative individuals. On initial recruitment, 10% of HIV-seronegative participants and 5% of HIV-seropositive participants were aged 50 years or older (table 1). Most of the HIV-seropositive participants aged 50 years or older were in their mid-50s, with very few participants older than 65 years (data not shown). More participants in the seropositive group than in the seronegative group had an educational level of high school or less (table 1). Similarly, university-level education or higher was more common in the HIV-seronegative subsample, and particularly in the older HIV-seronegative group, than in the seropositive sample (table 1). Significantly more participants in the HIV-seropositive group than in the seronegative group

	Full model on full sample					Full model with time since seroconversion				
	Information processing speed	Episodic memory	Executive function	Motor function	Working memory	Information processing speed	Episodic memory	Executive function	Motor function	Working memory
Age	−0·20 (0·01; −0·23 to −0·18; <0·0001)	−0·18 (0·02; −0·21 to −0·15; <0·0001)	−0·16 (0·01; −0·19 to −0·14; <0·0001)	−0·40 (0·02; −0·44 to −0·35; <0·0001	−0·13 (0·02; −0·17 to −0·08; <0·0001)	−0·20 (0·01; −0·23 to −0·18; <0·0001	−0·17 (0·02; −0·20 to −0·14; <0·0001)	−0·15 (0·01; −0·18 to −0·13; <0·0001)	−0·40 (0·02; −0·44 to −0·35; <0·0001)	−0·13 (0·02; −0·17 to −0·08; <0·0001)
HIV clinical disease stage*										
AIDS	−0·61 (0·37; −1·34 to 0·13; 0·10)	−0·64 (0·45; −1·51 to 0·24; 0·15)	−0·80 (0·39; −1·57 to −0·03; 0·042)	−3·40 (0·64; −4·66 to −2·14; <0·0001)	−2·45 (0·62; −3·66 to −1·24; <0·0001)	−1·39 (0·46; −2·28 to −0·49; 0·002)	−0·99 (0·55; −2·07 to 0·09; 0·07)	−2·41 (0·47; −3·33 to −1·50; <0·0001)	−3·46 (0·81; −5·05 to −1·88; <0·0001)	−2·49 (0·76; −3·98 to −1·00; 0·001)
Early symptomatic	0·38 (0·23; −0·06 to 0·82; 0·09)	0·35 (0·28; −0·20 to 0·90; 0·21)	0·38 (0·24; −0·09 to 0·85; 0·12)	0·35 (0·40; −0·43 to 1·14; 0·38)	−0·85 (0·38; −1·59 to −0·11; 0·025)	0·22 (0·29; −0·35 to 0·78; 0·45)	−0·01 (0·38; −0·75 to 0·74; 0·99)	−0·42 (0·30; −1·00 to 0·16; 0·16)	0·73 (0·56; −0·36 to 1·82; 0·19)	−0·87 (0·50; −1·86 to 0·11; 0·08)
Asymptomatic	0·43 (0·23; −0·02 to 0·87; 0·060)	−0·05 (0·28; −0·61 to 0·50; 0·86)	0·51 (0·24; 0·04 to 0·98; 0·034)	−0·02 (0·40; −0·81 to 0·77; 0·96)	−0·98 (0·38; −1·73 to −0·24; 0·010)	0·24 (0·28; −0·32 to 0·80; 0·39)	−0·52 (0·37; −1·26 to 0·21; 0·16)	−0·21 (0·29; −0·79 to 0·36; 0·47)	0·32 (0·55; −0·75 to 1·39; 0·56)	−0·86 (0·50; −1·84 to 0·12; 0·09)
Age by HIV clinical disease stage interaction										
Age by AIDS	0·11 (0·04; 0·03 to 0·18; 0·004)	0·03 (0·05; −0·06 to 0·13; 0·51)	0·18 (0·04; 0·10 to 0·25; <0·0001)	−0·03 (0·07; −0·17 to 0·12; 0·70)	0·002 (0·07; −0·13 to 0·14; 0·98)	0·06 (0·04; −0·03 to 0·15; 0·17)	−0·08 (0·06; −0·20 to 0·03; 0·13)	−0·02 (0·05; −0·11 to 0·07; 0·63)	−0·03 (0·08; −0·20 to 0·13; 0·70)	0·05 (0·08; −0·11 to 0·20; 0·54)
Age by symptomatic	0·05 (0·02) (0·01 to 0·08); 0·007	0·03 (0·02) (−0·01 to 0·08); 0·14	0·17 (0·02) (0·14 to 0·20) <0·0001	−0·08 (0·03) (−0·14 to −0·01); 0·019	0·08 (0·03) (0·02 to 0·14); 0·013	−0·02 (0·03) (−0·08 to 0·03); 0·42	−0·06 (0·03) (−0·13 to 0·01); 0·09	−0·03 (0·03) (−0·09 to 0·02); 0·28	−0·07 (0·05) (−0·17 to 0·03) ; 0·18	0·15 (0·05) (0·06 to 0·25; 0·001
Age by asymptomatic	0·07 (0·02; 0·04 to 0·10; <0·0001)	0·05 (0·02; 0·01 to 0·10; 0·018)	0·17 (0·02; 0·14 to 0·20; <0·0001)	−0·01 (0·03; −0·08 to 0·05; 0·73)	0·12 (0·03; 0·06 to 0·18; 0·0001)	0·01 (0·03; −0·04 to 0·06; 0·70)	0·001 (0·03; −0·07 to 0·07; 0·98)	−0·05 (0·03; −0·11 to 0·003; 0·07)	0·04 (0·05; −0·06 to 0·14; 0·47)	0·20 (0·05; 0·10 to 0·29; <0·0001)
Overall test for interaction	<0·0001	0·13	<0·0001	0·052	0·002	0·10	0·03	0·28	0·02	0·0004
Time since seroconversion (years)	..	..	..	..	..	0·11 (0·03; 0·05 to 0·16; <0·0001)	0·14 (0·03; 0·08 to 0·21; <0·0001)	0·30 (0·03; 0·24 to 0·35; <0·0001)	0·01 (0·05; −0·09 to 0·11; 0·84)	−0·02 (0·05; −0·11 to 0·07; 0·68)
Control variables										
Race and ethnicity†	−4·27 (0·30; −4·87 to −3·68; <0·0001)	−5·29 (0·36; −6·00 to −4·59; <0·0001)	−6·75 (0·33; −7·40 to −6·10; <0·0001)	−6·47 (0·51; −7·46 to −5·47; <0·0001)	−2·17 (0·49; −3·13 to −1·22; <0·0001)	−3·79 (0·36; −4·51 to −3·08; <0·0001)	−4·26 (0·43; −5·11 to −3·42; <0·0001)	−6·15 (0·39; −6·91 to −5·39; <0·0001)	−5·71 (0·61; −6·91 to −4·50; <0·0001)	−2·27 (0·60; −3·45 to −1·09; 0·0002)
Education‡										
Some university experience	4·16 (0·39; 3·39 to 4·92; <0·0001)	4·06 (0·46; 3·16 to 4·95; <0·0001)	5·19 (0·43; 4·36 to 6·03; <0·0001)	3·15 (0·64; 1·90 to 4·41; <0·0001)	0·54 (0·62; −0·66 to 1·75; 0·38)	3·60 (0·46; 2·70 to 4·49; <0·0001)	3·64 (0·54; 2·58 to 4·69; <0·0001)	4·58 (0·49; 3·63 to 5·54; <0·0001)	2·74 (0·76; 1·25 to 4·23; 0·0003)	1·13 (0·75; −0·35 to 2·61; 0·13)
University degree	5·21 (0·41; 4·40 to 6·03; <0·0001)	5·69 (0·49; 4·72 to 6·65; <0·0001)	6·15 (0·45; 5·27 to 7·04; <0·0001)	4·06 (0·69; 2·71 to 5·41; <0·0001)	1·04 (0·67; −0·27 to 2·34; 0·12)	4·79 (0·47; 3·87 to 5·71; <0·0001)	5·34 (0·55; 4·26 to 6·42; <0·0001)	5·93 (0·50; 4·96 to 6·91; <0·0001)	3·99 (0·78; 2·47 to 5·52; <0·0001)	1·42 (0·77; −0·09 to 2·94; 0·06)
Some postgraduate experience or postgraduate degree	5·69 (0·40; 4·90 to 6·48; <0·0001)	6·44 (0·49; 5·48 to 7·40; <0·0001)	6·13 (0·44; 5·27 to 7·00; <0·0001)	4·19 (0·69; 2·84 to 5·53; <0·0001)	1·14 (0·66; −0·16 to 2·45; 0·09)	5·54 (0·46; 4·65 to 6·44; <0·0001)	6·18 (0·55; 5·10 to 7·26; <0·0001)	6·19 (0·49; 5·24 to 7·14; <0·0001)	3·68 (0·78; 2·15 to 5·21; <0·0001)	1·57 (0·77; 0·06 to 3·09; 0·042)
Annual income (US$)§										
20 000–40 000	0·32 (0·13; 0·07 to 0·58; 0·014)	0·50 (0·17; 0·17 to 0·83; 0·003)	0·48 (0·13; 0·22 to 0·74; 0·0003)	0·72 (0·25; 0·23 to 1·21; 0·004)	0·42 (0·23; −0·02 to 0·87; 0·06)	0·25 (0·14; −0·03 to 0·53; 0·08)	0·39 (0·18; 0·04 to 0·75; 0·029)	0·32 (0·15; 0·03 to 0·60; 0·030)	0·49 (0·27; −0·04 to 1·02; 0·07)	0·40 (0·24; −0·08 to 0·87; 0·10)
≥40 000	0·70 (0·15; 0·40 to 1·00; <0·0001)	0·80 (0·20; 0·40 to 1·19; <0·0001)	1·20 (0·16; 0·90 to 1·51; <0·0001)	1·75 (0·29; 1·17 to 2·33; <0·0001)	0·71 (0·27; 0·18 to 1·23; 0·008)	0·63 (0·16; 0·31 to 0·95; 0·0001)	0·69 (0·21; 0·28 to 1·10; 0·0009)	1·08 (0·17; 0·75 to 1·41; <0·0001)	1·56 (0·31; 0·95 to 2·17; <0·0001)	0·60 (0·28; 0·06 to 1·15; 0·031)

(Table 3 continues on next page)

	Full model on full sample					Full model with time since seroconversion				
	Information processing speed	Episodic memory	Executive function	Motor function	Working memory	Information processing speed	Episodic memory	Executive function	Motor function	Working memory
(Continued from previous page)										
Antiretroviral therapy era (since Jan 1, 1996 *vs* before Jan 1, 1996)	0·58 (0·12; 0·35 to 0·82; <0·0001)	0·97 (0·15; 0·68 to 1·27; <0·0001)	1·81 (0·12; 1·56 to 2·05; <0·0001)	0·43 (0·22; −0·01 to 0·87; 0·055)	1·46 (0·20; 1·06 to 1·86; <0·0001)	0·60 (0·13; 0·35 to 0·85; <0·0001)	0·82 (0·16; 0·50 to 1·13; <0·0001)	1·62 (0·13; 1·36 to 1·88; <0·0001)	0·35 (0·24; −0·12 to 0·83; 0·15)	1·48 (0·22; 1·05 to 1·90; <0·0001)
Diabetes diagnosis	−0·09 (0·36; −0·80 to 0·62; 0·80)	−0·30 (0·59; −1·45 to 0·86; 0·62)	0·05 (0·37; −0·68 to 0·79; 0·88)	−4·08 (0·89; −5·83 to −2·34; <0·0001)	1·46 (0·78; −0·07 to 3·00; 0·06)	−0·41 (0·42; −1·23 to 0·41; 0·33)	−0·37 (0·66; −1·66 to 0·92; 0·57)	−0·56 (0·43; −1·40 to 0·28; 0·19)	−3·89 (1·00; −5·86 to −1·92; 0·0001)	1·95 (0·87; 0·26 to 3·65; 0·024)
Hypertension diagnosis	0·01 (0·14; −0·27 to 0·29; 0·92)	−0·45 (0·20; −0·85 to −0·06; 0·025	0·03 (0·15; −0·26 to 0·32; 0·83)	−0·84 (0·29; −1·42 to −0·27; 0·004)	0·05 (0·27; −0·48 to 0·57; 0·85)	−0·11 (0·15; −0·41 to 0·19; 0·47)	−0·47 (0·21; −0·89 to −0·05; 0·028)	−0·28 (0·16; −0·59 to 0·03; 0·08)	−0·72 (0·31; −1·34 to −0·11; 0·022)	0·09 (0·28; −0·47 to 0·64; 0·76)
Fatigue level	−0·65 (0·15; −0·95 to −0·35; <0·0001)	−0·07 (0·19; −0·44 to 0·30; 0·72)	−0·74 (0·16; −1·05 to −0·44; <0·0001)	−0·33 (0·28; −0·88 to 0·22; 0·24)	0·20 (0·26; −0·31 to 0·71; 0·45)	−0·76 (0·17; −1·09 to −0·43; <0·0001)	−0·13 (0·20; −0·52 to 0·26; 0·52)	−0·72 (0·17; −1·05 to −0·38; <0·0001)	−0·22 (0·30; −0·81 to 0·38; 0·48)	0·19 (0·27; −0·34 to 0·73; 0·48)
Pain	0·03 (0·11; −0·19 to 0·26; 0·78)	−0·36 (0·17; −0·69 to −0·03; 0·032)	−0·22 (0·12; −0·45 to 0·01; 0·06)	−0·32 (0·25; −0·82 to 0·17; 0·20)	−0·12 (0·23; −0·57 to 0·32; 0·59)	0·07 (0·13; −0·18 to 0·32; 0·58)	−0·43 (0·18; −0·79 to −0·08; 0·018)	−0·19 (0·13; −0·45 to 0·06; 0·14)	−0·09 (0·28; −0·64 to 0·46; 0·74)	−0·23 (0·25; −0·72 to 0·26; 0·36)
Psychotropic drug use	0·20 (0·10; 0·005 to 0·39; 0·045)	−0·11 (0·14; −0·37 to 0·16; 0·43)	−0·05 (0·10; −0·24 to 0·15; 0·66)	−0·43 (0·20; −0·83 to −0·03; 0·034)	0·002 (0·18; −0·36 to 0·36; 0·99)	0·31 (0·11; 0·10 to 0·52; 0·004)	−0·23 (0·15; −0·51 to 0·06; 0·12)	−0·06 (0·11; −0·27 to 0·15; 0·58)	−0·41 (0·22; −0·84 to 0·02; 0·06)	0·03 (0·19; −0·35 to 0·41; 0·88)
History of hepatitis B virus Infection	−0·20 (0·43; −1·04 to 0·63; 0·63)	−0·48 (0·57; −1·61 to 0·64; 0·40)	0·53 (0·46; −0·36 to 1·43; 0·24)	−0·98 (0·81; −2·56 to 0·60; 0·23)	0·12 (0·77; −1·38 to 1·62; 0·88)	−0·04 (0·48; −0·99 to 0·91; 0·94)	−0·06 (0·65; −1·34 to 1·22; 0·93)	0·04 (0·51; −0·95 to 1·04; 0·93)	−0·30 (0·93; −2·12 to 1·53; 0·75)	0·09 (0·89; −1·65 to 1·82; 0·92)
History of hepatitis C virus Infection	−1·25 (0·38; −1·99 to −0·50; 0·001)	−1·36 (0·49; −2·31 to −0·40; 0·005)	−1·36 (0·41; −2·16 to −0·56; 0·0008)	−3·05 (0·69; −4·41 to −1·69; <0·0001)	−1·84 (0·67; −3·15 to −0·53; 0·006)	−1·06 (0·45; −1·95 to −0·16; 0·020)	−1·50 (0·56; −2·60 to −0·39; 0·008)	−1·39 (0·48; −2·32 to −0·45; 0·004)	−2·17 (0·82; −3·77 to −0·57; 0·008)	−2·46 (0·79; −4·02 to −0·90; 0·002)
Cannabis use¶	0·13 (0·14; −0·15 to 0·41; 0·36)	−0·07 (0·19; −0·44 to 0·30; 0·72)	0·22 (0·15; −0·07 to 0·51; 0·13)	0·25 (0·28; −0·29 to 0·79; 0·36)	0·45 (0·25; −0·04 to 0·95; 0·07)	0·07 (0·15; −0·23 to 0·37; 0·65)	0·04 (0·20; −0·35 to 0·44; 0·82)	0·11 (0·16; −0·20 to 0·42; 0·49)	0·28 (0·30; −0·30 to 0·86; 0·34)	0·45 (0·27; −0·08 to 0·97; 0·09)
Nitrite inhalant use¶	0·48 (0·14; 0·21 to 0·75; 0·0006)	0·25 (0·19; −0·12 to 0·63; 0·19)	0·14 (0·14; −0·14 to 0·42; 0·34)	−0·07 (0·28; −0·61 to 0·48; 0·81)	0·07 (0·26; −0·43 to 0·58; 0·77)	0·45 (0·15; 0·16 to 0·74; 0·002)	0·17 (0·20; −0·22 to 0·56; 0·39)	0·14 (0·15; −0·16 to 0·43; 0·35)	−0·09 (0·29; −0·67 to 0·48; 0·76)	0·08 (0·27; −0·45 to 0·60; 0·77)
Total bodyweight (% change from previous visit)	−0·01 (0·01; −0·02 to 0·0007; 0·051)	−0·01 (0·01; −0·03 to 0·002; 0·09)	−0·01 (0·01; −0·02 to 0·01; 0·27)	−0·002 (0·01; −0·03 to 0·02; 0·86)	0·02 (0·01; 0·0005 to 0·04; 0·045)	−0·01 (0·01; −0·02 to 0·003; 0·12)	−0·01 (0·01; −0·03 to 0·01; 0·16)	−0·01 (0·01; −0·02 to 0·003; 0·15)	−0·004 (0·01; −0·03 to 0·02; 0·73)	0·03 (0·01; 0·01 to 0·05; 0·010)
Body-mass index	0·10 (0·02; 0·07 to 0·14; <0·0001)	−0·01 (0·02; −0·06 to 0·04; 0·59)	0·05 (0·02; 0·01 to 0·09; 0·009)	0·03 (0·04; −0·04 to 0·11; 0·34)	0·02 (0·03; −0·05 to 0·08; 0·65)	0·11 (0·02; 0·07 to 0·15; <0·0001)	−0·001 (0·03; −0·05 to 0·05; 0·94)	0·06 (0·02; 0·02 to 0·11; 0·004)	0·03 (0·04; −0·04 to 0·11; 0·40)	0·02 (0·04; −0·05 to 0·09; 0·58)
Depressed mood level	−0·03 (0·01; −0·04 to −0·02; <0·0001)	−0·03 (0·01; −0·04 to −0·01; 0·0002)	−0·03 (0·01; −0·04 to −0·02; <0·0001)	−0·004 (0·01; −0·02 to 0·02; 0·72)	−0·03 (0·01; −0·05 to −0·01; 0·002)	−0·03 (0·01; −0·04 to −0·02; <0·0001)	−0·03 (0·01; −0·04 to −0·02; <0·0001)	−0·03 (0·01; −0·04 to −0·02; <0·0001)	−0·01 (0·01; −0·03 to 0·01; 0·36)	−0·02 (0·01; −0·04 to −0·01; 0·012)

(Table 3 continues on next page)

were of non-white ethnicity (table 1), as expected from national demographics. HIV disease stage differed significantly by age at baseline, and more patients in the older age group had stage C disease than in the younger age group (table 1). CD4 cell nadir and concurrent CD4 cell counts were significantly higher in the older HIV-seropositive subgroup than in the younger subgroup (table 1), although these differences were probably not clinically important. The frequency of detectable plasma viral load was similar between age groups (table 1).

Neuropsychological domain scores were generally lower (but not always significantly so) in HIV-seropositive participants than in HIV-seronegative participants (table 2). However, when HIV disease stage was accounted for, lower performance on all five neuropsychological domain scores was significantly associated with advanced disease stage (table 2).

The full model on full sample (model 1) results showed that older age was significantly associated with lower performance in all five neuropsychological outcome domains ($p<0·0001$ for all; table 3). Deleterious HIV disease stage effects were maintained (table 3). We noted a significant age-by-disease-stage interaction in information processing speed, executive functioning, and working memory (table 3). In the reduced model on the entire sample (model 2), elimination of non-significant control variables recapitulated the results of the full models, including the effect of controls, which were in the expected directions (data not shown). Each control was significant in the analyses, except for cannabis use and lifetime history of hepatitis B virus infection (table 3).

The full model with the subsample analysis adding time since seroconversion as a special focus for control (model 3) included 4234 participants, 1638 of whom were HIV seropositive and 2596 of whom were seronegative. Of the seropositive participants, 1120 were seroprevalent at study baseline and 518 seroconverted while enrolled in the study. For seroprevalent participants, we conservatively used date of study baseline as time since seroconversion. Time since seroconversion was significant for information processing speed, episodic memory, and executive function (table 3). The negative effects of ageing from the full model were maintained in model 3 (table 3). The effect of HIV disease stage on neuropsychological performance was greater in the expected negative direction in this model than in the original model. The age-by-HIV-disease-stage interactions were eliminated for information processing speed and executive function (table 3). The interactions in this model (figure) between age and disease stage were significant and negative for motor function and episodic memory (which had changed in direction from positive to negative). A significant positive interaction was noted for working memory (table 3), but the directions of the changes noted with progression from HIV disease stages A to C were in the negative pattern consistently, as predicted. Analysis of

	Full model on full sample					Full model with time since seroconversion				
	Information processing speed	Episodic memory	Executive function	Motor function	Working memory	Information processing speed	Episodic memory	Executive function	Motor function	Working memory
(Continued from previous page)										
Alcohol use‖										
Weekly	−0·04 (0·14; −0·31 to 0·23; 0·79)	−0·60 (0·20; −0·99 to −0·21; 0·002)	−0·11 (0·14; −0·39 to 0·17; 0·43)	0·36 (0·29; −0·21 to 0·93; 0·22)	0·30 (0·27; −0·23 to 0·83; 0·27)	−0·03 (0·15; −0·32 to 0·25; 0·82)	−0·49 (0·20; −0·89 to −0·08; 0·018)	−0·07 (0·15; −0·36 to 0·22; 0·64)	0·57 (0·30; −0·03 to 1·17; 0·06)	0·16 (0·28; −0·39 to 0·70; 0·57)
Monthly	−0·13 (0·16; −0·45 to 0·19; 0·43)	−0·41 (0·23; −0·85 to 0·03; 0·07)	−0·08 (0·17; −0·41 to 0·25; 0·64)	0·37 (0·33; −0·28 to 1·03; 0·26)	0·45 (0·31; −0·15 to 1·05; 0·14)	−0·13 (0·17; −0·47 to 0·21; 0·46)	−0·39 (0·24; −0·85 to 0·07; 0·10)	−0·01 (0·18; −0·36 to 0·33; 0·94)	0·56 (0·35; −0·13 to 1·24; 0·11)	0·24 (0·32; −0·39 to 0·86; 0·45)
<Monthly	−0·38 (0·17; −0·72 to −0·04; 0·027)	−0·82 (0·24; −1·29 to −0·35; 0·0007)	−0·21 (0·18; −0·56 to 0·14; 0·24)	−0·63 (0·35; −1·32 to 0·06; 0·07)	−0·39 (0·32; −1·03 to 0·24; 0·23)	−0·43 (0·19; −0·79 to −0·06; 0·021)	−0·69 (0·25; −1·18 to −0·19; 0·006)	−0·09 (0·19; −0·46 to 0·29; 0·65)	−0·43 (0·37; −1·16 to 0·30; 0·25)	−0·53 (0·34; −1·20 to 0·14; 0·12)
Cigarette smoking pack-years	−0·02 (0·01; −0·03 to −0·01; 0·001)	−0·02 (0·01; −0·03 to −0·002; 0·031)	−0·04 (0·01; −0·05 to −0·03; <0·0001)	−0·03 (0·01; −0·05 to −0·01; 0·015)	−0·01 (0·01; −0·03 to 0·01; 0·28)	−0·02 (0·01; −0·03 to −0·003; 0·016)	−0·02 (0·01; −0·03 to −0·0009; 0·039)	−0·04 (0·01; −0·05 to −0·02; <0·0001)	−0·02 (0·01; −0·05 to 0·0007; 0·044)	−0·01 (0·01; −0·03 to 0·01; 0·43)

Data are estimated regression coefficients (SE; 95% CI; p value). *By the US Centers for Disease Control and Prevention staging system, adding parameterisation vs HIV-seronegative participants. †Predictors: all other participants vs white, non-Hispanic participants. ‡The reference group was the participants with high school education or less than high school education from table 1 combined. §The reference group was participants with an annual income of <$20 000. ¶The reference group was participants who did not use or rarely used cannabis or inhaled nitrites. ||The reference group was participants who drank alcohol daily.

Table 3: **Linear model analyses for full sample and full model sample plus time since seroconversion on a subsample**

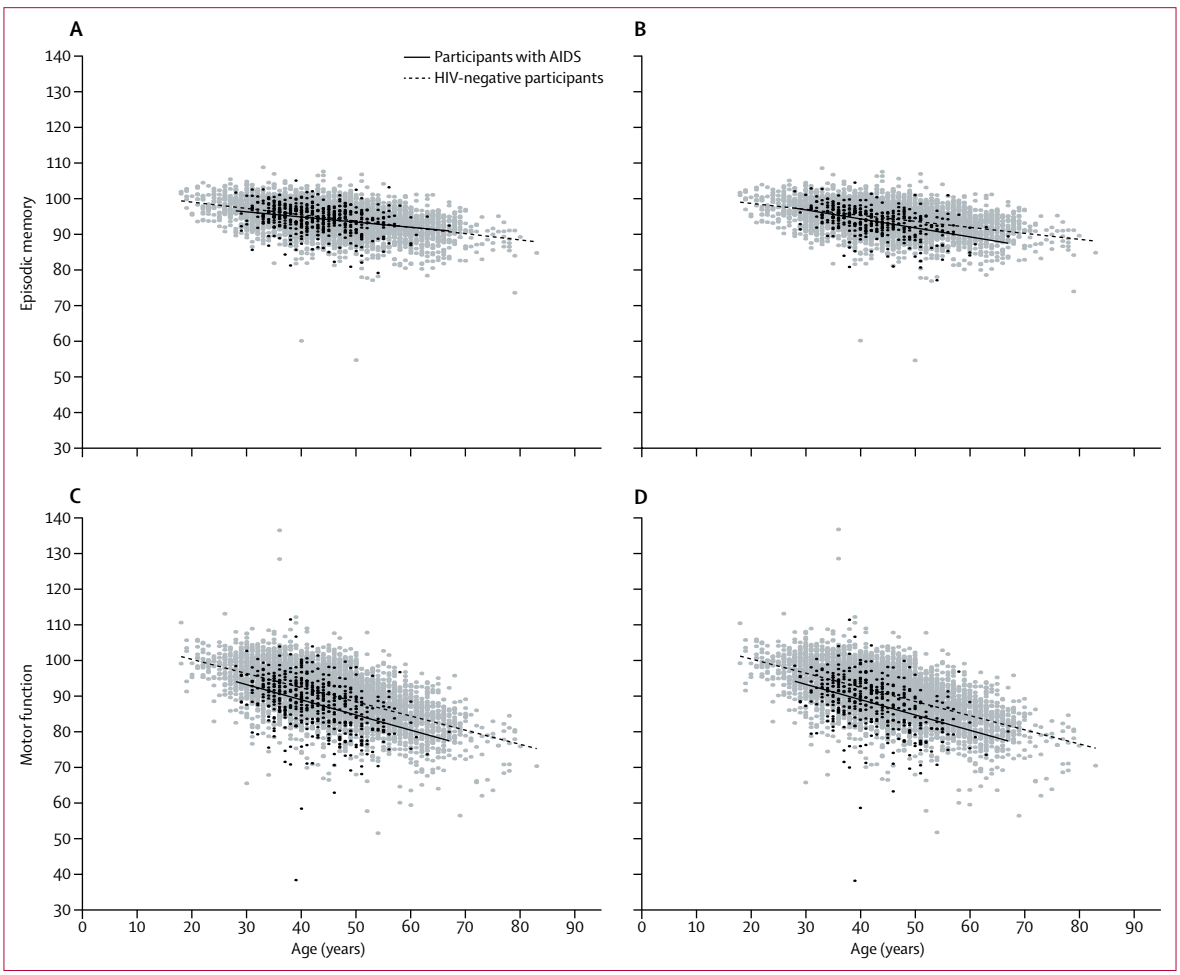

***Figure*: Plots of adjusted domain scores and fitted regression lines from the multivariable models for the relations between age and episodic memory and motor function, according to late Centers for Disease Control and Prevention disease stage or AIDS *vs* HIV seronegative status**

Plots of adjusted domain scores and fitted regression lines from multivariable models for relationships between age and episodic memory in the full model on the full sample (A) and model including time since seroconversion (B); and between age and motor function in the full model (C) and model including time since seroconversion (D). The AIDS and HIV-seronegative subsamples were selected to display the results from the opposite poles of the spectrum of HIV disease. In the model adding time since seroconversion, participants with AIDS did worse at older ages than HIV-seronegative control participants in both domains. The absence of any pattern in the residual error scattergrams of both groups (aside from the downward trends consistent with the regression on age) supports the validity of the analytic models used.

this subsample with the full model (ie, the fourth model, without including time since seroconversion) showed that results predominantly reverted to those of model 1 (data not shown), which, as anticipated, were once again contrary to prediction in the directions of the age by HIV disease stage interactions.

Discussion

As expected, we noted a primary effect of ageing across models, which consistently showed lower performance with older age on all five neurocognitive domains. Likewise, we noted a primary effect of systemic HIV disease severity (ie, HIV disease stage) consistently on all domains, with the lowest performance predominantly in the late symptomatic stage. The control variables (ethnicity, education, income, ART era, diabetes, hypertension, depressed mood level, pain, fatigue, body-mass index, total bodyweight, and history of hepatitis C virus infection) were predominantly consistently in the expected directions across the outcome domains. In the model 1 analysis, interactions of age with HIV disease stage were present in all domains but episodic memory and motor function. The direction of these interactions suggested that older HIV-seropositive individuals showed higher neurocognitive performance than their younger counterparts, with respect to how older HIV-seronegative controls compared with their younger counterparts, except in the motor domain. Similar positive interactions of age with HIV disease stage have been reported previously in models in which duration of HIV serostatus could not be controlled.[9]

The addition of the highlighted control for time since seroconversion to this model in a subsample in which these data were available in the MACS cohort showed higher performance with longer duration of HIV

infection in information processing speed, episodic memory, and executive function. Such an effect might be driven by variance in the lower end of the range of this period related to effective suppression of viral load on antiretroviral regimens and the associated greater immune reconstitution. In this analytic model, the significant interactions of ageing with HIV disease stage suggesting higher performance in older HIV-seropositive participants on information processing speed and executive function were eliminated. The non-significant interaction for episodic memory became significant and shifted to a negative direction. Motor function still showed lower performance, and working memory showed higher performance but decreasing associations toward late stage disease. Thus, with serostatus duration controlled, the results yielded the anticipated ageing interaction effect (ie, the lowest performance occurred with older age and late disease stage) in the specific domains of motor function and episodic memory, along with a similar direction by stage of disease in working memory. One limitation of the study is that participants undergoing neuropsychological testing could have experienced intercurrent medical events that affected their neurocognitive function between visits; however, our analytic model would have controlled for the effect of many of these events, and such events were recorded and uncommon. Overall, the results clearly show that controlling for the specific factor of time since infection separately from age has an effect of major importance. Furthermore, our results suggest that chronological age represents not only simply time since birth but also the onset of a specific physiological process of ageing, which has a debilitating neurocognitive effect beginning at about age 50 years in HIV infection.

This evidence showing an increased effect of ageing by HIV disease stage on motor function and episodic memory performance has specific neuroanatomical referents. For motor function, the neuroanatomical referent is the basal ganglia, which is affected early in HIV brain infection.[4] Of note, parkinsonism has been reported in individuals with HIV and is related to lowered dopamine concentrations in the cerebrospinal fluid and brain tissue.[25] For episodic memory, the neuroanatomical referent is the hippocampus, in which dysfunction and atrophy occur independently with both ageing[26] and HIV infection[27] and with a deleterious interaction between ageing and HIV infection.[28] Several studies have shown these regions to be of particular concern for damage in the setting of older individuals with HIV infection. The authors of a critical review[29] reported that HIV infection was associated with greater than age-related brain atrophy in the basal ganglia and hippocampus. This finding has been supported by those from a study[30] of brain morphometry in an older cohort with HIV. According to the critical review, functional MRI studies showed evidence for greater effects than those expected from ageing alone in individuals with HIV by brain region, although these effects varied when other neuroimaging techniques were used. In another neuroimaging study,[31] longitudinal analysis showed evidence for a greater-than-expected effect of ageing on selected brain regions over a period of 6 months to 8 years within a cohort of individuals with HIV infection who were in good overall health and did not have clinical evidence for dementia. Another relevant study[32] showed age-dependent changes in brain activation in response to tasks of increasing attentional load that differed among three groups, with HIV infection and ageing acting synergistically (ie, interactively) to exacerbate brain activation abnormalities in different brain regions. These results suggest that a neurologically adaptive mechanism in the attention network could be operating to compensate for decreased neural efficiency. Along a separate line, the protective role of neurocognitive reserve in older individuals with HIV infection also merits further study.[33]

In summary, our results show evidence for region-specific increases of deleterious ageing effects with worsening systemic stage of HIV infection. These results are supported by other studies in which changes in brain tissue were examined by neuroimaging. Our neuropsychological results provide evidence that there is a differential worsening of the deleterious effect of ageing on neurocognitive function when patients have a higher level of systemic HIV disease progression, most specifically on the neurocognitive domains of episodic memory and motor performance. That is, the magnitude of the impairment in these domains is greater than the sum of the independent, negative effects of age and HIV disease stage. Our results support the general clinical need to screen HIV-infected individuals for HIV-associated neurocognitive disorders and to do so particularly intensively for older HIV-infected individuals, ideally with tests sensitive to deficits in the episodic memory and motor domains.

Contributors

KG conceived the study design, was involved in data analysis and interpretation and preparation of the tables and figure, and led the writing of the Article. ENM was involved in study design; data collection, analysis, and interpretation; and writing of the Article. CC was involved in study design, data analysis and interpretation, and writing of the Article. SR was involved in data analysis and interpretation, and preparation of the figure. JTB was involved in study design, data collection and interpretation, and writing of the Article. EM was involved in data interpretation and writing of the Article. OAS was involved in study design and data collection. DGO was involved in the study design, data interpretation, and writing of the Article. NCS was involved in data collection and interpretation and writing of the Article.

Declaration of interests

EM is the author of the CalCAP Reaction Time program used in this study. All other authors declare no competing interests.

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