Longitudinal neuropsychological test performance among HIV seropositive individuals in Uganda

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Abstract

Objective—To evaluate longitudinal neuropsychological testing performance over a 12 month period among HIV+ individuals, and to evaluate the impact of antiretroviral therapy (ART) initiation on neuropsychological test changes in Uganda.

Methods—The study examined 77 HIV+ individuals recruited from the Infectious Diseases Clinic at Makerere University, Uganda. They underwent detailed sociodemographic, medical history, immune status, functional, neurologic, and neuropsychological evaluations at baseline and 12 months later. Thirty-one individuals initiated ART (ART group) after their baseline visit, whereas 46 individuals were not placed on ART (no-ART group) during those 12 months. Paired samples t-tests were used to evaluate longitudinal changes in neuropsychological test performance for the entire sample, as well as for groups defined by ART initiation and baseline neurocognitive status.

Results—The study evaluated 77 HIV individuals (62% women, mean age=37 years, mean education=8 years, mean CD4 count=235 cells/μL). Both the ART and no-ART groups showed significant improvements in tests of verbal memory, executive functioning, motor, and psychomotor speed performance, as well as depression symptoms. The ART group had significant improvements in CD4 count over the 12 months (p<.001) whereas the no-ART group had no CD4 count improvement.

Conclusion—ART use is associated with improvements in cognitive functioning among HIV+ individuals in Uganda. However, these improvements did not appear to be higher than those seen among HIV+ individuals who did not initiate ART. Possible reasons for this include practice effects among the no-ART group as well as improvements in their mood and overall quality of life.

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Search Terms

HIV; dementia; neurocognitive; neuropsychological assessment; Uganda

Human immunodeficiency virus-1 (HIV-) associated neurocognitive disorder (HAND) is characterized by disabling cognitive, behavioral, and motor dysfunction, and is a common neurological manifestation of advanced HIV infection. HAND in HIV+ individuals in Uganda is characterized by a relative decline in tests of verbal learning and memory, speed of information processing, executive function and attention compared to HIV seronegative controls [Robertson *et al.* 2007]. The prevalence of HIV- associated dementia (HIV dementia), the most severe form of HAND, in sub-Saharan Africa is largely unknown, but one study suggests that the prevalence in Uganda may be 31% among HIV+ individuals with advanced infection [Wong *et al.* 2007]. Previous studies of longitudinal neuropsychological test performance among HIV+ individuals in Uganda have included a follow-up period of only 6 months. This prior study among HIV+ individuals initiating stavudine-based combination active antiretroviral therapy (ART) demonstrated improvement in verbal memory, motor and psychomotor speed, executive functioning, and verbal fluency performance [Sacktor N *et al.* 2009]. No previous studies have evaluated neuropsychological test performance over a longer period.

The objective of this study was to evaluate longitudinal neuropsychological test performance over a twelve month period among HIV+ individuals, and to evaluate the impact of ART initiation and baseline neurocognitive status on neuropsychological test changes. Our hypotheses were that neuropsychological test performance among HIV+ individuals initiating ART would improve compared to baseline, and would show greater improvement compared to longitudinal neuropsychological test performance among HIV+ individuals who did not initiate ART.

METHODS

Participants

The study evaluated 104 HIV+ individuals followed over a 6 month period and 77 HIV+ individuals followed over a 12 month period from an Infectious Disease clinic in Kampala, Uganda, from August 2009 to October, 2010. The study procedures were approved by the Johns Hopkins University and Makerere University Institutional Review Boards and ethical standards committees. Written informed consent was obtained from all patients.

Consecutive ambulatory HIV+ individuals presenting to the Infectious Disease Clinic at the Infectious Disease Institute in Kampala, Uganda were contacted for participation in the longitudinal study. Inclusion criteria included HIV infection as documented by ELISA and confirmed by Western blot or a detectable plasma HIV RNA level. Exclusion criteria included age <18 years, an active or known past opportunistic infection of the CNS, fever (temperature >37.5 °C), a history of a chronic neurologic disorder, active psychiatric disorder, alcoholism, (defined as >30 standard drinks/week), physical deficit (*e.g.,* amputation), or severe medical illness that would interfere with the ability to perform the study evaluations. The evaluations were translated into the local language, Luganda. There was no targeted recruitment conducted during the enrollment process.

Clinical assessments

HIV+ individuals received clinical assessments using standardized questionnaires of demographic information and medical, psychiatric, and neurologic history, and underwent a neurologic examination [Wong *et al.* 2004; Wong *et al.* 2007] including assessments of

cranial nerves, limb strength and coordination, limb vibration and pin sensation, gait, and deep tendon reflexes in all extremities [Wong *et al.* 2007]. Patients were also evaluated for fever, headache, neck stiffness, and focal abnormalities. HIV+ patients with a suspected opportunistic infection of the central nervous system or neoplasm were excluded from the study.

The neurocognitive assessment included a screening test for HIV dementia, the International HIV Dementia Scale (IHDS) [Sacktor *et al.* 2005] and a full neuropsychological test battery. The neuropsychological tests for this battery were chosen to be culturally independent and predominantly non-language based tests that were appropriate for a sub-Saharan African population and also sensitive for detecting HAND [Wong *et al.* 2007]. The battery included predominantly motor and psychomotor speed/executive function tests, although a verbal memory tests and a simple verbal fluency test were also included. The neuropsychological testing battery included the World Health Organization–University of California–Los Angeles Auditory Verbal learning test (AVLT) for verbal memory [Maj *et al.* 1994]. The words used in the WHO-UCLA test have been chosen to be universally recognized objects independent of culture and language. The Timed Gait and Finger Tapping tests were used to assess motor performance, the Grooved Pegboard test was used to assess psychomotor speed performance, and the Symbol Digit modalities test [Smith 1982] and Color Trails Test [Maj *et al.* 1994] were used to assess executive function. The Digit Span Forward and Backward was used to assess attention, and the Category Naming test was used to assess verbal fluency. Functional assessment included the Karnofsky performance scale and the Instrumental Activities of Daily Living scale of Lawton and Brody [Karnofsky *et al.* 1948; Lawton and Brody 1969]. These assessments were used to assign a HAND stage of normal neurocognitive function, asymptomatic neurocognitive impairment (ANI), mild neurocognitive disorder (MND), or HIV dementia [Antinori *et al.* 2007]. A diagnosis of HIV dementia required impairment in 3 unrelated neurocognitive domains in which the subject scored >2.0 standard deviations below the locally determined mean for his or her normative age and education group. Depression symptoms were assessed with the Center for Epidemiologic Depression Scale (CES-D) [Beck *et al.* 1961]. CD4 lymphocyte counts and plasma HIV viral loads were determined for all HIV+ subjects on the same day as the neurocognitive assessment.

Data analysis—For each neuropsychological test, a Z score was calculated using age- and education-adjusted normative data obtained from 100 HIV- uninfected individuals in Uganda, [Robertson *et al.* 2007]. Distributional tests have confirmed that the resultant Z scores follow a normal distribution, and scores are summarized as mean ± (SD). Preliminary analyses showed that rate of change in cognition did not vary as a function of ART initiation or baseline neurocognitive status. Therefore, paired samples t-tests were used to evaluate longitudinal changes (baseline vs. twelve months) in neuropsychological test performance for the entire sample, as well as for groups defined by ART initiation and baseline neurocognitive status. Longitudinal changes in neuropsychological test performance adjusting for CD4 count and antiretroviral therapy initiation were assessed using a general linear model. An alpha of $p < 0.05$ was considered significant.

RESULTS

Frequency of HAND and demographic characteristics

At baseline, the HAND stage stratification for the 77 HIV+ individuals followed for twelve months was as follows: normal neurocognitive function: 11.7%, asymptomatic neurocognitive impairment (ANI): 15.6%, mild neurocognitive disorder (MND): 33.7%, HIV dementia: 39.0%. Thirty- one HIV+ individuals ("ART group") began ART during the

12 month follow-up period (39% during the first six months), and 46 HIV+ individuals ("no-ART group") never received ART during the 12 month follow-up period. The demographic characteristics of all 77 HIV+ individuals and for ART and no-ART groups are summarized in Table 1. Individuals in the ART group had a significantly lower mean CD4 count than no-ART individuals (p<.001). There were no differences between the ART and no-ART groups on age, education, gender, or plasma HIV RNA level.

Immunological and Virological response to ART

During the 12 month follow-up period, 18 HIV+ individuals initiated the ART combination of zidovudine, lamivudine, and nevirapine, 10 HIV+ individuals initiated the ART combination of zidovudine, lamivudine, and efavirenz, and 1 HIV+ individual initiated the combination of lamivudine and lopinavir. HIV+ individuals initiating ART during the 12 month follow-up period had a significant improvement in CD4 count [mean (SD), (cells/ μL), baseline= 166 (89), 6 month follow-up =221 (113), 12 month follow-up =319 (165)] (see Table 2) compared to HIV+ individuals not on ART [CD4 count [mean (SD) (cells/ μL)], baseline = 282 (100), 6 month follow-up period = 297 (106), 12 month follow-up period =251 (105)]. HIV+ individuals initiating ART during the 12 month follow-up period also had a significant improvement in the plasma HIV RNA level [mean (SD), (copies/ μL) baseline plasma HIV RNA level =159, 666 (190,455), 12 month follow-up period plasma HIV RNA level = 14,859 (56,833)] compared to HIV+ individuals not on ART, [mean (SD) baseline plasma HIV RNA level = 178,922 (239,037), mean (SD) 12 month follow-up period plasma HIV RNA level = 185,885 (227,224). (A 6 month follow-up plasma HIV RNA level was not performed). Eighty-eight percent of the HIV+ individuals initiating ART achieved plasma virologic suppression by 12 months.

Longitudinal neuropsychological test performance for the entire group and stratified by ART initiation

The performance for each neuropsychological test for the entire group and stratified by ART status is summarized in Table 3. The entire group showed improvement in tests of verbal memory (AVLT total, short delay, long delay, and recognition), executive functioning (Color Trails 1 and 2, Symbol Digit), motor (Timed Gait, Finger Tapping), and psychomotor speed (Grooved Pegboard) performance. Both the ART and no-ART groups showed improvement in tests of verbal memory, executive functioning, motor, and psychomotor speed performance, as well as depression symptoms assessed using the CES-D. The ART group had improvement in CD4 lymphocyte counts over the 12 months (p <.001) whereas the no-ART group had no CD4 lymphocyte count improvement. After adjusting for baseline CD4 cell count and ART initiation in the model, the improvements in tests of verbal memory, executive functioning, motor, and psychomotor speed performance, as well as depression symptoms remain significant.

Longitudinal neuropsychological test performance stratified by baseline HAND stage

The longitudinal neuropsychological test performance stratified by baseline HAND stage at 6 and 12 months are described in Tables 5 and 6 respectively.. For the HIV+ individuals with normal cognition at baseline (n=9), the only neuropsychological tests showing improvement over 12 months were the verbal fluency test (p=0.01) and a single test of motor speed [Timed Gait (p=0.04)]. For HIV+ individuals with ANI at baseline (n=12), the only tests showing improvement over 12 months were two tests of verbal memory [AVLT total (p=0.001), AVLT long delay (p=0.02)], a test of executive functioning [Symbol Digit (p-0.05)], and a test of motor speed [Timed Gait, p=0.001]. For HIV+ individuals with MND at baseline (n=26), many tests showed improvement including three tests of verbal memory [AVLT total, (p=0.05), AVLT short delay (p=0.01), AVLT long delay (p=0.02)], two tests of executive functioning [Color Trails 1 (p=0.008), and Color Trails 2 (p=0.005)],

two tests of motor speed [Timed Gait (p=0.01), and Finger Tapping (p=0.005)], and one test of psychomotor speed [Grooved Pegboard nondominant (p=0.004)]. For HIV+ individuals with dementia at baseline n=30), again many tests showed improvement including all four tests of verbal memory [AVLT total (p=0.008), AVLT short delay (p=0.02), AVLT long delay (p=0.004), and AVLT recognition (p=0.01)], three tests of executive functioning [Color Trails 1 (p=0.04), Color Trails 2 (<0.001), and Symbol Digit (p=0.03)], and two tests of psychomotor speed [(Grooved Pegboard dominant (p <0.001) and Grooved Pegboard nondominant (p< 0.001)].

DISCUSSION

Neuropsychological test performance among HIV+ individuals in sub-Saharan Africa was first evaluated in Kenya and Zaire in a cross-sectional study conducted by the World Health Organization in 1994 [Maj *et al.* 1994]. More recent studies of neuropsychological test performance among HIV+ adults in Africa using a detailed neuropsychological test battery have all been cross-sectional studies performed in Ethiopia [Clifford *et al.* 2007], Nigeria [Salawu *et al.* 2008] Botswanna [Lawler *et al.* 2010], Malawi [Patel *et al.* 2010], South Africa [Joska *et al.* 2011] Cameroon [Kanmogne *et al.* 2010] Kenya, [Kwasa *et al.* 2012], and Zambia [Hestad *et al.* 2012], [Birbeck *et al.* 2011]. A prior longitudinal study of neuropsychological test performance in sub-Saharan Africa was conducted in Uganda [Sacktor *et al.* 2009] over a six month period. In this study, HIV+ individuals with cognitive impairment at baseline demonstrated significant improvement on a test of executive function (the Color Trails 2 test) compared to HIV seronegative individuals also evaluated for a 6 month period. Another study, the AIDS Clinical Trials Group 5199 study, used an abbreviated neuropsychological test battery including tests of motor performance and verbal fluency every 6 months for a median of 16 weeks at multiple international sites, including locations in Malawi, South Africa, and Zimbabwe [Robertson *et al.* 2012]. There are no prior studies using a detailed neuropsychological test performance among HIV+ individuals over a 12 month period in sub-Saharan Africa.

Our results suggest that HAND continues to be a significant neurological condition among HIV+ individuals in Uganda. Thirty-nine percent of the HIV+ individuals entering our study were diagnosed with dementia at baseline which is slightly higher than the 31% of HIV+ individuals with dementia in a previous study performed by our group [Wong *et al.* 2007]. Both studies had HIV+ individuals with a mean CD4 lymphocyte count at baseline in the low 200's.

Our results also suggest that when HIV+ individuals in Uganda enter a clinical research study, they have significant improvement in their neuropsychological test performance over a 12 month period. This improvement in neuropsychological test performance at 12 months in HIV+ individuals initiating ART is similar to the improvement seen at 6 months in HIV+ individuals initiating ART in a prior study in Uganda [Sacktor N *et al.* 2009]. This improvement was seen predominantly in HIV+ individuals who had MND and dementia at baseline. Surprisingly, in contrast to our hypothesis, we did not see greater improvement in HIV+ individuals who initiated ART during the 12 month period compared to the HIV+ individuals who never started ART.

Several potential explanations could account for this finding. Practice effects from administration of the neuropsychological tests on multiple occasions could account for some of the improvement. Our study did not include an HIV seronegative (HIV-) control group for comparison to evaluate for practice effects. However, the improvement in neuropsychological test performance at six months among HIV+ individuals not on ART, exceeds the improvements due to practice effects at 6 months from HIV− individuals in a

previous study conducted by our group in Uganda (data not shown). Future longitudinal studies of neuropsychological test performance should include a demographically matched HIV- control group if feasible.

Although a subgroup of HIV+ individuals did not initiate ART, they were enrolled in a clinical research study at the Infectious Disease Institute in Kampala, Uganda, and received the medical and psychosocial support services available through the Institute. These services likely improved the overall quality of life for these HIV+ individuals, which could account for the neuropsychological test improvement seen with these individuals. Indeed, the HIV+ individuals who were not on ART did have significant improvement in their depression symptomatology on the CES-D, reflecting an overall improvement in their quality of life. This finding is an important consideration in future longitudinal studies of neuropsychological test performance in a resource limited country.

There are several limitations to this study which should be noted. We did not include an HIV- control group to evaluate for practice effects. Our assessments for functional status may not be ideal for examining functional status in a resource limited country such as Uganda. This limitation impacts the relative proportion of individuals assigned to each stage of HAND. Informant interviews for functional status were not available for the individuals in this study.

Our results are the first examination of longitudinal neuropsychological test performance over a twelve month period in well-characterized HIV+ individuals who started ART and those who did not in sub-Saharan Africa. Our results indicate that improvements in longitudinal neuropsychological test performance over twelve months can occur in both HIV + individuals who initiate ART and HIV+ individuals who do not initiate ART. Thus improvements in neuropsychological test performance in HIV+ individuals initiating ART in sub-Saharan Africa need to be interpreted with caution. Some of the neurocognitive improvement may be due to the effect of ART in suppressing virological replication and improving immunological function. However, some of the neurocognitive improvement may also be due to the impact of receiving medical and psychosocial support services, reduction in depression symptomatology, and improvements in overall quality of life. Practice effects could also account for some of the improvement. These factors need to be considered in future studies evaluating longitudinal neuropsychological test performance in HIV+ individuals initiating ART in resource limited countries. Future studies should also include a larger number of individuals followed over a long period of follow-up with the inclusion of demographically matched HIV- controls.

Acknowledgments

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Table 1

Demographic characteristics of HIV infected individuals, total and stratified by initiation of combination antiretroviral therapy (ART) during the 12 month follow-up period

Characteristic	Total	On ART	No ART
Age, years [Mean (SD)]	37.3 (7.4)	38.0 (8.3)	36.2 (6.5)
Education, years [Mean (SD)]	8.3 (3.8)	8.4 (4.2)	8.1 (3.6)
Gender, % male	38	36	39
CD4 lymphocyte count, cells/μL [Mean (SD)]	235 (111)	166 (89)	282 (100)
Plasma HIV RNA level, copies/mL [Mean (SD)]	171,170 (219,638)	159,666 (190,455)	178,922 (239,037)

Table 2

Longitudinal CD4 lymphocyte count and plasma HIV RNA changes among HIV+ individuals stratified by ART initiation

	On ART (n=31)	No ART (n=46)
CD4 count (cells/μL), Mean (SD)		
Baseline	166 (89)	282 (100)
6 month follow-up	221 (113)	297 (106)
12 month follow-up	319 (165)	251 (105)
Plasma HIV RNA level copies/μL, mean (SD) [*]		
Baseline	159,666 (190,455)	178,922 (239,037)
12 month follow-up	14,859 (56,833)	185,885 (227,224)

[*] 6 month follow-up plasma HIV RNA level was not performed.

ART=antiretroviral therapy

Table 3

Longitudinal neuropsychological test performance over 6 months for HIV+ individuals: total group and stratified by ART initiation

Test	Total (n=104)			On ART (n=12)			No ART (n=94)		
Mean (SD)	Baseline	12 month	p value	Baseline	12 month	p value	Baseline	12 month	p value
AVLT total	34.5 (7.1)	36.8 (7.6)	.002	33.8 (9.1)	35.4 (7.9)	ns	34.6 (6.9)	37.0 (7.5)	.004
AVLT short delay	6.6 (2.3)	7.3 (2.1)	.001	6.4 (2.9)	7.4 (2.4)	ns	6.6 (2.2)	7.3 (2.1)	.002
AVLT long delay	6.4 (2.2)	7.1 (2.5)	.002	6.1 (2.4)	6.8 (3.6)	ns	6.4 (2.1)	7.1 (2.3)	.004
AVLT recognition	12.5 (2.3)	13.4 (1.8)	<.001	12.0 (3.2)	12.8 (2.5)	ns	12.6 (2.1)	13.4 (1.7)	.001
Color Trails 1 (seconds)	122.3 (59.8)	102.9(50.4)	.002	120.3 (51.6)	85.2 (28.3)	ns	122.5 (61.0)	105.2 (52.2)	.01
Color Trails 2 (seconds)	217.4 (87.4)	188.3(82.3)	.002	217.3 (72.1)	156.3(35.9)	.02	217.4 (89.5)	192.5 (85.8)	.01
Symbol Digit	21.3 (11.1)	22.4 (10.5)	ns	22.4 (12.5)	24.0 (10.6)	ns	21.1 (11.0)	22.1(10.6)	ns
Verbal Fluency	11.5 (2.6)	11.7 (3.0)	ns	12.3 (3.0)	11.4 (2.5)	ns	11.4 (2.6)	11.8 (3.0)	ns
Digit Span Forward	7.7 (1.9)	7.7 (1.5)	ns	8.2 (1.8)	7.7 (1.2)	ns	7.6 (2.0)	7.7 (1.5)	ns
Digit Span Backward	2.9 (1.1)	3.0 (1.3)	ns	3.0 (1.2)	3.2 (0.7)	ns	2.9 (1.1)	3.0 (1.3)	ns
Digit Span Total	10.7 (2.5)	10.7 (2.2)	ns	11.2 (2.2)	10.8 (1.5)	ns	10.6 (2.6)	10.7 (2.3)	ns
Timed Gait	27.4 (5.2)	29.9 (6.0)	.001	28.0(5.1)	28.8 (8.0)	ns	27.3 (5.2)	30.0(5.8)	.001
Finger Tapping	31.3 (9.3)	33.8 (9.9)	.01	31.9 (7.8)	33.0 (11.0)	ns	31.3 (9.5)	33.9 (9.8)	.02
Grooved pegboard dominant (seconds)	102.3 (36.5)	89.5(27.1)	<.001	101.3 (20.6)	76.5 (19.2)	.02	102.5 (38.2)	91.2(27.6)	.001
Grooved pegboard non-dominant (seconds)	129.0 (61.7)	112.6 (44.0)	.002	120.7 (29.5)	103.1 (49.7)	ns	130.1 (64.8)	113.9 (43.4)	.006
CES-D	13.6 (9.6)	9.7 (9.3)	<.001	14.3 (9.5)	11.0 (10.0)	.039	13.2 (9.8)	9.0 (8.9)	.001

AVLT= World Health Organization Auditory Verbal Learning Test

CES-D= Center for Epidemiological Studies Depression Symptoms Scale

ns= not significant

Table 4

Longitudinal neuropsychological test performance over 12 months for HIV+ individuals: total group and stratified by ART initiation

Test	Total (n=77)			On ART (n=26)			No ART (n=51)		
Mean (SD)	**Baseline**	**12 month**	**p value**	**Baseline**	**12 month**	**p value**	**Baseline**	**12 month**	**p value**
AVLT total	34.7	38.5 (7.5)	<.001	34.1 (8.0)	39.3 (7.0)	.003	35.0 (7.0)	38.0 (7.8)	.002
AVLT short delay	6.8 (2.4)	7.9 (2.0)	<.001	6.6 (2.2)	7.9 (1.8)	.008	6.9 (2.5)	7.9 (2.0)	.003
AVLT long delay	6.4 (2.2)	7.6 (2.1)	<.001	6.6 (2.0)	7.4 (2.0)	ns	6.3 (2.3)	7.8 (2.1)	<.001
AVLT recognition	12.5 (2.2)	13.4 (1.9)	<.001	12.4 (2.4)	13.4 (2.2)	.05	12.5 (2.2)	13.4 (1.7)	.003
Color Trails 1 (seconds)	115.0 (46.9)	97.0 (41.5)	.003	114.9 (53.9)	86.7 (28.1)	.02	115.1 (43.6)	102.3 (46.3)	ns
Color Trails 2 (seconds)	217.6 (85.1)	164.6 (65.6)	<.001	220.3 (74.5)	160.5 (48.8)	<.001	216.2 (90.7)	166.7 (73.1)	<.001
Symbol Digit	22.1 (11.0)	24.6 (10.2)	.001	21.7 (13.0)	24.3 (11.0)	ns	22.4 (10.0)	24.7 (9.9)	.005
Verbal Fluency	11.5 (2.7)	11.8 (3.4)	ns	11.8 (2.9)	12.0 (2.8)	ns	11.3 (2.6)	11.7 (3.7)	ns
Digit Span Forward	7.6 (1.9)	7.9 (1.7)	ns	7.7 (2.1)	7.9 (1.8)	ns	7.6 (1.8)	7.9 (1.7)	ns
Digit Span Backward	2.9 (1.1)	3.1 (1.4)	ns	2.8 (1.2)	3.0 (1.2)	ns	3.0 (1.1)	3.1 (1.4)	ns
Digit Span Total	10.6 (2.4)	10.9 (2.7)	ns	10.6 (2.5)	10.9 (2.3)	ns	10.5 (2.4)	11.0 (2.8)	ns
Timed Gait	25.8 (4.4)	28.9 (5.0)	<.001	26.1 (4.4)	30.0 (5.5)	.01	25.7 (4.5)	28.4 (4.6)	<.001
Finger Tapping	31.0 (9.6)	33.7 (10.0)	.ns	30.2 (7.4)	31.7 (8.3)	ns	31.4 (10.5)	34.7 (10.7)	.07
Grooved pegboard dominant (seconds)	102.8 (40.6)	82.1 (23.5)	<.001	110.8 (54.6)	81.0 (22.5)	.003	98.7 (31.1)	82.8 (24.2)	<.001
Grooved Pegboard non-dominant (seconds)	128.0 (69.3)	96.5 (29.9)	<.001	136.7 (78.6)	97.7 (33.9)	.003	123.5 (64.4)	95.9 (27.9)	<.001
CES-D	13.61 (9.64)	9.74 (9.27)	<.001	14.29 (9.51)	11.04 (9.95)	.039	13.20 (9.80)	8.96 (8.85)	.001

AVLT= World Health Organization Auditory Verbal Learning Test

CES-D= Center for Epidemiological Studies Depression Symptoms Scale

ns= not significant

Table 5

Longitudinal neuropsychological test performance over 6 months for HIV+ individuals stratified by baseline diagnosis

HAND Stage	Normal (n=9)			ANI (n=20)			MND (n=34)			Dementia (n=41)		
Mean (SD)	Baseline	6 month	p value	Baseline	6 month	p value	Baseline	6 month	p value	Baseline	6 month	p value
AVLT total	42.4(5.6)	45.0 (6.5)	ns	36.8 (5.3)	38.1 (6.8)	ns	36.6 (6.2)	38.0 (7.6)	ns	30.1 (6.2)	33.3 (6.3)	.003
AVLT short delay	9.2 (2.2)	9.3 (2.6)	ns	6.4 (2.1)	7.2 (1.3)	.04	6.8 (2.4)	7.5 (1.8)	ns	5.9 (2.0)	6.8 (2.3)	.02
AVLT long delay	8.4 (1.6)	9.8 (2.5)	ns	6.6 (1.7)	7.3 (2.1)	ns	6.6 (2.2)	7.2 (2.3)	ns	5.7 (2.1)	6.4 (2.5)	ns
AVLT recognition	13.7 (1.1)	14.2 (1.0)	ns	12.8 (1.7)	13.8 (1.1)	.02	13.0 (2.0)	13.4 (1.9)	ns	11.7 (2.7)	12.9 (2.1)	.004
Color Trails 1 (seconds)	66.7 (21.4)	91.9 (54.1)	ns	84.5 (22.5)	75.6 (26.1)	ns	114.8 (32.0)	89.6 (40.2)	.007	159.0 (72.0)	129.7 (54.8)	.02
Color Trails 2 (seconds)	157.1 (480.5)	160.1 (85.9)	ns	159.7 (45.1)	153.0 (54.1)	ns	200.0 (68.8)	180.6 (88.2)	ns	273.2 (91.7)	218.2 (80.0)	.001
Symbol Digit	30.9 (14.4)	30.8 (11.8)	ns	26.8 (7.2)	29.1 (7.3)	ns	22.6 (10.2)	22.7 (9.2)	ns	15.4 (9.7)	17.0 (9.7)	ns
Verbal Fluency	13.2 (2.0)	14.6 (2.9)	ns	12.0 (2.0)	12.6 (3.5)	ns	11.9 (2.6)	11.4 (2.3)	ns	10.6 (2.7)	11.0 (2.8)	ns
Digit Span Forward	8.1 (1.5)	8.4 (1.1)	ns	8.1 (2.2)	7.7 (1.6)	ns	8.2 (1.9)	7.7 (1.8)	ns	7.0 (1.8)	7.5 (1.2)	ns
Digit Span Backward	4.0 (0.7)	4.0 (1.4)	ns	3.3 (0.8)	3.5 (1.2)	ns	3.2 (1.0)	3.3 (1.1)	ns	2.3 (1.2)	2.4 (1.1)	ns
Digit Span Total	12.1 (1.8)	12.4 (2.1)	ns	11.4 (2.4)	11.2 (2.3)	ns	11.4 (2.2)	11.0 (2.3)	ns	9.4 (2.4)	9.9 (1.9)	ns
Timed Gait	22.4 (1.4)	27.1 (5.6)	.03	25.9 (4.6)	30.0 (5.8)	.007	28.8 (5.1)	30.6 (6.5)	ns	28.8 (5.2)	29.9 (5.9)	ns
Finger Tapping	39.6 (4.7)	39.9 (9.6)	ns	38.4 (10.9)	36.6 (10.0)	ns	28.5 (6.8)	33.8 (11.8)	.008	28.5 (8.3)	31.2 (8.3)	ns
Grooved pegboard dominant (seconds)	80.0 (20.6)	91.3 (23.7)	ns	87.1 (22.0)	77.6 (21.6)	ns	92.9 (21.9)	84.3 (23.2)	ns	123.1 (44.7)	99.5 (30.4)	<.001
Grooved Pegboard non-dominant (seconds)	94.0 (25.1)	98.3 (26.5)	ns	99.8 (19.9)	97.1 (25.0)	ns	118.5 (34.4)	105.1 (38.8)	ns	160.4 (82.5)	130.0 (53.1)	.01
CES-D	11.0 (5.2)	7.6 (5.7)	ns	11.2 (8.3)	8.8 (7.6)	ns	10.9 (11.5)	13.3 (11.4)	ns	13.3 (10.0)	11.4 (9.7)	ns

ANI= asymptomatic neuropsychological impairment

MND= mild neurocognitive disorder

WHOAVLT= World Health Organization Auditory Verbal Learning test

CES-D= Center for Epidemiological Studies Depression Symptom Scale

ns= not significant

Table 6

Longitudinal neuropsychological test performance over 12 months for HIV+ individuals stratified by baseline diagnosis

HAND Stage	Normal (n=9)			ANI (n-12)			MND (n=27)			Dementia (n=29)		
Mean (SD)	Baseline	12 month	p value	Baseline	12 month	p value	Baseline	12 month	p value	Baseline	12 month	p value
AVLT total	42.4(5.6)	45.9 (7.9)	ns	36.7 (3.7)	42.4 (7.4)	.007	36.2 (6.4)	39.2 (6.7)	.05	30.0 (6.7)	33.9 (5.1)	.008
AVLT short delay	9.2 (2.2)	9.9 (1.5)	ns	7.1 (1.9)	8.3 (1.5)	ns	6.8 (2.5)	8.0 (2.1)	.01	6.0 (2.0)	7.0 (1.6)	.02
AVLT long delay	8.4 (1.6)	8.9 (2.3)	ns	6.7 (1.6)	8.3 (1.8)	.012	6.6 (2.3)	7.7 (2.0)	.02	5.6 (2.0)	6.9 (1.9)	.004
AVLT recognition	13.7 (1.1)	14.2 (0.8)	ns	12.4 (1.9)	13.8 (1.4)	ns	12.9(2.1)	13.4 (1.7)	ns	11.8 (2.5)	12.9 (2.3)	.01
Color Trails 1 (seconds)	66.7 (21.4)	78.7 (30.3)	ns	85.2 (23.1)	77.0 (27.0)	ns	110.6 (33.3)	85.5 (32.4)	.008	146.6 (49.2)	121.7 (46.0)	.04
Color Trails 2 (seconds)	157.1 (48.5)	138.8 (66.5)	ns	163.0 (52.3)	136.2 (42.0)	ns	198.9 (69.3)	148.5 (51.2)	005	276.3 (84.3)	199.3 (72.3)	.<00
Symbol Digit	30.1 (14.4)	33.4 (12.7)	ns	25.8 (6.4)	29.2 (8.1)	.05	23.2 (10.5)	25.0 (9.1)	ns	16.9 (9.6)	19.5 (8.5)	.03
Verbal Fluency	13.2 (2.0)	15.0 (2.9)	.01	12.0 (2.0)	12.8 (4.2)	ns	11.9 (2.8)	11.7 (2.4)	ns	10.3 (2.6)	10.5 (3.3)	ns
Digit Span Forward	8.1 (1.5)	8.3 (1.6)	ns	8.2 (1.1)	12.8 (4.2)	ns	7.9 (2.1)	7.7 (1.5)	ns	7.0 (19)	7.5 (1.6)	ns
Digit Span Backward	4.0 (0.7)	3.7 (1.4)	ns	3.3 (0.9)	3.4 (1.2)	ns	3.0 (0.9)	3.2 (1.2)	ns	2.3 (1.2)	2.6 (1.5)	ns
Digit Span Total	12.1 (1.8)	12.0 (2.8)	ns	11.4 (1.2)	12.1 (3.3)	ns	11.0 (2.7)	10.9 (2.3)	ns	9.3 (2.4)	10.1(2.5)	ns
Timed Gait	22.4 (1.4)	26.7 (5.4)	.04	23.6 (1.7)	30.8 (6.4)	.001	26.2 (4.4)	29.1 (4.1)	.01	27.6 (4.9)	28.7 (4.8)	ns
Finger Tapping	39.6 (4.7)	40.9 (11.0)	ns	38.1 (11.5)	33.0 (9.3)	ns	28.2 (7.3)	34.8 (9.6)	.005	28.0 (8.8)	30.6 (9.4)	ns
Grooved pegboard dominant (seconds)	80.0 (20.6)	70.3 (16.1)	ns	81.0 (19.7)	72.6 (20.2)	ns	89.8 (20.4)	82.7 (16.1)	ns	130.9 (49.7)	89.3 (29.7)	<.001
Grooved Pegboard non-dominant (seconds)	94.0 (25.1)	86.2 (23.0)	ns	93.4 (21.1)	89.5 (26.1)	ns	116.9 (35.5)	92.8 (23.6)	.004	163.1 (96.0)	106.0 (36.4)	<.001
CES-D	11.0 (5.2)	3.7 (2.7)	<.001	13.4 (9.8)	6.9 (6.5	<.001	13.4 (9.6)	11.3 (10.1)	ns	13.5 (9.6)	10.9 (7.5)	ns

ANI= asymptomatic neuropsychological impairment

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WHOAVLT= World Health Organization Auditory Verbal Learning test

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