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Changes in Cognition Precede Changes in HRQoL Among HIV+ Males: Longitudinal Analysis of the Multicenter AIDS Cohort Study

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Abstract

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Objectives: Despite treatment-related improvements in morbidity and mortality, HIV-1–infected (HIV+) individuals continue to face a wide range of HIV-associated medical and HIV-associated neurocognitive disorders. Little is known about the impact of cognitive impairment on patients' health-related quality of life (HRQoL). To address this, the current study examined the longitudinal relationship between cognitive functioning and HRQoL among HIV+ individuals.

Method: The sample consisted of 1,306 HIV + men enrolled in the Multicenter AIDS Cohort Study. Participants received biannual assessments of cognitive functioning (including tests of processing speed, executive functioning, attention/working memory, motor functioning, learning, and memory) and completed questionnaires assessing HRQoL and depression. Multilevel models were used to examine the longitudinal and cross-lagged relationship between HRQoL and cognition, independent of depression and HIV disease severity.

Results: There was a significant relationship between HRQoL and cognitive functioning both between and within subjects. Specifically, individuals who reported better HRQoL reported better cognitive functioning, and longitudinal change in cognition was positively related to change in HRQoL. There was a significant unidirectional-lagged relationship; cognition predicted HRQoL at subsequent visits, but HRQoL did not predict cognitive functioning at subsequent visits. Furthermore, analyses of severity of neurocognitive impairment revealed that transition to a more severe stage of cognitive impairment was associated with a decline in HRQoL.

Conclusions: Overall, the current study suggests that changes in HRQoL are partially driven by changes in cognitive functioning.

General Scientific Summary

Cognitive impairment is a common complication of HIV infection. The current study, based on a sample of 1,306 HIV+ adults followed longitudinally for up to 28 years, demonstrates that changes in cognitive functioning contribute, and predate, changes in quality of life among HIV+ individuals.

Keywords

HIV; quality of life; cognition; HIV-associated neurocognitive disorder; multilevel modeling

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Health-related quality of life (HRQoL) reflects individuals' perceptions of their overall well-being that can be influenced by illness (Wilson & Cleary, 1995). HRQoL is of particular relevance to the HIV-1–infected (HIV +) population (Tate et al., 2003). Despite the fact that advances in HIV treatments have greatly improved prognosis, patients continue to face challenges associated with HIV disease, including cognitive impairment, fatigue, neurologic/psychiatric comorbidities, physical limitations, and limited independent functioning (Leveille & Thapa, 2017). Indeed, previous studies have shown that individuals living with HIV report worse HRQoL relative to healthy uninfected controls and individuals with other chronic diseases such as epilepsy, gastroesophageal reflux disease, prostate cancer, depression, and diabetes (Bing et al., 2000; Hays et al., 2000). Among individuals with HIV, previous research has linked reduced QoL to depression, cognitive impairment, and markers of disease severity, such as lower current CD4 count, antiretroviral treatment interruptions, and more HIV-related symptoms (Liu et al., 2006; Parsons, Braaten, Hall, & Robertson,

2006; Tate et al., 2003). Thus, HRQoL is an important factor to evaluate and monitor in the treatment of HIV-infected individuals.

Cognitive impairment is a common complication of HIV infection, with a point prevalence of 40–50% (Heaton et al., 2011; Sanmarti et al., 2014). To date, a number of small cross-sectional studies (sample sizes range from 36 to 111) have investigated the contribution of cognitive impairment to HRQoL among HIV + individuals. Two studies demonstrated that a physical and mental health composite of HRQoL was associated with neuropsychological impairment and performance on all domains assessed (processing speed, mental flexibility, motor coordination, visuoconstruction, learning and delayed memory; Tozzi et al., 2003, 2004). Another study of HIV + women found that performance on tests of executive functioning and processing speed was associated with reduced HRQoL independent of emotional distress and current CD4 count (Osowiecki et al., 2000). Lastly, a fourth study showed that improvement in cognitive functioning following initiation of highly active antiretroviral therapy (HAART) was associated with improvements in HRQoL (Parsons et al., 2006). In addition to cognitive impairment, depression may be an important predictor of HRQoL (Jia, Uphold, Wu, Chen, & Duncan, 2005; Liu et al., 2006; Tate et al., 2003). Due to the potential overlap between depression, cognitive impairment, and HRQoL, depression may confound the relationship between cognitive impairment and HRQoL (Tate et al., 2003). Therefore, it is important to consider the independent effects of depression and cognition on HRQoL.

Although past studies provide initial support for a hypothesized relationship between cognitive functioning and HRQoL, the current study aims to expand upon the previous literature by examining the longitudinal and bidirectional relationship between cognitive functioning and HRQoL among a large cohort of HIV+ individuals followed for up to 28 years. There are three aims: (1) to determine the longitudinal relationship between HRQoL and cognition independent of depression and HIV disease severity, (2) to determine the bidirectional-lagged relationship between HRQoL and cognition to determine if changes in cognition predate changes in HRQoL or vice versa, and (3) to determine if transitions in severity of neurocognitive impairment (i.e., transitioning from no impairment to mild or severe impairment) relate to changes in HRQoL.

Method

Study Design

The study consisted of a subsample of participants recruited through the Multicenter AIDS Cohort Study (MACS), a longitudinal prospective multisite study of HIV+ and HIV-negative men. The details of the MACS have been described elsewhere (Detels et al., 2012; Kaslow et al., 1987). Participants were enrolled in one of four sites (Los Angeles, Pittsburgh, Chicago, and Baltimore/Washington). Enrollment occurred in three cohorts: in 1984–1985, 1987–1991, and 2001–2003. Of note, the measure of HRQoL (Short Form Health Survey [SF-36]) was incorporated into the MACS protocol in October 1994; thus, we used data collected after that date. The institutional review board at each of the clinical sites of the MACS approved all study activities.

We reviewed data from an initial pool of 2,143 HIV+ participants who completed neuropsychological testing. We excluded participants ($N = 837$) who never completed the measure of HRQoL during the course of the study or who demonstrated evidence of severe cognitive impairment (see below for criteria) at baseline. The final sample included 1,306 HIV+ participants (see online supplemental Table S1 for demographic and clinical characteristics of included and excluded participants). Participants in the current sample received biannual assessments and were followed longitudinally up to 28 years (median duration of study participation = 7 years, 7 months; see online supplemental Figure S1).

Neuropsychological Measures

The details of the neuropsychological testing have been described previously (Becker et al., 2015). Neuropsychological variables included tests from the following six domains: processing speed (Symbol Digit Modalities Test, Stroop Color Naming), executive functioning (Trail Making Test Part B, Stroop Interference), attention/working memory (simple and choice reaction time from the CalCAP Reaction Time program), motor functioning (dominant hand on the Grooved Pegboard Test), learning (Rey Auditory Verbal Learning Test, Trials 1–5; Rey Complex Figure immediate recall), and memory (Rey Auditory Verbal Learning Test delayed recall, Rey Complex Figure delayed recall).

Raw test scores were transformed into standardized scores using normative data derived from the MACS seronegative participants. Derived *z* scores were adjusted for age, years of education, ethnicity (Caucasian vs. other), and number of assessments. A global composite *z* score was computed at each assessment for each participant by averaging *z* scores for all cognitive domains.

Severity of neurocognitive impairment (cognitively intact, mild impairment, or severe impairment) was determined using cognitive cut-points established in previously published diagnostic criteria (Antinori et al., 2007). We used the following criteria: Severe impairment was defined if two or more tests, across two or more cognitive domains, scored two standard deviations below the mean (i.e., z score ≤ -2); mild impairment if two or more tests, across two or more cognitive domains, were one to two standard deviations below the mean; or no impairment if the above criteria were not met.

HRQoL

The SF-36 was used to measure HRQoL. The SF-36 contains 36 self-report items that assess health status across eight domains: vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, and mental health. Physical and mental health composite scores (Ware et al., 1995) were calculated, ranging from 0 to 100, with higher scores indicating better HRQoL.

Depression

Depression symptoms were measured using the Center for Epidemiological Studies Depression Scale (CES-D). The CES-D contains 20 self-report items on a 4-point Likert scale, with higher scores indicating greater depression severity.

Statistical Analyses

Multilevel modeling (MLM) was used to analyze the longitudinal relationship between cognitive functioning and HRQoL. Full-information maximum likelihood parameter estimation was used to account for missing data. For Aim 1, two MLM analyses were computed, with the mental health and physical HRQoL composite scores separately entered as the dependent variable for each analysis. Fixed predictors included within-person (Level 1; person-centered) global cognition, between-person (Level 2; mean-level) global cognition, within-person depression, between-person depression, age, nadir CD4 count, time (duration/months enrolled in study), and diagnosis pre/post-HAART (was the participant diagnosed with HIV prior to 1996). Random effects were also modeled for all time-varying variables (e.g., within-person depression, within-person global cognition and time). Random effects allow for the slopes/relationships between predictors and the dependent variable to differ across participants (i.e., does the relationship between depression and HRQoL differ between participants).

Because we were investigating the relationship between changes in QOL as a function of cognition, we included within- and between-subjects terms. The within-person and between-person terms were computed for cognition and depression in order to examine the following: (1) Do changes in a participant's cognition/depression relate to changes in HRQoL (i.e., within-person effect), or (2) do participants who on average have higher/lower values of cognitive functioning/depression across the duration of the study also tend to have higher/lower values of HRQoL (i.e., between-person effect)?

Aim 2 examined the bidirectional and lagged relationship between cognition and HRQoL. Similar MLM analyses were computed from Aim 1, except a lagged global cognition variable was computed and replaced the within-person global cognition variable. The lagged variable examines if HRQoL is predicted by a person's global cognitive performance at the previous assessment (i.e., does cognitive decline precede a decline in HRQoL). Additionally, further MLM analyses were conducted with global cognition entered as the dependent variable and HRQoL (both between person and lagged effects) entered as predictors in order to examine if global cognition was predicted by HRQoL at the previous visit.

Aim 3 examined if severity of neurocognitive impairment (i.e., cognitively intact, mild impairment, or severe impairment; Anti-nori et al., 2007) was related to HRQoL. MLM analyses were conducted, similar to Aim 1. The physical and mental health SF-36 composite scores were entered as the dependent variable for each MLM. Level of cognitive impairment (both within and between person) was entered as predictors in order to examine the following: (1) Does transitioning to a more severe level of cognitive impairment relate to worsening of HRQoL (i.e., within-person effect), and (2) do individuals who on average have more severe cognitive impairment tend to have worse HRQoL (i.e., between-person effect)? Additional predictors/covariates were similar to the previous aim and included within-person depression, between- person depression, age, nadir CD4 count, time, and pre/post-HAART era diagnosis.

For all analyses, all variables were transformed to *z* score metrics. This approach preserves all within-person and between-person differences and produces coefficients that can be

interpreted similar to traditional standardized regression coefficients (Bryk & Raudenbush, 1992).

Results

Table 1 displays sample and clinical characteristics and Table 2 displays characteristics for neuropsychological domains (see online supplemental Figure S2). There was no presence/history of stroke, heart attack, schizophrenia, or Alzheimer's disease among any participant in the sample.

A predictor-free model was implemented to calculate the intra-class correlation coefficient (ICC; σ^2 [between]/σ^2 [between + within]) and examine the within-person and between-person variability in physical and mental HRQoL. The ICC was 0.642 for the physical HRQoL composite and 0.567 for the mental HRQoL composite, meaning that 35.8% (physical HRQoL) and 43.3% (mental HRQoL) of the overall variance was a within-person (i.e., over time) effect. Online supplemental Table S2 displays the correlations between neuropsychological domains and mental and physical HRQoL at baseline.

Aim 1: Longitudinal Relationship Between HRQoL and Global Cognition

Table 3 displays results from the MLMs predicting physical HRQoL and mental HRQoL (dependent variable). Independent variables included global cognitive *z* score (within-and between-person effects), depression (within-and between-person effects), age, nadir CD4 count, time (duration/months enrolled in study), and a diagnosis of HIV pre/post-HAART era.

With respect to global cognition, physical HRQoL was significantly predicted by both the within- and between-person effect of cognition, meaning that individuals with better cognitive functioning tend to have better physical HRQoL (i.e., between-person effect) and that on occasions when participants tended to perform better on cognitive tasks, they also tended to report better physical HRQoL (i.e., within-person effect). Better physical HRQoL was also significantly related to time (physical HRQoL increased/improved over time on average), younger age, a diagnosis of HIV post-HAART, higher nadir CD4 levels, and fewer depressive symptoms (both within and between subjects).

Mental HRQoL was significantly related to global cognition between subjects but not within subjects. Specifically, individuals who reported better mental HRQoL throughout the study also had better global cognitive functioning, but changes in mental HRQoL were not associated with changes in cognition over time. Better mental HRQoL was also significantly predicted by older age and less severe symptoms of depression (both within-and between-subject effects).

See online supplemental Table S3 for models predicting physical and mental HRQoL from separate cognitive domain terms (executive functioning, processing speed, etc.).

Aim 2: Lagged MLM Models of Global Cognition and HRQoL

Lagged MLM models were computed with physical and mental HRQoL (dependent variables) being predicted by the global cognition *z* score at the previous assessment (see Table 4). Physical HRQoL was significantly predicted by lagged global cognition. Specifically, cognition at the previous assessment was positively related to physical HRQoL at the subsequent assessment. Better physical HRQoL was also associated with better mean-level cognition, lower severity of depression (both within and between subjects), lower age, and less severe nadir CD4.

Conversely, an additional MLM examined the alternative directionality of the above analysis: the relationship between lagged physical HRQoL (entered as an independent variable) and subsequent global cognition *z* scores (dependent variable). Results revealed that lagged physical HRQoL was not significantly related to global cognition at subsequent visits ($B = 0.010$, $SE = 0.025$, $p = .685$). Higher global cognition was significantly predicted by higher mean-level physical HRQoL ($B = 0.173$, $SE = 0.042$, $p < .001$), less severe mean-level depression ($B = –0.168$, $SE = 0.039$, $p < .001$), and younger age ($B = –0.103$, $SE = 0.045$, $p = .021$).

The above lagged analyses were repeated for mental HRQoL. Lagged global cognition *z* scores were not significantly associated with mental HRQoL at subsequent evaluations. Better mental HRQoL was associated with better mean-level cognitive *z* scores, less severe depression (within and between subjects), and older age. An additional MLM examined the alternative directionality (i.e., does lagged mental HRQoL predict global cognition at subsequent assessments). Lagged mental HRQoL was not predictive of subsequent cognitive functioning ($B = 0.004$, $SE = 0.022$, $p = .850$).

Aim 3: Longitudinal Relationship Between HRQoL and Severity of Neurocognitive Impairment

Participants were classified based on severity of neurocognitive impairment (i.e., cognitively intact, mild impairment, or severe impairment) based on previously established cut-points (Antinori et al., 2007). We investigated the stability of neurocognitive classifications among participants who had at least two neurocognitive assessments ($n = 869$). In total, 66.5% of participants ($n = 578$) were classified as cognitively intact at baseline. At the second assessment, 77.9% ($n = 450$) continued to be cognitively intact, 20.6% ($n = 119$) progressed to mild neurocognitive impairment, and 1.6% ($n = 9$) progressed to severe neurocognitive impairment. Of the participants, 33.5% ($n = 291$) were classified as having mild neurocognitive impairment at baseline. At the second assessment, 49.8% ($n = 145$) reverted to being cognitively intact, 42.6% ($n = 124$) continued to meet criteria for mild impairment, and 7.6% ($n = 22$) reverted to having severe impairment. The 4-year stability of HIV Associated Neurocognitive Disorder (HAND) classifications has previously been reported in the MACS cohort (Sacktor et al., 2016).

MLM analyses examined the longitudinal relationship between HRQoL and severity/stage of neurocognitive impairment (see Table 5). Physical HRQoL was significantly related to both the between-subjects and the within-subjects effects of neurocognitive impairment

stage. Specifically, participants who on average reported better physical HRQoL were more likely to be classified at a less severe stage of neurocognitive impairment (between-subjects effect), and transitioning to a more severe stage of neurocognitive impairment (i.e., cognitively intact to mild impairment or mild impairment to severe impairment) was associated with declines (or less improvement) in physical HRQoL. Regarding other predictors in the model, better physical HRQoL was also predicted by less severe depressive symptoms (within and between subjects), younger age, being diagnosed with HIV post-HAART era, and less severe nadir CD4.

Analyses examining mental HRQoL found a between-person association with neurocognitive impairment. Participants who on average reported better mental HRQoL had significantly less severe neurocognitive impairment. However, mental HRQoL was not predicted by the within-subjects neurocognitive impairment term. Better mental HRQoL was also significantly predicted by less severe depression (within and between subjects) and older age.

Discussion

This is the first study to show a longitudinal relationship between cognition and HRQoL among HIV+ individuals. Specifically, we found evidence of a unidirectional relationship; changes in cognitive functioning preceded and were predictive of future changes in HRQoL. Changes in HRQoL did not predict future changes in cognition. In addition to HRQoL being related to cognitive functioning, better HRQoL was also generally related to fewer symptoms of depression and less severe HIV disease (diagnosed with HIV post-HAART era and less severe nadir CD4 levels).

There is evidence that cognitive impairments are underrecognized by primary care physicians (Borson, Scanlan, Watanabe, Tu, & Lessig, 2006). Two possible reasons for inaccurate recognition of cognitive impairment include (1) inaccurate subjective reports of cognitive impairment by HIV+ patients, suggesting that clinicians should not depend solely on the patient's subjective report (Hinkin et al., 1996; Rourke, Halman, & Bassel, 1999), and (2) inaccurate detection of cognitive impairment, particularly milder forms of HAND, by cognitive screeners that lack sufficient sensitivity (Janssen, Bosch, Koopmans, & Kessels, 2015).

Ongoing monitoring of immunological/medical status is obviously important for the clinical care of patients with HIV infection. Indeed, measures of HIV severity, including receiving a diagnosis post-HAART, low nadir CD4, and better medication adherence, have been shown to be associated with better cognition and HRQoL (Becker, Thames, Woo, Castellon, & Hinkin, 2011; Hinkin et al., 2004; Kowal et al., 2008; Liu et al., 2006; Mannheimer et al., 2005). Our findings indicate that more stringent monitoring and maintenance of cognitive function may also help sustain HRQoL. Interventions, either behavioral or pharmaceutical, focused on improving cognitive functioning could prove useful; however, there have been few studies of restorative cognitive interventions in HIV+, and findings have been inconclusive (Becker et al., 2012; Vance, Fazeli, Ross, Wadley, & Ball, 2012; Weber,

Blackstone, & Woods, 2013). Alternatively, efforts to preserve cognitive functioning via compensatory interventions may prove more fruitful (Twamley et al., 2015).

Although HRQoL was significantly related to cognition (either within or between subjects), depression was generally the strongest predictor of HRQoL, particularly in the mental health domain. Our findings are consistent with past studies of HIV+ samples (Elliott, Russo, & Roy-Byrne, 2002; Liu et al., 2006; Tate et al., 2003), as well as in other progressive neurologic populations, including Parkinson's disease (Jones, Marsiske, Okun, & Bowers, 2015; Jones et al., 2015) and Alzheimer's disease (Gonzalez-Salvador et al., 2000; Shin, Carter, Masterman, Fairbanks, & Cummings, 2005). Due to the possible overlap between depression and cognitive functioning, it is important to highlight that depression and cognition both had independent/orthogonal effects on HRQoL. Therefore, it is unlikely that depression is confounding the relationship between cognition and HRQoL.

The strong relationship between depression and HRQoL suggests that adequate mental health assessment and treatment may be one of the most important clinical services in terms of preserving HRQoL. A prior study that found that depression is frequently underdiagnosed and undertreated by health care professionals further highlights the importance of improving mental health detection (Asch et al., 2003; Pence, O'Donnell, & Gaynes, 2012). Future studies are required to examine if interventions for depression have a positive effect on HRQoL. However, it is important to note that in the current study, the strong relationship between depression and HRQoL may be partially related to similar modalities; both depression and HRQoL were measured with self-reported questionnaires, whereas cognition and HIV disease severity were measured with more objective methods. Conversely, the sample reported minimal to mild symptoms of depression at baseline, on average. Therefore, the influence of depression on HRQoL could potentially be stronger among a group with more severe depression.

In the current study, cognitive functioning was related to HRQoL independent of possible confounders such as depression and measures of HIV severity. Past studies have shown a link between markers of cognitive impairment and functional problems in activities of daily living (Heaton et al., 2004; Morgan, Woods, & Grant, 2012). Future studies are needed to examine if the relationship between cognition and HRQoL is mediated by ability to independently engage in activities of daily living.

Limitations to the current study include relying on participant-reported HRQoL. Due to the high rates of apathy and cognitive impairment among HIV+ individuals, it is possible that informant/caregiver report of HRQoL may differ from the participant's report. Future studies may benefit by examining the contribution of cognitive impairment to caregiver burden. The current study focused on cognitive functioning as a "global" composite measure of multiple neuropsychological domains, although domain-level analyses are available in online supplemental Table S3. The finding of HRQoL being related to a global cognitive term is consistent with past cross-sectional studies that found HRQoL to be related to all neuropsychological domains assessed (Tozzi et al., 2003, 2004). Severity of neurocognitive impairment was based on the criteria by Antinori et al. (2007). Consistent with past MACS papers, the current study utilizes two tests within six domains (see Neuropsychological

Measures above), except for the motor domain, which only consisted of the grooved pegboard dominant hand performance (Levine et al., 2014; Sacktor et al., 2016). However, it is important to note that HAND criteria are sensitive to the overall number of tests used. The current estimation of neurocognitive impairment may differ from studies utilizing differing numbers of tests or different HAND criteria. The current study focused on the relationship between cognitive impairment and HRQoL, regardless of the cause of neurologic compromise. As such, we did not exclude participants on the basis of substance use. Future studies may wish to examine possible moderators of the relationship between cognition and HRQoL among HIV+ individuals. Finally, it is important to note that the sample consisted entirely of men, and findings may not generalize to women with HIV.

Overall, the current study demonstrates that longitudinal changes in HRQoL are partially driven by changes in cognitive functioning. Future efforts to improve the clinical care of HIV patients may profit through incorporating treatments/interventions for cognitive impairment and mental health, ultimately to the benefit of patients' quality of life.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Mean Baseline Sample Characteristics (N = 1,306)

Variable	Value
Age, *M* (SD)	42.0 (8.8)
Percent Caucasian	60.2
Mental Health SF-36 Composite, *M* (*SD*)	46.8 (12.8)
Physical SF-36 Composite, *M* (*SD*)	49.2 (10.3)
Global cognition (*z* score), *M (SD)*	−.13 (.95)
Percent diagnosed pre-HAART	93.3
Percent cognitively intact	62.5
Percent mild impairment	37.5
CES-D, *M* (*SD*)	12.7 (11.4)
Years with HIV, *M* (*SD*)	13.5 (4.5)
Percent with detectable viral load	57
CD4 at baseline, median (IQR)	456(269–647)
Nadir CD4, median (IQR)	265 (126–402)
Viral load at baseline, median (IQR)	269 (40–18,624)
Marijuana use, %[a]	48.8
Cocaine use, %[a]	23.7
Methamphetamine use, %[a]	13.8
Ecstasy/MDMA use, %[a]	7.1
Opiate use, %[a]	3.6

Note. HAART = highly active antiretroviral therapy; CES-D = Center for Epidemiological Studies Depression Scale; IQR = interquartile range; MDMA = Methylenedioxymethamphetamine.

[a]Percent reporting a past history of substance use or reporting use any time during the study duration.

Table 2

Mean Baseline Neuropsychological Characteristics

Value	Mean (*SD*)	Median	Interquartile range
Executive functioning	−.18 (.92)	−.07	−.6 to .4
Processing speed	−.12 (.90)	−.05	−.6 to .4
Attention/working memory	−.16 (.94)	−.19	−.7 to .5
Motor functioning	−.04 (.89)	.01	−.7 to .5
Learning	−.10 (.9)	−.01	−.7 to .6
Memory	−.10 (.9)	−.004	−.7 to .5

Note. Neuropsychological variables represent normative *z* score composites from the following six domains: processing speed (Symbol Digit Modalities Test, Stroop Color Naming), executive functioning (Trail Making Test Part B, Stroop Interference), attention/working memory (simple and choice reaction time from the CalCAP Reaction Time program), motor functioning (dominant hand on the Grooved Pegboard Test), learning (Rey Auditory Verbal Learning Test, Trials 1–5; Rey Complex Figure immediate recall), and memory (Rey Auditory Verbal Learning Test delayed recall, Rey Complex Figure delayed recall).

Table 3

Multilevel Models Predicting Health-Related Quality of Life From Global Cognition

Variable	Physical HRQoL			Mental HRQoL		
	B	*SE*	*p*	*B*	*SE*	*p*
Fixed effects						
Within-person (Level 1)						
Global cognition	.104	.016	<.001	−.019	.012	.125
Depression	−.056	.019	.003	−.637	.018	<.001
Time	.045	.022	.042	−.011	.013	.395
Between-person (Level 2)						
Global cognition	.125	.029	<.001	.038	.016	.015
Depression	−.274	.025	<.001	−.792	.014	<.001
Age	−.172	.028	<.001	.056	.015	<.001
HAART era	−.340	.104	.001	.001	.060	.988
Nadir CD4	.183	.029	<.001	.003	.016	.867
Random effects						
Within-person (Level 1)						
Global cognition	.040	.009	<.001	.016	.005	<.001
Depression	.075	.012	<.001	.092	.010	<.001
Time	.066	.010	<.001	.022	.005	<.001
Within-pseudo R^2			.254			.563
Between-pseudo R^2			.212			.810

Note. HRQoL = health-related quality of life; HAART = highly active antiretroviral therapy.

Table 4

Multilevel Models Predicting Health-Related Quality of Life From Lagged Global Cognition

Variable	Physical HRQoL			Mental HRQoL		
	B	*SE*	*p*	*B*	*SE*	*p*
Fixed effects						
Within-person (Level 1)						
Lagged cognition	.056	.017	.001	−.012	.013	.378
Depression	−.066	.019	.001	−.618	.019	<.001
Time	.035	.025	.161	−.013	.014	.366
Between-person (Level 2)						
Global cognition	.145	.033	<.001	.060	.017	<.001
Depression	−.305	.028	<.001	−.795	.015	<.001
Age	−.167	.032	<.001	.064	.017	<.001
HAART era	−.137	.157	.383	.044	.085	.609
Nadir CD4	.215	.034	<.001	.012	.018	.502
Random effects						
Within-person (Level 1)						
Lagged cognition	.025	.008	.001	.015	.005	.005
Depression	.065	.012	<.001	.099	.012	<.001
Time	.062	.010	<.001	.015	.004	<.001
Within-pseudo R^2			.239			.563
Between-pseudo R^2			.208			.821

Note. HRQoL = health-related quality of life; HAART = highly active antiretroviral therapy.

Table 5

Multilevel Models Predicting Health-Related Quality of Life From Global Cognitive Classifications

Variable	Physical HRQoL			Mental HRQoL		
	B	*SE*	*p*	*B*	*SE*	*p*
Fixed effects						
Within-person (Level 1)						
Lagged cognition	−.034	.009	<.001	−.003	.007	.672
Depression	−.068	.018	<.001	−.626	.017	<.001
Time	.042	.022	.058	−.006	.013	.629
Between-person (Level 2)						
Global cognition	−.115	.021	<.001	−.036	.012	.002
Depression	−.068	.018	<.001	−.792	.013	<.001
Age	−.164	.027	<.001	.053	.015	<.001
HAART era	−.330	.104	.002	−.018	.060	.761
Nadir CD4	.182	.029	<.001	.005	.016	.752
Random effects						
Within-person (Level 1)						
Cognitive Classification	.012	.003	<.001	.006	.002	<.001
Depression	.073	.011	<.001	.090	.010	<.001
Time	.072	.010	<.001	.021	.004	<.001
Within-pseudo R^2			.239			.560
Between-pseudo R^2			.201			.803

Note. HRQoL = health-related quality of life; HAART = highly active antiretroviral therapy.