Cardiovascular risk factors associated with lower baseline cognitive performance in HIV-positive persons

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ABSTRACT

Objective: To determine factors associated with baseline neurocognitive performance in HIV-infected participants enrolled in the Strategies for Management of Antiretroviral Therapy (SMART) neurology substudy.

Methods: Participants from Australia, North America, Brazil, and Thailand were administered a 5-test neurocognitive battery. *Z* scores and the neurocognitive performance outcome measure, the quantitative neurocognitive performance *z* score (QNPZ-5), were calculated using US norms. Neurocognitive impairment was defined as *z* scores <-2 in two or more cognitive domains. Associations of test scores, the QNPZ-5, and impairment with baseline factors including demographics and risk factors for HIV-associated dementia (HAD) and cardiovascular disease (CVD) were determined in multiple regression.

Results: The 292 participants had a median CD4 cell count of 536 cells/mm^3, 88% had an HIV viral load ≤400 copies/mL, and 92% were taking antiretrovirals. Demographics, HIV, and clinical factors differed between locations. The mean QNPZ-5 score was −0.72; 14% of participants had neurocognitive impairment. For most tests, scores and *z* scores differed significantly between locations, with and without adjustment for age, sex, education, and race. Prior CVD was associated with neurocognitive impairment. Prior CVD, hypercholesterolemia, and hypertension were associated with poorer neurocognitive performance but conventional HAD risk factors and the CNS penetration effectiveness rank of antiretroviral regimens were not.

Conclusions: In this HIV-positive population with high CD4 cell counts, neurocognitive impairment was associated with prior CVD. Lower neurocognitive performance was associated with prior CVD, hypertension, and hypercholesterolemia, but not conventional HAD risk factors. The contribution of CVD and cardiovascular risk factors to the neurocognition of HIV-positive populations warrants further investigation. *Neurology*® 2010;75:864–873

GLOSSARY

AD = Alzheimer disease; **ART** = antiretroviral therapy; **BP** = blood pressure; **CES-D** = Center for Epidemiologic Studies-Depression scale; **CT** = Color Trails; **CVD** = cardiovascular disease; **FTT** = Finger Tapping Test; **GPB** = Grooved Pegboard; **HAD** = HIV-associated dementia; **NCI** = neurocognitive impairment; **QNPZ-5** = quantitative neurocognitive performance *z* score; **SMART** = Strategies for Management of Antiretroviral Therapy; **TG** = Timed Gait.

In advanced untreated HIV disease, HIV-associated dementia (HAD) develops in approximately 15% of patients[1] and combination antiretroviral therapy (ART) has effectively reduced the incidence of HAD.[2] The Strategies for Management of Antiretroviral Therapy (SMART) study randomized participants to intermittent, CD4-guided ART or continuous ART.[3] In a neurology substudy, a neurocognitive test battery was administered. We hypothesized that neurocognitive

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performance would be superior in patients receiving continuous ART via its attendant benefits upon both peripheral and CNS immunity.

We present a cross-sectional analysis of 292 HIV-infected persons coenrolled in the SMART neurology substudy at sites in Australia, North America, Brazil, and Thailand. We sought to explore factors associated with neurocognitive performance. These included demographics, ART, HAD, and cardiovascular risk factors and cardiovascular disease (CVD). In HIV-negative populations, smoking,[4] hypertension,[5] high cholesterol,[6] obesity,[5] and diabetes[5] are the cardiovascular risk factors associated with increased risk of poor cognitive function, vascular dementia, and Alzheimer disease (AD). Prior myocardial infarction,[7] coronary artery bypass grafting,[8] and stroke[5] are also associated with poor cognitive function. In HIV-positive populations, diabetes has been associated with HAD,[9] and increased carotid intima media thickening[10] has been associated with poorer neurocognitive performance. CVD risk factors were common in the SMART study[3]: we hypothesized that they would be associated with lower baseline neurocognitive performance. We sought to describe and compare neuropsychological test results obtained in Australia, North America, Brazil, and Thailand and hypothesized that test scores, but not the standardized *z* scores, would differ across locations.

METHODS

Study design. The SMART study was an international randomized trial comparing continuous ART with CD4-cell count guided, intermittent ART in HIV-infected persons with CD4 cell count >350 cells/mm^3. The neurocognitive component of the SMART neurology substudy aimed to compare the 2 study arms for changes in neurocognitive function through follow-up. Baseline, month 6, and annual assessment of neurocognitive functioning in 600 participants would have provided 80% power to detect a difference of 0.27 in the primary outcome (change in the aggregate quantitative neurocognitive performance *z* score, QNPZ-5, described below). The neurology substudy commenced enrollment in July 2005. In January 2006, enrollment and the intermittent CD4-guided ART strategy of the SMART study were stopped due to increased risk of AIDS and serious non-AIDS complications. The primary results of the SMART study are published elsewhere.[3] At the time of this protocol change, only 292 of the 600 planned substudy participants were enrolled, and minimal follow-up data were available.

Forty-seven SMART study sites in Australia, North America, Brazil, and Thailand participated in the substudy. All eligible SMART participants were offered substudy coenrollment. Substudy eligibility criteria included age ≥18 years, and the ability to perform the study's neurocognitive tests in the site clinician's judgment.

Standard protocol approvals, registrations, and patient consents. Substudy approval was obtained by each site's institutional review board. Patient information and consent forms were translated into Thai, Portuguese, and Spanish, and back-translated into English. All participants provided written informed consent. The study was registered at clinical trials.gov: NCT00432003.

Outcome measures. The study's neurocognitive test battery comprised the Grooved Pegboard (GPB) (dominant hand),[11] Color Trails (CT) 1 and CT2,[12] Timed Gait (TG),[13] and Finger Tapping Test (FTT) (nondominant hand).[14] Details of these tests can be found in appendix e-1 on the *Neurology*® Web site at www.neurology.org. This test battery was chosen because it is sensitive to changes observed in HIV-associated neurocognitive disorders, brief, easy to administer and teach, and can be used internationally where little formal Western education exists[15]; our tests closely resemble the battery used in a large, randomized ART HIV treatment study.[16]

For all 5 tests, the raw scores of each participant were standardized to *z* scores by subtracting the mean test scores of matched, HIV-negative reference populations, and dividing by the reference SD. Therefore, *z* scores estimate how many SDs a test score is above or below the average score of the reference population; negative *z* scores denote below-average performance. For the TG, raw scores were standardized to *z* scores using previously published reference distributions,[13] matched by education level. For the other tests, *z* scores were calculated using scoring software by Psychological Assessment Resources, Inc., Odessa, FL.[17] Reference distributions were matched by education level for all 5 tests, and additionally by age, sex, and race/ethnicity for GPB and FTT,[18] and by age for CT. All reference populations were obtained in the United States.

Our primary neurocognitive performance outcome measure was the QNPZ-5, calculated as the average of the 5 *z* scores from the individual tests in the battery. A QNPZ-5 score below 0 denotes below-average neurocognitive performance. For the purpose of this study, we defined neurocognitive impairment (NCI) as *z* scores <−2 in at least 2 cognitive ability domains. Ability domains assessed were 1) speed/fine motor skills (GPB and FTT), 2) attention/speed of processing (CT1), 3) abstraction/executive function (CT2), and 4) gross motor skills (TG). The cutoff was chosen to reflect criteria for abnormal neurocognitive performance that are a required component for the diagnosis of HAD.[19]

We administered the Center for Epidemiologic Studies–Depression scale (CES-D)[20] to screen for depression at baseline. The CES-D has been used in international studies in HIV-infected[15] populations. We used the recommended cutoff score of ≥16 to define depression (sensitivity 86%–100%, specificity 53%–84%).[21]

Neuropsychological tests and the CES-D were administered to participants by site staff, including medical practitioners, specialists, and nurses. Site staff underwent centralized training and certification in the United States and Australia. Training was led by a neuropsychologist or neurologist and an infectious disease physician. Each trainee was required to administer the full test battery during training, and at least 3 times afterwards to non-study participants before administering it to study participants. Test instructions and training materials were available for site staff on the study Web site. Neuropsychological test instructions were translated into Portuguese, Spanish, and Thai. We used published translations of the Spanish[22] and Brazilian Portuguese[23] CES-D and an online Thai[24] translation.

Table 1 Baseline characteristics by location

Characteristics	Total (n = 292) % or median (IQR)	Location, % or median			p Value (location)
		Australia and North America (n = 102)	Brazil (n = 45)	Thailand (n = 145)	
Demographics					
Age, y	40 (35–45.5)	43	42	38	<0.001[a]
Female	41.8	18.6	37.8	59.3	<0.001[a]
Race/ethnicity					<0.001[a]
Asian	50.7	2.0	2.2	100.0	
Black	19.5	45.1	24.5	0	
Other or unknown	29.8	52.9	73.3	0	
Education (% with ≤12 y)	53.8	40.2	75.6	56.6	<0.001[a]
HIV-related factors					
CD4 count, cells/mm^3	536 (437–693)	522	628	517	0.003[a]
Nadir CD4 count, cells/mm^3	225 (158–296)	208	234	226	0.99
HIV RNA ≤400 copies/mL	87.6	69.6	88.6	100.0	<0.001[a]
Prior AIDS diagnosis	20.9	26.5	44.4	9.7	<0.001[a]
Preexisting conditions					
CVD[b]	3.4	5.9	4.4	1.4	0.15
Diabetes	3.8	4.9	4.4	2.8	0.66
ART use at baseline					
Years of prior ART use	4 (3–6)	5	6	3	<0.001[a]
Current ART use	92.5	82.4	97.8	97.9	<0.001[a]
CNS penetration effectiveness rank[c]	1.5 (1.5–2.0)	1.5	2.0	1.5	<0.001[a]
Cardiovascular risk factors					
Total cholesterol, mg/dL	196 (168–222)	190	180	203	0.02[a]
HDL cholesterol, mg/dL	44 (36–54)	41	37	49	<0.001[a]
Lipid-lowering drugs	8.6	18.6	6.7	2.1	<0.001[a]
Blood pressure–lowering drugs	11.0	21.6	13.3	2.8	<0.001[a]
Body mass index, kg/m^2	23.5 (21.1–26.6)	25.1	24.2	22.2	<0.001[a]
Current smoking	23.3	44.1	13.3	11.7	<0.001[a]
Recreational drug use	5.5	13.7	2.2	0.7	<0.001[a]
Predicted 10-y risk of CVD[d] (% per 10 y)	3 (2–7)	5	4	3	<0.001[a]

Abbreviations: ART = antiretroviral therapy; CVD = cardiovascular disease; HDL = high-density lipoprotein; IQR = interquartile range.
[a] Significant.
[b] Previous myocardial infarction (4), stroke (0), coronary heart disease (3), congestive heart failure (2), or peripheral vascular disease (5).
[c] Calculated using the CNS Penetration Effectiveness Rank.[26]
[d] Calculated using the Framingham score.[25]

Baseline data collected within the parent SMART study included demography, HIV history, general medical history, and laboratory values (summarized in table 1 and table e-1); additionally, alcohol and drug use were collected within the substudy. We summarized risk factors for CVD into a modified Framingham score; since blood pressure (BP) was not available, we assigned a systolic BP of 140 mm Hg to participants using antihypertensive drugs, and 120 mm Hg otherwise.[25] We calculated the CNS penetration effectiveness rank[26] of patients' ART regimens.

Statistical methods. Baseline characteristics, neuropsychological test scores, and CES-D scores were summarized by location of enrollment. The Kruskal-Wallis rank sum test was used to compare median values across locations, χ^2 tests to compare percentages. Mean test scores (raw scores and z scores) were compared across locations using analysis of variance and the Tukey Honest Significant Difference pairwise comparison method. In order to account for variability between clinical sites within countries, we also compared locations in hierarchical mixed effects models with sites nested in location.

Associations of baseline factors with raw test scores, z scores, the QNPZ-5 score, and having z scores <-2 in 2 or more cognitive domains (a total of 12 outcomes) were determined by multiple linear or logistic regression. In a first step, the following factors were included: HAD risk factors (age, current and nadir

CD4 cell counts, prior AIDS, diabetes); sex; race/ethnicity; location of enrollment; education; body mass index; smoking; alcohol abuse; recreational drug use; history of hepatitis B, hepatitis C, or CVD; viral load (HIV RNA ≤400 copies/mL); CNS penetration effectiveness rank; use of BP-lowering and lipid-lowering drugs; total cholesterol, high-density lipoprotein, and low-density lipoprotein; and CES-D score ≥16. Factors were then eliminated using backwards selection with the Akaike information criterion. We retained age, gender, race, and education in all models, because these factors were associated with neuropsychological test results in noninfected populations, and reference norms for calculating *z* scores are usually matched by these factors. We also retained location to consistently assess the location effect. Coefficients and *p* values from the final models were presented. In a separate model, lipids and use of BP-lowering drugs were replaced by Framingham risk estimates for CVD (4 categories),[25] extrapolating BP from use of BP-lowering drugs.

Analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC) and *R* version 2.9. All tests were 2-sided. *p* Values ≤0.05 were considered significant.

Table 2 Neuropsychological test performance and CES-D scores by location[a]

		Location				Hierarchical model[c]		
	Total (n = 292)	Australia and North America (n = 102)	Brazil (n = 45)	Thailand (n = 145)	*p* Value,[b] location (n = 292)	SD, between sites	SD, between patients	*p* Value,[c] location (n = 272)
Test scores, mean ± SD								
GPB, s	72.7 ± 25.8	83.9	70.4	65.5	<0.001[d]	4.0	23.0	0.004[d]
CT1, s	49.5 ± 22.5	48.8	60.2	46.7	0.002[d]	7.9	21.5	0.27
CT2, s	98.6 ± 43.0	92.3	127.1	94.1	<0.001[d]	15.8	40.2	0.08
TG, s	11.9 ± 2.1	11.8	11.2	12.1	0.04[d]	0.8	2.0	0.51
FTT, taps	39.4 ± 7.9	39.8	42.7	38.1	0.002[d]	3.7	7.4	0.45
***z* Scores,[e] mean ± SD**								
GPB	−0.26 ± 1.19	−0.62	−0.04	−0.08	<0.001[d]	0.22	1.10	0.04[d]
CT1	−0.63 ± 1.42	−0.63	−1.16	−0.47	0.02[d]	0.53	1.35	0.50
CT2	−0.15 ± 1.27	−0.06	−0.85	0.00	<0.001[d]	0.50	1.19	0.20
TG	−1.60 ± 1.74	−1.60	−0.94	−1.82	0.01[d]	0.58	1.62	0.29
FTT	−0.96 ± 1.10	−1.09	−0.41	−1.04	0.001[d]	0.45	1.04	0.25
QNPZ-5, mean ± SD	−0.72 ± 0.84	−0.80	−0.68	−0.68	0.53	0.35	0.79	0.81
No. (%) with *z* scores <−1 in 2 or more independent domains	150 (51.4)	52 (51.0)	18 (40.0)	80 (55.2)	0.21			
NCI: No. (%) with *z* scores <−2 in 2 or more independent domains	42 (14.4)	23 (22.5)	5 (11.1)	14 (9.7)	0.01[d]			
CES-D	11.2 ± 9.6	14.8	12.8	8.3	<0.001[d]	2.9	8.8	0.02[d]
Depression: No. (%) with CES-D ≥ 16	71 (25.5)	38 (41.3)	14 (31.1)	19 (13.5)	<0.001[d]			

Abbreviations: CES-D = Center for Epidemiologic Studies–Depression scale; CT = Color Trails; FTT = Finger Tapping Test (nondominant hand); GPB = Grooved Pegboard (dominant hand); NCI = neurocognitive impairment; QNPZ-5 = quantitative neurocognitive performance *z* score; TG = Timed Gait.

[a] Test scoring: GPB: time in seconds. CT1 and 2 tests: time in seconds. TG: 3 timed trials; scored as average time per trial, in seconds. FTT: each participant performed between 5 and 10 trials. The test score was the average of the 5 trials where the number of taps had the least spread. Outliers: We capped the time recorded for the GPB test at 300 seconds and for TG at 45 seconds (1 participant each). Test scores that corresponded to *z* scores that were more than 11 SD above or below the reference mean were considered recording errors and deleted from the analysis (1 CT1, and 2 TG records).

[b] Differences between locations were tested in an analysis of variance model.

[c] Differences between locations were tested in a mixed effects hierarchical model, with random effects for sites, nested in location, and fixed effects for the 3 locations. This analysis includes 272 participants at 15 sites (Australia 14/1, North America 68/7, Brazil 45/2, Thailand 145/5); clinical sites with less than 5 participants were pooled by city, or by country, or deleted.

[d] Significant.

[e] *z* Scores were standardized by subtracting the mean of reference distributions (test scores of healthy individuals matched for education [all tests], age [GPB, CT, FTT], gender [GPB, FTT], race/ethnicity [GPB, FTT]), and dividing by the reference distribution's standard deviation. In all locations, mean *z* scores were below 0 ($p < 0.001$); *z* scores below 0 denote below-average performance.

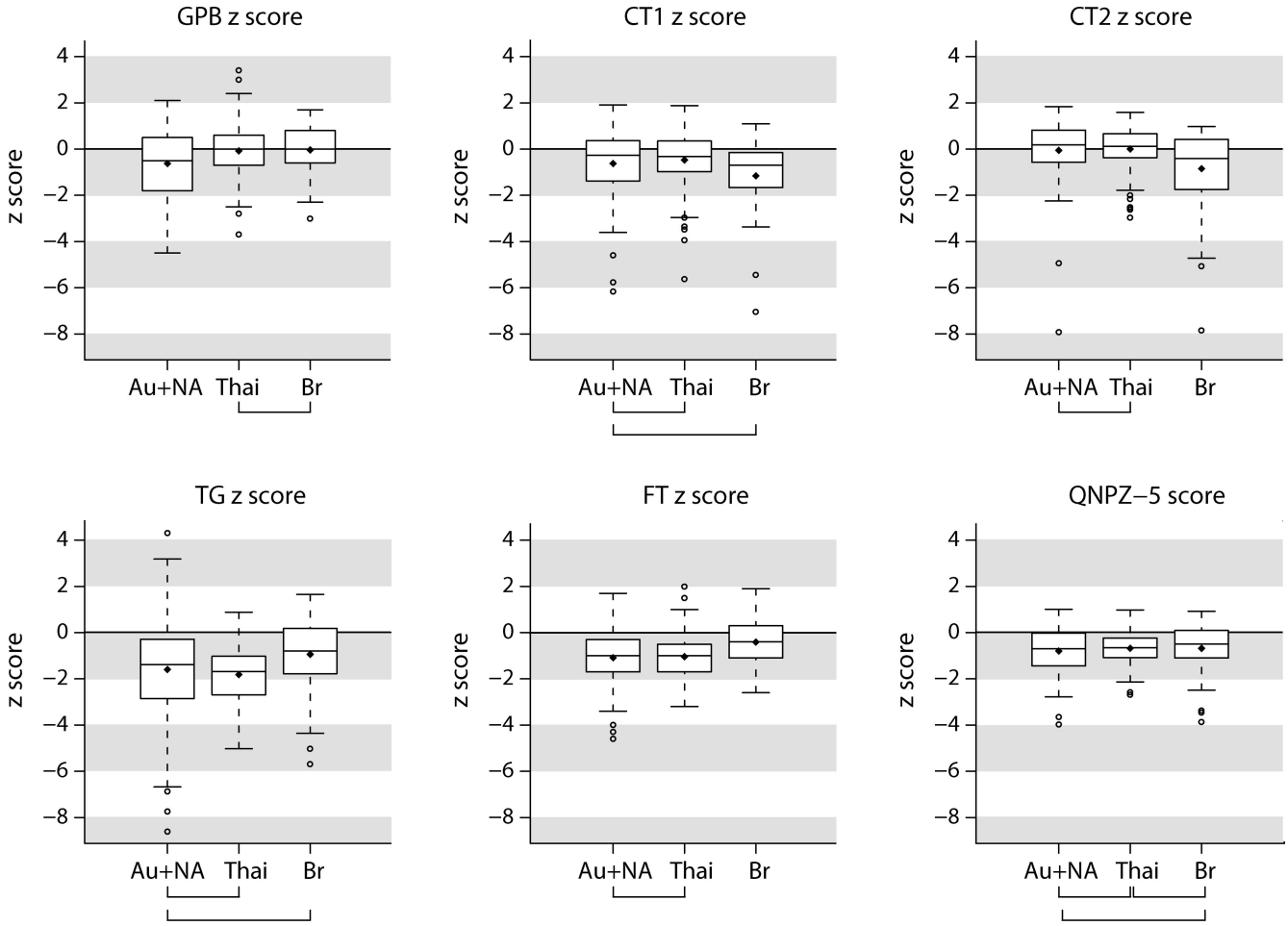
RESULTS **Baseline characteristics.** Baseline characteristics of the 292 study participants by their location of enrollment are shown in table 1 and table e-1. Participant characteristics differed across locations, including their demographics, HIV, and general medical history.

Baseline neurocognitive test scores are summarized by location in table 2 and the figure. Overall, the mean QNPZ-5 score was −0.72; in each location, the mean z score was below 0 ($p < 0.001$), denoting below-average performance compared to a healthy, matched population. Fourteen percent of patients met the study definition of NCI (z scores <-2 in 2 or more cognitive domains); 51% of participants had z scores <-1 in 2 or more cognitive domains. For each of the 5 tests, mean z scores differed between locations (all $p \leq 0.02$). There was no evidence, however, for regional differences in mean QNPZ-5 scores ($p = 0.53$), and no one region performed consistently higher or lower across all tests. In pairwise comparisons, there were no significant differences in test scores between Australia/North America and Thailand, except for the GPB (figure). Table 2 also shows the variability in test scores between clinical sites (between-site SD) in relation to the between-patient SD, estimated in hierarchical mixed models. For all tests except GPB, the between-site SD was about one-third to one-half of the between-patient SD, and remaining differences between locations (countries) were not statistically significant relative to the differences between sites ($p > 0.05$ in the hierarchical models).

The mean CES-D score was 11.2. Overall, 71 participants (26%) met the study definition of depression (table 2). The proportion of participants with depression was highest in Australia/North America (41%) and lowest in Thailand (14%).

Association between baseline factors and neurocognitive performance. The z scores for all 5 tests, but not

Figure **z Scores and summary QNPZ-5 for 5 neuropsychological tests, by location**



Box plots show the distributions of baseline z scores of 292 participants; 102 participants were enrolled in Australia and North America, 45 in Brazil, and 145 in Thailand. Brackets below the location labels connect pairs of locations where mean scores are not significantly different. Boxes show the interquartile range; the horizonta line in the box denotes the median; the diamond denotes the mean. Whiskers extend 1.5 times the interquartile range above and below the z score quartiles. Circles denote outliers. Au = Australia; Br = Brazil; CT = Color Trails Test; FT = Finger Tapping Test; GPB = Grooved Pegboard Test; NA = North America; QNPZ-5 = quantitative neurocognitive performance z score; TG = Timed Gait Test; Thai = Thailand.

the QNPZ-5 scores, differed by location after adjustment for age, gender, race/ethnicity, education, and selected other factors (table 3). Older age was associated with worse test performance in raw test scores except for TG, but not with any of the *z* scores, which are standardized by age. Women and black participants had lower estimated mean QNPZ-5 scores (by 0.21 and 0.48) after adjustment for the other covariates.

Patients with preexisting CVD had 6.2-fold higher odds of having NCI ($p = 0.01$, 95% CI 1.4–26.4), after adjustment for age, gender, race/ethnicity, education, location, prior AIDS, and total cholesterol (table 3). Prior CVD was also associated with lower QNPZ-5 scores (by −0.7; $p = 0.02$), as were use of antihypertensive agents (by −0.4, $p = 0.03$), higher total cholesterol (by −0.03 per 10 mg/mL, $p = 0.02$), and hepatitis B (by −0.7, $p = 0.05$); estimated mean QNPZ-5 scores were lower for women, black participants, and, borderline, for those with depression ($p = 0.07$) (table 3). Smoking, diabetes, higher body mass index, higher low-density lipoprotein, and use of lipid-lowering drugs were not independently associated with NCI or lower QNPZ-5 scores but were associated with lower *z* scores or worse test scores for some of the tests (table 3 and table e-2). Higher high-density lipoprotein was associated with lower *z* scores on GPB and CT1, but not with NCI or QNPZ-5 scores. In a sensitivity analysis, we included the Framingham CVD risk score as a factor instead of fitting cholesterol and BP-lowering drugs separately: there was no evidence for an association of the Framingham score with either the QNPZ-5 or NCI (data not shown). There was no evidence that major abnormalities on the baseline ECG, hepatitis C, or alcohol abuse were independently associated with any of the neurocognitive performance measures (table 3, footnote).

There was no evidence for an association of baseline or nadir CD4 cell counts, viral load, diabetes, or the CNS penetration effectiveness rank of ART regimens with QNPZ-5 scores or NCI.

DISCUSSION Our cross-sectional study of baseline neurocognitive performance included 292 SMART study participants from Australia, North America, Brazil, and Thailand with CD4 cell counts >350 cells/mm^3. At baseline, 14% of participants had NCI and prior CVD was the single associated factor. Participants with prior CVD, higher total cholesterol, and those using antihypertensive drugs had lower estimated mean baseline neurocognitive performance, but neither HIV-related risk factors commonly associated with HAD nor the CNS penetration effectiveness rank of ART were associated with NCI or neurocognitive performance measured by the QNPZ-5. The 10 participants (3.4%) with prior CVD in our study had experienced myocardial infarction, coronary heart disease, congestive heart failure, or peripheral vascular disease, but not stroke.

Our findings suggest that cardiovascular risk factors and disease may be key drivers of impairment in HIV-positive persons with high CD4 cell counts, more so than HIV-related HAD risk factors. These findings are important because HIV-positive populations have a high number of CVD risk factors including smoking,[3] hypertension,[3] diabetes,[3] hyperlipidemia,[3] metabolic syndrome,[27] insulin resistance,[28] and antiretroviral use.[29]

The mechanisms that might link lower neurocognitive performance with CVD and cardiovascular risk factors in HIV-positive populations are likely multifactorial. In HIV-negative populations increasing evidence suggests that cardiovascular risk factors contribute to the pathogenesis of both vascular dementia and AD.[4-6,30] Theoretically the pathogenesis of these 2 dementing illnesses may overlap. Recently it was proposed that insulin resistance, which underlies several of the abovementioned cardiovascular risk factors, may be one of the primary convergent mechanisms that links these risk factors to both vascular dementia and AD.[31]

Raised inflammatory markers, including IL-6 and C-reactive protein, are risk factors for dementia[32] and are common to CVD,[33] the metabolic syndrome,[34] aging, and HIV, including treated HIV infection.[35] However, we do not have inflammatory markers for study analysis.

The changes in the adaptive immune system of HIV-infected patients receiving long-term antiretroviral therapy resemble those seen in the elderly.[36] Key factors that may contribute to immune senescence in HIV-infected patients include persistent immune activation, inflammation, and poor CD4 cell response to antiretroviral treatment.[36] A recent study of HIV-infected patients measured coronary artery calcium accumulation and found an increased vascular age in over 40% of patients, with a mean increase of 15 years over their chronological age.[37] Increased vascular aging would help to explain why we found an association between lower neurocognitive performance and cardiovascular risk factors/CVD in a relatively young study population whereas cognitive decline and dementia associated with these factors in HIV-negative populations usually do not occur until at least the sixth decade. Similarly, the early expression of Parkinson disease in HIV infection has been reported recently.[38]

None of the conventional HIV-related HAD risk factors was associated with NCI or lower neurocogni-

Table 3 Association of participants' characteristics with neurocognitive performance: Regression coefficients and *p* values in multivariate linear (QNPZ-5) and logistic (NCI) regression[a]

				z Scores					Test scores (seconds or taps)				
Factors[b]	% of population	NCI[c]	QNPZ-5	GPB	CT1	CT2	TG	FTT	GPB	CT1	CT2	TG	FTT
Age (per 10 y)		NS	NS	NS	NS	NS	NS	NS	$p=0.009$[e] 4.5	$p<0.001$[e] 6.0	$p<0.001$[e] 12.2	NS	$p=0.007$[e] −1.5
Gender (female vs male)	41.7	NS	$p=0.05$[e] −0.21	NS	NS	NS	$p<0.001$[e] −1.13	$p=0.05$[e] 0.27	NS	NS	NS	$p<0.001$[e] 1.38	$p<0.001$[e] −5.2
Race/ethnicity (black vs other)	19.7	$p=0.08$ 2.25	$p<0.001$[e] −0.48	NS	$p<0.001$[e] −1.10	$p<0.001$[e] −1.03	NS	NS	$p=0.005$[e] 11.6	$p<0.001$[e] 17.6	$p<0.001$[e] 33.4	NS	NS
Education (>12 y)	46.6	NS	NS	NS	NS	NS	$p=0.002$[e] −0.59	NS	NS	$p<0.001$[e] −10.4	$p<0.001$[e] −20.5	$p=0.03$[e] −0.51	$p=0.007$[e] 2.4
Location		NS	NS	$p=0.007$[e]	$p=0.001$[e]	$p<0.001$[e]	$p=0.005$[e]	$p=0.004$[e]	$p=0.10$	$p<0.001$[e]	$p<0.001$[e]	$p=0.004$[e]	$p=0.003$[e]
Brazil[d]	15.2			0.41	−0.97	−1.04	0.16	0.54	−4.0	15.5	35.9	−0.40	3.9
Thailand[d]	50.0			0.60	−0.29	−0.43	−0.72	−0.09	−9.0	5.3	16.3	0.76	−0.4
Prior AIDS	20.7	$p=0.08$ 0.41	$p=0.05$[e] 0.24	—	$p=0.08$ 0.36	—	$p=0.03$[e] 0.51	—	—	$p=0.07$ −5.6	—	$p=0.05$[e] −0.58	—
Hepatitis B	2.1	—	$p=0.05$[e] −0.66	$p=0.03$[e] −1.05	$p=0.01$[e] −1.41	$p=0.08$ −0.85	—	—	$p=0.001$[e] 30.7	$p=0.06$ 15.5	NS	—	—
Prior CVD	3.5	$p=0.01$[e] 6.17	$p=0.02$[e] −0.65	$p=0.06$ −0.71	NS	—	$p=0.08$ −0.98	$p=0.09$ −0.62	$p=0.001$[e] 24.8	$p=0.06$ 12.6	—	$p=0.09$ 1.15	$p=0.06$ −4.6
Blood pressure-lowering drugs	11.0	—	$p=0.03$[e] −0.37	—	—	$p=0.03$[e] −0.53	$p=0.01$[e] −0.84	—	—	—	$p=0.05$[e] 15.4	$p=0.03$[e] 0.88	—
Total cholesterol (per 10 mg/mL)		$p=0.06$ 1.08	$p=0.02$[e] −0.03	—	$p=0.06$ −0.04	$p=0.06$ −0.03	—	—	—	$p=0.06$ 0.5	—	—	—
HDL (per 10 mg/mL)		—	—	$p=0.03$[e] −0.11	$p=0.05$[e] −0.12	—	—	—	$p=0.02$[e] 2.5	$p=0.05$[e] 1.9	NS	—	—
Depression (CES-D ≥ 16)	23.8	—	$p=0.07$ −0.21	—	—	—	$p<0.001$[e] −0.91	—	NS	—	—	$p<0.001$[e] 1.07	—

Abbreviations: ART = antiretroviral therapy; CES-D = Center for Epidemiologic Studies-Depression scale; CT = Color Trails; CVD = cardiovascular disease; FTT = Finger Tapping Test; GPB = Grooved Pegboard; HDL = high-density lipoprotein; NCI = neurocognitive impairment; NS = not significant ($p > 0.10$); QNPZ-5 = quantitative neurocognitive performance *z* score; TG = Timed Gait.

[a] For each outcome, associations with factors were determined in 2 steps: 1) starting from a comprehensive model with all factors, potentially relevant factors in addition to age, gender, race, education, and location were selected by backwards variable selection; 2) a model containing only the selected factors was fitted. All factors that had significant associations with NCI, the QNPZ-5 score, or at least 2 of the *z* scores were included in the table. Multiple regression coefficients with *p* values ≤0.10 were displayed, the remaining factors were labeled NS for nonsignificant; factors excluded by the backwards selection procedure were denoted by —.

[b] Additionally to the factors shown in the table, the comprehensive model contained the following: CD4 cell count, HIV RNA ≤400 copies/mL, smoking, body mass index, diabetes mellitus, low-density lipoprotein, lipid-lowering drugs, recreational drug use (these factors were not significantly associated with NCI or the QNPZ-5 score, but had $p \leq 0.10$ for at least 1 of the neurocognitive tests; details are shown in table e-2); CNS penetration effectiveness rank of the participants' ART; major ECG abnormality at baseline, hepatitis C, CD4 count nadir, alcohol abuse (no significant associations of any of these factors with any of the outcomes).

[c] Neurocognitive impairment was defined as a *z* score <−2 on at least 2 tests from independent domains. *p* Values and coefficients were obtained by logistic regression; the coefficient of 2.3 for black race, for example, indicates that for black participants, the odds for the presence of NCI were 2.3 times higher than for nonblack participants, after adjustment for the other factors in the model.

[d] Compared with North America and Australia.

[e] Significant.

tive performance and the reason for this is unclear. The median CD4 cell count was high (536 cells/mm^3) but there was also no association of NCI with nadir CD4 counts. There was no evidence for an association of diabetes with impairment or poorer neurocognitive performance, although the lack of evidence may have been due to the low number of participants with diabetes. There was also no evidence for an association of the ART CNS penetration effectiveness rank with any of the neurocognitive performance scores. ART regimens with CNS penetration effectiveness ranks ≥2 have been associated with improved neurocognitive performance[26]; in our study, 25% of participants had CNS penetration effectiveness ranks ≥2. Contrary to expectations, participants with prior AIDS had a slightly increased estimated mean QNPZ-5 score (by 0.24, $p = 0.05$, table 3). This may be a statistical artifact due to confounding; in univariate analysis, those with and without prior AIDS had similar QNPZ-5 scores ($p = 0.60$ for difference), but those with prior AIDS had more CVD risk factors, including a higher body mass index (mean 25 vs 23) and more use of BP-lowering drugs (18% vs 9%).

Mean *z* scores differed significantly between locations for each of the 5 neurocognitive tests; moreover, differences between locations persisted after adjusting for differences in age, sex, race, and education and other factors (table 3). At first glance, this leads to the hypothesis that the standard US norms were not appropriate for Brazil or Thailand. Within countries, however, *z* scores also varied considerably between clinical sites (table 2, hierarchical model). Further adjustment for age, race, sex, and education decreased between-site variability in raw test scores, but had only minimal effect on the between-site variability in *z* scores (data not shown). The latter suggests that our US norm *z* scores reasonably standardized the test scores for these 4 demographic factors, and that the remaining variability between countries may be largely due to other unmeasured factors such as nutritional status, urban vs rural residency, cultural/ethnic factors, and test administration. It may be that if we had been able to more accurately measure and adjust for the education of participants, for example by assessing their reading level[39] instead of using years of education, we may have seen less between-country variability.

Twenty-four percent of participants met the study definition of depression; this proportion is commensurate with some studies but lower than others.[15] Antidepressant use was not assessed.

One should interpret our study definition of NCI (*z* scores < -2 in 2 or more domains) with caution because 1) NCI was not confirmed clinically; 2) we used US norms in Brazilian and Thai populations; and 3) we assessed 4 cognitive domains only.[19] Moreover, NCI may not always represent HAD or other HIV-associated neurocognitive disorders because there is an overlap between the neurocognitive impairment associated with cerebrovascular disease[40] and HIV-associated CNS disease.

Study limitations include a moderate sample size, which limits the power to detect associations; a modest test battery; study-trained staff rather than neuropsychologists administering the neurocognitive tests; and the lack of local reference norms in Brazil and Thailand. Also, hypertension was not assessed directly, but extrapolated from the use of BP-lowering drugs. Finally, we evaluated multiple outcomes; some of the observed associations might be false-positives, in particular where statistical significance was borderline.

Our findings suggest that, in HIV-infected persons with high CD4 cell counts, cardiovascular-related insults may be more detrimental to neurocognitive functioning than factors more directly related to HIV. Given the high prevalence of cardiovascular risk factors in HIV-infected populations, this finding is important and warrants further investigation.

AUTHOR CONTRIBUTIONS

Statistical analysis was conducted by Dr. Grund and M. Roediger.

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