Title
Baseline neurocognitive test performance in START

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ORIGINAL RESEARCH

Factors associated with neurocognitive test performance at baseline: a substudy of the INSIGHT Strategic Timing of AntiRetroviral Treatment (START) trial

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Objectives

We describe neuropsychological test performance (NP) in antiretroviral treatment (ART)-naïve HIV-positive individuals with CD4 cell counts above 500 cells/μL.

Methods

In a neurology substudy of the International Network for Strategic Initiatives in Global HIV Trials (INSIGHT) Strategic Timing of AntiRetroviral Treatment (START) study, eight neurocognitive tests were administered. The primary measure of NP was the quantitative NP *z*-score (QNPZ-8), the average of the *z*-scores for the eight tests. Associations of baseline factors with QNPZ-8 scores were assessed by multiple regression. Mild neurocognitive impairment (NCI) was defined as *z*-scores < -1 in at least two of six cognitive domains.

Results

A total of 608 participants had a median age of 34 years; 11% were women and 15% were black; the median time since HIV diagnosis was 0.9 years; the median CD4 cell count was 633 cells/μL; 19.9% had mild NCI. Better NP was independently associated with younger age, being white, higher body mass index (0.10 per 10 kg/m^2 higher), and higher haematocrit percentage (0.19 per 10% higher). Worse NP was associated with longer time since HIV diagnosis (-0.17 per 10 years), diabetes (-0.29) and higher Framingham risk score (-0.15 per 10 points higher). QNPZ-8 scores differed significantly between geographical locations, with the lowest scores in Brazil and Argentina/Chile.

Conclusions

This is the largest study of NP in ART-naïve HIV-positive adults with CD4 counts > 500 cells/μL. Demographic factors and diabetes were most strongly associated with NP. Unmeasured educational/sociocultural factors may explain geographical differences. Poorer NP was independently associated with longer time since HIV diagnosis, suggesting that untreated HIV infection might deleteriously affect NP, but the effect was small.

Keywords: antiretroviral therapy naïve, HIV, HIV-associated neurocognitive disorders, neurocognitive performance

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Introduction

Neurocognitive performance and associated factors in antiretroviral therapy (ART)-naïve, HIV-positive adults with CD4 T-cell counts > 500 cells/μL have not been well described. In a number of studies, including several cohort studies, demographic factors [1–3], HIV-related parameters [1,4,5], clinical indices [6,7], cardiovascular risk factors [3,8,9], laboratory parameters [6,8,10–12] and neuroimaging indices [13,14] have been associated with neurocognitive performance in populations with partial or full HIV virological suppression.

The Neurology Substudy is embedded within the Strategic Timing of AntiRetroviral Treatment (START) study [15] and is designed to determine whether the change in the neurocognitive test performance (NP) of ART-naïve, HIV-positive participants with CD4 counts > 500 cells/μL, followed over an average of 4.5 years, will be superior in those participants who commence immediate versus deferred ART (CD4 cell count < 350 cells/μL). The Neurology Substudy also affords the unique opportunity to characterize, in a large sample, major baseline demographic factors, including location, age, education, sex and race/ethnicity, and clinical and HIV-related factors associated with NP in a population with relatively high CD4 cell counts. We hypothesized that baseline NP would be associated chiefly with demographic and cardiovascular risk factors given that participants had relative immune preservation and a high prevalence of risk factors for cardiovascular disease.

Methods

Study design

START is an ongoing multicentre, international trial [15]. The Neurology Substudy was designed to co-enrol 600 participants with the aim of comparing changes in NP in the immediate versus deferred study arms.

Study population

Between May 2009 and June 2012, 608 participants were co-enrolled into the substudy at 35 study sites in Australia, Thailand, Brazil, Argentina, Chile, the USA, the UK, Belgium, Italy, Switzerland and Germany (Fig. 1).

All eligible persons at participating sites were offered co-enrolment into the substudy. Eligibility criteria were simultaneous co-enrolment in START, provision of signed informed consent, age ≥ 18 years and ability to perform the protocol tests, in the clinician's judgment.

Each institution's institutional review board/ethics committee provided approval. Participant information and consent forms were translated as necessary.

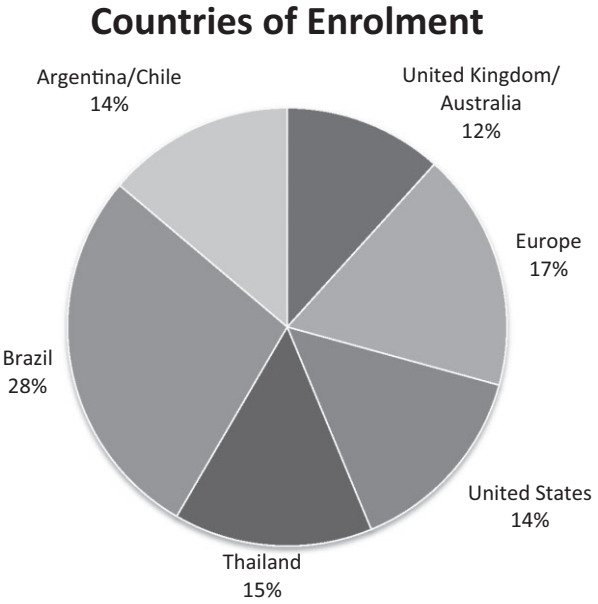

Fig. 1 Distribution of the study population across geographical locations. Europe: participants were enrolled in Belgium, Germany, Italy and Switzerland.

Neuropsychological tests

Neuropsychological tests were administered at baseline and will be administered at months 4, 8 and 12 and annually thereafter until the closing date of START. The test battery consists of 10 tests from six cognitive domains (Table 1).

Rationalization for the test battery included: (1) the tests being validated and sensitive to HIV-related neurocognitive impairment (NCI); (2) brevity and ease of administration and scoring; (3) high cross-cultural adaptation in international settings; (4) several cognitive domains requisite for a diagnosis of HIV-associated neurocognitive disorders (HAND) being represented [16,17] (Table 1).

Depressive symptomatology was assessed using the Centre for Epidemiologic Studies-Depression (CES-D) scale [18], which has been used in international studies in HIV-positive populations [3,19]. The CES-D is administered at each substudy visit; a score of ≥ 16 indicates depression [18].

Thai, Portuguese, Spanish, Italian, Flemish, French and German tests and questionnaires were provided by the tests' publishers or, if not available, culturally appropriate translations and back-translations into English were provided by bilingual staff at the International Network for Strategic Initiatives in Global HIV Trials (INSIGHT) international coordinating centres (ICCs). All translations were reviewed and approved by the test publishers. The CES-D has been translated into several languages, and the validity of each translation was checked by bilingual ICC staff.

Table 1 Strategic Timing of AntiRetroviral Treatment (START) neuropsychological test battery, and definitions of the global performance measures, the quantitative neuropsychological test performance *z*-score (QNPZ-8) and neurocognitive impairment (NCI)

Six cognitive domains	10 individual neuropsychological tests	QNPZ-8 components	Mild impairment	Moderate impairment
Speed of information processing	1. Color Trails 1 (completion time in seconds)	1. Color Trails 1 *z*-score	*z*-score < -1 in each test *or* < -1.5 SD in the domain average	*z*-score < -2 in each test *or* < -2.5 SD in the domain average
	2. WAIS III Digit Symbol (total correct in 120 seconds)	2. WAIS III Digit Symbol *z*-score		
Mental Flexibility	3. Color Trails 2 (completion time in seconds)	3. Color Trails 2 *z*-score	*z*-score < -1 for domain/test	*z*-score < -2 for domain/test
Verbal learning	4. HVLT-R Total Learning* (number correct in three learning trials)	4. HVLT-R Total Learning *z*-score	*z*-score < -1 for domain/test	*z*-score < -2 for domain/test
Verbal memory	5. HVLT-R, Delayed Recall* (total correct words after delay)	5. HVLT-R, Delayed Recall *z*-score	*z*-score < -1 for domain/test	*z*-score < -2 for domain/test
Language fluency	6. Semantic Fluency (number of words in category† in 60 seconds)	6. Semantic Fluency *z*-score	*z*-score < -1 for domain/test	*z*-score < -2 for domain/test
Fine motor skills and motor speed	7. Grooved pegboard dominant hand (completion time in seconds)	7. Grooved pegboard hand average *z*-score	*z*-score < -1 in each test *or* < -1.5 in the domain average	*z*-score < -2 in each test *or* < -2.5 in the domain average
	8. Grooved pegboard nondominant hand (completion time in seconds)			
	9. Finger tapping dominant hand (total taps in 10 seconds; five trials)	8. Finger tapping hand average *z*-score		
	10. Finger tapping nondominant hand (total taps in 10 seconds; five trials)			
Global measure		**QNPZ-8** = average of the 8 component *z*-scores	**Mild NCI** = at least mild impairment in at least two cognitive domains	**Moderate NCI** = at least moderate impairment in at least two cognitive domains

z-scores were calculated from individual test scores by subtracting the study mean, and dividing by the SD. The definitions of NCI are comparable to the definitions for asymptomatic NCI, mild NCI and HIV-associated dementia from the American Academy of Neurology (AAN) criteria 2007 [16] and follow the cognitive domains for multiple tests outlined in Woods *et al.* [17] as recommended in the AAN criteria 2007 [16]. In the absence of external normative data, the NCI definitions provide a descriptive overview of neuropsychological performance in our study population.
HVLT-R, Hopkins Verbal Learning Test-Revised; WAIS, Wechsler Adult Intelligence Scale; SD, standard deviation.
*Different wordlists were used at baseline, month 4, etc. †The category administered at baseline was vegetables; categories were rotated across visits to minimize a possible practice effect.

Procedure

Tests and questionnaires were administered by trained research staff at each clinical site. A train-the-trainer approach was used whereby staff from the ICCs received centralized training and certification in the USA or Australia. This training was provided by neuropsychologists for the standard neuropsychological tests, while the overall protocol was taught by a neurologist and an infectious diseases physician. ICC staff subsequently trained site coordinating centre (SCC) staff. Clinic staff were trained either on site or at centralized training conducted by the ICCs and SCCs. Clinic staff received accreditation for their training after they had: (1) successfully completed a multiple choice questionnaire, (2) watched a training video on the INSIGHT website that provided instructions for all tests and questionnaires, and (3) administered the test battery and the CES-D to at least three volunteers.

Outcome measures

In order to calculate a summary measure across all tests in the battery, the 10 individual raw test scores were standardized to *z*-scores [mean = 0; standard deviation (SD) = 1] by subtracting the mean test score over all participants, and dividing by the sample SD (internal standardization). The signs for the timed tests were changed so that higher *z*-scores always denote better performance. For the grooved pegboard and finger tapping tests, *z*-scores for the dominant and nondominant hands were averaged. Our primary outcome measure for NP is the summary quantitative neuropsychological performance *z*-score (QNPZ-8), calculated as the average of the eight *z*-scores for the individual tests. Secondary neurocognitive outcomes included the individual test scores, as well as NCI defined through the *z*-scores in six cognitive domains, as outlined in Table 1.

Rationale for the use of internal standardization and estimates of neurocognitive impairment

The primary aim of the START Neurology Substudy is to compare the two study arms for change in NP over time; when calculating change over time, study participants serve as their own controls. Hence, for the primary endpoint, normative data did not need to be collected in HIV-negative individuals to provide external neuropsychological references for major demographics.

The calculation of the summary QNPZ-8 score requires standardization of the individual test scores in order to measure performance in different tests on comparable scales. Because reference populations of HIV-negative adults were not available at international locations, we used internal standardization; that is, we calculated

z-scores for each test using the mean and SD of the study population. Differences in NP are known to be associated with age, sex, education and race/ethnicity; in order to account for such demographic differences, all analyses were adjusted by including these factors as independent variables in the statistical models.

The absence of normative data notwithstanding, to provide a 'descriptive' estimate of the prevalence of NCI at baseline, we calculated the proportion of participants whose internally standardized *z*-scores were −1 SD below the sample mean of zero in two or more of the six cognitive domains, which is comparable to mild NCI as per the Frascati criteria, for example, asymptomatic neurocognitive impairment (ANI) and early mild neurocognitive disorder (MND) [16] (Table 1). Scores below the cut-off of −2 SD are comparable to advanced MND and HIV-associated dementia (HAD) [16] (Table 1).

Other data collection

Baseline demographic and HIV factors, past medical history, cardiovascular risk factors and disease, viral hepatitis B and C serostatus, blood pressure (BP), fasting lipids, laboratory markers, concomitant medications and responses to a drug and alcohol questionnaire were collected for all START study participants. Duration of HIV seropositivity was determined by self-report. Years of education, most advanced formal education, current employment status, and rural or urban residence were collected additionally for Neurology Substudy participants.

Participants were defined as being hypertensive if they had a systolic BP of ≥140 mmHg, or a diastolic BP of ≥90 mmHg, or if they were receiving BP-lowering medications. Diabetes was defined as prior diagnosis, receiving drug therapy, or having fasting glucose levels of ≥ 126 mg/dL. Hyperlipidaemia was defined as receiving drug therapy or having low-density lipoprotein (LDL) cholesterol ≥ 160 mg/dL. The Framingham score was used to predict 10-year coronary heart disease (CHD) risk; in addition to age, sex and race, the score includes diabetes, smoking, total cholesterol, high-density lipoprotein (HDL) cholesterol, and left ventricular hypertrophy from baseline electrocardiogram (ECG) as variables [20].

Statistical methods

The means and SDs for raw test scores and the QNPZ-8 score were calculated overall and by geographical location. In order to obtain sufficiently large sample sizes, countries were pooled into geographical regions as shown in Table 2, with the intent to pool countries that have similar income levels, educational systems and culture/language. Mean test scores were compared between locations using analysis of covariance (ANCOVA) models adjusted for age (categories 18–29, 30–39, 40–49 and ≥ 50 years), sex, race/ethnicity (black, white and other), and education (no formal

Table 2 Demographic characteristics by location

Characteristic	Total (*n* = 608)	Location						*P*-value†
		UK/Australia (*n* = 71)	European countries* (*n* = 107)	USA (*n* = 88)	Thailand (*n* = 89)	Brazil (*n* = 169)	Argentina/ Chile (*n* = 84)	
Age (years)	34 (27–42)	37 (29.0–44.0)	42 (34.0–50.0)	36 (30.0–47.0)	31 (24.0–36.0)	29 (25.0–36.0)	32 (26.0–41.0)	< 0.001
Female	11.0	1.4	11.2	21.6	18.0	7.7	7.1	< 0.001
Race								< 0.001
Black	15.0	7.0	5.6	48.9	0.0	21.9	0.0	
Latino/Hispanic	16.3	2.8	1.9	9.1	0.0	16.6	70.2	
Asian	15.6	5.6	0.0	2.3	100	0.0	0.0	
White	47.9	78.9	91.6	38.6	0.0	46.2	29.8	
Other	5.3	5.6	0.9	1.1	0.0	15.4	0.0	
Most advanced formal education								< 0.001
No formal vocational/college/ university education	20.6	16.9	16.8	26.1	14.6	21.9	26.2	
Vocational training, with degree or certification	24.5	16.9	38.3	15.9	12.4	32.5	19.0	
Some college or university education	24.2	29.6	11.2	39.8	16.9	26.6	22.6	
Bachelor's degree or equivalent	22.9	28.2	18.7	11.4	48.3	14.8	25.0	
Master's degree or higher	7.9	8.5	15.0	6.8	7.9	4.1	7.1	
Currently employed	76.2	81.7	82.2	63.6	74.2	77.5	76.2	0.045
Urban residence	88.0	95.8	81.3	84.1	65.2	97.6	98.8	< 0.001

Values are percentage or median (interquartile range).
*Germany, Italy, Belgium and Switzerland. †Medians were compared using the Kruskal–Wallis rank sum test and percentages were compared using χ^2 tests.

vocational training or college education, vocational training/some college, Bachelor's degree, and Master's or higher degree). Asian and Latino/Hispanic race/ethnicity were not included separately because these were highly correlated with geographical location. Demographics and other baseline characteristics were summarized by median and interquartile range (IQR) or percentage; medians of continuous factors were compared across geographical regions using the Kruskal–Wallis rank sum test; proportions were compared using the Mantel–Haenzel χ^2 test.

Associations of baseline factors with the QNPZ-8 were assessed by multiple regression. Factors included in the final model were chosen through stepwise backwards variable selection using the Akaike information criterion (AIC) [21]. Age, sex, race/ethnicity and education level were included *a priori* in all models and were not subject to elimination through variable selection in order to ensure that estimated effect sizes for all factors were adjusted for demographic differences. For geographical regions, the USA was chosen as the reference category, because US norms have been commonly used as reference populations.

In addition to the traditional demographic factors, the starting model included the following: employment status; rural versus urban residence; HIV-related factors (known duration of HIV infection, baseline and nadir CD4 cell counts, the CD4:CD8 ratio, $\log_{10}$ HIV RNA and HIV RNA ≤ 400 copies/mL); cardiovascular risk factors [body mass index (BMI), smoking, hypertension, levels of fasting total cholesterol, HDL cholesterol, LDL cholesterol and triglycerides, hyperlipidaemia, glucose level, diabetes, and the 10-year Framingham risk score for CHD [20]]; laboratory measures (serum creatinine levels, liver function tests results, white blood cell count, haemoglobin level, haematocrit levels and lymphocyte count); extant conditions [hepatitis B or C, prior cardiovascular disease (myocardial infarction, stroke or CHD requiring revascularization) and psychiatric diagnoses]; concomitant medications; alcohol or other substance dependence; and depression by CES-D. Tables 2 and 3 provide summaries for selected factors. After the variable selection, any factors with *P*-values > 0.10 were also excluded from the final model. As sensitivity analyses, we tested whether the effects of age, sex and education on the QNPZ-8 differed by geographical region, by adding the corresponding interaction effects separately to the final model.

Mean QNPZ-8 scores were estimated for each geographical location by calculating the raw sample means as well as covariate-adjusted means in ANCOVA models. The first model adjusted the mean QNPZ-8 scores for differences in age and sex; the second model additionally adjusted for race/ethnicity and education, and the third model adjusted for all covariates in the final regression model.

All analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC) and R version 3.1 [22]. All *P*-values were two-sided; *P*-values ≤ 0.05 were considered significant.

Results

Demographics

Demographic characteristics, overall and by geographical location, are summarized in Table 2. The median age of the study population was 34 years; 11% were women. The study populations differed between locations in age, the proportion of women, the composition of race/ethnicity and the level of education ($P < 0.001$ for each) (Table 2). At participating sites, 74% of the START participants were co-enrolled in the Neurology Substudy.

Clinical characteristics and laboratory markers

Table 3 describes clinical characteristics and laboratory markers, overall and by geographical location. The median duration of self-reported known HIV seropositivity was 0.9 years (IQR 0.3–2.6 years), and the median baseline and nadir CD4 cell counts were 633 (IQR 575–741) cells/μL and 535 (IQR 473–631) cells/μL, respectively. Thirty-seven per cent of participants were smokers, 16% had hypertension, 11% had hyperlipidaemia and 4% had diabetes. The median Framingham 10-year risk of CHD was 1.8% (IQR 0.6–4.7%). The prevalence of cardiovascular risk factors varied significantly between the geographical locations ($P < 0.001$ for most). Rates of coinfection with hepatitis viruses were low (Table 3). Eight per cent of participants had a prior psychiatric diagnosis and 32% of participants had a CES-D score ≥ 16; the latter proportion did not vary by location ($P = 0.09$).

Neuropsychological test performance

Means of the raw scores for the 10 individual neuropsychological tests, the QNPZ-8 scores, and estimates for the prevalence of NCI are summarized overall and by geographical location in Table 4. The raw scores for each test as well as the QNPZ-8 scores differed between locations, with and without adjustment for age, sex, race/ethnicity and education level ($P \leq 0.006$ for each of the individual tests; $P < 0.001$ for the QNPZ-8) (Table 4). Across the locations, mean QNPZ-8 scores ranged from 0.19 (Thailand) to −0.17 (Brazil). Overall, 19.9% of study participants had performance consistent with at least mild NCI (range 10.1–29.5% across geographical locations); 2.6% had performance consistent with moderate–severe NCI (range 0–4.5%).

Table 3 HIV, medical and selected laboratory characteristics by geographical location

Characteristic	Total (n = 608)	Location						P-value[†]
		UK/Australia (n = 71)	European countries* (n = 107)	USA (n = 88)	Thailand (n = 89)	Brazil (n = 169)	Argentina/ Chile (n = 84)	
Time participant known to be HIV positive (years)	0.9 (0.3–2.6)	2.0	1.4	1.1	1.2	0.2	1.3	**< 0.001**
Likely mode of HIV infection								**< 0.001**
Injecting drug use	0.8	1.4	0.9	3.4	0.0	0.0	0.0	
Male sexual contact with person of same sex	75.2	88.7	71.0	48.9	70.8	83.4	84.5	
Sexual contact with person of opposite sex	18.9	7.0	19.6	31.8	27.0	15.4	13.1	
Other/unknown	5.1	2.8	8.4	15.9	2.2	1.2	2.4	
CD4 count (cells/μL)	633 [575–741]	651	644	647	593	641	637	**< 0.001**
Nadir CD4 count (cells/ μL)	535 [473–631]	524	530	557	518	556	533	**0.006**
CD4:CD8 ratio	0.64 (0.47–0.84)	0.61	0.55	0.70	0.55	0.68	0.62	**< 0.001**
HIV RNA ($\log_{10}$ copies/mL)	4.2 (3.7–4.7)	4.2	4.4	3.8	4.3	3.9	4.4	**< 0.001**
HIV RNA ≤ 400 copies/mL	4.1	4.2	2.8	9.2	6.7	1.2	3.6	**0.04**
Cardiovascular risk factors and disease								
Current smoker	36.7	39.4	51.4	36.4	16.9	29.6	51.2	**< 0.001**
Diabetes[†]	3.5	4.2	5.6	9.1	1.1	0.0	3.6	**0.004**
Hypertension	16.1	12.7	29.0	21.6	9.0	13.6	9.5	**< 0.001**
Hyperlipidaemia	10.7	9.9	15.0	19.3	16.9	4.7	2.4	**< 0.001**
Body mass index (kg/m^2)	23.7 (21.6–26.8)	23.9	23.8	26.4	21.2	23.6	24.6	**< 0.001**
Any prior CVD diagnosis[§]	1.3	1.4	2.8	2.3	1.1	0.6	0.0	0.51
Predicted 10-year Framingham risk of CHD (%)	1.8 (0.5–4.7)	2.2	4.9	2.2	0.7	1.0	2.2	**< 0.001**
Laboratory values								
Haematocrit (%)	43.6 (41.0–45.6)	44.0	43.0	43.6	41.9	44.1	43.9	**< 0.001**
AST/SGOT (U/L)	26.0 (21.0–32.0)	28.5	27.0	25.0	27.0	25.0	23.0	**< 0.001**
ALT/SGPT (U/L)	25.0 (18.0–37.0)	26.0	25.5	23.0	28.0	26.0	24.0	0.32
Hepatitis B or C	6.1	4.2	5.7	6.8	13.5	4.8	2.4	**0.042**
Alcoholism/other substance dependence	5.1	7.0	1.9	15.9	2.2	4.1	1.2	**< 0.001**
Psychiatric diagnosis[¶]	8.2	14.1	9.3	23.9	1.1	3.6	2.4	**< 0.001**
Depression (CES-D ≥ 16)	31.8	28.8	19.6	35.7	35.7	35.4	34.2	0.09

Values are percentage or median (interquartile range). Values in bold are significant at $P < 0.05$.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; BP, blood pressure; CES-D, Center for Epidemiologic Studies Depression Scale; CHD, coronary heart disease; CVD, cardiovascular disease; SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase.
*Germany, Italy, Belgium, Portugal and France. [†]Medians between locations were compared using the Kruskal–Wallis rank sum test, and percentages were compared using χ^2 tests. [†]Drug treatment for diabetes or fasting glucose levels ≥ 126 mg/dL. [§]History of myocardial infarction, stroke or CHD requiring revascularization. [¶]Major depression, bipolar disorder, schizophrenia or other psychotic disorder.

Associations between neuropsychological test performance and baseline factors

Several variables were independently associated with the QNPZ-8 score in a multiple regression model (Fig. 2).

Demographic factors

Younger age, male sex, being white, living in Australia, Europe, Thailand or the USA (versus living in Brazil or Argentina/Chile), higher education level and being employed were associated with better NP. Urban residence was associated with poorer NP (Fig. 2).

HIV, clinical and laboratory factors

Higher BMI, higher haematocrit percentage, higher aspartate aminotransferase (AST)/serum glutamic oxaloacetic transaminase (SGOT) and lower alanine aminotransferase (ALT)/serum glutamate-pyruvate transaminase (SGPT) levels were associated with better NP (Fig. 2). Longer known HIV infection duration, diabetes and a higher Framingham risk score were associated with worse NP.

Location and neuropsychological test performance

As shown in Figure 2, despite adjustment for several factors including age, sex, race/ethnicity, education and several HIV and clinical factors, QNPZ-8 scores differed substantially between geographical locations.

To further investigate how differences in demographic factors contribute to the differences in QNPZ-8 between locations, covariate-adjusted mean QNPZ-8 scores for each location were calculated (Fig. 3), adjusting first for age and sex, then for age, sex, education and race/ethnicity, and then for all variables shown in Figure 2. Here, the mean QNPZ-8 score across all study participants is 0 because we calculated z-scores relative to the mean and SD of our study population. After adjustment for age and sex, participants in Europe had mean QNPZ-8 scores that were 0.27

Table 4 Neuropsychological test scores and prevalence of neurocognitive impairment (NCI) by location

Characteristic	Total (n = 608)	Location						P-value[†] (location)
		UK/Australia (n = 71)	European countries* (n = 107)	USA (n = 88)	Thailand (n = 89)	Brazil (n = 169)	Argentina/ Chile (n = 84)	
Raw score								
Grooved pegboard (seconds)								
Dominant hand	68.6 (14.2)	67.2 (9.4)	69.0 (12.5)	72.5 (22.1)[¶]	59.8 (8.0)	71.7 (13.4)	68.3 (11.9)	**< 0.001**
Nondominant hand	75.8 (19.8)	73.2 (11.9)	73.9 (13.1)	81.9 (36.0)[¶]	67.0 (10.1)	80.0 (19.3)	74.8 (11.5)	**< 0.001**
Average	72.2 (16.2)	70.3 (9.8)	71.5 (12.0)	77.2 (28.5)[¶]	63.4 (8.5)	75.9 (15.4)	71.5 (10.7)	**< 0.001**
Finger tapping (no. of taps)								
Dominant hand	46.6 (9.8)	49.4 (7.1)	49.3 (8.8)	48.9 (13.2)[¶]	43.8 [8.0]	46.9 (8.6)	40.4 (9.7)	**< 0.001**
Nondominant hand	42.8 (8.5)	45.2 (5.6)	44.5 (7.6)	45.2 (12.0)[¶]	39.8 (6.6)	42.7 (8.1)	39.4 (7.9)	**< 0.001**
Average	44.7 (8.6)	47.3 (5.8)	46.9 (7.7)	47.1 (12.2)[¶]	41.8 (7.0)	44.8 (7.6)	39.9 (8.3)	**< 0.001**
WAIS-III Digit Symbol (no. correct)	65.9 (16.8)	65.5 (19.4)	66.7 (15.5)	65.2 (18.0)	73.4 (15.3)	62.9 (15.7)	64.3 (16.7)	**< 0.001**
Semantic Verbal Fluency (no. correct)	14.7 (4.3)	14.7 (3.6)	15.3 (5.2)	13.8 (4.1)	16.3 (4.7)	14.0 (3.8)	14.3 (3.6)	**0.005**
Color Trails 1 (seconds)	40.7 (18.1)	35.7 (12.2)	39.0 (14.8)	38.8 (28.6)[¶]	36.6 (10.3)	43.6 (17.0)	47.8 (17.6)	**< 0.001**
Color Trails 2 (seconds)	78.2 (28.7)	69.6 (20.3)	74.1 (25.6)	74.3 (40.9)[¶]	76.0 (19.7)	86.7 (29.7)	80.2 (24.9)	**< 0.001**
HVLT-R Learning Trials (no. correct)	26.2 (4.2)	26.7 (4.3)	27.5 (4.2)	25.3 (4.6)	26.7 (4.1)	25.4 (4.0)	26.5 (3.7)	**0.006**
HVLT-R Delayed Recall (no. correct)	9.4 (2.0)	9.4 (1.9)	10.1 (1.8)	9.3 (2.3)	9.4 (2.1)	9.1 (2.0)	9.2 (1.9)	**0.001**
Global performance measures								
QNPZ-8[†]	0 (0.59)	0.14 (0.52)	0.17 (0.57)	-0.04 (0.77)[¶]	0.19 (0.46)	-0.17 (0.59)	-0.14 (0.53)	**< 0.001**
NCI: at least mild[§]	19.9	14.1	13.1	29.5	10.1	27.8	17.9	**0.009**
NCI: at least moderate[§]	2.6	0.0	1.9	4.5	2.2	3.6	2.4	0.59

Values are percentage or mean (standard deviation [SD]).
ANCOVA, analysis of covariance; HVLT-R, Hopkin's Verbal Learning Test revised; NCI, neurocognitive impairment; QNPZ-8, quantitative neuropsychological performance z-score; WAIS, Wechsler Adult Intelligence Scale.
*Germany, Italy, Belgium and Switzerland. [†]Means were compared using analysis of covariance (ANCOVA), and percentages were compared using logistic regression, adjusted for age, sex, race/ethnicity, and education level. [†]QNPZ-8, the quantitative neuropsychological performance z-score, the average of the z-scores for the eight tests for each participant. z-scores for each test were calculated by subtracting the study mean, and dividing by the study SD (internal standardization); for grooved pegboard and finger tapping, z-scores for the dominant and nondominant hands were calculated separately and then averaged. [§]Defined in Table 1. [¶]The large SDs in the USA for the grooved pegboard, finger tapping and Color Trails tests are driven by outliers. Using a robust estimation method (SD = IQR/1.35), these SDs are estimated as follows: grooved pegboard, dominant hand 11.1, nondominant hand 16.3, average 11.9; finger tapping, dominant hand 9.5, nondominant hand 7.6, average 7.7; Color Trails 1, 14.4; Color Trails 2, 24.1; QNPZ-8, 0.63.

above the study average, followed by Thailand (0.15), Australia/UK (0.11), the USA (0.05) and Argentina/Chile (–0.17); scores were lowest in Brazil (–0.24).

After further adjustment for all factors listed in Figure 2, the covariate-adjusted mean QNPZ-8 score was highest in Thailand (0.18), followed by Europe (0.16), the USA (0.13), Australia/UK (0.10), Argentina/Chile (–0.10) and Brazil (–0.23) (Fig. 3). These findings show that none of the baseline variables could fully account for the difference in QNPZ-8 scores between the study's geographical locations.

In sensitivity analyses, we found no evidence for differences between geographical regions in the effects of age, sex and education level on the QNPZ-8; P = 0.65, 0.12 and 0.85 for the interaction between geographical region and age, sex and education level, respectively. The effect of race/ethnicity on the QNPZ-8 differed by geographical region.

Discussion

This is the largest study of the neurocognitive test performance of ART-naïve HIV-positive adults with CD4 cell counts > 500 cells/μL; it demonstrates that large, international neurology substudies with high co-enrolment rates are feasible. The results confirm our study hypothesis that demographic factors are associated with NP. Of the cardiovascular risk factors, however, only diabetes was associated with lower NP. We observed also that longer time since HIV diagnosis was associated with poorer NP.

Specifically, our findings were as follows. First, age had the greatest influence upon NP, wherein older age had a negative effect, similar to results in large clinical and nonclinical HIV-negative populations [23]. Next, in analyses including all demographic corrections and other covariates, white race/ethnicity was associated with better NP. In HIV-positive populations, differences in NP by race/ethnicity have been previously observed in national [24,25] and international studies [3]. However, irrespective of geographical boundaries, racial/ethnic effects on NP should be interpreted cautiously. Indeed, a number of socioeconomic factors that can affect general health and are otherwise associated with race/ethnicity were not measured in these studies [24,25] or ours. Moreover, it has been found in the USA that racial/ethnic influences on NP are significantly attenuated if reading level is taken into account [26].

Test scores differed between geographical locations (Table 4), and the difference between mean QNPZ-8 scores

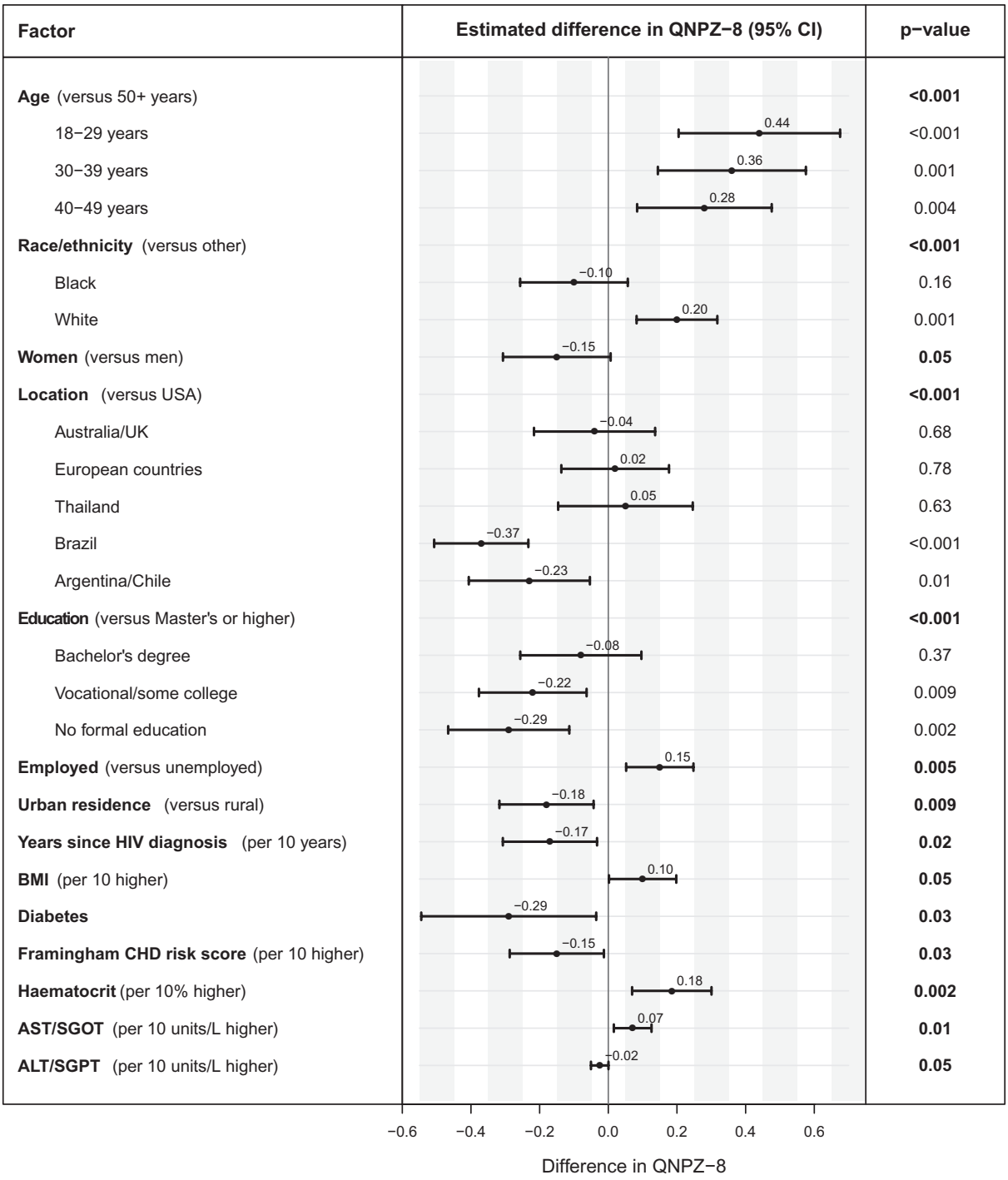

Fig. 2 Associations of demographic and clinical factors with the quantitative neuropsychological performance z-score (QNPZ-8), estimated in a multiple regression model. Factors in the model were determined through stepwise backwards variable selection; additionally, factors with *P*-values > 0.10 were excluded. The estimated differences are plotted with 95% confidence intervals (CIs). For factors with more than two categories, bolded *P*-values are for the factor, and unbolded *P*-values for individual categories. There is no evidence for an independent association of the following factors with neuropsychological test performance: baseline CD4 count, nadir CD4 count, the CD4:CD8 ratio, $\log_{10}$ HIV RNA, HIV RNA ≤ 400 copies/mL; smoking, hypertension, concentrations of fasting total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol and triglycerides, hyperlipidaemia, white blood cell count, haemoglobin level, lymphocyte count; hepatitis B or C, prior cardiovascular disease, psychiatric diagnoses; alcohol or other substance dependence; and depression by the Centre for Epidemiologic Studies-Depression Scale (CES-D). These factors were excluded from the final model by the automatic variable selection procedure. ALT, alanine aminotransferase; AST, aspartate aminotransferase; SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase.

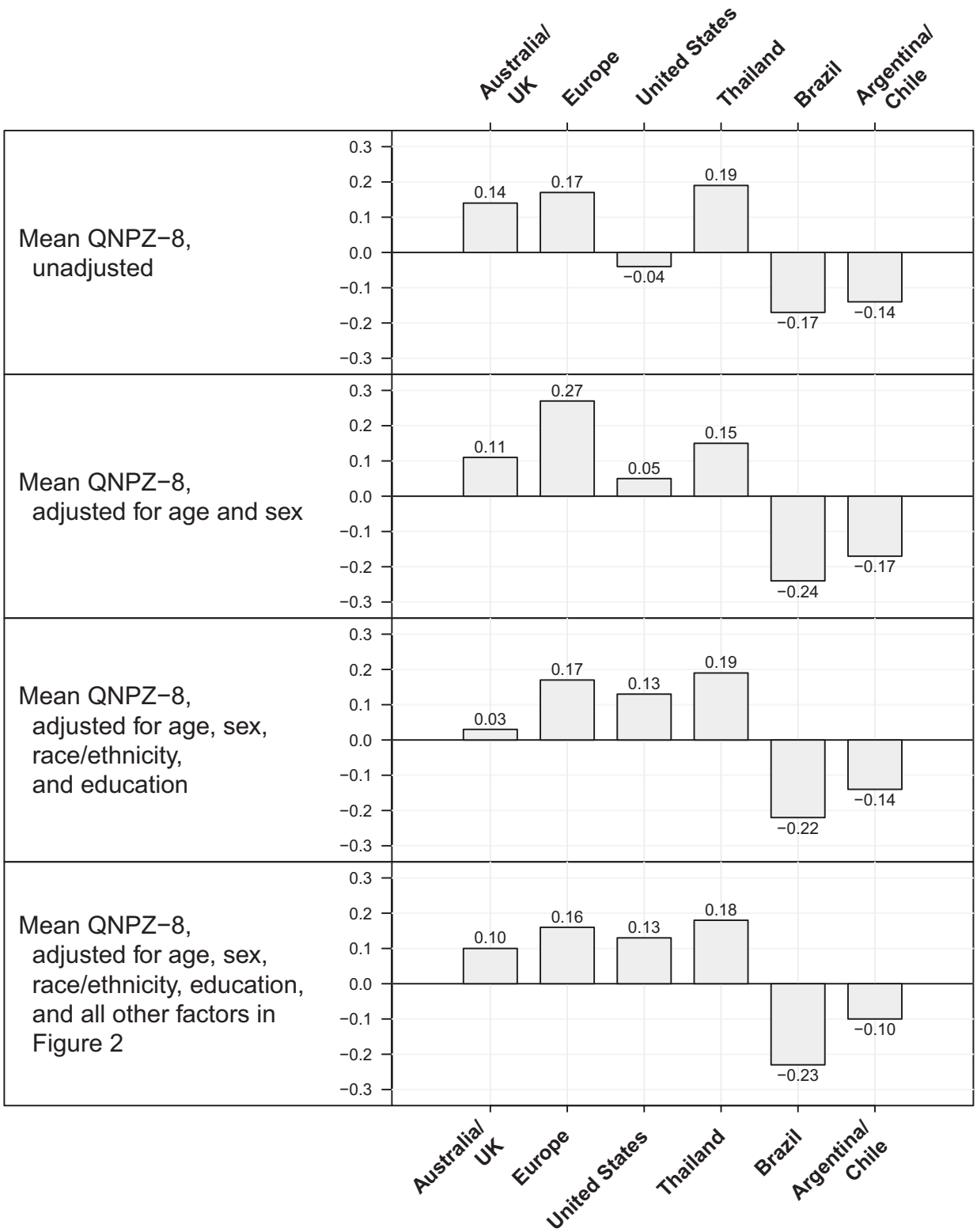

Fig. 3 Mean quantitative neuropsychological performance z-score (QNPZ-8) by geographical location, unadjusted and adjusted for selected demographic and clinical factors. The QNPZ-8 was calculated as the average of the *z*-scores for the individual neuropsychological tests (Table 1). The *z*-scores were standardized internally by subtracting the mean and dividing by the standard deviation (SD) for the 608 participants. Therefore, the overall mean QNPZ-8 is 0, and the bar graphs show the deviation of the mean QNPZ-8 at each location from the overall study mean. Estimated mean QNPZ-8 scores differ between geographical locations; $P < 0.001$ for each of the four models.

persisted after adjustment for demographic and clinical factors (Figs 2 and 3). Here also, it is possible that unmeasured socioeconomic, cultural and health-related factors could further account for differences in NP. Differences in baseline NP outcomes, however, will not interfere with the primary goal of the substudy, to compare longitudinal changes in NP between participants randomized to early versus deferred use of ART, because in the longitudinal analyses, each study participant will serve as their own control.

Second, diabetes was associated with poorer NP in our study population. Type 1 and type 2 diabetes carry risk for NCI involving cognitive domains that overlap with those involved in HAND [27,28]. It is not possible from our data to determine whether the HIV–diabetes dyad has an additive or synergistic impact on the degree of NCI, but it is cautionary that this association was found in our young study population, with a low prevalence of diabetes (< 4%). Because this study is cross-sectional, however, it is impossible to establish the temporal relationship between diabetes and lower NP. A higher Framingham 10-year CHD risk score was also associated with poorer NP, but with a small effect size; as diabetes was included as a variable in the Framingham calculation, it is possible that diabetes is driving this association.

Third, higher haematocrit level and BMI were associated with better NP. Low haematocrit level [10,11] and low BMI [6] have been associated with HAD in persons with advanced HIV disease. Our study shows that these factors are also associated with NP during earlier HIV infection. HIV infection is associated with a number of cytopaenias that may result from infection of CD34+ haematopoetic stem cells and cytokine-induced bone marrow dysfunction [29]. Reduced haematocrit levels and increased levels of tumour necrosis factor (TNF)-α and monocyte chemotactic protein were associated with basal ganglia injury in one magnetoresonance imaging study of HIV-positive persons [30]. Our finding that a higher haematocrit level was associated with higher NP may indicate that a milieu with less inflammation has attendant and perhaps interrelated benefits for both bone marrow and brain parenchymal integrity. Conversely, we found that a higher BMI, which is associated broadly with increased levels of inflammation in both HIV-positive and HIV-negative populations, was associated with better NP. After controlling for waist circumference, McCutchan *et al.* also found that high BMI was associated with better NP in HIV-positive persons with more advanced disease [7]. In HIV-positive and HIV-negative populations, adipose tissue produces cytokines with both pro- and anti-inflammatory properties [31,32]. The topography of adipose deposition in an individual influences the relative balance of cytokine production, where central (visceral) adipose tissue produces pro-inflammatory cytokines [32]. Central obesity and inflammatory markers were not evaluated in our study population.

Fourth, 19.9% of participants had at least mild NCI and 2.6% had moderate NCI based on our *z*-score criteria. These findings are in accord with data showing that damage to the central nervous system [14,33] and NCI [14] occur during early HIV infection. With the caveat of not having country-specific norms, this shows that our battery can detect a wide range of NP.

We are not able to compare the prevalence of NCI in our study with that in the general HIV-negative population, because NCI prevalence is not available for several of our international locations. In US HIV-negative populations, the prevalence of NCI is approximately 15%, compared with 28% according to our *z*-score criteria among the US participants in our study. Our ability to estimate the prevalence of NCI is further limited by the absence of data on clinical neurocognitive symptoms and functional ability of the substudy participants. Hence, although the diagnostic neuropsychological test criteria required by the Frascati criteria were used [16], the proportion of participants who had mild or moderate–severe HIV-associated dementia could not be ascertained.

The prevalence and aetiology of NCI during early HIV infection have not yet been fully elucidated. Substance use has been associated with NCI during early HIV infection [34], but substance and alcohol dependence was low in our study population (5.1%) and not associated with NP. Notably, 32% of participants met our study definition for depression, a rate very similar to our findings in studies of other international HIV-positive populations [3,19]. However, depression was not associated with NP in our analyses and, in our previous work, we have shown that incident depression is not associated with worsening of NP in HIV-positive populations [35]. It is noteworthy that only 8% of participants had a formal psychiatric diagnosis at baseline; this suggests that depression may be underdiagnosed in our substudy's populations.

Fifth, the only HIV-related baseline measure that was associated with NP was time since HIV diagnosis, which suggests that untreated HIV infection may have a cumulative deleterious effect on NP even early in the course of the disease, although the effect was small. In this cross-sectional analysis of participants selected for their high baseline CD4 cell counts, factors that are a function of time such as rate of CD4 decline from time of HIV acquisition were not captured. Further, the available laboratory measures may not be sensitive enough for an association between immune damage and NP to be detected in the context of uncontrolled HIV viraemia.

In addition to the limitations noted above, the chief limitations in our study were that some of the associations

may have been confounded by unmeasured factors as a consequence of the study's cross-sectional design, and that temporal relationships between NP and intercurrent associated conditions, such as diabetes, could not be ascertained. Also, normative data from HIV-negative controls were not available for most of our international sites, which limited the ability to estimate the prevalence of NCI based on *z*-scores. However, external reference populations were not needed to determine associations of baseline factors with NP, and we adjusted analyses for the demographic factors commonly used to match healthy controls. Finally, many factors were investigated, and hence some of the associations with borderline p-values may be spurious.

In summary, this is the largest international study of NP and associated factors in ART-naïve, HIV-positive individuals with high baseline and nadir CD4 cell counts. In addition to differences by geographical region, higher age, lower level of education and diabetes were associated most strongly with lower NP. High haematocrit levels and BMI were associated with better NP, while longer duration of known HIV seropositivity was associated with poorer NP. Mild NCI was present in 19.9% of participants. Future longitudinal analyses will evaluate the impact of the strategy of immediate versus deferred ART upon NP.

The START study is registered at clinicaltrials.gov (NCT00867048).

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