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Neuropsychological Test Performance Before and After HIV-1 Seroconversion: The Multicenter AIDS Cohort Study

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Abstract

Objectives—To compare neuropsychological test performance before and after HIV-1 seroconversion in order to identify possible acute changes in psychomotor speed, memory, attention, and concentration secondary to seroconversion.

Design—Mixed effects models to examine longitudinal neuropsychological test data.

Methods—We conducted a nested cohort study of 362 male HIV-1 seroconverters enrolled in the Multicenter AIDS Cohort Study. We used linear mixed models with random subject effects to

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Ms. Vo participated in the study design, data acquisition, data analysis, data interpretation, writing, and editing of the manuscript.

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compare repeated neuropsychological test outcomes from 5 years before seroconversion to 2 years after seroconversion on the Trail Making Test (Parts A & B), Symbol-Digit Test, Grooved Pegboard (dominant and non-dominant hands), Stroop Color-Interference Test, Rey Auditory Verbal Learning Test, and the CalCAP Reaction Time Test.

Results—We found no significant changes in the time-dependent score after seroconversion for the majority of neuropsychological tests used in the Multicenter AIDS Cohort Study. There was a significant change in time trend after seroconversion on part B of the Trail Making Test ($p=0.042$) but the difference only represented a 2% decrease in performance. We found the following characteristics to be associated with worse neuropsychological test performance: lower education levels, history of depression, older age, and no previous neurocognitive testing ($p<.05$).

Conclusion—Our results suggest that despite a 50% decrease in CD4 cell count immediately following infection, HIV-1 does not appear to have a measurable effect on psychomotor or complex cognitive processing for up to 2 years following infection, using this set of neurocognitive measures.

Keywords

HIV; neuropsychological test; seroconversion; CD4; neurocognition

Introduction

Most studies seeking to establish the optimal time to begin antiretroviral treatment (ART) have focused on the association of decreasing CD4 levels with immunological decline and patient survival (Ellis *et al*; Kitahata *et al*, 2009; Vivithanaporn *et al*). Few papers have focused on changes in CD4 and neuropsychological decline. Furthermore, most neuropsychological studies have examined late stage HIV and the effects of ART on the central nervous system (CNS) (Bhaskaran *et al*, 2008; Childs *et al*, 1999; Gazzard *et al*; Kanmogne *et al*; Robertson *et al*). Here we compare test scores pre- and post-seroconversion (SC) to examine whether there are acute neuropsychological effects soon after seroconversion.

Whether neuropsychological changes specifically attributable to the virus occur in early stages of HIV-infection has not been definitely determined (Marcotte *et al*, 2003; McArthur *et al*, 1989; Miller *et al*, 1990; Selnes *et al*, 1990; Spudich *et al*; Spudich *et al*, 2005). Although it is known that HIV-1 may enter the brain early after seroconversion, the effects of early infection on cognitive functioning are still not entirely clear (Spudich *et al*; Spudich *et al*, 2005). Studies of neuropsychological changes in early HIV have reported conflicting findings (Cole *et al*, 2007; Marcotte *et al*, 2003; McArthur *et al*, 1989; Miller *et al*, 1990; Selnes *et al*, 1990). A major limitation of these studies to detect significant early neuropsychological changes associated with seroconversion may be small sample sizes and limited pre-SC neuropsychological test data.

Accurate estimates of neuropsychological decline in otherwise healthy untreated patients with CD4 > 500 cells/ μ L are not available or limited in sample size (Marcotte *et al*, 2003; Selnes *et al*, 1990). The MACS data presented here are from seroconverters and represent one of the largest databases examining healthy, untreated patients with CD4 > 500 cells/ μ L. Using MACS longitudinal neuropsychological tests pre- and post-SC we created mixed models to determine if there is a threshold CD4 cell count at which the risk of neuropsychological decline increases.

Methods

The Multicenter AIDS Cohort Study began in 1984 to study the natural history of AIDS, identify risk factors for occurrence and clinical expression of the infection, and establish a repository of biologic specimens for future study (Kaslow *et al*, 1987). The MACS began the examination of longitudinal neuropsychological test performance in 1986 to study the effects of HIV/AIDS on the brain and central nervous system (Miller *et al*, 1990). The Trail Making and Symbol-Digit Modalities Tests are administered every six months and the full battery of neuropsychological tests is performed every two years.

We conducted a nested cohort study examining 431 MACS participants out of 580 seroconverters who had a seroconversion window of less than or equal to 1.5 years. Neuropsychological test data were collected over a period of 7 years, 5 years before seroconversion and 2 years after, yielding a maximum of 1,885 observations. Time was anchored at seroconversion (time pre-SC was negative and time post-SC was positive). A linear mixed model with random subject effects accounted for correlation among repeated test scores on the same subject. Categorical covariates in the models included education, race, number of previous tests, drug use, depression as defined by the Center for Epidemiologic Studies Depression Scale (CES-D), and current CD4 cell count/ μ L category as defined by the Centers for Disease Control and Prevention. Participants who reported the use of marijuana, poppers, crack, cocaine, uppers, injectable drugs, or other recreational drugs within 2 years of a visit were classified as positive for history of drug use. Participants who reported a score of greater than or equal to 16 on the CES-D were reported as depressed per CES-D guidelines. Age at 2 years pre-SC or first visit (if less than 2 years) was used as a time-fixed covariate in the model. Continuous covariates in the models included age (centered by subtracting the mean (35 years) from each participants age), duration on ART (years), and time trend (years) before and after SC.

The analyses used all person-visits for 3 primary outcomes: 1) Trail Making, part A; 2) Trail Making, part B; 3) Symbol-Digit raw score. Secondary outcomes included all person-visits from the following tests: 1) Grooved Pegboard, dominant hand; 1) Grooved Pegboard, non-dominant hand; 3) Stroop Task, interference; 4) Stroop Task, color naming; 5) Stroop Task, word reading; 6) Rey Auditory Verbal Learning Test, sum of trials 1–5; 7) CalCAP Mean Simple Reaction Time, task 1; 8) CalCAP Mean Complex Reaction Time, task 3; 9) CalCAP Mean Complex Reaction Time, task 4. The Trail-Making and Symbol-Digit Modalities Tests were designated as primary outcomes due to the more extensive data available for these tests. The secondary outcomes were used to further evaluate any associations found between the primary outcomes and predictors. With the exception of the Symbol-Digit and Rey Auditory Verbal Learning Tests, all test outcomes were log₁₀-transformed to stabilize the variance and to better approximate a normal distribution for our mixed linear models.

Sensitivity analyses were performed to examine the role of nadir CD4, HIV RNA viral load, and development of dementia in neurocognitive changes. We applied the same linear mixed model format used in our previous analyses for all sensitivity models. To examine the effects of nadir CD4 we replaced CD4 cell count category at the current visit with a variable to represent the time-varying nadir CD4 cell count. Prior to seroconversion, the time-varying nadir CD4 cell count was equal to the average CD4 count over all HIV negative visits. After seroconversion, the time-varying nadir CD4 cell count was equal to the lowest CD4 count prior to the current visit or nadir CD4 cell count (if nadir CD4 cell count occurred prior to the current visit).

Associations between test performance and viral load were examined for the post-SC period only. For this model, we used current CD4 levels, other variables from previous models, and the log10-transformed viral load for the first two years after seroconversion. As viral load could not be represented in our pre-SC timeline, a more thorough analysis of viral load in relationship to seroconversion and cognitive change was not possible.

Lastly, we examined neurocognitive test performance around the time of seroconversion among those who later developed dementia and the characteristics of persons lost-to-follow-up between the first and second year after seroconversion. Dementia diagnoses were verified by medical records or reported by trained clinicians in the MACS. Forty two cases of probable or possible dementia were reported among our participants but all diagnoses occurred 3 years or later after seroconversion.

Box-and-whisker plots were used to assess acute changes in CD4 cell counts, Trail Making (A&B), and Symbol-Digit outcomes over time. Residual plots from the mixed models were examined to check for normality of the distributed errors with constant variance. All statistical analyses were performed using SAS version 9.2 (SAS Institute Inc, Cary, North Carolina). Use of these routinely collected, de-identified, research data was approved by the ethical review committees at each site of the Multicenter AIDS Cohort Study.

Results

Of the initial 431 men, 69 men had incomplete neuropsychological tests and were excluded, resulting in 362 eligible participants. The participants contributed a maximum of 1,885 person-visits to each of our primary outcomes- Trail Making A and B and the Symbol-Digit Modalities Tests. Baseline characteristics were defined 2 years prior to seroconversion or at first visit for those who had less than 2 years of visits prior to seroconversion, Table 1. The mean age at baseline for our study population was 35 years (SD=7.9). The participants were primarily white, non-Hispanic males (80.9%, n=293) who had completed at least high school education (87.2%, n=312).

Among the majority of neuropsychological tests evaluated, we found no significant changes in the time-dependent score after seroconversion while controlling for age, duration on ART, years pre- and post-seroconversion, previous tests, education, race, current CD4 count, depression, and drug use, Table 2. There was a significant change in time trend after seroconversion on part B of the Trail Making Test ($p=0.042$) but the difference represented only a 2% decrease in performance.

The results of our longitudinal mixed effects models on the primary measures of Trail Making and Symbol-Digit are shown in Table 3. Lower neuropsychological test performance was associated with older age, lower education levels, and no previous neurocognitive testing ($p<0.05$). Depression was associated with worse performance on Trail Making, part B and Symbol-Digit Test. Duration on ART was associated with worse performance on the Symbol-Digit Test only ($p<0.05$). Blacks and Hispanics scored worse on our primary test outcomes when compared to non-Hispanic whites ($p<0.05$). Our mixed effects models of secondary outcomes also found lower scores to be associated lower education levels and having no previous test experience. History of drug use was associated with lower scores on the word reading and color naming conditions of the Stroop Task ($p<0.05$).

We found no associations between contemporaneous CD4 cell levels and test outcomes. Median CD4 cell counts dropped dramatically, from a pre-SC median of 1,000 cells/ μ L to slightly above or at 500 cells/ μ L post-SC. CD4 counts were relatively stable both before seroconversion and after the initial drop, Figure 1.

Sensitivity Models

When using nadir CD4 to predict test scores we found no significant changes in the time-dependent score after seroconversion. We did find a 13.8% decrease in performance among persons with low CD4 cell count levels (<200 cell/ μ L) when compared to persons with higher CD4 cell count levels on Trail Making, part A ($p=0.014$) but similar results were not reported in other tests. Other predictors such as the number of previous tests, race, depression, and education showed similar associations with test outcomes as in our previous models. HIV RNA viral load (log10-transformed) was not associated with any neuropsychological test outcomes for the first 2 years after seroconversion.

Finally, among persons who were later diagnosed with dementia ($n=42$) we found no significant changes in the time-dependent score after seroconversion. Our model of 163 person-visits showed similar associations as those reported earlier. Furthermore, we did not find discernible differences between participants lost-to-follow-up ($n=22$) and participants that remained in the study during the second year after seroconversion.

Discussion

Despite a 50% decrease in CD4 cell count immediately following HIV-1 infection, participants in the MACS did not demonstrate decreased psychomotor speed or complex cognitive processing within 2 years following HIV-1 infection. Neither the median test scores nor the CD4 cell count levels (except at seroconversion) changed substantially over time. Our data are consistent with previous research that has shown asymptomatic HIV-positive patients generally do not have clinically significant impairments in cognitive performance (Chang *et al*, 2002; Llorente *et al*, 1998). The observed stability of the overall test performance may be attributable to practice effects (Atkinson *et al*; Zalonis *et al*, 2008) but we controlled for this in our models by including the number of previous tests taken. The protective effect of ART may also have played a role in our results but duration of ART use was included in our models and only 5.1% of participants had initiated ART by the second year after seroconversion and ART duration was negatively associated with Symbol-Digit Test performance.

We found the following characteristics to be associated with lower neuropsychological test performance: older age, lower education levels, depression, and having no previous neuropsychological test experience. Blacks and Hispanics performed more poorly on the full battery of tests when compared to non-Hispanic whites, but non-Hispanic whites constituted the majority of our study population (80.9%). Our findings are consistent with results from previous studies that have reported age, education, and depression as major contributors to neuropsychological performance (Crimmins *et al*; Schmitter-Edgecombe *et al*).

The role ART may have in preventing or reversing neurocognitive decline caused by HIV-1 infection has been explored in previous literature (Gelbard *et al*; Sacktor *et al*, 1999; Tozzi *et al*, 1999). Recent findings regarding neurocognitive decline suggest, however, that neurologic damage caused by changes in declining CD4 levels may be permanent and sustained rather than acute and reversible (Becker *et al*). We modeled the effects of changes in both current and nadir CD4 cell count levels in predicting neurocognitive test performance. Consistent with our first model of CD4 cell count levels at the current visit, we found no associations between nadir CD4 cell count levels and neurological test outcomes. Only one measurement of neurocognitive functioning, Trail Making, part A, showed an association between nadir CD4 cell count levels and lower cognitive test performance. This result may suggest that some areas of the brain may be more likely to sustain injury during periods of severe immunosuppression or, depending on the severity of immunosuppression,

performance on the various neuropsychological tests may be impacted differently. Further research is needed to confirm these results.

The goal of our study was to compare neuropsychological test changes before and after seroconversion among participants in the MACS. To our knowledge this analysis provides the longest timeline of neuropsychological test performance data among HIV-infected participants before infection. In order to capture this time frame for the largest sample of seroconverters, we were limited in the breadth of data available to explain any observed neuropsychological decline. Specifically, our study did not account for the effects of traumatic brain injuries and diagnoses of peripheral nervous system (PNS) related deficits such as peripheral neuropathy (Becker *et al*; Llorente *et al*, 1998). These variables were not collected on all participants, particularly in the early years of the MACS, and inclusion would have significantly reduced the number of available participants. We further examined persons who later developed dementia, however, to explore whether these participants performed differently on neuropsychological test performance around the time of seroconversion. Our sub-analyses further confirmed that there was no change in neuropsychological test performance around the time of seroconversion in the MACS.

The presence of detectable HIV viral load in cerebrospinal fluid in both animal and human models have shown that increased viral load is associated with changes in the brain that could negatively impact cognitive functioning (Ernst *et al*, 2009; Zink *et al*, 1999). As viral load could not be represented in our pre-SC timeline, a more thorough analysis of viral load in relationship to seroconversion and cognitive change was not possible. We did examine the effects of viral load in our sensitivity analyses of post-SC data but found no associations with neuropsychological test performance, consistent with results from other studies (Robertson *et al*).

Finally, a recent cross-sectional study by Becker, et al. found asymptomatic HIV-infected patients who receive highly active antiretroviral therapy (HAART) had measurable atrophy in subcortical brain structures when compared to HIV negative controls that may result in cognitive impairment (Becker *et al*). The authors concluded that damage to the CNS prior to the initiation of HAART may improve with ART/HAART initiation but may not return to normal. Our results show that a dramatic decrease in CD4 cell count levels did not affect common behavioral measures of neurocognitive performance and thus, a dramatic decline in CD4 count may not cause significant cognitive impairment in early stage HIV-1 infection. The study by Becker et al. raises the possibility that the behavioral effects of HIV may express themselves at a slower rate than the anatomical effects of HIV. We recommend further research combining MRI, cerebrospinal fluid measures, and neuropsychological test assessments of long-term follow-up to increase our understanding of the neurological impact of HIV.

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Figure 1.
Plot of Mean CD4 Levels Around HIV-1 Seroconversion

Figure 2.
Plot of Mean Trail Making A Scores Around HIV-1 Seroconversion

Figure 3.
Plot of Mean Trail Making B Scores Around HIV-1 Seroconversion

Figure 4.
Plot of Mean Symbol-Digit Scores Around HIV-1 Seroconversion

Table 1

Baseline Characteristics of the Multicenter AIDS Cohort Study (n= 362)

Variables	M	(SD)
Age in Years at Baseline	35	7.9
CD4 Count (cells/uL)	823.4	404.7
	N	(%)
Race		
White, Hispanic	21	5.8
Black, non-Hispanic	40	11.1
Other ^a	8	2.2
White, non-Hispanic	293	80.9
Education		
<= 12th grade	46	12.9
HS degree	122	34.1
College degree	85	23.7
>College degree	105	29.3
Missing	4	--
History of Recreational Drug Use^b		
Yes	257	71.0
No	105	29.0
Depression (CES-D)^c		
Yes	76	22.1
No	268	77.9
Missing	18	--

^a includes black, Hispanic; American Indian/Native; Asian or Pacific Islander; other; other Hispanic

^b participants reported the use of marijuana, poppers, crack, cocaine, uppers, injectable drugs, or other recreational drugs within 2 years of

visit

^cCenter for Epidemiologic Studies Depression Scale: Depression defined as having scores ≥ 16

Table 2

Pre- and Post-Seroconversion Changes on Mean Neuropsychological Test Results - Results from Longitudinal Mixed Effect Models
 Est: parameter estimates from the model
 CI: confidence interval

	Personvisits (n)	B (10^Est.)	95% CI	p-value
<i>b</i>Trail Making				
Part A	1,600	1.003	0.982, 1.025	0.77
Part B	1,885	1.022	1.001, 1.043	0.042
^c Symbol-Digit	1,387	-0.555	-1.192, 0.082	0.09
<i>b</i>CPT				
Dominant	1,060	1.000	0.989, 1.012	0.97
Nondominant	1,057	0.992	0.980, 1.004	0.21
<i>b</i>CALCAP				
SRT1	690	0.992	0.966, 1.019	0.55
CRT3	691	0.999	0.987, 1.011	0.89
CRT4	691	0.992	0.974, 1.010	0.40
<i>b</i>Stroop Task				
Interference	415	1.012	0.990, 1.035	0.29
Color naming	391	1.017	0.998, 1.037	0.09
Word reading	392	1.004	0.988, 1.021	0.60
^cRAVT				
Trials 1-5	862	-0.499	-1.264, 0.267	0.20

^a covariates for these models included age, duration on ART, years pre- and postseroconversion, number of previous tests, education, race, current CD4 count, depression, and drug use

^b estimates less than 1 are better

^c estimates greater than 0 are better

* Estimates in this table represent the change in slope between the pre- and postseroconversion time trends from the longitudinal mixed models

Table 3

Parameter Estimates ($10^{\wedge}$ Est) from Longitudinal Mixed Effects Models Across Trail Making (Part A & B) and Symbol-Digit Tests

Est: parameter estimates from the model

CI: confidence interval

Parameter	Trail Making A (n=1,600) ^a			Trail Making B (n=1,885) ^a			Symbol-Digit (n=1,387) ^b		
	Estimates (Ratios = $10^{\wedge}$ Est)	95% CI	p-value	Estimates (Ratios = $10^{\wedge}$ Est)	95% CI	p-value	Estimates	95% CI	p-value
Age, per year increase	1.005	1.002, 1.010	0.005	1.006	1.002, 1.010	0.002	-0.358	-0.488, -0.228	<.0001
Duration on ART, per year increase	1.054	0.995, 1.117	0.07	1.045	0.985, 1.108	0.14	-1.954	-3.795, -0.113	0.037
Time trend before SC ^c , per year increase	0.990	0.986, 0.994	<.0001	0.988	0.985, 0.992	<.0001	-0.133	-0.265, -0.002	0.047
Time trend after SC ^c , per year increase	0.987	0.968, 1.007	0.21	0.967	0.948, 0.987	0.001	0.421	-0.178, 1.020	0.17
Number of previous tests									
0 vs. >= 2 tests	1.207	1.166, 1.249	<.0001	1.181	1.143, 1.221	<.0001	-1.741	-2.798, -0.683	0.001
1 vs. >= 2 tests	1.094	1.058, 1.132	<.0001	1.103	1.068, 1.138	<.0001	-0.432	-1.474, 0.610	0.42
Education									
<= 12th grade vs. > College degree	1.241	1.112, 1.384	0.0001	1.289	1.153, 1.442	<.0001	-9.957	-13.990, -5.923	<.0001
HS degree vs. > College degree	1.083	0.994, 1.179	0.07	1.113	1.019, 1.216	0.018	-3.159	-5.937, -0.381	0.026
College degree vs. > College degree	0.966	0.882, 1.058	0.45	0.922	0.839, 1.014	0.09	-0.811	-3.747, 2.125	0.59
Race									
White, Hispanic vs. White, non-Hispanic	1.238	1.080, 1.420	0.002	1.153	1.002, 1.327	0.047	-0.943	-5.369, 3.483	0.67
Black, non-Hispanic vs. White, non-Hispanic	1.134	1.028, 1.250	0.012	1.252	1.127, 1.392	<.0001	-5.120	-8.392, -1.848	0.002
Other ^d vs. White, non-Hispanic	1.103	0.912, 1.335	0.31	1.051	0.856, 1.290	0.64	0.140	-6.531, 6.811	0.97
CD4 count category									
< 200 cells/uL vs. > 500 cells/uL	1.112	0.987, 1.253	0.08	1.045	0.932, 1.172	0.45	-1.004	-4.281, 2.273	0.55
200–500 cells/uL vs. > 500 cells/uL	1.004	0.969, 1.041	0.81	1.027	0.992, 1.062	0.14	-0.537	-1.566, 0.492	0.31
History of depression	1.018	0.986, 1.051	0.28	1.034	1.003, 1.066	0.032	-1.816	-2.754, -0.878	0.0002
History of drug use	0.994	0.961, 1.028	0.74	1.000	0.968, 1.033	0.99	0.864	-0.198, 1.927	0.11

^a estimates less than 1 are better

^b estimates greater than 0 are better

c_{SC} = seroconversion

d_i includes black, Hispanic, American Indian/Native, Asian or Pacific Islander, other; other Hispanic