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HIV-1 Effects on Neuropsychological Performance in a Resource-Limited Country, Zambia

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Abstract Zambia has substantially been affected by the HIV/AIDS epidemic with prevalence rates at 14% in a population estimated at 12 million. Yet, the extent of HIV-associated neurocognitive disorders (HAND) in this population remains to be clearly understood. A series of culturally appropriate neuropsychological (NP) assessments [International HIV Dementia Scale (IHDS), Color Trails Test 1 and 2, Grooved pegboard Test, and Time Gait Test] were used to test the effects of HIV on NP performance of HIV seropositive and seronegative individuals. Twenty-two percent HIV positive individuals ARV naïve met the criteria for IHDS-defined NP impairment. Gender significantly influenced the performance on NP tests with females performing more poorly compared to males. Larger studies that will accommodate gender differences and age are necessary to generate appropriate norms in Zambia in order to better assess the prevalence of HAND in the developing country setting.

Keywords NeuroAIDs · Sub-Saharan Africa · HIV-associated neurocognitive disorders · HIV subtype C

Resumen Zambia ha sido significamente afectado por la epidemia de VIH/SIDA, con tasas de prevalencia del 14% en una población estimada en 12 millones. Sin embargo, en cuestión a los trastornos neurocognitivos asociados con el VIH (TNAV) aún se desconoce en esta población. Una serie de evaluaciones neuropsicológicas (NP) culturalmente apropiados [Escala Internacional de Demencia asociada a VIH (EIDAV), las Pruebas Color Trails™ 1 y 2, La prueba tablero ranurado de clavijas, y la prueba del tiempo de marcha] se utilizaron para probar los efectos del VIH en el rendimiento NP de personas VIH seropositivos y seronegativas. Veintidós por ciento de las personas VIH positivas sin manejo previo con antiretrovirales cumplieron con los criterios de un deterioro NP definido como EIDAV. El genero influyo importantemente en el desempeño en las pruebas NP, con un rendimiento mas pobre en las femeninas en comparación con los masculinos. Estudios de mayores dimensiones que tomen en cuenta las diferencias de género y edad son necesarios para generar normas adecuadas en Zambia con el fin de evaluar mejor la prevalencia de los TNAV en el escenario de los países en desarrollo.

Introduction

The global HIV epidemic has been most devastating in sub-Saharan Africa in which two-thirds of the estimated

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33.3 million of the HIV infected individuals reside [1]. One of the major challenges of the HIV epidemic is that there are surmountable medical complications [2] along with neurocognitive disorders [3]. In Western/developed countries, there is now a better appreciation for the effects of HIV on cognitive function. Initially, the neuropsychological (NP) profile was classified as a constellation of symptoms recognized as HIV associated dementia that manifested as cognitive, motor, and behavioral abnormalities in AIDS patients [4], with a yearly incidence rate of 7.3% [5]. Over the years and with the introduction of antiretroviral therapies (ARV) it became clearer that HIV infection leads to progressive impairment in brain function [6–9]. Since then, the description has been refined to include three main categories that ranged from less severe to more severe symptoms classified as HIV-associated asymptomatic neurocognitive impairment (ANI), HIV associated mild neurocognitive disorder (MND), and HIV associated dementia (HAD) collectively referred to as HIV-associated neurocognitive disorders or HAND [3]. The aforementioned literature is derived from regions where HIV subtype B predominates, however, less is known in other parts of the world where the epidemic is most concentrated, as in the case in sub-Saharan Africa.

Over the last 20 years, though sporadic, there are studies that addressed HIV associated neurocognitive impairment prevalence in sub-Saharan Africa with a wide range of HAND prevalence rates of 3.2–56% [8, 10–17]. This can be partly attributed to the methodological approaches of earlier studies that were based mostly on clinical assessments to determine HIV associated neurological and neurocognitive impairments [10–12]. The studies that followed used a series of culturally adapted NP assessments to screen for evidence of HAND [13, 14, 18, 19].

More recently, a few studies have investigated the neurological and neuropsychological impairments of HIV infected individuals from subtype C HIV predominant regions [20–23]. However, there were conflicting results regarding evidence for marked HAND. A study from Ethiopia concluded that for the exception of impaired psychomotor function, no marked cognitive disorders were evident in a predominately asymptomatic cohort [20]. In contrast, a study from South Africa reported a 23.5% HAND prevalence [22] defined by the HIV Dementia Scale (HDS) [24, 25]. Furthermore, a recent study from Botswana [21] reported that 38% of HIV infected individuals primarily on ARV treatment (97.5%) presented with HAND symptoms defined by the IHDS [18]. There are impoverished regions in sub-Saharan Africa in which HIV is endemic yet little is known about the effects of HIV on neurocognitive function such as in Zambia.

Zambia, a low income country and one of the poorest countries in sub-Saharan Africa (2005 Human Development Report), has been considerably affected by the HIV epidemic with prevalence rates of 14% in a population of 12 million [1, 26]. In Zambia, HIV subtype C is prevalent but the neurological and psychological effects of HIV are not defined. This is attributable to the lack of NP tools in this area as well as a lack of properly trained personnel to administer NP tests to patients. Furthermore, since 2002 ARV treatment has become available in Zambia and treatment programs were scaled up over the past several years [27]. The common regimen includes a combination of anti-retroviral regimen that consists of two nucleoside reverse transcriptase inhibitors (NRTI) and one non-NRTI, collectively referred to Trimune30. A recent study reported that HAND persists in the milder categories (ANI and MND) and to a lesser extent in the more severe form of HAD regardless of combination ARV treatment or CART [28]. Although the scaling up of ARV continues in developing countries in Zambia the effects of ARV treatment on neurcognitive function remain to be determined. Furthermore, the degree of HAND in asymptomatic and symptomatic individuals living in this country has not been systematically investigated. Thus, the overall objective in this study was to determine if evidence of HAND was present in a randomly selected cohort from a primarily subtype C region and a low resource country setting.

Methods

Study Site

This project was a collaborative effort between the United States (University of Nebraska, Lincoln (UNL) and University of Miami Leonard Miller School of Medicine and Zambia [University Teaching Hospital (UTH) and the University of Zambia (UNZA)]. The training of Zambian medical professionals and study were carried out at the UTH and Our Lady Hospice in Lusaka, Zambia.

Ethical Considerations

The UNL Institutional Review Board as well as the UNZA research ethics committee approved all procedures. Written consent was obtained from the participants before any procedures were performed. If the subject was a minor, written consent was obtained from the participant's parent and verbal consent from the minor as per requirements of the Zambian research ethics committees.

Training of Neuropsychological Administration in Zambia

A series of workshops and training sessions were developed at UTH to train local medical professionals in administering the series of NP tests. A U.S. based psychologist (EW) with expertise in NP assessment conducted the training. Nurses were recruited from the UTH adult wards and Our Lady Hospice in Kalingalinga.

The training spanned for approximately 2 months during which time the nurses were introduced to the testing materials and guidelines for administration of the measures. The nurses were required to demonstrate clinical competence by achieving an error score of <10% on test administration checklists according to the procedures outlined by Sattler for training new examiners [29]. Focus group sessions were organized to further validate the efficacy of the NP administration in the Zambian setting. The NP assessment was approximately 35–45 min in duration.

Subjects

Participants were recruited by referral through the collaborating medical doctors at UTH (MB, CM, and KOC) and an established community worker network to recruit both HIV positive and negative individuals from the periods of March 2008 through October 2008. The community worker network, established at UTH for the last 13 years, was utilized to recruit participants from the volunteer counseling HIV testing centers, community clinics, and compounds. Additionally, participants were also recruited from a private outpatient/inpatient clinic Our Lady Hospice by referral from MB. Participants were from 33 different townships distributed throughout Lusaka.

One hundred and forty-one HIV positive and negative participants were recruited. Participants received a full medical examination that included a physical, neurological, and psychological exam. General physical questions included, but were not limited to, history of brain injuries, diseases (i.e., tuberculosis, malaria, syphilis, diabetes, epilepsy, etc.), hospitalizations, surgeries, and alternative/traditional medicine. Additionally, questions also included queries related to social habits such as intake and frequency of alcohol (Care-Angry-Guilt-Eye opener survey), smoking and drugs. The psychological examination included, but was not limited to, queries of general appearance, social interactions, affect, mood, speech, thought process, perception, and orientation. The neurological examination included queries related to motor (i.e., movement, muscle bulk, reflex, power, co-ordination and sensation), orientation, and balance, in addition to full examination of the cranial nerves. Additionally, an adapted mini mental state examination was used to screen for general dementia [30, 31]. Furthermore, a history of ARV treatment was documented if the individual was HIV positive.

Neuropsychological (NP) Tests

The series of NP tests are short assessments that screen for sub-cortical dementia [International HIV Dementia Scale (IHDS)] [18], speed processing/attention and executive function [Color Trail Tests (CTT) 1 and 2] [32], and motor functions, both fine [Grooved Pegboard Test (GPT)] and gross (Time Gait Test) [33, 34]. The IHDS consists of four tasks that screen for acquisition, memory recall, motor speed, and psychomotor speed and a score between 1(poor) to 4 (best) was possible for each task [18]. All other tasks were scored according to time speeds measured in seconds (sec).

Serology

Five milliliters (ml) of blood was collected into sterile EDTA vacutainers (BD, USA). HIV-1 serostatus was verified using rapid HIV-1/2 test kits (Determine HIV 1/2, Abbott Laboratories). HIV serostatus was confirmed with HIV UniGold rapid test (Trinity Biotech, PLC). Laboratory assays were performed to detect antibodies against bacteria and parasites that cause syphilis or malaria, respectively.

Inclusion and Exclusion Criteria

Participants had to speak and understand English, Nyanja, or Bemba. The participants' main residences were within Lusaka province. This criterion was set because residents of Lusaka speak a looser Nyanja and Bemba, which are highly intermixed with English, whereas those individuals that mainly reside in the villages outside the city area speak a more traditional Nyanja (and/or Bemba). The translations were sensitive to these regional differences in language. All assessment related instructions and tasks were translated from English to Nyanja or Bemba and then reverse translated. Reverse translations were verified at the University of Miami, Miller School of Medicine. Exclusion criteria included history of brain injuries, concussions, and/or concomitant diseases (e.g., malaria, tuberculosis or syphilis). Also, a participant was excluded if the age was below 16 years old.

Statistical Analysis

The data were entered into ACCESS file and then transferred to SPSS version 19 for data analysis. The series of NP tests were evaluated to compare HIV status that accounted for covariance of sociodemographics and clinical symptoms using a multiple covariate analysis of

variance (MANCOVA). A *Z*-test for proportions was applied to determine the statistical significance of the percent differences on IHDS performance using a confidence level of 90%.

Results

There were 57 HIV seronegative (HIV− group), 54 HIV seropositive ARV naïve (HIV+ group), and 29 HIV-1 seropositive on ARV treatment (ARV group). The data was normally distributed. Social demographic parameters are shown on Table 1. According to the WHO clinical staging (CS) criteria [35] 49 were classified as CS 1, four as CS 3, and one as CS 4. In the ARV group 24 were classified as CS 1 and five as CS 3. There were no stage 2 classifications in this cohort. There was no evidence of malaria or syphilis from individuals who had blood specimens available for testing.

At a cut-off score of 10 the IHDS sensitivity is maximized at 80% with fewer false negatives and achieves a specificity of 55% [18]. Using the HIV− group's data to normalize the HIV+ group's data to account for non-specific effects [18], it was found that 22% of HIV+ ARV naïve individuals met the classification of IHDS-defined impairment. When the HIV+ and HIV− groups were compared to each other, it was found that 67% (36/54) of the HIV+ group fell at or below the cut-off point and this was significantly higher compared to 52% (30/57) of the HIV− group ($z = 1.31$, 90% confidence level). Gender

Table 1 Sociodemographics

	HIV−				HIV+				
	Mean	SEM	Range	%	Mean	SEM	Range	%	*P* value
Sex (M/F)	(30/27)				(32/51)				
Age-years	28	1.2	18–56		34	0.8	18–57		.00*
Education-years	9	0.3	2–14		9	0.2	2–16		.48
Dependents	4	0.4	0–12		3	0.3	0–9		.77
Marital status									
Single				44				21	
Married				46				45	
Separated				0				2	
Divorced				3				4	
Widowed				0				14	
Unknown				7				14	
Type of occupation									
Employed				84				84	
Unemployed				10				15	
Unknown				5				0	
Formal training				18				40	
Informal training				68				46	
Unknown				14				14	
Preferred language									
English				61				77	
Nyanja				30				23	
Bemba				9				0	
Income range(kwacha)									
<2,000,000 (poverty line)				84				94	
2,000,000–5,000,000				7				5	
>5,000,000				0				1	
Unknown				9				0	
Religious affiliation									
Christian				96				67	
Muslim				0				0	
Traditional				0				0	
Unknown				4				33	

Table 2 HIV status and covariates effects on NP performance

	IHDS Total	Motor Speed	Psychomotor Speed	Memory Recall	CTT 1	CTT 2	GPTdom	GPTnondom	TGT
HIV status									
P value	$P = .33$	$P = .06$	$P = .36$	$P = .21$	$P = .02$*	$P = .000$**	$P = .000$**	$P = .001$**	$P = .002$**
HIV+, mean (SE)	9.8 (.20)	3.1 (.10)	3.1 (.09)	3.5 (.07)	61.7 (2.76)	102.8 (4.29)	72.5 (1.81)	87.1 (1.79)	12.3 (.26)
ARV, mean (SE)	10.1 (.22)	3.4 (.09)	3.3 (.13)	3.4 (.20)	71.0 (.07)	140.3 (9.26)	91.6 (4.27)	108.7 (6.83)	10.8 (.59)
HIV−, mean (SE)	10.1 (.32)	3.5 (.12)	3.1 (.14)	3.4 (.11)	71.9 (3.64)	149.5 (6.47)	82.9 (2.41)	97.5 (3.07)	12.3 (.21)
Covariates									
Age	$P = .08$	$P = .61$	$P = .25$	$P = .13$	$P = .50$	$P = .06$	$P = .06$	$P = .78$	$P = .27$
Sex	$P = .15$	$P = .19$	$P = .23$	$P = .46$	$P = .01$**	$P = .16$	$P = .04$*	$P = .01$**	$P = .003$**
Education	$P = .07$	$P = .28$	$P = .21$	$P = .25$	$P = .18$	$P = .59$	$P = .49$	$P = .14$	$P = .55$
Clinical Symptoms	$P = .10$	$P = .25$	$P = .59$	$P = .09$	$P = .78$	$P = .65$	$P = .51$	$P = .37$	$P = .63$

Significant difference at * $P \leq .05$ or ** $P \leq .01$. HIV status = HIV−, HIV+, ARV. *IHDS* international HIV dementia scale

CTT 1 or 2 color trials test 1 or 2, *TGT* timed gait test, *GPT dom or nondom* grooved pegboard test dominant or nondominant hand

influenced the IHDS performance with significant differences between the HIV+ females and males. Eighty percent (28/35) of females scored at or below the cut-off point compared to 42% (8/19) of the males ($z = 2.51$, 99% confidence level). No other significant differences were observed.

A MANCOVA was applied to correlate HIV status with sociodemographics (age, sex, education) and clinical symptoms as covariates for the series of NP tests. The age category was classified into two groups 18–35 and >36 [26]. Clinical symptoms were assigned a categorical value of 1(symptom(s) not present) or 2 (symptom(s) present) [36]. The MANCOVA revealed significant differences of HIV status with covariance of sex as the strongest cofactor that significantly influenced NP performance with age showing some trends towards significance in the CTT 2 and GPTdom tasks (Table 2).

Discussion

There are two major findings in the present study. First, 22% of the HIV positive ARV naïve individuals demonstrated HAND according to IHDS-defined NP impairment, which suggests an underlying sub-cortical dementia. Second, the IHDS performance was greatly influenced by gender wherein NP impairment was more prevalent in females compared to the males.

The rate of prevalence of HAND reported here are lower compared to other studies from sub-Saharan Africa. A recent pilot study from Botswana reported that 38% of the HIV-infected individuals revealed HAND [21] defined by the IHDS [18]. The studies differed in that the Botswana cohort was mostly on ARV treatment (97%) and also evaluation of NP impairment was based on an IHDS cut-off point of 9.5 [21]. A study from South Africa reported rates of 24% NP impairment [22] defined by the HIV Dementia Scale (HDS) [24, 25]. It was noted that co-factors such as age, education, alcohol abuse, and post-traumatic stress disorder were associated with poor NP performance. A subsequent study of HIV positive individuals that were to commence ARV treatment had a high prevalence of HAND, specifically, 42.4% with MND and 25.4% with HAD. Again, co-factors of education and age contributed to the prevalence of HAND [23]. In the present study, although the medical examination included questions on alcohol intake and substance abuse there were very few responses. Hence, the influencing effects of alcohol intake and drug abuse may have gone undetected in the present study since it was not possible to include these factors as covariates in the analyses.

The NP impairment observed here appeared to be gender biased as females showed a higher rate of NP impairment as compared to the males. This observation was consistent throughout the series of NP tests in which females performed more poorly than males. A small collection of studies on gender and HIV show conflicting findings with some concluding no gender differences [37–40] and others suggesting that there is a higher risk for females in acquiring AIDS dementia complex [38] or that women manifest neurologic symptoms earlier than men [41]. Interestingly, most studies that do not show evidence for neuropsychological decline in asymptomatic patients are mostly comprised of male subjects [36, 42]. More recently, however, Joska et al. [23] found that males and lower education were significant predictors of HAD symptoms. It remains unclear why female and male participants from this study differed in their performance as no differences were found in their medical evaluation. In sub-Saharan Africa females have a higher rate of HIV

infections [1] and with the recent gender differences unraveling in NP assessments future studies should also examine the performance of genders independently with corresponding normative data.

In the present study it was also shown that ARV treatment did not have any significant effects except for slower scores in gross motor function (TGT). This may be due to a higher number of older participants in the ARV treated group than the HIV− and HIV+ ARV naïve groups. In Zambia, the peak age for HIV infection is mid-thirties [43] and this may be attributed to the older individuals in the ARV group.

It is established that associations exist between HIV disease and the ability to perform daily functions and/or fulfill occupational duties [7]. Furthermore, higher rates of unemployment are associated with HIV disease and poor performance on functional and neuropsychological tests. Our study did not survey daily living activities but occupational demographics showed that the unemployment rates were comparable between the HIV infected and uninfected groups. Formal occupations included that of teachers, electricians, and secretaries. However, there was also a high rate of informal work/occupations. The types of occupations that were common included those of maids, gardeners, security guards, drivers (taxi/bus) and market vendors (selling food). It is worth noting that these occupations are gender specific in the setting. In Zambia, there is an unemployment rate of 14% and with the higher rates in the urban cities, especially in Lusaka with a rate of 31% (www.zamstats.gov.zm). The inability to perform daily living activities and meet the demands of an occupation is not only a health/mental status concern but is also critical for the development of a country.

A caveat worth noting, since the HIV− group showed a little over 50% that scored at the cut-off point on the IHDS the prevalence of HAND in Zambia may be lower than the reported levels if factors such as age, gender, and social habits (alcohol abuse or drug abuse) are normalized. However, the sample size was limiting to formulate normative values. This limitation, also, may have influenced the unexpected outcome of the control group's performance on tasks of motor, attention, and dual processing functions. Additionally, although the IHDS Total mean score showed the same trend as the percent difference group comparisons in which the HIV+ group performed more poorly compared to the HIV− group, the sample size limited statistical power. Another limitation of this study is that the HIV− group was significantly younger than the HIV+ group though the age range was equally represented across the groups. NP performance and CD4 count associations remain controversial and though in the present study an attempt to collect blood specimens at the time of assessment was made, there were still too few samples to analyze and derive meaningful associations between the serological measures (CD4 count and viral load levels) and NP performance. The evaluation of immunological data is critical in comparing HIV infected individuals to "healthy" controls. Though Zambia is a region with high prevalence of malaria the negative results for parasitemia in our cohort appeared to be unusual. Nonetheless, no clinical signs were found to suggest an ongoing malaria or syphilis episode at time of the study visit.

Conclusion

The present study is the first to systematically assess NP performance administered by trained NP examiners in Zambia. It was found that HAND is present in HIV positive individuals in Zambia where subtype C infection is prevalent. However, the lack of normative data remains a challenge in the developing country setting. Since NP testing is now feasible in Zambia, future studies should include additional assessments that measure memory and language skills to achieve a more comprehensive neuropsychological profile to further examine the prevalence of HAND.

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