

# Older Age and Neurocognitive Function in the Multi-Center AIDS Cohort Study

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## Abstract

**Background:** Despite increasing numbers of research studies on aging, HIV disease and cognitive function, the extent to which HIV disease moderates the relationship between chronological age and cognitive functioning has remained unclear. The purpose of the present study was to examine this question in a large sample with extensive, longitudinal follow-up and a high level of control for other factors known to influence cognitive function.

**Methods:** Data from 5,086 participants in the Multicenter AIDS Cohort Study were used in this study; 2,278 were HIV infected (20/47 visits), and 2,808 were HIV seronegative (27,499 visits). Dependent variables included measures of cognitive functions from five domains: executive functions, information processing speed, working memory, episodic memory, and motor functions. Covariates in the models included ethnicity, education, household income, body mass index, body weight, depressed mood, antiretroviral therapy period, diabetes, hypertension, psychotropic medication use, and measures of pain and fatigue. History of infection with hepatitis C and B viruses were controlled for, as were a history of cigarette smoking, alcohol/substance use, and the duration of HIV infection (in a sub-sample).

**Results:** Older age was significantly associated with poor performance in all cognitive domains, after controlling for HIV disease stage. HIV Stage was significantly associated with NP outcome in all cognitive domains, independent of the effects of age. Clinical AIDS was associated with poorer performance in every case. Most important was the observation of a significant interaction between age and HIV disease stage in the episodic memory and motor function domains, after controlling for duration of HIV infection. Longer duration of HIV infection was associated with better function in each of these domains.

**Conclusion:** Based on these longitudinal data, we tentatively conclude that HIV disease severity shows a synergistic effect on the association between aging and cognitive function in the areas of episodic memory and motor function. The positive association between duration of infection and these cognitive functions suggests the possibility of a survivor bias, which needs to be addressed in all studies of this kind.

## Introduction

From the early studies of neurocognitive impairment (NCI) in HIV infection, it was reported that information processing speed, verbal memory, and motor function were the domains most likely to be impaired. Subsequent studies showed that impairment in information processing speed and verbal memory predicted earlier mortality in HIV+ persons who were predominantly otherwise asymptomatic. For the most part, the initial studies of NP impairment in HIV infection did not focus specifically on executive function and working memory (WM). Yet, these domains were later identified to be frequently adversely impacted by HIV infection as well related to the frontal lobes, such as with the basal ganglia. As with HIV infection, it has long been noted in the general population that there is considerable evidence of age-related changes in cognition occurring as early as 50 years of age, including slowing in information processing speed as measured by choice reaction time (RT), incompatible stimulus-response RT, and other complex speeded tasks. In the verbal memory domain, declines have likewise long been noted with aging ( $\geq 50$  years of age) in the general population. Since age-related differences are thought to be more quantitative than qualitative, the combination of aging and HIV infection was expected to be associated with differentially greater NP impairment than either factor taken alone. Of further interest, deficits have been reported in both HIV infected persons and older persons in working memory and executive functions. The hypothesis of this study was that there are age-associated differences in NP performance across the specific domains of attention, information processing speed, episodic memory, executive functions, working memory, and motor functions – when analyzed in the long-term, longitudinal study design of the MACS pre-highly active antiretroviral therapy (HAART) vs. post-HAART, with controls.

## Methods

**MACS Cohort. Inclusion Criteria:** A prospective longitudinal study of homosexual and bisexual men with and without HIV infection. The independent variables 1) HIV disease stage (A=1, B=2, or C=3), as per a CDC staging algorithm developed specifically for the MACS database, vs. HIV seronegative status (=0); 2) continuous age; and 3) HIV disease stage x age interaction.

### The NP Outcome Variables

**Attention / Information Processing Speed Domain.** The Symbol Digit Substitution Test measures visuospatial and motor processes (total raw score of correct entries) and Simple and Choice RT are assessed using the CaLpac reaction time test. For Complex Reaction time, subjects are asked to press a key only when they see two of the same number in sequence, for example, if they see the number 7 followed by a second occurrence of the number 7, adding a more complex element of memory, since the subject must learn the number that was seen.

**Episodic Memory Domain.** Verbal Episodic Memory Rey Auditory Verbal Learning Test (RAVLT). The average number correct over the first five learning trials (1 through V) of recall of 15 of words read aloud to the subject. Visual Episodic Memory Rey-Osterrieth Complex Figure. The subject is first instructed to copy this complex figure. This trial is followed by both immediate and 20-minute delayed recall trials.

**Executive Function.** The Trail Making Test (TMT) Part B involves alternatingly connecting consecutively numbered and lettered circles, which requires the shifting of cognitive sets (total time). The Stroop Color Word Task consists of three 100-item blocks of color patches, color names printed in black ink, and color names printed in incongruously colored ink. Time (sec.) to name the ink colors in the incongruent condition where the ink colors and color words conflict is referred to as the “Stroop Interference Measure”.

**Motor Functions.** The Grooved Pegboard Task measure here is the time (sec.) required to place small metal pegs into holes as quickly as possible with the non-dominant hand.

**Working Memory** is assessed with another RT Task in which subjects are asked to press a key only when they see two numbers in sequence (e.g., 10-10-10-10). For example, if they see the number 7 followed by the number 7, followed by the number 7, and so on.

**Exclusion criteria:** Acute, systemic opportunistic infection or tumor requiring chemotherapy; CNS infections or tumors associated with HIV infection; presence of non-HIV-associated neurological disease (e.g., history of epilepsy; non-correctable visual or hearing impairments; history of prior transient ischemic attack or cerebrovascular accident; Alzheimer’s disease; or multi-infarct dementia); history of major psychiatric disorder (i.e., schizophrenia; schizoaffective disorder; bipolar affective disorder); mental retardation; learning disorders; motor skill disorder; depressive behavior; attention deficit disorder; or pervasive personality disorder; any other condition that subjects would be unable to complete the study; severe chronic obstructive pulmonary disease; severe congestive heart failure; unstable angina; myocardial infarction (within the prior 6 months); daily use of systemic steroids (corticoids or anabolic); hepatic failure; renal failure; use of immunosuppressant therapies; or participation in trials of currently non-FDA-approved antiretroviral medications.

**Control variables:** ART time period was defined as the pre-HAART era, any time point until 1/96 and the post-HAART era; ethnicity (Caucasian or non-Caucasian); educational level (< HS, HS graduate, some college, college degree, or post-graduate); current annual income (< \$20,000, \$20,000- $<$  \$40,000, center for Epidemiological Studies of Depression Scale (CES-D) score; fatigue self rating over past two weeks; report of any pain (headache, joint, muscle, back, or other); subjective memory impairment; use of antiepileptic drugs; use of antipsychotic medications; use of antidepressants; use of cognitive health enhancer, hepatitis (C and B)); change in total body weight from prior MACS visit; % body mass index (BMI) in kg/m<sup>2</sup>; and alcohol and psychoactive substance use (marijuana/heroin and “poppers” only have sufficient variation to warrant inclusion) – captured by a categorical frequency variable. Medical disease status was not used in this analysis as a statistical control variable.

Known Duration of Positive HIV Serostatus: Time since first testing HIV seronegative to time of MACS study enrollment (for seroprevalent persons). ARV adherence, CNS Penetration Effectiveness (CPE), CD4 Cell Nadir, and plasma viral load measures could not be used, as they are meaningful specifically only for HIV+ persons.

All qualifying visits were included from the beginning of NP testing in the MACS. We analyzed four separate sets of models. Model 1 was the “Full Model on the Entire Sample” with independent variable predictors for age, CDC clinical disease stage, and an age x CDC disease stage interaction term as well as control variables. In Model 2 we used a “Reduced Model on the Entire Sample”, which eliminated all non-significant control variable predictors as a confirmatory model. Model 3 was the “Full Model adding Time since Seroconversion on a Sub-Sample”. Model 4 was the “Full Model without Time since Seroconversion on the Seroconversion Sub-Sample as a second confirmatory model to eliminate factors related to the sub-sample.

## Demographic Characteristics

Sample size at baseline	HIV- =200	HIV+ =50	HIV- =50	HIV+ =50	P value	Overall	
Color at baseline	1984 (47.0%)	1576 (60%)	209 (70%)	1856 (75%)	**	3489 (69%)	
1987	15 (0.4%)	208 (28%)	11 (4%)	187 (6%)		433 (9%)	
2001	15 (0.4%)	537 (22%)	47 (18%)	528 (21%)		1160 (23%)	
N Visits	1228	1732	682	2070			
Color at visit	1984 (22.1%)	1449 (66%)	616 (89%)	1628 (77%)	**	3612 (71%)	
1987	101 (0.9%)	242 (12%)	23 (1%)	116 (6%)		382 (9%)	
2001	107 (0.9%)	371 (22%)	409 (7%)	319 (16%)		794 (17%)	
Baseline age	54.0 (1.4)	53.3 (0.6)	55.1 (2.6)	56.2 (1.7)	**	57.2 (1.8)	
Age at visit	64.5 (4.1)	58.4 (6.2)	56.4 (7.5)	61.3 (6.5)	**	62.4 (5.2)	
Baseline education	less than HS	6 (0%)	13 (0%)	11 (4%)		26 (0%)	
HS	181 (6%)	327 (18%)	29 (11%)	248 (12%)		489 (10%)	
Some College	520 (10%)	741 (39%)	36 (13%)	605 (29%)		1161 (23%)	
College degree	13 (0.1%)	44 (2.1%)	3 (1.1%)	44 (2.1%)		100 (2.1%)	
College plus	42 (0.7%)	53 (2.4%)	14 (0.5%)	83 (3.9%)		154 (3.0%)	
Missing	11 (0.1%)	4 (0.0%)	1 (0.0%)	11 (0.0%)		26 (0.0%)	
Race	White, non-Hispanic	71 (0.9%)	1456 (67%)	223 (80%)	1918 (78%)	**	3672 (75%)
Other	401 (9%)	707 (33%)	44 (16%)	612 (24%)		1412 (28%)	
Missing	1 (0.0%)	1 (0.0%)	1 (0.0%)	1 (0.0%)		4 (0.0%)	
Baseline income	< \$20,000	31 (0.7%)	477 (22%)	39 (13%)	488 (19%)	**	1059 (20%)
\$20,000-\$39,999	21 (0.2%)	276 (13%)	46 (17%)	282 (13%)		499 (10%)	
\$40,000-\$59,999	27 (0.2%)	201 (9%)	36 (13%)	237 (11%)		391 (8%)	
Refused to answer	3 (0.0%)	56 (2%)	10 (4%)	52 (2%)		119 (2%)	
Missing	11 (0.1%)	173 (8%)	21 (8%)	193 (9%)		288 (6%)	
SP months from enrollment	23.3 (0.8)	24.1 (2.4)	24.1 (2.4)	24.1 (2.4)		25.9 (2.5)	
Months from SC	65.3 (4.6)	33.4 (2.6)	33.4 (2.6)	33.4 (2.6)		35.1 (3.2)	
From known or imputed SC	71.1 (4.4)	84.4 (8.3)	84.4 (8.3)	84.4 (8.3)		81.2 (7.1)	
Visits by age	Before 1.9/96	641 (21%)	980 (35%)	2231 (31%)	1406 (68%)	**	2674 (50%)
1.9/96-present	2484 (79%)	792 (44%)	460 (78%)	651 (32%)		2143 (44%)	
CDC clinical disease stage	A HIV+ seronegative	41 (0.8%)	161 (4.9%)	2 (0.0%)	163 (0.8%)	**	198 (0.4%)
B HIV+ seronegative	10 (0.1%)	161 (4.9%)	1 (0.0%)	162 (0.8%)		172 (0.4%)	
C HIV+ seronegative	4 (0.0%)	16 (0.0%)	1 (0.0%)	17 (0.0%)		18 (0.0%)	
C AIDS	10 (0.1%)	16 (0.0%)	1 (0.0%)	17 (0.0%)		18 (0.0%)	
CD4 count at visit	4182 (241.7)	404.2 (237.1)	418.2 (241.7)	404.2 (237.1)	**	409.8 (236.2)	
CD4 count at visit	530 (28.4)	491.1 (263.6)	491.1 (263.6)	491.1 (263.6)	**	491.9 (263.8)	
Undetectable HIV RNA at visit	No	197 (5.7%)	692 (4.9%)	692 (4.9%)	692 (4.9%)	**	849 (15.4%)
Yes	1386 (44%)	7623 (44%)	7623 (44%)	7623 (44%)		10809 (44%)	
Missing	173 (0.8%)	2407 (16%)	2407 (16%)	2407 (16%)		3088 (15%)	
Dabson	No	2964 (67%)	1687 (77%)	699 (96%)	2004 (78%)	**	4659 (97%)
Yes	179 (0.8%)	171 (1%)	16 (2%)	15 (1%)		164 (3%)	
Missing	42 (1%)	306 (2%)	7 (1%)	426 (2%)		617 (12%)	
Hypertension	No	1473 (46%)	1099 (57%)	515 (66%)	1279 (62%)	**	2675 (50%)
Yes	164 (2.5%)	483 (24%)	387 (51%)	552 (27%)		1407 (31%)	
Missing	58 (2%)	227 (11%)	17 (2%)	226 (11%)		478 (10%)	
Psychotropic drugs	No	2572 (62%)	1510 (68%)	889 (85%)	1815 (88%)	**	4186 (87%)
Yes	551 (10%)	2161 (12%)	1022 (15%)	2465 (12%)		4919 (10%)	
Missing	16 (0.0%)	1 (0.0%)	1 (0.0%)	1 (0.0%)		4 (0.0%)	
HIV	No	286 (0.9%)	1973 (22%)	675 (96%)	1988 (97%)	**	4524 (94%)
HIV+	Yes	319 (10%)	1379 (18%)	287 (41%)	717 (34%)	**	2022 (40%)
No	288 (0.8%)	1581 (66%)	642 (91%)	1883 (90%)	**	4487 (90%)	
Yes	44 (1.4%)	1481 (10%)	39 (5%)	724 (34%)	**	3199 (7%)	
Missing	11 (0.0%)	1 (0.0%)	1 (0.0%)	1 (0.0%)		4 (0.0%)	
Pain	No	2484 (77%)	1489 (68%)	542 (81%)	1872 (91%)	**	4150 (87%)
Yes	713 (21%)	2463 (14%)	129 (19%)	185 (9%)		638 (13%)	
Fatigue	No	2715 (67%)	1823 (68%)	645 (94%)	1972 (96%)	**	4421 (87%)
Yes	399 (10%)	230 (12%)	37 (5%)	84 (4%)		364 (8%)	
Missing	11 (0.0%)	1 (0.0%)	1 (0.0%)	1 (0.0%)		4 (0.0%)	
Alcohol	None or occasional	1005 (19%)	5385 (51%)	1881 (28%)	4295 (24%)	**	12522 (26%)
Used	2065 (49%)	1193 (9%)	4099 (72%)	1627 (78%)	**	3445 (72%)	
Missing	30 (1%)	74 (0.4%)	52 (1%)	74 (0.4%)		230 (0.5%)	
Cannabis	None or occasional	2383 (56%)	1220 (71%)	928 (87%)	1636 (80%)	**	3667 (77%)
Used	97 (0.2%)	465 (2%)	84 (12%)	352 (16%)	**	604 (12%)	
Missing	72 (2%)	456 (7%)	70 (1%)	280 (1%)		878 (2%)	
Poppers	None or occasional	243 (7%)	1380 (6%)	846 (86%)	1740 (85%)	**	3962 (86%)
Used	76 (2%)	298 (1%)	92 (10%)	278 (13%)	**	712 (15%)	
Missing	7 (0.0%)	58 (0.3%)	6 (0.1%)	45 (0.2%)		117 (0.2%)	

**Statistical Analyses** were by linear mixed models for longitudinal data. Each model included a random subject effect to account for repeated measurements on the same subjects. Analysis of residuals was used to check the required assumptions of normally distributed errors with constant variance; if necessary, outcome variables were log transformed to stabilize the variance or produce a more normal error distribution.

## RESULTS

Predictor:	Full Model Without Time Since Seroconversion					Model With Time Since Seroconversion				
	Information Processing	Speed	Episodic Memory	Executive Function	Motor	Information Processing Speed	Episodic Memory	Executive Function	Motor	Working Memory
Age	-0.399 (0.025)**	-0.335 (0.030)**	-0.343 (0.025)**	-0.743 (0.044)**	-0.241 (0.042)**	-0.404 (0.025)**	-0.318 (0.030)**	-0.326 (0.025)**	-0.743 (0.044)**	-0.246 (0.043)**
HIV disease stage										
Overall test p	.01	.01	<.001	<.001	<.001	<.001	.005	<.001	<.001	.013
AIDS	-0.996 (0.747)	-1.08 (0.828)	-0.792 (0.772)*	-1.196 (0.8*)	-0.698 (1.184)**	-2.695 (0.911)**	-1.772 (1.022)*	-5.356 (0.942)**	-6.478 (1.513)**	-4.782 (1.460)**
Symptomatic	0.812 (0.451)**	0.628 (0.526)	0.558 (0.483)	0.659 (0.750)	-1.629 (0.726)**	0.416 (0.574)	-0.031 (0.702)	-0.994 (0.595)**	1.364 (1.039)	-1.677 (0.967)*
Asymptomatic	0.898 (0.452)**	-0.092 (0.528)	0.855 (0.484)**	-0.036 (0.750)	-1.890 (0.729)**	0.451 (0.568)	-0.990 (0.696)	-0.561 (0.590)	0.600 (1.022)	-1.850 (0.958)**
AGE*HIV Stage										
Overall test p	<.001	.063	<.001	<.001	<.001	.02	.12	.02	.21	.02
Age*AIDS	0.212 (0.073)**	0.061 (0.092)	0.385 (0.075)**	-0.053 (0.137)	0.003 (0.131)	0.109 (0.088)	-0.162 (0.105)	-0.031 (0.091)	0.060 (0.156)	0.092 (0.150)
Age*Symptomatic	0.099 (0.033)**	0.075 (0.042)**	0.335 (0.033)**	-0.145 (0.062)*	0.146 (0.058)*	0.043 (0.055)	-0.103 (0.064)	-0.065 (0.057)	-0.126 (0.094)	0.293 (0.090)*
Age*Asymptomatic	0.148 (0.033)**	0.114 (0.042)**	0.331 (0.033)**	-0.021 (0.062)	0.224 (0.059)**	0.023 (0.055)	0.010 (0.065)	-0.112 (0.057)*	0.068 (0.094)	0.376 (0.077)**
Time Since Seroconversion										
Overall test p						0.235 (0.055)**	0.276 (0.065)**	0.586 (0.055)**	0.020 (0.096)	0.038 (0.091)
Ethnicity										
Other vs. White, non-Hispanic	-8.532 (0.612)**	-9.989 (0.679)**	-13.581 (0.669)**	-12.096 (0.950)**	-4.169 (0.936)**	-7.556 (0.734)**	-8.055 (0.807)**	-12.403 (0.779)**	-10.672 (1.149)**	-4.364 (1.156)**
Education										
Some college	8.281 (0.781)**	7.688 (0.838)**	10.396 (0.856)**	5.899 (1.195)**	1.044 (1.182)	7.129 (0.920)**	6.799 (1.010)**	9.204 (0.975)**	5.125 (1.422)**	2.171 (1.446)
College degree	10.384 (0.832)**	10.638 (0.924)**	12.331 (0.911)**	7.592 (1.286)**	1.994 (1.277)	10.949 (0.942)**	10.022 (1.034)**	11.303 (0.999)**	7.466 (1.455)**	2.734 (1.480)**
Post-Graduate	11.304 (0.811)**	12.005 (0.923)**	12.366 (0.867)**	8.183 (1.284)**	2.197 (1.275)**	11.004 (0.930)**	11.538 (1.038)**	12.502 (0.975)**	8.884 (1.438)**	3.015 (1.483)**
Income										
\$20,000 - \$40,000	0.683 (0.259)**	0.902 (0.311)**								