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

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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-naive individuals on long-term ART.

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

Methods: All participants underwent annual neurocognitive testing consisting of Trail making A and B, the wechsler adult intelligence scale-revised Digit Symbol and Hopkins Verbal Learning Tests. Uni and multivariable repeated measures regression models evaluated factors associated with neurocognitive performance. Predictors at parent study entry (ART naive) included entry demographics, smoking, injection drug use, hepatitis B surface antigen, hepatitis C virus serostatus, history of stroke, ART regimen type, pre-ART nadir $CD4^+$ cell count, and plasma viral load and as well as time-updated plasma viral load and $CD4^+$ cell count.

Results: The cohort comprised 3313 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.

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Keywords: aging, antiretroviral therapy, cognitive impairment, dementia, HIV-associated neurocognitive disorders, HIV

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Introduction

Effective combination antiretroviral therapy (ART) extends the life of individuals with 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 (center for disease control, 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].

Although 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 combination ART (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-infected under age 40 and 56 over age 50 years). Although the rate of incident cognitive disorders was higher in HIV-infected than in HIV-uninfected participants, there was no main effect of age or age by HIV interaction. The second longitudinal study [12] included 54 HIV-infected and 30 HIV-uninfected individuals over 1 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-naive 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 neuropsychological 4-test battery z-scores (NPZ4) score result. Discontinuing ART was defined as stopping for at least 3 weeks prior to neurocognitive evaluation. Additionally, as 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 wechsler adult intelligence scale-revised digit symbol subtest (DSY) [15], and the Hopkins verbal learning test revised (HVLT-R) [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 HVLT-R evaluates verbal learning. The HVLT-R was added to the battery to enhance its sensitivity to evolving changes in the pattern of neurocognitive impairment in the era of 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 HVLT-R, 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; HVLT-R was added in 2006). The primary outcome was overall impairment on the neuropsychological test battery, defined as -2.0 SD or less on one test or -1.0 SD or less on two tests. We sought to determine the impact of the predictor variable and covariates on neuropsychological outcome after expected virologic and immunologic effects of cART had been achieved. Thus, the analysis

Table 1. Participant demographic and disease characteristics, unadjusted and adjusted odds ratios and 95% confidence intervals for the association between risk factors and neurocognitive impairment.

Variables		*N* or median (IQR)	Unadjusted		Adjusted[a]	
			Odds ratio (95% CI)	*P* value	Odds ratio (95% CI)	*P* value
Years since ART initiation	Every 1 year increase	3.5 (2.5, 5.4)	0.95 (0.93,0.96)	<0.001	0.94 (0.92,0.96)	<0.001
Sex (ref: Male)	F	673 (20%)	1.44 (1.25,1.68)	<0.001	1.35 (1.15,1.59)	<0.001
Age at ART initiation	Every 10-year increase	38[b] (31, 45)	1.17 (1.10,1.25)	<0.001	1.18 (1.11,1.26)	<0.001
Ethnicity/Race (ref: White)	White non-Hispanic	1404 (42%)	n/a	n/a	n/a	n/a
	Black non-Hispanic	1172 (35%)	0.91 (0.79,1.05)	0.18	0.76 (0.65,0.89)	<0.001
	Hispanic	737 (22%)	2.93 (2.51,3.42)	<0.001	2.61 (2.22,3.07)	<0.001
Years of education (ref: >12 (post high school))	≤12 years	1258 (38%)	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%)	0.96 (0.80,1.16)	0.68	n/a	n/a
	PI + NNRTI	1,558 (47%)	1.08 (0.77,1.52)	0.66	n/a	n/a
	PI + NRTI	122 (4%)	1.04 (0.87,1.24)	0.68	n/a	n/a
	PI + NRTI + NNRTI	974 (29%)	0.84 (0.59,1.18)	0.31	n/a	n/a
Smoking history on/before 1st neurocognitive evaluation (ref: No)	Yes	1843 (56%)	1.08 (0.95,1.22)	0.23	n/a	n/a
IDU (ref: Not reported)	reported (currently or previously)	235 (7%)	1.35 (1.07,1.7)	0.01	1.12 (0.85,1.46)	0.42
Hepatitis B status (ref: Negative)	Positive	83 (3%)	1.21 (0.83,1.77)	0.32	n/a	n/a
Hepatitis C status (ref: Negative)	Positive	258 (8%)	1.64 (1.31,2.06)	<0.001	1.4 (1.08,1.82)	0.01
Nadir $CD4^+$ cell count [ref: >350 cells/μl, $n = 689$ (21%)]	0–50	656 (20%)	1.24 (1.02,1.50)	0.03	1.09 (0.87,1.35)	0.46
	51–200	855 (26%)	0.97 (0.81,1.16)	0.75	0.89 (0.73,1.08)	0.23
	201–350	1113 (34%)	1.06 (0.89,1.25)	0.54	1.00 (0.84,1.20)	>0.9
Baseline HIV RNA (ref: ≤100 000 copies/ml)	>100 000	1119 (34%)	1.02 (0.90,1.16)	0.78	n/a	n/a
Parent study [ref: A5257, $n = 1201$ (36%)]	384	273 (8%)	0.65 (0.52,0.81)	<0.001	1.13 (0.85,1.51)	0.41
	388	94 (3%)	0.77 (0.46,1.28)	0.31	1.15 (0.66,2.00)	0.62
	A5014	18 (1%)	0.79 (0.32,1.91)	0.6	1.01 (0.43,2.37)	>0.90
	A5095	406 (12%)	0.59 (0.48,0.72)	<0.001	0.82 (0.65,1.04)	0.1
	A5142	323 (10%)	0.75 (0.60,0.92)	0.007	0.93 (0.73,1.18)	0.54
	A5202	998 (30%)	0.80 (0.69,0.93)	0.004	0.82 (0.70,0.96)	0.01
Stroke history on/before 1st neurocognitive evaluation (ref: No)	Yes	24 (1%)	1.65 (0.82,3.33)	0.16	n/a	n/a
Lab toxicity with grade ≥3 before year 1 (ref: No)	Yes	664 (20%)	0.93 (0.79,1.09)	0.35	n/a	n/a
Adherence during year 1 (ref: 100% adherence)	<100%	979 (30%)	1.01 (0.89,1.15)	0.84	n/a	n/a
Time-varying $CD4^+$ cell count[c] (ref: >500 cells/μl)	0-350	699 (21%)	1.31 (1.16,1.49)	<0.001	1.21 (1.05,1.40)	0.008
	351–500	816 (25%)	1.15 (1.05,1.26)	0.002	1.12 (1.01,1.24)	0.03
Time-varying HIV RNA[c] (ref: ≤200 copies/ml)	>200	304 (9%)	1.09 (0.95,1.25)	0.22	n/a	n/a

ART, antiretroviral therapy; CI, confidence interval IQR, interquartile range; IDU, injection drug use; PI, protease inhibitors; n/a, not applicable; NRTI, nucleoside reverse transcriptase inhibitors; NNRTI, nonnucleoside reverse transcriptase inhibitors.
[a]Only covariates with unadjusted *P* value ≤0.1, are included.
[b]For time-varying $CD4^+$ cell count and HIV RNA, the frequencies represent these covariates at the first neurocognitive evaluation.
[c]12% of participants were over 50, 2% of the participants were over 60 years of age.

included only neuropsychological 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, intravenous drug use, years of education, history of smoking, history of stroke, ACTG study, initial ART regimens, $CD4^+$ T-cell counts at baseline and postbaseline, nadir $CD4^+$ cell count, HIV RNA viral load at baseline and postbaseline, 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 at least 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 (IQR) [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 $CD4^+$ cell count was 221 cells/μl (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 at least 200 copies/ml and 61% of $CD4^+$ cell counts were more than 500 cells/μl.

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% confidence interval 1.10–1.25, $P < 0.001$). The OR for hepatitis C coinfection 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 with men; 1.71 (1.51–1.94, $P < 0.001$) for 12 years or less of education compared to those with more than 12 years of education; 1.35 (1.07–1.70, $P = 0.01$) for history of injection drug use (IDU); 1.31 (1.16–1.49, $P < 0.001$) for those with time-varying $CD4^+$ cell counts less than 350 cells/μl and 1.15 (1.05–1.26, $P = 0.002$) for time-varying $CD4^+$ cell counts between 351 and 500 cells/μl, as compared with $CD4^+$ cell counts more than 500 cells/μl. 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 Fig. 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 study participants increased by nearly

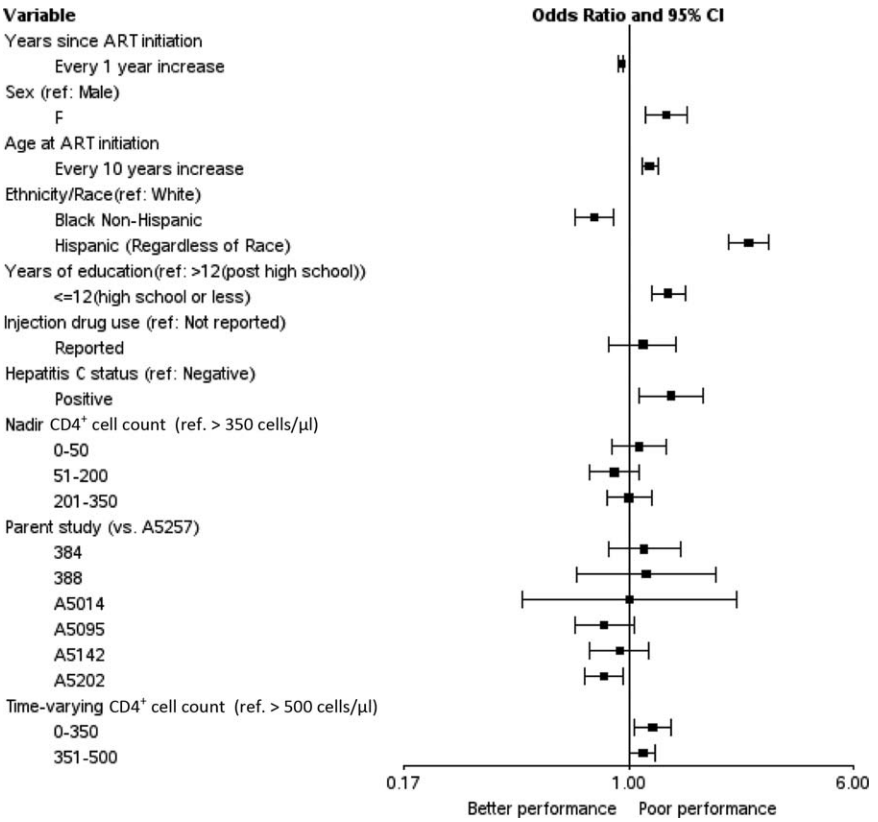

Fig. 1. Forest plot showing adjusted odds ratios and 95% CI for the association between risk factors and neurocognitive impairment. ART, antiretroviral therapy; CI, confidence interval. Forest plot showing adjusted odds ratios and 95% CI for the association between risk factors and neurocognitive impairment.

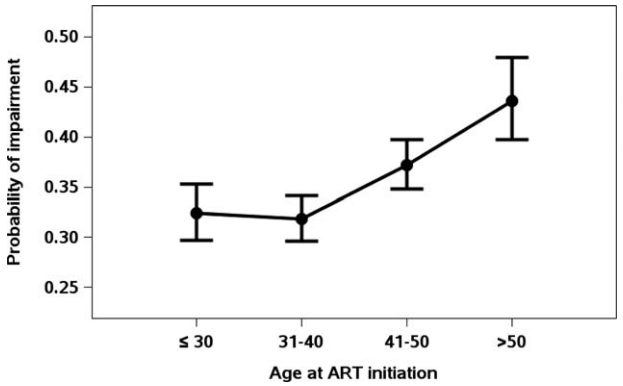

Fig. 2. Probability of cognitive impairment according to age decade at antiretroviral therapy initiation in the parent study. ART, antiretroviral therapy; CI, confidence interval.

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 fifth 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 $CD4^+$ cell count level less than 350 cells/μl [OR 1.21, (1.05–1.40), $P = 0.008$] and time-varying $CD4^+$ level between 351 and 500 cells/μl 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 IDU, 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 2 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 with 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-infected 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 central nervous system (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 coinfection 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 (nonnucleoside reverse transcriptase inhibitors) 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. As we used normative corrections for Hispanic ethnicity, and in the case of the HVLT-R, 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 ART. 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 HVLT-R, 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.

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Conflicts of interest

There are no conflicts of interest.

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