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Relationships between cognition, function, and quality of life among HIV+ Canadian men

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Abstract

Objective To estimate the extent to which HIV-related variables, cognition, and other brain health factors interrelate with other HIV-associated symptoms to influence function, health perception, and QOL in older HIV+ men in Canada.

Design Cross-sectional structural equation modelling (SEM) of data from the inaugural visit to the Positive Brain Health Now Cohort.

Setting HIV clinics at 5 Canadian sites.

Subjects 707 men, age ≥ 35 years, HIV+ for at least one year, without clinically diagnosed dementia.

Main outcome measures Five latent and 21 observed variables from the World Health Organization's biopsychosocial model for functioning and disability and the Wilson–Cleary Model were analysed. SEM was used to link disease factors to symptoms, impairments, function, health perception, and QOL with a focus on cognition.

Results QOL was explained directly by depression, social role, health perception, social support, and quality of the environment. Measured cognitive performance had direct effects on activity/function and indirect effects on participation, HP and QOL, acting through self-reported cognitive difficulties and meaningful activities.

Conclusion The biopsychosocial model showed good fit, with RMSEA < 0.05. This is the first time the full model has been tested in HIV. All of the domains included in the model are theoretically amenable to intervention and many have evidence-based interventions that could be harnessed to improve QOL.

Keywords Cognition · Quality of life · Disability · Health outcomes · Multivariable models

Abbreviations

ADI	AIDS-defining illnesses
B-CAM©	Brief Cognitive Ability Measure
cART	Combination antiretroviral therapy
CFI	Comparative Fit Index
CNS	Central nervous system
EQ-5D-3L	EuroQol 5 dimensions with 3 levels
EQ-5D-VAS	Visual analogue scale for health rating from EuroQol
HADS	Hospital Anxiety and Depression Scale
HADS-A	HADS anxiety items
HADS-D	HADS depression items
HIV_S&S	HIV-specific signs and symptoms
HP	Health perception
HRQL	Health-related quality of life
IAKL	Instrumental activities of daily living
ICF	International classification of functioning, disability and health
MHI	Mental Health Index
MHI-A	Anxiety items from MHI
MHI-D	Depression items from MHI
MLM	Maximum likelihood
MOT	Motivation
NP	Neuropsychological
PDQ	Perceived Deficits Questionnaire
PF	Physical function
PGI	Patient Generated Index
PRO	Patient-reported outcome
QOL	Quality of life

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RAND-36 GHP	General health perception
RMSEA	Root mean square error of approximation
SD	Standard deviation
SEM	Structural equation model
SRM	Standardized root mean squared residual
STDXY	Standardized regression coefficient
TICS	Trier inventory for chronic stress
TLI	Tucker–Lewis Fit Index
WHO	World Health Organization
W–C	Wilson–cleary
WHO5	World Health Organization 5-item well-being index

Introduction

The experience of living with HIV has changed substantially over the past two decades, as HIV infection has shifted from a disease with a dire prognosis to a manageable chronic condition [1–3]. Quality of life (QOL) is replacing survival as the central concern of patients and clinicians alike [1]. As people age with HIV, issues related to brain health, both mood and cognition, have emerged as preoccupations, with cognitive impairment a particular worry. Even with full viral suppression, cognitive challenges seem to be common, the underlying causes are debated, and prognosis is not yet clear [4–8].

Brain health is a multi-dimensional construct reflecting the brain's role in cognition, mood, emotional stability, motivation, and energy. Cognition can be characterized in terms of performance on neuropsychological tests (NP), here termed cognitive ability; and patient-reported difficulty in performing cognitively demanding activities, here termed cognitive difficulties. Lower cognitive ability may or may not be associated with cognitive difficulties [9]. Mental health comorbidities, notably anxiety and depression, are also very common, and may co-occur with or exacerbate cognitive difficulties, low cognitive ability, or both [10]. The inter-relationships between these aspects of brain health can be challenging to disentangle in clinical and research contexts. Moreover, brain health variables are only some of the many factors that affect QOL, either directly or indirectly, through a potentially complex structure.

Of the brain health constructs, cognition is perhaps that which can be most impactful as there is good evidence that cognition can affect important real-life activities in people with HIV, including adherence to medication [11–13], performance of tasks important for daily life, or role and social function [7, 13–16], driving [17], and employment [18]. Perhaps the largest study to date in HIV ($n = 267$) tracing the links between cognitive ability, difficulties, and function in everyday life found associations between NP test performance, reported cognitive difficulties, and performance-based tests of everyday activities using simulated shopping and financial tasks [19]. NP test performance sufficiently poor to support a diagnosis of HIV-Associated Neurocognitive Disorder (HAND) interferes with life roles and social function, as well as global QOL [13]. Likewise, lower cognitive ability on NP testing has been shown to have a negative impact on health-related and global QOL [20–22].

However, the links between cognition and QOL become less clear as additional variables are considered. The literature has not definitively established whether NP test performance or reported cognitive difficulty is most relevant for predicting downstream outcomes like function and QOL [19]. Other work argues that the apparent relationship between cognition and real-life function is explained by other, correlated, variables such as age, education, mood, or immune function [15].

This literature has used multiple regression, a method that has inherent limitations for such questions. Fully elucidating the complex structure and relationships between and among factors that contribute to QOL in HIV, and situating cognition within that structure, requires a comprehensive theoretical model and a statistical approach that goes beyond correlation or even multivariate regression models [23]. Structural equation modelling (SEM) is well-suited to address this complexity: it combines factor analysis, correlation, path analysis, and regression with the use of latent variables and is designed for testing a priori hypothesized relationships among multiple correlated variables [24]. SEM has been applied in HIV, using Wilson and Cleary's 1995 model (W–C Model) to link clinical variables and health domains of HRQL [25]. To illustrate, Vidrine et al. [26] used an SEM model to test the fit of the W–C model to data from 348 persons with HIV treated with combination antiretroviral therapy who were recruited in 2000 from urban centres in the United States. They demonstrated that disease status (nadir CD4 cell count) explained health-related QOL (HRQL: physical and mental health), through the presence (paths) of symptoms (pain), function (ability to maintain a household), and participation (ability to participate in meaningful life activities). Other constructs, education, occupation, smoking, alcohol, and illicit drug use also acted on these variables.

Several groups have used SEM to investigate contributors to aspects of QOL in women. Logie et al. [27] conducted an SEM linking stigma to health perception among 173 African and Caribbean Black women living with HIV in Ontario, Canada. This group used a theoretical model based on fundamental cause theory which conceptualizes the linkages between social contexts and health disparities. They also extended this model in a 2017 publication [28] to include QOL which was a latent construct formed by the 6 domains

of the WHOQOL-HIV [29]. They found that stigma, racism, social support, and depression had direct paths to QOL, which is not surprising given that the latent construct of QOL was formed by some of these constructs (psychological, social relationships, spirituality/beliefs). Alsayed et al. [30] applied SEM in a sample of 178 HIV+ American women, and found that overall QOL was influenced by depressive symptoms, social support, physical function, and self-perceived general health. Their measure of overall QOL was a single item with a 5-point ordinal scale. A 2018 study of Chinese pregnant women living with HIV ($n=101$) [31] found that depression and anxiety mediated perceived social support as a contributor of HRQL. Their measure of HRQL was the EQ-5D which includes an item for anxiety/depression. None of these SEM models for HRQL or QOL included constructs related to cognition.

Thus, while difficulty with cognitively demanding activities is an important concern for persons living with HIV, the contribution of cognitive impairment to cognitive difficulties, the relationships between cognitive difficulties and other brain health constructs, and the downstream effects of all these brain health domains on function and QOL has yet to be assessed within a comprehensive model. The aim of this analysis was to estimate the extent to which HIV-related variables, cognition, and other brain health factors interrelate with other HIV-associated symptoms to influence function, health perception, and QOL in older HIV + men in Canada.

Methods

A cross-sectional analysis was carried out on data from the inaugural assessment of participants in the Positive Brain Health Now (BHN) Cohort [32] with recruitment between 2014 and 2016 from five Canadian sites.

Population

Details on the sample have been reported previously [32]. Participants were ≥ 35 years old, HIV+ for at least 1 year, and able to communicate adequately in either French or English. Excluded were people with Stage 3 or more on the Memorial Sloan–Kettering dementia severity scale, [33], a non-HIV-related neurological disorder likely to affect cognition, active CNS opportunistic infection, known psychotic disorder, substance dependence or abuse within the past 12 months or life expectancy of < 3 years as judged by the treating physician. Owing to the preponderance of men in this cohort (≈ 85%) and the differences between men and women in terms of personal and environmental characteristics, the analysis was restricted to men only.

Model

The model tested in this study combines two theoretical models that are commonly applied in the health field to understand how a complex set of outcomes may be linked. The World Health Organization's 2001 International Classification of Functioning, Disability, and Health (ICF) [34] is a framework to explain links between body function/structure, activity/function, and participation, incorporating contextual factors (individual and environmental). The W–C Model incorporates these same elements, under different rubrics, and is a framework for linking clinical (biologic) variables, symptoms, functional status, through to health perceptions (HP) and overall QOL. The two models are complementary [25]. The combined ICF/W–C model shown in Fig. 1 comprises eight rubrics (categories of variables): Characteristics of the Individual, Characteristics of the Environment, and from left to right, Biological Variables, Impairment/Symptoms, Activity/Function, Participation, HP, and QOL.

Measurement

Figure 2 shows the variables or constructs situated under the eight rubrics of the ICF/W–C model. In addition to directly measured (manifest) variables, the specified model also includes five latent variables: anxiety, depression, sleep, QOL, and HP. Ten patient-reported outcome measures (PROs) contributed data for many of the constructs: RAND-36 [35], WHOQOL-HIV BREF [36], Hospital Anxiety and Depression Scale (HADS) [37], WHO5 Well-Being Index for mood [38], three items from Starkstein's Apathy Scale for motivation [39, 40], selected items from Revised Sign and Symptom Check-List for HIV [41], Perceived Deficits Questionnaire (PDQ) [42] for cognitive difficulties; EuroQol EQ-5D-3L [43]; Patient Generated Index (PGI) for individualized QOL [44], and the Trier Inventory for Chronic Stress (TICS) [45]. Total scores from measures such as the PDQ were entered directly under their respective constructs. Other measures contain test items that encompass more than one

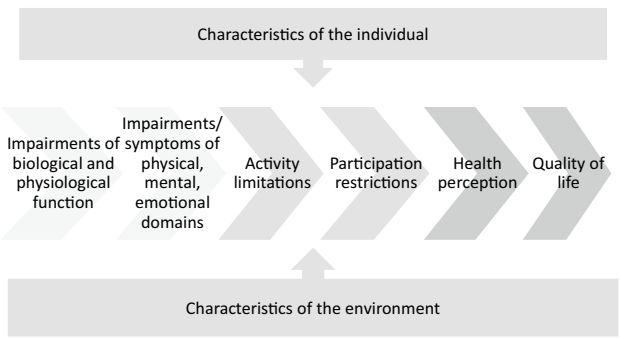

Fig. 1 Combined Wilson–Cleary and ICF models

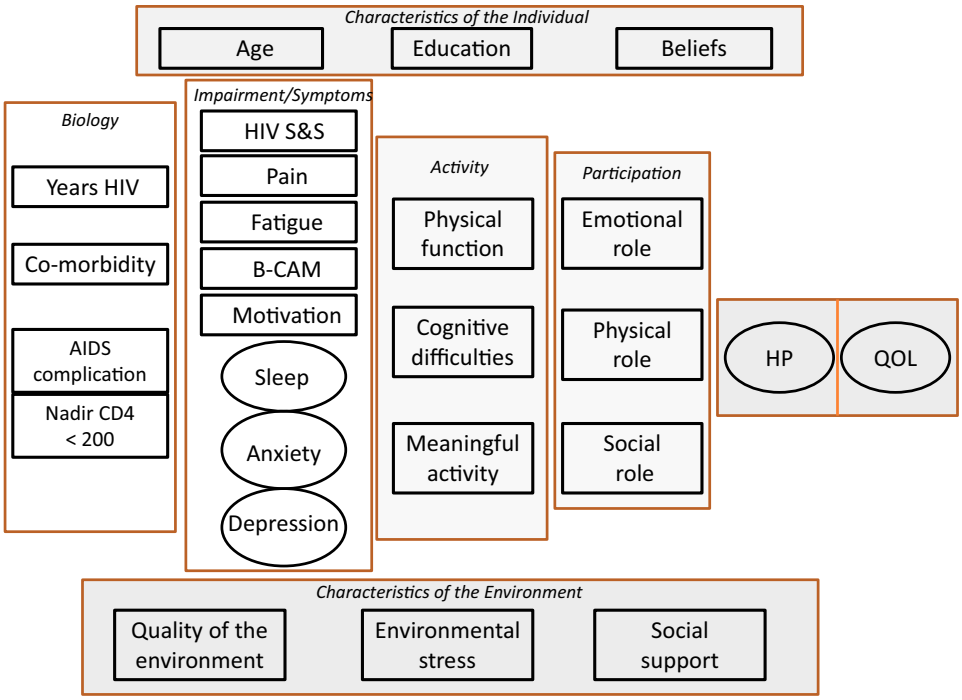

Fig. 2 Variables under each rubric of ICF/WC models

rubric represented in the model. These measures were disaggregated and their items were assigned to the appropriate construct. For example, the WHOQOL includes items assessing the environment, social support, and beliefs: these were extracted for inclusion under the relevant rubrics in the domain, with only a single item included under the rubric QOL ("How would you rate your quality of life?").

For ease of interpretation of the path coefficients, PROs were converted to a 0 to 100 scale with 100 indicating the most positively valenced value for the construct (e.g., better mood, higher function, less pain). This required reverse scoring of some.

Table 1 details the measures that contributed to each observed and latent variable:

Personal characteristics

This rubric includes age, education, and personal beliefs (Domain VI of the WHOQOL-HIV BREF) [36].

Environmental characteristics

This rubric includes social support, quality of the environment (Domain V of the WHOQOL-HIV BREF) [36], and external sources of stress as captured by the TICS [45].

Biologic variables

This rubric included a comorbidity index derived from the Charlson Index [46] and two HIV-related variables: duration of HIV infection and a diagnosis of AIDS. The latter was defined based on either: (i) a history of AIDS-defining illnesses (ADI) or; (ii) among those without (i), a nadir CD4 < 200 cells/μL.

Impairment/symptoms

Cognitive ability was measured with a computerized cognitive test battery, the Brief Cognitive Ability Measure (B-CAM). Properties of the B-CAM have been reported elsewhere [47]. Briefly, the B-CAM comprises the following tasks: Corsi block task (forward and backward) [48], mini Trail-Making Test B [49], Eriksen flanker task (incongruent reaction time) [50], phonemic fluency [51], and recall of a list of 8 words. It encompasses the cognitive domains known to be affected by HIV [52] and important for function and QOL: executive function, memory, attention, and processing speed. The assumption that performance on these cognitive tests reflects a single latent variable (cognitive ability) in HIV is supported by the fit of the data to the Rasch model [53]. Rasch analysis is applied to produce a total score that quantifies ability in these HIV-relevant domains and can also be used to track the evolution of cognitive impairment over time.

Other observed variables under the Impairment/Symptom rubric were motivation, pain, vitality (fatigue), and HIV-specific signs and symptoms [41]. Finally, this rubric also included three latent variables. Two latent variables representing anxiety and depression were formed from the relevant Mental Health Index items of the RAND-36 [35],

Table 1 Characteristics of the cohort on variables from the biopsychosocial model and interclass correlation coefficients across sites

Model variables	*N*	Mean (SD) or %	ICC
Personal characteristics (n = 707)			
Age (years)	703	53.4 (8.3)	.023
35–44	99	14.1%	
45–54	328	46.7%	
55–59	123	17.5%	
60–81	153	21.8%	
Education			.015
Years	701	14.0 (2.5)	.015
Primary	28	4.0%	
High school	179	25.5%	
Technical/pre-university college	238	34.0%	
University: bachelor's level	180	25.7%	
University: post-graduate/professional	76	10.8%	
Beliefs (WHOQOL-HIV: Domain VI)[a]			
Scored 0 to 100	696	70.6 (18.9)	.003
Environmental characteristics			
Social support (WHOQOL-HIV: Domain IV)[b]			
Scored 0 to 100	686	63.0 (20.0)	.022
Environmental concerns (WHOQOL-HIV: Domain V)[c]			
Scored 0 to 100	687	71.3 (16.4)	.004
Environmental sources of stress (TICS)[d]	675	16.3 (9.0)	.001
Reversed scored 0–100	700	65.8 (18.9)	.001
Biological variables			
Duration of HIV (years)	693	17.0 (8.1)	.040
Nadir CD4 cell count (cells/mm^3)	686	210.7 (166.6)	.010
Current CD4 count (cells/mm^3)	688	623.4 (273.2)	.005
CD4:CD8 ratio	682	0.8 (0.4)	.014
Progressed to AIDS	371	52.5%	.015
Comorbidity Index	707	1.1 (1.4)	.048
0	329	46.5%	
1	175	24.8%	
2	103	14.6%	
3	51	7.2%	
≥4	49	6.9%	
Impairment/symptoms (measure) [range]			
Cognitive Ability (B-CAM) [0–35]	641	20.0 (4.6)	.113
Pain(RAND-36) [0–100][e]	704	66.0 (24.7)	.014
Fatigue(Vitality:RAND-36) [0–100][f]	706	53.7 (22.2)	.008
Mental Health (MHI:RAND-36) [0–100][g]	706	67.3 (20.3)	.008
Anxiety (HADS 7 items) [0–21][h]	688	7.1 (4.2)	
Reversed scored [0–100]	688	66.1 (20.1)	.006
Depression (HADS) [0–21][h]	697	4.6 (3.6)	
Reversed scored [0–100]	697	78.1 (17.3)	.008
WHO well-being rescored [0–100][i]	706	58.1 (22.2)	.001
Sleep quality [0–11][j]	688	5.8 (2.3)	.007
Sleep satisfaction (HIV-WHOQOL) [1–5][k]	706	3.1 (1.2)	.000
Motivation [0–100][l]	674	61.9 (27.1)	.000
Number of HIV-specific symptoms[m]	707	4.4 (2.5)	.008
Activity/Function (Measure) [Range]			
Physical Function(PFI: RAND-36) [0–100][n]	704	82.4 (20.7)	.028
Self-reported cognitive deficits (PDQ)[o]	706	33.9 (17.5)	.020
Reversed rescored [0–100]	706	66.1 (17.5)	.020
Current engagement meaningful activity[p]	685	31.8 (23.6)	.034
Participation (Measure) [Range]			
Role Emotional (RE: RAND-36) [0–100][q]	703	59.0 (42.6)	.014

Table 1 (continued)

Model variables	*N*	Mean (SD) or %	ICC
Role Physical (RP: RAND-36) [0–100][r]	696	58.5 (41.4)	.017
Social Function (SF: RAND-36) [0–100][s]	705	69.0 (26.0)	.003
Health Perception (Measure) [Range]			
General Health Perception (GHP: RAND-36)[0–100][t]	692	62.3 (21.7)	.005
GH-HIV: WHOQOL-HIV2 [1–5] Rescored [0–100][u]	706	64.3 (26.2)	.002
EQ-5D-3L VAS Score [0–100][v]	696	76.2 (15.6)	.003
EQ-5D-3L index [0–100][w]	695	81.5 (16.4)	.000
Quality of Life (Measure) [Range]			
WHOQOL-HIV 1 [1–5] Rescored [0-100][x]	706	70.4 (23.6)	.004
Personalized QOL (PGI) [0–10][y]	683	5.4 (2.3)	.038

[a]WHOQOL-HIV Domain VI (Beliefs): To what extent do you feel your life to be meaningful? To what extent are you bothered by people blaming you for your HIV infection? How much do you fear the future? How much do you worry about death?

[b]WHOQOL-HIV Domain IV (Social relationships): To what extent do you feel accepted by the people you know? How satisfied are you with your personal relationships? How satisfied are you with your sex life? How satisfied are you with the support you get from your friends?

[c]WHOQOL-HIV Domain V (Environment): How safe do you feel in your daily life? How healthy is your physical environment? Do you have you enough money to meet your needs? How available to you is the information that you need in your day-to-day life? To what extent do you have the opportunity for leisure activities? How satisfied are you with the conditions of your living place? How satisfied are you with your access to health services? How satisfied are you with your transport?

[d]Trier Inventory for Chronic Stress: measures six aspects of chronic stress: Work overload, worries, social stress, lack of social recognition, work discontent, and intrusive memories. Original score (0–48) calculated only on persons who answered all 12 question; reversed score (0–100) calculated when at least half the questions were answered

[e]RAND-36 Bodily Pain: During the past 4 weeks: How much bodily pain have you had? How much did pain interfere with your normal work?

[f]RAND-36 Vitality: During the past 4 weeks: Did you feel full of pep? Did you have a lot of energy? Did you feel worn out? Did you feel tired?

[g]RAND-36 Mental Health with a mix of anxiety (A) and depression (D) items: During the past 4 weeks: Have you been a very nervous person (A)? Have you felt so down in the dumps that nothing could cheer you up (D)? Have you felt calm and peaceful (A)? Have you felt downhearted and blue (D)? Have you been a happy person (D)?

[h]HADS Anxiety (7 items): tense/wound up, frightened/nervous, worrying thoughts, restless, panic, relaxed; Depression (7 items): enjoy things (2 items), slowed down, lost interest in appearance, laugh, look forward, cheerful; 4-point frequency scale

[i]WHO well-being: Over the last 2 weeks, I have felt cheerful and in good spirits; I have felt calm and relaxed; I have felt active and vigorous; I woke feeling fresh and rested; My daily life has been filled with things that interest me

[j]Sleep: In the past month: Do you feel rested when you wake up? How long does it take you to fall asleep at night? Do you wake up in the middle of the night? Do you take a nap during the day?

[k]How satisfied are you with your sleep?

[l]Are you always looking for something to do? Do you have plans and goals for the future?

[m]HIV-specific symptoms: Today, presence and intensity: weakness, loose stools, diarrhoea, dizziness, headaches, weight gain in the stomach area, hump on the back of neck, skinny arms and legs, prominent leg veins, numbness/tingling of feet/toes

[n]RAND-36 Physical Functioning: Does your health now limit you in vigorous activities, moderate activities, lifting or carrying groceries, climbing stairs, bending, kneeling or stooping, walking (100 m, half a kilometre, more than one kilometre), bathing or dressing yourself; 3-point limitation scale

[o]PDQ: 20 self-report items on memory and concentration; 4-point frequency scale

[p]Current engagement meaningful activity: hours per week spent in recreation, leisure, household management, sports

[q]RAND-36 Role Emotional: During the past 4 weeks, have you had any of the following problems with work or other regular daily activities as a result of emotional problems (such as feeling depressed or anxious)? Cut down on the amount of time you spent on work or other activities; Accomplished less than you would like; Did not do work or other activities as carefully as usual

[r]RAND-36 Role Physical: During the past 4 weeks, have you had any of the following problems with your work (or other regular daily activities as a result of your physical health? Cut down on the amount of time you spent on work or other activities; Accomplished less than you would like; Were limited in the kind of work or other activities; Had difficulty performing the work or other activities

[s]RAND-36 Social Function: During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours or groups? Not at all; A little bit; Moderately; Quite a bit; Extremely

[t]RAND-36 General Health: In general, would you say your health is: Excellent, Very good, Good, Fair, Poor

[u]How is your health? Very poor, Poor, Neither poor nor good, Good, Very good

[v]Your own health today: 0 = Worst imaginable health state, 100 = Best imaginable health state

[w]From EuroQol EQ-5D

[x]How would you rate your quality of life? Very poor, Poor, Neither poor nor good, Good, Very good

[y]Nominate domains where HIV has affected life, rate severity, weight for desire to change

Table 2 Model progression

	Model	Description	RMSEA	CFI	χ^2	*df*
1a	Biology to symptoms	Initial, with all paths of symptoms on biology, personal and environmental factors, and centre	0.059	0.963	309.991	90
2		After removing non-significant paths of symptoms on biology, personal and environmental factors	0.047	0.960	388.553	151
3	Biology to symptoms to activity	After reducing model. Activities were added one at a time because of variance problems.	0.045	0.957	501.067	205
4		After adding cross-rubric paths to activity	0.044	0.959	486.08	204
5	Biology to symptoms to activity to function	Initial model, from model 5	0.054	0.938	779.507	252
6		After reducing model and adding cross-rubric paths to function	0.040	0.966	549.949	260
7	Biology to symptoms to activity to function to health perception	Initial model, from model 6	0.055	0.925	1171.469	375
8		After reducing model and adding cross-rubric paths to HP	0.042	0.955	853.479	375
9	Biology to symptoms to activity to function to health perception to quality of life	Initial model, from model 8	0.043	0.949	1006.298	433
10		After reducing model and adding cross-rubric paths to QOL	0.042	0.952	981.533	435

the HADS [37], and the WHO5 Well-Being [38]. A latent variable for sleep included a single item for sleep satisfaction from the WHOQOL-HIV BREF [36] and selected items from the Pittsburgh Sleep Quality Index [54], used in another context [55] and fit to a unidimensional and hierarchical model [53], and was scored from 0 to 11.

Activity/function

The self-reported frequency of cognitive difficulties in everyday activities was measured with the 20-item Perceived Deficits Questionnaire (PDQ) [42]. Other constructs under the Activity/Function rubric were physical functioning as measured by the corresponding index of the RAND-36 and number of hours per week of engagement in recreation and leisure activities as reported by the participant.

Participation

Limitation in fulfilling usual roles was measured by the three sub-scales of the RAND-36: Role Physical, Role Social, and Role Emotional.

HIV-associated HP and QOL

HP was assessed by a latent variable comprising the score from 0 to 100 on the EQ-5D VAS [43], one item from WHOQOL-HIV BREF, the General Health Perception subscale of the RAND-36 [35], scored from 0 to 100, and the EQ-5D utility score. QOL was represented by a latent variable comprised of the single item (5-point ordinal scale) for QOL from the WHOQOL-HIV BREF [36] and the score from 0 to 100 on the Patient Generated Index for individualized QOL (nominate, rate, and prioritize areas affecting QOL) [44].

Statistical methods

The ICF/W–C model was fit to the data using SEM with the software Mplus [20]. Robust maximum likelihood (MLM) estimation [24] was used as not all variables were normally distributed. As the population was gathered from five sites, this non-independence was adjusted for by including dummy variables in the model with paths to all other variables. Categorical variables with five or more levels were modelled as continuous variables; education was modelled as years. Variables within rubrics were allowed to correlate, as were items between personal and environmental characteristics. Personal and environmental factors were allowed paths to all variables in other rubrics. The model was developed sequentially, from left to right along the W–C model. Paths were allowed from left to right across each subsequent rubric, as well as from all personal and environmental factors. Correlations were added among all constructs within a single rubric as well as among all personal and environmental factors, and between the error terms of items arising from the same questionnaire. After removing non-significant paths, a rubric further along the left-to-right sequence was included along with all paths from the rubric immediately to the left and all personal and environmental factors. After removing non-significant paths to the newly added rubric, modification indices were examined and any suggested paths that crossed rubrics were added. This iterative procedure was followed until a final model including all seven rubrics was developed. Table 2 includes details on the model progression.

Two methods were used to handle missing data. People with missing data on more than half of the variables considered were removed from the analysis. Otherwise, single imputation was performed using Statistical Analysis System (SAS version 9.4) statistical software MI procedure. A single imputation was viewed as the most reasonable option as data from all visits (up to five) were used in the imputation; full information maximum likelihood (FIML) would not have used any data outside of what was included in the SEM model. The imputed value for the first visit was used in the current SEM.

Between site variation was examined using the intraclass correlation coefficient (ICC). ICCs were calculated using the random effects model that corresponded to the distribution of each variable: normal, binary, or multinomial.

Goodness of fit of the model was assessed using: root mean square error of approximation (RMSEA), Comparative Fit Index (CFI), and standardized root mean squared residual (SRMR). The Tucker–Lewis Fit Index was not considered since paths to the site variables from each of the variables in the model were retained regardless of their significance status.

When depicting these relationships only direct paths are shown; measured (manifest) variables are shown in rectangles and latent variables are shown in ovals. Paths were modelled only between variables in different rubrics and are shown as single-headed arrows, dark lines if the path is significant at $p < 0.05$, and dotted lines if $0.05 < p < 0.10$. Correlations between variables under the same rubric were numerous and are presented separately. Total effects are estimated from any and all direct and indirect paths.

Results

Five sites participated in the BHN cohort and provided data for this analysis on a total of 707 men, with two sites in Montreal contributing 173 and 225 men each, Vancouver 117, Hamilton 45, and Toronto 147. This sample excluded men ($n = 13$) who were missing more than half of the variables considered for the analysis. Overall, 74% had no missing data and, among the 34 variables included in the model, the number of missing variables never exceeded seven.

Table 1 presents the unimputed data on characteristics of the participants on the model variables corresponding to each rubric of the model, along with intraclass correlation coefficients across sites. The average age of the men was 53 years (SD: 8.3); the majority were between 45 and 59 years, and the oldest was 81 years; all were taking antiretroviral treatment. Cognitive ability was measured with the B-CAM, scored out of 35 (mean: 20.0; SD: 4.6). For the variables scored out of 100, means ranged from 54 (vitality) to 82 (physical function). All but two intraclass correlations were below 5%; cognitive ability and comorbidity index were between 5% and 10%. Fit of the model was good (RMSEA: 0.042; SRMR: 0.028, with an acceptable CFI: 0.952) [56].

The five latent variables forming the measurement portion of this model were constructed theoretically, and modelled along with paths from four variables representing the five sites. Three of the five latent variables fell in the Symptom/Impairment rubric. Depression was formed by the HADS depression scale, the WHO-5, and the sum of three RAND-36 depression items, and explained 65%, 80%, and 74% of each, respectively. The anxiety latent consisted of the HADS anxiety scale and the sum of two RAND-36 anxiety items, explaining 71% and 77%, respectively. Sleep was formed by an item from the HIV WHOQOL and a measure scored based on a Rasch model created with other data, and explained 55% and 47% of these two items. The HP latent variable explained 62% of the EuroQol VAS, 41% of the EuroQol utility score, 67% of the GH subscale of the RAND-36, and 60% of an HIV WHOQOL item. The QOL latent variable explained 61% of the WHOQOL item but only 25% of the PGI measure used to form it. Site explained between 0.7% and 1.6% of the variance of the latent variables. The measurement model had an adequate fit, with an RMSEA of 0.060, an SRMR of 0.029, and a CFI of 0.960.

Table 3 shows how each variable explained the others in the model via direct paths. The table is ordered from left to right starting from Personal and Environmental factors and then according to progression through the rubrics of the ICF/WC models.

The parameters of each path are given: beta (β) is interpreted as a regression coefficient (for every one unit difference in the exogenous x variable in the path, the endogenous y variable in the path changes by β units); the standard error (se) is interpreted as the standard deviation of the estimated β; the p value is determined from β/se, the equivalent of a t test, and the 'p' column indicates with a * if the path is significant at $p < 0.05$ and a ^ when $0.05 < p < 0.10$. The StdXY column provides the standardized regression coefficient which is needed to compare across paths as each combination of path variables, x and y, have different measurement scales; standardization is with respect to the standard deviation (SD) of the variable. The path with the highest StdXY is the path where the explanatory relationship is the strongest. As an illustration, the first path shown is from age to comorbidity with a β of 0.038 (se: 0.006) and a StdXY of 0.233. The β indicates that people who differ by one year of age score, on average, 0.038 points higher on the comorbidity index. The StdXY indicates that those who differ by 1 SD on age, differ by 0.233 of the SD of comorbidity; this path is significant at $p < 0.05$. Along with four paths to the biological variables (one of which is not significant), age has paths to four of the symptom/impairment variables, to one

Table 3 Direct path parameters for SEM model

Personal	Environment	Biology	Impairment/symptoms	Activity/function	Participation	HP	QOL	β	SE	p	StdYX
Age		Comorbidity						0.038	0.006	*	0.233
Age		Yrs with HIV[a]						0.312	0.032	*	0.322
Age		AIDS complication[a]						−0.001	0.001		−0.022
Age		Nadir < 200[a]						0.005	0.002	*	0.079
Age			Anxiety					0.137	0.043	*	0.065
Age			B-CAM					−0.156	0.018	*	−0.287
Age			Motivation					−0.247	0.120	*	−0.076
Age			Pain					−0.207	0.096	*	−0.070
Age				Physical				−0.300	0.067	*	−0.122
Age					Social role			0.261	0.077	*	0.083
Education			Anxiety					0.561	0.153	*	0.079
Education			B-CAM					0.271	0.057	*	0.149
Education			Pain					0.718	0.299	*	0.072
Education			Sleep					0.061	0.023	*	0.095
Education				Meaningful				1.733	0.329	*	0.182
Education					Emotional role			−1.016	0.452	*	−0.059
Education					Physical role			−0.845	0.429	*	−0.051
Education					Social role			−0.710	0.266	*	−0.067
Beliefs			Anxiety					0.247	0.032	*	0.266
Beliefs			Depression					0.175	0.025	*	0.236
Beliefs			Motivation					0.116	0.059	*	0.081
Beliefs			HIV S&S[a]					−0.017	0.005	*	−0.129
Beliefs			Vitality					0.177	0.043	*	0.149
Beliefs						HP		0.052	0.020	*	0.083
	Stress		Anxiety					0.464	0.028	*	0.499
	Stress		B-CAM					0.036	0.009	*	0.150
	Stress		Depression					0.219	0.023	*	0.295
	Stress		Pain					0.231	0.045	*	0.176
	Stress		Sleep					0.027	0.004	*	0.321
	Stress		HIV S&S[a]					−0.015	0.005	*	−0.115
	Stress		Vitality					0.373	0.041	*	0.314
	Stress			Cognitive				0.168	0.042	*	0.182
	Stress				Emotional role			0.285	0.084	*	0.126
	Stress				Physical role			0.327	0.071	*	0.150
	Stress				Social role			0.143	0.051	*	0.103
	Social support		Anxiety					0.094	0.029	*	0.107
	Social support		Depression					0.181	0.022	*	0.259

Table 3 (continued)

Personal	Environment	Biology	Impairment/symptoms	Activity/function	Participation	HP	QOL	β	SE	p	StdYX
	Social support		Sleep					0.018	0.004	*	0.230
	Social support		Vitality					0.126	0.038	*	0.113
	Social support						QOL	0.090	0.039	*	0.098
	Quality	Comorbidity[a]						−0.010	0.003	*	−0.122
	Quality		Anxiety					0.137	0.039	*	0.128
	Quality		B-CAM					0.060	0.010	*	0.220
	Quality		Depression					0.211	0.027	*	0.247
	Quality		Motivation					0.205	0.069	*	0.125
	Quality		Pain					0.428	0.059	*	0.285
	Quality		Sleep					0.017	0.005	*	0.173
	Quality		HIV S&S[a]					−0.028	0.006	*	−0.185
	Quality		Vitality					0.304	0.050	*	0.223
	Quality			Physical				0.217	0.042	*	0.174
	Quality					HP		0.061	0.022	*	0.084
	Quality						QOL	0.308	0.049	*	0.275
		Comorbidity[a]	HIV S&S[a]					0.221	0.060	*	0.120
		Comorbidity[a]		Physical				−1.930	0.497	*	−0.128
		Yrs with HIV[a]	Motivation					−0.237	0.120	*	−0.071
		Yrs with HIV[a]	Pain					−0.506	0.099	*	−0.165
		Yrs with HIV[a]	Sleep					−0.021	0.007	*	−0.106
		Yrs with HIV[a]	HIV S&S[a]					0.055	0.010	*	0.177
		Yrs with HIV[a]	Vitality					−0.218	0.059	*	−0.078
			Anxiety	Cognitive				0.247	0.059	*	0.248
			B-CAM	Meaningful				0.789	0.200	*	0.151
			B-CAM	Cognitive				0.801	0.113	*	0.207
			Depression		Emotional role			1.187	0.141	*	0.389
			Depression		Social role			0.683	0.107	*	0.366
			Depression			HP		0.286	0.053	*	0.335
			Depression				QOL	0.410	0.094	*	0.312
			Motivation	Meaningful				0.117	0.027	*	0.134
			Motivation			HP		0.026	0.010	*	0.059
			Pain	Cognitive				0.040	0.023	^	0.057
			Pain	Physical				0.306	0.028	*	0.369
			Pain		Emotional role			0.192	0.057	*	0.111
			Pain		Physical role			0.524	0.064	*	0.314
			Pain		Social role			0.211	0.033	*	0.200

Table 3 (continued)

Personal	Environment	Biology	Impairment/symptoms	Activity/function	Participation	HP	QOL	β	SE	p	StdYX
			Pain			HP		0.094	0.015	*	0.194
			HIV S&S[b]	Cognitive				−0.890	0.183	*	−0.128
			HIV S&S[b]	Physical				−1.458	0.277	*	−0.178
			Vitality	Cognitive				0.153	0.031	*	0.196
			Vitality		Physical role			0.378	0.068	*	0.205
			Vitality		Social role			0.143	0.058	*	0.122
			Vitality			HP		0.064	0.024	*	0.121
				Meaningful	Physical role			0.104	0.040	*	0.060
				Cognitive	Emotional role			0.478	0.096	*	0.195
				Cognitive	Physical role			0.258	0.088	*	0.109
				Cognitive	Social role			0.191	0.052	*	0.128
				Physical	Physical role			0.282	0.056	*	0.140
				Physical		HP		0.189	0.018	*	0.325
					Physical role	HP		0.016	0.008	^	0.055
					Social role		QOL	0.072	0.031	*	0.102
						HP	QOL	0.489	0.094	*	0.317

*$t > 1.96$ associated with p value < 0.05, ^$0.05 < p < 0.10$, − $p > 0.10$

[a]Higher is worse (more HIV signs and symptoms, more years with HIV, the presence of AIDS complications or nadir CD4 < 200)

Table 4 Total effects of variables to HP and QOL

	Total to HP					Total to QOL				
	Direct[a]	Indirect[a]	β	SE	StdYX	Direct[a]	Indirect[a]	β	SE	StdYX
Personal										
Age	N	Y	−0.152	0.023	−0.106	N	Y	−0.064	0.020	−0.029
Education	N	Y	0.107	0. 0.051	0.022	N	Y	0.017	0.039	0.002
Beliefs	Y	Y	0.123	0.020	0.195	N	Y	0.144	0.022	0.148
Environment										
Stress	N	Y	0.137	0.015	0.217	N	Y	0.190	0.021	0.195
Social support	N	Y	0.061	0.010	0.102	Y	Y	0.205	0.039	0.223
Quality	Y	Y	0.272	0.030	0.374	Y	Y	0.550	0.047	0.491
Biology										
Comorbidity	N	Y	−0.437	0.100	−0.050	N	Y	−0.216	0.060	−0.016
Yrs with HIV	N	Y	−0.119	0.020	−0.080	N	Y	−0.070	0.016	−0.030
AIDS complications	N	N				N	n			
Nadir < 200	N	N				N	N			
Impairment/symptoms										
B-Cam	N	Y	0.005	0.003	0.002	N	Y	0.013	0.006	0.003
Depression	Y	N	0.286	0.053	0.335	Y	Y	0.599	0.083	0.455
Anxiety	N	Y	0.001	0.001	0.001	N	Y	0.004	0.002	0.004
Sleep	N	N				N	N			
Motivation	Y	N	0.026	0.010	0.060	N	Y	0.013	0.005	0.019
Pain	Y	Y	0.161	0.015	0.334	N	Y	0.095	0.017	0.127
Vitality	Y	Y	0.071	0.024	0.133	N	Y	0.047	0.015	0.057
HIV s&s	N	Y	−0.286	0.059	−0.060	N	Y	−0.152	0.039	−0.021
Activity/function										
Cognitive	N	Y	0.004	0.003	0.006	N	Y	0.016	0.007	0.015
Meaningful	N	Y	0.002	0.001	0.003	N	Y	0.001	0.001	0.001
Physical	Y	Y	0.194	0.018	0.332	N	Y	0.095	0.020	0.105
Participation										
Social role	N	N				Y	N	0.072	0.031	0.102
Emotional role	N	N				N	N			
Physical role	Y	N	0.016	0.008	0.055	N	Y	0.008	0.004	0.017
HP						Y	–	0.489	0.094	0.317

[a]Y if they appear in the model, N if they do not

of the activity/function variables (physical), and to social role under participation. The path between environmental sources of stress and anxiety has the highest value of StdXY (0.499).

Table 4 presents total paths, calculated from both direct and indirect paths, to HP and to QOL. Table 5 shows the total paths to the cognitive constructs. The strongest paths to HP were from quality of the environment, depression, pain, and physical function, with StdXY of 0.374, 0.335. 0.334, and 0.332, respectively. Depression and quality of the environment were also strongly associated with QOL, along with health perception (StdXY of 0.599, 0.0.550, and 0.489, respectively).

The focus of this paper was on the role of cognition in the context of other brain health and functional outcomes in QOL and, therefore, the number of paths in our analysis is large. Because of this, the full model is shown in Fig. 3 in a supplementary file in a series of five panels showing direct paths from variables related to (a) personal factors; (b) environmental factors; (c) HIV-related biology variables; (d) symptoms and impairments; and (e) activity/function, participation, and HP. For this paper, we present models related to brain health constructs, particularly cognitive constructs. Supplementary Fig. 3a shows only those direct paths to and from cognitive constructs and to QOL. Paths between two variables are shown with black ($p < 0.05$) or dotted (p: $0.05 < p < 0.10$) lines; paths to or from a group of variables are shown in large blue lines and the groups are shown by a blue box enclosure (Fig. 3).

Table 5 Total effects of variables to cognitive ability and difficulties

	Total to cognitive ability (B-Cam)					Total to cognitive difficulties (PDQ)				
	Direct[a]	Indirect[a]	β	SE	StdYX	Direct[a]	Indirect[a]	β	SE	StdYX
Personal										
Age	Y	N	−0.156	0.018	−0.287	N	Y	−0.139	0.031	−0.066
Education	Y	N	0.271	0.057	0.149	N	Y	0.385	0.078	0.055
Beliefs	N	N				N	Y	0.103	0.017	0.112
Environment										
Stress	Y	N	0.036	0.009	0.150	Y	Y	0.391	0.030	0.423
Social support	N	N				N	Y	0.042	0.011	0.049
Quality	Y	N	0.060	0.010	0.220	N	Y	0.173	0.022	0.163
Biology										
Comorbidity	N	N				N	Y	−0.197	0.067	−0.015
Yrs with HIV	N	N				N	Y	−0.103	0.020	−0.047
AIDS complications	N	N				N	N			
Nadir < 200	N	N				N	N			
Impairment/symptoms										
B-CAM						Y	–	0.801	0.113	0.207
Depression						N	–			
Anxiety						Y	–	0.247	0.059	0.248
Sleep						N	–			
Motivation						N	–			
Pain						Y	–	0.040	0.023	0.057
Vitality						Y	–	0.153	0.031	0.196
HIV S&S						Y	–	−0.890	0.183	−0.128

[a]Y if they appear in the model, N if they do not; S&S: Signs and symptoms

Cognitive ability

Variables influencing the B-CAM measure of cognitive ability were age, education, quality of the environment, and environmental sources of stress. Cognitive ability in turn linked to cognitive difficulties (PDQ) and to the extent of engagement in meaningful activities. Cognitive ability affected participation, HP and QOL only indirectly, i.e., through its impact on cognitive difficulties and meaningful activities.

Cognitive difficulties

Multiple variables contributed to self-reported cognitive difficulties, including cognitive ability, anxiety, pain, vitality, a count of HIV signs and symptoms, and external sources of stress from the Environment rubric, all via direct paths. Indirect contributions were made by age, education, personal beliefs, external sources of stress, environmental quality, and social support (see Table 5). Interestingly, depression was not directly linked to cognitive difficulties, although it had a direct impact on HP and QOL. Cognitive difficulties influenced all aspects of Participation: fulfilment of social, emotional, and physical roles. Through the path to social role, cognitive difficulties had an (indirect) impact on QOL. The total effects (see Table 5) of cognitive performance and self-reported cognitive difficulties for both HP and QOL were very small (StdXY 0.002 and 0.006, respectively, for HP; 0.003 and 0.015, respectively, for QOL).

Other pathways to HP and QOL

Within the Biology rubric, comorbidity and duration of HIV had indirect effects on HP. Within the Impairment/symptoms rubric, depression and motivation influenced HP directly, anxiety and HIV symptoms influenced HP indirectly, and pain and vitality had both direct and indirect influences. Physical function, physical role, beliefs, and quality of the environment also contributed directly to HP, with 84% of the HP latent variable explained by model variables through direct and indirect paths. HP in turn directly explained QOL, as did depression, social role, quality of the environment, and the presence of social support, although many other symptoms/impairments and activity/function variables influenced QOL by way of indirect paths. The model explained 91% of the variance in the QOL latent variable.

Table 6 presents the correlations between variables under the Impairment/Symptom rubric, which includes cognitive

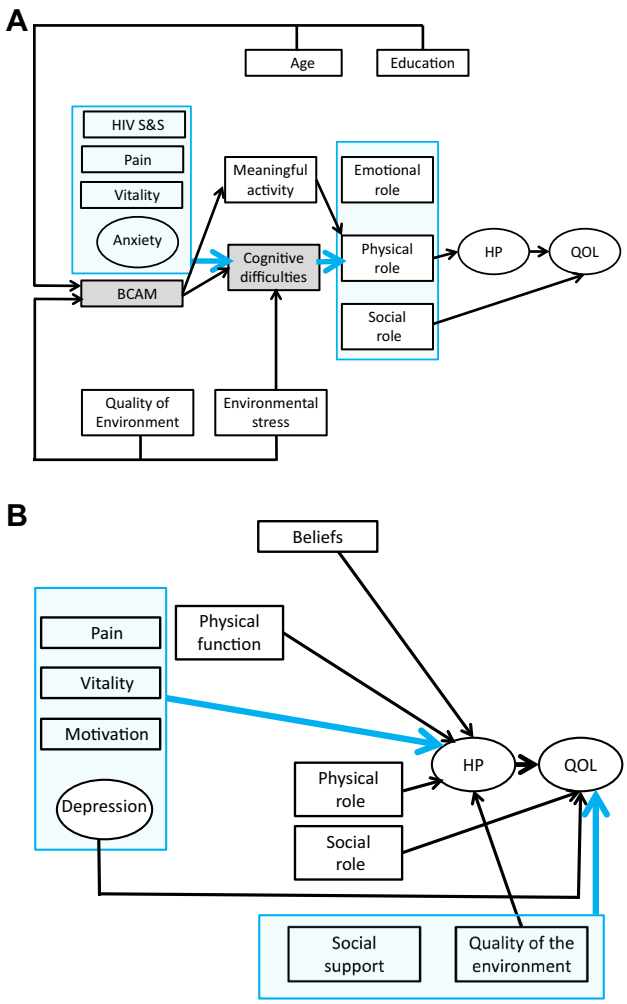

Fig. 3 **a** Direct paths to and from cognitive constructs leading to HP and QOL. **b** Direct paths to quality of life. Measured (manifest) variables are shown in rectangles and latent variables are shown in ovals. Paths shown in black or blue lines were significant at the $p<0.05$ level; paths in grey lines associated with values $0.05<p<0.10$. (Color figure online)

ability (B-CAM). The highest correlations (0.57 to 0.83) were observed among vitality, anxiety, and depression, as well as between the sleep latent, vitality, and the anxiety and depression latents (0.64 to 0.68). The correlations of cognitive ability with anxiety and depression were low ($r \approx 0.2$). Under the Activities and Participation rubrics, variables representing physical, cognitive, and meaningful activities showed little correlation, with the highest correlation, 0.31, observed between physical and cognitive activities (difficulties). In contrast, variables under the Participation rubric were correlated at approximately 0.6.

Alternative models

A feature of SEM is that multiple models can produce the same fit. An investigation into the lack of impact of a diagnosis of AIDS on variables subsequent in the model resulted in an alternative model with the same fit but significant paths from having an AIDS-defining illness to role physical ($\beta = -8.43$) and to HP ($\beta = -1.65$). These additions did not result in any other paths dropping out of the model.

Discussion

The ICF/WC-based biopsychosocial model tested here using SEM showed good fit to the data and 90% of the variation in the QOL latent variable was explained by model variables. The results showed that one or more aspects of brain health, the focus of the study, affected QOL through a cascade of health experiences linking biology, symptoms, activities, and participation, to HP and ultimately to QOL, although the total explanatory effects varied across the specific brain health constructs. While there have been other studies using SEM to explain complex relationships between constructs relevant to people living with HIV, this is the first that included cognitive constructs.

The BHN cohort was designed to disentangle the impact of cognition and other brain health variables on QOL in the presence of other impairments and limitations that also affect QOL. Cognitive ability, assessed based on performance tests included in the B-CAM, was influenced by age and education as well as characteristics of the environment. HIV-related variables were not influential. We also found that cognitive ability correlated only weakly (<0.3) with other variables and latents within the same rubric, including depression and anxiety. However, cognitive ability was strongly associated with cognitive difficulties (β: 0.801; se: 0.113; see Table 3). Self-reported cognitive difficulties were also influenced by HIV signs and symptoms, pain, vitality, anxiety and environmental stress, and indirectly by age, education, and beliefs. Through this pathway, cognitive ability had an indirect but widespread impact on all aspects of living with HIV, including decreased engagement in meaningful activities, impaired participation in life's roles, and through these, to impact QOL. Thus, in this non-demented sample, self-reported cognitive difficulties are good indicators of negative downstream effects on people's lives.

Although cognitive ability and self-reported cognitive difficulties were strongly related, the two variables showed distinctly different sets of associations with the variables located downstream (to the left) and upstream (to the right) in the model (see Supplementary Fig. 3a, b).

Table 6 Correlations between variables under the impairment (symptoms) rubric

	B-CAM	Pain	Vitality	Anxiety			Depression				Sleep			MOT
				Latent	MHI_A	HADS_A	Latent	MHI_D	HADS_D	WHO5	Latent	Sleep	WHO_HIV	
B-CAM	*1.00*													
Pain	0.22	*1.00*												
Vital	0.19	0.48	*1.00*											
Anxiety latent	0.24	0.38	0.67	*1.00*										
MHI_A	0.20	0.32	0.60		*1.00*									
HADS_A	0.23	0.32	0.57		0.75	*1.00*								
Depression latent	0.23	0.44	0.83	0.89			*1.00*							
MHI_D	0.18	0.32	0.69		0.75	0.71		*1.00*						
HADS_D	0.25	0.37	0.66		0.58	0.62		0.71	*1.00*					
WHO5	0.17	0.39	0.78		0.70	0.65		0.76	0.72	*1.00*				
Sleep latent	0.28	0.46	0.65	0.64			0.68				*1.00*			
Sleep	0.25	0.32	0.46		0.38	0.38		0.40	0.36	0.44		*1.00*		
WHO_HIV	0.17	0.34	0.49		0.41	0.41		0.40	0.39	0.53		0.51	*1.00*	
Motivation	0.07	0.05	0.27	0.11	0.14	0.06	0.28	0.20	0.29	0.25	0.09	0.08	0.06	*1.00*
HIV S&S	−0.22	−0.41	−0.40	−0.38	−0.31	−0.35	−0.38	−0.28	−0.36	−0.34	−0.43	−0.33	−0.31	−0.12

WHO-HIV for sleep is item 21: How satisfied are you with your sleep?

While it is often reported that mood states, such as anxiety and depression, explain cognitive difficulties [57, 58], the observations here suggest that cognitive ability, measured from test scores, contributes unique information to understanding the basis of cognitive difficulties, as correlations of B-CAM with measures of symptoms of anxiety and depression were low (see Table 4, 5).

Furthermore, our analysis revealed that depressive symptoms act directly on QOL, as well as on the intermediate constructs of role participation and HP. This means that depression and anxiety symptoms do not account for the lower QOL observed among HIV-positive men with lower cognitive ability and/or cognitive difficulties in everyday activities.

A strength of the SEM approach is the use of latent variables to represent constructs such as HP and QOL. This overcomes some of the limitations of the previous literature linking cognition to QOL that used social function or mental or physical health indices as proxies for QOL [22, 59, 60], or total scores from multi-item dimensional questionnaires in which items assess multiple constructs in addition to cognitive problems [20, 21].

The current results generally concord with those of other studies that have used different measures. Several groups have observed the correlation between measured and self-reported cognition [19, 22, 61–63]. Tozzi et al. concluded, in a study published in 2003 ($n = 111$) using a regression approach, that QOL is influenced by cognitive impairment and by the ability to engage in activities of everyday living [22]. This study differs from ours in that 33% were untreated with antiretrovirals and they had been referred for neuropsychological testing because of risk or suspicion of cognitive impairment and 33% were cognitively impaired. Our study was of an unselected population, although response rates indicated that the well were less likely to enter [64]. Our study identified only indirect effects (or paths) by which cognition affects QOL in HIV. Previously, Heaton et al. [19] observed that results on neuropsychological testing no longer predicted function (employment status) when self-report measures were included in a regression model. Our results suggest that impairment on cognitive testing is only associated with role participation and QOL through self-reported cognitive difficulties and its impact on meaningful activity. Simioni reached a similar conclusion by demonstrating that prevalence of functional impact secondary to cognitive impairment was higher among patients with cognitive complaints than among non-complainers, and predicted poorer QOL [13].

Although the focus of the study was on cognition, this construct was one of several falling under the umbrella term of brain health. The effects of cognitive constructs on HP and QOL were not as strong as the other brain health constructs of anxiety, depression, vitality, and motivation indicating that a global approach to brain health is needed rather than focusing on single symptoms. These findings have implications for designing interventions to mitigate the impact of brain health on QOL in men living with HIV. The current SEM analysis highlights that multi-modal interventions are likely to be more effective than those that target single symptoms or impairments. While there is interest in cognitive training and rehabilitation, interventions addressing the determinants of self-reported cognitive difficulties, such as anxiety and health beliefs about life's meaning and stigma (see Table 1) could also be of value. Symptoms of depression had a direct effect on QOL, highlighting the importance of treating this as well as considering this depression in trials of interventions targeting QOL either directly or indirectly. Interventions would also need to provide ways for to manage external sources of stress and environmental challenges as these were impactful at all levels of the biopsychosocial model.

A unique feature of this study was to consider cognition as a quantity rather than a classification (i.e., impaired or not). To this end, we used the B-CAM [47, 65] which is a computerized battery of neuropsychological tests [48–51], with a continuous score derived from the location of the item cut-points on the Rasch model. This is a mathematically valid and relatively low-burden approach for large-scale assessment.

A limitation of SEM is that even when a directional model fits the data, directionality in a causal sense can only be confirmed by analysis of longitudinal data or interventions aimed at modifying one of the variables in the cascade that links biology to QOL.

Conclusion

This is the first time that such a complete biopsychosocial model has been tested in HIV [66]. This view of HIV outcomes is very helpful in directing more specific analyses on key variables. For example, the "beliefs" domain in personal factors includes an item related to stigma and a second SEM paper focusing on this important experience has recently been completed [67]. In addition, all of the domains included in the model are theoretically amenable to intervention and many have evidence-based interventions that could be harnessed to improve QOL.

Measured cognitive performance is considered to have widespread effects and to be an important contributor to QOL. But in this non-demented and functional sample, other constructs contributed greater explanatory strength for QOL. Self-reported cognitive difficulties were an important source of information in understanding the negative impact of lower cognitive performance on patients' lives. The current results

add to growing evidence concerning the clinical impact of HIV-associated cognitive impairment.

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Compliance with ethical standards

Conflict of interest Authors declare that they have no conflicts of interest.

Ethical approval All procedures performed were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The project was approved by the Research Ethics Board of each of the participating institutions.

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