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Self-reported difficulties with everyday function, cognitive symptoms and cognitive function in people with HIV

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Running title: Self-reported symptoms and cognitive function in HIV

Background: We determined factors associated with self-reported decline in activities of daily living (ADLs) and symptoms of cognitive impairment in HIV positive (HIV+) adults in five European clinics.

Methods: HIV+ adults underwent computerized and pen-and-paper neuropsychological tests and questionnaires of cognitive symptoms and ADLs. We considered cognitive function in five domains, psychosocial factors and clinical parameters as potentially associated with symptoms. Separate regression analyses were used to determine factors associated with decline in ADL (defined as self-reported decline affecting ≥2 ADLs and attributed to cognitive difficulties) and self-reported frequency of symptoms of cognitive impairment. We also estimated the diagnostic accuracy of both questionnaires as tests for cognitive impairment.

Results: 448 patients completed the assessments (mean age 45.8 years, 84% male, 87% white, median CD4 count 550 cells/mm^3, median time since HIV diagnosis 9.9 years, 81% virologically suppressed [HIV-1 plasma RNA <50 copies/mL]). Ninety-six (21.4%) reported decline in ADLs and attributed this to cognitive difficulties. Self-reported decline in ADLs and increased symptoms of cognitive impairment were both associated with worse performance on some cognitive tests. There were also strong associations with financial difficulties, depressive and anxiety symptoms, unemployment, and longer time since HIV diagnosis. Both questionnaires performed poorly as diagnostic tests for cognitive impairment.

Conclusion: Patients' own assessments of everyday function and symptoms were associated with objectively-measured cognitive function. However, there were strong associations with other psychosocial issues including mood and anxiety disorders and socioeconomic hardship. This should be considered when assessing HIV-associated cognitive impairment in clinical care or research studies.

Key words: HIV; HIV dementia; neuropsychological assessment; MCI (mild cognitive impairment); activities of daily living.

INTRODUCTION

Several studies have reported high prevalence of cognitive impairment in HIV+ patients, with the highest estimates exceeding 50%.[1, 2] However, a large proportion of individuals scoring below specified thresholds on cognitive testing and meeting the criteria for HIV-associated neurocognitive disorder (HAND) have no interference with everyday functioning, and are categorised as having Asymptomatic Neurocognitive Impairment (ANI) by the Frascati criteria.[3] Others have used participant self-report methods such as the modified Lawton & Brody Instrumental Activities of Daily Living Scale (IADLS) to discriminate Mild Neurocognitive Disorder (MND) from ANI.[2, 4-6] Deterioriation, if defined as a change from ANI to MND, is based solely on the assessment of difficulties with activities of daily living (ADL), therefore discerning this change is highly important. Functional decline and cognitive symptoms may also be the main driver of patients coming to clinicians' attention in clinical settings.

Some studies have suggested limited validity of patient self-report with commonly-used questionnaires when used to predict objectively-measured cognitive function.[7-10] But even if symptoms are only weakly correlated with cognitive impairment, they are in some sense highly important to the patient. There are likely to be psychological and other factors underlying reported symptoms, and understanding these factors may steer the clinician away from investigations such as brain imaging and lumbar puncture and towards the patients' more pertinent needs. In this analysis, we aimed to measure the strength of association between self-reported decline in ADL, self-reported symptoms of cognitive impairment, and objectively-measured cognitive function. We then sought to determine which other factors were associated with these symptoms of cognitive difficulties.

Methods

Participants

CIPHER is a European study of cognitive function in HIV+ adult outpatients (two clinics in London, UK; one clinic in each of: Copenhagen, Denmark; Minsk, Belarus; Rome, Italy). We recently reported, along with detailed psychosocial and clinical cofactors, a 35% prevalence of cognitive impairment, of whom more than half met Frascati criteria for ANI and a quarter had confounding conditions, with the remaining 6% having MND or HAD.[11] Participants were recruited opportunistically from May 2011 to January 2013 regardless of symptoms, treatment and comorbidities. All questionnaires were self-completed in a written format by the participant in the local language, and participants had to be sufficiently cognitively intact to complete study procedures.

Ethical approval

The study was approved by the UK National Research Ethics Service – London Hampstead Committee (11/LO/0077), De Videnskabsetiske Komiteér for Region Hovedstaden (H-4-2011-105), the Ethics Committee of the Minsk Municipal Infectious Diseases Hospital (04/2011), and the Comitato Etico of Istituto Nazionale Malattie Infettive (66/2011). All study participants gave written informed consent prior to commencing the study.

Assessment of symptoms and self-reported function

Declining function in ADLs was measured using the Modified Lawton & Brody IADLS, which required participants to indicate their current and, retrospectively, their "best ever" level of function on sixteen activities, according to a 3- or 4-point scale (see Supplemental Digital Content 1). Where their current level was worse than their best ever level, participants recorded the perceived cause as "primarily cognitive problems", "primarily physical problems",

or “equally cognitive and physical problems”. The questionnaire has been used in large published studies of HAND.[2, 12, 13]

Symptoms of cognitive impairment were elicited using four questions from the Medical Outcomes Study in HIV (MOS-HIV)[14] (see Supplemental Digital Content 2). Participants were asked to indicate how much of the time in the past four weeks they had experienced difficulty reasoning and solving problems, forgetfulness, trouble keeping their attention, and difficulty in concentration. Possible responses were scored: 0, none of the time; 1, a little bit of the time; 2, some of the time; 3, a good bit of the time; 4, most of the time; 5, all of the time. Adding the four responses gave a total score of 0-20.

Participants completed the 9-item Patient Health Questionnaire (PHQ-9) for depression [15] and the 7-item Generalized Anxiety Disorder questionnaire (GAD-7) for anxiety.[16] These questionnaires elicit symptom frequency in the past two weeks: 0, not at all; 1, several days; 2, more than half the days; 3, nearly every day. PHQ-9 scores ranged from 0-27 and were graded: 0-4, none/minimal; 5-9, mild; 10-14, moderate; 15-19, moderate-severe; 20-27, severe. GAD-7 scores ranged from 0-21 and were graded: 0-4, none/minimal; 5-9, mild; 10-14, moderate; 15-21, severe.

Cognitive testing

The study used Cogstate, software adapted from standard NP tasks for assessment of multiple cognitive domains (http://cogstate.com/academic-2/measurement-of-cognition),[17-19] and two pen-and-paper NP tests. Cogstate is mainly non-language-based and the stimuli vary randomly between assessments, reducing the influence of cultural, educational, and practice effects. Several studies have used Cogstate in HIV+ patients in Anglophone countries,[20-26] with work demonstrating good construct validity and correlation with traditional pen-and-paper NP batteries,[21-23] and the method has been used in children and adults in diverse settings in Africa

and Asia [27-29] (although not in all countries where CIPHER was based). Ten tests were organized into five domains: psychomotor speed (Detection and Identification); verbal memory (Shopping List learning and recall); executive function (Groton Maze learning and recall; these tests also assess visuospatial learning and memory); working memory (One-Back speed and accuracy); verbal fluency (two pen-and-paper tests: Controlled Oral Word Association Test [COWAT] and Category Fluency Test [CFT]). Testing included a full practice run (not scored) on the same day as the main assessment.[30]

Each cognitive test was converted to an age-, sex-, and education-standardized *Z*-score using normative means and SD. Normative general population data for the computerized tests were provided by Cogstate from Europe, United States of America, South East Asia and Australia/New Zealand, frequency-matched for age (18-34, 35-50, and 51+ years; minimum cell size n=145), sex (157 female, 377 male), and education (university/further education, n=243, or secondary school, n=291). The normative population excluded individuals with clinical or functional impediments to test performance, and subsets of this data had been used previously to measure cognitive function in HIV+ adults.[20-22, 24, 26] Published norms were used for the COWAT and CFT.[31, 32] A continuous measure of neurocognitive function was calculated from the mean of all five domain Z scores (NPZ-5).

Other data collection

Drug and alcohol use, educational attainment and socioeconomic information were obtained from self-report. Medical and psychiatric history were obtained from both patient report and clinical notes. Clinical information included current HIV viral load (VL), CD4 count, ART history, HIV-related complications, laboratory markers, and neurological and psychiatric comorbidities. Hepatitis C (HCV) status was defined as the most recent HCV RNA assay, or the most recent antibody result in the absence of an RNA result. Participants with any of a pre-specified list of comorbid conditions (published as an appendix to the original criteria[3]) – including depressive

disorders, historical traumatic brain injury, developmental disabilities, alcohol and substance use disorders, certain HIV-related and non-HIV-related neurologic conditions, and systemic disease likely to affect cognition – were noted. We adopted the nomenclature used by the CHARTER group, where contributing conditions were those with potential for mild cognitive impairment, while confounding conditions were those likely to have a substantial effect on cognitive function.[2]

Statistical analyses

The first outcome measure was defined, using the IADLS, as self-reported decline in two or more ADLs out of the possible sixteen (designated "functionally dependent" by Obermeit *et al* [7]) *and* attribution to cognitive problems by the participant. In order to harmonize our results with Obermeit and others, we included ADLs that had been omitted in our previous analysis,[11] namely planning social activities, reading / watching television, and childcare. The associations of age, sex, ethnic group (white versus other ethnic groups), study site, educational attainment (as ordered categories of primary, secondary and higher education), employment status (as a categorical variable of in employment, unable to work, or unemployed for other reasons), cognitive function (as a continuous variable by domain and as a mean score), clinical data and psychosocial variables were estimated by odds ratios (OR) and 95% confidence intervals (CI). All cognitive function scores and factors found to be at least moderately associated with the outcome (at a threshold of $p<0.1$) were included in separate logistic regression models with adjustment for demographic variables (age, sex, ethnic group, study site and education). Education, site and ethnicity have been identified as factors associated with cognitive test scores in an earlier analysis of the same study sample.[11]

The second outcome measure was symptom score from the MOS-HIV questionnaire in five ordered categories. The base category was defined as asymptomatic (0 points on the questionnaire) and subsequent categories corresponded to four quartiles of the remaining values. Ordered logistic regression was used to calculate ORs and CI for each factor in the same way as the ADL decline outcome measure. The ordered logistic model assumes the same effect size for each unit increase in the outcome. Multivariable regression models were also constructed for factors with $p<0.1$ in the bivariate analyses, adjusted for demographic variables, in the same way as the first outcome measure.

Finally, we assessed the possible application of the IADLS and MOS-HIV symptom questionnaires as a diagnostic or screening tools for cognitive impairment. Two reference standards were employed, defined as low performance in two or more cognitive domains to a level of $Z \leq -1$ (mild cognitive impairment) or $Z \leq -2$ (severe cognitive impairment). Receiver operator curves (ROC) were generated from sensitivity and specificity statistics for all possible thresholds on each scale (number of ADLs of difficulty when attributed by the patient to cognitive problems, and MOS-HIV cognitive symptom score). Test accuracy statistics (positive and negative likelihood ratios [LR] and diagnostic odds ratios [DOR]) were calculated.

RESULTS

Study population

Of 486 patients recruited, 448 (92%) completed all cognitive assessments (London, 292 [65%]; Rome 90 [20%]; Copenhagen 42 [9.4%]; Minsk 24 [5.4%]), 15 participants only completed the practice assessment and 23 completed fewer than five cognitive domains. The sample was 87% white, 84% male, mean 45.8 years of age (SD 9.6), 89% on ART and 81% with VL <50 copies/mL. Participant characteristics are shown in Table 1 (breakdown by study site has already been published[11]).

Factors associated with self-reported decline in Activities of Daily Living

Self-reported functional decline in two or more ADLs was present in 138 participants (30.8%). This was attributed to cognitive problems, with or without physical problems, by 96 (69.6% of those reporting decline). The most frequent difficulties were socializing, work and housekeeping, affecting 55-72% of functionally impaired patients and 5-15% of patients with fewer than two areas of difficulty (Figure 1). Information on specific ADLs was not available for participants at the Italian site (n=90), and 134 of the remainder (37.4%) left the childcare item blank or responded "I do not have children"; these individuals were assumed not to have declined in this activity.

Several factors were associated with self-reported decline in ADLs attributed to cognitive impairment (Table 2). In models adjusted for age, sex, ethnic group, education and study site, a decline in ADLs was associated with speed / reaction time (aOR 0.68 per Z +1, 95% CI 0.55-0.83) and attention / working memory (aOR 0.57 per Z +1, 95% CI 0.42-0.78). Other associated factors were: ability to afford basic needs most of the time (aOR 2.71, 95% CI 1.52-4.80) or some of the time (aOR 4.44, 95% CI 2.01-9.81) compared to those who were always able to afford basic needs; being unable to work (aOR 3.99, 95% CI 1.94-8.22) or unemployed for other reasons (aOR 2.21, 95% CI 1.26-3.86) compared to those in employment; depressive symptoms (aOR 2.06 per grade on the PHQ-9 scale, 95% CI 1.66-2.55); anxiety symptoms (aOR 2.20 per grade on the GAD-7 scale, 95% CI 1.69-2.88); and HIV diagnosis 5-10 years ago (aOR 3.18, 95% CI 1.42-7.13) or ≥10 years ago (aOR 3.62, 95% CI 1.62-8.09).

To explore the interdependence of the effects of mood, cognition and functional abilities, we analyzed whether adjusting for relevant cognitive domains would change the association between PHQ-9 grade and self-reported decline in ADLs. The effect after including the speed domain was an adjusted odds ratio of 1.95 (95% CI 1.58-2.41), and the effect after including

attention and working memory was an aOR if 1.96 (95% CI 1.59-2.42), similar to the results of the simpler model. Additionally, there was no evidence of an interaction between depression and functional decline in their effects on the speed domain (p=0.37) or on the attention / working memory domain (p=0.84).

Factors associated with self-reported symptoms of cognitive impairment

MOS-HIV scores were available for 440 participants, with a median score of 4 (IQR 1-8). Numbers in each of the five ordered categories were: 86 asymptomatic (0 points, 19.6%); 115 with grade 1 (1-3 points, 26.1%); 70 with grade 2 (4-5 points, 15.9%); 85 with grade 3 (6-9 points, 19.3%); 84 with grade 4 (10-20 points, 19.1%). In multivariable ordered logistic regression models adjusted for age, sex, ethnic group, education and study site, increasing grade of symptom frequency was associated with impairment of speed / reaction time (aOR 0.68 per +1 in Z score, 95% CI 0.58-0.80), attention / working memory (aOR 0.60, 95% CI 0.47-0.77), verbal memory (aOR 0.87, 95% CI 0.77-0.98) and verbal fluency (aOR 0.84, 95% CI 0.71-1.00). Other associated factors were: being educated to only primary school level, compared to completing higher education (aOR 1.89, 95% CI 1.17-3.05); confounding (aOR 2.07, 95% CI 1.31-3.27) or contributing medical conditions (aOR 2.02, 95% CI 1.22-3.36); ability to afford basic needs most of the time (aOR 1.91, 95% CI 1.25-2.90), some of the time (aOR 3.56, 95% CI 1.86-6.82) or not at all (aOR 3.80, 95% CI 1.85-7.81); being unable to work (aOR 4.68, 95% CI 2.55-8.59) or unemployed for other reasons (aOR 2.11, 95% CI 1.41-3.14) compared to those in employment; depressive symptoms (aOR 2.75 per grade on the PHQ-9, 95% CI 2.28-3.32); anxiety symptoms (aOR 3.24 per grade on the GAD-7, 95% CI 2.58-4.07); and ≥10 years since HIV diagnosis (aOR 1.82, 95% CI 1.12-2.97).

Accuracy of the questionnaires as tests for cognitive impairment

After excluding participants with incomplete data, the IADLS had sensitivity 40%, specificity 78% when used as a test for severe cognitive impairment (prevalence 30/356, 8.4%) with a cut-off of decline in ≥ 2 ADLs (Figure 3). There were 12 true positives, 253 true negatives, 73 false positives and 18 false negatives, equating to positive LR 1.79, negative LR 0.77 and DOR 2.31. The questionnaire had worse sensitivity and better specificity when used with a cut-off of a higher number of ADLs, and LRs and DORs were consistently poor (close to 1).

The most balanced trade-off between sensitivity and specificity on the MOS-HIV symptom scale was at a cut-off of ≥7 points, giving sensitivity 48%, specificity 69% as a test for severe cognitive impairment (prevalence 48/440, 10.9%). There were 23 true positives, 271 true negatives, 121 false positives and 25 false negatives, giving positive LR 1.55, negative LR 0.75 and DOR 2.06. The questionnaire had better accuracy overall at higher cut-offs at the expense of poor sensitivity (high false negative rates). At lower cut-offs in the range of 2-5 points, sensitivity was improved at 50-73% but specificity was markedly down at 27-57% and both positive LR and DOR were consistently <2.

Both questionnaires were, in general, less sensitive and less specific when compared to a reference standard of mild cognitive impairment. We conducted exploratory analyses with exclusion of the most severely anxious or depressed participants, and this made no improvement to the diagnostic accuracy statistics for either outcome measure (IADLS or MOS-HIV score).

DISCUSSION

In this study of HIV+ outpatients at five clinics in Europe, 80% reported cognitive symptoms in the past four weeks, and just over 20% reported decline in their ADLs and attributed this to cognitive impairment. There were associations between poorer cognitive function (especially reaction time, speed and attention) and both self-reported decline in ADLs and increasing frequency of cognitive symptoms. However, symptoms of depression and anxiety, longer time since HIV diagnosis, unemployment, and difficulty affording basic needs were also strongly associated with cognition-related symptoms and functional decline. Additionally, lower educational attainment and comorbid medical conditions were associated with cognitive symptoms. All of our observed associations may have multiple explanations, and causality could be in either direction (particularly in the relationships between employment and financial means and the outcomes of interest). The accuracy of both questionnaires, modelled as diagnostic tests for cognitive impairment, was relatively poor and below a level likely to be acceptable for individual patient use.

These results imply that patients who report symptoms of cognitive impairment, or declining everyday function, should be assessed for depression, anxiety, concomitant medical conditions and financial difficulties. Failure to recognize these important elements of patients' lived experiences risks diagnostic delay, failure to address important needs, unnecessary investigations and further anxiety. This is similar to the conclusions of a large cohort study of HIV-negative older adults in Amsterdam: "when an older person complains about his or her memory and does not show actual cognitive impairment or cognitive decline, one should be aware that these complaints might reflect psycho-affective or health problems. Adequate intervention in these psycho-affective or health problems may improve quality of life".[33]

The relationships between cognitive impairment, low mood, and functional decline are complex and multidirectional. Secondary analyses suggested the effects of mood and cognition on everyday function were relatively independent, although we cannot exclude other explanations. In our recently-published report of the same study population, we showed that severe depressive symptoms were associated with cognitive impairment, particularly on timed tests.[11] A controlled intervention to improve patients' depression or anxiety symptoms might tease out the effect of low of mood on subjective and objective cognitive outcomes.

Limitations to CIPHER study methodology and Cogstate in general have been discussed in earlier reports [11, 25] but some deserve further mention here. Notably, selection biases may have arisen as a result of our opportunistic sampling strategy, with patients choosing to participate in the study on the basis of their own concerns and self-perceived cognitive symptoms. Also, the largely computerized neuropsychological methods did not provide as comprehensive an assessment as traditional assessment conducted by a neuropsychologist. Importantly, the lack of HIV-negative controls prevents us from determining whether our findings are specific to PLWH. However, there is a body of literature from the general population concluding that psychological and psychiatric factors are as important as cognitive function to subjective memory complaints. In their conceptual framework for research into subjective cognitive decline (SCD) in pre-clinical Alzheimer's disease, Jessen *et al* note that mood- and anxiety-related symptoms may be both a confounder of the relationship between SCD and subsequent dementia and an early symptom of dementia.[34] An analogous situation might be at work in HIV-related cognitive impairment.

Despite initially positive results with a three-question symptom tool [1] and the MOS-HIV cognitive questions,[35] several studies have reported poor test accuracy of ADL and cognitive symptom scales in HIV+ patients.[7-10] In 290 PLWH over 50 years in Great Britain and Ireland and 97 seronegative controls, other patient-reported outcome measures, including depression,

falls, sexual function and general health, correlated poorly with cognitive impairment.[8] Thames *et al* divided 107 HIV positive patients into 4 groups, on the basis of whether they were impaired or unimpaired, and whether they were accurate or inaccurate in their self-assessment of this. Notably, only 38% were accurate, 33% were impaired but did not report a decline, and 25% reported a decline but did not have cognitive impairment.[36] In similar studies, it was reported that only 33% [37] and 37% [38] of patients gave answers to symptom questions that concurred with their objective cognitive test scores. In an analysis of CNS HIV Anti-Retroviral Therapy Effects Research (CHARTER) cohort patients (n=277) in the United States, impaired everyday function was associated with depression, unemployment, findings on neuromedical examination and physician-assigned Karnofsky score. While patients were able to rate their own overall level of ability they were poor at correctly attributing their difficulties to cognitive versus physical problems.[7]

Patients' symptoms are important because they guide clinical decisions, but clearly there are reasons other than neurological disease why patients and study participants may report symptoms. First, PLWH may have psychiatric problems, excessive substance use, or some other reversible cause for their symptoms. Second, depression or anxiety may cause them to perceive a functional decline that is not present. Third, they may be hypervigilant for symptoms or worried about normal everyday experiences, although not suffering from any psychiatric disorder. Fourth, there may be desirability bias: they say what they think the clinician or researcher wants to hear. Fifth, there may be secondary gain as a result of misreporting their symptoms. And sixth, the measuring instruments may lack construct validity and fail to measure what they purport to measure.

Differentiation of asymptomatic from symptomatic HAND relies solely on estimating daily function at ADL, and most published research in this area relies predominantly on participants' self-report. There are limited data on more accurate and reliable measures of everyday performance, such as third-party observation or performance-based measures.[12, 13] This has crucial implications for the interpretation of longitudinal studies in which the risk of change from ANI to MND is measured, such as the United States CHARTER cohort,[39] the Canadian OHTN Cohort,[6] and the French Aquitaine cohort.[40] For example, in the Ottawa cohort, depression was a major risk factor for change from ANI to MND.[6] Since self-reported functional impairment is associated with depression, change from ANI to MND does not always indicate decline in neurocognitive abilities. Nor should change from ANI to MND in longitudinal studies be viewed as progressive, unidirectional deterioration (as is implied by the use of Kaplan-Meier plot analyses). The CHARTER cohort used a more robust method of both self-reported and performance-based assessments to discriminate ANI from MND.[39] These issues should be taken into consideration in the design and analysis of future HAND cohort studies.

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All authors contributed to the conception, conduct and analysis of the study, and have written and reviewed the final manuscript. Statistical analyses were conducted by LH, MD and FL.

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FIGURE LEGENDS

Figure 1. Proportion of patients reporting decline in specific activities of daily living who were functionally impaired (n=117) or not functionally impaired (n=241).

Figure 2. Receiver-operator curves showing sensitivity and specificity of (left) number of Activities of Daily Living affected and (right) symptom frequency score as tests for mild (dashed line) or severe (solid line) cognitive impairment. The dotted diagonal line shows the line of no diagnostic information.

Table 1. Characteristics of HIV Positive Study Participants (N=448).

	***n*/N**	**%**	**Mean (SD) or median (IQR)**
Age, years			45.8 (9.6)
Male sex	378/448	84.4	
MSM	306/429	71.3	
White ethnicity	389/440	88.4	
Migrant *	118/429	27.5	
Can always afford basic needs	247/429	57.6	
Educational attainment:			
University or other higher education	249/429	58.0	
Secondary school	101/429	23.5	
Primary school	79/429	18.4	
Employment status:			
In employment	255/421	60.6	
Unable to work	43/421	10.2	
Other reasons for unemployment	123/421	29.2	
Recent psychoactive drug use †	132/448	29.5	
Any previous IDU	40/448	8.9	
Problem drinking ‡	167/428	39.0	
Major depressive symptoms §	111/436	25.5	
Major anxiety symptoms §	87/435	20.0	
Latest CD4 count, cells/μL			550 (410, 750)
Nadir CD4 count, cells/μL			290 (160, 500)
Years since positive HIV result			9.9 (4.8, 16.2)
On ART	400/448	89.3	

HIV RNA <50 copies/mL	363/448	81.0
HCV ‖	64/441	14.5

* Defined as those not born in the country of assessment.

† Defined as self-reported consumption of amphetamines (including methamphetamine), cocaine, cannabis, opiates for non-medicinal use, ketamine, gamma-hydroxybutyrate, gamma-butyrolactone, psychedelics or mephedrone in the past 3 months.

‡ Defined by the modified (two-question) AUDIT-C questionnaire: a positive score was ≥4 points for men or ≥3 points for women.

§ Defined as ≥10 points on the PHQ-9 (depression) or GAD-7 (anxiety) scale.

‖ Defined as the most recent HCV RNA assay, or the most recent antibody result in the absence an RNA result.

ART, anti-retroviral therapy; HCV, hepatitis C virus; IDU, intravenous drug use; IQR, inter-quartile range; MSM, men who have sex with men; SD, standard deviation.

Table 2. Factors Associated with Self-Reported Decline in ADL Attributed to Cognitive Impairment.

	Unadjusted OR (95% CI)	***P***	**Adjusted OR (95% CI) ***	***P***
Age per +10 years	1.09 (0.86-1.38)	0.49	0.96 (0.73-1.26)	0.78
Gender and sexual orientation				
MSM	1		1	
Other men	1.25 (0.70-2.26)		1.66 (0.75-3.71)	
Women	0.52 (0.24-1.09)	0.13	0.93 (0.40-2.16)	0.39
Ethnic group				
White	1		1	
Other or not known	2.11 (1.17-3.83)	0.014	1.21 (0.59-2.48)	0.60
Education ‡				
University / higher	1		1	
Secondary	0.80 (0.44-1.47)		0.92 (0.48-1.78)	
Primary only	1.53 (0.85-2.73)	0.27	1.41 (0.76-2.62)	0.35
Employment status				
In employment	1		1	
Unable to work	5.47 (2.72-10.98)		3.99 (1.94-8.22)	
Other	2.36 (1.43-3.92)	<0.0001	2.21 (1.26-3.86)	0.0003
Site				
London	1		1	
Rome	0.36 (0.18-0.72)		0.33 (0.15-0.71)	
Copenhagen	0.20 (0.06-0.67)		0.23 (0.07-0.76)	
Minsk	0.11 (0.02-0.85)	0.0004	0.11 (0.01-0.92)	0.002

Mean Z (all domains) per +1 SD	0.76 (0.61-0.96)	0.019	0.70 (0.54-0.91)	0.009
Speed Z per +1 SD	0.75 (0.63-0.90)	0.002	0.68 (0.55-0.83)	<0.0005
Attention / working memory Z per +1 SD	0.68 (0.51-0.90)	0.006	0.57 (0.42-0.78)	<0.0005
Executive function Z per +1 SD	0.96 (0.88-1.05)	0.41	0.97 (0.88-1.07)	0.56
Verbal memory Z per +1 SD	0.92 (0.81-1.06)	0.26	0.90 (0.77-1.06)	0.22
Verbal fluency Z per +1 SD	0.87 (0.70-1.08)	0.21	0.87 (0.69-1.10)	0.24
Confounding co-morbid condition †				
No	1		1	
Yes	1.86 (1.09-0.51)	0.024	1.61 (0.91-2.84)	0.10
Contributing co-morbid condition †				
No	1			
Yes	1.57 (0.86-2.87)	0.14		
Can afford basic needs ‡				
Always	1		1	
Most of the time	2.64 (1.53-4.56)		2.71 (1.52-4.80)	
Some of the time	4.05 (1.93-8.51)		4.44 (2.01-9.81)	
No	2.47 (1.01-6.03)	0.0002	2.40 (0.94-6.11)	0.0003
Recreational psychoactive drugs in past 3 months				
No	1			

Yes	1.42 (0.88-2.29)	0.15		
Problem drinking §				
No	1			
Yes	1.41 (0.88-2.25)	0.15		
Depressive symptoms per grade ‡ ‖	2.11 (1.73-2.57)	<0.0005	2.06 (1.66-2.55)	<0.0005
Anxiety symptoms per grade ‡ ‖	1.98 (1.57-2.50)	<0.0005	2.20 (1.69-2.88)	<0.0005
Hepatitis C status ‡ ¶				
Negative	1			
Positive	1.63 (0.89-2.97)	0.11		
ART and VL status				
VL <50 on ART	1			
Detectable on ART	1.81 (0.87-3.77)			
Off ART	0.76 (0.34-1.68)	0.19		
Current CD4 count per +100 cells/mm^3	0.99 (0.91-1.09)	0.88		
Nadir CD4 count per +100 cells/mm^3	1.00 (0.91-1.09)	0.94		
Time since HIV diagnosis				
<5 years	1		1	
5-10 years	4.09 (1.90-8.77)		3.18 (1.42-7.13)	
≥10 years	3.36 (1.64-6.90)	0.001	3.62 (1.62-8.09)	0.005
Previous AIDS				
No	1			
Non-CNS	0.93 (0.49-1.77)			
CNS conditions	1.57 (0.40-6.22)	0.79		

* Adjusted models include age, sex, education, ethnic group and study site.

† Confounding and contributing medical conditions as defined by the Frascati criteria [3] and CHARTER cohort analysis.[2]

‡ Excludes missing data.

§ Defined by the modified (two-question) AUDIT-C questionnaire: a positive score was ≥4 points for men or ≥3 points for women.

‖ Depression (PHQ-9) grades were: 0-4, none/minimal; 5-9, mild; 10-14, moderate; 15-19, moderate-severe; 20-27, severe. Anxiety (GAD-7) grades were: 0-4, none/minimal; 5-9, mild; 10-14, moderate; 15-21, severe.

¶ Defined as the most recent HCV RNA assay, or the most recent antibody result in the absence an RNA result.

ART, antiretroviral therapy; CI, confidence interval; CNS, central nervous system; GAD-7, generalised anxiety disorder 7-item scale; MSM, men who have sex with men; OR, odds ratio; PHQ-9, patient health questionnaire 9-item scale; SD, standard deviation.

Table 3. Factors Associated with Frequency of Symptoms of Neurocognitive Impairment.

	Crude OR (95% CI)	***P***	**Adjusted OR (95% CI) ***	***P***
Age per +10 years	0.96 (0.81-1.13)	0.59	0.93 (0.77-1.12)	0.43
Gender and sexual orientation				
MSM	1		1	
Other men	1.14 (0.72-1.81)		1.23 (0.69-2.19)	
Women	1.12 (0.70-1.79)	0.79	1.75 (0.98-3.12)	0.16
Ethnic group				
White	1		1	
Other or not known	1.67 (1.00-2.77)	0.048	1.15 (0.65-2.02)	0.64
Education				
University / higher	1		1	
Secondary	1.22 (0.81-1.84)		1.25 (0.80-1.95)	
Primary only	1.77 (1.12-2.80)	0.016	1.89 (1.17-3.05)	0.010
Employment status				
In employment	1		1	
Unable to work	5.60 (3.12-10.1)		4.68 (2.55-8.59)	
Other	2.12 (1.47-3.08)	<0.0001	2.11 (1.41-3.14)	<0.0001
Site				
London	1		1	
Rome	0.47 (0.30-0.72)		0.38 (0.23-0.62)	
Copenhagen	0.36 (0.20-0.65)		0.41 (0.23-0.76)	
Minsk	0.54 (0.26-1.15)	0.0001	0.44 (0.18-1.10)	0.0002

Mean Z (all domains) per +1 SD	0.78 (0.65-0.92)	0.005	0.71 (0.58-0.87)	0.001
Speed Z per +1 SD	0.71 (0.62-0.82)	<0.0005	0.68 (0.58-0.80)	<0.0005
Attention / working memory Z per +1 SD	0.67 (0.54-0.84)	<0.0005	0.60 (0.47-0.77)	<0.0005
Executive function Z per +1 SD	0.99 (0.92-1.06)	0.73	0.99 (0.92-1.07)	0.86
Verbal memory Z per +1 SD	0.93 (0.84-1.03)	0.17	0.87 (0.77-0.98)	0.025
Verbal fluency Z per +1 SD	0.85 (0.72-1.00)	0.043	0.84 (0.71-1.00)	0.044
Confounding co-morbid condition †				
No	1		1	
Yes	2.30 (1.47-3.61)	<0.0005	2.07 (1.31-3.27)	0.002
Contributing co-morbid condition †				
No	1		1	
Yes	1.80 (1.12-2.89)	0.016	2.02 (1.22-3.36)	0.006
Can afford basic needs ‡				
Always	1		1	
Most of the time	1.98 (1.31-2.97)		1.91 (1.25-2.90)	
Some of the time	3.69 (1.95-6.96)		3.56 (1.86-6.82)	
No	4.25 (2.09-8.66)	<0.0001	3.80 (1.85-7.81)	<0.0001
Recreational psychoactive drugs in past 3 months				
No	1		1	
Yes	1.43 (0.99-2.05)	0.054	1.16 (0.79-1.72)	0.47
Problem drinking ‡ §				

No	1			
Yes	1.16 (0.82-1.64)	0.69		
Depressive symptoms per grade ‡ ‖	2.92 (2.43-3.50)	<0.0005	2.75 (2.28-3.32)	<0.0005
Anxiety symptoms per grade ‡ ‖	3.28 (2.63-4.07)	<0.0005	3.24 (2.58-4.07)	<0.0005
Hepatitis C status ‡ ¶				
Negative	1			
Positive	1.18 (0.75-1.87)	0.47		
ART and VL status				
VL <50 on ART	1			
Detectable on ART	1.37 (0.71-2.64)			
Off ART	0.93 (0.54-1.59)	0.61		
Current CD4 count per +100 cells	0.97 (0.91-1.04)	0.36		
Nadir CD4 count per +100 cells	0.99 (0.93-1.06)	0.83		
Time since HIV diagnosis				
<5 years	1		1	
5-10 years	1.45 (0.91-2.30)		1.26 (0.77-2.06)	
≥10 years	1.62 (1.08-2.43)	0.024	1.82 (1.12-2.97)	0.014
Previous AIDS				
None	1			
Non-CNS	1.36 (0.86-2.16)			
CNS condition	2.28 (0.73-7.10)	0.17		

* Adjusted models include age, sex, education, ethnic group and study site.

† Confounding and contributing medical conditions as defined by the Frascati criteria [3] and

CHARTER cohort analysis.[2]

‡ Excludes missing data.

§ Defined by the modified (two-question) AUDIT-C questionnaire: a positive score was ≥4 points for men or ≥3 points for women.

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