

Screening for HIV-Associated Neurocognitive Impairment: Relevance of Psychological Factors and Era of Commencement of Antiretroviral Therapy

Susan Herrmann, RN, BSc, MSc, PhD* • Elizabeth McKinnon, PhD • Matthew Skinner, MBBS, FRACP • Martin Duracinsky, MD, PhD • Richard Chaney, MBBS • Vance Locke, MPsych, PhD • Francis Mastaglia, MBBS, MD, FRACP, FRCP

Abstract

Neurocognitive impairment (NCI) is common in people aging with HIV and can adversely affect health-related quality of life. However, early NCI may be largely asymptomatic and neurocognitive function is rarely assessed in the context of routine clinical care. In this study, we considered the utility of two assessment tools as screens for NCI in patients attending a community-based clinic ($N = 58$; mean age = 57 years): the Montreal Cognitive Assessment (MoCA) and a 3-item cognitive concerns questionnaire derived from the HIV Dementia Scale. Health-related quality of life and depression/anxiety were also measured. Indication of NCI using the MoCA was more prevalent compared to the 3-item questionnaire and was associated with the patients' initial antiretroviral therapy commencing between the years of 1997 and 2001, independently of age. Findings of the MoCA were not confounded by existing mood disorders, unlike the 3-item questionnaire. Therefore, we suggest implementing the MoCA as an initial screen for NCI.

Key words: aging, depression, health-related quality of life, HIV nursing, neurocognitive screening

Access to potent and tolerable combination antiretroviral therapy (cART) has positively changed the health outlook for people living with HIV. However, despite effective treatment, there is increasing awareness of mild forms of neurocognitive impairment (NCI) affecting relatively young individuals living with HIV (Heaton et al., 2010). Determining whether cognitive impairment is attributable to the virus, to other aspects of treatment, and/or to comorbidities such as cardiovascular

diseases is important for persons living with HIV (PLWH) and health care providers.

Neurocognitive complications of HIV infection were recognized by clinicians as early as 1986 when PLWH in the late stages of HIV infection presented with dementia-like symptoms (Schouten, Cinque, Gisslen, Reiss, & Portegies, 2011). Postmortem brain studies conducted in that era indicated that harmful pathology was likely driven directly by viral proteins and neurochemically by secreted neurotoxins and other cellular products (Gelman et al., 2013; Schouten et al., 2011). Later, it was recognized that the virus could persist in CD4+T cells, macrophages, and astrocytes, even in the context of apparently effective cART introduced in the mid-1990s, creating a reservoir of “latent” infection (Deeks, Lewin, & Havlir, 2013; Simoes & Justino, 2015). Subsequently, concerns arose that antiretroviral penetration of the brain was possibly limited and varied between drug classes. A ranking of antiretroviral drugs, according to their capacity to cross the blood brain barrier and penetrate the central nervous system (CNS), was suggested to optimize the efficacy of combined regimens, and this ranking became known as the CNS penetration effect (CPE) score (Cusini et al., 2013; Letendre et al., 2008). However, some controversy continues as to whether neuronal damage occurs as a result of antiretroviral toxicity. Other researchers have reported that NCI can be associated with low CD4+T cell counts, cardiovascular diseases, metabolic disorders, and substance

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

Susan Herrmann, RN, BSc, MSc, PhD, is a Senior Research Officer in the School of Medicine, University of Western Australia, Australia. Elizabeth McKinnon, PhD, is a Biostatistician, Telethon Kids Institute in Western Australia, Australia. Matthew Skinner, MBBS, FRACP, is a Consultant Physician in the Department of Infectious Diseases, Sir Charles Gairdner Hospital, Western Australia, Australia. Martin Duracinsky, MD, PhD, is a Scientific Coordinator, EA 7334 Patient-Reported Outcomes Unit, Paris-Diderot University, Paris, France. Richard Chaney, MBBS, PhD, is a Clinician in Sexual Health, Sexual Health Clinic, Royal Perth Hospital, Western Australia, Australia. Vance Locke, MPsych, PhD, is a Translational Clinical Researcher, School of Psychology and Exercise Science, Murdoch University, Western Australia, Australia. Francis Mastaglia, MBBS, MD, FRACP, FRCP, is a Research Coordinator, Perron Institute for Neurological and Translational Science, Centre for Neuromuscular and Neurological Disorders, University of Western Australia, Australia.

*Corresponding author: Susan Herrmann, e-mail: Susan.Herrmann@uwa.edu.au
Copyright © 2018 The Authors. Published by Wolters Kluwer Health, Inc. on behalf of Association of Nurses in AIDS Care. This is an open-access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

<http://dx.doi.org/10.1097/JNC.000000000000040>

use (Anand, Springer, Copenhaver, & Altice, 2010; Simoes & Justino, 2015; Tedaldi, Minniti, & Fischer, 2015). Current cART is optimized to take into consideration the capacity of the virus to establish latent reservoirs in the brain.

Relevant for diagnosis and management of HIV-associated neurocognitive disorders are the potential confounding influences presented by the complex social and psychological dimensions of living with HIV, which can have a detrimental effect on health-related quality of life (HRQL), activities of daily living, mood and behavior, stable employment, and interpersonal relationships (Tedaldi et al., 2015). Importantly, NCI may particularly impact medication adherence, the keystone of effective viral suppression, as well as safe dosing (Kamal et al., 2017). Nurses, frontline clinicians caring for people living with chronic HIV, are well placed to implement screening that can detect early, and potentially fluctuating, neurocognitive deficits. Interventions to optimize brain health and quality of life can then be implemented. However, nurses need clear guidance concerning valid assessment tools that can be feasibly incorporated into routine care (Simoes & Justino, 2015).

The reported prevalence of HIV-associated NCI varies between studies with rates varying between 15% and 50% among PLWH (Schouten et al., 2011). However, severe forms of HIV-associated NCI are uncommon in the context of effective cART (Heaton et al., 2010; Tedaldi et al., 2015). Clinically, a subcortical profile of NCI is characterized by mental slowness and deficits in attention, memory, and executive functioning. These symptoms may be accompanied by impairment of fine motor skills, but in mild cases symptoms may not be apparent (Brew & Chan, 2014; Heaton et al., 2004).

In a busy practice environment, health care providers require brief, validated, and discriminating screening tools to support clinical decision making. However, expertise in their administration and interpretation may be lacking (Brouillette et al., 2014; Simoes & Justino, 2015). A number of screening tools to assess NCI have been proposed (Zipursky et al., 2013), including the CogState (Bloch et al., 2016) and the Montreal Cognitive Assessment (MoCA; Fazeli, Casaletto, Paolillo, Moore, & Moore, 2017). The European AIDS Clinical Society (2015) provides comprehensive guidelines for HIV management and recommends an initial screening for NCI that is comprised of three questions pertaining to memory, reasoning, and attention. Responses to these questions initiate a cascade of decision making, beginning with an assessment of depression/anxiety as a possible underlying cause, prior to undertaking any further assessment of cognitive function.

Consideration of these guidelines underpinned this study, which sought to identify individuals with early

cognitive changes in an aging cohort of PLWH attending a community-based specialist HIV clinic, staffed by a nurse and an infectious disease physician. We aimed to (a) assess the utility of the three-item cognitive concerns questionnaire (CCQ), as recommended by the European AIDS Clinical Society, alongside the MoCA, a brief screening instrument for mild cognitive impairment that had been used in geriatric populations (Nasreddine et al., 2005); (b) determine indicators of early NCI; and (c) assess the relationship between psychological distress, impaired cognitive performance, and HRQL. We considered that, from a clinical perspective, these assessments would be helpful in establishing baseline parameters against which we could monitor future changes in the individual patient.

Methods

Participants

Fifty-eight adult PLWH attending the clinic at the Institute for Immunology and Infectious Diseases at Murdoch University (Perth, Australia) for management of chronic HIV infection were recruited for participation in the study, which ran from September 2015 to December 2016. This convenience sample comprised more than 90% of clinic attendees visiting at 4-month intervals and who received a nurse consultation prior to seeing their HIV physician. During these consultations, adherence to medication, psychosocial issues, diet, and lifestyle were discussed; and blood pressure, weight, and records concerning comorbid medical conditions were updated. At this time, patients were offered the study information, which they took home to consider, and subsequently gave consent to participate in writing. At subsequent visits, participants were asked to complete a set of four validated instruments assessing neurocognition, mood (depression, anxiety, and stress), and HRQL prior to clinic consultations. Three of the instruments were self-report questionnaires and were completed independently by the participants, and the fourth, the MoCA, was administered by nurses or postgraduate clinical psychology students who were trained to conduct the data collection. The study was approved by the Murdoch University Human Research Ethics Committee (Reference ID: 2015-112).

Measurement

Three-item cognitive concerns questionnaire. The three-item questionnaire recommended in the European AIDS Clinical Society Guidelines (2015) for use as an initial screen for neurocognitive deficits in HIV infection was derived from the HIV Dementia Scale (Power,

Selnes, Grim, & McArthur, 1995). For the purposes of clarity in this study, we refer to this screen as the cognitive concerns questionnaire or the CCQ. The three questions are as follows: (a) Do you experience frequent memory loss (e.g., do you forget the occurrence of special events, even the more recent ones, appointments, etc.?). (b) Do you feel you are slower when reasoning, planning activities, or solving problems? (c) Do you have difficulties paying attention (e.g., to a conversation, a book, a movie)? The questions are designed to elicit cognitive complaints with respondents indicating the presence and frequency of such difficulties. An answer is considered “actionable” when the response is *yes, definitely* to at least one question. In addition to this clinic-based assessment of the need for further follow-up, we calculated the sum of the three responses to the three-item questionnaire as: 0 if *never*, one if *sometimes*, and two if *yes, definitely* to obtain a score ranging from 0 to 6 for the frequency of cognitive concerns as expressed at that visit.

The Montreal Cognitive Assessment. The MoCA (Nasreddine et al., 2005) is a brief screen used in varied clinical contexts, including HIV infection, to assess cognitive domains, including attention, memory, conceptual thinking, and orientation. The test is brief and takes about 10–12 min to complete. The test taker is asked to complete a series of tasks that assess short-term memory, visuospatial ability, abstract reasoning, concentration, and language abilities. Each of these tasks is scored separately, and the maximum possible total is 30/30 points with scores 26 and above indicating better cognitive functioning. Accordingly, consistent with the scoring guide for the instrument and its use by other researchers, we considered a score of less than 26 as being “actionable” and suggestive of a degree of cognitive impairment. Staff were trained to administer the MoCA, and alternative versions of the validated instrument containing slightly modified content, for example the choice of words in a five-word delayed recall, but measuring the same domains, were used at each visit. This was done to minimize the likelihood of the test result being affected by the participants’ previous use of the instrument.

The Depression Anxiety Stress Scales. The Depression Anxiety Stress Scales (DASS) (Lovibond & Lovibond, 1995) is a self-report instrument to assess psychological distress across the domains of depression, anxiety, and stress. Scores are calculated across domains, with higher scores indicating higher levels of distress. The questionnaire can be completed in a 42- or 21-item format over 5–10 min. A four-point response scale rates severity and frequency. The scores ranged from 0, meaning that the patient believed the

item “*did not apply to them at all*,” to 3, meaning that the respondent considered the item to “*apply to them very much, or most of the time*.” Domain scores are categorized by general population percentiles (normal: <78th percentile, mild: 78th–87th percentile, moderate: 87th–95th, severe: 95th–98th, extremely severe: >98th), with scores above the 78th percentile considered to be clinically significant. For the analysis here, we utilized *z*-scores as normalized by insertion of appropriate general population domain parameters (Crawford, Cayley, Lovibond, Wilson, & Hartley, 2011) into the formula: $z\text{-score} = (\text{raw score} - \text{domain mean}) / (\text{domain standard deviation } [SD])$.

The Patient-Reported Outcomes & Health-Related Quality of Life instrument specific for HIV. The PRO-QOL-HIV (Duracinsky et al., 2012) is a self-report questionnaire used to assess the HRQL of people living with HIV. It reflects people’s perceptions over the previous 2 weeks, and a five-point scale rates either frequency or level of agreement. There is one global health self-report item and a further 32 questions reflecting three global dimensions: physical health, psychological health, and social health. The fourth dimension (10 items), encapsulating treatment impact, can be omitted without affecting the instrument’s psychometric properties; thus, the instrument is equally valid for use by people not taking cART. The subscale scores are summed and expressed as a final score on a 0–100 scale with higher values indicating better HRQL.

Central nervous system penetration effect. The CNS penetration effect score for participants’ current cART was calculated for each visit. These scores were derived by summing assigned values of 1—*below average*, 2—*average*, 3—*above average*, and 4—*much above average* to each component antiretroviral drug according to the criteria established by Letendre et al. (2008).

Statistical Analysis

Positive indication of NCI was defined by the “actionability” of the screening measures: The CCQ was deemed actionable when any of the three items had a response of *yes, definitely*, while the MoCA was deemed actionable for a score less than 26. The proportion of positive agreement between responses to the CCQ and MoCA screening tools was calculated as stated in, for example, Spitzer and Fleiss (1974): $(2 \times \text{number both screens actionable}) / (\text{number of CCQ actionable} + \text{number MoCA actionable})$. Actionability of screening responses at study entry according to demographics, and the baseline clinical and psychological characteristics of

participants were assessed by Fisher's exact test and analysis of variance as appropriate.

Mixed effect regression models, which can accommodate a varying number of visits per person, were utilized for longitudinal analyses of the screening assessments, the MoCA and cognitive concerns frequency scores, and associations with measures of psychological distress. The models assumed individual measures fluctuate from visit to visit about patient-average values, which may in turn vary around group means or trend over time, or according to other covariate values. Assessment of bivariate associations with HRQL was based on Pearson correlation coefficients, calculated from the respective individual mean measures. *p* Values $\leq .05$ were considered statistically significant.

Baseline actionability comparisons and regression analyses included consideration of the impact of demographic characteristics (age, sex, race), psychological characteristics (diagnosed depression, DASS scores), and baseline clinical measures (years since diagnosis and treatment start date, CD4+T cell measures, CPE score). In a reflection of changing cohort prescribing practices over the years, era of treatment initiation was also considered in analyses, as defined by the calendar periods of 1990–1996 (pre-cART), 1997–2001 (early cART), and 2002–2014 (later cART).

Results

Data that included concurrent responses to the NCI screening tools and the DASS and PROQOL questionnaires were obtained from 58 individuals (87% male) over 1–3 visits per person ($M = 2$), approximately 4 months apart to coincide with clinic visits. At baseline, patients had a mean (*SD*) age of 57 (9) years and time since diagnosis ranged from 2 to 32 ($M = 19$) years. All patients were receiving effective cART and had undetectable plasma viral loads. More females than males were non-Caucasian (6/9 = 67% vs. 9/49 = 18%, $p = .006$ Fisher's test). Prevalence of documented depression was similar between males and females (18% vs. 22%, $p > .9$), and at the time of the study, none of the participants were diagnosed with dementia or any other neurological disorder.

Relative Frequency of Actionable Responses to the Montreal Cognitive Assessment and Cognitive Concerns Questionnaire

There was low overall agreement between the MoCA and CCQ as indicators of NCI, with the proportion of positive agreement in the contemporaneous screening

assessments being approximately 25%. In particular, 54/115 (47%) of MoCA results, which ranged from 17 to 30, fell below the threshold of 26, as compared to the 25/115 (21.7%) of actionable responses to the CCQ. In all, while at least one below-threshold MoCA screen was observed in 63.8% (37/58) of study participants, and at least one actionable CCQ result in 32.8% (19/58) of participants, there were only 10 individuals (17.2%) in whom neurocognitive dysfunction was indicated by both screens. Furthermore, patient-average MoCA scores (M [*SD*] = 25.4 [2.7]) showed little correlation with the average CCQ frequency scores ($R = 0.11$).

Clinical and Demographic Indicators of Neurocognitive Impairment

No baseline clinical and demographic variables showed a consistent association with positive outcomes across the two screening measures at study entry (Table 1). Age was the strongest predictor of an actionable CCQ response ($p = .03$) but did not significantly differentiate the MoCA responses. However, older age particularly characterized those with concordant indication of NCI by both screens (both CCQ and MoCA positive at baseline: $n = 7$, M [standard error] age = 63.9 [2.4] years; neither screen positive: $n = 20$, 53.2 [2.0] years; $p = .004$). There was a strong association between the era of commencing therapy and likelihood of an actionable MoCA response at baseline ($p = .002$). In particular, a lower MoCA score at baseline was observed in those whose initial therapy was in the era of early cART (1997–2001) independently of age, time since diagnosis, or length of time on treatment ($p < .003$, linear regression analyses). Notably, more than 75% of patients who had commenced initial treatment in the early cART era (1997–2001) scored below the MoCA threshold, a finding that did not appear to be driven by older age (Figure 1).

In the longitudinal analysis, era of therapy initiation remained strongly associated with scoring on the MoCA ($p = .005$; estimated M [standard error] score 1990–1996: 26.4 [0.6], 1997–2001: 24.1 [0.6], 2002–2014: 25.8 [0.5]), but not frequency of cognitive concerns ($p = .2$). A below-threshold MoCA result was more prevalent in patients who commenced therapy in the earlier years of cART (1997–2001), irrespective of age, with patients starting treatment in this era significantly more likely to have an actionable response than those whose first antiretroviral therapy was pre-cART (odds ratio [OR] = 3.4, $p = .04$; age-adjusted: OR = 3.7, $p = .03$) or those who commenced treatment after 2001 (OR = 5.6, $p = .003$;

Table 1. Actionability of Screening Responses at Study Entry According to Demographics and Baseline Clinical and Psychological Characteristics of Individuals

	Cognitive Concerns Questionnaire ^a			Montreal Cognitive Assessment ^b		
	Not Actionable <i>n</i> = 40	Actionable <i>n</i> = 18	<i>p</i> -Value ^c	Not Actionable <i>n</i> = 31	Actionable <i>n</i> = 27	<i>p</i> -Value ^c
Demographics						
Male gender (vs. female)	31 (77.5%)	18 (100.0%)	.05	28 (90.3%)	21 (77.8%)	.3
Caucasian race (vs. other)	28 (70.0%)	15 (83.3%)	.3	25 (80.6%)	18 (66.7%)	.2
Era of therapy initiation			.4			.002
Prior to 1997 (pre-cART)	9 (22.5%)	7 (38.9%)		10 (32.3%)	6 (22.2%)	
1997–2001 (early cART)	14 (35%)	5 (27.8%)		4 (12.9%)	15 (55.6%)	
2002–2014	17 (42.5%)	6 (33.3%)		17 (54.8%)	6 (22.2%)	
Documented depression	5 (12.5%)	6 (33.3%)	.08	8 (25.8%)	3 (11.1%)	.2
Baseline characteristics						
Age (years)	54.73 ± 8.3	61.47 ± 10.5	.03	55.10 ± 10.6	57.63 ± 7.7	.3
Years since diagnosis	17.47 ± 8.1	19.88 ± 10.4	.5	16.83 ± 10.1	19.82 ± 6.9	.2
Years on therapy	14.38 ± 6.6	16.37 ± 8.3	.5	13.58 ± 8.2	16.63 ± 5.5	.1
Antiretroviral regimen			.7			.7
NNRTI-based	22 (55%)	8 (44.4%)		17 (54.8%)	13 (48.1%)	
PI-based	6 (15%)	4 (22.2%)		6 (19.4%)	4 (14.8%)	
Other ^d	12 (30%)	6 (33.3%)		8 (25.8%)	10 (37.0%)	
CPE score	8.07 ± 1.2	7.5 ± 1.5	.08	7.87 ± 1.2	7.93 ± 1.4	.9
Nadir CD4+ T cells/mm ³	303 ± 155	246 ± 178	.2	280 ± 175	291 ± 152	.8
Nadir CD4+ % of lymphocytes	17.4 ± 8.4	15.0 ± 8.8	.3	15.6 ± 9.2	17.8 ± 7.7	.3
CD4+ T cell count/mm ³	795 ± 344	691 ± 306	.3	723 ± 377	810 ± 278	.3
CD4+ % of lymphocytes	35.4 ± 8.4	32.6 ± 10.7	.4	33.2 ± 8.9	36.2 ± 9.4	.2
CD4+/CD8+T cell ratio	1.02 ± 0.4	0.93 ± 0.5	.5	0.93 ± 0.5	1.07 ± 0.5	.2
Depression z-score ^e	−0.20 ± 0.80	0.70 ± 1.42	.01	0.22 ± 1.04	0.06 ± 1.15	.6
Anxiety z-score ^e	−0.07 ± 0.52	0.56 ± 1.51	.01	0.08 ± 0.65	0.19 ± 1.27	.7
Stress z-score ^e	−0.10 ± 0.14	−0.15 ± 0.16	.22	−0.11 ± 0.10	−0.12 ± 0.18	.9

Note. Data values are *n* (%) or *M* ± standard deviation. cART = combination antiretroviral therapy; CPE = central nervous system penetration effect; NNRTI = non-nucleoside reverse transcriptase inhibitor; PI = protease inhibitor.

^a An answer is considered “actionable” in the cognitive concerns questionnaire when the response is “yes, definitely” to at least one question.

^b The Montreal Cognitive Assessment is deemed positive for a score < 26.

^c *p* Values are derived from comparisons assessed by Fisher’s exact test or analysis of variance.

^d Includes individuals who were on both PI and NNRTI drugs.

^e Derived from normalized scores of the Depression Anxiety Stress Scales (DASS).

age-adjusted: OR = 5.3, *p* = .003). For both screens, neither antiretroviral regimen nor any of the CD4+ measures were associated with odds of returning an

actionable result, either with or without adjustment for age or treatment era, nor were there significant trends in time over the period considered.

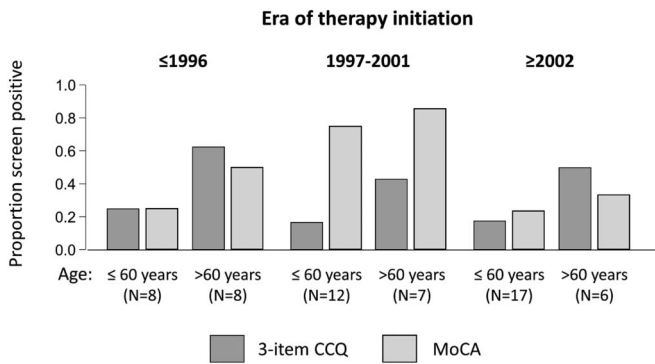


Figure 1. Comparison between the three-item CCQ and the MoCA as indicators of neurocognitive impairment according to era of first treatment and age category (data from baseline scores). CCQ = cognitive concerns questionnaire; MoCA = Montreal Cognitive Assessment.

Prevalence of Psychological Distress and Impact on Neurocognitive Impairment

Psychological distress was notably prevalent in the cohort; observed rates of clinically significant symptoms of depression and anxiety, as profiled by responses to the DASS at study entry were 21% and 15%, respectively. Individuals with an actionable response to the three-item CCQ screening questions were more likely to report greater psychological distress, with higher scores in both the depression and anxiety domains compared with patients with nonactionable responses ($p = .007$ and $p = .02$, respectively). Of the CCQ-actionable responses at baseline, 7/18 (39%) and 4/18 (22%) coincided with DASS scores indicative of clinically significant depression and anxiety, respectively. In contrast to the CCQ, baseline indication of NCI by the MoCA did not associate with higher scores across any of the domains ($p > .5$).

In longitudinal analyses, impact of psychological distress on performance in the CCQ screening test was particularly apparent in younger patients. Notably, increased anxiety and depressive symptomology were associated with having an actionable CCQ screen among patients with ages younger than 60 years ($p = .004$ and $p = .01$, respectively). The impact of mood on MoCA results was less marked; although average scores were moderately lower when patients reported increased anxiety levels ($p = .04$, adjusted for age and era of therapy initiation), there was no significant association between the MoCA scores and depressive symptomology ($p > .6$).

Health-Related Quality of Life Correlations with Psychological Distress and Neurocognitive Impairment

Patient-average HRQL measures across physical health, psychological health, and social health domains were

significantly correlated with the mean self-reported psychological distress scores as measured by the three DASS scales ($p \leq .0001$). Overall HRQL, and particularly general psychological health, was notably reduced in patients reporting the most depressive symptoms ($R = -0.81$ and $R = -0.76$, respectively, $p < .0001$). Increased frequency of self-reported cognitive concerns was also significantly associated with poorer HRQL ($p = .002$), correlating inversely with both the physical and social domains ($R = -0.59$, $p < .0001$, and $R = -0.36$, $p = .005$, respectively). This was in contrast to the MoCA results, which failed to show any significant relationship with HRQL measures.

Discussion

In this study, the three-item self-report questionnaire addressing patients' cognitive concerns, which was recommended by the European AIDS Clinical Society as an initial assessment for HIV-associated NCI, showed poor concordance with performance on the MoCA. The discrepancy between the two screens calls into question the utility of the CCQ as a "procedural" step in the screening for NCI, at least its ability to discriminate early asymptomatic cognitive impairment. Of note, the CCQ indicated that about one third of patients may have subjective memory or other cognitive complaints, but these scores were more closely associated with depression/anxiety and HRQL. In contrast, about two thirds of the cohort had subthreshold (<26) scores with the MoCA screen, a validated instrument for detecting asymptomatic NCI in patients ages 50–60 years (Fazeli et al., 2017), and these results were found to be largely independent of coexisting psychological factors. These findings suggest prevalent and largely asymptomatic NCI in our cohort, notably in patients who commenced therapy in the cART era defined by the years from 1997 to 2001.

The threshold chosen for the MoCA is consistent with the recommended application of the tool as a brief screen for mild cognitive impairment in a geriatric population (Nasreddine et al., 2005) and has subsequently been used in the HIV context (Janssen, Bosch, Koopmans, & Kessels, 2015; Milanini et al., 2014; Simoes & Justino, 2015). This threshold could be considered conservative in comparison with the study of Fazeli et al. (2017) in which a cutoff of ≤ 26 was used; however, the sensitivity observed in their study of 84.2% was balanced by a reduced specificity of 55.8%. Accordingly, while we may have missed some cases of early NCI by the use of the higher cutoff, it is less likely that NCI was incorrectly assigned due to a reduced specificity.

We acknowledge that the NCI observed in some participants cannot be attributed to HIV-related causes alone, because older participants had more consistent associations with both screens. However, it is noteworthy that patients who commenced therapy in the early cART era (1997–2001) were more likely to return an impaired MoCA score than those commencing drugs in pre-cART (prior to 1997) or later cART (after 2001) eras, and this association persisted even after adjusting for age. This finding is not altogether surprising. Although the incidence of HIV-associated dementia has fallen following the introduction of potent combinations, early studies found that neuropsychological deficits remained common, indicating an active and damaging intracerebral process (Cysique, Maruff, & Brew, 2004; Heaton et al., 2010; Sacktor et al., 2002). Later, studies of larger cohorts (Heaton et al., 2011), defined by era of cART (1988–1995 vs. 2000–2007) and disease stage, showed a different pattern of impairment between eras. Our current study delineates these three eras and reflects antiretroviral prescribing practices in our clinical context. Our finding is consistent with the current thinking that latent virus, which is established when infected monocytes and lymphocytes cross the blood brain barrier, activates ongoing systemic inflammation (Deeks et al., 2013). Subsequently, the unique immunological compartment of the CNS shapes host–virus interaction, leading to a differential response to treatment, distinct from the peripheral circulation. This understanding provided a plausible explanation for viremia in cerebrospinal fluid in the context of otherwise suppressive cART (Strain et al., 2005) and led to the development of the antiretroviral CPE ranking scale to guide the selection of regimens protective of the brain (Letendre et al., 2008). The guidelines for starting cART in the late 1990s recommended delaying treatment until the CD4+ T cell count fell to 200 mm³/L; therefore, it is likely that our participants would have established latency in the CNS, which drove systemic inflammation. Furthermore, the recommended first-line regimens at the time included the lowly CPE-ranked nelfinavir and saquinavir, with a backbone of stavudine and didanosine or lamivudine, nucleosides having a neuropenetrance capacity inferior to that of zidovudine and abacavir (Letendre et al., 2008). In contrast, those participants who had received monotherapy before the introduction of cART, and earlier in their disease trajectory, may have benefited from the strong neuroprotective effect of zidovudine.

In addition to prolonged CNS exposure to virus, suboptimal adherence to early cART may also have contributed to the development of NCI (Castillo-

Mancilla et al., 2016). Early combination drug regimens were tissue toxic, particularly affecting mitochondria and metabolic pathways (John, Mallal, & French, 1998), with frequent and multiple adverse side effects, especially gastrointestinal (Mocroft et al., 2001). Our observational study in 2002 (Herrmann et al., 2008) showed that more than 50% of patients reported missed doses in the month prior to their appointment, but by 2008, only 18% of patients in the same cohort reported less than 100% adherence. An alternative explanation is that neurotoxicity was induced by antiretrovirals used in that era (Caniglia et al., 2014; Underwood, Robertson, & Winston, 2015). This theory arose because studies, *in vitro*, showed that intracellular accumulation of toxic proteins arising from proteasome dysfunction, and caused by protease inhibitors, could be a mechanism for cell damage. Equally, it was thought that efavirenz may be neurotoxic, but studies are conflicting (Caniglia et al., 2014; Letendre, Ellis, Ances, & McCutchan, 2010).

Limitations

Firstly, the patient cohort was relatively small and, therefore, may have lacked power to detect associations with T cell measures, and the ability to assess categorical associations of NCI with cardiovascular diseases, metabolic disorders, and history of substance use, as observed by others. However, our observations were able to confirm the findings seen in larger studies in other contexts. Secondly, although our study did not include an HIV-negative control group, our data are enriched by the comprehensive clinical and treatment histories of the participants and continued follow-up over time, which will benefit individual patients and inform future cohort studies. Thirdly, not all participants contributed longitudinal data, and the 16-month study period was too short to assess the stability of the neurocognitive status or the trajectory of any decline in relation to age. Lastly, information on family history of dementia and other risk markers was lacking.

Conclusions

Our study points to the MoCA as a useful screen for detecting early NCI and has found it to be largely unaffected by associated depression or anxiety, whereas reliance on the self-reported CCQ alone appears an inadequate strategy. Addressing psychological distress is a key component of HIV management, and clarifying the potential contribution of depression/anxiety, common in people living with HIV, is necessary when assessing neurocognitive function. Of concern for many patients, is uncertainty about the future and aging in the context of

Key Considerations

- Despite effective treatment, NCI is affecting relatively young individuals, especially those exposed during the early years of cART.
- Nurses can implement simple, reliable, and valid tools in their practices to recognize early neurological deficits that may impact HRQL and medication adherence.
- Assessment of NCI is confounded by complex social and psychological dimensions of living with HIV infection; therefore, self-reported cognitive concerns are inadequate as an assessment of NCI.
- The MoCA is largely unaffected by mood but can be administered contemporaneously with the DASS to address and differentiate impaired neurocognitive functioning from mood disorders as well as support clinical decision-making.
- Monitoring of HRQL on a regular basis, to complement the MoCA and the DASS, can reveal early cues that something is amiss. Nurses are well placed to observe these cues.

HIV infection. We suggest the MoCA be administered with the DASS to discriminate impaired neurocognitive functioning from mood disorders and identify patients who may require further psychological assessment and/or specialist referral. These screening tools are simple and quick to administer in a practice setting, and the immediacy of the feedback may serve to either validate or alleviate patient concerns. Furthermore, this can provide nurses with an opportunity to engage patients in a discussion of lifestyle interventions such as exercise and social engagement. Finally, based on our findings, we recommend monitoring HRQL on a regular basis to complement the MoCA and the DASS and to reveal early cues that something is amiss. This holistic approach is feasible in a community practice setting.

Disclosures

The authors report no real or perceived vested interests related to this article that could be construed as a conflict of interest.

Acknowledgments

The authors would like to thank the patients for their willing participation; Amy Grace, Aminah Rashidi, and Debbie

Norman, who helped with the testing and recruitment of patients; Associate Professor Marie-Josée Brouillette for helpful guidance on use of the MoCA, and Dr. Michelle Byrnes, who advised regarding the selection of tests.

References

- Anand, P., Springer, S. A., Copenhaver, M. M., & Altice, F. L. (2010). Neurocognitive impairment and HIV risk factors: A reciprocal relationship. *AIDS and Behavior, 14*(6), 1213-1226. doi:10.1007/s10461-010-9684-1
- Bloch, M., Kamminga, J., Jayewardene, A., Bailey, M., Carberry, A., Vincent, T., ... Cysique, L. A. (2016). A screening strategy for HIV-associated neurocognitive disorders that accurately identifies patients requiring neurological review. *Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America, 63*(5), 687-693. doi:10.1093/cid/ciw399
- Brew, B. J., & Chan, P. (2014). Update on HIV dementia and HIV-associated neurocognitive disorders. *Current Neurology and Neuroscience Reports, 14*(8). doi:10.1007/s11910-014-0468-2
- Brouillette, M. J., Mayo, N., Fellows, L. K., Lebedeva, E., Higgins, J., Overton, E. T., ... Koski, L. (2014). A better screening tool for HIV-associated neurocognitive disorders: is it what clinicians need? *AIDS, 29*(8), 895-902.
- Caniglia, E. C., Cain, L. E., Justice, A., Tate, J., Logan, R., Sabin, C., ... On behalf of the HIV-CAUSAL Collaboration. (2014). Antiretroviral penetration into the CNS and incidence of AIDS-defining neurologic conditions. *Neurology, 83*(2), 134-141. doi:10.1212/wnl.0000000000000564
- Castillo-Mancilla, J. R., Brown, T. T., Erlandson, K. M., Palella, F. J., Gardner, E. M., Macatangay, B. J. C., ... Wada, N. I. (2016). Suboptimal cART adherence is associated with higher levels of inflammation despite HIV suppression. *Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America, 63*(12), 1661-1667 doi:10.1093/cid/ciw650
- Crawford, J., Cayley, C., Lovibond, P. F., Wilson, P. H., & Hartley, C. (2011). Percentile norms and accompanying interval estimates from an Australian general adult population sample for Self-Report Mood Scales (BAI, BDI, CRS-D, CES-D, DASS, DASS-21, STAI-X, STAI-Y, SRDS, and SRAS). *Australian Psychologist, 46*(1), 3-14. doi:10.1111/j.1742-9544.2010.00003.x
- Cusini, A., Vernazza, P. L., Yerly, S., Decosterd, L. A., Ledergerber, B., Fux, C. A., ... Gunthard, H. F. (2013). Higher CNS penetration-effectiveness of long-term combination antiretroviral therapy is associated with better HIV-1 viral suppression in cerebrospinal fluid. *Journal of Acquired Immune Deficiency Syndromes, 62*(1):28-35 doi: 10.1097/QAI.0b013e318274e2b0
- Cysique, L. A., Maruff, P., & Brew, B. J. (2004). Prevalence and pattern of neuropsychological impairment in human immunodeficiency virus-infected/acquired immunodeficiency syndrome (HIV/AIDS) patients across pre- and post-highly active antiretroviral therapy eras: A combined study of two cohorts. *Journal of NeuroVirology, 10*(6), 350-357. doi:10.1080/13550280490521078
- Deeks, S. G., Lewin, S. R., & Havlir, D. V. (2013). The end of AIDS: HIV infection as a chronic disease. *Lancet, 382*(9903), 1525-1533.
- Duracinsky, M., Lalanne, C., Le Coeur, S., Herrmann, S., Berzins, B., Armstrong, A., ... Chassany, O. (2012). Psychometric validation of the PROQOL-HIV questionnaire, a new health-related quality of life instrument specific to HIV disease. *Journal of Acquired Immune Deficiency Syndromes, 59*(5), 506-515.
- European AIDS Clinical Society (EACS). (2015) *European AIDS Clinical Society Guidelines*. In Lundgren, J., Gatell, J., & Rockstroh, J. (Eds.) (pp. 1-92): European AIDS Clinical Society (EACS).
- Fazeli, P. L., Casaletto, K. B., Paolillo, E., Moore, R. C., Moore, D. J., The Hnrp Group. (2017). Screening for neurocognitive impairment in

- HIV-positive adults aged 50 years and older: Montreal Cognitive Assessment relates to self-reported and clinician-rated everyday functioning. *Journal of Clinical and Experimental Neuropsychology*, 39(9), 842-853. doi:10.1080/13803395.2016.1273319
- Gelman, B. B., Lisinicchia, J. G., Morgello, S., Masliah, E., Commins, D., Achim, C. L., ... Soukup, V. M. (2013). Neurovirological correlation with HIV-associated neurocognitive disorders and encephalitis in a HAART-era cohort. *Journal of the Society of Laparoendoscopic Surgeons*, 62(5), 487-495.
- Heaton, R. K., Clifford, D. B., Franklin, D. R., Woods, S. P., Ake, C., Vaida, F., ... Grant, I. (2010). HIV-associated neurocognitive disorders persist in the era of potent antiretroviral therapy: Charter Study. *Neurology*, 75(23), 2087-2096.
- Heaton, R. K., Franklin, D. R., Ellis, R. J., McCutchan, J. A., Letendre, S. L., Leblanc, S., ... Grant, I. (2011). HIV-associated neurocognitive disorders before and during the era of combination antiretroviral therapy: differences in rates, nature, and predictors. *Journal of NeuroVirology*, 17(1), 3-16. doi:10.1007/s13365-010-0006-1
- Heaton, R. K., Marcotte, T. D., Rivera Mindt, M., Sadek, J., Moore, D. J., Bentley, H., ... Wolfson, T. (2004). The impact of HIV-associated neuropsychological impairment on everyday functioning. *Journal of the International Neuropsychological Society*, 10(3), 317-331.
- Herrmann, S., McKinnon, E., John, M., Hyland, N., Martinez, O., Cain, A., ... Mallal, S. (2008). Evidence-based, multifactorial approach to addressing non-adherence to antiretroviral therapy and improving standards of care. *Internal Medicine Journal*, 38(1), 8-15.
- Janssen, M. A. M., Bosch, M., Koopmans, P. P., & Kessels, R. P. C. (2015). Validity of the Montreal Cognitive Assessment and the HIV Dementia Scale in the assessment of cognitive impairment in HIV-1 infected patients. *Journal of NeuroVirology*, 21(4), 383-390. doi: 10.1007/s13365-015-0324-4
- John, M., Mallal, S., & French, M. (1998). Emerging toxicity of long term anti-retroviral therapy. *Journal of HIV Therapy*, 3(3), 58-63.
- Kamal, S., Locatelli, I., Wandeler, G., Sehat, A., Bugnon, O., Metral, M., ... Schneider, M. P. (2017). The presence of Human Immunodeficiency Virus-associated neurocognitive disorders is associated with a lower adherence to combined antiretroviral treatment. *Open Forum Infectious Diseases*, 4(2), ofx070. doi:10.1093/ofid/ofx070
- Letendre, S. L., Ellis, R. J., Ances, B. M., & McCutchan, J. A. (2010). Neurologic complications of HIV. *Topics in HIV Medicine*, 18(2), 45-55.
- Letendre, S., Marquie-Beck, J., Capparelli, E., Best, B., Clifford, D., Collier, A. C., ... Ellis, R. J. (2008). Validation of the CNS penetration-effectiveness rank for quantifying antiretroviral penetration into the central nervous system. *Archives of Neurology*, 65(1), 65-70.
- Lovibond, S. H., & Lovibond, P. F. (1995). *Manual for the Depression Anxiety Stress Scales* (2nd ed.). Sydney, Australia: Psychology Foundation.
- Milanini, B., Wendelken, L. A., Esmaili-Firidouni, P., Chartier, M., Crouch, P. C., & Valcour, V. (2014). The Montreal Cognitive Assessment to screen for cognitive impairment in HIV patients older than 60 years. *Journal of Acquired Immune Deficiency Syndromes*, 67(1), 67-70. doi:10.1097/QAI.0000000000000220
- Mocroft, A., Youle, M., Moore, A., Sabin, C. A., Madge, S., Lepri, A. C., ... Phillips, A. N. (2001). Reasons for modification and discontinuation of antiretrovirals: results from a single treatment centre. *AIDS*, 15(2), 185-194.
- Nasreddine, Z., Phillips, N., Bédirian, V., Charbonneau, S., Whitehead, V., Collin, I., ... Chertkow, H. (2005). The Montreal Cognitive Assessment, MoCA: A brief screening tool for mild cognitive impairment. *Journal of the American Geriatrics Society*, 53(4), 695-699.
- Power, C., Selnes, O. A., Grim, J. A., & McArthur, J. C. (1995). HIV Dementia Scale: a rapid screening test. *Journal of Acquired Immune Deficiency Syndromes Human Retrovirology*, 8(3), 273-278.
- Sacktor, N., McDermott, M. P., Marder, K., Schifitto, G., Selnes, O. A., McArthur, J. C., ... Epstein, L. (2002). HIV-associated cognitive impairment before and after the advent of combination therapy. *Journal of NeuroVirology*, 8(2), 136-142.
- Schouten, J., Cinque, P., Gisslen, M., Reiss, P., Portegies, P. (2011) HIV-1 infection and cognitive impairment in the cART era: a review. *AIDS*, 25(5), 561-575.
- Simoes, E., & Justino, J. D. (2015). HIV-associated neurocognitive disorders: A review for NPs. *Nurse Practitioner*, 40(7), 1-7. doi: 10.1097/01.npr.0000466501.42049.99
- Spitzer, R. L., & Fleiss, J. L. (1974). A re-analysis of the reliability of psychiatric diagnosis. *British Journal of Psychiatry*, 125, 341-347.
- Strain, M. C., Letendre, S., Pillai, S. K., Russell, T., Ignacio, C. C., Günthard, H. F., ... Wong, J. K. (2005). Genetic composition of human immunodeficiency virus type 1 in cerebrospinal fluid and blood without treatment and during failing antiretroviral therapy. *Journal of Virology*, 79(3), 1772-1788. doi:10.1128/JVI.79.3.1772-1788.2005
- Tedaldi, E. M., Minniti, N. L., & Fischer, T. (2015). HIV-Associated neurocognitive disorders: The relationship of HIV Infection with physical and social comorbidities. *BioMed Research International*. Retrieved from <http://dx.doi.org/10.1155/2015/641913>
- Underwood, J., Robertson, K. R., & Winston, A. (2015). Could antiretroviral neurotoxicity play a role in the pathogenesis of cognitive impairment in treated HIV disease? *AIDS*, 29(3), 253-261. doi: 10.1097/qad.0000000000000538
- Zipursky, A. R., Gogolishvili, D., Rueda, S., Brunetta, J., Carvalhal, A., McCombe, J. A., ... Rourke, S. B. (2013). Evaluation of brief screening tools for neurocognitive impairment in HIV/AIDS: a systematic review of the literature. *AIDS*, 27(15), 2385-2401. doi:10.1097/QAD.0b013e328363bf56