

## Pattern of neuropsychological performance among HIV positive patients in Uganda

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**Sponsorship:**

Supported by Bill and Melinda Gates Foundation and the Academic Alliance Foundation (which has received support from Pfizer Pharmaceuticals). MH62690, AI25868, AI50410, RR00046.

Further support for this work: RO1NSMH34243, RO1MH62690, RO1MH71150.

**Declaration of Competing Interests:**

The author(s) declare that they have no competing interests.

## ABSTRACT

**Background.** Few studies have examined cognitive functioning of HIV positive patients in sub-Saharan Africa. It cannot be assumed that HIV positive patients in Africa exhibit the same declines as patients in high-resource settings, since there are differences that may influence cognitive functioning including nutrition, history of concomitant disease, and varying HIV strains, among other possibilities. Part of the difficulty of specifying abnormalities in neuropsychological functioning among African HIV positive patients is that there are no readily available African normative databases. The purpose of the current study was to evaluate the pattern of neuropsychological performance in a sample of HIV positive patients in comparison to HIV negative control subjects in Uganda. **Methods.** The neuropsychological test scores of 110 HIV positive patients (WHO Stage 2, n = 21; WHO Stage 3, n = 69; WHO Stage 4, n = 20) were contrasted with those of 100 control subjects on measures of attention/concentration, mental flexibility, learning/memory, and motor functioning. **Results.** Analysis of variance (ANOVA) revealed significant group differences on measures of verbal learning and memory, speed of processing, attention and executive functioning. Post hoc analyses comparing the performance of normal controls to each WHO Stage group showed these differences existed primarily between the Stage 4 group and normal controls. Though neuropsychological performance generally declined as the stage of illness progressed, ANOVA indicated that differences within the HIV+ WHO stages were not significant. **Conclusions.** Ugandan patients with HIV demonstrated a relative decline on measures of verbal learning and memory, speed of processing, attention, and executive functioning compared to HIV negative controls.

Studies done in the developed world in the era prior to Highly Active Anti-Retroviral Therapy (HAART) have shown prevalence rates of dementia ranging from 7.3%-27.3% in patients with advanced infection [1-3]. Despite the high prevalence of HIV in many African countries, very few studies have examined cognitive functioning in these patients. It cannot be assumed that HIV positive patients in Africa exhibit the same declines as patients in high-resource settings, since there are differences that may influence cognitive functioning including nutrition, history of concomitant disease, and varying HIV strains, among other possibilities.

Cognitive impairments are relatively common in HIV infection. The most striking picture is of frank dementia. HIV dementia afflicts 10-15% of patients with advanced infection in the United States [3], but there is also a high incidence of less severe dysfunction that has been labeled minor cognitive motor dysfunction (MCMD). HIV-associated cognitive impairment is characterized by a subcortical pattern with primary deficits in psychomotor speed and information processing speed [3-7]. Consequently, patients have higher rates of unemployment [8] and difficulty completing instrumental activities of daily living [9].

In 2005, access to highly active antiretroviral therapy in Sub-Saharan Africa is increasing significantly. HAART can improve cognitive performance in individuals with HIV-associated cognitive impairment in the United States [10, 11], but the effect of HAART on individuals with HIV-associated cognitive impairment in Sub-Saharan Africa is largely unknown. As access to AIDS care and highly active antiretroviral therapy (HAART) increases, greater numbers of individuals are receiving care at ambulatory HIV clinics [12]. Studies have shown that HAART can halt the cognitive decline associated with HIV dementia, and in some cases may reverse it [10, 11, 13].

HIV Clade B is found in the United States, Europe, and Australia where almost all

neuropsychological studies have been completed. In Uganda HIV clades D and A predominate over clade B [14]. Variations in HIV clade could lead to different expression of HIV Dementia. Both prevalence and characterization could be altered. A higher or lower prevalence of AIDS Dementia could exist in non B clade endemic areas, due to possible increased neurotropism. The pattern of neurological and neuropsychological deficits could also be altered in non B clade endemic areas. If the underlying neuropathological areas affected are different in non B clade, then the pattern of functional impairments will change.

The purpose of the current study was to evaluate the pattern of neuropsychological performance in a sample of HIV positive patients in comparison to HIV negative control subjects in Uganda.

## METHODS

### **Participating Centers:**

The study took place at two sites in Kampala, Uganda. HIV+ subjects were seen at the Infectious Disease Clinic (IDC) at the Mulago Hospital Complex. This clinic provides care to HIV+ patients at all stages of their illness. It is partially funded by the Academic Alliance Foundation.

HIV- subjects were recruited from the AIDS Information Centre (AIC) in Kampala, Uganda. The AIC provides a voluntary counseling and testing centre for individuals who wish to know their HIV infection status. The AIC tests approximately 120 individuals daily of which about 80% are HIV-.

### **Participants:**

One hundred ten HIV+ (WHO Stage 2, n = 21; WHO Stage 3, n = 69; WHO Stage 4, n = 20) participants were recruited from the IDC. Eighty-one HIV+ subjects were recruited using a

random clustered sample from attendees of the IDC. The remaining subjects were recruited for a pilot study to evaluate the effect of HAART and had CD4 counts < 200. Exclusion criteria included HIV+ individuals less than 18 years of age, HIV+ individuals with an active or known past CNS opportunistic infection, fever > 37.5°C, a history of a chronic neurological disorder, active psychiatric disorder, alcoholism, physical deficit (e.g., amputation), severe functional impairment (Karnofsky < 50), or severe medical illness that would interfere with the ability to perform the study evaluations.

100 HIV- individuals were recruited from the client base of the AIC. In order to be considered HIV- the individual had to have a negative HIV ELISA test in the last year. HIV- subjects were selected to match the mean age and education of the randomly selected HIV+ sample. Applicable exclusion criteria for the HIV+ subjects were used for the HIV- subjects.

The neuropsychological test scores of 110 HIV positive participants (age: mean = 36.72, standard deviation = 8.71; education: mean = 9.11, standard deviation = 5.02; gender: 69.57 percent female) were contrasted with those of 100 control participants (age: mean = 27.48, standard deviation = 9.14; education: mean = 12.08, standard deviation = 4.05; gender: 40.00 percent female) on measures of attention/concentration, mental flexibility, learning/memory, and motor functioning.

#### **Data Collection Instrument:**

Data collection included five sections: (1) A sociodemographic survey, (2) medical history and functional status survey, (3) subjective neurological symptoms questionnaire, (4) neuropsychological test battery, and a (5) neurological assessment.

#### **WHO Disease Staging System**

Given the fact that our research was conducted in the African Region, we utilized the

World Health Organization's (WHO) clinical staging and case definition of HIV in resource-constrained settings. The WHO disease staging system for HIV Infection was first produced in 1990 and updated in September 2005 (World Health Organization, 2005). WHO clinical stages are categorized as Stage 1 through Stage 4, and reflect progression from primary HIV infection to advanced HIV/AIDS. Each stage is defined by specific clinical conditions or symptoms: In Stage I, HIV disease is asymptomatic and not categorized as AIDS. In Stage II: minor mucocutaneous manifestations and recurrent upper respiratory tract infections are included. In Stage III, unexplained chronic diarrhea (longer than a month), and severe bacterial infections and pulmonary tuberculosis are included. In Stage IV, diseases used as indicators of AIDS (brain toxoplasmosis, candidiasis of the esophagus, trachea, bronchi or lungs, and Kaposi's sarcoma) are included.

### **Neuropsychological Battery:**

The neuropsychological instruments administered to both HIV+ and HIV- patients were chosen for their cultural independence as well as their sensitivity for detecting HIV dementia in HIV+ patients (Miller et al., 1990). The tests include assessments in the domains of functioning of Gross motor (Timed Gait), Fine motor (Grooved pegboard), Executive Functioning (Color Trails 2), Speed of Processing (Color Trails 1, Symbol Digit modalities), Verbal Learning/Memory (WHO-UCLA Auditory Verbal Learning Test), and Attention/Working Memory (Digit Span, Forward and Backward).

The WHO-UCLA Auditory Verbal Learning Test is similar to the Rey Auditory Verbal Learning Test [15, 16]. These tests both measure verbal learning and memory through a scored immediate and delayed recall of a 15 word list. While the structure of each test is the same, the words used in the WHO-UCLA test have been chosen to be universally recognized

objects independent of culture and language [17]. Color Trails 1 and 2 test an individual's speed of processing and are designed as cross-cultural variants of the Trail Making tests [15, 17-19].

All the tests had their instructions and content translated into Luganda. Tests were administered in either Luganda or English, depending on the main language of the subject. Test administrators were fluent in both languages. There was no bias to language, an individual was tested in the language they spoke most of the time and were most comfortable. Once the instructions were clear the two groups did not differ in performance. In addition the questionnaire would inquire as to how well the participant spoke and/or wrote English and/or their primary language. The score was "excellent," "very good," "good," or "poor." Hence, on the basis of this the administrator chose the main language. Scores for the individual tests were summed then averaged into a Total z-score. Note that, we multiplied the Timed Gait, Grooved pegboard, Color Trails 1 & 2, and Symbol Digit modalities scores by (-1) so that all positive z-scores indicate improvement and negative scores denote a decline in performance.

### **Determination of Dementia:**

Each HIV+ individual had their demographics, past medical history, neurological symptoms, functional status, neuropsychological test scores and neurological exam assessed by the primary examiners, HIV neurologist and HIV neuropsychologist in a consensus conference. Using this information a Memorial Sloan-Kettering (MSK) HIV dementia score of 0, 0.5, and greater than or equal to 1 was assigned to each HIV+ individual [20]. The scores of 0, 0.5 and 1 represent no cognitive impairment, sub-clinical dementia and mild –moderate dementia respectively. In order to be given a diagnosis of HIV dementia (MSK score = 1), a patient had to

be impaired in two separate neuropsychological domains, as well as have significant functional impairment.

### **Data Analytic Plan:**

HIV+ subjects were stratified based on MSK score (0, 0.5 and greater than 1.0). To explore differences on cognitive domains between groups analysis of variance was utilized. To examine the relationship between continuous variables of interest Spearman correlations were calculated. Statistical analysis was done in SAS 9.1.3 (SAS Institute Inc., Cary, NC).

## **RESULTS**

There was a significant difference in neuropsychological total z-scores between the HIV seronegatives and seropositives ( $F(1, 209) = 28.36, p < .0001$ ) as shown in Table 1 (see Figure 1). Significant differences between HIV- and HIV+ subjects were found for AVLT total ( $F(1, 209) = 31.94, p < .0001$ ); AVLT Delayed Recall ( $F = 34.92, p < .0001$ ); Symbol Digit ( $F = 19.44, p < .0001$ ); Color Trails 1 ( $F = 12.34, p < .0005$ ); Color Trails 2 ( $F = 33.94, p < .0001$ ); Digit Span Forward ( $F = 9.30, p < .005$ ), and Digit Span Backward ( $F = 11.80, p < .001$ ). Grooved Pegboard using the dominant hand ( $p < .15$ ), Grooved Pegboard using the nondominant hand (not significant), and Modified Timed Gait ( $p < .20$ ), did not reach significance between HIV- and HIV+ subjects in this study.

With respect to disease staging, there were significant correlations between neuropsychological tests and WHO HIV disease stages. As disease stage progressed, poorer neuropsychological functioning on the tests of AVLT total ( $r(209) = -.35, p < .0001$ ), Delayed Recall ( $r = -.35, p < .0001$ ), Symbol Digit ( $r = .27, p < .0001$ ), Color Trails 1 ( $r = .17, p < .05$ ), Digit Span Forward/Backward ( $r = -.16, p < .05$  for both) and Color Trails 2 ( $r = .35, p < .0001$ ) were found (see Figures 2, 3). For immune functioning in the HIV+ subjects, there were trends for absolute

CD4+ cells to be decreased with poorer outcomes on the neuropsychological tests of AVLT Total ( $r(99)=-.19$ ,  $p<.07$ ) and Grooved Pegboard dominant ( $r=-.18$ ,  $p<.08$ ).

There were significant differences found in neuropsychological tests between MSK AIDS Dementia Stage (see Table 2). As expected, as AIDS Dementia Stage increased, poorer outcomes on the neuropsychological tests were found for AVLT Total ( $p<.0001$ ), Delayed Recall ( $p<.0001$ ), Symbol Digit ( $p<.0001$ ), Grooved Pegboard Dominant ( $p<.001$ ), Nondominant ( $p<.005$ ), Timed Gait ( $p<.0005$ ), Color Trails 1 and 2 ( $p<.0001$ , both), and Digit Span backward ( $p<.001$ ) and forward ( $p<.06$ ). On most neuropsychological tests, post hoc analysis found that No AIDS Dementia was equivalent to Subclinical, and AIDS Dementia Stage had poorer functioning than both groups. On Symbol Digit, Color Trails 2, the No Dementia group was significantly better than the Subclinical group which was significantly better than those with AIDS Dementia, providing the most separation between groups. On Timed Gait, No Dementia Stage was better than the Subclinical Dementia group, which was equivalent to the AIDS Dementia group.

## **DISCUSSION**

HIV Dementia has been associated with CNS white matter disease, and affects speed of processing and motor functioning. HIV Clade B is found in the United States, Europe, and Australia where almost all neuropsychological studies have been completed. Here, we assessed performance between seronegative controls and HIV seropositives in Uganda where HIV clades D and A predominate over clade B [14]. Variations in HIV clade could lead to different expression of HIV Dementia. Both prevalence and characterization could be altered. A higher or lower prevalence of AIDS Dementia could exist in non B clade endemic areas, due to possible

increased neurotropism. The pattern of neurological and neuropsychological deficits could also be altered in non B clade endemic areas. If the underlying neuropathological areas affected are different in non B clade, then the pattern of functional impairments will change. Our primary objective was to characterize the pattern of neuropsychological functioning in this Ugandan cohort.

In Uganda, a setting of predominantly HIV Clade D and A in sub-Saharan Africa, our study found significant group differences between the HIV seronegatives and HIV seropositives on measures of verbal learning and memory, speed of processing, attention and executive functioning. As HIV disease stage progressed, poorer verbal learning and memory, speed of processing, attention/working memory, and executive function were found. Characterization of neuropsychological performance across AIDS Dementia Stage found that all tests were poorer in those with AIDS Dementia compared to those without. Executive function, Speed of processing, and Gross Motor functioning was poorer in those with Subclinical Dementia than those HIV+ individuals with no evidence of dementia.

HIV+ Ugandans demonstrated a relative decline, in measures of verbal learning and memory, speed of processing, attention, and executive functioning compared to HIV negative controls. This is a similar pattern to what has been found in the US, Europe and Australian settings, and would suggest that the pattern of neuropsychological loss will be the same with Clade A and D HIV infection. In turn, this would suggest that HIV Clade A and D have the same underlying pattern of neuropathology. We found no significant difference in the fine and gross motor tests between the HIV positive and HIV negative groups in this setting. However, in this study we found that both fine and gross motor performance become more impaired in those with AIDS Dementia, and may be useful in separating those with Subclinical Dementia from

normals. In a separate study using a screening test for HIV dementia which evaluates motor and psychomotor speed performance, the International HIV Dementia Scale, (IHDS), we have found that motor functioning remains important in determining AIDS Dementia Stage in these Ugandan patients [21].

AIDS related neurological disease has a very high cost in terms of loss of functional ability. Patients have higher rates of unemployment, decreased ability to perform their activities of daily living including difficulty completing such tasks as meal preparation and housework [8, 9]. These data suggest that Ugandan patients demonstrate a relative decline on measures of verbal learning and memory, speed of processing, attention, and executive functioning compared to HIV negative controls. These deficits are likely to have an impact on a patient's ability to maintain employment outside of the home, or to complete activities to maintain the household. When this happens, many others are affected as well. Dependent children or parents will also experience the losses associated with these deficits: less income, food and caretaking ability. Initiation of antiretroviral therapy in these individuals may reverse some of these neuropsychological deficits, and allow continued employment and household maintenance.

There are noteworthy limitations that should be considered when interpreting the current study's findings. While there is a need for neurocognitive assessments in resource limited settings, our battery was relatively brief, which may limit its sensitivity to HIV-related neurocognitive impairment [22]. Further, we suspect that speaking Luganda is a surrogate marker for multiple factors, possibly including lower socioeconomic status, decreased access to healthcare and decreased nutritional status. These factors were not measured in the current study, but inclusion of these factors in future work may determine whether they individually affect the risk of HIV dementia.

Further studies to characterize AIDS Dementia and neuropsychological functioning in resource limited settings are necessary. The response of neurological disease to treatment will also be important to characterize. These studies will be particularly difficult to engage in, but can be aided by committed researchers on the ground who are competent and bring the necessary local experience to successfully complete them.

Table 1. Descriptives of Neuropsychological Functioning of HIV seronegatives and HIV seropositives

		HIV seropositives			HIV seronegatives			p value
		Valid			Valid			
		N	Mean	SD	N	Mean	SD	
Recall	AVLT	109	7.25	2.48	100	9.2	2.27	< .0001
total	AVLT	110	37.25	8.66	100	43.57	7.41	< .0001
ol Dig	Symb	105	24.13	11.41	100	31.12	11.27	< .0001
Dom	Pegs	108	91.58	26.9	100	86.48	21.33	< .15
Nond	Pegs	108	102.78	37.52	100	102.71	25.23	ns
	Gait	108	7.21	1.65	98	6.95	0.82	< .20
1	Trails	107	92.67	49.71	99	74.38	22.21	< .0005
2	Trails	106	166.97	57.67	99	124.51	37.01	< .0001
forward	Dig	110	4.91	0.89	100	5.28	0.87	< .005
back	Dig	110	2.99	1.1	100	3.47	0.9	< .001

**Note:** AVLT = WHO-UCLA Auditory Verbal Learning Test is similar to the Rey Auditory Verbal Learning Test; Symbol Dig = Symbol Digit Modalities; Pegs Dom = Grooved Pegboard using dominant hand; Pegs Nond = Grooved Pegboard using nondominant hand; Gait = Modified Timed Gait; Trails = Color Trails; Dig forward = WAIS Digit Span Forward; Dig Back = WAIS Digit Span Backward.

**Table 2: Neurocognitive performance by ADC Stage**

Stage	0 (Normal)		.5 (subclinical)		1 (mild)		F	p	Group difference ADC STAGE
	Mean	SD	Mean	SD	Mean	SD			
RAVLT Total	43	5.52	40.7	7.7	33.8	6.18	11.77	0.0001	0=.5<1
RAVLT Delayed Recall	8.84	1.71	8.14	2.23	5.5	2.06	16.99	0.0001	0=.5<1
Symbol Digit Grooved Pegs	36.63	7.85	25.77	10.78	17.33	9.81	20.36	0.0001	0>.5>1
Dominant Grooved Pegs	78.47	8.44	86.73	21.62	106.2	35.69	7.55	0.001	0=.5>1
Nondom	86.53	9.43	93.97	18.68	122.68	64.06	6.08	0.005	0=.5>1
Timed Gait	6.6	0.71	6.82	0.71	7.64	1.22	8.85	0.0005	0<.5=1
Color Trails 1	60.47	20.87	81.43	39.08	117.56	52.68	11.35	0.0001	0=.5<1
Color Trails 2	109.11	23.27	159.77	46.64	216.08	55.56	30.23	0.0001	0<.5<1
Digit Span Forward	5.26	0.99	5.03	0.83	4.64	0.81	2.99	0.06	0=.5,.5=1, 0<1
Digit Span Backward	3.79	0.85	3.08	1.06	2.64	0.86	7.79	0.001	0<.5=1

**Note.** ADC Stage is the Memorial Sloan Kettering AIDS Dementia Staging.

**Table 3: Neuropsychological Domains Tested**

<b>Domain</b>	<b>Test</b>
Verbal	
Memory/Learning	Delayed Recall -AVLT Total Recall -AVLT
Attention/Concentration	Symbol Digit Digit Span Forward and Backward
Fine Motor	Grooved Pegboard
Gross Motor	Timed Gait
Information Processing	
Speed	Trails 1
Abstraction/Reasoning	Trails 2

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