Proteinuria is Associated With Neurocognitive Impairment in Antiretroviral Therapy Treated HIV-Infected Individuals

Robert C. Kalayjian, MD,§ Kunling Wu, MS,† Scott Evans, PhD, MS,† David B. Clifford, MD,‡ Muraldihar Pallaki, MD,§ Judith S. Currier, MD, MSc,‖ and Marlene Smryzynski, PhD, MSPH†¶*

Background: Proteinuria is a marker of vascular dysfunction that predicted increased cardiovascular mortality and is associated with neurocognitive impairment (NCI) in population-based studies. We examined associations between proteinuria and HIV-associated NCI.

Methods: Multivariable logistic regression was used to examine associations between NCI at the first neurocognitive assessment (baseline) and simultaneous, clinically significant proteinuria [as random spot urine protein-to-creatinine ratios (UP/Cr) ≥200 mg/g] in a prospective multicenter observational cohort study. Generalized estimating equations were used to examine associations between baseline proteinuria and subsequent NCI among subjects without NCI at baseline. NCI was defined as a Z-score, derived from the combination of normalized scores from the Trailmaking A and B and the Wechsler Adult Intelligence Scale-Revised Digit Symbol tests.

Results: A total of 1972 subjects were included in this analysis. Baseline proteinuria was associated with increased odds of NCI [odds ratio (OR): 1.41, 95% confidence interval (CI): 1.08 to 1.85; $P = 0.01$] and with subsequent NCI among subjects without NCI at baseline (OR: 1.39, 95% CI: 1.01 to 1.93; $P = 0.046$) in multivariable models adjusted for risk factors and potential confounders. Similar associations were evident when these analyses were limited to visits at which time study subjects maintained plasma HIV RNA levels <200 copies per milliliter.

Conclusions: The association between proteinuria and NCI observed in this study adds to a growing body of evidence implicating contributions by vascular disease to NCI in antiretroviral treated individuals. Studies examining interventions that improve vascular function are warranted.

Key Words: neurocognitive impairment, proteinuria, vascular disease, HIV-associated neurocognitive disorders

(*J Acquir Immune Defic Syndr* 2014;67:30–35)

INTRODUCTION

HIV-associated neurocognitive disorders (HAND) encompass a spectrum of neurologic conditions ranging from asymptomatic neurocognitive impairment (NCI) to HIV-associated dementia.[1] Antiretroviral therapy (ART) substantially improves neurocognitive function and was associated with dramatic declines in the incidence of HIV-associated dementia,[2–7] but neurocognitive dysfunction that was predominately mild or asymptomatic could be detected in 22%–59% of ART-treated patients.[4,8,9] Neither plasma nor cerebrospinal fluid HIV RNA concentrations was associated with the presence or severity of NCI in ART-treated patients,[4,10] but associations between vascular disease and NCI are increasingly recognized.[11–14]

Proteinuria is a marker of kidney injury and vascular dysfunction. Comprised predominately of albumin, proteinuria, or albuminuria predicted increased risks of cardiovascular and all-cause mortality in population-based studies,[15–18] and similar associations also were observed in large observational studies of HIV-infected individuals.[19–22] Herein, we explored the relationship between proteinuria and NCI in ART-treated HIV-infected participants of a multicenter prospective observational study who underwent annual neurocognitive testing and urine protein measurements.

METHODS

Study Participants

Established in 2000, the AIDS Clinical Trials Group (ACTG) Longitudinal Linked Randomized Trials (ALLRT) study is a multicenter observational cohort study that co-enrolled participants from ACTG randomized clinical trials of ART (parent clinical trial) for longitudinal follow-up.[23] Participants underwent neurocognitive testing soon after entry to ALLRT, and every 48 weeks later.

Received for publication February 12, 2014; accepted May 1, 2014.

From the *Department of Medicine, MetroHealth Medical Center; Cleveland, OH; †Geriatric Research Education and Clinical Centers, Louis Stokes Cleveland Veterans Administration, Cleveland, OH; ‡Statistical and Data Analysis Center, Harvard School of Public Health; Boston, MA; §Department of Neurology and Neurological Surgery, Washington University of St. Louis, St. Louis, MO; ‖UCLA CARE Center, David Geffen School of Medicine, University of California Los Angeles, Los Angeles, CA; and ¶Department of Epidemiology, Milken Institute School of Public Health, George Washington University, Washington, DC.

Supported by NIH AI 069501, AI 036219, AI 069424 and the Veterans Administration: VISN10 Geriatric Research Education and Clinical Centers, Louis Stokes Cleveland Veterans Administration Medical Center.

D.B.C. serves a consultant for Biogen, Idec, Millennium, Bristol Myers Squibb, Pfizer, Genzyme, Amgen, Quintiles, Genetech, and AstraZeneca and received honoraria for lectures from Sun Biopharma; R.C.K. is currently receiving a grant from Gilead (GS-US-292-0112). The other authors have no conflicts of interest to disclose.

Presented at the 20th Conference on Retroviruses and Opportunistic Infections, 2013, March 6, 2013. Atlanta, GA, Abstract No. 460.

Correspondence to: Robert C. Kalayjian, MD, Division of Infectious Diseases, 2500 MetroHealth Drive, Cleveland, OH 44108 (e-mail: rkalayjian@metrohealth.org).

NCI was assessed using normalized NPZ-3 scores, derived from the Trailmaking A and B and the Wechsler Adult Intelligence Scale-Revised Digit Symbol tests. Raw scores for each of these 3 tests were normalized by age, sex, and race/ethnicity (as black non-Hispanic, white non-Hispanic or Hispanic) as Z-scores (NPZ-3 score).[24] NCI was defined as 1 SD below zero on at least 2 normalized scores, or 2 SDs below zero on at least 1 normalized score. Written and verbal instructions were primarily given in English, whereas there was an option for bilingual and monolingual Spanish-speaking subjects to receive written and verbal instructions in Spanish.

Urine protein and creatinine concentrations were measured from random spot urine samples that were collected every 48 weeks and calculated as the ratio of urine protein-to-creatinine (UP/Cr). UP/Cr measurements were included if urine protein was measured ≤3 months before or after the first neurocognitive assessment (baseline); clinically significant proteinuria was defined by a UP/Cr ratio ≥200 mg/g.[25] Glomerular filtration rates were estimated (eGFR) from simultaneously collected serum creatinine measurements using the chronic kidney disease (CKD)-Epidemiology equation.[26]

All participants provided written informed consent at their local ACTG clinical trials site. This study was conducted with oversight from the ACTG and the MetroHealth Medical Center Institutional Review Board and adhered to the Declaration of Helsinki.

Statistical Analysis

The aims of this analysis were to examine the relationship between NCI at the time of the initial neurocognitive assessment in ALLRT (baseline) with simultaneous proteinuria and to examine the relationship between subsequent NCI during follow-up and baseline proteinuria among participants who did not have NCI at the baseline visit.

Included in the baseline cross-sectional analysis were 1972 participants who had their initial neurocognitive testing and a simultaneous UP/Cr at baseline as of June 2010. Multivariable logistic regression models were used to assess the association [odds ratios (ORs) and 95% confidence intervals (CIs)] between UP/Cr (≥200 vs. <200 mg/g) and NCI, controlling for other potential confounders and risk factors including eGFR, age, sex, race/ethnicity, education duration, injection drug use (as previous, current, or never), smoking history, ART experience upon entry to the parent study, CD4 cell counts and plasma HIV RNA concentrations; and diagnoses of cardiovascular disease (defined by a history of myocardial infarction, stroke, and other cardiovascular diseases), hypertension (defined as a blood pressure >140/90 mm Hg on more than one occasion and receipt of antihypertensive medications), hypercholesterolemia (defined as a fasting low-density lipoprotein cholesterol >160 mg/dL and receipt of lipid-lowering medications), diabetes (defined as diagnosis of any hyperglycemia and receipt of hypoglycemic agents), and grade ≥3 anemia or thrombocytopenia (using the Division of AIDS Toxicity Scale, defined as a hemoglobin ≤4.61 mmol/L, or a platelet count $<50 \times 10^9$ per liter). An adjusted final model retained UP/Cr, the demographic variables, injection drug use history, ART experience, and other variables from univariate models with unadjusted $P < 0.2$. In a sensitivity analysis, only participants with baseline HIV RNA <200 copies per milliliter were assessed. An additional analysis examined potential confounding effects by tenofovir, an antiretroviral drug with low central nervous system penetration that is specifically associated with increased risk of proteinuria.

A total of 1372 subjects with normal baseline NPZ-3 scores and at least 1 follow-up neurocognitive visit were included in a longitudinal analysis. To investigate the association between baseline UP/Cr and incident NCI over time, multivariable logistic regression models using generalized estimating equations that were similarly constructed as described above were assessed. The models included all the previously listed variables, of which the following were time updated: eGFR, CD4 cell counts, HIV RNA concentrations, grade ≥3 anemia or thrombocytopenia, and time-updated diagnoses of cardiovascular disease, hypertension, hypercholesterolemia, and diabetes. In a sensitivity analysis, only time points where participants had HIV RNA <200 copies per milliliter were assessed.

RESULTS

Characteristics of the Population

Among the 1972 participants included in this analysis, median time between entry to the parent clinical trial and the first neurocognitive assessment (ie, the baseline evaluation) was 16 weeks [interquartile range (IQR), 8–24 weeks], median age was 40 years, and 82% were men. Four hundred one participants (20%) had a UP/Cr ≥200 mg/g at baseline but only 41 (2%) had an eGFR <60 mL/min per 1.73 m^2 (Table 1). Two hundred twelve subjects (11%) were ART naive at the baseline evaluation, whereas 1683 (85%) subjects had recently initiated ART upon entry to their parent clinical trial. Median baseline CD4 count was 319 cells per microliter, and 60% of subjects were virologically suppressed (to <200 copies/mL) at baseline; 52% were past or current cigarette smokers, 11% had hypertension, 8% had a history of cardiovascular disease, and 4% and 3% had diabetes or hypercholesterolemia at baseline, respectively.

Baseline Cross-sectional Analysis

NCI was detected in 481 of 1972 (24%) subjects, of whom 116 (24%) had clinically significant proteinuria (UP/Cr ratio ≥200 mg/g), compared with 285 (19%) of 1491 subjects with clinically significant proteinuria but without NCI (unadjusted OR: 1.34, 95% CI: 1.05 to 1.72; $P = 0.02$). When proteinuria was assessed as a continuous variable it was negatively correlated with eGFR ($r = -0.13$, $P < 0.001$). Proteinuria as a categorical variable (UP/Cr ≥200 mg/g) remained significantly associated with increased odds of NCI in a fully adjusted model that included eGFR (OR: 1.41, 95% CI: 1.08 to 1.85; $P = 0.01$; Table 2), wherein higher eGFR also was associated with increased odds of NCI (OR: 1.08, 95% CI: 1.01 to 1.16 per every 10 mL/min per 1.73 m^2 eGFR increase; $P = 0.02$). Proteinuria remained

TABLE 1. Demographics and Baseline Variables by Baseline NCI Status

Characteristics	Total (N = 1972)	NCI at Baseline		
		Normal (N = 1491)	Impaired (N = 481)	*P*
UP/Cr, median (IQR), mg/g	99 (69–168)	97 (67–161)	104 (73–194)	0.009*
UP/Cr ≥200 mg/g, n (%)	401 (20)	285 (19)	116 (24)	0.02†
eGFR, median (IQR), mL/min per 1.73 m^2	104.2 (89.4–116.3)	103.2 (88.5–114.9)	109.2 (92.4–119.7)	<0.001*
eGFR <60 mL/min per 1.73 m^2, n (%)	41 (2)	27 (2)	14 (3)	0.14†
Male, n (%)	1616 (82)	1251 (84)	365 (76)	<0.001†
Race/ethnicity, n (%)				<0.001†
White non-Hispanic	892 (45)	735 (49)	157 (33)	
Black non-Hispanic	659 (33)	515 (35)	144 (30)	
Hispanic (regardless of race)	421 (21)	241 (16)	180 (37)	
Years of education, median (IQR)	14 (12–16)	14 (12–16)	12 (11–15)	<0.001*
Age, median (IQR), yrs	40 (33–47)	40 (33–47)	39 (32–46)	0.10*
Previous or current injection drug use, n (%)	184 (9)	138 (9)	46 (10)	0.84†
Antiretroviral naive at baseline, n (%)	212 (11%)	182 (12%)	30 (7%)	0.02†
CD4 cell counts, median (IQR), cells/μL	319 (184–454)	324 (191–461)	296 (166–426)	0.01*
HIV RNA <200 copies/mL, n (%)	1186 (60)	897 (60)	289 (60)	0.98†
Grade ≥3 hemoglobin toxicity, n (%)	6 (<1)	2 (<1)	4 (1)	0.03‡
Grade ≥3 thrombocytopenia, n (%)	5 (<1)	5 (<1)	0 (0)	0.34‡
Smoking history, n (%)	1026 (52)	787 (53)	239 (50)	0.21†
History of cardiovascular diseases, n (%)	150 (8)	119 (8)	31 (6)	0.27†
Pharmacologically treated hypercholesterolemia, n (%)	52 (3)	39 (3)	13 (3)	0.92†
Pharmacologically treated hypertension, n (%)	219 (11)	170 (11)	49 (10)	0.46†
Pharmacologically treated diabetes, n (%)	82 (4)	50 (3)	32 (7)	0.002†
Hepatitis C antibody positive	168 (9)	128 (9)	40 (8)	0.85†

*Wilcoxon test.
†χ^2 test.
‡Fisher exact test.

significantly associated with NCI in the same adjusted model when the highest versus the lowest quartile of UP/Cr concentrations were compared (OR: 1.55, 95% CI: 1.13 to 2.14; P = 0.007 for UP/Cr >168 vs. ≤69 mg/g).

Additional factors associated with increased odds of NCI in the prevalent model included female sex (OR: 1.55, 95% CI: 1.18 to 2.05; P = 0.002), Hispanic ethnicity (OR: 2.67, 95% CI: 2.00 to 3.55; P < 0.001 vs. black) and pharmacologically treated diabetes (OR: 1.89, 95% CI: 1.14 to 3.13; P = 0.01); increased odds was associated with a grade ≥3 anemia though not statistically significant (OR: 4.89, 95% CI: 0.85 to 28.22; P = 0.08). A lower risk of NCI was associated with more years of formal education (OR: 0.95, 95% CI: 0.92 to 0.98 per year of education; P = 0.004). When the analysis was restricted to include the 1186 subjects with a baseline HIV RNA <200 copies per milliliter, proteinuria (as UP/Cr ≥200 mg/g) was not statistically associated with increased odds of NCI (OR: 1.34, 95% CI: 0.94 to 1.92; P = 0.11). In additional sensitivity analyses, current tenofovir use was not associated with increased risk of NCI (OR: 0.94, 95% CI: 0.68 to 1.30; P = 0.70) and a "U-shaped" association was suggested when eGFR was analyzed as a categorical variable in unadjusted models (OR: 2.25, 95% CI: 1.13 to 4.47; OR: 1.38, 95% CI: 1.05 to 1.81; and OR: 2.04, 95% CI: 1.48 to 2.81) for associations with eGFR ≤60, 91 to 120, and >120, versus 61 to 90 mL/min per 1.73 m^2, respectively.

Incident NCI Among Subjects Without NCI at Baseline

Among the 1491 subjects without NCI at the initial assessment, 1372 had at least 1 postbaseline neurocognitive assessment and were followed for a median of 3.3 years (IQR, 2.4–4.2 years). NCI was subsequently detected in 250 subjects (18%) a median of 1.7 years (IQR, 0.9–2.7 years) after the baseline assessment. In multivariable longitudinal analysis, baseline UP/Cr ≥200 mg/g was associated with increased odds of incident NCI (OR: 1.39, 95% CI: 1.01 to 1.93; P = 0.045; Table 2). Consistent with the baseline analyses, Hispanic ethnicity remained associated with increased odds of subsequent NCI (OR: 2.70, 95% CI: 1.82 to 4.00 vs. black; P < 0.001); other significant correlates in this model included older age (OR: 1.22, 95% CI: 1.03 to 1.45 per each 10 years older; P = 0.02) and a grade ≥3 thrombocytopenia (OR: 7.66, 95% CI: 1.85 to 31.75; P = 0.005).

When the longitudinal analysis was restricted only to assessments during which time subjects achieved viral suppression to HIV RNA <200 copies per milliliter (n = 1280), baseline proteinuria ≥200 mg/g was significantly associated with increased odds of subsequent NCI (OR: 1.45, 95% CI: 1.02 to 2.08; P = 0.04). In contrast to the cross-sectional, prevalent analysis, baseline eGFR was not associated with incident NCI risk among all subjects in this longitudinal cohort (OR: 1.00, 95% CI: 0.99 to 1.0; P = 0.28),

TABLE 2. Associations Between Baseline Proteinuria (Urine Protein/Creatinine >200 mg/g at the Initial Neurocognitive Assessment) and Prevalent and Incident NCI, Estimated as Odds Ratios and 95% CI Adjusting for Diabetes and Other Baseline and Longitudinal Risk Factors

	Prevalent NCI (Baseline)*		Incident NCI (Longitudinal)†	
	N = 1972		N = 1372	
Variables	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***
UP/Cr at baseline (≥200 vs. <200 mg/g)	1.41 (1.08 to 1.85)	0.01	1.39 (1.01 to 1.93)	0.046
eGFR at baseline (per 10 mL/min per 1.73 m^2 increase)	1.08 (1.01 to 1.16)	0.02	—	—
Age at baseline (per 10 year increase)	1.00 (0.87 to 1.14)	>0.90	1.22 (1.03 to 1.45)	0.02
Sex (female vs. male)	1.55 (1.18 to 2.05)	0.002	1.39 (0.99 to 1.95)	0.05
Race/ethnicity				
White vs. black	1.02 (0.78 to 1.35)	0.87	1.09 (0.76 to 1.55)	0.65
Hispanic vs. black	2.67 (2.00 to 3.55)	<0.001	2.70 (1.82 to 4.00)	<0.001
Years of education at baseline (per year increase)	0.95 (0.92 to 0.98)	0.004	1.01 (0.95 to 1.06)	0.85
Grade ≥3 anemia at baseline	4.89 (0.85 to 28.22)	0.08	—	—
Grade ≥3 thrombocytopenia at follow-up (time updated)	—	—	7.66 (1.85 to 31.75)	0.005
Pharmacologically treated diabetes at baseline	1.89 (1.14 to 3.13)	0.01	—	—

*Based on logistic regression; model also included previous or current injection drug use history and ART experience at entry to ALLRT; baseline CD4 (>200 vs. ≤200 cells/μL).
†Based on logistic generalized estimating equations regression modeling; model also included previous or current injection drug use history and ART experience at entry to ALLRT, hepatitis B and hepatitis C status, baseline HIV RNA (>200 vs. ≤200 copies/mL), HIV RNA copies at follow-up and time-updated diagnosis of hypertension.

or in the subset of subjects with viral suppression during follow-up (OR: 1.00, 95% CI: 0.99 to 1.01; $P = 0.61$).

DISCUSSION

We identified an association between NCI and concurrent, clinically significant proteinuria (UP/Cr ≥200 mg/g) among ART-treated HIV-infected participants of a large prospective multicenter observational study. Baseline proteinuria also was associated with subsequent NCI among subjects in whom NCI was not detected during the initial evaluation in a longitudinal analysis. The association between this level of proteinuria and NCI was evident in multivariable models adjusted for additional risk factors and potential confounders including eGFR and comorbidities, and when UP/Cr concentrations were categorized within quartiles.

As a marker of vascular dysfunction, numerous studies have identified strong and consistent associations between proteinuria or albuminuria with fatal cardiovascular events that were independent of the levels of GFR.[15–18] Similar associations also were evident in studies of HIV-infected individuals.[19–22] Although it is possible that residual confounding from common risk factors that are shared between patients with both cardiovascular and kidney disease could contribute to these associations, this relationship also may imply common pathogenic mechanisms underlying both disease processes.[27,28] One such common mechanism may involve disruption of the glycocalyx lining that is present on all endovascular cells, including fenestrated glomerular cells, which limits endothelial activation by preventing leukocyte and platelet adhesion while also preventing negatively charged proteins including albumin to escape from the capillary lumen. This lining can be disrupted by oxidative stress, hyperglycemia, or laminar shear leading to albuminuria and endovascular inflammation.[29] Although we identified significant associations with proteinuria, albuminuria is a more specific marker for glomerular dysfunction and may be a better marker of endothelial dysfunction than is proteinuria, whereas renal tubular dysfunction also contributes to proteinuria.[30]

Albuminuria also was associated with an increased risk of NCI in the general population and with increased risk of subsequent NCI in patients with diabetes.[31–35] Common microvascular changes in the brains and kidneys of patients with cognitive impairment and proteinuria may similarly imply common pathogenic mechanisms involving both disorders. Renin–angiotensin blockade with angiotensin converting enzyme inhibitors or angiotensin-II receptor blockers are consistently effective in lowering albuminuria.[36] In 1 analysis of 2 large clinical trials that included participants with vascular disease and diabetes, telmisartan use (an angiotensin-II receptor blockers) was associated with significantly reduced odds of neurocognitive decline among subjects with baseline macroalbuminuria.[37]

In HIV-associated NCI, vascular risk factors have been increasingly recognized including associations with increased carotid intima-media thickness,[11] a history of cardiovascular comorbidities,[12–14] or elevated CD163 plasma concentrations, a marker of arterial inflammation.[38] HIV infection was associated with reduced cerebral blood flow by magnetic resonance imaging[39] and with small vessel ischemic vascular disease as determined by periventricular leukoaraiosis by magnetic resonance imaging[40] suggesting important contributions by vascular disease to HAND.

In the present analysis, we also identified a significant association between NCI and increased eGFR in the cross-sectional analysis (but not in the longitudinal analyses) that is consistent with a previous study from the Multicenter AIDS Cohort Study.[11] By contrast, lower eGFR was associated with cognitive impairment in studies from the general population.[41,42] Many studies have described U-shaped associations

between cardiovascular outcomes and eGFR with adverse outcomes associated with both the ends of the eGFR spectrum.[43,44] Non-GFR determinates of serum creatinine levels including muscle mass, diet, age, and systemic illness may confound associations with creatinine-based GFR estimates, where it is hypothesized that serum creatinine may be lower than expected for the level of GFR.[45] Glomerular hyperfiltration was also more common among HIV-infected subjects in a recent study from the Multicenter AIDS Cohort Study, and this was associated with indicators of hyperglycemia and hypertension.[46] It is possible that confounding or hyperfiltration may have contributed to the observed associations between higher eGFR and NCI in this study. Because only 41 subjects (2%) had a baseline eGFR <60 mL/min per 1.73 m^2, our ability to detect associations between NCI and lower eGFR levels was limited in this study.

Associations between years of formal education or ethnic minority status with HIV-associated NCI are consistent with some,[3,11,12] but not all previous studies[8,10] and may represent differences in available educational opportunities. Most English-speaking subjects were instructed in English, including those for whom Spanish may have been their primary language. Because we did not adjust for Spanish-dominant language or the degree of bilingualism, this may have introduced an important source of bias in the association with ethnicity that we observed. The validity of the neurocognitive testing and the normative adjustments that were used in this study are nevertheless supported by favorable performance characteristics when compared with more comprehensive, reference standard neuropsychological testing.[47]

Although all levels of hemoglobin and platelet counts were not routinely captured in the database of this study, a small number of subjects had grade ≥ 3 toxicities of each. These were, respectively, associated with NCI in the baseline and longitudinal analyses and are consistent with previous studies that reported associations between anemia or thrombocytopenia with HIV-associated dementia complex.[48,49] In addition, the association between diabetes and NCI in the baseline evaluation of the present analysis is consistent with a previous association between self-reported diabetes and NCI among older ART-treated HIV-infected subjects in a multicenter study.[14] Our study enrolled predominantly treatment naive individuals who recently started ART but the interval between ART initiation and the measurement of proteinuria varied across the cohort (median 8 weeks after ART initiation, IQR: 8–24 weeks). Finally, proteinuria was previously associated with elevated plasma HIV RNA concentrations in individual receiving ART and with heightened immune activation markers.[50–52] The finding of reduced significance in the baseline association between proteinuria and NCI among the group with HIV RNA <200 copies per milliliter may suggest possible contributions by incomplete viral suppression to the relationship between proteinuria and NCI.

Strengths of this analysis include the prospective longitudinal design with regular simultaneous measurements of proteinuria and neurocognitive function in this large well-characterized cohort of HIV-infected individuals on ART that allowed us to adjust for multiple potential confounding factors. We used a brief and simple battery of 3 tests to determine NCI that was administered by trained staff, but not by neuropsychologists. More comprehensive testing would be required to define more subtle degrees of impairment and to assess all the domains of neurocognitive function. However, we also cannot exclude residual confounding from unmeasured factors that could contribute to the observed association between proteinuria and NCI.

In conclusion, we observed a significantly increased risk of NCI in persons with elevated proteinuria in both cross-sectional and longitudinal analyses of this prospective observational study of ART-treated HIV-infected participants. Because of the previous strong associations from population-based studies between proteinuria and disease processes that are characterized by vascular dysfunction, these associations also suggest an important role of vascular disease in HAND, adding to a growing number of similar associations implicating vascular contributions to this morbidity. Studies examining the effects on HAND by interventions that reduce vascular dysfunction are warranted.

REFERENCES

1. Antinori A, Arendt G, Becker JT, et al. Updated research nosology for HIV-associated neurocognitive disorders. *Neurology*. 2007;69:1789–1799.
2. Cohen RA, Boland R, Paul R, et al. Neurocognitive performance enhanced by highly active antiretroviral therapy in HIV-infected women. *AIDS*. 2001;15:341–345.
3. Ferrando S, van Gorp W, McElhiney M, et al. Highly active antiretroviral treatment in HIV infection: benefits for neuropsychological function. *AIDS*. 1998;12:F65–F70.
4. Heaton RK, Franklin DR, Ellis RJ, et al. HIV-associated neurocognitive disorders before and during the era of combination antiretroviral therapy: differences in rates, nature, and predictors. *J Neurovirol*. 2011;17:3–16.
5. Robertson K, Jiang H, Kumwenda J, et al. Improved neuropsychological and neurological functioning across three antiretroviral regimens in diverse resource-limited settings: AIDS Clinical Trials Group study a5199, the International Neurological Study. *Clin Infect Dis*. 2012;55:868–876.
6. Suarez S, Baril L, Stankoff B, et al. Outcome of patients with HIV-1-related cognitive impairment on highly active antiretroviral therapy. *AIDS*. 2001;15:195–200.
7. Tozzi V, Balestra P, Galgani S, et al. Positive and sustained effects of highly active antiretroviral therapy on HIV-1-associated neurocognitive impairment. *AIDS*. 1999;13:1889–1897.
8. Robertson KR, Smurzynski M, Parsons TD, et al. The prevalence and incidence of neurocognitive impairment in the HAART era. *AIDS*. 2007;21:1915–1921.
9. Simioni S, Cavassini M, Annoni JM, et al. Cognitive dysfunction in HIV patients despite long-standing suppression of viremia. *AIDS*. 2010;24:1243–1250.
10. Marra CM, Zhao Y, Clifford DB, et al. Impact of combination antiretroviral therapy on cerebrospinal fluid HIV RNA and neurocognitive performance. *AIDS*. 2009;23:1359–1366.
11. Becker JT, Kingsley L, Mullen J, et al. Vascular risk factors, HIV serostatus, and cognitive dysfunction in gay and bisexual men. *Neurology*. 2009;73:1292–1299.
12. Wright EJ, Grund B, Robertson K, et al. Cardiovascular risk factors associated with lower baseline cognitive performance in HIV-positive persons. *Neurology*. 2010;75:864–873.
13. Foley J, Ettenhofer M, Wright MJ, et al. Neurocognitive functioning in HIV-1 infection: effects of cerebrovascular risk factors and age. *Clin Neuropsychol*. 2010;24:265–285.
14. McCutchan JA, Marquie-Beck JA, Fitzsimons CA, et al. Role of obesity, metabolic variables, and diabetes in HIV-associated neurocognitive disorder. *Neurology*. 2012;78:485–492.
15. Hemmelgarn BR, Manns BJ, Lloyd A, et al. Relation between kidney function, proteinuria, and adverse outcomes. *JAMA*. 2010;303:423–429.

16. Perkovic V, Verdon C, Ninomiya T, et al. The relationship between proteinuria and coronary risk: a systematic review and meta-analysis. *PLoS Med.* 2008;5:e207.
17. Bouchi R, Babazono T, Yoshida N, et al. Association of albuminuria and reduced estimated glomerular filtration rate with incident stroke and coronary artery disease in patients with type 2 diabetes. *Hypertens Res.* 2010;33:1298–1304.
18. Matsushita K, van der Velde M, Astor BC, et al. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. *Lancet*. 2010;375:2073–2081.
19. Choi A, Scherzer R, Bacchetti P, et al. Cystatin C, albuminuria, and 5-year all-cause mortality in HIV-infected persons. *Am J Kidney Dis.* 2010; 56:872–882.
20. Choi AI, Li Y, Deeks SG, et al. Association between kidney function and albuminuria with cardiovascular events in HIV-infected persons. *Circulation*. 2010;121:651–658.
21. Wyatt CM, Hoover DR, Shi Q, et al. Microalbuminuria is associated with all-cause and AIDS mortality in women with HIV infection. *J Acquir Immune Defic Syndr*. 2010;55:73–77.
22. Gardner LI, Holmberg SD, Williamson JM, et al. Development of proteinuria or elevated serum creatinine and mortality in HIV-infected women. *J Acquir Immune Defic Syndr.* 2003;32:203–209.
23. Smurzynski M, Collier AC, Koletar SL, et al. AIDS clinical trials group longitudinal linked randomized trials (ALLRT): rationale, design, and baseline characteristics. *HIV Clin Trials.* 2008;9:269–282.
24. Heaton RK, Miller SW, Taylor MJ, et al. *Revised Comprehensive Norms for an Expanded Halstead-reitan Battery: Demographically Adjusted Neuropsychological Norms for African American and Caucasian Adults. Professional Manual*. Lutz, FL: Psychological Assessment Resources, Inc.; 2006.
25. Eknoyan G, Hostetter T, Bakris GL, et al. Proteinuria and other markers of chronic kidney disease: a position statement of the national kidney foundation (NKF) and the national institute of diabetes and digestive and kidney diseases (NIDDK). *Am J Kidney Dis.* 2003;42:617–622.
26. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med.* 2009;150:604–612.
27. Garg P, Rabelink T. Glomerular proteinuria: a complex interplay between unique players. *Adv Chronic Kidney Dis.* 2011;18:233–242.
28. Singh A, Satchell SC. Microalbuminuria: causes and implications. *Pediatr Nephrol.* 2011;26:1957–1965.
29. Singh A, Friden V, Dasgupta I, et al. High glucose causes dysfunction of the human glomerular endothelial glycocalyx. *Am J Physiol Renal Physiol.* 2011;300:F40–F48.
30. Smith ER, Cai MM, McMahon LP, et al. The value of simultaneous measurements of urinary albumin and total protein in proteinuric patients. *Nephrol Dial Transplant.* 2012;27:1534–1541.
31. Barzilay JI, Fitzpatrick AL, Luchsinger J, et al. Albuminuria and dementia in the elderly: a community study. *Am J Kidney Dis.* 2008;52:216–226.
32. Jassal SK, Kritz-Silverstein D, Barrett-Connor E. A prospective study of albuminuria and cognitive function in older adults: the Rancho Bernardo study. *Am J Epidemiol.* 2010;171:277–286.
33. Joosten H, Izaks GJ, Slaets JP, et al. Association of cognitive function with albuminuria and eGFR in the general population. *Clin J Am Soc Nephrol.* 2011;6:1400–1409.
34. Vupputuri S, Shoham DA, Hogan SL, et al. Microalbuminuria, peripheral artery disease, and cognitive function. *Kidney Int.* 2008;73:341–346.
35. Weiner DE, Bartolomei K, Scott T, et al. Albuminuria, cognitive functioning, and white matter hyperintensities in homebound elders. *Am J Kidney Dis.* 2009;53:438–447.
36. Maione A, Navaneethan SD, Graziano G, et al. Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers and combined therapy in patients with micro- and macroalbuminuria and other cardiovascular risk factors: a systematic review of randomized controlled trials. *Nephrol Dial Transplant.* 2011;26:2827–2847.
37. Barzilay JI, Gao P, O'Donnell M, et al. Albuminuria and decline in cognitive function: the ONTARGET/TRANSCEND studies. *Arch Intern Med.* 2011;171:142–150.
38. Burdo TH, Weiffenbach A, Woods SP, et al. Elevated sCD163 in plasma but not cerebrospinal fluid is a marker of neurocognitive impairment in HIV infection. *AIDS*. 2013;27:1387–1395.
39. Ances BM, Vaida F, Yeh MJ, et al. HIV infection and aging independently affect brain function as measured by functional magnetic resonance imaging. *J Infect Dis.* 2010;201:336–340.
40. McMurtray A, Nakamoto B, Shikuma C, et al. Small-vessel vascular disease in human immunodeficiency virus infection: the Hawaii aging with HIV cohort study. *Cerebrovasc Dis.* 2007;24:236–241.
41. Feng L, Yap KB, Yeoh LY, et al. Kidney function and cognitive and functional decline in elderly adults: findings from the Singapore longitudinal aging study. *J Am Geriatr Soc.* 2012;60:1208–1214.
42. Kurella Tamura M, Wadley V, Yaffe K, et al. Kidney function and cognitive impairment in US adults: the Reasons for Geographic and Racial Differences in Stroke (REGARDS) Study. *Am J Kidney Dis.* 2008;52:227–234.
43. Hallan SI, Matsushita K, Sang Y, et al. Age and association of kidney measures with mortality and end-stage renal disease. *JAMA*. 2012;308: 2349–2360.
44. Inrig JK, Gillespie BS, Patel UD, et al. Risk for cardiovascular outcomes among subjects with atherosclerotic cardiovascular disease and greater-than-normal estimated glomerular filtration rate. *Clin J Am Soc Nephrol.* 2007;2:1215–1222.
45. Shlipak MG, Matsushita K, Arnlov J, et al. Cystatin C versus creatinine in determining risk based on kidney function. *N Engl J Med.* 2013;369: 932–943.
46. Ng DK, Jacobson LP, Brown TT, et al. HIV therapy, metabolic and cardiovascular health are associated with glomerular hyperfiltration among men with and without HIV infection. *AIDS*. 2014;28:377–386.
47. Ellis RJ, Evans SR, Clifford DB, et al. Clinical validation of the NeuroScreen. *J Neurovirol.* 2005;11:503–511.
48. McArthur JC, Hoover DR, Bacellar H, et al. Dementia in AIDS patients: incidence and risk factors. Multicenter AIDS Cohort Study. *Neurology*. 1993;43:2245–2252.
49. Wachtman LM, Skolasky RL, Tarwater PM, et al. Platelet decline: an avenue for investigation into the pathogenesis of human immunodeficiency virus—associated dementia. *Arch Neurol.* 2007;64:1264–1272.
50. Bruggeman LA, O'Toole JF, Ross MD, et al. Plasma apolipoprotein L1 levels do not correlate with CKD. *J Am Soc Nephrol.* 2014;25:634–644.
51. Gupta SK, Komarow L, Gulick RM, et al. Proteinuria, creatinine clearance, and immune activation in antiretroviral-naive HIV-infected subjects. *J Infect Dis.* 2009;200:614–618.
52. Gupta SK, Smurzynski M, Franceschini N, et al. The effects of HIV type-1 viral suppression and non-viral factors on quantitative proteinuria in the highly active antiretroviral therapy era. *Antivir Ther.* 2009;14:543–549.