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Journal

AIDS, 31(11)

ISSN

0269-9370

Authors

Coban, Hamza
Robertson, Kevin
Smurzynski, Marlene
[et al.](#)

Publication Date

2017-07-17

DOI

10.1097/qad.0000000000001523

Peer reviewed



Published in final edited form as:

AIDS. 2017 July 17; 31(11): 1565–1571. doi:10.1097/QAD.0000000000001523.

Impact of aging on neurocognitive performance in previously antiretroviral-naïve HIV+ individuals on their first suppressive regimen

Hamza Coban¹, Kevin Robertson², Marlene Smurzynski³, Supriya Krishnan³, Kunling Wu³, Ronald J. Bosch³, Ann C. Collier⁴, and Ronald J. Ellis^{1,5}

¹University of California San Diego, Department of Psychiatry, San Diego, CA

²University of North Carolina at Chapel Hill, Department of Neurology, Chapel Hill, NC

³Harvard TH Chan School of Public Health, Center for Biostatistics in AIDS Research, Boston, MA

⁴University of Washington School of Medicine, Seattle, WA

⁵University of California San Diego, Department of Neuroscience, San Diego, CA

Abstract

Background—Despite treatment with virologically suppressive antiretroviral therapy (ART), neurocognitive impairment may persist or develop de novo in aging HIV-infected individuals. We evaluated advancing age as a predictor of neurocognitive impairment in a large cohort of previously ART-naïve individuals on long-term ART

Design—The AIDS Clinical Trials Group (ACTG) Longitudinal Linked Randomized Trials (ALLRT) was a prospective cohort study of HIV-infected individuals originally enrolled in randomized ART trials. This analysis examined neurocognitive outcomes 2 years after ART initiation.

Methods—All participants underwent annual neurocognitive testing consisting of Trail making A and B, the WAIS-R Digit Symbol and Hopkins Verbal Learning Tests. Uni- and multi-variable repeated measures regression models evaluated factors associated with neurocognitive performance. Predictors at parent study entry (ART naïve) included entry demographics, smoking, injection drug use, hepatitis B surface antigen, hepatitis C virus serostatus, history of stroke, ART regimen type, pre-ART nadir CD4 and plasma viral load (PVL) and as well as time-updated PVL and CD4.

Results—The cohort comprised 3,313 individuals with median pre-ART age of 38 years, 20% women; 36% Black, non-Hispanic; 22% Hispanic. Virologic suppression was maintained at 91% of follow-up visits. Neurocognitive performance improved with years of ART. After adjusting for the expected effects of age using norms from HIV–negative individuals, the odds of

neurocognitive impairment at follow-up visits among the HIV-infected increased by nearly 20% for each decade of advancing age.

Conclusion—Despite continued virologic suppression and neurocognitive improvement in the cohort as a whole, older individuals were more likely to have neurocognitive impairment than younger individuals.

Keywords

HIV; cognitive impairment; dementia; aging; ART; HAND

INTRODUCTION

Effective combination antiretroviral therapy (ART) extends the life of individuals with human immunodeficiency virus (HIV), and the infected population is aging.^[1] Treatment with ART can result in significant neurocognitive improvement in many individuals with HIV-associated neurocognitive disorders (HAND).^[2] However, improvement varies by person and several cohort studies have demonstrated that HAND can persist despite virologic suppression and immune recovery on ART^[3, 4]. A number of risk factors for HAND have been identified including older age, less education, the presence of depression, hepatitis C virus (HCV) infection, a diagnosis of AIDS (CDC 1993), and the presence of other severe medical comorbidities.^[5] Recent reports indicate that more than 50% of persons living with HIV are over age 50 years of age, and 30% are over the age of 60.^[1, 6] These trends raise the importance of understanding the impact of aging on the course of HAND.^[7]

While several studies have evaluated the impact of aging on risk of cognitive impairment in HIV, most of these studies have been cross-sectional^[8], included substantial proportions of individuals lacking viral suppression on cART^[9] and used neurocognitive measures with very limited sensitivity and specificity^[10]. Two longitudinal studies^[11, 12] have evaluated the relationship of neurocognitive impairment to declining cognition. In the first study^[11], two assessments were performed – baseline and 14-month follow-up. The number of participants was small (27 HIV+ under age 40 and 56 over age 50 years). While the rate of incident cognitive disorders was higher in HIV+ than in HIV– participants, there was no main effect of age or age by HIV interaction. The second longitudinal study^[12] included 54 HIV+ and 30 HIV– individuals over one year and concluded that age and HIV infection interact to produce larger declines in verbal memory over time. Thus, important gaps in the literature include whether decline in neurocognitive function occurs in virologically suppressed participants followed for several years, and when decline occurs, at what age does it begin.

To address these gaps, we evaluated the relationship of advancing age to neurocognitive decline, after adjusting for other relevant covariates, in a cohort of previously ART-naïve individuals, a large proportion of whom were virologically suppressed for 2 or more years after initiating their first ART regimen.

METHODS

Study population

This was an analysis of prospectively collected data from The AIDS Clinical Trials Group (ACTG) Longitudinal Linked Randomized Trials (ALLRT) study. Participants were drawn from seven randomized clinical trials of antiretrovirals (Table 1), referred to here as the “parent studies” [13]. Participants agreed to long-term follow up with the purpose of evaluating clinical, virologic, immunologic and neurologic outcomes associated with treatment of HIV. Individuals were selected for this analysis if they were ART-naïve when they entered their parent studies and had at least one NPZ4 score result. Discontinuing ART was defined as stopping for at least 3 weeks prior to neurocognitive evaluation. Additionally, since normative neurocognitive data were not available for all race/ethnicity groups, we further restricted the study population to white non-Hispanic (N=1965), black non-Hispanic (N=1595) and Hispanic (N=1015). To achieve the study goal of examining individuals during long-term ART, only neurocognitive assessments done at least 2 years after ART initiation were included in this analysis.

Neurocognitive Testing

The 4-test neurocognitive battery (NPZ4) included the Trail-making Tests A and B (TMA, TMB) [14], the WAIS-R Digit Symbol subtest (DSY) [15], and the Hopkins Verbal Learning Test - Revised (HVLTR). [16] These tests were chosen because they are sensitive in detecting HIV-related neurocognitive changes. [17, 18] Briefly, TMA and DSY assess psychomotor speed, TMB assesses executive function, and the HVLTR evaluates verbal learning. The HVLTR was added to the battery to enhance its sensitivity to evolving changes in the pattern of neurocognitive impairment in the era of combination antiretroviral therapy (cART). [12] The raw score for each test was standardized using demographically-adjusted (age, sex, years of education, race/ethnicity as appropriate) normative means. A standardized score was calculated by subtracting the appropriate normative mean, then dividing by the appropriate normative standard deviation. For TMA, TMB and DSY, norms were available for White, Black and Hispanic ethnicities. [19, 20] The parent clinical trials included no HIV uninfected individuals, and therefore did not yield norms. We used the best available normative data. For the HVLTR, existing norms were available for Whites and Blacks tested in English [19, 20], and for Hispanic participants tested in Spanish. [21] Participants completed the NPZ4 at ALLRT entry and approximately every 48 weeks thereafter (TMA, TMB and DSY were assessed in ALLRT throughout the study (since 2000); HVLTR was added in 2006). The primary outcome was overall impairment on the NP test battery, defined as -2.0 SD on one test or -1.0 SD on two tests. We sought to determine the impact of the predictor variable and covariates on NP outcome after expected virologic and immunologic effects of cART had been achieved. Thus, the analysis included only NP scores from visits at least 2 years after cART was initiated in the parent studies.

Age and other covariates

For each participant, baseline characteristics were defined at cART initiation (at parent study entry). Ascertainment methods for clinical and laboratory variables have been previously described in detail. [13] The primary predictor was age and covariates included in the

analysis were sex, race/ethnicity, IV drug use, years of education, history of smoking, history of stroke, ACTG study, initial ART regimens, CD4+ T-cell counts at baseline and post-baseline, nadir CD4 count, HIV RNA viral load at baseline and post-baseline, antiretroviral adherence (ACTG adherence questionnaire), hepatitis C status (diagnosis or antibody positive), and hepatitis B status (surface antigen positive) at first available time point.

Statistical analysis

We used unadjusted (univariate) and adjusted (multivariable) generalized estimating equations (GEE) models to identify risk factors associated with neurocognitive impairment deficits. The outcome variable was neurocognitive impairment as a binary variable based on NPZ4. In multivariable adjusted models, variables with p-value from the univariate models 0.1 were included as covariates. Repeated measures logistic regression (GEE) estimated the odds of neurocognitive impairment at an NPZ4 evaluation.

RESULTS

Baseline (pre-ART) characteristics defined at the parent study entry (ART initiation) for each participant are shown in Table 1. The median age of the 3313 HIV+ individuals was 38 years (interquartile range [22] 31, 45); 2% were over 60, 12% were over 50 years of age; 42% were white non-Hispanic; and 20% were females (N= 673). The median nadir CD4 was 221 cells/ μ L (IQR 80, 324). The median number of visits at which the neurocognitive tests were administered to each participant after 2 years on ART was 3 (IQR 2, 6). During follow-up, participants remained on ART at 97% of visits, 91% of HIV RNA measures were \leq 200 copies/ml and 61% of CD4 counts were $>$ 500 cells/ μ L.

Univariable and multivariable GEE regression models on binary NPZ4 impairment are shown in Table 1. In the unadjusted model, the odds ratio (OR) of neurocognitive impairment for each decade of advancing age at parent study entry was 1.17 (95% CI 1.10–1.25, $p < 0.001$). The OR for hepatitis C co-infection was 1.64 (1.31–2.06, $p < 0.001$). ORs for other significant covariates included 1.44 (1.25–1.68, $p < 0.001$) for women as compared to men; 1.71 (1.51–1.94, $p < 0.001$) for \leq 12 years of education compared to those with $>$ 12 years of education; 1.35 (1.07–1.70, $p = 0.01$) for history of injection drug use; 1.31 (1.16–1.49, $p < 0.001$) for those with time-varying CD4 counts less than 350 cells/ μ L and 1.15 (1.05–1.26, $p = 0.002$) for time-varying CD4 counts between 351–500 cells/ μ L, as compared to CD4 counts $>$ 500 cells/ μ L. In the cohort as a whole, neurocognitive impairment rates diminished with increasing years on ART 0.95 (0.93–0.96, $p < 0.001$).

In the multivariable adjusted model (Table 1 and Figure 1), after correcting for the expected effects of age using norms from HIV–negative individuals, the odds of neurocognitive impairment at follow-up visits among our HIV-infected subjects increased by nearly 20% for each decade of advancing age at parent study entry (OR 1.18, [1.11–1.26], $p < 0.001$). Figure 2. shows that the age-related increase in neurocognitive impairment began in the 5th decade (age 41–50). Hepatitis C infection was also associated with neurocognitive impairment (OR 1.40, [1.08–1.82], $p = 0.01$) along with less education (OR 1.37, [1.20–1.57], $p < 0.001$) time-varying CD4 level less than 350 cells/ μ L (OR 1.21, [1.05–1.40], $p = 0.008$) and time-varying

CD4 level between 351–500 cells/ μ L during follow up (OR 1.12, [1.01–1.24], $p=0.03$). Women had greater odds of impairment than men (OR 1.35, [1.15–1.59], $p<0.001$). Variables for which the odds of impairment were not significant in the adjusted models included injection drug use, initial ART drug class and parent study and nadir CD4 level.

DISCUSSION

We found that advancing age was a significant risk factor for neurocognitive impairment, even two or more years after starting initial ART treatment. This was true despite normative adjustment of neurocognitive scores for age from HIV-negative individuals, and after adjusting for a variety of covariates in multivariable models. This elevated risk of neurocognitive impairment with age was seen despite continued virologic suppression in most and despite overall neurocognitive improvement in the cohort as a whole. In contrast to a recent study that found that increased cognitive impairment began in the seventh decade [11], we observed an increase in risk beginning in the fifth decade.

Analyses showed that women were more likely than men to show neurocognitive impairment during follow-up after 2 years of cART. Some previous cross-sectional studies have reported higher frequencies of neurocognitive impairment among women as compared to men [23, 24] but others have not [25]. Another study showed no difference in longitudinal worsening between men and women [26]. There were important differences between the cohorts in these prior reports and our own, including absence of cART [24, 26] and differences in neurocognitive tests used [25]. Our cohort is unique in its size and the high proportion of individuals studied after 2 years of virally suppressive ART.

Our findings have implications for the aging HIV+ population on cART. Numerous prior studies have postulated premature or accelerated aging in HIV [27], but the exact mechanisms by which this might occur are unclear. Several mechanisms have been proposed. First, cART has been shown to magnify adverse effects on neurocognition of common comorbidities associated with aging, such as diabetes mellitus, hypertension and abdominal obesity. [28–31] Second, older individuals may require higher CNS-penetration ART regimens to benefit neurocognitively than younger individuals, as was shown in an older subgroup in a recent clinical trial. [32] Third, CNS toxicities of ART may have a greater impact in older participants than younger ones, [33].

Although a recent study [34] did not find HCV co-infection to be significantly associated with poorer neurocognitive outcomes, our study found HCV to be a significant risk factor. Of note, our study was conducted before direct-acting antiviral HCV agents were in use. Differences in findings between our study and previous studies may reflect our larger cohort size and greater power to detect an effect.

We did not find a statistically significant association between initial ART drug class and neurocognitive impairment. This contrasts with some recent studies in which efavirenz (NNRTI) based regimens were found to be associated with worse neurocognitive functioning. [35, 36] A caveat is that some of our study participants might have switched ART regimens during follow-up.

We observed a higher rate of impairment among participants of Latino/Hispanic ethnicity. Since we used normative corrections for Hispanic ethnicity, and in the case of the HVLTR, for Spanish language, poorer performance of Hispanics is not attributable to inadequate demographic corrections. Similar findings have been reported previously, and are not completely explained by worse HIV disease characteristics or comorbidities. [37–40] These findings might be related to culturally-relevant psychosocial and biomedical factors that have not been adequately explored to date.

Strengths of this study include a large, prospective longitudinal cohort with more than 3000 participants taking randomly assigned initial antiretroviral therapy. The vast majority achieved high rates of sustained virologic suppression. Care was taken to minimize practice effects as a result of repeated testing – in the case of the HVLTR, by using different word lists, and in the case of the other tests, by using norms corrected for practice effects. A limitation of this study, as with all observational studies, is that the observed relationships represent associations, which may not be causative. Few subjects were over age 60, limiting the generalizability of our findings to older populations. The majority of the cohort began neurocognitive testing subsequent to initiation of cART^[13] thus the impact of cART initiation on neurocognition was not assessed.

Future studies should evaluate potential mediators of the adverse effects of age on neurocognitive trajectories, such as inflammation, coinfections such as syphilis and cytomegalovirus, and vascular risk factors including diabetes, hypercholesterolemia and central obesity. Novel treatments will depend in part on which factors or combinations of these factors are driving neurocognitive impairment in HIV.

Acknowledgments

The manuscript was submitted by Hamza Coban, MD. He is a fellow at Interdisciplinary Research Fellowship in NeuroAIDS (IRFN) program which is funded by NIH (MH 081482). He is also supported by funds from NIH MH 105319 (Cristian L. Achim)

The project described was supported by Award Number U01AI068636 from the National Institute of Allergy and Infectious Diseases and supported by National Institute of Mental Health (NIMH), National Institute of Dental and Craniofacial Research (NIDCR). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute of Allergy and Infectious Diseases or the National Institutes of Health.

Data in this manuscript were collected by the AIDS Clinical Trials Group (ACTG) Longitudinal Linked Randomized Trials (ALLRT) study. ALLRT was supported by the AIDS Clinical Trials Group of the National Institute for Allergy and Infectious Diseases (AI 68634, AI 38858, AI 38855, AI 069481)

We would also like to acknowledge the study coordinators at the ACTG sites and all the research participants.

Funding: This study funded by NIH grants AI 68634, AI 38858, AI 68636, AI 38855, AI069481, AI 27757

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Variable

- Years since ART initiation
 - Every 1 year increase
- Sex (ref: Male)
 - F
- Age at ART initiation
 - Every 10 years increase
- Ethnicity/Race(ref: White)
 - Black Non-Hispanic
 - Hispanic (Regardless of Race)
- Years of education(ref: >12(post high school))
 - <=12(high school or less)
- Injection drug use (ref: Not reported)
 - Reported
- Hepatitis C status (ref: Negative)
 - Positive
- Nadir CD4 (ref: >350 cells/uL)
 - 0-50
 - 51-200
 - 201-350
- Parent study (vs. A5257)
 - 384
 - 388
 - A5014
 - A5095
 - A5142
 - A5202
- Time-varying CD4 (ref: >500 cells/uL)
 - 0-350
 - 351-500

Odds Ratio and 95% CI

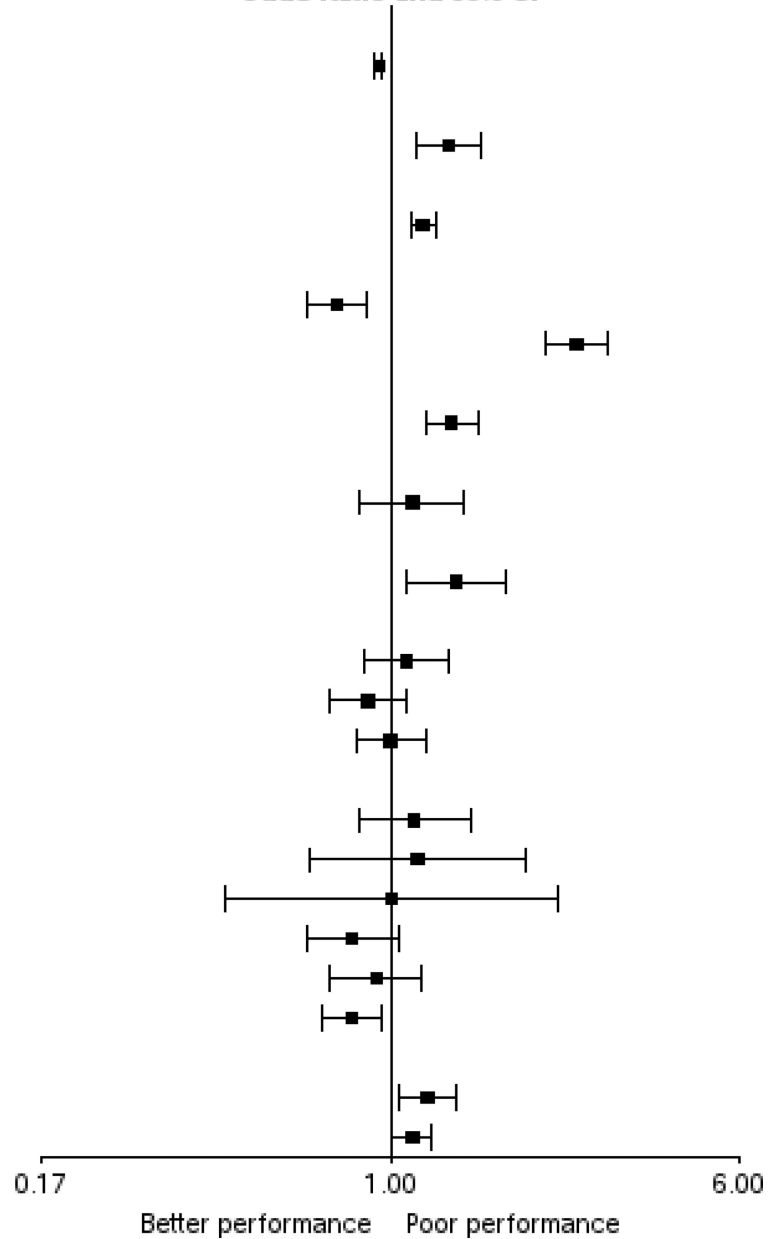


Figure 1. Forest plot showing adjusted odds ratios and 95 percent confidence intervals for the association between risk factors and neurocognitive impairment.

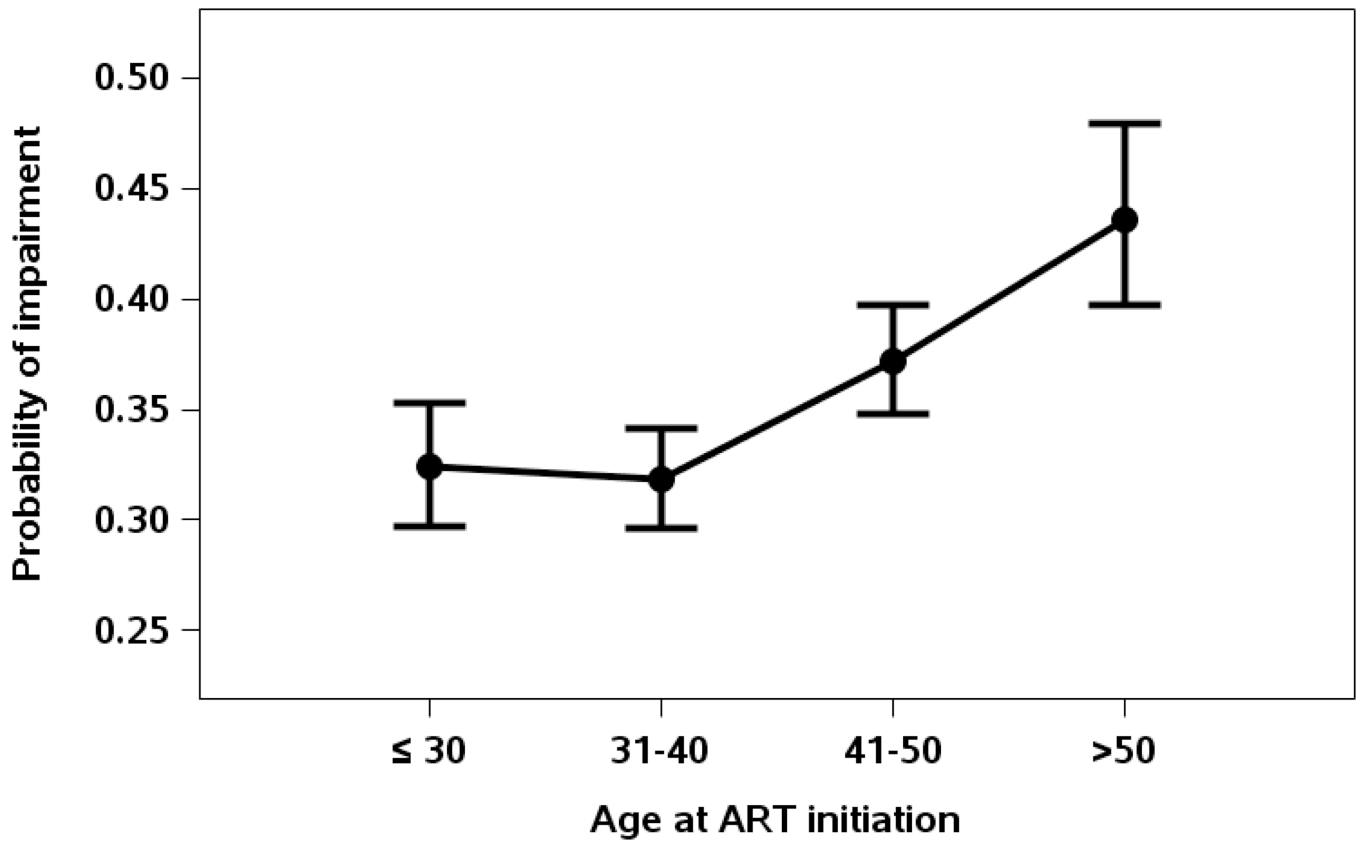


Figure 2.
Probability of cognitive impairment according to age decade at parent study entry.

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Table 1

Participant demographic and disease characteristics, unadjusted and adjusted odds ratios and 95 percent confidence intervals for the association between risk factors and neurocognitive impairment.

Variables	N or MEDIAN (IQR)	UNADJUSTED		ADJUSTED [†]	
		Odds Ratio (95% CI)	P-value	Odds Ratio (95% CI)	P-value
Years since ART initiation	Every 1 year increase	0.95 (0.93,0.96)	<0.001	0.94 (0.92,0.96)	<0.001
Sex (ref: Male)	F	1.44 (1.25,1.68)	<0.001	1.35 (1.15,1.59)	<0.001
Age at ART initiation	Every 10-year increase	1.17 (1.10,1.25)	<0.001	1.18 (1.11,1.26)	<0.001
Ethnicity/Race (ref: White)	White Non-Hispanic	n/a	n/a	n/a	n/a
	Black Non-Hispanic	1,172 (35%)	0.18	0.76 (0.65,0.89)	<0.001
	Hispanic	737 (22%)	<0.001	2.61 (2.22,3.07)	<0.001
Years of education (ref: >12(post high school))	12 years	1.71 (1.51,1.94)	<0.001	1.37 (1.2,1.57)	<0.001
Initial ART drug class (ref: NRTI only)	NRTI+NNRTI	536 (16%)	0.68	n/a	n/a
	PI+NNRTI	1,558 (47%)	0.66	n/a	n/a
	PI+NRTI	122 (4%)	0.68	n/a	n/a
	PI+NRTI+NNRTI	974 (29%)	0.31	n/a	n/a
Smoking history on/before 1st neurocognitive evaluation (ref: No)	Yes	1,843 (56%)	0.23	n/a	n/a
Injection drug use (ref: Not reported)	reported (currently or previously)	235 (7%)	0.01	1.12 (0.85,1.46)	0.42
Hepatitis B status (ref: Negative)	Positive	83 (3%)	0.32	n/a	n/a
Hepatitis C status (ref: Negative)	Positive	258 (8%)	<0.001	1.4 (1.08,1.82)	0.01
Nadir CD4 (ref: >350 cells/ μ L, n=689 (21%))	0-50	656 (20%)	0.03	1.09 (0.87,1.35)	0.46
	51-200	855 (26%)	0.75	0.89 (0.73,1.08)	0.23
	201-350	1,113 (34%)	0.54	1.00 (0.84,1.20)	>0.9
Baseline HIV RNA (ref: 100,000 copies/ml)	>100,000	1,119 (34%)	0.78	n/a	n/a
Parent study (ref: A5257, n=1201(36%))	384	273 (8%)	<0.001	1.13 (0.85,1.51)	0.41
	388	94 (3%)	0.31	1.15 (0.66,2.00)	0.62
	A5014	18 (1%)	0.6	1.01 (0.43,2.37)	>0.90
	A5095	406 (12%)	<0.001	0.82 (0.65,1.04)	0.1
	A5142	323 (10%)	0.007	0.93 (0.73,1.18)	0.54

Variables	N or MEDIAN (IQR)	UNADJUSTED		ADJUSTED [‡]	
		Odds Ratio (95% CI)	P-value	Odds Ratio (95% CI)	P-value
Stroke history on/before 1st neurocognitive evaluation (ref: No)	A5202	0.80 (0.69,0.93)	0.004	0.82 (0.70,0.96)	0.01
Lab toxicity with grade 3 before year 1 (ref: No)	Yes	1.65 (0.82,3.33)	0.16	n/a	n/a
Adherence during year 1 (ref: 100% adherence)	Yes	0.93 (0.79,1.09)	0.35	n/a	n/a
Time-varying CD4 [‡] (ref: >500 cells/ μ L)	<100%	1.01 (0.89,1.15)	0.84	n/a	n/a
Time-varying HIV RNA [^] (ref: >200 copies/ml)	0-350	1.31 (1.16,1.49)	<0.001	1.21 (1.05,1.40)	0.008
	351-500	1.15 (1.05,1.26)	0.002	1.12 (1.01,1.24)	0.03
	>200	1.09 (0.95,1.25)	0.22	n/a	n/a

Abbreviations: IQR: interquartile range; CI: confidence interval; PI: protease inhibitors; NRTI: nucleoside reverse transcriptase inhibitors; NNRTI: non-nucleoside reverse transcriptase inhibitors. n/a: not applicable.

[‡] Only covariates with unadjusted p-value ≤ 0.1 , are included.

[^] For time-varying CD4 and HIV RNA, the frequencies represent these covariates at the 1st neurocognitive evaluation

* 12% of participants were over 50, 2% of the participants were over 60 years of age.