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The Association Between Neurocognitive Impairment and Health-Related Quality of Life Among People Living with Human Immunodeficiency Virus (HIV).

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Abstract

Background: Despite the use of combination antiretroviral therapy, HIV associated neurocognitive impairment (NCI) persists in HIV seropositive persons, albeit in milder forms than before therapy was available. Nevertheless, the relationship between NCI and health-related quality of life (HRQoL) is not well known.

Method: Baseline data from the CHARTER study was used to investigate the association between NCI and HRQoL. Factor analysis was employed to summarize the 35-item Medical Outcome Survey questionnaire into physical and mental HRQoL scores. General linear models were employed to investigate the association between NCI, as measured by global deficit scores (GDS), and HRQoL, and to control for confounding.

Results: A total of 1,340 HIV participants were analyzed, including 35.6% NCI, 77.2% males, 70.5% unemployed, and 42.2% depressed. The mean (standard deviation) mental HRQoL scores (lower scores are worse) for impaired and unimpaired participants were 64.0 (18.4) and 67.9 (18.6) and mean physical HRQoL scores for impaired and unimpaired participants were 60.3 (24.7) and 65.1 (25.9), respectively. There was an inverse association between NCI and mental HRQoL in unadjusted [-4.38 (-6.70 to -2.06)] and adjusted analysis [-2.56 (-4.83 to -0.30)], controlling for unemployment and current psychotropic medication use. The association between NCI and physical HRQoL was significant in unadjusted analysis [-4.62 (-7.45 to -1.78)] but not in adjusted analysis [2.20 (-4.81 to 0.40)], controlling for unemployment, CD4 nadir and positive opiate test results and other covariates.

Conclusion. The inverse association between NCI and HRQoL was confounded mainly by employment and mediated by depression. Interventions aimed at the comprehensive treatment of HIV patients should include the management of depression and maintenance of employment.

Key Words: Neurocognitive impairment. Quality of life. Medical outcome survey questionnaire. Human Immunodeficiency Virus (HIV). Global deficit scores (GDS).

Introduction

HIV-1 enters the brain early during infection [1] when infected monocytes, lymphocytes [2] or viral particles cross the blood brain barrier (BBB) [3]. The virus can then infected macrophages and microglia in the central nervous system (CNS) and cause immune activation and indirect damage to neurons [3, 4].

HIV-1 replication and continuous immune activation in the CNS causes alterations in brain structure, the degeneration of brain cells and alterations in brain gray and white matter volume, and brain abnormalities [5]. Persistent immune activation can result in immune dysfunction, neuro-inflammation, and injury to synapses and dendrites [1, 6, 7]. Injury to synapses affects the functioning of neurotransmitters, the transmission of electrical impulses from one neuron to the other, and may contribute to neurocognitive impairment, neuropathy and decline in health-related quality of life [1, 8, 9]. Although the introduction of combination antiretroviral therapy (cART) in the late 1990s has resulted in decreased HIV related mortality, morbidity and HIV related dementia, mild to asymptomatic forms of HIV associated neurological disorders (HAND) remain a problem [11]. HAND may be due to the direct neurotoxic effects of combination antiretroviral therapy (cART) that cause neuronal damage or dysfunction [1]. Additionally, once macrophages and microglial cells are infected, they serve as reservoirs for the virus in the brain where it can continue to replicate, evading HIV-drugs with limited CNS penetration [12].

HIV in the CNS and the neurotoxic effect of cART are not the only risk factors for cognitive impairment and the associated impact on quality of life of HIV patients. Studies have shown that substance abuse and drug use aggravate the deleterious effect of HIV on brain metabolites [13], lead to neuronal injury [14] and negatively affect neuropsychological functioning [15]. Hepatitis C virus coinfection is associated with cognitive impairment and domain specific dysfunction [16, 17]. HIV positive individuals with a syphilis co-infection or history of prior syphilis infection are at increased risk of neurocognitive impairment and neuropsychological dysfunction compared to HIV negative individuals with no history of syphilis [18, 19]. Cardiovascular risk factors associated with

aging can influence cognitive dysfunction particularly slowing of psychomotor speed and cognitive performance [2]. Coronary heart disease increases the likelihood of developing cognitive impairment [20, 21]. Depression, hypertension, physical inactivity, diabetes, obesity, hyperlipidemia, and smoking are strong risk factors for dementia [22]. A higher body mass index (BMI) is associated with cognitive dysfunction in healthy individuals [23, 24], alterations in cortical gray and white matter volumes [25] and slower processing speed [26]. Dyslipidemia caused by high LDL cholesterol and triglyceride concentrations in the blood is associated with sensory neuropathy and cognitive impairment in people infected with HIV [27]. Psychiatric disorders have a deleterious effect on cognitive function [28-31] and psychotropic drug use may negatively affect memory, attention, psychomotor performance and cognitive function [32]. Age has effect on brain gray and white matter volume and results in degeneration of brain cells [33]. Additionally, genetic factors such as polymorphisms in host immune response genes have been associated with CNS inflammation and the effect of antiretroviral therapy on viral replication, suppression and side-effects on the brain [34].

The deleterious effect of HIV infection and associated comorbidities on quality of life of HIV participants are well documented [19, 28, 35-39]. Nevertheless, few studies have investigated the relationship between HIV-associated neurocognitive impairment (NCI) and health-related quality of life or the neurotoxic effects of cART on health-related quality of life in HIV participants. We analyzed the Central Nervous System HIV Antiretroviral Therapy Effects Research (CHARTER) study to investigate the relationship between HIV-associated NCI and health-related quality of life (HRQoL). An understanding of the predictors of HRQoL of HIV participants with NCI can contribute to the knowledge based necessary to inform comprehensive HIV management.

Study Objectives

The main objective of this study was to examine the relationship between neurocognitive impairment, as measured by global deficit scores (GDS), and HRQoL using baseline data from the CHARTER study. We hypothesized that HIV-associated (NCI) is

associated with HRQoL and there is a significant difference in HRQoL between impaired and unimpaired participants. A secondary objective of this analysis was to determine whether the Medical Outcome Survey (MOS) questionnaire can be summarized into physical and mental health summary scores using factor analysis.

Methods

Data Source and Participants

We analyzed data from the CHARTER study, a prospective, observational study conducted from 2004 to 2015 in three phases [18, 42]. The primary aim of the CHARTER study was "to determine how central and peripheral nervous system complications of HIV are affected by different histories and regimens of antiretroviral therapy" (https://charternntc.org/). The study design is described in detail in [42, 44]. Baseline data collected from 2004 to 2007 at the time of recruitment was analyzed. All participants for this study were HIV infected individuals recruited from six university research clinics in the United States [42, 44]. The Institutional Review Board of each participating Institution reviewed and approved the study [44].

The CHARTER study used a volunteer sample. A total of 2,016 HIV participants that attended a clinic at the participating university centers were screened at baseline and invited to participate in the study, with minimal exclusion criteria [42, 43]. Participants were excluded from the study only if they declined to participate or if they could not complete the assessment at the time of evaluation [42, 44]. Of the participants screened, 40 (2.0%) were not asked to continue while 366 (18.2%) declined to participate. Cross sectional baseline data were collected from 1,610 HIV infected participants from six centers. For the current study, 1,587 participants who had complete data on HRQoL were included in the factor analysis. Participants with missing data on study variables and those with confounding comorbidities were excluded from the final analysis (Figure 1). Confounding comorbidities were determined based on expert ratings of the comorbidity status of participants in all six centers using standard guidelines [44]. All participants were classified as having incidental, contributing or confounding comorbidities. *"Confounding*

conditions that could fully explain significant neuropsychological impairment and currently observed problems with everyday functioning" [44] preclude the attribution of NCI solely to the effects of HIV on the brain so persons with confounding comorbidities were removed from the analysis [44].

Dependent and Independent Variables

HRQoL was measured by the standardized 35-item MOS questionnaire, which is based on patients' self-reports of their subjective wellbeing [46]. The main outcome variables were physical and mental HRQoL summary scores derived from the questionnaire. The 35-item questionnaire was summarized into ten scales: pain, physical functioning, social functioning, mental health, energy or fatigue, health distress, cognitive functioning, general health, role functioning and quality of life scales. Previous studies have shown that these scales can be reduced into distinct physical and mental health summary scores for a sample of HIV participants [47]. Following procedures in [47], the 35-item questionnaire was reduced into physical and mental HRQoL summary scores, which served as the main outcome variables. The main independent variable was HIV-associated NCI as measured by GDS. Data to compute cognitive impairment were collected using a comprehensive set of neuropsychological tests covering seven cognitive domains [18]. Standard methods were used to compute cognitive impairment using GDS described elsewhere [44,45].

Statistical Analysis

Exploratory and confirmatory factor analysis was conducted to reduce the 35-item MOS questionnaire to physical and mental health dimensions. Factor analysis was based on a complete case analysis of 1,587 participants using SAS version 9.4, after deleting 23 (1.4%) cases with missing data. Data reduction to compute summary scores for the MOS questionnaire followed a three-step process. In the first step, eleven of the 35 items of the MOS questionnaire were reverse coded to ensure that higher scores reflect a more favorable health status. The 35 items were then summarized into eleven scales by adding questionnaire items designed to

measure common constructs. The scales were; pain (2 items), physical functioning (6 items), role functioning (2 items), social functioning (1 item), mental health (5 items), energy or fatigue (4 items), health distress (4 items), cognitive functioning (4 items), general health perception (5 items), quality of life (1 item) and health transition (1 item). The scales were transformed to 0 to 100 scores with 100 representing best health status [47]. In the second step, we performed exploratory factor analysis on a subsample of 794 participants representing half of the full dataset randomly selected from the total sample using the SAS PROC SURVEYSELECT procedure. The exploratory factor analysis procedure used squared multiple correlations as prior communality estimates. Two factors were extracted by the principal factor method followed by a promax rotation [48]. Health transition did not load on any factor, so it was not included in the confirmatory factor analysis. In the third stage, the extracted factors were validated using confirmatory factor analysis applied to the full dataset of 1,587 participants. A measurement model that describes the relationship between the 2 latent factors and the 10 scales was developed and confirmatory factor analysis was conducted to demonstrate that the model fits the data [48-51]. The maximum likelihood method (MLM) was used for parameter estimation.

Model development followed a structured approach. We conducted comprehensive literature review that informed the development of a causal directed acyclic graph (DAG) exhibiting the theoretical relationships among potential confounders of the relationship between NCI and HRQoL. This information was used to identify potential confounders to be included in the model [52]. ‘Change- in-estimate’ approach was used to determine confounders to be included in the model. The aim was to derive the most accurate estimates (as measured by mean square error) of the relationship between NCI and HRQOL and obtain a parsimonious model that controls most confounding [52]. Bivariate analysis using independent sample t-tests, Pearson correlation coefficients, and one-way analysis of variance (ANOVA) was conducted to investigate the relationship between NCI and candidate confounders and between HRQoL and candidate confounders. All variables associated with NCI ($p = 0.10$) and at the same time

associated with HRQoL (p = 0.10) were retained as potential confounders. A test for confounding was conducted in two steps. Firstly, the mean difference of the relationship between HRQoL (physical and mental) and NCI for a reduced model comprising of NCI, age, gender at birth and race/ethnicity was estimated. Secondly, potential confounders were added one after the other and the change in the estimate was observed for each variable added. If the percentage change in the estimate for the reduced model compared to the model with the added confounder was greater than 10%, we considered the variable as a confounder and included it in the model, if no it was ignored.

Results

Characteristics of Participants at Enrollment

Of the 1,857 participants with complete data on the outcome variable, 15.6% had severe comorbidities, 54.0% had incidental comorbidities while 30.0% had contributing comorbidities. Comorbid conditions included brain trauma, epilepsy, low reading levels, major depression, lifetime or current substance use or alcohol disorder to name but a few. Severe comorbidities confound NCI diagnosis so 247 participants with severe comorbidities were excluded from the study [44]. The final sample (n = 1,340) included 77.2% males, 46.9% Black or African Americans, 41.1% Whites and 70.5% unemployed participants. The mean age was 43.0 years (SD = 8.65). Approximately one third of the participants were neurocognitively impaired as determined by their GDS scores (table 2).

Factor Analysis

The results of the exploratory factor analysis confirmed that two factors could be extracted from the 10 scales of the MOS questionnaire (the scale health transition did not load on any factor in exploratory factor analysis). The rotated factor pattern was used to determine scales that loaded on which factor. A scale was said to load on physical health and not on mental health if a factor loading of the scale was 0.4 or higher on the physical health factor but less than 0.4 on the mental health factor [48]. Five factors loaded on mental health and five factors loaded on physical

health. The factor pattern showed simple structure (i.e., no scale loaded on more than one factor). A review of the eigenvalues, proportion of variance explained, and the scree plots combined with the rotated factor pattern demonstrated that the MOS questionnaire can be summarized into two factors; mental health and physical health.

Means, standard deviations and Pearson correlation coefficients for the 10 scales of the MOS questionnaire using the full sample were computed (table 1). The Pearson correlation coefficients ranged from 0.33 to 0.66, indicating a relatively strong positive association among the variables. The standardized path coefficients for the factor loadings are shown on figure 2. The t-values for all standardized path coefficients were statistically significant ($p < 0.001$) and all the standardized path coefficients were greater than 0.65, providing support for the convergent validity of the scales [48].

Differences in Clinical Characteristics Between HIV Impaired and Unimpaired Participants. The Mann Whitney test was conducted to determine whether there are differences between impaired and unimpaired participants on main clinical variables. Compared to unimpaired participants, impaired participants had higher median white blood cell count ($Z = 2.12$, $p = 0.034$), lower hematocrit percentage in blood ($Z = -2.10$, $p = 0.036$), lower blood hemoglobin levels ($Z = -2.09$, $p = 0.037$), higher mean corpuscular (cell) volume ($Z = 3.08$, $p = 0.002$), higher alkaline phosphatase levels ($Z = 2.81$, $p = 0.005$), higher serum triglycerides ($Z = 2.19$, $p = 0.029$), higher white blood cell counts in cerebrospinal fluid ($Z = -2.97$, $p < 0.003$), and higher monocyte percentage in CSF ($Z = 3.14$, $p = 0.001$). Nevertheless, the average values were within normal clinical range for both impaired and unimpaired groups.

Differences in HRQoL Between HIV Neurocognitive Impaired and Unimpaired Participants.

The results of t-tests showed that unimpaired participants had higher physical ($p = 0.001$) and mental HRQoL composite scores ($p < 0.001$) than impaired participants, with higher scores indicating better quality of life perception, less pain or role limitation. Specifically, unimpaired participants reported higher mean scores for mental health ($p = 0.004$),

energy/fatigue (p = 0.006), health distress (p = 0.001), cognitive function (p < 0.001), physical function (p < 0.001), role function (p = 0.002), and social function (p = 0.009) compared to impaired participants. However, impaired and unimpaired participants had similar quality of life perception (p = 0.175), pain (p = 0.164) and general health perception (p = 0.141).

Confounders of the Relationship Between HIV-Associated Neurocognitive Impairment and HRQoL.

In unadjusted analyses, the following were identified as potential confounders of the relationship between HIV associated neurocognitive impairment (NCI) and HRQOL at the 5% level of significance: gender at birth, race/ethnicity, employment, highly active antiretroviral therapy, lowest CD4 count (cells/mm^3), current psychotropic medication use, life time alcohol abuse or dependence, current opiate test result, high cholesterol, cerebrospinal fluid (CSF) glucose, CSF total protein, hematocrit percentage (g/dl) in blood, hemoglobin (g/dl) in blood, mean corpuscular (cell) volume (x10^-15 L (fL)) in blood, basophil percentage in blood and serum alkaline phosphatase level (IU/L). Age and education where associated with physical but not mental HRQoL or impairment. The potential confounders that met the criteria for inclusion in the models for mental and physical HRQoL are shown on tables 2 and 3.

The Relationship Between Impairment and Mental and Physical HRQoL in Adjusted Analysis.

The relationship between mental health related quality of life (HRQoL) and HIV-associated NCI as measured by global deficit scores was significant in unadjusted and adjusted analysis. Impaired participants had lower mental health related quality of life compared to unimpaired participants. The association between NCI and HRQoL was lower in unadjusted [-4.38 (-6.70 to -2.06)] than in adjusted analysis [-2.56 (-4.83 to -0.30)] and remain significant when controlled for age, gender at birth, race/ethnicity, unemployment and current psychotropic medication use. In adjusted analysis, female gender, white and Hispanic race/ethnicity, current unemployment or

part-time employment and current prescribed psychotropic medication use were associated with lower mental HRQoL (table 2).

The association between NCI and physical HRQoL was significant in crude analysis [-4.62 (-7.45 to -1.78)] but not significant when adjusted for gender, age, race/ethnicity, employment, lowest CD4 count (cells/mm^3) and positive opiate test results [-2.20 (-4.81 to 0.40)]. In adjusted analysis, female gender, white race/ethnicity, ages 40 to 59, unemployment, lowest CD4 below 500 cells/mm^3 and positive opiate test results were associated with lower physical HRQoL (table 3).

The Durbin-Watson test coefficients for the mental and physical HRQoL models were less than 2.0 indicating that the residuals were uncorrelated. An analysis of the model residual plots against predicted values showed no patterns implying homogeneity of variance. The Q-Q plots showed a linear trend with only minor deviations at the upper tail, satisfying the assumptions of normality of residuals. Additionally, the variance inflation factors were below 1.2 meaning that there was no multicollinearity in the model. The predicted values were reasonable, within the range of the response variable indicating that the models fit the data.

The Mediation Effect of Depression.

Depression was not included in the models because we hypothesized that depression was a mediator of the relationship between impairment and HRQoL. To test this assumption, we used the approach in [53] to investigate the extent to which depression mediated the relationship between HIV neurocognitive impairment (NCI) and HRQoL using ordinary least squares in SAS version 9.4. To established mediation, NCI (independent variable) must be associated with depression (mediator), NCI must be associated with HRQoL (dependent variable) and depression must be associated with HRQoL [53, 55]. We regressed (a) depression on impairment (b) HRQoL on NCI (c) HRQoL on NCI controlling for depression and (d) depression on HRQoL.

The results of the ordinary least squares regression show that NCI was negatively associated with depression (B = -1.583, p = 0.020) and depression was negatively associated

with mental (B = -0.450, p < 0.001) and physical HRQoL (B = -0.261, p < 0.001). Controlling for depression, neurocognitive impairment was associated with mental (B = 2.048, p = 0.005) and physical HRQoL (B = 0.826, p = 0.528) although the relationship for physical health was not significant. The indirect effect of impairment on mental health (Sobel z = 2.236, p = 0.020) and physical health (Sobel z = 2.074, p = 0.038) as indicated by the Sobel test was significant. The proportion of the total effect mediated was higher for physical health (72.2%) than for mental health (51.5%). These results suggest that depression was a mediator of the relationship between HIV-associated NCI and mental and physical health related quality of life [53].

There was a significant relationship between depression as measured by the Beck's depression index and employment. Among participants with mild to severe depressive symptomatology, 78.1% were unemployed compared to 10.5% that were fully employed. Mild to severe depression was regarded as having a score of greater than 13 points on the Beck's depression index. In crude analysis, being unemployed increases the odds of mild to severe depression by 2.83 (1.96 to 4.08) and being employed part-time increases the odds of mild to severe depression by 1.97 (1.20 to 3.21) compared to being fully employed. However, employment was not a mediator of the relationship between HIV-associated NCI and HRQoL (z = 1.603, p = 0.109).

Discussion.

Among HIV-positive CHARTER participants without confounding comorbidities we found a significant relationship between HIV-associated neurocognitive impairment (NCI) and health related quality of life (HRQoL). In unadjusted and adjusted analysis, impaired participants had significantly lower mental HRQoL scores compared to unimpaired participants. The results also suggest that impaired participants had lower physical HRQoL in crude analysis. The association between NCI and physical HRQoL remained negative when controlled for employment and other covariates but was no longer significant.

Unemployment was a stronger predictor of lower physical and mental HRQoL in this population than HIV-associated NCI. The strong association of employment with HRQoL may partly be explained by the association between employment and depression reflected in the mediation effect of depression on HIV-associated NCI and HRQoL. The beneficial effect of employment on depression and general mental health is well established. Employment has a protective effect on depression and general mental health and well-being [56, 57, 59], and psychological distress [58, 59]. Employment improves quality of life because it provides the means to acquire the necessities of life, improves consumption of goods and services, enhance economic and social status, and reduce physical and mental distress arising from worry associated with economic insecurity.

In adjusted analysis, we also found that prescribed psychotropic drug use was significantly associated with mental HRQoL but not with physical health. Prescribed psychotropic medication use is partly induced by psychiatric problems such as depression. Some of the psychotropic drugs used to ameliorate the harmful health effects of psychiatric problems can affect cognitive function. Psychotropic drug use negatively affects memory, attention and psychomotor performance and is associated with lower cognitive scores in the elderly [62] and lower health related quality of life [60-63].

The results of our study suggest that HRQoL significantly decreases with increasing severity of depression and depression mediates the relationship between HIV-associated NCI and HRQoL . This is consistent with findings from several studies that demonstrated that depression has a deleterious effect on mental health, role, emotional and social functioning of various patient groups [60, 61], decreases cognitive function [28] and mediates the relationship between NCI and HRQoL [53].

In both unadjusted and adjusted analysis, opiate use was significantly associated with lower physical HRQoL but not with mental HRQoL. Participants with positive opiate test results

had significantly lower physical HRQoL compared to persons with a negative result. The association between opiate addiction, substance use and alcohol abuse and neurocognitive functioning are well established. Opiate addiction, chronic substance or alcohol abuse can aggravate the deleterious effect of HIV on brain metabolites and can lead to neuronal injury, affects neuropsychological functioning, alter health behavior and results in low levels of medication adherence [13- 15, 37, 64].

With 30 million people projected to be on combination antiretroviral therapy (cART) by 2020 (UNAIDS, 2016), and given the observed increase in life expectancy of HIV seropositive individuals on cART, the potential collective impact of HIV-associated NCI, depression, substance abuse, psychotropic medication use and unemployment on a large proportion of these population should be of serious concern. This is particularly important because HIV and age-related cognitive impairment, substance abuse and depression affect the individual's ability to adhere to medication, perform activities of daily living, hold, or maintain a job, and live a normal productive life. HIV seropositive persons on cART are living longer implying that HIV is becoming a chronic disease, requiring continuous management. The combined effect of neurocognitive deficits, substance abuse, unemployment and depression are likely to contribute significantly to decline in HRQoL with significant impact on healthy aging. There is need to design specific interventions aimed at the optimal management and improvement in the quality of life of persons living with HIV, including the management of depression and maintenance of employment.

In this study, HRQoL was conceptualized within the framework of the Medical Outcome Survey (MOS) questionnaire which measures HRQoL using 35 items that require individuals to provide a subjective evaluation of their health and wellbeing. The questionnaire was designed to measure11 scales of HRQoL (mental health, energy or fatigue, health distress, cognitive function, quality of life, pain, physical functioning, role functioning, social functioning, general health and health transition). Consistent with our secondary objectives and in harmony with previous research findings in [47], we established using factor analysis that the 35-item MOS questionnaire

can be summarized into two dimensions, physical and mental HRQoL and is a reliable and valid measure of HRQoL.

Limitations

The study has some limitations. First the CHARTER study was based on a volunteer sample comprising of individuals attending clinics in the study centers. This implies that the sample is not representative of HIV-patients in other clinics or patients who would not volunteer for such studies (see https://neuroaids-dcc.unmc.edu/CharterResDesc). To address this concern, and to ensure that the CHARTER sample was as inclusive as possible of the population of HIV participants visiting the study clinics, minimal exclusion criteria was used. Participants were recruited from six sites widely distributed within the United States.

Data was collected using mix methods involving patient self-reports for outcome variable, and a mixture of clinician ratings and self- report for the exposure variable. This implies that the data is subject to mode effects. The relationship between neurocognitive impairment and quality of life is influenced by a mesh of factors, which confound , mediate or moderate the relationship. This may be a source of bias. To limit the impact of confounding on the analysis, structured approach to bias was applied by analyzing the various causal pathways of the relationship between the two variables. The directed acyclic graph (DAG) approach was used to identify the most important confounders and statistical tests were conducted with these variables to determine confounding effects.

Conclusion

We used baseline data from the prospective, observational CHARTER study to investigate the relationship between HIV-associated NCI, as measured by GDS, and HRQoL. We hypothesized that NCI is associated with lower physical and mental HRQoL and that NCI participants have lower HRQoL than unimpaired HIV participants in the CHARTER study. Our central hypothesis was supported in unadjusted and adjusted analysis for mental health, but the

inverse relationship between HIV associated neurocognitive impairment and physical HRQoL was no longer significant when adjusted for other covariates. Depression is a strong mediator of the relationship between HIV associated neurocognitive impairment and HRQoL. The implication of the mediation effect of depression is that in the CHARTER population, managing depression should be a potential target to lessen the risk of HIV neurocognitive impairment and improve HRQoL.

Figure1

Flow chart showing final sample sizes

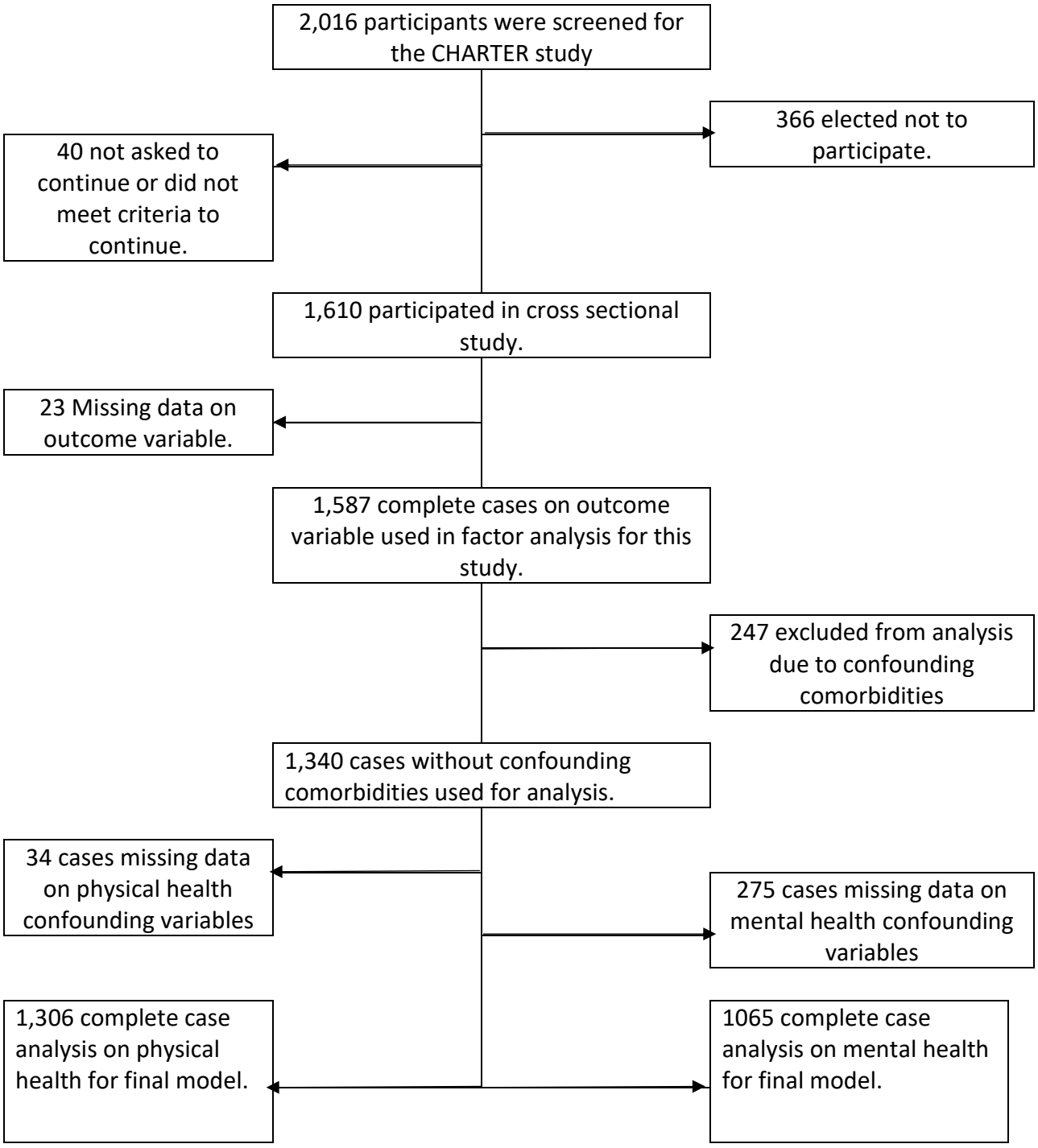
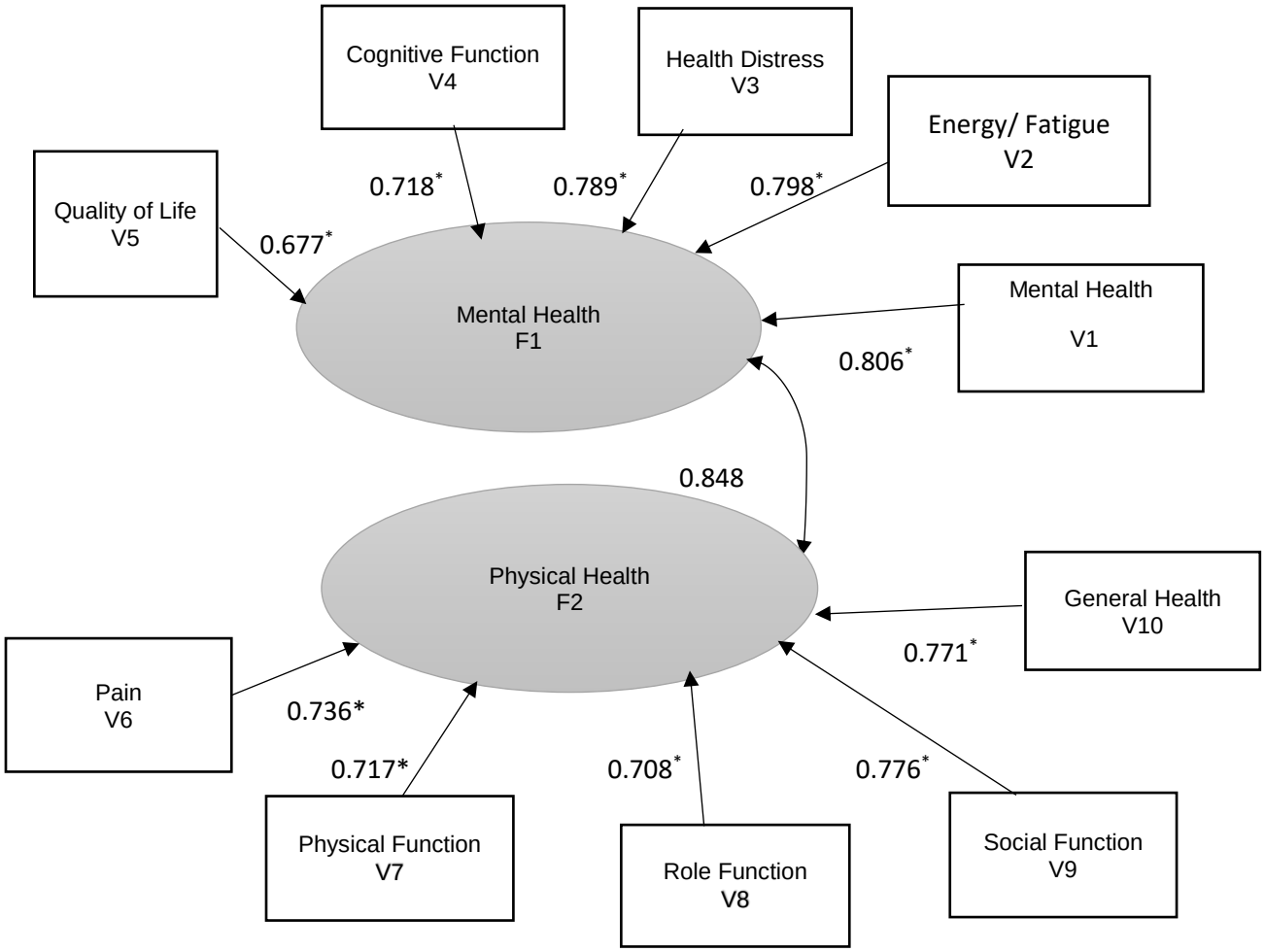


Figure 2:

Path model of health-related quality of life of CHARTER participants (n = 1,587)



Single headed arrows show standardized path coefficients; Curved double headed arrow shows covariance for two factors. * $p < 0.001$. F1, Factor 1; F2, Factor 2; V1…V10, represents variable name.

Table 1

Means, standard deviations and Pearson correlation coefficients for the health-related quality of life (HRQoL) scales of the medical outcome survey questionnaire (n=1,587).

No	Scales	Mean	SD	1	2	3	4	5	6	7	8	9	10
1	Mental health	66.55	21.66	1									
2	Energy/Fatigue	53.28	22.21	.66	1								
3	Health distress	72.10	26.33	.66	.57	1							
4	Cognitive function	72.13	23.80	.59	.56	.59	1						
5	Quality of life	64.44	22.06	.59	.55	.50	.43	1					
6	Pain	66.24	26.73	.42	.52	.50	.41	.42	1				
7	Physical function	69.02	27.47	.35	.49	.45	.43	.33	.58	1			
8	Role function	54.09	45.32	.38	.49	.47	.41	.36	.51	.55	1		
9	Social function	74.12	28.45	.53	.56	.60	.54	.44	.55	.58	.56	1	
10	General health	48.25	26.91	.52	.59	.60	.46	.56	.58	.52	.56	.54	1

Note: Higher mean scores indicate better quality of life perception, lower pain and limitations in role function; the scale health transition did not load on any factor.

Table 2

The relationship between neurocognitive impairment and mental-related quality of life (HRQoL) of CHARTER participants
(n = 1,065).

Variable	n (%)	Mental HRQoL composite scores Mean (SD)[a]	Unadjusted mean difference (95% CI)[c]	Adjusted mean difference[c] (95% CI)
Neurocognitive impairment (GDS)[d]			p < 0.002	
No	679 (63.8)	65.82 (18.82)	ref	ref
Yes	386 (36.2)	61.45 (18.11)	-4.38 (-6.70 to -2.06)	-2.56 (-4.83 to -0.30)
Gender at Birth			p = 0.273	
Male	807 (75.8)	64.59 (18.35)		
Female	258 (24.2)	63.12 (19.66)	-1.47 (-4.09 to 1.15)	-2.14 (-4.75 to 0.46)
Age (years)			p = 0.571	
≤ 39	321 (30.2)	64.87 (19.08)	ref	ref
40-49	504 (47.3)	64.05 (18.38)	-0.82 (-3.44 to 1.80)	-0.11 (-2.65 to 2.42)
50-59	212 (19.9)	63.24 (18.35)	-1.63 (-4.88 to 1.61)	-0.09 (-3.22 to 3.04)
≥ 60	28 (2.6)	67.74 (21.84)	2.86 (-4.36 to 10.09)	4.23 (-2.68 to 11.14)
Race/Ethnicity			p = 0.001	
Black or African	479 (45.0)	66.75 (18.07)		
American			ref	ref
White	462 (43.4)	62.05 (18.97)	-4.69 (-7.07 to -2.32)	-5.86 (-8.28 to -3.44)
Hispanic	99 (9.3)	62.58 (17.56)	-4.17 (-8.19 to -0.15)	-4.17 (-8.09 to -0.25)
Other	25 (2.3)	63.09 (23.76)	-3.66 (-11.13 to 3.81)	-5.05 (-12.25 to 2.15)
Employment			p < 0.001	
Full time	152 (14.2)	71.96 (16.53)	ref	ref
Part-time	137 (12.9)	65.50 (18.57)	-6.46 (-10.71 to -2.20)	-6.64 (-10.78 to -2.50)
Not currently employed	776 (72.9)	62.50 (18.71)	-9.46 (-12.66 to -6.26)	-8.96 (-12.17 to -5.75)
Current psychotropic medication use			p < 0.001	
No	310 (29.1)	71.28 (16.21)	ref	ref
Yes	755 (70.9)	61.34 (18.86)	-9.93 (-12.33 to -7.53)	-8.21 (-10.63 to -5.80)

n = sample size with percentage of respondents in bracket; ref means the reference category. [a]SD, Standard deviation, [b]CI, Confidence interval. [c]Adjusted for other covariates in the table using general linear model analysis.; [e]GDS, global deficit scores, were used to determine impairment.

Table 3

The relationship between HIV associated neurocognitive impairment and physical health-related quality of life (HRQoL) of CHARTER participants (n = 1,306).

Variable	n (%)	Physical HRQoL composite scores Mean (SD)[c]	Unadjusted mean difference (95% CI)[a]	Adjusted mean difference[b] (95% CI)
Neurocognitive impairment (GDS)[e]			p = 0.001	
No	843 (64.5)	65.17 (25.04)	ref	ref
Yes	463 (35.5)	60.55 (24.92)	-4.62 (-7.45 to -1.78)	-2.20 (-4.81 to 0.40)
Gender at Birth			p < 0.001	
Male	1,008 (77.2)	65.00 (24.96)	ref	ref
Female	298 (22.8)	58.55 (24.92)	-6.45 (-9.67 to -3.22)	-6.53 (-9.57 to -3.49)
Age (years)			p < 0.001	
≤ 39	422 (32.3)	70.60 (23.83)	ref	ref
40-49	594 (45.5)	61.42 (24.65)	-9.19 (-12.25 to -6.12)	-6.32 (-4.28 to -9.21)
50-59	254 (19.4)	56.43 (24.96)	-14.17 (-18.00 to -10.35)	-10.49 (-14.-8 to -6.91)
≥ 60	36 (2.8)	65.50 (28.10)	-5.11 (-13.47 to 3.26)	-2.36 (-10.10 to 5.38)
Race/Ethnicity			p = 0.606	
Black or African American	605 (46.3)	62.79 (23.98)	ref	ref
White	544 (41.7)	63.69 (26.23)	0.90 (-2.01 to 3.81)	-4.45 (-7.22 to -1.68)
Hispanic	124 (9.5)	65.69 (24.30)	2.95 (-1.96 to 7.75)	0.51 (-3.93 to 4.96)
Other	33 (2.5)	66.22 (28.76)	3.42 (-5.38 to 12.23)	-3.21 (-11.21 to 4.79)
Employment[e]			p < 0.001	
Full time	222 (17.0)	82.31 (17.45)	ref	ref
Part-time	163 (12.5)	68.66 (21.23)	-13.65 (-18.38 to -8.92)	-11.95 (-16.58 to -7.33)
Not currently employed	921 (70.5)	58.09 (24.91)	-24.22 (-27.65 to -20.79)	-21.97 (-25.44 to -18.50)
Lowest CD4 count (cells/mm^3)			p < 0.001	
≥ 500	121 (9.3)	72.77 (24.49)	ref	ref
200-499	481 (36.8)	65.74 (25.84)	-12.34 (-17.13 to -7.55)	-6.08 (-10.60 to -1.56)
< 200	704 (53.9)	60.43 (24.13)	-7.04 (-12.00 to -2.09)	-7.20 (-11.64 to -2.77)
Current opiate test results			p < 0.001	
Positive	95 (7.3)	48.61 (24.92)	ref	ref
Negative	1,211 (92.7)	64.70 (24.73)	16.09 (10.91 to 21.26)	11.12 (6.35 to 15.90)

n = sample size with percentage of respondents in bracket; ref means the reference category. [a]SD, Standard deviation, [b]CI, Confidence interval. [c]Adjusted for other covariates in the table using general linear model analysis. [e]GDS, global deficit scores, were used to determine impairment.

Supplementary Tables

Table 4: CHARTER[a] study neuropsychological test battery by cognitive domain.

Domain	Test
1. Speed of Information Processing	Wechsler Adult Intelligence Scale [WAIS]-II Digit Symbol WAIS-III -Symbol Search Trail Making Test Part A
2. Learning	Hopkins Verbal Learning Tests Revised [HVLT-R] Learning Trials Brief Visuospatial Memory Test Revised [BVMT-R] Learning Trials Story Memory Test (Learning Component); Figure Memory Test (Learning Component)
3. Memory	HVLT-R Delayed Recall, BVMT-R Delayed Recall, Story Memory Test (with delayed recall), Figure Memory Test (delayed recall component); Brief Visuospatial Memory Test Revised,
4. Executive Function	Category Fluency Test, Wisconsin Card Sorting Computerized Test [64-item version], Trail Making Test Part B
5. Verbal Fluency	Verbal Fluency-Controlled Oral Word Association Test [F-A-S letters] Category Fluency Test [animals]
6. Attention and Working Memory	Paced Auditory Serial Addition Test-50 WAIS-III Letter-Number Sequencing
7. Motor Function	Grooved Pegboard Test, Dominant and Non-Dominant Hands.

[a]CHARTER, Central nervous system HIV antiretroviral therapy effects research

Table 5 Differences in health-related quality of life (HRQoL) between HIV neurocognitive impaired and unimpaired CHARTER participants.

Scales	Impaired (n = 477)	Unimpaired (n = 863)	p-value[a]
	Mean (SD)	Mean (SD)	
Mental			
Mental health	64.9 (21.5)	68.4 (21.2)	.004
Energy/Fatigue	51.4 (22.6)	54.9 (22.0)	.006
Health distress	70.8 (25.6)	75.0 (25.5)	.004
Cognitive function	69.4 (24.1)	75.9 (22.1)	< .001
Quality of life	63.5 (22.2)	65.2 (21.5)	.175
Mental composite[b]	64.0 (18.4)	67.9 (18.6)	< .001
Physical			
Pain	65.6 (27.6)	67.7 (26.0)	.164
Physical function	65.5 (27.8)	72.7 (26.7)	<.001
Role function	50.4 (45.6)	58.3 (45.0)	.002
Social function	72.3 (28.5)	76.5 (27.4)	.009
General health	47.9 (25.7)	50.2 (27.7)	.141
Physical composite	60.3 (24.7)	65.1 (25.9)	.001

[a]p-value based on t-test, p-value > 0.05 means not significant, SD, Standard deviation, CHARTER means , Central nervous system (CNS) HIV antiretroviral therapy effects research study. [b]Mental and physical health-related quality of life composite scores were computed as factor-based scores by adding the average HRQoL scores on all preceding scales that loaded on same factor during the factor analysis

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