The Longitudinal Effects of Blood Pressure and Hypertension on Neurocognitive Performance in People Living With HIV

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Background: Hypertension (HTN) and HIV are salient risk factors for cerebral small vessel disease and neurocognitive (NC) impairment, yet the effects of HTN on NC performance in persons living with HIV remain poorly understood. This is the first study to examine the longitudinal associations between blood pressure (BP), HTN, and pulse pressure (PP) with NC performance in persons living with HIV.

Setting: New York City.

Methods: Analysis of medical, NC, and virologic data from 485 HIV+ participants was collected by the Manhattan HIV Brain Bank, a prospective, observational, longitudinal study of neuroHIV. A series of multilevel linear growth curve models with random intercepts and slopes were estimated for BP, HTN status, and PP to predict the change in NC performance.

Results: The baseline prevalence of HTN was 23%. Longitudinal changes in diastolic and systolic pressure were associated with a 10.5-second and 4-second increase in the Grooved Pegboard Test nondominant hand performance, respectively. A longitudinal change in diastolic BP was also associated with a 0.3-point decline in correct categories and 3-point increase in perseverative responses and total errors on the Wisconsin Card Sorting Test. Increasing odds of prevalent and/or incident HTN were associated with a 0.1-point decrease in correct categories and a 0.8-point increase in total errors on the Wisconsin Card Sorting Test. There was no association between PP and NC performance.

Conclusions: The results indicate linear longitudinal relations for BP and HTN with poorer NC test performance, particularly in psychomotor and executive functions in persons with HIV.

Key Words: cerebral small vessel disease, blood pressure, hypertension, pulse pressure, neurocognitive, HIV-associated neurocognitive disorders

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INTRODUCTION

The global prevalence of hypertension (HTN) in persons living with HIV (PLWH) is ~25%.[1] However, HTN prevalence is expected to rise with aging, chronic inflammation, and/or prolonged exposure to antiretroviral therapies (ARTs).[2] The increase of HTN in PLWH is noteworthy because HTN and HIV are salient risk factors for stroke,[3,4] cerebral small vessel disease (cSVD),[5–7] and neurocognitive (NC) impairment, including vascular cognitive impairment and dementia (VCID)[8,9] and HIV-associated neurocognitive disorders (HAND).[10–12] There is also substantial overlap in the clinical and neuropathological manifestations of VCID and HAND.[12–14] Thus, improved understanding of the relationship between cSVD risk factors and NC performance in PLWH is critical to determine how cSVD risk factors may contribute to the evolution of HAND and/or VCID over time.

Although the literature is not definitive, research suggests that cSVD risk factors, such as HTN, may better predict HAND than traditional HIV biomarkers,[15] perhaps at least in part because of higher rates of age-related comorbid conditions,[16–18] particularly cardiovascular disease and its related risk factors.[18,19] Research also suggests that HIV may be an independent vascular risk factor, given the greater risk and incidence of adverse cardiovascular-related events (eg, heart disease, stroke, or death) despite viral suppression,[20] possibly because of chronic inflammation and immunosenescence.[21–24] Conversely, there may be additive and/or synergistic effects of HTN and HIV on vascular functioning and integrity that increase the risk for NC impairment in PLWH.

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However, little research has examined the relationship between more granular markers of HTN [eg, blood pressure (BP) and pulse pressure (PP)] and NC impairment in PLWH. The few available studies on HTN and/or PP with NC impairment in PLWH[25–29] suggest the following: (1) Antihypertensive medication use was associated with greater NC impairment among hypertensive PLWH compared with their normotensive counterparts[28] and (2) HTN was also associated with poorer psychomotor performance.[26] By contrast, other studies revealed no significant associations between HTN and PP with NC impairment.[25,27,29]

Overall, the relationship between HTN and NC impairment in PLWH remains equivocal. The aforementioned studies are limited and merit cautious interpretation because all but one study[26] were cross-sectional, and each lacked comprehensive BP data. Specifically, BP data consisted of either only BP measurement with self-reported diagnosis or confirmed antihypertensive use,[25] self-reported diagnosis with a medical record review,[26,27] or confirmed antihypertensive use.[28] Thus, investigation of the long-term effects of HTN, and its components, on NC impairment in PLWH is needed, with well-characterized BP and HTN diagnosis data as well as comprehensive examination of their associations with NC performance over time.

This study aimed to evaluate the longitudinal associations between BP, HTN status, and PP with the change in NC performance, in a diverse cohort of PLWH with well-characterized cardiovascular and neuropsychological test data. We hypothesized that longitudinal increases in BP and PP would be associated with declines in NC performance over time. We also hypothesized that the change in HTN status, specifically higher likelihood of being hypertensive, would be associated with worse NC performance over time.

METHODS

Participants

Data from 485 of 501 HIV+ adults enrolled in the Manhattan HIV Brain Bank (MHBB; U24MH100931) between the years 1999–2017 were used for this study. The MHBB conducts a longitudinal, observational, neuroHIV study for individuals willing to be organ donors on demise. Sixteen participants with no available BP and neuropsychological testing data were excluded.

Procedures

Study design and eligibility criteria for the MHBB study have been previously described.[30] Participants received comprehensive neurologic, neuropsychologic, and psychiatric examinations at baseline and follow-up visits by trained medical staff. Participants were prospectively followed at visit intervals of 6, 12, or 24 months depending on the medical acuity. Data from all baseline and follow-up visits were used in this study. General medical information and antiretroviral histories were also obtained through participant interview and chart review. All research activities were reviewed and approved by the Institutional Review Board of Icahn School of Medicine at Mount Sinai.

Cardiovascular Variables

Cardiovascular variables included diastolic BP (DBP), systolic BP (SBP), PP, and HTN status. Both BP and HTN status data were collected at each in-person neuromedical evaluation. BP data were obtained by licensed clinical research nurses at each in-person neuromedical evaluation using a calibrated sphygmomanometer and included DBP and SBP measurements, which were used continuously. BP data were used to compute PP, which was the difference between SBP and DBP. HTN status was determined by the research nurses through medical record review and/or patient self-reported diagnosis of HTN with use of antihypertensive medication. For this study, active HTN was operationalized as stage 2 or greater (SBP $\geq$ 140 mm Hg and DBP $\geq$ 90 mm Hg) or by documenting the use of antihypertensive medication. Data regarding diagnostic status for diabetes and dyslipidemia were also available and determined using either participant self-report and/or medical record review by the research nurse.

Neuropsychological Assessment

Participants were administered an extensive and well-validated neuropsychological test battery that has been widely used to assess a broad range of NC functions in PLWH.[31] Neuropsychological tests were administered and scored by trained psychometrists at all visits. Raw scores from 6 neuropsychological tests, that collectively comprised 14 component scores, were used to assess NC performance in the putative domains of learning, memory, executive functions, processing speed, and psychomotor functioning (Table 1). Raw scores were used to examine the longitudinal change in NC performance and their associations with longitudinal changes in BP, HTN status, and PP. Standardized scores were not used to eliminate the risk of variance depletion in longitudinal analysis.[32] An estimate of premorbid intellectual functioning was obtained at baseline visit from performance on the Wide Range Achievement Test-third edition (WRAT-3), Reading-Recognition Subtest.

HIV Clinical Variables

Blood samples were drawn for laboratory analysis to obtain CD4 T-cell count and plasma HIV viral loads at each in-person visit; laboratory reports were also obtained from the medical record review when available. Plasma viral load was log transformed before use and reported using log10 copies/mL.

Covariates

Time-varying and time-invariant covariates were selected a priori based on theoretical or empirical rationale and included in all statistical analyses. Log_{10}-transformed HIV viral load and urine toxicology results for cocaine and opiates (0 = negative and 1 = positive) were included as time-varying covariates to account for possible intraindividual differences of HIV infection severity and substance use on cardiovascular and NC performance growth trajectories. Sex, years of

TABLE 1. Summary of the Neuropsychological Test Battery by NC Domains

Neurocognitive Domain	Neuropsychological Tests and Their Performance Scores	Summary
Executive functioning	Wisconsin Card Sorting Task-64 Item Version	Measure of cognitive flexibility, abstract reasoning, and novel problem solving.
	Categories completed	
	Perseverative responses	
	Total errors	
	Trail Making Test Part B	Measure of cognitive flexibility and mental sequencing.
Attention/ working memory	WAIS-III Letter Number Sequencing Total score	Measure of ability to process and sequence information.
	Trail Making Test Part A	Measure of attention and speed.
Learning and memory	Hopkins Verbal Learning Test Revised	Measure of verbal learning and memory recall.
	Total recall	
	Delayed recall	Measure of visual learning and memory recall.
	Brief Visuospatial Memory Test-Revised	
	Total recall	
	Delayed recall	
Speed of information processing	WAIS-III Digit Symbol Total score	Measures of psychomotor speed and cognitive efficiency.
	WAIS-III Symbol Search Total score	
Psychomotor functioning	Grooved Pegboard Test Dominant hand	Measure of psychomotor speed and fine motor dexterity.
	Nondominant hand	

WAIS-III, Wechsler Adult Intelligence Scale-third Edition.

education (self-reported), and baseline WRAT-3 Reading-Recognition Scores were included as time-invariant covariates to account for interindividual differences on the growth trajectories. A lifetime history of depression was also examined as a potential covariate, given mixed findings regarding its association with NC functions.[33] Depression was diagnosed by study personnel using either the Psychiatric Research Interview for Substance and Mental Disorders (PRISM) or the Composite International Diagnostic Interview based on DSM-IV-TR criteria.[34,35] The result patterns were consistent with those without depression. Thus, depression was not included as a covariate.

Statistical Analysis

Baseline descriptive statistics was calculated for all demographic, clinical, anthropomorphic, and NC variables. Univariate analysis of variance and χ^2 tests were also performed to examine baseline differences in demographic characteristics and NC performance between the hypertensive and normotensive groups. Hierarchical linear modeling (HLM) was used to test the effects of the longitudinal change in each cardiovascular variable (ie, DBP, SBP, HTN status, and PP) on the change in NC performance over time. HLM was selected because of its ability to manage an unbalanced design and randomly missing data,[36] and it also does not require adjustment for multiple comparisons.[37] The average missing data rate of analyzed variables was 35.4% (range from 0% to 45%). Variables with >31% missing data were excluded from inferential analysis to minimize statistical error and sample bias.[36] All models were estimated using maximum likelihood with robust standard errors (MLR in Mplus 7.4; Muthén & Muthén, 1998–2015), which assumes data were missing at random.

First, we used graphs (mean and spaghetti plots) to examine the longitudinal growth pattern of each predictor (DBP, SBP, HTN status, and PP) and outcome (NC performance scores). No variables demonstrated nonlinear growth patterns. We used HLM to estimate the unconditional linear growth curve models (GCMs) with random intercept and slope for each predictor and outcome. Age (years) was used to index time in all GCMs,[38] with the intercept centered at 30 years because that was the youngest age in the sample. Logit link function was used for HTN status (0 = normotensive and 1 = hypertensive) in GCMs. The results revealed significant random slope variance for each variable, supporting the inclusion of random slopes in the GCMs. Next, all time-varying and time-invariant covariates were added to the GCMs to account for intraindividual and interindividual differences in the growth trajectories of the predictors and outcomes. Finally, we estimated a series of GCMs where the random intercept and slope of each predictor was used to account for the random intercept and slope of each outcome. Each model included one pair of predictor and outcome (56 models in total), with all covariates adjusted for the GCM of the outcome variable. Models were examined for significant-level and trend-level effects; only one model reached trend-level significance ($P < 0.10$). For brevity, only significant findings were reported ($\alpha = 0.05$). The results neither revealed any significant associations between PP and NC performance nor any associations between their longitudinal changes.

RESULTS

The study sample included 485 participants. The sample had 45% non-Latinx Black participants, 32% Latinx, and 23% non-Latinx White; 38% were women with a mean of 12 years (SD = 3) education completed.

Baseline Characteristics

At baseline, the average age of the sample was 47 years (SD = 8.8). The prevalence of HTN was 23%, and the mean BP measurements included a SBP of 119 mm Hg, DBP of 75 mm HG, and PP of 44 mm Hg. Univariate analysis of variance and χ^2 tests were performed to examine baseline differences between the hypertensive and normotensive groups pertaining to demographic characteristics (Table 2). Compared with the normotensive participants, the hypertensive participants were older and

more likely to be non-Latinx Black. The hypertensive group had significantly higher weight, body mass index, BP, PP, and prevalent diabetes than the normotensive group. The hypertensive group was also more likely to be on ART at baseline and exhibited higher absolute CD4 counts, lower HIV viral loads, and longer duration of infection at entry, compared with the normotensive group. Approximately 77% of the cohort was on ART at baseline. Of the 23% participants (N = 103) who were not on ART at baseline, 60% started ART during follow-up and 40% were never on ART. The mean interval to ART initiation during follow-up was 1.7 years (median = 0.57, IQR = 1.4). Baseline differences in NC performance between the hypertensive and normotensive groups were also examined (see Table 1, Supplemental Digital Content 1, http://links.lww.com/QAI/B685, which presents results of group comparison) and found groups were comparable on all but one measure.

Longitudinal Characteristics

For the study sample, the average number of completed visits was 5 (*SD* = 4.3) and the average years of participation was 5 (*SD* = 4). The visit periods spanned up to 210 months (median = 30, IQR = 68). Approximately 75% of the sample completed ≥ 2 visits, 40% ≥ 5 visits, 16% ≥ 10 visits, and 6% ≥ 15 visits. Over the course of the study, the average age was 51.5 years (*SD* = 9, range 30–84 years). The total number of study observations was 2442, and of these observations, 9% were derived from participants aged 30–39 years, 33% from ages 40–49 years, 39% from ages 50–59 years, 17% from ages 60–69 years, and 2% from ages 70 or older. Among the 328 normotensive participants at baseline, 75 cases of new-onset HTN were identified in the period up to 2017, during 1067 PYFU, yielding an overall incidence of 7.02 per 100 PYFU. The mean BP components by age for all available data from each

TABLE 2. Baseline Demographic and Clinical Characteristics by HTN Diagnosis Status

Variable	Total Sample (N = 485) M (SD) or n (%)	Hypertension Dx (n = 113) M (SD) or n (%)	No HTN Dx (n = 328) M (SD) or n (%)	Group Comparisons (F/χ^2)
Demographic characteristics				
Age	47.0 (8.8)	51.5 (7.7)	45.6 (8.8)	39.0*
Sex				
Male	299 (61.6%)	65 (55.9%)	206 (63.2%)	1.0
Race/ethnicity				
Non-Latinx Black	220 (45.4%)	64 (56.8%)	137 (41.9%)	7.7†
Latinx	153 (31.5%)	30 (27.0%)	109 (32.8%)	
Non-Latinx White	112 (23.1%)	19 (16.2%)	82 (25.2%)	
Education (yr)	12.4 (3.0)	12.2 (3.2)	12.4 (2.9)	0.3
Anthropomorphic data				
Height (m)	1.7 (0.1)	1.7 (0.1)	1.71 (0.1)	0.1
Weight (lbs)	170.0 (43.7)	187.5 (50.6)	161.6 (37.6)	19.8*
BMI	27.0 (7.2)	29.4 (8.1)	25.5 (6.5)	15.4*
Systolic BP (mm HG)	119.0 (16.0)	128.0 (18.0)	114.5 (12.8)	49.2*
Diastolic BP (mm HG)	75.0 (10.6)	79.0 (11.3)	72.8 (9.7)	19.3*
Pulse pressure (mm HG)	44.0 (11.8)	49.0 (13.3)	42.0 (9.9)	27.0*
Comorbid conditions				
Diabetes	59 (12%)	36 (30%)	23 (8%)	44.7*
Hyperlipidemia	106 (22%)	48 (44%)	58 (18%)	28.3*
Hx of hepatitis C infection	184 (38%)	47 (24%)	130 (30%)	0.1
HIV characteristics				
Abs CD4 count; Mdn (IQR)	223.2 (389)	325.0 (415)	197.0 (373)	16.8*
Plasma viral load; Mdn (IQR)	3.9 (2.7)	3.3 (2.6)	4.1 (2.7)	7.8*
Viral load ≤50 copies/mL	70 (14%)	24 (21%)	46 (14%)	—
Nadir CD4	127 (184.4)	156 (175.8)	119 (184.4)	3.4
Baseline care status				
ART experienced at entry	376 (77%)	96 (86%)	251 (76%)	3.8†
Duration of infection at entry (yr)	12.8 (6.4)	15 (6.8)	12 (6.0)	17.0*
Substance use characteristics				
Positive Utox cocaine	86 (17.7%)	17 (17.5%)	63 (21.8%)	1.0
Positive Utox opiates	87 (17.9%)	20 (20.6%)	60 (20.8%)	0.0
Psychiatric characteristics				
Lifetime history of MDD	222 (45.8%)	50 (50.5%)	152 (55.3%)	0.5

Plasma viral load was log transformed before use and is reported in log10 copies/mL. Pairwise deletion was used in these analyses.
*$P < 0.01$.
†$P < 0.05$.
Dx, diagnosis status; BMI, body mass index; Mdn, median; Utox, urinary toxicology; MDD, major depressive disorder.

participant are presented in 10-year age intervals (see Fig. 1, Supplemental Digital Content 2, http://links.lww.com/QAI/B685) and generally shows a consistent rise in BP components from age 30–39 years to 60–69 years.

Change in NC Performance Associated With DBP

Table 2 presents the significant results of the random intercept and slope of DBP predicting the random intercept and slope of NC performance, adjusted for all covariates. The results revealed a significant relationship between the longitudinal change of DBP and the longitudinal change of NC performance on the Grooved Pegboard Test (GPT) and Wisconsin Card Sorting Test (WCST). At baseline (intercept), participants with higher DBP performed slower on the GPT nondominant hand and made more perseverative responses and total errors on WCST. The linear slope of DBP was also significantly associated with the slope of GPT-NDH and WCST performance. Specifically, the increase of the slope of DBP was associated with a 10.5-second increase in the slope of GPT-NDH performance, indicating slower performance over time. While on the WCST, the slope of DBP was associated with a 3-point increase in the slope of perseverative responses and total errors as well as a 0.3-point decline in the slope of number of correct categories completed over time. Additional details regarding NC performance on the GPT and WCST by age is provided in the Supplemental Digital Content (see Figs. 2 and 3, Supplemental Digital Content 3, http://links.lww.com/QAI/B685, which present the mean performance scores on the GPT and WCST for all available data from each participant in 10-year age intervals). Of the covariates, significant intercept scores were observed for baseline WRAT-3 reading scores, education, cocaine, and HIV viral load on NC performance. Specifically, at baseline (intercept, age 30 years), lower reading scores were associated with slower GPT-NDH performance ($\beta = 1.2$, $P < 0.01$) as well as fewer perseverative responses ($\beta = -0.3$, $P = 0.01$) and total errors ($\beta = -0.4$, $P < 0.01$) on the WCST. The higher number of years of education completed was also associated with fewer total errors ($\beta = -0.5$, $P < 0.05$) on the WCST. Furthermore, those who tested positive for cocaine at baseline had fewer total errors ($\beta = -1.6$, $P < 0.01$) on the WCST, and those with lower HIV viral loads at baseline completed fewer categories ($\beta = -0.06$, $P < 0.05$) on the WCST.

Change in NC Performance Associated With SBP

Table 3 presents the significant findings of the random intercept and slope of SBP predicting the random intercept and slope of NC performance outcomes, adjusted for all covariates. The results revealed a significant relationship between the longitudinal change of SBP and the longitudinal change of NC performance on the GPT-NDH. Specifically, the slope of SBP was associated with a 4-second increase in the slope of GPT-NDH, indicating slower performance over time. However, SBP, at the intercept, did not significantly predict GPT-NDH performance. Significant intercept scores were observed for baseline WRAT-3 reading scores ($\beta = -1.2$, $P < 0.01$) and HIV viral load ($\beta = 1.5$, $P < 0.05$) on the GPT-NDH. A trend-level association was also observed for the slope of SBP on the slope of WCST perseverative responses ($P = 0.08$). Although this finding was not significant, the results suggest the change in the slope of SBP may be associated with an increase in perseverative responses on the WCST over time.

Change in NC Performance Associated With HTN Status

Table 4 presents the significant findings of the random intercepts and slopes of HTN status predicting the random intercept and slope of NC performance outcomes, adjusted for all covariates. The slope of hypertensive status (ie, increasing odds of being hypertensive over time) was associated with a 0.1-point decline in the slope of the WCST number of correct categories and a 0.8-point increase in the slope of WCST number of total errors over time. Of the time-invariant covariates, significant intercept scores were observed for baseline WRAT-3 reading scores ($\beta = -0.4$, $P < 0.01$) and education ($\beta = -0.5$, $P < 0.05$) with NC performance on the WCST. Sex was also significantly associated with HTN status ($\beta = 1.8$, $P < 0.05$), indicating that at baseline, women demonstrated increased odds of having HTN. Of the time-varying covariates, significant intercept scores were observed for cocaine with both NC performance ($\beta = -1.6$, $P < 0.01$) and HTN status ($\beta = -0.9$, $P < 0.05$), indicating that at baseline, those who tested positive for cocaine had fewer total errors on the WCST and exhibited lower odds of having HTN (Table 5).

Finally, we repeated the analyses with diabetes, hyperlipidemia, and history of hepatitis C virus coinfection included as covariates to account for the potential interaction between BP and HTN with other vascular risk factors (see Tables 2–4, Supplemental Digital Content 4, http://links.lww.com/QAI/B685) and found the results were not attenuated after additional adjustment for these risk factors.

DISCUSSION

This prospective longitudinal study examined the independent effects of change in BP, HTN status, and PP on the change in NC performance across 14 NC outcomes in PLWH, adjusted for HIV viral load, substance use, sex, education years, and baseline WRAT-3 Reading-Recognition scores. The results revealed significant relationships between the change in BP and HTN status with the change in NC performance over time. Specifically, longitudinal increases in both DBP and SBP were associated with performance declines in (nondominant hand) psychomotor speed and fine motor dexterity. The longitudinal increase in DBP was also associated with performance declines on a measure of executive functions, particularly in the areas of abstract reasoning, cognitive flexibility, and set shifting. Similarly, greater odds of being hypertensive were significantly associated with poorer NC

TABLE 3. Linear GCM for Diastolic BP Predicting Linear GCM of NC Test Performance

	Neurocognitive Test Performance (NCP)							
	GPT Nondominant Hand		WCST Categories		WCST Perseverative Responses		WCST Total Errors	
Parameters	ß	SE	ß	SE	ß	SE	ß	SE
Change in NCP on change in DBP								
Change in NCP on change in DBP	10.5*	3.9	−0.3†	0.1	2.9†	1.2	3.0*	1.0
Change in NCP on intercept of DBP	0.2*	0.1	−0.0†	0.0	0.0†	0.0	0.0*	0.0
Intercept of NCP on change in DBP	−569.9*	202.6	13.7†	6.6	−164.5†	70.5	−147.5*	53.9
Intercept of NCP on intercept of DBP	−8.3*	2.8	0.2	0.1	−2.2†	0.9	−1.8†	0.7
Mean intercept of NCP	704.7*	204.2	−12.0	6.6	202.7†	68.8	177.6*	51.8
Mean change in NCP	−10.8*	4.0	0.3	0.1	−3.0*	1.2	−2.7*	0.9
Mean intercept of DBP	73.1*	4.0	72.2*	4.3	73.2*	4.3	72.8*	4.3
Mean change in DBP	−0.0	0.1	0.0†	0.1	0.0	0.1	0.0	0.1
Residual variance								
Residual variance of change in DBP	0.1†	0.1	0.1†	0.1	0.1	0.1	0.1†	0.1
Residual variance of change in NCP	4.8*	1.8	0.0†	0.0	0.1	0.1	0.1	0.1
R^2	0.2		0.3		0.3		0.7	

Age was used to index time, with intercept set at age 30 years. Models were adjusted for HIV viral load and urine toxicology results for cocaine and opiates at Level 1 and for sex, education yr, and baseline Wide Range Achievement Test-third Edition (WRAT-3) Reading-Recognition Subtest scores at Level 2.

*$P < 0.01$.

†$P < 0.05$.

DBP, diastolic BP; GPB, Grooved Pegboard Test; WCST, Wisconsin Card Sorting Test.

performance in abstract reasoning and cognitive flexibility on a measure of executive functions. Neither PP nor change in PP was associated with NC performance over time.

TABLE 4. Linear GCM for Systolic BP Predicting Linear GCM of NC Test Performance

	Neurocognitive Test Performance (NCP)			
	GPB Nondominant Hand		WCST Perseverative Responses	
Parameters	ß	SE	ß	SE
Change in NCP on change in SBP				
Change of NCP on change in SBP	3.9†	1.6	0.8‡	0.4
Change of NCP on intercept of SBP	0.1	0.0	0.0	0.0
Intercept of NCP on change in SBP	−185.0†	75.5	−44.6	23.7
Intercept of NCP on intercept of SBP	−2.3	1.8	−0.7‡	0.5
Mean intercept of NCP	396.3	205.7	124.9	54.3
Mean change in NCP	−5.6	4.4	−1.6*	1.1
Mean intercept of SBP	91.6*	6.3	91.4*	6.7
Mean change in SBP	0.5*	0.1	0.5*	0.1
Residual variance				
Residual variance of change in SBP	0.4†	0.2	0.4*	0.2
Residual variance of change in NCP	5.3*	1.8	0.2†	0.1
R^2	0.1		0.1	

Age was used to index time, with intercept set at age 30 years. Models were adjusted for HIV viral load and urine toxicology results for cocaine and opiates at Level 1 and for sex, education yr, and baseline Wide Range Achievement Test-third edition (WRAT-3) Reading-Recognition Subtest scores at Level 2.

*$P < 0.01$.

†$P < 0.05$.

‡$P < 0.10$.

SBP, systolic BP; GPB, Grooved Pegboard Test; WCST, Wisconsin Card Sorting Test; SE = standard error.

Covariate analysis revealed significant intercepts for education, WRAT-3 reading scores, cocaine-positive urine toxicology, and HIV RNA load with NC performance, as well as sex and cocaine-positive urine toxicology with HTN status.

TABLE 5. Linear GCM for HTN Status Predicting Linear GCM of NC Test Performance

	Neurocognitive Test Performance (NCP)			
	WCST Categories		WCST Total Errors	
Parameters	ß	SE	ß	SE
Change in NCP on change in HTN status (0 = no, 1 = yes)				
Change in NCP on change in HTN status	−0.1†	0.1	0.8†	0.3
Intercept of NCP on change in HTN status	5.0	2.6	−35.5†	16.7
Intercept of HTN status on change in NCP	0.0	0.1	−0.2	0.4
Intercept of HTN status on intercept of NCP	−1.2	2.9	13.8	20.6
Mean intercept of NCP	−2.1	1.1	63.3*	8.5
Mean change in NCP	0.0	0.0	−0.3†	0.1
Mean change in HTN status	0.4*	0.0	0.5*	0.0
Residual variance				
Residual variance of change in HTN status	0.1*	0.0	0.1*	0.0
Residual variance of change in NCP	0.0*	0.0	0.2*	0.1
R^2	0.3		0.3	

Age was used to index time, with intercept set at age 30 years. Models were adjusted for HIV viral load and urine toxicology results for cocaine and opiates at Level 1 and for sex, education yr, and baseline Wide Range Achievement Test-third Edition (WRAT-3) Reading-Recognition Subtest scores at Level 2.

*$P < 0.01$.

†$P < 0.05$.

WCST, Wisconsin Card Sorting Test.

Previous studies examining the relationship between HTN and NC impairment in PLWH have been equivocal overall.[25–29] Our finding of a significant longitudinal association between the change in HTN status and the change in NC performance is consistent with some previous literature[6,8,9,39–43] bolstering previous cross-sectional observations of a potential link between HTN and NC impairment in PLWH.[13,25,28] However, it is unknown how our study relates more broadly to the general population of PLWH because the MHBB cohort is medically multimorbid, with relatively advanced indices of HIV disease, as demonstrated by a median baseline CD4 T-cell count of 223 cells/mm3. This study is also the first to examine these longitudinal associations in a diverse cohort of adult PLWH, so we have no previous comparators. The significant longitudinal association between increases in DBP and SBP with performance declines in psychomotor speed partially aligns with recent findings from our group indicating HTN was associated with declines in psychomotor speed within a subgroup of this cohort.[26,30] Although our results slightly contrast with the aforementioned study in that elevations, BP, but not HTN, was associated with declines in psychomotor speed, and HTN was not associated with reduced executive functions performance; absence of BP data in the previous study precludes improved understanding of these relationships including how their results relate to the present findings. Still, it is notable that negative trends in NC performance, across multiple domains, with HTN were also reported in the previous study[26] because those trends are consistent with the current results indicating higher BP, and HTN may negatively impact NC performance in PLWH. Discrepancies between these results may be attributable to insufficient power and/or the relatively small sample size in the aforementioned study. In addition, a BP-related decline in motor functions is also consistent with our previous finding of an association of motor function decline and cerebrovascular disease, which is an important consequence of HTN.[30]

Although the association between SBP and DBP conformed to what would be predicted based on the literature of HTN, cSVD, and cognition, the null association between PP, an indirect marker of arterial stiffness, and NC performance was unexpected. However, there is some evidence to suggest that PP may not carry the same predictive power for cSVD as direct measurement of BP.[44] As this study is the first to explore longitudinal relations between PP and NC performance in PLWH, we cannot comment on the validity of our negative observation. Only one cross-sectional investigation has examined relationships between PP and NC performance in the context of HIV.[29] In this previous cross-sectional analysis, a significant quadratic association between PP and NC functioning in PLWH and seronegative adults was observed, wherein both lower and higher PPs were associated with worse global, psychomotor, and executive functions. Notably, HIV+ serostatus did not moderate the relationship between PP and NC functioning, and PP was comparable between groups in this study.[29]

Our study is the first to examine the longitudinal relations between BP and PP on NC performance in PLWH. Strengths of this investigation include its longitudinal design, advanced statistical approach, diverse sample, lengthy follow-up, number of repeated assessments, and use of professionally ascertained medical and NC data. Limitations of this study include inability to account for other known risk factors for cSVD and NC impairment in PLWH, such as smoking and metabolic syndrome, because of incomplete data in the early epoch (years 1999–2002) of the study. Effects of variable ART classes over time was also not examined because we could not reliably estimate prestudy exposures through the patient report, and varying drugs within classes had different metabolic profiles over time. This limitation warrants further study, given the conflicting findings regarding the influence of ART on HTN and/or NC functions.[45–50] We also did not assess the mean arterial pressure, the steady component of BP. Lack of an HIV sample precluded our ability to make substantive conclusions regarding HIV-specific relative risk and impact of HTN, and its components, on cSVD and NC performance in PLWH. The absence of antihypertensive data also prohibited examination of the longitudinal effects of HTN control on NC performance, although direct measurement of BP can be considered a surrogate. Future research would benefit from longitudinal investigations on the effects of various antihypertensive therapies, including their associations with NC performance, to potentially mitigate disparities in NC impairment and/or HAND in PLWH. Longitudinal investigations detecting change in neuroimaging biomarkers of sCVD dysfunction, including their relations with NC performance, are also warranted because this work has been largely cross-sectional.[51] Such work would further benefit from incorporation of norms for change[52] to better characterize NC trajectories and impairment in relation with sCVD in PLWH. Finally, an important future direction of this work includes careful examination of the role of racial disparities on the relationship between HTN and NC impairment in this diverse cohort of PLWH, given the differential burden of cognitive and health disparities in underrepresented minority PLWH.

The results of this longitudinal study provide a significant contribution to the limited and largely cross-sectional literature on the relationship between HTN, and its components, with NC performance in PLWH. These findings also meaningfully extend the previous work examining the influence of cSVD risk factors on HAND, which has mostly focused on metabolic risk factors and biomarkers of arterial dysfunction[13,51,53] despite the robust association between HTN and cSVD in HIV+ and seronegative populations.[3,11,20,54,55] This is notable as HTN has also recently been implicated as an important prognostic indicator of decreased vascular integrity and arterial compliance, including increased carotid intima media thickness and arterial wall thickness,[56,57] 2 significant predictors of NC impairment in PLWH.[25–27,58] Although the relationships between BP, HTN, and PP with biomarkers of vascular integrity and arterial compliance could not be assessed in this study, accumulating support-linking biomarkers of vascular and arterial dysfunction with HTN as well as cSVD and NC impairment in PLWH suggests elevations in BP and HTN may impose unique and/or additive effects on NC impairment and/or HAND in PLWH. This may be due to alterations in

neurovascular coupling, secondary to HTN, that increase the brain's vulnerability to ischemia, cSVD, and, thereby also, NC impairment due to increased hypoperfusion and cerebral autodysregulation.[6,59] Furthermore, observed associations between performance declines in psychomotor speed and executive functions with longitudinal increases in BP and HTN risk in this cohort also suggest HTN and HIV may interact to exacerbate HIV-associated neurologic dysfunction, which disproportionately and adversely affects the cerebral white matter, particularly subcortical and frontostriatal networks,[60] to increase the risk for NC impairment and/or HAND in PLWH.[61]

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