Personalized Risk Index for Neurocognitive Decline Among People With Well-Controlled HIV Infection

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Background: Little is known about the predictors of neurocognitive decline in HIV+ individuals with good virological control. Identification of modifiable risk factors would allow targeted interventions to reduce the risk of decline in higher risk individuals. The objective of this study was to develop a risk index to predict neurocognitive decline over 3 years in aviremic HIV+ individuals.

Methods: As part of the CNS HIV Anti-Retroviral Therapy Effects Research (CHARTER) study, HIV+ adults completed clinical evaluation and neuropsychological tests every 6 months. Group-based trajectory analysis was used to detect patterns of neurocognitive change; individuals who deteriorated ≥ 0.5 SD on at least one neuropsychological test were considered decliners. Multiple logistic regression was used to identify baseline sociodemographic, clinical, biological, and lifestyle factors associated with decline in the subgroup that was consistently aviremic during the first 3 years. A risk index was developed using the beta-coefficients from the final regression model.

Results: Neurocognitive decline occurred in 23 of 191 (12%) participants followed longitudinally. The baseline factors that predicted decline were glomerular filtration rate ≤50 mL/min, known duration of HIV infection ≥15 years, education ≤12 years, and cerebrospinal fluid protein >45 mg/dL.

Conclusions: Using this analytic approach, neurocognitive decline was uncommon in this sample of aviremic HIV+ individuals. The 3-year risk of decline ranged from 2% in those with no risk factors to 95% in those with all 4. The strongest predictor was glomerular filtration rate, also a predictor of cardiovascular disease. This raises the possibility that controlling vascular risk factors could reduce the risk of neurocognitive decline.

Key Words: HIV, HIV-associated neurocognitive disorder, neurocognitive decline, risk index

(*J Acquir Immune Defic Syndr* 2017;76:48–54)

INTRODUCTION

In recent years, the burden of neurocognitive complications associated with HIV infection has shifted from HIV-associated dementia to milder forms of impairment.[1] Though mild, neurocognitive impairment remains of clinical concern, as it is associated with functional impairment,[2] and maybe a harbinger of future deterioration.[2,3] The clinical management of HIV infection has also changed, with antiretroviral therapy (ART) being initiated earlier in the course of the disease.[4] A larger proportion of HIV+ individuals are now expected to live longer while remaining aviremic.

Neurocognitive decline is not completely averted in aviremic HIV+ individuals.[5] For clinicians, this persistent risk brings up an important question: once an individual is aviremic, are additional measures required to maintain brain health? Identification of risk factors for neurocognitive decline among aviremic individuals could suggest potential targets for intervention to reduce this risk, beyond the control of the infection itself.

At the individual level, estimating the risk of decline in HIV+ individuals is complicated by the simultaneous presence of multiple risk factors for neurocognitive impairment or decline. Although some risk factors (eg, age) are immutable, modifiable risk factors can guide interventions aimed at reducing the risk of neurocognitive decline. Quantification of each risk factor's contribution to the overall risk of neurocognitive deterioration would allow clinicians to focus on high-risk individuals and target-specific risk factors, as opposed to implementing a generic approach.

Received for publication December 5, 2016; accepted May 17, 2017.

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This work was supported by the grants from the Canadian Institutes of Health Research (L.K.F., M.-J.B., and N.M., TCO-125272), the Research Institute of the McGill University Health Centre (M.-J.B.), and the CNS HIV Anti-Retroviral Therapy Effects Research was supported by awards N01 MH22005, HHSN271201000036C and HHSN271201000030C from the National Institutes of Health. The remaining authors have no conflicts of interest to disclose.

The views expressed in this article are those of the authors and do not reflect the official policy or position of the United States Government.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.jaids.com).

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A risk index enables clinicians to compute the conjoint risk of an outcome (eg, neurocognitive decline) and the contribution of each risk factor associated with a patient's current clinical profile. This provides easily interpretable numbers that can facilitate the development of a personalized management strategy for brain health. Although risk indices for neurocognitive decline exist for the general population,[6–9] there is no published information on their validity in the HIV+ population.

The aim of this study was to develop a risk index for neurocognitive decline within 3 years among aviremic HIV+ individuals based on sociodemographic, clinical, and lifestyle factors measured at the time of cohort entry.

METHODS

Study Sample

Participants were in the longitudinal component of the CNS HIV Anti-Retroviral Therapy Effects Research (CHARTER) cohort study. Seven hundred one HIV+ adults, recruited between September 2003 and August 2007, underwent neuropsychological (NP) testing and medical examination every 6 months.[10] Written informed consent was obtained from all study participants. For the development of the risk index, only the data up to 3 years (median follow-up time) were used, and only participants who underwent NP testing on at least 2 occasions and remained aviremic during the first 3 years of follow-up were considered for the analysis. A total of 191 participants fulfilled both the criteria. The Psychiatry/Psychology Research Ethics Board of the McGill University Health Centre (13-214-PSY) approved the secondary analysis of the data.

Measurement

The outcome, neurocognitive decline, was a binary variable. The predictors were categorical variables representing sociodemographic and lifestyle characteristics and selected HIV and non–HIV-related clinical variables, measured at baseline.

Outcome

Participants completed a battery of 15 NP tests.[1] Raw scores of each test were modeled using group-based trajectory analysis (GBTA)[11] to identify groups with similar changes in test scores over time. Individuals with missing follow-up assessments were included, as GBTA can be performed with missing information. For each NP test, models with different numbers of trajectory groups and parameterization of time were compared using fit statistics and posterior group probabilities. The model with the best fit was selected. Each trajectory from the 15 selected GBTA models (one for each NP test) was categorized into 3 groups based on the estimated regression parameters: stable, improved, or declined. An individual was categorized as a decliner if he or she was assigned to a trajectory of deteriorating performance of $\geq$0.5 SD on at least one NP test. The method has been described in detail elsewhere.[12]

Predictors

At baseline, all participants completed a medical evaluation, and 166 (86.9%) underwent lumbar puncture. The glomerular filtration rate (eGFR) was estimated using the Modification of Diet in Renal Disease (MDRD) Study equation, taking into account the creatinine level, age, sex, and race. The predictors considered for the risk index were selected based on published risk factors of neurocognitive impairment or decline in HIV+ adults or the general population.[13–23] To develop a risk score with widespread applicability, only variables that are commonly available clinically were included. The exception to this rule was the inclusion of cerebrospinal fluid (CSF) markers. Although lumbar puncture is not part of routine care for HIV+ adults, a strong predictive finding could justify a change in practice for select high-risk patients. The selected continuous risk factors were then categorized using normal ranges for laboratory values or in consultation with HIV clinicians. A separate category was used for missing data.

Statistical Analysis

Multiple logistic regression was used to identify risk factors that were predictive of neurocognitive decline. First, each risk factor was modeled using univariate logistic regression. Then, a multiple logistic regression model was performed using all risk factors. Risk factors were retained in the final logistic regression model if the associated odds ratio was $>$3.0 and the lower bound of the 95% confidence interval exceeded 0.8; factors that reached statistical significance ($P <$ 0.05) were also included.

The fit and predictive accuracy of the final model was tested using the Hosmer–Lemeshow test. Internal validity was assessed using the bootstrap method with 1000 replications. Each unique risk profile yields a unique risk index derived from summing the regression weights ($\times$10), which is used to calculate the risk of decline over 3 years. All analyses were performed using SAS version 9.3.[24]

RESULTS

Study Population

Table 1 describes the sociodemographic and clinical characteristics of the 191 participants at the time of initial assessment. The cohort was largely composed of adult men with a median of 12 years of education. Fewer than 25% of the participants were older than 50 years. Twelve participants (6.3%) were missing information on one or more predictors. There were neither statistically significant differences in clinical profile nor observed systematic differences between those with and without missing values.

Trajectories of NP Test Performance

The proportion of aviremic individuals assigned to each trajectory type on each of the 15 NP tests is summarized in Table 2. Across all 15 tests, 88.0% of the cohort had stable or improved performance over the course of follow-up. Twenty-three individuals (12.0%) declined on at least one NP test and

TABLE 1. Sociodemographic and Clinical Characteristics at Study Entry in 191 CHARTER Participants Who Completed at Least 2 Neuropsychological Assessments and Were Aviremic Throughout the First 3 Years of Follow-Up

	Median [IQR] or N (%)
Demographics	
Age, yrs	45 [40–50]
Education, yrs	12 [11–15]
Sex, male	141 (73.8%)
Non-black	97 (51.8%)
HIV disease parameters	
Duration of HIV infection, yrs	10.4 [5.0–14.6]
Current $CD4^+$ T-cell count, /mm^3	514 [360–708]
Nadir $CD4^+$ T-cell count, /mm^3	121 [25–235]
Currently on ART	188 (98.3%)
Taking efavirenz	58 (30.4%)
Taking tenofovir DF	121 (63.4%)
CPE score	
≥7	131 (68.6%)
≥8	87 (45.6%)
CSF biomarkers (on N = 166)	
CSF WBC > 5 cells/μL	18 (10.8%)
CSF Protein > 45 mg/dL	53 (31.9%)
CSF HIV RNA ≥ 50 copies/mL	3 (1.8%)
Selected clinical parameters	
BMI, kg/m^2	
<18.5	2 (1.01%)
18.5–24.9	68 (36.0%)
25–29.9	76 (39.7%)
≥30	38 (19.9%)
Systolic blood pressure, mm/Hg	
<120	67 (35.1%)
120–140	95 (49.7%)
≥140	28 (14.7%)
Diastolic blood pressure, mm/Hg	
<80	98 (51.3%)
80–89.9	67 (35.1%)
90–99.9	20 (10.5%)
≥100	5 (2.6%)
eGFR ≤ 50 mL/min	14 (7.3%)
Comorbidities	
Hepatitis C seropositive	60 (31.4%)
Diagnosis of hypertension	18 (9.4%)
Diagnosis of diabetes	10 (5.2%)
Hyperlipidemia	7 (3.7%)
Cardiovascular disease	2 (1.1%)
Cerebrovascular disease	6 (3.1%)
Current or history of depression	107 (56.2%)
Current or history of dysthymic disorder	4 (2.1%)
History of substance and/or alcohol abuse	97 (50.8%)
Psychotropic use	82 (42.9)
Antidepressant use	69 (36.1%)
Tobacco smoking in past 30 d	90 (47.1%)

BMI, body mass index; CPE, central nervous system penetration effectiveness; DF, disoproxil fumarate; IQF, interquartile range; WBC, white blood cell.

only 4 of whom declined on more than one test. The highest proportion of decliners was observed in the Grooved Pegboard test, dominant hand (n = 15, 7.9%), followed by the Trail Making Test-B (n = 7, 3.7%), with remaining tests identifying 2% or less of decliners. No participant declined on tests for memory recall.

Risk Factors for Neurocognitive Decline

Results of the univariate and final logistic regression models are presented in Table 3 (the full model can be found in the Supplemental Digital Content, Table 1, http://links.lww.com/QAI/B47). In the univariate analysis, 6 factors met the criteria for prediction of neurocognitive decline. While smoking in the last 30 days, body mass index ≥ 30 kg/m^2, cerebrovascular disease and low hemoglobin levels were predictive in the univariate analyses, they did not remain statistically significant in the presence of decreased eGFR. The final model included 4 risk factors: eGFR ≤ 50 mL/min was the strongest predictor, followed by a known duration of HIV infection ≥15 years, education ≤12 years, and CSF protein level > 45 mg/dL. CSF viremia ≥50 copies/mL at baseline was very rare and was not predictive of decline. The presence of cardiovascular or cerebrovascular disease was also rare and their effect could not be tested.

The final multiple logistic regression model was internally validated using bootstrap simulation with 1000 replications. All estimates were robust and c-statistics was estimated to be 0.83, indicating strong predictive accuracy.[25] The Hosmer–Lemeshow test for goodness of fit indicates good model fit throughout the range of the observed data.

Risk Index for Neurocognitive Decline

Table 4 describes the personalized risk index of neurocognitive decline among aviremic HIV+ individuals in CHARTER. A higher score indicates increased 3-year risk of neurocognitive decline. To further illustrate the clinical application of the risk index, clinical profiles with different combinations of the risk factors, their corresponding risk score, and the estimated 3-year risk of neurocognitive decline are presented in Table 5. The estimated background risk of neurocognitive decline over 3 years was 2% for individuals without any of the selected risk factors. Having only eGFR ≤ 50 mL/min increases the risk from 2% to 21%; having all 4 risk factors increases the risk to 95%.

DISCUSSION

Neurocognitive decline, defined as deterioration in performance ≥ 0.5 SD on at least one NP test in the first 3 years of follow-up, was identified in 12% of the study cohort using GBTA. The personalized risk index included 4 clinical factors that were significant predictors of neurocognitive decline. Lower eGFR was the strongest predictor. Consistent with published literature, longer HIV duration and fewer years of education also increased the risk of neurocognitive decline in this study.[26–28] Moreover, we found that individuals with a CSF protein concentration greater than 45 mg/dL were also at heightened risk of decline.

TABLE 2. Classification of the 191 HIV+ Aviremic CHARTER Participants in the 15 Group-Based Trajectory Analysis Models

	Declined		Improved		Stable	
	N	%	N	%	N	%
Speed of information processing						
Trail Making Test-A	1	0.5	6	3.1	184	96.3
Digit symbol	0		4	2.1	187	97.9
Symbol search	0		7	3.7	184	96.3
Executive function						
Trail Making Test-B	7	3.7	30	15.7	154	80.6
Wisconsin card sorting test	2	1.1	0		174	91.1
Verbal fluency						
Category fluency	0		0		191	100
Letter fluency	0		0		191	100
Attention/working memory						
PASAT	0		25	13.1	166	86.9
Letter number sequencing	1	0.5	8	4.2	182	95.3
Memory learning						
BVMT total learning	0		0		191	100
HVLT total learning	1	0.5	0		190	99.5
Memory recall						
BVMT delayed recall	0		0		191	100
HVLT delayed recall	0		43	22.5	148	77.5
Motor function						
Grooved Pegboard-dominant	15	7.9	4	2.1	172	90.1
Grooved Pegboard nondominant	2	1.1	0		189	98.9

BVMT, brief visuospatial memory test; HVLT, Hopkins verbal learning and memory test; PASAT, paced auditory serial addition test.

The mechanism that underpins the correlation between lower baseline eGFR and future cognitive decline is unclear, but could reflect the presence of vascular pathology in the kidney and the brain. Several lines of observation support this hypothesis. Lower eGFR is a known independent predictor of atherosclerotic vascular disease.[29] In non-HIV individuals, lower eGFR has been independently associated with lower cerebral blood flow,[30] cognitive decline,[31] and increases the risk of recurrent stroke and small brain infarctions, both risk factors for cognitive decline.[32] Another biomarker of GFR, cystatin C, is also associated with neurocognitive impairment in individuals without[33] and with HIV.[34] The contribution of vascular disease has also been suggested as an explanation of the observed association between proteinuria and neurocognitive impairment in antiretroviral-treated HIV+ individuals.[35]

Vascular risk factors in middle age are predictors of dementia in later life in the general population, although this effect is seen over decades, not years.[8] These risk factors, such as hypertension, diabetes, or smoking, are more common in HIV+ individuals than in the general population, and could be contributing to higher rates of neurocognitive decline. Individual vascular risk factors were not associated with neurocognitive decline in our sample. One possible reason for this lack of association is that, in this clinical sample, people would be treated for hypertension and diabetes, which could attenuate their negative consequences. Perhaps eGFR is serving as a more biologically relevant marker of accumulated vascular damage than the individual vascular risk clinical diagnoses. The accumulated vascular risk of smoking may likewise not have been fully captured by measuring smoking in only the last 30 days.

Although the vascular hypothesis to explain the association between eGFR and declining cognition is attractive, there are other causes of lower eGFR in HIV+ individuals: it may reflect exposure to tenofovir disoproxil fumarate or other antiretroviral agents that can elevate creatinine, or be explained by HIV-associated nephropathy and glomerulonephritis.[36] Further work is needed before concluding that the link between eGFR and neurocognitive decline reflects a vascular mechanism. Clarification of this issue is clinically important because many vascular risk factors are modifiable, unlike the other risk factors for cognitive decline identified here.

The association between increased CSF protein levels and cognitive decline is difficult to interpret. It may reflect a disruption in blood–brain barrier (BBB). CSF protein levels are elevated in a variety of inflammatory and neurodegenerative disorders. In the general population, an age-dependent increase in BBB permeability has been reported in neurologically healthy individuals, with a greater increase in patients with vascular or Alzheimer disease type dementia. The temporal relationship between breakdown of the barrier and neurodegeneration remains uncertain, but evidence is accumulating that the barrier fails first.[37] HIV infection is known to disrupt the BBB and alterations in the integrity of the BBB have been associated with the severity of HIV-associated dementia[38] and with CSF markers of neuronal damage in ART-treated individuals.[39] The additional risk conferred by the presence of a CSF protein level $>$ 45 mg/dL is large, particularly when combined with decreased eGFR or with 2 other risk factors. However, because the presence of this risk does not suggest any clinical intervention, the decision to perform a lumbar puncture solely for the purpose of clarifying the level of risk of future cognitive decline is not indicated.

Surprisingly, none of the usual HIV biomarkers (nadir or current $CD4^+$ T-cell count, detectable viral load in CSF) or ART characteristics was predictive of neurocognitive decline. However, 2 of the 4 predictors may relate to direct effects of HIV on the brain. Higher CSF protein may reflect inflammation or other causes of BBB breakdown plausibly linked directly to HIV presence within the central nervous system, with inflammation reported in postmortem brain tissue even in the cART era.[40] The relationship between neurocognitive decline and estimated duration of infection $\geq$15 years is more complex to interpret, as it may in part reflect the changing treatment in the pre-cART to cART era and be influenced by survivor biases. These predictors may be less important in patients who initiate ART earlier in the disease, but this needs active study.

Lower education is a risk factor for neurocognitive decline or dementia in studies in the general population,[11] and we identified it here as well. Higher education likely reflects many socioeconomic factors and cognitive reserve. It is a reminder that personal "resilience" factors in general may have the potential in modifying the natural history of the neurocognitive effects of HIV infection.

This study has several strengths. The CHARTER cohort constitutes a unique data source: a large representative sample of

TABLE 3. Results of Univariate and Final Logistic Regression Models of Predictive Sociodemographic and Clinical Factors at Initial Assessment Predictive of NC Decline Within First 3 Years in 191 Aviremic HIV+ CHARTER Participants

	Univariate Model		Final Model		Validation	
	OR	95% CI	OR	95% CI	OR	95% CI
Sociodemographics						
Education ≤ 12 yrs	3.04	1.14 to 8.10	3.78	1.31 to 10.94	5.45	1.44 to 24.09
HIV disease parameters						
Duration of HIV infection						
<5	Referent		Referent		Referent	
5–10	0.33	0.03 to 0.33	0.33	0.03 to 3.50	0.78	0.08 to 9.40
10–15	1.1	0.23 to 0.87	0.87	0.16 to 4.83	1.49	0.20 to 14.28
15+	4.13	1.01 to 5.97	5.97	1.29 to 27.60	11.14	1.61 to 88.08
Nadir $CD4^+$ T-cell count, /mm^3						
<200	2.9	0.37 to 22.85				
200–350	3.53	0.34 to 37.10				
350+	Referent		Referent		Referent	
CSF biomarkers						
CSF protein > 45 mg/dL	3.03	1.17 to 7.83	3.17	1.12 to 8.97	4.55	1.36 to 15.74
Selected clinical parameters						
eGFR ≤ 50 mL/min	5.18	0.82 to 32.80	13.06	1.27 to 133.98	18.14	1.53 to 254.43
Hemoglobin (<12.7 g/dL for men, <10.5 g/dL for women)	3.31	0.94 to 11.58	2.26	0.54 to 9.45		
BMI, kg/m^2						
25–29.5	2.42	0.72 to 8.13				
≥30	3.00	0.79 to 11.39				
Current comorbidities						
Hepatitis C seropositive	1.19	0.48 to 2.98				
Diagnosis of cerebrovascular disease	8.25	1.56 to 43.66	3.87	0.52 to 28.79		
Diagnosis of hypertension	1.53	0.41 to 5.75				
Hyperlipidemia	3.11	0.57 to 17.03				
Diabetes	1.91	0.38 to 9.58				
Smoking in the last 30 d	1.00	0.98 to 1.02				

BMI, body mass index; CI, confidence interval; OR, odds ratio.

HIV+ individuals in the United States who are well characterized. Selecting the aviremic subsample allowed us to test a comprehensive set of predictors in a population that is relevant to settings where most patients are effectively treated with cART. The use of GBTA to detect neurocognitive decline is novel in HIV research. This is a sensitive method, well suited to longitudinal data sets including those with missing data. The risk index has strong predictive accuracy, comparable to similar risk indexes for dementia in the general population.[11]

This study also has limitations. First, the cohort was relatively young with fewer than 25% of the cohort older than 50 years of age and change was assessed over 3 years only. Also, in the absence of a gold standard, we used deterioration in the performance of ≥0.5 SD on one or more NP test as a definition of neurocognitive decline. We address the merits and drawback of this approach in detail elsewhere.[12] Although this magnitude of change in general meets conventional standards for clinical relevance, we do not know if this change is clinically meaningful here. The test in which decline was detected most often was the Grooved Pegboard, a test of dexterity and processing speed that could also reflect peripheral neuropathy or even mechanical factors. Whether a change in this magnitude on this test, or any of the individual NP tests, relates to real-world function is not established. However, the fact that plausible biological and demographic risk factors were identified as predicting neurocognitive decline defined in this "liberal" way argues that this outcome reflects a biologically meaningful phenomenon. Thus, the risk factors we identified here point to important directions for further study.

We would be cautious in applying this information in the clinical setting now; it is important to keep in mind that this risk index predicts decline in a single NP test over 3 years. The predictive value of some previously reported risk factors could not be included as the traits were present in only a few study participants, and some potentially relevant

TABLE 4. Personalized Risk Index of NC Decline Over 3 Years in 191 HIV+ Aviremic CHARTER Participants

Risk Factor	β*	Risk Score (=β × 10)
eGFR ≤ 50 mL/min	0.257	2.57
HIV infection ≥ 15 yrs	0.179	1.79
Education ≤ 12 yrs	0.133	1.33
CSF protein > 45 mg/dL	0.115	1.15

*e^{β} = OR (Table 3).

TABLE 5. Observed Clinical Profiles, Corresponding Risk Score, and the Predicted 3-Year Risk of NC Decline for the 191 HIV+ Aviremic CHARTER Participants

No. of Risk Factors	Prevalence, %	Duration of HIV ≥ 15 yrs	CSF Protein > 45 mg/dL	eGFR≤ 50 mL/min	Education ≤ 12 yrs	Total Score	3-Year Risk of Decline
0	35					0	0.02
1	15		•			1.15	0.06
	43				•	1.33	0.07
	28	•				1.79	0.11
	9			•		2.57	0.21
2	13		•		•	2.48	0.2
	11	•	•			2.94	0.28
	24	•			•	3.12	0.32
	0		•	•		3.72	0.46
	3			•	•	3.9	0.51
	0	•		•		4.36	0.62
3	13	•	•		•	4.27	0.6
	0		•	•	•	5.05	0.76
	0	•	•	•		5.51	0.84
	1	•		•	•	5.69	0.86
4	1	•	•	•	•	6.84	0.95

predictors (eg, waist-to-hip ratio) were not measured at the initial assessment. Given the multifactorial nature of neurocognitive risk, there are likely other risk factors not included in our study that contributed to neurocognitive risk.

Although this risk index was developed from a well-characterized representative sample of HIV+ patients in the United States, it needs to be validated in other HIV+ populations. Longer follow-up and assessment of real-life functional changes will be important in establishing the clinical importance of the risk factors identified here.

CONCLUSIONS

In summary, neurocognitive decline among aviremic HIV+ individuals in the CHARTER cohort was uncommon over a period of 3 years, with a background risk of 2% only. The results suggest at least one potential direction for efforts to prevent neurocognitive decline, that is, addressing modifiable vascular risk factors. For example, the Study to Improve Quality of Care and Patient Health in the Field of Cardiovascular Risk Factors in General Practice (ESCAPE) trial an interventional cluster randomized trial, in which family physicians were trained to deliver a multifaceted intervention aimed at addressing cardiovascular risk factors in high-risk hypertensive patients, significantly increased the proportion of patients who achieved their recommended therapeutic targets; the eGFR decreased over 2 years in the usual care group but did not in the intervention group ($P < 0.001$).[41] Although the link between lower eGFR and vascular disease remains to be clarified, and that the beneficial effect of interventions to modify vascular risk factors on cognition remains to be formally tested, lack of empirical evidence should not delay their implementation in view of their benefits on cardiovascular morbidity and mortality. These interventions are likely to be widely applicable as smoking or obesity was present in as many as 80% of CHARTER cohort participants: smoking cessation and avoidance of obesity would be obvious starting points to maintain brain health. Providing patients with their individualized risk of cognitive decline may increase their motivation for behavioral changes and adherence to treatment. This case will become more compelling as the findings are replicated in other samples, and the link between the neurocognitive outcome we studied and real-life function is established.

ACKNOWLEDGMENTS

The CNS HIV Anti-Retroviral Therapy Effects Research (CHARTER) group is affiliated with Johns Hopkins University; the Icahn School of Medicine at Mount Sinai; University of California, San Diego; University of Texas, Galveston; University of Washington, Seattle; Washington University, St. Louis; and is headquartered at the University of California, San Diego and includes: Director: Igor Grant, MD; Co-Directors: Scott L. Letendre, MD, Ronald J. Ellis, MD, PhD, Thomas D. Marcotte, PhD; Center Manager: Donald Franklin, Jr.; Neuromedical Component: Ronald J. Ellis, MD, PhD (P.I.), J. Allen McCutchan, MD; Laboratory and Virology Component: Scott Letendre, MD (Co-P.I.), Davey M. Smith, MD (Co-P.I.).; Neurobehavioral Component: Robert K. Heaton, PhD (P.I.), J. Hampton Atkinson, MD, Matthew Dawson; Imaging Component: Christine Fennema-Notestine, PhD (P.I.), Michael J. Taylor, PhD, Rebecca Theilmann, PhD; Data Management Component: Anthony C. Gamst, PhD (P.I.), Clint Cushman; Statistics Component: Ian Abramson, PhD (P.I.), Florin Vaida, PhD, Reena Deutsch, PhD; Johns Hopkins University Site: Ned Sacktor (P.I.), Vincent Rogalski; Icahn School of Medicine at Mount Sinai Site: Susan Morgello, MD (Co-P.I.) and David Simpson, MD (Co-P.I.), Letty Mintz, NP; University of California, San Diego Site: J. Allen McCutchan, MD (P.I.), Kaori Phillips, BSN; University of Washington, Seattle Site: Ann Collier, MD (Co-P.I.) and Christina Marra, MD (Co-P.I.), Sher Storey, PA-C; University of Texas, Galveston

Site: Benjamin Gelman, MD, PhD (P.I.), Eleanor Head, RN, BSN; and Washington University, St. Louis Site: David Clifford, MD (P.I.), Muhammad Al-Lozi, MD, Mengesha Teshome, MD.

REFERENCES

1. Heaton RK, Clifford DB, Franklin DR, et al. HIV-associated neurocognitive disorders persist in the era of potent antiretroviral therapy: CHARTER Study. *Neurology*. 2010;75:2087–2096.
2. Heaton RK, Marcotte TD, Mindt MR, et al. The impact of HIV-associated neuropsychological impairment on everyday functioning. *J Int Neuropsychol Soc.* 2004;10:317–331.
3. Grant I, Franklin DR, Deutsch R, et al. Asymptomatic HIV-associated neurocognitive impairment increases risk for symptomatic decline. *Neurology*. 2014;82:2055–2062.
4. *Guideline on When to Start Antiretroviral Therapy and on Pre-exposure Prophylaxis for HIV*. Geneva, Switzerland: World Health Organization; 2015.
5. Robertson KR, Smurzynski M, Parsons TD, et al. The prevalence and incidence of neurocognitive impairment in the HAART era. *AIDS*. 2007; 21:1915–1921.
6. Barnes DE, Covinsky KE, Whitmer RA, et al. Commentary on "Developing a national strategy to prevent dementia: Leon Thal Symposium 2009." Dementia risk indices: a framework for identifying individuals with a high dementia risk. *Alzheimers Dement.* 2010;6:138–141.
7. Barnes DE, Yaffe K, Byers AL, et al. Midlife vs late-life depressive symptoms and risk of dementia: differential effects for Alzheimer disease and vascular dementia. *Arch Gen Psychiatry.* 2012;69:493–498.
8. Kivipelto M, Ngandu T, Laatikainen T, et al. Risk score for the prediction of dementia risk in 20 years among middle aged people: a longitudinal, population-based study. *Lancet Neurol.* 2006;5:735–741.
9. Matsuzawa T, Takata T, Yokono K, et al. A warning index used in prescreening for Alzheimer's disease, based on self-reported cognitive deficits and vascular risk factors for dementia in elderly patients with type 2 diabetes. *Int J Alzheimers Dis.* 2012;2012:124215.
10. Cysique LA, Murray JM, Dunbar M, et al. A screening algorithm for HIV-associated neurocognitive disorders. *HIV Med.* 2010;11:642–649.
11. Nagin DS, Tremblay RE. Analyzing developmental trajectories of distinct but related behaviors: a group-based method. *Psychol Methods.* 2001;6:18–34.
12. Brouillette MJ, Yuen T, Fellows LK, et al. Identifying neurocognitive decline at 36 months among HIV-positive participants in the CHARTER cohort using group-based trajectory analysis. *PLOS One*. 2016;11: e0155766.
13. McCombe JA, Vivithanaporn P, Gill MJ, et al. Predictors of symptomatic HIV-associated neurocognitive disorders in universal health care. *HIV Med.* 2013;14:99–107.
14. Espinosa A, Alegret M, Valero S, et al. A longitudinal follow-up of 550 mild cognitive impairment patients: evidence for large conversion to dementia rates and detection of major risk factors involved. *J Alzheimers Dis.* 2013;34:769–780.
15. Ciccarelli N, Fabbiani M, Colafigli M, et al. Revised central nervous system neuropenetration-effectiveness score is associated with cognitive disorders in HIV-infected patients with controlled plasma viraemia. *Antivir Ther*. 2013;18:153–160.
16. Vivithanaporn P, Nelles K, DeBlock L, et al. Hepatitis C virus co-infection increases neurocognitive impairment severity and risk of death in treated HIV/AIDS. *J Neurol Sci.* 2012;312:45–51.
17. Viticchi G, Falsetti L, Vernieri F, et al. Vascular predictors of cognitive decline in patients with mild cognitive impairment. *Neurobiol Aging.* 2012;33:1127.e1–1127.e9.
18. Sona A, Zhang P, Ames D, et al. Predictors of rapid cognitive decline in Alzheimer's disease: results from the Australian Imaging, Biomarkers and Lifestyle (AIBL) study of ageing. *Int Psychogeriatr.* 2012;24: 197–204.
19. Mackin RS, Insel P, Aisen PS, et al; Alzheimer's Disease Neuroimaging I. Longitudinal stability of subsyndromal symptoms of depression in individuals with mild cognitive impairment: relationship to conversion to dementia after 3 years. *Int J Geriatr Psychiatry.* 2012;27:355–363.
20. Li L, Wang Y, Yan J, et al. Clinical predictors of cognitive decline in patients with mild cognitive impairment: the Chongqing aging study. *J Neurol.* 2012;259:1303–1311.
21. Leoutsakos JM, Han D, Mielke MM, et al. Effects of general medical health on Alzheimer's progression: the cache county dementia progression study. *Int Psychogeriatr.* 2012;24:1561–1570.
22. Xie H, Mayo N, Koski L. Predictors of future cognitive decline in persons with mild cognitive impairment. *Dement Geriatr Cogn Disord.* 2011;32:308–317.
23. Cysique LA, Letendre SL, Ake C, et al. Incidence and nature of cognitive decline over 1 year among HIV-infected former plasma donors in China. *AIDS Lond Engl.* 2010;24:983–990.
24. SAS/STAT Software. Version 9.3. Cary, NC: SAS Institute Inc.; 2011.
25. Hosmer D, Lemeshow S. *Applied Logistic Regression*. 2nd ed. New York, NY: John Wiley & Sons, Inc; 2000.
26. Bhaskaran K, Mussini C, Antinori A, et al. Changes in the incidence and predictors of human immunodeficiency virus-associated dementia in the era of highly active antiretroviral therapy. *Ann Neurol.* 2008;63: 213–221.
27. Mindt MR, Byrd D, Ryan EL, et al. Characterization and sociocultural predictors of neuropsychological test performance in HIV+ Hispanic individuals. *Cultur Divers Ethnic Minor Psychol.* 2008;14:315–325.
28. De Ronchi D, Faranca I, Berardi D, et al. Risk factors for cognitive impairment in HIV-1-infected persons with different risk behaviors. *Arch Neurol.* 2002;59:812–818.
29. Go AS, Chertow GM, Fan D, et al. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med.* 2004; 351:1296–1305.
30. Sedaghat S, Vernooij MW, Loehrer E, et al. Kidney function and cerebral blood flow: the Rotterdam study. *J Am Soc Nephrol.* 2016;27: 715–721.
31. Helmer C, Stengel B, Metzger M, et al. Chronic kidney disease, cognitive decline, and incident dementia: the 3C Study. *Neurology*. 2011;77:2043–2051.
32. Lee M, Saver JL, Chang KH, et al. Low glomerular filtration rate and risk of stroke: meta-analysis. *BMJ*. 2010;341:c4249.
33. Yaffe K, Kurella-Tamura M, Ackerson L, et al. Higher levels of cystatin C are associated with worse cognitive function in older adults with chronic kidney disease: the chronic renal insufficiency cohort cognitive study. *J Am Geriatr Soc.* 2014;62:1623–1629.
34. Sakoda M, Fazeli P, Letendre S, et al. Cystatin C is associated with neurocognitive impairment in older HIV+ adults (P2.313). *Neurology*. 2015;84(suppl 14). Available at: http://www.neurology.org/content/84/14_Supplement/P2.313.. Accessed November 1, 2016.
35. Kalayjian RC, Wu K, Evans S, et al. Proteinuria is associated with neurocognitive impairment in antiretroviral therapy treated HIV-infected individuals. *J Acquir Immune Defic Syndr.* 2014;67:30–35.
36. Wyatt CM, Morgello S, Katz-Malamed R, et al. The spectrum of kidney disease in patients with AIDS in the era of antiretroviral therapy. *Kidney Int.* 2009;75:428–434.
37. The Lancet Psychiatry. The blood–brain barrier: frontier science. *Lancet Psychiatry.* 2016;3:389.
38. Boven LA, Middel J, Breij EC, et al. Interactions between HIV-infected monocyte-derived macrophages and human brain microvascular endothelial cells result in increased expression of CC chemokines. *J Neurovirol.* 2000;6:382–389.
39. Calcagno A, Atzori C, Romito A, et al. Blood brain barrier impairment is associated with cerebrospinal fluid markers of neuronal damage in HIV-positive patients. *J Neurovirol.* 2016;22:88–92.
40. Langford TD, Letendre SL, Larrea GJ, et al. Changing patterns in the neuropathogenesis of HIV during the HAART era. *Brain Pathol Zurich Switz.* 2003;13:195–210.
41. Pouchain D, Lievre M, Huas D, et al. Effects of a multifaceted intervention on cardiovascular risk factors in high-risk hypertensive patients: the ESCAPE trial, a pragmatic cluster randomized trial in general practice. *Trials*. 2013;14:318.