Meaningful cognitive decline is uncommon in virally suppressed HIV, but sustained impairment, subtle decline and abnormal cognitive aging are not

Htein Linn Aung,[a,b] Krista J. Siefried,[a,c,d] Thomas M. Gates,[a,e] Bruce J. Brew,[a,b,e,f] Limin Mao,[g] Andrew Carr,[a,c] and Lucette A. Cysique[a,e,h,*]

[a]St Vincent's Centre for Applied Medical Research, Sydney, Australia
[b]Faculty of Medicine, UNSW, Australia
[c]Immunology and HIV Unit, St Vincent's Hospital, Sydney, Australia
[d]The National Centre for Clinical Research on Emerging Drugs, Sydney, Australia
[e]Departments of Neurology and HIV Medicine, St Vincent's Hospital, Australia
[f]Faculty of Medicine, University of Notre Dame, Sydney, Australia
[g]Centre for Social Research in Health, UNSW, Sydney, Australia
[h]School of Psychology, University of New South Wales, Sydney, NSW, Australia

eClinicalMedicine
2023;56: 101792
Published Online
https://doi.org/10.1016/j.eclinm.2022.101792

Summary

Background High antiretroviral therapy (ART) coverage and viral suppression among people with HIV (PWH) in Australia provide a unique context to study individual cognitive trajectories, cognitive aging and factors associated with longitudinal cognitive function during chronic and stable HIV disease.

Methods Participants from the Predictors of Adherence to Antiretroviral Therapy study (n = 457, recruited between September 2013 and November 2015, median age = 52 years, and all with HIV RNA <50 copies mL) completed a cognitive assessment with CogState Computerized Battery (CCB) at baseline, Month-12, and Month-24. Demographics, psycho-social and socioeconomic factors, healthcare seeking behaviors, HIV disease characteristics and comorbidities were assessed. The CCB data were corrected for age, sex and practice effect and averaged into a global z-score (GZS). Cognitive impairment was defined with the global deficit score method (GDS>0.5). Meaningful cognitive change was statistically defined (decline or improvement versus stability, i.e., 90% CI, that is $p < 0.05$, 2-tailed) using a novel evidence-based change score: the linear mixed-effect regression (LMER)-based GZS change score. A separate LMER model with a top-down variable selection approach identified the independent effects of age and other demographic, HIV disease characteristics, socioeconomic and health-related factors on the demographically corrected GZS. The combined definitions of change and cross-sectional impairment enabled the identification of cognitive trajectories.

Findings At Month-12 and Month-24, 6% and 7% showed meaningful cognitive decline and 4% and 3% improved respectively. Only 1% showed sustained decline. Incident impairment due to subtle cognitive decline (i.e., below the threshold of meaningful cognitive decline) was 31% and 25% at Month-12 and Month-24, while 14% showed sustained impairment (i.e., cognitively impaired at all study visits). Older age (≥50 years) and time interaction was associated with lower demographically corrected GZS ($\beta = -0.31$, $p < 0.001$). Having a regular relationship, excellent English proficiency, and perceived stigma (avoidance) were associated with higher GZS (all $p < 0.05$). Relying on government subsidy, severe depression, and lower belief in ART necessity and higher concerns were associated with lower GZS (all $p < 0.05$). No HIV disease characteristics had a significant effect.

Interpretations Meaningful cognitive decline was not different from normal expectation in chronic stable HIV disease. Despite this, subtle cognitive decline, sustained cognitive impairment, and greater than normative-age cognitive aging were evident.

Funding Funding for the PAART study was provided in part by unrestricted educational grants from Gilead Sciences (www.gilead.com) (Grant Number: IN-AU-264- 0131), the Balnaves Foundation (www.balnavesfoundation.com), the Victorian Department of Health and Human Services (Australia) (www.dhs.vic.gov.au/home), Western Australia

*Corresponding author. School of Psychology, The University of New South Wales, Matthews Building, Room 1012, 11 Botany Street, Sydney, NSW, 2052, Australia.
E-mail address: lcysique@unsw.edu.au (L.A. Cysique).

Health (www.health.wa.gov.au), the ACT Ministry of Health (Australia) (www.health.act.gov.au), and in-kind support from the Queensland Department of Health (Australia) (www.health.qld.gov.au), and NHMRC Partnership grant APP1058474 (PI: Carr, Andrew).

Keywords: HIV; Neurocognition; Trajectories; Aging; Psychosocial factors

Research in context

Evidence before this study

We searched the PubMed database on Oct 30, 2021 using the following search terms: HIV AND (neurocognitive OR cognitive) AND (longitudinal OR change OR trajector*). Based on our review, there were six studies reporting cognitive decline using evidenced-based change scores. Among them, only two studies: one from Australia from our group and one from the Netherlands, included participants who were all virally suppressed. However, the Australian study lasting 18 months was conducted among participants (N = 102) who were all over 45 years of age, had nadir CD4 counts less than 350/μL, and historical AIDS prevalence of 70%, hence making the study relevant only to those with historical advanced HIV. In the Dutch study, the sample size was relatively small (N = 82), and the duration of follow-up was relatively short (one year). In addition, we also identified that the majority of previous longitudinal NeuroHIV studies did not consider socioeconomic factors (e.g., income and having a regular partner or not) and healthcare seeking behaviors (e.g., ART adherence) while identifying factors associated with longitudinal neurocognitive performance.

Added value of this study

Unlike previous studies which mainly used standard regression-based change score method to define meaningful cognitive change, our study used a more robust method named linear mixed-effect regression (LMER)-based change score method which is better at dealing with longitudinal data because it allows for inclusion of all available data, rather than only participants with complete follow-up, which introduces significant bias. In addition, our study includes a larger sample size (excepting the longitudinal CHARTER study), and importantly a representative national sample that is one of the most optimally treated in the world with high viral suppression rate. Moreover, this study simultaneously considered a comprehensive set of demographics, socioeconomic factors, healthcare seeking behaviors, and health status as well as HIV disease characteristics to identify factors influencing longitudinal cognitive performance. We observed that statistically significant cognitive decline rates in this virally suppressed people with HIV (PWH) sample are low and not different from what is normally expected (that is 5% improve and 5% decline). However, there is other concerning signals that cognitive health remains vulnerable such as sustained cognitive impairment, abnormal cognitive aging and effects of complex psychosocial and socioeconomic factors impacting cognitive health.

Implications of all the available evidence

The fact that virally suppressed PWH are unlikely to show severe cognitive deterioration with stable HIV infection is reassuring to millions of PWH and further highlights the importance of early treatment and achieving and maintaining viral suppression not only for physical health but also for cognitive health. On the other hand, as PWH are aging, cognitive health should be prioritized because despite early and successful ART, there are signals for abnormal cognitive aging among PWH based on our finding and findings from previous studies. In practical terms, it means that greater resources should start to be allocated to aging PWH to provide multi-disciplinary services integrating physical, mental, and cognitive health care. Further, cognitive health is a complex concept and depends on both HIV and non-HIV factors including factors that have been less considered in the NeuroHIV literature such as health seeking behavior and social isolation. As loneliness and financial difficulties showed a negative impact on the cognitive health in our study, expansion and maintenance of psychosocial services and peer-support strategies will be necessary for PWH.

Introduction

Along with the growing access to combination antiretroviral therapy (cART), an increasing proportion of people with HIV (PWH) are achieving viral suppression.[1] Thus, it is becoming critically important to understand what long-term cognitive functioning may be in virally suppressed and clinically stable PWH because milder forms of HIV associated neurocognitive disorder (HAND) still persist in the cART era. Indeed, we are only starting to explore longitudinal cognitive trajectories in chronic and stable HIV disease.[2,3] Most international epidemiological figures in NeuroHIV are from cross-sectional studies and from samples that are heterogenous in terms of viral suppression and clinical stability.[4] This has contributed to

inconsistent findings and resulted in confusing messages to the HIV community and clinicians.

In addition, the existing longitudinal NeuroHIV studies do not always consider a comprehensive set of risk factors.[4] Besides HIV disease factors,[5] a myriad of other factors can impact the longitudinal neurocognitive performance among PWH (and more so with increased life expectancy)[6–9]: 1. cognitive aging (both normal and abnormal patterns of premature, accentuated, and accelerated aging)[10,11]; 2. demographic and socioeconomic factors (e.g., education, income, housing, social support, stigma and discrimination)[4,12,13]; 3. medical comorbidities (e.g., cardiovascular diseases and hepatitis C infection)[9]; 4. mental health (e.g., depression and stressful life events)[14]; 5. healthcare-seeking behaviors (e.g., engagement in care and ART adherence)[15]; and 6. smoking and drug and alcohol use disorders.[16–20] In general, previous longitudinal NeuroHIV studies have assessed mental health conditions, medical comorbidities, demographic and alcohol and drug use problems, but not socioeconomic factors or healthcare-seeking behaviors.[4]

Moreover, there are some methodological limitations in previous longitudinal NeuroHIV studies regarding how cognitive trajectories were assessed at the individual level, although more appropriate methods have been used at the group level.[4] At the individual level, most studies have not determined meaningful cognitive change (i.e., statistically defined cognitive change rather than functional change or change due by chance or normal fluctuations, see also Fig. 1). Some research, including studies from our group, used standard regression-based change score methods, an established evidence-based method for detecting individual cognitive change.[4,21] However, the standard regression methods have limitations, as they are impractical when there is more than one follow-up assessment and when follow-up durations vary.[22] In addition, these methods require complete follow-up of all participants to yield unbiased estimates.[4] When participants with incomplete follow-ups are excluded, the data have to be missing completely at random to produce unbiased results.[22] Complete longitudinal data are the exception rather than the rule in clinical research. Further, excluding incomplete follow-up cases reduces study power and generalizability.[22] On the other hand, linear mixed-effect (LME) models are robust in dealing with attrition and unbalanced data and work seamlessly with data that has multiple follow-up time points.[22] Van der Elst and colleagues have demonstrated the possibility of using an LME model as an alternative to traditional methods to compute regression-based change scores.[22]

Thus, to address the limitations in the previous literature and to improve our understanding of cognitive trajectories in people living with chronic stable HIV infection, we analyzed data from an Australian cohort study known as the Predictors of Adherence to

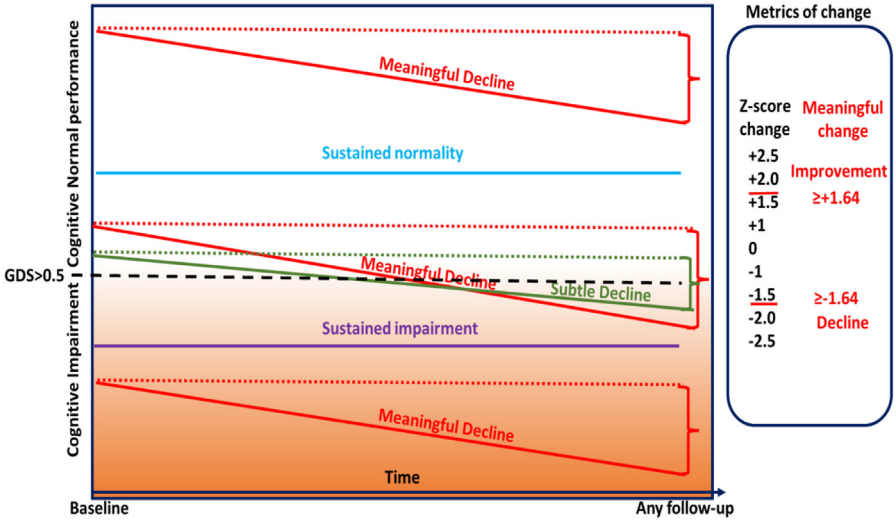

Fig. 1: **Illustrations of different concepts of cognitive decline and trajectories. Meaningful cognitive change** is a statistically defined threshold of cognitive change on an evidenced-based cognitive change score. The convention is to detect both decline and improvement with a 90% CI, that is $p < .05$ two-tailed, that is ±1.64 change across the normative mean of zero. Meaningful decline is only a longitudinal definition and only applies to cognitive change. Hence it is possible to have meaningful cognitive decline across different levels of performance range as illustrated in 3 arbitrary examples. In this figure for simplicity, we only presented decline and not improvement. But the same reasoning applies to **meaningful cognitive improvement**. In this framework, **subtle cognitive decline** is a decline that is large enough for a progression between normal to impaired performance, but the magnitude of the decline is not large enough to be ≥−1.64, cut-off for meaningful cognitive decline. As such, subtle cognitive decline takes into account both the cross-sectional impairment rating and longitudinal change status. **Sustained impairment** is a cross-sectional definition of change where impaired performance is detected at all tested time points. The same reasoning applies for **sustained normality**.

Antiretroviral Therapy (PAART) study as planned in the study original protocol.[23] The PAART study was conducted in a cohort of clinically stable and virally suppressed PWH and collected data across cognitive functions, demographics and socioeconomic factors, healthcare seeking behaviors, HIV disease markers, and medical comorbidities. We used the LME regression-based change score method to classify meaningful cognitive change profiles (statistically defined decline or improvement versus stability, $p < 0.05$ two-tailed). Further, using these change profiles and cognitive impairment classifications, we determined cognitive trajectories of whether cognitive decline and impairment are incident, sustained or fluctuant. Note that, using this approach, it is possible to detect incident cognitive impairment without having a meaningful decline, but subtle decline (see Fig. 1). Subtle cognitive decline represents the combination of longitudinal and cross-sectional information in the data and the instance in which a participant declined but did not reach the threshold of meaningful cognitive decline and yet progressed from having normal cognitive performance to impairment performance. Finally, we use an LME model to determine factors influencing longitudinal cognitive performance at the group level while focusing on the effect of cognitive aging.

Methods

Study population

The PAART study[23] recruited 523 PWH from 17 HIV healthcare facilities across Australia. The detailed description of the study has been published elsewhere.[23,24] To be eligible, participants had to be taking ART and attained viral suppression (plasma HIV RNA <50 copies/mL) for at least three months prior to recruitment. Ethic approval was obtained from the following Human Research Ethics Committees (HRECs): ACT Health Canberra HREC (ETH.7.13.178), St Vincent's Hospital HREC (HREC/12/SVH/186), The Alfred Hospital HREC (444/14), Government of Western Australia South Metropolitan Health Service HREC (ref 13/70), and Monash Health HREC (15O28X). Written informed consent was taken from the participants. Recruitment started in September 2013 and participants were followed up every six months for two years.

The current study sample included all participants with valid cognitive data, which comprised 457 participants at baseline, 316 participants at Month-12 follow-up, and 276 participants at Month-24 follow-up (see also Supplementary File 1). According to the sample size calculation method developed by Lu, Luo, and Chen for LME models,[25] our sample size has enough power (i.e., 80%) to run an LME model with autoregressive correlation structure using the cognitive score as the outcome, age as the main predictor, and assuming the effect size as 0.33.

Assessments

The following data were collected on annual visits through a computer-based self-administered questionnaire: demographics, socioeconomic factors, physical health, mental health, quality of life, life stressors, social support, alcohol and drug use, HIV disclosure, stigma and discrimination, healthcare access, and treatment adherence.[23] Quality of life was assessed with the Professional Quality of Life Scale (PROQOL-HIV scale),[25] mood status or depression was assessed with Patient Health Questionnaire (PHQ-9),[26] alcohol dependence was assessed with CAGE questionnaire,[27] attitude to ART was assessed with Beliefs About Medications Questionnaire (BMQ-HAART),[28] and ART adherence was assessed with Simplified Medication Adherence Questionnaire (SMAQ).[29] Medical information such as current HIV treatment, comorbidities and laboratory findings and biomarkers were collected from clinical notes and from ART-dispensing pharmacies.

Cognitive performance was assessed with the CogState Computerized Battery (CCB),[30] which has been validated in NeuroHIV research.[31] CCB consists of four tasks and five measures known as detection (speed), identification (speed), one back (speed and accuracy), and one-card learning (accuracy). The tasks assess speed of simple and divided attention and speed of working memory, in addition to accuracy of continuous learning and working memory. The tasks of attention/working memory and continuous learning embed executive functioning.

Definitions of cross-sectional cognitive impairment

The five individual CCB test scores were transformed to demographically corrected z-scores using Cogstate normative data correcting for age, education, and sex.[32] Then, global z-scores (GZS) were computed by averaging the individual test z-scores.[32] Practice effect correction was applied for Month-12 and Month-24 data using longitudinal normative data that our group has developed.[32] We determined cognitive impairment at all time-points, where deficit scores were applied to the individual z-scores and then averaged into a Global Deficit Score (GDS). A GDS >0.5 was defined as cognitively impaired.[33,34]

Definitions of meaningful cognitive change (i.e., decline or improve versus stable) and determination of cognitive trajectories (incident impairment, incident meaningful decline, subtle decline, sustained impairment, sustained decline, sustained improvement, and fluctuant performance)

We selected the LME regression framework to compute change scores in order to identify meaningful cognitive change[22] (see Fig. 1 and Supplementary File 2 for

detailed procedure). Per convention,[35] meaningful cognitive change for each follow-up time point was rated based on whether the change score was within or above/below 90% confidence interval (i.e., ± 1.64 SD to the mean, that is $p < 0.05$, 2-tailed). Participants who had a change score above 1.64 SD were classified as "improve" while participants with a change score below –1.64 SD were classified as "decline". The remaining participants were classified as "stable".

Afterwards, using the cross-sectional impairment rating and longitudinal change status, we determined cognitive trajectories (incident impairment, incident meaningful decline, subtle decline, sustained impairment, sustained decline, sustained improvement, and fluctuant performance). We determined the incidence of cognitive decline (i.e., participants who were normal at baseline and had a meaningful decline at Month-12 or Month-24), incidence of cognitive impairment by subtle decline (i.e., participants who were normal at baseline and became impaired at Month-12 or Month 24 but did not reach the threshold of meaningful cognitive decline; see Fig. 1), and the prevalence of sustained cognitive impairment (i.e., participants who were impaired at baseline and stayed impaired at both Month-12 and Month-24), sustained cognitive decline (i.e., participants who declined at both Month-12 and Month-24), sustained cognitive improvement (i.e., participants who improved at both Month-12 and Month-24), and fluctuant performance (i.e., participants who were impaired or normal at baseline and declined at Month-12 but then became stable/improved again at Month-24).

Determination of cognitive aging effects and factors influencing longitudinal neurocognitive performance

Firstly, descriptive analyses were conducted using t-test, Mann–Whitney U test, and Chi–Square test to compare all the baseline information between those who were cognitively impaired at baseline according to the GDS and those who were cognitively normal. Comparisons were also made between young (<50) and old (≥50) participants. Normality of the continuous variables was checked using Shapiro–Wilk test to determine whether to use t-test or Mann–Whitney U test.

Next, to determine any abnormal cognitive aging effect, in addition to which factors predicted longitudinal cognitive performance, we carried out an additional LME model using age-corrected GZS as the outcome, and all the other variables as delineated above as predictors. The age-corrected GZS was used in order to take into account normal aging and this identifies abnormal cognitive ageing which by definition is above and beyond the normal ageing effect.[11] Age groups (i.e., young; <50 years or old; ≥50 years),[9] time and their interaction were used as main fixed-effect variables. Younger and older participants were classified based on the 50 years of age cut-off because age-related conditions are likely to increase exponentially starting from the age of 50 among PWH. Covariates were chosen based on a backwards selection approach. Namely, variables which had a p-value >0.5 were sequentially removed from the model. The final model adopted only random intercept because it outperformed the model with random slope. Nlme[36] package in R statistical software was used for these analyses.

Role of the funding source

The funders had no role in the design of the study, collection and analysis of data, and preparation of manuscript.

Results

Participants' baseline characteristics are presented in Table 1. Among 457 participants with valid baseline data, 270 participants (59%) were over 50 years of age. All participants had undetectable plasma HIV RNA (<50 copies mL) at baseline and only three participants had a viral rebound (increase back to >200 copies mL) over the follow-up. The median duration of being diagnosed with HIV was 15 years and only 22% (n = 100) had a history of previous AIDS illness. Thirty one percent (n = 142) were classified as cognitively impaired at baseline.

Individual cognitive change profiles

Actual cognitive performance of each participant over the study follow-up is presented in the Supplementary File 3 in a spaghetti plot. Six percent of the participants at Month-12 and 7% at Month-24 were classified as having a "decline" from baseline, while 3% were classified as "improve" at both Month-12 and Month-24 follow-ups. Therefore, the remaining 91% at Month-12 and 90% at Month-24 were classified as "stable". Participants who were cognitively impaired at baseline had a greater chance of cognitive decline at both Month-12 12 ($p < 0.001$) and Month-24 ($p < 0.05$) in comparison with those who were cognitively normal at baseline (Figs. 2 and 3).

Cognitive trajectories combining cross-sectional impairment status at baseline and across the study period with magnitude of longitudinal cognitive decline (meaningful or subtle)

Among the participants who were cognitively normal at baseline, the incidence of cognitive decline over one- and two-year follow-up periods were 2% and 5%, respectively, while the incident cognitive impairment (implying a subtle cognitive decline that is below the clinically meaningful cut-off) rates were 31% at Month-12 and 25% at Month-24 respectively. Among 226 participants with follow-up data at both Month-12

	Normal or impaired cognition		Young (<50 years) or Old (≥50 years)		Total (457)
	Normal (315)	Impaired (142)	Young (187)	Old (270)	
Demographics					
Age (mean, SD)	51.2 (12.12)	49.6 (12.66)	38.8 (8.12)	58.9 (6.66)***	50.7 (12.3)
Gender (male)	306 (97%)	130 (92%)*	168 (90%)	268 (99%)***	436 (95%)
Men who have sex with men	259 (82%)	103 (73%)*	145 (78%)	217 (80%)	362 (79%)
Born in Australia	202 (64%)	82 (58%)	106 (57%)	178 (70%)	284 (62%)
Australian citizen	307 (97%)	128 (90%)*	168 (90%)	267 (99%)***	435 (95%)
Speaks English at home	272 (82%)	108 (76%)*	158 (84%)	222 (82%)	380 (83%)
Excellent English	284 (90%)	122 (86%)	149 (80%)	257 (95%)***	406 (89%)
Has a Medicare card	308 (98%)	138 (97%)	178 (95%)	268 (99%)*	446 (98%)
Reached the Medicare safety net in the past 12-months	52 (20%)	24 (18%)	23 (14%)	53 (22%)**	76 (19%)
Private health insurance (yes)	147 (47%)	48 (34%)*	84 (45%)	111 (41%)	195 (43%)
Completed year 12	255 (81%)	111 (78%)	159 (85%)	207 (77%)*	366 (80%)
Social structure and support					
Married/de facto/in a regular relationship	146 (46%)	56 (39%)	93 (50%)	109 (40%)	202 (44%)
In a sexual relationship	135 (43%)	61 (43%)	95 (51%)	101 (37%)**	196 (43%)
Lives alone	119 (38%)	62 (44%)	60 (32%)	121 (45%)**	181 (40%)
Received less social support than wanted/needed	183 (58%)	83 (58%)	75 (40%)	115 (43%)	266 (58%)
Not involved in any HIV support organization	237 (75%)	102 (2%)	132 (71%)	207 (77%)	339 (74%)
HIV disclosure, stigma, and discrimination					
Has not disclosed HIV status to anyone	12 (4%)	9 (6%)	9 (5%)	12 (4%)	21 (4%)
Has been made to feel ashamed of HIV diagnosis	135 (43%)	64 (45%)	100 (53%)	99 (37%)***	199 (44%)
Has felt blamed for having HIV	100 (32%)	56 (39%)	80 (43%)	76 (28%)**	156 (34%)
Has felt avoided, excluded, or rejected for having HIV	129 (41%)	59 (42%)	86 (46%)	102 (38%)*	188 (41%)
Has had awkward interactions for having HIV	153 (49%)	67 (47%)	106 (57%)	114 (42%)**	220 (48%)
Financial/employment status					
Social welfare as the main source of income	113 (36%)	66 (46%)*	53 (28%)	126 (47%)***	179 (39%)
Received financial assistance in the past 12 months	106 (34%)	63 (44%)*	73 (39%)	96 (36%)	169 (70%)
Employed	169 (54%)	65 (46%)	124 (66%)	110 (41%)***	234 (51%)
Work hours per week (median, IQR)	20 (40)	4 (38) ***	35 (15)	0 (32)***	15 (39.25)
Weekly income after tax (median, IQR)	600 (770)	500 (697)*	746 (464)	500 (500)**	600 (690)
Lives in a public-subsidized accommodation	54 (17%)	37 (26%)*	29 (16%)	62 (23%)	91 (20%)
Lives with someone who is financially dependent	26 (8%)	17 (12%)	21 (11%)	22 (8%)	43 (9%)
Had financial difficulties to meet basic needs in the past 12 months	60 (19%)	31 (22%)	45 (24%)	46 (17%)	91 (20%)
HIV healthcare and treatment access					
Used more than three HIV management health services	101 (32%)	47 (33%)	57 (30%)	91 (34%)	148 (32%)
Uses the following HIV care and treatment services:					
Hospital based HIV clinic	145 (46%)	79 (56%)	102 (55%)	122 (45%)	224 (49%)
Health center specialized in HIV treatment	85 (27%)	34 (24%)	33 (18%)	86 (32%)**	119 (26%)
Community based general practice	105 (33)	47 (33%)	45 (24%)	107 (40%)***	152 (33%)
Sexual health clinic/center	103 (33%)	43 (30%)	73 (39%)	73 (27%)**	146 (32%)
Naturopath	15 (5%)	9 (6%)	8 (4%)	16 (6%)	24 (5%)
Hospital pharmacy	170 (54%)	63 (44%)	88 (47%)	145 (54%)	233 (51%)
Home or community care	6 (2%)	6 (4%)	5 (3%)	7 (3%)	12 (3%)
Drug or alcohol services	4 (1%)	2 (1%)	4 (2%)	2 (1%)	6 (1%)
HIV-related community organizations or support groups	41 (13%)	25 (18%)	24 (13%)	42 (16%)	66 (14%)
Actively involved in the management of HIV	306 (97%)	137 (96%)	183 (98%)	260 (97%)	443 (97%)
Primary HIV physician					
General practitioner	113 (36%)	48 (33%)	49 (26%)	112 (42%)**	161 (35%)
Hospital physician	129 (41%)	68 (48%)	91 (49%)	106 (39%)	197 (43%)
Sexual health physician	70 (22%)	24 (17%)	43 (23%)	51 (19%)	94 (20%)
Cost prevented to access a medical service for the management of HIV infection in the past 12 months	41 (13%)	24 (17%)	36 (19%)	29 (11%)*	65 (14%)

(Table 1 continues on next page)

	Normal or impaired cognition		Young (<50 years) or Old (≥50 years)		Total (457)
	Normal (315)	Impaired (142)	Young (187)	Old (270)	
(Continued from previous page)					
HIV history					
Duration of HIV diagnosis (median, IQR)	13 (19)	16 (16.25)	9.19 (7.31)	19.08 (9.14)***	15 (17)
Duration of ART (median, IQR)	9 (14)	12 (13.5)	6.52 (5.88)	14.34 (7.36)***	10 (14)
Male-to-male sexual transmission of HIV	258 (85%)	98 (74%)*	143 (78%)	213 (84%)	356 (81%)
Nadir CD4+ T-lymphocyte count <200 cells/mm^3	119 (39%)	52 (38%)	50 (27%)	121 (46%)***	171 (38%)
Previous AIDS	62 (20%)	38 (27%)	30 (16%)	70 (26%)*	100 (22%)
HIV brain Involvement history	10 (3%)	8 (6%)	7 (4%)	11 (4%)	18 (4%)
Comorbidities					
Hep B coinfection	10 (3%)	9 (6%)	6 (3%)	13 (5%)	19 (4%)
Hep C coinfection	26 (8%)	18 (13%)	18 (10%)	26 (10%)	44 (10%)
Heart disease	33 (10%)	15 (11%)	5 (3%)	43 (16%)***	48 (11%)
Hypertension	63 (20%)	29 (20%)	15 (8%)	77 (29%)***	92 (20%)
Stroke	6 (2%)	3 (2%)	2 (1%)	7 (2%)	9 (2%)
Peripheral vascular disease	7 (2%)	1 (1%)	0 (0%)	8 (3%)*	8 (2%)
Diabetes	17 (5%)	10 (7%)	2 (1%)	25 (9%)***	27 (6%)
Chronic liver failure	0 (0%)	1 (1%)	0 (0%)	1 (0.4%)	1 (0.2%)
Chronic kidney disease	6 (2%)	4 (3%)	0 (0%)	10 (4%)**	10 (2%)
Psychiatric	89 (28%)	45 (32%)	56 (30%)	78 (29%)	134 (29%)
Other diagnosed comorbidity	77 (25%)	36 (26%)	23 (12%)	90 (33%)***	113 (25%)
Cumulative number of age-related comorbidities (≥2%)	29 (9%)	15 (11%)	3 (2%)	41 (15%)***	44 (10%)
Current health					
Current CD4+ T-lymphocyte count (median, IQR)	461 (300.14)	587 (305.50)	712.28 (273.39)	632.62 (275.33)**	630 (355)
Length of undetectable HIV viral load in months (median, IQR)	40 (67.5)	42 (65)	24 (30)	55 (41)***	42 (64)
Anemia	19 (6%)	10 (7%)	12 (6%)	17 (6%)	29 (6%)
Elevated ALT (>40 U/L males, >35 U/L females, %)	84 (27%)	26 (18%)	44 (24%)	66 (25%)	110 (24%)
eGFR <60 ml/min/1.73 m^2	21 (7%)	13 (9%)	6 (3%)	28 (10%)**	34 (7%)
Hepatitis co-infection	40 (13%)	29 (20%)*	25 (13%)	44 (16%)	69 (15%)
Syphilis infection in the past 12 months	18 (6%)	4 (3%)	15 (8%)	7 (3%)**	22 (5%)
Physical health					
Self-reported good/very good overall health	264 (84%)	117 (82%)	162 (87%)	219 (81%)	381 (83%)
One or more bed days due to illness in the past 12 months	172 (54%)	82 (59%)	120 (65%)	134 (50%)*	254 (56%)
One or more doctor visits due to illness in the past 12 months	216 (69%)	102 (72%)	126 (69%)	192 (72%)	318 (70%)
One or more hospital inpatient days in the past 12 months	55 (17%)	32 (23%)	29 (16%)	58 (21%)	87 (19%)
Mental health					
Severe depression on PHQ-9[a]	23 (7%)	12 (10%)	15 (8%)	20 (7%)	35 (8%)
Depressive symptoms make daily living difficult	103 (33%)	48 (34%)	73 (39%)	78 (29%)*	151 (33%)
Currently clinically active psychiatric illness	68 (22%)	33 (23%)	45 (24%)	56 (21%)	101 (22%)
Alcohol and drug use					
Alcohol use in the past 12 months	270 (90%)	110 (86%)	160 (90%)	220 (87%)	380 (89%)
Alcohol dependent (CAGE)[b]	69 (21%)	22 (15%)	44 (24%)	47 (17%)	91 (21%)
Use a drug at least once a week in the past 12 months (yes)	65 (24.16%)	51 (27.27%)	51 (27%)	65 (24%)	163 (36%)
Smoking at least once a week in the past 12 Months (yes)	84 (27%)	34 (24%)	62 (33%)	56 (21%)**	118 (26%)
Use an injecting drug weekly or more in the past 12 months	12 (4%)	9 (6%)	13 (7%)	8 (3%)	12 (4%)
Life stressors					
More than 2 major stress events in the past 12 months	82 (26%)	34 (24%)	64 (34%)	52 (19%)***	116 (25%)
Antiretroviral therapy					
Started ART because of high viral load	141 (45%)	69 (49%)	93 (50%)	117 (44%)	210 (46%)
Started ART because of low CD4 count	165 (53%)	70 (50%)	104 (56%)	131 (49%)	235 (52%)
ART as a single tablet regimen	94 (30%)	43 (30%)	75 (40%)	62 (23%)***	137 (30%)
CPE (mean, SD)	7.71 (1.93)	7.8 (1.81)	7.4 (1.63)	7.97 (2.02)***	7.74 (1.89)
SMAQ score (mean, SD)[c]	0.89 (1.12)	1.05 (1.38)	1.14 (1.33)	0.79 (1.09)**	1.65 (2.15)
Missed at least one dose of ART in the last three months (yes)	144 (46%)	57 (40%)	88 (47%)	113 (42%)	201 (44%)
Delayed/interrupted ART in the past 12 months	18 (6%)	11 (8%)	15 (8%)	14 (5%)	29 (6%)

(Table 1 continues on next page)

	Normal or impaired cognition		Young (<50 years) or Old (≥50 years)		Total (457)
	Normal (315)	Impaired (142)	Young (187)	Old (270)	
(Continued from previous page)					
Delayed/interrupted ART ever	45 (17%)	23 (16%)	30 (16%)	45 (17%)	75 (16%)
Delayed/interrupted ART ever for ≥1 week	41 (13%)	17 (12%)	20 (11%)	38 (14%)	58 (13%)
BMQ-HAART score (mean, SD)[d]	38.54 (9.08)	40.25 (9.38)	39.7 (9)	38.64 (10)	39.07 (9.2)
Concomitant medications					
Daily concomitant medication pill burden (mean, SD)	3.63 (4.5)	3.67 (3.94)	2.16 (3.46)	4.66 (4.58)***	3.64 (4.33)
PRO-QOL HIV					
PRO-QOL HIV summary score (mean, SD)[e]	44.88 (23.21)	47.83 (25.88)	49.11 (25.23)	44.5 (23.02)*	45.8 (24.08)
Cognitive scores					
Mean T-score (mean)	−0.01 (0.40)	−1.0 (0.53) ***	−0.46 (0.65)	−0.22 (0.62) ***	−0.32 (0.64)
Global Deficit score (mean)	0.14 (0.16)	1.21 (0.67) ***	0.57 (0.69)	0.41 (0.59) *	0.47 (0.63)
Cognitively impaired			72 (39%)	70 (26%)**	142 (31%)

'***'p < 0.001, '**'p < 0.01, '*'p < 0.05. Data are presented as n (%) for categorical variables and mean (SD) or median (interquartile range) for continuous variables. Chi-square test was used for categorical, and t-test and Mann–Whitney U Test were used for continuous variables. ALT = alanine aminotransferase, BMQ-HAART = Beliefs About Medications Scales, PHQ = Patient Health Questionnaire, CPE = CNS penetrative effectiveness score, SMAQ = Simplified Medication Adherence Questionnaire, PRO-QOL = Professional Quality of Life Scale.[a]PHQ-9 score ≥15. [b]CAGE score ≥2. [c]Higher score means poorer adherence. [d]Higher score means less belief in necessity and acceptability of ART. [e]Higher score means lower QOL.

Table 1: **Differences in baseline characteristics between those who were cognitively normal or impaired at baseline and between younger and older participants.**

and Month-24, 32 participants (14%) had sustained impairment, three (1%) had sustained cognitive decline and two (1%) had sustained cognitive improvement. The majority, 195 out of 226 (86%), remained stable over the follow-up period. Lastly, seven participants (3%) had a fluctuating performance over the follow-up (i.e., impaired, or normal at baseline and declined at Month-12, but then became stable again at Month-24).

Effects of aging and other demographic, socioeconomic, psychosocial, treatment and clinical factors on longitudinal cognitive performance

Table 2 shows the results from the LME model which determined factors associated with change in neurocognitive performance. Older age was associated with higher neurocognitive performance (β = 0.23, CI = 0.03, 0.43, p < 0.001), but its interaction with follow-up time was associated with lower cognitive performance (β = −0.31, CI = −0.39, −0.22, p < 0.001). Among covariates, having a regular relationship (β = 0.14, CI = 0.00, 0.28, p < 0.05) and having excellent English proficiency (β = 0.22, CI = 0.04, 0.41, p < 0.05) were associated with higher cognitive performance. Unexpectedly, having felt avoided because of HIV status (β = 0.15, CI = 0.01, 0.30, p < 0.05) was associated with better cognitive performance. On the other hand, social welfare as the main source of income (β = −0.27, CI = −0.52, −0.03, p < 0.05), severe depression (β = −0.28, CI = −0.53, −0.03, p < 0.05), and less belief in the necessity and higher concerns in ART (higher BMQ-HAART score) (β = −0.09, CI = −0.16, −0.02, p < 0.05) were associated with poorer cognitive performance.

Discussion

There is a paucity of studies assessing individual cognitive trajectories in virally suppressed PWH with a chronic and stable HIV disease. The current study aimed to address inconsistencies in previous literature by optimally assessing cognitive trajectories, cognitive aging, and the effects of a comprehensive set of health, social and lifestyle factors on cognition in a representative national sample of virally suppressed Australian PWH.

Our study used a comprehensive framework to determine cognitive trajectories combining cross-sectional and longitudinal impairment classification, and for the first time, a LME method to develop norms for change and compute regression-based change scores. Unlike some previous longitudinal NeuroHIV studies,[37,38] our study also corrected follow-up cognitive data for practice effects to reliably estimate sustained and incident cognitive impairment.

Overall, most participants were cognitively stable over the follow-up period. Only a small proportion of participants (6% at Month-12 and 7% at Month-24) had a meaningful cognitive decline and just one percent of participants had sustained cognitive decline over the two-year follow-up period. These low cognitive decline rates are probably afforded by the ongoing viral suppression among the participants. While previous studies have also reported that lower viral load reduces the risk for cognitive decline,[39,40] we are the first to provide a clear epidemiological figure.

However, despite no evidence for severe cognitive decline, 31% and 25% of participants showed subtle cognitive decline resulting in them crossing the threshold from normal to impaired cognition at Month-

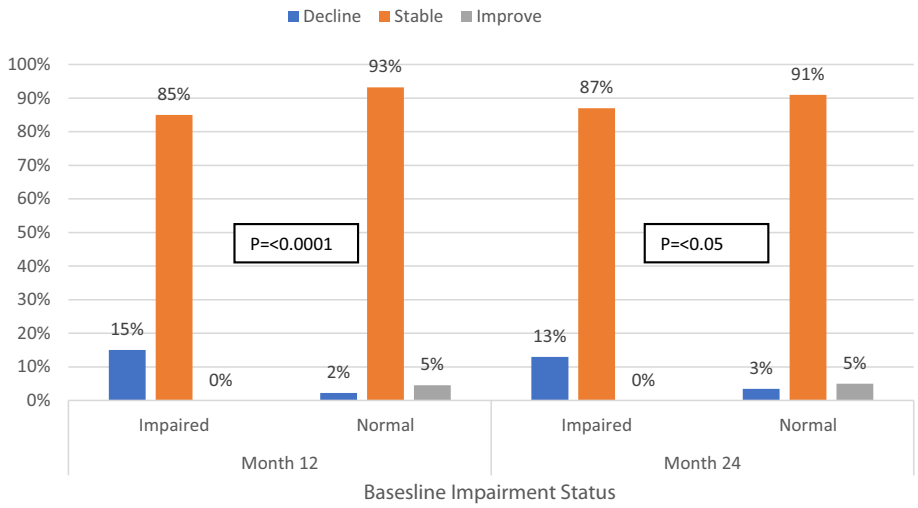

***Fig. 2:* Cognitive change status at month-12 and month-24 based on baseline impairment status.** Data was presented only for those who attended month-12 (n = 316) and month-24 (n = 276) follow-ups, Chi-square tests were used to compare the proportions of decline, stable and improve between those who were cognitively normal and who were cognitively impaired at the baseline. P-values were drawn from the chi-square tests and a significant p-value shows that the proportions of decline, stable and improve are significantly different between those who were cognitively normal and who were cognitively impaired at the baseline.

12 and Month-24 respectively. This subtle cognitive decline may be related to ongoing subtle brain changes among PWH despite viral suppression. Our group has previously demonstrated that despite viral suppression, there are signs of progressing subtle brain damage among PWH characterized by abnormal cellular energy, neuronal and axonal injury and restricted neuroinflammation.[41] Future neuroimaging studies specifically targeting subtle cognitive change as defined in the current study are warranted. Possible precipitating factors for ongoing brain injury among PWH despite plasma viral suppression include direct HIV effects (activity of the reservoir, chronic immune activation and inflammation), indirect or partial HIV effects (increased comorbidities and abnormal cognitive aging), and non-HIV effects that can be partially, but not always compounded by HIV (mental health and alcohol and drug use disorders).[41,42]

Compared to the previous studies which used standard regression-based change score method, the meaningful cognitive decline rate reported in our study is lower. In our other study[2] where we assessed

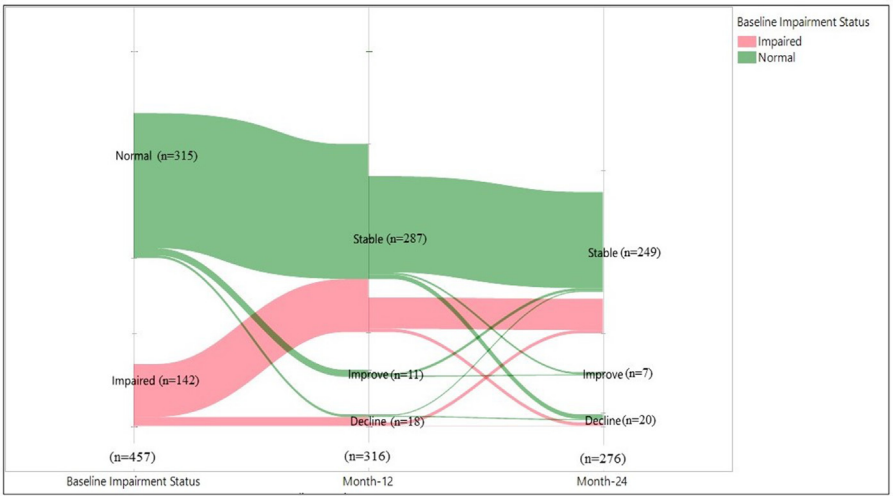

***Fig. 3:* Cognitive trajectories among study participants over the study follow-up based on the baseline impairment status.** Participants who were impaired at baseline did not improve over the study follow-up period.

Variable	B	Standard error (SE)	95% CI	β	95% CI
Age group (young vs old)	0.33***	0.07	0.20, 0.47	0.23	0.03, 0.43
Time (year)	0.08**	0.03	0.03, 0.13	0.11	0.04, 0.18
Gender (female vs male)	0.16	0.14	−0.11, 0.43	0.25	−0.19, 0.69
Homosexual (yes)	0.10	0.07	−0.03, 0.24	0.16	−0.08, 0.36
Married or in a regular relationship (yes)	0.09*	0.04	0.002, 0.17	0.14	0.00, 0.28
Excellent English (yes)	0.14*	0.06	0.03, 0.25	0.22	0.04, 0.41
Eligible for Medicare (yes)	−0.20	0.14	−0.47, 0.07	−0.32	−0.76, 0.12
Completed year 12 (yes)	0.10	0.06	−0.02, 0.22	0.16	−0.04, 0.36
Social welfare as the main source of income (yes)	−0.18*	0.08	−0.33, −0.02	−0.27	−0.52, −0.03
Receiving financial support (yes)	−0.06	0.05	−0.15, 0.03	−0.09	−0.23, 0.05
Employed (yes)	0.06	0.07	−0.08, 0.19	0.09	−0.13, 0.31
Self-perceived health status (poor/average vs good/very good)	−0.07	0.05	−0.17, 0.03	−0.11	−0.28, 0.05
Hospital admission in the last 12 months (yes)	−0.04	0.04	−0.12, 0.05	−0.06	−0.20, 0.08
Severe depression[a] (Yes)	−0.17*	0.08	−0.33, −0.02	−0.28	−0.53, −0.03
More than 2 major stress events in previous 12 months (yes)	−0.07	0.05	−0.16, 0.01	−0.12	−0.26, 0.02
Alcohol use in the past 12 months (yes)	0.06	0.06	−0.06, 0.18	0.09	−0.10, 0.28
Smoking at least once a week in the past 12 months (yes)	0.09	0.05	−0.01, 0.20	0.15	−0.02, 0.32
Use a drug at least once a week in the past 12 months (yes)	0.04	0.04	−0.05, 0.13	0.05	−0.10, 0.21
Has disclosed HIV status to someone (yes)	0.11	0.08	−0.05, 0.26	0.17	−0.08, 0.42
Has felt avoided, excluded, or rejected for having HIV (yes)	0.10*	0.05	0.008, 0.18	0.15	0.01, 0.30
Has had awkward interactions for having HIV (yes)	0.04	0.04	−0.05, 0.12	0.06	−0.08, 0.20
SMAQ score	0.04	0.02	−0.004, 0.08	0.07	−0.01, 0.15
Missed at least one dose of ART in the last three months (yes)	0.06	0.05	−0.01, 0.16	0.12	−0.02, 0.27
BMQ-HAART score	−0.006*	0.002	−0.01, −0.002	−0.09	−0.16, −0.02
History of psychiatric disorder (yes)	0.05	0.06	−0.06, 0.16	0.08	−0.09, 0.26
Normal ALT[b] (yes)	−0.04	0.04	−0.12, 0.04	−0.07	−0.20, 0.06
History of Syphilis (yes)	0.11	0.09	−0.06, 0.29	0.18	−0.10, 0.6
Other comorbidity[c] (yes)	0.03	0.04	−0.04, 0.11	0.06	−0.07, 0.18
Hypertension (yes)	−0.07	0.06	−0.19, 0.05	−0.11	−0.30, 0.09
Diabetes (yes)	−0.18	0.10	−0.38, 0.02	−0.28	−0.61, 0.05
HIV brain involvement history (yes)	−0.16	0.14	−0.43, 0.11	−0.26	−0.69, 0.18
History of Hepatitis C Virus infection (yes)	−0.08	0.09	−0.26, 0.09	−0.14	−0.41, 0.14
Duration of living with HIV (year)	−0.005	0.003	−0.01, 0.001	−0.08	−0.18, 0.02
Age group (young vs old)* time (year)	−0.23***	0.03	−0.30, −0.17	−0.31	−0.39, −0.22

A positive B or β means a positive association and a negative B or β means a negative association. The higher the level of B or β, the higher the magnitude of association. '***'p < 0.001, '**'p < 0.01, '*'p < 0.05, B = the unstandardized beta coefficient; β = standardized beta coefficient. [a]PHQ-9 score ≥15. [b]>40 U/L males, >35 U/L females. [c]Other diagnosed age-related comorbidity apart from hypertension, diabetes, heart disease, stroke, peripheral vascular disease, chronic liver failure and chronic kidney disease.

Table 2: **Linear mixed effects model results to identify the effects of age and other factors on longitudinal cognitive performance.**

cognitive decline over 18 months among 96 clinically stable and virally undetectable PWH, we found that 14% of participants declined. In the CHARTER study,[40] 22.7% of participants were classified as a "decliner" (defined if a participant had a decline status over the follow-up period and did not improve in any of the visits) over three years. A Cysique et al., study in China[39] which followed 192 treated PWH over one year reported a cognitive decline rate of 27%. The differences in the neurocognitive decline rate between our study and the previous studies may be due to differences in participant characteristics. Although the participants in our previous Australian study were virally suppressed, they were older (≥45 years old was an inclusion criterion) and had a higher proportion of participants with historical AIDS compared to the participants in the current study. In the CHARTER study, only 70% of participants were on cART and only 41% were virally suppressed at baseline. Similarly, only 56% of the Chinese study participants were taking cART and only 34% had an undetectable viral load. Further, the baseline cognitive impairment rate, which significantly influences cognitive decline[2,43] was higher among these previous studies (Australian study (55%), the CHARTER study (46%), and Chinese-based study (around 36%) compared to 31% in our study). When taken together with the other studies,[4] this pool of research indicated that at the international level where viral suppression rates are lower than those in Australia, cognitive decline is likely to be more common than in the current study.

Unlike previous studies,[11] age ≥50 years was associated with better cognitive performance at baseline in our

study. However, its association with follow-up time was associated with lower cognitive performance meaning older PWH have a higher risk for decline in cognitive function over time. The cross–sectional association between older age and better neurocognitive performance may be due to poorer social, physical, and mental health statuses among younger participants compared to older participants in this study. A lower proportion of younger participants had excellent English and health care access; and a larger proportion of them had felt ashamed, blamed, awkward, avoided, and excluded because of HIV, had suffered disturbing depressive symptoms and major stress events, had had more than one bed day due to an illness, lower ART adherence level and finally lower quality of life compared to the older participants. On the other hand, the increased risk for cognitive decline over time among older PWH may subsequently heighten their susceptibility to cognitive deterioration as accelerated cognitive decline has been reported as a prodromal phase for subsequent cognitive impairment or neurodegenerative diseases.[44] And this higher chance for cognitive decline among the older participants could not merely be interpreted as normal cognitive aging because the GZS which was used as the outcome was corrected for normal aging effect.

Being married or in a regular relationship was associated with better cognitive performance compared to those who are single/widowed/separated/divorced. The negative effect of being single/widowed/separated/divorced on cognition may be related to loneliness which has been consistently associated with lower cognitive function in previous studies among both PWH and the general population.[45–47] This finding has important implications for PWH and those who are aging in particular.[48] HIV care and psychosocial services may promote social engagement among PWH especially those who are not in a regular relationship to alleviate loneliness.[48]

Excellent English was associated with better cognitive function in this study. Evidence of poorer performance on neuropsychological tests in non-English speakers despite similar demographics is well-established and this effect was seen on verbal as well as non-verbal tasks with lower language requirements.[49–51] In general, this is likely to reflect cultural differences in education style and less familiarity with formal testing that is more common in Western societies.[52] In addition, the negative effect of lower English proficiency on cognitive performance may be a mediation effect of lower educational achievement because participants with lower English proficiency level were significantly likely to have lower education level in this study.

Our study found that lower socioeconomic status (defined as social welfare as the major source of income) was associated with lower longitudinal performance. This finding reinforces the evidence in the existing literature that socioeconomic disparities can contribute negatively not only to physical health but also to cognitive health.[53,54] This finding highlights the need to endorse a holistic life course approach to diagnose cognitive health problems among PWH taking into consideration social and structural factors as well.[55]

As reported in previous research,[14,56] we found that severe depression was associated with poorer cognitive performance. Given that depression is common among PWH and can often be effectively treated with pharmacological and non-pharmacological interventions such as cognitive behavioral therapy, depression should be regularly screened among PWH.[14,56]

Less belief in ART necessity and more concerns about negative impacts of ART, measured with BMQ-HAART, were associated with lower cognitive performance. The effect of less belief in necessity and acceptability of ART on poor cognitive performance may represent a proxy for lower ART adherence levels. Indeed, the BMQ-HAART has been reported to be able to reliably predict drug adherence in previous research[28,57,58] and its score was significantly correlated with adherence measures in this study. Importantly, recent studies found that suboptimal ART adherence increases systemic immune activation and inflammation even in the context of plasma viral suppression as in the current study.[59,60] This finding has important implications for HIV services. Clinicians and counselling services should regularly assess the perception on necessity and acceptability of ART among PWH and address any concerns and false beliefs if possible.[61]

Unexpectedly, having felt avoided because of HIV status was associated with better cognitive performance. One possible reason is that participants who had experienced HIV stigma were more likely to be receiving social support such as engagement with NGOs or home and community care, thus leading to improved cognition and heightened HIV stigma awareness.[62] In addition, the questionnaire used in this study to assess stigma does not necessarily investigate how severely and how frequent the stigmatized experiences (enacted HIV stigma) have been. Future studies should further explore the complex and possible dose response relationship between stigma experiences and cognition among PWH.

Our study has limitations. First, underrepresentation of female participants in this study limits the generalizability of study findings, although women with stable HIV are also likely to benefit in terms of cognitive health. Second, the cognitive decline rates reported in this study should be interpreted with some nuance because participants who were lost to follow up at Month-12 and Month-24 were more likely to be from a socioeconomically disadvantaged group which is reported to be associated with poorer cognition. Third, our study did not include a HIV-negative control sample and therefore, the aging effect in our study should be

interpreted as only indicative of premature/accelerated aging effect. Nevertheless, we corrected the cognitive scores for normal aging effect. Fourth, lack of a HIV-negative control group may also attenuate the validity of normative sample selection. However, this is unlikely since we selected participants whose cognitive performance was within normal limits (based on large normative data in healthy controls) for computing the LME regression-based formula; a method that has been successfully used in previous studies to estimate normal longitudinal performance.[35] Fourth, our study did not assess functional decline or activities of daily living, and therefore, could not be evaluated whether cognitive decline and changes among the participants were correlated with functional impairment or decline. Nevertheless, previous studies have reported that cognitive impairment is associated with functional decline among PWH,[63,64] and the regression-based change score method used in this study is widely accepted as a way to measure meaningful cognitive change among both PWH and other disease populations.[4,65–67] Lastly, our study is subject to self-report bias and recall bias since the information on demographics, socioeconomic status, healthcare seeking behavior and general health status were collected through self-reports. However, recall bias was minimized as the recall period was always ≤12 month and PWH were actively engaged in care. However, self-report bias, is a common element of most NeuroHIV studies because PWH usually come to the clinics on their own without an informant to corroborate their history. In our study, this is however minimized by the fact that patients are highly engaged in care and were therefore known to the staff at each clinic minimizing responses that do not match the medical history of the patients. Finally, one of the main contributors to self-report bias is anxio-depressive symptoms[14] which were measured and considered in multivariate analyses in this study.

In this sample of virally suppressed PWH, clinically meaningful cognitive decline is not different from normal expectation. This finding should be reassuring to the millions of people who are living with stable HIV infection. However, we also identified several instances of cognitive vulnerabilities meaning that cognitive health should remain a focus even in these successfully treated people. Of concern was evidence for abnormal aging on cognitive decline (i.e., decline greater than expected for the normative age). In addition, we observed the negative effect of not having a regular relationship, severe depression, and less belief in necessity and acceptability of ART on longitudinal cognitive performance. These finding warrant integrated multidisciplinary care from clinicians, mental healthcare providers, and psychosocial support workers and counselors for persons living with chronic HIV infection to maintain not only their physical health but also social, mental, and cognitive health which could have a large influence on their QOL and activities of daily living. Future studies should also consider socioeconomic and psychosocial factors and attitude to the treatment in addition to the physical health and clinical factors while evaluating cognitive health among PWH.

Contributors

Conceptualization: Htein Linn Aung, Lucette A. Cysique; Data Collection: Krista J. Siefried; Accessed the raw data: Krista J. Siefried, Thomas M. Gates, Lucette A. Cysique, Htein Linn Aung; Methodology: Htein Linn Aung, Thomas M. Gates, Lucette A. Cysique; Formal Analysis and investigation: Thomas M. Gates, Lucette A. Cysique, Htein Linn Aung; Writing - original draft preparation: Htein Linn Aung; Writing - review and editing: Krista J. Siefried, Thomas M. Gates, Limin Mao, Bruce Brew, Andrew Carr, Lucette A. Cysique; Supervision: Bruce Brew, Limin Mao, Lucette A. Cysique.

Data sharing statement

Study data is freely available on the public repository of UNSW Australia named UNSWorks at the following link: https://doi.org/10.26190/unsworks/24031.

Declaration of interests

Andrew Carr received consulting fees from Gilead and ViiV; honoraria for lectures or presentations from Gilead; and payment for participation on a Data Safety Monitoring Board or Advisory Board from Gilead, ViiV and MSD. Krista Siefried received travel support/sponsorship to attend conferences from Gilead. Bruce Brew received payment or honoraria for lectures or presentations from Jasnssen. All the other authors declare no conflicts of interest.

Acknowledgment

Funding for the PAART study was provided in part by unrestricted educational grants from Gilead Sciences (www.gilead.com) (Grant Number: IN-AU-264- 0131), the Balnaves Foundation (www.balnavesfoundation.com), the Victorian Department of Health and Human Services (Australia) (www.dhs.vic.gov.au/home), Western Australia Health (www.health.wa.gov.au), the ACT Ministry of Health (Australia) (www.health.act.gov.au), and in-kind support from the Queensland Department of Health (Australia) (www.health.qld.gov.au). NHMRC Partnership grant APP1058474 (PI Carr, Andrew). The funders were not involved in the conception, analysis, and interpretation of the current study.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2022.101792.

References

1 UNAIDS. AIDSINFO. https://aidsinfo.unaids.org/; 2021. Accessed February 22, 2022.
2 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(3):e0171887.
3 Janssen MA, Koopmans PP, Kessels RP. Cognitive decline in relation to psychological wellbeing and HIV disease-and treatment characteristics in HIV-infected patients on cART: a one-year follow-up study. *AIDS Behav*. 2017;21(6):1728–1734.
4 Cysique LA, Casaletto KB, Heaton RK. Reliably measuring cognitive change in the era of chronic HIV infection and chronic HIV-

associated neurocognitive disorders. *Curr Top Behav Neurosci*. 2019;50:271–298.
5 Brew BJ, Garber JY. Neurologic sequelae of primary HIV infection. *Handb Clin Neurol*. 2018;152:65–74.
6 Kim M, Park J-M. Factors affecting cognitive function according to gender in community-dwelling elderly individuals. *Epidemiol Health*. 2017;39:e2017054.
7 Nyberg L, Boraxbekk C-J, Sörman DE, et al. Biological and environmental predictors of heterogeneity in neurocognitive ageing: evidence from Betula and other longitudinal studies. *Ageing Res Rev*. 2020;64:101184.
8 Zhu S, Zhao J, Chen Z, Wang Y. Influential factors on cognitive performance in middle-aged cohort: third national health and nutrition examination survey-based study. *Medicine*. 2018;97(37):e12033.
9 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(2):227–238.
10 Valcour VG. HIV, aging, and cognition: emerging issues. *Top Antivir Med*. 2013;21(3):119–123.
11 Aung HL, Cysique LA. What is the level of evidence for premature and accelerated aging effects on neurocognition in people living with HIV? A systematic review and meta-analysis. *AIDS Behav*. 2019;25(3):917–960.
12 Daly S, Allen JJ. *Inequalities in mental health, cognitive impairement and dementia among older people*. London: Insitute of Health Equity; 2016.
13 Rubin LH, Maki PM, Springer G, et al. Cognitive trajectories over 4 years among HIV-infected women with optimal viral suppression. *Neurology*. 2017;89(15):1594–1603.
14 Muñoz-Moreno JA, Cysique LA, Rourke SB. Neuropsychiatric disorders, emotional disturbances, and their associations with HIV-associated neurocognitive disorder. *Curr Top Behav Neurosci*. 2021;50:347–366.
15 Moore DJ, Montoya JL, Casaletto KB, Hampton Atkinson J. Medication adherence and HIV-associated neurocognitive disorders (HAND). In: Hope TJ, Richman DD, Stevenson M, eds. *Encyclopedia of AIDS*. New York, NY: Springer New York; 2018:1312–1318.
16 Chang L, Liang H, Kandel SR, He JJ. Independent and combined effects of nicotine or chronic tobacco smoking and HIV on the brain: a review of preclinical and clinical studies. *J Neuroimmune Pharmacol*. 2020;15:1–36.
17 Hauser KF, Fitting S, Dever SM, Podhaizer EM, Knapp PE. Opiate drug use and the pathophysiology of neuroAIDS. *Curr HIV Res*. 2012;10(5):435–452.
18 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(2):143–156.
19 Selnes OA. Impact of HIV infection and alcohol on cognition: a review. *Neurobehav HIV Med*. 2010;2:85–94.
20 Liang H-J, Ernst T, Cunningham E, Chang L. Contributions of chronic tobacco smoking to HIV-associated brain atrophy and cognitive deficits. *AIDS*. 2022;36(4):513–524.
21 Duff K. Evidence-based indicators of neuropsychological change in the individual patient: relevant concepts and methods. *Arch Clin Neuropsychol*. 2012;27(3):248–261.
22 Van der Elst W, Molenberghs G, Van Boxtel MP, Jolles J. Establishing normative data for repeated cognitive assessment: a comparison of different statistical methods. *Behav Res Methods*. 2013;45(4):1073–1086.
23 Siefried KJ, Mao L, Kerr S, et al. Socioeconomic factors explain suboptimal adherence to antiretroviral therapy among HIV-infected Australian adults with viral suppression. *PLoS One*. 2017;12(4):e0174613.
24 Siefried KJ, Mao L, Cysique LA, et al. Concomitant medication polypharmacy, interactions and imperfect adherence are common in Australian adults on suppressive antiretroviral therapy. *AIDS (London, England)*. 2018;32(1):35.
25 Duracinsky M, Herrmann S, Berzins B, et al. The development of PROQOL-HIV: an international instrument to assess the health-related quality of life of persons living with HIV/AIDS. *J Acquir Immune Defic Syndr*. 2012;59(5):498–505.
26 Kroenke K, Spitzer R, William J. The PHQ-9: validity of a brief depression severity measure [online] [diunduh 4 September 2017]. Tersedia dari. http://www.ncbi.nlm.nih.gov; 2001.
27 Ewing JA. Detecting alcoholism: the CAGE questionnaire. *JAMA*. 1984;252(14):1905–1907.
28 Horne R, Buick D, Fisher M, Leake H, Cooper V, Weinman J. Doubts about necessity and concerns about adverse effects: identifying the types of beliefs that are associated with non-adherence to HAART. *Int J STD AIDS*. 2004;15(1):38–44.
29 Knobel H, Alonso J, Casado JL, et al. Validation of a simplified medication adherence questionnaire in a large cohort of HIV-infected patients: the GEEMA Study. *AIDS*. 2002;16(4):605–613.
30 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(2):165–178.
31 Kamminga J, Lal L, Wright EJ, Bloch M, Brew BJ, Cysique LA. Monitoring HIV-associated neurocognitive disorder using screenings: a critical review including guidelines for clinical and research use. *Curr HIV AIDS Rep*. 2017;14(3):83–92.
32 Gates TM, Kamminga J, Jayewardene A, et al. An examination of reliable change methods for measuring cognitive change with the Cogstate computerized battery: research and clinical implications. *Arch Clin Neuropsychol*. 2020;36(4):597–612.
33 Blackstone K, Moore D, Franklin D, et al. Defining neurocognitive impairment in HIV: deficit scores versus clinical ratings. *Clin Neuropsychol*. 2012;26(6):894–908.
34 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(8):753–767.
35 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(5):505–522.
36 Pinheiro J, Bates D, DebRoy S, et al. *Package 'nlme'*. 2017;3(1).
37 Brouillette M-J, Yuen T, Fellows LK, Cysique LA, Heaton RK, Mayo NE. Identifying neurocognitive decline at 36 months among HIV-positive participants in the CHARTER cohort using group-based trajectory analysis. *PLoS One*. 2016;11(5):e0155766.
38 Seider TR, Luo X, Gongvatana A, et al. Verbal memory declines more rapidly with age in HIV infected versus uninfected adults. *J Clin Exp Neuropsychol*. 2014;36(4):356–367.
39 Cysique LA, Letendre SL, Ake C, et al. Incidence and nature of cognitive decline over one year among HIV-infected former plasma donors in China. *AIDS*. 2010;24(7):983.
40 Heaton RK, Franklin Jr DR, Deutsch R, et al. Neurocognitive change in the era of HIV combination antiretroviral therapy: the longitudinal CHARTER study. *Clin Infect Dis*. 2014;60(3):473–480.
41 Cysique LA, Jugé L, Gates T, et al. Covertly active and progressing neurochemical abnormalities in suppressed HIV infection. *Neurol Neuroimmunol Neuroinflamm*. 2018;5(1):e430.
42 Suzuki K, Levert A, Yeung J, et al. HIV-1 viral blips are associated with repeated and increasingly high levels of cell-associated HIV-1 RNA transcriptional activity. *AIDS*. 2021;35(13):2095.
43 Cysique LAJ, Maruff P, Brew BJ. Variable benefit in neuropsychological function in HIV-infected HAART-treated patients. *Neurology*. 2006;66(9):1447–1450.
44 Karr JE, Graham RB, Hofer SM, Muniz-Terrera G. When does cognitive decline begin? A systematic review of change point studies on accelerated decline in cognitive and neurological outcomes preceding mild cognitive impairment, dementia, and death. *Psychol Aging*. 2018;33(2):195–218.
45 Harris M, Brouillette M-J, Scott SC, et al. Impact of loneliness on brain health and quality of life among adults living with HIV in Canada. *J Acquir Immune Defic Syndr*. 2020;84(4):336–344.
46 Han SD, Adeyemi O, Wilson RS, et al. Loneliness in older black adults with human immunodeficiency virus is associated with poorer cognition. *Gerontology*. 2017;63(3):253–262.
47 Lara E, Martín-María N, De la Torre-Luque A, et al. Does loneliness contribute to mild cognitive impairment and dementia? A systematic review and meta-analysis of longitudinal studies. *Ageing Res Rev*. 2019;52:7–16.
48 Greene M, Hessol NA, Perissinotto C, et al. Loneliness in older adults living with HIV. *AIDS Behav*. 2018;22(5):1475–1484.
49 Carstairs JR, Myors B, Shores EA, Fogarty GJ. Influence of language background on tests of cognitive abilities: Australian data. *Aust Psychol*. 2006;41(1):48–54.

50 Kisser JE, Wendell CR, Spencer RJ, Waldstein SR. Neuropsychological performance of native versus non-native English speakers. *Arch Clin Neuropsychol*. 2012;27(7):749–755.

51 Low L-F, Harrison F, Kochan NA, et al. Can mild cognitive impairment be accurately diagnosed in English speakers from linguistic minorities? Results from the Sydney Memory and Ageing Study. *Am J Geriatr Psychiatry*. 2012;20(10):866–877.

52 Rosselli M, Ardila AJ. The impact of culture and education on non-verbal neuropsychological measurements: a critical review. *Brain Cogn*. 2003;52(3):326–333.

53 Majoka MA, Schimming CJ. Effect of social determinants of health on cognition and risk of alzheimer disease and related dementias. *Clin Ther*. 2021;43(6):922–929.

54 Do TC, Avihingsanon A, Suksawek S, et al. HIV-associated cognitive performance and psychomotor impairment in a Thai cohort on long-term cART. *J Virus Erad*. 2018;4(1):41–47.

55 Anstey KJ. Optimizing cognitive development over the life course and preventing cognitive decline: introducing the cognitive health environment life course model (CHELM). *SAGE*. 2014;38(1):1–10.

56 Rubin LH, Maki PM. HIV, depression, and cognitive impairment in the era of effective antiretroviral therapy. *Curr HIV AIDS Rep*. 2019;16(1):82–95.

57 Gauchet A, Tarquinio C, Fischer G. Psychosocial predictors of medication adherence among persons living with HIV. *Int J Behav Med*. 2007;14(3):141–150.

58 Horne R, Chapman SC, Parham R, Freemantle N, Forbes A, Cooper V. Understanding patients' adherence-related beliefs about medicines prescribed for long-term conditions: a meta-analytic review of the Necessity-Concerns Framework. *PLoS One*. 2013;8(12):e80633.

59 Castillo-Mancilla JR, Phillips AN, Neaton JD, et al. Association of suboptimal antiretroviral therapy adherence with inflammation in virologically suppressed individuals enrolled in the SMART study. *Open Forum Infect Dis*. 2018;5(1):ofx275.

60 Castillo-Mancilla JR, Phillips AN, Neaton JD, et al. Incomplete ART adherence is associated with higher inflammation in individuals who achieved virologic suppression in the START study. *J Int AIDS Soc*. 2019;22(6):e25297.

61 Gellaitry G, Cooper V, Davis C, Fisher M, Leake Date H, Horne RJ. Patients' perception of information about HAART: impact on treatment decisions. *AIDS Care*. 2005;17(3):367–376.

62 Emlet CA. An examination of the social networks and social isolation in older and younger adults living with HIV/AIDS. *Health Soc Work*. 2006;31(4):299–308.

63 Kordovski VM, Tierney SM, Woods SP. Conceptualizing and assessing everyday functioning in the context of HIV-associated neurocognitive disorders. In: Cysique LA, Rourke SB, eds. *Neurocognitive complications of HIV-infection: neuropathogenesis to implications for clinical practice*. Cham: Springer International Publishing; 2021:329–346.

64 Laverick R, Haddow L, Daskalopoulou M, et al. Self-reported decline in everyday function, cognitive symptoms, and cognitive function in people with HIV. *JAIDS J Acquired Immune Defic Syndromes*. 2017;76(3):e74–e83.

65 Sawrie SM, Chelune GJ, Naugle RI, Lüders HO. Empirical methods for assessing meaningful neuropsychological change following epilepsy surgery. *J Int Neuropsychol Soc*. 1996;2(6):556–564.

66 Combs HL, Wyman-Chick KA, Erickson LO, York MK. Development of standardized regression-based formulas to assess meaningful cognitive change in early Parkinson's disease. *Arch Clin Neuropsychol*. 2020;36(5):734–745.

67 Sawrie SM, Marson DC, Boothe AL, Harrell LE. A method for assessing clinically relevant individual cognitive change in older adult populations. *J Gerontol: Series B*. 1999;54B(2):P116–P124.