IMPACT OF ADVANCING AGE ON COGNITION IN HIV+ PERSONS ON A FIRST SUPPRESSIVE REGIMEN

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Background and Objectives

- Effective combination antiretroviral therapy (ART) extends the life of individuals with HIV
- The HIV+ population is aging, with more than 50% over age 50 years.
- While many individuals show neurocognitive improvement after ART initiation, HIV-associated neurocognitive disorders (HAND) can persist or occur de novo despite virologic suppression and immune recovery.
- Aging is a risk factor for HAND in untreated individuals.
- The impact of age on longitudinal changes in neurocognitive function after initiating a first ART regimen have not previously been examined in large cohorts.
- This study sought to compare changes in neurocognitive performance ≥ 2 years after ART initiation in older and younger individuals in a large cohort.

Methods

- The AIDS Clinical Trials Group (ACTG) Longitudinal Linked Randomized Trials (ALLRT) study was a prospective cohort of HIV+ individuals enrolled in randomized ART parent trials.
- Participants (n=3313) were ART-naïve individuals from 7 parent trials.
- Annual neurocognitive (NC) testing:
  - Trail making Test A
  - Trail making Test B
  - WAIS-R Digit Symbol subtest
  - Hopkins Verbal Learning Test (HVLT)
- Neurocognitive tests after 2 or more years of ART were analyzed.
- Global impairment = z score ≤ -2.0 SD on 1 test or ≤ -1.0 on 2 tests
- Uni- and multi-variable repeated measures regression models evaluated predictors of neurocognitive impairment
- Variables with p<0.10 eligible to enter multivariable models.
- Odds ratios adjusted for covariates with univariate p ≤ 0.10.

Results

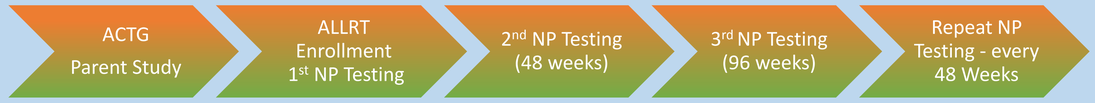
Table 1. Demographics and baseline characteristics, n=3313.

Parent study entry		Median (IQR) or N (%)
Age	Median	38 (31, 45)
	≤30	790 (24%)
	31-40	1,128 (34%)
	41-50	992 (30%)
	51-60	335 (10%)
	>60	68 (2%)
Nadir CD4 cell count (cells/µL)		221 (80, 324)
Years of education (>12 years)		2,055 (62%)
Injection drug use ever		235 (7%)
Hepatitis C Antibody (+)		258 (8%)

Table 2. HIV disease characteristics

At 1st HVLT date on or after 2 years of ART initiation	Median (IQR) or N (%)
HIV RNA (<200 copies/ml)	2,996 (91%)
CD4 cell count (0-350 cells/µL)	699 (21%)
CD4 cell count (351-500 cells/µL)	816 (25%)
CD4 cell count (>500 cells/µL)	1784 (54%)
Average NPZ4 Score	-0.23 (-0.83, 0.43)
HVLT impairment	1,402 (42%)
NPZ-4 impairment	1,284 (39%)

Timeline for ascertainment of predictors and outcomes



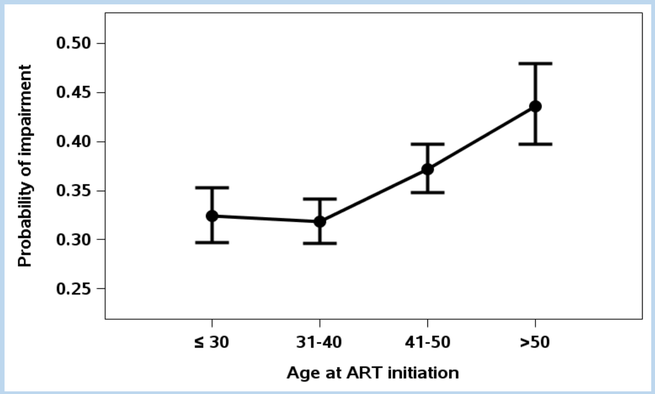


Fig 1. Probability of cognitive impairment according to age decade at parent study entry. Neurocognitive impairment rate is higher in older compared to younger individuals.

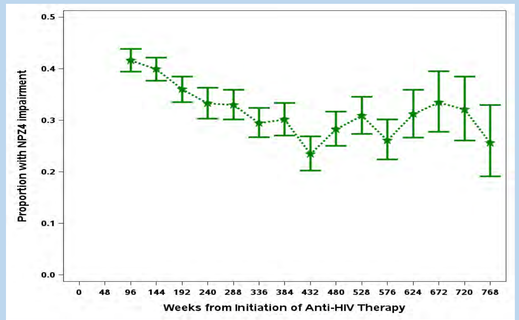
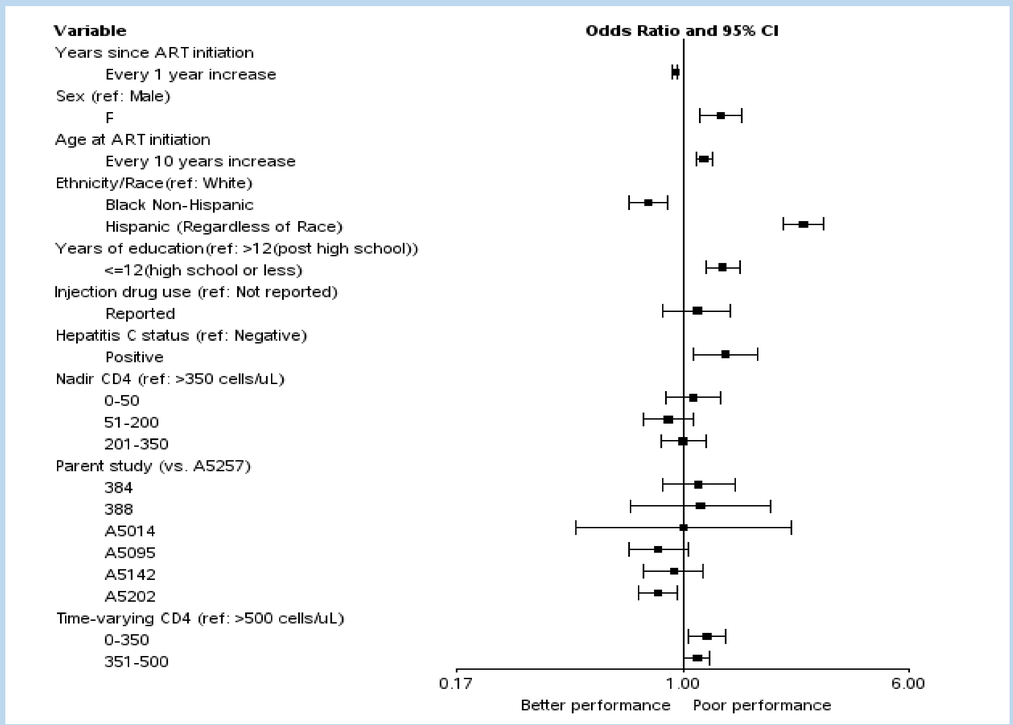


Fig 2. Neurocognitive Impairments by Week. NPZ4 impairment gradually decreased over time.

Fig 3. Forest plot showing adjusted odds ratios and 95 percent confidence intervals for the association between risk factors and neurocognitive impairment.



Additional non-significant covariates considered in univariate analysis were: ARV regimen type (PI + NNRTI; NRTI only; PI + NRTI; NNRTI + NRTI; PI + NRTI + NNRTI) cigarette smoking, stroke history, Hepatitis B Ag+, ARV adherence <100% vs 100%)

Results, continued

- Median follow-up duration after 2 years on ART was 3.5 (2.5, 5.4) years.
- Participants remained on ART at 97% of neuro-visits. Virologic suppression was maintained at 91% of follow-up visits.
- In the cohort as a whole, rates of neurocognitive impairment declined over time (**Fig 2**)
- In multivariable model the odds ratio for neurocognitive impairment increased 1.18 (95% CI 1.11, 1.26) for each decade of older age (**Fig 3**)
- Inspection of a plot of the probability of neurocognitive impairment according to age revealed an inflection after 31-40 years (**Fig 1**)
- HCV co-infection was significantly associated with poorer neurocognitive outcomes
- No significant association of initial ART drug class with neurocognitive impairment
- Multivariable-adjusted odds ratios for other predictors of neurocognitive impairment are demonstrated in the Forest plot (**Fig 3**)

Conclusions, Limitations

- In the context of long-term ART (2 or more years after starting initial treatment), older age was a significant risk factor for neurocognitive impairment
- Age-related neurocognitive impairment was seen despite continued virologic suppression in most and despite neurocognitive improvement (lower impairment rate at later follow-up visits) in the cohort as a whole.

<u>Potential causes of age-related neurocognitive impairment</u>

- ART-related adverse effects of common age-related comorbidities (diabetes, hypertension, hyperlipidemia)
- Greater CNS toxicities of ART in older versus younger participants

<u>Limitations</u>

- Although neurocognitive test scores are adjusted for age, we did not study contemporaneous HIV negative individuals

Future Directions

- 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 in order to focus treatment and management on the most important aspects.

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