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Neurocognitive impairment in people living with human immunodeficiency virus (HIV): Risk factors and mortality

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NEUROCOGNITIVE IMPAIRMENT IN PEOPLE LIVING WITH HUMAN IMMUNODEFICIENCY VIRUS (HIV): RISK FACTORS AND MORTALITY

by

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ABSTRACT

NEUROCOGNITIVE IMPAIRMENT IN PEOPLE LIVING WITH HUMAN IMMUNODEFICIENCY VIRUS (HIV): RISK FACTORS AND MORTALITY

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Despite the widespread use of combination antiretroviral therapy (cART), HIV-associated neurocognitive impairment (NCI) persists in people living with HIV (PLWH) with clinical and public health implications. Studies have generated inconsistent results regarding etiological factors for NCI in PLWH and a brief user-friendly predictive tool is desirable in clinical practice to assess the probability of having NCI in PLWH. Furthermore, factors associated with clinically meaningful decline in neurocognitive status and survival disadvantage for patients with NCI are understudied in the post-cART era. The goal of this dissertation was to investigate factors associated with baseline NCI and neurocognitive decline and the association of baseline NCI with mortality in PLWH. Further, we aimed to construct a predictive tool for NCI and to examine the association between longitudinal changes in neurocognitive status and mortality in PLWH. We used two large databases, the National NeuroAIDS Tissue Consortium (NNTC) and the CNS HIV Antiretroviral Therapy Effects Research (CHARTER), to carry out this research project. Statistical procedures such as Bayesian network analysis, multiple logistic regression, joint modeling, and multivariable Cox proportional hazards modeling were employed.

Results of first study indicated that neurocognitive impairment had positive associations with older age, current unemployment, difficulty in bathing, dressing, eating, or using the toilet, impaired use of hands, history of high cholesterol, current psychotropic medication use, presence of any AIDS-defining illness and lifetime history of stroke. In the second study we noted that lifetime depression, hepatitis-C infection, lifetime methamphetamine and cannabis use Hispanic ethnicity, no baseline ARV use, and difficulty eating, dressing, bathing, or using the toilet were positively associated with neurocognitive decline. Finally, the third study exhibited a significant interaction between age and neurocognitive status in relation to mortality. Also, non-Hispanic ethnicity, lower baseline serum hemoglobin and higher baseline plasma viral load were positively associated with higher hazard of death. By knowing associated factors, the results of this study could assist clinicians identify patients needing comprehensive neuropsychological examination resulting in timely diagnosis and appropriate management. Furthermore, through targeted interventions, the results of this study may assist in improving the quality of life and disease outcomes (decline and mortality) among PLWH.

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LIST OF ABBREVIATIONS

CDC	Center for Disease Control and Prevention
HIV	Human Immunodeficiency Virus
HAND	HIV-associated neurocognitive disorders
cART	combination Antiretroviral Therapy
CNS	Central Nervous System
NCI	Neurocognitive Impairment
GDS	Global Deficit Scores
CR	Clinical Ratings
NP	Neuropsychological
AAN	American Academy of Neurology
ANI	Asymptomatic Neurocognitive Disorder
MND	Mild Neurocognitive Disorder
HAD	HIV Associated Dementia
NNTC	National NeuroAIDS Tissue Consortium
CHARTER	The CNS HIV Antiretroviral Therapy Effects Research
SD	Standard Deviation
OR	Odds Ratio
IHDS	International HIV dementia scale
MMSE	Mini-Mental State Examination
HAART	Highly Active Antiretroviral Therapy
WAIS-R	Wechsler Adult Intelligence Scale-Revised
HCV	Hepatitis-C Virus

MDD	Major Depressive Disorder
MA	Methamphetamine
EACS	European AIDS Clinical Society
MCA	Montreal Cognitive Assessment
HDS	HIV dementia scale
GBTA	Group Based Trajectory Analysis
CSF	Cerebrospinal Fluid
ART	Antiretroviral Therapy
RR	Relative Risk
HR	Hazards Ratio
PLWH	People Living With HIV
BDI	Beck depression inventory
AIDS	Acquired Immunodeficiency Syndrome
AST	Aspartate Aminotransferase
ALT	Alanine Aminotransferase
RCI	Reliable Change Indices
MB	Markov Blanket
ROC	Receiver Operating Characteristic
CIDI	Composite International Diagnostic Interview
DSM	Diagnostic and Statistical Manual of Mental Disorders

CHAPTER 1. INTRODUCTION

The Center for Disease Control and Prevention (CDC) estimates that at the end of 2018, 1.2 million Human Immunodeficiency virus (HIV) infected people, aged 13 and above, were living in the United States (US). The incidence in the US was 37,968 people. Further, in 2018, an estimated 15,820 people with HIV died in the US [1]. HIV epidemic has been characterized by the presence of HIV-associated neurocognitive disorders (HAND) in the infected populations since the beginning. In fact, brain is the second most infected organ after lungs [2]. The areas primarily affected in the brain are basal ganglia, frontal neocortex, hippocampus, and the cerebral white matter [3]. The disorders have ranged between the asymptomatic impairment to profoundly incapacitating HIV-associated dementia (HAD) [4]. The advent (1996) of combination antiretroviral therapy (cART) has resulted in an overall reduction in morbidity and increased life expectancy in HIV patients through viral suppression [5], but neurocognitive disorders persist with a change in phenotype and continue to embody a public health problem. HAD has been largely replaced by an increased prevalence of milder forms of impairment, and the HIV-positive individuals are living longer [6-11]. However, increased life expectancy can bring the onset of additional central nervous system (CNS) risk factors including comorbidities (hepatitis C infection), substance use and treatment-related medical issues (hyperlipidemia associated with cART) [12]. Thus, with the combination of enhanced survival and aging, the chronically HIV-infected population may exhibit an increased prevalence of impairment [13].

According to recent studies, 30-50% of chronically HIV-infected people receiving cART suffer from milder forms of HAND [11, 12]. A significant monotonic trend exists with best neurocognitive functioning in HIV-negative persons, intermediate functioning in persons with acute or early HIV infection and worst functioning in chronically HIV infected person [14]. In the

pre-cART era, HAND was majorly found to be significantly associated with low CD4 counts and high viral loads, which is not the case today. Currently, neurocognitive impairment (NCI) may be present in patients with no evidence of productive infection [15] Furthermore, the pattern of NCI has changed with increased impairment of memory, learning and executive functioning in cART era compared to highly prevalent impairment in motor skills, cognitive speed and verbal fluency in the pre-cART era [15, 16]. The cause of persistent presence and the change in phenotype and pattern is uncertain and a number of possibilities such as irreversible brain injury prior to cART initiation, insufficient viral suppression due to poor CNS penetration of antiviral drugs, drug-resistant strains, and other comorbid conditions have been suggested [16-20]. Thus, it is vital to explore and recognize factors associated with NCI in the cART era.

Measurement of NCI in HIV

There are three popular approaches to measure NCI in the literature; Global Deficit Scores (GDS), Clinical Ratings (CR) and HAND classification also called “Frascati criteria”. In the GDS approach, individual test scores from a comprehensive NP battery (Appendix A) are each converted to demographically corrected T-scores that are further converted to a deficit score ranging from 0 (no impairment) to 5 (severe impairment) (Appendix B). The deficit scores (based on 1 standard deviation (SD) difference form the norm) are then averaged across all tests in the battery to create the GDS [21]. Literature indicates that a GDS cutoff of ≥0.5, to indicate abnormal NP functioning, yields the most optimal balance between sensitivity and specificity (with CR as the standard measure) [22].

In the CR approach, test scores from a comprehensive neuropsychological (NP) battery are converted to demographically corrected T-scores, generating T-scores for each functional domain. Clinical ratings (based on 1SD difference from the norm) for each domain is then assigned

a scale that ranges from 1 (above average) to 9 (severely impaired), with a cutoff score of 5 indicating definite mild impairment and a score of 4 denoting borderline NP performance (Appendix C). For an individual to be classified as ‘‘impaired’’ overall, he must exhibit definite impairment in at least two ability domains. Global clinical rating is assigned to an individual based on the values of the domain ratings [21].

HAND classification or Frascati criteria developed in 2007, is a modification of the 1991 American Academy of Neurology (AAN) criteria. It defines an individual as having asymptomatic neurocognitive disorder (ANI), mild neurocognitive disorder (MND) or HIV associated dementia (HAD). ANI is defined by performance of at least 1 SD below the normative mean in two or more cognitive domains (attention-information processing, language, abstraction-executive, complex perceptual motor skills, memory, including learning and recall, simple motor skills or sensory perceptual abilities). MND, in addition to the impairment criteria of ANI, requires at least mild interference of NCI with activities of daily life, impairment not meeting the criteria for delirium or dementia and impairment not fully explained by comorbid conditions. Finally, HAD requires acquired moderate-to-severe cognitive impairment, documented by a score at least 2 SD below demographically corrected normative means in at least two different cognitive areas, marked difficulty in ADLs due to the cognitive impairment, impairment not meeting criteria for delirium, and the impairment not being adequately explained by comorbid conditions [15]. Woods et al. operationalized the Frascati criteria for HAND classification using the clinical ratings (flow chart as Appendix D) [21, 23].

Association of Demographic Factors With NCI

Several factors have been assessed over time in association with NCI and depending on the sample size, study eligibility criteria and statistical approach, inconsistencies have been

observed in the findings. Studies have been conducted to explore the association of NCI with age, gender, race, and education. The literature on age and NCI exhibits conflicting result with some studies obtaining a significant independent association between age and NCI in HIV patients while others demonstrating no association. A recently published study with age (10-year intervals) as the primary predictor and neurocognitive impairment as a binary outcome, found a significant positive association between the two (OR =1.18, 95%CI=1.11-1.26, p value<0.001). Additionally, it was seen that the age-related decline in neurocognitive status began in the 5th decade (age 41-50) [24]. The study used a battery comprising four tests to ascertain neurocognitive status and had generalizability limited to HIV patients on cART and those aged less than 60 years. Another recent study conducted in China used International HIV dementia scale (IHDS) and Mini-Mental State Examination (MMSE) to ascertain NCI and found a significant positive association with age in HIV-positive participants. The findings of the study were interesting as they noticed different risk factors being associated with NCI while using different scales (IHDS/MMSE) to establish impairment [25]. The effect on age on individual neurocognitive domains was established by a study conducted in 2017. Goodkin et al. found a significant positive association (p<0.0001) between age and neurocognitive domain impairment for all five domains (information processing speed, executive functioning, episodic memory, working memory, and motor functions) that they explored. Significant interactions between HIV stage and age were noted for episodic memory and motor function [26]. The study used men who have sex with men as participants and is thus generalizable only to them.

Somewhat contrasting results were obtained by a study including male seropositive patients and seronegative controls when overall NCI was used as an outcome and not the domains. Age and serostatus were independently associated with overall NCI, but there was no interaction between the two [27]. Similarly, Valcour et al. found no significant interaction

between age and HIV serostatus in association with NCI in a cohort of HIV infected and uninfected controls [28]. Regarding incident neurocognitive impairment, a study conducted in 2015 did not find any significant main effect for age nor an interaction with HIV as an association and concluded that over a period of one year, HIV infection confers a fivefold risk of incident NCI independent of age [29]. Studies have also established conflicting results for gender where some found no difference between men and women in relation to NCI [30] while others concluded women to have higher odds of NCI compared to men [24, 31]. Regarding education and NCI, a significant negative association has been reported by some studies [32, 33].

HIV Specific Factors and NCI

Among disease-related factors, biomarkers (CD4 counts), disease stage and viral loads have been studied substantially, however, the results from different studies have not always supported each other. Robertson et al. did not find baseline CD4 nadir, viral load, and current CD4 to be significantly associated with mild baseline NCI. However, they found a significant association of prevalent sustained mild NCI with every 50 cells decrease in total CD4 cell count at baseline (p value<0.01, OR=1.04, 95% CI=1.01-1.08) and every 50 cells decrease in CD4 cell nadir before the baseline (p value<0.01, OR=1.08, 95% CI=1.03-1.13) [10]. The study had some limitations. It included only two ethnicities, i.e., Caucasians and African American and excluded Hispanics. Only participants on highly active antiretroviral therapy (HAART, a term previously used for cART) were recruited. The neurocognitive status was evaluated with a very brief battery using only three tests (Trail making test A, Trail making test B and Wechsler Adult Intelligence Scale-Revised (WAIS-R) Digit symbol subset) potentially missing information regarding learning, memory, verbal fluency, and motor aspects of neurocognitive functioning. The definitions of persistent prevalence and incidental impairment were based on a single follow up after 48 weeks from baseline. Given the

transient nature of NCI, likely practice effect and participant's state at the time of testing, conclusions based on a single follow up assessment with a gap of 48 weeks raise reliability concerns. Lastly, there was no mention of other comorbid condition that might have acted as confounders in association between various factors and NCI. Studies also found no significant association between current CD4 count and NCI when explored cross-sectionally [34] but did establish a significant association between baseline CD4 counts with NCI at follow-up in longitudinal studies [35].

In contrast, a study published recently (2017) found a significant negative association between CD4 nadir and an abnormal neuropsychological assessment (based on a 0.5 cut off for GDS, p-value =0.01) [36]. The study, however, was characterized by relatively small sample size (96 HIV+ participants) and included only the cART users. Similar significant findings (CD4 Nadir and plasma viral loads in association with NCI) were established by certain other studies characterized by residual potential confounding [37, 38], limited generalizability [39, 40], and relatively small sample size [41]. As far as the stage/progression of HIV-infection is concerned, studies have found a significant positive association between disease stage and NCI [42, 43].

Comorbidities in Association With NCI

Among comorbidities, anemia, brain injury, opportunistic CNS infections, syphilis, blood cholesterol, diabetes, depression, proteinuria, and Hepatitis-C virus infection (HCV) have been studied previously. Two recently published studies conducted in the US found a significant positive association between anemia and NCI. Specifically, in one of the studies, worse performance in executive functioning or executive speed tests was associated with anemia in a clinic-based sample of older HIV participants [44]. The second study used the CHARTER dataset (with demographically diverse subjects thought to represent those receiving care in academic

medical centers) and employed a cross-sectional as well as longitudinal design methodology and found that, mean corpuscular volume and mean corpuscular hemoglobin were significantly associated positively with NCI ($p<0.01$) and anemia independently predicted the development of HAND during a 27 month follow up [45]. Injury to brain in the form of head injury or concussion accompanied by loss of consciousness was significantly associated with lower executive functioning and working memory in a CHARTER study [46]. Among infections, history of toxoplasmosis encephalitis [47] and current latent toxoplasma infection [48] have been found to be associated with higher NCI. In another CHARTER study, history of syphilis was positively associated with NCI [49], but a recently published study did not find any association between current neurosyphilis with NCI [50]. Metabolic disorders including high blood cholesterol, HDL (high-density lipoprotein) studied in ART adherent men [51] and diabetes have also been associated with a NCI [52, 53].

Depression specified both as lifetime history of major depressive disorder (MDD) [54] and current major depression, has been significantly associated with worse NCI. A recent study from Brazil used IHDS to ascertain the neurocognitive status and reported a significant positive association between overall NCI and current depression [55]. Another study explored individual domains of neurocognition and found a significantly higher deficit in processing speed, motor, and global cognitive functioning in relation to current depression [56]. Inconsistent results were observed when only men were included as participants. Cysique et al. found no association between history of depression or incidental depression with NCI [57]. Goggin et al. found a significant positive association only between the memory domain impairment and current depression with no association between overall impairment and depression [58]. Most studies exploring the association of HCV infection with NCI documented a significant positive association [59-61]. However, Clifford et al. using the CHARTER database, found no significant association

between HCV seropositive status and NCI [62]. The studies differed with respect to the study populations, exclusion criteria and NCI definitions.

Behavioral Risk Factors in Association With NCI

Behavioral risk factors in the form of smoking and substance abuse have been widely studied in association with NCI in HIV participants with mixed results. Regarding smoking, two studies conducted on men as study participants found no significant association of smoking history with overall NCI [63, 64]. However, further analysis by one of them revealed a negative association of smoking with verbal learning ($p=0.04$) and processing speed ($p=0.001$) [64]. Both, histories of alcohol abuse [65] and heavy current drinking [66] have shown significant positive association with impairment in HIV-positive individuals. Alcohol dependence has also been found to exert a significant positive effect on NC status interacting with age in older HIV participants [67] and with HIV serostatus in African American men [68]. According to Thame et al., moderate to heavy marijuana use is the past 12 months in HIV-positive participants was associated with poor learning/memory in comparison to HIV-negative controls [69] and a significant interaction between HIV stage and marijuana in association with NCI, was reported by another study [70]. About cocaine, literature again has mixed results. Active cocaine use had been found to be positively associated with NCI in a cross-sectional study conducted on HIV-positive individuals on cART [71] and with neurocognitive decline by a longitudinal study [72]. Another study published in 2015 only found a positive association between lifetime dependence of cocaine and poor performance in the domains of processing speed and executive functioning but not with overall NC status [73]. However, a more recent study conducted in New York found no association between current cocaine use and NCI [74]. An interesting finding was observed from a study conducted on CHARTER data and published in 2011 when they found a positive association

between lifetime cocaine use and better verbal fluency [75]. Lastly, according to the published literature, history of methamphetamine (MA) [76] and remote MA dependence have a significant association with NCI [77]. Furthermore, significant interactions have been found between lifetime MA dependence and CD4 cell count [78] and between MA and HIV serostatus in association with NCI [79].

Screening/Predictive Tool for HAND

The European AIDS Clinical Society (EACS) recommends physicians to screen HIV infected patients for cognitive complaints so that the eligible ones may be referred to a neuropsychologist [80]. The traditional neuropsychological batteries are lengthy, consume a lot of time and require trained psychometrists and thus may not be feasible to administer them at HIV primary care clinics [81]. A screening tool may help a physician in timely identification and further evaluation of patients at risk. Additionally, it is recognized that HAND is a highly underdiagnosed problem especially in its milder forms and can escape detection without formal assessment and testing, thus prompting an early screening for detection of patients with a higher probability of having it [82]. Although, a number of tools exist to assess the cognitive functioning including Montreal Cognitive Assessment (MCA), Mini-Mental State Exam (MMSE), HIV dementia scale (HDS) and the International HIV dementia scale (IHDS), but, they are either not specific to NCI in people living with HIV (PLWH), are more suitable for detecting severe forms of impairment, do not exhibit decent sensitivity and specificity with respect to the gold standard battery of tests, need revised score cut-offs or have not been fully validated to be used in a clinical context [83-88].

A study published in 2010 proposed a screening algorithm for HAND based on the documented risk factors using support vector machine methodology. Considering the standard NP battery (defined as including 14 individual NP measures) results as the gold standard, they

found a sensitivity of 78% and specificity of 70% [89]. The algorithm, however, has generalizability limitations as the participants (total sample size=97) included only men with advanced disease. Another recently published study assessed the validity of a modified cogState battery as a screening tool against the full-scale NP testing. The authors used both battery wide summary score (GDS) and Frascati classification (based on CR) as gold standards and found higher sensitivity (GDS=73%, CRS=68%) and specificity (GDS=82% AND 69%) using the former. However, when including only participants that were unimpaired or had a mild impairment, the sensitivity (50%) and specificity (77%) dropped with respect to GDS [85]. The study was characterized by a small sample size (55 HIV-infected participants and 22 controls) and included only men as participants, limiting its generalizability.

The search for an optimal screening tool for NCI in HIV remains a major challenge. According to a systematic review, different studies exhibited a wide variation between the sensitivity and specificity values depending on their eligibility criteria without a rationale, variation in overall gold standard impairment rate, non-standard definitions of impairment and inclusion/non-inclusion of a control group [90]. Another systematic review based on 31 studies with evaluation of 39 tools concluded that none of the tools differentiated HAND well enough to suggest broader use. The review further concluded that most studies had methodological shortcomings [88]. Screening tools for HIV associated NCI should be able to account for comorbidities, demographic characteristics, and disease-specific factors such as age, duration of disease, duration of treatment and severity of the disease. A predictive tool based on multiple logistic regression model can reduce statistical predictive models into a single numeric estimate of the probability of an event. A nomogram is one such tool that has been widely used in cancer studies [91]. The user-friendly interface, potential widespread availability via the web and the

ability of a nomogram to generate individualized predictions may be useful in identification and stratification of HIV-infected participants with NCI for expert diagnostic evaluation.

Detection of Longitudinal Changes in NCI

A considerable proportion (about 20%) of HIV infected individuals exhibit bidirectional changes in neurocognitive symptomatology, shifting from impairment to normal and vice versa [15]. Unlike a neurodegenerative disease such as Alzheimer's, HAND is not stable and can follow a fluctuating course. Detecting a change, particularly a decline, in the neurocognitive status and exploring determinants associated with it, has clinical significance as it may advocate further clinical investigation and a potential change in disease management. However, for a longitudinal study, the definition of clinically meaningful change needs keen deliberation. An observed change in NP status may be due to unstandardized measurements, regression towards the mean, practice effect or intraindividual variations in performance and motivation [92]. Few longitudinal studies with different methodologies have been conducted to detect the magnitude and pattern of neurocognitive changes over time and its determinants, the issue remaining understudied. Furthermore, the studies are not entirely free of potential erroneous and clinically irrelevant measures of decline.

For example, a recently published study on the CHARTER study database used the group-based trajectory analysis (GBTA) and found that 15.8% participants declined on at least one neuropsychological (NP) test over a period of 36 months with a majority (83.8%) declining on a single test [93]. Although the study used a novel methodology that works well with datasets with attrition, there were certain limitations. The definition of change (0.5 SD) was adopted from research focused on change in the quality of life for patients with chronic disease and may not be valid or clinically meaningful for neurocognitive status of HIV-positive participants. No norms

were applied to the raw scores. Thus, the data had not been contrasted against an expected performance for interpretation. Lastly, the statistical analysis did not include any model building to explore the association of change in NP profile and risk factors. A similar study with similar limitations found a low glomerular filtration, a higher duration of HIV infection, lower education, and high cerebrospinal fluid (CSF) protein levels to be significantly associated with neurocognitive decline [94].

Another recent CHARTER study used summary regression change scores to determine the neurocognitive change and conducted a survival analysis. They found that 22.7% participants declined, 60.8% remained stable while 16.5% improved. As for the predictor of change, Hispanic ethnicity (vs. non-Hispanic: RR= 2.16, 95% CI=1.29-3.61), confounded comorbidity status (vs. incidental: RR, 2.12, 95% CI=1.22–3.67), being off antiretroviral therapy (ART) (vs. on ART: RR, 1.94, 95% CI=1.26–3.00), low albumin (vs. 1 unit higher: RR, 1.58, 95% CI=0.99–2.52), low hematocrit (vs. 1 unit higher: RR, 1.08, 95% CI=1.03–1.13), having a lifetime methamphetamine use diagnosis (vs. none: RR, 1.87, 95% CI=1.16–3.02) and more depressive symptoms (vs. 1 unit lower: RR, 1.02, 95% CI=1.00–1.04) were associated with earlier time to NC decline [95]. The study employed a robust methodology to reduce practice effect. However, the methodology of merging individual change status for each participant into an overall change status and defining decline and improvement could have potentially involved chance. Two studies used regression-based summary scores to define a significant change but used only a single follow-up visit [96, 97]. However, one of them found a significant association of decline with current CD4 count (follow-up) [96] while the other found no association [97]. Additionally, a study with a small sample size (37 HIV-positive participants) using similar regression-based change scores to assess change, found higher severity of NP impairment at baseline and higher cART CNS penetration index to be significantly associated with neurocognitive improvement [98].

Mortality and NCI

NCI has been found to be an independent risk factor for mortality in the pre-cART period [99-101]. However, the association has not been very well documented in the post-cART era, and few studies have been conducted. Availability of more advanced treatments has altered the natural history of HIV, as is evident from an increased survival among the infected population. With a decreased severity, HAND may no longer be an independent risk factor but involved in multiple interactions with demographic, behavioral or disease-related factors to impact survival. In a study of participants with diagnosed HIV-associated neurologic disease (including the opportunistic CNS infections), women had a significantly higher hazard of dying (HR=2.3, 95% CI= 1.22-4.35) compared to men. Although the study did not explore the association of HAND with mortality, it highlighted the need to explore gender further in relation to mortality and NCI [102]. Two studies, conducted in 2007 and 2011, found that severe forms of neurocognitive impairment were associated with higher mortality [103, 104]. Tozzi et al. found an increased risk of death for neurocognitively impaired participants with virologic failure (HR=2.9, 95% CI=1.2-7.1) [105]. Apart from the dearth of research on the topic, statistical analyses have been performed with a single baseline value of NCI thus failing to incorporate intra-individual variability in NCI. A survival disadvantage for patients with NCI has not been established in the cART era particularly taking into consideration the reversible nature of the impairment and demands further evaluation.

Specific Aims

Among other complications, HAND have been highly prevalent as the virus is recognized to adversely affect the brain since early stages of the infection. The disorders range from mild asymptomatic impairment to HAD. The advent of cART ensued a dramatic decrease in HIV related morbidity and mortality, but mild to moderate HIV-associated NCI still represents a public health

issue with a prevalence ranging between 30-50%. NCI in HIV is an independent predictor of death and has a significant negative impact on independence in daily activities and health-related quality of life. The problem has become exacerbated in recent years because the infected population is living longer with chronic HIV, resulting in an increase in the prevalence of NCI and adverse influence on medical and physical independence. Certain demographic, clinical and psychological factors have been investigated as potential etiological/risk factors for HIV-related NCI. However, methodological differences, including inadequately elucidated eligibility criteria, differences in testing modalities and variable degree of control for confounding factors, have led to inconsistent results. Thus, there is a need for a comprehensive assessment of etiological factors to develop an optimal prediction model for NCI in HIV. Also, longitudinal studies to identify determinants of a change in neurocognitive status in HIV are limited in number and utilize different definitions of NC change, most of which have unclear clinical significance. Lastly, there is a scarcity of research about the association of NCI with mortality. None of the mortality studies has taken the reversible nature of NC status into account. Our study aims to fill the gaps mentioned above.

The long-term goal of this research was to contribute to the existing knowledge of factors associated with HIV-related NCI and the association of NCI with mortality to provide an evidence base for potential prevention/management strategies in the future. The overall objective was to examine how specific factors associate with neurocognitive status and how NC status affects mortality in PLWH. The central hypothesis based on biological plausibility and available literature, was that specific demographic, clinical and behavioral factors are significantly associated with NCI and neurocognitive status is significantly associated with mortality in PLWH. The primary aims and hypotheses of the three studies were as follows:

Specific Aim 1: To identify the factors associated with neurocognitive impairment in PLWH

Hypothesis: Specific demographic, socio-behavioral, clinical, and biological factors are associated with neurocognitive impairment in PLWH either independently or interacting with one another

Specific Aim 2: To build a predictive tool (nomogram) to assess the probability of having NCI in PLWH.

Hypothesis: The probability of having NCI in PLWH can be assessed using a predictive tool based on demographic, behavioral and clinical factors

Specific Aim 3: To investigate time to neurocognitive decline and related factors in PLWH.

Hypothesis: Specific demographic, behavioral and clinical factors independently influence time to neurocognitive decline in PLWH

Specific Aim 4: To examine the association between baseline and longitudinal changes in neurocognitive status and mortality in PLWH.

Hypothesis: A poorer neurocognitive status is associated with a higher hazard of death among PLWH

Data Sources:

The following two databases were used to answer the research questions.

The CNS HIV Antiretroviral Therapy Effects Research (CHARTER) Study

CHARTER is a prospective cohort study that was conducted at six academic medical centers including Johns Hopkins University (Baltimore, MD), Mt. Sinai School of Medicine (New York, NY), University of California at San Diego (San Diego, CA), University of Washington (Seattle, WA), University of Texas Medical Branch (Galveston, TX), and Washington University (St. Louis,

MO). The study was funded in 2002 to explore the changing presentation of HIV neurological complications in the context of emerging antiviral treatments such as highly active antiretroviral therapy (HAART) [106]. During the cross-sectional phase of the study, HIV positive volunteer participants were recruited during 2003-2007 with minimal exclusion criteria (i.e., if they declined to participate or if their screening interviewer doubted their ability to participate). Of the 2,016 potential participants screened, 1,610 (79.9%) participated in the cross-sectional phase of the study. About 366 screened individuals refused to participate and another 40 (2%) were excluded due to doubt in their ability to participate. A subset of participants (n=722) entered a longitudinal pathogenesis study with a follow-up every six months. The use of minimal exclusion criteria was to broadly represent the population of HIV-positive patients being followed in the site's university-based clinics [107]. Comprehensive demographic, neuropsychological, neurobehavioral, substance use and clinical (laboratory assessment and examination) data were collected at baseline as well as at each follow-up visits [7].

The National NeuroAIDS Tissue Consortium (NNTC)

NNTC was established in 1998 to collect, store, and distribute samples of central and peripheral nervous system tissue, cerebrospinal fluid, blood, and other organs collected from HIV positive and negative patients, to support researchers. The participants with advanced HIV disease and willingness to participate in post-mortem organ donation program are recruited at one of the four participating sites; Texas NeuroAIDS Research Center (University of Texas Medical Branch, Galveston), California NeuroAIDS Tissue Network (University of California, San Diego), National Neurological AIDS Bank (University of California, Los Angeles), Manhattan HIV Brain Bank (Mount Sinai Medical Center, New York). Subjects are volunteers recruited from clinics, hospitals, and local communities to a longitudinal observational study with detailed neurologic and neuropsychological evaluations at every 6-month interval. Furthermore, assessment such as

demographics, medication history (ARV and others), CSF, blood plasma and urine laboratory testing for HIV specific and ancillary markers, co-morbidities and substance use are also conducted at baseline as well as during the longitudinal phase. Medical history updates, examinations, and laboratory tests were repeated every 6–24 months depending on participants' health (those in declining health are seen more frequently to increase the chance of assessment before tissue donation) and likelihood of loss to follow-up (those who are more likely to be lost to follow-up were seen more frequently to minimize attrition). A total of 3,150 participants have been enrolled in the cohort including 2,812 HIV-positive and 338-HIV-negative individuals. Of the HIV-positive participants, 385 were anatomical gifts at recruitment (i.e., deceased individuals without assessments), 2427 entered the longitudinal cohort and as of November 1, 2018, the consortium is actively following 602 HIV-positive individuals [108-110].

CHAPTER 2. DEVELOPMENT OF A NOMOGRAM-BASED TOOL TO PREDICT NEUROCOGNITIVE IMPAIRMENT IN PEOPLE LIVING WITH HIV (PLWH)

Abstract

Background: Despite the widespread use of combination antiretroviral therapy (cART), HIV-associated neurocognitive impairment (NCI) persists in people living with HIV (PLWH). Studies have generated inconsistent results regarding etiological factors for NCI in PLWH. Furthermore, a brief, user-friendly, and readily available predictive tool is desirable in clinical practice to assess the probability of having neurocognitive impairment in PLWH. This study aimed to identify factors associated with NCI using a large and diverse sample of PLWH and build a nomogram based on demographic, clinical, and behavioral variables.

Methods: We performed Bayesian network analysis using a supervised learning technique (neurocognitive impairment as the target variable) with the Markov Blanket algorithm for predictive modeling. Finally, multivariable logistic regression analysis was conducted to obtain the adjusted regression coefficients to construct the nomogram.

Results: Among a sample of 1,307 participants, 21.6% were neurocognitively impaired at baseline. Among the variables included in the Markov blanket of the target variable (neurocognitive status), age provided the highest amount of mutual information (0.0333) and lifetime history of stroke the least (0.0088). Multiple logistic regression also indicated old age (>50 vs. ≤50 years) to have the strongest association (OR=2.77, 95% CI=1.99-3.85) with NCI, and thus was assigned 100 points in the nomogram. The highest possible points on the nomogram were 626, translated to a nomogram-predicted probability of NCI to be approximately 0.95. The receiver operating

characteristic (ROC) curve's concordance index was 0.75, and the nomogram's calibration plot exhibited an excellent agreement between observed and predicted probabilities.

Conclusion: The nomogram used variables that can be easily measured in clinical settings and, thus, easy to implement within a clinic or web-interface platform. Following external validation, the nomogram may potentially help clinicians identify patients with a high probability of having NCI and thus needing a comprehensive neurocognitive assessment for an early diagnosis and appropriate management.

Introduction

The development of highly active combination antiretroviral therapy (cART) has resulted in a remarkable decline in HIV-associated morbidity and mortality [111]. HIV has become a chronic disease with a life expectancy of the medication-compliant infected population approaching the uninfected population [112]. With the changing course of HIV infection, the pattern of HIV-associated neurocognitive disorders (HAND) has also altered [9]. The adverse consequences of HIV on the central nervous system have reduced in severity but are still prevalent as milder forms of neurocognitive impairment (NCI) [113, 114]. Even in the milder forms, NCI is disabling and constitutes a public health issue due to its adverse effect on everyday functioning. NCI has been found to be associated with poor medication management [115], low self-efficacy for healthcare interactions [116], unemployment [117], poor health-related quality of life [118], and higher mortality [119].

The pathogenesis of NCI in people living with HIV (PLWH) is multifaceted, including direct viral replication, chronic inflammation, treatment-related adverse effects, comorbidities, and aging, and is not well recognized [120]. A number of risk factor associations with NCI have been studied in the HIV infected population. However, the studies have generated inconsistent results. While some studies reported older age, female gender, Hispanic ethnicity, substance use, comorbidities (depression, hepatitis-C co-infection, metabolic disorders, and anemia), high viral load, and low CD4 T-cell counts to be positively associated with NCI in PLWH [24, 64, 121-128], others reported contradicting results [28, 34, 73, 129-132]. The findings' inconsistencies may be due to methodological differences, including differences in study population and eligibility criteria, small sample size, differences in testing modalities, and a variable degree of control for confounding factors. There is still a need for a comprehensive assessment of etiological factors to develop an optimal prediction model for NCI in PLWH.

Neuropsychologic testing remains the "gold standard" of NCI diagnosis; however, it is time consuming, costly, and requires interpretation by a neuropsychologist. Thus, a brief and readily available screening tool is desirable in clinical practice. The current screening tools such as CogState battery, revised HIV dementia scale, and Montreal Cognitive Assessment are either robust in detecting more severe forms of impairment (e.g., HIV-associated dementia) [133] or did not have good screening accuracy for HAND [134]. Furthermore, these screening tools require neurocognitive testing for implementation. Given that demographic and clinical data can be readily collected, they may be valuable in developing user-friendly nomograms to predict NCI in PLWH. These predictive tools could potentially serve as adjunct procedures when determining whether a patient may require further neuropsychological assessments. Our study's first objective was to identify factors associated with NCI using a large and diverse sample of PLWH. The second objective of our study was to build a user-friendly predictive tool (nomogram) based on demographic, clinical, and behavioral variables to identify PLWH at risk of NCI.

Methods

Data source and participants

The CNS HIV Antiretroviral Therapy Effects Research (CHARTER) study baseline database was used to examine risk factors associated with NCI in HIV patients and to develop the nomogram. The CHARTER study was a prospective observational study conducted with the primary aim to determine how central and peripheral nervous system complications of HIV are affected by different histories and regimens of antiretroviral therapy. Participants were enrolled between 2003 to 2007, with minimal exclusion criteria (i.e., if they declined to participate or if their screening interviewer doubted their ability to participate), at six participating sites, including Johns Hopkins University, Mt. Sinai School of Medicine, University of California San Diego,

University of Texas Medical Branch, University of Washington, and Washington University. The study concluded in 2015, and in addition to collecting demographic and clinical data, participants received comprehensive neuro-medical, neurocognitive, and laboratory examinations [7, 135].

Variables

The primary outcome was neurocognitive impairment (NCI). NCI was ascertained at enrollment through a comprehensive neurocognitive test battery covering seven domains, abstraction/executive functioning, speed of information processing, attention and working memory, learning, memory, verbal fluency, and motor functioning. Individual raw test scores were converted to demographically corrected standard scores (T-scores), which were then averaged to generate the global T-score. Best available normative standards were used to correct the effects of age, education, sex, and ethnicity, as appropriate [16]. The tests with references are given in Appendix A. An impaired neurocognitive status was assigned to those with a global T-score value of <40 [136-138].

Based on prior literature and biological plausibility, the independent variables included in the analyses were demographic factors (age, education, gender, race, ethnicity and employment), HIV-related factors (disease severity, duration of HIV infection, antiretroviral (ARV) drug use, CD4 nadir, current CD4 and plasma viral loads), activities of daily living (eating, bathing, dressing, using the toilet and taking medication), comorbidities (depressive symptoms assessed through Beck depression index (BDI-II), anemia, syphilis, history of head injury, history of coma, history of seizures, diabetes, hyperlipidemia, hypercholesterolemia, viral hepatitis and any AIDS-defining comorbidity), laboratory measures (urine proteins, hepatitis C viral loads, serum glucose, blood urea nitrogen, serum creatinine, serum sodium, serum chloride, serum potassium, serum calcium, serum total protein, serum bilirubin, serum aspartate aminotransferase (AST), serum alanine

aminotransferase (ALT), serum hemoglobin, blood monocyte percent), medication history (antidiabetics, lipid lowering drugs, psychotropic medication) and substance use (history of alcohol, opiate, hallucinogen, inhalant, sedative, methamphetamine, cannabis and cocaine use). Among the activities of daily living, selected variables (eating, bathing, dressing, using the toilet, and taking medication) were included as they were universally applicable to all the participants. The severity of HIV infection was measured using the 1993 Centers for Disease Control and Prevention (CDC) classification system. The variable "any AIDS-defining comorbidity" was categorized "yes" if the participant had a diagnosis of any of Cryptococcus (extrapulmonary), cytomegalovirus disease (other than liver, spleen, or nodes), cytomegalovirus retinitis, HIV-related encephalopathy, herpes simplex, disseminated histoplasmosis, Kaposi sarcoma, Burkitt's lymphoma, disseminated mycobacterium avium complex, any site mycobacterium tuberculosis, pneumocystis carinii pneumonia, recurrent pneumonia or progressive multifocal leukoencephalopathy. For more detail on the definitions of all variables in the final dataset, see Appendix E.

Statistical analyses

Descriptive statistics were performed for categorical (frequencies and percentages) and numeric variables (means, medians, and standard deviations) to assess the sample's overall demographic and clinical characteristics. All continuous clinical variables (duration of HIV infection, CD4 nadir, current CD4, plasma viral loads, depressive symptoms assessed through BDI-II, urine proteins, hepatitis C viral loads, serum glucose, blood urea nitrogen, serum creatinine, serum sodium, serum chloride, serum potassium, serum calcium, serum total protein, serum bilirubin, serum AST, serum ALT, serum hemoglobin and blood monocyte percent) were converted to meaningful categorical variables using standard clinical cutoffs taken from MedlinePlus [139]. A cutoff value of 50 (≤50 years or >50 years) was used to categorize age as a

binary variable as nearly half of PLWH in the US are aged 50 years or older [140]. The duration of HIV infection was categorized as ≤15 years or >15 years based on the median. Chi-squared tests were performed to determine the outcome variable's association with individual predictors. A Bayesian network analysis using a supervised learning technique with the Markov Blanket (MB) algorithm was employed for predictive modeling. Bayesian networks are non-parametric probabilistic models that identify predictors qualitatively through a graphical diagram with nodes (representing variables) and edges (arrows representing relationships) [141]. Bayesian network analyses do not require conventional statistical assumptions, and they can handle a large number of predictors [141, 142]. The MB is the smallest subset of the Bayesian network characterized by the property that all variables outside the MB could be deleted without influence on the target node and thus will have no impact on the accuracy of classification [143]. Mutual information was generated between the nodes (independent variables) and the target node (outcome variable). K-fold cross-validation was used to evaluate network performance.

With NCI as the outcome variable (binary), multivariable logistic regression analysis was conducted to obtain the adjusted regression coefficients for the independent variables identified through the Bayesian network analysis. All variables identified by the Bayesian network analyses were included in the multivariable logistic model. Additionally, among the demographic variables (gender, race/ethnicity, and education) that dropped out in the network analysis but were associated with primary covariate at 2-sided α=0.1 (race/ethnicity) in univariable logistic regression were also included. A nomogram was built using techniques described by Iasonos et al., Brittain E, and Zhang et al. [91, 144, 145]. The nomogram's predictive accuracy (discrimination) was measured via a concordance index (c-index). The nomogram's calibration was assessed by reviewing the plot of predicted probabilities from the nomogram versus the actual probabilities.

The analyses were performed using SAS 9.4 (SAS Institute, Inc., Cary, NC) software and R software-3.5.0 (RMS package).

Results

A total of 1610 participants were enrolled in the CHARTER study; of these, 1,595 participants (99.1%) had complete baseline data on the outcome variable. After excluding 288 participants (18.0%) with missing information on covariates of interest, the final sample analyzed included 1,307 participants. Figure 1 shows the flow chart of participation.

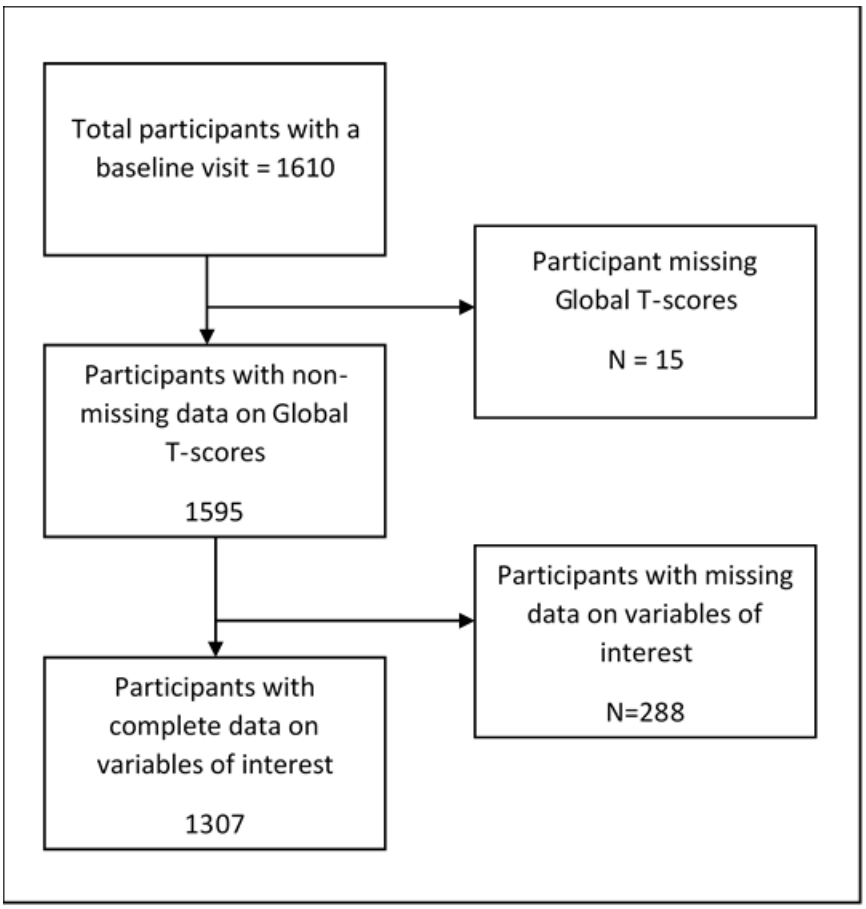

Figure 1: Flow chart of participation

Most participants were under 50 years of age (81.6%), males (77.4%), and non-Hispanic African Americans (47.4%; Table 1). At baseline, 21.6% of participants had global T-scores under

40 (impaired), and 65.1% were using highly active antiretroviral therapy (HAART). Furthermore, among those who were older than 50 years old, 41.2% were neurocognitively impaired compared to 17.2% of those at or below 50 years of age (Table 1).

Table 1: Baseline characteristics by neurocognitive status among HIV-infected participants of the CNS HIV Antiretroviral Therapy Effects Research (CHARTER) study, 2003-2007

Characteristics	Sample	Neurocognitive status n (%)		P Value
	n (%)	Impaired T-score<40	Unimpaired T-score≥40	
Total	1,307 (100.0)	283 (21.6)	1,024 (78.3)	
Age (years)				
≤50	1,067 (81.6)	184 (65.0)	883 (86.2)	<0.001
>50	240 (18.4)	99 (35.0)	141 (13.8)	
Education				
Less than high school	242 (18.5)	50 (17.7)	192 (18.7)	
High school or equivalent	336 (25.7)	72 (25.4)	264 (25.8)	
Certificate or Associates degree	169 (12.9)	39 (13.8)	130 (12.7)	0.167
Some college	328 (25.1)	65 (23.0)	263 (25.7)	
Bachelor's degree	151 (11.6)	30 (10.6)	121 (11.8)	
Graduate degree or graduate work	81 (6.2)	27 (9.5)	54 (5.3)	
Race/Ethnicity				
Non-Hispanic African American	620 (47.4)	109 (38.5)	511 (49.9)	
Non-Hispanic White	537 (41.1)	131 (46.3)	406 (39.7)	0.005
Hispanic	116 (8.9)	33 (11.7)	83 (8.1)	
Other	34 (2.6)	10 (3.5)	24 (2.3)	
Gender				
Male	1,012 (77.4)	212 (74.9)	800 (78.1)	0.252
Female	295 (22.6)	71 (25.1)	224 (21.9)	
Currently employed				
No	952 (72.8)	238 (84.1)	714 (69.7)	<0.001
Yes	355 (27.2)	45 (15.9)	310 (30.3)	
Lifetime diagnosis of diabetes mellitus				
No	1,185 (90.7)	244 (86.2)	941 (98.9)	0.004
Yes	122 (9.3)	39 (13.8)	83 (8.1)	
Current diabetes medication				
No	1,181 (90.4)	242 (85.5)	939 (91.7)	0.002
Yes	126 (9.6)	41 (14.5)	85 (8.3)	
History of high cholesterol				
No	1,039 (79.5)	195 (68.9)	844 (82.4)	<0.001
Yes	268 (20.5)	88 (31.1)	180 (17.6)	
History of high triglycerides				
No	1,078 (82.5)	222 (78.5)	856 (83.6)	0.044
Yes	229 (17.5)	61 (21.5)	168 (16.4)	
Current hyperlipidemia medication				
No	1,078 (82.5)	211 (74.6)	867 (84.7)	<0.001
Yes	229 (17.5)	72 (25.4)	157 (15.3)	
Ever used psychotropic drugs				
No	248 (19.0)	43 (15.2)	205 (20.0)	0.067
Yes	1,059 (81.0)	240 (84.8)	819 (80.0)	
Current psychotropic drugs				
No	547 (41.8)	85 (30.0)	462 (45.1)	<0.001
Yes	760 (58.2)	198 (70.0)	562 (54.9)	

Lifetime major depressive disorder				
No	631 (48.3)	145 (51.2)	486 (47.5)	0.261
Yes	676 (51.7)	138 (48.8)	538 (52.5)	
Beck Depression Inventory-II				
0-13 (minimal)	728 (55.7)	145 (51.3)	583 (56.9)	
14-19 (mild)	209 (16.0)	49 (17.3)	160 (15.6)	0.078
20-28 (moderate)	227 (17.4)	47 (16.6)	180 (17.6)	
29-63 (severe)	143 (10.9)	42 (14.8)	101 (9.9)	
History of head injury				
No	825 (63.1)	178 (62.9)	647 (63.2)	0.929
Yes	482 (36.9)	105 (37.1)	377 (36.8)	
History of coma				0.025
No	1,232 (94.3)	259 (91.5)	973 (95.0)	
Yes	75 (5.7)	24 (8.5)	51 (5.0)	
History of stroke				
No	1,232 (94.3)	252 (89.1)	980 (95.7)	<0.001
Yes	75 (5.7)	31 (10.9)	44 (4.3)	
Family history of neurologic disease[1]				
No	946 (71.4)	201 (71.0)	745 (72.8)	0.565
Yes	361 (27.6)	82 (29.0)	279 (27.2)	
Duration of HIV infection (years)				
≤15	1,007 (77.1)	210 (74.2)	797 (77.8)	0.199
>15	300 (22.9)	73 (25.8)	227 (22.2)	
HIV severity (1993 CDC classification)[2]				
1=A1+A2+A3	494 (37.8)	86 (30.4)	408 (39.8)	0.001
2=B1+B2+B3	339 (25.9)	64 (22.6)	275 (26.9)	
3=C1+C2+C3	474 (36.3)	133 (47.0)	341 (33.3)	
ARV use				
HAART	851 (65.1)	212 (74.9)	639 (62.4)	
Non-HAART	93 (7.1)	23 (8.1)	70 (6.8)	<0.001
No Current ARVs	175 (13.4)	28 (9.9)	147 (14.4)	
ARV Naïve	188 (14.4)	20 (7.1)	168 (16.4)	
Plasma viral load (IU/mL)				
<51	527 (40.3)	143 (50.5)	384 (37.5)	<0.001
51-10,000	448 (34.3)	91 (32.2)	357 (34.9)	
>10,000	332 (25.4)	49 (17.3)	283 (27.6)	
Any AIDS defining illness[3]				
No	857 (65.6)	155 (54.8)	702 (68.5)	<0.001
Yes	450 (34.4)	128 (45.2)	322 (31.5)	
Last CD4 count				
<200	225 (17.2)	44 (15.6)	181 (17.7)	0.115
200-500	628 (48.1)	126 (44.5)	502 (49.0)	
>500	454 (34.7)	113 (39.9)	341 (33.3)	
CD4 nadir				
<200	740 (56.6)	188 (66.4)	552 (53.9)	0.006
200-500	466 (35.7)	81 (28.6)	385 (37.6)	
>500	101 (7.7)	14 (5.0)	87 (8.5)	
ARV drug adherence				
No	506 (38.7)	87 (30.7)	419 (40.9)	0.002
Yes	801 (61.3)	196 (69.3)	605 (59.1)	
Hepatitis C lab result (Antibody)				
Negative	975 (74.6)	203 (71.7)	772 (75.4)	0.211
Positive	332 (25.4)	80 (28.3)	252 (24.6)	
Serum glucose (mg/dL)				
<140	1,211 (92.7)	250 (88.3)	961 (93.8)	0.002
≥140	96 (7.3)	33 (11.7)	63 (6.2)	
Blood urea nitrogen (mg/dL)				0.024
≤20	1,217 (93.1)	255 (90.1)	962 (93.9)	

>20	90 (6.9)	28 (9.9)	62 (6.1)	
Serum creatinine (mg/dL)				
≤1.3	1,242 (95.0)	263 (92.9)	979 (95.6)	0.067
>1.3	65 (5.0)	20 (7.1)	45 (4.4)	
Serum chloride (mmol/L)[4]				
<106	1,120 (85.7)	244 (86.2)	876 (85.6)	0.775
≥106	187 (14.3)	39 (13.8)	148 (14.4)	
Serum sodium (mmol/L)[5]				
≥135	70 (5.4)	258 (91.2)	979 (95.6)	0.003
<135	1,237 (94.6)	25 (8.8)	45 (4.4)	
Serum potassium (mmol/L)[6]				
≥3.6	165 (12.6)	247 (87.3)	895 (87.4)	0.956
<3.6	1,142 (87.4)	36 (12.7)	129 (12.6)	
Serum calcium (mg/dL)				
<8.9	158 (12.1)	28 (9.9)	130 (12.7)	0.003
8.9-10.1	1,030 (78.8)	215 (76.0)	815 (79.6)	
>10.1	119 (9.1)	40 (14.1)	79 (7.7)	
Serum total protein (g/dL)				
<6.4	36 (2.8)	12 (4.2)	24 (2.3)	0.074
6.4-8.3	873 (66.8)	176 (62.2)	697 (68.1)	
>8.3	398 (30.4)	95 (33.6)	303 (29.6)	
Serum total bilirubin (mg/dL)				
≤1.2	1,093 (83.6)	236 (83.4)	857 (83.7)	0.904
>1.2	214 (16.4)	47 (16.6)	167 (16.3)	
Serum aspartate aminotransferase (iu/L)				
≤40	945 (72.3)	198 (69.9)	747 (72.9)	0.321
>40	362 (27.7)	85 (30.1)	277 (27.1)	
Serum alanine aminotransferase (iu/L)				
≤55	1,036 (79.3)	222 (78.5)	814 (79.5)	0.701
>55	271 (20.7)	61 (21.5)	210 (20.5)	
Serum alkaline phosphatase (iu/L)				
≤140	1,177 (90.1)	243 (85.9)	934 (91.2)	0.007
>140	130 (9.9)	40 (14.1)	90 (8.8)	
Total cholesterol (mg/dL)				
≤200	964 (73.8)	196 (69.3)	768 (75.0)	0.052
>200	343 (26.2)	87 (30.7)	256 (25.0)	
Blood WBCs (1000/uL)				
<4	298 (22.8)	58 (20.5)	240 (23.4)	0.119
4-11	988 (75.6)	217 (76.7)	771 (75.3)	
>11	21 (1.6)	8 (2.8)	13 (1.3)	
Serum hemoglobin (g/dL)				
≥13	973 (74.5)	202 (71.4)	771 (75.3)	0.181
<13	334 (25.5)	81 (28.6)	253 (24.7)	
Blood monocytes (%)				
≤8	623 (47.7)	148 (52.3)	475 (46.4)	0.078
>8	684 (52.3)	135 (47.7)	549 (53.6)	
Absolute blood CD4 (cells/ul)				
>500)	493 (37.7)	110 (38.9)	383 (37.4)	0.704
200-500	604 (46.2)	132 (46.6)	472 (46.1)	
<200	210 (16.1)	41 (14.5)	169 (16.5)	
Rapid plasma reagin (syphilis) result				
Negative	1,199 (91.7)	255 (90.1)	944 (92.2)	0.260
Positive	108 (8.3)	28 (9.9)	80 (7.8)	
Urine proteins analysis (mg/dl)				
Negative	853 (65.3)	171 (60.4)	682 (66.6)	0.135
Trace-30	395 (30.2)	99 (35.0)	296 (28.9)	
>30	59 9 (4.5)	13 (4.6)	46 (4.5)	

Lifetime alcohol use				
No	585 (44.8)	145 (51.2)	440 (43.0)	0.013
Yes	722 (55.2)	138 (48.8)	584 (57.0)	
Lifetime cocaine use				
No	736 (56.3)	200 (70.7)	536 (52.3)	<0.001
Yes	571 (43.7)	83 (29.3)	488 (47.7)	
Lifetime hallucinogen use				
No	1,206 (92.3)	266 (94.0)	940 (91.8)	0.221
Yes	101 (7.7)	17 (6.0)	84 (8.2)	
Lifetime inhalant use				
No	1,260 (96.4)	279 (98.6)	981 (95.8)	0.026
Yes	47 (3.6)	4 (1.4)	43 (4.2)	
Lifetime cannabis use				
No	918 (70.2)	214 (75.6)	704 (68.8)	0.025
Yes	389 (29.8)	69 (24.4)	320 (31.2)	
Lifetime methamphetamine use				
No	1,080 (82.6)	245 (86.6)	835 (81.5)	0.048
Yes	227 (17.4)	38 (13.4)	189 (18.5)	
Lifetime opioid use				
No	1,091 (83.5)	243 (85.9)	848 (82.8)	0.221
Yes	216 (16.5)	40 (14.1)	176 (17.2)	
Lifetime PCP use				
No	1,280 (97.9)	279 (98.6)	1001 (97.8)	0.383
Yes	27 (2.1)	4 (1.4)	23 (2.2)	
Lifetime sedative use				
No	1,209 (92.5)	263 (92.9)	946 (92.4)	0.756
Yes	98 (7.5)	20 (7.1)	78 (7.6)	
Difficulty eating, dressing, bathing, or using the toilet	1,098 (84.0)	208 (73.5)	890 (86.9)	<0.001
No	209 (16.0)	75 (26.5)	134 (13.1)	
Yes				
Management of medication				
Independent	1,201 (91.9)	255 (90.1)	946 (92.4)	0.214
Dependent	106 (8.1)	28 (9.9)	78 (7.6)	
Impaired use of hands				
No	1,141 (87.3)	221 (78.1)	920 (89.8)	<0.001
Yes	166 (12.7)	62 (21.9)	104 (10.2)	

[1]Includes Parkinson's, Alzheimer's, Huntington's, multiple sclerosis and epilepsy recurrent Salmonella septicemia, Toxoplasmosis of brain or HIV related wasting syndrome. [2] A1=Asymptomatic HIV infection or acute HIV infection with accompanying illness PGL CD4 >500/mm^3 T-lymphocyte >29%, A2=Asymptomatic HIV infection or acute HIV infection with accompanying illness PGL CD4 200-499/mm^3 T-lymphocyte 14-28%, A3=Asymptomatic HIV infection or acute HIV infection with accompanying illness PGL CD4 <200/mm^3 T-lymphocyte <14%, B1=Symptomatic HIV infection with accompanying illness CD4 >500/mm^3 T-lymphocyte >29%, B2=Symptomatic HIV infection with accompanying illness CD4 200-499/mm^3 T-lymphocyte 14-28%, B3=Symptomatic HIV infection with accompanying illness CD4 <200/mm^3 T-lymphocyte <14%, C1=AIDS indicator condition CD4 >500/mm^3 T-lymphocyte >29%, C2=AIDS indicator condition CD4 200-499/mm^3 T-lymphocyte 14-28%, C3=AIDS indicator condition CD4 <200/mm^3 T-lymphocyte <14%. [3]Includes diagnosis of Cryptococcus (extra pulmonary), Cytomegalovirus disease (other than liver, spleen or nodes) Cytomegalovirus retinitis, HIV related encephalopathy, herpes simplex, disseminated histoplasmosis, Kaposi sarcoma, Burkitt's lymphoma, disseminated mycobacterium avium complex, any site mycobacterium tuberculosis, Pneumocystis carinii pneumonia, recurrent pneumonia and Progressive multifocal leukoencephalopathy. [4]Originally coded as; hypo<96, normal=96-105, hyper>=106. Less than 5 had hypo so were combined into normal. [5]Originally coded as hypo <135, normal 135-147, hyper >147. Less than 5 had hyper so were combined with normal. [6]Originally coded as; hypo<3.6, normal 3.6-5.2, hyper >5.2. Less than 5 had hyper so were combined into normal. PCP=Phenylcyclohexyl Piperidine. ARV=Antiretroviral.

The Bayesian network analysis identified that neurocognitive impairment has a direct probabilistic relationship, in descending order, with age, lifetime cocaine use, current employment status, difficulty in bathing, dressing, eating, or using the toilet, impaired use of hands, diagnosis of abnormally high cholesterol, current psychotropic medication use, presence of any AIDS-defining illness and lifetime history of stroke (Figure 2). The number at the top (within each box) in Figure 2 is the mutual information (predictive importance) between outcome and covariate. The middle number is the relative mutual information with regard to the child node (i.e., the amount of uncertainty reduced regarding the parent node by knowing the child node). The bottom number is the relative mutual information with regard to the parent node (i.e., the amount of uncertainty reduced regarding the child node by knowing the parent node). Among the variables included in the Markov blanket of the target variable (neurocognitive status), age provided the highest amount of mutual information (0.0333) and lifetime history of stroke the least (0.0088). Specifically, by knowing age, the uncertainty regarding neurocognitive status was reduced by 4.4% on average (Figure 2). The K-fold cross-validation yielded an overall accuracy of 78%.

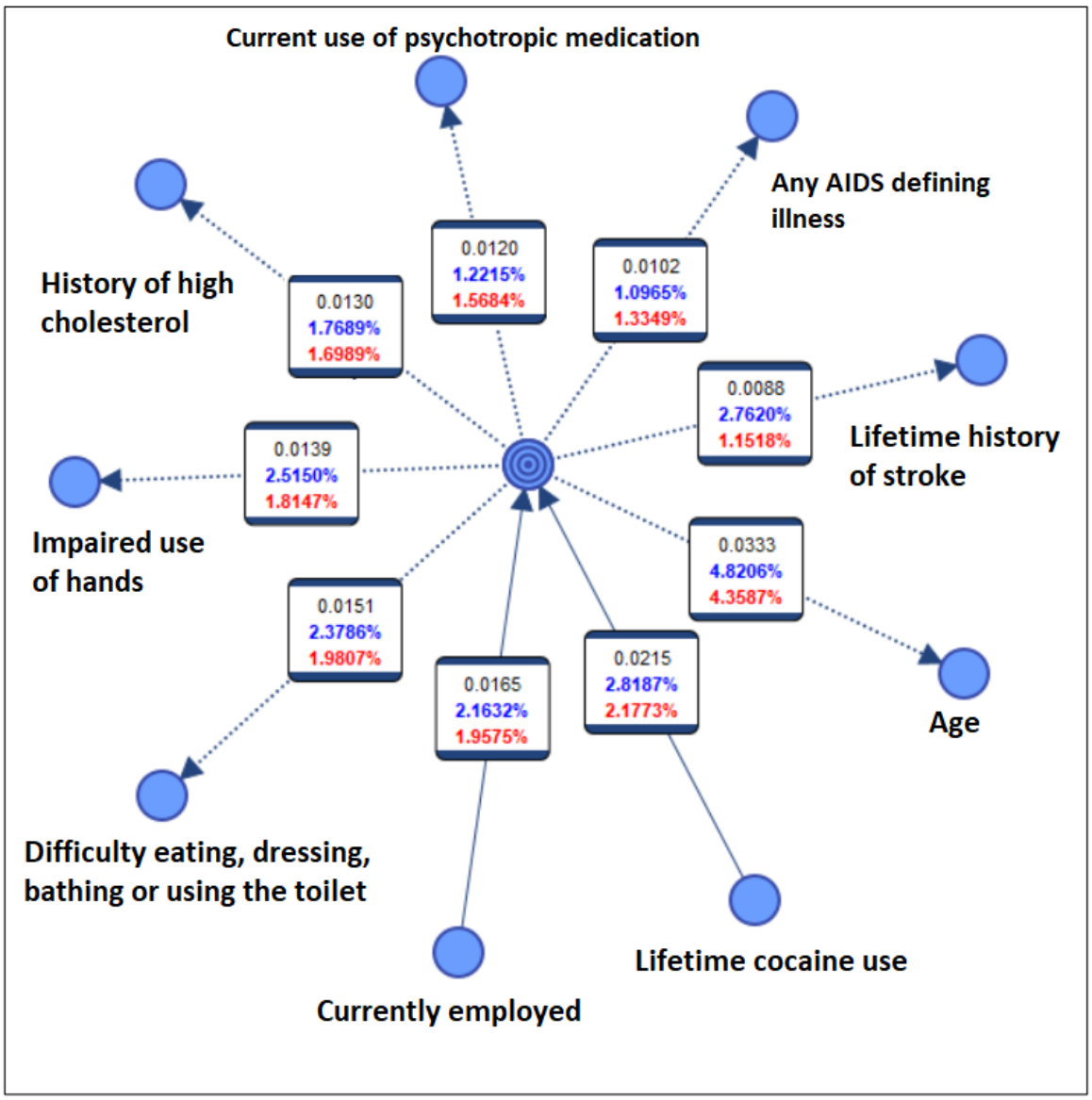

Figure 2: Markov Blanket model with mutual information between neurocognitive impairment (central node) and other covariates

Results of the multiple logistic regression indicated age to have the strongest association with NCI. Specifically, the adjusted odds of NCI among those above 50 years of age was 2.77 times (95% CI=1.99-3.85) those at or below 50 years of age (Table 2). History of high cholesterol, current psychotropic drug use, history of stroke, history of any AIDS-defining illness, current difficulty eating, dressing, bathing, or using the toilet, and impaired use of hands were also positively

associated with NCI (Table 2). Being employed and cocaine use were negatively associated with NCI (Table 2).

Table 2: Crude and adjusted Odds Ratios (OR) for neurocognitive impairment by selected variables among HIV-infected participants of CNS HIV Antiretroviral Therapy Effects Research (CHARTER) study (n=1,307)

Characteristics	n (%)	Neurocognitive impairment	
		Crude OR (95% CI)	Adjusted OR (95% CI)[1]
Age (years)			
≤50	1,067 (81.6)	Ref	Ref
>50	240 (18.4)	3.37 (2.49 – 4.56)	2.77 (1.99 – 3.85)
Race/Ethnicity			
Non-Hispanic African American	620 (47.4)	Ref	Ref
Non-Hispanic White	537 (41.1)	1.51 (1.14 – 2.01)	1.45 (1.04 – 2.02)
Hispanic	116 (8.9)	1.86 (1.18 – 2.93)	1.99 (1.22 – 3.28)
Other	34 (2.6)	1.95 (0.91 – 4.20)	2.09 (0.90 – 4.88)
Currently employed			
No	952 (72.8)	Ref	Ref
Yes	355 (27.2)	0.43 (0.31 – 0.61)	0.48 (0.33 – 0.71)
History of high cholesterol			
No	1,039 (79.5)	Ref	Ref
Yes	268 (20.5)	2.12 (1.57 – 2.85)	1.48 (1.06 – 2.08)
Current use of psychotropic medication			
No	547 (41.8)	Ref	Ref
Yes	760 (58.2)	1.91 (1.44 – 2.54)	1.42 (1.04 – 1.94)
History of stroke			
No	1,232 (94.3)	Ref	Ref
Yes	75 (5.7)	2.74 (1.69 – 4.43)	2.22 (1.29 – 3.81)
Any AIDS defining illness[1]			
No	857 (65.6)	Ref	Ref
Yes	450 (34.4)	1.80 (1.37 – 2.35)	1.43 (1.06 – 1.93)
Lifetime cocaine use			
No	736 (56.3)	Ref	Ref
Yes	571 (43.7)	0.45 (0.34 - 0.60)	0.47 (0.34 – 0.64)
Difficulty eating, dressing, bathing, or using the toilet			
No	1,098 (84.0)	Ref	Ref
Yes	209 (15.9)	2.39 (1.74 – 3.29)	1.83 (1.28 – 2.62)
Impaired use of hands			
No	1,141 (87.3)	Ref	Ref
Yes	166 (12.7)	2.48 (1.75 – 3.51)	1.90 (1.28 – 2.81)
Gender			
Male	1,012 (77.4)	Ref	NA
Female	295 (22.6)	1.19 (0.88 – 1.63)	
ARV use			
HAART	851 (65.1)	Ref	NA
Non-HAART	93 (7.1)	0.99 (0.60 – 1.63)	
No Current ARVs	175 (13.4)	0.57 (0.37 – 0.88)	
ARV Naïve	188 (14.4)	0.36 (0.22 – 0.58)	
Duration of HIV infection (years)			
≤15	1,007 (77.1)	Ref	NA
>15	300 (22.9)	1.22 (0.90 – 1.65)	

[1]Each variable is adjusted for all other variables in the table for which an adjusted odds ratio has been calculated. [2]Includes diagnosis of Cryptococcus (extra pulmonary), Cytomegalovirus disease (other than liver, spleen or nodes) Cytomegalovirus retinitis, HIV related

encephalopathy, herpes simplex, disseminated histoplasmosis, Kaposi sarcoma, Burkitt's lymphoma, disseminated mycobacterium avium complex, any site mycobacterium tuberculosis, Pneumocystis carinii pneumonia, recurrent pneumonia and Progressive multifocal leukoencephalopathy.

Since age had the highest adjusted regression coefficient (β=1.02), it was assigned 100 points in the nomogram (Figure 3). The points per variable are added together for each person and then converted into a probability of having NCI. For example, for a non-Hispanic white, aged below 50 years, with no employment, current use of psychotropic drugs, AIDS-defining illness, history of stroke, impaired use of hands and difficulty eating, dressing, bathing, or using the toilet and positive histories of high cholesterol and lifetime cocaine use will have total points of 146 converted to a probability of approximately 0.13. The highest possible points on the nomogram were 626, translated to a nomogram-predicted probability of NCI to be approximately 0.95.

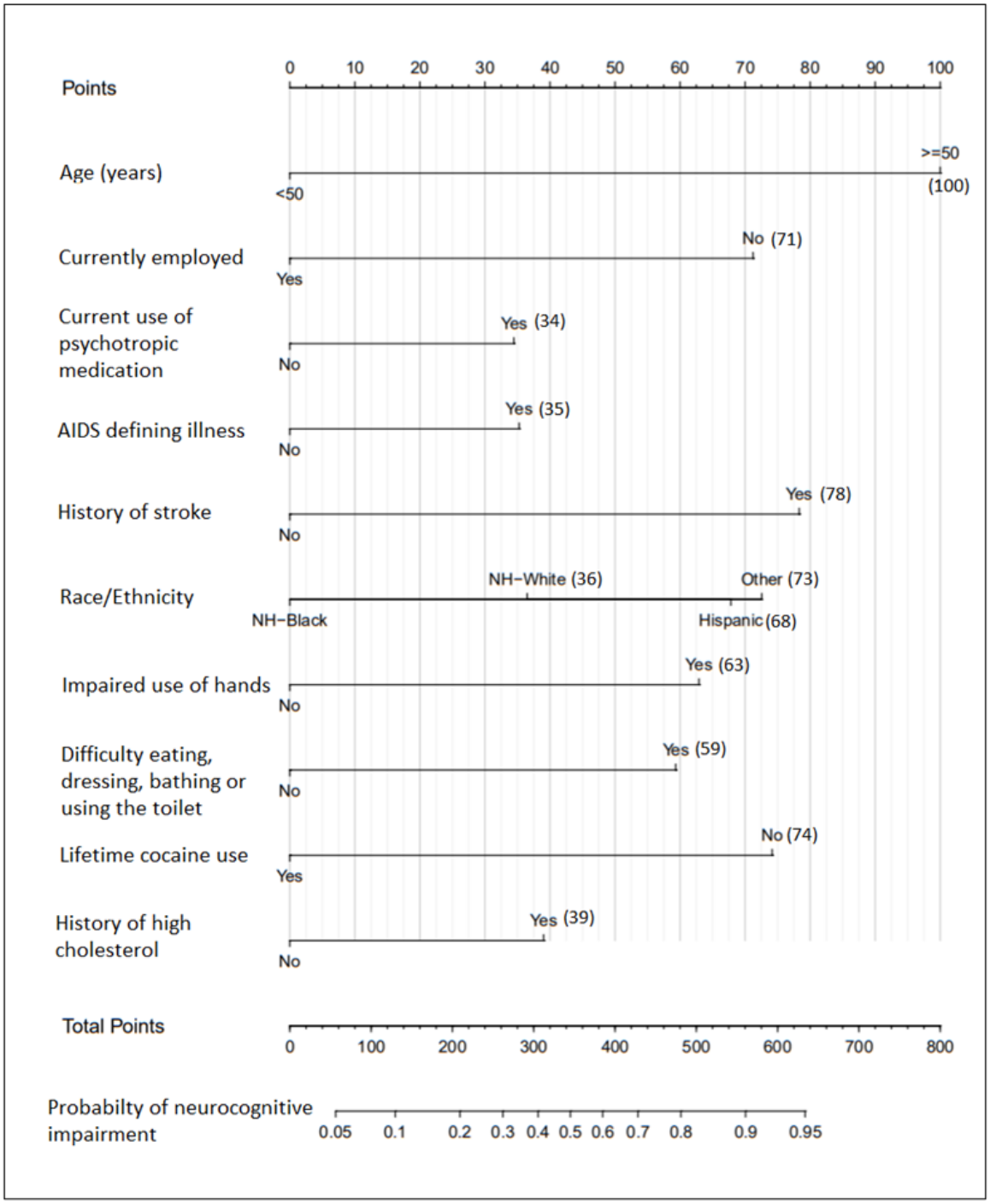

Figure 3: Nomogram for predicting the probability of neurocognitive impairment among HIV-infected participants of the CNS HIV Antiretroviral Therapy Effects Research (CHARTER) study (n=1,307)

Note: The number at the top (within each box) is the mutual information (predictive importance) between outcome and covariate. The middle number is the relative mutual information regarding the child node. The bottom number is the relative mutual information regarding the parent node

The receiver operating characteristic (ROC) curve's concordance index was 0.75 (Fig. 4), and there was excellent agreement between observed and predicted probabilities, as shown by the nomogram's calibration plot (Fig. 5).

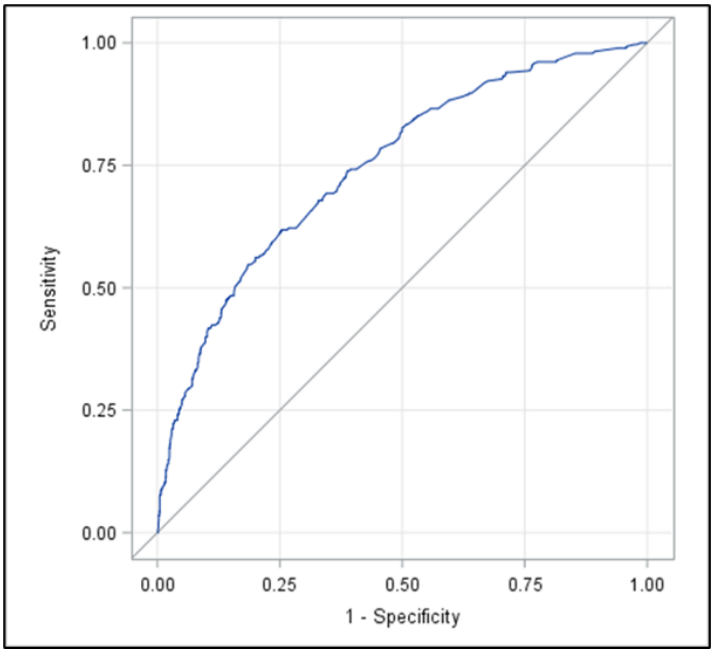

Figure 4: Receiver operating characteristic (ROC) curve; AUC= 0.7473

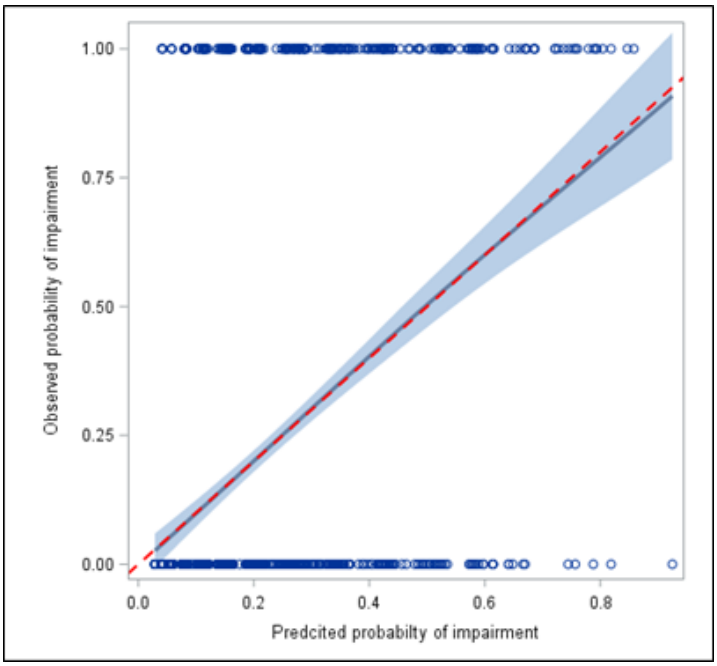

Figure 5: Calibration plot of observed verses nomogram predicted probabilities

Discussion

Despite the availability of potent antiretroviral medications, mild to moderate neurocognitive impairment persists in PLWH [7]. There is a limited agreement in the literature about the risk factors for NCI in PLWH. Our first objective was to use a large sample of HIV-infected patients with NCI status assessed through a comprehensive battery of neuropsychological tests to examine the factors associated with NCI. The search for an optimal screening tool for NCI in PLWH is still ongoing. Traditional neuropsychological test batteries are lengthy, time-consuming, and require trained psychometrists and thus may not be feasible for use in primary care clinics. We hypothesized that the probability of having HIV-related NCI during a clinic visit may be assessed using a predictive tool based on demographic, behavioral, and clinical factors and thus created a nomogram.

The results of both Bayesian network analysis and multivariable logistic regression demonstrated age to be the most important predictor of NCI (highest mutual information and highest adjusted odds ratios). As we used demographically corrected (age-adjusted) T-scores based on standardized normative data, the association specifically embodies changes beyond the normal age-related neurocognitive function. The association between age and NCI among PLWH is crucial as HIV has been found to lead to premature and accelerated aging [146]. However, as we did not use a HIV-negative control group, we cannot comment on the interaction between HIV status and age in association with NCI. Our finding regarding age is in line with a recent US-based study that found older age (>50 years) to be associated with weaker overall cognitive performance among PLWH [147]. Another recent systematic review of HIV-infected adults reported that the odds ratio (OR) of having NCI among older participants compared to their younger counterparts varied between 1.18 and 4.8 [148].

Interestingly, cocaine use was associated with lower odds of NCI (OR=0.46, 95% CI=0.33-0.63). As we had combined lifetime cocaine abuse and lifetime cocaine dependence to generate the cocaine use variable, we may have underestimated the findings in active drug users. A possible explanation is that some participants might have used cocaine only in the past, and this may account for reversal of cocaine use effects. The literature exhibits mixed results regarding the association between NCI and cocaine use among PLWH. Meade et al. did not find any association between current (past three months) cocaine use and a global neurocognitive measure (Global Deficit Scores); however, they did find higher impairment in processing speed and executive functioning among cocaine users compared to non-users [73]. Similarly, Attonito et al. did not find any association between cocaine use and neurocognition among 370 HIV-positive participants living in Florida [149]. Interestingly, another study using CHARTER data combined lifetime and current use of cocaine to define cocaine use variable, and although it did not detect any association between global impairment and cocaine use, they did report a weak association between cocaine use and improved verbal fluency [75].

Although limited research has been done on the topic, the inverse association between employment and NCI found in our study is consistent with the literature. Blackstone et al. demonstrated higher unemployment among those with NCI, and Rabkin et al. found that impairment in executive functioning represented significant employment barriers in HIV-infected men [21, 150]. Not only may NCI render PLWH unable to be efficiently employed; but unemployment itself may also reduce neurocognitive ability, as being employed provides cognitive stimulation, facilitating enhanced cognitive functioning [151].

We ascertained difficulty in daily living by combining difficulty in bathing, dressing, eating, or using the toilet and found a positive association with NCI. The finding is not surprising, as an ample body of literature indicates that HIV-associated neurocognitive disorders are a significant

risk factor for the everyday functioning decline [115-117, 152]. Our result that Hispanics and non-Hispanic Whites have higher adjusted odds of NCI than non-Hispanic African Americans is generally in contrast with prior reports of higher impairment among African Americans [153-155]. However, prior studies differ from ours regarding the included samples (gender or ART use specific) and NCI measures. Our finding may be sample dependent as it was a multicenter study and had voluntary participation, however, stratification by individual sites showed similar findings across sites (Appendix F). Heaton et al., in a longitudinal analysis using CHARTER data, also found higher neurocognitive decline (RR=2.35) among Hispanics compared to non-Hispanics (Whites and African Americans combined). Previous studies have demonstrated that Hispanic adults are diagnosed late for HIV and thus have a delayed HIV care initiation [156, 157], which may be an explanation of our finding.

Among the comorbidities, we found impaired use of hands, abnormally high cholesterol, current psychotropic drug use, presence of any AIDS-defining illness, and lifetime history of stroke to be positively associated with NCI. The specific reasons for hand impairment were not available. Hand impairment may result from HIV-induced brain injury, aging, external trauma, systemic disease, or other CNS infections and vascular diseases [158-161]. Thus, in some participants with hand impairment, poor motor-domain performance may not truly represent NCI and may need further evaluation. Previous studies have consistently found hypercholesterolemia to be positively associated with NCI in PLWH. A recent longitudinal study using CHARTER data found that participants with declining cognition exhibited a higher baseline cholesterol/HDL ratio compared to patients with stably normal cognition [162]. Another longitudinal study established elevated cholesterol to be an independent risk factor for cognitive decline in ART-adherent HIV-infected men [51]. The most plausible explanation for this association may be HIV-induced endothelial dysfunction leading to cholesterol oxidation and thus sub-clinical cerebrovascular

damage [163-165]. Psychotropic drug use may commonly indicate a diagnosis of anxiety, depression, psychosis, or sleep disorders, and hence an association with poor cognition. Although the literature is limited for other conditions, depression has been amply studied and, according to a recent comprehensive review, was associated positively with NCI in PLWH [166]. Depression may act directly or indirectly through poor ARV adherence to affect neurocognition in PLWH [166]. The presence of AIDS-defining comorbidities indicates higher severity of HIV-infection and is rather plausibly associated with NCI. In addition to HIV-infection acting itself, certain AIDs-defining infections such as HIV related encephalopathy, disseminated histoplasmosis, disseminated mycobacterium avium complex, and progressive multifocal leukoencephalopathy may directly affect the brain leading to impairment [167].

Specialists have recommended conducting routine and regular screening for NCI for early detection, treatment adjustment, and management in PLWH. However, most screening tools are based on neurocognitive testing that requires clinicians to be suitably trained in its administration and interpretation. Furthermore, currently available screening tools are generally unable to detect milder forms of NCI [168, 169]. We created a nomogram based on easily recordable demographic, clinical, and behavioral factors to serve as a user-friendly screening tool and predict NCI in PLWH. There is one study by Cysique et al. that attempted to develop a screening algorithm with demographic and clinical factors using support vector machine methodology [89] using a sample of 97 HIV-infected individuals on CART and with advanced HIV infection. The study included age, current CD4 cell count, past central nervous system HIV-related diseases, and current treatment duration in the algorithm. However, they did not convert their algorithm into a ready-to-use screening tool. Another study by Muñoz-Moreno et al. used a tree-structured approach and created four classification models to predict NCI in PLWH and identified age, employment status, CD4 cell count, highest viral load, comorbidities, HIV duration, and duration

of current treatment as potential predictors [170]. However, their statistical approach (classification and regression trees) differed from our Bayesian network analysis.

Our study had some limitations. The clinic-based volunteer and predominantly male participation may limit generalizability. However, this study is one of its kind, conducted at six centers in the US with information available on a wide range of demographic, behavioral, clinical, and laboratory measures and NCI status assessed through a comprehensive neuropsychological test battery. Our study cannot detect any temporal associations between the factors and the outcome being cross-sectional in nature. The nomograms convert complex statistical modeling into an easily understandable interface. The nomogram we created is a preliminary limited to sociodemographic, medical, and cognitive variables in the CHARTER database and needs to be validated externally in other samples of PLWH.

Conclusion

In conclusion, we investigated factors associated with NCI in PLWH and developed a preliminary nomogram to predict NCI in the HIV-infected population. The nomogram used variables that can be easily measured in clinical settings and, thus, easy to implement within a clinic or web-interface platform. Our goal with such a tool is to help clinicians predict specific patients who might have a high probability of NCI and be further evaluated by a comprehensive neuropsychological examination resulting in timely diagnosis and appropriate management. Future research should focus on external validation of the nomogram in different populations to assess external generalizability.

CHAPTER 3. AN ASSESSMENT OF FACTORS ASSOCIATED WITH NEUROCOGNITIVE DECLINE IN PEOPLE LIVING WITH HIV (PLWH)

Abstract

Background: Despite the widespread use of combination antiretroviral therapy (cART), HIV-associated neurocognitive impairment (NCI) is still prevalent in milder forms and remains a clinical and public health concern. NCI progression is highly variable in people living with HIV (PLWH), but the definition of clinically meaningful change, particularly a decline, in neurocognitive status needs further deliberation. Furthermore, limited research has been done to identify risk factors associated with neurocognitive decline. This study was conducted to identify the risk factors associated with neurocognitive decline in PLWH using a potentially clinically relevant definition of decline.

Methods: We used the CNS HIV Antiretroviral Therapy Effects Research (CHARTER) study longitudinal database and performed Cox proportional hazards modeling with time to neurocognitive decline as the primary outcome variable. Neurocognitive decline was defined as a drop in global T-scores of at least 2.67. The global T-scores were calculated form a comprehensive neurocognitive test battery. Demographic, clinical, and behavioral variables were assessed as potential risk factors.

Results: Among a sample of 581 HIV-positive participants, 23.2% experienced the event (decline). Multivariable cox regression analysis indicated that being of Hispanic ethnicity, no ARV medication use, lifetime major depressive disorder, Lifetime methamphetamine use, lifetime cannabis use, hepatitis-C infection, and difficulty eating, dressing, bathing, or using the toilet (all measured at baseline) were positively associated with neurocognitive decline.

Conclusion: Our results indicate that neurocognitive decline in PLWH is driven by a combination of demographic, clinical, and behavioral factors and that consistent use of ART may be of high significance to preserving neurocognition. Furthermore, Hispanic patients, those with a history of depression and substance use, and those having difficulty in essential activities of daily living may require particular clinical attention and follow-up for better neurocognitive outcomes among PLWH.

Introduction

The advent of combination antiretroviral therapy (cART) has resulted in the effective management of HIV viremia and an enhanced immune function, thus remarkably declining HIV associated morbidity and mortality [111, 171]. Despite the widespread use of cART, HIV associated neurocognitive impairment (NCI) is still prevalent in milder forms [113]. Even in milder forms, NCI remains a clinical and public health concern as it is associated with poor medication management, low self-efficacy for healthcare interactions, unemployment, poor health-related quality of life, and higher mortality [115-119]. Furthermore, mild impairment may be associated with future deterioration in neurocognitive status [172]. With an enhanced life expectancy of people living with HIV (PLWH), an increase in NCI prevalence is expected.

NCI progression is highly variable in PLWH, with individuals displaying considerable recovery of cognitive functions, worsening of impairment, static impairment, or a fluctuating course [9]. Few longitudinal studies with different methodologies have been conducted to detect the magnitude and pattern of neurocognitive changes over time and its determinants, though the issue remaining understudied. Most studies have used multilevel modeling or linear mixed-effect modeling (repeated measures), regression based change scores, generalized estimating equation, and group-based trajectory analysis (GBTA) to ascertain decline [121, 173-175]. Although statistically robust, the methodologies may be limited when it comes to defining neurocognitive decline in a clinically relevant manner. Yuen et al., used GBTA to ascertain neurocognitive change among aviremic participants of the CNS HIV Anti-Retroviral Therapy Effects Research (CHARTER) cohort study and defined meaningful change as at least 0.5 standard deviations (SD) from the baseline test score [94]. However, the definition of change was adopted from research focused on studies computing the minimally important difference (MID) for health-related quality of life

instruments and may not be valid or clinically meaningful for the neurocognitive status of HIV-positive participants [176].

Detecting a change, particularly a decline, in neurocognitive status and exploring determinants associated with it has clinical significance as it may support further clinical investigation and a potential change in disease management. Furthermore, modifiable risk factors can guide interventions aimed at reducing the risk of neurocognitive decline. However, for a longitudinal study, the definition of clinically meaningful change needs further deliberation. Our main objective was to identify risk factors associated with decline in neurocognitive status in PLWH using a potentially clinically relevant definition of decline. Identification of modifiable risk factors may allow targeted interventions to reduce the risk of decline in higher-risk individuals.

Methods

Data source and participants

The CNS HIV Antiretroviral Therapy Effects Research (CHARTER) study longitudinal database was used to examine the risk factor associated with a decline in NCI. The CHARTER study was a prospective observational study conducted with the primary aim to determine how central and peripheral nervous system complications of HIV are affected by different clinical histories and regimens of antiretroviral therapy. Participants were HIV-positive volunteers enrolled between 2003 to 2007 at six participating US sites, including Johns Hopkins University, Mt. Sinai School of Medicine, University of California San Diego, University of Texas Medical Branch, University of Washington, and Washington University. Minimal exclusion criteria (i.e., if they declined to participate or their screening interviewer doubted their ability to participate) were used for enrollment. Participants received comprehensive neuro-medical, neurocognitive, and laboratory examinations in addition to collecting demographic and clinical data and the study concluded in

2015 [135]. For analyses, we included participants with complete baseline data on the variables of interest and at least two visits.

Variables

The primary outcome was time to neurocognitive decline (event). Neurocognitive status was assessed through a continuous score (demographically corrected T-score) derived from a comprehensive neurocognitive test battery comprising fourteen test scores. The battery included neuropsychological tests for seven cognitive domains, including executive functioning, speed of information processing, attention and working memory, learning, memory, verbal fluency, and motor functioning (Appendix A). Raw scores from individual tests were converted to demographically corrected T-scores, which were then averaged together to calculate a global T-score for each participant [7]. A >10 unit (or 1 SD) decrease below the mean for any neurocognitive test score in the comprehensive battery of tests is a commonly accepted value to indicate impairment [15, 21, 22]. This implies that a 10-unit change in a neurocognitive test score may be clinically relevant. To remain consistent with previous literature, we considered a change in global T-score of 2.67 to be clinically relevant. The value of 2.67 is based on the theoretical standard error for the mean of 14 neurocognitive tests, each with a standard deviation of 10 ($10/\sqrt{14}$).

The independent variables included in the analyses were demographic factors (age, education, gender, race, ethnicity, and employment), HIV-related factors (disease severity, duration of HIV infection, antiretroviral (ARV) drug use, CD4 nadir, current CD4 and plasma viral loads), activities of daily living (eating, dressing, bathing or using the toilet), comorbidities (depressive symptoms assessed through Beck Depression Inventory (BDI-II), anemia, syphilis, history of head injury, diabetes, hyperlipidemia, hypercholesterolemia, hepatitis C status and any

AIDS-defining comorbidity), laboratory measures (serum bilirubin, serum Aspartate Aminotransferase (AST), serum Alanine Aminotransferase (ALT), and serum hemoglobin), medication history (antidiabetics, lipid-lowering drugs, psychotropic medication) and substance use (history of alcohol, opiate, hallucinogen, inhalant, sedative, methamphetamine, cannabis, and cocaine use). The severity of HIV infection was measured using the 1993 CDC classification system. The variable "any AIDS-defining comorbidity" was categorized as "yes" if the participant had a diagnosis of any of cryptococcus (extrapulmonary), cytomegalovirus disease (other than liver, spleen, or nodes), cytomegalovirus retinitis, HIV related encephalopathy, herpes simplex, disseminated histoplasmosis, Kaposi sarcoma, Burkitt's lymphoma, disseminated mycobacterium avium complex, any site mycobacterium tuberculosis, pneumocystis carinii pneumonia, recurrent pneumonia or progressive multifocal leukoencephalopathy. The Composite International Diagnostic Interview (CIDI, v2.1), consistent with the diagnostic and statistical manual of mental disorders-4th edition (DSM-IV), was used to assess substance use and lifetime major depressive disorders.

Statistical analyses

Descriptive statistics were generated for categorical (frequencies and percentages) and numeric variables (means, standard deviations, medians, and interquartile ranges) to assess the sample's overall demographic and clinical characteristics. Survival analysis was conducted using Cox proportional hazards regression. Kaplan-Meier analysis was used to compute the overall median survival time and to visualize survival time distributions. Univariable Cox proportional hazards models were employed to explore the association between the covariates and the outcome. Only those variables associated with the outcome variable at 2-sided $\alpha \leq 0.2$ were entered in the multivariable Cox proportional hazards model for further analysis. A stepwise

approach was used where variables were entered into the model in descending order of strength of association (ascertained by hazard ratios, HR). The elimination of variables from the multivariable cox regression model was based on the association with the outcome at 2-sided $\alpha \leq 0.2$ and Akaike Information Criterion (AIC). The proportional hazards assumption was assessed using the graphical method (log-log survival curve approach) and goodness of fit test (based on martingale residuals). Crude and adjusted HR and 95% confidence intervals (95% CI) were reported as the measures of association for the Cox proportional hazards regression analyses. The analyses were performed using SAS version 9.4 (SAS Institute, Inc., Cary, NC) software.

Results

Participants' characteristics

A total of 722 participants were enrolled in the longitudinal arm of the CHARTER study; of these, 680 participants (94.2%) completed neurocognitive test battery at least twice. After excluding 99 participants (14.5%) with missing information on covariates of interest, the final sample analyzed included 581 participants. The median time between the first and second visit was 6.17 months. Overall, the median interval between any visit was 6.67 months. The average number of visits among the participants was 7 (SD=4.8) with a minimum of 2 and a maximum of 19 visits.

The mean age was 43.4 years (SD=8.5), and most participants were males (79.2%) and non-Hispanic African Americans (44.4%). The median self-reported duration of HIV infection was 9.7 years (SD=6.3). At baseline, 72.6% of participants were on ARV therapy (including both highly active antiretroviral therapy (HAART) and non-HAART regimens).

There was a higher percentage of females (23.0% vs 20.2%), Hispanics (12.6% vs 8.3%), unemployed (71.8% vs 66.6%) and participants not on ARV therapy (34.8% vs 25.1%) among participants who declined (i.e., had a drop in global T-scores of at least 2.67 since baseline) compared to those who did not (Table 3). Furthermore, participants who declined were slightly older (mean = 43.6 years), had lower hemoglobin levels (mean = 13.9 g/dl), and a higher plasma viral load (mean = 2.6 copies/ml).

Table 3: Participants' baseline characteristics by event (neurocognitive decline) among HIV-infected participants of CNS HIV Antiretroviral Therapy Effects Research (CHARTER) study, 2003-2007. (N=581)

Variable	Frequency	Neurocognitive decline	
	n (%)	Yes n (%)	No n (%)
Total	581 (100)	135 (23.2)	446 (76.8)
Gender			
Male	460 (79.2)	104 (77.0)	356 (79.8)
Race/Ethnicity			
Black or African American	258 (44.4)	56 (41.5)	202 (45.3)
White	252 (43.4)	55 (40.7)	197 (44.2)
Hispanic	54 (9.3)	17 (12.6)	37 (8.3)
Other	17 (2.9)	7 (5.2)	10 (2.2)
Currently employed	187 (32.2)	38 (28.2)	149 (33.4)
HIV severity (1993 CDC classification)[1]			
1=A1+A2+A3	230 (39.6)	53 (39.2)	177 (39.7)
2=B1+B2+B3	156 (26.8)	36 (26.7)	120 (26.9)
3=C1+C2+C3	195 (33.6)	46 (34.1)	149 (33.4)
Last cd4 count (cells/mm3)			
<200	89 (15.3)	20 (14.8)	69 (15.5)
200-500	279 (48.0)	63 (46.7)	216 (48.4)
>500	213 (36.7)	52 (38.5)	161 (36.1)
Cd4 nadir (cells/mm3)			
<200	322 (55.4)	66 (48.9)	256 (57.4)
≥200	259 (44.6)	69 (51.1)	190 (42.6)
Current ARV use	422 (72.6)	88 (65.2)	334 (74.9)
ARV drug adherence	367 (63.2)	77 (57.0)	290 (65.0)
Any AIDS defining illness[2]	187 (32.2)	45 (33.3)	142 (31.8)
Lifetime diagnosis of diabetes mellitus	54 (9.3)	15 (11.1)	39 (8.7)
Current diabetes medication	56 (9.6)	17 (12.6)	39 (8.7)
History of high cholesterol	125 (21.5)	24 (17.8)	101 (22.7)
History of high triglycerides	106 (18.2)	23 (17.0)	83 (18.6)
Current hyperlipidemia medication	98 (16.9)	20 (14.8)	78 (17.5)
History of head injury	200 (34.4)	50 (37.0)	150 (33.6)
Ever used psychotropic drugs	474 (81.6)	118 (87.4)	356 (79.8)
Current psychotropic drugs	338 (58.2)	90 (66.7)	248 (55.6)
Beck Depression Inventory-II			
1= 0-13 (minimal)	343 (59.0)	72 (53.3)	271 (60.8)
2= 14-19 (mild)	84 (14.5)	24 (17.8)	60 (13.5)
3= 20-28 (moderate)	96 (16.5)	20 (14.8)	76 (17.0)
4= 29-63 (severe)	58 (10.0)	19 (14.1)	39 (8.7)

Hepatitis C lab result (Antibody)			
Negative	429 (73.8)	93 (68.9)	336 (75.3)
Positive	152 (26.2)	42 (31.1)	110 (24.7)
Serum total bilirubin (mg/dL)			
≤1.2	477 (82.1)	111 (82.2)	366 (82.1)
>1.2	104 (17.9)	24 (17.8)	80 (17.9)
Serum aspartate aminotransferase (iu/L)			
≤40	426 (73.3)	94 (69.6)	332 (74.4)
>40	155 (26.7)	41 (30.4)	114 (25.6)
Serum alanine aminotransferase (iu/L)			
≤55	465 (80.0)	102 (75.6)	363 (81.4)
>55	116 (20.0)	33 (24.4)	83 (18.6)
Total cholesterol (mg/dL)			
≤200	426 (73.3)	106 (78.5)	320 (71.8)
>200	155 (26.7)	29 (21.5)	126 (28.2)
Rapid plasma reagin (syphilis) result			
Negative	536 (92.3)	124 (91.8)	412 (92.4)
Positive	45 (7.7)	11 (8.2)	34 (7.6)
History of coma	34 (5.9)	11 (8.2)	23 (5.2)
History of stroke	29 (5.0)	6 (4.4)	23 (5.2)
Family history of neurologic disease[3]	157 (27.0)	34 (25.2)	123 (27.6)
Lifetime alcohol use	326 (56.1)	70 (51.8)	256 (57.4)
Lifetime cocaine use	247 (42.5)	59 (43.7)	188 (42.2)
Lifetime hallucinogen use	39 (6.7)	11 (8.2)	28 (6.3)
Lifetime inhalant use	16 (2.7)	5 (3.7)	11 (2.5)
Lifetime cannabis use	159 (27.4)	45 (33.3)	114 (25.6)
Lifetime methamphetamine use	99 (17.0)	32 (23.7)	67 (15.0)
Lifetime opioid use	98 (16.9)	27 (20.0)	71 (15.9)
Lifetime sedative use	40 (6.9)	10 (7.4)	30 (6.7)
Lifetime major depressive disorder	291 (50.1)	81 (60.0)	210 (47.1)
Difficulty eating dressing bating or using the toilet	80 (13.8)	24 (17.8)	56 (12.6)
Impaired use of hands	73 (12.6)	16 (11.8)	57 (12.8)
	Mean (SD)	**Mean (SD)**	**Mean (SD)**
Age (years)	43.4 (8.5)	43.6 (8.7)	43.3 (8.5)
Education (years)	12.8 (2.6)	12.8 (2.5)	12.8 (2.6)
Blood hemoglobin g/dL	14.1 (1.6)	13.9 (1.5)	14.1 (1.6)
Plasma viral load (Log10 copies/mL)	2.2 (1.9)	2.6 (1.9)	2.0 (1.8)
Duration of HIV infection (years)	9.7 (6.3)	9.8 (6.2)	9.7 (5.3)

[1]A1=Asymptomatic HIV infection or acute HIV infection with accompanying illness PGL CD4 >500/mm^3 T-lymphocyte >29%, A2=Asymptomatic HIV infection or acute HIV infection with accompanying illness PGL CD4 200-499/mm^3 T-lymphocyte 14-28%, A3=Asymptomatic HIV infection or acute HIV infection with accompanying illness PGL CD4 <200/mm^3 T-lymphocyte <14%, B1=Symptomatic HIV infection with accompanying illness CD4 >500/mm^3 T-lymphocyte >29%, B2=Symptomatic HIV infection with accompanying illness CD4 200-499/mm^3 T-lymphocyte 14-28%, B3=Symptomatic HIV infection with accompanying illness CD4 <200/mm^3 T-lymphocyte <14%, C1=AIDS indicator condition CD4 >500/mm^3 T-lymphocyte >29%, C2=AIDS indicator condition CD4 200-499/mm^3 T-lymphocyte 14-28%, C3=AIDS indicator condition CD4 <200/mm^3 T-lymphocyte <14%. [2]Includes diagnosis of Cryptococcus (extrapulmonary), Cytomegalovirus disease (other than liver, spleen or nodes) Cytomegalovirus retinitis, HIV related encephalopathy, herpes simplex, disseminated histoplasmosis, Kaposi sarcoma, Burkitt's lymphoma, disseminated mycobacterium avium complex, any site mycobacterium tuberculosis, Pneumocystis carinii pneumonia, recurrent pneumonia, Progressive multifocal leukoencephalopathy, recurrent Salmonella septicemia, Toxoplasmosis of brain or HIV related wasting syndrome [3]Includes Parkinson's, Alzheimer's, Huntington's, multiple sclerosis, and epilepsy

Survival analysis (Kaplan-Meier method and Cox proportional hazards regression)

The participants were followed for up to 12 years. During the study, 135 of 851 participants (23.2%) had a decline in neurocognitive status. The overall median time to cognitive decline was 11.4 years (Figure 6).

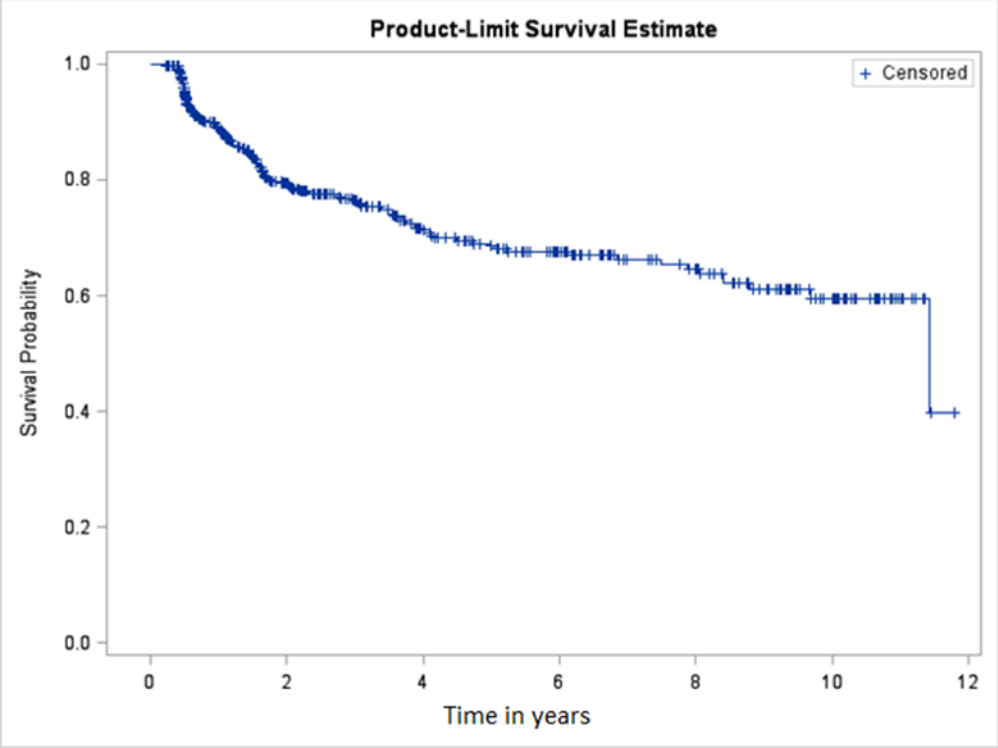

Figure 6: Kaplan-Meier plot for overall survival
Median survival time=11.4 years (95% CI = 11.4 - .)

A total of sixteen variables (current psychotropic drug use, BDI-II, hepatitis-C infection, serum AST, total serum cholesterol, history of head injury, current ARV medication use, race/ethnicity, history of lifetime cannabis use, history of lifetime inhalant use, history of lifetime opioid use, history of lifetime methamphetamine use, lifetime major depressive disorder, CD4 nadir, plasma viral loads and difficulty in essential activities of daily life including eating, dressing, bathing or using the toilet) were assessed as potential covariates in a stepwise approach in the adjusted model. The final multivariable Cox proportional hazards model included race/ethnicity,

current ARV use, lifetime major depressive disorder, lifetime methamphetamine use, lifetime cannabis use, hepatitis-c infection, and difficulty eating, dressing, bathing, or using the toilet (Table 4). The multivariable model showed a higher hazard of decline among Hispanics (HR=1.72, 95% CI=0.97-3.05) and a lower hazard among non-Hispanic Whites (HR=0.98, 95% CI=0.64-1.50) compared to non-Hispanic African Americans. Furthermore, non-use of ARV medication, lifetime major depressive disorder, lifetime methamphetamine use, lifetime cannabis use, hepatitis-C infection, and presence of difficulty eating, dressing, bathing, or using the toilet (all measured at baseline) were positively associated with neurocognitive decline.

Table 4: Crude and adjusted Hazard Ratios (HR) for neurocognitive impairment by selected variables among HIV-infected participants of CNS HIV Antiretroviral Therapy Effects Research (CHARTER) study (n=581)

Variable (at baseline)	Neurocognitive impairment	
	Crude HR (95% CI)	Adjusted HR (95% CI)[1]
Race/Ethnicity		
Non-Hispanic African American	Ref	Ref
Non-Hispanic White	1.05 (0.72 – 1.53)	0.98 (0.64 – 1.50)
Hispanic	1.49 (0.87 – 2.57)	1.72 (0.97 – 3.05)
Other	2.27 (1.04 – 4.99)	2.18 (0.96 – 4.97)
Current ARV use		
Yes	Ref	Ref
No	1.51 (1.06 – 2.16)	1.57 (1.09 – 2.26)
Lifetime major depressive disorder		
No	Ref	Ref
Yes	1.53 (1.08 – 2.16)	1.41 (0.98 – 2.01)
Lifetime methamphetamine use		
No	Ref	Ref
Yes	1.89 (1.27 – 2.82)	1.79 (1.14 – 2.79)
Lifetime cannabis use		
No	Ref	Ref
Yes	1.45 (1.02 – 2.08)	1.29 (0.89 – 1.87)
Hepatitis C lab result (Antibody)		
Negative	Ref	Ref
Positive	1.34 (0.93 – 1.93)	1.49 (1.01 – 2.22)
Difficulty eating, dressing, bathing, or using the toilet		
No	Ref	Ref
Yes	1.40 (0.90 – 2.18)	1.45 (0.92 – 2.28)

[1]Each variable is adjusted for all other variables in the table.

Discussion

Despite the availability and use of potent antiretroviral medications, mild to moderate HIV-associated NCI persists and holds substantial public health implications by being a disabling consequence of HIV infection. Limited longitudinal studies have been conducted to assess the demographic, behavioral, and clinical factors associated with a neurocognitive decline in PLWH. Furthermore, the definition of decline adopted by various studies may not hold clinical significance. The present study aimed to examine the association between relevant baseline factors and neurocognitive decline in a diverse HIV-infected patient sample using a potentially clinically relevant definition of decline.

Nonusers of ARV medication at baseline had a higher hazard (adjusted HR=1.57, 95% CI=1.09-2.26) of neurocognitive decline compared to those using the medication; the finding being rather plausible as the beneficial effects of antiretroviral therapy (ART) on viral load and immune functions are well-known [98, 177, 178]. A study conducted by Heaton et al., utilizing CHARTER data but using summary regression change scores (RCS) to define neurocognitive decline, also found not being on ART to be positively associated with the decline (RR=1.94, 95% CI=1.26–3.00) [175].

Among comorbidities, lifetime history of major depressive disorder and hepatitis C infection were positively associated with neurocognitive decline. The positive association between the lifetime history of major depressive disorder and neurocognitive decline (adjusted HR=1.41, 95% CI=0.98-2.01) is consistent with the literature. A recent study utilized multilevel modeling to assess the association between the cumulative burden of depression and neurocognitive decline and found a positive association between the two [121]. The chronic neuroinflammation and glucocorticoid cascade caused by sustained depressive symptoms and

stress leading to subsequent neuronal damage may be a potential mechanism of the observed association [179]. Heaton et al., in a longitudinal study, also found the absence of a lifetime history of depressive disorder to be associated positively with neurocognitive improvement [175]. Regarding the association between hepatitis C infection and neurocognitive decline, a study by Grant et al., that used CHARTER data but included only neurocognitively normal participants or those with asymptomatic NCI at baseline found consistent results [172]. Apart from the direct brain tissue damage ensued by HCV through neurotoxicity and inflammation [180], the treatment (specially interferons) related neurotoxicity may also be a contributing factor [181]. Furthermore, a normally functioning liver is essential to eliminate free radicals in the plasma, thus protecting the brain from damage due to oxidative stress [182]. Although HCV infection may have the same neurocognitive consequences in the general population, HIV infection may enhance the vulnerability, as a cross-sectional study conducted by Ciccarelli et al. found higher odds of neurocognitive impairment in HIV/HCV co-infected participants compared to HIV mono-infected and HCV mono-infected participants [183].

Our results showed positive associations between lifetime methamphetamine (MA) use and neurocognitive decline and between lifetime cannabis use and neurocognitive decline. Janssen et al., conducted a longitudinal study and used reliable change indices (RCI) as a measure of significant change in neurocognitive status [184]. The results of the study revealed a positive association between recreational drug use and neurocognitive decline. However, the types of recreational drugs that were combined for analysis were not specified. Similarly, there was no indication if the drug use was current, past, or lifetime. A cross-sectional study conducted by Rippeth et al., found that HIV infection and MA dependence were not only independently associated with neurocognitive deficits but also, in combination, had additive deleterious cognitive effects [79]. Although the exact mechanism is not known, the toxic effects of MA on

neurocognition may partly be attributed to glutamate dysregulation [185]. Furthermore, as we measured lifetime use, some participants may have used MA in the past only. This may be suggestive of early MA associated CNS damage resistant to recovery, thus needing further evaluation. Regarding cannabis use, limited research has been conducted, and findings are inconsistent. Recent cross-sectional studies have shown a positive association between cannabis use and better neurocognition that they attribute to the potential anti-inflammatory properties of cannabis [186, 187]. On the other hand, a longitudinal study including only HIV-infected men found a positive association between cannabis use and neurocognitive decline; however, they concluded that the association might not be clinically meaningful [188]. The inconsistent findings may be due to methodological differences, including differences in study population and eligibility criteria and differences in the measurement of cannabis use, and thus the phenomenon merits further investigation.

Our finding that, compared to non-Hispanic blacks, Hispanics have a higher hazard of neurocognitive decline while non-Hispanic whites have a lower hazard of neurocognitive decline is in line with the literature. Our findings may be attributed to delayed HIV-care initiation among Hispanics due to lower healthcare access as observed by other studies [156, 157]. Prior studies have also shown that among HIV-positive adults, survival disparities resulting from late initiation and early discontinuation of therapy are most pronounced for Hispanics [189]. A longitudinal study conducted using CHARTER study participants who underwent 4–7 study visits, and a different definition of neurocognitive change also exhibited consistent results where Hispanic ethnicity was positively associated with neurocognitive decline [175].

We ascertained difficulty in daily living by combining difficulty in bathing, dressing, eating, or using the toilet and found a positive association with neurocognitive decline. The finding is not surprising, as an ample body of literature indicates that HIV-associated neurocognitive disorders

are a significant risk factor for everyday functioning decline [96, 117, 152]. Although the presence of difficulty in daily life's essential activities may indicate the severity of neurocognition, the poor daily functioning may be a result of other medical/psychiatric factors as well, outside of HIV.

Our study has certain limitations. The clinic-based volunteer and predominantly male participation may limit generalizability. However, this study is one of its kind, conducted at six centers in the US with information available on a wide range of demographic, behavioral, clinical, and laboratory measures and NCI status assessed through a comprehensive neuropsychological test battery. Our analysis was done considering the first incidence of decline, irrespective of the rest of the follow-up period. Our findings should not be interpreted as a linear trend towards decline. As neurocognitive status may fluctuate over time in patients with HIV, participants who initially declined might have improved cognitively later in the study. The definition of decline assumes independence among the neurocognitive test scores. However, the test scores from certain tests (e.g., Grooved Pegboard) may not entirely be independent. Our study cannot prove causation as it is observational in nature; however, being longitudinal, we may assume temporality of associations between the factors and the outcome. Our sample only included PLWH, so no comparisons were made to the HIV-negative population. However, the study aimed to specifically study the factors associated with neurocognitive decline in the HIV positive population. Lastly, as the repeated neurocognitive assessments were not corrected for practice effect, we might have underestimated the decline.

Conclusion

Our study results indicate that the neurocognitive decline in PLWH is driven by a combination of demographic, clinical, and behavioral factors. We found comorbidities, such as lifetime depression and hepatitis infection and substances including methamphetamine and

cannabis, to be positively associated with neurocognitive decline. Furthermore, Hispanic ethnicity, no baseline ARV use, and difficulty eating, dressing, bathing, or using the toilet were also positively associated with neurocognitive decline. Thus, our findings indicate that consistent use of ART may be of high significance in preserving neurocognition. Furthermore, Hispanic patients, those with a history of depression and substance use, and those having difficulty in essential activities of daily living may require particular clinical attention and follow-up for better neurocognitive outcomes among PLWH.

CHAPTER 4. NEUROCOGNITIVE STATUS AND MORTALITY AMONG PEOPLE LIVING WITH HUMAN IMMUNODEFICIENCY VIRUS (HIV)

Abstract

Background: HIV-related neurocognitive impairment (NCI) may increase the risk of death. However, a survival disadvantage for patients with NCI has not been well studied in the post-cART era. Specifically, limited research has been conducted considering the reversible nature and variable progression of the impairment and this area demands further evaluation.

Methods: We performed multivariable Cox proportional hazards modeling to assess the association between baseline NCI (global T-scores) and mortality. A joint modeling approach was then used to model the trajectory of global neurocognitive functioning over time and the association between neurocognitive trajectory and mortality.

Results: Among NNTC participants, we found a strong negative association between NCI and mortality in the older age groups (e.g., at age=55, HR=0.79; 95% CI=0.64-0.99). Three neurocognitive sub-domains (abstraction and executive functioning, speed of information processing, and motor) had the strongest negative association with mortality. Joint modelling indicated a 33% lower hazard for every 10-unit increase in global T-scores (HR=0.67; 95% CI=0.56-0.80).

Conclusion: The study identified older HIV-infected individuals with NCI as a group needing special attention for the longevity of life. The study has considerable prognostic utility by not only predicting mortality hazard, but also future cognitive status.

Introduction

Since the outset of the human immunodeficiency virus (HIV) epidemic, HIV-associated neurocognitive disorders (HAND) have been prevalent in infected populations, ranging from subtle neuropsychological impairments to profoundly disabling HIV-associated dementia (HAD) [15]. The advent of combination antiretroviral therapy (cART) has transformed HIV infection from a deadly acute disease to a chronic tractable condition by effective management of HIV viremia and enhanced immune function [171]. Yet, despite the widespread use of cART, HIV-associated neurocognitive impairment (NCI) and brain injury persist with a change in phenotype and pattern. There has been a significant decrease in HAD in the cART era. Nevertheless, less severe forms of HAND continue to have a prevalence of 20-50% [7, 34]. The pattern of NCI also differs between the two eras. In the pre-cART era impairment in motor skills, cognitive speed, and verbal fluency were more common, whereas in the cART era memory and executive function impairment are more prominent [7, 15, 168].

HIV enters the brain early in its course by crossing the blood-brain barrier inside migrating monocytes and lymphocytes. Infected monocytes are converted to perivascular macrophages that express neurotoxic molecules leading to increased blood-brain barrier permeability. Neuronal damage and death are ensued both by direct viral proteins interaction and indirect inflammatory response mounted by inflammatory cells against the viral proteins [190, 191]. The brain alterations during early HIV infection have also been validated by neuroimaging [192]. In the past, subcortical regions of the brain were thought to be primarily infected by HIV, giving rise to subcortical dementia. However, heterogeneous findings from both neuropsychological and neuroimaging studies have now recognized the cognitive impairment to be present across various brain regions and cognitive domains [23]. The exact mechanism of persistence of milder forms of impairment is not clear; though, two potential explanations may include the lingering

consequences of advanced immunosuppression during the early stages of the disease (before initiation of cART) and ongoing viral replication within the brain, even when systemic viral suppression has been achieved [17, 113].

NCI progression is highly variable, with individuals displaying considerable recovery of cognitive functions, worsening of impairment, static impairment, or a fluctuating course [9]. Understanding the consequences of HIV associated NCI is vital because even in milder forms, it is associated with lower medication adherence, a decreased ability to perform the daily tasks, poorer quality of life, and difficulty obtaining employment [193]. Moreover, HIV infected individuals with mild cognitive impairment may have an increased risk of dementia and death [16, 99]. Although HIV related morbidity and mortality have decreased over time, people living with HIV continue to face an increased risk of mortality compared to the non-infected counterparts, even among those with a successful response to cART [194, 195]. There are several well-established predictors of mortality in HIV [196-198]; however, limited research has been conducted to investigate the association between NCI and mortality in HIV infected people. In the pre-cART era, NCI ascertained through a comprehensive battery of neuropsychological tests was found to be an independent risk factor of death [99-101]. A recent cross-sectional study with hospitalized HIV infected patients as the study sample found higher inpatient mortality among those who had been diagnosed with HIV associated NCI compared to those who had not [199]. Three other studies conducted in the cART era found a positive association between NCI and mortality but were limited to participants with advanced HIV infection or severe cognitive disorders only [103, 104, 200]. Banerjee et al. recently reported NCI to be an independent prognostic marker of mortality in an HIV infected cognitive cohort [119]. The study used the HIV-Dementia scale (HDS) to assess NCI. However, studies have demonstrated inconsistent results pertaining to the ability of HDS to detect subtle types of NCI [201, 202].

Apart from the limited research on the association between NCI and mortality, all the previous studies have examined cognitive impairment at a single time-point (i.e., baseline). As it is likely that cognitive status changes over time, it is vital to account for this variability in relation to mortality. A survival disadvantage for patients with NCI has not been well studied in the cART era, particularly taking into consideration the reversible nature of the impairment and demands further evaluation. The present study aims to fill the research gap by examining the association between baseline neurocognitive status as well as longitudinal changes in neurocognitive status and mortality in a diverse HIV-infected sample. We hypothesize that NCI and its progression increase the hazard of death in HIV patients either independently or in association with specific patient-related factors.

Methods

Data source and participants

The National NeuroAIDS Tissue Consortium (NNTC) database was used to investigate the association between neurocognitive status and mortality in HIV patients. NNTC is an ongoing, prospective observational study established in 1998 with the primary aim of collecting, storing, and distributing samples of central and peripheral nervous system tissue, cerebrospinal fluid, blood, and other organs collected from HIV positive and negative patients for research purposes [110]. Adult participants with advanced HIV disease willing to participate in a post-mortem organ donation program were recruited at one of the four participating sites: Texas NeuroAIDS Research Center (University of Texas Medical Branch, Galveston), California NeuroAIDS Tissue Network (University of California, San Diego), National Neurological AIDS Bank (University of California, Los Angeles) and Manhattan HIV Brain Bank (Mount Sinai Medical Center, New York). Participants were volunteers recruited from clinics, hospitals, and local communities into a longitudinal

observational study with detailed neurologic and neuropsychological evaluations at 6-, 12- or 24-month intervals depending on the clinical judgment of a participant's health.

Variables such as demographics, medication history (ARV and others), cerebrospinal fluid, blood, plasma, and urine laboratory testing for HIV specific and ancillary markers, comorbidities and substance use were collected at baseline and during the longitudinal phase [108, 203].

For the analysis, we included participants enrolled between January 2000 to November 2017, with complete baseline data on the variables of interest, and with at least two follow-up visits (n=1,325). Seventy-seven participants did not have information available on neurocognitive status at the baseline and were excluded (n=1,248). Further exclusions were made based on missing baseline information on covariates of interest. The reporting of this observational study has been guided by the STROBE instrument.

Variables:

The primary outcome was time to event (death). The primary exposures were neurocognitive status at baseline (for Cox proportional hazards modeling) and repeated measures of neurocognitive status (for joint modeling). Neurocognitive status was assessed through a continuous score (demographically corrected T-score) derived from a comprehensive neurocognitive test battery comprising of fourteen test scores. The tests with references are given in Appendix 1. The battery covers seven cognitive domains, including executive functioning, speed of information processing, attention and working memory, learning, memory, verbal fluency, and motor functioning. Raw scores from individual tests were converted to demographically corrected T-scores [7] which were than averaged together to generate the global T-score. For descriptive analysis, an impaired neurocognitive status was assigned to those with a global T-score value of <40 [136]. The best available normative standards were used, which correct for the effects of age,

education, sex, and ethnicity, as appropriate [16]. Based on prior literature and biological plausibility, other groups of variables included in the study were demographic factors (age, education, gender, race, and ethnicity), HIV related factors (disease severity, duration of HIV infection, antiretroviral (ARV) drug use, CD4 nadir, current CD4 cell count, plasma viral loads and CSF viral loads), comorbidities (anemia, cerebrovascular disease, hypertension, diabetes, hyperlipidemia, viral hepatitis, chronic renal disease, chronic obstructive pulmonary disease, AIDS-defining comorbidity, any CNS comorbidity and a composite measure of any non-AIDS defining comorbidity) and substance use (history of alcohol, opiate, hallucinogen, cannabis and cocaine use). The Composite International Diagnostic Interview (CIDI, v2.1) that is consistent with the diagnostic and statistical manual of mental disorders-4th Edition (DSM-IV), was used to measure substance use. For more detail on the definitions of all variables in the final dataset, see Appendix G.

Statistical analyses:

Descriptive statistics were generated for categorical (frequencies and percentages) and continuous variables (means, medians, and standard deviations) to assess the overall demographic and clinical characteristics of the sample. Traditional survival analysis was conducted using Cox proportional hazards regression. Kaplan-Meier analysis was used to compute the overall median survival time and to visualize survival time distributions. Univariable Cox proportional hazards models were employed to explore the association between the covariates (primary exposure and potential confounders) and outcome. Furthermore, univariable analyses using one-way analysis of variance (ANOVA) for continuous variables and Cochran Mantel-Haenszel statistics (with modified ridit scores) for categorical variables were conducted to identify the association between primary covariate (neurocognitive status) and other potential covariates. Only those variables associated with, both with the primary outcome and primary covariate at 2-

sided α=0.2, were entered in the multivariable Cox proportional hazards model for further analysis. One-way interactions between the primary predictor and other covariates were also assessed using the proportional hazards model.

For multivariable Cox proportional hazards modeling, a stepwise approach was used. The initial model included neurocognitive status, age, and the interaction term between them. Other potential confounders were then added to the model, and the change in the estimate for the association between neurocognitive status and outcome was recorded. The variable was considered a confounder if the percent change in the estimate of the reduced model compared to the model with the added variable was more than 5%. Finally, HIV duration was forced into the model. The proportional hazards assumption was assessed using the graphical method (log-log survival curve approach) and goodness of fit test (based on martingale residuals). The same model was fitted for all seven domains as sub-analyses. Crude and adjusted hazard ratios (HR) and 95% confidence intervals (95% CI) were reported as the measures of association for the Cox proportional hazards regression analyses. A sub-analysis of participants with complete data on Beck Depression Inventory-II (BDI-II) scores was conducted to investigate potential confounding effects of depressive symptoms.

A joint modeling approach was then used to model the trajectory of global neurocognitive functioning (global T-score) over time and the association between neurocognitive trajectory and mortality at the same time. The temporal evolution of longitudinal T-score measurements was estimated using a linear mixed-effects model. To model cognitive trajectories, we employed both linear and quadratic functions to observe if the results differed. Residual diagnostics were conducted to check the linear mixed models' assumptions. The final joint model used a Weibull baseline hazard function and was adjusted for covariates used in the traditional survival analysis.

The analyses were performed using SAS 9.4 (SAS Institute, Inc., Cary, NC) software and R software-3.5.0 (JM package).

Results

Participants' characteristics

The original enrolled sample (n=1,901) had a median age of 45 years (IQR=39-53), and was 81.1% males, 55.8% whites and 73.2% non-Hispanics. Fifty nine percent of the original sample had a global T-score above 40. A total of 877 participants were included in the final analyses (Figure 7).

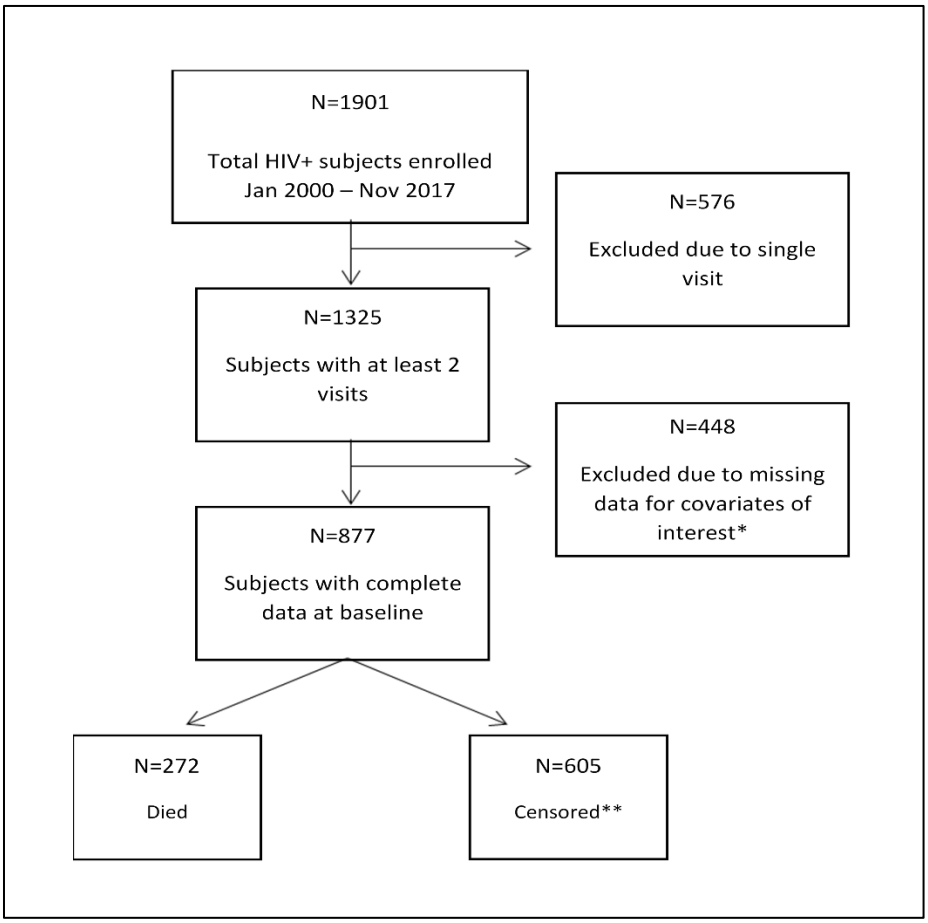

Figure 7: Flow chart of participation

*Descriptive analysis comparing those with missing data for covariates of interest to those with complete data showed no difference in demographic variables and baseline global T-scores

**There is a 12% loss to follow-up

The median age was 45 years (IQR=40-53), and most participants were males (79.2%), whites (55.8%) and non-Hispanics/Latinos (72.1%). Sixty percent of participants in the analytic sample had a global T-score above 40. The median duration of HIV infection was 12.6 years (IQR= 7.4-17.8). At baseline, 78% of participants were on a highly active antiretroviral therapy (HAART) regimen, 13% were on the non-HAART regimen, and the rest 9% were not using any antiretroviral therapy (ART). The median CD4+ cell count was 203.5 cells/µl (IQR=75-406) and the median Log10 viral load was 2.6 (IQR=1.7-4.2). Table 5 shows the baseline characteristics of participants by neurocognitive status. Most males (80.5%), participants on HAART (81.1%), Blacks (42.0%), and non-Hispanics/Latinos (77.4%) were in the neurocognitively unimpaired category. Furthermore, participants in the unimpaired category were marginally older (mean = 47.1 years) with higher education (mean = 12.3 years), higher hemoglobin levels (mean = 13.4 g/dl), higher CD4 count (mean = 301.9 cells/µl), lower blood Log10 viral load (mean = 2.9 copies/ml), longer duration of HIV disease (mean = 13.3 years) and fewer CNS comorbidities (mean = 0.05) compared to those in impaired group. Descriptive statistics for the neurocognitive battery of tests (individual and domain specific T-tests) are included as Appendix H. Participants that died during the follow-up had marginally lower baseline T-scores for the domains of abstraction/executive functioning, speed of information processing, verbal fluency and motor and marginally higher T-scores for the domains of attention and working memory, learning and working memory compared to those that were censored.

Table 5: Participant's baseline characteristics by neurocognitive status among HIV-infected participants of National NeuroAIDS Tissue Consortium (NNTC)

	Global T-scores[a]		
Variable	***Unimpaired >40***	***Impaired ≤40***	***p-value***
	n (%)[b]	**n (%)**[b]	
Total	527[c] (60.1)	350[c] (39.1)	
Gender			
Male	424 (80.5)	271 (77.4)	0.2791*
ARV medication use			
No current ARV	45 (9.1)	29 (8.9)	0.0157*
Current non-cART	49 (9.8)	59 (18.0)	
Current Cart	402 (81.1)	239 (73.1)	
Race			
White	266 (51.9)	211 (61.7)	0.003*
Black	215 (42.0)	98 (28.6)	
Other	33 (9.6)	33 (9.6)	
Ethnicity			
Hispanic or Latino	119 (22.6)	126 (36.0)	<.0001*
Not Hispanic or Latino	408 (77.4)	224 (64.0)	
Hypertension history	121 (29.9)	62 (25.4)	0.2138*
Diabetes history	46 (11.39)	43 (17.7)	0.0242*
Hyperlipidemia history	100 (24.7)	48 (19.6)	0.1291*
Viral hepatitis history	139 (34.5)	104 (42.8)	0.0340*
End stage liver disease history	9 (2.2)	8 (3.3)	0.4157*
Chronic renal disease history	30 (7.5)	17 (7.0)	0.8252*
Cardiac disease history	40 (9.9)	26 (10.7)	0.7611*
Chronic obstructive pulmonary disease	44 (10.9)	24 (9.8)	0.6563*
Cerebrovascular disease history	33 (8.2)	43 (17.7)	0.0005*
Non-AIDS defining cancers	31 (7.7)	15 (6.2)	0.4622*
Any non-AIDS defining comorbidity[d]	287 (70.7)	181 (73.9)	0.3811*
Any CNS comorbidity[e]	29 (5.9)	44 (13.4)	0.0002*
Alcohol use history	224 (61.5)	98 (45.5)	0.0030*
Cannabis use history	151 (41.5)	62 (28.6)	0.0379*
Cocaine use history	198 (54.4)	87 (40.1)	0.0008*
Hallucinogens use history	28 (7.7)	16 (7.4)	0.8883*
Opiate use history	63 (17.3)	42 (19.3)	0.5345*
Sedative use history	38 (10.4)	24 (11.1)	0.8149*
Stimulant use history[e]	86 (23.6)	39 (17.9)	0.1089*
	Mean (SD)	**Mean (SD)**	
Age (years)	47.1 (10.7)	46.5 (10.6)	0.5779**
Years of education (years)	12.3 (3.6)	12.2 (3.2)	0.5779**
Beck's Depression Inventory (BDI) total score	13.1 (10.1)	15.4 (10.4)	0.0001**
Hemoglobin (g/dl)	13.4 (1.8)	13.2 (1.9)	0.0395**
CD4 Nadir (cells/µl)	138.7 (213.6)	138.1 (210.0)	0.9744**
CD4 cell count (cells/µl)	301.9 (298.8)	273.1 (273.5)	0.1565**
Plasma viral load (log10 copies/mL)	2.9 (1.3)	3.1 (1.4)	0.0561**
Number of non-AIDS defining comorbidities[d]	1.4 (1.3)	1.6 (1.5)	0.2521**
Number of CNS comorbidities[f]	0.05 (0.2)	0.1 (0.4)	<.0001**
Duration of HIV (years)	13.3 (7.4)	12.7 (7.6)	0.1615**
Number of substances used[g]	2.1 (1.7)	1.6 (1.7)	0.0323**

[a] Scores range between 0-100 and higher T-scores imply better neurocognitive status. [b] Column percentages. [c]Sample size may be lower for variables due to missing data. [d]Includes history of hypertension, diabetes, viral hepatitis, end-stage liver disease, hyperlipidemia, chronic renal disease, cardiac disease, chronic obstructive pulmonary disease, and cerebrovascular disease. [e]Defined as use of amphetamines, diet pills, ice, khat, methamphetamine, Ritalin, speed and uppers. [f]Primary CNS lymphoma, toxoplasma encephalitis, progressive multifocal leukoencephalopathy, CMV ventriculo-encephalitis, cryptococcal meningitis, histoplasma meningitis, coccidiodes meningitis, tuberculous meningitis, syphilitic meningitis,

*lymphomatous meningitis, and other specific meningitis. [9]Includes history of alcohol, cannabis, cocaine, hallucinogen, opiate, sedative and stimulant use. *Cochran Mantel-Haenszel statistics (score= modified ridit). **Analysis of variance*

Survival analysis (Kaplan-Meier method and Cox proportional hazards regression)

The participants were followed for up to 18 years. During the study duration, of the 877 participants, 272 (31%) died. The overall median survival time was 13.2 years (Figure 8).

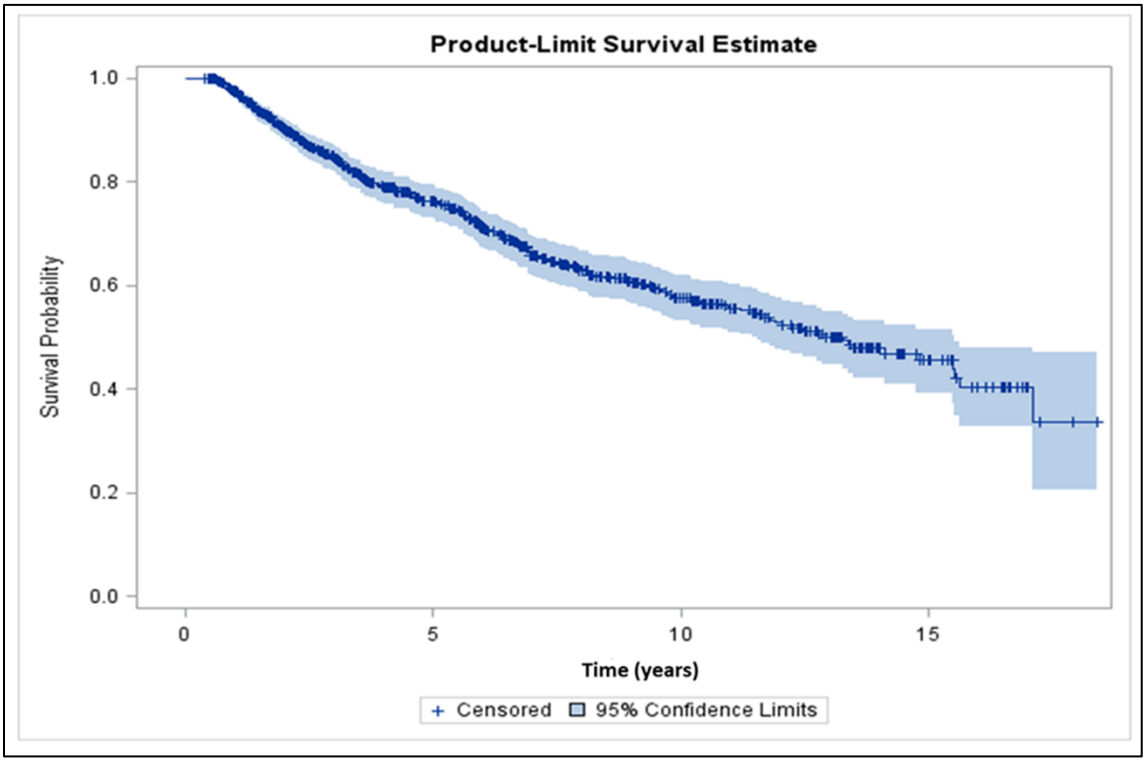

Figure 8: Kaplan-Meier plot for overall survival
Median survival time = 13.2 years (95% CI= 11.4 – 15.5)

The survival plot (Figure 9) stratified by neurocognitive status, exhibited lower median survival time (median=11.8 years) for neurocognitively impaired participants compared to the median survival time (14.1 years) for unimpaired participants. Unadjusted analyses for interaction and identification of potential confounders showed a significant interaction between age and neurocognitive status in association with mortality. Furthermore, 11 variables (current ARV medication use, ethnicity, history of hyperlipidemia, history of cerebrovascular disease, history of

cannabis use, history of cocaine use, history of opiate use, serum hemoglobin, CD4 nadir, plasma viral loads and duration of HIV infection) were assessed as potential confounders in a stepwise approach in the adjusted model.

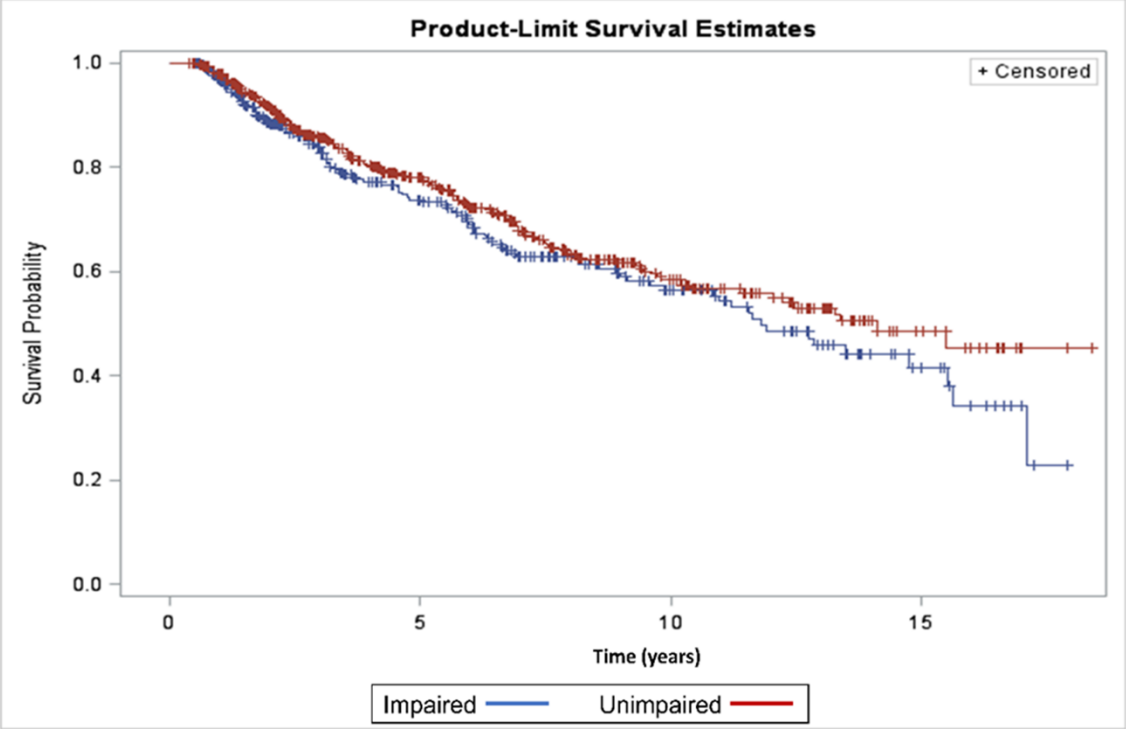

Figure 9: Kaplan-Meier plot stratified by neurocognitive status
Median survival time impaired (global T-score≤40) = 11.8 years (95% CI= 9.6 – 15.5)
Median survival time unimpaired (global T-score>40) = 14.1 years (95% CI= 9.6 - .)*
*The upper limit of confidence interval for median survival time in unimpaired group is not estimable because of censored data

The final multivariable Cox proportional hazards model included duration of HIV infection, ethnicity, serum hemoglobin, plasma viral load and an interaction term between neurocognitive status and age (Table 6). The adjusted model revealed a strong negative association between mortality and NCI in the older age groups. For example, among those who were 55 years old, the hazard of dying for those with higher (10 units) global T-score was 0.79 times (21% lower) the hazard for those with lower global T-score. However, the association was not evident in the younger age groups. Apart from the interaction term, being non-Hispanic/Latino (HR=1.38, 95%

CI=1.02-1.86) and having a higher baseline log10 viral load (HR=1.27, 95% CI=1.16-1.39) were associated with a higher hazard of dying whereas, a higher baseline serum hemoglobin was associated with a lower hazard of dying (HR=0.91, 95% CI=0.85-0.97).

Table 6: Crude and adjusted hazard ratios (HR) for mortality by selected variables among HIV-infected participants of National NeuroAIDS Tissue Consortium (NNTC; n=877)

Variable (at baseline)	*Crude HR (95% CI)*	*Adjusted HR (95% CI) model*[a]
Global T-score[b]	0.99 (0.97 - 1.01)	NA
Age (years)	1.01 (0.99 - 1.02)	NA
Gender		
Female	Ref	NA
Male	1.20 (0.90 – 1.61)	
Race		
White	Ref	NA
Black	1.15 (0.89 – 1.48)	
Other	1.02 (0.63 – 1.66)	
Duration of HIV infection (years)	1.02 (1.01 - 1.03)	1.01 (0.99 - 1.03)
Ethnicity		
Hispanic or Latino	Ref	Ref
Not Hispanic or Latino	1.41 (1.05 – 1.88)	1.38 (1.02 - 1.86)
ARV medication use		NA
No current ARV use	Ref	
Current non-cART	0.52 (0.32 - 0.86)	
Current cART	0.53 (0.37 - 0.76)	
Serum hemoglobin (g/dl)	0.89 (0.83 - 0.95)	0.91 (0.85 - 0.97)
Plasma viral load (log10 copies/mL)	1.28 (1.17 - 1.39)	1.27 (1.16 - 1.39)
T-scores x Age[c]		
35 years	1.13 (0.88 - 1.46)	1.09 (0.85 - 1.41)
55 years	0.76 (0.61 - 9.95)	0.79 (0.64 - 0.99)
75 years	0.51 (0.31 – 0.85)	0.58 (0.35 - 0.97)

[a]Each variable is adjusted for all other variables listed in the column
[b]Hazard Ratio corresponds to a 10-unit increase in global-t scores
[c]Interaction term between global T-scores and age. Hazard ratio corresponds to a 10-unit increase in global T-scores for a given age.

Domain-specific Cox proportional hazards modeling (Table 7) showed that T-scores for abstraction and executive functioning, speed of information processing, and motor domains, had stronger negative associations with mortality compared to the other domains, particularly among older participants. As seen with the global neurocognitive status, the association between individual neurocognitive domain and mortality was not evident among younger participants.

Table 7: Neurocognitive domain specific crude and adjusted hazard ratios for mortality by selected variables among HIV-infected participants of National NeuroAIDS Tissue Consortium (NNTC; n=877)

Variable (at baseline)[a]	Domain specific T-score Adjusted HR (95% CI)[a]						
	Abstraction executive functioning	**Speed of information processing**	**Motor**	**Attention and working memory**	**Learning**	**Memory**	**Verbal Fluency**
T-scores[b]	NA	NA	NA	NA	NA	NA	NA
Age (years)	NA	NA	NA	NA	NA	NA	NA
Duration of HIV infection (years)	1.01 (0.99-1.03)	1.01 (0.99 – 1.03)	1.01 (0.99 - 1.03)	1.01 (0.99 - 1.03)	1.01 (0.99 - 1.03)	1.01 (0.99 - 1.03)	1.01 (0.99 - 1.03)
Ethnicity							
Hispanic or Latino	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Not Hispanic or Latino	1.37 (1.01-1.84)	1.35 (0.99 – 1.82)	1.33 (0.99 - 1.79)	1.29 (0.95 - 1.74)	1.33 (0.99 - 1.80)	1.29 (0.96 - 1.74)	1.35 (1.00 - 1.81)
Serum hemoglobin (g/dl)	0.91 (0.85-0.97)	0.91 (0.85 – 0.97)	0.91 (0.85 - 0.97)	0.89 (0.84 - 0.96)	0.90 (0.84 - 0.96)	0.90 (0.84 - 0.96)	0.90 (0.85 - 0.97)
Plasma viral load (log10 copies/mL)	1.27 (1.16-1.39)	1.27 (1.16 – 1.39)	1.28 (1.16 - 1.40)	1.28 (1.17 - 1.41)	1.27 (1.16 - 1.39)	1.27 (1.16 - 1.39)	1.25 (1.14 - 1.37)
T-scores X Age[c]							
35 years	1.08 (0.90 - 1.30)	1.09 (0.90 - 1.33)	0.98 (0.84 - 1.14)	0.99 (0.80 - 1.24)	1.11 (0.89 - 1.37)	1.16 (0.95 - 1.41)	0.99 (0.82 - 1.18)
55 years	0.83 (0.71 - 0.97)	0.84 (0.71 - 0.98)	0.80 (0.68 - 0.94)	0.95 (0.79 - 1.14)	0.93 (0.77 - 1.12)	1.01 (0.85 - 1.20)	0.89 (0.77 - 1.03)
75 years	0.64 (0.45 - 0.93)	0.64 (0.43 - 0.94)	0.65 (0.45 - 0.94)	0.91 (0.59 - 1.40)	0.78 (0.50 - 1.20)	0.88 (0.59 - 1.32)	0.81 (0.57 - 1.14)

[a]Each variable is adjusted for all other variables listed in the column

[b]Hazard Ratio correspond to a 10-unit increase in T-scores

[c]Interaction term between T-scores and age. Hazard ratio corresponds to a 10-unit increase in T-scores for given age.

A sub-analysis of participants with complete data on Beck Depression Inventory-II (BDI-II) scores showed a similar association between NCI and mortality than without BDI-II in the model (Appendix I). For example, for participants aged 55 years, the adjusted HR was 0.83 (95% CI=0.62-1.12) for the sub-analysis compared to 0.79 (95% CI=0.64-0.99; Table 6) for the model without BDI-II.

Joint modeling (shared random effects model)

The joint analysis estimated the individual-specific random effects of the longitudinal process simultaneously and specified them as covariates of mortality in the survival process. The linear mixed effect model generated an average regression coefficient of 0.033 (SE=0.003) (not shown) for the time variable suggesting an increase in global T-scores over the study period. The linear slope estimate of the global T-score was -0.39 (SE=0.089), which indicates a negative association with the risk of mortality (Table 8). The adjusted HR of the slope was 0.67 (95% CI = 0.56-0.80), indicating that for every 10-unit increase in global T-score, the hazard of death decreased by 33%. The baseline covariates included in the final model (duration of HIV infection, plasma viral load, ethnicity, and serum hemoglobin) were same as those in the traditional Cox regression.

Table 8: Table V: Results of multivariable joint modeling of repeated measures (Global T-score)

Predictor	β (SE)	Adjusted HR (95% CI)[a]
Intercept	-2.34 (0.71)	0.09 (0.02 – 0.38)
Global T-score slope	-0.39 (0.08)	0.67[a] (0.56 – 0.80)
Age (years)	0.01 (0.01)	1.01 (0.99 – 1.02)
Duration of HIV infection (years)	0.02 (0.01)	1.02 (0.99 – 1.03)
Ethnicity		
Hispanic or Latino	Ref	Ref
Not Hispanic or Latino	0.41 (0.15)	1.50 (1.11 – 2.02)
Serum Hemoglobin (g/dl)	-0.10 (0.03)	0.90 (0.84 – 0.96)
Plasma viral load (log10 copies/mL)	0.22 (0.04)	1.25 (1.14 – 1.36)

[a]Adjusted for all other variables in the model
[b]Hazard Ratio corresponds to a 10-unit increase in global T-scores

Discussion

Despite the availability and use of potent antiretroviral medications, mild to moderate HIV-associated NCI is still prevalent [7, 15]. Apart from being a disabling consequence of HIV infection, NCI has been found to be an independent predictor of mortality in the pre-cART era [99]. Limited research has been conducted on the association between mortality and NCI in the HAART era, with little consideration given to the substantial variability that the course of NCI over time in the HIV infected population [9, 99]. The present study aimed to examine the association between baseline neurocognitive status as well as longitudinal changes in neurocognitive status and mortality in a diverse HIV-infected patient sample. Our research adds to this limited body of literature by investigating the link between HIV-associated NCI and mortality among HIV-infected participants.

The crude survival analysis results demonstrated no association between neurocognitive status and mortality (HR = 0.99). In adjusted analyses, we detected a significant interaction between neurocognitive status and age in relation to mortality. Specifically, among older participants, higher global T-scores (i.e., better neurocognitive status) were associated with a lower hazard of death, whereas neurocognitive status was not associated with mortality among younger participants. This finding was independent of plasma viral load, ethnicity, duration of HIV infection, and serum hemoglobin as these variables were adjusted for in the final model. Unlike our study, none of the previous studies have reported an interaction between age and neurocognitive status in relation to mortality. However, studies have observed independent associations between age and mortality and age and neurocognitive status [199, 200]. Specifically, in the pre-cART era, studies had found NCI to be an independent risk factor for mortality [99]. The association was also found in the cART-era, in a limited number of studies. However, the association was explored either between severe forms of NCI and mortality or only among those

with the severe form of HIV infection [103, 104]. Our findings differ from cART-era studies because we did not exclude any participants based on severity.

The most plausible mechanism underlying the interaction between age and neurocognitive status in association with mortality may be the age-related exacerbation of co-morbidities, such as metabolic disorders and vascular diseases [204-206]. Since the initiation of cART, the prevalence of vascular and metabolic disorders among HIV infected individuals has increased because of improved life expectancy [207]; nearly half of people living with HIV in the United States are aged 50 and older. The synergy between age (and, indirectly, age-related comorbidities) and NCI in HIV probably ensues a vicious cycle. Comorbidities adversely affect the neurocognitive status, which may lead to reduced ability to manage daily life activities, lower medication adherence, and poorer healthcare utilization, thus further progressing comorbidities [208, 209]. Therefore, age may be acting as a proxy for certain comorbidities.

We found a stronger negative association between mortality and domain-specific T-scores for abstraction and executive functioning during domain-specific analyses, speed of information processing, and motor compared to other domains. The finding is not surprising given the recognition that HIV-related NCI tends to impact frontal-subcortical regions of the brain. To our knowledge, only one other study has conducted an analysis based on subsets of a brief screening instrument that assesses global HIV-related cognitive impairment [119]. Banerjee et al. used the HIV dementia scale (HDS) as a measure of NCI and assessed psychomotor speed, memory, visual-spatial constructional praxis, and executive inhibitory control in relation to mortality. Among the four subset scores, executive inhibitory control (antisaccade subset) was associated with time to death, consistent with the frontal-subcortical impairment pattern. Lastly, recent studies have found heightened variability within or between neuropsychological test

scores associated with a higher risk of death [210, 211]. Such variability may also point to dysfunction related to attention and/or executive functions.

Apart from neurocognitive status, we also found that HIV-infected participants of non-Hispanic ethnicity with higher viral loads or lower hemoglobin had a higher hazard of mortality. These findings are adjusted for each other as well as for the neurocognitive status and are consistent with the literature. High plasma viral load and low serum hemoglobin are well-established independent risk factors of mortality in the HIV-infected population. Sempa et al. found a higher hazard of death per unit increase in the log10 viral load (HR=1.63; 95% CI = 1.02–2.60) [212], and a recent study found that viral load was a stronger predictor of mortality compared to CD4 cell count [196]. Lower hemoglobin has also been associated with a higher hazard (HR= 1.32, 95% CI =1.12–1.55) of dying in the HIV-infected population [213]. Multiple studies have found a higher hazard of death among non-Hispanic blacks than non-Hispanic whites or overall Hispanics [214, 215]. Our findings are somewhat consistent as 72% of NNTC participants were non-Hispanics, and 46% of the non-Hispanics were blacks.

To account for the variability in the course of NCI over time and its reversible nature in relation to mortality, joint modeling was performed. Joint modeling enables the repeated NCI measurements and survival to be modeled while accounting for interrelationships between the two processes [216]. We found that a linear change (increase/decrease) in global T-scores is an independent predictor of mortality. To our knowledge, this is the first study to examine repeated measures of NCI in relation to mortality in the HIV-infected population. Our results provide useful predictive information of longitudinal measures of NC status on mortality. The model can be used to predict future survival outcomes as well as future neurocognitive status in terms of T-scores when the T-scores are known up to the current time (dynamic prediction). Clinicians can use this information for timely detection and appropriate mitigation of NCI based on prediction.

The current study has certain limitations. This is a clinic-based study with a volunteer and predominantly male participation that may limit generalizability. This study, however, is one of its kind, conducted at four centers in the US with information available on a wide range of demographic, behavioral, and clinical and laboratory measures. The study did not exclude anyone based on the presence of other contributing central nervous system (CNS) infections; thus, the NCI may, in part, be imparted by them and not exclusively by HIV infection. However, the prevalence of other CNS infections in the study population was low (9%). An additional limitation was that some variables were incompletely described (e.g., unclear type of hepatitis or cerebrovascular disease), or were based on self-reports (e.g., duration of HIV infection). Among the neurocognitive domains, verbal fluency was a single task domain, which may not be ideal. However, we were limited by the variables available for these secondary analyses, and this is consistent with past work by the NNTC group. Loss to follow up (12%) in the study may have underestimated overall mortality. The final Cox proportional hazards model was not adjusted for additional confounders like depressive symptoms due to missing data. Yet, a sub-analysis of participants with complete data on Beck Depression Inventory-II (BDI-II) scores showed a similar association between NCI and mortality then without BDI-II in the model, although the results cannot be directly compared due to sample size differences. We did not investigate cause-specific mortality, as there was no relevant information available. This may have overestimated mortality in association with NCI. Furthermore, we were not able to assess the potential confounding effects of unmeasured variables, such as comorbidity treatments. Joint modeling was conducted under the assumption of a linear form for the global T-score trajectories and censoring being independent of the random effects that may lead to model misspecifications. However, we obtained similar results with splines in the model. The positive average regression coefficient (0.033) for the time variable in the longitudinal sub-model within joint modelling might have been

related to practice effects and not to an actual increase in global T-scores over the study period. Practice effect is typically stronger between the between 1st and 2nd assessments and less evident in subsequent assessments [217]. Thus, we conducted a sub-analysis excluding the 1st visit. The linear mixed effect model starting at the 2nd visit still generated a positive average regression coefficient (0.022). Lastly, repeated measures were used only for the primary exposure (global T-scores), and all other covariates were assessed only at the baseline. Future research may consider including multiple covariates with repeated measures.

Conclusion

Overall, this study provides evidence that neurocognitive status interacts with age in relation to mortality and thus may have considerable prognostic utility for assessing mortality risk, particularly among older HIV-infected population. The current study identified older HIV-infected population as a group needing special attention for the longevity of life. The finding is substantial given that nearly half of people in the United States living with diagnosed HIV are aged 50 and older and that the neurocognitive status is associated with quality of life. The preliminary findings of the domain-specific analysis may suggest abstraction and executive functioning, speed of information processing, and motor domains to be particularly sensitive in relation to the hazard of mortality. The study further provides evidence that the increase in T-scores over time is associated with lower mortality. The joint model provides useful predictive information not only about the hazard of mortality but also future cognitive scores. The study findings may be used to develop a predictive tool and thus may be used for patient-specific timely management strategies and future clinical interventions (lifestyle remedies, optimizing disease and comorbidity management and ARV management). The approach is particularly useful in clinical settings as repeated measures on biomarkers are very commonly generated for monitoring of chronic medical conditions. In conclusion, optimal management (treatment/rehabilitation) strategies,

particularly based on the dynamic predictions and targeting not only the neurocognitive status but also age-related co-morbidities, may lead to an improved outcome in the HIV-infected population.

CHAPTER 5. DISCUSSION

Though cART has revolutionized HIV-management [10, 15, 200, 218, 219], PLWH continues to experience relatively milder forms of cognitive impairment [7, 10, 16, 177], which not only compromises their quality of life but also imposes serious implications on public health [118, 220]. Neurocognitive status is highly relevant to long-term survivors of HIV infection because it may carry important prognostic value for mental and physical outcomes that are important to patients.

The focus of this dissertation was to investigate risk factors associated with neurocognitive impairment and to assess the survival implications of neurocognitive status in PLWH. First, we investigated clinical, demographic, and behavioral risk factors associated with neurocognitive impairments in PLWH and constructed a user-friendly predictive tool based on the factors. Second, we investigated the factors associated with neurocognitive decline. Lastly, we investigated the association between neurocognitive status and mortality in PLWH.

Study findings and their relevance to literature

Given that despite a broad literature on NCI in PLWH, the underlying risk factors remain inconclusive and that the search for an optimal screening tool for NCI in PLWH is still ongoing, the objectives of our first study were to identify factors associated with NCI using a large and diverse sample of PLWH and to build a user-friendly predictive tool. To this end, we used the CHARTER study baseline database and created a nomogram. The global T-scores were used to designate impairment as an outcome variable, and Bayesian network analyses followed by multiple logistic regression modeling were performed.

We found a strong positive association between age and NCI that is beyond the normal age-related neurocognitive function as we used age-adjusted T-scores. Although the general population may have the finding, this association is vital for PLWH as they may be experiencing HIV-associated accelerated aging [146, 148, 221]. In contrast, unexpectedly, cocaine usage exhibited an inverse relation with NCI. However, this finding may be attributed to the inconsistent timings of cocaine use in some of our participants, with its effects having worn out at the time of the study. Notably, past studies on PLWH have obtained mixed results. Meade et al. and Attonito et al. found no association between cocaine use and global neurocognitive measure. However, Meade et al. did find higher impairment in processing speed and executive functioning. On the other hand, Byrd et al. reported a weak association between cocaine use and improved verbal fluency in PLWH [73, 75, 149]. The majority of the studies conducted in HIV-negative population have found either no association [222] or a positive association between cocaine use and neurocognitive impairment [223, 224] that is understandable as per biological plausibility. Further, a similar directionality of association was found between employment and NCI in the current study, which corroborates and expands on the previous literature that demonstrated a negative association between them [21, 150]. Neurocognitive status and employment may exhibit a bidirectional association where NCI may render PLWH unable to be efficiently employed, and unemployment may also reduce neurocognitive ability due to lack of job-dependent increased use of cognitive skills [151].

Besides age, selected activities of daily life (ADL) also showed a positive association with NCI, which again fits well with the large volume of past studies [115-117]. Of note, to gauge ADL, we used only the universally applicable essential activities of daily life, i.e., a combination of difficulty in bathing, dressing, eating, or using the toilet. Nevertheless, our race/ethnicity-dependent finding of Hispanic and Non-Hispanic Whites showing higher odds of NCI versus non-

Hispanic African Americans partially conflicted with the prior studies [153-155]. Although the delayed diagnosis may explain higher NCI in Hispanics and thus untimely management of the disease [156, 157], the higher NCI among Non-Hispanic Whites needs further investigation. Finally, we found impaired use of hands, abnormally high cholesterol, current psychotropic drug use, presence of any AIDS-defining illness, and lifetime history of stroke to be positively associated with NCI. Regarding motor disability of hands, since this impairment could be multicausal [158-160] and our data lacked the detailed information on causation, other factors mediating or moderating this relationship could not be ruled out and require further studies.

The positive association between hypercholesterolemia and NCI was anticipated and repeatedly reported [51, 162, 164]. Though not fully understood, the underlying mechanism may encompass cholesterol oxidation-induced cerebrovascular insults, secondary to endothelial redox perturbation caused by HIV [163-165]. Regarding psychotropic drug use, though not direct, previous studies have found associations between mental disorders (e.g., anxiety, depression, psychosis, or sleep disorders) and cognitive abilities [166]. Therefore, it seems probable that the observed association between psychotropic drugs and NCI in the current study is due to the mediatory role of such disorders, which can severely interfere with ART adherence. AIDS-defining comorbidities may serve as a proxy for the severity of HIV infection, and thus the positive association with NCI is not surprising and consistent with the literature [167].

As mentioned earlier, the extant screening/predictive tools for NCI are not as convenient and require rigorous training, experience, and time which warrants an efficient, concise, economical, and user-friendly alternative. Our proposed nomogram meets such requirements and considers many indispensable variables, including demographic, clinical, and behavioral factors, and can be employed in clinical settings to facilitate the assessment of cognitive status.

Not only that, the prompt availability and ease of use of such algorithms may specifically aid in early detection and thus better management of NCI in PLWH.

The second study's primary aims were to bridge the gap in the literature about a potential definition of neurocognitive decline that may be pertinent to the clinical criteria and probe the associated etiology accordingly. As alluded to earlier, cART has resulted in a dramatic increase in the life expectancy of PLWH, which equates to healthy individuals; however, this increase parallels the prevalence of NCI in such a population. Not only is there a paucity of longitudinal studies that investigated multiple factors linked to the cognitive decline in PLWH, using different methodologies, but also their measure of cognitive decline may not apply to the clinical setting.

As expected, ART non-users showed a stronger association with the cognitive decline versus their medicated counterparts. This adds to the existing literature by supporting the positive impact of ART on cognition in PLWH, possibly by suppressing viremia [95, 98, 177, 178]. Moreover, we observed a positive association between NCI and history of major depressive disorder and NCI and Hepatitis C in the population of interest. The finding is in accordance with the past studies [121, 172, 175] and can be tied back to the neuronal injury caused by chronic neuroinflammatory processes and oxidative stress, combined with the therapy-induced neurotoxicity (Hepatitis C treatment) [179, 182]. Though HCV infection in solitude has also been known to cause neurocognitive impairment, its concomitance with HIV infection may increase the vulnerability and risk of neurocognitive decline [183].

We also found a positive relationship between lifetime methamphetamine (MA) and cannabis use with a decrease in cognition, which largely agrees with the literature. A handful of studies that examined the relationship between recreational drug use and cognitive status reported not only neurotoxic effects of MA but also deleterious interactive effects of MA and HIV

infection on neurocognition in PLWH [79]. As far as cannabis is concerned, the results of different studies remain inconclusive, as some suggest a positive [186, 187] while others a negative association with cognitive status [188]. Notably, the aforementioned studies differed inherently in methodology, sample selection, and cannabis use (time, frequency, mode), and thus the results should be compared with caution.

Our findings also showed significant differences in the association of neurocognitive decline race/ethnicity-wise. Briefly, Hispanics exhibited a comparatively greater while non-Hispanic whites had a lower risk of neurocognitive decline than the non-Hispanic black population. This may be explained by the limited provision of health care, delayed diagnosis, and subpar management in Hispanics, as reported widely [156, 157, 175, 189]. Finally, our selected ADL parameters also exhibited a positive association with the decrement in cognition. Though previous studies have documented the association between the two [96, 117, 152], physical disabilities should be ruled out prior to investigating the association. In summary, our second study delineates the key etiological factors of neurocognitive decline in PLWH, which may be valuable for effective management and better ART adherence in patients.

Before the advent of cART, NCI in PLWH was linked, among other detrimental outcomes, to mortality [99]. However, in the post-cART era, the association between mortality and neurocognitive status, as well as the trajectory of neurocognitive status over time, remains an area of active investigation [9, 99]. The foremost objective of our final study was to probe mortality in relation to baseline as well as longitudinal neurocognitive status in PLWH. Crude and adjusted survival analyses were performed to assess our research question. Using the former analysis, we did not find any significant relation between neurocognitive status and mortality. In contrast, later analysis revealed a significant interactive effect of neurocognitive status and age on mortality such that no association was found in the younger group while older participants

showed an inverse relation (i.e., better neurocognitive status inversely related to mortality) above and beyond viral load, ethnicity, HIV infection duration, and serum hemoglobin. Our study, to our best knowledge, is the first to demonstrate such an interaction. Moreover, unlike previous studies [103, 104], in our study, no exclusions were made based on infection severity, which makes our sample comparatively more generalizable and representative of the disease. Though cART has led to an increase in the life expectancy in PLWH, the age-related comorbidities and their consequences (e.g., on cognition) have surged as well [204-206]. Thus, age may act as a proxy for the comorbidities that affect neurocognition, which in turn exacerbates the comorbidities (e.g., through the decreased ability of management) [208, 209], and probably explains our finding of synergistic effects of aging and NCI on mortality in patients.

Additionally, we also performed domain-specific exploration and found a stronger inverse relationship between mortality and the domains of abstract reasoning, executive functioning, information processing speed, and moto. Such cognitive processes rely heavily on the frontal cortex and subcortical regions known to be affected by NCI in PLWH. Our finding partially agrees with a recent study that documented a decline in executive control related to mortality [119]. Other important factors that showed a positive association with mortality in PLWH were non-Hispanic ethnicity, higher viral load, and lower serum hemoglobin. The ethnicity results partially correspond with the prior studies that indexed higher mortality among non-Hispanic blacks versus non-Hispanic whites/ overall Hispanics [213, 214]. However, higher mortality among non-Hispanic Whites compared to Hispanics cannot be explained and needs further investigation. The findings regarding high plasma viral load and low serum hemoglobin are inline with the literature [196].

Neurocognitive status exhibits divergent patterns ranging from substantial convalescence to massive deterioration [9]. This variability in the trajectory of NCI was accounted for by joint

modeling, and we found that the linear decrease in global T-scores was an independent predictor of mortality.

Implications of current research

The research project focused on investigating the factors associated with neurocognitive status and longitudinal neurocognitive change in PLWH. Furthermore, this dissertation aimed to construct a predictive tool to assess the probability of having a neurocognitive impairment. Lastly, we assessed if neurocognitive status was an independent predictor of death in PLWH. The aims of this research have important clinical and public health implications.

Age appears to be an essential factor when it comes to neurocognitive impairment, thus rendering the elderly PLWH a group requiring keen attention. Given the fact that age is a non-modifiable factor and that PLWH may have accelerated aging compared to the general population, the association cannot be eradicated. However, timely targeted actions and management plans may improve the quality of life among this group. Neurocognition and employment may have a bidirectional association. It may be challenging to complete the assigned job-related tasks if cognition is affected, while on the other hand, being unemployed reduces task-related cognitive stimulation, thus further reducing the neurocognitive ability. Therefore, as a part of the management plan, the unemployed PLWH may benefit from activities that deliver cognitive stimulation. The Hispanic HIV-infected population may be another group that needs supplementary consideration when it comes to neurocognition. Among this group, an effort may need to be made in improving healthcare utilization for the early detection of disease and early initiation of management. Our findings show that PLWH with high cholesterol, current psychotropic drug use, AIDS-defining illness, and history of stroke exhibit a positive association

with neurocognitive impairment. A diligent emphasis on patients with such comorbidities may lead to better health outcomes.

The nomogram that we developed has a user-friendly interface. It uses variables that can be easily measured in clinical settings and easy to implement within a clinic or web-interface platform. Our goal with such a tool is to help clinicians predict specific patients who might have a high probability of NCI and be further evaluated by a comprehensive neuropsychological examination resulting in timely diagnosis and appropriate management.

Results of the second study highlight the use of ART to prevent a future decline in neurocognitive status. A regular evaluation of the effectiveness of the ART regimen and continual use may be vital for PLWH to have a better quality of life and a potentially reduced or delayed incidence of neurocognitive impairment. Furthermore, delayed progression and remission of neurocognitive impairment may potentially be achieved for the prevalent cases through proper management.

Our third study provides evidence that neurocognitive status interacts with age in relation to mortality and thus may have substantial prognostic utility for assessing mortality risk, particularly among older HIV-infected population. Our results identified the older HIV-infected population as a group needing special attention for the longevity of life. The finding is substantial given that nearly half of people in the United States living with diagnosed HIV are aged 50 and older and that the neurocognitive status is associated with quality of life. The study further provides evidence that the increase in T-scores over time is associated with lower mortality. The joint model provides useful predictive information about the hazard of mortality and future cognitive scores. The study findings may be used to develop a predictive tool and thus may be used for patient-specific timely management strategies and future clinical interventions (lifestyle

remedies, optimizing disease and comorbidity management, and ARV management). The approach is instrumental in clinical settings, as repeated measures on biomarkers are commonly generated to monitor chronic medical conditions. In conclusion, optimal management (treatment/rehabilitation) strategies, particularly based on the dynamic predictions and targeting not only the neurocognitive status but also age-related co-morbidities, may lead to an improved outcome in the HIV-infected population.

Future considerations

Future studies should be focused on enhanced generalizability of the findings. However, given the time and expertise required to administer the comprehensive neurocognitive test battery to assess neurocognitive status, it may not be feasible to design and conduct studies generalized to the entire HIV-infected populations in the US. Nevertheless, studies may be designed and conducted to extend generalizability to at least the clinical HIV-infected population through incorporating a random selection of the participants rather than volunteer selection. Regarding the nomogram, a future direction is to external validation for broader applicability. We used age as a binary variable in the nomogram as about 50% of PLWH in the US are above the age of 50 years. Future studies may incorporate age with more categories. Unexpectedly we found a negative association between cocaine use and NCI. Given our findings and the literature's mixed results, the association between cocaine use and NCI in PLWH should be considered in future research. Although we understandably found that the odds of having NCI are higher among Hispanics vs. non-Hispanic Blacks, the higher odds among non-Hispanic Whites vs. non-Hispanic blacks was not clear. These findings may be sample dependent but still, need further exploration. On the other hand, we observed a higher hazard of mortality among non-Hispanics than Hispanics, which may also be sample dependent and should be studied further.

We found a positive association between cannabis use and neurocognitive decline. Limited research has been conducted to explore this association, and the studies have been inconsistent in their findings, and some of them suggested cannabis use to be beneficial for neurocognition. Given the dearth of research and inconsistent findings, the phenomenon merits further investigation. We could not assess cause-specific mortality, but future research may aim to collect information about the cause of death as well. While conducting joint modeling, repeated measures were used only for the primary exposure (global T-scores), and all other covariates were assessed only at the baseline. Future research may consider including multiple covariates with repeated measures.

Conclusion

Overall, this dissertation provides valuable evidence of factors associated with neurocognitive impairment and neurocognitive decline in PLWH. It further provides evidence that neurocognitive status interacts with age in relation to mortality and identifies other factors associated with mortality in PLWH. Older age (>50 years) was positively associated with neurocognitive impairment, and age interacted with neurocognitive status (global T-score) in relation to mortality such that among older participants, higher global T-scores (i.e., better neurocognitive status) were associated with a lower hazard of death. Compared to non-Hispanic Blacks, Hispanics had higher odds of baseline NCI and higher neurocognitive decline hazard. However, compared to non-Hispanic Blacks, although non-Hispanic Whites had higher odds of NCI, they had a lower hazard of neurocognitive decline (although negligible). Further, non-Hispanics had a higher hazard of mortality compared to Hispanics. Current employment was negatively associated with neurocognitive impairment. Among substance use, lifetime cocaine use was negatively associated with NCI, whereas lifetime methamphetamine use and lifetime cannabis use were positively associated with neurocognitive decline. No baseline ARV use was

positively related to neurocognitive decline and having a high baseline viral load that may act as a proxy for the effectiveness of ARV therapy was associated with a higher hazard of dying. Difficulty eating, dressing, bathing, or using the toilet was positively associated with both NCI and neurocognitive decline. Lifetime depression had a positive association with the neurocognitive decline, while current psychotropic drug use that may be a proxy for diseases like depression and anxiety had a positive association with baseline NCI. Among other comorbidities, history of stroke, any AIDS-defining illness, and impaired use of hands were positively associated with baseline NCI, the hepatitis-C infection was positively associated with neurocognitive decline, and a higher baseline serum hemoglobin was associated with a lower hazard of dying.

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APPENDICES

APPENDIX A: Neurocognitive battery used to generate T-scores among HIV-infected participants of CHARTER/NNTC

Cognitive Domain	Neuropsychological Test
Abstraction/ Executive Functioning	Trail Making Test, Part B [225]
	Wisconsin Card Sorting Test-64, Perseverative Responses [225, 226]
Speed of Information Processing	Wechsler Adult Intelligence Scale-3rd ed. (WAIS-III) Digit Symbol [227]
	WAIS-III Symbol Search [227]
	Trail Making Test, Part A [225]
Attention and Working Memory	Paced Auditory Serial Addition Task (PASAT) (first channel only) [228]
	WAIS-III Letter Number Sequencing [227]
Learning	Brief Visuospatial Memory Test-Revised (BVMT-R) Total Recall [226, 229]
	Hopkins Verbal Learning Test-Revised (HVLT-R) Total Recall [226, 230]
Memory	BVMT-R Delayed Recall [226, 229]
	HVLT-R Delayed Recall [226, 230]
Verbal fluency	Controlled Oral Word Association Test (COWAT-FAS) [225]
Motor	Grooved Pegboard dominant [225]
	Grooved Pegboard non-dominant [225]

APPENDIX B: Conversion table for transforming T-scores into deficit scores.

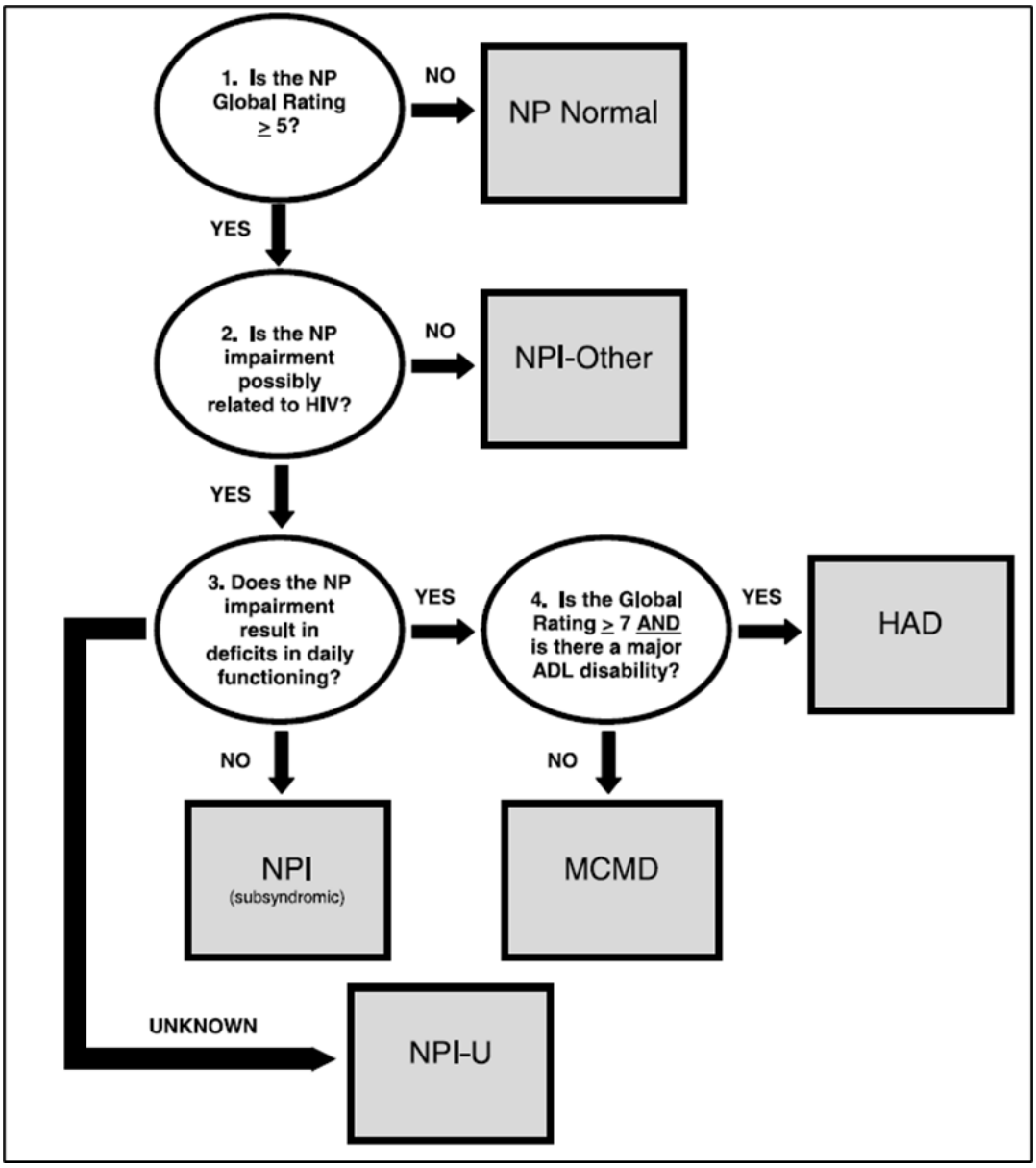
T score	Deficit Score	Impairment Descriptor
≥ 40	0	Normal
39 – 35	1	Mild
34 – 30	2	Mild-moderate
29 – 25	3	Moderate
24 – 20	4	Moderate-severe
≤ 19	5	Severe

APPENDIX C: Conversion table for transforming T-scores into clinical ratings

T score	Deficit Score	Impairment Descriptor
≥ 55	1	Above average
45 – 54	2	Average
40 – 44	3	Low average
–	4	Borderline*
35 – 39	5	Definite mild impairment
30 – 34	6	Mild-to-moderate impairment
25 – 29	7	Moderate impairment
20 – 24	8	Moderate-to-severe impairment
≤ 19	9	Severe impairment

*''Borderline'' used only for Domain and Global summary ratings (not individual test scores)

APPENDIX D: Flow chart depicting the decision-making process in assigning a neurocognitive diagnosis



Printed from: Woods, S.P., Rippeth, J.D., Frol, A.B., Levy, J.K., Ryan, E., Soukup, V.M., Hinkin, C.H., Lazzaretto, D., Cherner, M., Marcotte, T.D. and Gelman, B.B., 2004. Interrater reliability of clinical ratings and neurocognitive diagnoses in HIV. Journal of Clinical and Experimental Neuropsychology, 26(6), pp.759-778.

APPENDIX E: SAS Codebook for CHARTER data (This codebook was created and edited as needed to identify variables in the final dataset used for analysis).

CHARTER FORM	OIGINAL VARIABLE	ORIGINAL VARIABLE LABEL	ORIGINAL CODING	SAS VARIABLE (Label)	SAS CODING
chqrlipf	qrdiabe	Have you been diagnosed with diabetes mellitus?	-9: Missing 0: No 1: Yes	qrdiabe	0: No 1: Yes
chqrlipf	qrdiadg	Have you ever or are you currently taking any of these medications for diabetes?	-9: Missing 0: No 1: Yes	Qrdiadg	0: No 1: Yes
chqrlipf	qrhighc	Do you have abnormally high cholesterol?	-9: Missing 0: No 1: Yes	Qrhighc	0: No 1: Yes
chqrlipf	qrhight	Do you have abnormally high triglycerides?	-9: Missing 0: No 1: Yes	Qrhight	0: No 1: Yes
chqrlipf	qrmedhi	Have you ever or are you currently taking medication for hyperlipidemia?	-9: Missing 0: No 1: Yes	qrmedhi	0: No 1: Yes
chqrlipf	qrdiabe qrhighc qrhight	Have you ever been diagnosed with diabetes mellitus? Do you have abnormal high cholesterol? Do you have abnormal high triglycerides?	-9: Missing 0: No 1: Yes	Metdisorder (Any metabolic disorder)	0: No 1: Yes
chqurin	quprote	Urine test protein analysis	0: Negative 1: trace-5mg/dl 2: 30mg/dl 3: 100mg/dl 4: 300mg/dl 5: 2000mg/dl	Quprote	0: Negative 1: Trace-30mg/dl 2: >30mg/dl
chqurin	qubtme1	Blood Lactate: 1st Value (mMol/L)	Continuous	Qubtmecat	0: 0.1-1.5 mmol/l 1: > 1.5 mmol/l
chqurin	qultme1	CSF Lactate: 1st Value (mMol/L)	Continuous	qultme1cat	0: <0 - 2.3 mmol/l 1: >2.3 mmol/l
chqzpsy	qzpsyrx	Have you ever used psychotropic medications?	-9: Missing 0: No 1: Yes	Qzpsyrx	0: No 1: Yes
chqzpsy	qzcurrx	Are you currently taking any psychotropic medications?	-9: Missing -8: NA value 0: No 1: Yes	Qzcurrx	0: No 1: Yes

chybbk2	ybtotal	Total BDI Score	Continuous	Ybtotalc	1: 0-13 (minimal) 2: 14-19 (mild) 3: 20-28 (moderate) 4: 29-63 (severe)
ctadliv	adbathn	Bathing: Now	0: I handle all of my bathing needs by myself 1: I need occasional assistance with bathing (getting in and out of the tub or shower) 2: I always need help from others when bathing -9: missing	adbathn	0: Independent (0) 1: Dependent (1,2)
ctadliv	addresn	Dressing: Now	0: I am able to dress myself and pick out my own clothes 1: I dress myself but someone else must pick out my clothes for me 2: I need occasional assistance getting dressed or frequently make mistakes in choosing clothes 3: I need frequent assistance getting dressed -9: missing	addresn	0: Independent (0,1) 1: Dependent (2,3)
ctadliv	admedsn	Taking medication: Now	0: I take sole responsibility for taking medications in correct dosages at the correct time 1: I take medications that are prepared in individual doses by someone else 2: I am unable to take my own medications 0.5: I am able to take my own medications but choose to have someone else do it for me -9: missing	admedsn	0: Independent (0,0.5) 1: Dependent (1, 2)
chczhhs	czeatin	Does health limit eating dressing bating or using the toilet	1: Yes limits a lot 2: Yes limits a little 3: No not limited	czeatin2	0: No (3) 1: Yes (1,2)
dmcdcws	cd93cdc	1993 CDC Classification	A1: Asymptomatic HIV infection or acute HIV infection with accompanying illness PGL CD4 >500/mm3 T-lymphocyte >29% A2: Asymptomatic HIV infection or acute HIV infection with accompanying illness PGL CD4 200-499/mm3 T-	cd93cdc	1: A1+A2+A3 2: B1+B2+B3 3: C1+C2+C3

			lymphocyte 14-28% A3: Asymptomatic HIV infection or acute HIV infection with accompanying illness PGL CD4 <200/mm3 T-lymphocyte <14% B1:Symptomatic HIV infection with accompanying illness CD4 >500/mm3 T-lymphocyte >29% B2: Symptomatic HIV infection with accompanying illness CD4 200-499/mm3 T-lymphocyte 14-28% B3: Symptomatic HIV infection with accompanying illness CD4 <200/mm3 T-lymphocyte <14% C1: AIDS indicator condition CD4 >500/mm3 T-lymphocyte >29% C2: AIDS indicator condition CD4 200-499/mm3 T-lymphocyte 14-28% C3: AIDS indicator condition CD4 <200/mm3 T-lymphocyte <14%		
dmcdcws	cd93rec	Value of most recent viral load	Continuous	cd93recat	0: =<50 1: 51-10000 2: >10000
dmcdcws	cd93can	Diagnosis of Candidiasis (THRUSH) - bronchial pulmonary or esophageal	-9: Missing -8: Na value 0: No diagnosis reported 1: Diagnosis reported	Aidscomorb (Any AIDS defining comorbidity)	0: No 1: Yes
	cd93coc	Diagnosis of Cryptococcus extra pulmonary			
	cd93cmd	Diagnosis of Cytomegalovirus disease (CMV) (other than liver spleen or nodes)			
	cd93cmv	Diagnosis of Cytomegalovirus retinitis (CMV) (with loss of vision)			
	cd93enc	Diagnosis of Encephalopathy HIV related			
	cd93hrp	Diagnosis of Herpes simplex: chronic ulcer(s) (>1 month`s duration); or bronchitis pneumonitis or esophagitis			
	cd93his	Diagnosis of Histoplasmosis disseminated or extra pulmonary			
	cd93kap	Diagnosis of Kaposi's Sarcoma			
	cd93brk	Diagnosis of Lymphoma Burkitt`s (or equivalent term) immunoblastic (or equivalent term) and primary of brain			
	cd93mal	Diagnosis of Mycobacterium avium complex (MAC) or M. kansasii (MAI) disseminated or extra pulmonary			

	cd93mtb	Diagnosis of Mycobacterium tuberculosis (TB) any site (pulmonary or extra pulmonary)			
	cd93pcp	Diagnosis of Pneumocystis carinii pneumonia (PCP)			
	cd93pne	Diagnosis of Pneumonia recurrent			
	cd93pml	Diagnosis of Progressive multifocal leukoencephalopathy (PML)			
	cd93sal	Diagnosis of Salmonella septicemia recurrent			
	cd93tox	Diagnosis of Toxoplasmosis of brain			
	cd93was	Diagnosis of Wasting syndrome due to HIV			
dmcdcws	cd93lat	Value of last CD4 Count	Continuous	cd93latcat	0: >500 1: 200-500 2: <200
dmcdcws	cd93lot	Value of lowest CD4 Count	Continuous	cd93lotcat	0: >500 1: 200-500 2: <200
hcvlabs	vlhcvab	Hepatitis C laboratory results	POS NEG	Vlhcvab	1: Yes (POS) 0: No (NEG)
nhcvrna	cvrnavl	Hepatitis C Viral load (IU/mL)	Continuous	cvrnavlcat	0: <=800000 1: >800000
nmcnnrp	cnbgluc	Glucose (serum) (mg/dL)	Continuous	cnbglucat	-9: missing 0: <140 1: >=140
nmcnnrp	cnburea	Blood urea nitrogen (serum) (mg/dL)	Continuous	cnbureacat	-9: missing 0: <=20 1: >20
nmcnnrp	cnbcrea	Creatinine (serum) (mg/dL)	Continuous	cnbcreacat	-9: missing 0: <=1.3 1: >1.3
nmcnnrp	cnbchlo	Chloride (serum) (mmol/L)	Continuous	cnbchlocat	-9: missing 0: <106 1: =>106
nmcnnrp	cnbsodi	Sodium (serum) (mmol/L)	Continuous	cnbsodicat	-9: missing 1: <135 (hyponatremia) 0: =>135
nmcnnrp	cnbpota	Potassium (serum) (mmol/L)	Continuous	cnbpotacat	-9: missing 1: <3.6 (hypokalemia) 0: =>3.6
nmcnnrp	cnbcalc	Calcium (serum) (mg/dL)	Continuous	cnbcalcat	-9: missing 0: 8.9-10.1 1: <8.9 2: >10.1

nmcnnrp	cnbprot	Total protein (serum) (g/dL)	Continuous	cnbprotcat	-9: missing 0: 6.4-8.3 1: <6.4 2: >8.3
nmcnnrp	cnbbilt	Bilirubin Total (serum) (mg/dL)	Continuous	cnbbiltcat	-9: missing 0: <=1.2 1: >1.2
nmcnnrp	cnbsgot	Aspartate aminotransferase level (AST/SGOT) (serum) (IU/L)	Continuous	cnbsgotcat	-9: missing 0: <=40 1: >40
nmcnnrp	cnbsgpt	Alanine aminotransferase level (ALT/SGPT) (serum) (IU/L)	Continuous	cnbsgptcat	0: <=55 1: >55
nmcnnrp	cnbalka	Alkaline Phosphatase level (serum) (IU/L)	Continuous	cnbalkacat	-9: missing 0: <=140 1: >140
nmcnnrp	cnbchol	Total cholesterol (serum) (mg/dL)	Continuous	cnbcholcat	0: <=200 1: >200
nmhcmrp	hcbwbc	White blood cell count (x10^3/uL) (Blood)	Continuous	hcbwbcat	0: 4-11 1: <4 2: >11
nmhcmrp	hcbhgb	Hemoglobin (g/dL) (Blood)	Continuous	hcbhgbcat	Missing=-9 0: =>13 1: <13
nmhcmrp	hcbmono	Monocyte (%) (Blood)	Continuous	hcbmonocat	missing=-9 0: <=8 1: >8
nmigmrp	igit4a	CD4 Absolute (cells/uL) (Blood)	Continuous	igit4acat	MISSING=-9 0: <500 1: 200-500 2: <200
nmserrp	sereslt	Rapid plasma reagin (syphilis screen) test result	Neg Pos	Sereslt	0: Neg 1: Pos
npbmdsn	bmlifa1	In your lifetime have you ever Had an open or closed head injury	0: No 1: Yes	bmlifa1	0: No 1: Yes
npbmdsn	bmlifc1	In your lifetime have you ever Been in a coma	0: No 1: Yes -9: Missing	bmlifc1	0: No 1: Yes -9: .
npbmdsn	bmlifi1	In your lifetime have you ever Had a stroke	0: No 1: Yes -9: Missing	bmlifi1	0: No 1: Yes -9: .
npbmdsn	bmnillfa	Is there a history of neurologic illness such as Parkinson's Alzheimer's Huntington's multiple	Adopted - unknown Aunt or Uncle	Bmnillfa	0: No (combined none, adopted-unknown and

		sclerosis epilepsy in your family? What is your closest familial relationship to someone with neurological illness?	Both sets grandparents Child Cousin Father Maternal grandparent mother mother/uncle/aunt nephew none Paternal grandparent Sibling unknown		unknown) 1: Yes (all others)
npbmdsn	bmyedi1	Educational attainment (categorical)	1: Less than a high school diploma or high school equivalency 2: High school diploma or high school equivalency 3: Certificate or Associates degree 4: Some college 5: Bachelor's degree 6: Graduate degree or graduate work -9: missing	bmyedi1	1: Less than a high school diploma or high school equivalency 2: High school diploma or high school equivalency 3: Certificate or Associates degree 4: Some college 5: Bachelor's degree 6: Graduate degree or graduate work -9: .
npbnote	bnviage	Age (years)	Continuous	bnviagecat	10-year intervals 1: 18-27 2: 28-37 3: 38-47 4: 48-57 5: =>58
npbnote	bnviage	Age (years)	Continuous	Agebi	0: <=50 1: >50
npbnote	bngendr	Gender at Birth	0: MALE 1: FEMALE	bngendr	0: MALE 1: FEMALE
npbnote	bnethco	Ethnicity Code	1: Black or African American 2: White 3: Hispanic 4: Other 5: Asian	bnethco	1: Black or African American 2: White 3: Hispanic 4: Other (4+5)
npbnote	bnuohan	Impaired use of hands	1: Sever impairment of hands 2: Moderate Impairment of hands 3: moderate/mild impairment of hands	bnuohan2	0: No (5) 1: Yes (1,2,3,4)

			4: Mild impairment of hands 5: No impairment of hands		
npclchr	CGLOBLDS	Global Deficit Score (NNTC-DCC value)	Continuous	CGLOBLDScat	0: <0.5 1: >=0.5 -9: .
npclchr	CAVRGTS	Global T score	Continuous	CAVRGTSBI	1: <40 0: >=40
nppaofi	pawkemp	Currently Employed	1: Yes full time 2: Yes part time 3: Not currently employed	pawkemp	1: Yes (combined 1 & 2) 0: No
tbdwsh2	dws2220	Clinical judgement of cause of neurocognitive impairment	-9: MISSING -8: Neurocognitively normal 0: No abnormalities other than HIV infection noted that might contribute to neurocognitive impairment 1: One or more abnormalities present but considered not likely to contribute to impairment 2: One or more abnormalities above considered contributory but not primary cause of impairment 3: One or more abnormalities above were considered to be the primary cause of impairment	dws2220	0: No (combined 0,1,2) 1: Yes (3 coded as 1)
ARV_Summary_Scores	ARVhistory	ARV use history (derived from chazarv)	ARV Naïve Current ARV use Past ARV use	ARVhistory	0=Current ARV use 1=Past ARV use 2=ARV naïve
ARV_Summary_Scores	HAART	HAART regimen classification (derived from chazarv)	ARV Naïve HAART No Current ARVs Non-HAART	HAART	0: HAART 1: Non-HAART 2: No Current ARVs 3: ARV Naïve
VL_Summary_Scores	csfvl	CSF viral load (IU/mL) (derived from nmrnarp) (derived from nmrnarp)	Continuous	Csfvlcat	Missing: . 0: <200 1: >=200
VL_Summary_Scores	bloodvl	Plasma viral load (IU/mL) (derived from nmrnarp) (derived from nmrnarp)	Continuous	bloodvlcat	Missing=. 0: <=50 1: 51-10000 2: >10000
CIDI_Summary_Scores	Lifetime_MDD	Lifetime DX Major depressive disorder (derived from chdsmiv)	YES NO	lifetime_mddc	1: Yes 0: No
CIDI_Summary_Scores	Lifetime_ALCAbuse	Lifetime DX Alcohol abuse (derived from chdsmiv)	YES NO	lifetime_alc	

CIDI_Summary_Scores	Lifetime_ALCDependence	Lifetime DX Alcohol dependence (derived from chdsmiv)	YES NO		Combined the two 1: if any one is yes 0: else
CIDI_Summary_Scores	Lifetime_MARAbuse	Lifetime DX Cannabis abuse (derived from chdsmiv)	YES NO	lifetime_mar	Combined the two 1: if any one is yes 0: else
CIDI_Summary_Scores	Lifetime_MARDependence	Lifetime DX Cannabis dependence (derived from chdsmiv)	YES NO		
CIDI_Summary_Scores	Lifetime_COCAbuse	Lifetime DX Cocaine abuse (derived from chdsmiv)	YES NO	lifetime_coc	Combined the two 1: if any one is yes 0: else
CIDI_Summary_Scores	Lifetime_COCDependence	Lifetime DX Cocaine dependence (derived from chdsmiv)	YES NO		
CIDI_Summary_Scores	Lifetime_HALAbuse	Lifetime DX Hallucinogen abuse (derived from chdsmiv)	YES NO	lifetime_hal	Combined the two 1: if any one is yes 0: else
CIDI_Summary_Scores	Lifetime_HALDependence	Lifetime DX Hallucinogen dependence (derived from chdsmiv)	YES NO		
CIDI_Summary_Scores	Lifetime_INHAbuse	Lifetime DX Inhalant abuse (derived from chdsmiv)	YES NO	lifetime_inh	Combined the two 1: if any one is yes 0: else
CIDI_Summary_Scores	Lifetime_INHDependence	Lifetime DX Inhalant dependence (derived from chdsmiv)	YES NO		
CIDI_Summary_Scores	Lifetime_METAbuse	Lifetime DX Methamphetamine abuse (derived from chdsmiv)	YES NO	lifetime_met	Combined the two 1: if any one is yes 0: else
CIDI_Summary_Scores	Lifetime_METDependence	Lifetime DX Methamphetamine dependence (derived from chdsmiv)	YES NO		
CIDI_Summary_Scores	Lifetime_OOPAbuse	Lifetime DX Opioid abuse (derived from chdsmiv)	YES NO	lifetime_oop	Combined the two 1: if any one is yes 0: else
CIDI_Summary_Scores	Lifetime_OOPDependence	Lifetime DX Opioid dependence (derived from chdsmiv)	YES NO		
CIDI_Summary_Scores	Lifetime_PCPAbuse	Lifetime DX PCP abuse (derived from chdsmiv)	YES NO	lifetime_pcp	Combined the two 1: if any one is yes 0: else
CIDI_Summary_Scores	Lifetime_PCPDependence	Lifetime DX PCP dependence (derived from chdsmiv)	YES NO		
CIDI_Summary_Scores	Lifetime_SEDAbuse	Lifetime DX Sedative abuse (derived from chdsmiv)	YES NO	lifetime_sed	Combined the two 1: if any one is yes 0: else
CIDI_Summary_Scores	Lifetime_SEDDependence	Lifetime DX Sedative dependence (derived from chdsmiv)	YES NO		
CIDI_Summary_Scores	Combined the variables from above to create any substance use			Anysub (Any substance use)	0: No 1: Yes
Dmcdcws	cd93psz	First positive HIV test date	Continuous	Posyears (HIV duration)	0: <=15 1: >15 Posyears was further converted to duration as above
npclchr	clexamz	Assessment date	Continuous		

APPENDIX F: Adjusted Odds Ratios (OR) for neurocognitive impairment stratified by Site among HIV-infected participants of CNS HIV Antiretroviral Therapy Effects Research (CHARTER) study (n=1,307)

Characteristics	Neurocognitive Impairment					
	Adjusted OR (95% CI)					
	Site 1	Site 2	Site 3	Site 4	Site 5	Site 6
Age (years)						
≤50	Ref	Ref	Ref	Ref	Ref	Ref
>50	1.86 (0.74-4.64)	2.28 (0.94-5.50)	1.77 (0.73-4.27)	4.75 (2.26-9.98)	4.32 (1.55-12.00)	4.61 (1.69-12.49)
Race/Ethnicity						
Non-Hispanic African American	Ref	Ref	Ref	Ref	Ref	Ref
Non-Hispanic White	1.55 (0.73-3.27)	1.19 (0.48-2.93)	2.30 (0.64-8.22)	1.59 (0.65-3.87)	3.46 (0.74-16.15)	4.08 (1.05-15.82)
Hispanic	1.24 (0.08-19.01)	0.85 (0.19-3.70)	NA	5.06 (2.08-12.30)	3.56 (0.60-21.05)	5.43 (0.73-40.23)
Other	18.5 (1.51-227.1)	NA	NA	NA	3.30 (0.31-34.52)	6.35 (1.04-38.68)
Currently employed						
No	Ref	Ref	Ref	Ref	Ref	Ref
Yes	0.44 (0.18-1.01)	0.45 (0.16-1.24)	0.64 (0.18-2.17)	0.77 (0.32-1.85)	0.42 (0.14-1.18)	0.45 (0.16-1.28)
History of high cholesterol						
No	Ref	Ref	Ref	Ref	Ref	Ref
Yes	1.85 (0.78-4.39)	1.03 (0.41-2.59)	1.14 (0.47-2.77)	1.66 (0.78-3.52)	1.63 (0.61-4.36)	1.89 (0.76-4.72)
Current use of psychotropic medication						
No	Ref	Ref	Ref	Ref	Ref	Ref
Yes	1.21 (0.58-2.52)	1.17 (0.49-2.75)	1.76 (0.73-4.24)	0.99 (0.46-2.14)	1.65 (0.71-3.88)	1.72 (0.70-4.26)
History of stroke						
No	Ref	Ref	Ref	Ref	Ref	Ref
Yes	1.56 (0.46-5.27)	3.79 (0.81-17.87)	3.10 (0.94-10.24)	1.51 (0.45-5.03)	6.68 (0.97-46.05)	0.64 (0.05-8.21)
Any AIDS defining illness						
No	Ref	Ref	Ref	Ref	Ref	Ref
Yes	1.96 (0.97-3.91)	0.60 (0.25-1.47)	1.33 (0.62-2.86)	1.41 (0.71-2.81)	2.59 (1.08-6.20)	1.32 (0.57-3.06)
Lifetime cocaine use						
No	Ref	Ref	Ref	Ref	Ref	Ref
Yes	0.58 (0.27-1.26)	0.22 (0.08-0.60)	0.43 (0.20-0.95)	0.55 (0.27-1.12)	0.62 (0.25-1.51)	0.41 (0.15-1.10)
Difficulty eating, dressing, bathing, or using the toilet						
No	Ref	Ref	Ref	Ref	Ref	Ref
Yes	4.54 (2.11-9.77)	2.04 (0.74-5.60)	0.72 (0.29-1.78)	1.52 (0.63-3.69)	1.78 (0.51-6.18)	1.28 (0.42-3.91)
Impaired use of hands						
No	Ref	Ref	Ref	Ref	Ref	Ref
Yes	2.32 (0.84-6.35)	1.21 (0.39-3.75)	1.39 (0.61-3.18)	2.38 (0.82-6.94)	2.40 (0.74-7.79)	4.34 (1.34-14.09)

APPENDIX G: SAS Codebook for NNTC data (This codebook was created and edited as needed to identify variables in the final dataset used for analysis).

MAJOR CATEGORY	TABLE	OIGINAL VARIABLE	ORIGINAL VARIABLE LABEL	ORIGINAL CODING	SAS VARIABLE	SAS LABEL	SAS CODING
PATIENT ID	ANY	PATID	Participant ID	NONE	PATID	Participant ID	NONE
COMORBIDITY	BDI	BDITOTAL	BDI Total Score	NONE	BDITOTAL	BDI Total Score	NONE
	COM	COHYPTEN	Hypertension	1=Unable to obtain info 2=No evidence of disease 3=Evidence of disease	COHYPTEN2	Hypertension	0=No evidence of disease 1=Evidence of disease (3=1, 2=0, 1=.)
	COM	CODIABTS	Diabetes	1=Unable to obtain info 2=No evidence of disease 3=Evidence of disease	CODIABTS2	Diabetes	0=No evidence of disease 1=Evidence of disease (3=1, 2=0, 1=.)
	COM	COHYPLIP	Hyperlipidemia	1=Unable to obtain info 2=No evidence of disease 3=Evidence of disease	COHYPLIP2	Hyperlipidemia	0=No evidence of disease 1=Evidence of disease (3=1, 2=0, 1=.)
	COM	COVIRHEP	Viral Hepatitis	1=Unable to obtain info 2=No evidence of disease 3=Evidence of disease	COVIRHEP2	Viral Hepatitis	0=No evidence of disease 1=Evidence of disease (3=1, 2=0, 1=.)
	COM	COESLD	End Stage Liver Disease	1=Unable to obtain info 2=No evidence of disease	COESLD2	End Stage Liver Disease	0=No evidence of disease 1=Evidence of disease (3=1, 2=0, 1=.)

MAJOR CATEGORY	TABLE	OIGINAL VARIABLE	ORIGINAL VARIABLE LABEL	ORIGINAL CODING	SAS VARIABLE	SAS LABEL	SAS CODING
				3=Evidence of disease			
	COM	COCRD	Chronic Renal Disease	1=Unable to obtain info 2=No evidence of disease 3=Evidence of disease	COCRD2	Chronic Renal Disease	0=No evidence of disease 1=Evidence of disease (3=1, 2=0, 1=.)
	COM	COCARDDS	Cardiac Disease	1=Unable to obtain info 2=No evidence of disease 3=Evidence of disease	COCARDDS2	Cardiac Disease	0=No evidence of disease 1=Evidence of disease (3=1, 2=0, 1=.)
	COM	COCOPD	Chr Obstructive Pulmon Dis	1=Unable to obtain info 2=No evidence of disease 3=Evidence of disease	COCOPD2	Chr Obstructive Pulmon Dis	0=No evidence of disease 1=Evidence of disease (3=1, 2=0, 1=.)
	COM	COCVD	Cerebrovascular Disease	1=Unable to obtain info 2=No evidence of disease 3=Evidence of disease	COCVD2	Cerebrovascular Disease	0=No evidence of disease 1=Evidence of disease (3=1, 2=0, 1=.)
	COM	CONONADC	Non-AIDS Defining Cancer	1=Unable to obtain info 2=No evidence of disease 3=Evidence of disease	CONONADC2	Non-AIDS Defining Cancer	0=No evidence of disease 1=Evidence of disease (3=1, 2=0, 1=.)

MAJOR CATEGORY	TABLE	OIGINAL VARIABLE	ORIGINAL VARIABLE LABEL	ORIGINAL CODING	SAS VARIABLE	SAS LABEL	SAS CODING
	COM	COHYPTEN, CODIABTS, COHYPLIP, COVIRHEP, COESLD, COCRD, COCARDDS, COCOPD, COCVD, CONONADC	GIVEN ABOVE	GIVEN ABOVE	COMORBNUMBER	Number of non-AIDS defining comorbidities	Sum of all original variables
	COM	COHYPTEN, CODIABTS, COHYPLIP, COVIRHEP, COESLD, COCRD, COCARDDS, COCOPD, COCVD, CONONADC	GIVEN ABOVE	GIVEN ABOVE	ANYCOMORB	Any non-AIDS defining comorbidity	0=no 1=yes If sum of original sas variables is equal to or more than 1 then anycomorb=1.
CSF LABS	CSF	CSFGLUC	CSF Glucose	NONE	CSFGLUC	CSF Glucose	NONE
	CSF	CSFPROT	CSF Protein	NONE	CSFPROT	CSF Protein	NONE
	CSF	CSFRBC	CSF Red Blood Cells	NONE	CSFRBC	CSF Red Blood Cells	NONE
	CSF	CSFWBC	CSF White Blood Cells	NONE	CSFWBC	CSF White Blood Cells	NONE
	CSF	CSFLOGVL	CSF Log 10 Viral Load	NONE	CSFLOGVL	CSF Log 10 Viral Load	NONE
	CSF	csfvln	CSF Viral Load	NONE	csfvln	CSF Viral Load	NONE
BLOOD LABS	CBC	CBCHGB	Hemoglobin	NONE	CBCHGB	Hemoglobin	NONE

MAJOR CATEGORY	TABLE	OIGINAL VARIABLE	ORIGINAL VARIABLE LABEL	ORIGINAL CODING	SAS VARIABLE	SAS LABEL	SAS CODING

	LAB	**LABFIELDN**
		BLDGLUCOSE
		BLDCREAT
		BLDBILI
		BLDAST
		BLDALT
		BLDCHOL
		BLDHDL
		BLDCLDL
		
		BLDHCVAB
			DCC Laboratory Test
			Glucose
			Creatinine
			Bilirubin
			AST
			ALT
			Cholesterol
			HDL
			LDL
			
			Blood Hepatitis C Antibodies
					bldglucose
					bldcreatinine
					bldbilirubin
					bldast
					bldalt
					bldchol
					bldhdlchol
					bldldlchol
					
					bldhcvab2
						Blood Glucose
						Blood Creatinine
						Serum Bilirubin
						Serum AST
						Serum ALT
						Blood Cholesterol
						Blood HDL
						Blood LDL
						
						Blood Hepatitis C Antibodies
							The table had mutiple observation per observation for baseline visit and different labs were recorded as longitudinal.
							Example: data table7a;set table7;where LABFIELDN= "BLDGLUCOSE";run;
							proc sort data=table7a;by patid dtassess;run;
							data table7b;set table7a;by patid dtassess;if first.patid;bldglucose=labvalue;keep patid bldglucose;run;
							Merged all the tables at the end
							
							0=non-reactive
							1=reactive

	TCL	TCLCD4C	CD4 Count	NONE	TCLCD4C	CD4 Count	NONE
	VLD	VIRALLDN	Viral Load	NONE	VIRALLDN	Viral Load	NONE
	VLD	VIRALLOGN	Log 10 Viral Load	NONE	VIRALLOGN	Log 10 Viral Load	NONE
	NDR	NDRCD4	Nadir CD4	NONE	NDRCD4	Nadir CD4	NONE
ARV MEDICATION	MEDARV	CURRENT	Medication status	0=PAST 1=ARV md is current	ARV	ARV med use	0=no current ARV use 1= non-HAART 2=HAART if current=. then ARV=.; else if current=1 and HAART=0 then ARV=1; else if current =1 and HAART=1 then ARV=2; else ARV=0;
		HAART	Regimen at visit consisted of highly active antiretroviral therapy (HAART)	0=no 1=yes			

MAJOR CATEGORY	TABLE	OIGINAL VARIABLE	ORIGINAL VARIABLE LABEL	ORIGINAL CODING	SAS VARIABLE	SAS LABEL	SAS CODING
DEMOGRAPHICS	NPV	DTASSESS	Date of assessment	none	Indexdate	indexdate	Indexdate=dtassess
	NPV	NPVEDUC	Years of Education	NONE	NPVEDUC	Years of Education	
	NPV	NPVGEND	Patient Gender	1=female 2=male	NPVGEND	Patient Gender	1=female 2=male
	NPV	NPVAGE	Age	NONE	NPVAGE	Age	NONE
	PTD	ETHNCTY	Ethnicity	1=Hispanic/Latino 2=Not Hispanic/Latino	Ethncty	Ethnicity	1=Hispanic/latino 2=Not Hispanic/Latino
	PTD	Asian, black, nativeal, nativeha, white, raceunk	Different variables for each race	1=yes 2=No	Race	Race	Asian =(0) Black =(1) Native Alaskan/American Indian =(2) Native Hawaiian/Pacific Islander =(3) White =(4) Unknown =(5)
	Row above	Race		Asian =(0) Black =(1) Native Alaskan/American Indian =(2) Native Hawaiian/Pacific Islander =(3) White =(4) Unknown =(5)	race2	Race	White=1 Black=2 Other=3
NEUROPSYCH TESTS AND DATES	NPV	CABSTTS	Abstract Exec Domain T-score	NONE	CABSTTS	Abstract Exec Domain T-score	NONE

MAJOR CATEGORY	TABLE	OIGINAL VARIABLE	ORIGINAL VARIABLE LABEL	ORIGINAL CODING	SAS VARIABLE	SAS LABEL	SAS CODING
	NPV	CINFPRTS	Speed of Info Processing Domain T-score	NONE	CINFPRTS	Speed of Info Processing Domain T-score	NONE
	NPV	CATTNTS	Attention Working Memory T-score	NONE	CATTNTS	Attention Working Memory T-score	NONE
	NPV	CLERNTS	Learning Domain T-score	NONE	CLERNTS	Learning Domain T-score	NONE
	NPV	CMEMTS	Memory Domain T-score	NONE	CMEMTS	Memory Domain T-score	NONE
	NPV	CVERBTS	Verbal Fluency Domain T-score	NONE	CVERBTS	Verbal Fluency Domain T-score	NONE
	NPV	CMOTORTS	Motor Domain T-score	NONE	CMOTORTS	Motor Domain T-score	NONE
	NPV	CAVRGTS	Global T Score	NONE	CAVRGTS	Global T Score	NONE
	NPV	DTASSESS	Assessment date	NONE	DTASSESS	Assessment date	NONE
	NPV	DTASSESS	Assessment date	NONE	DLASTVISIT	Date of last visit	NONE

SUBSTANCE ABUSE	PSY	ALCLDP	Alcohol Dependence	1=current
				2=past
				3=past and current
				4=normal
				5=not administered
				9=unable to rate
					alcuse	Alcohol use	1=yes
							0=no
							
							combine 1,2,3 into 1 and 4=0 and 5, 9, .=.
							if ALCLDP in(1 2 3) or ALCLAB in(1 2 3) then alcuse=1;
							else if ALCLDP in(4) or ALCLAB in(4) then alcuse=0;
							else alcuse=.;

		ALCLAB	Alcohol Abuse				

MAJOR CATEGORY	TABLE	OIGINAL VARIABLE	ORIGINAL VARIABLE LABEL	ORIGINAL CODING	SAS VARIABLE	SAS LABEL	SAS CODING
	PSY	CANBSDP	Cannabis Dependence	1=current 2=past 3=past and current 4=normal 5=not administered 9=unable to rate	canbuse	Cannabis use	1=yes 0=no
		CANBSAB	Cannabis Abuse				
	PSY	COCNDP	Cocaine Dependence	1=current 2=past 3=past and current 4=normal 5=not administered 9=unable to rate	cocuse	Cocaine use	1=yes 0=no
		COCNAB	Cocaine Abuse				
	PSY	HALCNDP	Hallucinogen Dependence	1=current 2=past 3=past and current 4=normal 5=not administered 9=unable to rate	haluse	Hallucinogen use	1=yes 0=no
		HALCNAB	Hallucinogen Abuse				

MAJOR CATEGORY	TABLE	OIGINAL VARIABLE	ORIGINAL VARIABLE LABEL	ORIGINAL CODING	SAS VARIABLE	SAS LABEL	SAS CODING
	PSY	OPIATDP	Opiate Dependence	1=current 2=past 3=past and current 4=normal 5=not administered 9=unable to rate	opiatuse	Opiate use	1=yes 0=no
		OPIATAB	Opiate Abuse				
	PSY	SEDATDP	Sedative Dependence	1=current 2=past 3=past and current 4=normal 5=not administered 9=unable to rate	sedatuse	Sedative use	1=yes 0=no
		SEDATAB	Sedative Abuse				
	PSY	STMULDP	Stimulant Dependence	1=current 2=past 3=past and current 4=normal 5=not administered 9=unable to rate	stmuse	Stimulant use	1=yes 0=no
		STMULAB	Stimulant Abuse				
DATES	PTD	DOD	Date of Death	NONE	DOD	Date of Death	NONE
	PTD NPV	YHIVDGN DTASSESS	1st evidence of HIV Date of assessment	NONE	hivdur	Duration of HIV infection (years)	NONE
	PTD	DBSLVIS	Date of baseline visit	NONE	DBSLVIS	Date of baseline visit	NONE
	STA	DSTATCH	Date of Status Change	NONE	DSTATCH	Date of Status Change	NONE

MAJOR CATEGORY	TABLE	OIGINAL VARIABLE	ORIGINAL VARIABLE LABEL	ORIGINAL CODING	SAS VARIABLE	SAS LABEL	SAS CODING
SURVIVAL ANALYSIS	NPV PTD STA	DTASSESS DOD DSATCH	Date of assessment Date of death Date of status change	none	Time	Time	For status=1 time from baseline to date of last visit. For Status=2 date of baseline visit to date of last visit. For status 3,4, date of baseline visit to date of death. For status = 5, date of baseline visit to the date of last visit. For status=6, date of baseline visit to date of last visit. For status=7, date of baseline visit to the date of status change.
	STA	STDSTAT	Study Status	1=ABBREVIATED 2=ACTIVE 3=DECEASED WITH AUTOPSY 4=DECEASED WITHOUT AUTOPSY 5=LOST TO FOLLOW UP 6=ADMINISTRATIVELY CENSORED 7=WITHDRAWN	Event	death	1=yes 0=no
PARTICIPANTS HEALTH CONDITION	SUB	SERIOUS	Serious/grave condition	0=NO 1=YES 9=UNKNOWN	SERIOUS2	Serious/grave condition	0=no 1=yes 9 and . = .
NEUROLOGICAL DISEASE DAGNOSIS / CNS INFECTIONS	NDX	FRSCTIDX	Frascati Neurocognitive Diagnosis	0=neurocognitively normal 1=ANI 2=Possible MILD	NPIO	Neuropsychological impairment- other	1=yes (6,7,8) 0=no .= 9, 99, .

MAJOR CATEGORY	TABLE	OIGINAL VARIABLE	ORIGINAL VARIABLE LABEL	ORIGINAL CODING	SAS VARIABLE	SAS LABEL	SAS CODING

				MND
				3=Probable mild MND
				4=Possible HAD
				5=Probable HAD
				6=NPI-other
				7=NPI-Uncertain
				9=test not done
				99=Unable to reliably assign diagnosis
							Combined both variables
							if FRSCTIDX in(9,99,.)then diagnosis=PRMNCGDG;
							else if PRMNCGDG in (9,99,.) then diagnosis=FRSCTIDX;
							else diagnosis=FRSCTIDX;
							if diagnosis in (9,99,.) then NPIO=.;
							else if diagnosis in (6,7,8)then NPIO=1;
							ELSE NPIO=0;
							run;

		PRMNCGDG	AAN Neurocognitive Diagnosis	0=neurocognitively normal 1=NPI; does not meet criteria for syndromic disorder 2=Possible MCMD 3=Probable MCMD 4=Possible HAD 5=Probable HAD 6=Probable CMVE 7=NPIO-other 8=NPI-uncertain 9=tests not done 99=unable to assign diagnosis			
	NDX	PRMCLYMP	Primary CNS Lymphoma	0=no evidence of disease 1=possible disease 2=probable disease 3=definite disease 9=na	PRMCLYMP2	Primary CNS Lymphoma	1=yes 0=no combined 1,2,3 into 1 0=0 na and .=.

MAJOR CATEGORY	TABLE	OIGINAL VARIABLE	ORIGINAL VARIABLE LABEL	ORIGINAL CODING	SAS VARIABLE	SAS LABEL	SAS CODING
	NDX	TOXPENC	Toxoplasma Encephalitis	0=no evidence of disease 1=possible disease 2=probable disease 3=definite disease 9=na	TOXPENC2	Toxoplasma Encephalitis	1=yes 0=no
	NDX	PML	PML	0=no evidence of disease 1=possible disease 2=probable disease 3=definite disease 9=na	PML2	PML	1=yes 0=no
	NDX	CMVNTENC	CMV Ventriculoencephalitis	0=no evidence of disease 1=possible disease 2=probable disease 3=definite disease 9=na	CMVNTENC2	CMV Ventriculoencephalitis	1=yes 0=no
	NDX	DEFCRYPT	Definite Cryptococcal	1= yes 2=no	DEFCRYPT2	Definite Cryptococcal	1=yes 0=no
	NDX	DEFHISTO	Definite Histoplasma	1= yes 2=no	DEFHISTO2	Definite Histoplasma	1=yes 0=no
	NDX	DEFCOCCI	Definite Coccidioides	1= yes 2=no	DEFCOCCI2	Definite Coccidioides	1=yes 0=no
	NDX	DEFTUBM	Definite Tuberculous	1= yes 2=no	DEFTUBM2	Definite Tuberculous	1=yes 0=no
	NDX	DEFSYPHM	Definite Syphilitic	1= yes 2=no	DEFSYPHM2	Definite Syphilitic	1=yes 0=no
	NDX	DEFLYMPH	Definite Lymphomatous	1= yes 2=no	DEFLYMPH2	Definite Lymphomatous	1=yes 0=no
	NDX	OTHSPCM	Other Specific Meningitis	1= yes 2=no	OTHSPCM2	Other Specific Meningitis	1=yes 0=no
	NDX	11 VARIABLES ABOVE	GIVEN ABOVE	GIVEN ABOVE	CNSMORBNUM	Number of CNS comorbidities	sum of all original variables

MAJOR CATEGORY	TABLE	OIGINAL VARIABLE	ORIGINAL VARIABLE LABEL	ORIGINAL CODING	SAS VARIABLE	SAS LABEL	SAS CODING
	NDX	12 VARIABLES ABOVE	GIVEN ABOVE	GIVEN ABOVE	anycnscomorb	Any CNS comorbidity	0=no 1=yes If sum of original SAS variables is equal to or more than 1 then anycomorb=1.

APPENDIX H: Descriptive statistics for battery of individual tests and neurocognitive domains among HIV-infected participants of the National NeuroAIDS Tissue Consortium (NNTC), n=877

Test/Domain	T-score, mean (SD)		
	Overall	Died*	Survived*
Global T-score	41.8 (7.4)	41.6 (7.9)	41.9 (7.2)
Abstraction/executive functioning	43.7 (10.4)	43.2 (10.4)	43.9 (10.4)
Trail Making Test, Part B	41.8 (12.4)	41.5 (12.7)	42.0 (12.3)
Wisconsin Card Sorting Test-64, Perseverative Responses	45.9 (12.3)	45.6 (11.6)	46.0 (12.6)
Speed of information processing	42.7 (9.8)	42.3 (10.1)	42.9 (9.7)
Wechsler Adult Intelligence Scale-3rd ed. (WAIS-III) Digit Symbol	42.2 (10.4)	41.7 (10.5)	42.4 (10.4)
WAIS-III Symbol Search	43.8 (11.4)	43.5 (11.6)	43.9 (11.3)
Trail Making Test, Part A	42.5 (12.4)	42.1 (12.9)	42.6 (12.1)
Attention and working memory	43.2 (8.9)	43.5 (9.5)	43.0 (8.8)
Paced Auditory Serial Addition Task (PASAT)	40.8 (11.4)	41.1 (11.6)	40.8 (11.3)
WAIS-III Letter Number Sequencing	45.7 (9.8)	45.9 (10.1)	45.6 (9.6)
Learning	40.3 (8.7)	40.8 (8.9)	40.1 (8.6)
Brief Visuospatial Memory Test-Revised (BVMT-R) Total Recall	41.8 (9.2)	42.7 (9.9)	41.5 (8.8)
Hopkins Verbal Learning Test-Revised (HVLT-R) Total Recall	38.8 (11.4)	38.9 (10.9)	38.8 (11.6)
Memory	40.1 (9.7)	40.9 (10.1)	39.7 (9.4)
BVMT-R Delayed Recall	40.7 (11.2)	41.8 (12.2)	41.0 (10.7)
HVLT-R Delayed Recall	39.6 (11.4)	40.1 (11.4)	39.4 (11.4)
Verbal fluency	45.7 (11.5)	45.1 (11.9)	45.9 (11.2)
Controlled Oral Word Association Test (COWAT-FAS)	45.7 (11.5)	45.1 (11.9)	45.9 (11.2)
Motor	38.9 (11.4)	37.1 (11.4)	39.7 (11.3)
Grooved Pegboard dominant	39.2 (12.5)	36.9 (12.0)	40.3 (12.5)
Grooved Pegboard non-dominant	38.9 (11.5)	37.6 (11.6)	39.6 (11.4)

*The death/survival is based on the study duration i.e., between Jan 2000 – Aug 2018.

APPENDIX I: Crude and adjusted hazard ratios (HR) for mortality by selected variables among HIV-infected participants of National NeuroAIDS Tissue Consortium (NNTC; n=877)

Variable (at baseline)	*Adjusted HR (95% CI) model[a] without BDI*	*Adjusted HR (95% CI) model[a] with BDI*
Global T-score[b]	0.99 (0.97 - 1.01)	NA
Duration of HIV infection (years)	1.01 (0.99 - 1.03)	1.01 (0.98 - 1.04)
Ethnicity		
Hispanic or Latino	Ref	Ref
Not Hispanic or Latino	1.38 (1.02 - 1.86)	1.31 (0.79 – 2.18)
ARV medication use	NA	NA
No current ARV use		
Current non-cART		
Current cART		
Serum hemoglobin (g/dl)	0.91 (0.85 - 0.97)	0.88 (0.79 - 0.98)
Plasma viral load (log10 copies/mL)	1.27 (1.16 - 1.39)	1.29 (1.09 - 1.53)
Beck depression inventory (BDI)	NA	1.03 (1.01 – 1.05)
T-scores x Age[c]		
35 years	1.09 (0.85 - 1.41)	1.55 (0.85 – 2.84)
55 years	0.79 (0.64 - 0.99)	0.83 (0.62 – 1.12)
75 years	0.58 (0.35 - 0.97)	0.44 (0.23 - 0.84)

[a]Each variable is adjusted for all other variables listed in the column

[b]Hazard Ratio corresponds to a 10-unit increase in global-t scores

[c]Interaction term between global T-scores and age. Hazard ratio corresponds to a 10-unit increase in global T-scores for a given age.