Neurocognitive functioning in women with HIV: a comparative study in a low/middle-income country

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Objective: In untreated HIV infection, the prevalence of HIV-associated neurocognitive disorders was high. Studies from the ART era with appropriate controls from a resource-limited setting are lacking. Neurocognitive functioning of young women with HIV (WWH) was compared to women without HIV (WWOH) in South Africa between 2018 and 2019.

Design: A cross-sectional study.

Methods: WWH from the **Pro**mise **O**ngoing **T**reatment **E**valuation (PROMOTE) study and WWOH completed a neuropsychological battery targeted at domains affected by HIV. Factors known to be associated with neurocognitive impairment (NCI) were assessed by generalized linear model adjusting for covariates. Clinical symptoms were evaluated using WHODAS.

Results: Of 451 women, with a median age of 35 (IQR: 31–39) years, 224 (49.7%) were WWH. More WWH had NCI (46 vs. 36%, $P = 0.06$) and mild to severe deficits in verbal learning and memory (51 vs. 30%, $P < 0.001$), motor speed (32 vs. 19%, $P = 0.002$), language (55 vs. 44%, $P = 0.021$), and information processing (40 vs. 25%, $P = 0.001$). The risk of NCI was higher in women aged at least 35 years [relative risk (RR): 1.46, 95% confidence interval (95% CI): 1.16–1.84, $P = 0.001$], incomplete secondary education (RR: 1.26, 95% CI: 1.01–1.58, $P = 0.04$), HIV infection (RR: 1.26, 95% CI: 1.02–1.56, $P = 0.03$), and high alcohol use (RR: 1.42, 95% CI: 1.13–1.78, $P = 0.003$).

Conclusion: WWH on long-term ART had a high prevalence of NCI. High alcohol use and incomplete secondary education were significant risk factors in all women. This study highlights the higher risk of NCI in this population despite a younger age and successful ART.

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Introduction

Neuropsychiatric complications are considered common comorbidities in people with HIV despite successful antiretroviral therapy (ART). This may be due to HIV-1 persistence in the central nervous system (CNS) [1]. Persistent CNS immune activation has been linked to the development of HIV-associated neurocognitive disorders (HAND) [2]; however, in the era of ART, the incidence of severe neurocognitive impairment (NCI) has decreased, but the prevalence of milder forms of NCI have increased [1]. Data in low and middle-income countries (LMIC) are limited, but rates may be higher than high-income countries [3].

In contrast to other forms of neurocognitive disorders, a lower chronological age may not be a protective factor because the virus is thought to cause accentuated aging, possibly due to chronic inflammation [4]. New approaches to aging in HIV take into account that aging is a heterogeneous process, including biological, metabolic, cognitive, and psychosocial aging, which includes contextual factors and comorbidities such as alcohol use [5,6].

Recent global data suggest that women with HIV (WWH) have an increased risk of NCI when compared to women without HIV (WWOH) and men with HIV (MWH) [7,8]. This is especially important in Southern Africa, where the epidemic is greater among women [9]. WWH appear to be more vulnerable to developing verbal learning and verbal memory deficits, decreased speed of information processing, and poor psychomotor abilities compared to MWH [8]. This increased burden in women is thought to be due to psychosocial and biological causes. Compared to men, women have more exposure to trauma, physical and sexual abuse, lower education, income attainment, and depression, factors that also contribute to neurocognitive decline [7]. Biologically, the differences are suggested to be due to immunological responses, which affect the size of viral reservoir in the CNS and hormonal patterns that can affect cognition [6,10].

This study describes the neurocognitive functioning of WWH and compares this to WWOH. We sought to establish the prevalence and type of impairment specifically within a young female population in a LMIC setting, on long-term ART, who would not be considered at a high risk for NCI due to their chronological age. The study addresses an important gap by providing data in a young, female population from a low-resource country.

Methodology

Study design

This was a cross-sectional, one-center study to assess neurocognitive functioning among two cohorts: A cohort of South African WWH participating in the **Pro**mise **O**ngoing **T**reatment **E**valuation (PROMOTE) study and a cohort of age-group matched WWOH, who were recruited from the same community. PROMOTE is a longitudinal, multisite cohort study providing data on comorbidities, safety, adherence, and long-term effectiveness of ART among WWH followed across eight research sites in four countries (South Africa, Malawi, Uganda, Zimbabwe) [11]. The characteristics of the WWH enrolled in PROMOTE have been described previously, but importantly, 96.7% were on ART with 92.6% of those having an undetectable viral load and 99.6% were assessed as WHO clinical stage one. These women had originally been recruited from antenatal clinics while pregnant for the IMPAACT PROMISE 1077BF/1077FF randomized trial [12]. This study required a pre-ART $CD4^+$ cell count more than 350 cells/μl and diagnosis was during pregnancy, not perinatally. The clinical course of these participants was therefore well known since 2011.

Participants

The neurocognitive study was conducted at the Perinatal HIV Research Unit (PHRU), in Soweto, a peri-urban setting in South Africa from 2018 to 2019. All 273 women participating in PROMOTE at the PHRU site were invited to participate. The age-group matched WWOH cohort comprised of mothers recruited from local immunization clinics (58%), word of mouth (19%), and a Voluntary Counselling and Testing (VCT) program (11%) (see Fig. 1). Because many physical, emotional, and cognitive changes can occur during pregnancy and postpartum, matching for maternal age group and pregnancy/postpartum status was deemed important. Participants were excluded if they had a history of a traumatic brain injury that resulted in hospitalization or loss of consciousness for more than 20 min, and/or there was a current diagnosis of epilepsy. Participants self-reported their ability to read, were over 18 years of age, and provided written informed consent. Permission for the study was obtained from University of the Witwatersrand Human Research Ethics Committee (Clearance certificate number M180709).

Definitions

We chose to use the DSM 5 (Diagnostic and Statistical Manual of Mental Disorders) criteria for classification of

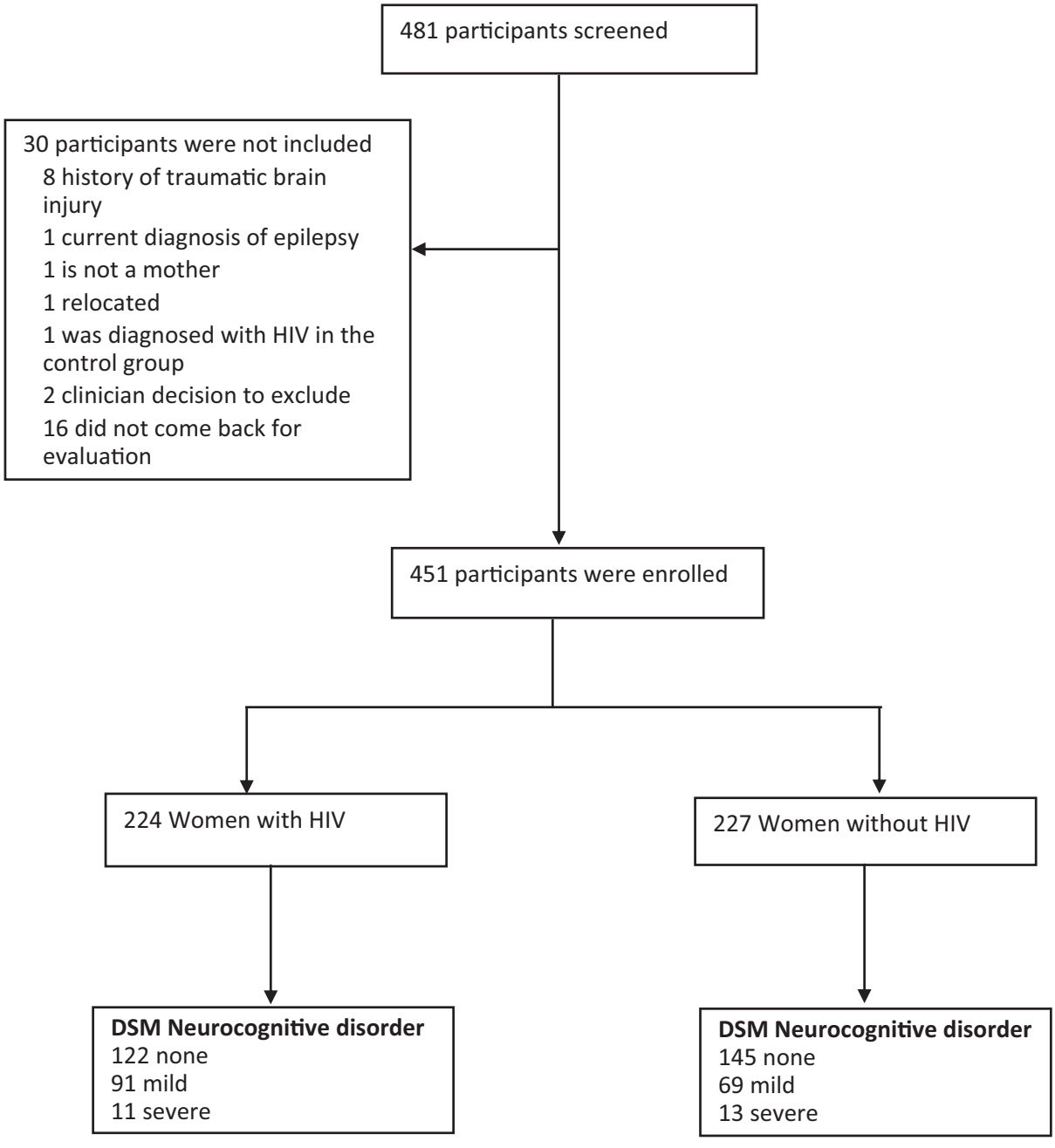

Fig. 1. CONSORT flow diagram of participants screened, enrolled, and likely neurocognitive disorder cases by HIV status.

NCI, which categorizes NCI as mild or major neurocognitive disorders, with a specifier of HIV [13]. The definition of a major neurocognitive disorder according to DSM 5 requires evidence of significant cognitive decline from previous level of performance, as shown by a substantial impairment on standardized neuropsychological tests in one or more cognitive domains and the deficit needs to interfere with independence in daily activities. We defined this as two standard deviations below the mean for each cognitive domain score. Mild disorders have a similar definition but only have a modest cognitive decline, require modest impairment, defined here as one standard deviation below the mean, and the deficits do not interfere with daily activities. Importantly, because interference in daily activities is required for the diagnosis of major NCI, the WHO Disability Assessment Schedule (WHODAS) was included. HIV-associated neurocognitive disorders have previously often been classified according to the Frascati diagnostic criteria [14]; however, we chose the above because we included a cohort living without HIV and because DSM 5 includes a change in daily activities.

Procedure

A battery of psychometric assessments was administered by qualified and trained psychologists. In accordance with standard testing guidelines, testing took place in a quiet and private room. Participants did wear hearing and visual aids if applicable. Tests were administered in English by a psychometrist who was also fluent in local languages. Instructions, clarifications, and verbal translations into a language of the participant's choice was available where needed. The psychologists scored the neuropsychiatric assessments and these were quality-controlled by a second psychologist or psychiatrist. Discrepancies in scores were discussed and agreed upon.

Demographic data and medical history were collected using a questionnaire designed by the team. Clinical characteristics were obtained from the PROMOTE database for the WWH. Screening for hazardous drinking was done using the Alcohol Use Disorder Identification Test (AUDIT), a self-reported questionnaire, where low-risk drinking is a score between 1 and 7, a score of 8–14 suggests hazardous drinking and anything from 15 is suggestive of alcohol dependence. We classified a score of 8 or above as high-risk drinking. It has been used extensively in South Africa, including in people with HIV (PWH) [15]. The Patient Health Questionnaire (PHQ-9), a widely-used, self-report screening tool [16] was used to screen for depression. It has good specificity and can be used to identify comorbid depression in individuals with chronic conditions [17,18]. A score of 10 or above was used to diagnose possible depression. The WHODAS Version 2.0, short 12-item version, was used to assess various areas of clinical functioning including mobility and self-care [19]. All 12 items were summed to create an overall WHODAS score, and thereafter, the score was used to classify participants in the disability categories.

All assessments were scored on the same day before participants left to ensure timely referrals. Participants identified as being at risk were assessed by the team psychologist or psychiatrist and referred as needed. Anyone identified with impairment in functioning was referred to occupational therapy at Chris Hani Baragwanath Academic Hospital for further assessment and management.

Neuropsychological test battery

The neuropsychological battery included tests that are sensitive to domains affected in HAND, as demonstrated in a review of neuropsychological testing in Africa [20]. Two tests (The Purdue pegboard and RAVLT) are not as commonly used but adequately test the chosen domains and were used in the current study.

The Rey Auditory Verbal Learning Test (RAVLT) [21] measures immediate memory span and provides information on one's learning curve, short-term, and longer-term memory retention. Each trial is scored out of 15, with a higher score indicating better learning ability. The delayed score correlates with longer-term memory. The Digit Span Test [22] is a measure of immediate verbal recall, as well as auditory attention, double tracking and working memory. The higher the score, the better these modalities are functioning. The Complex Figure of Rey (CFR) [23] provides information regarding organization and planning ability. There is an immediate recall, providing information about visual memory abilities and a delayed recall trial assessing the ability to recall complex visual information. The figure drawn by the participant is scored out of 36 points, based on standardized scoring. The Digit Symbol Coding Test (DSCT) [22] tests visual attention, sustained concentration, and directed visual shifting abilities. Scores range from 0 to 100, with higher scores indicating better cognitive functioning. Trail Making Test Part A and B [24] measures psychomotor speed, agility, attention, sequencing, mental flexibility, as well as visual search abilities and motor function. This is a timed test, with the longer one takes to complete the trial, the worse the functioning of this domain. Purdue Pegboard [21] measures manual dexterity. The more pegs placed correctly during the prescribed time, the better the participants manual dexterity. Wisconsin Card Sorting Test (WCST) [22,25] is a computerized task that requires strategic planning, organized searching, maintained goal-directed behavior, and the monitoring of impulsive responses. The fewer trials administered, the higher the correct score and the lower the errors score, the better the neurocognitive functioning. Verbal Fluency [26] measures verbal functioning and is reported to be a sensitive indicator of brain dysfunction. Both a word generating and a category fluency task is used and the more words the participant can generate in a minute, the better the neurocognitive functioning.

Domains

Verbal Learning and Memory was assessed using Rey Auditory Learning Test (RAVLT). Means and standard deviations were created from raw scores and were scored as 2 = severe if SD of -2 or less, 1 = mild if SD ranged between -1 and -2 SD and 0 = none if SD at least 2. The new scores were summed into a verbal learning and memory overall score with a score of at least 4 indicating severe, score of 3 indicating mild, and 2 or less indicating none.

Visual Learning and Memory was determined from the Complex Figure of Rey (CFR) using delayed recall percentile. If the percentile was less than 10, then it was classified as severe, 10–24 was classified as mild, and more than 24 was classified as none.

Motor Speed was assessed using Digital Symbol Coding Test (DSCT), Trail Making Test Part A and B, and Purdue Pegboard. DSCT scaled score; standard deviation for Trail making PART A and standard deviation for dominant hand in Purdue Pegboard were scored as severe (2) if SD

of -2 or less, mild (1) if SD ranged between -1 and -2, and none (0) if SD at least 2, 1 to 2, or 0. Thereafter, they were summed to create an overall motor speed score, which was then classified as severe (score $\geq$4), mild (score = 3), and none (score$\leq$2).

Executive Function was determined using perseverative response *T* score and perseverative errors *T* scores from Wisconsin Card Sorting Test. Participants who were "Severely impaired" or "Moderate-severely impaired" were classified as severe (2), those who were "Mildly impaired," "Mildly-moderate impaired," or "Moderate impaired" were classified as mild (1) and "Below average," "Average," and "Above average" was classified and none (0).

Language was assessed using Verbal Fluency, standard deviation of -2 SD or less for animals indicated severe language, -1 to -2 SD indicated mild language, and at least 2 SD, 1 to 2 SD, and 0 indicated none.

Information Processing was determined using Digit Span Backwards, Trail Making Test Part B, RAVLT, and Digit Symbol Coding. DSCT scaled score; standard deviation for Trail making PART B and standard deviation for digital span backwards were scored as severe (2) if SD of -2 or less, mild (1) if SD ranged between -1 and -2, and none (0) if SD at least 2, 1 to 2, or 0. Thereafter, they were summed to create an overall information processing score, which was then classified as severe (score $\geq$4), mild (score = 3), and none (score$\leq$2).

Data analysis

Data were summarized descriptively by HIV status. Summary tables of categorical variables, frequencies, and percentages are presented together with the denominators. The denominator refers to the number of women who responded to an item. Summary tables for continuous measures, medians and interquartile ranges (IQR), as well as median differences are presented.

Categorical variables were compared by chi-square analysis stratified by HIV status, neurocognitive status, education level, and alcohol use, whereas Kruskal–Wallis was used to compare continuous variables by HIV status as unadjusted analysis. For adjusted analysis, we compared neurocognitive domains by HIV status using logistic regression controlling for parity, depression, ability to read, and BMI. The statistical comparison of NCIs by education level and alcohol use was done separately for WWH and WWOH and presented as supplementary tables.

Standardized neurocognitive scores, which are normed for age, were compared between the WWH and WWOH using both adjusted and unadjusted methods. Since the neurocognitive scores are continuous, normality was assessed using Shapiro–Wilk test and only two variables were normally distributed. Therefore, we determined medians and interquartile ranges (IQRs) and used quantile regression, a nonparametric method, to compare the neurocognitive median scores by HIV status (unadjusted) and by HIV status controlling for parity, depression, ability to read, and BMI (adjusted).

Risk factors for NCI for both cohorts were determined by fitting univariate and multivariate generalized linear model (with a log binomial distribution link function), since the neurocognitive impaired proportion was more than 10%. Several variables derived from the literature on NCI were tested at the univariate level, such as age, alcohol use (AUDIT), depression (PHQ-9), BMI, number of pregnancies, HIV status, and other clinical characteristics [3,27,28]. Findings are reported as relative risks (RRs), 95% confidence intervals, and *P* values. Univariate variables with *P* values less than 0.05 were used to form the full multivariate model that was reduced by the backward selection procedure to retain the final set of significant variables. Deviance statistics/degrees of freedom [29] was used to determine model fit. Statistical significance was defined as a *P* value of 0.05 or less. Statistical analysis was conducted using SAS Enterprise Guide 7.1 (SAS Institute Inc., Cary, North Carolina, USA).

Results

Demographics characteristics of participants

Four hundred fifty-one women were enrolled in the study, 224 (49.7%) WWH and 227 (50.3%) WWOH. The median age was 35 years (IQR: 31–39), with similar median age between the groups (Table 1). The level of education was similar, with most having completed secondary education or higher (56% overall), but a higher proportion of WWH were formally employed compared to the WWOH group (48 vs. 10%). Most women were classified as overweight or obese in both groups (Table 1). More WWOH were classified as having high-risk alcohol use in the AUDIT scale than WWH (22 vs. 15%). Depression was detected in 8.5% WWH compared with 8.4% WWOH (Table 1).

Neurocognitive functioning by HIV status

Analysis was adjusted, as shown in Table 2. In the overall assessment of cognitive functioning according to the DSM 5 criteria, a higher proportion of WWH had mild to major NCI (46 vs. 36%, $P = 0.06$), though this was not statistically significant. The distribution of mild versus major NCI was 40.6% mild, 4.9% major for WWH, and 30.4% mild, 5.7% major for WWOH. WWH had significantly more deficits in verbal learning and memory (51 vs. 30%, $P < 0.001$), motor speed (32 vs. 19%, $P = 0.002$), and speed of information processing (40 vs. 25%, $P = 0.001$) compared to the WWOH (Table 2). Deficits in language were higher in WWH (55 vs. 44%, $P = 0.02$) compared to WWOH.

Table 1. Demographic characteristics of participants by HIV status.

Variable	Overall	Women with HIV	Women without HIV	*P*
Age in years				
21–34 (%)	221/451 (49)	106/224 (47.3)	115/227 (50.7)	0.54
≥35 (%)	230/451 (51)	118/224 (52.7)	112/227 (49.3)	
Median (IQR)	35 (31–39)	35 (31–38.5)	34 (31–39)	0.55
Marital status				
No regular partner (%)	90/450 (20.0)	52/223 (23.3)	38/227 (16.7)	0.29
Primary regular partner (%)	280/450 (62.2)	133/223 (59.6)	147/227 (64.8)	
Married (%)	72/450 (16.0)	36/223 (16.1)	36/227 (15.9)	
Separated (%)	3/450 (0.7)	1/223 (0.5)	2/227 (0.9)	
Divorced (%)	3/450 (0.7)	0/223 (0.0)	3/227 (1.3)	
Widowed (%)	2/450 (0.4)	1/223 (0.5)	1/227 (0.4)	
Highest level of education				
Primary-partially completed (%)	12/450 (2.7)	3/223 (1.4)	9/227 (4.0)	0.26
Primary completed (%)	2/450 (0.4)	2/223 (0.9)	0/227 (0.0)	
Secondary-partially completed (%)	186/450 (41.3)	92/223 (41.3)	94/227 (41.4)	
Secondary completed (%)	200/450 (44.4)	99/223 (44.4)	101/227 (44.5)	
College/University (%)	50/450 (11.1)	27/223 (12.1)	23/227 (10.1)	
Self-reported reading ability				
Minimal (%)	11/449 (2.5)	6/223 (2.7)	5/226 (2.2)	0.74
Quite well/very well (%)	438/449 (97.6)	217/223 (97.3)	221/226 (97.8)	
Employment				
Formal employment (%)	128/445 (28.8)	105/221 (47.5)	23/224 (10.3)	<0.0001
Self-employment (small business) (%)	32/445 (7.2)	12/221 (5.4)	20/224 (8.9)	
Not employed/housewife (%)	285/445 (64.0)	104/221 (47.1)	181/224 (80.8)	
Median number of children (IQR)	2 (1–3)	2 (1–3)	2 (2–3)	0.57
BMI				
Underweight (%)	7/446 (1.6)	5/223 (2.2)	2/223 (0.9)	0.06
Normal (%)	99/446 (22.2)	60/223 (26.9)	39/223 (17.5)	
Overweight (%)	126/44 (28.3)	59/223 (26.5)	67/223 (30.0)	
Obese (%)	214/446 (48.0)	99/223 (44.4)	115/223 (51.6)	
Median (IQR)	29.7 (25.3–34.7)	29.3 (24.5–34.6)	30.2 (26.4–34.9)	0.05
WHODAS (Cronbach alpha = 0.83)				
No difficulty (%)	258/451 (57.2)	139/224 (62.1)	119/227 (52.4)	0.07
Mild difficulty (%)	26/451 (5.8)	8/224 (3.6)	18/227 (7.9)	
Moderate difficulty (%)	163/451 (36.1)	76/224 (33.9)	87/227 (38.3)	
Severe difficulty (%)	4/451 (0.9)	1/224 (0.5)	3/227 (1.3)	
Median (IQR)	1 (0–4)	2 (0–4)	1 (0–4)	
AUDIT score (Cronbach alpha = 0.84)				
Low risk (%)	367/451 (81.4)	190/224 (84.8)	177/227 (78)	0.06
High risk (%)	84/451 (18.6)	34/224 (15.2)	50/227 (22)	
Median (IQR)	3 (0–6)	3 (0–6)	4 (0–7)	
Cannabis use in the past month				
Yes (%)	10/447 (2.2)	1/222 (0.5)	9/225 (4)	0.01
No (%)	437/447 (97.8)	221/222 (99.6)	216/225 (96)	
PHQ-9 (Cronbach alpha = 0.81)				
None/minimal depression (%)	413/451 (91.6)	205/224 (91.5)	208/227 (91.6)	0.97
Depressive symptoms (%)	38/451 (8.4)	19/224 (8.5)	19/227 (8.4)	
Median (IQR)	3 (1–6)	3 (1–5)	3 (1–6)	

Neuropsychological tests by HIV status

All tests were adjusted, as shown in Table 3.

RAVLT: (immediate and longer-term memory)

Compared to the WWOH, WWH had a significantly lower median score in the summed RAVLT scores [55 (48–60.5) vs. 58 (49–66), $P = 0.010$] and on the delayed trial of the RAVLT [9 (7–11) vs. 10 (8–12), $P = 0.004$], indicating deficits in longer-term verbal memory and possibly some short-term verbal memory deficits (Table 3 and Supplementary Figure 1, http://links.lww.com/QAD/D605).

DSCT: (visual attention, sustained concentration)

WWH had decreased scoring compared to WWOH (7 vs. 8, $P = 0.006$), and as higher scores indicate better overall cognitive functioning, this suggests lower global neurocognitive functioning.

Verbal fluency

The F total number correct (9 vs. 10, $P = 0.04$) and the A total number correct (5 vs. 6, $P = 0.003$) was decreased in WWH in comparison to the other cohort, which could be due to the language of testing or worse language functioning. Animal verbal fluency was not significantly different between groups.

Trail Making Test: (psychomotor speed, agility, attention, sequencing, mental flexibility) The median total time was significantly higher in the WWH relative to the WWOH for Part A (56 vs. 47, $P = 0.003$) and Part B

Table 2. Neurocognitive domains by HIV status.

Variable	Overall	Women with HIV	Women without HIV	Unadjusted *P*	Adjusted *P*
Verbal learning and memory					
None (%)	271/451 (60.1)	111/224 (49.6)	160/227 (70.5)	<0.0001	<0.0001
Mild/Severe (%)	180/451 (39.9)	113/224 (50.5)	67/227 (29.5)		
Visual learning and memory					
None (%)	296/449 (65.9)	151/222 (68.0)	145/227 (63.9)	0.36	0.29
Mild/Severe (%)	153/449 (34.1)	71/222 (32.0)	82/227 (36.1)		
Motor speed					
None (%)	335/451 (74.3)	152/224 (67.9)	183/227 (80.6)	0.002	0.001
Mild/Severe (%)	116/451 (25.7)	72/224 (32.1)	44/227 (19.4)		
Executive function					
None (%)	269/451 (59.7)	134/224 (59.8)	135/227 (59.5)	0.94	0.79
Mild/Severe (%)	182/451 (40.3)	90/224 (40.2)	92/227 (40.5)		
Language					
None (%)	226/451 (50.1)	100/224 (44.6)	126/227 (55.5)	0.02	0.07
Mild/Severe (%)	225/451 (49.9)	124/224 (55.4)	101/227 (44.5)		
Speed of information processing					
None (%)	305/451 (67.6)	135/224 (60.3)	170/227 (74.9)	0.001	0.003
Mild/Severe (%)	146/451 (32.4)	89/224 (39.7)	57/227 (25.1)		
DSM neurocognitive disorder					
Mild/Major (%)	184/451 (40.8)	102/224 (45.5)	82/227 (36.1)	0.04	0.08
None (%)	267/451 (59.2)	122/224 (54.5)	145/227 (63.9)		

Adjusted by parity, depression, ability to read, and BMI. Tests used to assess domains: Verbal Learning and Memory – RAVLT and Digit Span; Visual Learning and Memory - Complex figure of Rey; Motor Speed - Digit Symbol Substitution Coding, Trail Making Part A and B, Purdue Pegboard; Executive Functioning - Wisconsin Card sorting test; Language – Verbal Fluency; Speed of Information Processing – RAVLT, Digit span backwards, Digit Symbol Substitution Coding, Trail Making Part B. DSM neurocognitive disorder (One or more domains): Mild= 1 standard deviation below the norm in at least 1 domain, Major=2 standard deviations below the norm in at least 1 domain and functional impairment.

(103 vs. 88, $P<0.001$), which suggests decreased motor speed and speed of information processing. There were no differences between groups for the Wisconsin card sorting test, the complex figure of Rey, Purdue pegboard, or digit span test.

Risk factors associated with neurocognitive impairment in all women

univariate model

Those who were at least 35 years of age (RR: 1.53, 95% CI: 1.21–1.93; $P<0.001$) did not complete secondary schooling (RR: 1.38, 95% CI: 1.10–1.72; $P=0.005$), were able to read only a little (RR: 1.83, 95% CI: 1.25–2.68; $P=0.002$), were living with HIV (RR: 1.26, 95% CI: 1.007–1.58; $P=0.043$), and were considered high-risk alcohol users (RR: 1.33, 95% CI: 1.04–1.70; $P=0.022$) had an elevated risk of NCI (Table 4).

Multivariate model

The risk of NCI was elevated in women at least 35 years of age (RR: 1.46, 95% CI: 1.16–1.84, $P=0.001$), those with incomplete secondary education (RR: 1.26, 95% CI: 1.01–1.58, $P=0.04$), HIV infection (RR: 1.26, 95% CI: 1.02–1.56, $P=0.03$), and high alcohol use (RR: 1.42, 95% CI: 1.13–1.78, $P=0.003$). The model fit assessment, measured by deviance/degrees of freedom, yielded a value of 0.7160, suggesting an acceptable model.

Neurocognitive tests by education level among women with HIV and women without HIV

Among WWH, those who did not complete secondary school had significantly more deficits in verbal learning and memory (60 vs. 44%, $P=0.017$), speed of information processing (51 vs. 31%, $P=0.003$), and more diagnosis of NCI (54 vs. 39%, $P=0.029$) than those who completed secondary school or had higher education (Supplementary Table 1, http://links.lww.com/QAD/D606). Deficits in motor speed (26 vs. 14%, $P=0.018$), language (55 vs. 35%, $P=0.003$), and speed of information processing (36 vs. 16%, $P=0.001$) were significantly higher in WWOH who did not complete secondary school compared to those who completed or had higher education. There was no statistical difference in diagnosis of NCI (Supplementary Table 1, http://links.lww.com/QAD/D606).

Neurocognitive tests by alcohol use among women with HIV and women without HIV

WWH with higher alcohol use had significant NCI (65 vs. 42%, $P=0.015$) compared to WWH with lower alcohol use. There was no significant difference in tests of specific cognitive domains between groups. There was no significant difference in NCI or specific cognitive domains for WWOH by alcohol use (Supplementary Table 2, http://links.lww.com/QAD/D606).

Discussion

This study showed important findings in all women irrespective of HIV status. We found that 40.8% of all women had NCI based on DSM 5 criteria (35.8% mild, 5.3% major), and 8.4% of all women had depressive

Table 3. Complex figure of Rey, Rey auditory verbal learning test, Digit symbol, Purdue pegboard, Trail making test, digit span test, verbal fluency, and WCST test by HIV status.

Variable	Overall Median (IQR)	Women with HIV Median (IQR)	Women without HIV ($n = 227$) Median (IQR)	Comparison of groups Median difference	Unadjusted *P*	Adjusted *P*
Complex figure of Rey						
Copy Score (Max 36)	34 (32–36)	34 (32–36)	34 (31–35)	0.00	0.91	0.32
Immediate Recall Score (Max 36)	19.5 (16–23)	19.5 (16–23)	19.5 (16–23.5)	0.00	0.91	0.88
Delayed Recall Score (Max 36)	19.5 (16.5–23.5)	19.8 (17–23)	19.5 (16–24)	0.25	0.91	0.94
Rey auditory verbal learning test						
Trial 1 Total Number (Max 15)	5 (4–7)	5 (4–6)	6 (4–7)	−1.00	<0.001	0.35
Trial 2 Total Number (Max 15)	9 (7–10)	8 (7–10)	9 (7–10)	−1.00	0.001	0.42
Trial 3 Total Number (Max 15)	10 (9–11)	10 (9–11)	10 (9–12)	0.00	0.91	<0.001
Trial 4 Total Number (Max 15)	11 (9–12)	11 (9–12)	11 (10–13)	0.00	0.91	0.91
Trial 5 Total Number (Max 15)	11 (10–13)	11 (10–12)	12 (10–14)	−1.00	0.001	0.001
Trial 6 Total Number (Max 15)	10 (8–11)	9 (7–11)	10 (8–12)	−1.00	0.01	0.01
Delayed Total Number (Max 15)	10 (8–12)	9 (7–11)	10 (8–12)	−1.00	0.01	0.004
Digital symbol coding test						
Raw Scores	47.5 (39–56)	45 (36–55)	50 (42–59)	−5.00	0.01	<0.001
Scaled Score	7 (6–9)	7 (5–9)	8 (6–9)	−1.00	0.001	0.01
Purdue pegboard						
Dominant Hand Total Number of Pegs (Max 25)	16 (15–17)	16 (15–17)	16 (15–18)	0.00	0.91	0.24
Nondominant Hand Total Number of Pegs (Max 25)	15 (14–16)	15 (14–16)	15 (14–16)	0.00	0.91	0.91
Both Hands Total Number of Pegs (Max 25)	12 (11–13)	12 (11–13)	12 (11–13)	0.00	0.91	0.91
Trail making test						
PART A Total Time (Seconds)	52 (41–66)	56 (43–70)	47 (37–60)	9.00	0.002	0.003
PART B Total Time (Seconds)	94 (73–123)	103 (81–136)	88 (68–111)	15.00	0.001	<0.001
Digit span test						
Forwards (Max 9)	5 (4–5)	5 (4–5)	5 (4–6)	0.00	0.91	0.91
Backwards (Max 8)	3 (3–4)	3 (2–4)	3 (3–4)	0.00	0.91	0.91
Verbal fluency						
''F'' Total Number	9 (7–12)	9 (7–11.5)	10 (8–13)	−1.00	0.01	0.04
''A'' Total Number	6 (4–8)	5 (3–7)	6 (4–8)	−1.00	0.01	0.003
Animals Total Number	13 (10–15)	12 (10–14)	13 (11–16)	−1.00	0.04	0.12
Wisconsin Card Sorting Test						
Trials Administered Raw Scores	128 (93–128)	128 (98–128)	124 (89–128)	4.00	0.23	0.50
Total Correct Raw Scores	72 (64–81)	72 (63–79.5)	72 (65–82)	0.00	0.91	0.77
Total Errors Raw Scores	39 (19–58)	42.5 (21.5–62.5)	34 (17–54)	8.50	0.04	0.2
Total Errors T score	40 (31–51)	39 (30–49)	43 (33–51)	−4.00	0.02	0.13
Total errors standard score	85 (72–101)	83.0 (70–98)	89 (75–102)	−6.00	0.02	0.08
Conceptual level responses						
Raw scores	64 (48–71)	63 (43–70)	66 (56–72)	−3.00	0.04	0.04
T score	41 (31–50)	39.0 (30–47)	43 (33–51)	−4.00	0.01	0.08
Standard Score	86 (72–100)	84 (70–96)	89 (75–101)	−5.00	0.04	0.13
Categories completed raw scores	5 (2–6)	5 (2–6)	6 (3–6)	−1.00	0.04	0.07
Trials to complete first category raw score	11 (11–17)	11.5 (11–16.5)	11 (11–17)	0.50	0.91	0.53
Failure to maintain set raw scores	1 (0–2)	1 (0–2)	1.00 (0–2)	0.00	0.91	0.91
Learning to learn raw scores	−2.2 (−7.90)	−2.2 (−9.20)	−2.2 (−6.90)	0.04	0.94	0.71

NB: Quantile regression adjusted comparisons controlled for parity, depression, ability to read, and BMI.

symptoms, slightly higher than the global average of 6% in women [30]. However, WWH had statistically lower test scores in four of six neurocognitive domains tested. Risk factors associated with NCI were age over 35 years, HIV status, incomplete secondary education, and higher alcohol use.

A lower level of education has been negatively associated with neurocognitive performance in PWH (31), while higher education is protective against later cognitive decline in the general population, but importantly more so among women [31]. While a lower education level was detrimental for neurocognitive functioning in all women in our study, WWH who also had a lower level of education had significantly more NCI than WWH with greater educational achievements. This difference was not seen in varying education levels in WWOH. It is possible that a lower level of education may be more detrimental in WWH, therefore education in this group of women is of outmost importance. (Supplementary Table 1, http://links.lww.com/QAD/D606).

Table 4. Risk factors associated with neurocognitive impairment.

	Univariable		Multivariable	
Variable	RR (95% CI)	*P*	RR (95% CI)	*P*
Age (in years)				
≥35 vs. 21–34	1.53 (1.21–1.93)	<0.001	1.45 (1.14–1.85)	0.003
Marital status				
Married vs. Other	0.94 (0.64–1.39)	0.76	–	–
Primary regular partner vs. Other	1.05 (0.79–1.39)	0.73	–	–
Level of education				
Incomplete secondary vs. Completed secondary/college	1.38 (1.10–1.72)	0.005	1.26 (1.01–1.58)	0.04
Employment status				
Not employed/housewife vs. formal/self employed	0.93 (0.74–1.17)	0.52	–	–
Do you receive a grant/pension?				
Yes vs. No	1.02 (0.74–1.41)	0.91	–	–
BMI				
Underweight vs. Normal	0.67 (0.20–2.22)	0.52	–	–
Overweight/Obese vs. Normal	0.96 (0.74–1.25)	0.73	–	–
How well are you able to read?				
A little vs. Quite well/very well	1.83 (1.25–2.68)	0.002	–	–
Total number of pregnancies	1.07 (0.99–1.17)	0.11	1 (0.92–1.1)	0.92
HIV status				
Women with HIV vs. Women without HIV	1.26 (1.01 -1.58)	0.04	1.25 (1.01–1.55)	0.04
Have you ever been diagnosed with a problem like anxiety or depression?				
Yes vs. No	0.84 (0.48–1.49)	0.56	–	–
Do you currently (within the last 30 days) use hormonal contraception?				
No vs. Yes	1.04 (0.83–1.3)	0.74	–	–
Alcohol use				
Higher risk (8+) vs. Lower risk (0–7)	1.33 (1.04–1.70)	0.02	1.44 (1.15–1.79)	0.002
Depressive symptoms vs. No depressive symptoms	0.76 (0.47–1.23)	0.26	0.76 (0.47–1.22)	0.25

Living with HIV was associated with a higher risk of NCI, RR: 1.25 (95% CI: 1.01−1.55), in our study. A meta-analysis from 2020 showed a high burden of cognitive deficits linked to HIV globally, with a global prevalence of 42.6% [3]. A study from Zimbabwe in a healthy cohort of people on ART, but with a female predominance (70%), found a rate of NCI of 49.7% [32]. Our study confirms the high burden of disease with a prevalence of 46% in WWH despite a median age of 35 years.

The CHARTER study showed an increased probability of NCI among PWH with other comorbidities [1]. In our study, poor neurocognitive functioning was seen in all women with higher alcohol use, a known risk factor for NCI [33]. A higher percentage of WWOH were using alcohol heavily. Interestingly, those WWH with high alcohol use were more likely to be diagnosed with NCI, suggesting the additive effect of alcohol and HIV on the brain (Supplementary Table 2, http://links.lww.com/QAD/D606). It appears that comorbidities interact with HIV to accelerate and accentuate cognitive aging [7].

Mental health is an important variable when looking at neurocognitive functioning. Depression is known to be independently associated with NCI in PWH and WWOH, with speed of information processing, executive functioning, learning, memory and motor functioning affected [28,34]. We did not find a link between NCI and depression in both WWH and WWOH, possibly due to different methodologies and pathways involved in NCI. Another finding that may need further study was that 48% of all participants were classified as obese. Obesity has been linked to increased inflammation and NCI [35], but was not an independent risk factor in our study.

This study specifically chose to examine neurocognitive functioning among young women who were mothers, a population not often focused upon. The high rate of cognitive difficulties among this group of younger WWH is alarming, given their responsibilities as caregivers of children, some of whom may have complicated medical needs.

This study has strengths and limitations. First, it was cross-sectional in design. Repeated assessments over time can be helpful to more fully determine impairment and its effect on daily functioning. CNS infections were not included as an exclusion criterion, and if present, could have had an impact on neurocognitive functioning. However, WWH had been followed up for many years as part of the PROMISE and PROMOTE studies and almost all had WHO Stage 1 at baseline. The likelihood of a serious CNS infection was considered extremely low. Despite efforts to match the two groups, we found a substantial difference in employment status as WWOH with formal employment appear to have declined to join the study, citing time constraints. The specific ART regimens of the WWH were not analyzed. Other psychiatric conditions, specifically PTSD, were not screened for this. The sample size was based on the

number of women who participated in the PROMOTE study at the PHRU site, which was fixed. All tests were conducted in English, which is not the first language of the participants. Linguistic bias was decreased by selecting tests that have been shown to have less reliance on language. One of the psychologists involved was fluent in the participants primary language to translate as needed. The mode of testing may have impacted on results. Some participants had low levels of education. Having less exposure to testing situations is known to impact on one's ability to perform during testing. In terms of methods, the use of the DSM 5 criteria for diagnosis may have over-represented NCI, as suggested in Tierney *et al*. [36]. However, we had low rates of depression and all participants completed the WHODAS. We have shown several test results in Table 3 without conducting multiple comparison testing because our aim was to show trends in descriptive fashion rather than comparing hypotheses. Strengths include the use of a matched control group and a thorough neuropsychological assessment performed by highly skilled personal and a supportive environment with attention to participants' needs during testing such as breaks between tests.

Conclusion

We found a high rate of poor neurocognitive functioning among young WWH in South Africa despite long-term ART and well controlled HIV. The inclusion of a control group, as well as the high rate of NCI within this group, has helped to highlight other factors that affect brain health, such as heavy alcohol use and level of education, and public health initiatives should focus on these. The use of the DSM 5 classification system may be a useful tool for assessing neurocognitive functioning in PWH and future studies could look at the different classifications and outcomes of neurocognitive testing. Future research should examine the perceived difficulties in functioning and parenting from the WWH's perspective, the stability of the neurocognitive functioning over time, and the impact brain-health interventions could have on functioning and quality of life.

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Conflicts of interest

There are no conflicts of interests for any authors included in this manuscript.

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