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Cognitive deficits and HIV associated psychotic disorders in Uganda

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Cover: Illustration: "engraffiti"
The management of cognitive impairment, psychosis and HIV disease have to be collectively appreciated in order to effect management of affected individuals.
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We can't solve problems by using the same kind of thinking we used when we created them."

Albert Einstein

To Noel, Mary-Julia, Jemimah-Angella and Daddy

ABSTRACT

Introduction: HIV infection is known to cause neuro-psychiatric disturbances whose prevalence ranges between 74-83%. The prevalence of HIV in patients with psychosis has been found at 18%. Cognitive dysfunction occurs in 37% of HIV individuals with advanced HIV/AIDS even after the initiation of antiretroviral therapy. This thesis presents the feasibility of a rapid screening test for HIV dementia in a resource limited setting; the nature of HIV related psychoses and the impact of HIV infection on the cognitive function of patients with and without psychosis.

Methods: Four studies (1-IV) were conducted using multiple methods. We determined the validity of the International HIV Dementia Scale (IHDS) through administering standardized neurological and neuropsychological assessments to 66 HIV-positive individuals in the USA, 81 HIV positive individuals and 100 HIV negative individuals in Uganda (Study I). We recruited 102 HIV positive individuals from the Infectious Diseases Institute and 25 HIV negative individuals from the AIDS Information Centre. Depression and cognitive function were assessed at 0, 3 and 6 months (Study II). One hundred and fifty six HIV positive and 322 HIV negative patients with psychosis were consecutively recruited from two national referral hospitals. Psychiatric, physical, and laboratory assessments were conducted at 0, 3 and 6 months (Study III & Study IV). Data was analyzed using univariate, bivariate and multivariable methods including linear and logistic regression analysis to test for predictors of the different types of psychosis and the relationship to cognitive impairment.

Results: The sensitivity and specificity for HIV dementia with the IHDS was 80% and 57% in the US part of the study, and 80% and 55% in the Uganda part of the study (I). We found higher scores (equal to or greater than 16) on the Centre for Epidemiologic Depression Scale in the HIV-positive group at all 3 clinic visits (54% vs 28%; 36% vs 13%; and 30% vs 24% respectively; all $p < 0.05$ (II). The HIV positive group had higher likelihood for cognitive impairment (OR 8.9; 95% CI 2.6-29.9). Mania, major depression and schizophrenia occurred more in the HIV negative group, 67%:62%:80% respectively, while psychotic disorder not otherwise specified occurred more in the HIV positive individuals 88% vs 12 %, ($p < 0.001$) (III). The HIV positive individuals were more likely to be impaired in the following domains, verbal memory (OR 1.8, 95% CI 1.0-2.9), verbal fluency (OR 3.4; 95% CI 2.2-5.2), Colour trails 1(OR 2.0; 95% CI 1.3-3.0 and Colour trail 2 (OR 3.5; 95% CI 2.0-6.1).

Conclusion: We found it feasible to screen for HIV dementia using the IHDS and suggest this is implemented in routine clinical care. Depression symptomatology and the presentation of psychosis are distinct and common among HIV infected individuals compared to HIV negative individuals. The cognitive function of individuals with psychosis is worsened by HIV infection. Treatment algorithms for the different types of psychoses and the cognitive impairment that occur in HIV infection should be developed. There is need for policy changes that can improve guidelines for the care of HIV infected individuals with neuropsychiatric complications in resource limited settings.
Keywords: HIV/AIDS, cognition, HIV associated psychosis, depression.

LIST OF PUBLICATIONS

I.   Sacktor N, Wong M, **Nakasujja N**, Skolasky RL, Selnes O, Musisi S, Robertson K, McArthur J, Ronald A, Katabira E. The International HIV Dementia Scale: a new rapid screening test for HIV dementia. <u>AIDS</u> 2005;19:1367-1374

II.   **Nakasujja N**, Skolasky RL, Musisi S, Allebeck P, Robertson K, Ronald A, Katabira E, Clifford BD, Sacktor N. Depression symptoms and cognitive function among individuals with advanced HIV infection initiating HAART in Uganda. <u>BMC Psychiatry</u> 2010; 10:44

III.   **Nakasujja N**, Musisi S, Agren H, Katabira E, Allebeck P. Psychotic disorders in HIV positive versus HIV negative patients: A comparative study of clinical characteristics. *Manuscript*

IV.   **Nakasujja N**, Allebeck P, Agren H, Musisi S, Katabira E. Cognitive dysfunction among HIV positive and HIV negative patients with psychosis in Uganda. *Manuscript*

CONTENTS

LIST OF ABBREVIATIONS

AIC	AIDS Information Centre
AIDS	Acquired Immune Deficiency Syndrome
ART	Antiretroviral therapy
BPRS	Brief Psychotic Rating Scale
CD4	Cluster of differentiation 4
IHDS	International HIV Dementia scale
HAART	Highly active antiretroviral therapy
HIV	Human Immunodeficiency Virus
MINI	Mini International Neuropsychiatric Interview
PHQ-9	Patient Health Questionnaire-9
SIDA	Swedish International Development Agency
UNAIDS	Joint United Nations Programme on HIV/AIDS
WHO	World Health Organisation
WHO-UCLA	World Health Organisation- University of California Los Angeles
YMRS	Young Mania Rating Scale

LIST OF TABLES AND FIGURES

OPERATIONAL DEFINITIONS

Cognitive impairment: A disturbance in the process of obtaining, organizing and using intellectual knowledge. It also implies an understanding of the connection between cause and effect as well as between action and consequence.

Psychosis: This is a generic psychiatric term for a mental state in which thought and perceptions are severely impaired. Psychosis is a symptom of severe mental illness rather than a diagnosis in itself (Kaplan and Sadock, 1998). There is an inability to distinguish reality from fantasy: with a creation of a new reality (i.e. the objective evaluation and judgment of the world outside the self). In the Diagnostic and Statistical Manual IV (DSM-IV) psychotic disorders are operationally defined as to comprise hallucinations, delusions, and/or formal thought disturbances. Persons experiencing a psychotic episode may experience hallucinations or hold delusional beliefs, demonstrate personality changes, exhibit disorganized thinking and disturbed behavior. This is often accompanied by lack of insight into the unusual or bizarre nature of such behavior, thinking or difficulties in social interaction and impairments in carrying out activities of daily living. Though not exclusively linked to any particular psychological disorder, it is particularly associated with schizophrenia, bipolar disorder and severe clinical depression and some forms of organic brain impairments (Kaplan and Sadock, 1998).

PREFACE

"I wish to explore at the cognitive function of individuals with psychosis" I said to one of the members of my research team. His reply was "Am not sure that will be totally easy, the patients are usually non-compliant to sit through the evaluation, it may turn out a very difficult task". And a difficult task it was but I had the belief that this was something that was achievable. Having previously conducted numerous cognitive assessments in HIV and non HIV infected individuals, it was time to attempt what was considered a most difficult task. Looking back now, that was a journey which has finally culminated into this thesis. I hope the information in this book will fill the gap in knowledge of the cognitive function in HIV infected individuals with mental illness.

1   INTRODUCTION

1.1   HIV INFECTION IN UGANDA

The HIV/AIDS epidemic is entering its forth decade (UNAIDS, 2010). The disease which was first described in America in 1981 was documented as the SILIMU disease in Uganda in 1982. It was characterized by extreme wasting, mental confusion and subsequent death (Musisi and Kinyanda, 2009). Over the past three decades the disease spread to epidemic proportions in all continents. The peak HIV prevalence occurred in the early 1990's for the Ugandan population (MOF, 2010). Even though the millennium development goal for the global reduction in the spread of HIV prevalence has been achieved by a 19% drop in infection rates, some countries have not experienced the continuous downward trend.

In Uganda, the prevalence of HIV infection had tremendously dropped from 30% in the early 1990's to 6.4 %, in the early 2000's however in recent years the trend has again been noted to be increasing (MOH and Macro, 2006, Eggertson, 2010, Shafer et al., 2010, UNAIDS, 2010). Indeed the burden of individuals affected by the virus remains high with a staggering 110,000 new infection per day (Figure 1). In a country where the fertility rate has stagnated at 6.7 births for women in the reproductive age group, the population has continued to escalate with a growth rate of 3.3% to a current estimate of 32.7 million people. This places Uganda as one of the countries with the fastest growing population in the world (UAC, 2007, UBOS, 2009, The World Bank, 2010). This presents a challenge to the management of HIV infection and its associated complications given the scarcity of antiretroviral therapy (ART) in this setting. Worldwide, there only 5.2 million (36%) of the 15 million people who have access to ART. In Uganda it is estimated that of the 373,000 individuals in need of ART, about 200,000 have access to the treatment (MOF, 2010).

Figure 1: The trend of new HIV infections in Uganda.
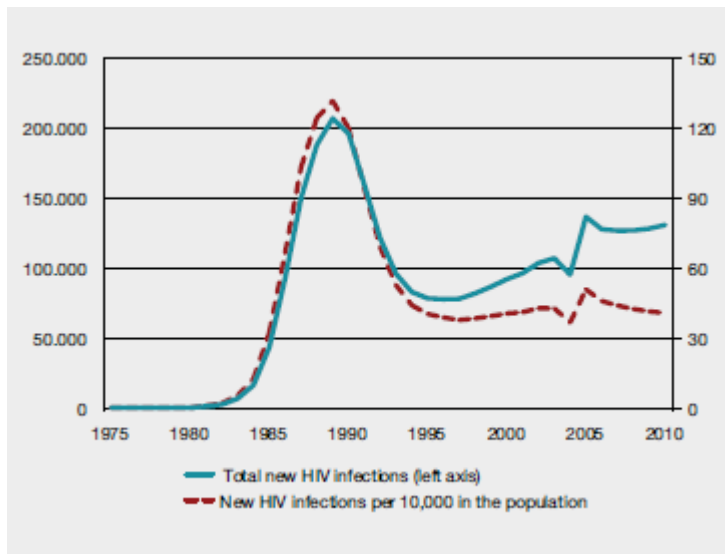
Source: Hladik 2009, (as cited) in Uganda Millennium Development Goal

Report 2010

Coupled with this problem, it has been observed that most of the patients present for

health care service in advanced stages of the AIDS illness. As a result there is a

multiplicity of occurrence of HIV associated illnesses including neuropsychiatric

disorders (Halstead et al., 1988). This creates an enormous disease burden for the health

care system (UNAIDS, 2010).

1.2   HIV INFECTION AND NEUROPSYCHIATRIC DISORDERS

Neuropsychiatric disorders can occur at any stage of HIV illness (Musisi and

Kinyanda, 2009). The disorders manifest in a number of ways and require appropriate

intervention. HIV related psychosis, dementia and cognitive impairment are common

complications of HIV which are poorly researched in Sub Saharan Africa.

Consequently there is little attention given to their management in the health care

system where the HIV affected individuals receive care. The prevalence of these

disorders has been reported to be as high as 74% (Kinyanda and Musisi, 2002) and 82.6% (Petrushkin et al., 2005) among ambulatory patients attending the AIDS Support Organization (TASO), clinic in Uganda.

1.3   COGNITIVE IMPAIRMENT AND HIV INFECTION

Prior the introduction of highly active antiretroviral therapy (HAART) in 1996, the prevalence of HIV associated dementia was as high as 50-70% in high income countries (Cysique et al., 2006) while others estimated it at 7.3% - 37% (Janssen et al., 1992, Portegies et al., 1993, Sacktor et al., 2002). The prevalence in low income countries varied due to inconsistencies in the methodologies used to measure the cognitive impairment. There was also a lack of standardized cross cultural instruments whose use could not be replicated in these settings where the literacy rate was low (Wong et al., 2007). The World Health Organization (WHO) conducted a study in Congo and Kenya where they indicated the prevalence among inpatients as 5.9 and 6.9% respectively (Maj et al., 1994).

Cognitive impairment is associated with low CD4 count and usually occurs in the later stages of HIV infection (Robertson et al., 2007). Unfortunately for patients in Uganda, ART has often been initiated if one had an opportunistic infection or if their CD4 cell count dropped as low as 50 cells/uL. Recently, there has been a revision of the country's treatment guidelines for HIV infection in liaison with the WHO. The current cut off for initiation for ART is now CD4 250 cells/uL if one is not pregnant or if they do not have WHO stage III or IV disease (MOH, 2009). Realistically this is hard to implement given the scarcity of ART. Indeed most centers initiate the ART when the CD4 cell count is ≤ 200 cells/uL. Due to the scarcity of ART therapy, lack of recognition and proper management of cognitive disorders in low resource countries, many would succumb to the disorder.

It has been shown that HAART improves cognitive function (Sacktor et al., 2006, Robertson et al., 2007, Shapshak et al., 2011). However the actual management of the cognitive impairment in resource limited settings leaves a lot to be desired as in most cases the condition is not even looked out for. Most HIV positive individuals do not even receive such a diagnosis in HIV clinics due to a lack of personnel that can make the true diagnosis. Compounding the difficulty in diagnosis is the high prevalence of depression among HIV patients (Sherbourne et al., 2000). It has been noted that depression symptomatology rises as AIDS progresses (Lyketsos et al., 1996, Nath et al., 2008). Its rates are 2-3 times higher than those of the general community (Norton, 2000, Sherbourne et al., 2000, World Health Organisation, 2004). Among recently diagnosed HIV patients in South Africa the prevalence of major depression was found to be 35% (Olley et al., 2003). However most clinics do not routinely screen for it and therefore it is often missed. The symptoms of depression may at times mimic the presentation of cognitive impairment (Akena et al., 2010). In some situations depression may be the initial presentation of HIV dementia further making it difficult to distinguish the two conditions (Dubé et al., 2005, Nath et al., 2008).

When cognitively impaired, there are challenges that arise for the individuals and community as a whole. Firstly, there is always a concern on how individuals will handle their ART regimen given that memory impairment is a major presenting feature of cognitive impairment (Anand et al., 2010). Secondly, the effects of the impairment impact on work and hence the economic productivity of the individual and income for their families gets to be largely compromised. Thirdly, as the condition progresses, the functionality of the individuals is affected and they became less able to perform Activities of Daily Living. Consequently the affected individual becomes largely dependent on others within their family or community.

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1.4 HIV AND PSYCHOSIS

Psychosis secondary to the HIV infection, as is the case with HIV secondary mania, has been characterized to by late onset, with usually a close temporal relationship of an organic insult to the brain, and predominantly with a negative family history as well as a negative pre-morbid history of psychosis the individuals (Krauthammer and Klerman, 1978, Lyketsos et al., 1993, Sewell et al., 1994, Maling et al., 2005, Nakimuli-Mpungu et al., 2006). While individuals may coincidentally develop psychosis when HIV infected and the HIV virus increases the chance of an individual developing neuropsychiatric complications, it is worth noting that not all individuals get such complications.

Specifically, the evidence of an etiologic association of HIV with mania, that can present as psychosis was shown in a study in which it was demonstrated that a protective effect from an ART agent able to penetrate the central nervous system could prevent the development of mania (Mijch et al., 1999).

The psychosis develops directly or indirectly through opportunistic infection (Asselman et al., 2010), neoplasm, metabolic disorders or as a result of drugs used in the management of HIV disease (Halstead et al., 1988, Ewald, 2002, Horwah, 2002, Dolder et al., 2004, Dubé et al., 2005, Nilsson et al., 2005, Arendt et al., 2007). The presentation of HIV-associated psychotic disorders is varied. Generally it mimics the functional psychoses though distinct characteristics have been observed in some of the disorders like mania (Nakimuli-Mpungu et al., 2006).

1.5 COGNITION AND PSYCHOSIS

Cognitive dysfunction in patients having primary psychiatric illness like schizophrenia has been well documented (Goldberg et al., 1995, Tabares-Seisdedos et al., 2003, Fitzgerald et al., 2004). However there is limited literature on cognitive

impairment in patients that get HIV associated psychoses (Buhrich et al., 1988), noting that patients with AIDS who developed psychosis do not always have cognitive impairment. This author detailed case studies of three psychotic patients, one with AIDS, and two with AIDS-related complex (ARC), who showed no evidence of cognitive impairment, and suggested that the HIV virus may produce symptoms indistinguishable from those seen in the functional psychoses. In a study by Fitzgerald et al., (2004), verbal memory deficits differentiated individuals with schizophrenia from those with psychotic affective disorders. The patients with schizophrenia appeared to have more generalized impairment across a broad array of cognitive functions than other psychotic disorders.

Various researchers have studied the psychoses caused by HIV (Harris et al., 1992, De Ronchi et al., 2000, Dolder et al., 2004, Maling et al., 2005). In Uganda, among the first studies to be conducted on HIV psychosis, Maling et al., (2005) focused on the HIV infection rate among first episode psychosis, which was found at 18.4%. This rate was almost three times higher than that of the HIV negative population. Nakimuli-Mpungu et al., (2006) looked at the correlates of HIV related secondary mania. Both studies were conducted at Mulago and Butabika hospitals, the national general and psychiatric referral hospitals respectively.

Though mention of cognitive functioning was made on the patients included in these studies, there was no conduction of definitive detailed cognitive assessment. Indeed the primary objective of those studies was not the assessment of cognitive function. Researchers are often hesitant to attempt detailed neuropsychological testing in low resource settings as this usually requires a lot of resources in terms of human resource, skill and time as well as culturally relevant test instruments.

Among patients with HIV infection, clinical depression is the most frequently observed psychiatric disorder, affecting between 4% and 14% of men and women

respectively in some studies (Maj, 1996, Sacks et al., 2005, Singh et al., 2008). The few studies that have attempted to assess cognition have only used the Mini Mental State Examination (MMSE), a test that is best for detecting cortical cognitive dysfunction. The HIV virus attacks the sub-cortical structures hence causing a sub-cortical type of dementia (Brew, 2001). Thus the aspects of cognition that are usually affected first in HIV positive individuals are the motor, executive and affective functioning. It is therefore necessary to have a more appropriate instrument that is sensitive enough to detect this type of dementia.

In a retrospective chart review of HIV positive patients with mania, Lyketsos et al., (1993), found that none of the patients with a personal or family history of mood disorder had coexistent dementia. All but one of the patients without a personal or family history of mood disorder had coexistent dementia. In addition, among the 8% of the patients who experienced manic episodes, CD4 cell count was significantly higher in those individuals without a personal history of mood disorder.

1.6   TREATMENT OF PATIENTS WITH HIV ASSOCIATED PSYCHOSIS

Psychosis may be more frequently found in patients with significant AIDS-related neurocognitive impairment than in patients in earlier stages of the disease. In one retrospective chart review of 46 patients identified with HIV-1-associated dementia, (Navia and Price, 1986) found that 15% had developed psychotic symptoms. However, none of these studies described the effect of HIV on the course of treatment of these disorders or on the cognitive impairment itself. Although the retrospective chart review demonstrated no significant increase in extrapyramidal symptoms in AIDS patients treated with dopamine antagonists as compared to non-HIV-1-infected control patients, the small sample size and the general methodology of this study would only allow for the detection of large differences in prevalence of extrapyramidal symptoms;

moderate, but clinically relevant, differences could not be detected. Therefore, when treating psychotic symptoms in symptomatic HIV-1-infected patients it appears clinically prudent to slowly titrate neuroleptic medications, minimize drug dose, and carefully monitor for side effects.

ART has been shown to significantly improve cognitive impairment in HIV/AIDS (Sacktor et al., 2000, Musisi and Kinyanda, 2009). In Uganda, a cohort of 100 HIV positive patients with cognitive impairment was followed up for 6 months at the Infectious Disease Institute (IDI). Participants received an ART regimen of trioimmune (stavudine (d4T), lamivudine (3TC) and nevirapine (Nvp). There were improvements on all neuropsychological tests at 3 and 6 months (Sacktor et al., 2006). It has been reported that the use of Zidovudine in the long-term treatment of HIV patients could have a neuroprotective effect on cognitive function though this effect vanishes shortly after medication is discontinued (Pereda et al., 2000).

Studies have suggested that drug metabolism is different between ethnic groups. Polymorphisms of cytochrome P450s, CYP1A2, 2C8, 2C9, and 2C19 in African populations demonstrate interethnic differences in allelic variant frequencies compared to the Caucasian or Oriental populations (Aklillu et al., 2007, Miura et al., 2009). Such variation has implications on the drug metabolism of administered drugs and hence dosage and disease outcome of affected individuals. It is therefore important to find the nature and treatment outcome of psychosis and cognitive impairment among HIV affected individuals in Africa, especially Uganda where the HIV infection rates are still high.

1.7   AETIOLOGY OF COGNITIVE IMPAIRMENT AND PSYCHOSIS IN HIV

It has been established that the HIV/AIDS infection is associated with the development of cognitive impairment and psychosis (Halstead et al., 1988, Sewell et

al., 1994, Shapshak et al., 2011). The amount of evidence to support this finding has increased over the years to show that the onset of the psychosis occurs via both direct and indirect pathways. Directly, the virus attacks brain tissue, specifically sequestering in the microglial tissues where an immune response results in neurotoxin production. The damage which then ensues is a result of the produced toxins (Brew, 2001). Indirectly the HIV virus can induce psychosis through opportunistic infection, neoplasm, metabolic disorders or as a result of drugs used in the management of HIV disease (Nilsson et al., 2005, Ewald, 2002, Dolder et al., 2004, Arendt et al., 2007).

The cognitive functioning of an individual with psychosis is affected by a number of factors including the severity of psychosis or the anti-psychotic medication being taken among other things (Dolder et al., 2004). However, cognitive and other neurological impairment have been well documented in patients with functional psychoses such as schizophrenia (Goldberg et al., 1995). Schmand et al., (1993) have argued that cognitive disorders of psychosis are not of a 'computational' i.e. comprehension and processing but of an 'energetical' i.e. motivational nature. The cognitive impairments are not secondary to psychological issues that involve delusions, distracting effects of hallucinations or gross motivational defects. This has been shown by several approaches. First, correlations between symptoms and cognition are weak in schizophrenia; they are, however, very strong in bipolar disorder. Second, critical impairments in working memory and executive functions in schizophrenia do not respond to teaching or cognitive rehabilitation to a marked degree. Third, symptoms and cognition can be dissociated using pharmacological tools: A study of clozapine among individuals with schizophrenia has found that while symptoms showed significant improvement over a one-year interval, cognitive impairment remained stable and marked, this has also been observed in other studies (Albus et al., 2002).

Other researchers have found that the cognitive impairment in schizophrenia sometimes even precedes the onset of the disorder (Keefe et al., 2010).

At the biochemical level, research has suggested that HIV-related psychosis may occur as a result of the disruption of the glutamate–N-methyl-D-aspartic-acid (NMDA)–calcium pathway. Glutamate induces the NMDA receptor to open channels which allow calcium into the cell. If the receptor is blocked then one can develop psychosis. Quinolinic acid is an NMDA agonist, released from macrophages when induced by HIV proteins and it is found in increased concentrations in the central nervous system of HIV-positive patients (Smith et al., 2001). Kynurenic acid, an endogenous NMDA antagonist, is present in raised concentrations in the cerebral spinal fluid of patients with schizophrenia (Nilsson et al., 2005). It is also found raised in HIV positive patients (Dolder et al., 2004) and in even higher levels in the HIV positive who have psychosis (Atlas et al., 2007).

Other theories implicate HIV as a predisposing factor to psychosis, either because of the psychological stress of having a stigmatized chronic and ultimately fatal disease, or through HIV-related neuropathological mechanisms as may occur if an individual has opportunistic infections (Musisi and Kinyanda, 2009).

1.8   DIAGNOSIS OF HIV ASSOCIATED COGNITIVE IMPAIRMENT

Previously, lack of knowledge about the problem, as well as lack of screening for cognitive impairment created diagnostic dilemmas for clinicians managing HIV infected individuals. A variety of tools had been used including the Mini Mental State Examination (MMSE); however this tool was specifically designed for screening for cortical dementia such as Alzheimer's disease. Assessing comprehensive cognitive function often involves the administration of a variety of tests by trained personnel.

This process requires time and human resource which is are often lacking in the HIV clinics in Sub Saharan Africa yet performing neurocognitive examination is a sensitive and relevant approach to detecting neurological disorders (Grant, 2008).

The American Academy of Neurology defined the terms *HIV-1 associated dementia* (HAD) and *HIV-1 minor cognitive/motor disorder*(MCMD), in order to differentiate between severe impairment impacting performance of the patient's activities of daily living (ADLs) and mild cognitive impairment respectively (AAN, 1996). Formerly HAD and MCMD were differentiated by whether they affected patient function. However, it is now known that even the minor changes that accompany MCMD have been shown to affect patient function as well as the patient's overall quality of life (Heaton et al., 1994, McArthur et al., 2003, Gorman et al., 2009). There are 3 recognized HIV Associated Neurocognitive Disorders (HAND): HIV Associated Asymptomatic Neurocognitive Impairment (ANI), HIV-1 Associated Mild Neurocognitive Disorder (MND) and HIV-1 Associated Dementia (HAD). The classification has therefore been modified as indicated in the summarized criteria below for the spectrum of HIV Associated Neurocognitive Disorders (HAND) (Antinori et al., 2007, Foley et al., 2010).

1.8.1 HIV Associated Asymptomatic Neurocognitive Impairment (ANI)

1. Acquired impairment in cognitive functioning must involve at least two ability domains, documented by performance of at least 1.0 standard deviation (SD) below the mean for age-education-appropriate norms on standardized neuropsychological tests. The neuropsychological assessment must survey at least the following abilities: verbal/language; attention/working memory; abstraction/executive; memory (learning; recall); speed of information processing; sensory-perceptual, motor skills.
2. The cognitive impairment does not interfere with everyday functioning.

3. The cognitive impairment does not meet criteria for delirium or dementia.

4. There is no evidence of another preexisting cause (like depression or substance abuse) for the ANI.

1.8.2 HIV-1 Associated Mild Neurocognitive Disorder (MND)

1. Acquired impairment in cognitive functioning must involve at least two ability domains, documented by performance of at least 1.0 standard deviation below the mean for age-education-appropriate norms on standardized neuropsychological tests. The neuropsychological assessment must survey at least the following abilities: verbal/language; attention/working memory; abstraction/executive; memory (learning; recall); speed of information processing; sensory-perceptual, motor skills. *Typically, this would correspond to an Memorial Sloan Kettering (MSK) scale stage of 0.5 – 1.0.*

2. The cognitive impairment produces at least mild interference in daily functioning (at least one of the following):

> i. Self-report of reduced mental acuity, inefficiency in work, homemaking, or social functioning.
>
> ii. Observation by knowledgeable others that the individual has undergone at least mild decline in mental acuity with resultant inefficiency in work, homemaking, or social functioning.

3. The cognitive impairment does not meet criteria for delirium or dementia.

4. There is no evidence of another preexisting cause for the MND.

1.8.3 HIV-1 Associated Dementia (HAD)

1. There is marked acquired impairment in cognitive functioning, involving at least two ability domains; typically the impairment is in multiple domains, especially in learning

of new information, slowed information processing, and defective attention/concentration.

2. The cognitive impairment must be ascertained by neuropsychological testing with at least two domains 2 SD or greater than demographically corrected means. (If neuropsychological testing is not available, standard neurological evaluation and simple bedside testing may be used. *Typically, this would correspond to an MSK scale stage of 2.0 or greater.*

3. The cognitive impairment produces marked interference with day-to-day functioning (work, home life, social activities).

4. The marked cognitive impairment has been present for at least one month.

5. The pattern of cognitive impairment does not meet criteria for delirium or, if delirium is present, criteria for dementia need to have been met on a prior examination when delirium was not present.

6. There is no evidence of another, preexisting cause for the dementia (e.g., other central nervous system (CNS) infection, CNS neoplasm, cerebrovascular disease, preexisting neurological disease, or severe substance abuse compatible with CNS disorder).

If the individual with suspected HAD also satisfies criteria for a severe episode of major depression with significant functional limitations or psychotic features, or substance dependence, the diagnosis of HAD should be deferred to a subsequent examination conducted at a time when the major depression has remitted or at least 1 month has elapsed following cessation of substance use. When major depression and HAD occurred together, there is little evidence that 'pseudodementia' exists and the cognitive deficits do not generally improve with treatment of depression. If there is a prior diagnosis of HAD, but currently the individual does not meet criteria, the diagnosis of HAD in remission can be made.

2 RATIONALE FOR THE STUDIES

The presentation of neuropsychiatric disorders associated with HIV disease is largely unknown in the African setting where the prevalence of HIV is still high. The debate on whether or not the presentation of psychosis in HIV/AIDS is a manifestation of cognitive deterioration (i.e. a dementing process in individuals that are infected with HIV) has not yet been conclusively resolved so far from the studies that have been conducted. The development of a quick screening test for HIV dementia is therefore essential in a setting where most individuals are at risk of HIV associated cognitive impairment . Often these are hardly ever diagnosed thereby missing out on essential services. Depression, even to psychotic extent, is common in HIV/AIDS. The condition is at times difficult to differentiate from HIV dementia. In some situations, depression may be the initial presentation of HIV dementia and can make cognitive impairment worse. This creates a situation in which the depression often goes undetected and untreated in many of the patients hence the need for establishment of the distinction between the two conditions for each of them to receive the management that is due.

While the prevalence of HIV infection among patients with psychosis (18%) has been found high (Maling et al., 2005), there are only a few studies that have attempted at addressing the relationship of cognitive impairment in individuals who are co-morbid with HIV and psychosis. There is need for further documentation of what cognitive domains get impaired among HIV positive individuals. This thesis will therefore comprehensively document the occurrence of as well as types of cognitive dysfunction with a detailed test battery of neuropsychological assessment among patients with and without psychosis. Subsequent clinical intervention can then be specifically and appropriately directed for the affected individuals.

3 CONCEPTUAL FRAME WORK

Factors that affect the cognitive functioning of an individual with psychosis may occur in the following different ways:

1. Antecedents: These include disease factors e.g. HIV infection, the presence of psychotic illness or the presence of any other physical illness. Antecedents also include patient factors like the exposure experienced by the individual in their environment as well as their upbringing and level of education.

2. Modulating mechanisms: These include drug factor e.g. a sedating antipsychotic may affect the level of cognition of an individual and their subsequent performance on a cognitive test. The presence of a CNS lesion will also modify the performance on cognitive testing.

Below is a diagram representing the interaction of the above described factors.

Figure 2: Conceptual framework.
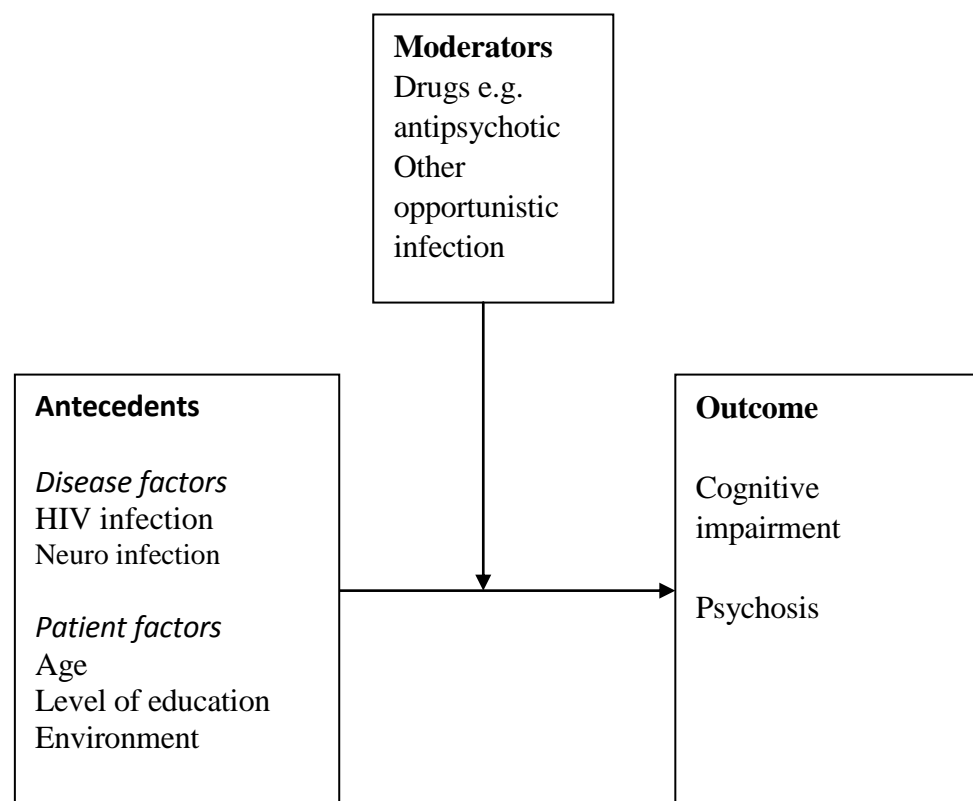
4   AIMS AND OBJECTIVES

4.1   GENERAL AIM

This research aimed at describing the feasibility of screening for HIV cognitive impairment as well as describing the impact of HIV on cognitive function in patients with and without psychosis in Uganda.

4.2   SPECIFIC OBJECTIVES

1. To evaluate the sensitivity and specificity of a new screening test for HIV dementia.

2. To determine the association of depression symptomatology and cognitive function among HIV positive and HIV negative individuals.

3. To compare the clinical characteristics of psychoses among HIV positive and HIV negative individuals.

4. To compare the cognitive deficits among psychotic HIV positive and psychotic HIV negative individuals.

5 METHODS

Table 1. Showing study design, setting and participants.

Article	Design	Period	Setting	Participants
I	Cross-sectional	2003-2005 2002	Infectious Diseases Institute and AIDS Information Centre Johns Hopkins Hospital.	81 HIV positive 100 HIV negative 66 HIV positive
II	Prospective	2005-2007	Infectious Diseases Institute and AIDS Information Centre	102 HIV positive 25 HIV negative
III	Cross sectional	2008	Mulago and Butabika Hospitals,	156 HIV positive and 322 HIV negative
IV	Prospective	2008-2009	Mulago and Butabika Hospitals,	156 HIV positive and 322 HIV negative

5.1 STUDY SETTINGS

The studies in this thesis were conducted in Uganda and the United States. Uganda is a land-locked country found in East Africa, measuring 241,550.7 sq.

km sq. km. The country's total population is estimated at 32.7 million with over 50% of the people below the age of 35 and most are poor rural peasants. Uganda's fertility rate of 6.7 children per woman in the reproductive age is among the highest in the world. The annual growth rate estimate as of 2009 was 3.5% and the average life expectancy was 53 years. The gross domestic product (GDP) of central government expenditure (1998–2007) allocated to health is 2%. The doctor patient ratio is 1: 18,000 and there are only 28 psychiatrists for the whole country.

The majority of the population (99%) is made up of related ethnic groups which consist of about 40 tribes. Luganda and Swahili are the widely used languages. However there are other Bantu and Nilotic languages. English is the official language of use. The literacy rate is 69% (UBOS, 2009). The country has been ravaged by war and was hard hit by the AIDS epidemic. There was a positive response to the epidemic through a number of strategies that included public awareness efforts, promotion of abstinence and monogamy ("ABC" policy) and free HIV testing. . The "ABC" policy emphasized "Abstinence" (A) for those who are not sexually active, "Being faithful" (B) to one's sexual partner and use of "Condoms" (C) in case one is to have sexual intercourse outside a steady relationship.

During the 1990s, HIV rates among pregnant women declined by nearly two-thirds, and the National HIV rate was cut nearly in half (UNAIDS, 2005). In spite of making considerable progress in decreasing the infection rate from 18 % in the early 1990 to 7% in the recent Sero-behavioural demographic survey (MOH and Macro, 2006, UAC, 2007) there are reports of recent increasing prevalence especially in the married group (UNAIDS, 2010). The number of people infected with HIV is high possibly due to the chronicity of the disease and more people survive due to treatment with ART.

The number of individuals (18%) who present with HIV infection in patients with psychosis is high. Psychiatric in-patient services can be accessed through the different levels health system (Kigozi et al., 2010).

Maryland is one of the fifty states that make up the Unites States of America. Its capital city Baltimore has an estimated population of 5,615,727 people. The initial report of HIV infection came from the United States. At that time HIV/AIDS was observed among men who had sex with other men. Eventually, the epidemic spread to involve all groups of society.

5.2   STUDY SITES

Infectious Diseases Institute

This specialized out-patient HIV health unit provides free care including anti-retroviral therapy for general HIV cases. It is located adjacent to Mulago National Referral Hospital in Kampala, Uganda. The Institute also serves as a national referral centre, providing specialist consultations for patients who are not responding well to treatment from other health facilities. Over 9,000 HIV/AIDS clients have been registered in the clinic since its establishment in 2004. Approximately 5,900 of these clients receive lifesaving antiretroviral therapy and prophylaxis for opportunistic infections provided through drug donations programs and grant funding. Approximately 250-300 patients are seen each day at the Adult IDI clinic.

The focus of the Institute is to strengthen care and treatment of HIV and related infectious diseases for people living with HIV across Africa. This is achieved through   a number of strategies that include;- high quality training for health workers; research on best practices related to HIV in low resource settings; and advanced clinical services that support the development of new models of care. Since its establishment, there has been expansion into programs for HIV prevention, malaria, tuberculosis and

capacity building in research and laboratory services. Outreach programmes on prevention care, treatment, research training and laboratory training are also conducted in several districts across Uganda.

AIDS Information Center (AIC)

This is a voluntary counseling and testing centre located in Kampala, Uganda which was established in 1990. It was the first of its kind in Sub Saharan Africa. It provides services for the whole country and in 2009 alone 420,000 people were tested for HIV.

Johns Hopkins Hospital

The Johns Hopkins hospital is located to the east of the city of Baltimore, Maryland. The facility is a leader in patient care, medical, teaching and research. It serves as the teaching unit for the Johns Hopkins University School of Medicine.

Mulago General Hospital

This is the national referral hospital for Uganda and is located in Kampala, the centrally located capital city. It is the teaching hospital for Makerere University, College of Health Sciences and it has facilities for the training of undergraduates, postgraduates, nurses, pharmacists, dentists and other allied health professionals.

On average 462,604 patients are seen at Mulago Hospital per year of which 85,932 are inpatients. The hospital offers services in many different specialties. It has in-patient, outpatient, investigative and research facilities. The psychiatry in-patients ward has a 50 bed capacity. ART therapy is provided through a number of units in the hospital namely, the HIV clinic, the Infectious diseases Institute, Baylor College of Medicine Children's Foundation and the Makerere University Joint Aids Program clinic all situated within the Hospital complex.

Butabika Psychiatric Hospital

This is the national Psychiatric referral hospital and is located 12 kilometers from the Kampala city centre. The hospital was built in 1950 with an initial bed capacity of 700 for the civil (open) wing and 250 for the forensic wing. The current bed capacity is 450. The reduction in capacity is a result of community programmes that advocate for the treatment of the mentally ill in the community. The hospital has an out-patients' HIV clinic which provides service to HIV positive patients with mental illness and as well as the general population that needs HIV care even though they may not have psychiatric illness.

In order to allow for easy follow up of patients the main districts that were targeted for the study were those surrounding Kampala city i.e. the districts of Kampala, Wakiso, Mukono and Mpigi which were within a maximum 20km (I & II) or 30 km ((III & IV) radius of Kampala.

5.3   DATA COLLECTION AND ANALYSIS

5.3.1 HIV testing

All patients received an HIV test performed using the Abbot determine HIV ½ Qualitative immmunochromatographic test (ABBOT JAPAN Co. LTD, Mito-ku, Tokyo, Japan. Those who were positive were again subjected to confirmatory test by the ChemBio HIV ½ Sta-Pak Dipstick (Chembio, Diagnostics Systems, Inc., 3661 Horseblock Road, Medford, NY 11763, USA). The third test, Trinity Biotech Uni-Gold HIV test was used as a tiebreaker if there were conflicting results from the first two tests.

5.3.2 Measurements

All study instruments were translated into the main local language, Luganda. During the piloting stage of the studies questions that were irrelevant or too hard were edited. Laboratory investigations were carried out from the Butabika clinical laboratory, the Microbiology laboratory of the College of Health Sciences and the Makerere University Johns Hopkins laboratory in Mulago Hospital complex.

1. To diagnose psychiatric disorder-

The Mini International Neuropsychiatric Interview (MINI) was used (Sheehan and Lecrubier, 2006). This is a short diagnostic instrument which takes 15 minutes to administer. It has been validated against the Structured Clinical Interview for the Diagnostic and Statistical Manual (DSM) IV–TR Axis I and the Composite International Diagnostic Interview(CIDI) and has been well accepted by patients for the diagnosis of (DSM) IV–TR major axis I diagnosis. It is based on the DSM and International Classification of Disease diagnostic criteria.

2. To assess severity of psychiatric symptoms-

a) Manic symptoms:

Young Mania rating scale (YMRS): The YMRS is a brief, easy and widely accepted instrument used in the evaluation of manic symptoms at baseline and over time in individuals diagnosed with the disorder. It was developed by Young and others and is probably the most frequently utilized rating scale to assess mania (Young et al., 1978).

b) Depressive symptoms:

Patient Health Questionnaire-9 (PHQ 9): This is a 9 item scale used for the evaluation of a major depressive episode (Kroenke et al., 2001). The grading of

scores is 1-4 and any total score equal to or greater than 10 indicates a moderate or severe depressive condition.

Centre for Epidemiologic Studies Depression Scale (CES-D): This is a 20 items scale. A score of $\geq$ 16 suggests clinically significant levels of distress (Radloff, 1977).

c) Schizophrenic-like psychosis:

Brief Psychiatric Rating Scale (BPRS): This is a widely used brief scale that measures major psychotic and non- psychotic symptoms in individuals with major psychiatric disorder. The rating is based on observations made by the clinician. It is an 18 item scale which documents the severity of symptoms (Overall and Gorham, 1962).

3. To assess cognitive dysfunction-

a) International HIV Dementia Scale, (IHDS): This is a cognitive screening tool. It is a 3 item tool which takes about 5 minutes to administer. The maximum score is 12.

b) The Mini Mental State Examination (MMSE): This is an 11 item scale developed by (Folstein et al., 1975) scored out of 30. It takes about 10 minutes to administer.

c) Neuropsychiatric battery and the domains tested:

   i)   symbol digit for visual motor coordination ,

   ii) animal recall for verbal fluency,

   iii) digit span backward for working memory

   iv) digit span forwards for attention

   v) Color trails 1 and 2 for abstraction/executive and speed of information processing

vi) WHO UCLA verbal learning test for verbal memory and learning visual memory and logical memory.

4. To assess HIV clinical stage-

WHO Clinical Staging for HIV Disease: Classification of HIV clinical disease progression is made possible with the use of this scale. This instrument was first produced by the WHO in 1990 and was updated in 2005 (WHO, 2005). It is a useful research tool in studies of progression to symptomatic HIV disease in resource limited settings.

5. To assess immunological status and exclude other medical disorders-

CD4 count, complete blood count, viral load, Venereal Disease Research Laboratory (VDRL) test for syphilis, cryptococcal antigen test and toxoplasmosis titers.

6. To exclude substance abuse-

Alcohol Use Disorders Identification Test (AUDIT). This screening test commended by the WHO was used to detect different patterns and levels of drinking (Saunders et al., 1993). It is widely used in many countries among medical and psychiatric in-patients. It is relatively free from gender and cultural bias.

5.3.3 Data collection procedures and data analysis

PAPER 1

To determine the feasibility of the International HIV dementia scale we enrolled sixty-six HIV positive participants over a period of 5 months from July 2002 to November 2002 at the Johns Hopkins Hospital. They underwent assessments for, neurological, neuropsychological including the IHDS, and functional assessments as part of the NorthEastern AIDS Dementia (NEAD) cohort at Johns Hopkins Hospital (Sacktor et al., 2002). The participants were at high risk for HIV dementia with either a CD4 cell count < 200 cells/ul or a CD4 cell count < 300 cells/ul and demonstrating

cognitive impairment defined as performance on neuropsychological testing that was 2 SD below the appropriate mean on one test or 1 SD below the mean on two tests. Exclusion criteria for the US study participants were current or past opportunistic central nervous system (CNS) infection at study entry, or history of severe medical, psychiatric, or neurologic disorder believed to interfere with the ability to perform the study evaluations.

In the Uganda part of the study, eighty-one HIV positive individuals also received standardized neurological, neuropsychological, and functional assessments over a period of 8 months from August 2003 to March 2004. Exclusion criteria included HIV positive individuals less than 18 years of age, those with an active or known past CNS opportunistic infection, fever of $> 37.5°C$, a history of a chronic neurological disorder, active psychiatric disorder, alcoholism, physical deficit (e.g., amputation), severe functional impairment (Karnofsky < 50), or severe medical illness that would interfere with the ability to perform the study evaluations. Normative data were also collected on 100 HIV seronegative individuals recruited at the AIC. Inclusion and exclusion criteria were identical to the Uganda HIV positive participants except that the HIV negative individuals had documentation of a negative HIV test within 1 year preceding the evaluation.

Mean values for demographic and laboratory variables of the US part of the study were compared using t tests. Chi-square tests were used to compare proportions among the groups. IHDS results and performance on the Grooved Pegboard test with the non-dominant hand were each evaluated as a screening instrument. The difference in performance on these tests was stratified by the Memorial Sloan Kettering (MSK) scale stage using a t test. The IHDS and Grooved Pegboard results also were correlated with a correlation coefficient. A receiver–operator characteristic (ROC) curve was performed to determine the cut-off which maximizing sensitivity and specificity for the

diagnosis of HIV dementia in the US study (Phelps, 1993). This same cut-off was then evaluated in the Uganda study.

The HIV positive and HIV negative individuals in the Uganda study were compared with respect to demographic, neuropsychological test, functional, and IHDS performance. Using the entire battery of assessments to assign the MSK dementia stage, the IHDS score was then compared to the MSK dementia stage to define the sensitivity and specificity of the IHDS in the Uganda study using the cut-off points.

PAPER II

The aim of this paper was to determine the association of depression symptomatology and cognitive function after the initiation of HAART. A cohort of HIV positive patients at risk for cognitive impairment (as defined by a CD4 count < 200 or poor performance on a screening test for HIV dementia and HIV negative individuals was enrolled for longitudinal assessment of depression symptomatology, cognitive function and functional status. Between September 2005 and January 2007, we recruited 102 HIV positive individuals from the IDI and 25 HIV negative age and education-matched controls were recruited from the AIC. Selection criteria for the HIV positive individuals included: CD4 lymphocyte count < 200, ability to speak Luganda or English, clinic attendance of ≥ 2 visits in the past 6 months, residence within a 20 km radius of Kampala for the previous 6 to 12 months and being unlikely to move out of the area. The exclusion criteria included age less than 18 years, an active or known past central nervous system opportunistic infection, fever of > 37.5ºC, a history of a chronic neurologic disorder, active psychotic disorder, alcoholism (CAGE score of ≥2), physical deficit (e.g., amputation), a Karnofsky Performance Scale < 50 or a severe medical illness that would interfere with the ability to perform study evaluations. All above applicable criteria were also used for the HIV negative group. There was no need

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for prior visits to the AIC however they were required to have an ELISA confirmed HIV negative test. All HIV positive subjects had a baseline CD4 lymphocyte count, viral load and were initiated on the generic co-formulated HAART regimen [stavudine, lamivudine and nevirapine]. Depression symptoms were assessed using the CES-D, the cut-off score was ≥ 16. The number of individuals meeting screening criteria on either the CES-D or the IHDS was compared for the HIV positive and HIV negative individuals in order to obtain the baseline prevalence of depression symptomatology and cognitive impairment in the two groups.

Chi square and Fisher's exact tests were used to compare the MSK score for cognition and the CES-D score for depressive symptoms. A 95% confidence interval (CI) for this prevalence estimate was calculated. The proportion of HIV positive and HIV negative individuals with dual prevalence of depressive symptomatology and cognitive impairment was also estimated. These estimates were compared using logistic regression methods with prevalence as the dependent measure and HIV status as the independent measure to determine the likelihood of depression symptoms given HIV infection. A logistic regression model adjusted for age and gender was then generated to determine the likelihood of the dual prevalence of depressive symptoms and cognitive impairment as the dependent measure and HIV status as the independent variable.

Participants were classified as having depression symptoms, cognitive impairment, or both at baseline and at 3- and 6-months follow-up. Differences in the likelihood of these conditions were modelled using a repeated measures logistic regression model. The model was adjusted for baseline characteristics of age, gender and HIV status. The potential for interaction between HIV status and follow-up time was tested.

PAPER III

The objective of this study wase achieved through a cross-sectional study design. We compared the clinical presentation of the types of psychosis and the level of cognitive function among consecutively enrolled HIV positive and HIV negative individuals. The research assistants were psychiatric clinical assistants or psychiatric nursed who had received training in HIV pre and post test counselling. They identified newly admitted patients with psychosis who had delusions, hallucinations or disturbed behaviour to select those that satisfied the study selection criteria. Written informed consent was sought from the patient once they were calm. Consented individuals were then recruited and were administered a pre-tested standardized demographics, laboratory and psychiatric assessments. Cognitive functioning and psychosis were assessed as the main outcome variables.

The specific psychiatric diagnoses were made with the aid of the MINI instrument while the level of psychosis was determined by use of the rating scales mentioned above. Physical examination and appropriate laboratory investigations were carried out. The participants consent to continue participating in the study was again sought when the patients gained insight into their illness after initiation of treatment. This usually happened approximately 2 weeks from the time of admission. The WHO clinical staging (for the HIV positives) were then determined with the help of the WHO clinical criteria for Adults with HIV/AIDS. Post-test counseling was done before the HIV test results were given to the study participants. Individuals found to be HIV positive and who met criteria for starting ARVs, has their treatment initiated at the HIV clinics at the respective study site.

To assess differences in the social and clinical characteristic presentation between the HIV positive and HIV negative groups, bivariate analysis was performed using chi square test. Means and medians where appropriate were generated. Multivariate

analysis employing discriminant analysis was employed to test for differences between the two groups i.e. HIV positive and HIV negative on the presence or absence of specific clinical characteristics. The Mann–Whitney U test was used to compare scores on performance and severity on the psychiatric rating scales between the two groups.

The scores obtained on a specific clinical characteristic were categorized into mild or severe. The variables found to be severe were entered into a logistic regression model to determine the odds ratios of presentation of the characteristics in HIV positive and HIV negative individuals. Multivariable models were constructed for each psychotic disorder using the forward stepwise approach while adjusting for HIV status, gender, age, and education level.

PAPER IV

The objective of this study was achieved through a prospective study design. Study participants were recruited as detailed above in paper III. The cognitive function was assessed using the IHDS together with a battery of neuropsychiatric tests as described above. The HIV positive and HIV negative participants were followed up at 3 and 6 months. Computed Z scores on neuropsychological scores were based on the mean and standard deviation (SD) of the HIV negatives. An individual was described as neuropsychologically impaired if they performed 2SD below the mean one of more tests of or if they had 1 SD below the mean on 2 or more tests. Each specific test represented a cognitive domain. The normative data against which the performance was made was obtained from the general HIV negative, non-psychotic population. The primary end point was the level of cognitive function which was determined by the presence or absence of cognitive impairment. The impairment was categorized into mild, moderate or severe depending on the number of deviations obtained on multiple tests.

Participants were assessed at the subsequent reviews for the presence of depression and the severity of psychosis using the psychiatric scales described above. Participant's response to conventional anti-psychotic treatment and the degree of cognitive impairment were also determined. The treatment response was determined based on whether there was change i.e. improvement, no change and worsening on rating scales.

We tested for associations and risk factors of psychosis and cognitive function as health outcomes of the affected individuals. The likelihood of cognitive impairment was determined using logistic regression using a stepwise approach while controlling for age, gender, HIV status and educational level.

Contact with patients was maintained with the use of monthly reviews at the two hospitals as well as through telephone contact (where possible) to minimize loss to follow up.

5.4   DATA MANAGEMENT

All data was collected using questionnaires which were cross checked for completeness. In case of missing or unclear data the research assistants would seek clarification with the individual that was interviewed whenever possible. Data for studies I and II was entered into Excel data sheets and later transferred into SAS statistical software package (SAS Institute, Carey, NC). Data for studies III and IV was entered in Epidata and later transferred to STATA version 10 (StataCorp, College Station, TX USA).

5.5 ETHICAL CONSIDERATIONS

All studies had clearance from the institutional review committees at Department of psychiatry, The Ethics and Research Committee of the Faculty of Medicine Makerere University, the Uganda National Council for Science and Technology, the Resident District Commissioner, Kampala district, Uganda as well as the Institutional Review Board of Johns Hopkins Hospital, Baltimore, USA.

In addition we observed the following ethical issues during the conduct of studies. Informed consent was obtained from the study participants before they were enrolled into the study. Any participant who was unable to consent by themselves had a next of kin consenting on their behalf. Participants had pre- and post-test counseling for HIV. Individuals with a positive HIV test were channeled into HIV care in the respective hospitals. All collected data was kept under secured locks. Any individual who declined to participate would have their refusal respected and all their previously collected data discarded. They would continue to receive all the appropriate care with no prejudice. At each of the study visits consent was again obtained from the patients for their continued participation in the study.

6   RESULTS

6.1   VALIDITY OF THE INTERNATIONAL HIV DEMENTIA SCALE (I)

Among the US study participants the mean IHDS score for both the MSK 0 (no impairment) and MSK 0.5 (equivocal/subclinical dementia) groups was 10.6 whereas the mean IHDS score for the MSK 1 (mild dementia) group was 9.3, suggesting that 10.0 was a useful cut-off to distinguish HIV positive individuals with and without dementia. The cut-off value of 9.5 for the IHDS maximized the sensitivity (71%) and specificity (79%) for HIV dementia. However, the cut-off value of 10.0 for the IHDS improved the sensitivity (80%) with fewer false negative results. In the Uganda participants the sensitivity of the IHDS for HIV dementia was 80%, and the specificity for HIV dementia was 55% using a cut-off of ≤ 10. Cut-off values in 0.5 increments from 8.0 to 12.0 are shown in Table 1 below. The mean age of the Uganda HIV positive participants was 37 years while that for the US individuals with dementia was 48 years.

HIV positive individuals performed worse on the IHDS total score and each of the three IHDS subscores (the fingertapping, alternating hand position, and verbal recall subtests) compared to HIV negative individuals. In the full neuropsychological test battery, HIV positive individuals performed worse on the Auditory Verbal Learning Test (AVLT) total score test, AVLT Delayed Recall score, the Color Trails 1 and 2 tests, and the Symbol Digit Modalities test. Using normative data from HIV negative individuals in Uganda, 31% of the HIV positive individuals in this study were diagnosed with dementia.

Table 2. Sensitivity and specificity of varying cut- off scores on the IHDS

Cut-off value	Sensitivity %	Specificity %
US Participants		
12.0	100	0
11.5	92	22
11.0	92	31
10.5	83	52
10.0	80	57
9.5	71	79
9.0	63	88
8.5	46	95
8.0	46	100
Uganda Participants		
12.0	100	0
11.5	100	20
11.0	96	23
10.5	88	48
10.0	80	55
9.5	64	71
9.0	60	79
8.5	40	89
8.0	36	89

6.2 DEPRESSION SYMPTOMS AND COGNITIVE FUNCTION AFTER HAART (II)

The prevalence of depressive symptoms was 53.9% (55/102) among the HIV positive individuals and 28% (7/25) among the HIV negative individuals. After adjusting for differences in age and gender, the likelihood of depression symptoms was significantly higher among HIV-positive individuals compared to HIV-negative individuals (OR 2.8, 95% CI: 1.0, 7.9). Prevalence of cognitive impairment was 68.6% in the HIV positive while among the HIV negative Individuals it was 16%. A general trend for improvement on the neuropsychological function occurred more among the HIV positive subjects but the only significant change was in Color Trails 2 test ($p = 0.02$) after adjusting for differences in sex.

Dual prevalence of depression symptoms and cognitive impairment in the HIV positive individuals was 39.2% (40/102) while among the HIV negative individuals it was 4% (1/25). Adjusting for age and gender, the likelihood of both depression symptoms and cognitive impairment among HIV positive individuals was significantly higher in this group compared to HIV negative individuals (OR 13.9; 95% CI 1.7 -111.7).

HIV positive individuals experienced a significant decrease in the prevalence of depression symptomatology (p = 0.003) (Figure 3). There was also significant decrease in cognitive impairment (p < 0.001), and dual prevalence of these two conditions (p = 0.004) compared to HIV negative individuals.

Figure 3: Mean CES-D scores among HIV-negative and HIV-positive individuals
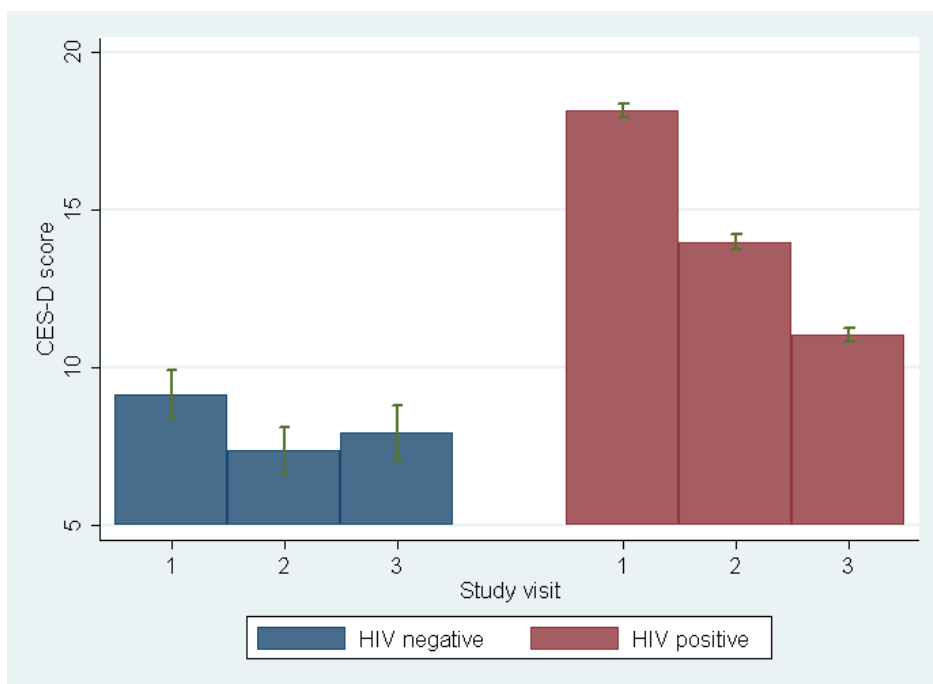
6.3 CLINICAL CHARACTERISTICS OF PSYCHOSIS (III)

Among the 156 HIV positive patients who had psychosis, 64% presented in WHO clinical stages 3 and 4 while 20% of the individuals presented in WHO clinical stage 1. The HIV positive individuals were almost three times (OR 2.6; 95% CI 1.7 – 4.1) as likely to be cognitively impaired on the MMSE compared to the HIV negative group. Mania, major depression and schizophrenia were more common in HIV negative patients. Although with small numbers psychotic disorder not otherwise specified was more common in the HIV positive group. The median score for mania symptoms was higher in the HIV positive group however this was only marginally significant with a Mann-Whitney test score (p = 0.065). On regression analysis each unit increase in the YMRS score was affected by being HIV positive (β coef 4.1; 95% CI 1.9 - 6.4,) while increasing age > 30 years and female gender (β coef -2.1; CI -4.2 - 0.1, and β coef -6.0; 95% CI -8.1 – 3.9, p = < 0.001) decreased the score respectively. On the BPRS, being female decreased the score (β coef -8.1; 95% CI -10.6 -5.6) while the PHQ score was increased if one were HIV positive (β coef 2.3; 95% CI 1.4 – 3.2). The HIV positives were more likely to have the following characteristics on linear logistic regression: irritability (OR 3.0; 95% CI 1.3-7.0,), impaired content of thought (OR 2.3; 95% CI 1.3 -4.2), guilt feelings (OR 2.9; 95% CI 1.5- 5.5,) and disorientation (OR 2.9; 95% CI 1.5- 5.7).

6.4 COGNITIVE FUNCTION AND HIV ASSOCIATED PSYCHOSIS (IV)

At the baseline evaluation there were more cognitively impaired individuals within the HIV positive group 64.7%vs 35.3% than within the HIV negative group 49.4%vs 50.6%, (p <0.000). The females 270 (58.82%) were more impaired than the males 189 (41.18%) p = 0.018. All tested cognitive domains apart from digit span were more likely to be impaired in the HIV positive group. The HIV

positive individuals were more likely to be impaired in the following domains: verbal memory (OR 1.7; 95% CI 1.0 - 2.9), verbal fluency (OR 3.4; 95% CI 2.2 - 5.2), Colour trails 1(OR 2.0; 95% CI 1.2 - 3.0) and Colour trail 2 (OR 3.5; 95% CI 2.0 - 6.1) all p = 0.005. Adjusted odds ratios revealed female gender (OR 2.8; 95% CI 1.0 - 7.9) and older age (OR 1.6; 95% CI 0.5 – 4.4) to be associated with cognitive impairment. Cognitive function improved in both HIV positive and HIV negative group during follow up however the HIV positive had higher levels of severe impairment even at 6 months of follow up (Table 3).

Table 3: Cognitive function in HIV positive and HIV negative patients at 3 and 6 months of follow up.

	Baseline		3 months		6 months	
	HIV-	HIV +	HIV-	HIV+	HIV-	HIV+
	n =322	n = 156	n =262	n = 116	n = 205	n = 97
Normal	16 (4.97)	3 (1.92)	25 (64.10)	14 (35.90)	33(68.75)	15(31.25)
Mild	147(45.65)	52 (33.33)	130 72.22)	50 (27.78)	101(74.81)	34 (25.19)
Severe	159 49.48)	101(64.74)	107(67.30)	52 (32.70	71 (59.66)	48 (40.34)

7 DISCUSSION

7.1 APPRAISAL OF MAIN FINDINGS

Our results suggest that the IHDS is a useful screening test for HIV dementia in both the industrialized world and the developing world. The sensitivity (80%) and specificity (55%) of the IHDS are comparable to the sensitivity (71%) and specificity (46%) of the Grooved Pegboard non-dominant hand test, an established test for HIV dementia (using a cut-off of 1.5 SD below the age- and education-adjusted mean) (Miller et al., 1990, Davis et al., 2002). HIV dementia is an important complication to diagnose in patients with AIDS for several reasons:

(i) it is associated with an increased risk of mortality (Sacktor et al., 1996, McArthur, 2004)

(ii) the presence of dementia can affect antiretroviral medication adherence which is essential for suppression of virological replication (Hinkin et al., 2004) and development of resistance to ARVs;

(iii) HIV dementia is a potentially treatable condition with HAART (Robertson et al., 2010).

The presence of the depressive symptomatology and cognitive impairment was higher at baseline among HIV positive individuals at risk of cognitive impairment compared to HIV negative individuals (II). The scores generated on the cognitive tests in both groups of individuals were not biased by literacy level as the sample had a high literacy rate. Both the depression symptomatology and cognitive impairment improved after initiation of highly active antiretroviral therapy as has been shown in other studies (Grant, 2008).

In keeping with previous research studies (Dolder et al., 2004, De Ronchi et al., 2006), we found differences in clinical characteristics between HIV negative and HIV positive individuals (III). Whereas we may partly agree that some of the

symptoms are indistinguishable from those of a functional psychosis (Buhrich et al., 1988), there were many differences from these functional psychoses. This has also been shown by other studies (Dubé et al., 2005, Llorente and Malphurs, 2006, Adewuya et al., 2007) We also found that the HIV positive individuals tended to have more symptoms that would best fit the picture of the DSM IV category of "psychotic disorder not otherwise specified". This kind of presentation, which was more or less seen as an organic insult on the brain, is better likened to the presentation of cerebral syphilis and other organic psychoses (Hotson, 1981, Friedrich et al., 2009). The occurrence of this "psychotic disorder not otherwise specified" makes the presentation of HIV-associated psychosis a rather distinct entity apart from the primary functional psychoses.

Previous studies have shown that individuals with primary psychosis can have cognitive impairment (Hill et al., 2009). We have shown that cognitive impairment occurs in psychotic HIV negative individuals. However the severity of the impairment was more in the HIV positive individuals even after the symptoms of the psychotic illness decrease during follow up (IV).

Uganda still has a high number of HIV infected individuals despite the prior reported decrease in prevalence (MOH and Macro, 2006)Recent reports show there is a risk of increasing prevalence (UNAIDS, 2010). The reasons for this are many and include risky sexual behavior in a country with a growing population and long survival due to HIV/AIDS treatment. So even though the prevalence of the HIV infected may decrease, the actual numbers HIV infected individuals still remains high (UNAIDS, 2005, UNAIDS, 2010). The presence of cognitive dysfunction in patients who are HIV positive further decreases their ability to adequately function in society and to fulfill their activities of daily living i.e. reduced social functioning including inability to adhere to prescribed medications including ART. Cognitive impairment

associated with HIV-related psychosis compounds this problem and unless addressed and properly managed, it will interfere with the scaling up program for HIV prevention and treatment.

ART provision done according to WHO guidelines (MOH, 2003, MOH, 2009) in Uganda is now universally accepted and practised. Unfortunately health workers are still very cautious with providing anti-retroviral treatment to psychotic patients from any cause. Yet HIV infection causes psychosis especially in advanced (Stage III and IV) HIV disease. Thus on many occasions the treatment of late stage HIV infected patients with psychosis will be delayed or never started because of the individual's associated mental illness.

The National Health Policy of Uganda does recognise that mental disorders confer a heavy non-fatal disease burden on the nation. However they do not appear on the country's Burden of Disease Study because that study relied on mortality indices rather than morbidity data (MOH, 1999). The policy also advocates for the strengthening of mental health services through addressing the heavy and increasing burden of mental illness in the country. Part of the increase in the mental illness and general disease burden is due to consequences of HIV infection and also on those affected by the HIV/AIDS such as orphans and widows/widowers. The government also promotes and supports a basic primary health programme (the Minimum Health Care package) as well as appropriate referral services at the regional and national levels. It is therefore implied in this policy that all individuals with mental illness should be appropriately treated and this includes individuals that may be infected with HIV. Yet the group of individuals who have HIV and psychosis and thus are more vulnerable, are not currently being given the special attention they deserve due to their unique presentation. Moreover they continue to pose a special risk group for HIV infection spread.

Preliminary studies have shown ART to be effective in decreasing (but not eradicating) cognitive impairment among HIV sero-positive individuals (Robertson et al., 2007). However, for those HIV positive individuals that have psychosis, the outcome for the psychosis, the cognitive impairment and the general HIV disease progression is generally not known. The question of how long one should administer antipsychotic treatment for HIV positive individuals that develop psychosis is also unclear. There exists no current ART policy or guideline on the management of HIV positive individuals with mild neurocognitive disorder whose CD4 count is above 250 with or without psychosis.

Even though it is generally believed that cognitive impairment occurs in stage 3 or stage 4 of HIV disease a few studies have found that indeed some patients develop cognitive impairment in the early stages of HIV infection (Wong et al., 2007). We found (Paper III) that about one third (1/3) of the patients with psychosis presented in the early WHO stages of HIV infection, i.e. they had not had any serious ailments prior the onset of the psychosis. This raises the question of when to best to start ART or rather when to include cognitive impairment, however early, as an indication to start ART despite CD4 cell counts being >250. The findings of this study thus fill an information gap on cognitive impairment and psychosis as related to HIV/AIDS. This should provide an insight in the management of HIV sero-positive individuals that develop psychosis and/or cognitive impairment. With the high prevalence of HIV positive individuals that develop psychosis, the findings serve to help in the better planning at policy level for those affected HIV positive individuals to ensure best practises management in our setting.

7.2 METHODOLOGIES

7.2.1 Internal validity

A daily list of all patients that were coming to the clinic would be printed out and all patients who were ART naive would be identified (I & II). They were then screened for involvement in the study and were enrolled if they fulfilled the study criteria. We would have preferred a more random method of selection however the daily routine of the clinic did not allow for this method of selection. Though we may have represented individuals living in the urban areas of the country we may have missed the rural representation.

The IHDS also has some limitations. It is not very useful for detecting mild cognitive impairment associated with HIV infection. Indeed there was no difference between HIV positive individuals with normal neuropsychological testing (MSK stage 0) and HIV positive individuals with mild impairment on neuropsychological testing who were not severe enough to meet criteria for dementia (MSK stage 0.5). Identifying patients with mild impairment is a challenge even with the development of a shorter algorithm for the detection of HIV associated neurocognitive disorders (Cysique et al., 2010). The IHDS cannot thus be used to distinguish between different stages of HIV dementia, although progressively lower mean IHDS scores did correspond to greater dementia severity.

The study in Uganda had other limitations. The HIV positive individuals were older than the HIV negative individuals. The differences noted were mainly in motor performance tests, and age is associated with motor performance decline therefore one cannot rule out the possibility that the differences between the two groups could have been due to age and not HIV infection. However the mean age for the study group was below 50 years there by limiting the effect of senility as a cause for the observations. The low specificity of the IHDS yields a high positive rate for HIV

dementia creating a high burden of individuals to screen. A more refined instrument could be developed.

The comparison group in Paper II included only 25 HIV-negative individuals for statistical and practical reasons. Practically it was more difficult to recruit the HIV-negative individuals and retain them in the follow-up. These individuals were neurologically normal and exhibited less variability on the outcome measures. Two research assistants were used for the cognitive testing so as to maximize the precision of the findings in each individual tested.

All consenting admitted patients were enrolled (III & IV). This was so given the large sample size that had to be accrued with consideration of loss to follow up as would certainly be as evidenced by previous studies. We excluded patients admitted with drug and alcohol related psychoses as possible cognitive impairment could stem from the substance dependence. Therefore a comparison of this group was missed since these individuals are also part of the general community.

A number of tools were used to arrive at a diagnosis of a particular psychotic disorder using research criteria hence the possibility of a person being misdiagnosed with a disorder was indeed very minimal. The inter-rater variability was minimized by the administration of standardized instruments and rating scales. Some of the evaluations were performed within a specific time frame with the aid of a stop clock. In addition, for one to be diagnosed as cognitively impaired, they had to perform below the standard on multiple tests for cognition. We thus minimized misclassification of study participants' diagnostic categories.

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7.2.2 External validity

We would have preferred a wider sampling from different parts of the country. However time and logistics limited us to Kampala district and the nearby districts of Mukono, Mpigi and Wakiso which are within a 30 Km radius. However the population in Kampala city is widely represented in both ethnicity and social class. Therefore the sample that was collected was representative of the study population of Uganda. Longer time for follow up of the individuals would yield more information. However the 6 months of follow up was deemed enough for us to detect a significant change in these types of clinical studies of participants.

Confounding/Effect modifiers

A confounder is a variable that is associated with the exposure and outcome of interest. There were possible modifiers to the study outcome of cognitive function and these included the use of antipsychotic treatment and the presence of opportunistic infections (Figure 4). The medicines used may have affected the level of cognitive function of an individual and therefore the results could have been interpreted with this fact under consideration. Secondly if an individual had an undetected central nervous system opportunistic infection like cryptococcal meningitis this could also affect the level of cognitive function. These opportunistic infections were therefore looked out for with the help of laboratory investigations.

Figure 4: Effect modifiers for cognitive impairment in psychosis.

Cause
HIV

Outcome
Cognitive impairment

Modifier
Antipsychotic treatment
Presence of opportunistic infections
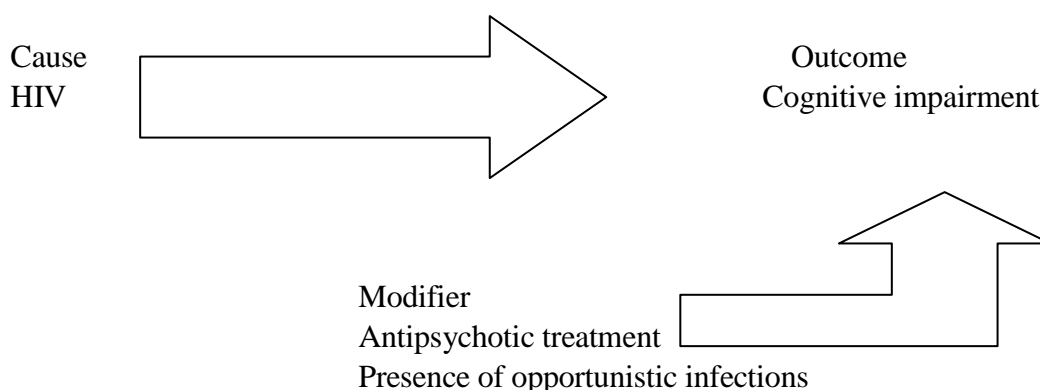
We therefore performed laboratory test to rule out concurrent infections and we also excluded all patients with alcohol and substance related disorders.

Generalizability of findings

The HIV clinic and the referral hospitals have highly selected groups of patients in their care. A large number of HIV patients may not come for care in these units yet they could have the outcome of interest. However Kampala, the area that is served by the clinic has a diversity of individuals from all ethnicities and social classes as found in Uganda. These are therefore representative of the urban population. However the study findings may not be generalizable to the rural population.

The rural population may have lower rates of literacy compared to the urban population. The level of literacy can affect performance on neuropsychological instruments. We however used cross cultural instruments that required minimal education.

We also had an over representation of the female gender in the HIV positive group. There are more females that are affected by HIV infection (McArthur, 2004, UNAIDS, 2010). The females have also been noted to be more vigilant in attending HIV care (Kipp et al., 2010) and this could explain their higher numbers in the non-psychotic HIV population (I& II). But also, the high number of HIV positive

females among the patients with psychosis is probably explained by the higher prevalence of HIV among the females in the Ugandan population (MOH and Macro, 2006).

When enrolling patients with psychosis, we excluded patients who had any other co morbid conditions like substance abuse and hence these findings may not apply to that group of the population. These excluded patient groups might have cognitive impairment for other reasons and would require separate studies.

8 CONCLUSIONS

❖ We established that the IHDS was a sensitive tool for the detection of HIV dementia (I)

❖ Depression symptomatology was distinct and common among cognitively impaired HIV patients (II). Even though depressive symptomatology decreases after the initiation of HAART, a large number of individual remained with persisting depressive symptoms.

❖ There were differences in clinical characteristics between HIV positive and HIV negative patients. Patients infected with HIV had a distinctly higher representation of psychosis not otherwise specified (III).

❖ Cognitive impairment in psychosis was worsened by HIV infection (IV).

9 POLICY IMPLICATIONS

The IHDS may have great value as a screening test for HIV dementia in the industrialized world and the developing world. The diagnosis of HIV dementia may then be an indication for initiation of antiretroviral therapy which could have enormous benefit for patients and the society.

It is important that individuals in HIV care are screened for depression symptoms and cognitive dysfunction. This would make it possible to manage both conditions appropriately so as to improve patient outcomes. Even after initiation of HAART a few patients remain with high depressive score thereby confirming the need for antidepressant therapy. Strategies to improve management of these patients and to follow prognosis after antiretroviral treatment need to be put in place

Initiation of HAART should begin early for patients that have cognitive impairment even before their CD4 drop to low. Strategies for the early management of cognitive impairment especially in HIV positive patients with psychosis need to be put in place to improve patient care.

10 ACKNOWLEDGEMENTS

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