Benefits and risks of stavudine therapy for HIV-associated neurologic complications in Uganda

N. Sacktor, MD
N. Nakasujja, MB, ChB
R.L. Skolasky, ScD
K. Robertson, PhD
S. Musisi, FRCP
A. Ronald, MD
E. Katabira, FRCP
D.B. Clifford, MD, FAAN

Address correspondence and reprint requests to Dr. Ned Sacktor, Department of Neurology, Johns Hopkins Bayview Medical Center, 4940 Eastern Avenue, B Bldg. Rm. 123, Baltimore, MD 21224
sacktor@jhmi.edu

ABSTRACT

Background: The frequency of HIV dementia in a recent study of HIV+ individuals at the Infectious Disease Institute in Kampala, Uganda, was 31%. Coformulated generic drugs, which include stavudine, are the most common regimens to treat HIV infection in Uganda and many other parts of Africa.

Objective: To evaluate the benefits and risks of stavudine-based highly active antiretroviral therapy (HAART) for HIV-associated cognitive impairment and distal sensory neuropathy. The study compared neuropsychological performance changes in HIV+ individuals initiating HAART for 6 months and HIV− individuals receiving no treatment for 6 months. The risk of antiretroviral toxic neuropathy as a result of the initiation of stavudine-based HAART was also examined.

Methods: At baseline, 102 HIV+ individuals in Uganda received neurologic, neuropsychological, and functional assessments; began HAART; and were followed up for 6 months. Twenty-five HIV− individuals received identical clinical assessments and were followed up for 6 months.

Results: In HIV+ individuals, there was improvement in verbal memory, motor and psychomotor speed, executive thinking, and verbal fluency. After adjusting for differences in sex, HIV+ individuals demonstrated significant improvement in the Color Trails 2 test ($p = 0.025$) compared with HIV− individuals. Symptoms of neuropathy developed in 38% of previously asymptomatic HIV+ patients after initiation of the stavudine-based HAART.

Conclusions: After the initiation of highly active antiretroviral therapy (HAART) including stavudine, HIV+ individuals with cognitive impairment improve significantly as demonstrated by improved performance on a test of executive function. However, peripheral neurotoxicity occurred in 30 patients, presumably because of stavudine-based HAART, suggesting the need for less toxic therapy. ***Neurology*® 2009;72:165–170**

GLOSSARY

AVLT = Auditory Verbal Learning Test; **CES-D** = Center for Epidemiologic Studies–Depression Scale; **D-drug** = dideoxynucleoside antiretroviral drug; **GEE** = generalized estimating equation; **GP** = Grooved Pegboard test; **HAART** = highly active antiretroviral therapy; **HIV-SN** = HIV-associated sensory neuropathy; **IHDS** = International HIV Dementia Scale; **MSK** = Memorial Sloan-Kettering; **NA** = not applicable; **NS** = not significant; **SDMT** = Symbol Digit Modalities Test; **UCLA** = University of California-Los Angeles; **WHO = World Health Organization.**

The majority of HIV cases globally, an estimated 25 million people, are in sub-Saharan Africa.[1] HIV-1–associated dementia complex (HIV dementia) is characterized by disabling cognitive, behavioral, and motor dysfunction.[2] HIV-associated sensory neuropathies (HIV-SNs) are another common neurologic manifestation of advanced HIV infection seen in approximately 35% of HIV-infected patients.[3-5] HIV-SNs can be caused by HIV infection itself as a distal symmetric polyneuropathy or by exposure to dideoxynucleoside antiretroviral drugs (D-drugs), which include d4T (stavudine) as an antiretroviral toxic neuropathy. The frequency of HIV

From the Departments of Neurology (N.S.) and Orthopedic Surgery (R.L.S.), Johns Hopkins University School of Medicine, Baltimore, MD; Departments of Psychiatry (N.N., S.M.), and Medicine (E.K.), Makerere University, Kampala, Uganda; Department of Neurology (K.R.), University of North Carolina, Chapel Hill, NC; Department of Internal Medicine (A.R.), University of Manitoba, Winnipeg, Canada; and Department of Neurology (D.B.C.), Washington University, St. Louis, MO.

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dementia, the most severe form of HIV-associated neurocognitive disorders, in a recent study of ambulatory HIV+ patients in an Infectious Disease Clinic in Kampala, Uganda, was 31%.[6] The frequency of HIV-SN in this same study was 32%.

Highly active antiretroviral therapy (HAART) can improve cognitive performance in some patients with HIV dementia in the United States.[7-9] In a pilot study of 23 HIV+ individuals in Uganda, HAART also was associated with improvement in neuropsychological test performance.[10] This pilot study was without a control group so that the study was limited by the possibility of "practice effects." Furthermore, it is possible that HAART may improve peripheral neuropathy in some individuals, whereas it is a recognized toxicity in others.[11]

Generic drugs are the most commonly used antiretroviral drugs in sub-Saharan Africa. Triommune is a coformulation of stavudine, lamivudine, and nevirapine. Because of cost and availability, it is the most frequent generic regimen prescribed.

The objective of this study was to evaluate the benefits and risks of stavudine-based HAART for HIV-associated neurologic complications, namely HIV-associated cognitive impairment and HIV-SN in Uganda. Specifically, the study compared neuropsychological test performance changes in HIV+ individuals initiating Triommune for 6 months and HIV− individuals receiving no treatment for 6 months. The risk of antiretroviral toxic neuropathy as a result of the initiation of Triommune was also examined.

METHODS

Participants. The study was conducted, from September 2005 to January 2007, with 102 HIV+ individuals at the Infectious Disease clinic in Mulago Hospital and with 25 HIV− individuals from the AIDS Information Center in Kampala, Uganda.[12] The study was approved by the institutional review boards and ethical standards committees at Johns Hopkins University in Baltimore, Maryland, and Makerere University in Kampala, Uganda. Written patient consent was obtained from all individuals. All HIV− subjects had a documented negative ELISA HIV-1 test result. HIV+ individuals in the clinic were chosen to receive HAART using the following inclusion criteria: advanced HIV infection with a CD4 lymphocyte count <200 cells/μL, attendance of at least two clinic visits in the past 6 months, residence within a 20-km radius of Kampala, antiretroviral drug naive, performance on a screening test for HIV dementia (International HIV Dementia Scale [IHDS] score ≤ 10) suggestive of HIV-associated cognitive impairment,[13] and ability to provide written informed consent. Exclusion criteria included age less than 18 years, an active or known past CNS opportunistic infection, fever >37.5°C, a history of a chronic neurologic disorder, active psychiatric disorder, alcoholism, physical deficit (e.g., amputation), severe functional impairment (Karnofsky Performance Scale score <50),[14] or severe medical illness that would interfere with the ability to perform the study evaluations. The evaluations were translated into the local language, Luganda.

Clinical assessments. HIV+ individuals received clinical assessments using standardized questionnaires assessing demographic information, including primary language and reading abilities; medical, psychiatric, and neurologic history, including an assessment of peripheral neuropathy symptoms; and a neurologic examination, including assessments of vibration and pin sensation, limb strength and coordination, and deep tendon reflexes. The neurocognitive assessment included the IHDS[13] and a full neuropsychological test battery. The neuropsychological testing battery included the World Health Organization (WHO)–University of California-Los Angeles (UCLA) Auditory Verbal Learning Test (AVLT) for verbal memory[15]; the Timed Gait, Finger Tapping, and Grooved Pegboard tests to assess motor performance; the Symbol Digit Modalities test[16] and the Color Trails test[15] to assess psychomotor speed and executive functioning performance; Digit Span Forward and Backward to assess attention; and the category naming test to assess verbal fluency. The functional assessment included the Karnofsky Performance Scale.[14] These assessments were used to assign a Memorial Sloan-Kettering (MSK) dementia stage of 0, 0.5, or ≥ 1 by a consensus conference including a neurologist, a psychiatrist, and a neuropsychologist.[17]

All HIV+ subjects received a baseline CD4 lymphocyte count. Follow-up CD4 counts were obtained at 3 and 6 months after baseline. Plasma and CSF HIV RNA as well as neuroimaging were not available in this study.

HIV− individuals received identical clinical assessments except for the absence of CD4 lymphocyte counts. HIV− individuals were also followed up for 6 months.

Antiretroviral treatment. After the baseline visit, all of the HIV+ subjects began Triommune (stavudine, lamivudine, and nevirapine). HIV− individuals received no treatment.

Data analysis. For each neuropsychological test, a Z score was calculated using age- and education-adjusted normative data obtained from 100 HIV− individuals in Uganda.[6] Distributional tests have confirmed that the resultant Z scores follow a normal distribution, and scores are summarized as mean (SE). To account for loss-to-follow-up, longitudinal changes in the mean Z score for each neuropsychological test were evaluated at 3 and 6 months using generalized linear models for handling nonignorable dropouts for continuous outcomes.[18] Statistical inference for the model parameters was based on generalized estimating equations (GEEs).[19] The GEE model included HIV serostatus, study visit, and the interaction between HIV serostatus and study visit as important parameters. Significance of the interaction term was taken as inferential evidence of a difference in longitudinal performance between the HIV− and HIV+ groups. Type I error rates were adjusted for multiple comparisons using a Bonferroni correction. Distributional tests have confirmed that CD4 count, IHDS screening test, and Karnofsky Performance Scale scores did not follow a normal distribution, and scores were summarized as median and interquartile range (25th and 75th per-

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Table 1 Demographics of HIV+ and HIV− individuals

	HIV+ (n = 102)	HIV− (n = 25)	*p* Value
Age, mean (SD), y	34.2 (6.4)	30.3 (4.0)	0.004
Education, mean (SD), y	9.1 (4.3)	10.3 (4.2)	NS
Male, n (%)	29 (28)	15 (60)	0.003
CD4 count, mean (SD)	129 (79.0)	NA	
Karnofsky score, mean (SD)	84 (8.5)	98 (4.1)	<0.001
MSK HIV dementia stage, baseline, n (%)			
0 = no impairment	12 (12)	NA	
0.5 = equivocal/subclinical	48 (48)	NA	
1 = mild dementia	33 (33)	NA	
2 = moderate dementia	7 (7)	NA	

NS = not significant; NA = not applicable; MSK = Memorial Sloan-Kettering.

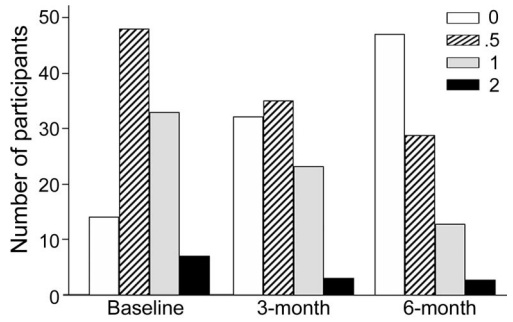
centiles). Longitudinal changes in these measures were evaluated using a nonparametric one-way analysis of variance.

RESULTS The demographics for the 102 HIV+ subjects and 25 HIV− subjects are summarized in table 1. The HIV+ subjects [mean (SD) age = 34.2 (6.4) years] were slightly older than the HIV− subjects [mean (SD) age = 30.3 (4.0) years] ($p = 0.004$). There were no differences in level of education between the two groups. The HIV+ group (28% male) had a greater proportion of women than the HIV− group (60% male) ($p = 0.003$). The HIV+ subjects in our study are representative of the demographics of HIV infection in Uganda.

Using the inclusion criteria of an IHDS score ≤10 suggesting HIV-associated neurocognitive disorders, the frequency of HIV dementia at baseline was high, with 33% presenting to the ambulatory clinic with mild HIV dementia (MSK dementia stage 1) and 7% presenting with moderate HIV dementia (MSK dementia stage 2). None of the HIV− individuals had impairment on their neuropsychological testing to consider a diagnosis of dementia. The HIV+ individuals also had more functional impairment at baseline as measured by the Karnofsky score [HIV+ group Karnofsky mean (SD) = 84 (8.5) vs HIV− group Karnofsky mean (SD) = 98 (4.1); $p < 0.001$].

The follow-up rates for the HIV+ and HIV− subjects were excellent. Among the HIV+ patients, 92% returned for their 6-month follow-up visit. Among the HIV− subjects, 84% returned for their 6-month follow-up visit. There was improvement in the mean CD4 count among the HIV+ subjects at both 3 and 6 months after the initiation of HAART. The mean CD4 count improved from 129 at baseline to 268 at 3 months ($p < 0.001$) and to 272 at 6 months ($p < 0.01$).

Figure 1 Memorial Sloan-Kettering HIV dementia stage changes after 3 and 6 months of highly active antiretroviral therapy



0 = Memorial Sloan-Kettering (MSK) 0 (normal cognitive function); 0.5 = MSK 0.5 (equivocal symptoms or signs without impairment in capacity to perform activities of daily living); 1 = MSK 1 (mild HIV dementia); 2 = MSK 2 (moderate HIV dementia).

Neurocognitive improvement with HAART. As shown in the figure 1, improvements in the MSK HIV dementia stage were noted among the HIV+ subjects after 6 months of HAART. After 3 months, 23% of the HIV individuals had mild HIV dementia (MSK dementia stage 1) and 3% had moderate HIV dementia (MSK dementia stage 2). After 6 months, 13% of the HIV+ individuals had mild HIV dementia (MSK dementia stage 1) and 3% had moderate HIV dementia (MSK dementia stage 2) ($p < 0.001$).

Table 2 shows the changes in the mean neuropsychological test performance for each of the neuropsychological tests after 3 and 6 months of HAART among the HIV+ subjects. Compared with baseline, improvement was seen in tests of verbal memory (WHO–UCLA AVLT total score and delayed recall at 3 and 6 months), psychomotor speed and executive functioning (Color Trails 1 and 2 at 3 and 6 months, Symbol Digit Modalities test at 6 months only), motor performance (Timed Gait and Grooved Pegboard dominant hand at 6 months only, Grooved Pegboard nondominant hand and Finger Tapping at 3 and 6 months), and verbal fluency (category naming at 3 and 6 months).

Table 3 shows the changes in the mean neuropsychological test performance for each of the neuropsychological tests after 6 months among the untreated HIV− subjects. Compared with baseline, among the HIV− subjects, improvement was seen in a test of motor speed (Grooved Pegboard nondominant hand at 3 months, Grooved Pegboard dominant hand at 6 months) and psychomotor speed (Color Trails 1 at 6 months only). Also, there was borderline improvement in tests of verbal memory [AVLT total score ($p = 0.09$) and delayed recall ($p = 0.08$) at 6 months]. No other neuropsychological test showed improvement compared with baseline among the HIV− subjects.

Compared with the HIV− subjects, HIV+ subjects showed improvement on the Color Trails 2 test ($p = 0.02$) after adjusting for differences in sex (fig-

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Table 2 Neuropsychological test performance at baseline and 3 and 6 months after HAART among HIV+ patients

Neuropsychological test	Baseline Z score* (n = 102)	3-Month Z score* (n = 94)	p Value†	6-Month Z score* (n = 95)	p Value†
AVLT total score	−1.2 (0.1)	−0.4 (0.1)	<0.001	−0.1 (0.2)	<0.001
AVLT delayed recall	−1.2 (0.1)	−0.4 (0.2)	0.003	−0.1 (0.1)	<0.001
Color Trails 1	−1.7 (0.3)	−0.7 (0.2)	<0.001	−0.4 (0.3)	<0.001
Color Trails 2	−2.8 (0.3)	−1.9 (0.4)	0.001	−1.3 (0.2)	<0.001
SDMT	−0.8 (0.1)	−0.5 (0.1)	NS	−0.3 (0.1)	0.002
GP, dominant hand	0 (0.2)	−0.2 (0.1)	NS	0.4 (0.1)	0.014
GP, nondominant hand	−0.7 (0.2)	0.1 (0.1)	<0.001	0.3 (0.1)	<0.001
Finger tapping	−1.0 (0.1)	−0.5 (0.1)	0.001	−0.5 (0.1)	0.002
Timed gait	−2.7 (0.3)	−2.3 (0.3)	NS	−1.8 (0.3)	0.028
Verbal fluency	−0.4 (0.4)	−0.1 (0.1)	0.007	0 (0.1)	<0.001

*Mean (SE).
†Compared with performance at baseline.
HAART = highly active antiretroviral therapy; AVLT = Auditory Verbal Learning Test; SDMT = Symbol Digit Modalities Test; NS = not significant; GP = Grooved Pegboard test.

ure 2). Other tests, e.g., WHO–UCLA AVLT, showed trends for greater improvement among the HIV+ subjects compared with the HIV− subjects, but this difference was not significant.

Functional improvement with HAART. There was improvement in the functional performance (Karnofsky scale) at both 3 and 6 months after the initiation of HAART among HIV+ subjects. The mean Karnofsky score improved from 84 at baseline to 87 at 3 months ($p = 0.002$) and to 89 at 6 months ($p < 0.001$). A Karnofsky score of 80 indicates an individual who is able to do normal activity with effort but shows some disease symptoms or signs. A Karnofsky score of 90 indicates an individual who is able to do normal activity without effort but shows minor disease symptoms or signs.

Table 3 Neuropsychological test performance at baseline and 3 and 6 months after HAART among HIV− patients

Neuropsychological test	Baseline Z score* (n = 25)	3-Month Z score* (n = 25)	p Value†	6-Month Z score* (n = 25)	p Value†
AVLT total score	−0.4 (0.3)	−0.4 (0.4)	NS	0.2 (0.2)	NS
AVLT delayed recall	−0.6 (0.2)	−1.1 (0.6)	NS	0.1 (0.2)	NS
Color Trails 1	−0.3 (0.3)	0.2 (0.3)	NS	0.8 (0.2)	0.006
Color Trails 2	−0.8 (0.3)	−0.4 (0.4)	NS	−0.4 (0.3)	NS
SDMT	−0.4 (0.3)	−0.2 (0.3)	NS	0.4 (0.3)	NS
GP, dominant hand	0.3 (0.3)	0.9 (0.2)	NS	0.8 (0.2)	0.032
GP, nondominant hand	−0.1 (0.2)	0.7 (0.2)	0.011	0.6 (0.2)	NS
Finger tapping	−0.0 (0.2)	−0.1 (0.3)	NS	0.1 (0.2)	NS
Timed gait	−1.5 (0.5)	−0.4 (0.5)	NS	−1.7 (0.4)	NS
Verbal fluency	−0.0 (0.2)	−0.2 (0.3)	NS	0.4 (0.3)	NS

*Mean (SE).
†Compared with performance at baseline.
HAART = highly active antiretroviral therapy; NS = not significant; AVLT = Auditory Verbal Learning Test; SDMT = Symbol Digit Modalities Test; GP = Grooved Pegboard test.

Neuropathy changes over time. Among the HIV+ subjects, 37% had foot numbness at baseline.[20] Signs of neuropathy (loss of vibration or pinprick sensation, decreased or absent ankle reflexes) were present in 43% of the HIV+ subjects at baseline. In contrast, only 1 (4%) of the HIV− controls had foot numbness at baseline, and 1 (4%) of the HIV− controls had signs of neuropathy at baseline. After 6 months, 54% of the HIV+ subjects had numbness in the feet. Symptoms of neuropathy were described in 38% (n = 30) of previously asymptomatic HIV+ patients after initiation of the stavudine-based HAART. Signs of neuropathy were detected in 31% ($p = 0.03$) of the HIV+ individuals who did not have signs at baseline after initiation of HAART. There were no differences in the age, education, sex, or CD4 count among asymptomatic HIV+ patients who developed symptoms of neuropathy and asymptomatic HIV+ patients who did not develop symptoms of neuropathy after initiation of the stavudine-based HAART. Similarly, there were no differences in the age, education, sex, or CD4 count among HIV+ patients without signs of neuropathy at baseline who developed signs of neuropathy and HIV+ patients who never developed signs of neuropathy after initiation of the stavudine-based therapy. In contrast, only 1 (4%) of the HIV− controls had an increase in neuropathy symptoms from baseline, and only 1 (4%) had an increase in neuropathy signs from baseline.

After the initiation of the stavudine-based HAART, some HIV+ subjects had improvement in neuropathy symptoms and signs present at baseline. Among HIV+ subjects with foot numbness at baseline, 22% no longer had numbness after 6 months of the stavudine-based HAART. Among HIV+ subjects with signs of neuropathy at baseline, 23% no longer had neuropathy signs after 6 months of the stavudine-based HAART.

DISCUSSION

The results from this study support the clinical benefit of HAART for stavudine-based therapy in HIV+ individuals in Uganda. After the initiation of HAART, HIV+ individuals had improvement in their level of immune suppression with increased CD4 counts. HIV+ individuals had improvement in their overall functional performance as measured by the Karnofsky scale. HIV+ individuals also had improvements in their neurocognitive performance in tests of verbal memory, psychomotor and motor speed performance, executive functioning, and verbal fluency similar to the results of a prior

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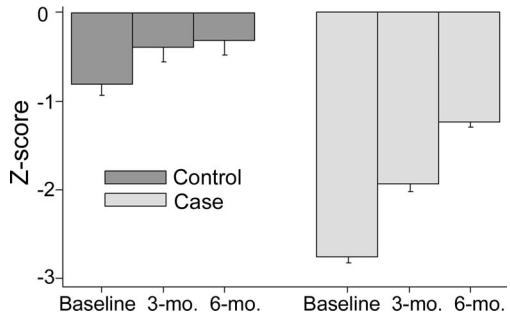
Figure 2 **Color Trails 2 changes over 6 months**



Case = HIV+ individual; control = HIV− individual. Y-axis corresponds to the *Z* score on the Color Trails 2 test.

pilot study in Uganda evaluating the effect of HAART on neurocognitive performance.[10]

The neuropsychological test improvement among HIV+ individuals is likely due to a combination of both HAART-associated improvements in immune suppression and neurocognitive function as well as practice effects. Compared with HIV− individuals, HIV+ individuals showed greater improvement in Color Trails 2, a test of executive functioning, suggesting that practice effects alone cannot account for the improvements seen in executive functioning. However, a ceiling effect for performance on this test, where the HIV− subjects could not improve significantly from baseline normal function, could have limited the learning effects relevant to the control group. Other cognitive domains, e.g., verbal memory, showed trends for greater improvement among HIV+ individuals compared with HIV− individuals. However, the sample size of the study may not have been large enough to detect a difference between the two groups. In addition, it is possible that some of the neurocognitive impairment among the HIV+ individuals at baseline may have been due to confounding factors other than HIV infection itself, and thus unlikely to improve with HAART.

The prevalence of neuropathy symptoms and signs at baseline in our study is similar to the prevalence of neuropathy symptoms and signs in Western countries among HIV+ patients with advanced immunosuppression,[3-5] because the mean CD4 count of our HIV+ cohort was 129 cells. Stavudine-based HAART is also associated with some measurable neurologic morbidity. In Western countries, D-drug based HAART is rarely used now because of the risk of peripheral neuropathy. In our study in Uganda among HIV+ patients without peripheral neuropathy at baseline, 31% to 38% of these patients developed either symptoms or signs of neuropathy during the study. The onset of the symptomatic neuropathy experienced after starting therapy was prompt within the first 3 months of the trial, suggesting that stavudine may have been the cause of the neuropathy or stavudine decreased the threshold for developing an HIV-related neuropathy. The severity of these symptoms did not lead to HAART discontinuation in any of these patients. However, the study duration was only 6 months. At present, it is unclear whether a cumulative toxicity of stavudine over longer periods of treatment might result in a greater proportion affected or more severe neuropathy in those taking this therapy. Future studies of neuropathy should include a more extensive period of follow-up.

There are limitations to the study. The study was conducted among HIV+ patients from an urban setting in Kampala, Uganda, which is likely to be representative of the urban HIV+ community in Uganda. However, it may not necessarily reflect the HIV+ population in rural Uganda.

All study participants received a screening test for depression symptomatology, the Center for Epidemiologic Studies–Depression Scale (CES-D).[21] At baseline, the mean CES-D score for the HIV+ group was 18.1 (SD 11.4). Thus, some patients may have had major depression. However, a psychiatrist on site evaluated any patient in which an active psychiatric condition was a concern.

HIV subtypes D and A are the predominant subtypes in Uganda, whereas subtype C is the predominant subtype in southern Africa. If HIV subtype has an effect on HIV neuropathogenesis, our results in Uganda may not necessarily reflect the HIV+ population throughout Africa.

HIV+ patients did not receive either neuroimaging or CSF examinations to rule out another CNS disease as the cause for an individual's cognitive impairment. Other infectious diseases, such as tuberculosis, syphilis, or malaria, or malnutrition could have contributed to the cognitive impairment in our study participants. However, all HIV+ patients did receive a detailed neurologic history and examination (including an evaluation of fever, headache, neck stiffness, and focal abnormalities). Any HIV+ patient with a suspected CNS opportunistic infection or neoplasm was excluded from the study.

The neuropsychological tests that showed the largest improvement among the HIV+ patients were the tests that had the largest baseline *Z* score deficits. Thus, regression to the mean may have been a contributing factor for some of the neurocognitive improvement seen among the HIV+ patients.

HIV+ individuals demonstrated greater improvement in functional performance compared with HIV− individuals. However, the HIV− individuals had normal functional performance in gen-

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eral, so this group had little capacity for further improvement.

The cause of the neuropathy could not be fully determined due to the design of the study. A screening question for diabetes was included, and two HIV+ individuals reported a history of diabetes. Screening tests for other causes of neuropathy and electrophysiological studies were not available in Uganda. Ideally, a group of HIV+ individuals with the same inclusion criteria at study entry who were not on a stavudine-based regimen could have been evaluated, but this group of patients did not exist at the time of the study.

HAART is a lifesaving therapy for HIV+ patients with advanced immunosuppression in sub-Saharan Africa, and if a patient meets clinical criteria, HAART should be initiated without delay. If no other antiretroviral drug options are available, stavudine-based HAART can provide benefit with respect to immune system restoration and improvement in executive functioning in HIV+ individuals with neurocognitive impairment. However, this study provides data demonstrating that peripheral neurotoxicity is a significant problem from stavudine-based HAART, and if possible, alternative antiretroviral drug combinations should be provided. It is anticipated that future trends will have decreased use of stavudine-based therapies in resource limited countries. Additional resources to provide HAART regimens without stavudine would provide a great benefit by preventing a potential increase in the prevalence of painful peripheral neuropathy among millions of HIV+ individuals who will need HAART within the next several years in sub-Saharan Africa.

AUTHOR CONTRIBUTIONS

Statistical analysis was conducted by R.L.S.

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