Cognitive Impairment and Psychiatric Morbidity in HIV+ Zambians with New-Onset Seizure

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Abstract. A prospective cohort study of new-onset seizure in people with human immunodeficiency virus (HIV) in Zambia is ongoing to determine the incidence of subsequent epilepsy and risk factors for epileptogenesis in this population. At enrollment, we evaluated this cohort for cognitive impairment and psychiatric morbidity. Over 50% of participants had cognitive impairment and significant psychiatric morbidity. Most participants had advanced HIV disease based on CD4+ T-cell count and World Health Organization stage, but we found no association between cognitive impairment or psychiatric morbidity and HIV disease staging.

INTRODUCTION

With the introduction of combined antiretroviral therapy (cART), there has been a global increase in the number of people living with human immunodeficiency virus (HIV). In the developed and developing world, longer survival has been accompanied by improved quality of life among people living with HIV.^{1,2} However, cART improves but does not fully eliminate impaired cognitive functioning of people with HIV.³

HIV-associated neurologic disorders (HANDs) are a common complication of HIV in sub-Saharan Africa.^{4–6} Before the availability of cART in Lusaka, Zambia, at least 55% of HIV+ hospice patients had significant cognitive impairment.⁷ Psychiatric morbidity (anxiety and depression symptoms), present in approximately 80% of individuals, was an independent predictor of early mortality, even after controlling for HIV stage.⁸ Even if cART reduces HAND by approximately 60%, over 8 million HIV-infected adults in sub-Saharan Africa will be cognitively impaired at some level.⁹ Some have hypothesized that people with HIV experience early aging.¹⁰ If African populations with HIV experience such early aging effects, the burden of cognitive disabilities in the region will substantially increase in the coming years.

Early and more intense central nervous system (CNS) viral invasion/replication could potentially pre-dispose to HAND,¹¹ but how different neuropsychiatric morbidities impact the overall health and functional capacity of long-standing HIV survivors is not well-understood. Although HIV-associated dementia is an acquired immunodeficiency syndrome (AIDS)-defining illness that indicates the need for cART, most African HIV clinics do not routinely screen for it, because culturally relevant screening tools are not readily available and neurologic expertise is sparse.^{7,12}

Seizures and epilepsy are also common neurologic problems among people with HIV.¹³ Seizures caused by opportunistic infections (OIs) can occur in advanced HIV disease but may also occur early in the course of the illness.¹⁴ Epilepsy management in HIV-infected individuals is especially chal-

lenging in resource-limited African settings, because only enzyme-inducing antiepileptic drugs (EI-AEDs), which interact with antiretroviral medications (ARVs) in adverse and unpredictable ways, are readily available/affordable.^{15,16}

To better understand the neuropsychiatric health of people with HIV in an HIV-endemic African setting, we assessed baseline cognitive function and psychiatric symptom burden of participants in the Cohort of HIV-Associated Seizures and Epilepsy (CHASE) Study, an ongoing prospective cohort study of HIV-positive adult Zambians presenting with new-onset seizure.

METHODS

Participants. Participants were recruited from the University Teaching Hospital in Lusaka. Between August 8, 2011 and May 10, 2013, 95 individuals provided informed consent to participate. Inclusion criteria required that study participants be at least 18 years old and HIV+ with a seizure in the past 14 days and no history of prior seizures, except for childhood febrile seizures. Evaluation during the index admission included history and seizure presentation, neurological examination, Glasgow Coma Score (GCS) at enrollment, World Health Organization (WHO) HIV/AIDS staging, CD4+ T-cell count, lumbar puncture for cerebrospinal fluid (CSF) polymerase chain reaction (PCR) analyses, serum cryptococcal (crypto) antigen, and other clinical laboratory studies as indicated and available. CSF cryptococcal antigen was not obtained. Any laboratory evidence of a CNS OI, whether by CSF PCR, serum cryptococcal antigen, or serum rapid plasma reagin was accepted as evidence of a CNS infection. We also assessed for past histories of malaria severe enough to require hospitalization, meningitis, and traumatic brain injury with loss of consciousness, because these past exposures could also impact cognitive function.

Cognitive and psychiatric evaluations. Participants were scheduled for cognitive and psychiatric assessments approximately 2 weeks to 2 months post-discharge from the index seizure-related admission. The neuropsychiatric assessments were not evaluated in the inpatient setting, because such evaluations may have been unduly influenced by the recent seizure/acute illness. Transport funds or actual transportation were provided to facilitate evaluations for all participants.

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Assessments were conducted by a graduate-level trained neuropsychologist (L.K.) in a quiet private office setting.

The Zambian Mini Mental State Examination (zMMSE) and the International HIV Dementia Scale (IHDS) were used to assess cognitive function. The Shona Symptom Questionnaire (SSQ) was used to identify psychiatric morbidity. The zMMSE is an adaptation of the standard MMSE with minor item substitutions made to accommodate individuals with limited literacy. The zMMSE is commonly used by clinicians and researchers in Zambia.^{4,7,8} The IHDS is a widely used scale for assessing HIV-associated dementia. The scale measures three neuropsychological domains, which include (1) memory and registration, (2) psychomotor speed, and (3) memory recall. The IHDS has been used in Zambia to assess HAND with previously established norms using a cutoff of 10.^{4,7,8} The SSQ is a 14-item instrument initially developed in neighboring Zimbabwe to identify symptoms of anxiety and depression.^{17,18} Questions capture the presence or absence of specific anxiety and depressive symptoms, with a higher score indicating greater burden (maximum of 14). A score of five or higher indicates the need for additional psychiatric assessment and support.¹⁸

Data management and analysis. Demographic, clinical, and neuropsychiatric data were collected on paper forms before data entry into Microsoft Excel. The data were then reviewed for accuracy before being imported into EPI INFO, version 7.0 for analysis. Descriptive statistics were evaluated, and *t* and χ^2 tests were used to examine the association between demographic and clinical characteristics and cognitive or psychiatric morbidity based on mean test scores without reference to prior normative data. For comparison of two continuous variables, analysis of variance (ANOVA) was used unless Bartlett's test for inequality of population variance indicated the need to use the Mann-Whitney/Wilcoxon test.

Ethical considerations. Ethical approvals were obtained from the University of Zambia's Biomedical Research Ethics Committee (UNZA BREC) and Michigan State University's Biomedical Institutional Review Board (MSU BIRB) before study initiation.

RESULTS

Among 95 CHASE participants, 58 (61%) participants underwent cognitive and psychiatric evaluations. Of 58 participants, 31 (53%) participants were male; mean age was 36.8 years (interquartile range [IQR] = 28–47 years). Of 37 participants not tested, 1 participant came for testing but was unable to participate because of severe cognitive compromise, 29 participants died before testing could occur, 2 participants withdrew from study participation, 1 participant moved out of Lusaka, and 4 participants were lost to follow-up, despite multiple attempts to contact them. Neuropsychiatric assessments were conducted a median of 50 days after the index seizure (mean = 72 days; SD = 75 days; modes = 18 and 21 days). Demographic and clinical data are provided in Table 1. At enrollment, just over one-third of participants were on cART, with most being WHO stage III or IV and having a mean CD4+ T-cell count of 187 (IQR = 32–246). Over one-half experienced complex seizures, which were defined as seizures that lasted longer than 15 minutes or multiple or prolonged seizures at presentation that were not status epilepticus. Prolonged seizures were defined as

TABLE 1
Demographic and clinical characteristics (N = 58)

Characteristic	Measurement
Sex (male), n (%)	31 (53)
Age, mean years (IQR)	36.8 (28–47)
Family history of epilepsy (N = 56), n (%) positive)	9 (16)
History of severe malaria, n (%)	4 (7)
History of meningitis, n (%)	5 (9)
History of traumatic brain injury, n (%)	1 (2)
WHO stage (N = 57), n (%)	
I	8 (14)
II	2 (4)
III	22 (39)
IV	25 (44)
CD4+ T-cell count, mean (IQR)	187 (32–246)
ARV use, n (%)	
Never	33 (57)
At enrollment	21 (36)
Defaulted	4 (7)
Fever during admission, n (%)	21 (36)
Seizure severity, n (%)	
Brief, single	20 (34)
Multiple or prolonged, not status	32 (55)
Status epilepticus	6 (10)
Focal seizure, n (%)	26 (45)
GCS 15 at time of enrollment (N = 57), n (%)	49 (86)
RPR+ (N = 57), n (%)	11 (19)*
Cryptococcus neoformans+† (N = 51), n (%)	8 (14)
Toxoplasmosis antibody (N = 9), n (%)	3 (33)
Tuberculosis (N = 40), n (%)	2 (5)
JC virus (N = 40), n (%)	3 (8)
CMV (N = 40), n (%)	3 (8)
Epstein-barr virus‡ (N = 40), n (%)	11 (28)
Varicella zoster virus (N = 40), n (%)	2 (4)
Any PCR+ (N = 40), n (%)	17 (43)
Any CNS OI identified (N = 40), n (%)	19 (48)

* *Treponema pallidum* hemagglutination assay in 5 (45%) of 11 participants.

† By India ink or antigen on serum sample.

‡ EBV positivity may be a marker for either viral encephalitis or CNS lymphoma.

seizures that lasted more than 15 minutes at presentation. Ten percent experienced *status epilepticus*. Focal seizures occurred in almost one-half of participants; underlying CNS infections were evident in about one-half of participants.

The mean scores for the zMMSE, IHDS, and SSQ are shown in Table 2 along with details on the proportion that met previously established cutoffs for cognitive impairment and/or the need for additional psychiatric evaluation; 48 (83%) of 58 participants had an abnormal score on at least one of the instruments. Figure 1 illustrates the distribution of cognitive impairment and psychiatric morbidity in the study population. About one-half of the participants had evidence of cognitive impairment on the IHDS and zMMSE, with the results of these assessments being highly correlated ($P = 0.0004$). Psychiatric morbidity exceeding the established cutoff for additional evaluation was evident in 55% of participants. The SSQ score did not correlate with either the zMMSE or the IHDS (P values > 0.05).

Clinical and demographic characteristics associated with cognitive impairment and psychiatric morbidity are shown

TABLE 2
Neuropsychiatric evaluations (N = 58)

Evaluation	Mean score (IQR)	Cutoff for abnormal	Abnormal
zMMSE	20.0 (19.5–23.5)	< 22	29 (50%)
IHDS	8.5 (8.5–10.5)	< 10	31 (53%)
SSQ	5.0 (7.5–10.0)	> 4	32 (55%)

FIGURE 1. Number of participants showing impairment on neuropsychiatric measures ($N = 48$).

in Table 3. Men had better cognitive function and less psychiatric morbidity than women based on the IHDS and SSQ ($P = 0.04$ and $P = 0.02$, respectively). Men and women did not differ significantly on mean CD4+ T-cell count or WHO stage. Greater psychiatric morbidity was also associated with a GCS of 15 at admission ($P = 0.01$).

Test results were not dichotomized into normal and below normal, because we do not have fully validated norms for these instruments in the Zambian population. Given this limitation, we conducted a sensitivity analysis with dichotomous outcome using cutoffs from other African populations. The only difference in findings was that the sex difference on the zMMSE was no longer significant; also, on the zMMSE, poorer scores were seen among patients who had focal neu-

rologic findings on admission. The sex difference on psychiatric burden and the association between a normal GCS and higher psychiatric morbidity remained significant.

DISCUSSION

This study identified evidence of cognitive impairment and significant psychiatric morbidity in 50% of people with HIV and new-onset seizure. Compared with a large cohort of approximately 500 rural Zambians commencing cART as part of the Rural ART Adherence in Zambia (RAAZ) study,⁸ where the mean IHDS was 9.0 (42.1% of participants scored below the norm) and the mean zMMSE was 21.6 (34.4% of participants scored below the norm), the means in the RAAZ and CHASE populations were fairly comparable, but more people in the CHASE cohort were below the norm, suggesting that they are, indeed, more impacted by cognitive impairment. All of the CHASE patients had seizures, and therefore, it is reasonable to consider that CHASE patients had a relatively higher level of CNS involvement (prior HIV, OI, etc.) from their HIV infection relative to HIV+ populations without a history of seizure. Given the intentional delay between index seizure and testing, it is unlikely the poor cognitive scores are related to the index seizures.

There is a great deal of overlap in neuropsychiatric morbidity, with 16 (26%) of 58 participants having impairment on all three measures (zMMSE, IHDS, and SSQ). However, as was shown previously in Uganda,¹⁹ cognitive impairment and psychiatric morbidities are independent clinical entities. Correlations on the three measures show a significant relationship between the two dementia scales ($P = 0.01$) and an inverse non-significant relationship between the dementia scales and SSQ.

Although the study population had a high prevalence of advanced HIV disease based on CD4+ T-cell count and WHO stage, we found no association between cognitive impairment or psychiatric morbidity and HIV disease stage. Other studies in Zambia using more sophisticated mental health assessments reported a similar absence of association.²⁰

TABLE 3
Association between patient characteristics at the time of new-onset seizure and neuropsychiatric morbidities ($N = 58$)

Characteristics	IHDS P value (mean)	zMMSE P value (mean)	SSQ P value (mean)
Sex (male)	0.78	0.04 (20.8 vs. 18.5)*	0.02 (4.1 vs. 6.1)*
Age (mean years)	0.39	0.22	0.60
History of severe malaria	0.92	0.95	—
History of meningitis	0.34	0.58	—
History of traumatic brain injury	0.56	0.35	—
Seizure severity (categories)	0.72	0.48	0.76
Focal seizure ($\pm$)	0.09	0.58	0.71
Antiretroviral use (3 categories)	0.47	0.10	0.34
Fever during index admission ($\pm$)	0.42	0.95	0.53
Glasgow Coma Score 15 at enrollment	0.76	0.30	0.001 (5.6 vs. 1.9)*
WHO stage†	0.40	0.50	0.60
CD4 (mean)	0.52	0.97	0.14
Rapid plasmin reagin ($\pm$)	0.33	0.29	0.36
Cryptococcal neoformans ($\pm$)	0.10	0.82	0.61
Tuberculosis by PCR ($\pm$)	0.29	0.25	0.09
Varicella zoster virus by PCR ($\pm$)	0.64	0.48	0.94
Epstein-barr virus by PCR ($\pm$)	0.93	0.71	0.48
JC virus by PCR ($\pm$)	0.32	0.36	0.93
Cytomegalovirus by PCR ($\pm$)	0.15	0.11	0.80
Any PCR ($\pm$)	0.59	0.40	0.58
Any CNS OI ($\pm$)‡	0.27	0.50	0.19

* $P < 0.05$.

† Stages I and II as a single category.

‡ Note that five patients had two OIs detected (crypto + JC, EBV + CMV, crypto + EBV, and two cases of crypto + VZV).

The state of immune suppression in our study population probably explains the finding that 50% of participants had an OI identified as the likely underlying seizure cause.

The prevalence of neuropsychiatric morbidity in this urban Zambian population is comparable with rates reported in studies conducted in general populations of people with HIV before cART was available.^{4,7,8,21} However, 83% of patients in our study were WHO stage III or IV compared with 55% of the rural population of people with HIV accessing cART as cART initially became available. New-onset seizure in HIV+ individuals may be evidence for more advanced disease, prompting consideration of cART initiation and/or regimen adjustments.

There are several limitations of this work. We have data for only approximately 60% of the CHASE cohort. Neuropsychiatric data were not available for those who died, making it a survival cohort analysis. We also were not able to complete the evaluation within the planned 2-month window, and it is possible that cognitive and psychiatric problems identified were not present at the time of the index seizure and enrollment. Forty percent of assessments occurred outside of the 60-day window (range = 5–427 days). Finally, the structure of the SSQ is such that patients must answer affirmatively to questions for the detection of symptoms of anxiety or depression. As such, less engaged or attentive patients responding passively would likely be scored as not having a particular symptom. This is an inherent feature of the SSQ, but it may also explain why patients with a higher GCS on admission scored higher on the SSQ.

In this study, men had better cognitive function based on the zMMSE (although not the IHDS), and women suffered from more psychiatric symptoms. Sex differences in the zMMSE were no longer significant in our sensitivity analysis using dichotomous test outcomes. Other studies of neuropsychological effects of HIV in Zambia also found that women suffer more in the neuropsychological domains.^{4,21} Hestad and others²¹ found that women score poorly compared with men on the Beck Depression Scale and argue that HIV is more likely to cause affective disturbance in women than men. This may be because of the disproportionate burden of stigma and discrimination faced by women who contract HIV.²² Because psychiatric morbidity has been shown in at least one study to be associated with early mortality,⁸ additional research warranted.

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