OPEN

AIDS, Publish Ahead of Print

DOI: 10.1097/QAD.0000000000003230

Abnormal cognitive aging in people living with HIV: Evidence from Data integration between two countries' cohort studies

Short Title: Abnormal cognitive aging in people living with HIV

Htein Linn AUNG[1,2], Thomas M. GATES[1,3], Limin MAO[4], Bruce J. BREW[1,2,5], Sean. B ROURKE[6,7], Lucette A. CYSIQUE[1,3,6]*

[1] Departments of Neurology and HIV Medicine, St Vincent's Hospital and Peter Duncan Neurosciences Unit, St Vincent's Centre for Applied Medical Research, Sydney, Australia

[2] Faculty of Medicine, UNSW, Sydney, Australia

[3] School of Psychology, University of New South Wales, Sydney, NSW, Australia

[4] Centre for Social Research in Health, UNSW, Sydney, Australia

[5] Faculty of Medicine, University of Notre Dame, Sydney, Australia

[6] MAP Centre for Urban Health Solutions, Li Ka Shing Knowledge Institute, St. Michael's Hospital

[7] Department of Psychiatry, University of Toronto

*** Corresponding author**

E-mail: lcysique@unsw.edu.au

Address: 11 Botany Street, School of Psychology, Matthews Building, Room 1012

The University of New South Wales, Sydney, NSW, 2052, Australia

Funding: Nil

Author Contributions

Conceptualization: Htein Linn Aung, Lucette A. Cysique;

Methodology: Htein Linn Aung, Thomas M. Gates, Lucette A. Cysique;

Formal Analysis and investigation: Htein Linn Aung;

Writing - original draft preparation: Htein Linn Aung;

Writing - review and editing: Thomas M. Gates, Limin Mao, Bruce Brew, Sean. B Rourke, Lucette A. Cysique;

Supervision: Bruce Brew, Limin Mao, Lucette A. Cysique.

Abstract

Objectives: Previous research has shown inconsistent results on whether cognitive aging is abnormal in people living with HIV (PLHIV) because of low sample size, cross-sectional design, and non-standard neuropsychological methods. To address these issues, we integrated data from two longitudinal studies: Australian HIV and Brain Ageing Research Program (N=102) and CNS HIV Antiretroviral Therapy Effects Research (CHARTER) study (N=924) and determined the effect of abnormal aging on neurocognitive impairment (NCI) among PLHIV.

Methods: Both studies used the same neuropsychological test battery. NCI was defined based on demographically-corrected global deficit score (≥0.5=impaired). Both studies also assessed comorbidities, neuropsychiatric conditions and functional status using similar tools. To determine the cross-sectional and longitudinal effects of age on the risk of NCI, a generalized linear mixed-effect model tested main and interaction effects of age group (young, <50 VS old, ≥50) and time on NCI adjusting the effects of covariates.

Results: Older PLHIV had 83% higher chance of NCI compared to younger PLHIV (OR=1.83(1.15-2.90), p<0.05). Older participants also had a greater risk of increases in NCI over the follow-up (OR=1.66(1.05-2.64), p<0.05) than younger participants. Non-White ethnicity (p<0.05), having a contributing (p<0.05) or confounding (p<0.001) comorbidity, greater cognitive symptoms (p<0.001), and abnormal creatinine level (p<0.05), plasma viral load >200copies/ml (p<0.05), being from the Australian cohort (p<0.05) were also associated with a higher risk of NCI.

Conclusions: Data integration may serve as a strategy to increase sample size and study power to better assess abnormal cognitive aging effect in PLHIV which was significant in the current study.

Keywords: HIV, AIDS, Aging, Cognition, Cognitive Impairment, Data Integration

Introduction

Aging among people living with HIV (PLHIV) adds additional risks for neurocognitive impairment (NCI) [1]. Previous research has suggested that cognitive aging can be accentuated and accelerated among PLHIV [1, 2]. However, based on a systematic review [3] our group has recently conducted, current available evidence on these abnormal patterns of neurocognitive aging among PLHIV have been inconclusive. Low sample size, cross-

sectional study design and heterogeneity in neuropsychological methods in previous research have led to conflicting results[3]. In addition, only a few studies considered the effect of comorbidities while examining the abnormal cognitive aging effects among PLHIV. Large scale multidimensional longitudinal data are needed to detect a small-medium effect of chronological age among PLHIV [4].

The recruitment of large samples is always challenging. One possible solution to achieve higher sample sizes is to integrate data from individual studies across the world to form a larger dataset as in the dementia research [3, 5, 6]. This strategy for data integration has the benefit of leveraging the cost-effective use of data that are for public use [7]. Importantly, it will also improve the generalizability of research output since the sample will become more heterogeneous [5]. Moreover, there is merit to minimizing the effects of study-level factors through data integration between studies [7]. The NeuroHIV field could also establish a similar mechanism for data integration and harmonization internationally to help resolve emerging research questions.

For successful data integration and harmonization, it is ideal that individual studies use not only the same neuropsychological tests but also the same testing and norming procedures. The HIV Neurobehavioral Research Centre (HNRC) neuropsychological test battery and its testing, scoring and norming procedures have been commonly used among many NeuroHIV studies across the world [8-10] including the HNRC CNS HIV Antiretroviral Therapy Effects Research (CHARTER) study [11, 12]. In Australia, our group set up the HIV and Brain Aging Research Program in 2009 [13] using a shortened version of this battery. Data from the CHARTER study are accessible upon request from the National NeuroAIDS Tissue Consortium (NNTC) (www.nntc.org). We therefore combined data from these two studies to: 1. demonstrate the feasibility of data integration in the NeuroHIV field. 2. To determine whether older age increases the risk for NCI among PLHIV both cross-sectionally and

longitudinally while assessing for potential cohort effects and 3. To identify biomarkers and health conditions associated with cognitive impairment among PLHIV.

Methods

Study cohorts

This study used data from two longitudinal NeuroHIV studies which have been extensively described: the HIV and Brain Aging Research Program in Australia [13] and the CHARTER study from the US [14]. Access to CHARTER data was obtained through a formal request to the NNTC. The Australian study recruited 102 PLHIV from St Vincent's Hospital, Sydney between 2009 and 2011 [13]. Inclusion criteria were ≥45 years of age, had been diagnosed with HIV more than five years ago, had been stable on cART for a minimum of six months, and had a nadir CD4 lymphocyte T cell count ≤350 cells/mm3. Data were collected at baseline and at month 18. Ninety six participants attended the 18 month follow-up visit (average follow-up duration = 22 months, SD=3.82) [15].

The CHARTER study [14] was conducted across six sites in the US. It recruited a total of 1,600 PLHIV between 2003 and 2007. A subset of samples was followed-up six monthly for the longitudinal study up to a maximum of 11.5 years [16]. For our study, participants with pre-morbid Schizophrenia, non-HIV dementia or neurodegenerative disease, substance or alcohol intoxication, poor English proficiency level and those who were not taking cART at the time of cognitive testing were excluded. After exclusion of ineligible cases, 924 participants remained in the CHARTER cohort. Follow-up visits from the CHARTER cohort were included only up to 36 months for the current study.

Data integration

Detailed data collection processes for each study cohort have been published elsewhere [11-13, 15, 17]. Only information which was collected in both studies were incorporated in this study

and included demographic factors, comorbidities (comorbidity rating for HAND, current depression, substance use disorder, diabetes, anemia, history of heart attack and history of stroke), blood tests (cholesterol, triglyceride, and creatinine), HIV biomarkers and clinical information, cognitive symptoms, and functional status. For the current study analyses, Hispanic (N=59) and other ethnicity (N=15) were categorized as "Other" because on their own their prevalence was low. Lifetime and current (last 12 months) alcohol and drug use disorders were assessed with the Composite International Diagnostic Interview (CIDI) [18] in the CHARTER study and with the Mini International Neuropsychiatric Interview (MINI) [19] in the Australian study. Both semi-structured interviews yield standard DSM-IV diagnoses which were used in rating psychiatric comorbidities. In both studies, the effect of medical and psychiatric comorbidities on NCI was classified into either no/incidental, contributing, or confounding as operationalized by Heaton et al. [20] (detailed steps are described in S1, http://links.lww.com/QAD/C488). Both studies used the Patient's Assessment of Own Functioning Inventory (PAOFI) [21] to assess self-perceived cognitive symptoms, the Beck Depression Inventory-II (BDI-II) scale [22] to assess depressive symptoms, and the modified version of the Lawton and Brody (1969) instrumental activities of daily living (IADL) scale [23, 24] to assess functional decline.

Regarding neuropsychological testing, the CHARTER study used a battery containing 15 tests and the Australian study used a battery containing 13 tests. We used 10 neuropsychological tests which were common between two studies (Table S2, http://links.lww.com/QAD/C489). Raw scores were converted to demographically-corrected T-scores applying standard normative data from the respective populations. Specifically, regression-based US norms [25] were used for the US cohort. For the Australian cohort, we used locally-derived regression-based Australian norms (generated from demographically, lifestyle, and geographically comparable HIV-negative controls [13] plus more recently

collected normative data) in participants with high literacy levels (≥15 years of education or pre-morbid full-scale IQ (FSIQ)≥110) because the US norms underperform in the Australian HIV-negative with high education (cognitive domains T-scores are statistically different from Mean = 50 and SD =10) . We used the regression-based US norms [25] in participants with lower literacy level (<15 years of education or pre-morbid FSIQ<110) as the US norms perform optimally in the Australian HIV-negative with low education (cognitive domains T-scores are not statistically different from Mean =50 and SD =10). Follow-up cognitive data were corrected for practice effect as well [26]. T-scores were then transformed to deficit scores ranging from 0-5 (0 means no impairment and 5 means severe impairment). Next, the mean T-score and global deficit score (GDS) were computed by averaging across individual tests. Conventionally, a GDS of ≥0.5 was defined as neurocognitively impaired. A GDS of ≥0.5 not only has optimal specificity and sensitivity to detect impairment in clinical populations [27] but also handles tests' correlations across the test battery and optimally balances Type I and II errors [28]. The consideration of clinically relevant NCI is important because at this threshold, both patients and HIV physicians may start to notice that cognitive changes interfere with everyday activities [29].

Data Analysis

First, descriptively, all of the baseline information were compared between the US and Australian cohorts, between young (<50) and old (≥50) participants (this cut-off is seen as a biologically meaningful cut-off in PLHIV [1]), and between those classified as cognitively normal and impaired using t-test, Mann-Whitney U Test, and chi-square test. Afterwards, to detect and extract the magnitude and significance of the cross-sectional and longitudinal effects of chronological age on the risk of NCI, generalized linear mixed-effect regression (GLMER) models were conducted. Mixed-effect models are robust in dealing with unbalanced data with varied number of follow-ups and varied duration between follow-up

visits among participants by treating the follow-up time as a continuous variable [30]. Using random effects, a mixed-effect model accounts for correlation between repeated measurements within a person and variations of the outcome measure at the baseline among individual participants [31, 32]. NCI (No versus Yes) derived from the demographically corrected T-scores was used as the primary outcome to assess whether aging imposes additional risk of NCI among PLHIV even after correcting for the normal aging effect (per use of the country-based regression norms correcting for a normal aging effect). Age group (young VS old) and follow-up time in years, and their interaction were chosen as the main fixed effects. Subject was used as the random effect. Covariates were selected based on a top-down selection process. Variables with $p>0.5$ were gradually removed from the model. Model performance was measured with the Akaike Information criteria (AIC) value. Models with and without random slope were tested. Since the model with the random slope outperformed, the final model was run with the random slope. A sensitivity analysis was conducted by testing a model confined to the participants who had at least a follow-up visit because only 48% of the participants had a follow-up visit. In addition, another model was tested among those who were virally-suppressed (VL<1,000 copies/ml) to assess if the age effect changes in the context of viral suppression. LME4 package [33] from R version 3.6.1 [34] was used for all the statistical analysis.

Results

After combining the eligible participants from the two cohorts, a total of 1,026 participants remained in this study (mean age=45.22 years±8.66). Table 1 shows the baseline characteristics of study participants in the entire sample and in young versus old participants and impaired versus unimpaired participants at the baseline. Results from the generalized linear mixed-effect model with NCI as the outcome were presented in Table 2 and Fig 1. Both older age (OR=1.83 (1.15, 2.90), $p<0.05$) and the interaction between older age and

follow-up time (OR=1.66 (1.05, 2.64), p<0.05) were associated with a higher risk of NCI. Longer follow-up duration was associated with a lower risk of NCI (OR=0.64 (0.45, 0.90), p<0.01).

Among covariates, Black/African American (OR=1.60 (1.01, 2.53), p<0.05) and "Other" ethnicity (OR=2.41 (1.12, 5.17), p<0.05) were associated with a higher risk of NCI compared with White ethnicity. In terms of comorbidities, having a contributing (OR=1.59 (1.03, 2.46), p<0.05) or confounding (OR=11.9 (5.77, 24.70), p<0.001) comorbidity rating was associated with a higher chance of NCI compared to having incidental/no comorbidity rating. In addition, higher PAOFI score (OR=1.07 (1.04, 1.11), p<0.001) and having abnormal creatinine level (>90 μmol/L for Females and >110 μmol/L for Males) (OR=1.83 (1.08, 3.08), P<0.05) were also associated with a greater likelihood of NCI. On the other hand, plasma viral count <200 copies/ml (OR=0.63 (0.43, 0.92), p<0.05) and being from the US cohort (OR=0.48 (0.24, 0.98), p<0.05) were associated with a lower risk of NCI.

Two sensitivity analyses were conducted (Table S3, http://links.lww.com/QAD/C490) with one model confined to those who had at least one follow-up visit (N=488 inclusive of all Australians) and one model among those who had achieved viral suppression at the time of their visits (N=793 inclusive of all Australians). The effect of age remained significant in both models. Both the individual effect of age group and the interaction between age group and follow-up time were associated with a higher risk of NCI in both the model that included only participants with at least one follow-up visit (OR for older age =1.97 (1.00, 3.85), p<0.05) (OR for older age * follow-up time interaction=1.70 (1.03, 2.80), p<0.05), and in the model which included participants who had achieved viral suppression at the time of their visits (OR for older age =1.65 (1.05, 2.61), p<0.05) (OR for older age * follow-up time interaction=1.68 (1.05, 2.70), p<0.05).

Discussion

To our knowledge, this is the first study which combined and harmonized data between NeuroHIV studies from two different countries. We successfully combined data from the HIV and Brain Aging Research Program in Australia and the CHARTER study from the US and robustly determined the effects of abnormal cognitive aging on the risk of NCI among PLHIV. A total of 1,026 participants (102 from the Australian study and 924 from the CHARTER study) were included in this study.

Large sample sizes are needed to achieve a "conventional" power of 80% to detect small to medium sized effects, especially when outcomes are expressed as count/categorical variables such as clinically relevant NCI [2, 3]. Our study provides a pragmatic solution to increase sample size through data integration among studies internationally. Based on the sample size calculation in our review [3], the current study sample size had at least 80% power to detect a small-medium effect size of age on NCI at a statistically significant level ($p<0.05$). While the Australian sample size was much smaller than the US sample, the study represents evidence of feasibility and proof of concept for larger data pooling not only for neuropsychological and IADL data, but also for clinical and biomarker data, demonstrating feasibility for data integration in several types of NeuroHIV data sciences. Further, the data integration enhanced the heterogeneity of the final sample [7] as there were clear demographic, clinical and HIV disease differences between the two cohorts. The Australian group was mostly composed of older, white, high functioning gay and bisexual men who had achieved long-term viral suppression whereas the US cohort was younger and included a considerable proportion of African Americans, females and a sizeable proportion that had not achieved viral suppression.

Data pooling can be done in two ways: a posteriori and a priori. For a posteriori scenario, studies which used similar neuropsychological testing methods and collected similar data items could be integrated as we did in this study. We hope that the requirements for the data merging can be followed using the steps that we have provided, and our group is open to providing further guidance in the eventual uptake of the current work including for the development of regression-based norms. For a priori scenarios, the NeuroHIV research community would need to agree on a core set of neuropsychological tests [35] (e.g., the international HNRC neuropsychological test battery which has already been adapted and used in different countries such as China [8], India [10] and Brazil [36]) and a minimum set of data items to be collected provisionally. In both a posteriori and a priori scenarios, a consortium with a steering committee may need to be established to determine how and where the data repository may be developed and maintained. Such efforts have been successfully established in the neuroimaging community (e.g., ENIGMA [37]) and dementia research (e.g., ADNI [38]) and will be useful for the newly established NIMH Biotypes of CNS Complications in PLHIV project [39].

Our study further confirms that older age is associated with increased risk for NCI both cross-sectionally and longitudinally even after considering for cohort, demographic factors, comorbidities, and HIV disease factors. Our analyses reveal that participants older than 50 years of age had 83% higher chance of NCI compared to the younger participants. Older participants also had a higher probability of increases in NCI over the follow-up compared to the younger participants (OR=1.66). These effects were still significant when the analysis was confined to participants who had already achieved viral suppression: 65% increased risk cross-sectionally and 68% increased risk longitudinally among older participants in relation to younger participants. While we did not have HIV-negative controls in this study, cognitive scores were corrected for demographic effects with robust regression-based norms derived

from appropriate controls' sample, and we are therefore confident that the residual age effect detected was representative of pathological cognitive aging above and beyond that of normal aging.

Despite detection of the significant age effects on NCI in our study, the original longitudinal CHARTER analyses published in 2015 [40] did not identify a significant age effect on neurocognitive decline. This may be explained by relative differences in samples' demographic and clinical characteristics. First, our study results are based on a larger sample compared to the original CHARTER (N=436 versus N=1,026), which may have improved the power in our study to detect small-medium sized age effects at a statistically significant level. Second, we used a dichotomous age grouping (50+ as a cut-off for older) while the original CHARTER used a linear age strategy. Third, the inclusion of Australians who were all older than 40 years of age increased the overall number of people age 50+ at baseline by about 5% (23.8% in the 2014 CHARTER study sample VS 29.4% in our study sample) (additional data on age group breakdown and characteristics of the older and younger samples in the original CHARTER analysis were sought from the CHARTER team). Lastly, younger participants in the 2015 CHARTER study were less likely to be on treatment, which might have predisposed them to have higher neurocognitive decline over older participants. Critically, in our study, we included only participants on cART, and have therefore excluded the complex effect of no treatment and its association between younger age and NCI.

Despite normative correction of cognitive scores for racial/ethnic background, we still found much higher risk of NCI among Black/African American participants (1.60 times higher risk compared to White participants) and those from "Other" racial/ethnic backgrounds (2.41 times greater risk compared to White participants). We interpret these results not so much as the "imperfect" corrections of the norms, but as effects that the norms cannot correct because

they represent the cumulative or synergistic impact of racial/ethnic disparities impacting many aspects of a person's life (e.g., lower quality of education, lower socio-economic status and intergenerational poverty, poorer housing, lower social opportunities, and psychosocial stress associated with racial discrimination) [41-44]. This interpretation is supported by the fact that African American and other racial/ethnic background participants also had higher contributing and confounding comorbidities.

More severe comorbidity ratings were associated with a significant higher risk of NCI. Specifically, having a contributing or confounding comorbidity increased the chance of NCI by 1.59 times and 11.9 times respectively compared to incidental or no comorbidity rating. The Australian cohort included 30% of people with contributing comorbidities and only 2% with confounding comorbidities. Therefore, the confounding effect essentially came from the US cohort. Previous research has also reported such an association between comorbidities and cognitive performance in both PLHIV [45] and the general population [46]. Since age-related comorbidities such as cardiovascular diseases and diabetes, and non-age-related comorbidities such as depression, substance and alcohol use disorders and hepatitis C infection (which can all have an impact on cognition) are more common among PLHIV than in the general population, risk for NCI may be much higher among PLHIV, especially in elders [1]. However, it also follows that minimization of NCI is possible via early detection and management of these comorbidities. With the aging of the HIV population, screening and management strategies for these comorbidities is probably best considered within the context of an HIV geriatric clinic [47, 48].

Our study also showed that abnormal creatinine level is associated with increased risk of NCI. Having abnormal creatinine level was associated with 83% higher chance of NCI. Previous studies have reported an association between renal dysfunction and cognitive

impairment in both PLHIV [49] and general population [50, 51]. Renal impairment is often associated with other risk factors for cognitive impairment such as hypertension, diabetes, cerebrovascular disease, and anemia; these conditions are likely to mediate the effect of renal impairment on cognition [50]. In our study, participants who had renal impairment were more likely to have higher comorbidity rating, diabetes, history of myocardial infarction and stroke and abnormal hemoglobin level.

Lower self-perceived cognitive functioning (higher PAOFI score) was associated with an increased risk for NCI. This finding supports results from previous studies indicating that objective cognitive impairment is associated with subjective cognitive symptoms in PLHIV [52-54]. The PAOFI is often associated with depressive symptoms in PLHIV and thus, cognitive deficit among those with higher PAOFI score may partly be mediated by depression [55, 56]. In the current study, PAOFI score was significantly higher among those who were depressed at baseline (P=<0.0001).

Lastly, a plasma viral count <200 copies/ml reduced the risk for cognitive impairment by 37%. This is congruent with previous studies [57-59]. This finding reinforces the importance of access and adherence to ART to keep HIV viral replication suppressed [60]. Yet it is important to note that even in virally suppressed individuals, the abnormal aging effects were also detected.

Our study has several methodological limitations. During data integration, some of the variables could not be included because of lack of information in either of the studies. The participants included in the study were still overall relatively young (mean age = 45.22, SD =8.86; 29% 50+ years of age). It is therefore possible that as PLHIV are getting older, a stronger effect of age on cognitive deficit may be observed. Lastly, time periods which the US (2003-2007) and Australian (2009-2011) studies were conducted were different, and

variances in HIV treatment advancements over these periods may have affected the cognitive health of participants differently between the two cohorts. Nonetheless, the adjustment of cohort effect in the regression model may have corrected any residual effect of cohort which could not be explained by individual participant level characteristics such as viral load and history of AIDS illnesses.

To conclude, our study demonstrates the feasibility of integrating data between NeuroHIV studies. Data integration or pooling may serve as a cost-effective way to obtain adequate power in the NeuroHIV field. Harmonization of neuropsychological measurement tools and data collection tools are urgently needed to be able to pool data prospectively in the future studies. Our study advocates for HIV clinics to immediately implement routine cognitive screening in all PLHIV age 50+ years, especially those with comorbidities, subjective cognitive complaints, and those who fall into a vulnerable demographic group within their countries.

Acknowledgements

We thank the National NeuroAIDS Tissue Consortium (NNTC) for sharing the CHARTER study data and responding to our query in a timely fashion.

References

1. 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?** *European Geriatric Medicine* 2019.
2. Cysique LA, Brew BJ. **The effects of HIV and aging on brain functions: proposing a research framework and update on last 3 years' findings**. *Current opinion in HIV and AIDS* 2014; 9(4):355-364.
3. 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. In: PROPSERO; 2019.
4. Stephan BCM, Siervo M, Brayne C. How can population-based studies best be utilized to reduce the global impact of dementia? Recommendations for researchers, funders, and policymakers. Alzheimer's & Dementia 2020; 16(10):1448-1456.

5. Brodaty H, Woolf C, Andersen S, Barzilai N, Brayne C, Cheung KS-L, et al. ICC-dementia (International Centenarian Consortium-dementia): an international consortium to determine the prevalence and incidence of dementia in centenarians across diverse ethnoracial and sociocultural groups. BMC Neurol 2016; 16(1):1-10.
6. Sachdev PS, Lipnicki DM, Kochan NA, Crawford JD, Rockwood K, Xiao S, et al. COSMIC (Cohort Studies of Memory in an International Consortium): an international consortium to identify risk and protective factors and biomarkers of cognitive ageing and dementia in diverse ethnic and sociocultural groups. BMC neurology 2013; 13(1):1-8.
7. Hofer SM, Piccinin AM. Integrative data analysis through coordination of measurement and analysis protocol across independent longitudinal studies. Psychological methods 2009; 14(2):150.
8. Cysique LA, Jin H, Franklin Jr DR, Morgan EE, Shi C, Yu X, et al. Neurobehavioral effects of HIV-1 infection in China and the United States: a pilot study. Journal of the International Neuropsychological Society: JINS 2007; 13(5):781.
9. Kabuba N, Menon JA, Franklin DR, Heaton RK, Hestad KA. Use of western neuropsychological test battery in detecting HIV-associated neurocognitive disorders (HAND) in Zambia. AIDS and behavior 2017; 21(6):1717-1727.
10. Kamat R, McCutchan A, Kumarasamy N, Marcotte TD, Umlauf A, Selvamuthu P, et al. Neurocognitive functioning among HIV-positive adults in southern India. Journal of neurovirology 2017; 23(5):750-755.
11. Heaton RK, Clifford DB, Franklin DR, Jr., Woods SP, Ake C, Vaida F, et al. HIV-associated neurocognitive disorders persist in the era of potent antiretroviral therapy: CHARTER Study. Neurology 2010; 75(23):2087-2096.
12. Heaton RK, Franklin DR, Ellis RJ, McCutchan JA, Letendre SL, Leblanc S, et al. HIV-associated neurocognitive disorders before and during the era of combination antiretroviral therapy: differences in rates, nature, and predictors. Journal of neurovirology 2011; 17(1):3-16.
13. Cysique LA, Heaton RK, Kamminga J, Lane T, Gates TM, Moore DM, et al. HIV-associated neurocognitive disorder in Australia: a case of a high-functioning and optimally treated cohort and implications for international neuroHIV research. Journal of neurovirology 2014; 20(3):258-268.
14. Jernigan TL, Archibald SL, Fennema-Notestine C, Taylor MJ, Theilmann RJ, Julaton MD, et al. Clinical factors related to brain structure in HIV: the CHARTER study. Journal of neurovirology 2011; 17(3):248.
15. 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.
16. 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).
17. Grant I, Franklin DR, Deutsch R, Woods SP, Vaida F, Ellis RJ, et al. Asymptomatic HIV-associated neurocognitive impairment increases risk for symptomatic decline. Neurology 2014; 82(23):2055-2062.
18. Kessler RC, Üstün TB. The world mental health (WMH) survey initiative version of the world health organization (WHO) composite international diagnostic interview (CIDI). International journal of methods in psychiatric research 2004; 13(2):93-121.
19. Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, et al. The Mini-International Neuropsychiatric Interview (MINI): the development and validation of a

structured diagnostic psychiatric interview for DSM-IV and ICD-10. Journal of clinical psychiatry 1998; 59(20):22-33.
20. Heaton R, Clifford D, Franklin D, Woods S, Ake C, Vaida F, et al. HIV-associated neurocognitive disorders persist in the era of potent antiretroviral therapy CHARTER Study. Neurology 2010; 75(23):2087-2096.
21. Bell MJ, Terhorst L, Bender CM. Psychometric analysis of the Patient Assessment of Own Functioning Inventory in women with breast cancer. Journal of nursing measurement 2013; 21(2):320-334.
22. Beck AT, Steer RA, Brown G. Beck depression inventory–II. Psychological Assessment 1996.
23. Heaton RK, Marcotte TD, Mindt MR, Sadek J, Moore DJ, Bentley H, et al. The impact of HIV-associated neuropsychological impairment on everyday functioning. Journal of the international neuropsychological society 2004; 10(3):317-331.
24. Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. The Gerontologist 1969.
25. Heaton RK. Revised comprehensive norms for an expanded Halstead-Reitan Battery: Demographically adjusted neuropsychological norms for African American and Caucasian adults, professional manual. Psychological Assessment Resources; 2004.
26. Cysique LA, Franklin Jr D, Abramson I, Ellis RJ, Letendre S, Collier A, et al. Normative data and validation of a regression based summary score for assessing meaningful neuropsychological change. Journal of clinical and experimental neuropsychology 2011; 33(5):505-522.
27. Carey CL, Woods SP, Gonzalez R, Conover E, Marcotte TD, Grant I, et al. Predictive validity of global deficit scores in detecting neuropsychological impairment in HIV infection. 2004; 26(3):307-319.
28. 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(1):53-69.
29. Matchanova A, Woods SP, Kordovski VM. Operationalizing and evaluating the Frascati criteria for functional decline in diagnosing HIV-associated neurocognitive disorders in adults. Journal of neurovirology 2020; 26(2):155-167.
30. Cysique LA, Casaletto KB, Heaton RK. Reliably measuring cognitive change in the era of chronic HIV infection and chronic HIV-associated neurocognitive disorders. 2019.
31. Fitzmaurice GM, Ravichandran C. A primer in longitudinal data analysis. Circulation 2008; 118(19):2005-2010.
32. Singmann H, Kellen D. An introduction to mixed models for experimental psychology. New methods in cognitive psychology 2019; 28(4).
33. Bates D, Sarkar D, Bates MD, Matrix L. The lme4 package. R package version 2007; 2(1):74.
34. Team RC. R: A language and environment for statistical computing. 2013.
35. Saloner R, Cysique LA. HIV-Associated Neurocognitive Disorders: A Global Perspective. Journal of the International Neuropsychological Society : JINS 2017; 23(9-10):860-869.
36. de Almeida SM, Ribeiro CE, de Pereira AP, Badiee J, Cherner M, Smith D, et al. Neurocognitive impairment in HIV-1 clade C-versus B-infected individuals in Southern Brazil. Journal of neurovirology 2013; 19(6):550-556.
37. Thompson PM, Stein JL, Medland SE, Hibar DP, Vasquez AA, Renteria ME, et al. The ENIGMA Consortium: large-scale collaborative analyses of neuroimaging and genetic data. Brain imaging and behavior 2014; 8(2):153-182.

38. Jack Jr CR, Bernstein MA, Fox NC, Thompson P, Alexander G, Harvey D, et al. The Alzheimer's disease neuroimaging initiative (ADNI): MRI methods. Journal of Magnetic Resonance Imaging: An Official Journal of the International Society for Magnetic Resonance in Medicine 2008; 27(4):685-691.
39. Rubin LH, Ances BM. Working HAND in HAND: Central nervous system complications in people with HIV. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 2021.
40. Heaton RK, Group ftC, Franklin DR, Jr, Group ftC, Deutsch R, Group ftC, et al. Neurocognitive Change in the Era of HIV Combination Antiretroviral Therapy: The Longitudinal CHARTER Study. Clinical Infectious Diseases 2014; 60(3):473-480.
41. Fiscella K, Franks P, Gold MR, Clancy CM. Inequality in quality: addressing socioeconomic, racial, and ethnic disparities in health care. Jama 2000; 283(19):2579-2584.
42. Zhang Z, Hayward MD, Yu Y-L. Life course pathways to racial disparities in cognitive impairment among older Americans. Journal of health and social behavior 2016; 57(2):184-199.
43. Glymour MM, Manly JJ. Lifecourse social conditions and racial and ethnic patterns of cognitive aging. Neuropsychology review 2008; 18(3):223-254.
44. Singer B, Ryff C. Racial and Ethnic Inequalities in Health: Environmental, Psychosocial, and Physiological Pathways. In: Intelligence, Genes, and Success: Scientists Respond to The Bell Curve. Devlin B, Fienberg SE, Resnick DP, Roeder K (editors). New York, NY: Springer New York; 1997. pp. 89-122.
45. Tedaldi EM, Minniti NL, Fischer T. HIV-associated neurocognitive disorders: the relationship of HIV infection with physical and social comorbidities. BioMed research international 2015; 2015.
46. Vance D, Larsen KI, Eagerton G, Wright MA. Comorbidities and cognitive functioning: implications for nursing research and practice. Journal of Neuroscience Nursing 2011; 43(4):215-224.
47. Lerner AM, Eisinger RW, Fauci AS. Comorbidities in persons with HIV: the lingering challenge. Jama 2020; 323(1):19-20.
48. Guaraldi G, Palella FJ, Jr. Clinical implications of aging with HIV infection: perspectives and the future medical care agenda. Aids 2017; 31 Suppl 2:S129-s135.
49. Schouten J, Su T, Wit FW, Kootstra NA, Caan MW, Geurtsen GJ, et al. Determinants of reduced cognitive performance in HIV-1-infected middle-aged men on combination antiretroviral therapy. Aids 2016; 30(7):1027-1038.
50. Seliger SL, Siscovick DS, Stehman-Breen CO, Gillen DL, Fitzpatrick A, Bleyer A, et al. Moderate renal impairment and risk of dementia among older adults: the Cardiovascular Health Cognition Study. Journal of the American Society of Nephrology 2004; 15(7):1904-1911.
51. Tamura MK, Xie D, Yaffe K, Cohen DL, Teal V, Kasner SE, et al. Vascular risk factors and cognitive impairment in chronic kidney disease: the Chronic Renal Insufficiency Cohort (CRIC) study. Clinical journal of the American Society of Nephrology 2011; 6(2):248-256.
52. Merriman JD, Sereika SM, Brufsky AM, McAuliffe PF, McGuire KP, Myers JS, et al. Trajectories of self-reported cognitive function in postmenopausal women during adjuvant systemic therapy for breast cancer. Psycho-oncology 2017; 26(1):44-52.
53. Rourke SB, Halman MH, Bassel C. Neurocognitive complaints in HIV-infection and their relationship to depressive symptoms and neuropsychological functioning. Journal of Clinical and Experimental Neuropsychology 1999; 21(6):737-756.

54. Marquine MJ, Flores I, Kamat R, Johnson N, Umlauf A, Letendre S, et al. A composite of multisystem injury and neurocognitive impairment in HIV infection: association with everyday functioning. Journal of neurovirology 2018; 24(5):549-556.
55. Kamat R, Woods SP, Marcotte TD, Ellis RJ, Grant I. Implications of apathy for everyday functioning outcomes in persons living with HIV infection. Archives of Clinical Neuropsychology 2012; 27(5):520-531.
56. Jang HJS. Cognitive function and health-related quality of life in older adults with HIV: University of California, San Francisco; 2016.
57. Chang L, Ernst T, Witt MD, Ames N, Gaiefsky M, Miller E. Relationships among brain metabolites, cognitive function, and viral loads in antiretroviral-naive HIV patients. Neuroimage 2002; 17(3):1638-1648.
58. Childs E, Lyles R, Selnes O, Chen B, Miller E, Cohen B, et al. Plasma viral load and CD4 lymphocytes predict HIV-associated dementia and sensory neuropathy. Neurology 1999; 52(3):607-607.
59. Sacktor N, Skolasky R, Tarwater P, McArthur J, Selnes O, Becker J, et al. Response to systemic HIV viral load suppression correlates with psychomotor speed performance. Neurology 2003; 61(4):567-569.
60. Schaecher KL. The importance of treatment adherence in HIV. The American journal of managed care 2013; 19(12 Suppl):s231-237.

Figure 1: Odds ratio figure for risk of neurocognitive impairment. .Odds ratios were presented only for variables, which are statistically significant. IADL, Instrumental activities of daily living; PAOFI, Patient's Assessment of Own Functioning Inventory.

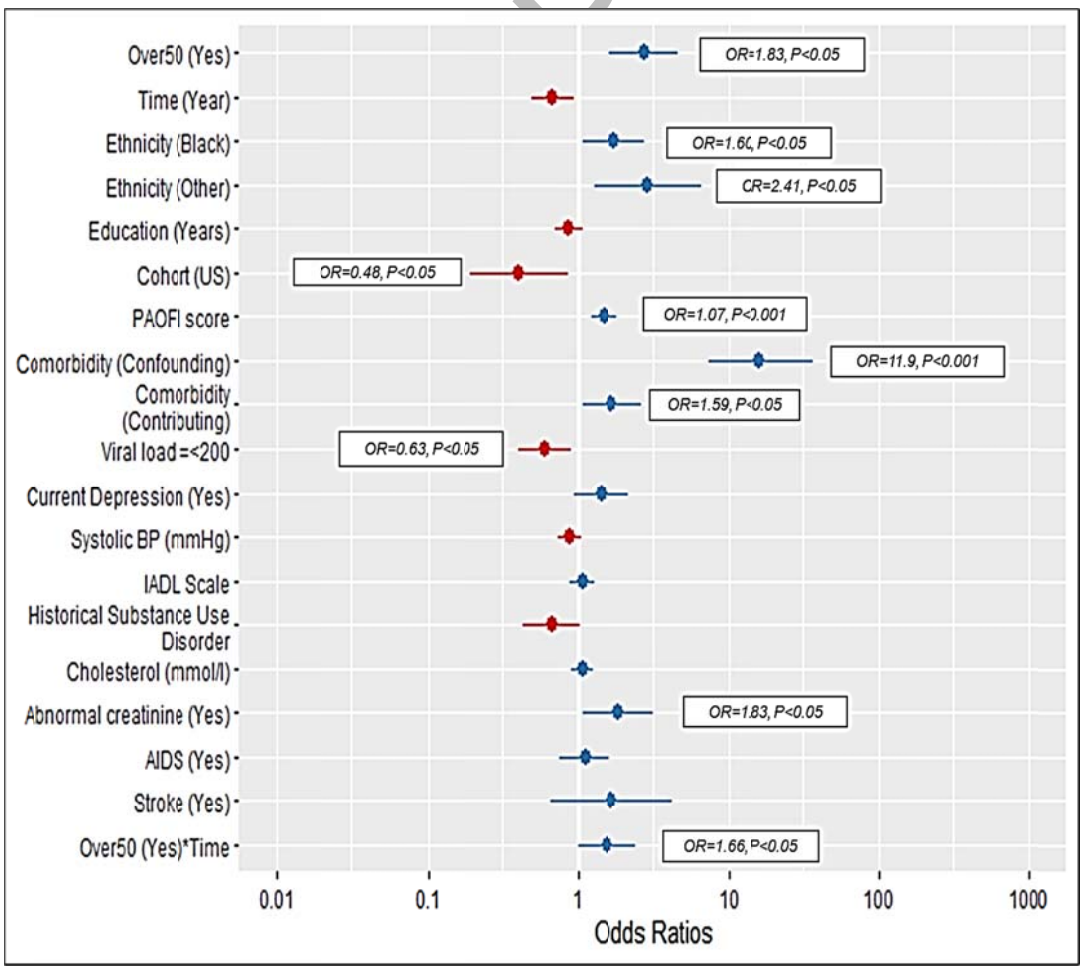

Table 1: Baseline characteristics of study participants

	Young VS Old		Australian VS US cohort		Cognitively impaired VS Normal		Total
	Young (724)	Old (302)	Australia (102)	US (924)	Impaired (449)	Normal (577)	
Age (Mean)	40.93 (6.1)	55.51 (5.24)***	55.98 (7.97)	44.03 (8.13)***	45.92 (8.72)	44.68 (8.94)*	45.22 (8.86)
Male	559 (77%)	253 (84%)*	99 (97%)	713 (77%)***	342 (76%)	470 (81%)*	812 (79%)
Years of education (Mean)	12.53 (2.47)	13.28 (2.81)***	13.93 (2.89)	12.62 (2.53)***	12.50 (2.70)	12.95 (2.49)**	12.75 (2.59)
Ethnicity							
White	294 (41%)	173 (57%)***	100 (98%)	367 (40%)***	187 (41%)	280 (49%)	467 (46%)
Black/African American	368 (51%)	115 (38%)	0 (0%)	483 (53%)	223 (50%)	260 (45%)	483 (47%)
Other	62 (8%)	14 (5%)	2 (2%)	74 (7%)	39 (9%)	37 (6%)	76 (7%)
Employed	138 (33%)	74 (38%)	55 (54%)	157 (31%)***	74 (29%)	138 (39%)**	212 (34%)

Current depression [a]	257 (36%)	86 (29%)*	18 (18%)	325 (35%)***	181 (40%)	161 (28%)***	343 (34%)
Use of psychotropic medication ever	554 (77%)	200 (68%)**	30 (33%)	724 (79%)***	330 (74%)	424 (75%)	754 (75%)
Lifetime substance use disorder	317 (44%)	103 (34%)**	11 (11%)	409 (44%)***	178 (40%)	242 (42%)	420 (41%)
Current substance use disorder	28 (4%)	1 (0.5%)**	0 (0%)	29 (3%)*	13 (3%)	16 (3%)	29 (3%)
PAOFI score (Mean)	5.29 (6.88)	4.72 (6.6)	3.89 (4.99)	5.26 (6.96)*	6.84 (8.02)	3.80 (5.32)***	5.12 (6.8)
IADL score	0.96 (1.51)	1.27 (1.94)*	1.07 (1.64)	1.05 (1.66)	1.24 (1.89)	0.92 (1.45)**	1.06 (1.66)
Comorbidity rating							
No/Incid	432	177	69	540	210	399	609

ental	(60%)	(59%)*	(68%)	(58%)**	(47%)	(69%)***	(59%)
Contributing	189 (26%)	96 (31%)	31 (30%)	254 (28%)	133 (30%)	152 (26%)	285 (28%)
Confounding	103 (14%)	29 (10%)	2 (2%)	130 (14%)	106 (23%)	26 (5%)	132 (13%)
CD4 (Median)	403.5 (363.5)	456 (328.5)***	527.5 (361.5)	407 (343)***	405 (374)	433.5 (340.25)	418 (351)
CD8 (Median)	858.5 (583.25)	871 (547)	822 (533.25)	862 (558.5)	874 (589)	846.5 (523.75)	861 (554)
CD4:CD8 ratio (Median)	0.45 (0.47)	0.5 (0.45)	0.58 (0.44)	0.46 (0.47)***	0.48 (0.45)	0.47 (0.46)	0.47 (0.45)
HIV viral load < 200 copies/ml	429 (62%)	233 (80%)***	101 (99%)	561 (63%)***	291 (68%)	371 (66%)	662 (67%)
Duration of current ART in	8.25 (21)	18.98 (32.09)***	26 (30.75)	9.3 (22.82)***	11.42 (24.57)	10.00 (22.76)	11.03 (23.49)

months (Median)							
Duration of HIV diagnosis in years (Mean)	10.37 (6.35)	14.02 (7.03)***	19.32 (6.67)	10.56 (6.17)***	11.68 (6.66)	11.26 (6.84)	133 (124.11)
CPE (Mean)	7.82 (1.96)	8.07 (2.1)	7.97 (2.34)	7.88 (1.2)	8.11 (2.10)	7.71 (1.92)**	7.89 (2)
Nadir CD4 < 200 cells/mm3	482 (67%)	200 (66%)	57 (56%)	625 (68%)*	316 (71%)	366 (64%)*	682 (67%)
AIDS	318 (44%)	160 (53%)**	71 (70%)	407 (44%)***	228 (51%)	250 (43%)*	478 (47%)
Risk Group							
Heterosexual	179 (32%)	53 (21%)*	5 (5%)	227 (32%)***	109 (31%)	123 (26%)*	232 (28%)
MSM	306 (54%)	149 (60%)	87 (91%)	368 (51%)	176 (50%)	279 (60%)	455 (56%)

Intravenous drug use	58 (10%)	38 (15%)	1 (1%)	95 (13%)	52 (15%)	44 (10%)	96 (12%)
Other	23 (4%)	10 (4%)	3 (3%)	30 (4%)	14 (4%)	19 (4%)	33 (4%)
History of myocardial infarction	19 (3%)	30 (10%)**	17 (17%)	32 (3%)***	24 (5%)	25 (4%)	49 (5%)
History of stroke	31(4%)	23 (8%)*	0 (0%)	54 (6%)*	38 (8%)	16 (3%)***	54 (5%)
Systolic blood pressure in mmHg (Mean)	123.85 (15.83)	128.81 (16.27)***	130.67 (16.08)	124.71 (16.01)***	124.56 (16.98)	125.90 (15.39)	125.31 (16.11)
Cholesterol in mmol/L (Mean)	4.69 (1.2)	4.77 (1.17)	4.99 (1.11)	4.68 (1.2)**	4.71 (1.29)	4.72 (1.11)	4.72 (1.19)
Triglyceride	2.03 (1.63)	1.97 (1.43)	2.26 (2.21)	1.98 (1.45)	2.01 (1.44)	2.01 (1.68)	2.01 (1.58)

mmol/L (Mean)							
Abnormal creatinine [b]	58 (8%)	47 (16%)***	13 (13%)	92 (10%)	60 (13%)	45 (8%)**	105 (10%)
Anemia [c]	192 (27%)	80 (27%)	19 (20%)	253 (28%)	128 (29%)	144 (25%)	272 (27%)
Diabetes	61 (8%)	38 (13%)*	7 (7%)	92 (10%)	52 (12%)	47 (8%)	99 (10%)
Cognitive Scores							
Mean T-score (Mean)	46.74 (7.50)	46.39 (6.75)	47.44 (6.99)	46.55 (7.32)	40.72 (5.41)	51.11 (4.89)***	46.64 (7.29)
Global Deficit Score (Mean)	0.52 (0.60)	0.54 (0.56)	0.46 (0.62)	0.53 (0.58)	1.01 (0.59)	0.15 (0.14)***	0.52 (0.59)
Cognitively impaired	298 (41%)	143 (47%)	36 (35%)	405 (44%)[π]			441 (43%)

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.
**p<0.05; **p<0.01, ***p<0.001*

PAOFI= Patient's Assessment of Own Functioning Inventory, IADL=Instrumental Activities of Daily Living, CPE=CNS penetrative effectiveness score
[a]≥14 in Beck Depression Inventory score, [b]>90mmol/L for Females and >110 mmol/L for Males, [c]Hemoglobin <12g/dl for Females and <13.5g/dl for Males
[π] In the original CHARTER study, the NCI rate is 52%. This difference may be due to that we included only participants on cART.

Table 2: Generalized linear mixed effects model results with NCI as the outcome (NCI is a normative age-corrected outcome)

Variable	Odds Ratio	Standard Error (SE)	95% CI
Age group (Young VS Old)	1.83*	0.43	1.15, 2.90
Time (Year)	0.64**	0.11	0.45, 0.90
Ethnicity			
White VS Black/African American	1.60*	0.37	1.01, 2.53
White VS Other	2.41*	0.94	1.12, 5.17
Education	0.95	0.04	0.87, 1.03
Cohort (US)	0.48*	0.17	0.24, 0.98
Comorbidity			
Incidental VS Contributing	1.59*	0.35	1.03, 2.46
Incidental VS Confounding	11.9***	4.43	5.77, 24.70
Viral Load < 200 copies/ml	0.63*	0.12	0.43, 0.92
PAOFI (continuous) [a]	1.07***	0.02	1.04, 1.11

IADL (continuous) [b]	1.04	0.06	0.93, 1.16
Historical substance used disorder (Yes)	0.70	0.15	0.46, 1.05
Systolic Blood Pressure (mmHg)	0.99	0.005	0.98, 1.00
Historical AIDS (Yes)	1.13	0.21	0.78, 1.64
Current Depression (Yes)	1.40	0.29	0.94, 2.10
Cholesterol (mmol/L)	1.06	0.08	0.91, 1.22
Abnormal Creatinine (Yes) [c]	1.83*	0.49	1.08, 3.08
History of Stroke (Yes)	1.56	0.71	0.64, 3.81
Age group * Time	1.66*	0.39	1.05, 2.64

Apart from demographic variables, all the other variables were treated as time-varying covariates.
**p<0.05; **p<0.01, ***p<0.001*
PAOFI= Patient's Assessment of Own Functioning Inventory
IADL=Instrumental activities of daily living
[a] *Higher score means greater cognitive symptoms*
[b] *Higher score means greater functional decline*
[c] *>90µmol/L for Females and >110 µmol/L for Males*