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SCREENING INSTRUMENTS FOR NEUROCOGNITIVE IMPAIRMENT IN HIV/AIDS PATIENTS: A PILOT STUDY UTILIZING NON-PHYSICIAN HEALTHCARE PROVIDERS IN KALINGALINGA, LUSAKA, ZAMBIA

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Michelle Powell Kvalsund

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SCREENING INSTRUMENTS FOR NEUROCOGNITIVE IMPAIRMENT IN HIV/AIDS PATIENTS: A PILOT STUDY UTILIZING NON-PHYSICIAN HEALTHCARE PROVIDERS IN KALINGALINGA, LUSAKA, ZAMBIA

By

Michelle Powell Kvalsund

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ABSTRACT

SCREENING INSTRUMENTS FOR NEUROCOGNITIVE IMPAIRMENT IN HIV/AIDS PATIENTS: A PILOT STUDY UTILIZING NON-PHYSICIAN HEALTHCARE PROVIDERS IN KALINGALINGA, LUSAKA, ZAMBIA

By

Michelle Powell Kvalsund

HIV-related neurocognitive impairments (NCI) have important clinical, public health, and economic implications, particularly in light of the rapid expansion of antiretroviral access in sub-Saharan Africa. Obstacles to the clinical identification of these disorders in resource-limited settings are multi-factorial, including limited access to physician-experts for diagnosis and lack of ecologically-sound screening instruments and normative data. Screening instruments for HIV-related NCI have been utilized in some investigations in Africa, but none using the primary non-physician healthcare workers (NPHW) staffing antiretroviral therapy clinics. This study conducted steps for the formal evaluation of three locally-adapted screening instruments in Zambia, a Zambian Mini-Mental Status Examination (ZMMSE), HIV Dementia Scale, and Color Trails tests. Instruments were administered by NPHW to a group of AIDS patients (n=48) admitted to an urban hospice and a group of healthy subjects (n=15) from the same community. Hospice patients performed significantly worse (all p's <0.001) on all instruments. In addition, 24 of 48 (50%) hospice patients, 55% of patients with WHO HIV Stage IV disease, and 33% of patients with WHO HIV Stage III disease met the study definition for significant cognitive impairment. Evaluation of individual test items revealed that the ZMMSE was more easily administered and had better face and content validity than other instruments. Future steps for formal validation of the ZMMSE in Zambia are outlined.

Dedicated to the patients at Our Lady's Hospice
who graciously donated their time to participate in this study

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LIST OF ABBREVIATIONS

ADI: AIDS Defining Illness

AAN: American Academy of Neurology

ART: Antiretroviral Therapies

CI: Cognitive Impairment

HAART: Highly Active Antiretroviral Therapy

HDS: HIV Dementia Scale

HIV-D: HIV-associated Dementia

HBC: Home-based care

IHDS: International HIV Dementia Scale

MCMD: Mild cognitive motor disorder

MMSE: Mini Mental State Examination

NCI: Neurocognitive impairments

NP: Neuropsychological

NPHW: Non-physician Healthcare Workers

PEPFAR: President's Emergency Plan for AIDS Relief

PLWAs: Person Living With AIDS

SSA: Sub-Saharan Africa

WHOCCD: World Health Organization Clinical Case Definition

ZMMSE: Zambian Mini-Mental State Examination

CHAPTER 1: INTRODUCTION

1.1 Overview:

HIV-associated neurocognitive impairments (NCI) range among a continuum from subtle, even subclinical deficits in psychomotor speed, memory, and attention to a fulminant subcortical dementia with marked impairment of cognitive capacity and functional ability. The evolution of HIV/AIDS care, and most particularly the advent of Highly Active Antiretroviral Therapy (HAART)* in 1996, has brought shifting patterns of HIV-associated NCI including changing incidence and prevalence, and variable progression and clinical features. The pathogenesis and best therapeutic approach to HIV-related NCI remains ill-defined more than twenty years since these syndromes were first described. The epidemiology of HIV-related NCI in developing countries, where the majority of HIV/AIDS patients reside, remains largely unknown.

The course and clinical features of HIV-related NCI appear to be changing with HAART. In the pre-HAART era, the course of HIV dementia (HIV-D), the most severe form of HIV-related NCI, was generally that of a subacute, progressive dementia with prominent subcortical features, such as psychomotor slowing. Since the advent of HAART, longitudinal cohort studies have reported increased frequency of milder NCI with phenotypic features of both cortical and subcortical dementias in HAART treated patients[1-3]. HIV-D often now results in a more static or chronic dementia state with

* Highly Active Antiretroviral Therapy (HAART) refers to the use of three or more antiretroviral agents to suppress systemic HIV replication. The use of HAART in clinical practice became widespread in 1996 when the first protease inhibitor (third class of antiretroviral agents) was approved for clinical use.

varying degrees of reversibility, resulting in some clinicians and researchers to propose new HIV-D categories to more adequately describe HIV-D subtypes[4].

Along with changes in the course and clinical profile of HIV-related NCI, HAART has reduced the incidence of HIV-related NCI. Before the HAART era, approximately 20 to 30% of AIDS patients in the United States suffered from HIV-D[5,6]. An additional 30% of symptomatic HIV patients in the U.S. suffered from a less severe form of NCI known as Mild Cognitive Motor Disorder (MCMD).[1,3] The incidence of HIV-D has decreased by roughly 50% in the post-HAART era from 21/1000 person-years to 10/1000 person-years[7-10]. However, patients with advanced HIV disease, despite HAART therapy, are still at significant risk for the development of HIV-related NCI. In the Northeastern AIDS Dementia (NEAD) cohort (a group of high risk HIV patients with CD4 counts less than 200 cells/mm^3 identified through four university infectious disease clinics in New York and Maryland), incidence rates remained nearly identical to a similar pre-HAART cohort; both groups exhibited a 25% cumulative incidence of HIV-D at one year, and 38% versus 40% cumulative incidence for the NEAD and pre-HAART cohort respectively after two years[3]. In addition, a rising incidence of HIV-D was noted amongst Johns Hopkins HIV clinic attendees in 2003[11]. This finding may lend support to previous concerns that poor antiretroviral drug penetration in the Central Nervous System (CNS) combined with the immunologic peculiarities of the CNS may led to a differential impact of HAART on the neurological complications of HIV relative to other HIV-related illnesses (i.e. "CNS escape.")[11].

Overall, prevalence studies in developed countries have suggested static to increasing prevalence of all HIV-related NCI with improved survival following HAART[3,12-14].

There is some concern that prevalence rates will continue to rise with aging of the HIV population, as well as with the development of other co-morbid conditions[15-18]. Investigators at Johns Hopkins University reported an increasing prevalence of HIV-D among 1300 HIV clinic attendees from 6.6:100 person-years in 1994 up to 10.1:100 person-years in 2000, although the statistical significance of this trend was not reported[19,20]. In Australia, Dore et al utilized the National AIDS Registry to follow survival after a diagnosis of HIV-D as an initial AIDS defining illness (ADI). They found that HIV-D represented 4.4% of all ADIs in 1992-1995, but this prevalence increased significantly following the introduction of HAART in 1996 and 1997, with HIV-D cases representing 6.0% and 6.5% of ADIs, respectively (p=0.02)[21]. Neuropathological studies conducted in the U.S. in early HAART treated patients also found a trend towards increased prevalence of HIV encephalitis (HIV-E), the pathological correlate of HIV-D, although this trend was not statistically significant[22,23].

Other studies have found static pre- and post-HAART prevalence rates of HIV-related NCI[12,14]. A cross-sectional study from a tertiary HIV center in Australia found that, among patients with advanced HIV disease, but without HIV-D, the prevalence of milder forms of HIV-related NCI remained unchanged between pre- and post-HAART cohorts[12]. In another study of 432 HIV patients attending a large HIV referral clinic in Rome, Italy, the prevalence of both mild HIV-related NCI and HIV-D remained unchanged after seven years of follow-up with HAART[14]. These findings suggest that studies conducted early in the post-HAART era may be impacted by increased survival in patients with fixed neurological deficits or "burn-out" disease[24], while patients identified and treated earlier with HAART may have more reversible cognitive deficits and/or a higher likelihood of

halting disease progression to more severe forms of HIV-related NCI. The true reasons for these differences remain speculative, but may become more clear with increased duration of follow-up in HAART-treated cohorts with milder HIV disease, higher nadir CD4 counts (a marker of less severe HIV disease), and increased age. Still, whether the prevalence of HIV-related NCI remains static or increasing, these neurocognitive deficits clearly remain important consequences of HIV infection in developed countries despite the most effective combinations of HIV therapies available today.

Our current understanding of HIV-related NCI epidemiology comes almost exclusively from well-educated, homosexual Caucasian men[5,25], who may not be reflective of HIV-related NCI in other groups within the U.S. or globally. There are many reasons to suspect that the profile and frequency of HIV-related NCI may differ in developing countries. Different HIV subtypes found in different world regions may have variations in degrees of neurotropism. Co-factors such as poor nutrition, low education, different HIV transmission patterns and patterns of concomitant disease may all result in different frequency and severity of these impairments. Unfortunately, the true impact of these co-factors on HIV-related NCI epidemiology is largely unknown. Studies from low and middle income countries assessing HIV-related NCI have varied widely in the neuropsychological batteries used, guidelines for diagnosis, and the range of neuropsychological impairment included in their figures. Variations in HIV-related NCI nomenclature over time have led to the use of a variety of terminology in these studies and vague categorizations of impairments. The inclusion of patients with mild cognitive impairment can inflate prevalence figures compared to studies that exclude these patients. The neuropsychological battery employed for each study may also alter prevalence rates,

raising the prevalence with increasing cognitive domains tested. The proportion of patients with end stage AIDS among a study population will also impact the prevalence rate, as HIV-D typically occurs with advanced HIV disease[1,5].

The result of these differences in study design has been a wide range of HIV-D prevalence estimates, both internationally and within geographic regions. In Latin America and the Caribbean, HIV-related NCI prevalence estimates have ranged from 2.6% to 28.6%[26-31]. Studies from Asia have reported HIV-D prevalence estimates from 0.1% in Thailand[32] to 16.7% in China,[33] and within India studies have ranged from 8% to as high as 35%[16,34-37]. In sub-Saharan Africa, where 22.5 (68%) of the 33.2 million persons living with HIV reside[38], prevalence estimates ranging from 3.2 to 54% have been reported[39-44].

Only an estimated 2 million (28%) of the 7.1 million PLWAs globally who require treatment with antiretroviral therapies (ART) today are able to access these life-saving treatments[45]. However, access to ART is rapidly expanding as a result of efforts by WHO/UNAIDS and increased financial commitment from funders such as the Global Fund to fight AIDS, Tuberculosis and Malaria; the President's Emergency Plan for AIDS Relief (PEPFAR); the World Bank; and others[45]. Our inability to anticipate the impact of widespread distribution of ART on the prevalence of HIV-related NCI may result in inadequate allocation of resources and significant distress to informal care systems, like Home-Based Care* (HBC)[46].

* Home based care programs offer community-based HIV/AIDS care via volunteer healthcare workers and community members. By providing care to HIV/AIDS patients at home, these programs have offered non-institutional care services, lessening the burden of HIV/AIDS on government hospitals, while shifting the burden of care to families and communities.

The high demand for antiretroviral treatments, coupled with geographic, socioeconomic, and infrastructural limitations in sub-Saharan Africa have necessitated policies that limit ART initiation to patients with very low CD4 counts (<200 cells/mm^3), when available, or clinical evidence of advanced HIV disease (i.e. WHO Stage III or Stage IV). HIV-associated dementia (HIV-D) is a qualifying indication for antiretroviral therapy (ART) initiation according to World Health Organization (WHO) guidelines for resource-limited settings[45], but is not routinely screened for in ART clinics in sub-Saharan Africa (SSA) due to a lack of valid instruments with population-based normative data. HIV-D frequently goes unrecognized by clinicians inexperienced in diagnosing such disorders and may lead to delays in treatment initiation. A recent editorial highlighting experience from Uganda has pointed out that 6 of 16 HIV-D patients had CD4 counts above 200 cells/mm^3, making a clinical-based diagnosis essential for ART commencement in 37.5% of HIV-D patients identified[47]. Such delays in ART initiation may result in significant and irreversible CNS damage that complicates future HIV management[48].

In sub-Saharan Africa, where economic development has nearly halted under the strain of HIV-associated mortality and morbidity, HIV-related NCI may prevent desperately needed employees from returning to the workforce[49]. HIV-related NCI has important implications for individual households as well, when significant neurocognitive impairment strikes the main provider or results in other family members exiting the workforce to provide care to these individuals[50]. The success of large-scale, heavily subsidized antiretroviral treatment initiatives may also be hindered, as HIV-related NCI has been associated with poor adherence to antiretroviral therapies (ART)[51]. Poor

adherence is frequently associated with ART failures and development of drug resistance[52]. Thus, enabling healthcare workers to diagnose HIV-related NCI is of urgent importance in planning appropriate HIV treatment and prevention initiatives.

1.2 Rationale

Improved access to antiretroviral therapies in sub-Saharan Africa and other regions with resource limitations are likely to cause significant shifts in the epidemiology of HIV and HIV-associated illnesses. As more prominent systemic infections decline and HIV survival increases, HIV-related NCI are likely to become increasingly prevalent though the healthcare sector may be slow or unable to recognize this readily. The ability of the primary non-physician healthcare workers who staff ART clinics in sub-Saharan Africa to diagnose HIV-related NCI is limited by the lack of valid instruments to identify these impairments. The use of extensive neuropsychological batteries administered by neurologists, psychiatrists, and neuropsychologists in previous investigations of HIV-D make these methods impractical for routine surveillance of HIV-D in understaffed, overcrowded ART Clinics in Africa. For example, the WHO Neuropsychiatric AIDS study reported a mean time required for experienced neuropsychologists to conduct the neuropsychological battery of 2 hours[53]. The development of a simple instrument reasonably sensitive and specific to identifying the cognitive deficits seen in HIV-related NCI that could be administered by non-physicians would prove more feasible for screening and surveillance in countries with a lack of general or specialist physicians, limited financial means, and already overburdened medical resources.

In the U.S., there are several instruments used in routine clinical settings to assess cognitive status. The Mini Mental Status Examination (MMSE) is a brief screening instrument typically used to identify patients with cortical dementia syndromes, such as Alzheimer's disease[54]. Cognitive domains assessed include orientation, attention, language, constructional praxis, and memory and recall. The MMSE is generally considered to be insensitive to the cognitive deficits seen in HIV-D, although the clinical utility may perform better in post-HAART cohorts with more cortical features of HIV-related NCI[48,55]. MMSE performance is known to be impacted by factors like respondent education and many items may be culturally dependent[56]. However, the MMSE has been modified and validated in several resource limited-settings and illiterate populations[57-61]. The MMSE has the advantage of widespread familiarity and frequent informal use. In Zambia, neuropsychiatric officers, clinical officers with specialized training in neuropsychiatry, often use questions adapted from the MMSE for cognitive assessment in their patients (personal reference). Unfortunately, there has never been a formal translation or validation of these questions for NCI assessment in the Zambian population.

Color Trails 1 & 2 are designed specifically for cross-cultural use and assess attention, psychomotor speed, and executive function[53]. These are all cognitive domains that are frequently compromised in HIV-D. Color Trail tests are variations of the better-known Trail Making A & B tests, but replace the use of the English alphabet in Trail Making B. In Color Trails 1, patients are required to draw lines connecting numbers consecutively from one to 25 during a timed trial. Color Trails 2 contains two sets of numbers, each of different colors, and patients must alternate each advancing number with a different color

(i.e. yellow 1, pink 2, yellow 3). This test (also timed) requires higher executive functioning skills to sort and retrieve correct responses and inhibit selection of incorrect items. A disadvantage of Color Trails 1 & 2 is the need for instrumentation, most notably color copies of the test document.

The HIV Dementia Scale (HDS) has been widely used as a sensitive screening tool for HIV-D in the U.S.[62], but its utility in other populations has not been evaluated. The HDS includes tests of motor speed (timed written alphabet), memory (recall four words at 5 minutes), constructional praxis (timed drawing of 3D cube), and its original form also included a test of executive function (antisaccadic error test). The antisaccadic error test, however, was noted to be poorly administered by non-neurologists and was subsequently removed from the HDS[63].

Another scale for HIV Dementia, the International HIV Dementia scale (IHDS)[64], has recently been developed specifically for cross-cultural use. The IHDS contains tests of motor speed (timed finger tapping), psychomotor speed (timed alternating hand sequence test), and memory (recall of four words). The IDHS was shown to have 64% sensitivity and 71% specificity for identifying HIV-D in a group of ambulatory HIV patients (n=81) in Kampala, Uganda[64]. Although the neuropsychological (NP) instruments utilized in this study for HIV-D consensus diagnosis and for comparative performance on the IHDS have never been validated in Uganda, the authors were able to collect data on a group of 100 seronegative controls from the same clinic to provide some normative data for diagnosis and comparison purposes[64]. The IHDS was also able to identify significant differences in performance between HIV patients and a group of normative controls in an Indian population based on IHDS cut-off scores derived from studies in the U.S. and

Uganda[34]. In a recently published study from Ethiopia, the IHDS failed to identify significant differences in performance between patients with untreated, moderately advanced HIV disease (i.e. median CD4 <300) and a group of seronegative controls[41]. This finding suggests a decreased prevalence of HIV-related NCI or insensitivity of the IHDS to milder NCI in this population.

It is notable that in all studies utilizing the IHDS the test has been administered by physicians, although physician-level care represents only a small minority of primary HIV care in many resource-limited settings. In sub-Saharan Africa, clinical officers, who receive three years of post-secondary clinical training, provide the bulk of medical and HIV care[38,65]. If an instrument is to be feasibly incorporated into the routine care setting in Africa, then studies of this instrument should be conducted utilizing clinical officers for administration and scoring procedures. There may also be a need to expand the IHDS to include assessment of the mixed phenotypic presentation of HIV-D noted in U.S. populations following widespread introduction of HAART (i.e. with both subcortical and cortical deficits seen).

1.3 Specific Aims

This study aims to investigate the feasibility of using screening instruments including a locally-adapted Zambian MMSE (ZMMSE), the HIV Dementia Scale (HDS), and Color Trails 1 & 2 in identifying HIV-related NCI among AIDS patients admitted to Our Lady's Hospice, in Kalingalinga, Lusaka, Zambia. The IHDS was not available at the time of this study and was therefore not assessed. This study will also describe the prevalence of HIV-related NCI among these patients. If successful, these instruments

may be used by paramedical healthcare workers in clinical settings, as a method for surveillance of HIV-related NCI, and may be adaptable to other African populations as well.

The specific aims of this study are:

1) To assess cultural relevance and adaptability of screening instruments, including the ZMMSE, HDS and Color Trails 1 & 2, to identify cognitive impairment among Persons Living with AIDS (PLWAs) in Lusaka, Zambia through focus group discussions with local medical professionals, community piloting, and in study participants.

2) To evaluate the distribution of individual neuropsychological test items between PLWAs and healthy community members in Lusaka, Zambia.

3) To evaluate differences in mean ZMMSE, HDS, and Color Trails 1 & 2 between PLWAs admitted to Our Lady's Hospice in Lusaka, Zambia and healthy persons from the same community without evidence of HIV/AIDS

4) To evaluate WHO HIV Stage as a potential effect modifier of performance on the ZMMSE, HDS, and Color Trails 1 & 2 among PLWAs admitted to Our Lady's Hospice in Lusaka, Zambia.

5) To determine the prevalence of HIV-related NCI among PLWAs admitted to Our Lady's Hospice in Lusaka, Zambia, as defined by scoring ≥ 2 standard

deviations (SD) below the comparison group on the ZMMSE alone, or $\geq$ 2 SD below the mean on both the HDS and Color Trails 1.

6) To provide an overview of potential methods for formal cross-cultural validation of locally-adapted screening instruments for HIV-related NCI in Lusaka, Zambia based on pilot study findings.

1.4 Organization of Paper

This thesis includes an introduction, background and literature review, methods, results, and conclusions. In addition, Appendix 1 includes a copy of the ZMMSE. Appendix 2 includes a manuscript for submission to a peer-reviewed journal, and thus contains information redundant to the thesis manuscript.

CHAPTER 2: BACKGROUND

2.1 HIV-related NCI Nomenclature

HIV-D has been and continues to be described in the literature under various terminology. HIV encephalopathy, AIDS Dementia Complex (ADC), and HIV-D are all synonymous terms to describe the clinical triad of cognitive, motor, and behavioral abnormalities that result in functional impairment in HIV patients. Minor cognitive motor disorder (MCMD) is used to describe HIV patients who have significant changes in cognition, motor dysfunction, and behavioral abnormalities when these changes are not severe enough to interfere with activities of daily living[66]. HIV Encephalitis (HIV-E) is a pathologic diagnosis reserved to describe the hallmark neuropathologic features of clinically evident HIV-D, including white matter pallor, microglial nodules, multinucleated giant cells, and gliosis[67].

2.2 Diagnostic Criteria

The gold standard for diagnosing HIV-D is the American Academy of Neurology (AAN) clinical criteria[68]. According to the AAN guidelines, a diagnosis of HIV-D can be reached in patients with at least a one month history of cognitive decline resulting in impairment of activities of daily living in at least two of the following cognitive domains: attention/concentration, speed of processing of information, abstraction/reasoning, visuospatial skills, memory/learning, and speech/language. Impairment is usually identified through neuropsychiatric testing batteries. In addition, a diagnosis requires finding either objective motor dysfunction or behavioral abnormalities. Objective motor

dysfunction may be identified on neurological exam as slowed rapid movements, abnormal gait, limb incoordination, hyperreflexia, hypertonia, or weakness. Behavioral abnormalities include change in personality with apathy, inertia, irritability, emotional lability, impaired judgment, or disinhibition[68]. The diagnosis of HIV-D also requires exclusion of other potential causes of cognitive impairment through CSF evaluation and neuroimaging. The diagnosis of MCMD would require all of the above evidence in the absence of functional impairment.

The AAN guidelines, as proposed in 1991, have been criticized for a number of limitations that restrict, complicate, and lead to overlap between the clinical diagnoses of HIV-D and MCMD. For example, motor and behavioral abnormalities must be present to lead to a diagnosis of HIV-D. Thus, patients with severe NCI, but without motor or behavioral symptoms cannot be diagnosed with HIV-D. Although previous research had indicated that NCI without behavioral or motor symptoms was rare in the natural history of HIV-D, this may be changing with HAART[55]. Conversely, patients without NCI can receive a diagnosis of MCMD if there is evidence of motor or behavioral abnormalities. While a diagnosis of HIV-D requires impairment in two cognitive domains, the number of domains impaired in MCMD is not delineated. In addition, the AAN criteria fail to specify the degree of neuropsychiatric (NP) impairment required to differentiate HIV-D from MCMD. This allows the same NP presentation to qualify for both HIV-D and MCMD diagnoses. Quantification of degrees of functional impairment are also lacking. Further, patients with reliably documented cognitive difficulties that do not interfere with activities of daily living may not meet criteria for either diagnosis. Recently, the HIV Neurobehavioral Research Center (HNRC), an independent research institution in San

Diego, California, has proposed new categories to reduce overlap of diagnoses of mild HIV-D and MCMD, to reflect changes in the clinical profile of HIV-D cases since widespread HAART use, and to improve identification of asymptomatic NCI that correlates with HIV-E findings at autopsy and yields important prognostic value for clinicans[55]. The HNRC proposes three categories including 1) HIV-D; 2) Mild Neurocognitive Disorder; and 3) Asymptomatic neurocognitive impairment. In contrast to the AAN criteria, the HNRC criteria place added emphasis on NCI manifestations in HAART treated patients. HNRC criteria include categorization of NCI as normal, mild to moderate, or moderate to severe global NP impairment based on a standard NP battery with demographically adjusted normative means. There is also specification about the degree of functional impairment required for each diagnosis. Differences between the AAN and HNRC criteria are summarized in Table 1. When comparing AAN and HNRC categories to 39 autopsy cases with evidence of HIV-E, the HNRC categories had improved sensitivity (67% versus 56%), improved specificity (92% versus 83%), and improved positive predictive power (95% versus 88%), though the authors did not compare these differences statistically. Since these guidelines have only recently been published (2007), all studies to date have used the AAN criteria as the gold standard for HIV-related NCI. However, future research may benefit from using the HNRC criteria.

2.3 Clinical Features.

2.3.1 Common Symptoms

Early in HIV-D, patients often complain of lack of concentration, decreased attentiveness, and a general slowing of thought processes[25]. Motor complaints are also a

prominent feature of the disease. In one case series of 111 HIV-D patients, 75% of HIV-D patients complained of gait unsteadiness and 50% noted clumsiness and changes in handwriting[69]. Among behavioral symptoms, apathy and social withdrawal are the most common early manifestations, with agitation, mania, and hallucinations occurring less frequently[25]. Depression has been reported to be present in up to 30% of HIV-D cases[70]. Amongst the very limited studies that present clinical features of HIV-related NCI outside the U.S, Europe, and Australia, the pattern (i.e. early and late symptoms) of clinical complaints seems to be consistent. In an Indian series of ADC cases, forgetfulness associated with slowed mental abilities, motor signs including loss of balance and leg weakness, and apathy and social withdrawal were frequently reported[36]. A case series of 6 ADC cases in Shanghai, China reported forgetfulness and inattention as common early symptoms[33]. Other symptoms encountered included inability to calculate, disorientation to time and place, difficulty recognizing family members, and reduced external responsiveness. As ADC advanced, personality change, apathy, and social withdrawal were common. Two patients reported incontinence, one had visual hallucinations, and one was unable to write.

2.3.2 Neurological Findings

Neurological signs are non-focal and may include gait disturbance, impaired rapid eye movements, hyperreflexia, and frontal lobe release signs[2]. Additional findings may include slowing of fine finger movements, mild leg weakness, and inability to perform tandem gait. An estimated one third of patients will also have a peripheral neuropathy associated with depressed or absent ankle jerks[69]. In the pre-HAART era, these disturbances invariably progressed over a period of weeks to months to involve

significant global dysfunction including mutism, abulia, and ataxia, often accompanied by hypertonia, paraplegia, and bladder/bowel incontinence.

2.3.3 Neuropsychological Assessments

Neuropsychological assessments are important in HIV-D because the results provide important information about the types of deficits patients encounter, and provide temporal information regarding progression of deficits and response to treatment when testing is repeated over time. A recent meta-analysis of studies characterizing the neuropsychological profile of HIV-D in the pre-HAART era has reported that domains of learning, motor coordination, language fluency, and memory were the most severely impaired, followed by complex attention and simple processing speed which were moderately to severely impaired[71]. AIDS patients without HIV-D also had significant impairments compared to seronegative controls on neuropsychological test performance, especially in the domains of complex attention and psychomotor speed. Similar, but milder impairments were found in patients with symptomatic HIV infection. The WHO Neuropyschiatric AIDS study, conducted in the pre-HAART era, reported a consistent pattern of deficits in fine motor control, sustained and selective attention, cognitive flexibility, and verbal learning across five geographically diverse countries including, Germany, Brazil, former Zaire, Kenya, and Thailand[72]. In Kampala, Uganda similar patterns of neuropsychological testing abnormalities in verbal learning and memory, speed of processing, attention, and executive functioning were seen amongst HIV outpatients with 28% receiving HAART therapy[73].

There is some indication, although indirect, that the pattern of deficits seen in HIV-related NCI may be changing with HAART. For example, Cysique et al found that

HAART treated patients had an increased frequency of verbal memory impairment compared to pre-HAART patients[12]. Brew et al found that characteristic hypermetabolism of the basal ganglia found on positron emission tomography (PET) of HIV-D patients in the pre-HAART era is now much less prominent[24]. Instead, there appears to be more mesial temporal lobe hypometabolism in HAART treated patients on PET scan. Further research will need to be conducted to identify if these preliminary findings represent true variations in the neuropsychological profiles of HIV-related NCI related to ART.

2.3.4 Course

In the pre-HAART era, the onset of HIV-D occurred insidiously with progressively worsening cognitive function and death over a period of months. Mean survival following a diagnosis of HIV-D was 3 to 6 months[25,74]. Since HAART, the progression of deficits seen in HIV-related NCI is much more variable leading some to propose new HIV-D subtype categories, such as subacute aggressive, chronic active, chronic inactive, and reversible dementia[2].

2.3.5 Risk Factors

In the pre-HAART era, risk factors for HIV-D were highly associated with markers of advanced immunosuppression, including high viral load, low CD4 count, constitutional symptoms[5], clinical features like depression[69] and sustained declines in psychomotor slowing[75]. Some of these risk factors have changed with HAART treatment, namely HIV-D cases are more equally distributed over a range of CD4 cell counts[10,21,76]. Screening for HIV-related NCI is still recommended among HIV/AIDS care providers.

Age has been investigated as a risk factor for development of HIV-D. A study of Michigan HIV/AIDS registry patients found that 5.6% of patients aged >50 at HIV diagnosis compared to only 3.3% of persons between 13-49 years of age at HIV diagnosis received a diagnosis of HIV-D ($p=0.001$)[15]. Failure to control for duration and stage of HIV infection may play a role in study, as older HIV patients were significantly more likely to present with CD4 counts below 200 than younger HIV patients at diagnosis. However, the Hawaii Aging with HIV-1 Cohort found that even after adjusting for differences in education, race, substance abuse, HAART status, viral load, and CD4 count, older patients were 3.3 (1.32-8.07) times more likely to meet criteria for HIV-D.[17] A study of HIV patients in Kampala, Uganda has also reported that age was a significant risk factor for HIV-D, with each additional 10 years of age conferring a 2.06 increased odds of HIV-D ($p<0.05$).[44] These findings have led to concerns that aging of the HIV population may lead to additional increases in HIV-D prevalence.

Female gender has also been investigated as a risk factor for HIV-D, but many studies have been limited by failure to control for care-seeking patterns or patterns of care received by HIV positive women that may be associated with increased risk for HIV-related NCI. A recent study of Puerto Rican women, almost all of who where receiving HAART, reported an extremely high prevalence of HIV-D at 28.6%[31]. The authors found that many women in this study had detectable plasma (82.3%) and CSF (37.5%) HIV viral loads, suggesting poor HIV control and treatment failure. In a large multicenter retrospective study of European patients, HIV-D was present in 8.9% of women compared to 4.1% of men ($p=0.0002$)[77]. Historically recognized patterns of homosexual transmission may have resulted in more advanced HIV disease at diagnosis

among women in this study of HIV cases between 1979 and 1989. Indeed, Robertson et al reported no gender differences in neuropsychological test performance or progression of neurological disease in a prospective cohort of HIV patients followed for three years and matched for disease duration and markers of immunosuppression at a university clinic in North Carolina[78]. Given the high prevalence of HIV infection of women in many developing countries, these findings warrant further investigation of gender differences in HIV-related NCI.

2.4 Frequency of HIV-related NCI in Low and Middle Income Countries

In the U.S., studies of the pre-HAART prevalence of HIV-D revealed that approximately 20-30% of HIV patients suffered from HIV-D[3], with an annual incidence of 7% among AIDS patients[5]. HAART has resulted in significant decreases in the incidence of HIV-D, although prevalence estimates have remained unchanged and in some reports increased with improved survival[3,8,13]. If similar trends are seen in resource-limited settings, then HIV-D will likely become the leading cause of dementia in adults under 40 worldwide[79].

Unfortunately, very little is known about the epidemiology of HIV-D in low and middle income countries. Obstacles to identification and understanding of these disorders include universal non-resource related factors, limitations of infrastructure and human resources, as well as factors related to healthcare worker perceptions (Table 2). Variations in terminology, ambiguities in the current AAN criteria, and variable severity of HIV illness among the population being studied can all impact research findings and limit comparability. In addition, there has been a tradition of dependence on physician-

specialists for diagnosis of these disorders. In the U.S., Europe, and Australia, investigations of HIV-related NCI often employ a series of physicians and other specialists, including neurologists, psychiatrists, and neuropsychologists for diagnosis and interpretation of findings. Specialist services are far out of reach in many regions of the world, where non-physician healthcare workers are responsible for HIV primary care and management. These investigations also employ neuropsychiatric tests batteries that are lengthy and time-consuming, and not likely to be employed for routine clinical purposes in resource-limited settings. Even more importantly, NP test instruments are known to be age, education, and culturally dependent. Thus, NP tool development and validation in the population of interest are necessary first tasks in HIV-related NCI studies, which are expensive and ambitious research agendas in themselves. Healthcare worker perceptions may also play a role, particularly in retrospective studies. Mental health disorders are highly stigmatized conditions and frequently blamed upon witchcraft in sub-Saharan Africa and perhaps other regions. Thus, healthcare workers may fear that labeling patients with such disorders will result in withdrawal of care and/or pursuit of traditional medicine. Anecdotal beliefs among healthcare workers that short survivorship among HIV/AIDS patients in Africa and other regions make HIV-related NCI rare, if not unimportant, also likely contribute to under-identification of the disorder. Another factor may be that, in contrast to other HIV-associated opportunistic infections, there is no treatment for HIV-related NCI beyond the use of HAART. Thus, the impetus among healthcare workers to identify these conditions, at least in the past, has been low.

Still, review of the literature from low and middle income countries suggests that HIV-related NCI are important manifestations of HIV in these settings (Table 3). The

following section, organized by world region, summarizes findings, strengths, and limitations of these studies. The studies reported were identified through all PubMed entries submitted through August 2007, utilizing the term HIV plus one of the following terms: cognition; neuropsychiatric, or dementia. Additional articles were identified through review of citations from the full articles retrieved via PubMed.

2.4.1 Latin America and the Caribbean

Studies of HIV-D from Latin America and the Caribbean have been conducted in Mexico, Puerto Rico, and Brazil (see Table 3). Studies within Mexico have revealed very consistent prevalence estimates, ranging from 8.5-10.8%. Still, there are many limitations and factors that are not accounted for in these studies. A study of 120 HIV patients (all of whom met Center for Disease Control criteria for AIDS) referred for neurological evaluation to two main neurological institutes in Mexico City, Mexico reported 13 cases (10.8%) of ADC between 1986 to 1988[30]. A strength of this study was that other causes of cognitive impairment in HIV patients were able to be excluded via CSF analysis and computed tomography (CT) scan in all ADC cases. In addition, one third of the ADC cases underwent Magnetic Resonance Imaging (MRI), and four cases had postmortem histopathologic examinations. However, it is unlikely that all HIV patients have equitable access to neurological services in Mexico, so this study population may represent only a subset of Mexican HIV patients that can access specialist services. Thus, the external validity of this study is difficult to assess. Another concern is that this study was conducted before any standardized guidelines were published to diagnose HIV-D. The authors use the terms HIV encephalopathy and ADC interchangeably, and it is unclear if this estimate includes patients with MCMD. It is also

unclear if neuropsychological tests were employed for evaluation of cognitive function. Another study conducted in Mexico City, Mexico by Gongora-Rivera et al, retrospectively evaluated all HIV patients evaluated at the National Institute of Neurology and Neurosurgery between 1990 and 1998.[28] This study identified 13 cases (8.7%) of ADC amongst 149 HIV/AIDS patients. The ability of the investigators to exclude other causes of altered cognition was again excellent, as all patients were evaluated by a neurologist and had access to a wide variety of diagnostic studies including CSF analysis, CT, and MRI. However, abnormal mental status was an initial complaint in 21 (14.1%), including 15 patients with subacute behavioral abnormalities, four cases with acute confusional state, and two patients with chronic cognitive impairment. It is possible that some of these cases may have represented early manifestations of ADC or milder forms such as MCMD that did not fulfill the study definition for ADC. Conversely, it is possible that the additional cases were found to have other causes for altered mental status, such as CNS-opportunistic infections, but the final diagnoses of these cases were not reported or unknown due to loss of follow-up or insufficient documentation. Similar to the previously mentioned study, the generalizability of the study findings are difficult to assess because information about systems of referral and access to this institute are not reported. In addition, if any objective measures were used to identify cognitive impairment, the authors do not report NP assessments. There are several additional factors that may impact HIV-D prevalence that are not addressed in this study. Firstly, this study evaluated HIV cases from 1990 and 1998 and therefore some patients may have been receiving monotherapy, dual therapy, or even HAART, but ART usage is not reported. Another concern is that there

is also no indication of stage of HIV infection of study participants, a factor known to impact prevalence rates. In another study from Mexico, HIV encephalopathy was found as an initial ADI in 101 (8.5%) of 1,175 AIDS cases reported to the Yucatán State Department of Health between 1983 to 2001[27]. This estimate is slightly higher than reports in U.S. populations in which ADC represents only 3% of all initial ADIs[1,25]. Although stage of HIV infection is not reported, patients with neurological manifestations had lower mean CD4 cell counts and higher viral load compared to patients without neurological manifestations, suggesting advanced immunosuppression of these cases. Neurological manifestations between the time period 1983-1992 were much higher compared to 1993-2001. The authors interpret this finding as related to earlier diagnosis of HIV during the latter time period, but this may also reflect increases in ART usage that may have occurred. However, ART usage is not reported. HIV encephalopathy diagnosis was "based on clinical data of patients with deterioration of motor and behavioral cognitive functions, having ruled out opportunistic infections or neoplasms." How cognitive function was assessed or the criteria used to define cognitive impairment are not reported in this article.

Neurological manifestations of HIV in Brazilian HIV/AIDS patients have also been reported in several studies. In Rio de Janeiro, Brazil a retrospective review of 653 patients admitted to a university hospital between 1985 and 1989 reported 17 (2.6%) cases of "subacute encephalitis"[29]. Diagnosis was based on clinical history, neurological exam findings, and exclusion of other causes of HIV-related NCI through CT scan or CSF analysis. Neuropsychiatric tests, if utilized, are not reported. Emilio Hibas Hospital in São Paulo, Brazil participated in the WHO Neuropsychiatric AIDS study, the only

international study of neuropsychiatric manifestations of HIV to date[72,80]. Between October 1990 and August 1991, every third patient attending medical or infectious disease clinics were invited to undergo a comprehensive neuropsychological battery covering 8 cognitive domains, as well as a neurological evaluation and a psychiatric evaluation. HIV positive subjects were categorized as asymptomatic and symptomatic and matched by gender, age, education, and HIV at-risk group to HIV negative subjects from the same clinic. Global NP impairment, defined as scoring $\geq$2 SD below the mean of the HIV negative group on 3 or more tests, was identified in 9.1% of asymptomatic and 13% of symptomatic HIV patients. Although the AAN clinical criteria were not available at the time of this study, Maj et al reported a 6.5% prevalence of dementia applying both DSM-III-R and ICD-10 criteria for dementia. All cases were identified among symptomatic HIV patients. Among symptomatic HIV patients with a mean CD4 count of 350 (370) cells/mm^3, 40.1% meet CDC criteria for AIDS, and 4.3% were receiving Zidovudine. This study was strengthened by the use of a comprehensive neuropsychiatric battery piloted before study commencement and access to a wide range of diagnostic capabilities as a result of access to neurologists, psychiatrists, experienced neuropsychologists, access to a microbiological unit and neuroimaging (CT scan). However, the study population may not have been reflective of the HIV population generally as a result of site selection and exclusion criteria, which included number literacy. In 1995, Camara et al reported clinico-pathologic correlations of 154 AIDS patients with evidence of CNS pathology at autopsy from a university hospital in Niteroi, Brazil[26]. Among ten cases (6.5%) with HIV encephalitis identified on histopathologic examination, retrospective review of clinic and in-patient records revealed dementia

syndromes in nine patients (5.8%). Unfortunately, definitions for dementia are not provided in this study. In the post-HAART era, a cross-sectional study of all adult HIV patients admitted to Hospital Eduarado de Menezes, the main tertiary hospital for HIV/AIDS patients in the large metropolitan area of Belo Horizonte, found HIV dementia in 9 (2.2%) of 417 HIV cases[81]. This study utilized the AAN criteria for HIV-D diagnosis, though like previous studies from this region, neuropsychological assessment descriptions are lacking. This study focused on the prevalence of all neurological manifestations of HIV. Therefore, descriptive data about HIV-D specifically are not reported. However, amongst the patients with neurological conditions, the mean CD4 count was 93.9 (SD=110.6) suggesting these patients had advanced HIV disease. Additionally, 76.1% had been on ART in the past 6 months including 79.3% on HAART, 10.8% on dual therapy, and in 9.9% there was no information regarding antiretroviral use available.

A recent study investigated the prevalence of a range of HIV-related NCI amongst women attending two HIV clinics in Puerto Rico[31]. This study clearly delineates both the neuropsychological assessment instruments used, and cut-off criteria for HIV-related NCI. Another strength of this study was the use of normative data from 34 seronegative Puerto Rican women of similar age and education to assess HIV-related NCI performance. HIV dementia was diagnosed in 14 (28.6%), MCMD was diagnosed in 8 (16.3%), and asymptomatic NCI was apparent in 16 (32.7%) of 49 HIV positive women. No significant differences were found between HIV-related NCI and CD4 cell count or ART treatment.

2.4.2 Asia

The frequency of HIV-related NCI in Indian HIV/AIDS patients has varied in the literature over time. Initial reports suggested a very low prevalence of the disorder. For example, two studies of HIV patients attending neurological institutes reported HIV-D prevalence estimates of less than or equal to 2%[35,37]. These studies suffered from lack of normative data for HIV dementia diagnosis and possibly from referral bias. For example, patients with HIV dementia have reduced survival and might not survive inpatient admissions leading to underestimated prevalence rates in outpatient referral clinics. Indeed, recent publications suggest that HIV-D prevalence in India approaches numbers closer to those seen the U.S. and other developed countries. A retrospective study investigating the neurological manifestations of disease amongst 1,606 HIV inpatients admitted to an Indian hospital between 1993 and 2003, reported an HIV-D prevalence of 8.03%[36]. In 2006, Yepthomi et al compared 30 treatment-naïve HIV patients with median CD4 cell count 97 cells/mm^3 (range 14-209) and 30 healthy controls matched for age, education, and gender on neuropsychological test performance.[82]. Significant differences were identified between the groups on tests of verbal learning, motor speed, attention, and executive function. Using a cut-off of 1.5 standard deviations below the control group on at least two cognitive domains to define impairment, impairment was present in 56% of the HIV patients. Although HIV-D prevalence was not able to be measured in this study directly because of lack of other information (i.e. activities of daily living), this study suggests that HIV-related NCI are also extremely prevalent in treatment naïve Indian patients with advanced HIV disease. Similarly, significant

differences in performance on the IHDS were identified between HIV patients with CD4 counts less than 200 cells/mm^3 and seronegative controls in Pune, India[34]. The overall prevalence of impairment on the IHDS was 35% amongst HIV patients, suggesting a high prevalence of HIV-related NCI in this area of west India. In a study from South India conducted between October 2003 and December 2004, 119 treatment naïve HIV outpatients attending two clinics in Bangalore were administered a comprehensive neuropsychological battery[83]. These patients had a mean CD4 count of 396.8 cells/mm^3 (SD 212.5), suggesting mild to moderate immunosuppression. The NP test battery included tests of motor speed, verbal fluency, working memory, planning, and verbal learning and memory. This study was strengthened by the availability of age, gender, and education adjusted normative data on 540 healthy subjects recruited from the same community. A deficit on NP test items was defined as falling 1 standard deviation below the mean score of the normative group, and further categorized as mild to moderate (deficits on 4-6 of 12 items), moderate to severe (deficits on 7-9 of 12 items), and severe (deficits on >9 of 12 items). Despite specifically excluding patients with neurological manifestations (n=18), including patients with HIV-D (n=2), this study found mild to moderate cognitive deficits in 57.2% of patients, and moderate to severe cognitive deficits in 3.3%. No cases of severe cognitive deficits were identified, likely owing to the study's exclusion criteria.

Only three studies of HIV-D frequency in Asian countries outside of India were identified. One of these studies identified 36 AIDS patients managed at two hospitals in Shanghai, China between 1999 and 2003[33]. Amongst this group, 6 (16.7%) cases of "ADC" were diagnosed according to AAN criteria, although this nomenclature is not

recommended under the current AAN diagnostic guidelines. Therefore, it is possible that AIDS patients with mild NCI may have not been included. Indeed, staging of cases revealed only patients with moderate and severe ADC. MMSE and HDS evaluations were used for neuropsychological assessment, but normative data on these scales in this population are not provided. Nevertheless, MMSE scores ranged from 22 to 29 and suggested mild deficits in attention and short term memory in 50% of patients. HDS scores ranged from 3-9, with a median HDS score of 6.17 out of 16 maximum points. All ADC cases had CD4 counts below 200 cells/mm^3. Only one case out of six had received HAART prior to hospital admission.

A study from Bangkok, Thailand has reported the lowest frequency of HIV-D of all studies from around the globe at less than 0.1%[32]. This study identified 2,261 HIV cases admitted for the first time to medical wards, infectious disease wards, private wards, a gynecology ward and a diarrheal disease ward at a public hospital in Bangkok between 1993 and 1996. On-going chart reviews were conducted during each admission as part of an increased internal HIV surveillance system. Patients in this study had evidence of advanced HIV illness, with 1,553 (68.7%) cases presenting with an ADI. Of 509 patients in which CD4 counts were available, 88% had CD4 counts <200 cells/mm^3. Only two cases of HIV encephalopathy were definitively diagnosed, although 19 additional cases were suspected by clinicians but could not be confirmed because of lack of diagnostic capabilities. No information is provided as to what criteria or tools are utilized for HIV-related NCI diagnosis at this hospital. The very low prevalence in this study is likely related to study design, which utilized chart reviews to identify the frequencies of all HIV-related illnesses. Such a design, versus an active screening protocol for HIV-D, is

likely to result in under-identification of HIV-related NCI. This may be especially pertinent given the severity of HIV disease in this population and high likelihood of treatment for more conspicuous systemic illnesses overshadowing HIV-related NCI identification.

The previously mentioned WHO Neuropsychiatric AIDS study was also conducted at Chulalongkorn University outpatient clinics in Bangkok, Thailand[72,80]. Global neuropsychiatric impairments were common, with 5.7% and 22.1% impaired amongst asymptomatic and asymptomatic HIV patients, respectively. However, no cases of dementia were identified. This may be related to the mild HIV disease seen in this population, as reflected by mean CD4 counts of 640 cells/mm^3 for asymptomatic and 460 cells/mm^3 for symptomatic HIV patients. Only 25.3% of patients meet criteria for AIDS at this site.

2.4.3 Africa

An estimated 68% of all persons living with HIV/AIDS reside in SSA, yet only a handful of studies have examined HIV-related NCI in these populations, and populations studied are likely highly selected and not necessarily representative of most people with HIV in the region. Bélec et al conducted an investigation of the prevalence of neurological complications among seropositive inpatients meeting the World Health Organization Clinical Case Definition (WHOCCD) for AIDS in Bangui, Central African Republic and reported a prevalence of severe dementia of 3.2%, but it is unclear what clinical assessments were used for dementia diagnosis[40]. In Tanzania, 54% of hospital patients were reported to have ADC[42]. However, this estimate included patients with psychomotor retardation and confusion, as well as frank dementia. Both of these studies

were conducted before any standardized guidelines were developed for diagnosing HIV-D and thus are difficult, if not erroneous, to compare. CSF analysis was conducted in the study from Central African Republic, but not in the Tanzanian study, and neither study had access to neuroimaging facilities for exclusion of other causes of cognitive impairment in AIDS patients. In 1992, Perriëns et al found an 8.7% (95% CI 4-16%) prevalence of possible HIV-D among hospital patients in Kinshasa, former Zaire using the AAN criteria for diagnosis[43]. The WHO Neuropsychiatric AIDS study found significant differences on numerous neuropsychological tests between symptomatic HIV positive outpatients and HIV negative controls in Kinshasa, former Zaire and Nairobi, Kenya[53,84]. The overall prevalence of dementia was estimated at between 4.4 and 6.9% in both countries[72]. A retrospective review of HIV/AIDS patients with neurological disease attending an HIV clinic and medical in-patient ward at a Nigerian hospital reported a 10.5% prevalence of AIDS Dementia Complex[39]. A clinical definition of ADC was provided, but a description of how clinicians at this hospital reach this diagnosis was not reported. Another study, conducted in 2004 at a university hospital in Benin City, Nigeria, reported significant differences in mean verbal and nonverbal memory NP scores between symptomatic HIV patients ($p<0.001$), but not asymptomatic patients ($p>0.05$), and a group of seronegative controls[85]. Tests of psychomotor speed and attention were significantly impaired in both groups compared to controls (both p-values <0.001). All patients were ART-naïve in this study. This study used a computerized neuropsychological test battery, which consisted of tests of reaction time, memory recognition, visual scanning, and abstraction tests. The authors are quick to point out that computer literacy is not necessary for administration of this test, however

clearly accessibility and need for maintenance of testing equipment make computerized NP testing a poor choice for routine use in resource-limited settings. A group of controls were identified through HIV-negative hospital staff members for comparison purposes that were "randomly" selected, although the randomization procedures for healthy controls, and patients for that matter, are not reported. This study did not attempt to exclude opportunistic CNS infections as causes for impairment. The prevalence rates of neuropsychiatric testing abnormalities, MCMD, or HIV-D are not reported.

Pierotti et al conducted a study at a hospital in northern Uganda, the only study based in an rural African setting to date[86]. Amongst 44 antiretroviral naïve HIV patients with neurological impairments admitted to the internal medicine ward over a seven month period, seven (15.9%) cases "consistent with ADC" were identified. Cases were identified through neurological exam, but neuropsychiatric measures are not reported. Also, this study did not have access to neuroimaging or CD4 counts, but CSF analysis was performed for all patients. Another Ugandan study of 78 ambulatory HIV patients in Kampala, Uganda has reported a very high prevalence of HIV-related NCI, 31% for mild HIV dementia or worse and 47% for MCMD. In this study, HIV-D and MCMD diagnoses were based on comparison of mean scores on NP tests between HIV patients (28% of whom were receiving HAART) and a seronegative group from the same clinic base, followed by assessment by two primary physician examiners, a HIV neurologist, and an HIV neuropsychologist.

In 2004, a study of a well-characterized cohort of 1400 Ethiopian textile and sugarcane factory workers attending free clinics in two communities outside Addis Ababa failed to find differences between 73 ART-naïve HIV positive and 87 HIV

negative clinic attendees on total or sub-item IHDS scores, timed gait, grooved pegboard, or verbal fluency tests. In this study, only timed dominant-hand finger tapping performance was significantly different between HIV positive and HIV negative groups ($p = 0.01$). The authors point to the potential differential impact of clade C and C' virus on HIV-related neurological manifestations as a potential explanation for the very low prevalence of NP deficits in this Ethiopian cohort. However, 61 (86%) patients reported full time working status, suggesting relatively mild HIV illness. Indeed, markers of immunosuppression indicated only mild to moderate HIV illness with CD4 counts ranging from 168 to 451 (median=260) cells/mm^3 and mean HIV viral load at 4.3 log copies/ml. Functional abilities of the cohort were also extremely good with a mean Karnofsky score of 95.7 out of a maximum score of 100 among HIV patients. Another important concern is that receiving free healthcare based on factory employment may lead to patients with more severe systemic illness or NP manifestations seeking care elsewhere for fear of job insecurity, although this study captured greater than 70% of all HIV cases in these communities.

In a cross-sectional study of black South African patients admitted to inpatient medical wards at Helen Joseph Hospital in Johannesburg, HIV-D was the most common neurological disorder with 108 (38%) cases of HIV-D diagnosed in 506 consecutive HIV positive patients[87]. Decreasing CD4 count correlated with HIV-D diagnoses, with 108 cases having CD4 below 50 cells/mm^3, 38 between 51 and 100 cells/mm, 29 between 101 and 200 cells/mm^3, 12 between 201 and 500 cells/mm^3, and in 5 cases CD4 count was >500 cells/mm^3 (p for trend not reported). None of the patients had received ART. Other causes of cognitive impairment were excluded through CSF analysis and CT scans. The

MMSE was utilized for neuropsychological assessment, though it is unclear how cognitive impairment was defined or if normative data was available for this screening instrument in South Africa. In addition, the AAN criteria were utilized for diagnosis, but no cases of MCMD were reported. It is therefore unclear if mild cognitive impairments were excluded from this analysis or simply included in the HIV-D diagnoses.

2.4.4 Summary

When excluding studies conducted before any standardized guidelines for HIV-D diagnosis had been published, the prevalence estimates of most studies appears within the range from 8.5 to 38% in most regions of the world[27,28,30,31,33,34,36,87], and are similar to prevalence estimates from the U.S. in the pre-HAART era (i.e. 20-30%)[3]. Notable exceptions are Brazil and Thailand, which have reported significantly lower estimates[26,29,32,81]. It is unclear if these are true differences related to the neuropathogenesis of HIV in these countries or reflect differences in diagnosis, sampling, or other methodological differences. Although comparisons of these studies are difficult at best, HIV-related NCI appear to be common amongst HIV patients in low and middle income countries. In addition, the only cross-cultural investigation, the WHO neuropsychiatric AIDS study, found similar prevalences of global neuropsychiatric impairments in asymptomatic and symptomatic HIV patients in Brazil, former Zaire, Kenya, and Thailand[72,80]. Trends similar to those seen in developed countries following availability of HAART may also be seen, highlighting the need for improved identification and surveillance of HIV-D in resource poor countries.

2.5 Importance of Identifying HIV-D in sub-Saharan Africa

Most of the burden of HIV/AIDS lies outside the developed world. An estimated 22.5 million (68%) of the 33.2 million persons infected with HIV globally are found in SSA[38]. It is estimated that 2.8 million new HIV infections occurred in SSA in 2006, and accounted for more than 2 million deaths that same year.

The burden of HIV/AIDS in SSA has lead to a dramatic increase in funding for ART and infrastructures to support ART distribution. In 2003, it was estimated that less than 100,000 Persons Living With AIDS (PLWAs) in Africa had access to these life saving treatments[45]. By 2005, approximately 810,000 PLWAs were receiving ART thanks to efforts by the WHO '3 by 5' initiative. Improving access to ART is likely to significantly improve mortality of HIV-related infections. However, morbidity from HIV infection may increase as patients gain systemic control, but live to bear the more chronic stigmata of HIV infection, such as HIV-related NCI. Our ability to understand and respond to these changes is essential for planning and program development, and for allocation of preciously limited resources. Sadly, the impact ART may have on the prevalence of neurological disease and other chronic health conditions related to HIV infection were more or less omitted from the long, political discourses that preceded the widespread entry of ART into African healthcare systems. The lack of background knowledge we have about these conditions in sub-Saharan Africa and other resource-limited settings makes it difficult to anticipate the impact ART will have. However, there are several areas of concern that speak to the need for increased clinical identification and improved surveillance of HIV-related NCI in such countries.

2.5.1 Initiation of Antiretroviral Therapy

The limited supply and high demand for ART in sub-Saharan Africa and other resource-limited settings has resulted in clinical guidelines that support initiation in PLWAs who are in the most need of ART treatment. The WHO recommends ART initiation in patients who 1) have a WHO stage IV disease, regardless of CD4 count, 2) have WHO stage III disease and CD4 count <350 cells/mm^3, or 3) patients at any WHO stage with CD4 count <200 cells/mm[388]. **HIV-D is considered a stage IV WHO illness and is an indication for ART initation[89].** It is estimated that HIV-D occurs as the initial manifestation of HIV/AIDS in approximately 3% of cases[1,25], although estimates as high as 8.5% were seen in a Mexican population[27]. However, clinical officers, who provide most of the care in ART clinics in SSA[38,65], have little training in identifying HIV-D and it is likely that the condition generally goes unrecognized. Changes in cognition, behavior, and personality may be wrongly attributed to depression, other psychiatric disease or even witchcraft by healthcare workers and family members. Thus, patients may receive treatment for psychiatric disorders or seek help from traditional healers, leading to delays in ART initiation. Such delays may allow progression of CNS injury and result in reduced efficacy of ART to reverse neurocognitive deficits. A prospective cohort of HAART-treated patients with HIV-related NCI identified through the National Institute of Infectious Diseases Lazzaro Spallanzani in Rome, Italy found that the best predictor of reversibility of NP deficits was baseline neuropsychiatric test peformance[48]. After controlling for gender, education, Hepatitis C-positive serology, and CD4 count, poor performance on the baseline composite NP score was associated with a 3.07 (1.54-6.08, p=0.001) increased odds of having persistent NP deficits after HAART initiation.

This finding suggests that early HAART treatment in patients with HIV-related NCI may be essential to avoid irreversible neurological damage.

2.5.2 Optimizing Treatment for Patients with HIV-related NCI

HAART appears to be at least partially effective in improving HIV-related NCI, but there remains little empirical evidence or consensus among experts on how to optimize treatment. The main goal of treatment is the same for all HIV patients (i.e. reduce the systemic burden of HIV as measured by HIV viral load and CD4 count). The importance of CNS-penetrant drugs, defined as drugs with cerebrospinal fluid (CSF) concentrations that exceed the level necessary to inhibit replication of HIV[4], is largely unknown. In a study among Johns Hopkins University HIV neurology clinic attendees, no difference was found between patients receiving HAART regimens with single versus multiple CNS-penetrant drugs on tests of motor and psychomotor function[90]. In contrast, another study found that HAART regimens containing two CNS-penetrant drugs were associated with transient improvements in motor and psychomotor speed in individuals with moderately advanced HIV illness[91]. Cysique et al found that amongst a group of impaired patients (i.e. scoring 2 SD below the mean on 2 NP measures), those receiving HAART with 3 or more CNS-penetrant drugs performed significantly better on tests of memory learning ($p = 0.04$), short-term recall ($p = 0.03$), and long-term recall ($p = 0.02$) than patients with other HAART regimens[92].

It is generally agreed that patients with HIV-related NCI should receive HAART therapies with good CNS penetration[2,4]. In the U.S., this has become an important consideration among HIV/AIDS healthcare providers in the planning and selection of HAART regimens[4]. This individualized care is in stark contrast to the situation in SSA,

where cost-saving, simplified regimens considered safe and effective in *most* patients are emphasized. Triomune, containing the antiretroviral agents stavudine, lamivudine, and nevirapine, is the only regimen available in many public ART clinics in sub-Saharan Africa[93]. Stavudine and nevirapine are considered CNS-active drugs, but the efficacy of a two CNS-penetrant drug cocktail in controlling HIV replication in the CNS has not been established. Thus, limited access to alternate treatments may differentially impact HIV-related NCI in SSA.

2.5.3 Communication of Medical Information and Medication Adherence

As mentioned earlier, symptoms of HIV-D may be subtle and go unrecognized or confused with depression by healthcare workers. This speaks to the need for healthcare workers to adequately assess cognition in their patients in order to ensure that proper medical information is accurately conveyed to the patient, or a caregiver if needed. This is of great importance for HIV/AIDS patients, who may be on complicated medication regimens such as ART, anti-tuberculosis medications, other antimicrobials, psychotropic drugs, and others. Medication adherence is known to be compromised in cognitively impaired HIV patients in the U.S.[51,94]. Hinkin et al found that cognitive impairment in HIV patients increased the odds of poor adherence to HAART regimens by 2.5 (95% CI 1.19-5.35) compared to HIV patients without cognitive impairment[51]. Complexity of treatment regimen was also found to interact with cognitive impairment to further increase the likelihood of poor adherence[94]. Therefore, HIV-D patients may be at risk for development of drug resistance, ART regimen failure, and death if not properly assessed. Adherence to ART must exceed 95% to prevent development of drug-resistant virus and subsequent regimen failure[52]. Improved ability to diagnose HIV-D patients would allow

healthcare workers in SSA to identify appropriate caregivers to administer ART, or at the very least simplify regimen complexity. The development of drug-resistant HIV has far reaching public health implications, and could impact the success of large-scale ART intervention efforts.

2.5.4 Quality of Life

As ART access becomes more equitable in developing countries, quality of life measures will become increasingly important. Several studies have found an association with decreased quality of life in patients with HIV-D, even after adjustment for other confounding factors such as depression and other comorbid medical conditions[95-97]. In an Italian HIV cohort, Tozzi et al. found that cognitively impaired patients reported significantly lower quality of life measures ($p<0.05$) in all domains tested, including social functioning, health distress, and general health perceptions, among others[96]. Identification of HIV-related NCI facilitates the ability of clinicians to plan and implement interventions that can improve quality of life and functional abilities, including HAART initiation. HAART has been shown to reverse or stabilize NCI in some patients with HIV-D[98-100] and can improve patient quality of life[101]. Patient quality of life may also be impacted by stigma surrounding HIV/AIDS. HIV-related NCI patients may be more likely to experience abuse, neglect, and abandonment. In Zambia, patients with epilepsy, a highly stigmatized chronic health condition, are more likely to experience physical violence and rape than persons with non-stigmatized chronic health conditions, and were found to be significantly disadvantaged both socially and economically[102]. Although formal investigations of stigma and HIV-D have not been

formally carried out, HIV-related chronic health conditions are likely to be highly stigmatized conditions as well.

2.5.5 Caregiver Burden

As cognitive functioning progressively worsens, HIV-D patients often need 24 hour care to meet their daily needs and maintain safety. In a case series of 11 caregivers of patients with HIV-D, caregivers reported similar stresses and concerns of caregivers of patients with other types of dementia. Some common themes reported were feelings of social isolation, difficulty coping with problematic behaviors, and practical problems of care (i.e. eating, bathing, toileting)[103]. However, there are also important differences between caregiving for HIV-D patients and patients with other dementias. For example, the onset of dementia often occurs during young or middle adulthood. HIV-D patients are more likely to have financial or family responsibilities (i.e. dependent children at home). In this circumstance, HIV-D caregivers must remedy the financial or child care consequences of losing a spouse or other member of their household, while at the same time attending to the needs of an increasingly dependent loved-one[104]. Caregivers of HIV-D patients must also cope not only with dementia, but also with societal attitudes and stigma surrounding HIV/AIDS. This may strain social networks for caregivers, leading to increased feelings of despair and isolation. Further, caregivers of HIV-D patients may be living with HIV themselves, increasing their own anxieties about dementia and dying[105]. Other important and unique cultural factors may be important in SSA and other resource-limited countries, but the impact of HIV-relate NCI on caregiver burden has never been formally assessed in these environments. Still, many of these factors are likely to be important in such countries, and the clinical identification of HIV-

D would allow clinicians the opportunity to provide advice and prognostic information about the disorder, including how to handle difficult behaviors such as combativeness or agitation. In addition, HBC resources could be prioritized to these patients to allow caregiver respite.

2.5.6 Impact on Employment

At a macroeconomic level, the HIV/AIDS epidemic has led to a dramatic decrease in economic growth and development in African countries, reducing national growth rates to 2-4% across Africa[106]. While access to ART is likely to reduce mortality and morbidity of HIV illness, increasing HIV-D prevalence may prevent employee (re)entry or reduce worker productivity. Patients with HIV-related NCI are more likely to be unemployed than cognitively normal HIV patients with similar HIV stage in the U.S[50,107]. When comparing employment rates in HIV patients with NCI to unimpaired HIV patients, Heaton et al found that HIV patients with NCI were three times more likely to be unemployed ($p= 0.0001$)[50,107]. Unemployment rates remained higher even when considering patients with only mild impairment ($p<0.05$). In addition, HIV patients with NCI who were employed were significantly more likely to complain of difficulty with work tasks ($p<0.001$). Since ART may improve neuropsychological function or stabilize HIV-related NCI, identification of HIV-D may allow some patients to return to work and improve productivity amongst those who are employed.

2.5.7 Understanding HIV-D Pathogenesis

The opportunity to identify HIV-D patients in regions with non-B HIV clades (or subtypes), the most common clade found in the U.S., Europe, and Australia would provide valuable information about HIV-D pathogenesis and may lead to further

elucidation of clinical treatments. The infidelity of the HIV reverse transcriptase enzyme and lack of a proof-reading mechanism has led to diversity of HIV in different world regions[108]. There are three phylogenetic groups, including M (major), O (outlier), and N (new). Groups O and N are found only in central Africa, especially Cameroon. Group M accounts for roughly 90% of HIV infections globally and is subdivided further into 9 subtypes based on phylogenetic classifications of variations in HIV envelope nucleotide sequences. Group M subtypes (or clades) include A-D, F-H, J and K. Some of these subtypes have been shown to preferentially influence disease progression and death and thus may impact HIV-related disease epidemiology, including HIV-related neurological complications. In Rakai, Uganda, a retrospective study found that 59% of patients with clade D progressed or died compared with only 29% of patients with clade A who progressed (and none died) during a 5.1 year mean follow-up period ($p<0.01$)[109]. Similar findings were seen among a group of pregnant mothers in Dar es Salaam, Tanzania, with HIV positive women with clade D experiencing more rapid disease progression to death (HR 2.27, 95% CI 1.46-3.52) compared to HIV positive women with clade A, even after adjusting for viral load and CD4 cell count[110].

Animal retrovirus models have also shown that different HIV strains can preferentially induce brain pathology[111-116]. Further support for the importance of clade diversity on neurological outcomes comes from *ex vivo* findings indicating decreased viral fitness of Clade C virus in macrophages relative to Clade B isolates[117]. Since macrophages are a predominant HIV-infected cell within the central nervous system, some authors have extended this finding to explain the regional differences in HIV-related NCI prevalence between the previously mentioned Ethiopian cohort (where clade C predominates) and

Ugandan cohort (where clades A and D predominate)[108]. However, recent studies from South India, also a Clade C predominant region, have indicated that HIV-related NCI are extremely common manifestations among Indian HIV/AIDS patients, with estimates ranging from 35% to 60.5%[34,83]. These conflicting findings are likely to result from differences in population sampling, selection of control subjects for normative data, and neuropsychological assessment batteries utilized. No studies have formally investigated the impact of HIV clade on HIV-related neurological manifestations. Further research would provide valuable information about HIV-D pathogenesis and may lead to further elucidation of clinical treatments.

Table 1. Comparison of American Academy of Neurology and HIV Neurobehavioral Research Center Guidelines for Diagnosing HIV-related NCI[a]

	HIV-D		Other HIV-Related NCI Disorders		
	AAN HIV-D	HNRC HIV-D	AAN MCMD	HNRC MND	HNRC ANI
Cognitive/motor/behavorial abnormality by history At least 2 of: 1)impaired attention/concentration; 2) mental slowing; 3) impaired memory; 4) slowed movements; 5) incoordination; 6) personality change, irritability, lability	R	N	R	N	N
Number of self-reported cognitive complaints	US	3+	US	3+	<3
Verified cognitive abnormality	R	R	R	R	R
# of domains impaired	2+	2+	US	2+	2+
Mild to moderate Global NP Severity	US	N	US	R	R
Moderate to severe global NP Severity	US	R	US	R	R
Verified motor or behavioral abnormality	R	N	N	N	N
ADL Impairment: None	N	N	N	N	R
ADL Impairment: Mild	US	N	R	R	N
ADL Impairment: Moderate to Severe	R	R	N	R	N
Sufficient consciousness for testing	R	R	R	R	R
Duration at least 1 month	R	R	R	R	R
No other etiology for observed problems	R	R	R	R	R

[a]Adapted from Cherner et al. Neuropathologic confirmation of definitional criteria for human immunodeficiency virus-associated neurocognitive disorders. J Neurovirol 2007;13: 25[55].

R= Required for diagnosis; N= not required for diagnosis; US= Unspecified

Table 2. Barriers to Knowledge and Comparability of Previous Investigations of HIV-Related NCI in Low and Middle Income Countries

Universal Limitations	• Variations in HIV-related NCI terminology over time • AAN Criteria Limitations • No consensus definition of cognitive impairment • Comprehensiveness of neuropsychiatric tests instruments • Severity of HIV illness in populations studied impacts HIV-related NCI prevalence • Prevalence of HAART, dual-therapy, or monotherapy in study population
Resource Limitations	• Physician/specialist "brain drain" • Neuropsychiatric tool development and validation • Need for exclusion of other causes of NCI (i.e. MRI, CT, CSF, etc) • Preferential selection of populations at urban centers
Healthcare worker/researcher barriers	• Beliefs of survivorship bias • No treatment or cure for HIV-related NCI without ART availability • Stigmatization of mental health disorders

Table 3. Summary of HIV-related NCI Studies in Low and Middle Income Countries by World Region

World Region: Latin America & Caribbean						
Country: Mexico						
Author (year)	City, State/Province, or Region	Study Design and Population	Diagnostic criteria for NCI	Sample Size	% receiving ARV therapy	Results
Trujillo (1995)	Mexico City, Mexico	Cross-sectional study of AIDS pts admitted to two main hospitals	Clinical diagnosis, not otherwise specified	n=120	None	HIV-E/ADC 10.8%
Gongora-Rivera (2000)	Mexico City, Mexico	Retrospective cohort of HIV/AIDS pts seen at Neurological Institute	Clinical diagnosis, not specified	n= 149	not reported	ADC 8.7%
Castro-Sansores (2004)	Yucatán State	Retrospective cohort of Initial ADIs reported to Health Dept	Clinical diagnosis, not specified	n= 1,175	not reported	HIV-E 8.5%
Country: Puerto Rico						
Wojna (2006)	Puerto Rico	Cross-sectional study of Women screened at two HIV clinics	AAN with m-AAN for milder NCI, 8 NP instruments testing 5 cognitive domains. Impairment = ≥1 SD below the mean on ≥2 tests or ≥2 SD on any test	n=49	94%	Asymptomatic CI 32.7% MCMD 16.3% HIV-D 28.6%
Country: Brazil						
Puccioni-Sohler (1991)	Rio de Janiero, Brazil	Retrospective cohort of HIV pts admitted to University Hospital	Clinical diagnosis, not otherwise specified	n=653	none	Subacute encephalitis 2.6%
Maj (1994)	São Paulo, Brazil	Cross-sectional study of asymptomatic and symptomatic HIV outpatients	DSM-III-R/ ICD-10 dementia criteria, NP tests assessing 8 cognitive domains. Global NCI defined as scoring ≥2 SD below HIV- controls on ≥3 of 10 tests	n=101	4.3% of symptomatic HIV pts on Zidovudine	Global NCI 22.1% Dementia 6.5%
Camara (1995)	Niteroi, Brazil	Retrospective cohort of AIDS pts with CNS pathology at autopsy	Clinical diagnosis, not otherwise specified	n=154		Dementia 5.8% HIV-E s 6.4%
Oliveira (2006)	Belo Horizonte, Brazil	Cross-sectional study of HIV+ patients admitted to University Hospital	AAN criteria, assessment instruments not reported	n=417	HAART 79.3%; Dual therapy10.8%; Unknown 9.9%	HIV-D 2.2%

Table 3 (cont'd).

Author (year)	City, State/Province, or Region	Study Design & Population	Diagnostic criteria for NCI	Sample Size	% receiving ARV therapy	Results
World Region: Asia						
Country: India						
Satishchandra (2000)	Bangalore, South India	Retrospective cohort of HIV+ pts attending neurology clinic	Clinical diagnosis, not otherwise specified	n= 20	not reported	Dementia 2%
Wadia (2001)	Bangalore, South India	Cross-sectional study of HIV pts referred for neurological examination	Clinical diagnosis based on MMSE and exclusion of other causes via CT scan	n=1,527	not reported	HIV-D 1.3%
Teja (2005)	South India	Retrospective cohort of HIV inpatients	Clinical diagnosis, not otherwise specified	n=1606	not reported	HIV-D 8.03%
Riedel (2006)	Pune, West India	Cross-sectional study of HIV pts with CD4 count <200 at research institute	International HIV Dementia Scale	n=48	not reported	Possible HIV-D 35%
Yepthomi (2006)	Chennai, South India	Cross-sectional study of HIV pts with CD4 cell counts below 250 at tertiary HIV referral center.	Standardized NP exam (not otherwise specified). Impairment defined as 1.5 SD below comparison group on two cognitive domains	n=30	none	Cognitive Impairment 56%
Gupta (2007)	Bangalore, South India	Cross-sectional study of HIV outpatients without neurological impairment or HIV-D	Comprehensive NP Exam Impairment defined as >1 SD below mean of normative controls on any test item	n=119	none	Cognitive Deficits 60.5%
Country: China						
Wu (2007)	Shanghai	Cross-sectional study of AIDS patients at two urban hospitals	AAN criteria, MMSE and HDS for NP assessment	n=36	2.7%	ADC 16.7%
Country: Thailand						
Maj (1994)	Bangkok	Cross-sectional study of asymptomatic and symptomatic HIV outpatients	DSM-III-R/ ICD-10 dementia criteria, NP exam of 8 domains. Global NCI defined as scoring ≥2 SD below HIV-controls on ≥3 of 10 tests	n=127	none	Global NCI 27.8% No dementia identified
Tansuphasawadikul (2000)	Bangkok	Retrospective cohort of HIV+ pts at infectious disease	Not specified	n= 2,261	not reported	HIV-E <0.1%

		hospital				

Table 3 (cont'd).

World Region: Africa (1)						
Author (year)	City, State/Province, or Region	Study Design & Population	Diagnostic criteria for NCI	Sample Size	% receiving ARV therapy	Results
Bélec (1989)	Bangui, Central African Republic	Cross-sectional study of inpatients meeting WHOCCD for AIDS at urban hospital	Clinical criteria, not otherwise specified	n= 93	none	Dementia 3.2%
Howlett (1989)	Northern Zone, Tanzania	Cross-sectional study of AIDS inpatients at urban hospital	Impairment in >1 NP test = dementia NP tests not reported but tested orientation, memory, attention, and calculation	n=200	none	ADC 54% Psychomotor retardation 24%
Perriens (1992)	Nairobi, Kenya/ Kinshasa, Former Zaire	Cross-sectional study of HIV inpatients at urban hospital	AAN criteria, NP tests not specified	n=104	none	NCI 43% MCMD 2.9% HIV-D 8.7%
Maj (1994)	Kinshasa, Former Zaire and Nairobi, Kenya	Cross-sectional study of asymptomatic and symptomatic HIV outpatients	DSM-III-R/ ICD-10 dementia criteria, NP tests assessing 8 cognitive domains. Global NCI defined as scoring ≥2 SD below HIV- controls on ≥3 of 10 tests	Former Zaire: n=120 Kenya: n= 138	none	Former Zaire: Global NCI 28.7%; Dementia 4.4-5.9% Kenya: Global NCI 22.8%; Dementia 5.5-6.9%
Pierotti (2002)	Northern Uganda	Cross-sectional study of HIV patients with neurological impairments at rural hospital	Neurological examination, not otherwise specified	n=44	none	ADC 15.9%
Abayomi (2005)	Nigeria	Retrospective cohort of HIV/AIDS pts attending HIV clinic and medical inpatient ward	Clinical criteria, not otherwise specified	n= 362	not reported	ADC 10.5%

Table 3 (cont'd).

World Region: Africa (2)						
Author (year)	City, State/Province, or Region	Study Design and Population	Diagnostic criteria for NCI	Sample Size	% receiving ARV therapy	Results
Wong (2007)	Kampala, Uganda	Cross-sectional study of HIV+ patients attending urban clinic	AAN criteria, 6 NP assessment instrument testing 8 cognitive domains	n=78	28%	MCMD 47% HIV-D 31%
Clifford (2007)	Ethiopia	Cross-sectional study of factory worker clinic attendees	Not specified	n=160	none	No HIV-D or MCMD
Modi (2007)	Johannesburg, South Africa	Cross-sectional study of HIV+ inpatients at urban hospital	AAN criteria, utilizing MMSE	n=506	none	HIV-D 38%

CHAPTER 3: METHODS

3.1 Setting

3.1.1 Overview of Zambia

The Republic of Zambia is a landlocked country in southern Africa bordered by seven countries including Democratic Republic of Congo in the north; Tanzania, Malawi and Mozambique to the east; Zimbabwe, Botswana, and Namibia to the south; and Angola to the west (Figure 1). The country is slightly larger in size than the state of Texas. Zambia has a population of 11.5 million, of which approximately 44% reside in urban centers and 1.2 million (10%) reside in the capital city, Lusaka[118]. English is the official language of Zambia, but there are over 70 local languages and dialects. Chibemba is the most widely spoken language in Zambia (30.1%), but Chinyanja was identified as the predominant language spoken at home in Lusaka (52.8%) during the 2000 national census and is considered the lingua franca by most[119].

Zambia ranks among the poorest countries in the world. According to the United Nations Development Programme's Human Development Report 2006, 75.8% of the population live on less than $1.00 a day[120] and Zambia ranks 87th out of 102 developing countries on the Human Poverty Index.*

Many factors have contributed to Zambia's economic struggles including high unemployment, falling copper prices, foreign debt, droughts and food insecurity, and the HIV/AIDS epidemic. The HIV/AIDS epidemic continues to ravage Zambia, with an

* The Human Poverty Index is calculated based on the following indicators: probability at birth of not surviving to age 40, adult literacy rate, population without sustainable access to an improved water source, children underweight for age, population below income poverty line

estimated 1.1-1.2 million HIV infected individuals and an HIV prevalence between 13.3 and 20% in 2004[120].

3.1.2 Kalingalinga

This study took place in Kalingalinga, a shantytown settlement wedged between the University of Zambia and the Government Airport on the west-side of Lusaka, on the south side of the main Great East Road (Figure 2). It is a densely populated area with extreme poverty, poor sanitation, and limited access to healthcare. The official population of Kalingalinga is unknown, but was widely quoted by hospice administration staff to number around 100,000 during the study period. The HIV seroprevalence in Kalingalinga, as estimated from antenatal clinic attendees, was reported at 26.5% in 2002[121].

3.2 Population

At the time of this study (2004), Our Lady's Hospice was a newly opened facility with a blossoming community outreach program in Kalingalinga and surrounding areas. Patients were identified through key community members employed by the hospice, who also resided within the communities. Once identified, patients were evaluated and followed at home by a team of hospice healthcare workers. Depending on need and availability of beds, patients could then be referred to the hospice for in-patient admission. The hospice administration placed emphasis on home-based care and generally restricted in-patient admissions to five days or less. However, longer stays were common. During the study period, the hospice recruited over 500 hundred patients within Kalingalinga and three surrounding communities, and had a 24 inpatient

admission capacity. The hospice was dependent upon donor funding and governmental support for medications and supplies, and at the time of this study had no available laboratory or radiological equipment on site.

3.3 Interview Procedures

Each morning, a list of admissions occurring the evening before was reviewed for eligibility. All patients aged 18 or older, and admitted for the first time to the in-patient ward between January 21, 2004 and March 22, 2004, were invited to participate. Readmissions were not evaluated because of the high turnover of patients and the heavy clinical responsibilities of study interviewers. Other exclusion criteria included a past medical history of a chronic neurologic disorder, psychiatric disorder, alcohol abuse, or a physical deficit or severe medical illness that would interfere with study performance. After informed consent procedures, patients underwent a structured interview to assess demographic information, medical history, history of changes in memory and thinking, and cognitive and neurological status. A medical chart review was also undertaken and all information regarding medical history, medications, and available laboratory testing was recorded. No laboratory testing was done as part of this study. In cases in which a patient was unable to provide informed consent, a family member or friend provided informed consent, and answered questions on behalf of the patient regarding demographic characteristics and medical history. The interview was conducted in the patient's or advocate's language of choice between Chinyanja, the most prevalent vernacular language in Lusaka, and English, the official language and the language of instruction in schools. Several hospice volunteers fluent in these languages were trained

to conduct the interview procedures. An additional group of healthy individuals also underwent the neuropsychiatric assessment to provide normative data. These individuals were family members or friends of patients attending the outpatient clinics at the hospice and other interested members of the community. All interviews were conducted by clinical officers and hospice volunteers who underwent training in administration of the standardized study instrument. The author of this thesis was present during all interview procedures.

3.4 Language and Cultural Considerations

3.4.1 Translation of Study Instruments

A group of translators with extensive experience in translating clinical research instruments were employed to translate consent documents and interview instruments into Chinyanja. This group has been previously employed by the WHO for translation of research instruments. A team of local professionals including a psychiatrist, internists, and medical students, among others, were also asked for their input. A linguist then translated the documents back into English. Following back-translation, discrepancies were assessed and corrected and documents were then carried into the community to fine-tune the documents. This procedure was repeated until content was preserved and vocabulary was easily understandable to all parties.

3.4.2 Neuropsychological Assessment

No instruments were formally available for the assessment of cognition in Zambian HIV patients. Therefore, several neuropsychological assessment instruments were chosen, including the MMSE[54], the HDS[62], and Color Trails 1 and 2[122]. These

instruments were chosen because of their familiarity to healthcare workers (MMSE) and sensitivity to the cognitive deficits seen in HIV-related NCI (HDS and Color Trails 1). In addition, these instruments had the advantage of simplicity of application and short time for administration, which was considered of fundamental importance for this population of terminally ill patients, who would be unlikely to tolerate a lengthy and complex examination. Local physicians, including a psychiatrist and two internists, medical students, and clinical officers were consulted regarding the cross-cultural applicability and appropriateness of the instruments. Items of concern were identified through group meetings, piloting in the community, and finally during data collection for the study. Table 4 summarizes the neuropsychological instruments and the respective cognitive domains assessed following modifications to the instruments for cultural appropriateness.

3.5 HIV/AIDS Diagnosis

Patients were interviewed regarding knowledge of their HIV/AIDS status. It was anticipated that very few patients would be aware of their HIV status, and so patients were also assessed using the World Health Organization Clinical Case Definition (WHOCCD) for AIDS[123] using a previously described algorithm.[124] The sensitivity and specificity of this algorithm has been reported at 71% and 80% respectively[124]. Patients who did not meet the WHOCCD for AIDS were excluded from the analysis. All patients who meet WHOCCD for AIDS and consented to participation were included in the study analysis and also assessed for stage of HIV infection accordingly. Stage 2 (mild), Stage 3 (moderate), and Stage 4 (severe) were the possible staging categories. Stage 1 (asymptomatic) was not assessed because of the reliance of WHOCCD on symptomatic

HIV infection. WHOCCD for AIDS was preferred over conducting HIV testing because of the expense of such tests, limited access to HIV serological testing and appropriate counselors for consenting procedures, lack of access to antiretroviral treatment, and the overall sensitivity of the issue during the time this study was conducted.

3.6 Definition of Cognitive Impairment

Cognitive impairment (CI) was defined as scoring two or more standard deviations below the mean of the normative group on the ZMMSE, or scoring greater than two standard deviations below the mean of the comparison group on the HDS and Color Trails 1. Impairment on neuropsychological test performance has previously been defined as greater than two standard deviations below healthy subjects in other cross-cultural investagions[72,84]. The term cognitive impairment, as opposed to neurocognitive impairment, is utilized because of the lack of diagnostic capabilities available for differentiating the cause of cognitive impairment in hospice patients at the time of this study.

3.7 Sample Size Calculation

In a U.S. study on the validity of the HDS comparing AIDS patient with and without dementia, asymptomatic HIV patients, and normal controls, an effect size of >1 was identified between groups on scores of both the HDS and MMSE[62]. Extrapolating this effect size to this population, an estimated 17 patients per group are needed to identify significant differences in mean NP test scores with α=.05 and β=.20 for Specific Aim 3. For specific aim 5, a sample size of 88 is anticipated to be necessary to establish 95%

confidence that between 5% and 20% of AIDS patients have suspected HIV-D in this population, assuming that Zambian AIDS patients have a similar incidence of HIV-D as U.S. AIDS patients in the pre-HAART era (i.e. 15%)[5].

3.73.8 Statistical Analysis

3.8.1 Overview

Data was coded and entered into an Excel spread sheet. All statistical analyses were carried out using SPSS version 13.0 or SAS version 9.1. Demographic variables were compared using Student's t-tests for continuous variables including age and education. Chi-square tests were performed to identify differences between groups for categorical variables such as gender and language of interview. Patients and comparison controls with missing data points for neuropsychological tests were evaluated and cases removed from data analysis when necessary. Color Trails 1 was the only test in which missing data values were problematic, with one (6.7%) comparison group participant in which a poor copy of the testing material was administered with missing numeric values; and in three PLWAs Color Trails 1 was not assessed because of patient refusal (n=2) or inadequate test documents (n=1). On occasions in which participants were unable to complete the task at the five-minute mark, a test time of 300 seconds was imputed (PLWAs, n=16; Comparison group, n=2).

3.8.2 Data Analysis by Specific Aim

3.8.2.1 Aim 1

To assess cultural relevance and adaptability of screening instruments, including the ZMMSE, HDS and Color Trails 1 & 2, to identify cognitive impairment among PLWAs in

Lusaka, Zambia through focus group discussions with local medical professionals, community piloting, and in study participants.

Evaluations of study instruments for cultural relevance and adaptability were conducted through:

- Focus group discussions with local medical professionals, including a psychiatrist, and two internists, as well as medical students to assess individual neuropsychological test items for cultural, contextual, and linguistic appropriateness
- Consensus agreement amongst local healthcare professionals regarding appropriate adaptations for items identified as culturally problematic in focus group discussions
- Forward and back translations of study instruments from English into Chinyanja, the most prevalent vernacular language in Lusaka, Zambia, utilizing emic translation procedures
- Interview-based field piloting of the adapted and translated study documents and neuropsychiatric instruments to volunteer community members prior to study commencement, and finally, with study participant administration.

3.8.2.2 Aim 2

To evaluate the distribution of individual neuropsychological test items between PLWAs and healthy community members in Lusaka, Zambia.

The frequency (%) of correct responses on sub-items of the neuropsychiatric tests were evaluated in both PLWAs and the healthy comparison group. In addition, the distribution of each individual neuropsychiatric test score was evaluated graphically.

3.8.2.3 Aim 3

To evaluate differences in mean ZMMSE, HDS, and Color Trails 1 & 2 between PLWAs admitted to Our Lady's Hospice in Lusaka, Zambia and healthy persons from the same community without evidence of HIV/AIDS.

Mann-Whitney U Tests and Student's t-tests were performed to compare ZMMSE, HDS, and Color Trails 1 scores between PLWAs and the comparison group using $p \leq 0.05$ as the level of statistical significance.

3.8.2.4 Aim 4

To evaluate WHO HIV Stage as a potential effect modifier of performance on the ZMMSE, HDS, and Color Trails 1 & 2 among PLWAs admitted to Our Lady's Hospice in Lusaka, Zambia.

To assess the impact of WHO Stage on neuropsychological test performance, Kruskal-Wallis and one-way ANOVA tests were performed to evaluate between group and within group differences. In addition, a chi-square test for trend in binomial proportions was used to assess the relationship between CI and WHO staging of HIV infection. A significance level of 0.05 was considered statistically significant.

3.8.2.5 Aim 5

To determine the prevalence of HIV-related NCI among PLWAs admitted to Our Lady's Hospice in Lusaka, Zambia, as defined by scoring $\geq$ 2 standard deviations (SD)

below the comparison group on the ZMMSE alone, or ≥ 2 SD below the mean on both the HDS and Color Trails 1.

The prevalence of HIV-related NCI is reported as the proportion (%) of hospice patients identified meeting the study definition for significant cognitive impairment.

3.9 Protection of Human Rights

This project was approved by both the Michigan State University Committee on Research Involving Human Subjects and the University of Zambia Research Ethics Committee.

TABLES

Table 4. Neuropsychological Instruments and Cognitive Domains Assessed

Instrument	Domains Assessed
ZMMSE	Orientation, memory registration, language, attention, memory recall
HDS	Psychomotor speed, and memory recall
Color Trails 1 & 2	Attention and concentration, motor speed/fine motor control, executive function

Table 5. World Health Organization Screening Algorithm for HIV Infection*

Definition of Suspected HIV infection: 1) 1 cardinal OR 2) 2 characteristic OR 3) 1 characteristic and 2 associated 4) OR 3 associated		
Symptoms, Signs, & Diagnosis Categories		
Cardinal	**Characteristic**	**Associated**
Kaposi's sarcoma	Oral Candidiasis	Weight loss >10%
Pneumocystis carinii pneumonia	Hairy leukoplakia	Fever >1 month
Toxoplasmic Encephalitis	Tuberculosis	Diarrhea > 1 month
Esophageal candidiasis	Herpes Zoster	Genital Ulcers >1 month
Cytomegalovirus retinitis	Pruritic dermatitis	Cough >1 month
Cryptococcal Meningitis	B cell lymphoma	Drug reactions
		Skin infections
		Seborrheic dermatitis
		Neurologic symptoms

*Adapted from Miller et al. Diagnosis and screening of HIV/AIDS using clinical criteria in Tanzanian adults. J Acquir Immune Defic Syndr Hum Retrovirol 1995; 9(4):410.[124]

FIGURES

Figure 1. Map of Zambia

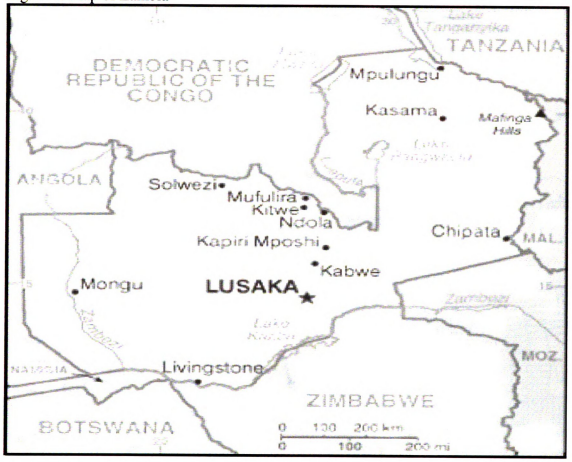


Figure 2. Map of Lusaka, Zambia and Location of Kalingalinga Compound*

*Arrow indicates location of Kalingalinga

CHAPTER 4: RESULTS

4.1 Overview and Descriptive Statistics

Patient flow is summarized in Figure 3. The final study group was comprised of 48 PLWAs. Only one patient was currently receiving antiretroviral therapy, and none of the study group reported previous use of antiretroviral therapy. A group of 18 healthy volunteer individuals from the Kalingalinga community underwent the same evaluation. Three volunteers reported a past medical history of possible signs/symptoms of HIV including herpes zoster, cryptococcal meningitis, and a history of chronic persistent diarrhea. These volunteers were excluded from the analysis and the remaining 15 formed the comparison group. As suspected, very few participants were aware of their HIV status, with only 5 (10.4%) PLWAs reporting having had an HIV test in the past (4 positive, 1 negative). Only one comparison group participant (6%) reported knowledge of HIV status, having had a negative HIV test in the past. Baseline characteristics for the PLWAs and comparison groups are summarized in Table 5. No significant differences were found between or within PLWAs and comparison subjects with regard to age, education, or gender. Among all PLWAs, 25 (52.1%) reported noticing changes in memory and 16 (33.3%) reported noticing changes in thinking. No one in the comparison group reported problems with memory or thinking. Three PLWAs (6%) were identified as having WHO Stage II, 14 (29%) WHO Stage III, and 31 (65%) WHO Stage IV HIV disease.

4.2 Results by Specific Aim

4.2.1 Aim 1

To assess cultural relevance and adaptability of screening instruments, including the ZMMSE, HDS and Color Trails 1 & 2, to identify cognitive impairment among PLWAs in Lusaka, Zambia through focus group discussions with local medical professionals, community piloting, and in study participants.

4.2.1.1 Zambian Mini Mental State Examination

Several modifications were made for cultural appropriateness on the locally adapted ZMMSE. Amongst items assessing orientation to time, season ascertainment was noted to be an item of difficulty because the Chinyanja translation for "what season is it," literally translates as "what time is it?" The result was that patients were often confused if the item referred to time of day or time of year. To circumvent this confusion and provide context to the question, patients were provided with cues. Cues included all possible correct answers to the question, including hot, cold, rainy, or dry. During the study period, the only correct answer to this question was "rainy." No difficulties were encountered with other time orientation assessments including year, date, day, and month. The MMSE as designed by Folstein et al, includes five items assessing orientation to place, such as state, county, city or town, place (i.e. hospital or clinic), and floor of building. These items were altered on the ZMMSE to include province, city, area of city, name of hospice, and floor of building. No changes were made regarding item naming, including identifying a wristwatch and pencil by the appropriate names. However, while assessment of language repetition and fluency with the statement, "no ifs ands or buts," was maintained in interviews conducted in English, another statement

needed to be identified for Chinyanja interviews. "Kulibe kuchita, kulibe kusachita," which translates to "there is no doing, there is no not doing," was identified as a potential phrase through another group in Lusaka conducting a concurrent HIV-D study, and was utilized because of the lexical and syntactical similarities to the English phrase.

Education and rate of literacy were assumed to be relatively low in Kalingalinga and items requiring reading and writing were considered to be inappropriate in such a population. Attention tasks such as spelling world backwards or serial 7s were therefore replaced with a different task, which required study participants to name the days of the week backwards, starting with Sunday. Another item of concern because of education and literacy rates was a visual command task in which patients are asked to read the visual command, "close your eyes." Instead, patients were asked by the examiner to "look at me and do exactly as I do." The examiner then closes his/her eyes for three seconds, and observes and records the patient response. This procedure has been used in other studies of the MMSE in illiterate populations[60].

Similarly, the sentence-writing task was identified as another problematic item in this population. In a Hindi adaptation of the MMSE in an illiterate population, this item was replaced with "Tell me something about your house"[60]. However, in our community piloting of the tests, this item often lead to confusion and required additional explanation. Another appropriate substitution was never identified, so we decided to include the sentence-writing task for completeness. All other items were maintained as originally described. The final ZMMSE is shown in Appendix 1.

4.2.1.2 HIV Dementia Scale

Previous investigations have indicated that most adults are able to count numbers from one through twenty-five, regardless of literacy level[122]. Therefore, the HDS timed-alphabet task was changed to a timed-number writing task. The 3D cube drawing was dropped from the HDS because very few participants, healthy or otherwise, could complete the drawing accurately. Thus, the maximum HDS score was six points versus twelve on the original HDS scale.

4.2.1.3 Color Trails 1 & 2

No modifications were made to Color Trails 1 & 2. While field piloting and testing in the comparison group revealed no administrative difficulties, Color Trails 2 was revealed to be poorly tolerated by hospice patients. A significant number declined to complete the task, were unable to complete in the allotted seven minutes or made five or more errors resulting in discontinuation of the test. Thus, only Color Trails 1 was included in the data analysis.

4.2.2 Aim 2

To evaluate the distribution of individual neuropsychological test items between PLWAs and healthy community members in Lusaka, Zambia.

4.2.2.1 Zambian Mini-Mental State Exam

The frequency of correct response to ZMMSE test items among comparison group participants and PLWAs are reported in Table 7. The ZMMSE appeared to have good face validity among the healthy comparison group. Items including assessment of year, day of week, name of place, item naming, pentagon drawing, and word registration were answered correctly by 15 (100%) of the comparison group. Other items including

season, month, floor, town, compound, phrase repetition, naming days of the week backwards, and follows a 3-step command also performed reasonable well, with at least 13 (86.7%) of comparison participants providing the correct response. Other items proved less reliable. As suspected, sentence writing proved to be one of the most difficult tasks with only 11 (73.3%) able to complete the task correctly. Day of month, province, and word recall items were also less reliable with 11 (73.3%), 12 (80%), and 12 (80%) of comparison group participants answering these items appropriately, respectively. These items might be considered for revision in future cross-cultural validation studies.

PLWAs performed worse than the comparison group on all ZMMSE items. There were no items on which all PLWAs were able to answer correctly. PLWAs performed reasonably well on orientation questions, with the exception of day of month and day of week in which only 17 (35.4%) answered correctly. Language naming items, including naming "chair" and "pen," appeared to be intact among PLWAs with 46 (95.8%) able to generate correct responses. Other language tasks such as phrase repetition, following a three-step command, and sentence-writing proved more difficult for PLWAs with 33 (68.6%), 31 (65.6%), and 20 (41.7%) providing correct responses, respectively. PLWAs performed very poorly overall on items of attention, constructional praxis, and memory recall (table 7).

The distribution of ZMMSE total scores for both the comparison group and PLWAs showed left-skewing, as seen in Figure 4.

4.2.2.2 HIV Dementia Scale

Performance on the HDS was markedly difficult for both PLWAs and the comparison group. The distribution of time in seconds to complete the HDS timed number writing task are provided in Figure 5 for both groups. Ten PLWAs (20.8%) and one (6.7%) comparison group participant were unable to complete the timed number writing task correctly. Among those completing the task, timed number writing was significantly slower among the comparison group participants compared to data from U.S. normative controls on timed alphabet number writing, and point distributions based on U.S.-derived scores required reassessment. As seen in Figure 5, no comparison group participants were able to complete timed number writing in under 25 seconds, resulting in maximum task score of 1 based on U.S. derived cut-off scores. Thus, the distribution of time in seconds for normal controls was reassessed, and a new scoring system was derived, as outlined in table 8. Memory recall task also proved difficult, with only 3 of 15 (20%) comparison subjects and 7 of 48 (14.3%) PLWAs able to correctly recall all four items. HDS summary score distributions for the comparison group and PLWAs are summarized graphically in Figure 6.

4.2.2.3 Color Trails 1

The distribution of time in seconds required to complete Color Trails 1 are shown in Figure 7 for both study groups. Time to complete Color Trails 1 among comparison group participants, ranged from 42 seconds to a maximum of 300 seconds. In two instances comparison group participants were unable to complete the task in the allotted 5 minute time period, resulting in imputed scores of 300 seconds. The remaining 12 (85.7%) performed the task correctly. Among PLWAs, time in seconds ranged from 32

seconds to 300 seconds. However, 12 (25%) PLWAs were unable to complete the task in 5 minutes resulting in a 300 second imputed value.

4.2.3 Aim 3

To evaluate differences in mean ZMMSE, HDS, and Color Trails 1 & 2 between PLWAs admitted to Our Lady's Hospice in Lusaka, Zambia and healthy persons from the same community without evidence of HIV/AIDS.

Mean and median scores of PLWAs and comparison group participants on the screening instruments are summarized in Table 9. PLWAs scored significantly worse than the comparison group on all neuropsychological tests as a group (all p's <0.001).

4.2.4 Aim 4

To evaluate WHO HIV Stage as a potential effect modifier of performance on the ZMMSE, HDS, and Color Trails 1 & 2 among PLWAs admitted to Our Lady's Hospice in Lusaka, Zambia.

After stratifying by WHO stage, highly significant differences were identified between the comparison group and WHO Stage IV PLWAs on all tests (all p's < 0.001), as seen in Table 9. No statistically significant differences were identified between the comparison group and WHO Stage II/III on the ZMMSE (p =.081), HDS (p =.086), or Color Trails 1 (p =.093). However, WHO Stage IV patients differed significantly from the comparison group on the ZMMSE (p<0.001), the HDS (p<0.001), and Color Trails 1 (p<0.003). WHO Stage IV differed from WHO Stage II/III on the HDS only (p =.011).

4.2.5 Aim 5

To determine the prevalence of HIV-related NCI among PLWAs admitted to Our Lady's Hospice in Lusaka, Zambia, as defined by scoring ≥ 2 standard deviations (SD)

below the comparison group on the ZMMSE alone, or ≥ 2 SD below the mean on both the HDS and Color Trails 1.

Twenty-four PLWAs (50%) scored >2 SD below the comparison mean on the ZMMSE, and 8 of those 24 also scored >2 SD below the comparison mean on both the HDS and Color Trails 1. No additional CI cases were identified using the latter criteria alone. Twenty-four PLWAs (50%) scored >2 SD below the comparison mean on the HDS. Finally, 13 PLWAs (27%) scored >2 SD below the comparison mean on Color Trails 1. Overall, 24 (50%) PLWAs in this Lusaka-based hospice met the study definition for significant NCI. Among WHO staging categories, there was one stage II (33%), 6 stage III (42%), and 17 stage IV (55%) patients with significant NCI, but this trend was not statistically significant ($p = 0.24$).

4.2.6 Aim 6

To provide an overview of potential methods for formal cross-cultural validation of locally-adapted screening instruments for HIV-related NCI in Lusaka, Zambia based on pilot study findings.

This pilot study represented a first step in cross-cultural validation of a neuropsychiatric instrument useful for identification of CI in HIV/AIDS patients by non-physician healthcare workers. Based on our initial findings of high face and content validity of the ZMMSE, the following steps, as outlined by other researchers adapting Western instruments for cross-cultural use[125], will need to be undertaken for formal cross-cultural validation:

1) Standardization of the instrument among a normal HIV seronegative population sample to determine normal age, gender, and education-specific performance distributions on ZMMSE performance.
    a. Using logistic regression analysis with age, sex, and education included as explanatory variables, the predicted probability of answering each item correctly should be assessed. Identification of items with significant age, gender, and education effects should be further modified to ensure that this item can be used on all HIV patients irrespective of these factors.
    b. Create graphical representations of observed and predictive probabilities of answering a given test item correct for visual inspection and identification of discrepancies.
    c. Calculation of a "goodness of fit" statistic to evaluate statistical significance of the fitted curve to representative data.
2) Reliability of Each Item
    a. Clinical officer interobserver and intraobserver reliability should be assessed by calculating Kappa statistics for each ZMMSE test item. Items with poor interobserver and intraobserver reliability among clinical officers should be further modified to ensure the instrument can be used in routine care settings.
3) Consensus Meeting
    a. Further revisions and modifications as determined by standardization and reliability findings.

4) Further evaluation in the HIV population, including asymptomatic and symptomatic patients, to evaluate the sensitivity, specificity, and positive predictive value of the instrument for identifying HIV-D, MCMD, and other HIV-related NCI compared to the American Academy of Neurology Clinical Criteria.

Tables

Table 6. Baseline Characteristics of Persons Living With AIDS (PLWAs) and Comparison Group

Characteristic	PLWAs n = 48	Comparison n = 15	*p-value**
Age, yrs; mean (SD)	34.7 (9.53)	32.4 (7.39)	0.32
Education, yrs; mean (SD)	7.2 (4.35)	7.5 (3.11)	0.71
Sex, female (%)	30 (62.5)	9 (60)	0.87
Language of Interview (Chinyanja) (%)	32 (67)	10 (67)	0.30

**p*-value based on Students T-tests for age and education, Chi square tests for gender and language of interview

Table 7. Number of Correct Responses (%) to Zambian Mini-Mental State Exam Items by Group and Cognitive Domain Assessed

	PLWAs (n= 48)	Comparison (n=15)		PLWAs (n=48)	Comparison (n=15)
Orientation Year			**Language**		
Year (1)	34 (70.8%)	15 (100%)	Names "chair" (1)	46 (95.8%)	15 (100%)
Season (1)	35 (72.9%)	13 (86.7%)	Names "pen" (1)	46 (95.8%)	15(100%)
Month (1)	36 (75%)	13 (86.7%)	Repeats phrase (1)	33 (68.8%)	14 (93.3%)
Day of Month (1)	17 (35.4%)	11 (73.3%)	Sentence Writing (1)	20 (41.7%)	11 (73.3%)
Day of week (1)	29 (60.4%)	15 (100%)	Follows 3-step command (3)	31 (65.6%)	13 (86.7%)
Name of place (1)	39 (81.3%)	15 (100%)	**Constructional Praxis**		
Floor (1)	30 (62.5%)	14 (93.3%)	Pentagon Drawing (1)	16 (33.3%)	15 (100%)
Town (1)	44 (89.8%)	14 (93.3%)	**Memory and Recall**		
Compound (1)	33 (68.8%)	14 (93.3%)	Word Registratio n (3)	39 (81.3%)	15 (100%)
Province (1)	37 (77.1%)	12 (80%)	Word Recall (3)	20 (41.7%)	12 (80%)
Attention					
Days of week backward (5)	32 (66.7%)	13 (86.7%)			

PLWAs= Persons Living with AIDS; Comparison= Comparison Group

Table 8. Number of Correct Responses (%) to HIV Dementia Scale Items by Group and Cognitive Domain Assessed

	PLWAs	**Comparison Group**
Motor Speed		
Timed Number Writing		
<30 seconds (2 point)	9 (18.8%)	8 (53.3%)
31-40 seconds (1 points)	5 (10.4)	4 (26.7%)
>40 seconds (0 points)	34 (70.8%)	3 (20%)
Verbal Learning		
Memory Recall (4 points)	7 (14.3%)	3 (20%)
Memory Recall (3 points)	13 (27%)	9 (60%)
Memory Recall (2 points)	10 (20.8%)	3 (20%)
Memory Recall (1 point)	5 (10.4%)	0
Memory Recall (0 points)	13 (27%)	0

PLWAs= Persons Living with AIDS

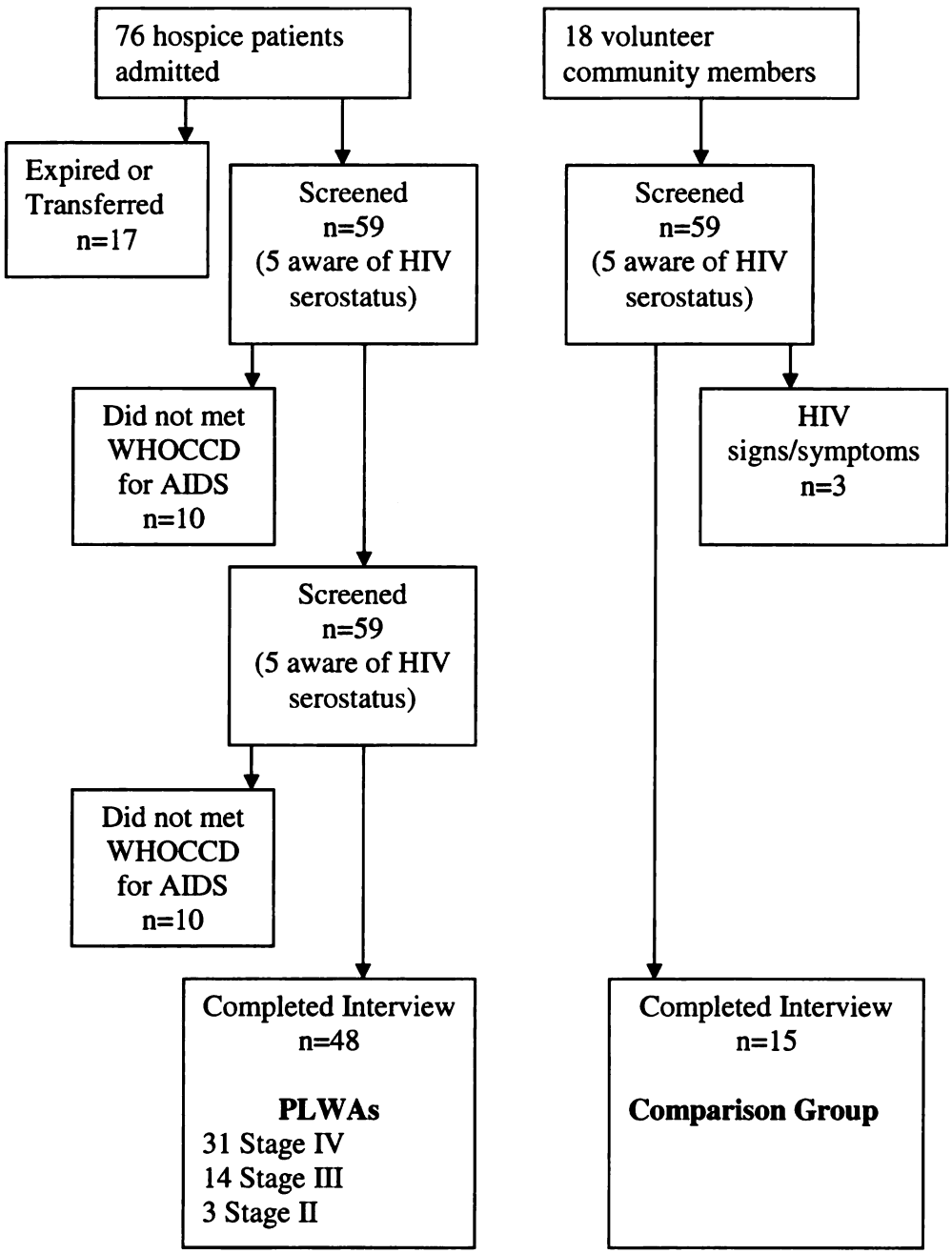
Table 9. Neuropsychological Assessments for Persons Living With AIDS (PLWAs) and Comparison Group

		Comparison n=15	WHO Stage II/III n=17	WHO Stage IV n=31	All PLWAs
ZMMSE	Mean (SD)	28.2 (1.8)	23.8 (5.1)	20.1 (9.0)*	21.4 (8.0)‡
	Median (range)	29 (24-30)	25 (12-30)	24 (0-29)	25 (0-30)
HDS	Mean (SD)	4.2 (1.1)	3.2 (1.7)	1.9 (1.8)*†	2.4 (1.9) ‡
	Median (range)	4 (3-6)	3 (0-6)	2 (0-6)	2 (0-6)
Color Trails 1[§]	Mean (SD)	104.4 (71.6)	162.3 (95.4)	195.1 (91.4)*	182.7 (93.2) ‡
	Median (range)	81 (44-300)	141 (32-300)	206.5 (52-300)	164 (32-300)

*Comparison vs. WHO Stage IV, p<0.001 on ZMMSE and HDS; p< 0.003 on Color Trails 1 by ANOVA
†WHO Stage II/III vs. WHO Stage IV, $p < 0.05$ by ANOVA
‡Comparison vs. All PLWAs (WHO Stage II-IV), $p < 0.001$ by ANOVA
§Missing values: Comparison group (n=14), WHO Stage IV (n=28), PLWAs (n=45)

FIGURES

Figure 3. Flow Chart for Patients and Comparison Group.



WHOCCD= World Health Organization Clinical Case Definition
Stage defined by WHO classification criteria[20]

Figure 4. Distribution of Persons Living With AIDS (PLWAs) and Comparison Group Zambian Mini-Mental State Exam Total Scores

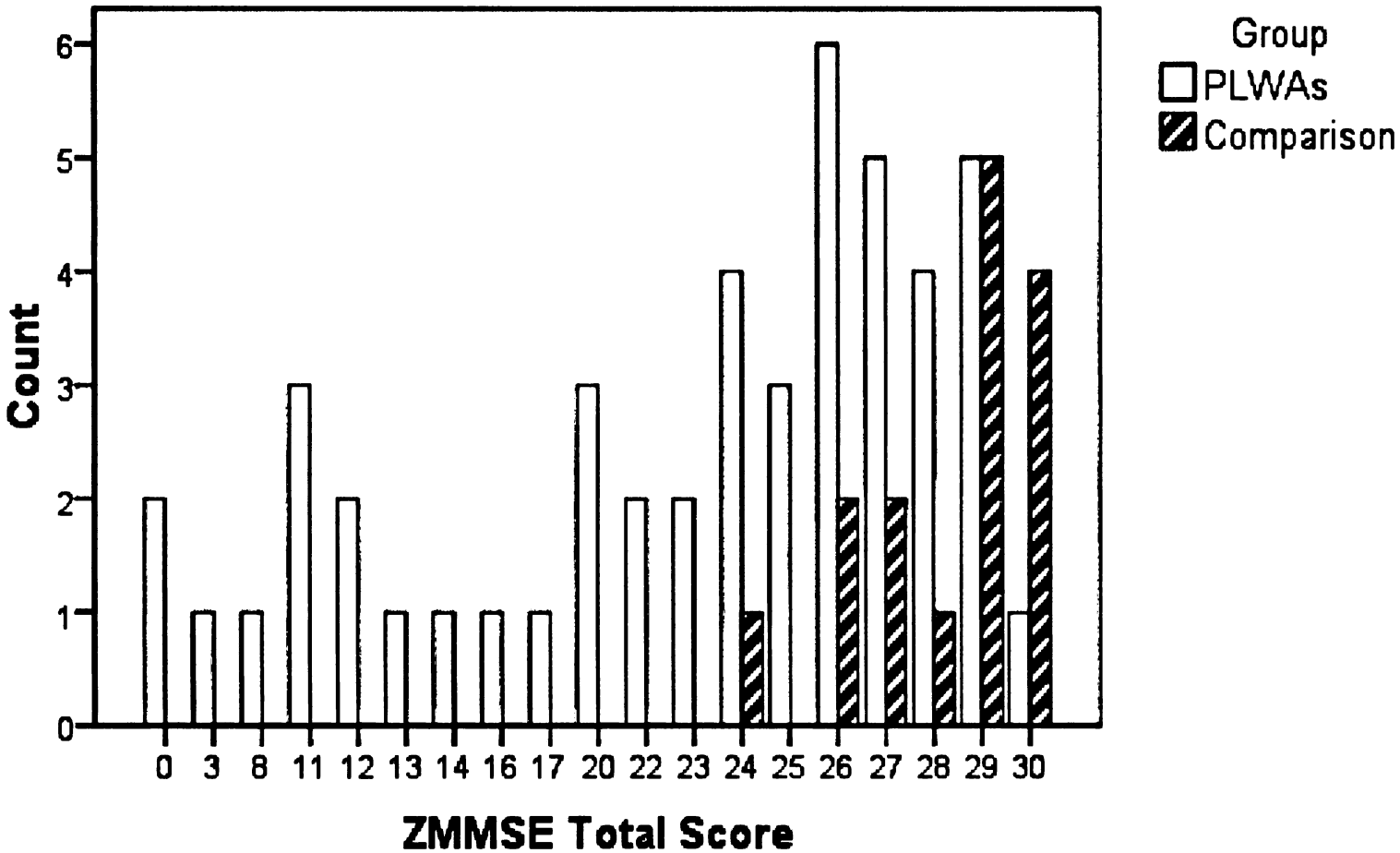
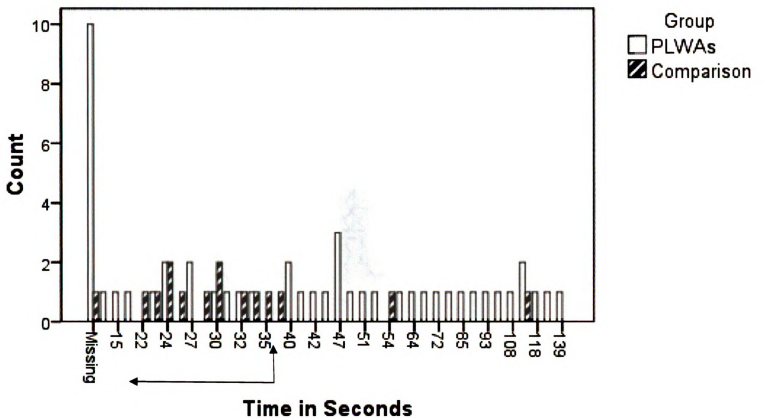


Figure 5. Distribution of Time (in seconds) to Complete the HIV Dementia Scale Timed Number Writing Task for Persons Living With AIDS (PLWAs) and Comparison Group



*Arrows indicate U.S.-derived cut-offs for timed alphabet writing scores: <21 sec=6; >21-24 sec=5; >24-27 sec=4; >27-30 sec=3; >30-33 sec=2; >33-36=1; >36 sec=0

Figure 6. Distribution of Persons Living With AIDS (PLWAs) and Comparison Group HIV Dementia Scale Total Scores

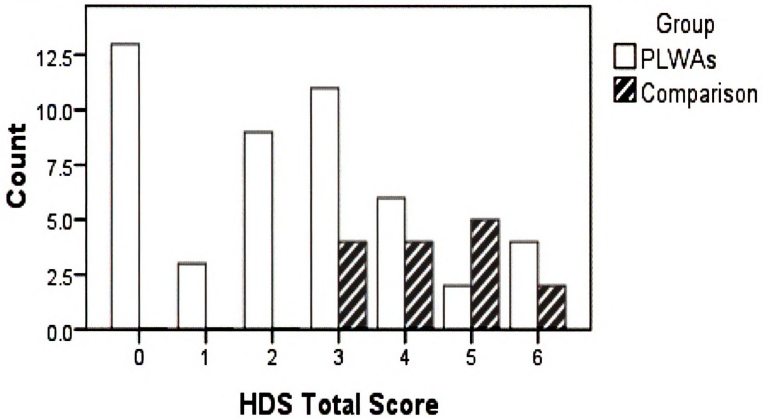
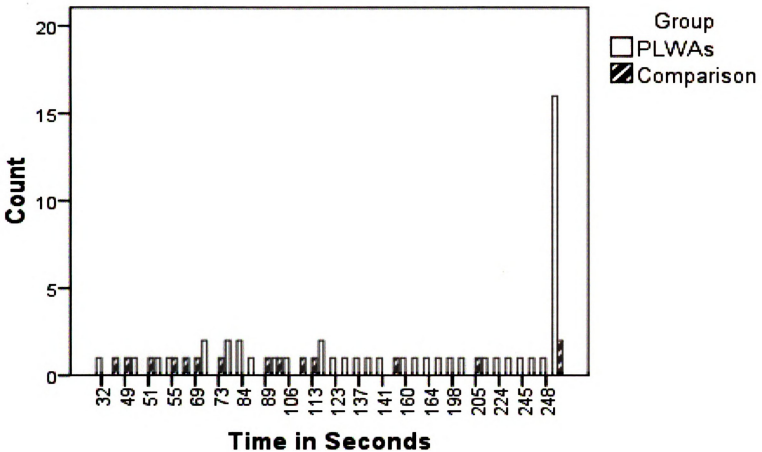


Figure 7. Distribution of Time (in seconds) to Complete Color Trails 1 among Persons Living With AIDS (PLWAs) and Comparison Group



CHAPTER 5: CONCLUSIONS

5.1 Summary of Findings

In this pilot study, non-physician healthcare workers utilized brief screening instruments to identify significant differences in neuropsychological test performance between PLWAs and a healthy comparison group. We found that 50% of all PLWAs, and 55% of patients with WHO Stage IV HIV disease met our study definition of CI. Among the study instruments tested, the ZMMSE was able to identify more cases of CI compared to the use of the m-HDS and Color Trails 1. Comparison group participants also performed more reliably on the ZMMSE, indicating improved cultural relevance in this population.

5.2 Comparison of Findings to Prior Literature

5.2.1 Screening Instruments for HIV-related NCI

The pattern of deficits on the ZMMSE, including impaired attention and verbal memory recall among PLWAs is consistent with previous investigations of HIV-related NCI[69,71,73]. Verbal fluency tests are frequently impaired in patients with HIV-related NCI, and other HIV-D investigations have employed timed semantic and phonemic fluency tasks, which are likely more specific to the psychomotor slowing deficits seen in HIV-D and might be considered as an appendix to the ZMMSE in future investigations of HIV-D.

The patterns of deficits seen in HIV-related NCI in regions outside of the U.S., Europe, and Australia have not been well documented and tests of cortical impairment were also included for evaluation on the ZMMSE. Orientation and constructional praxis

were preserved amongst PLWAs, but these items may still have clinical utility in identifying patients with other co-morbidities that result in cognitive impairment in HIV/AIDS patients with or without ART treatment.

Neuropsychiatry officers in Zambia commonly use questions adapted from the MMSE for cognitive status assessment in their patients. Thus, the MMSE has the benefit of widespread familiarity in Zambia, and perhaps in other African settings as well. An MMSE was utilized for neuropsychiatric assessment in a study of HIV inpatients in Johannesburg, South Africa[87]. This study does not report if the instrument was adapted for local use and normative data was not provided. In fact, no previous studies have examined the reliability or validity of the MMSE in Africa. An addition to the ZMMSE of more culturally appropriate tests of psychomotor retardation may improve identification of HIV-related CI in such populations and should be considered in future investigations.

Although the HDS is considered more specific to the cognitive deficits seen among HIV/AIDS patients in the U.S., few study participants, healthy or otherwise, were able to complete timed 3-D cube drawing in this study, and timed number writing also appeared to be a difficult task. It was observed that PLWAs frequently omitted numbers and/or wrote numbers backwards, suggesting that number writing requirements and possibly the paper and pencil format are unfamiliar tasks amongst patients in this community.

Similarly, our normative comparison group performed much more slowly on Color Trails 1 than other cross-cultural studies of healthy subjects[126,127], emphasizing the need for population-specific normative data. In a Chinese study of mandarin-speaking volunteers with mean age of 35.77 and mean years of education of 9.06, the mean time in

seconds to complete Color Trails 1 was 44.7 seconds, compared to our healthy comparison group with a mean of 104.4 seconds[127]. Although designed to minimize cultural bias by eliminating the use of the English alphabet, the Color Trail tests were originally validated amongst populations with high educational ascertainment, with all participants having at least 10 years of education and a mean and standard deviations of 16.4 years in Bangkok, Thailand; 15.7 years in Kinshasa, former Zaire; and 17.2 years in Naples, Italy, whilst our normative controls and PLWAs had a mean education of 7.5 and 7.2, respectively[122]. In addition, 13 study participants, including 12 (25%) PLWAs and 1 (6.7%) normative control, were unable to complete the task in the recommended allotted time of 5 minutes. Thus, the paper and pencil format of the Color Trails test may produce a significant educational bias and reduce the sensitivity of the test for identifying HIV-D in areas with low education and literacy rates, reducing the cross-cultural relevance for use. In addition, the cost of purchasing the colored documents is prohibitive to routine use in resource-limited settings. This study did not formally evaluate the correlation between education, HDS score, and Color Trails 1 time, and thus the causes of the administrative difficulties observed remain speculative, but suggest that both are poor choices for use in resource-limited settings.

The International HIV Dementia Scale (IHDS) may prove to be a useful screening instrument, but was not available at the time of this study[64]. The IHDS contains tests of motor speed (timed finger tapping), psychomotor speed (timed alternating hand sequence test), and memory (recall of four words). The IDHS was shown to have 64% sensitivity and 71% specificity for identifying HIV-D in a group of 81 ambulatory HIV patients (mean CD4 219 cells/mm^3) in Kampala, Uganda[64]. However, the IHDS failed to identify

any significant differences in performance between factory and sugarcane workers in Ethiopia with untreated and moderately advanced HIV disease (i.e. median CD4 <300 cells/mm^3) and a group of seronegative controls[41]. This may be related to selection of control patients for normative data, who were slightly younger in the Ugandan study, or suggests that the IHDS may be insensitive to milder HIV-related NCI. Application of the ZMMSE and the IHDS in another larger study in a rural Zambian population may help elucidate further strengths and limitations of these two instruments.

5.2.2 Prevalence of Cognitive Impairment

This study found a very high prevalence of cognitive impairment (50%) among a group of high-risk, antiretroviral naïve AIDS patients in Lusaka, Zambia. Statistical power was not sufficient to ensure that this finding was not due to chance alone. However, other African investigations have found equally high prevalence estimates in hospitalized patients[40,42,44,84]. In Tanzania, 54% of PLWAs had neuropsychiatric abnormalities including psychomotor slowing, confusion, and dementia utilizing unspecified neuropsychological tests of orientation, memory, attention, and calculation[42]. Although the WHO staging scheme was not utilized in the Tanzanian study, 62% of patients with greater than three months duration since AIDS diagnosis and 65% of PLWAs that died in the hospital (suggesting advanced HIV disease) were identified as having CI. A study from former Zaire identified neuropsychiatric abnormalities in 43 of 104 (41%) HIV inpatients[43]. However, the neuropsychiatric instruments utilized are not reported in this study. Among the HIV seropositive patients, nine cases of HIV-D and three cases of MCMD were identified. All of theses cases were identified among WHO stage III (41%) and stage IV (58%) PLWAs. In Johannesburg, South Africa, HIV-D was

the most common neurological disorder with 108 (38%) cases of HIV-D diagnosed in 506 consecutive antiretroviral-naïve HIV positive inpatients as assessed by MMSE[87]. Decreasing CD4 count correlated with HIV-D diagnoses, with 108 cases having CD4 below 50, 38 between 51 and 100, 29 between 101 and 200, 12 between 201 and 500, and in 5 cases CD4 count was >500 (*p* for trend not reported). Belec et al found a very low occurrence of dementia at 3.2% amongst 93 hospitalized patients in Bangui, Central Africa Republic[40]. The reasons for this disparate finding are unclear, owing to lack of specification of clinical criteria for diagnosis in this study. It is reasonable that HIV-D patients may be overrepresented among hospitalized patients, owing to the increased caregiving and dependency needs of patients with cognitive impairment.

Studies of non-hospitalized HIV/AIDS patients also suggest that HIV-related NCI are common in ambulatory HIV patients in SSA(i.e. 4.5-31%)[39,44,72], with the exception of an Ethiopian study which failed to find any significant HIV-related NCI[41]. It is important to note, however, that this study utilized employer-based free clinics for patient identification. Thus, patients with more disabling neurological manifestations may have sought care elsewhere for fear of employment insecurity (although >70% of the HIV population is characterized in this study). HIV-D patients also have reduced survival without access to HAART and may also have contributed to the absence of significant impairments in this cohort.

In the U.S., several studies have shown that subtle cognitive deficits among asymptomatic HIV patients (equivalent to WHO stage I) increase in magnitude with progression to symptomatic HIV (equivalent to WHO stage II and III) and full-blown AIDS (equivalent to WHO stage IV) [128-130]. In this study, there appeared to be important

differences between the Stage II/III and Stage IV PLWAs on all neuropsychological tests, but this trend did not reach statistical significance. This latter finding may reflect the limited number of patients among the study population with Stage II or Stage III HIV disease. Studies with larger sample size will be needed to further examine the relationship between stage of HIV disease and CI among African PLWAs.

5.3 Strengths and Limitations

This study was limited by small sample size. Another limitation of our study was that causes of CI likely included HIV-D, opportunistic infections of the CNS, metabolic encephalopathy, as well as mixed cases. Our ability to define the cause of CI was hindered by the lack of available diagnostic testing and the expense of conducting such tests, but these conditions reflect the reality of HIV care provisions in SSA. Lack of access to diagnostic and physician level healthcare are challenges faced daily by African patients and their healthcare providers. In addition, the screening instruments utilized in this study only assessed cognition, but behavioral abnormalities and functional abilities are also important components of the clinical triad of HIV-related NCI. Still, identification of patients with CI may prompt additional referral and/or lead to identification of other potentially treatable causes, such as neurosphyillis or depression.

In comparison to previous investigations of CI among African PLWAs that utilized extensive neuropsychiatric tests administered and interpreted by neuropsychologists and physician-specialists, a strength of this study is that the methodology is reproducible in other resource-limited setting. These preliminary findings indicate that the ZMMSE is easily administered and interpreted by non-physician healthcare workers and that further

modifications to the instrument and evaluations may allow routine screening for cognitive impairment in HIV patients in SSA.

5.4 Suggestions for Future Research

As ART becomes increasingly available in SSA, HIV-related NCI have important pubic health implications and may become increasingly prevalent. Enabling clinical identification of the disorder is crucial to monitoring shifts in the epidemiology of these disorders and planning appropriate resource allocations.

This pilot study conducted preliminary steps for formal validation of the ZMMSE in Zambia. Additional studies will need to be conducted to standardize the instrument, and will likely result in further modifications and improvements. Further, reliability of test items within and between observers should be assessed if the instrument is to be used for routine surveillance of HIV-related NCI by clinical officers or other paramedical healthcare workers. Screening instruments for identifying HIV-related NCI provide a viable opportunity to improve diagnosis in resource-limited settings where physician-experts are most often unavailable.

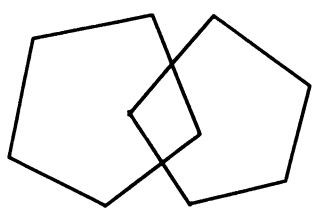
Many aspects of HIV-related NCI remain unknown, including optimal treatment schemes and diagnostic importance of CSF markers of HIV suppression and inflammation (i.e. CSF viral load and cytokines) in guiding treatment decisions. The pathogenesis of the disorder may be further elucidated by studies of frequency, clinical features, and course of HIV-related NCI in patients with different patterns of disease transmission and HIV-related disease, as well as diverse HIV clades. Enabling early clinical identification of HIV-related NCI by clinical officers is a first step in improving

understanding of the epidemiology of these disorders in SSA, as well as providing maximal clinical benefit to patients through ART initiation.

APPENDICES

APPENDIX A

Incorrect Response	Correct Response	**Zambian Mini-Mental State Examination**
		Kuyambisa (Orientation)
0	1	Ndi caka bwanji (*what is the year*)?_____
0	1	Ndi ntawu bwanji (ntawi ya mpepo, maiza, chi la la) (*what is the season*)?_____
0	1	Ndi mwezi bwanji (*what is the month*)? _____
0	1	Ndi siku la bwanji mu mwezi (*what day of the month is it*)? _____
0	1	Ndi siku la bwanji mu week (*what day of the week is it*)? _____
0	1	Tili muziko bwanji *(what is the name of this place)*? _____
0	1	Kodi tili pa floor bwanji? *(what floor are we on?)* _____
0	1	Kodi tili mumuzinda bwanji *(what city are we in)*? _____
0	1	Kodi tili muyumba btani *(what are of that city are we in)*? _____
0	1	Tili muprovince bwanji *(what province are we in)*? _____
		Cilankulidwe (Language)
		Kodi nicani ici?/Kambani zina la cisulo ici (*What is the name of this (Show item))*?
0	1	Nkoloko (wrist watch)
0	1	Pensulu (pen)
0	1	Mubwezepo pambuyo panga: 'kulibe kuchita kulibe kusachita' Ask the patient to repeat this phrase, only one trial: 'no ifs, ands, or buts'
		Khalani cete (Attention)
		Can you name the days of the week backward? For example, before Sunday comes Saturday; what comes before that?
0	1	Friday
0	1	Thursday
0	1	Wednesday
0	1	Tuesday
0	1	Monday

Incorrect Response	Correct Response	**Zambian Mini-Mental State Examination (Page 2)**
		Konkani njila zitatu (3-Stage Command)
		Tenga iyi pepala mukwanja yamanja, upeteke pakati ndipo uike pansi. *(Take this paper in your right hand, fold it in half and put it on the floor. Do NOT prompt or repeat command when patient is performing task)*
0	1	Right hand
0	1	Folds
0	1	Places on floor
		Lamulo lolembedwa (Written Command)
0	1	Welengani mau aya ndi kucita zimene inena (MVALANI MASO ANU) *(say look at me and do exactly what I do. DO NOT TELL PATIENT TO CLOSE EYES).*
		Lembani mau (Write a Sentence)
0	1	Lembani mau Lembani mau aliyense (*Have the patient write a sentence*)
		Cigwilizano (Coordination)
0	1	Lembani ici cintuzi bwinobwino mwamene mungalembele *(All ten angles must be present and the two pentagons must intersect)*
		
_____		TOTAL

APPENDIX B

Introduction

HIV-associated dementia (HIV-D) is a qualifying indication for antiretroviral therapy (ART) initiation according to World Health Organization (WHO) guidelines for resource-limited settings[45], but is not routinely screened for in ART clinics in sub-Saharan Africa (SSA) due to a lack of valid instruments with population-based normative data. Delays in treatment initiation may lead to irreversible neurologic damage that complicates future HIV management[48], but the non-physician healthcare workers (NPHW) providing the bulk of HIV care in SSA[38,65,131], have little experience in diagnosing these disorders.

Previous investigations for HIV-D in SSA have utilized physician specialists for evaluation[41,64,87]. No previous studies have utilized NPHW for cognitive assessments. We trained NPHW in administration of locally-adapted screening instruments. We report cross-sectional results of performance and frequency of cognitive impairment (CI) in Persons Living With AIDS (PLWAs) admitted to an urban hospice facility in Lusaka, Zambia.

Methods

Population

PLWAs were recruited from a hospice in Kalingalinga, Lusaka, Zambia and controls were recruited from the same community. HIV seroprevalence in Kalingalinga was reported at 26% in 2002[121]. The hospice had a 24-bed capacity, but no laboratory or radiological equipment available on site.

Participants

All PLWAs, aged 18 or older, admitted for the first time to the hospice between January 21, 2004 and March 22, 2004 were interviewed. Exclusion criteria included failure to meet World Health Organization Clinical Case Definition for AIDS (WHOCCD)[89], past medical history of a chronic neurologic disorder, psychiatric disorder, substance abuse, or a physical deficit or severe medical illness that would interfere with study performance. Family members of patients attending outpatient clinics also underwent the evaluation to provide normative data.

Interview Procedures

This project was approved by the Michigan State University Committee on Research Involving Human Subjects and the University of Zambia Research Ethics Committee. Twelve NPHW were trained in administration of study instruments. After informed consent procedures, participants underwent a structured interview assessing demographic information and past medical history. A chart review was also undertaken. Interviews were conducted in the patient's language of choice between Chinyanja (67%) and English (33%).

HIV/AIDS Diagnosis

HIV status was assessed by the WHOCCD[89,124]. Comparison group participants with signs/symptoms of HIV were excluded from analysis (n=3). WHOCCD for AIDS was preferred over conducting HIV testing because of limited access to HIV testing. Patients were also assessed by WHO HIV staging criteria[89]. Subsidized ART were generally not available in Zambia during the study period.

Neuropsychological Screening Instruments

The Mini Mental State Exam[54] (MMSE) was selected because of frequent informal use among clinical psychiatric officers in Lusaka. The HIV Dementia Scale[62] (HDS) and Color Trails 1[122] (CT1) were chosen because of the specificity of each in assessing HIV-D deficits. To adapt these instruments, focus group discussions were conducted with a local psychiatrist (A.H.), internists, and medical students to identify test items likely to be culturally or otherwise problematic. Once identified, the cognitive domain tested by each item and relationship to HIV-D was discussed and adaptation suggestions were provided. Adapted items involved tasks requiring reading and writing and were replaced with more appropriate items deemed to have content validity by the focus group. However, an adaptation for 3-D cube drawing was not identified and this item was omitted from the summary score. Following a careful emic translation procedure by experienced medical translators, instruments were back-translated into English by a linguist and medical professionals and pre-piloted in the community prior to study commencement.

Statistical Analysis

Data was coded and entered into an Excel spread sheet. All statistical analyses were carried out using SPSS version 13.0 or SAS version 9.1. Demographic variables were compared using Student's T-tests or Chi-square tests. Mann-Whitney U tests and Student's t-tests were performed to compare MMSE, HDS, and CT1 scores between PLWAs and the comparison group. Very few patients had evidence of only mild HIV disease and patients with WHO Stage II Illness and WHO Stage III together for comparisons. Kruskal-Wallis tests and one-way ANOVA tests were performed to evaluate between group differences on WHO Stage II/III, WHO Stage IV, and the comparison group. Since all nonparametric tests supported the findings of the Student's

t-tests and ANOVA, only the latter are reported to maintain the raw data in original scale. Significant CI was defined as scoring >2 SD below the mean of the comparison group on the MMSE, or >2 SD below the mean of the comparison group on both the HDS and CT1, similar to previous investigations[72,84]. The prevalence of CI is reported as the proportion (%) of PLWAs meeting the study criteria for significant CI. A chi-square test for trend in binomial proportions was used to assess the relationship between CI and WHO HIV stage. A significance level of 0.05 was considered statistically significant for all tests.

Results

The final study group was comprised of 48 PLWAs (Figure 3). One patient was currently receiving ART, and none reported previous use of ART. Only one comparison group volunteer (6%) reported having a negative HIV test. No significant differences were found between PLWAs and healthy subjects with regard to age, education, or gender (see Table 6). Among all PLWAs, 25 (52.1%) reported noticing changes in memory and 16 (33.3%) reported changes in thinking. No one in the comparison group had these complaints.

Neuropsychological Comparisons

PLWAs scored significantly worse than the comparison group on all tests as a group, as summarized in Table 9. Overall, three PLWAs (6%) were identified as having WHO Stage II, 14 (29%) WHO Stage III, and 31 (65%) WHO Stage IV disease. After stratifying by WHO stage, highly significant differences were identified between the comparison group and WHO Stage IV PLWAs on the MMSE ($p<0.001$), HDS ($p<0.001$), and CT1 ($p<0.003$). No statistically significant differences were identified between the

comparison group and WHO Stage II/III on the MMSE (p =.081), HDS (p =.086), or CT1 (p =.093). WHO Stage IV differed from WHO Stage II/III on the HDS only (p =.011). Twenty-four PLWAs (50%) scored >2 SDs below the comparison mean on the MMSE, and 8 of those 24 also scored >2 SD below the comparison mean on both the HDS and CT1. No additional cases were identified using the latter criteria alone. Twenty-four PLWAs (50%) scored >2 SD below the comparison mean on the HDS. Finally, 13 PLWAs (27%) scored >2 SD below the comparison mean on CT1. **Overall, 24 (50%) PLWAs met the study definition for significant CI.** Among WHO staging categories, there was one stage II (33%), 6 stage III (42%), and 17 stage IV (55%) patients with significant CI, but this trend was not statistically significant (p = 0.24).

Discussion

In our pilot study, NPHW utilized locally adapted screening instruments to identify significant differences in neuropsychological performance between PLWAs and a healthy comparison group. The MMSE was noted to be most easily administered and have better face validity among control subjects. An addition to the MMSE of more culturally appropriate tests of psychomotor retardation and visuo-spatial abilities may improve identification of HIV-related CI and should be considered in future investigations. Clinical psychiatry officers in Zambia commonly use MMSE items for cognitive assessments, and therefore the MMSE has the benefit of widespread familiarity. The International HIV Dementia Scale (IHDS) may also prove to be a useful screening instrument, but was not available at the time of our study[64]. We are applying the adapted MMSE and the IHDS in another larger study in a rural Zambian population utilizing

NPHW, which may help elucidate further strengths and limitations of these two instruments for routine clinical assessments.

We found that 50% of all PLWAs, and 55% of patients with WHO Stage IV HIV disease met our study definition of CI. In addition, the identification of one stage II (33%) and 6 stage III (42%) patients with CI suggests that screening is important for all symptomatic HIV patients. Other African investigations have found equally high prevalence estimates in hospitalized patients[40,42,44,84]. HIV patients with CI may be overrepresented among hospitalized patients owing to the increased dependency and caregiving needs, but our findings suggest that CI in PLWAs are disorders that consume a great deal of hospital resources in SSA. Given that delayed treatment may result in irreversible CI, resources should be allocated to allow increased training in identifying and managing such cases, as well as allowing for caregiver respite.

Screening instruments alone cannot be used alone for HIV-D identification, but may help to narrow the ART access gap for patients that would not otherwise qualify for ART initiation. In Kampala, Uganda, 6 of 16 HIV-D patients had CD4 counts greater than 200, making a clinical-based diagnosis essential for ART commencement in 37.5% of HIV-D patients identified[47]. Use of such screening instruments may facilitate triage to specialists or diagnosis of other causes of CI in PLWAs. The time to enable clinical identification is now, so that these important disorders can be considered in public health policy planning and resource allocation. Our preliminary findings indicate that simple screening examinations performed by NPHW can identify HIV patients with significant CI.

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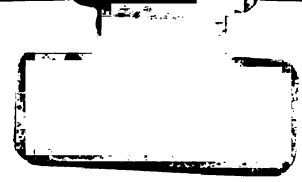

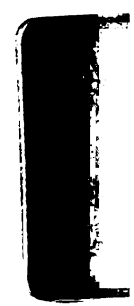

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