DOI: 10.1111/hiv.12980
HIV Medicine (2020)

ORIGINAL RESEARCH

Cognitive ageing is premature among a community sample of optimally treated people living with HIV

HL Aung [1,2,3] M Bloch [3,4] T Vincent,[4] D Quan,[4] A Jayewardene [4,5] Z Liu [6] TM Gates [1] B Brew [1,3,7] L Mao [8] and LA Cysique [1,2,3]

[1]*Department of Neurology and HIV Medicine, St Vincent's Hospital and Peter Duncan Neurosciences Unit, St Vincent's Centre for Applied Medical Research, Sydney, NSW, Australia,* [2]*Neuroscience Research Australia, Sydney, NSW, Australia,* [3]*Faculty of Medicine, UNSW, Sydney, NSW, Australia,* [4]*Holdsworth House Medical Practice, Sydney, NSW, Australia,* [5]*Charles Perkins Centre, University of Sydney, Sydney, NSW, Australia,* [6]*Stats Central, UNSW, Sydney, NSW, Australia,* [7]*Faculty of Medicine, University of Notre Dame, Sydney, NSW, Australia and* [8]*Centre for Social Research in Health, UNSW, Sydney, NSW, Australia*

Objectives

Evidence of premature cognitive ageing amongst people living with HIV (PLHIV) remains controversial due to previous research limitations including underpowered studies, samples with suboptimal antiretroviral access, varying rate of virological control, high rate of AIDS, over-representation of non-community samples, and inclusion of inappropriate controls. The current study addresses these limitations, while also considering mental health and non-HIV comorbidity burden to determine whether PLHIV showed premature cognitive ageing compared with closely comparable HIV-negative controls.

Methods

This study enrolled 254 PLHIV [92% on antiretroviral therapy; 84% with HIV RNA < 50 copies/mL; 15% with AIDS) and 72 HIV-negative gay and bisexual men [mean (SD) age = 49 (10.2) years] from a single primary care clinic in Sydney, Australia. Neurocognitive function was evaluated with the Cogstate Computerized Battery (CCB) at baseline and 6 months after. Linear mixed-effects (LME) models examined main and interaction effects of HIV status and chronological age on the CCB demographically uncorrected global neurocognitive *z*-score (GZS), adjusting for repeated testing, and then adjusting sequentially for HIV disease markers, mental health and comorbidities.

Results

HIV status and age interacted with a lower GZS ($\beta = -0.43$, $P < 0.05$). Higher level of anxiety symptoms ($\beta = -0.11$, $P < 0.01$), historical AIDS ($\beta = -0.12$, $P < 0.05$) and historical HIV brain involvement ($\beta = -0.12$, $P < 0.05$) were associated with lower GZS.

Conclusions

We found a robust medium-sized premature ageing effect on cognition in a community sample with optimal HIV care. Our study supports routine screening of cognitive and mental health among PLHIV aged ≥ 50 years.

Keywords: cognitive ageing, HIV, premature ageing

Accepted 17 September 2020

Correspondence: Dr Htein Linn Aung, Peter Duncan Neurosciences Unit, St Vincent's Centre for Applied Medical Research (AMR), Level 8, Lowy Packer Building, 405 Liverpool St, Darlinghurst NSW 2010, Australia.
Tel: +61 2 8382 4930; fax: +61 2 8382 4901; e-mail: h.aung@amr.org.au

Introduction

Globally, people living with HIV (PLHIV) are ageing at an unprecedented rate [1] because of the accelerated decrease in AIDS-related morbidity and general mortality afforded by combination antiretroviral therapy (cART) [2,3]. In Australia, the number of older PLHIV increased from 5564 in 2008 to 11 361 in 2017, with a dramatic increase in the proportion aged > 50 years from 5% to

46% between 1986 and 2017 [4]. Within the next 20–30 years, > 70% of the Australian PLHIV will be aged 50+ years [5].

With ageing, neurological and psychological health is becoming increasingly relevant for PLHIV. First, cognitive ageing may be premature among PLHIV because of persistent immune activation and inflammation along with an increased prevalence of other age-related comorbidities [especially cardiovascular diseases (CVD) and stroke], all of which are known risk factors for dementia in the general population [6]. Second, age is the number one risk factor for cognitive decline and dementia in the general population [7] and even mild evidence of premature cognitive ageing could have serious public health implications for the ageing HIV epidemic. Third, PLHIV carry a significant mental health burden such as anxiety and depression [8,9], which are also known risk factors for cognitive decline and dementia [10,11].

In our recently completed systematic review, we found that previous HIV and cognitive ageing studies have identified signals for premature neurocognitive ageing [12]. Premature cognitive ageing was defined as lower cross-sectional neurocognitive performance amongst PLHIV compared with age-matched HIV-negative people (i.e. there is significant interaction effect of HIV and age on cross-sectional continuous neurocognitive performance). However, findings of this abnormal pattern of cognitive ageing have been inconsistent across studies due to certain methodological limitations. These included small sample size, lack of age-matched HIV-negative controls, clinical heterogeneity and suboptimal representation of PLHIV aged ≥ 50 years.

Furthermore, there was an ascertainment bias towards cohorts that included a high proportion of cases with historical AIDS, and non-community samples with disparities in cART access and degree of virological control [13,14]. Community samples are healthier and more representative of the current HIV epidemic, especially in countries where ART is subsidized [15].

Our review [12] also demonstrated that only a minority of cognitive ageing studies adjusted for the effects of age-related comorbidities and other comorbidities that may affect neurocognitive performance. Indeed, in addition to the effect of chronological age, an array of other factors such as HIV clinical characteristics (e.g. clinical stage, nadir and current CD4 counts and HIV viral load), previous HIV brain involvement [i.e. historical central nervous system (CNS) opportunistic infection (OI) and HIV-associated neurocognitive disorder (HAND)], age-related comorbidities, mental health burden and lifestyle factors will complicate the degree to which premature ageing can be ascribed [16,17].

The present study sought to assess the evidence of premature cognitive ageing amongst PLHIV addressing the previous studies' limitations. For this, we tested whether there is an interaction effect of HIV and age on neurocognitive performance in a community sample of HIV-positive bisexual and gay men with low AIDS rate and high ART access and a cohort of age- and lifestyle-matched HIV-negative people. All participants were recruited from a single primary care practice in Sydney, Australia. Half of the participants were aged ≥ 50 years.

Methods

Participants

Details of the study cohort enrolled from a primary care clinic in Sydney, Australia, have been reported previously [18,19]. Briefly, the recruitment and baseline assessment took place between October 2011 and October 2012. Participants were reassessed 6 months later to assess any potential short-term cognitive changes. A total of 326 participants (254 HIV-positive and 72 HIV-negative) participated in this study and 266 participants (208 HIV-positive and 58 HIV-negative) attended for follow-up. The attrition rate was 18%.

Participants included allcomers except for evidence of alcohol or substance intoxication at the time of assessment. These relaxed criteria of inclusion were designed to improve the study's representativeness and the generalizability of results to similar primary care cohorts in Australia and other countries with cART access and universal health coverage. Nevertheless, we note that in this community sample, no participants had a history of non-HIV dementia, major traumatic brain injury (TBI) or other advanced neurological disorder, and no participants had a psychiatric disorder on the psychotic axis. Milder forms of neurological and psychiatric conditions were recorded, including mild TBI, non-advanced multiple sclerosis, non-advanced Parkinson's disease and minor stroke. In the HIV-positive participants, a history of HIV brain involvement (treated CNS OI, HAND) was not set as an exclusion criterion and recorded. Medical history, psychiatric/psychological, and alcohol/drug use history were also carefully recorded (see details later).

Procedures

Demographic and medical inventories

Procedures have been reported in detail in previous publications [18,19]. Briefly, the visit included medical and demographic inventories. The following conditions were

recorded: lifetime depression, history of anxiety or panic attack, history of non-HIV neurological disorders, history of HIV-related neurological disorder (past treated HAND or CNS OI), coinfections (treated syphilis and treated HCV), vascular risk factors and conditions (hypertension, angina, myocardial infarct, vascular disease and coronary artery disease, smoking and diabetes). HIV route of transmission, date of diagnosis, cART treatment, and cART duration were also collected from the HIV-positive participants. HIV-related medical and laboratory information such as current CD4 and CD8 levels, nadir CD4 count, plasma HIV RNA viral load result and HIV clinical stage were measured within a week of the assessment.

Mood and functional assessments

Current mood was evaluated with a 21-item depression, anxiety, stress scale (DASS-21) [20]. Standard Australian cut-offs were applied to determine clinically relevant mood changes: scores of > 13 in the depression component, > 9 in anxiety component, and > 18 in stress component were defined as having clinically significant levels of depressive, anxiety or stress symptoms. The Mini-International Neuropsychiatric Interview alcohol and substance use sections [21] were administered to determine the presence of any alcohol use disorder (AUD) or substance use disorder (SUD). Instrumental activities of daily living (IADLs) were measured with a modified version of the Lawton and Brody scale [22].

Neurocognitive assessment

Neurocognitive performance was assessed using the Cogstate Computerized Battery (CCB) [23]. The CCB is a cognitive screening tool that can be conducted by non-specialists and covers the cognitive domains commonly affected by HAND [19]. Details of the assessment have also been reported before [18,19]. The CCB version for this study covered information processing speed, attention and working memory, verbal learning and memory [24], and included six measures: detection speed, identification speed, one back accuracy, two back accuracy, international shopping list (ISL) task learning total correct and ISL task delayed recall total correct.

For our primary aim analyses on the age effect on cognition, we used the age-uncorrected global *z*-score (GZS). For this, raw scores were converted to *z*-scores centred to the mean age of the entire sample using norms provided by Cogstate for Australians of the same education level and sex as the current sample [18]. We then applied a practice effect correction on the individual tasks on the 6-month age-uncorrected *z*-scores, where the practice effect was extracted from the same normative sample. Both baseline and 6-month follow-up individual age-uncorrected *z*-scores were then averaged into a GZS. A low GZS indicates lower performance.

While not the main aim of our study, we determined the CCB-based HAND prevalence at baseline and follow-up for future references. Rate of neurocognitive impairment (NCI) was also determined in the HIV-negative controls. For this, raw scores were converted to age- and gender-standardized *z*-scores [18]. For the follow-up, a practice effect correction was included. These z-scores were then converted to deficit scores ranging from 0 to 5 as follows: 0 (z-score ≥ -1.0); 1 (z-score < -1.0 to -1.5); 2 (z-score < -1.5 to -2.0); 3 (z-score < -2.0 to -2.5); 4 (z-score < -2.5 to -3.0); and 5 (z-score < -3.0). A global deficit score (GDS) was computed by averaging the six individual tasks' deficit scores. A high GDS indicates greater impairment level. Based on our previous work with the CCB and its sensitivity/specificity to HAND against standard neuropsychological testing, we used a GDS cut-off of > 0.5 rather than ≥ 0.5 to define NCI [18,19]. HAND was classified according to the methods developed in our previous study [18]: asymptomatic neurocognitive impairment (ANI), GDS > 0.5 and no IADL decline; mild neurocognitive disorder (MND), GDS > 0.5–1.5 and mild to moderate IADL decline; HIV-associated dementia (HAD), GDS ≥ 1.5 and severe IADL decline. In the HIV-negative controls, NCI was rated as mild NCI, GDS > 0.5 and no IADL decline; moderate NCI, GDS > 0.5–1.5 and mild-to-moderate IADL decline; severe NCI, GDS ≥ 1.5 and severe IADL decline.

Statistical analysis

To estimate the effect of HIV-related neurological conditions and other neurological conditions, two categorical variables were created: HIV neurological involvement history coded as 'yes' or 'no' (previous history of CNS OI or previous history of HAND) and non-HIV-related neurological history (history of head injury, history of stroke, any history of neurological/CNS conditions such as multiple sclerosis and Parkinson's disease). A categorical variable termed CVD was created and rated 'yes' if the participant had any history of hypertension, angina, myocardial infarct, vascular disease and coronary artery disease *vs*. 'no'. HIV-negative participants were coded as 'no' for CDC stage C and HIV-related neurological history and '0' for HIV duration to be able to control and assess the effect of these variables in the analysis with HIV-negative controls.

To assess our primary aim, the study participants were divided *a priori* into four groups by age category and HIV status (younger, < 50 years; older, ≥ 50). This cut-off of 50 years old was used based on previous evidence that

this age represents a clinically meaningful cut-off in HIV and ageing research [25]. Student's *t*-test, ANOVA and χ^2 tests were used to compare the mean and group differences of demographics, HIV-related characteristics and comorbidities. These variables were also compared between those who came back for the 6-month follow-up and those who did not (Tables S1 and S2). HIV-positive participants who came back for follow-up were more likely to be Australian of Anglo-English-speaking background ($P < 0.001$), have longer duration living with HIV ($P = 0.02$), longer duration of ART ($P = 0.04$), and higher proportion of HIV-related neurological involvement history compared with those who did not ($P = 0.004$). Among HIV-negative participants, there was no significant difference in terms of demographic and clinical characteristics between those who came back at the 6-month follow-up and those who did not.

We then used a LME model to assess the main and interaction effects of age and HIV status on the GZS. All the baseline and 6-month follow-up visits were included in the analysis. The model was built using the restricted maximum likelihood method. Variables were fitted into the model through forward selection. Subjects were included as a random effect. Fixed linear effects included were the individual terms of HIV status and age (continuous) and their interaction.

To determine the effects of covariates while selecting the best model fit, we included all the covariates that were significantly different among the four HIV/age groups. All the other relevant covariates, such as lifetime history of depression, history of mental illness and non-HIV-related neurological history, were also incorporated into the model in addition to the primary predictors and their interactions. Next, covariates with a $P > 0.3$ were taken out of the model step by step while assessing the model's fitness with the Akaike information criterion (AIC). The variables fitted into the model were adjusted until there was no significant decrease in the AIC value. A total of nine covariates remained in the final model in addition to the three primary predictors and their interaction. The residual plots of the final model were examined to check whether any model broke the assumption of the linearity, normality and homoscedasticity. No deviation was detected. Collinearity between the variables in the final model was assessed with the variance inflation factor (VIF). The VIF was < 5 for all the tested variables except the interaction terms. A similar LME model was also conducted, restricting only to the HIV-positive participants and including all the HIV biomarkers (e.g. CD4, viral load and duration of cART). The analyses were conducted with the lme4 package in R statistical software [26]. For all the analyses, $P < 0.05$ was set as the statistically significant threshold, while effect sizes and confidence interval (CI) were reported to aid in the interpretation of any statistically significant result.

Results

Table 1 presents the demographic and clinical characteristics in the four HIV/age study groups. Younger HIV-positive self-reported the highest anxiety symptoms at baseline. They also had the highest prevalence of AUD/SUD at both baseline and follow-up compared with all other groups. The proportion with treated syphilis, CVD and low glomerular filtration rate (i.e. eGFR < 60) was at its highest amongst older HIV-positive participants *vs.* all other groups. Diabetes was the most prevalent amongst older HIV-negative people.

Table 2 presents the HIV disease characteristics between younger HIV-positive and older HIV-positive participants. Older HIV-positive participants had lower nadir and current CD4 T cell counts, higher ART uptake, and longer HIV duration compared with the younger HIV-positive participants at $P < 0.05$.

Table 3 presents the HIV/age group comparisons for the age-uncorrected GZS. The older HIV-positive participants had the lowest performance on the GZS at both baseline and follow-up compared with all other groups. CCB-based HAND prevalence (demographically corrected plus practice effect-corrected at follow-up) was compared between HIV-negative and HIV-positive participants and is presented in Tables S3 and S4. HAND/NCI prevalence was significantly higher among HIV-positive than among HIV-negative participants at both baseline (42% *vs.* 22%) and follow-up (43% *vs.* 23%) ($P < 0.05$).

Table 4 presents the results for the final LME model. The iterative model building and comparisons are provided in Tables S5 and S6. Neither HIV status ($\beta = 0.27$) nor age ($\beta = -0.13$) main effect was significantly associated with the GZS at $P < 0.05$. However, their interaction was significantly associated with a lower GZS ($\beta = -0.43$, 95% CI: −0.85 to −0.02, $P < 0.05$) on GZS. Three covariates were significantly associated with lower GZS across the study period. These included having a history of HIV brain involvement ($\beta = -0.12$, 95% CI: −0.22 to −0.01, $P < 0.05$); having been diagnosed with CDC stage C ($\beta = -0.12$, 95% CI: −0.22, −0.03, $P < 0.05$) and having higher anxiety score ($\beta = -0.11$, 95% CI: −0.19 to −0.04, $P < 0.01$). By contrast, current SUD was associated with higher GZS in an unexpected direction ($\beta = 0.07$, 95% CI: 0.004–0.14).

Figure 1 presents the interaction effect of HIV and age on cross-sectional GZS predicted by the regression model. It is evident that neurocognitive performance deteriorated

Table 1 Demographic and clinical characteristics

Variable	Young HIV-negative (38)	Old HIV-negative (34)	Young HIV-positive (138)	Old HIV-positive (116)	All (326)	*P*
Demographics						
Ethnicity						
Anglo-ESB-Australian	34 (89%)	31 (91%)	114 (83%)	106 (91%)	285 (87%)	0.16
Other	4 (1%)	3 (9%)	24 (7%)	10 (9%)	41 (13%)	
Age	38.5 (7.9)	58.7 (6)	42.6 (5.7)	57.4 (6.4)	49 (10.2)	0.29
Education						
Above secondary school	27 (71%)	28 (82%)	103 (75%)	73 (63%)	231 (71%)	0.08
Below secondary school	11 (29%)	6 (18%)	35 (25%)	43 (37%)	95 (29%)	
Comorbidities						
DASS anxiety (baseline)						
Yes	7 (18%)	3 (9%)	45 (32%)	26 (22%)	81 (25%)	0.02
No	31 (82%)	31 (91%)	93 (68%)	90 (78%)	245 (75%)	
DASS stress (baseline)						
Yes	7 (18%)	2 (6%)	30 (22%)	16 (14%)	55 (17%)	0.11
No	31 (82%)	32 (94%)	108 (78%)	100 (86%)	271 (83%)	
DASS depression (baseline)						
Yes	11 (29%)	3 (9%)	39 (28%)	27 (23%)	80 (25%)	0.11
No	27 (71%)	31 (91%)	99 (72%)	89 (77%)	246 (75%)	
DASS depression (month 6)						
Yes	6 (22%)	4 (13%)	29 (27%)	21 (21%)	60 (23%)	0.43
No	21 (78%)	27 (87%)	80 (73%)	77 (79%)	205 (77%)	
DASS anxiety (month 6)						
Yes	7 (26%)	2 (6%)	27(25%)	23 (23%)	59 (22%)	0.16
No	20 (74%)	29 (97%)	82 (75%)	75 (77%)	206 (78%)	
DASS stress (month 6)						
Yes	5 (19%)	3 (10%)	21 (19%)	12 (12%)	41(15%)	0.4
No	22 (81%)	28 (90%)	88 (81%)	86 (88%)	224 (85%)	
Non-HIV neurological history*						
Yes	6 (16%)	7 (21%)	34 (25%)	31 (27%)	78 (24%)	0.55
No	32 (84%)	27 (79%)	104 (75%)	73 (66%)	248 (76%)	
Current AUD (baseline)						
Yes	1 (3%)	3 (9%)	17 (12%)	18 (7%)	29 (9%)	0.22
No	37 (97%)	31 (91%)	121(88%)	108 (93%)	297 (99%)	
Current SUD (baseline)						
Yes	2 (5%)	0 (0%)	39 (28%)	12 (10%)	53 (16%)	< 0.0001
No	36(95%)	34 (100%)	99 (72%)	104 (90%)	273 (84%)	
Current AUD (month 6)						
Yes	5 (19%)	1 (3%)	11 (10%)	2 (2%)	19 (7%)	0.01
No	22 (81%)	30 (97%)	98 (90%)	97 (98%)	247 (93%)	
Current SUD (month 6)						
Yes	2 (7%)	0 (0%)	20 (18%)	6 (6%)	28 (11%)	0.004
No	25 (93%)	31 (100%)	89 (82%)	93 (94%)	238 (89%)	
Smoking						
Yes	9 (24%)	5 (15%)	33 (24%)	24 (21%)	71 (22%)	0.68
No	29 (76%)	29 (85%)	105 (76%)	92 (79%)	255 (78%)	
Total cholesterol						
High (> 5.5 mmol/L)	6 (35%)	11 (46%)	36 (31%)	35 (37%)	88 (35%)	0.56
Low	11 (65%)	13 (54%)	79 (69%)	60 (63%)	163 (65%)	
eGFR rate (low)						
Yes (< 60 mL/min/1.73m2)	0 (0%)	0 (0%)	4 (3%)	12 (12%)	16 (6%)	0.02
No	17 (100%)	20 (100%)	113 (97%)	87 (88%)	237 (94%)	
Hepatitis C RNA-positive						
Yes	0 (0%)	0 (0%)	4 (3%)	5 (5%)	9 (4%)	0.59
No	22 (100%)	9 (100%)	121 (97%)	92 (95%)	244 (96%)	
CVD†						
Yes	5 (13%)	15 (44%)	19 (14%)	53 (46%)	92 (28%)	< 0.0001
No	33 (87%)	19 (56%)	119 (86%)	63 (54%)	234 (72%)	
Diabetes						
Yes	0 (0%)	4 (12%)	3 (2%)	9 (8%)	16 (5%)	0.02
No	38 (100%)	30 (88%)	135 (98%)	107(92%)	310 (95%)	
History of lifetime depression						
Yes	12 (32%)	14 (41%)	61 (44%)	44 (38%)	131 (40%)	0.5
No	26 (68%)	20 (59%)	77 (56%)	72 (62%)	195 (60%)	

Table 1 (*Continued*)

Variable	Young HIV-negative (38)	Old HIV-negative (34)	Young HIV-positive (138)	Old HIV-positive (116)	All (326)	*P*
History of anxiety or panic attack‡						
Yes	4 (11%)	3 (9%)	24 (17%)	12 (10%)	43 (13%)	0.29
No	34 (89%)	31 (91%)	114 (72%)	104 (90%)	283 (87%)	
Treated syphilis						
Yes	1 (3%)	8 (24%)	35 (25%)	35 (30%)	79 (24%)	0.007
No	37 (97%)	26 (76%)	103 (75%)	81 (70%)	247 (76%)	

Data are presented as *n* (%) for categorical variables and mean (SD) for continuous variables. χ^2 test was used for categorical and Student's *t*-test and ANOVA were used for continuous variables. For variables that are not mentioned either month 0 or 6 are month 0 data.
AUD, alcohol use disorder; CVD, cardiovascular disease; DASS, Depression Anxiety Stress Scale; eGFR, estimated glomerular filtration rate; ESB, English-speaking background, PTSD, post-traumatic stress disorder; SUD, substance use disorder.
*Minor stroke or minor traumatic brain injury (TBI), non-advanced multiple sclerosis and non-advanced Parkinson's disease (no dementia, major TBI, or any other advanced neurological conditions)
†Any history of hypertension, angina, myocardial infarct, vascular disease and coronary artery disease.
‡Does not include any psychiatric conditions on the psychotic axis.

with increasing age at a significantly higher rate among HIV-positive than among HIV-negative participants.

The final model that was restricted to the HIV-positive participants is presented in Table 5. Older age ($\beta = -0.32$, 95% CI: −0.45 to −0.19, $P < 0.001$) was associated with lower GZS. Having a history of non-HIV neurological condition ($\beta = -0.11$, 95% CI: −0.22 to −0.001, $P < 0.05$), having been diagnosed with CDC stage C ($\beta = -0.10$, 95% CI: −0.21 to −0.02, $P < 0.05$), and having a higher anxiety score ($\beta = -0.17$, 95% CI: −0.25 to −0.08, $P < 0.001$) were also associated with a lower GZS. In addition, compared with baseline testing, cognitive testing at 6 months was negatively associated with lower GZS among HIV-positive participants ($\beta = -0.05$, 95% CI: −0.11 to −0.03, $P < 0.05$). On the other hand, duration of ART ($\beta = 0.19$, 95% CI: 0.004–0.37, $P < 0.05$) was associated with a higher GZS.

Discussion

The current study aim was to identify whether there is any evidence of premature cognitive ageing among a community sample of well-treated HIV-positive participants with low historical AIDS *vs.* demographically, geographically and lifestyle-comparable HIV-negative controls. Importantly, younger (< 50 years) and older (≥ 50 years) age groups were evenly represented across the study population.

The main study finding was evidence of premature cognitive ageing. Essentially, the HIV and age interaction effect size was the largest (medium effect size) compared with all the variables that were significantly associated with neurocognitive performance. Several factors were also independently associated with neurocognitive performance, although they all had small effect sizes. In the analyses including both HIV-negative and HIV-positive samples, a higher degree of anxiety symptoms, a history of HIV-related brain involvement, and a past CDC stage C diagnosis were associated with lower neurocognitive performance, while SUD was associated with higher cognitive performance. In the analyses restricted to the HIV-positive sample, in addition to age, which has a small to medium effect size, a history of non-HIV-related neurological disorder, a past CDC stage C diagnosis and a shorter duration of ART were associated with poorer neurocognitive performance, all representing small effect sizes.

The HAND CCB-based prevalence in the treated HIV-positive sample in the current study was in line with previously published studies (in independent samples) using the CCB and/or standard neuropsychological testing [27]. This prevalence rate is also similar to international cohorts which have used appropriate demographically corrected norms and reported mild-to-moderate degree of comorbidity burden [28]. The NCI rate amongst HIV-negative participants was higher than in a typical control sample (i.e. 16%) [29], because all HIV-negative comers were included in this study, and some had NCI risk factors, including a slightly higher rate of diabetes. This further corroborates that the CCB is a sensitive instrument to cognitive difficulties [30].

Our study supports and extends previous reports of premature cognitive ageing amongst PLHIV [31,32]. Goodkin *et al.* [31] identified premature cognitive ageing in a longitudinal cohort of 2278 HIV-positive and 2808 HIV-negative participants (average baseline age = 37.2 years) from the Multicenter AIDS Cohort Study (MACS) who had been followed up 6-monthly for an average duration of 7.4 years. More specifically, this study found a negative interaction effect between chronological age and CDC HIV clinical disease stage on motor function and episodic memory that were measured

Table 2 HIV disease characteristics

Variable	Younger HIV-positive (138)	Older HIV-positive (116)	All (326)	*P*
Mode of HIV transmission				
Homosexual	128 (92%)	108 (93%)	236 (93%)	0.91
Heterosexual	3 (2%)	1 (1%)	4 (2%)	0.40
Intravenous drug use	2 (1%)	0 (0%)	2 (0.8%)	0.19
Blood transfusion	2 (1%)	3 (3%)	5 (2%)	0.52
Others	7 (4%)	4 (3%)	11 (4%)	0.53
CDC stage C (baseline)				
Yes	19 (14%)	20 (17%)	39 (15%)	0.44
No	119 (86%)	96 (83%)	215 (85%)	
CDC stage C (month 6)				
Yes	18 (17%)	19 (20%)	37 (18%)	0.63
No	87 (83%)	77 (80%)	164 (82%)	
CD4 cell count (baseline) (copies/mL)	667 (278)	590 (238)	632 (263)	0.02
CD4 cell count (month 6) (copies/mL)	689 (269)	608 (219)	650 (249)	0.02
Nadir CD4 cell count (copies/mL)	346 (210)	278(169)	315 (195)	0.005
Nadir CD4 cell count (< 200) (copies/mL)				
Yes	33 (24%)	42 (37%)	75 (30%)	0.03
No	102(76%)	71 (63%)	173 (70%)	
CD8 cell count (copies/mL)	986 (531)	982 (501)	984 (517)	0.95
Viral load (< 200 copies/mL) at baseline				
Yes	110 (80%)	101 (88%)	211 (84%)	0.11
No	27 (20%)	14 (12%)	41 (16%)	
Viral Load (< 200 copies/mL) at month 6				
Yes	92 (89%)	90 (95%)	172 (92%)	0.16
No	11 (11%)	5 (5%)	26 (8%)	
On ART (yes/no)				
Yes	122 (88%)	111 (96%)	233 (92%)	0.04
No	16 (12%)	5 (4%)	21 (8%)	
Duration diagnosed with HIV (years)	11.2 (7.7)	17.4 (8.4)	14.05 (8.6)	< 0.0001
Duration of antiretroviral therapy (years)	7.5 (7.2)	12.1 (7.1)	9.61 (7.5)	< 0.0001
HIV brain involvement history*				
Yes	10 (7%)	22 (19%)	32 (13%)	0.005
No	128 (93%)	94 (81%)	222 (87%)	

Data are presented as *n* (%) for categorical variables and mean (SD) for continuous variables. χ^2 test was used for categorical and Student's *t*-test and ANOVA were used for continuous variables. For variables that are not mentioned either month 0 or 6 are month 0 data.
*Previous history of HIV-associated neurocognitive disorder or central nervous system opportunistic infection that was treated with combination antiretroviral therapy and other appropriate prophylaxis.

through standard neuropsychological testing. Another study conducted by Ding *et al.* [32] in China also detected premature cognitive ageing in their HIV-positive sample. The study included a community cohort of 345 HIV-positive and 345 HIV-negative participants from Taizhou prefecture of the Zhejiang province in China who were over 40 years of age (range: 40–82 years). The study detected an interaction effect of age and HIV status on lower performance in the International HIV Dementia Scale and the Chinese version of the Mini-Mental State Examination for the domains of motor speed, orientation, registration and recall.

Previous studies that did not identify a similar premature cognitive ageing effect were different from the current study in terms of demographic and clinical characteristics of the study participants. Studies that recruited unrepresentatively healthy HIV participants within their country (i.e. highly educated, stable on cART, with undetectable viral load and no neuropsychological confounds) did not observe premature cognitive ageing [33,34]. A Polish study [33] did not observe the premature cognitive ageing effect amongst 91 HIV-positive and 95 HIV-negative participants (age range: 23–75 years) who were recruited from an infectious disease hospital and received standard neuropsychological testing. All the participants in this study were males who were highly educated (≥12 years of education), and clinically stable (no active OI, active syphilis, current hepatitis C coinfection, alcohol or substance abuse, major psychiatric illnesses, liver or renal insufficiency, and had viral load < 60 copies/mL). Towgood *et al.* [34] also did not identify a premature cognitive ageing effect in their study conducted in the UK in a sample of 40 HIV-positive and 42 HIV-negative participants (age range: 20–75 years) who were white/Caucasian, had CD4 count > 200 cells/μL and viral load < 50 copies/mL for 6 months, and did not have any neuropsychological confounds (i.e. history of HIV brain involvement, hepatitis B or C coinfection, any neurological disorder, history of TBI with loss of consciousness for more than 10 min, any history of alcohol or substance abuse, major psychiatric disorder, and any chronic condition related to cardiac, renal or liver). HIV-positive participants in these studies represent the well-controlled elite of the HIV epidemic. While results in similar populations may hold true, they are not representative of the typically multi-comorbid PLHIV and may be substantially biased by a survivor effect [35]. Further, we should remain critical of the conceptual circularity in pre-selecting the healthiest patients from a clinical population with a chronic disease and then determining that those people are mostly cognitively healthy. This

Table 3 Comparisons of Cogstate Computerized Battery global scores across HIV status and age groups

	Younger HIV-negative	Older HIV-negative	Younger HIV-positive	Older HIV-positive	All	*P*
	***N* = 38**	***N* = 34**	***N* = 138**	***N* = 116**	***N* = 326**	
Baseline global *z*-score	−0.6 (0.4)	−0.7 (0.4)	−0.7 (0.5)	−1 (0.7)	−0.80 (0.59)	< 0.0001
	***N* = 27**	***N* = 31**	***N* = 109**	***N* = 99**	***N* = 266**	
Month 6 global *z*-score (practice effect corrected)	−0.5 (0.4)	−0.6 (0.3)	−0.8 (0.5)	−1 (0.7)	−0.84 (0.59)	< 0.0001

Data are presented as mean (SD). ANOVA test was used to compare the global *z*-score between four HIV and age groups at both baseline and follow-up.

Table 4 Linear mixed-effects model results in the entire study population

Variable	*B*	Standard error (SE)	95% CI	*β*	95% CI
Baseline HIV status (positive)	0.39	0.29	−0.18–0.95	0.27	−0.13–0.67
Baseline age (continuous)	−0.008	0.005	−0.02–0.002	−0.13	−0.29–0.03
Time (month 0 *vs.* month 6)	−0.04	0.02	−0.08–0.01	−0.03	−0.07–0.01
HIV brain involvement history (yes)	−0.22*	0.1	−0.43 to −0.02	−0.12	−0.22 to −0.01
Non-HIV neurology history (yes)	−0.09	0.07	−0.22–0.04	−0.07	−0.16–0.03
AUD (yes)	−0.07	0.06	−0.18–0.05	−0.03	−0.08–0.02
SUD (yes)	0.13*	0.06	0.07–0.24	0.07	0.004–0.14
History of mental illness (yes)	−0.13	0.08	−0.29–0.03	−0.08	−0.17–0.02
CDC stage C (yes)	−0.22*	0.09	−0.38 to −0.05	−0.12	−0.22 to −0.03
DASS anxiety score	−0.01**	0.003	−0.02 to −0.004	−0.11	−0.19 to −0.04
Lifetime history of depression (yes)	−0.08	0.06	−0.19–0.04	−0.06	−0.16–0.03
HIV status (positive) * baseline age	−0.01*	0.006	−0.02 to −0.0006	−0.43	−0.85 to −0.02

AUD, alcohol use disorder; CI, confidence interval; DASS, Depression Anxiety Stress Scale; SUD, substance use disorder.
*$P < 0.05$.
**$P < 0.01$.

pre-emptively removes a large number of people with age-related comorbidities, some of whom may be driven by HIV, and selects patients who are the most biologically resilient, making the detection of any age and HIV interaction effect very difficult, if not *a priori* undermining.

Other studies may have failed to detect an effect of premature cognitive ageing because the proportion of participants included who were aged > 50 years was low. In a study in the US [36] that included only participants under 60 (only 13% were over 45), no interaction effect of HIV and age was identified in either the composite or individual standard neuropsychological test scores. Another US study [37] where only 33% of their sample (91 HIV-positive and 184 HIV-negative participants) were older than 50 years, also did not identify the premature ageing effect in the executive function they tested.

A history of HIV brain involvement such as previous history of HAND and treated CNS OI, and previous history of non-HIV neurological disorders (e.g. mild TBI and stroke) were associated with poorer neurocognitive performance in the current study. These results bring cumulative evidence with previous studies [38,39] that any history of neurological insult can have lasting consequences on one's cognitive health. As stated in Frascati criteria for HAND diagnosis [40], a history of HIV and non-HIV-related neurological conditions could have a profound impact on the long-term neurocognitive health in PLHIV and needs to be accounted for in the diagnostic process. Our study showed that the effect of such conditions on neurocognitive performance was small overall, but this was probably because only 13–24% of them had previous HIV or non-HIV neurological disorder.

In the current study, we found that anxiety symptoms rather than depressive symptoms were associated with poorer neurocognitive function. This result may be due to the fact that anxiety and depressive symptoms were correlated ($r = 0.66$, $P < 0.0001$), and that the iterative selection for a final best-fit model retained the stronger of the two. Nevertheless, previous studies have also identified an association between anxiety and cognitive decline and impairment in PLHIV. Malaspina *et al.* [41] reported that lower symptoms of depression and anxiety were associated with a higher chance of successful cognitive ageing (defined as lack of NCI) among a sample of 74 HIV-positive people. Anxiety has been less studied than depression in PLHIV [9]. It would be important to more systematically include anxiety assessment in neuro-HIV studies, as higher anxiety symptoms have been associated with lower ART adherence, as shown in a study conducted by Servellen *et al.* [42] among 182 PLHIV who were recruited from community-based clinics in Los

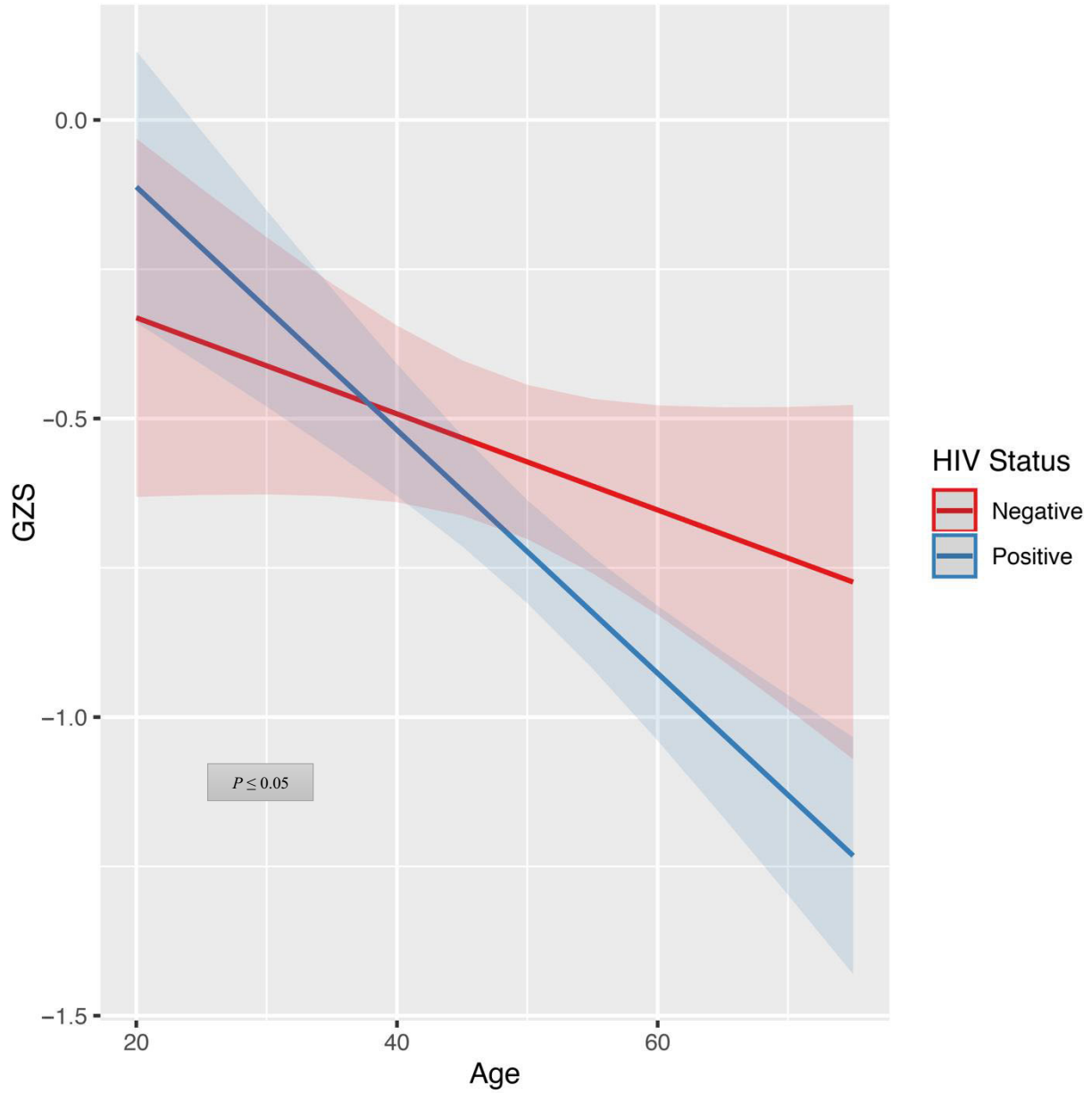

Fig. 1 Global *z*-score predicted by the linear mixed-effects model for the HIV-negative and HIV-positive groups by age. The interaction effect of HIV and age on global *z*-score predicted by the linear mixed-effects model presented. The effect size β is −0.43 (95% confidence interval: −0.85 to −0.02) and it is statistically significant at $P \leq 0.05$.

Angeles, USA [43]. The clinical implication of our results is that provision of regular mental health support, including for anxiety, remains critical in ageing PLHIV [38,44,45]. Importantly, stress management and cognitive behavioural therapies have been reported to be effective in alleviating anxiety symptoms among PLHIV [46].

Our finding that having CDC stage C was negatively associated with neurocognitive function represents cumulative evidence that AIDS is a risk factor for NCI [47]. Heaton *et al.* [48] also showed, when focusing on CDC stage, that NCI rate increased with the advancing CDC stage in both the pre-cART and cART cohorts. CDC stage C implies that PLHIV may have experienced high viral load and/or low nadir CD4 and/or an AIDS-defining illness. As our analysis also included nadir and current CD4 counts, as well as viral load, it suggests that the CDC stage may be the strongest predictor for NCI.

Table 5 Linear mixed-effects model results in the HIV-positive sample

Variable	*B*	SE	95% CI	*β*	95% CI
Baseline age	−0.02***	0.004	−0.03 to −0.01	−0.30	−0.42 to −0.18
Time (month 0 *vs.* month 6)	−0.07*	0.03	−0.6 to −0.1	−0.05	−0.11 to −0.003
Non-HIV neurology history	−0.17*	0.08	−0.32 to −0.02	−0.12	−0.23 to −0.001
SUD (yes)	0.124	0.07	−0.01–0.26	0.07	−0.008–0.15
CDC stage C (yes)	−0.18*	0.09	−0.35 to −0.03	−0.11	−0.22–0.02
Duration of ART (months)	0.001*	0.001	0.00009–0.003	0.2	0.01–0.38
Duration of HIV diagnosis (months)	−0.001	0.001	−0.002–0.0002	−0.19	−0.37–0.03
CD4 count	−0.0002	0.0001	−0.0005–0.000004	−0.09	−0.19–0.002
Viral load < 200 (yes)	−0.11	0.08	−0.3–0.05	−0.05	−0.12–0.02
DASS anxiety score	−0.02***	0.004	−0.02 to −0.008	−0.17	−0.28 to −0.09

ART, antiretroviral therapy; CI, confidence interval; DASS, Depression Anxiety Stress Scale; SUD, substance use disorder.
*$P < 0.05$.
***$P < 0.001$.

Unexpectedly, current SUD, which was assessed with the Mini International Neuropsychiatric Interview alcohol and substance use sections, was associated with higher neurocognitive performance. This unexpected result may be explained by the significantly higher representation of younger participants among those with SUD in both HIV-positive (5% among young *vs.* 0% among old) and HIV-negative groups (28% among young people *vs.* 10% among old people) groups. Neurocognitive consequences of substance use depend on the type and dose of the drug, duration that the substance has been used, and whether it is single or polydrug use [49]. It is possible that substance users in this study, while meeting the SUD criteria, remained high-functioning individuals.

Interestingly, we found that longer duration of ART was associated with better neurocognitive performance within the HIV-positive sample when the effects of chronological age and HIV duration were controlled for. This finding supports the evidence that stability on ART is associated with better and/or stable cognitive function [50,51]. Longer duration of ART implies longer disease stability, better viral control and greater immune reconstitution [52]. In all, this means that besides early cART initiation and low AIDS, stability on treatment is another major factor for cognitive health.

A potential explanation for premature cognitive ageing in HIV includes chronic immune activation and immune senescence [53,54]. This mechanism is similar to what has been found in the normal ageing process, so that it has been postulated that the ageing phenomenon starts early among PLHIV [55]. Importantly, there is evidence of chronic neuroimmune activation and associated neuroinflammation despite successful cART and viral suppression [56]. Altogether, ageing and HIV may lead to brain damage via excitotoxicity, mitochondrial dysfunction and oxidative stress [53,57].

Evidence of premature cognitive ageing in a cohort that is optimally treated and is representative of the multiple comorbidities found in a community sample has serious public health ramifications. As age is the number one factor for all-type dementia, it will be very important to follow this kind of cohort into their 70s, the age at which the dementia risk increases exponentially in the general population [6]. More worryingly, at the global level, because PLHIV who have this level of healthcare and cART access, and low AIDS proportion are in the minority [58], it can be expected that in less healthy PLHIV, the premature ageing effect may be even larger, as would be the dementia risk [13].

The implications of premature ageing are not only related to dementia risk. Poor cognitive health negatively affects physical and social functioning in ageing PLHIV [59,60]. This, in turn, impacts quality of life [61]. Poor cognitive health may also lead to less cART adherence [62], potentially reducing the high compliance rate among older PLHIV [63]. Although there is no evidence of this in the current cohort, this is a possibility that cannot be ignored in general. Importantly, cognitive decline remains independently associated with mortality in the cART-treated cohort [64]. A higher mortality rate in people with HAND or other dementia may falsely lead the HIV research community to think that cognitive issues are less represented than they actually are due to a survivor effect [65].

Our study supports that PLHIV aged ≥ 50 years should undergo regular neurocognitive and mental health screen and further investigation when this screen is positive [66]. However, implementation research is urgently needed to enable a realistic clinical translation. For example, while the CCB is a screening option especially for repeated testing [67], we have found that involvement of neuropsychologists for the training of the non-specialist staff is needed as in the current

study. This may represent a new type of work for clinical neuropsychologists in the future, but other options will need to be explored given the resource implications. Lastly, it would also be important to assess the value of cognitive remediation strategies (e.g. SmartBrain [68] and InSight [69]) as a way to prevent further deterioration [70] as pharmaceutical treatment has shown variable efficacy.

Limitations

Our study has a number of limitations. First, the attrition rate was 18% (19% among HIV-negative and 18% among HIV-negative participants) that is higher than previous studies conducted by our research group in cohorts recruited from tertiary healthcare centres [39,71] where the attrition rate was never > 10%. Paradoxically, this could be due to the fact that primary healthcare has a higher number of healthier participants who are busy and have limited amount of time for follow-up visits. However, the level of baseline cognitive performance was similar between those who did and did not attend the follow-up. Finally, the LME model enabled the inclusion of all the visits in the analysis and produced estimates corrected for attrition.

Second, it is very likely that this study embeds some degree of survivor bias among the HIV-positive samples. Some of the older PLHIV who had survived and participated in this study might represent, to some extent, an elite group who are less likely to present with premature or accelerated cognitive ageing. This effect may be further amplified compared with other international locations, or even rural Australian locations, because the study sample is composed of urban and highly educated gay and bisexual men who are receiving the optimal HIV care that is possible in a high-income country. Nevertheless, we included highly comparable HIV-negative gay and bisexual men as controls from the same primary care location which together with the low AIDS prevalence may have partially limited a survivor effect. Third, our study included only men and therefore the findings may not be applicable to female PLHIV. This is, however, representative of the Australian HIV population, which comprises mainly males [4].

Lastly, while the CCB is a useful cognitive computerized battery that was well adapted to the current primary care setting, CCB remains a screening tool that is best used as a composite global cognitive ability score [19]. This means that some cognitive functions were not assessed (e.g. fine motor coordination) and some participants may have declined in one particular cognitive function that was not reflected in the global composite *z*-score. This, however, should be considered against the evidence showing that the CCB is sensitive to HAND and HIV-related cognitive decline [18,19] whilst the composite score is highly reliable on repeated testing [72].

Conclusion

The current study identified premature cognitive ageing in a community sample of well-educated and well-treated HIV-positive gay and bisexual men with low AIDS rate, compared with demographically comparable HIV-negative counterparts. The study was conducted at a primary care clinic in Sydney, Australia, and included allcomers in the HIV-positive group. However, the effects of psychiatric, HIV and non-HIV neurological and other medical comorbidities were adjusted in the analyses. In terms of clinical implications, our study supports regular neurocognitive screening in treated (even if virally suppressed) PLHIV aged ≥ 50 years, particularly in those with a historical CDC stage C, or a history of HIV-related and non-HIV-related neurological conditions. Concurrent monitoring and intervention on mental health burden should also be considered for PLHIV to prevent additional risk to neurocognitive decline. In terms of research implications, it is critical that further resources and research funding be allocated to the follow-up of such cohorts.

Acknowledgements

We thank the treating physicians, nursing staff and study coordinators at Holdsworth House Medical Practice who enrolled patients in this study. We also deeply thank all the patients who participated in this study.

Conflict of interest: BB contributes to the Natalizumab advisory board (Australia, 2006–); Biogen Idec PML advisory board (Natalizumab) International (2008–); GlaxoSmithKline national advisory board (2009–); Merck Serono PML international advisory board (2009–) and contributed to the Biogen Alzheimer's advisory board in 2018. He has received speaker honorarium from Johnson & Johnson in 2018. He has been on the IDS editorial board since 2018; Lancet HIV; and the *Journal for Neurovirology*. MB has served as an advisory board member and/or educational speaker for Gilead Sciences, ViiV Healthcare, Janssen and AbbVie and has received travel assistance from Gilead Sciences. All the other authors declare no conflicts of interest.

Financial disclosure: ViiV Healthcare provided funding to conduct the primary research project, but the authors did not receive any funding support to conduct the analysis for the current manuscript.

Author contributions

MB, TV, DQ AND AJ carried out data collection. The study was conceived by HLA, MB, BB, LM and LAC. HLA, ZL, TMG and LAC developed the methodology. HLA carried out the formal analysis and investigation. HLA prepared the original draft manuscript, while HLA, MB, TMG, BB, LM and LAC reviewed and edited versions. This work was supervised by BB, LM and LAC.

References

1 Autenrieth CS, Beck EJ, Stelzle D, Mallouris C, Mahy M, Ghys P. Global and regional trends of people living with HIV aged 50 and over: Estimates and projections for 2000–2020. *PLoS One* 2018; **13**: e0207005.

2 Palella Jr FJ, Delaney KM, Moorman AC *et al.* Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. *N Engl J Med* 1998; **338**: 853–860.

3 Lima VD, Harrigan R, Bangsberg DR *et al.* The combined effect of modern highly active antiretroviral therapy regimens and adherence on mortality over time. *J Acquir Immune Defic Syndr (1999)* 2009; **50**: 529.

4 Institute K. *HIV, Viral Hepatitis and Sexually Transmissible Infections in Australia: Annual Surveillance Report 2018*. Sydney, Kirby Institute, UNSW Sydney, 2018.

5 Bretaña NA, Gray R, Law M, Guy R. Aging of the HIV population in Australia: a modeling study. *JAIDS J Acquired Immune Defic Syndromes* 2018; **79**: e115-e6.

6 Aung HL, Kootar S, Gates TM, Brew BJ, Cysique LA. How all-type dementia risk factors and modifiable risk interventions may be relevant to the first-generation aging with HIV infection? *Eur Geriatr Med* 2019; **10**: 227–238.

7 Aronson MK, Ooi WL, Geva DL, Masur D, Blau A, Frishman W. Dementia: age-dependent incidence, prevalence, and mortality in the old old. *Arch Intern Med* 1991; **151**: 989–992.

8 Basu S, Chwastiak LA, Bruce RD. Clinical management of depression and anxiety in HIV-infected adults. *AIDS* 2005; **19**: 2057–2067.

9 Watkins CC, Treisman GJ. Neuropsychiatric complications of aging with HIV. *J Neurovirol* 2012; **18**: 277–290.

10 Gulpers B, Ramakers I, Hamel R, Köhler S, Voshaar RO, Verhey F. Anxiety as a predictor for cognitive decline and dementia: a systematic review and meta-analysis. *Am J Geriat Psychiat* 2016; **24**: 823–842.

11 Ownby RL, Crocco E, Acevedo A, John V, Loewenstein D. Depression and risk for Alzheimer disease: systematic review, meta-analysis, and metaregression analysis. *Arch Gen Psychiatry* 2006; **63**: 530–538.

12 Aung HL, Aghvinian M, Gouse H, Robbins RN, Brew BJ, Mao L, Cysique LA. Is There Any Evidence of Premature, Accentuated and Accelerated Aging Effects on Neurocognition in People Living with HIV? A Systematic Review. AIDS and Behavior. 2020 Oct 6:1-44.

13 Cysique LA, Brew BJ. The effects of HIV and aging on brain functions: proposing a research framework and update on last 3 years' findings. *Curr Opin HIV AIDS* 2014; **9**: 355–364.

14 Valcour V, Paul R, Neuhaus J, Shikuma C. The effects of age and HIV on neuropsychological performance. *J Int Neuropsychol Soc.* 2011; **17**: 190–195.

15 Garsia R. HIV treatment, care and support in NSW: a work necessarily still in progress. *NSW Public Health Bull* 2010; **21**: 89–92.

16 Rosenthal J, Tyor W. Aging, comorbidities, and the importance of finding biomarkers for HIV-associated neurocognitive disorders. *J Neurovirol* 2019; **25**: 673–685.

17 Hardy DJ, Vance DE. The neuropsychology of HIV/AIDS in older adults. *Neuropsychol Rev* 2009; **19**: 263.

18 Bloch M, Kamminga J, Jayewardene A *et al.* A screening strategy for HIV-associated neurocognitive disorders that accurately identifies patients requiring neurological review. *Clin Infect Dis* 2016; **63**: 687–693.

19 Kamminga J, Bloch M, Vincent T, Carberry A, Brew BJ, Cysique LA. Determining optimal impairment rating methodology for a new HIV-associated neurocognitive disorder screening procedure. *J Clin Exp Neuropsychol* 2017; **39**: 753–767.

20 Lovibond PF, Lovibond SH. The structure of negative emotional states: comparison of the depression anxiety stress scales (DASS) with the beck depression and anxiety inventories. *Behav Res Ther* 1995; **33**: 335–343.

21 Sheehan DV, Lecrubier Y, Sheehan KH *et al.* The Mini-International Neuropsychiatric Interview (MINI): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiat* 1998; **59**: 22–33.

22 Heaton RK, Marcotte TD, Mindt MR *et al.* The impact of HIV-associated neuropsychological impairment on everyday functioning. *J Int Neuropsychol Soc* 2004; **10**: 317–331.

23 Cysique LA, Maruff P, Darby D, Brew BJ. The assessment of cognitive function in advanced HIV-1 infection and AIDS dementia complex using a new computerised cognitive test battery. *Arch Clin Neuropsychol* 2006; **21**: 185–194.

24 Maruff P, Thomas E, Cysique L *et al.* Validity of the CogState brief battery: relationship to standardized tests and sensitivity to cognitive impairment in mild traumatic brain injury, schizophrenia, and AIDS dementia complex. *Arch Clin Neuropsychol.* 2009; **24**: 165–178.

25 Blanco JR, Jarrín I, Vallejo M *et al.* Definition of advanced age in HIV infection: looking for an age cut-off. *AIDS Res Hum Retroviruses* 2012; **28**: 1000–1006.

26 Bates D, Sarkar D, Bates MD, Matrix L. The lme4 package. *R Package Version* 2007; **2**: 74.

27 Saloner R, Cysique LA. HIV-Associated Neurocognitive Disorders: A Global Perspective. *J Int Neuropsychol Soc*. 2017; **23** (9–10): 860–9.
28 Heaton RK, Clifford DB, Franklin Jr DR *et al*. HIV-associated neurocognitive disorders persist in the era of potent antiretroviral therapy: CHARTER Study. *Neurology* 2010; **75**: 2087–2096.
29 Gates TM, Cysique LA. The chronicity of HIV infection should drive the research strategy of NeuroHIV treatment studies: a critical review. *CNS Drugs* 2016; **30**: 53–69.
30 Maruff P, Lim YY, Darby D *et al*. Clinical utility of the cogstate brief battery in identifying cognitive impairment in mild cognitive impairment and Alzheimer's disease. *BMC Psychol* 2013; **1**: 30.
31 Goodkin K, Miller EN, Cox C *et al*. Effect of ageing on neurocognitive function by stage of HIV infection: evidence from the Multicenter AIDS Cohort Study. *Lancet HIV* 2017; **4** (9): e411–e422.
32 Ding Y, Lin H, Shen W, Wu Q, Gao M, He N. Interaction effects between HIV and aging on selective neurocognitive impairment. *J Neuroimmune Pharmacol* 2017; **12**: 661–669.
33 Gawron N, Choinski M, Szymanska-Kotwica B *et al*. Effects of age, HIV, and HIV-associated clinical factors on neuropsychological functioning and brain regional volume in HIV+ patients on effective treatment. *J Neurovirol* 2018; **25**: 9–21.
34 Towgood KJ, Pitkanen M, Kulasegaram R *et al*. Mapping the brain in younger and older asymptomatic HIV-1 men: Frontal volume changes in the absence of other cortical or diffusion tensor abnormalities. *Cortex A J Devot Study Nerv Syst Behav* 2012; **48**: 230–241.
35 Deeks SG, Lewin SR, Havlir DV. The end of AIDS: HIV infection as a chronic disease. *Lancet* 2013; **382**: 1525–1533.
36 Kissel EC, Pukay-Martin ND, Bornstein RA. The relationship between age and cognitive function in HIV-infected men. *J Neuropsychiatry Clin Neurosci* 2005; **17**: 180–184.
37 Kim S, Miles T, Huber R, Feit MD. Executive cognitive function of older people with HIV/AIDS. *J Hum Behav Soc Environ* 2008; **18**: 48–63.
38 Bonnet F, Amieva H, Marquant F *et al*. Cognitive disorders in HIV-infected patients: are they HIV-related? *AIDS* 2013; **27**: 391–400.
39 Cysique LA, Maruff P, Brew BJ. Variable benefit in neuropsychological function in HIV-infected HAART-treated patients. *Neurology* 2006; **66**: 1447–1450.
40 Antinori A, Arendt G, Becker JT *et al*. Updated research nosology for HIV-associated neurocognitive disorders. *Neurology* 2007; **69**: 1789–1799.
41 Malaspina L, Woods SP, Moore DJ *et al*. Successful cognitive aging in persons living with HIV infection. *J Neurovirol* 2011; **17**: 110–119.
42 Van Servellen G, Chang B, Garcia L, Lombardi E. Individual and system level factors associated with treatment nonadherence in human immunodeficiency virus-infected men and women. *AIDS Patient Care STDs* 2002; **16**: 269–281.
43 Brandt CP, Paulus DJ, Garza M, Lemaire C, Norton PJ, Zvolensky MJ. A novel integrated cognitive-behavioral therapy for anxiety and medication adherence among persons living with HIV/AIDS. *Cogn Behav Pract* 2018; **25**: 105–118.
44 Milanini B, Catella S, Perkovich B *et al*. Psychiatric symptom burden in older people living with HIV with and without cognitive impairment: the UCSF HIV over 60 cohort study. *AIDS Care* 2017; **29**: 1178–1185.
45 Morrison MF, Petitto JM, Have TT *et al*. Depressive and anxiety disorders in women with HIV infection. *Am J Psychiatry* 2002; **159**: 789–96.
46 Clucas C, Sibley E, Harding R, Liu L, Catalan J, Sherr L. A systematic review of interventions for anxiety in people with HIV. *Psychol Health Med* 2011; **16**: 528–547.
47 Bhaskaran K, Mussini C, Antinori A *et al*. Changes in the incidence and predictors of human immunodeficiency virus-associated dementia in the era of highly active antiretroviral therapy. *Ann Neurol* 2008; **63**: 213–221.
48 Heaton RK, Franklin DR, Ellis RJ *et al*. HIV-associated neurocognitive disorders before and during the era of combination antiretroviral therapy: differences in rates, nature, and predictors. *J Neurovirol* 2011; **17**: 3–16.
49 Norman LR, Basso M, Kumar A, Malow R. Neuropsychological consequences of HIV and substance abuse: a literature review and implications for treatment and future research. *Curr Drug Abuse Rev* 2009; **2**: 143–156.
50 Kumar S, Himanshu D, Tandon R, Atam V, Sawlani KK, Verma SK. Prevalence of HIV associated neurocognitive disorder using modified mini mental state examination and its correlation with CD4 counts and anti-retroviral therapy. *J Assoc Physicians India* 2019; **67**: 47.
51 Cole M, Margolick JB, Cox C *et al*. Longitudinally preserved psychomotor performance in long-term asymptomatic HIV-infected individuals. *Neurology* 2007; **69**: 2213–2220.
52 Brennan AT, Maskew M, Sanne I, Fox MP. The interplay between CD 4 cell count, viral load suppression and duration of antiretroviral therapy on mortality in a resource-limited setting. *Trop Med Int Health*. 2013; **18**: 619–631.
53 Cohen RA, Seider TR, Navia B. HIV effects on age-associated neurocognitive dysfunction: premature cognitive aging or neurodegenerative disease? *Alzheimers Res Ther* 2015; **7**: 37.
54 Brew BJ, Crowe SM, Landay A, Cysique LA, Guillemin G. Neurodegeneration and ageing in the HAART era. *J Neuroimmune Pharmacol* 2009; **4**: 163–174.

55 Aberg JA. Aging, inflammation, and HIV infection. *Top Antivir Med*. 2012; **20**: 101.
56 Nasi M, Pinti M, De Biasi S *et al*. Aging with HIV infection: a journey to the center of inflammAIDS, immunosenescence and neuroHIV. *Immunol Lett* 2014; **162**: 329–333.
57 Farhadian S, Patel P, Spudich S. Neurological complications of HIV infection. *Curr Infect Dis Rep* 2017; **19**: 50.
58 Fettig J, Swaminathan M, Murrill CS, Kaplan JE. Global epidemiology of HIV. *Infect Dis Clin* 2014; **28**: 323–337.
59 Vance DE, Fazeli PL, Ball DA, Slater LZ, Ross LA. Cognitive functioning and driving simulator performance in middle-aged and older adults with HIV. *J Assoc Nurses AIDS Care* 2014; **25**: e11–e26.
60 Widera E, Steenpass V, Marson D, Sudore R. Finances in the older patient with cognitive impairment:"He didn't want me to take over". *JAMA* 2011; **305**: 698–706.
61 Jang HJS. *Cognitive function and health-related quality of life in older adults with HIV*. Ann Arbor: University of California, San Francisco. 2016.
62 Barclay TR, Hinkin CH, Castellon SA *et al*. Age-associated predictors of medication adherence in HIV-positive adults: health beliefs, self-efficacy, and neurocognitive status. *Health Psychol* 2007; **26**: 40.
63 Hinkin CH, Hardy DJ, Mason KI *et al*. Medication adherence in HIV-infected adults: effect of patient age, cognitive status, and substance abuse. *AIDS (London, England)* 2004; **18** (Suppl 1): S19.
64 Ellis RJ, Deutsch R, Heaton RK *et al*. Neurocognitive impairment is an independent risk factor for death in HIV infection. San Diego HIV Neurobehavioral Research Center Group. *Arch Neurol* 1997; **54**: 416–424.
65 Mayeda ER, Tchetgen Tchetgen EJ, Power MC *et al*. A simulation platform for quantifying survival bias: an application to research on determinants of cognitive decline. *Am J Epidemiol* 2016; **184**: 378–387.
66 Vance DE, Farr KF, Struzick T. Assessing the clinical value of cognitive appraisal in adults aging with HIV. *J Gerontol Nurs* 2008; **34**: 36–41.
67 Hammers D, Spurgeon E, Ryan K *et al*. Reliability of repeated cognitive assessment of dementia using a brief computerized battery. *Am J Alzheim Dis Other Dement* 2011; **26**: 326–333.
68 Becker JT, Dew MA, Aizenstein HJ *et al*. A pilot study of the effects of internet-based cognitive stimulation on neuropsychological function in HIV disease. *Disabil Rehabil* 2012; **34**: 1848–1852.
69 Vance DE, Fazeli PL, Ross LA, Wadley VG, Ball KK. Speed of processing training with middle-age and older adults with HIV: a pilot study. *J Assoc Nurses AIDS Care* 2012; **23**: 500–510.
70 Kaur J, Dodson JE, Steadman L, Vance DE. Predictors of improvement following speed of processing training in middle-aged and older adults with HIV: a pilot study. *J Neurosci Nurs* 2014; **46**: 23.
71 Gott C, Gates T, Dermody N, Brew BJ, Cysique LA. Cognitive change trajectories in virally suppressed HIV-infected individuals indicate high prevalence of disease activity. *PLoS One* 2017; **12**: e0171887.
72 Cysique LA, Franklin Jr D, Abramson I *et al*. Normative data and validation of a regression based summary score for assessing meaningful neuropsychological change. *J Clin Exp Neuropsychol* 2011; **33**: 505–522.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1 Baseline demographic, clinical, HIV disease characteristics and neuropsychological outcome difference between the HIV-positive participants who attended and did not attend for 6-month follow-up.

Table S2 Baseline demographic, clinical characteristics and neuropsychological outcome difference between the HIV-negative participants who attended and who did not attend the 6-month follow-up

Table S3 Baseline HAND prevalence among the HIV-negative and HIV-positive participants.

Table S4 Six-month follow-up HAND prevalence (corrected for practice effect) among HIV-negative and HIV-positive participants.

Table S5 Details of the iterative LME model building.

Table S6 Comparisons of the fitness of the models.