Neuropsychiatric Features of HIV/AIDS

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Thesis presented for the Degree of

DOCTOR OF PHILOSOPHY

in the Department of Psychiatry and Mental Health,

Faculty of Health Sciences,

UNIVERSITY OF CAPE TOWN

October 2006

In memory of those for whom we were too late

"This is the story of the invisible people.
It is the tragedy within the tragedy."

The Invisible People, Greg Behrman, 2004, Free Press

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Abstract

Title: Neuropsychiatric Features of HIV/AIDS

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Submission date: 10 October 2006

The central hypothesis of this thesis was that HIV psychosis and mania are overlapping manifestations of the neuropathophysiological consequences of HIV characterized by symptoms suggestive of a sub-acute delirium and cognitive impairment. It was also hypothesised that HIV-associated mania and psychosis are AIDS-defining features and should be indications for antiretroviral treatment. The thesis includes four main components. Firstly, the diagnostic validity of psychiatric disorders presenting with psychosis and mania as well as those presenting with symptom fluctuation was critically appraised. Secondly, a systematic review of HIV psychosis and mania was conducted. Thirdly, a cross-sectional study of the clinical features, special investigations and treatment of 81 HIV-positive and 30 HIV-negative patients with psychotic and manic symptoms was conducted. The fourth component was a cohort study examining the treatment of patients with HIV psychosis and mania with antiretroviral medication. The analysis of the study included the development of a cluster analytic model to identify latent classes of psychiatric symptoms. The findings suggest that HIV-associated psychosis and mania are overlapping clinical manifestations of HIV-related neuropsychiatric disease and that they are AIDS-defining phenomena. Patients with advanced HIV comprised three groups. The largest group consisted of patients with symptoms in keeping with a sub-acute delirium. They had a high prevalence of multiple hallucinations, severe thought disorder, movement abnormalities, attentional deficits, disorientation, sub-cortical cognitive impairment and symptom fluctuation. The second group was comprised of nine patients who had severe depression, severe psychomotor retardation, sub-cortical cognitive impairment and high viral loads. The third group consisted of patients with probable co-existent primary psychiatric illnesses with advanced HIV but without HIV-consequent neuropsychiatric involvement. In the cohort study, patients responded very well to ART. Good adherence was achieved through the use of directly observed treatment and adequate social support.

Abbreviations

AADL/IADL	Advanced (instrumental) activity of daily living
AIDS	Acquired Immunodeficiency Syndrome
ART	Antiretroviral treatment (used synonymously with HAART in this thesis)
BADL	Basic activity of daily living
CDC	Centers for Disease Control and Prevention
CT	Computerized tomography
CXR	Chest X-ray
DRS	Delirium Rating Scale
DRS-98	Delirium Rating Scale Revised-98
DSM	Diagnostic and Statistical Manual of Mental Disorders
Early HIV	HIV-positive patients with World Health Organization stage 1 or 2 disease and with CD4+ counts over 200 cells/mm^3
HAART	Highly active antiretroviral treatment (used synonymously with ART in this thesis)
HDS	HIV Dementia Scale
HIV	Human Immunodeficiency Virus
HIV-D	HIV-associated Dementia
ICD	International Classification of Diseases
IHDS	International HIV Dementia Scale
Late HIV	HIV-positive patients with World Health Organization stage 3 or 4 disease and/or with CD4+ counts below 200 cells/mm^3
LCA	Latent Class Analysis
LDB	Lewy Body dementia
MINIPLUS	Expanded Mini-International Neuropsychiatric Interview
MRI	Magnetic resonance imaging
PTB	Pulmonary tuberculosis
TPHA	Treponema pallidum haemaglutination test
VDRL	Venereal Disease Research Laboratory
WHO	World Health Organization
YMRS	Young Mania Rating Scale

Acknowledgements

The work reported in this thesis was funded by the South African National Research Foundation Thuthuka Programme, the Medical Research Council of South Africa, the Colleges of Medicine of South Africa Phyllis-Knocker Bradlow Award, the Provincial Government of the Western Cape HIV/AIDS Directorate and the Associated Psychiatric Hospitals, and the Hendrik Vrouwes Scholarship.

I would like to acknowledge and thank the following people: the patients and their families for agreeing to participate in this study; Dr Michele Rogers for her invaluable assistance with patient interviews and management, her contribution towards addressing issues of language and culture in this study and her unwavering commitment to patient care; Ms Indira Moodley for conducting the neuropsychological assessments as well as her insightful support; Ms Nazeema Ahmed for her assistance with planning the project; Dr Bev Edwards for her assistance with the field work; Ms Munirah Mangerah and Mr Antonio Lentoor for their administrative assistance; Dr Sally Candy for reading the computerized tomography and magnetic resonance images; Dr Francis Hemp and Ms Helena Thornton for their assistance with regard to the selection of the neuropsychological tests and supervision of the neuropsychological assessments; Prof Simon Lovestone for his enthusiastic support and for introducing me to cluster analytic methodology; Dr Landon Myer for his patient assistance with the statistical analysis and for conducting the Latent Class Analysis; the staff of the sites where this work was conducted, particularly Dr John Parker and Sister Lizette Robins; Dr Rory Leisegang for designing the database and his assistance with data management; and Ms Jenni Horn for her assistance with proof-reading and editing.

I should also like to thank the staff at Desmond Tutu HIV Centre, including Dr Jen Pitt, Dr Catherine Orrell, Ms Nicky Killa, Ms Elizabeth Fielder, Ms Joan Aploon, Ms Anne Witbooi, Ms Phyllisty Smith, Dr Roland Croxford, Dr Linda-Gail Bekker, Professor Robin Wood and the community HIV counsellors, who supported this project and generously gave of their time and expertise.

Thank you also to Dr Linda Hering from the Associated Psychiatric Hospitals and Dr Fareed Abdullah and Dr Keith Cloete from HIV directorate of the Provincial Administration of the Western Cape for their support and generous funding.

I would particularly like to thank my supervisor, Prof Alan Flisher, for the considerable time and effort he put into supervision and for his academic rigor, considered feedback and personal support.

I would specially like to thank my friends and family for their ongoing support and encouragement. To my husband, Brendan, my profound thanks for his unflagging support and love and for the many hours spent entertaining three small children so that I could work. Finally to my children, Jemma, Ben and Liam, for the light and joy they bring me, my gratitude for which there are no words.

Jane Saunders
Cape Town
October 2006

Chapter 1. Introduction

1.1 Context

Human immuno-deficiency virus (HIV) infection constitutes a global pandemic with approximately 50 million HIV-positive people worldwide (1). The majority of HIV-positive people live in sub-Saharan Africa and South Africa has one of the highest infection rates in the world. According to data gathered during the National HIV and Syphilis Antenatal Sero-prevalence Survey in 2005, the national rate of HIV infection in South Africa was 30.2% (confidence interval 29.1%–31.2%). The rate in the Western Cape province, where this study was conducted, was reported as 15.7 (CI 11.3–20.1%). At the time of writing this thesis, there were approximately 800-1 000 HIV-related deaths per day in South Africa (1).

HIV/AIDS has a profound effect on the mental health of those infected. HIV–associated mental illnesses range from anxiety and depression to psychosis and dementia. These problems are common and may have a negative impact on the quality of life, immunological status and economic productivity of infected people (2). A model was developed by Struthers in Gauteng Province (which includes Johannesburg and Pretoria) to predict the likely impact of HIV/AIDS on service provision for people with mental illness. Struthers described the seriousness of this impact with the associated need to increase both the number of acute psychiatric beds and professional staff at all levels (2). For example, Struthers predicted that admission rates would double when HIV/AIDS rates reached 20%.

Very few data exist with respect to the nature of the severe mental health consequences of HIV/AIDS in developing countries. The data from developed countries are of limited use as they are generally derived from resource-rich communities and from different high-risk populations who have extensive social resources and wide-spread access to antiretroviral treatment (ART). Guidelines are especially necessary in primary- and secondary-care facilities where clinicians may not have ready access to many investigations such as viral loads and computer imaging tomography (CT) scans. The paucity of data has been emphasised repeatedly by South African health service planners and clinicians as a serious source of concern

and describing AIDS-related morbidity and mortality was an objective of the Department of Health's Strategic Plan, South Africa 2000–2005 (3).

Diagnostic clarity is important as it informs prognosis and management. It can be very difficult to differentiate HIV-associated psychosis and mania from other psychiatric disorders (such as bipolar disorder, schizophrenia and psychotic depression) in a patient who is incidentally HIV-positive. Antiretroviral treatment is becoming increasingly available in South Africa. The ART roll-out guidelines used in South Africa at the time of writing this thesis were that treatment should be offered to patients with AIDS-defining illnesses or CD4+ counts below 200 cells/mm^3 (4). In line with international trends, psychiatric patients in South Africa are an underserved population with respect to access to health care (5). They are at risk of being excluded from the benefits of antiretroviral treatment unless clear practical guidelines are provided at primary and secondary care levels. A further compounding factor is the strict requirements for adherence to antiretrovirals, which may be difficult for patients with serious mental illness. It is therefore important that appropriate models for assisting with adherence be developed in this patient population.

1.2 HIV-associated psychosis and mania – a new diagnostic entity

During the mid 1990s, we began to treat increasing numbers of HIV-positive patients with psychotic and mood disorders at the University of Cape Town-linked psychiatric facilities. This became particularly striking while I was working as a registrar (resident) in the psychiatric emergency and medical psychiatry wards and subsequently while I was working as a junior specialist in the women's admission wards at Valkenberg Hospital. My interest in HIV-related neuropsychiatric disease began in 1996 when I presented a series of three HIV-positive women with post-partum psychosis at a local academic meeting. All three presented with affective psychoses that took a long time to settle in the acute phase and had multiple recurrences until their deaths. Over the last 10 years, it has become clear that HIV-positive psychotic and manic patients posed a number of clinical challenges.

1.3 Clinical Challenges

1.3.1 Atypical presentation

The clinical features manifested by many patients with late stage HIV did not conform to a clear categorical diagnostic entity. Their symptoms appeared to fluctuate, with a mixture of affective and psychotic symptoms and they were very sensitive to the side-effects of psychotropic agents (particularly extra-pyramidal and anti-cholinergic effects). Many patients appeared to have progressive cognitive impairment. They appear to have a poor prognosis both the respect to psychiatric symptomatology and mortality. Some clinicians raised the possibility that these patients may be more aggressive and behaviourally disturbed than HIV-negative patients. Even though we excluded the possibility of an acute delirium or any acute medical illness, other than HIV itself, some of the patients appeared to be less orientated at times. The fluctuation and disorientation was apparent over days and weeks in the ward rather than over 24 hours as is characteristically seen in acute delirium. Even though the medical literature deals with HIV-associated psychosis and mania as separate entities, our clinical experience was that most of the patients had both affective and psychotic symptoms. As my main areas of interest lies in neuropsychiatry and psychogeriatrics, I was struck by the many similarities in the clinical presentations between the behavioural and psychological symptoms of dementia in the elderly and those of what appeared to be HIV-consequent mania and psychosis. As I read more about HIV neuropsychiatric pathophysiology, I recognised the similarities with other neuropsychiatric diseases such as Lewy Body Disease as well as with clinical and pathophysiological characteristics of a delirium. To my knowledge, at the time of planning this study, only occasional case-reports had been published from Africa. Subsequent to the commencement of field work in this study, one study from Uganda, focussing on new-onset mania, was published (6).

1.3.2 Investigations

There was no information as to which special investigations would be appropriate in our context and practice varied enormously between facilities. As the epidemic grew, there was a growing urgency to try and distinguish AIDS-related neuropsychiatric disease from other mood and psychotic disorders so that patients could receive appropriate treatment.

1.3.3 Treatment resistance

Patients appeared to be resistant to psychotropic treatment and often developed prohibitive side-effects which prevented dose increases. Their hospital stays were longer than most other patients and there was a high re-admission rate. Management was complicated by the co-existence of complex medical problems. Evidence with regard to treatment, both with psychotropics and antiretrovirals, was emerging from the resource-rich countries but there were no local guidelines.

1.3.4 Access to antiretroviral treatment

Over 95% adherence is required for adequate viral suppression and the prevention of drug resistance and adherence thus plays a pivotal role in the treatment of patients with AIDS. Treatment readiness programmes emphasise the importance of patients taking responsibility for their treatment and the need for them to understand the medication and the illness. Mental disorders such as depression, psychosis, dementia and substance abuse affect adherence negatively (7;8). An appropriate model for ARV treatment and adherence maximisation was urgently needed for our patients.

1.4 Theoretical considerations with respect to the diagnostic validity of HIV-associated psychosis and mania

The atypical presentation of HIV-positive psychotic and manic patients poses a broader question, probing one of the most vexing problems facing psychiatry today: the lack of diagnostic validity in psychiatric diagnoses within the current categorical models which frame our understanding of psychiatric disorders. As I became more interested in describing the clinical characteristics of HIV psychosis and mania, it became clear that it would be necessary to understand the context within which categorical models of psychiatric disorders operate with particular reference to diagnostic validity and reliability. I therefore conducted a critical examination of the literature in this regard, presented in chapter 2, focussing in particular on the possible conceptualisation of HIV psychosis and mania within the context of other psychiatric disorders manifesting with psychotic, mood and fluctuating symptoms. This appraisal included both clinical and neurobiological evidence with respect to diagnostic validity in disorders characterised by manic and psychotic symptoms, with particular

reference to HIV-related disorders. HIV-associated psychosis and mania, delirium in HIV-positive patients, and HIV-associated dementia (HIV-D) can all present with psychotic symptoms. I focussed on these disorders, critically evaluating the possible relationship between them. As will be argued in this chapter, the categorical diagnostic models we employ in psychiatry have poor validity and are not supported as discrete entities by clinical or neurobiological evidence. HIV psychosis and mania are therefore not discrete diagnostic entities, but rather represent a spectrum of clinical phenotypes, the susceptibility to which is conferred by overlapping genes interacting with the immunological consequences of HIV infecting the central nervous system. With respect to the nosological description of HIV-associated neuropsychiatric disease in this thesis, HIV-associated psychosis and/or mania, HIV psychosis/mania and HIV consequent psychosis and or mania are used to describe neuropsychiatric disease secondary to HIV infection. This is in distinction from HIV infection and a psychotic or manic illness arising incidentally in the same patient.

Methodological mechanisms, such as cluster analytic methods, will be proposed for improving diagnostic validity, and the chapter will conclude with the proposal of an integrated model of psychosis that enhances the diagnostic validity of psychosis and mania in general and HIV psychosis and mania in particular.

1.5 Systematic review

I present a systematic review of HIV-associated mania and psychosis in Chapter 3, in which I address four main questions:

1. What is the evidence for the existence of HIV-related mania and psychosis?
2. If they do exist, what features characterise their clinical presentations?
3. What is their relationship to HIV staging?
4. Do they have a role in indicating the need for antiretroviral treatment (ART)?

From an examination of the available evidence, it will be argued that HIV-related mania and psychosis do exist but not as discrete entities. Both have increased prevalence in HIV-positive populations. Affective symptoms were reported to be prominent in psychotic patients while psychotic symptoms were prominent in manic patients. They both occur in late-stage HIV disease and are associated with cognitive impairment and a poor prognosis. There is some evidence that ART may provide

some protection against developing HIV-associated mania and psychosis and that it is important for successful treatment of HIV-related manic and psychotic symptoms. This evidence supports the argument that HIV mania and psychosis should be regarded as AIDS-defining phenomena and are therefore indications for ART.

The systematic review describes the paucity of literature in this area as only six comparative studies were identified. Apart form the Ugandan study, sample sizes were small. Methodologies and sample selection varied between studies and no studies examined the possibility that HIV-associated mania and psychosis may be a sub-acute delirium. No studies were found that focussed on both manic and psychotic symptoms and there were no studies that had used cluster analytic methods to identify possible latent variables in these disorders. Neuropsychological findings, neuroradiology and other investigations were reported in very small samples and no studies reported viral loads. The review concludes with suggestions of some ways in which the methodological constraints and gaps in the literature, described in the review, can be addressed in future studies.

1.6 Hypotheses

1. If a patient with advanced HIV disease has psychotic and manic symptoms, they are more likely to have features of a sub-acute delirium than patients with early HIV disease or HIV-negative patients.
2. If a patient has HIV-mania or psychosis, they are more likely to have features of cognitive impairment than patients with early HIV disease or HIV-negative patients.
3. HIV-associated mania and psychosis are AIDS-defining phenomena

1.7 Aims

1. To determine whether the clinical features, and relevant laboratory data, of manic and psychotic patients who have late-stage HIV, early HIV or who are HIV negative, differ; and, if so, what features characterise those differences.
2. To evaluate, in particular, whether patients with HIV psychosis and mania have features of a sub-acute delirium as compared to the other two groups.

3. To determine whether HIV-associated mania and psychosis are AIDS-defining phenomena.
4. Arising from points 1–3 above, to provide information that will be useful in developing practical guidelines for the diagnosis, differential diagnosis, investigation and treatment of these disorders within the South African context.

1.8 Objectives

1.8.1 Research Objectives

1. To conduct a critical examination of the clinical and neurobiological evidence with respect to diagnostic validity in disorders characterized by manic and psychotic symptoms with particular reference HIV-related disorders and disorders characterized by symptom fluctuation.

2. To conduct a systematic review, in all languages, of HIV-associated psychosis and HIV-associated mania.

3. To develop a clear ethical framework for the study.
    a) To develop an appropriate consent form and information sheet.
    b) To develop an appropriate patient-information document.
    c) To translate and back-translate these documents into Afrikaans and Xhosa[1].

2. To review cognitive, psychiatric and functional assessment tools pertinent to this study, and to select appropriate tools for use in the neuropsychiatric evaluation of patients in the study.

3. To document the clinical features, (i.e. presenting complaints, symptoms, signs, co-morbidity, diagnosis, relevant special investigations and treatment

[1] The majority of people living in Cape Town speak at least one of the following languages: English, Afrikaans and Xhosa

considerations) with respect to HIV-positive and negative patients presenting with psychotic and manic symptoms.

4. To perform a detailed clinical assessment involving a neuropsychiatric and neuropsychological assessment and physical examination of each patient. To perform the following special investigations on each HIV-positive patient and, where clinically appropriate, on the HIV- negative patients;

   a) A full blood count and differential count, CD4+ count, serum viral load, lumbar puncture (chemistry, microscopy, culture and sensitivity, cryptoccocal latex agglutination test (CLAT), Venereal Disease Research Laboratory (VDRL) and treponema pallidum haemaglutination test (TPHA), acid fast bacilli (AFB) culture, viral load), serum VDRL and TPHA, thyroid stimulating hormone (TSH), vitamin B12 and folate, electrolytes and liver function tests.

   b) Radiology: Chest X-rays (CXR) on all HIV-positive patients and on HIV negative patients where indicated. To perform CT brain scans on as many patients is possible and magnetic resonance imaging (MRI's) of the brain in HIV-positive patients with advanced disease (due to budgetary constraints).

   c) Any other clinically relevant investigations, for example, sputum acid-fast bacilli (AFB), skin or lymph node biopsy, abdominal ultrasound, electroencephalogram (EEG) .

5. To compare the clinical and laboratory features of manic and psychotic patients with late stage HIV to those with early HIV as well as with a group who are HIV negative.

6. To conduct a latent class analysis, a cluster analytic statistical method, to help identify underlying patterns of symptoms among patients in the study:

   a) To describe and analyse the underlying latent classes.

   b) To then compare the latent classes according to participant demographic, psychiatric and HIV-related factors, using descriptive and analytic approaches.

   c) To compare the latent classes according to their DSM-IV diagnoses.

7. To conduct a small pilot study of a cohort of patients with advanced disease who were given antiretroviral treatment, focusing on adherence and treatment response, following the patients for at least six months. Although this does not form part of the main aims and objectives of this thesis, it provides important additional information with respect to the main arguments presented in this study. For example, response to ART will be informative with respect to determining the relationship between HIV and psychotic and manic symptoms as well as the whether the features are AIDS-defining and should be indications for ART.

1.8.2 Implementation objectives

1. To use this study to initiate the development of clinical services for HIV-related mental illness in Cape Town.
    a) To provide practical guidelines with respect to the diagnosis, appropriate investigations and treatment of patients with HIV-related neuropsychiatric illness, including guidelines concerning the co-administration of psychotropics and antiretrovirals.
    b) To offer a consultation-liaison service with regard to HIV- related mental illness to health professionals working in this field in psychiatric and general medical hospitals in Cape Town.
    c) To provide teaching and in-service training to increase the proficiency of health professionals in HIV-related mental health.
    d) To provide information gathered as described above to improve access to antiretrovirals in patients with serious AIDS-related mental illness.

1.9 Methodology

The methodology employed in this study will be described in Chapter 4, together with a description of the methodological challenges which arose. Specific attention will be paid to the complex ethical considerations in a study of this nature. The study sites were located in a multicultural community where three main languages are spoken and many people are poor and have low standards of education. The methodology therefore needed to accommodate these factors as much as possible.

1.10 Results

In chapter 5, this thesis will report a study of 111 patients who presented with manic and/or psychotic symptoms to psychiatric and general medical hospitals in Cape Town over an 18 month period between October 2004 and March 2006. The three selection groups (late HIV-positive / early HIV-positive / HIV-negative) will be described and an analysis of differences between these groups will be presented. This will be followed by a description of the latent class analysis (LCA) model to identify any patterns in the underlying (latent) classes of psychiatric symptoms. A description and analysis of the latent classes of psychiatric symptoms, according to participant demographic characteristics, features of HIV disease, and psychiatric symptoms not used to define the latent classes will be presented. The findings of the pilot cohort study with respect to the use of ART in patients with HIV-associated psychosis and mania will then be presented.

1.11 Discussion

The discussion will be described in chapter 6 and will begin with the presentation of a summary of the thesis and a discussion of the findings with respect to the manner in which they concur with, or differ from, the literature. Possible neurobiological implications will be discussed as well as practical implications of the findings. Limitations of the study will be described as well as a description of areas in which this study may contribute to new knowledge in the field. Suggestions with respect to possible future research will be made.

Chapter 2. Diagnostic validity in HIV-associated psychosis and mania: Theoretical considerations

2.1 Introduction

A description of the clinical features of a new diagnostic entity such as HIV-associated psychosis or mania requires a clear understanding of the diagnostic systems within which psychiatric disorders are described. As HIV-associated psychosis and mania do not fit well into current diagnostic systems, they highlight the clinical heterogeneity within psychiatric disorders and the significant challenges this poses for both clinical practice and research. Although much of the discussion in this chapter could apply to a number of psychiatric disorders, including depression in HIV-positive patients, the focus of this chapter is on the diagnostic validity of psychiatric disorders presenting with psychosis and mania as well as those presenting with symptom fluctuation.

In this chapter, I will critically appraise categorical models of disorders characterised by manic and psychotic symptoms in order to understand their conceptualisation. The specific focus will be on establishing the basis for determining diagnostic validity in these disorders to provide a clear frame of reference for the description of HIV-related psychosis and mania. If primary psychiatric disorders such as bipolar affective disorder and schizophrenia are distinct diagnostic entities, it would provide a basis for arguing that HIV-associated psychosis and mania may also be mutually exclusive. However, if this distinction cannot be made for schizophrenia and bipolar disorder, it is unlikely to be made for HIV-related disorders, unless there is clinical or neurobiological evidence differentiating HIV-associated psychosis from HIV-associated mania.

I will therefore examine the clinical and neurobiological evidence for diagnostic distinction between primary psychiatric disorders such as schizophrenia and bipolar disorder. My appraisal will then include disorders secondary to HIV that commonly

present with psychotic and manic symptoms. This includes HIV-associated psychosis and mania, delirium and dementia. The appraisal will be conducted with four questions in mind:

1. Are the current diagnostic systems valid in that they describe discrete diagnostic entities?
2. If there are problems with diagnostic validity in primary psychiatric disorders presenting with psychotic or manic symptoms, is there a model available that may improve their diagnostic validity?
3. How are HIV-associated psychosis and mania conceptualised within this new model?
4. What methodological approaches would be useful to address the challenges surrounding the examination of HIV-associated psychosis and mania as diagnostic entities?

2.2 Categorical models of psychiatric disorders

The primary aim of developing classification systems is to increase diagnostic validity and to facilitate appropriate effective treatment (9). Relative to other disciplines in medicine, the maturation of the brain sciences has been relatively slow (10). Psychiatry thus had to develop classification systems without the benefits of concomitant developments in neuroscience.

There have been fundamental changes in the conceptualisation of mental disorders over the past three decades with the development of two main categorical diagnostic systems in psychiatry, namely the International Classification of Diseases (ICD) (11) and the Diagnostic and Statistical Manual of Mental Disorders (DSM)(12). These explicit criterion- and rule-based classification systems provide an international frame of reference for clinical practice and research. They have been developed from syndromic categorical descriptions following extensive field trials, which have greatly improved their reliability, and they have become very similar. They have led to advances in clinical care, reduced idiosyncrasies, and have helped to demystify psychiatry. They have also facilitated scientific research into the aetiology, pathophysiology and treatment of psychiatric disorders (13). As categorical models, their validity would be maximal in the context of homogenous mutually exclusive disorders distinguished by clear boundaries.

The ICD and DSM systems have been criticised for reifying diagnostic categories. There is no empirical basis for most of the categories and many of the thresholds have been criticised as being arbitrary. While there is little evidence of discontinuity between categories, evidence for spectrum disorders and symptoms lying along a continuum is increasing (14-17). The inability of the DSM and ICD to reflect the heterogeneity found in clinical psychiatric practice has resulted in a proliferation of categories and co-morbidities. As they are not based on underlying pathophysiological and etiological factors, the current systems will remain vulnerable to these problems.

Many of the criticisms are a consequence of misguided expectations and the misuse of categorical models. The authors of the DSM-IV warn that "there is no assumption that each category of mental disorder is a completely discrete entity with absolute boundaries dividing it from other mental disorders or from no mental disorder" (DSM-IV pxxii) (12). They also warn against a "cookbook" approach to the use of the DSM, emphasising that it is to be used "to serve as a guideline to be informed by clinical judgement' (DSM-IV pxxiii) (12). Despite these warnings, psychiatric diagnoses as described in the DSM have been reified. This "reification fallacy" through which psychiatric disorders as defined by the DSM-IV or ICD 10 are viewed as quasi disease entities, has increased conceptual confusion and can hinder the advancement of knowledge, stifle conceptual innovation and lead to the impoverishment of clinical care (9). A summary of the strengths and weaknesses of categorical models of psychiatric disorders is listed in Table 2.1.

Table 2-1 A summary of the strengths and weaknesses of current categorical systems in psychiatry (9;13;16;18;19)

Strengths
• Standard international frame of reference for clinical practice with increased diagnostic agreement and improved communication • Advances in clinical care • Reduced idiosyncrasies and improved reliability in psychiatric research • Demystification of psychiatry and reduction in stigma with improved communication with the public and health care uses • Facilitated groundbreaking scientific research into the actiology and pathophysiology of psychiatric disorders • Facilitated the development and application of psychotropic medication
Weaknesses
• Reification of DSM categories can result in the impoverishment of clinical care and the stifling of conceptual innovation • Lack of empirical basis for some categories and some thresholds arbitrary • Reliability at the expense of validity • Vulnerable to manipulation by external forces such as managed-care systems and medical insurance • Does not make room for the possibility of continuum of disease • Not based on underlying pathophysiological and aetiological factors • Response to psychotropic medication is non-specific • Categories may be epiphenomena of underlying dimensions • Little evidence for natural boundaries between disorders • Does not reflect the heterogeneity found in clinical practice, resulting in the proliferation of "atypical" diagnoses and co morbidities • Category fallacy whereby a category is formulated within a specific framework (such as a western categorical diagnostic system) thereby excluding those feature that do not fit into its narrow categorical definitions.

2.3 Establishing diagnostic validity

Much of the criticism of the DSM and ICD arises from the difficulties surrounding the validity of psychiatric diagnoses. Validity is, however, a complex construct, comprising multiple components, each of which may be more important in defining the validity of the disorder depending on the context. Robins and Guze's original paper in 1970 assumed that the validity of syndromes would be established over time by refining clinical descriptions and delimitation from other disorders which would be informed by laboratory, family and outcome studies (20). This would ultimately result in valid homogeneous diagnoses characterised by familial aggregation. Kendler differentiated between antecedent validators (for example, pre-morbid personality, family aggregation and risk, demographics and possible precipitants), concurrent validators (for example, psychological and biological test results) and predictive validators (for example, consistency of diagnosis, prognosis and functioning longitudinally, including treatment response) (21). Emphasis on different validators such as symptom clusters versus treatment response, results in different sets of criteria.(22).

The extent to which validity informs clinical utility is dependent on the veracity of the underlying diagnostic constructs. It is not possible to validate the construct using an instrument derived from it as no mechanisms exist for validation beyond the conceptual framework of the construct itself (23,24). For example, if one defines HIV psychosis by a set of parameters including no previous history of psychosis together with a set of clinical symptoms and then formulates an instrument for rating HIV psychosis based on those parameters, the instrument cannot validate the diagnosis of HIV psychosis unless the assumptions in the formulation of the instrument are true. In this example, the exclusion of patients with a previous psychiatry history presumes that HIV psychosis and previous psychiatric disorders are mutually exclusive. Furthermore, if these patients are then compared to another group (such as HIV-negative patients), which includes patients with a past history of psychosis, there may be characteristics of first episode disease *per se* rather than HIV psychosis that bias

the results. There may also be clinical features that characterise HIV psychosis, such as depression, that were not selected in the initial description and therefore remain unknown. The description of psychiatric disorders using instruments (such as the Structured Diagnostic Interview (135)) derived from categorical models thus improves reliability but results in the perpetuation of circular arguments incapable of establishing or improving the validity of the disorders. The risk of deviating prematurely from the use of these instruments is that research findings may be idiosyncratic and unreliable.

2.4 Diagnostic validity in disorders with psychotic and manic symptoms

2.4.1 Absence of natural boundaries between psychotic and manic disorders

The absence of natural boundaries between diagnoses is well demonstrated across the psychotic disorders and the evidence of an overlap between bipolar disorder and schizophrenia is now well established (16;23). The extensive overlap in symptomatology extends from behavioral disturbance to perceptual changes, delusions and affective symptoms (15;17;23). In the last decade, there has been growing evidence of the significance of abnormalities of cognition in most psychotic disorders. The patterns of impairment vary between disorders. They range from "cognitive dysmetria" in schizophrenia characterised by dysfunctional synchronisation, or co-ordination of thought and action, to evidence of neurocognitive impairment in euthymic patients with bipolar disorder (25-27). Psychotic and affective symptoms are common to a variety of disorders, ranging from Alzheimer's disease and HIV-associated dementia to HIV-associated psychosis and mania, bipolar disorder and schizophrenia. The overlapping clinical features with respect to these disorders also extend to impairment in social functioning, increased morbidity, and in some disorders, to increased mortality. Furthermore, most treatments of psychotic and manic symptoms are not diagnosis-specific in that the same medications are used to treat different disorders and treatment responses are variable (28-30). The high rates of co-morbidity in psychotic and manic disorders are also suggestive of the heterogeneity of psychopathology (31). The distinction between true co-morbidity

(that is, the co-occurrence of an independent disorder with a different aetiology) and spurious co-morbidity has become blurred and reflects the inability of the current classification syndromes to describe common aetiologies or spectrum disorders (9).

Diagnostic validity, however, extends beyond the clinical similarities and differences between disorders. Both the breadth (array) and depth (severity) of symptomatology need to be adequately addressed as does the waxing and waning nature of many of these disorders. A valid diagnostic model for disorders presenting with psychotic and manic symptoms should also explain shared genetic susceptibility, psychosocial factors, neurobiological evidence and treatment response (32;33).

2.4.2 Primary and secondary psychoses

The DSM and ICD systems have historically distinguished between primary and secondary psychoses. Primary psychoses have been termed "functional" whereas secondary psychoses were conceptualised as being "organic", although this distinction is conceptually erroneous as primary psychoses are also secondary to underlying pathological processes within the brain (34). Secondary psychoses are most commonly conceptualised as arising from general medical illnesses, medication or substance use (11;12).

2.4.3 Psychosis and mania due to an underlying general medical condition

The DSM-IV allows for the diagnosis of a psychosis due to an underlying general medical condition (GMC) only if there are prominent hallucinations or delusions. A delirium or dementia need to be excluded (12). A summary of the diagnostic criteria for psychosis and a mood disorder due to a medical condition are described in Tables 2.2 and 2.3 respectively.

Table 2-2 Summary of the DSM-IV criteria for the diagnosis of psychosis due to a General Medical Condition (12)

1. Prominent hallucinations or delusions
2. Evidence from history, physical examination, or laboratory findings that the disturbance is the direct physiological consequence of a GMC.
3. The disturbance is not better accounted for by another mental disorder, such as a brief psychotic reaction to the diagnosis of a medical illness.
4. The disorder does not occur exclusively in the course of a delirium.
5. The diagnosis is not given if the symptoms occur as part of Alzheimer's disease or vascular dementia.

Table 2-3 Summary of the DSM-IV criteria for the diagnosis of mood disorder due to a General Medical Condition (12)

1. A prominent and persistent disturbance in mood predominates in the clinical picture and is characterised by one or both of the following:
    a) depressed mood or markedly diminished interest or pleasure in all, or almost all, activities
    b) elevated, expansive, or irritable mood
2. There is evidence from the history, physical examination, or laboratory findings that the disturbance is the direct physiological consequence of a general medical condition.
3. The disturbance is not better accounted for by another mental disorder.
4. The disturbance does not occur exclusively in the course of a delirium.
5. The symptoms result in clinical significant distress or dysfunction.

While cautioning that there are no infallible guidelines for determining an etiological relationship between psychotic or manic symptoms and a GMC, the authors of the DSM-IV give some guidelines for making the diagnosis which are described in Table 2.4.

Table 2-4 DSM-IV guidelines for determining whether psychotic symptoms are due to a General Medical Condition (12)

1. Temporal association between the onset, exacerbation or remission of the GMC and that of the psychotic symptoms.
2. Features atypical of a primary psychiatric disorder, such as visual or olfactory hallucinations.
3. Evidence from the literature that a causative relationship exists.
4. Exclusion of other mental disorders, particularly a primary substance disorder or a brief psychotic episode.
5. Late age of onset (first psychotic episode over 35 years of age)
6. Absence of a personal or family history
7. The DSM-IV lists associated general medical conditions known to cause psychotic symptoms and lists central nervous system (CNS) infections, such as HIV, among them.

For a psychiatric disorder to be secondary to a GMC, a defined clinical syndrome with identifiable clinical manifestations needs to be established that is associated with evidence of cerebral disease and has an increased prevalence in the population with the disorder (35). Krauthammer and Klerman (36) proposed criteria for distinguishing primary from secondary mania. They suggested that the absence of a personal or family history of mania, temporal relationship between the illness and psychiatric symptoms and an older age of onset would indicate the likelihood of secondary mania (36). Although the diagnoses of secondary disorders do not escape the poor validity and circularity inherent in all psychiatric diagnoses, they can potentially move beyond them if causality with the underlying medical illness can be established and neurophysiological mechanisms identified. Establishing the diagnosis, however, is often difficult as psychotic or manic symptoms can also arise within the context of a delirium or dementia and the distinction between these disorders is not always clear.

2.4.4 Delirium versus psychosis

The estimated rate of acute delirium in patients with HIV is high with some estimates in excess of 65% in patients with advanced disease (37;38). The literature is very sparse and I found that all the studies addressing delirium in HIV-positive patients were conducted among patients admitted to acute medical facilities (39;40) . Most studies characterise the aetiology of delirium in HIV-positive patients to be multifactorial (including acute infections, malignancy or metabolic complications of HIV, as well as their treatments) with a poor prognosis (39-41). There is a large overlap in symptomatology between psychosis, mania and delirium (40). They share common features such as distractibility, hallucinations, delusions, sleep changes, agitation, disinhibition, and affective symptoms (42;43). This overlap is reflected in the synonyms for delirium, eight of which include the word "psychosis (including exogenous psychosis, acute organic psychosis, acute brain syndrome with psychosis, acute secondary psychosis, acute reversible psychosis) (44). Other synonyms such as acute organic brain syndrome and encephalopathy are still widely used. There have been suggestions that severe delirium differs from a milder form (termed an "acute confusional state") although there is little evidence pathophysiologically for this distinction, thus further complicating the nosological confusion (45).

Distinguishing features of delirium as opposed to other psychiatric illnesses, particularly dementia, are thought to be the acute symptom onset and fluctuation of symptoms over a 24-hour period (46). The core feature is described as being that of cognitive dysfunction which may present in a number of forms, including disorientation, impaired attention, memory deficits and diffuse cognitive deficits or clouding of consciousness (46). There is growing evidence that, in addition to these core symptoms, delirium can be divided clinically into three motoric sub-types: hyperactive, hypoactive and mixed presentations. There is, however, lack of consensus with regard to different sub-typing methods which limits the comparability of different studies (47). Using the Delirium Rating Scale, Meagher *et al.* (48) found that patients with hyperactive delirium had higher scores for delusions, mood lability, sleep-wake disturbances and variability of symptoms than those with the hypoactive form. Ross *et al.* (49) found that hyperactive patients are also more likely to have hallucinations, delusions and agitation.

Table 2-5 Summary of the DSM-IV diagnostic criteria for a delirium due to a General Medical Condition (12)

1. Disturbance of consciousness (reduced clarity of awareness of the environment) with reduced ability to focus, sustain or shift attention.

2. A change in cognition (for example, impaired memory or language, disorientation) or perceptual disturbance that is not better accounted for by a dementia.

3. Symptoms develop over a short period (usually hours to days) and tend to fluctuate during the course of the day.

4. Evidence from history, physical examination, or laboratory findings that the disturbance is a direct consequence of a GMC.

Although acute delirium can often be more readily identified, the DSM-IV categorisation of delirium has been criticised as being too narrow (50). The phenomenological distinction between psychosis and delirium becomes particularly difficult in the context of repeated acute medical illnesses superimposed on a chronic illness affecting the brain, such as occurs in HIV infection. Rosen *et al.* (51) found a 32% false-positive score using the Delirium Rating Scale in geriatric patients with organic mental disorders. The scores were particularly high for patients who had higher scores on the Brief Psychiatric Rating Scale (BPRS). The question of possible misassignment of patients with delirium into the organic mental disorder group was raised in the literature, indicating the difficulty in distinguishing these disorders (52). Acute delirium is often characterised by the electroencephalogram (EEG) findings of diffuse slowing of the dominant posterior rhythm. The exception to this appears to be hyperactive delirium in alcohol withdrawal, which is associated with fast wave activity and increased cerebral blood flow. There is a paucity of information with regard to EEG changes in other forms of hyperactive delirium (43). One study

reported that 60% of the patients with delirium had abnormal EEG's as opposed to 41% of the patients with organic mental disorders and 12% of patients with non-organic symptoms (51). Although serial EEG's demonstrating diffuse slowing may be one of the most sensitive diagnostic tools in delirium (53), they are often not very practical as they are very difficult to do in behaviourally disturbed patients and there may be a lag between the clinical and EEG changes. They are also costly and time consuming (54).

The development of the Delirium Rating Scale by Trzepacz *et al.* (54), and other similar instruments over the past twenty years, has helped to clarify the clinical features of acute delirium. Serial EEG's and some clinical features, including for example, fluctuation of symptoms over 24-hour periods, changes in level of consciousness and acute onset, may be useful in distinguishing delirium from other sources of psychosis. Overlapping clinical features, however, demonstrate the possibility of some shared pathophysiological processes and underlying genetic susceptibility (43). Although delirium is commonly recognised as being a transient disorder, there is evidence that symptoms may persist for more than six months (55). Levkoff *et al.* (56) found that only 4% of elderly patients with delirium have symptom resolution prior to discharge from hospital while fewer than 25% HIV-D have symptom resolution by six months. They concluded that incomplete manifestations of the syndrome may be frequent. The possibility of a sub-acute delirium occurring in patients with AIDS has not been explored in the literature.

There is some evidence that psychotic symptoms may be associated with an increased number of active medical problems and multiple aetiologies for the delirium. This may be particularly true in patients presenting with visual hallucinations (57). In the same study, Levkoff *et al.* (56) found no correlation between concurrent psychiatric diagnoses and the presence of psychotic symptoms. Although the study is a retrospective chart review, it nevertheless suggests that there may be interesting pathophysiological differences in the generation of psychotic symptoms in delirium as opposed to other psychotic disorders (57).

Table 2-6 Range of report frequency of clinical features of delirium (%) (58)

Poor attention/vigilance	17–100
Clouding of consciousness	58–100
Disorientation	43–100
Diffuse cognitive impairment	77
Poor memory	64–90
Delusions	18–68
Perceptual changes/ hallucinations	17–55
Language disorder	41–93
Disorganised thinking/thought disorder	95
Mood lability	43–63
Sleep disturbances	25–96
Psychomotor changes	38–55

2.4.5 Delirium, psychosis and dementia

Pre-existing cognitive impairment is a risk factor for the development of delirium (52). The association between psychotic symptoms and dementia suggests that the underlying illnesses are playing a role in facilitating the expression of psychotic symptomatology. A significant overlap in scores with delirium is also found patients with Lewy Body dementia (LBD) and those with end-stage Alzheimer's Disease (52). LBD is characterised is by the central feature of progressive cognitive decline with deficits of attention, executive function and visuospatial ability. In addition to this, it has three core features: fluctuating cognition, recurrent visual hallucinations and spontaneous features of parkinsonism. Severe neuroleptic sensitivity has been described in 50% of patients with the LBD. Features such as autonomic instability, repeated falls, delusions and depression have also been described (59-61). It is likely that neurodegenerative or infective states such as Alzheimer's disease, LBD or HIV infection constitute additional susceptibility factors which act synergistically with other vulnerability factors for the expression of psychotic symptoms (62;63). This could occur as the unmasking of a vulnerability to psychosis as the brain is progressively affected and loses reserve. Another factor may be that the underlying

inflammatory or neurodegenerative process more directly affects the pathophysiology of psychotic symptoms. The clinical features observed in patients in Cape Town described in Chapter 1, suggest that patients with HIV psychosis and mania have symptom fluctuation, episodes of disorientation, cognitive impairment and neuroleptic sensitivity and that they have features in keeping with a sub-acute delirium.

2.5 Clinical features of HIV-associated dementia

HIV-associated Dementia (HIV-D) is predominantly a sub-cortical dementia and, as such, presents with cognitive, motor and behavioural symptoms. For an HIV-positive patient, the cumulative lifetime risk of developing HIV-D was between 5 and 20% before the introduction of highly active antiretroviral treatment (HAART) in the late 1990's in developed countries (64). However, as people have lived longer with HIV, it has risen again and the cumulative incidence of HIV-D at one year was 25% in patients with AIDS in a study in 2003 in such countries (65). HIV-D is a sub-cortical dementia and cognitive deficits differ from cortical dementias, such as Alzheimer's disease and are more closely related to Parkinson's disease and Lewy Body Dementia(60;66). HIV-D is characterised by difficulty in switching tasks, decreased cognitive agility, recognition being better preserved than recall, frontal lobe symptoms and problem-solving impairment (67). The affective and behavioural symptoms are most commonly present with what initially appears to be depression but leads to marked cognitive slowing and other features of HIV-D. Slow response times and psychomotor retardation are very common features. Almost any psychiatric symptom can accompany HIV-D. The early apathy, depression and mild psychotic symptoms can progress to severe psychosis with manic and persecutory features and associated delusions and behavioural disturbance may occur (65).

The movement abnormalities characteristic of HIV-D vary from clumsiness, motor slowing and tremor to inco-ordination, myoclonus, choreiform and athetoid movements and fine motor difficulties (68). Eventually, patients become rigid (69), completely psychomotor retarded, and mute with severe dementia affecting multiple cognitive domains. HIV-associated minor cognitive disorder is characterised by milder symptoms in the same domains as HIV-D and do not invariably progress to

HIV-D (65). A summary of the symptoms and signs of HIV-D presented in Table 2.7 below illustrates the considerable overlap they present with HIV-associated psychosis, mania or delirium. The evidence with regard to the clinical features of HIV-associated psychosis and mania will be presented in the next chapter.

Table 2-7 A summary of the American Academy of Neurology AIDS working group diagnostic criteria for HIV-D (70)

1. Acquired abnormality in at least two of the following cognitive abilities which must have been present for a month and be resulting in dysfunction:
    - Attention or concentration
    - Speed of information processing
    - Abstraction or reasoning
    - Visuospatial skills
    - Memory or learning
    - Speech or language

2. At least one of the following:
    - Acquired motor abnormality
    - Decreased motivation or emotional control or change in social behaviour

3. Symptoms must not only occur during a delirium.

4. Symptoms must not be secondary to another cause such as a complication of HIV (such as an infection or malignancy), a psychiatric disorder or substance abuse.

2.6 Neurobiological evidence in psychosis

A critical appraisal of the clinical features of psychiatric disorders is one component of evaluating their diagnostic validity. Neurobiological evidence is, however, becoming increasingly important in establishing antecedent, concurrent and predictive validators of psychotic and manic syndromes. Neurobiological studies into the etiology and pathophysiology of psychosis and mania report non-specific results. For example, most neurotransmitter studies demonstrate an overlap between diagnostic and control groups, as well as overlap between disorders, including bipolar disorder and schizophrenia (71;72).

2.6.1 Genetics

Genes constitute the potential of neuronal functioning, both in terms of maximal normal capacity, as well as in terms of potential pathological vulnerability. As the relationship between genes and the environment, both internal and external, is dynamic and circular, physical and psychosocial events are incorporated into cells altering the expression of specific genes within the brain (32;73). There is growing evidence of shared genetic susceptibility across many psychotic disorders. Shared susceptibility in bipolar disorder and schizophrenia has been demonstrated repeatedly (33;74-76). Loci involved in a number of neurotransmitters, including dopamine, and serotonin and catechol-o-methyltransferase (COMT) have been implicated in numerous psychiatric disorders (72;77;78). In addition to this lack of specificity, there is evidence that there are ethnic variations in many of these biological markers and that may be associated with risk in some populations, but protection in others (79).

Evidence also exists of shared susceptibility to psychosis in primary and secondary psychotic disorders, with the demonstration of shared susceptibility regions in patients with Alzheimer's disease who experience psychotic symptoms and those with schizophrenia (63;80). Furthermore, apolipoprotein E4, a risk factor in Alzheimer's disease, has been identified as an independent risk factor for the development of HIV-associated dementia in older patients (81). A preliminary review of gene expression studies in HIV-associated dementia, Alzheimer's disease, multiple sclerosis and schizophrenia has demonstrated some overlap across these disorders (82). Some of this information is difficult to interpret as most studies have been

retrospective and use different techniques with no clinical, neuropathological, or biostatistical algorithmic standardisation (82). The genetic evidence does, however, suggest that psychosis is best conceptualised as a spectrum of clinical phenotypes, the susceptibility to which is conferred by number of overlapping sets of genes.

2.6.2 The role of inflammation, immunology and vasculopathy in psychosis and mania

Other pathophysiological processes such as inflammation and vascular damage occur in a number of neuropsychiatric disorders such as HIV, systemic lupus erythematosis (SLE), neurosyphilis, post-streptococcal syndrome, Alzheimer's disease and vascular dementia (83-87). There is evidence that other psychotic disorders such as schizophrenia may have an inflammatory vascular component. Cytokines and other inflammatory modifiers, influenced by factors such as a vulnerable genotype, infection or anoxia, may result in oxidative stress and microvascular damage in the brain with associated disruption to the blood-brain barrier. Hanson and Gottesman have used the pathophysiology of post-streptococcal neuropsychiatric illness as a possible model for inflammatory and microvascular mechanisms in psychotic disorders. Within this model, subtle microvascular disruptions disrupt CNS homeostasis through widespread effects resulting in oxidative stress. These disruptions are a consequence of a number of vulnerability factors acting synergistically to produce episode of psychosis (87). The increasing body of evidence of the role of immunological factors in the pathophysiology of psychosis may help to explain the intermittent nature of many psychotic and affective symptoms akin to those in auto-immune disorders such as SLE (88).

2.6.3 Neuropathogenesis of HIV

The precise neuropathogenesis of AIDS is still uncertain. Neuropathological processes in HIV brain disease are thought to arise from infected perivascular macrophages crossing the blood-brain barrier and initiating an inflammatory cascade which leads to glutamatergic and neurotoxically mediated neuronal apoptosis. Although astrocytes, neurons and oligodendrocytes can be infected by HIV, perivascular macrophages and microglia are the most susceptible cells. It has been suggested that HIV crosses the blood brain barrier by a "Trojan Horse" mechanism whereby infected monocytes migrate into the brain and differentiate into perivascular

macrophages (89;90). Cell-to-cell fusion of macrophages and microglia is mediated by HIV-envelope glycoproteins to produce large multinucleated giant cells (syncytia), which are the pathological hallmark of HIV encephalitis and the main neuropathological finding in HIV-D. HIV may also enter the brain in infected CD4+ T cells but the importance of this in the neuropathogenesis of HIV is unclear (83).

Figure 2-1 Mechanisms of neurodegeneration and neuroprotection in AIDS [2] (83)

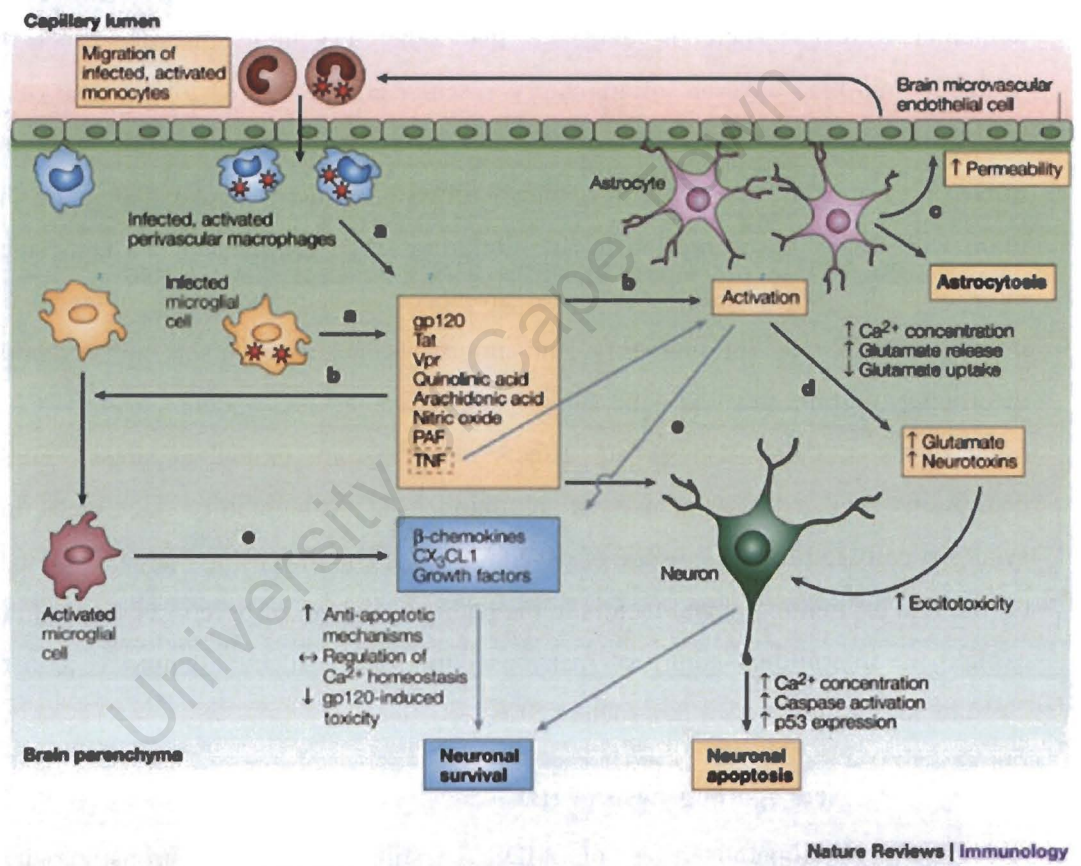


Figure 2.1 above illustrates the fact that infected perivascular macrophages and monocytes, in addition to producing HIV, may release neurotoxin viral proteins and other factors such as nitric oxide (a). These factors promote further activation of microglial cells, as well as astrocyte activation (b). Activated astrocytes change the permeability of the blood-brain barrier, increasing its permeability to monocytes (c)

[2] Gonzalez-Scarano and Julio Martin-Garcia , 2005, p 71

and result in increased calcium and glutamate induced neurotoxicity and excitotoxic neuronal death and demyelination (d). The degree to which the brain is protected from this process is probably related to the degree to which activated microglial cells release β-chemokines and other factors which decrease the HIV-envelope glycoprotein 120 (gp120)-induced toxicity, regulate calcium homeostasis and promote anti-apoptotic mechanisms (83). This explains why neurotoxicty can occur in the absence of high viral loads.

Glyoprotein 120, important in HIV docking onto CD4+ cells, has been shown to increase intraneuronal calcium in a dose-dependent response (91;92). This may be a mechanism in the dysregulation of neurotransmitters and other neuromodulators resulting in psychosis and mania (92). Chemokines such as CXCL12 are present at increased levels in the brain and CSF of HIV-positive patients. CXCL12 has been implicated in the dysregulation of cholingeric and dopaminergic systems as well as the promotion glutamate release and cytokine promotion (83). Although depletion of dopaminergic neurones in the substantia nigra has been demonstrated in HIV-positive patients, it has been suggested that increased dopamine availability may be a mediator of HIV consequent central nervous system deficits as dopamine is important in neural-immune communication. This has led to interest with respect to the possible neuroprotective role of neuroleptics, as dopamine blocking agents and studies in this regard are ongoing (93).

Sewell *et al.* (94) found that psychotic HIV-positive-patients have lower CSF protein and white cell counts when compared to aspychotic matched HIV-positive patients. Although the numbers in this study were small, it is possible that psychotic patients have a relatively impaired immune response, rendering them more vulnerable to neuronal damage. Several hypotheses have been proposed to explain the pathogenesis of new onset psychotic symptoms in HIV-positive patients. It has been suggested that psychosis is secondary to HIV-D and may be linked to sub-cortical degeneration (95;96). Occult infections in the context of an inferior CNS immune response has also been suggested (94). It has been hypothesised that high levels of intracellular free calcium mediating inappropriate neurotransmitter release may cause mood dysregulation and psychotic symptoms. The neuropathogenetic mechanisms illustrated in Figure 2.1 provide an explanatory model for mechanisms by which

patients with vulnerable genotypes develop HIV-related neuropsychiatric diseases and may be useful in understanding the genesis of neurospychiatric symptomatology in other disorders where inflammatory processes play a role.

2.6.4 Neuropathophysiology of Lewy Body Dementia (LBD)

LBD is associated with abnormal dopamine transporter on functional imaging and is characterised by the presence of Lewy bodies as a pathological diagnostic feature with depletion of dopaminergic neurons in the substantia nigra (66). The response of visual hallucinations in Lewy Body dementia to agents such as clozapine and quetiapine is indicative of more complex dysregulation in dopamine and other neurotransmitters (97). This is also supported by evidence that dopaminergic drugs may worsen the hallucinations in patients with LBD (98). There is extensive overlap clinically and neuropathologically between LBD, Alzheimer's disease and Parkinson's disease (99). In addition to cortical and hippocampal degeneration, LBD is characterized by severe degeneration of the nucleus basalis and the forebrain cholinergic nuclei occurring together with basal ganglia involvement. Cholinergic and dopaminergic mechanisms have been implicated in the pathogenesis of the characteristic symptomatology described in this disease (100;101). Inflammation and oxidative stress have been implicated in the development of Lewy Body disease (102). There are therefore shared neuroanatomical and neurotransmitter abnormalities in LBD and HIV brain involvement in the form of subcortical neuropathology and dysregulation of acetylcholine and dopamine.

2.6.5 Neuropathophysiology of delirium

Interestingly, there is evidence that the underlying pathophysiology of delirium may involve, at least in part, subcortical structures, including the basal ganglia and orbitofrontal-subcortical circuitry (103). Inflammation is thought to be the central in the pathogenesis of delirium with the increased cerebral secretion of cytokines which, together with other factors, activate neurotransmitter systems resulting in decreased cholinergic function and increased release of dopamine, as well as changes in other neurotransmitters (104). It has been suggested that delirium may constitute a final common pathway for heterogeneous aetiological agents, probably mediated through dopamine and acetylcholine dysregulation (43;58).

2.7 Methodological approaches to improve diagnostic validity in psychosis

The clinical and neurobiological evidence discussed thus far indicates commonality in psychotic and manic disorders. Specific methodological approaches are required to improve the conceptualisation of these disorders. Phenomenological studies crossing traditional categorical boundaries enable the identification of correlations between symptom clusters and underlying neurobiological processes, thus elucidating commonality and differences in etiology, neuropathophysiology and neuronal circuitry (32;43). Applying statistical techniques such as cluster analytic methods (including principal component analysis and latent class analysis) can facilitate the identification of cross-category latent variables thereby establishing clinically valid and stable diagnostic phenotypes. Because these methods enable the identification of clusters of symptoms that cross categorical boundaries, identified clusters or latent variables, once identified, can be correlated with possible underlying physiological mechanisms and genetic determinants of susceptibility or resilience. Any such correlations would facilitate the reorganisation of psychiatric diagnoses to accommodate the heterogeneity and complexity of psychiatric nosology (33;105).

2.8 New models for the conceptualisation of psychosis and mania

A number of models and systems have been proposed to accommodate various aspects of the emerging lines of evidence described above. Satisfactory models will need to accommodate the dimensional aspects of psychosis and mania as there are no clear boundaries between psychiatric disorders and changes between disorders are imperceptible. Multi-dimensional representations of psychiatric phenomenology are not new (106), but are now being given impetus by the genetic and neurophysiological evidence of shared susceptibility and common pathophysiological pathways (107). Categorical models reflect the lack of sophistication of the understanding of the pathophysiology of psychosis and mania and may obscure underlying continuities (17). This will change as more clarifying biological and psychosocial evidence accrues. Categorical distinctions may still be necessary for

practical reasons and medicine is full of such examples. For example, blood sugar levels lie on a continuum but reference values are determined to construct categories which lead to medical intervention. This process is more delicate and complex when the nature of human behaviour and experience, rather than a physiological parameter, is at issue.

Psychotic disorders, as most psychiatric disorders, are therefore probably better conceptualised as neurobiological syndromes with a number of different aetiologies. Psychotic symptoms are therefore indicative of common underlying neural network dysfunction. A better understanding of the aetiology, neuropathology and pathophysiology of different psychotic disorders will help to address the heterogeneity in their clinical presentation.

However, psychiatric illness is not unique in being the consequence of multifactorial determinants. A useful model for understanding multifactorial aetiology has been available for some time. Andreasen has proposed the use of a cancer "multi-hit" model for psychiatric illnesses (32). In terms of this model, underlying genetic vulnerability does not necessarily express itself as a full form of the disorder. The extent to which this occurs depends on a number of co-factors, both biological and psychosocial (32). A similar model has been proposed with respect to the possible role of microvascular damage and inflammation in schizophrenia (87). Within this model, the multiple "hits" are mediated through inflammatory pathways. There are multiple possible points within the neuropathogenesis of HIV where such "hits" may take place. This ranges from the viral load and penetration of the virus across the blood-brain barrier to the activation of various inflammatory cascades. Common symptoms may therefore result from shared and different "hits", conferring vulnerability in some contexts but not in others. For example some individuals may become psychotic or manic only if vulnerable inflammatory pathways which affect neurotransmitters and other mediators of disease are activated. In other individuals, the same inflammatory pathways may function normally but they may have other abnormal neurophysiological processes mediated by different inflammatory different combinations of mediators of psychosis and mania. Susceptibility to psychosis or mania in one context may therefore not apply in another.

Shared biological and psychosocial susceptibility for many psychiatric illnesses, many of which are likely to be spectrum disorders, potentially results in an extremely complex conceptualisation of these disorders. Different individuals will have different thresholds across different symptom clusters as a result of varying susceptibility affecting both the breadth and the extent (or depth) of symptomatology. For example, some people may have genotypes susceptible to dysregulation in neurotransmitters, neurodegeneration, inflammatory processes or psychosocial stressors. An individual's susceptibility will therefore convey variable vulnerability or protection depending on the nature and strength of all the contributory factors. Some factors, such as subtle changes in inflammatory and or other molecular processes, could have a powerful impact resulting in a direct shift in vulnerability or resilience, while other factors may have less noticeable influences. The propensity to psychosis or mania is therefore possibly a quantitative trait in a population revealed by numerous factors (63).

HIV-associated psychosis and mania are useful examples of the complex heterogeneity of contributory factors in psychotic and manic disorders. The risk of becoming HIV positive is determined by a number of factors such as the prevalence of the disease in the population, poverty, social dislocation, poor health services, substance abuse, religious and community beliefs and practices and levels of sexual abuse and rape. These factors have direct biological consequences. For example, untreated sexually transmitted infections (STI's) and early sexual debut increase the risk of transmission (108). People homozygous for the 32-bp deletion of the chemokine receptor CCR5 (a receptor important in HIV docking onto CD4+ cells), do not develop AIDS while those heterozygous for the receptor are slow progressors (109). Multiple factors therefore determine whether a person becomes HIV positive and develops AIDS. Should they become HIV positive, these factors then intersect with their relative vulnerability to, or protection from, neurodegeneration and psychosis. Patients respond differently to the virus depending on another set of factors such as immunological and inflammatory responses, including the activation of inflammatory neurotoxic cascades in the brain (83). The result is the relative vulnerability to HIV-associated psychosis or mania. HIV-associated psychosis and mania can therefore serve as models for identifying aetiological and pathophysiological pathways in the generation of psychotic and manic symptoms,

thereby indicating possible pathophysiological mechanisms in disorders such as schizophrenia and bipolar affective disorder.

Cross-category studies identifying correlations between clusters of symptoms and underlying neurobiological substrates and pathways will further elucidate a more valid diagnostic understanding of psychosis and mania (17). During this process, many existing categorical models will disaggregate and symptom clusters will coalesce in new ways with a variable degree of change depending on the evidence at hand.

2.9 Conclusions

The heterogeneity of clinical presentation, lack of diagnostic discontinuity between disorders, the proliferation of co-morbidity, common neurobiological determinants and non-specific responses to treatment demonstrate that the current categorical systems in psychiatry have poor diagnostic validity.

A more satisfactory conceptual model is one in which the original genetic propensity to develop psychotic or manic symptoms is modified through epigenetic processes and other genetic modifications. The process leading to an individual's resultant vulnerability or resilience at any given time is immensely complex. Susceptibility genes, including regulatory genes, modulated by diverse factors ranging from social deprivation to infection and neurodegeneration, are offset by those conferring resilience. Psychotic and manic symptoms therefore reflect some final common pathways for a number of different disorders, all of which have a widespread impact on the central nervous system. This model reaches behind categorical systems and addresses the vexing problem of the validation of disorders presenting with psychotic and manic symptoms. It also provides a conceptual basis for understanding HIV psychosis and mania, which do not fit easily within categorical systems. The proposed model potentially explains the overlap in symptomatology, the heterogeneity of psychiatric symptoms, the non-specific response to current treatments, high rates of co-morbidity within the current categorical models, as well as the waxing and waning nature of many disorders characterised by psychotic and manic symptoms. Furthermore, it accommodates the complexity of multiple

neuropathophysiological mechanisms, ranging from inflammation and infection to sociopolitical stressors. It is the interaction between various constituents of these pathways and between the pathways themselves that will ultimately confer protection or pathology. It is therefore possible that a symptom may be the consequence of a number of different pathophysiological pathways.

A satisfactory diagnostic system needs to be practical in order that it may have clinical utility. Underlying concepts and principles therefore need to be generalisable to the clinical context in order that such a system remains true to its primary purpose: that is, to understand psychiatric disorders so that valid diagnoses and appropriate effective treatment strategies can be instituted. In the light of the above critique, planning a study focusing on the diagnostic features of HIV psychosis and mania needs to address a number of issues. It needs to establish the evidence with regard to the antecedent, concurrent and predictive validators of HIV-associated psychosis and mania with careful attention to clinical symptomatology and relevant laboratory and radiological findings. An appropriate statistical methodology incorporating descriptive and cluster analytic approaches can then examine areas of interest. It is important that the findings be applicable in countries such as South Africa where the prevalence of HIV is very high and resources are scarce.

Chapter 3. A systematic review of HIV-associated psychosis and mania

3.1 Introduction

The relationship between HIV, psychosis and mania is complex. In the early 1980s, case reports began to emerge discussing manic and psychotic symptoms in HIV-positive patients. As the terms HIV-associated psychosis and AIDS mania began to emerge, these entities became increasingly reified. On reading the literature, it was easy to assume that these were two mutually exclusive entities with discrete pathophysiological pathways. In parallel with this, the World Health Organization (WHO) and Centers for Disease Control and Prevention (CDC) have continued to refine the clinical and laboratory definitions of HIV/AIDS (110-112). This is of particular importance because of the increasing accessibility of antiretroviral treatment (ART). Clear guidelines need to be given to clinicians as to when ART should be started. At the time of writing this thesis, neither HIV-associated psychosis or AIDS mania are recognised as AIDS-defining features and therefore do not, of themselves, result in the initiation of treatment with ART according to most guidelines.

3.1.1 Mechanisms for psychosis and mania in HIV-positive patients

When an HIV-positive patient presents with manic or psychotic symptoms, it raises a number of questions about the relationship between psychiatric illness and HIV. The psychotic or manic symptoms may be due to any combination of the following possibilities:

1. HIV and mental illness may co-exist in the same patient. Mental illnesses are common and HIV has reached pandemic proportions in many countries, including South Africa. Both major psychiatric illnesses and HIV are prevalent in young people and mental illness is a risk factor for contracting HIV (113). Substance abuse in an HIV-positive patient may also result in manic or psychotic symptoms (114).
2. Mental illness may be secondary to the neuropathophysiological consequences of HIV itself as discussed in the previous chapter.

3. Complications of HIV can cause mania and/or psychosis. Examples of this include cerebral toxoplasmosis, tuberculomas and other infections, metabolic abnormalities, malignancy, seizures, dehydration and hypoxia (115-118).

4. ART or medication to treat the complications of HIV can cause mental illness. These include drugs such as isoniazid, antibiotics, antivirals such as gancylovir and antiretrovirals, particularly efavirenz and zidovudine. Anti-depressants, particularly amitriptyline used in the treatment of HIV-related neuropathic pain, have also been implicated (119-125).

3.1.2 Criteria for the maximisation of diagnostic validity with respect to HIV-associated psychosis and mania

It is important that the contributions to mania or psychosis resulting from the complications of HIV or its treatment be separated from any that arise from the virus itself. Some authors, writing early in the HIV epidemic, questioned the existence of HIV psychosis or mania. They suggested that co-morbidity with primary psychiatric disorders, substance use or symptoms secondary to the complications of HIV might explain the increased prevalence of manic and psychotic symptoms in HIV-positive people (126;127). The central issue is to establish the evidence with regard to the diagnostic validity of HIV psychosis and mania. Criteria for the maximisation of diagnostic validity of HIV-associated mania and psychosis, as discussed in chapter 2, are summarized as follows:

1. The presence of a defined clinical syndrome.
2. Increased prevalence of the syndrome in the population with the disorder
3. Laboratory or other investigative evidence (such as neuroimaging or neuropsychology) of cerebral disease arising from HIV infection itself and its neurotoxic consequences rather than from complications of immuno-suppression or the treatment thereof.
4. A temporal relationship between HIV infection or stage of disease and the onset of manic or psychotic symptoms.
5. The exclusion of an acute delirium
6. Late age of symptoms onset (>35 years)
7. Atypical features such as prominent visual or olfactory hallucinations
8. An identifiable clinical course response to ART.

9. The absence of a personal or family history of mania (or psychosis). (9;12;36;128)

3.1.3 Prevalence of HIV psychosis and mania

Although definitions of HIV-associated mania and psychosis have often been vague and sample sizes small, some prevalence data have emerged. Prevalence rates for new onset psychosis in patients with HIV vary from 0.2% and 1.2% in patients in all stages of the disease to 15.2% in patients with AIDS (129;130). De Ronchi *et al.* (131) found that the prevalence of new-onset psychosis in HIV-infected patients was 3.7% (95% CI 1.6–5.7) and Lyketsos *et al.* (132) found a prevalence of mania in an HIV clinic to be at least ten fold more than in the general population. There is strong evidence of an increased prevalence of psychosis and mania in patients with advanced disease (130). The prevalences of bipolar disorder and non-affective psychosis (both 17.4%) in HIV-positive patients were high in a study in Uganda (133). Further evidence with respect to HIV psychosis and mania would help characterise their clinical characteristics and relationship to HIV and its disease progression.

Focus of the review

This systematic review addresses the following questions:

1. What is the evidence of the existence of HIV-related mania and psychosis?
2. If they do exist, what features characterise their clinical presentation?
3. Are they distinct entities? If not, how do they relate to each other?
4. What is their relationship to HIV staging and do they have a role in indicating the need for ART?

3.2 Methods

I searched MEDLINE, EMBASE, PsychINFO and Web of Science databases using combinations of the following terms: HIV or AIDS *and*: mania, psychosis, psychotic, schizophrenia, bipolar disorder, mood disorders, catatonia, neuropsychiatric and neuropsychiatry. Other terms included AIDS dementia complex, HIV-associated dementia, HIV encephalopathy and cognitive impairment and delirium. After the initial search for various combinations of these terms, I performed a manual search of the references cited in relevant articles. In addition, I also obtained further references by contacting some authors. I identified articles published in all languages until May 2006, including papers in press, which were published thereafter. I included empirical studies focusing on the clinical features of HIV psychosis and/or mania. Articles in languages other than English were reviewed with the assistance of health professionals proficient in the language concerned.

I excluded review and duplicate articles as well as studies in which:

1. there were identifiable medical causes for the mania or psychosis other than HIV itself, including the complications of HIV such as infections, malignancies and metabolic abnormalities;
2. there were medications used by patients at the time of symptomatology that have been implicated in mania or psychosis (cross-sectional and case-control studies controlling for medication were included);
3. there were substances implicated in the psychotic symptomatology including substance intoxication and withdrawal;
4. seizures were a possible cause of symptomatology;
5. there was insufficient information to establish inclusion (for example, in some case reports and letters where very little information was documented while other studies focused on treatment with anti-psychotics but contained very little clinical information), and
6. patients were on ART prior to the onset of symptoms.

Once all the relevant articles had been collected, it was apparent that there was a paucity of articles that satisfied the inclusion criteria. I therefore decided to include case reports and letters to gather as much information as possible. Some studies

focusing on psychotropic treatment did not meet the inclusion criteria for the review because they did not report sufficient clinical information. These studies are referred to in the discussion where relevant. I found no recent reviews in the area.

Definitions of HIV staging differed across the studies with the systems established by Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO) being applied (110-112). To facilitate clarity of presentation, I grouped the patients into two groups: those with early and those with late disease clinically. This was done after consultation with HIV clinicians and internal medicine specialists. The early disease group is the equivalent of the WHO 2005 stage 1 and 2 disease, whereas the late group implies stage 3 or 4 disease. These groups were chosen as they help to address the review question relating to the relationship between HIV staging and HIV mania and psychosis where stage 3 and 4 are indicative of advanced immuno-suppression. Of the comparative studies, five were DSM-IIIR based (40;62;94;131;134) and one was DSM-IV based (6). The Structured Clinical Interview (SCID) for the DSM-IIIR was used in three studies (SCID) (94;134;135) and two studies used the mini-mental state examination (MMSE) (6;131;136). Other instruments varied across studies (Table 3.3). Most of the studies excluded patients with features of acute delirium using DSM criteria (134).

3.3 Results

Fifty eight studies were included in this review. Of these, 52 studies (90%) were case reports, letters or case series. (One case report, published in English, was not located as its citation was incorrect). The remaining six studies reported comparisons between patients with HIV psychosis or mania and another condition. They were comprised of two case-control studies, three cross-sectional studies and one chart review. Of all the studies, 48 (83%) were published before 1995.

3.3.1 Evaluation of the quality of the studies

Careful documentation of manic and psychotic symptoms in case reports resulted in the recognition that these symptoms may relate to HIV in some manner. This led to larger chart reviews, case-control and cross-sectional studies, each of which have contributed to clarifying various aspects of neuropsychiatric HIV disease. There are numerous methodological problems with the studies in this review, which though often unavoidable, complicate the interpretation of their findings. First are the small sample sizes. Apart from the Ugandan study (N = 125) (6), the other samples sizes were small (N=20–75). Although Lyketsos *et al.* (134) had 75 patients in their study only 19 were HIV-positive patients with mania as the remainder were controls. The second problem was the variation in the manner in which it was decided that patients had HIV-associated mania or psychosis. Some studies suggested a probable causal relationship between the HIV and psychiatric symptomatology in the absence of a personal and/or family history of psychiatric disorders. Other studies were more specific depending on the clinical focus. For example, Nakimuli-Mpungu *et al.*(6) excluded patients from the HIV-positive group with a family or personal history of mood disorders as they were focusing on manic symptoms whereas Alciati *et al.*(40) excluded patients with a previous psychotic illness, as well as those with mood symptoms. The third problem is that terminology to describe symptomatology and diagnoses were often loosely applied. This was particularly noticeable in the letters and case reports where information was kept brief and positive findings or features of interest were presented. Absent symptoms and symptoms that are not the focus of the report were often not reported. For example, reports about patients with mania frequently gave very little information about psychotic symptomatology and those focusing on psychotic symptoms were often vague about affective symptoms.

3.3.2 Case reports, letters and case series

Ninety five patients were included from the 52 studies. There were 40 single case reports, six describing two cases, two describing three cases and four with more than three patients (4, 5, 8 and 19 cases). Forty studies were in English, ten in German, three each in Swedish and French and one each in Polish and Portuguese. Forty seven (91%) were published before 1995.

The main findings are tabulated in Table 3.1. All patients were described as having a probable HIV-related psychiatric disorder and most patients had advanced disease clinically (79%). With regard to gender and age, 88% of the patients were male with a mean age of 34. Psychotic symptoms were reported in 75%, manic symptoms in 68% and depressive symptoms in 26% of patients. The most frequently reported delusions were persecutory and grandiose delusions (50% and 55% respectively) and the most frequently described hallucinations were auditory and visual (71% and 55% respectively). Cognitive impairment was described in 28% of patients and 19% were reported as having abnormal neurological examinations. The presence or absence of disorientation was reported in 24 patients, 15 (63%) of whom were disorientated. Many patients were reported as having been diagnosed with AIDS as a consequence of being admitted with psychotic or manic symptoms (20 reports/series). Side-effects to medication were reported in 27 patients, 70% of whom had extra-pyramidal side-effects. The dose of medication was reported infrequently with doses ranging from the equivalent of 1.5 mg to 60 mg of haloperidol/day. One case described the successful use of electroconvulsive therapy (137). With regard to antiretroviral treatment, six patients were on AZT monotherapy which had either been discontinued prior to the onset of the psychosis or was started after admission. Two patients were started on antiretroviral treatment after the onset of their psychiatric symptomatology. Cerebral atrophy was found in 25% of patients on computerised tomography (CT) scan and 17% on magnetic resonance scan (MRI) with 33% of patients who had MRI's had white matter changes. EEG's were abnormal in 39% (N = 7/18) but the abnormalities varied. In 20 studies, psychosis or mania was the presenting illness that resulted in the diagnosis of AIDS.

Table 3-1 Findings reported in case reports and case series (127; 137-186)

(Total no of cases = 95, mean age = 34 years)

Clinical feature	N=95 *	%	References
Positive previous IVI drug use (N=83)*	10	12	Alexius 1986; Alexius *et al.* 1993; Bassetti 1998; Beckett *et al.* 1987; Belec *et al.* 1989; Bernhard *et al.* 1989; Budman & Vanders *et al.* 1990; Bulrich *et al.* 1988; Cummings *et al.* 1987; Dauncey 1988; Dettling 1998; Ellen *et al.* 1999; Fernandez & Levy 1993; Frei & Kruger 1997; Gabel *et al.* 1986; Gawlitza & Reuter 1988; Grehl & Kaschka 1994; Halevie-Goldman *et al.* 1987; Halstead *et al.* 1988; Hoffman 1984; Huffman & Fricchione 2005; Hutchinson 2005; Jones *et al.* 1987; Jost 1989; Kermani *et al.* 1984; Kermani *et al.* 1985; Kessing, *et al.* 1994; Kieburtz *et al.* 1991; Lazarus 1992; Maccario & Scharre 1987; Maha & Goetz 2006; McGowan *et al.* 1991; Milner 1989; Moller *et al.* 1988; Nasierowski *et al.* 1991; Nurnberg *et al.* 1984; Patricio F E 1991; Perry *et al.* 1986; Peters *et al.* 1989; Polan *et al.* 1985; RachBeisel & Weintraub 1997; Rosenbaum 1992; Röttgers *et al.* 2000; Scamvougeras & Rosebush 1992; Schmidt & Miller 1988; Scurlock *et al.* 1995; Shedlack *et al.* 1994; Snyder *et al.* 1992; Soyka *et al.* 1991; Vamos 1992; Zumbrunnen *et al.* 1984.
Positive family history (N=45)*	3	7	
Positive personal psychiatric history (excluding IVI substances) (N=40)*	11	28	
Psychotic symptoms	71	75	
Delusions	66	70	
Types of Delusions (N=66)*			
Persecutory	33	50	
Grandiose	36	55	
Religious	10	15	
Control	9	14	
Other	12	18	
Hallucinations	38	40	
Types of hallucinations (N=38)*			
Auditory	27	71	
Visual	19	50	
Olfactory	1	3	
Manic symptoms	65	68	
Depressive symptoms	25	26	
Irritability	32	34	
Mood lability	16	17	
Thought disorder	18	19	
Behavioural disturbance/agitation	41	43	
Cognitive impairment clinically (N=39)*	11	28	
Impairment on formal neuropsychological testing (N=9)*	2	22	
Duration of symptoms prior to admission (N=23)*	12	44	
Days	6	22	
Weeks	8	30	
Months	1	4	
Years			
Sleep disturbance (N=46)*			
Decreased sleep	41	89	
Patients with late disease (N=79)*	71	90	
Mean CD4+ count (cells/mm^3) (N =19)* (SD)	76 (1–220)		
Disorientation (N=24)*			
Disorientation present	15	63	
Fluctuation	6	6	
Bizarre symptoms	23	24	
Abnormal neurological examination (N=72)*	14	19	

Clinical feature	N=95*	%
Pharmacological treatment (N=72)*		
Anti-depressants	9	13
Mood stabilisers	8	8
Benzodiazepines	21	31
Anti-psychotics	62	93
Haloperidol	39	63
Chlorpromazine	8	13
Thioridazine	4	6
Risperidone	4	6
Rest (10 different antipsychotics)	19	31
Side-effects (N=27)*		
Extrapyramidal side-effects	19	70
Generalised seizure	2	7
Delirium	2	7

* indicates where a denominator other than 95 is used. Alternative denominator is the indicated in that cell.

3.3.3 Comparative studies

The comparative studies are more recent with five (83%) having been published since 1995. Only one study emanated from a developing country (Uganda) (6). Patient selection varied between studies. Psychosis and mania were the primary focus in three studies each (40;62;94;131;134). Of the psychosis-focused studies, one was a cross-sectional study, comparing HIV-positive patients with psychotic symptoms to HIV-positive patients with psychosis who also had metabolic or infective complications of HIV (40) (Table 3.2). The second was a cross-sectional study comparing patients with new onset psychosis with apsychotic HIV-positive patients (131). The third was a case-control study comparing HIV-positive patients with psychosis with HIV-positive apsychotic patients (94). The first study focusing on mania was a chart review comparing HIV-positive manic patients with CD4+ counts below and above 200cells/mm^3 (134). The second was a case control study comparing manic HIV-positive patients with those without mania (62) and the last was a study comparing HIV-positive patients with first episode mania with HIV-negative patients with mania (6).

3.3.3.1 Patient characteristics

The mean patient age was between 33 and 37 years for all studies apart from Nakimuli-Mpungu's study where the mean age for the HIV-positive group was 35

years but for the negative group, was 25 years (6). The samples in the studies from the developed world consisted mainly of males (50–90%) whereas the minority of the HIV-positive patients in the Ugandan study (18%) were male (6). Education differed at different sites with patients in the Ugandan study having lower levels of education compared to the HIV-negative patients (6). Most patients described as having HIV-associated mania or psychosis had late-stage disease (53%–91%) and low CD4+ counts although this varied depending on how groups were defined (range of means: 45–392 cells/mm^3). Lyketsos *et al.* (134) reported a family history of mood disorders in 50% of manic patients with CD4+ counts less than 200 cells/mm^3 as opposed to 90% for those with CD4+ counts > 200cells/ mm^3. Previous intravenous drug use was reported in the five studies from western countries (range 5–88%) (Table 3.2).

3.3.3.2 Summary of clinical findings

In the study comparing patients with HIV complications and psychosis to HIV-positive patients without complications, the group with complications were more likely to have the diagnosis of a delirium (Table 3.3) (40). Patients with HIV-associated mania were found to be more irritable and psychotic than HIV-negative patients or patients with early HIV disease in two studies (6;134). Mood symptoms in patients with HIV-associated psychosis were only described in any detail in one study (94), in which 13 out of 20 of the patients with HIV-associated psychosis (65%) had mood symptoms which were noted to be prominent. Cognitive impairment was reported in two studies in HIV-associated psychosis (94;131) and two in HIV-associated mania (6;134). One study in each group conducted formal neuropsychological assessment (94;134) whereas the others used the MMSE (6;131). Psychomotor speed was particularly reduced in these studies (134). The studies focusing on psychotic symptomatology found similar frequencies for visual hallucinations (42% and 45%). Mijch *et al.* (62) found that patients with mania were less likely to be receiving zidovudine (AZT) and De Ronchi (131) found that the only two patients to have full remission of psychotic symptoms were on ART.

Table 3-2 Comparative studies: patient characteristics

Authors and clinical focus	N	Sample description	Mean age (yrs)	(%) male	Level of education	Patients with late disease clinically (%)[b]	CD4+ counts in HIV+ group (cells/mm^3)	Past psychiatric history (%) (PH)	Family Psychiatric History (%) (FH)	Past History of IVI Drug Use (%)
Alciati *et al.* 2001(40)[a] *Psychosis*	26	Cross-sectional study: All HIV-positive patients: 13 with secondary metabolic or CNS infection (B), 13 without (A)*	A: 34.8 B: 35	77	Grade: A: 9.5 B: 8.0	Late: A: 92 B: 92	Mean: A: 45.8 B: 72	Not reported	Not reported	A: 62 B: 69
De Ronchi D *et al.* 2000 (131) *Psychosis*	27	Cross-sectional study: All HIV-positive patients: 13 with new onset psychosis (P) 15 apsychotic (AP) 22 patients followed up at 2 years	AP: 34 P: 36.1	AP: 73 P: 67	Mean (yrs) AP: 10 P: 9.3	AP: 33 P: 55	Mean: AP: 243.8 P: 207.5	AP: 33 P: 83	AP: NR P:8	AP: 40 P: 64
Sewell *et al.* 1994 (94) *Psychosis*	40	Case-control study. All HIV-positive patients, 20 with psychosis and 20 apsychotic	AP: 34.2 P: 35.6	100% for both groups	Mean (yrs): AP:14 P: 13.7	AP: 90 P: 90	AP: 372.8 P: 267.8	>1 diagnosis per patient-cannot be documented in this format	AP: 79 P: 83	AP: 0 P: 5
Lyketsos CG *et al.* 1997 (134) *Mania*	20	Chart review: All HIV-positive patients, divided into early (CD4+count > 200) and late (CD4+count < 200)	Early: 34.7 Late: 35.5	Early: 50 Late: 82	Mean (yrs) Early: 10.6 Late: 12.5	Early: 38 Late: 91	> 200: Early < 200: Late	PH for mood disorders: Early: 100 Late: 19	FH for mood disorders: Early: 90 Late: 50	Early: 88 Late: 55
Mijch AM *et al.* 1999 (62) *Mania*	75	Case-control study: All HIV-positive patients, 19 with mania secondary to HIV and 57 non-manic controls. matched by age. CD4+ count and date of treatment.	Manic: 37.1 Control: 37.2	Manic: 90 Control: 95	Not reported	Defined as with AIDS: Manic: 53 Control: 67	Manic: 44.9 Control: 48.1	Not reported	Not reported	Mania: 11 Control: 15
Nakimuli-Mpungu E *et al.* 2006 (6) *Mania*	125	Cross-sectional study: All patients were manic: 61 HIV-positive patients compared with 64 HIV-negative patients	HIV-: 35.2 HIV+: 25.2	HIV- : 45 HIV+: 18	% primary education or less: HIV-negative: 28 HIV-positive: 61	Late : 52	Mean: 392 Median: 272 > 350: 43% < 200: 46%	PH mania: HIV-: 66 HIV+: NA (0)	FH mood disorders: HIV-: 85 HIV+: NA (0)	Not applicable – exclusion criteria

[a] Defined the group with CNS infection or metabolic disruption as "secondary" and the other group as " primary". In this table Alciati's "primary =A and "secondary"=B. This avoids confusion as the term "primary" refers to disease in which HIVis not thought to be playing a role in all the other studies. [b] Late Disease: CDC category C and WHO stages 3 and 4 (111;112)

Table 3-3 Comparative studies: main findings

Authors and clinical focus	N	Instruments used	Clinical features	Neuroradiology (%)	Other investigations	Treatment and side- effects	Comments
Alciati *et al.* 2001 (40) *Psychosis*	26	DSM-III-R and PAS; AMDP 4*	All patients had psychotic symptoms. "Primary" group less likely to have the diagnosis of an acute delirium as defined by the DSM- III-R	CT: Cerebral atrophy: 42% Space-occupying lesions: 27% Normal: 41%	Not reported	Not reported	Previous psychotic illness and substantial mood symptoms excluded. "Primary psychoses defined as the absence of an infective or metabolic cause other than HIV. Non-lesional psychosis mean time to death = 31 days. "Primary" group mean time to death 160 days.
De Ronchi D *et al.* 2000 (131) *Psychosis*	27	SCID-NP, BPRS, PANSS, HRS-D, HRS-A, MMSE**	In patients with psychosis: 75% with delusions; three had less organised persecutory beliefs; 16% were cognitively impaired; one patient depressed: 42% had visual hallucinations and one had visual and auditory hallucinations. The psychotic group score significantly higher scores on the Brief Psychiatric Rating Scale (BPRS) (187)	CT: Cerebral atrophy: Psychotic group: 33 Apsychotic group: 0	Not reported	83% of psychotic patients had not received ART as opposed to 20% of apsychotic patients	One patient in the psychotic group had a CNS opportunistic infection 22 % had remission of psychotic symptoms but only after ART initiated two psychotic patients (22%) died. Both autopsies demonstrated cerebral atrophy. One had a brain viral burden whereas the other had no detectable virus.
Sewell *et al.* 1994a (94) *Psychosis*	40	SCID-P for DSM-III-R, semi-structured family interview, expanded version of the Halstead-Reitan neuropsychologic al test battery (188)	Psychotic symptomatology: 20 (100%) had delusions, thirteen (65%) more than one delusion (paranoid and persecutory thirteen, grandiose eight, bizarre six, guilt and control two, ideas of reference five, other two) eighteen (90%) had hallucinations: twelve auditory, nine visual , one each tactile and olfactory thirteen (65%) had mood symptoms: nine depressed, two euphoria and two mixed affective symptoms. Mood symptoms prominent clinical feature	No significant difference between groups on lumbar puncture or neuroradiology findings. (Radiologists blinded to clinical diagnoses.)	Neuropsychology: psychotic group demonstrated higher average impairment. Scores were not influenced by neuroleptic use. Patients evaluated neuropsychologically once their psychotic symptoms had been reduced sufficiently to enable them to participate in the testing. Mean length of time from study entry to testing = 114 days (SD=86)	Mean dose of chlorpromazine equivalent = 265mg/day (SD=569) Treatment complicated by side-effects (anticholinergic and EPSE), drug interactions and medical complications	No difference between groups for family psychiatric illness or part history of a mood disorder. Current substance use excluded but the psychotic group had a higher lifetime prevalence of substance use. Psychotic symptoms persisted (mean duration at last follow up = 29 months.) Diagnoses if HIV had not been assumed to be the cause: Psychotic disorders eight, bipolar disorder, manic five, major depression with psychosis four, schizoaffective disorder two, schizophrenia one Mean survival in months: Apsychotic group: 50.8 (4.6) Psychotic group: 22.6 (3.3)

Authors and Clinical Focus	N	Instruments Used	Clinical Features	Neuroradiology (%)	Other Investigations	Treatment and side- effects	Comments
Lyketsos CG *et al.* 1997 (134) *Mania*	20	SCID for DSM-III-R, CDC Criteria for Clinical Staging. Neuropsychiatric Interview.	Patients with CD4+ counts < 200 were more likely to be irritable (82% vs. 56%, p = 0.02), talkative (100% vs. 64%, p = 0.04), and have psychomotor slowing (90% vs. 13%, p = 0.001) and dementia (60% vs. 0%, p = 0.0073)	Not reported	Not reported	Not reported	Introduced the term, "AIDS Mania" as a manic syndrome arising from the neuropathophysiological consequences of HIV infection in the brain, supported by the association with cognitive impairment and psychomotor slowing.
Mijch AM *et al.* 1999 (62) *Mania*	75	DSM-III-R Clinical Criteria. Used the Krauthammer and Klerman criteria for identifying patients with secondary mania (36): no personal or family history of psychiatric illness and onset of symptoms after the diagnosis of HIV. Age of onset was not applied.	No specific clinical details described. Mean length of psychiatric illness 20 days	In patients with mania, CT ± MRI: 9/19 (47%) normal 5/19 (26%) mild cerebral atrophy 5/19 (26%) high T_2 signal foci One patient had a porencephalic cyst Control group 8/10 normal, One mild atrophy and one progressive multifocal leukoencephalopathy	All patients had lumbar punctures: reported as no infections or malignancies	Both groups on a number of agents that have been implicated in mania but no significant differences between the groups. Also no difference in medical complications that could be implicated but still possible that one or more of the manic patients may have had drug-induced mania.	Excluded patients with acute delirium and current substance use. At follow up, two patients (13%) had had another manic episode and (13%) a depressive episode. No controls had developed mania and 14.3% had developed depression. Median survival in group with mania: 7.9 months vs. 13.5 months in the control group Patients with mania were significantly less likely to be receiving concurrent AZT which has good CNS penetrance.

Authors and Clinical Focus	N	Instruments Used	Clinical Features	Neuroradiology (%)	Other Investigations	Treatment and side- effects	Comments
Nakimuli-Mpungu E *et al.* 2006 (6) *Mania*	125	DSM-IV criteria for mania Young Mania Rating Scale (189) MMSE	The second mania group had shorter hospital stays, were significantly less likely to have an elated mood, more likely to be irritable and have visual or auditory hallucinations, paranoid delusions and behavioural disturbance as well as a higher total YMRS score (all p values < 0.001) They had more cognitive impairment on MMSE, even after correction for education (p=0.001).	Not reported	Not reported	Not reported	Patients with substance abuse, puerperium, the DSM-IV diagnosis of delirium, or medical condition other than HIV and it complications that could be related to the manic episode were excluded. A multivariate regression model indicated that age 30-49 years, loss of a partner to AIDS and a history of a cough for > 1 month was associated with having secondary mania. High rates of HIV-related symptoms and signs described. Possible influence HIV complications and treatment as well as brain pathology not assessed.

3.3.3.3 Neuroradiology

Neuroradiological findings were reported in three studies on HIV-associated psychosis, but findings in one study were not distinguishable from patients with metabolic or CNS infections (40). It was thus not possible to determine the results of the patients who did not have secondary complications. In another study, there was no difference between psychotic and apsychotic HIV-positive patients (94). The third study (131) found cerebral atrophy in 33% of patients with HIV-associated psychosis. One study reports neuroradiological findings in HIV-positive patients with mania. Atrophy was described in 26% of patients with mania opposed to 10% in the patients without mania. White matter abnormalities were described in 26% of the patients with mania (62).

3.3.3.4 Clinical course

The clinical course of psychotic and manic symptoms was reported to be variable with some studies reporting the persistence and recurrence of symptoms (94;131). These studies did not, however, comment formally on whether there was fluctuation in symptoms (symptom variability) over the course of the psychotic or manic episode. In other studies, patients responded well in the short term and were discharged (6). The prognosis of both HIV-associated psychosis and mania without ART is poor. Mijch found that the median survival time for HIV-positive patients with mania was 7.9 months as opposed to 13.5 months for matched HIV-positive patients without mania (62). Alciati found a mean survival of 5.5 months (160 days)(40) and Sewell *et al.* (94) found a mean survival of 22.6 months in the patients with HIV-associated psychosis and 50.8 months for apsychotic HIV-positive patients.

3.3.4 Summary of the main findings of the review

A summary of the main findings from the all the studies is presented in Table 3.4 below.

Table 3-4 Summary of the main findings of studies involving HIV-associated psychosis and mania

Parameter	HIV-associated mania	HIV-associated psychosis
Prevalence of condition	Increased compared to general population	Increased compared to the general population
HIV clinical stage in which it occurs	Late	Late
CD4+ counts	Low	Low
Clinical features	Irritability and psychotic symptoms prominent	Affective symptoms prominent
Radiology (1 study each)	Cerebral atrophy 26%	Cerebral atrophy 33%
Cognition	Impaired	Impaired
Tolerability of psychotropic side-effects	Poor	Poor
Prognosis	Poor compared to controls	Poor compared to controls
Role of ART	May be protective	Two patients psychosis resolved when give ART

Additional findings from case reports, letters and case series:

- Persecutory and grandiose delusions are common (50 and 55% respectively)
- Cerebral atrophy found in 25% of patients on CT scan and 17% on MRI with 33% of patients who had MRI's having white matter changes
- EEG's were abnormal in 39% (N = 7/18) but the abnormalities were nonspecific
- Psychotic and manic symptoms may be the presenting symptoms which lead to the diagnosis of AIDS

3.4 Discussion

There is a paucity of literature with regard to the nature of HIV-associated psychosis and mania, their relationship to each other and to HIV disease progression. The studies identified are limited by small sample sizes and heterogeneity with respect to definitions of terms, patient selection and methodology. In many respects, they reflect the history of HIV as an emerging illness from the early descriptions in gay men and intravenous substance users in the developed world to the heterosexual pandemic in sub-Saharan Africa.

3.4.1 Do HIV psychosis and mania exist, and if so, what are their clinical characteristics?

As was argued in the preceding chapter, HIV-associated psychosis and mania are examples of the complex heterogeneity of contributory factors in psychotic and manic disorders. Attributing causation and the establishment of diagnostic validity within this context is especially challenging.

3.4.1.1 Clinical characteristics

An evaluation of the evidence in this review indicates that there is an increased frequency of manic and psychotic symptoms in HIV-positive patients and that they present with psychotic or manic symptoms when they have advanced HIV disease. The temporal relationship with the time of infection, usually helpful in identifying secondary psychiatric symptoms, is therefore not helpful here. Although the late onset of symptoms (35 years) has been used as an indicator of a possible underlying medical illness, this parameter is not as useful in HIV-related psychiatric disorders as HIV affects predominantly young people (1). Nakimuli-Mpungu *et al.*'s (6) finding that HIV-positive patients in Uganda were older than HIV controls was surprising. Nakimuli-Mpungu *et al.* (60) also found that the HIV-positive manic patients had lower education and associated lower socio-economic levels than their HIV-negative counterparts. These findings may well relate to HIV prevention strategies and educational programmes undertaken in Uganda since 1990, rather than to the nature of the HI virus itself. Uganda is one of the few countries in sub-Saharan Africa to have a significant reduction in HIV prevalence

and parallel evidence of changes in sexual behaviour. In a seven-year trend study from 1989 to 1996, Kamali *et al.* (190) found a reduction in seroprevalence in young men and women (13–24 years) and an increase in prevalence in women aged between 25 and 34 years. These two groups would have been 22–33 and 34–43 years old respectively at the time of Nakimuli-Mpungu *et al.'s* study. There has also been an increase in education levels and an associated reduction in poverty levels in Uganda since 1990 (191). These factors could explain the older age group, lower education and lower socio-economic levels in the HIV-positive group in Nakimuli-Mpungu *et al.'s* study, which was conducted in 2004/2005. The findings are probably not related to HIV-associated mania itself and thus may not be generalisable.

Three studies focused on new onset psychosis or mania in HIV-positive patients. One study compared HIV-positive patients with new onset mania and no family history of mania, with HIV-negative manic patients, including those with a personal or past history of mania (6). Patients without a personal or family history of mania were found to be more likely to present with advanced HIV and to have associated dementia, supporting the concept of HIV-consequent mania (132). One of the problems with comparing patients with first episode disease in one group with those with previous episodes in another is that there may be factors unique to first presentations, irrespective of cause, that differ from subsequent presentations. Including patients with personal history and family histories of psychosis and mania in a large study would be useful to explore the role of genetic susceptibility (192). A sub-group comparison between HIV-positive and HIV-negative patients with new onset mania or psychosis could then be done to help distinguish symptoms which characterise first episode mania or psychosis from those that were secondary to HIV. As discussed in Chapter 2, there is overlap in the genetic susceptibility to psychosis and mania and lack of diagnostic distinction between the manic and psychotic disorders. A positive personal or family history may therefore indicate a vulnerability to secondary psychosis or mania. Patients could therefore present clinically depending on the degree of their vulnerability to psychotic or manic symptoms. For instance, patients with a strong genetic vulnerability would develop a primary psychotic or affective disorder (14;193). Those with a moderate degree of vulnerability

would develop symptoms only when they were exposed to other potentiators of disease, such as the infection of the CNS by HIV and its neurotoxic consequences. HIV-positive patients could therefore have a co-existent psychiatric disorder without substantial HIV brain disease, they could have HIV-consequent disease or they could have both a primary disorder with superimposed HIV brain disease.

Depressive symptoms were reported in 25% of patients in the case reports, letters and case series (Table3.1). Irritability was more prominent than euphoria in manic patients (6;134) and depressive and manic symptomatology was prominent in patients with psychosis (94). The possibility of mixed affective symptoms was not discussed in any of the studies. Depression is the most extensively studied psychiatric disorder associated with HIV and the prevalence rates in HIV of up to 36% have been reported (194). Depression impedes adherence, impairs quality of life and accelerates immune suppression and disease progression (195). It also predisposes to sexual risk behaviour and thus possible re-infection. Major depressive disorder has been reported as being even more prevalent in patients with advanced HIV disease and depressive symptoms have been reported to improve in patients on HAART (196). It had also been reported as being a predictor for future HIV-associated dementia (197). Although the relationship of HIV and depression is complicated more by psychosocial factors than by mania and psychosis, the possibility of depressive symptoms as a direct neuropathophysiological consequence of HIV remains largely unexplored.

3.4.1.2 Sensitivity to neuroleptic medication

Studies in this review reported patients to be have a low tolerance for the side-effects of psychotropics, particularly the extrapyramidal side-effects, which is consistent with other findings in the literature (198;198-201) although low dose risperidone was reportedly well tolerated in one study (202). A pilot study with clozapine in psychotic HIV-positive patients with drug-induced parkinsonism reported a reduction in psychopathology with reduced parkinsonism (201). One patient was withdrawn from the study because of leucopenia. The rate of sensitivity to extra-pyramidal side-effects (EPSEs) has been reported to be 2.4 times higher in AIDS patients compared to psychotic patients without

AIDS (203) and 7.0 times higher than a comparison group of medically ill patients (204). There have also been a number of reports of catatonia and Neuroleptic Malignant Syndrome (NMS) in patients with HIV, usually in the context of advanced disease, HIV-associated dementia and medical co-morbidity (37;205;206).

3.4.1.3 Neuroimaging

Small white matter changes, evident on T2-weighted MRI scans have been reported in about a third of asymptomatic seropositive patients (207). These changes occur early in the disease and are scattered to a variable extent throughout the cerebral white matter. In patients who develop significant HIV brain disease, cerebral atrophy is commonly found, and is present in virtually all patients with severe dementia. Central atrophy with ventricular enlargement predominates rather than cortical atrophy (207). The findings reported in this review are in keeping with this literature, supporting other evidence presented here of the relationship between HIV dementia, HIV-associated psychosis and HIV-associated mania.

3.4.1.4 Other investigations

Electroencephalograms (EEG's) were reported in a very small group of the studies reviewed. This is not surprising as it is extremely difficult to perform EEG's on psychotic and manic patients who struggle to lie still and may be behaviourally disturbed. The results of the EEG's are also difficult to interpret as patients are usually on psychotropic agents and, in particular, may require benzodiazepines to facilitate co-operation with the procedure. Baldeweg *et al.* (208) reported an increase in background activity in EEG's of patients with psychiatric symptoms as they develop symptomatic brain disease and suggests that this may be indicative of the development of sub-cortical CNS disease. The CSF findings reported in this review are non-specific and are commonly found in HIV-positive patients (209;210). None of the studies reviewed reported either serum or CSF viral loads.

3.4.1.5 Cognitive impairment

Cognitive assessments were conducted on small numbers of patients reported in this review. Two studies used the MMSE as screening tools for cognitive impairment. This instrument was developed as a screen for cortical dementia such as Alzheimer's disease (136) and is less useful for patients with predominantly sub-cortical disease. There are screening tests such as the HIV Dementia Scale and its international version which may be more useful to use (211;212). The studies reviewed do provide evidence of cognitive impairment, particularly reduced psychomotor speed. This finding is in keeping with those found in HIV-associated dementia, which has reduction in psychomotor speed as a prominent feature. The American Academy of Neurology AIDS Task Force (AAN) criteria for HIV-associated dementia include both manic and psychotic symptoms as possible features of the behavioural symptoms of the disease, suggesting a relationship between HIV-associated dementia, mania and psychosis.

The symptom array expressed phenotypically in each patient is a product of their underlying genetic vulnerability or resilience, together with other contributors including co-morbid disease and psychosocial stressors. El-Mallakh has suggested that there may be a window of opportunity for the development of HIV-related manic or psychotic symptoms, possibility secondary to an increase in intracellular calcium. As CNS damage progresses, more serious neuronal damage and death occurs and the likelihood of psychosis then lessons (95).

3.4.2 The diagnostic validity of HIV-associated psychosis and mania

The studies presented in this review were all subject to a logical circularity. Groups of people with a disorder such as HIV-associated mania, were assembled and then examined using definitions, instruments and methodological approaches that were pertinent when deciding who should be included in the group. This approach, while potentially improving diagnostic reliability if methodologies are consistently applied, cannot improve diagnostic validity. As was argued in Chapter 2, the selection of a group such as HIV-positive patients with mania and the subsequent application of the DSM-IV or an instrument based on the DSM to confirm that the patients have HIV-associated mania,

does not in fact do so. In terms of this approach, a potential diagnostic entity such as HIV-associated mania is defined by a set of parameters, which, it is assumed, constitute it as an entity. Those same parameters are then used to confirm its existence. If a common definition is used, there will be good reliability in that there will be agreement about what constitutes HIV-associated mania. This, however, does not necessarily make the underlying presumptions in the original selection of descriptive parameters true. One way of establishing the possible validity of these parameters can only be established if clinical features are examined by identifying possible latent underlying variables, rather than by the primary selection group.

3.4.3 Are HIV psychosis and mania distinct entities? If not, how do they relate to each other?

One of the central assumptions implicit in the studies is that HIV-associated mania and psychosis are distinct entities. This review, however, demonstrates that they share overlapping clinical features, are both associated with cognitive impairment, cerebral atrophy and advanced HIV disease. This is in keeping with the literature discussed in Chapter 2 with respect to other disorders presenting with psychotic and manic symptoms. Given that diagnostic distinction is absent in primary and other secondary psychotic and manic disorders, it is likely that manic and psychotic symptoms arise from overlapping neuropathophysiological processes in patients with HIV brain disease.

3.4.4 What is the relationship of HIV-associated psychosis and mania to the stage of HIV progression?

The studies reported in this review suggest that HIV psychosis and mania are associated with advanced HIV disease and a have a poor prognosis when compared to matched HIV-positive patients without psychosis or mania. This suggests that, like HIV-associated dementia, they should possibly be considered as AIDS-defining phenomena and would therefore be indications for ART. This is particularly important as mania and psychosis can be the presenting features of advanced disease in the absence of other AIDS-defining symptoms that would otherwise lead patients to seek treatment.

The second important reason is that there is some evidence from this review that the psychiatric symptomatology responds to ART and that ART may protect against developing mania or psychosis. Treating patients with HIV-associated mania and psychosis with ART will treat the underlying etiology of the symptoms rather than using psychotropics alone, which treat epiphenomena in the form or psychotic or manic symptoms. Treating HIV psychosis and mania with ART as early as possible is important in reversing existing CNS damage and in preventing any further damage from occurring, thereby reducing morbidity and mortality and maximising function and quality of life.

3.5 Conclusions

Despite the small sample sizes, paucity of studies and methodological problems in the studies reported in this review, there is a sufficient evidence to begin to answer the review questions. Current evidence suggests that HIV psychosis and mania do exist but are not mutually exclusive entities. It is more likely that they represent differing manifestations of underlying HIV-related CNS damage and are closely related to each other and to HIV-associated dementia. Clinically, there is an overlap in symptomatology with both psychotic and affective symptoms being prominent, poor tolerability of neuroleptic side-effects, as well as associated cognitive impairment, particularly psychomotor slowing, in some patients. HIV psychosis and mania occur late in the disease, are associated with a poor prognosis, appear to be AIDS-defining and to respond to ART.

Further studies are required to clarify the issues raised in this review. For example, the study described in the following chapters examines both mania and psychosis, incorporating standardised instruments and close attention to clinical features, neuropsychology, neuroimaging and disease staging (including viral loads). A cluster analytic method will be used to identify possible latent neurobehavioural dimensions underlying the clinical features of HIV psychosis and mania. This prevents some of the circularity inherent in many for the studies in this review. Sub-analyses will be conducted to evaluate the possible role of language, personal history and family history. The role of

ART will be examined in a preliminary cohort study involving patients with AIDS who are psychotic or manic. Should patients' psychotic and manic symptoms respond to ART, a strong argument can be made for a causal relationship between HIV and psychotic and manic symptoms.

Chapter 4. Methodology

4.1 Introduction

This thesis reports a cross-sectional study of the clinical features, co-morbidity, differential diagnosis, relevant special investigations and treatment of HIV-positive and negative patients presenting with psychotic and manic symptoms. The analysis of the study included a cluster analytic model to identify patterns in the distributions of psychiatric symptoms in the three groups: late HIV-positive (Late HIV), early HIV-positive (Early HIV) and HIV-negative, and the identification of latent classes of the psychiatric symptoms. Aspects of a pilot study of 16 patients who were given ART and followed up over six months are described where relevant to the arguments in this thesis.

4.2 Sample

4.2.1 Sample Selection and Sites

The study was conducted in Cape Town, which is the southern-most city in Africa and the capital city of the Western Cape Province of South Africa. It has the lowest prevalence of HIV in the country, with 13–15% of adults being HIV-positive (1). Cape Town is a multi-cultural city with three main languages spoken: Afrikaans, English and Xhosa. Racial categories have no scientific or anthropological validity. In South Africa, the socially defined racial categories of black, coloured (mixed descent) and white are legacies of the repealed Population Registration Act under the Apartheid government. However, they can still serve as proxies for language, culture and socioeconomic status (213), and one's racial category thus still partially determines health outcomes. HIV prevalence rates are highest among black people and these categories are thus included in this thesis as they have implications for focusing interventions with respect to HIV (214). A consecutive sample was selected from the in-patients at the three psychiatric hospitals and all general medical hospitals and hospices in the Cape Metropole over an 18 month period between October 2004 and March 2006. As described in the procedures below, all the clinicians at the sites were informed about the study. All patients who met the criteria

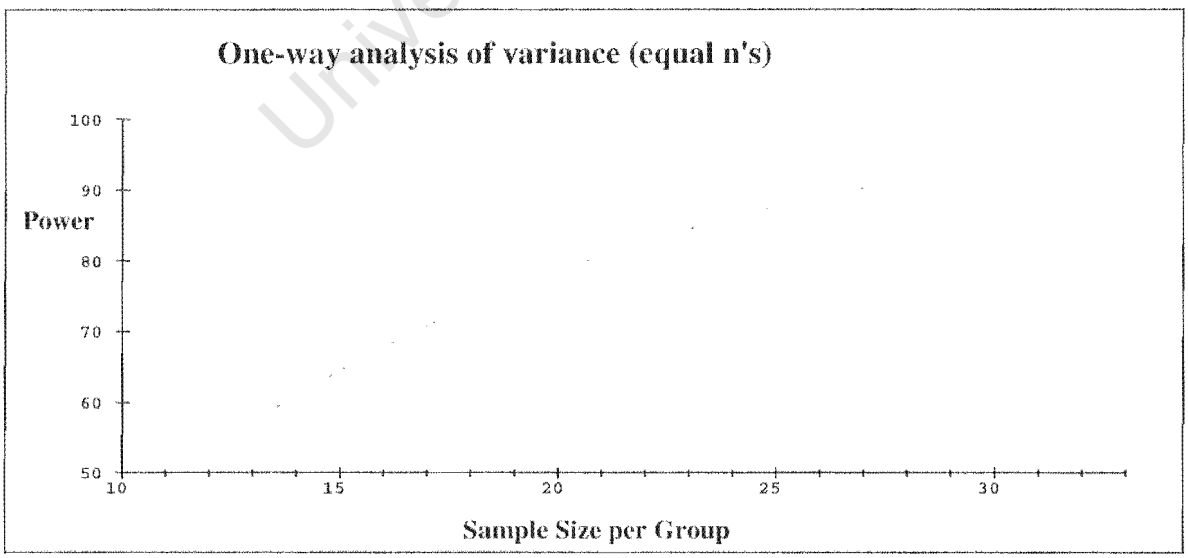
for selection and were referred to the study were included. There were a total of 12 sites: Lentegeur Hospital, Valkenberg Hospital, Stikland Hospital, Nazareth House, St Luke's Hospice, Groote Schuur Hospital, Tygerberg Hospital, Victoria Hospital, Somerset Hospital, False Bay Hospital, GF Jooste Hospital, and Karl Bremmer Hospital.

4.2.2 Sample size calculation

The sample size calculation was based on a two-sided test of a one-way analysis of variance (ANOVA) based on three groups, a type 1 error rate (alpha) of 0.05, a type 2 error rate (beta) of 0.10 (i.e., 90% power), an estimated variance of means of 8.0, and an estimated pooled standard deviation of 7.0 (i.e., an effect size of 0.16). Using these parameters, a desired minimum sample size of 28 individuals per selection group was calculated. Figure 4.1 below shows the relationship between sample size and statistical power based on these parameters for the delirium rating scale.

This sample size was attained for the HIV-negative (N = 30) and Early HIV-positive groups (N = 29) but was exceeded for the HIV-positive group as entry into the study was the only means of accessing ART for many patients which resulted in an ethical imperative to accept patients with advanced HIV into the study.

Figure 4-1 The relationship between the sample size and statistical power



4.2.3 Inclusion and exclusion criteria

4.2.3.1 Inclusion criteria for HIV-positive patients

- All stages of HIV with mania or psychosis

4.2.3.2 Exclusion criteria for HIV-positive patients

- Patients less than 18 years old
- Patients with an acute delirium as defined by the DSM-IV. This definition includes patients with an abrupt onset of a disturbance in consciousness and is usually associated with a change in cognition and fluctuation over a 24-hour period. There has to be evidence of a direct consequence of a general medical condition or substance use (c.f. Chapter 2 for detailed diagnostic criteria). All medical conditions apart from HIV itself were excluded. Any clinical, laboratory or radiological indicator that suggested the possibility of a medical complication or additional medical problem, temporally related to the onset of the psychiatric symptoms, led to the patient being excluded, even if there were no obvious signs of an acute delirium. Examples included patients with a primary causative medical illness. (for example sub-dural haematoma, Alzheimer's disease or vascular dementia, epilepsy or seizures prior to the onset of symptoms, cerebral infections such as toxoplasmosis, tuberculosis (TB), metabolic abnormalities, Huntington's disease, head injury). Patients whose symptoms were attributed to medication were also excluded. For example, patients on isoniazid, a medication commonly used for treating TB, which can cause psychotic symptoms were excluded (215).
- Active substance abuse/dependence. The substance use module of the MINI-Plus was used to evaluate substance use. This was confirmed using laboratory tests such as urinary tetrahydrocannibanol (THC) levels.
- HIV-positive patients not requiring antiretroviral treatment (ART) who were not able to consent and for whom proxy consent was not possible. The inclusion of patients with advanced HIV will be discussed in the ethics section of this chapter.

- Patients who declined to participate
- Patients with mental handicap as mental handicap often results in atypical clinical presentations.
- Patients on ART which would introduce bias.

4.2.3.3 Inclusion criteria for HIV-negative patients

- Patients with primary psychiatric disorders presenting with psychotic or manic symptoms, such as schizophrenia, schizo-affective disorder, schizophreniform disorder, bipolar affective disorder and major depressive disorder.

4.2.3.4 Exclusion criteria for HIV-negative patients

- Patients less than 18 years old
- Patients with an acute delirium or primary causative medical illness as described above for the HIV-positive patients.
- Current substance abuse/dependence
- Patients not able to consent
- Patients who declined to participate
- Patients with mental handicap

4.3 Procedures

4.3.1 Selection of groups

The patients were staged clinically in accordance with the World Health Organization (WHO) Interim clinical staging of HIV/AIDS and HIV/AIDS case definitions for surveillance criteria (112). The evidence from the literature review indicated that patients with HIV-mania and HIV-psychosis present with advanced HIV (WHO stages 3 and 4) and are associated with severe immuno-suppression. The patients were therefore selected such that some had early HIV disease, some had late HIV disease and the remainder were HIV-negative. Patients with early HIV disease (early HIV) were defined as having WHO clinical stage 1 or 2 disease and CD4+ counts over 200 cells/mm^3 while patients with late HIV disease (late HIV) were defined as having WHO stage 3 or 4 and/or CD4+ counts of less than or equal to 200 cells/mm^3. Patients presenting with psychotic or manic symptoms whose HIV status has been established for clinical reasons were referred for evaluation to the research team. For the HIV-positive patients, this occurred after they had been evaluated by internal medicine specialists with specific expertise in HIV, and any underlying medical causes for psychosis and mania, other than HIV alone, had been excluded.

4.3.2 Assessments

Following referral for assessment, the initial evaluation consisted of an interview to determine suitability for inclusion on clinical grounds and an evaluation of the competency of the patient to consent to participating in the study. Following a discussion about the study, the patient was asked whether they would be willing to participate. All psychiatric interviews were conducted in the patient's first language. Patients were seen as soon as possible after admission, but some required time to be become well enough to be competent to consent. In order to get as much information as possible and to determine whether symptoms varied over time (fluctuation), patients were evaluated on numerous occasions over the course of their admission. Collateral was sought from as many sources as possible, including the daily nursing notes, which were very helpful in assessing fluctuation. The sources of information were documented for each patient. All patients

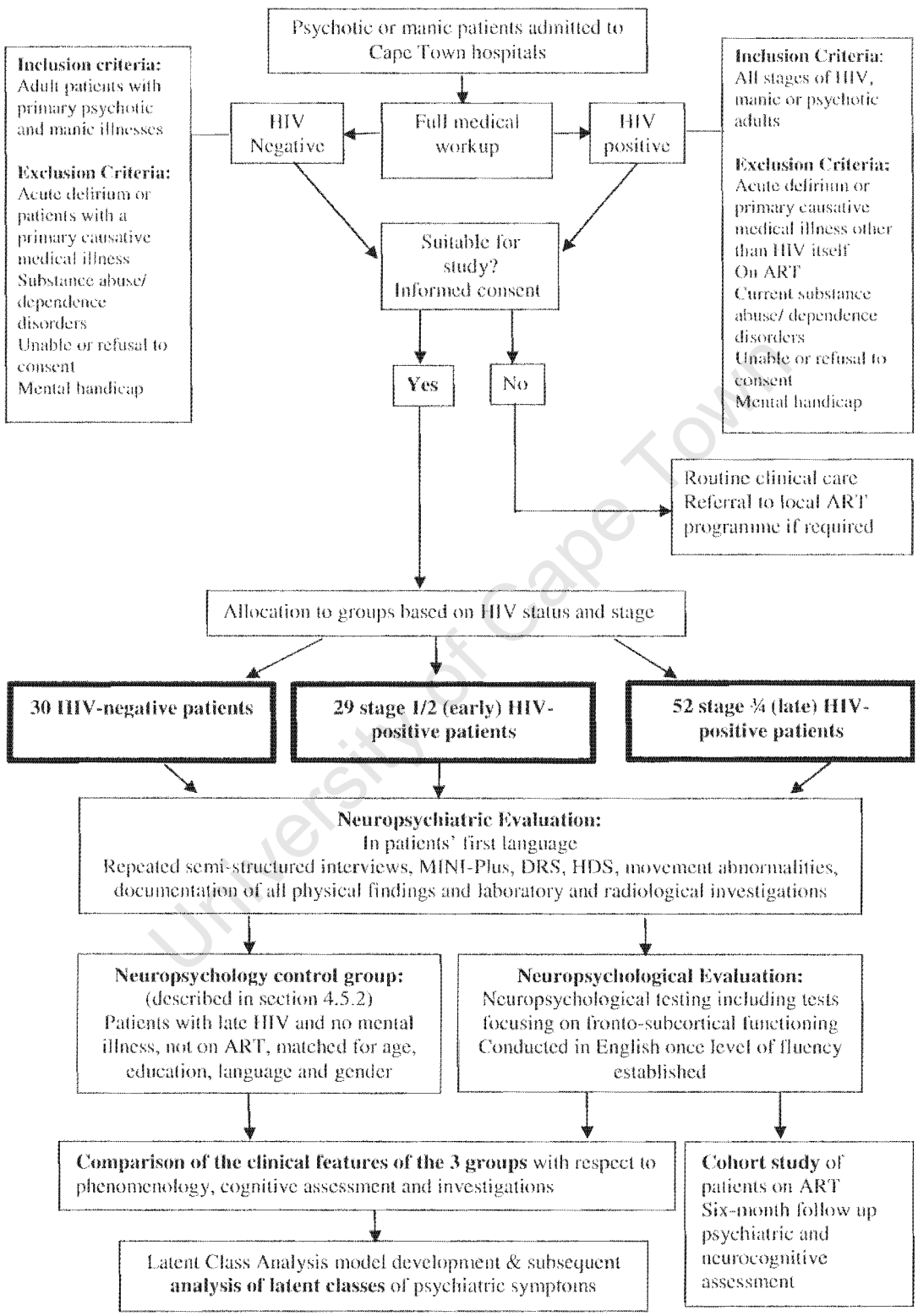
had detailed physical examinations prior to referral to the study. They were examined again by medical staff from the Desmond Tutu HIV Centre. Where necessary, patients were sent for other sub-specialist appraisals, such as neurology, respiratory medicine and haematology. Assessments also involved cultural formulations, which will not be discussed in this thesis.

All laboratory and radiological findings were recorded. CT (brain) scans were performed on as many HIV-positive patients as possible and MRI (brain) scans were performed on as many as possible patients with late stage HIV disease. The CT scans were initially performed without contrast which was then used if necessary. With respect to MRI, axial T2, sagittal T1 images without gadolinium, and axial flair images were done. Although it would have been ideal to perform MRI's on patients with early HIV and on HIV-negative patients, this was not possible for financial reasons. HIV-negative patients had CT scans as clinically indicated, in keeping with the current local standard of care.

Laboratory data included routine clinically relevant investigations such as full blood counts and differential counts, CD4+ counts, viral load, lumbar puncture (chemistry , microscopy, culture and sensitivity, cryptoccocal latex agglutination (CLAT), Venereal Disease Research Laboratory VDRL and treponema pallidum haemaglutination (TPHA) tests, acid fast bacilli (AFB) culture and possibly viral load and other markers), serum VDRL and TPHA, thyroid stimulating hormone (TSH), vitamin B12 and folate, electrolytes and liver function tests. The results of any other clinically relevant investigations, for example sputum AFB's, skin or lymph node biopsy and abdominal ultra-sound were documented. EEG's were performed if clinically indicated once the patients were no longer behaviourally disturbed.

Patient records were kept in folders identified by number and the information was then transferred into an MS Access database. The neuropsychological data were kept separately. Separate notes were also kept at the University of Cape Town Desmond Tutu HIV Centre for those patients who received ART.

Figure 4-2 Summary of procedures



I was assisted in the fieldwork by a psychiatrist, Dr M Rogers, who is fluent in all three languages commonly spoken in the Cape Town (Afrikaans and English and Xhosa). I am fluent in Afrikaans and English and speak some Xhosa. At the time of this research, there was no formal HIV-related mental health service in Cape Town and we were therefore ethically obliged to provide a clinical service. During the last six months of the study, an additional psychiatrist, Dr B Edwards, who is fluent in English and Afrikaans, assisted us (part-time) as we were overwhelmed with clinical demands. In accordance with the Health Professions Council of South Africa regulations, all neuropsychological assessments must be done by a registered clinical psychologist or psychometrist (216). A clinical psychologist, Ms I Moodley, trained in the administration of the neuropsychological tests used in this study, and fluent in English and Afrikaans, conducted the neuropsychological assessments. She was supervised by a senior neuropsychologist, Dr F Hemp, at the University of Cape Town. The medical staff of the University of Cape Town Desmond Tutu HIV Centre conducted the physical examinations of the patients, co-ordinated the treatment counselling, administered the ART and managed the patients medically. All decisions with regard to medical management of HIV-positive patients were supervised by the directors of the Desmond Tutu Centre, Dr L-G Bekker and Prof R Wood, both of whom are international HIV experts. Trained HIV counsellors assisted patients for whom ART was indicated with ART readiness counselling. All CT scans and MRI's were read by Dr S Candy, the senior neuroradiologist at the Division of Neuroradiology, University of Cape Town, based at Groote Schuur Hospital.

4.3.3 Access to the study sample

Public hospitals in Cape Town are frequently filled to capacity, with the result that there are serious time constraints with respect to the amount of time that clinicians can spend with their patients, as well as to the duration of hospital stays. Within this context, there is tension between the need to move patients through the system rapidly and ensuring appropriate patient care. Both the psychiatric and medical hospitals in Cape Town discharge patients prematurely in the need to create space for patients who may be even more ill and who are waiting to get into hospital. This results in territoriality developing

where clinicians set strict boundaries around their disciplines in an attempt to manage the patient load. Physically ill manic or psychotic patients who are frequently behaviourally disturbed, presented a problem within this context. Clinicians in medical wards were reluctant to admit patients with serious psychiatric symptomatology as they were concerned that other patients would be at risk. On the one hand, there were misconceptions about psychiatric symptoms and patients in medical wards were frequently prescribed very high doses of psychotropic medication. On the other hand, psychiatrists were also unhappy about looking after these patients because of their co-morbid physical illnesses. They were concerned that the patients' requirements for physical care could not be met in psychiatric wards. As a discipline, psychiatry is not as exposed to issues surrounding death as are other fields of medicine and psychiatric colleagues struggled with the notion that some patients would inevitably die as a consequence of AIDS-related complications in their wards. Within this context, patients were frequently transferred back and forth between hospitals and wards.

In order to gain access to patients at different sites, I held meetings with the hospital administrators and senior clinicians at all of the sites. Ease of access varied across institutions and some sites required a number of meetings to gain access to patients for the study. One of the main concerns of hospital administrators and clinicians was that the study might bring about changes in the way in which HIV-positive psychiatric patients were treated. Many facilities had adopted a passive approach to the management of psychiatric patients with HIV. For example many patients did not have appropriate medical investigations or referrals for medical intervention. There were concerns that staff did not have the skills to manage these patients actively. There was also concern that changing from a passive to an active approach to patient management would raise the cost of patient care. The meetings were time-consuming and required a diplomatic approach in order to persuade colleagues that it was important to engage actively in the process of caring for HIV-positive patients with mental disorders. Meetings were also held with pharmacists at psychiatric hospitals to facilitate the storage of antiretrovirals and to clarify the logistics of antiretroviral administration. It became apparent that many mental health professionals would benefit from in-service training in a number of aspects

of managing HIV-positive patients. I therefore organised an HIV and mental health workshop in Cape Town on the 30th of November 2004 which was attended by approximately 150 mental health professionals, including health managers, specialist psychiatrists, psychiatric registrars, psychologists, intern psychologists, occupational therapists and psychiatric nurses. The day began with an overview of HIV and mental health. Experts then gave presentations on HIV staging, medical complications and the important medical aspects of care, antiretroviral treatment and adherence. A panel discussion on ethical issues surrounding HIV and mental illness was held in the afternoon. The panel consisted of medical and psychiatric ethicists, infectious disease specialists and pharmacologists. The workshop served as a base for further in-service training at the various sites. I found that once mental health professionals had more information about HIV, they were more willing to engage in the act of caring the patients and to refer patients to the study. As the HIV epidemic escalated in Cape Town, both physicians and our psychiatric colleagues became increasingly dependent on field staff working on this study to provide HIV-related mental health advice. Ongoing in-service training was provided by the study staff to health professionals in the Cape Metropolitan area. As antiretroviral therapy has become more widely available, the role of the HIV hospices in Cape Town has changed. They now assist with the initiation of antiretroviral treatment and look after patients until they are well enough to live independently. Of all the sites of the study, the hospices were the most flexible, and, despite having the least medical and psychiatric resources, were willing to accommodate patients with co-morbid medical and serious psychiatric disorders. Registrars (residents) at the teaching hospitals move to different wards every three to six months. This required regular meetings with new staff in order to familiarise them with the study in general and the inclusion and exclusion criteria in particular.

4.3.4 Culture and language

Language and cultural issues affected the procedures in the study. For example, it was found that patients' names were frequently spelt in a number of different ways and, as a result, often had more than one folder number. This happened most often when hospital clerks and patients spoke different languages, leading to the misspelling of names and the misidentification of first names as surnames. This led to confusion with respect to whether investigations had been done on patients or not and investigations were often unnecessarily repeated. All neuropsychiatric measures were translated into Afrikaans and Xhosa and back-translated into English. The initial translations were done by professional translators and the translations were then examined by teams of mental health professionals, fluent in either Afrikaans or Xhosa, and amended so that they were accurate within a mental health context. The instruments were then back translated into English. The translations were further amended after the pilot study, which is described below. Some English concepts were found to be incommensurable in Xhosa and needed careful conceptualisation so that the correct intention of the question was conveyed. For example, there is no word for depression or bingeing in Xhosa. There is also considerable regional variation in both Afrikaans and Xhosa and care was taken to ensure that this was reflected in the translations used in the study. It was necessary to ensure that the language used in the instruments was colloquial rather than academic.

4.3.5 Pilot study

The pilot study involved eight patients (four HIV-positive and four HIV-negative). Instruments were piloted in all three languages. Any logistical problems were identified and addressed. The length of different components of the full battery was determined and the instruments were examined further with respect to language, culture and educational issues. Inter-rater reliability was maximised by the psychiatrists being blinded to one another's ratings while evaluating patients simultaneously. Detailed discussions on the intent behind each question were important, particularly when using the translations. Many questions needed qualification and agreement was reached on how this would be done to maximise reliability. If any question did require clarification, it was clearly documented next to the patient's answer. The inter-rater reliability was good, in that there

was more than 95% agreement between raters. Any differences in the interpretation of questions were clarified. Parts of the neuropsychiatric battery required rephrasing since questions were at times very lengthy and wording in the passive voice was sometimes difficult to comprehend. Questions were rephrased in a standardised manner ensuring that the accurate intent of the question was conveyed. For example, for the questions in the Expanded Mini-International Neuropsychiatric Interview (MINI-Plus), the same wording as the MINI-Plus was used wherever possible but changed into the active voice for easier comprehension. Patients experienced difficulties in the neuropsychological battery when attempting to comprehend the arithmetic subtest, particularly because of the verbose sentence structures used in this subtest. This test was omitted from the battery since changing the sentence structure would have had implications for the standardisation of the test and other methods of testing working memory had already been included in the battery. The period of administration of both the neuropsychological and neuropsychiatric battery was time consuming, as patients with AIDS tire easily and need time to rest. It was often necessary to conduct the interviews over two or three visits. The time of administration of the battery was also noted to be important. For example, it is necessary to ensure that patients have not been medicated immediately prior to testing. The importance of obtaining collateral and a clinical history was highlighted as patients were often unable to give accurate accounts of their symptomatology and medical histories. The value of qualitative data collection arose in the pilot study. Although this was time consuming, it added value to the nature of data collected. A formal mechanism for collecting this data was therefore added whereby qualitative data was recorded for each patient. A number of quality-of-life instruments were included but it was found that patients' psychotic and manic symptoms interfered with their ability to evaluate the questions and to give consistent answers and they were therefore discontinued.

4.3.6 Cohort study

In accordance with the Western Cape guidelines on the administration of antiretrovirals, all patients with a CD4+ count <200cells/mm^3 or WHO stage 4 (112), were assessed with a view to commencing ART (4;217). The antiretroviral regimens used were those prescribed as part of the roll-out of ART in the Western Cape (217). Consistently high-level adherence to ART (>95%) is required for adequate sustained viral suppression. Poor adherence leads to the development of drug resistance, which can potentially spread through populations (218;219). There is evidence to suggest that high levels of treatment adherence are ensured through multi-disciplinary efforts involving family and social networks and medical staff (220). A challenge in this study was that most of our patients were initially unable to adhere to treatment. Patients therefore selected a family member or close friend as a treatment partner who attended treatment readiness counselling with them prior to the initiation of ART. If patients were too manic or psychotic to benefit from the counselling, the treatment partner would attend and the patients would attend when they were able to participate. Each patient and treatment partner attended at least two treatment readiness sessions with a trained HIV counsellor. The first session was on HIV and positive living and the second on ART. In addition to this, they received ongoing counselling from the research and clinical staff in the wards. Adherence was measured using a combination of self-reports, treatment partner reports, clinician assessments, viral load monitoring and pill counting. Directly observed therapy (DOT) was used while the patients were psychiatrically ill and unable to adhere without assistance (221). Patients and their treatment partners saw their counsellors when necessary during the six-month period if they were struggling with adherence. HIV clinicians saw the patients for a screening visit and then the baseline visit after treatment readiness counselling had been successfully completed. Viral loads and CD4+ counts were measured at baseline.

After the initiation of ART, patients were seen again at the Desmond Tutu HIV Centre after two weeks and then monthly thereafter. Viral loads were repeated after two months of treatment. Patients were managed jointly by our research team and the HIV clinicians

and we referred them to the Desmond Tutu HIV Centre if any medical problems arose. For instance, some patients experienced clinical deterioration following the initiation of ART as a result of restored immunity (immune reconstitution syndrome) (222) while others developed hepatitis and their ART regimen needed to be adjusted accordingly. Adequate viral suppression was defined as a viral load of less than 400 copies/ml (log 2.60) (223). Once patients were well, usually between three and six months after the initiation of ART, they were referred to their community ART roll-out sites for ongoing treatment. Formal re-evaluation of sixteen patients was conducted after six months on ART. At this visit, patients were interviewed using a semi-structured interview, enquiring about their psychiatric and physical health, how they were managing with adherence, as well as evaluating their level of functioning. Some structured instruments were repeated where appropriate. CD4+ counts and viral loads were recorded. Bedside neurocognitive tests and neuropsychological assessments were not repeated before this to minimise practice effect.

4.3.7 Ethical procedures

The objectives of this study reflect paragraph 6 of the Helsinki declaration as follows: "The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the actiology and pathogenesis of disease" (224). The declaration states that research involving people belonging to vulnerable groups, such as mentally ill people, should only be conducted if it is not possible to conduct this research in subjects who are not vulnerable or incompetent. HIV-vaccine research in seriously mentally ill patients would therefore be unacceptable whereas research into serious mental illness as a consequence of HIV infection can only be done in this patient population. This study has been formulated in compliance with principles delineated in the World Health Organization Helsinki Declaration (2002) (224). It is imperative that current research in HIV/AIDS research informs policy decisions. In this regard, Benatar has described the need for justice in the distribution of the knowledge and resources that stem from research (225). This necessitates that research that is performed on disadvantaged and vulnerable patients has beneficial results to them and to their communities through influencing policy makers

(225). The methodology of the study was therefore directed at informing clinical practice in developing countries and in South Africa in particular. For example, the antiretroviral regimens used in the study were those prescribed by the government roll-out of antiretrovirals (ART) in the Western Cape Province and patients were treated with psychotropic medication which constituted the standard of care in state hospitals in South Africa at the time of the study.

At the time of the field work of this study, very few HIV-positive patients with psychosis or mania had access to ART. Psychiatric disorders, such as depression, psychosis, cognitive impairment and substance use can all have a negative impact on adherence to ART (8;226;227). This posed a serious ethical problem as we had received funding for ART for patients with advanced HIV who participated in the study. Patients who were not eligible for the study therefore had little chance of getting access to ART. We therefore offered a clinical service to these patients, including referral for ART but they were not enrolled in the study and any data pertaining to them were excluded from any analysis. Although this placed a significant clinical burden on the study staff, we agreed that this was the only ethical manner in which to proceed. When this study was initially planned, it was envisaged that it would be conducted in the hospitals associated with the University of Cape Town only. However, this would mean that psychiatric patients presenting at facilities at other hospitals in Cape Town would not have access to antiretrovirals. The study was therefore extended to involve all patients presenting within the Cape Metropolitan area. The University of Cape Town Research Committee supplied funding for cellular phones which enabled the field staff to work at 12 sites, in order to be accessible for screening calls, to liaise with one another with regard to patient care and research logistics, and to provide a consultation liaison service for HIV-related mental illness in the Cape Metropolitan area.

This study was performed with informed consent by the participants. A person's competence to consent may vary with time and depend on the complexity and seriousness of the decision at hand. Many of the patients in the study were not competent to give

consent to a complex medical procedure or a complicated invasive study, but most patients were able to give informed consent for this study, which was minimally invasive and of direct benefit to them. Some patients were too psychotic to consent initially. If patients were unable to consent and were either HIV-negative or HIV-positive but antiretrovirals were not clinically indicated, the clinical staff looking after them liaised with the research team when they were well enough to consent. If they continued to be unable to consent, they were not enrolled in the study. With respect to patients with advanced HIV who required ART, consent was sought from family members who had pre-existing knowledge of the patient's HIV status. No family members were informed of the patient's status for the purposes of the study. There were two patients who did not have family members with such knowledge and who were not able to consent but required antiretroviral treatment. With respect to these two patients, consent was given by the senior psychiatrist and medical superintendent (chief hospital administrator) responsible for the patients' clinical care.

Given that participation in the study was the only way that patients would get antiretrovirals, the clinical staff looking after the patients, in discussion with senior hospital management, gave consent for the patients to be enrolled in the study. As soon as the patients were able to consent themselves, informed consent was taken from them. All records were identified by number and the identity of the patients was known only to the research team and clinical staff involved in their care. The study was approved by the University of Cape Town Health Sciences Faculty Research Ethics Committee (no 232/2003). In keeping with the University of Cape Town Research Ethics Committee and South African Department of Health Ethical guidelines, patients were not tested for the purposes of the study. Patients were tested for clinical purposes and then referred to the study. The relevant health authorities and senior clinicians at each site granted permission for the study and all medical personnel were given a pamphlet documenting the inclusion and exclusion criteria. Patients were renumerated for transport costs if they came for outpatient visits after discharge from hospital and all patients were given refreshments at each interview.

4.4 Neuropsychiatric measures

4.4.1 Measurement Selection

A combination of a DSM-IV-based semi-structured psychiatric interview and formal psychiatric and psychological measures were selected to gain as complete an understanding of the characteristics of HIV-psychosis and HIV-mania as possible. Most of the neuropsychiatric diagnostic measures were categorical but often contained continuous components. The choice of measures was primarily determined by three factors: reliability, validity and feasibility (228). No measure is perfect in all respects, particularly when the nosology of the measured phenomena is poorly delineated as is the case in HIV-psychosis and HIV-mania. The validity of measures is profoundly affected by language, culture and educational factors, as well as other less obvious confounders such as the perceptions of the interviewer and interviewee towards the interview (228;229). Following a review of the literature and e-mail discussions with the authors of many neuropsychiatric instruments, I held meetings with linguists, translators and mental health professionals fluent in English, Afrikaans and Xhosa, who assisted with the selection of the instruments.

4.4.2 Semi-structured psychiatric interview

The semi-structured interview consisted of a detailed history, from multiple sources and repeated mental state examinations. The findings were documented in detail to ensure that information not captured by the formal instruments would still be documented. Demographic information, including information with regard to risk factors for contracting HIV was recorded. Each patient was interviewed on several occasions in order to gain a detailed account of their clinical features. Details concerning past psychiatric histories were recorded with particular attention being paid to whether the onset of symptoms was before or after other stigmata of advancing HIV disease. Behavioural disturbance was defined as socially and culturally inappropriate behaviours and included behaviours such as agitation, disinhibition, intrusiveness, verbal threats and aggression. A separate variable measured the presence or absence of aggression alone.

4.4.3 The Expanded Mini-International Neuropsychiatric Interview

The purpose of making DSM-related diagnoses was to determine which diagnoses, other than those due to a medical condition, would have been made if it was not assumed that HIV was aetiologically related to the clinical presentation. DSM-IV diagnoses were examined after the Latent Class Analysis to determine how patients' symptoms in different clusters related to primary diagnostic categories. The Expanded Mini-International Neuropsychiatric Interview (MINI-Plus) is a structured neuropsychiatric interview used to standardise data collection. It is compatible with the ICD 10 and DSM-IV and is able to capture sub-syndromal variants (230). It has been designed by psychiatrists for use in clinical research and is more detailed than the original MINI (230;231). The format is less complex than other longer interviews, such as the Structured Clinical Interview for DSM-IV (SCID) (135), which are difficult to administer cross culturally in psychotic medically ill patients due to factors such as difficulty in understanding sentence structure, distractibility and fatigue. The Composite International Diagnostic Interview (CIDI) (232) is designed for use by lay people and was not detailed enough for the purposes of this study. There is good concordance between the MINI-Plus, the SCID and the CIDI with the MINI-Plus having very good sensitivity and specificity compared to the longer instruments (230;231;233;234).

The MINI-Plus is user-friendly, allows for co-morbidity and is modularised allowing for the use of relevant components directed by screening questions, but does not have a cognitive component. Compared to some other instruments that are very expensive, the authors provide it free of charge. It has good inter-rater and retest reliability (230;231). Additional questions to expand the section on psychotic symptomatology were developed using the MINI-Plus format. The authors of the MINI-Plus gave permission to use it and it was translated into Xhosa and Afrikaans. Although the MINI-Plus allows for gathering information from other sources, patients' self-reports are the main source of information.

It was not possible to use the MINI-Plus on 16 patients, and the diagnosis was then based on the semi-structured interview and collateral information using the DSM-IV diagnostic criteria. Reasons for not being able to use the Mini-Plus included patients not being able to give consistent accounts, distractibility, cognitive impairment and thought disorder. The MINI-Plus was incomplete in two patients who died. Although it would have been possible to use the MINI-Plus at a later stage for many of the patients with advanced HIV disease, because of ongoing contact with the study through ART, this was not done as this was not possible for patients with early HIV or HIV-negative patients.

4.4.4 HIV Dementia Scale and International HIV Dementia Scale

The HIV Dementia Scale (HDS), developed by Power *et al.* in 1995 (212), has been useful as a screen for HIV-related cognitive impairment as an alternative to the mini-mental state examination as the latter was designed to detect cortical rather than sub-cortical dementia (Appendix A1) (136;235). The HDS is a brief sensitive screening instrument used to identify patients at risk of sub-cortical dementias such as HIV dementia and sub-cortical ischaemic vascular disease (211;236). There have, however, been criticisms of the use HDS in developing countries because of its potential educational and cultural bias. This particularly applies to the alphabet writing, cube copying and anti-saccadic eye movement subtests (211). Sacktor *et al.* (211) have attempted to rectify this and have developed the International HIV Dementia Scale (IHDS) (Appendix B1). This test excludes the anti-saccades and uses subtests of motor and psychomotor speed rather than the alphabet and cube copy time subtests. Sacktor *et al.* evaluated the IHDS in HIV-positive people in the United States and Kampala, Uganda. They compared the IHDS to standard neuropsychological tests and reported it to be a useful screening test for HIV-D in the industrialised and developing world. Its limitations are that it is not useful for detecting minor cognitive impairment, that it cannot be used to grade the stages of dementia and that its vulnerability to practice effects have not been determined (211). The maximum score for this test is 12 and the US cohort with a dementia scored a mean of 10.6 whereas those with dementia scored a mean of 9.3. In a Ugandan cohort, the sensitivity was 80% and the specificity 55% using a cut-off of less

than or equal to 10 for abnormal performance (211). Although the area under the curve analysis suggested that a cut-off of less than or equal to 9.5 would maximise the sensitivity and specificity of this test, the sensitivity would then only be 71% which would result in a significant false-negative rate which is undesirable in screening instruments (211). Both the HDS and the IHDS were translated and back-translated into Afrikaans and Xhosa.

4.4.5 The Delirium Rating Scale and the Delirium Rating Scale-Revised–98

Both the Delirium Rating Scale (DRS) and the Delirium Rating Scale-Revised–98 (DRS Revised–98) (R-98) were used in this study (Appendices C and D) (54;237). As discussed in Chapter two, the diagnostic conceptualisation of delirium has changed over the past 20 years resulting in a considerable difference between the DSM III and current thinking that will be reflected in the DSM-V (58). The DRS and DRS (R-98) reflected these changes (58;237). The DRS has been used in patients with dementia as opposed to other scales such as the Confusion Assessment Method (CAM) and has good inter-rater reliability and validity (54;238). The DRS has also been used in hospitalised medically ill patients with AIDS (239). Although there is considerable overlap in the two scales, both are used in this study because of the importance of describing phenomenology as fully and precisely as possible. In most studies, delirious patients score between 20 and 23 on the DRS (54;240), including one in HIV-positive hospitalised patients (239). Others have set cut off points much lower, for example at 10, in studies of geriatric patients with mild to moderate severity of disease as measured by the Brief Psychiatric Rating Scale (BPRS) (51;241).

In the DRS-98, cutoff scores of 17.75 had a 92% sensitivity and 95% specificity when delirious patients were compared to patients with dementia, schizophrenia, depression and "other" psychiatric disorders. The severity of disease as measured by the mean Clinical Global Impression Score (CGI) (242) in the group with schizophrenia was 3.7 (SD=1.7) indicating mild to moderate illness. The mean CGI score for the delirious group was 4.9 (SD=0.9), that is, where a score of 5 indicates serious illness (237). These scales rate fluctuation over minutes to hours, including symptoms worsening at night, but do not

evaluate whether patients fluctuate over days. An additional categorical measure was used to include the presence or absence of fluctuation over a period of more than 24 hours. For this measure, fluctuation was defined as a marked periodic variability in symptoms. For example, a patient presented agitated and psychotic with no affective symptoms on day one, appeared depressed and labile with irritability on days two to four and then displayed affective symptoms but was psychotic and agitated for the next few days. On both scales, the presence of a physical disorder that can be temporally associated with the symptoms is given one to two points depending on the strength of the association. This resulted in patients with early HIV being given 1 point and those with late HIV getting 2 points, thus inflating their scores based on factors other than nosology and symptom severity. The means of both tests were determined with and without this item to determine whether this made any significant difference to the scores.

4.4.6 Movement abnormality assessment scales

Abnormal movements were assessed using three instruments, each of which focuses on different abnormal movements, namely the Barnes Akathisia Rating Scale (BARS) (243), the Abnormal Involuntary Movement Scale (AIMS) (242) and the Simpson-Angus Rating Scale (SARS) (244). All three tests have been extensively used and have good validity and reliability (228). During the pilot study, concerns were raised about the second item (arm dropping) on the SARS as patients consistently had difficulty carrying out this instruction and so this item was removed from the test. A composite categorical evaluation was made for the presence or absence of any movement abnormality over the course of the admission to offset any false negatives that could have arisen as a result of the formal measure being administered on only one visit. This was decided by referring to the formal measures as well as to the clinical notes kept by the research team for ongoing evaluations during the course of the admission. The type of movement abnormality was then stipulated. The presence or absence of catatonia was recorded separately.

4.4.7 The Young Mania Rating Scale

In addition to the MINI-Plus, the Young Mania Rating Scale (YMRS) was used to rate the severity of manic symptomatology in patients presenting with mania (189). The YMRS is a checklist of 11 items and is one the most commonly used mania rating scales and has acceptable reliability and validity although the studies evaluating these parameters involved very small numbers (228). There were difficulties with three items in this test. The first was item three, which rates sexual interest. Patients were reluctant to discuss changes in sexual interest and mild to moderate increases in sexual interest may have been underreported. The more severe forms (which would rate 3 or 4 on a scale of 0 to 4), are based on observation and would therefore have been more accurately reported. Item eight on the scale scores between 0 and 8, with 8 being recorded when patients had delusions or hallucinations. All patients in the study had either delusions or hallucinations and therefore all scored 8 on this item. Item ten (scored as 0 to 4), rated patients' grooming. It was difficult to rate patients accurately as many patients were in hospital attire, while the manner in which others dressed may have been a consequence of poverty rather than of a lack of grooming. Other instruments for rating mania which were considered had similar problems. The YMRS was used in the study as an adjunct rather than as one of the main instruments such as the MINI-Plus. I therefore decided to keep using it to rate the severity of mania and it was determined both with and without the subtests.

4.4.8 Activities of daily living

Patients' capacities for self-care and functioning were assessed by rating the activities of daily living (ADL's). These were divided into basic activities of living covering the domains of bathing, dressing, toilet use, transferring, urine and bowel continence and eating, as described in the Katz Index of Activities of Daily Living Scale (Katz ADL) (245). Based on the parameters in the Katz ADL index, patients' basic ADL scores were rated as being intact, mild to moderately impaired, or severely impaired. The instrumental (advanced) ADL's were also rated as being intact, mild to moderately impaired or severely impaired. They were based on the Lawton Instrumental Activities of Daily Living Scale (Lawton IADL) that assesses domains such as the ability to drive a car or

use public transportation, the ability to shop, prepare meals, do housework, use medication correctly and manage money (246). The seventh domain used in this assessment of being able to use the telephone book was excluded as it was strongly influenced by education.

4.5 Neuropsychological tests

4.5.1 Instrument selection

As HIV-associated dementia is a predominantly sub-cortical disease (197), the neuropsychological instruments chosen for this study focus on the following domains: attention, memory, executive functioning (planning, attention shifting, initiation and abstract thinking), constructional abilities and psychomotor speed. Although the National Institute for Health (NIMH) has suggested that a battery of 25 different neuropsychological tests be used for the neuropsychological assessment of AIDS-related cognitive changes (247), it takes between seven and nine hours to complete, is not well tolerated by patients and is impractical (69). A subtest of tests, termed the MACRO, was developed by Sidtis in 1994 for brevity and repeatability (248). The neuropsychological test battery used in this study was developed in conjunction with a team of senior neuropsychologists (Dr F Hemp and Ms H Thornton) at the University of Cape Town and includes all the subtests in the MACRO but was amended to ensure that all appropriate domains were covered within a cross-cultural context with associated language and educational biases. The grooved pegboard has been widely used in assessing HIV-related cognitive decline and the grooved pegboard non-dominant hand test has been found to be particularly useful in evaluating HIV-D (249-251).

The tests were administered in English. The South African Human Sciences Research Council (HSRC) has standardised the South African Wechsler Adult Intelligence Scale III (SAWAIS III) in South African populations. Over 1000 subjects were tested and the majority spoke English as a second language (252). There is substantial literature to support the administration of the tests chosen for this study in the patients' second language as they have been used extensively in this manner throughout South Africa

(253;254). Although all the patients in this study had some knowledge of English, the battery was adapted according to their English fluency. Vocabulary tests were used to establish the level of fluency. If a patient had poor English fluency, the battery was adapted by leaving out more language intensive tests such as similarities and Rey Auditory Verbal Learning Test (RAVLT) (255;256). A number of tests were administered which have not been included in the analysis as they were found to problematic with respect to language and education. For example, the Mental Alternation Test (which assesses working memory) (257) and the Trail Making Test-Part B (which requires switching from letters to numbers) (255;256) were found to be too education dependent. Another problem was fatigue, particularly in very ill patients. For instance, the Symbol Search Test (which tests visual scanning, attention and cognitive flexibility) requires patients to withstand fatigue had to be removed from the battery (252;258;259). The results were interpreted within the context of the patients' level of fluency and educational level. The neuropsychological battery took approximately two and a half hours to administer. Patients were given the opportunity to have as many breaks as required and the test was often administered in more than one sitting.

The 10-metre walking test, used in the MACRO, was administered at the end of each patient's physical examination. It measures the length of time taken to walk 10 metres, as well as the number of steps taken. Norms for normal adults are a mean time of 6.73 seconds (SD 0.59 seconds, CI 5.55-7.91 seconds) with a median value of 13 steps (range 11-16 steps) (260). The 10-metre walking test was administered in 94 out of a possible 111 patients. Some patients had difficulty walking due to the presence of a peripheral neuropathy, severe parkinsonism or catatonia. The scores of some disinhibited and behaviourally disturbed patients had to be discarded as they danced or skipped the 10-metre length.

Table 4-1 Summary of the neuropsychological instruments

Domain	Test	Description
Memory Executive Functioning	Rey Complex Figure (255;256)	Visuo-constructional ability and visual memory. Examines the ability to construct a complex figure and remember it for later recall. Also evaluates executive functioning relating to planning, problem-solving abilities and motor abilities.
Memory	Rey-Auditory Verbal Learning Test (255;256)	Immediate memory span, verbal learning, short-term and long-term retention, as well as assessing retrieval and learning strategies. It evaluates the ability to learn word lists and is an excellent measure of auditory memory but most patients were reluctant to continue beyond the third trial.
Memory	Digit Span (252;258;259)	Digit forwards assesses attention and verbal memory whereas backwards assesses mental manipulation and working memory. It is not timed and is a scaled score.
Attention	Mental Control (255;256)	A subtest taken from the Wechsler Memory Scale. Detects attention and concentration problems. Only reciting the alphabet and counting backwards from 20 components were useful. Score achieved within a set time is noted.
Attention	Trail Making Test (255;256)	Visual attention, visual scanning, neglect, sequencing and cognitive flexibility. Part A of the trails was more useful as it is less education dependent.
Motor	Successive Finger Tapping (255;256)	Fine motor speed by tapping successive fingers against the thumb. It is a timed test and is very useful in the context of patients with low levels of literacy and where language is a confounder as it is easy to administer, easily understood by the patient and does not have a verbal component.
Motor	Grooved Pegboard (261)	Tests manual dexterity requiring complex visual-motor co-ordination as it measures performance speed of a fine motor task. It is culture fair.
Language	SA-WAIS Vocabulary Test (252;258;259)	Fluency in English. Use to assess patients level of language proficiency and not part of the testing *per se*.

4.5.2 Neuropsychology control group without mental illness

The HIV-negative patients with psychosis on the one hand and the HIV-positive patients with late stage disease and no mental illness on the other served as controls for the two main variables in this study: HIV disease and psychosis/mania. This compensated to some extent for the absence of local neuropsychological norms. The control group was selected from three HIV clinics: Masiphumelele, Gugulethu and Victoria Hospital.

Patients with advanced HIV who were being evaluated for ART were included. Patients were therefore not on ART at the time of evaluation. The late HIV-positive patients with no mental illness were matched to the patients in the late HIV-positive group with psychosis /mania according to age (within 5 years), race, language, education (exact matches) and gender. They were interviewed using as semi-structured interview and the MINI-Plus screening questionnaire. Patients with mental illness or cognitive impairment were not included in the control group. The neuropsychological findings are useful in the context of comparing groups rather than viewing them in isolation.

4.5.3 Patients who were unable to attempt neuropsychological testing

Apart from language and education, some patients with severe cognitive impairment were too ill to be assessed when they were first admitted to hospital and referred to the study. Assessments were conducted as soon as possible but this time frame varied depending on symptom severity. The true baseline of these patients' cognitive function with respect to formal neuropsychological assessment and screening tests such as the International HIV Dementia Scale could therefore not be recorded. This particularly applied to patients with advanced HIV disease, some of whom could not have baseline neuropsychological assessments conducted as they improved only after antiretroviral treatment had been initiated. This was not reflected in the results if one only considered the scores. Patients were therefore rated by the neuropsychologist based on the results of the testing, taking into account those patients who were not able to attempt testing at all, as being normal to mild or moderate to severe cognitive impairment. This global measure of cognition was very useful as it reflected the cognitive ability of all the patients including those who were too ill to be tested.

4.6 Statistical Analysis

4.6.1 Stages of statistical analysis

The statistical analysis had three main stages:

1. the description of the three selection groups (Late HIV-positive / Early HIV-positive / HIV-negative) and analysis of differences between these groups;
2. the development of a Latent Class Analysis (LCA) model to identify any patterns in the distribution of psychiatric symptoms underlying the three groups; and
3. the description and analysis of the underlying (latent) classes of psychiatric symptoms, according to other participant demographic characteristics, features of HIV disease, and psychiatric symptoms not used to define the latent classes.

4.6.2 Description and analysis of the selection groups

The unit of comparison chosen for these analyses is the selection group (late HIV, Early HIV, HIV-negative). Means (with standard deviations) and medians (with interquartile ranges) were used to describe normally and non-normally distributed continuous data respectively; percentages were used to describe categorical data. Normally distributed continuous variables were compared using Student's t-Tests (for comparing two groups) or Analysis of Variance (for comparison involving more than two factors) and non-normally distributed continuous variables were compared using Wilcoxon Rank-Sum tests (for two-way comparisons) or Kruskall-Wallis tests (for more than two-way comparisons. Categorical variables were compared using Fisher's Exact (Hypergeometric) tests. The Fisher's Exact Test was preferred over the chi-square test as it determines true probability, is more conservative, and more suited to small sample sizes. The chi-square is a computationally simpler asymptotic test suitable for large sample sizes where results approximate results using the Fisher's Exact Test. As it was easy to compute using STATA (262), there were no disadvantages to using the Fisher's Exact Test in this context even though most of the cell sizes were greater than five (263; 264). All statistical tests were two-sided at alpha (the Type 1 error rate = 0.05). Throughout, global comparisons (2 x N) were preferred to two-way (2 x 2) comparisons, to reduce the overall number of statistical comparisons made. Because there was the

potential to make many statistical comparisons with a relatively small sample size, it was necessary to limit the number of statistical comparisons (264-266). Therefore no corrections for multiple statistical comparisons were used.

4.6.3 Latent Class Analysis

Latent Class Analysis (LCA) is a cluster analytic method used primarily for categorical variables, based on maximum likelihood estimation (using similar statistical principles as logistic regression modelling). Given observed data, LCA can be used to infer a set of unobserved (latent) classes around which observations are clustered, and to assign individual observations to the most appropriate latent class. Cluster analytic methods are being used more often in psychiatry to help identify underlying symptom clusters and improve diagnostic validity. For instance, it has been used to identify dimensions and classes of psychosis, depression and delirium tremens (17;267;268). Trzepacz (52) used principal components analysis, a cluster analytic method, used primarily for continuous variables, to identify relationships between items on the delirium rating scale. She identified a single underlying dimension that could be divided into two components: one comprising temporal onset of symptoms, perceptual disturbances, hallucinations and symptom fluctuation and the other delusions, psychomotor behaviour, cognition and sleep-cycle disturbance.

In this study, a series of latent class models (LCMs) were developed using the LEM (log-linear and event history analysis with missing data using the EM (event maximization) algorithm) statistical programme (269). The observed (manifest) variables and cutpoints considered for inclusion in the LCA analysis were selected based on a review of the literature (Chapter 3), the measures available in this study and clinical experience. For instance, patients with mania and psychosis commonly experience mild lability, attentional deficits, problems with registration and minor sleep disturbances. Furthermore, as many the patients in the study sample were on classical neuroleptics, mild deficits in motor speed and psychomotor speed were anticipated. As discussed in Chapter 2, mild cognitive deficits have been documented in patients with bipolar disorder and schizophrenia. It was therefore important to distinguish severe impairment from mild

impairment in order to improve specificity. Clinical experience, together with the literature review, suggested that these symptoms were more severe in patients with possible HIV-associated psychosis and dementia. The variables initially considered were:

- the duration of symptoms: both comparing days-weeks versus months-years, and days versus weeks-years
- depressive symptoms
- manic symptoms
- depressive and manic symptoms
- suicidal ideation
- fluctuation, including fluctuation over days versus fluctuation over weeks or no fluctuation
- behavioural disturbances
- marked irritability, defined as irritability with either behavioural disturbances or violence/aggression
- multiple delusions (analysed at cutpoints for >1 or >2 different types)
- multiple hallucinations (analysed at cutpoints for >1 or >2 different types)
- catatonia
- episode/s of disorientation
- movement abnormality/ies
- sleep disturbances
- lability
- irritability
- severe lability (based on item 9 on the DRS, comparing scores of 0/1 with scores of 2/3)
- sleep-wake disturbances (based on DRS- R-98 Item1, comparing scores of 0/1 with scores of 2/3)
- severe thought process disturbances (based on DRS- R-98 Item 6, thought process abnormalities, comparing scores of 0/1/2 with scores of 3)
- severe attention deficits (based on DRS-R-98 Item 10, attention, comparing scores of 0/1/2 with scores of 3)

- motor speed disturbances (based on International HIV Dementia Scale Item 2, comparing scores of 0/1 with scores of 2/3)
- psychomotor speed disturbances (based on International HIV Dementia Scale item 3, comparing scores of 0/1/2 with scores of 3)
- the total score for the International HIV Dementia Scale, with cutpoints at 8 and 9 evaluated separately
- registration (based on International and Original HIV Dementia Scale Item 1, comparing scores of 0/1/2/3 with scores of 4 taken from the original version and the international version does not score this item).

Different model parameters (combinations of manifest variables, numbers of latent variables and numbers of latent classes within each variable) were examined through the construction of separate models in LEM (269). The subset of variables included in the analysis was selected through multiple iterations of a model with one latent variable with two classes. Model fit was determined based on:

- the likelihood ratio test (G^2) for overall goodness-of-fit
- the model chi-square statistic summarising the amount of variability in the manifest variables that is not explained by the latent classes (compared to a critical point chi-squared value based on the degrees of freedom of the model, itself a function of the number of parameters estimated)
- the Wald statistic and R-squared entropy statistic were used to guide individual parameter selection

For selection of individual variables retained in the model, items which were likely to be intercorrelated (such as sleep disturbances and sleep-wake disturbances) or items which could be defined using different criteria (for example, multiple delusions defined as >1 vs. >2 different types) were considered in separate models (with identical covariate sets); the preferred item was selected based on overall goodness-of-fit as well as individual Wald statistics. Additional goodness-of-fit analyses, including the ideal number of latent variables and classes per variable, were conducted using parsimony indices based on |-2*log(likelihood)| statistics, in particular the Akaike Information Criterion (AIC).

Using these model-building strategies, the best-fit model was found to be one with one latent variable comprised of two classes. The best-fit model was predicted by 12 latent variables.

4.6.4 Description and analysis of the underlying (latent) classes

The two latent classes were then compared according to participant demographic, psychiatric and HIV-related factors, using the descriptive and analytic approaches described above. For this, it is clearly inappropriate to compare latent classes according to the phenomena used to describe them. Latent classes were also compared according to their DSM-IV diagnoses, either through the MINI or from review of psychiatric notes and evaluation using DSM-IV criteria.

4.6.5 Pilot cohort study

Patients' CD4+ counts, viral loads and IHDS scores at baseline and at six months were documented for each patient and compared using the Paired T-Test.

Chapter 5. Results

5.1 Introduction

The results of the study will be discussed in six sections, covering:

1. a brief description of the patients who were excluded from the study sample
2. a description of the three selection groups (late HIV+ / Early HIV + / HIV-) and analysis of differences between these groups
3. the development of a Latent Class Analysis (LCA) model to identify any patterns in the distribution of psychiatric symptoms underlying the three groups
4. the description and analysis of the underlying (latent) classes of psychiatric symptoms, according to other participant demographic characteristics, features of HIV disease, and psychiatric symptoms not used to define the latent classes
5. the neuroimaging findings, including computerised tomography (CT) scan and magnetic resonance imaging (MRI) results
6. a description of the six month follow-up results for patients in the cohort study and analysis of differences for participants from baseline to six months

5.2 Details of the sample

The total sample consisted of 285 patients presenting with manic or psychotic symptoms, of whom, 171 were excluded as outlined below. Three patients were enrolled in the study but were unable to complete the assessment as they had been discharged and had either moved away from Cape Town or were unable to return for follow up as they were not able to get time off work. The study sample therefore comprised 111 patients, 52 patients with late (advanced) HIV disease, 29 with early HIV disease and 30 who were HIV-negative, all of whom were recruited between October 2004 and March 2006.

The patients were screened between October 2004 and April 2006. The number of patients referred to the study who met the exclusion criteria decreased as the referring clinicians became more aware of the inclusion and exclusion criteria. Following screening assessments, 171 patients were excluded from the study including 34 HIV-negative patients and 137 HIV-positive patients.

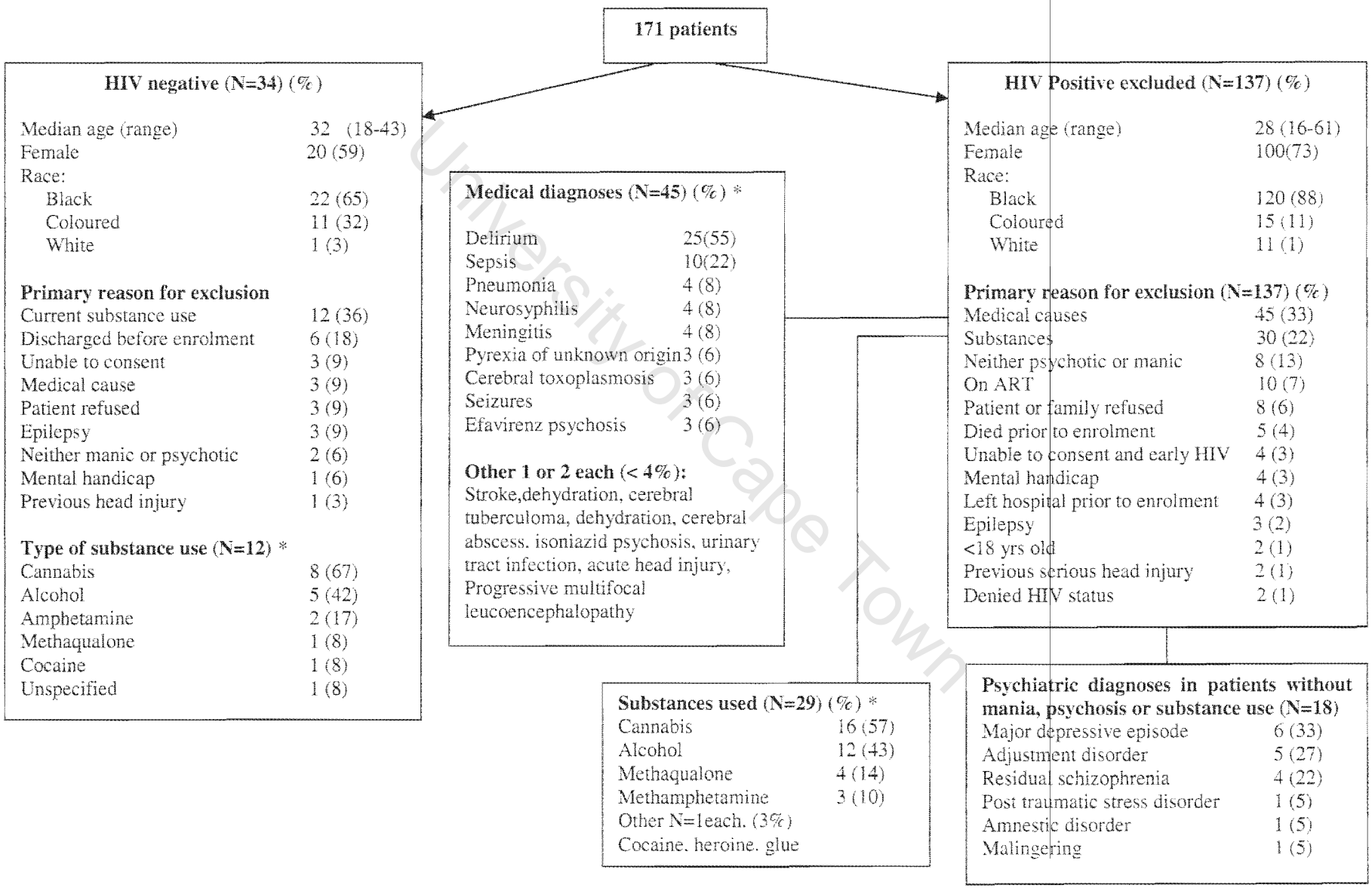
Routine HIV testing was not occurring at the time of the study, resulting in most HIV-negative patients being tested because clinicians suspected that they may be HIV positive. Figure 5.1 summarises the characteristics of patients who were excluded. The median ages of the HIV-positive and negative groups are similar, with the HIV-negative group in a slightly older (32 vs.28) age range. There were 100 women in the HIV-positive group (73%) as opposed to 20 in the HIV-negative group (59%). With respect to race, 120 HIV-positive patients were black (88%) as opposed to 22 of the HIV-negative patients (65%).

The most common reason for exclusion in the HIV-negative group were current substance abuse (N=12, or 36%) and patients being discharged prior to enrolment (N=6, or 18%). The latter occurred when field staff were informed of the patients' status late in their admission or when the patients discharged themselves from hospital early. Only three patients (9%) in this group were excluded for acute medical reasons and three (9%) for a history of epilepsy. With respect to the patients who were using substances, the most common substance of abuse was cannabis (N= 8) followed by alcohol (N=5).

Patients in the HIV-positive group were more likely to be excluded for acute medical reasons, with 45 patients (31%) being so excluded. Of these patients, 40% (N=18) had more than one medical reason for exclusion. Delirium occurred in 25 patients (55%), followed by septicaemia in 10 patients (22%). Other causes included pneumonia (N=4), meningitis (N=4) and efavirenz psychosis (N=3). Current substance abuse was reported by 30 patients (22%) and was the second most common reason for the exclusion of HIV-positive patients. The most common substance of abuse was cannabis (N=16, or 57%) followed by alcohol (N=12, or 43%).

A total of 15% of patients in the HIV-positive group were neither manic nor psychotic. This arose as clinicians were initially unfamiliar with the exclusion criteria and referred the patients to the study because they were HIV-positive. Within this group, six patients (33%) had a major depressive episode, five patients had an adjustment disorder and four patients had residual schizophrenia. There were 10 patients (7%) who were already on antiretroviral therapy and eight patients (6%) or their families refused to participate in the study. Two patients denied that they were HIV-positive, even when apsychotic, and refused to participate, four patients died before they could be enrolled and three patients had a history of epilepsy. Of those patients who were excluded, 46% had advanced HIV/AIDS, 28% had early HIV and 26% had not yet been staged.

Figure 5-1 Patients excluded from the study sample



* *More than one medical condition or substance occurred in some patients*

5.3 A description and analysis of the three selection groups

Patients were selected by group in the following manner: late HIV-positive (late HIV+), early HIV-positive (early HIV+) and HIV-negative (HIV-). The initial sample included 114 patients, but was reduced to 111 patients as three patients withdrew from the study (they were discharged prior to their assessments being completed and were unable to come for follow up due to work commitments or because they were transferred to hospitals out of Cape Town). On initial assessment, there were 44 patients in the late HIV-positive group and 37 patients in the early HIV-positive group. However, after formal staging and considering laboratory investigations, such as CD4+ counts and viral loads, there were 52 patients in the late group and 29 in the early group. The HIV-negative group consisted of 30 patients.

The numbers of patients in each group reflects the practice in Cape Town hospitals whereby patients are only tested for HIV if attending clinicians find clinical grounds to suspect that they may be HIV positive. The reported sample size (N) varies in the tables presented in this chapter, particularly with respect to the personal demographic information, where some patients were not able to give an accurate account and collateral information would either be inappropriate (such as for sexual risk questions) or was not available. The other main area where N varies is in the neuropsychology testing. As discussed in chapter four, it was not possible to test some patients as they were not able to attempt the testing due to problems with language and education or because of disease severity. When the N varied, it was noted in the text and tables.

5.3.1 Sources of information

Serial psychiatric examinations, including mental state examination were conducted for each patient |(mean 5.3 (SD=2.3) examinations, median 5 (IQR 4-6) examinations|. Numerous sources were used to provide as much information as possible. As described in Table 5.1, the mean total number of sources of information for patients with late HIV was 5.1 (SD=0.92) sources, whereas it was 3.9 (SD=0.95) and 3.7 (SD=0.60) sources for those with early HIV and the HIV-negative patients respectively The patients with late

HIV disease who were eligible for ART attended the Desmond Tutu HIV Centre, and the staff there provided additional collateral information thus resulting in a slightly higher mean in that group.

Table 5-1 Sources of information, by selection group

	Late HIV N=52		Early HIV N=29		HIV-Negative N=30		p-value
	N	%	N	%	N	%	
Patient	52	100	29	100	30	100	1.000
Family	29	56	14	48	10	33	0.153
Referral	34	65	11	38	12	40	0.021
Ward notes and personnel	52	100	29	100	30	100	1.000
Nursing personnel	49	94	27	93	29	97	0.877
Desmond Tutu HIV Centre	47	90	2	7	0	0	<0.001

5.3.2 Socio-demographic information

The ages of patients across the three groups were similar, with the median age being 30 (IQR 25–34.5) years in the late HIV group as opposed to 29 (IQR 24–35) years in the early HIV group and 34 (IQR 24–38) years in the HIV-negative group. The socio-demographic characteristics are described in Table 5.2. With respect to gender, 44 (85%) of the patients with late HIV disease, 22 of those with early disease were female (75%) as opposed to 19 of the HIV-negative patients (63%), but the differences were not significant (p=0.082). There was no significant difference with regard to education, employment, or income, but 47 of patients in the late HIV group (90%) and 27 in the early group (93%) were Black, as opposed to 57% in the HIV-negative group (p=0.001). This difference was reflected across language groups, where 44 and 27 of the patients in the late and early HIV group respectively were Xhosa speaking (86% and (93%) as opposed to 17 (57%) in the HIV-negative group (p=0.009).

Table 5-2 Socio-demographics characteristics, by selection group

	Late HIV N=52		Early HIV N=29		HIV-negative N=30		p-value
	N	%	N	%	N	%	
Female	44	85	22	75	19	63	0.082
Education							
None/illiterate	1	2	0	0	0	0	0.235
Grades 1–7	17	33	10	34	10	33	
Grades 8–11	28	54	12	41	9	30	
Grade 12 (completed schooling)	4	8	3	10	6	20	
Technical education/college	2	4	4	14	4	13	
University	0	0	0	0	1	3	
Employment							
Employed	6	12	4	14	5	19	0.894
Unemployed	31	61	18	62	14	52	
Unemployed on grant	14	27	7	24	8	30	
Race							
Black	47	90	27	93	17	57	0.001
Coloured	5	10	2	7	11	37	
Other	0	0	0	0	2	7	
Language							
English	2	4	0	0	3	10	0.009
Afrikaans	4	8	2	7	9	30	
Xhosa	44	86	27	93	17	57	
Other	1	2	0		1	3	
Income (in Rand)							
1–499	5	17	5	22	2	10	0.571
500–999	10	33	7	30	7	33	
1000–1999	8	27	5	22	4	19	
2000–4999	6	20	5	22	3	14	
5000+	1	3	1	4	5	24	

5.3.3 Sexual orientation and behaviour

There were no significant differences across the groups with respect to sexual orientation and behaviour (Table 5.3). The majority of patients in the sample were heterosexual and the median age of sexual debut was at 15.0 (IQR 14-19) years for patients with late HIV, 17.5 (IQR 15-18.5) years for patients with early HIV and 16.0 (IQR 15-20) years for HIV-negative patients. With respect to the number of sexual partners or condom use, 19 patients with late HIV (56%), 14 with early HIV (58%) and 16 of the HIV-negative patients (62%) had less than five sexual partners. The number of patients having had 10 sexual partners was 8 in the late HIV group (24%), 8 in the early HIV group (33%) and 7 in the HIV-negative group (27%). There was also no significant difference with regard to condom use with 20 patients with late HIV (59%), 10 of patients with early HIV (42%) and 15 of HIV-negative patients (56%) reporting that they had never used condoms.

Table 5-3 Sexual orientation and behaviour, by selection group

	Late HIV N=52		**Early HIV N=29**		**HIV-Negative N=30**		**p-value**
	N	**%**	**N**	**%**	**N**	**%**	
Sexual orientation:	42		28		29		
Heterosexual	40	96	27	96	29	100	0.894
Homosexual	1	2	1	4	0	0	
Bisexual	1	2	0	0	0	0	
Lifetime number of sexual partners	34		24		26		
<5	19	56	14	58	16	62	0.908
5–9	7	21	5	21	3	12	
10	8	24	5	21	7	27	
Condom use:							
Regular	6	18	6	25	5	19	0.775
Inconsistent	8	24	8	33	7	26	
Never	20	59	10	42	15	56	

5.3.4 HIV characteristics

The early HIV-positive group was made up of patients with WHO stage 1 and 2 disease (Table 5.4). There were four patients in the late group who had either WHO stage 1 (two patients) or WHO stage 2 (two patients) disease clinically but had CD4+ counts below 200 cells/mm^3. The median CD4+ count was 89 cells/mm^3 (IQR 36–172) in the late HIV group and 390 cells/mm^3 (IQR 301–622) in the early group, with the median viral loads being log 5.08 (IQR= 4.40–5.65) copies/ml and log 4.11 (IQR= 3.11–4.58) copies/ml in the late and early group respectively.

Table 5-4 HIV disease characteristics, by selection group

		Late HIV N=52		Early HIV N=29		p-value
		N=52	**%**	**N=29**	**%**	
WHO stage:	1	2	4	18	62	<0.001
	2	2	4	11	38	
	3	24	46	0	0	
	4	24	46	0	0	
		Median	**IQR**	**Median**	**IQR**	
Median CD4+ count		89	36–172	390	301–622	<0.001
Median HIV viral load (log, copies/ml)		5.08	4.40–5.65	4.11	3.11–4.58	<0.001

5.3.5 Medical co-morbidity

Medical findings by selection group are tabulated in Table 5.5. These findings reflect the domains used by the WHO for the HIV staging and indicate the high medical morbidity in this population. Co-morbidity in the patients with late HIV was dominated by pulmonary tuberculosis (PTB) which had been diagnosed in 71% of patients within the preceding two years.[3] Two of the patients with early HIV and one HIV-negative patient had had PTB more than 2 years before evaluation. In the late HIV-positive group, six patients had extra-pulmonary tuberculosis (12%) and nine patients had either primary or

[3] Pulmonary tuberculosis (PTB) is not used as a staging criterion in patients who have had TB more than two years prior to evaluation. This is because of the high prevalence of PTB in sub-Saharan Africa and is in accordance with the WHO interim staging for Africa (112).

secondary syphilis (17%). Many patients were unable to quantify how much weight they had lost and the reported findings with respect to weight loss are probably inaccurate. Within the HIV-negative group, one patient had a sexually transmitted infection, two patients had some cervical lymphadenopathy and one patient had lost more than 10 kg in weight.

Table 5-5 Medical findings, by selection group

Medical findings	Late HIV N=52		Early HIV N=29	
	N	%	N	%
Pulmonary tuberculosis in previous 24 months	37	71	0	0
Pulmonary tuberculosis > 24 months ago	1	2	2	7
Extrapulmonary TB	6	12	0	0
Oral candidiasis	32	62	0	0
Oesophageal candida	3	6	0	0
Oral hairy leukoplakia	14	27	0	0
Weight loss <10 kg	8	15	5	18
Weigh loss >10 kg	12	23	0	0
Severe gingivitis	12	23	4	14
Fungal infection of nails or skin	10	19	1	4
Sexually transmitted disease other than syphilis	7	13	1	4
Primary syphilis	1	2	0	0
Secondary syphilis	2	4	2	7
Papular pruritic eruptions	27	52	0	0
Seborrhoeic dermatitis	3	6	3	11
Generalised lymphadenopathy	37	71	15	54
Cytomegalovirus retinitis	3	6	0	0
Peripheral neuropathy	10	19	0	0
Oral ulcers	3	6	1	4
Drug induced hepatitis	2	4	0	0
Anaemia	20	38	2	7
Leucopaenia	3	6	0	0
Pancytopaenia	1	2	0	0
Probable Karposi Sarcoma	2	4	0	0
Herpes zoster	5	10	0	0

5.3.6 Family and personal history of psychiatric illness

HIV-negative patients were more likely to have a family history of psychiatric illness, although this was marginally significant (p=0.060) (Table 5.6). The difference in previous admission rate was significant with 18 patients with early HIV (62%) and 18 HIV-patients (60%) having had a previous admission as opposed to 5 patients with late HIV (10%) reporting having had a psychiatric admission prior to the onset of AIDS (p<0.001).

Table 5-6 Personal and family history, by selection group

	Late HIV N=52		Early HIV N=29		HIV-Negative N=30		p-value
	N	%	N	%	N	%	
All previous admissions	15	29	18	62	18	60	0.003
Previous admissions excluding those occurring after stigmata of AIDS had developed	8	15	18	62	18	60	<0.001
Family history of psychiatric illness	5	10	6	21	9	30	0.060

5.3.7 Duration of symptoms prior to admission and duration of hospital stay

As described in Table 5.7, although patients with late HIV disease were more likely to present acutely over a period of days, 26 of patients in this group (50%) presented sub-acutely over weeks. HIV-negative patients were more likely to present over months (17, or 57%) rather than weeks or days. All patients in the sample had psychotic symptoms. There was no difference in the duration of admission across groups with the median duration of admission being 58 days (IQR 33–106) for patients with late HIV, 58 days (IQR 38–104) for those with early HIV and 51 days (IQR 33–103) for the HIV-negative patients.

5.3.8 Psychiatric symptoms

All the patients in the sample had at least one psychotic symptom and manic symptoms were common across all three groups, occurring in 29 patients with late HIV (56%), 19 patients with early HIV (66%) and 23 in HIV-patients (77%). The psychiatric symptoms by selection group are described in Table 5.7. Although there was a trend toward increased prevalence of manic symptoms from the late HIV-positive group to the HIV-negative group, it was not significant (p for trend=0.085). Depressive symptoms occurred in 34 patients in the late HIV-positive group (65%) as opposed to 11 in the early HIV-positive group (38%) and 9 in the HIV-negative group (30%). Here the trend towards the increased prevalence of depressive symptoms from the HIV-negative group to the HIV group was significant (p for trend = 0.001). There was no significant difference across the groups with respect to patients having mixed affective states (manic and depressive symptoms) (p=0.876). There was also no significant difference across groups with respect to suicidal ideation (p=0.125) or intent (p=0.144), although HIV-positive patients were more likely to have suicidal ideation with 25 patients with late disease (48%), 14 of patients with early HIV disease (48%) and eight patients (27%) of the HIV-negative patients reporting suicidal ideation (p for trend=0.079). Lability, but not irritability, was more prevalent in the late HIV group with 37 patients (71%) exhibiting affective lability compared to 13 in the early HIV group (45%) and 15 in the HIV-negative patients (50%).

Patients with late HIV were more likely to be behaviourally disturbed (with symptoms such as agitation, disinhibition, intrusiveness or socially inappropriate behaviour) (N=49, or 94%), compared to the other two groups, with 23 of patients in the HIV-negative group (79%) and 22 of patients in the HIV-negative group (77%) having behavioural disturbance (p=0.036, p for trend= 0.021). This did not translate into violent or aggressive behaviour, where patient with late HIV were less likely to be aggressive than the other two groups (p=0.686).

Delusions were highly prevalent, occurring in all but two patients (both with late HIV). Persecutory delusions were documented in 46 patients with late HIV (88%), 28 with early HIV (97%) and 26 of the HIV-negative patients (87%) (p=0.499). There were, however significant differences with respect to the prevalence of grandiose and religious delusions with a trend to increased prevalence from late HIV to HIV negative for both parameters. Grandiose delusions occurred in 19 patients with late HIV (35%), 15 patients with early HIV (52%) and 21 of the HIV-negative patients (70%) (p for trend=0.004). Religious delusions were documented in seven patients (13%) with late HIV, 9 with early HIV (31%) and 13 of the HIV-negative patients (43%). There was a trend across the means scores of different types of delusions. The late HIV-positive group had fewer delusions [mean of different types of delusions: 1.7 (SD 1.00)] than those with early HIV disease [mean of different types of delusions: 2.1 (SD 0.98)] and HIV-negative patients were found to have the most delusions [mean of different types of delusions: 2.5 (SD 0.90)] (p=0.001).

Hallucinations were very common across all groups, occurring in more than 80% of patients overall. There was a trend towards decreasing prevalence of visual and tactile hallucinations from the late HIV group to the HIV-negative group (p for trend = 0.004 and 0.014 respectively). Patients with late HIV disease were most likely to have visual hallucinations (N= 31, or 60%) followed by those with early disease (N=13, or 45%) and then the HIV group (N=8, or 27%) (p=0.015). Tactile hallucinations were documented in 14 patients with late HIV (27%), three with early HIV (10%) and one HIV-negative patient (3%). There was a trend across the group mean scores towards a decrease in the prevalence of the different types of delusions. In this respect, patients in the late HIV-positive group had a mean of 1.87 (SD=1.04) different types of hallucinations, those with early HIV had a mean of 1.52 (SD=0.78) and HIV-negative patients a mean of 1.20 (SD= 0.89).

Of those patients with late HIV disease, 27 had symptom fluctuation (52%), as opposed to 3 in both the other groups (10%) ($p< 0.001$). Patients with late HIV were more likely to report memory impairment, (24, or 49%), which was uncommon in the other two groups which comprised one patient with early HIV and two HIV-negative patients) ($p<0.001$). Patient in the late group were also significantly more likely to have episodes of disorientation (N=31, or 60%) than those in the early HIV group (N= 6, or 21%) or the HIV-negative patients (N=5, or 17%), with a trend towards decreasing prevalence from the late group to the negative group (p for trend <0.001).

Table 5-7 Psychiatric symptoms, by selection group

	Late HIV N=52		Early HIV N=29		HIV-Negative N=30		p-value
	N	%	N	%	N	%	
Duration of symptoms:							
Days	12	23	2	7	3	10	0.002
Weeks	26	50	13	45	6	20	
Months	14	27	11	38	17	57	
Years	0	0	3	10	4	13	
Affective symptoms:							
Depression	34	65	11	38	9	30	0.003
Mania	29	56	19	66	23	77	0.171
Depressive and manic symptoms	13	25	6	21	6	20	0.876
Lability	37	71	13	45	15	50	0.037
Irritability	38	73	21	72	22	73	0.999
Suicidal ideation	25	48	14	48	8	27	0.125
Suicidal intent	12	23	12	41	6	20	0.144
Behavioural disturbance	49	94	23	79	22	77	0.036
Aggression	27	52	18	62	17	57	0.686
Any delusions present	50	96	29	100	30	100	0.497
Types of delusions							
Persecutory	46	88	28	97	26	87	0.499
Grandiose	19	37	15	52	21	70	0.015
Religious	7	13	9	31	13	43	0.008
Somatic	5	10	1	3	6	20	0.116
Erotomanic	1	2	0	0	2	7	0.443
Jealousy	1	2	1	3	2	7	0.697
Guilt	4	8	3	10	2	7	0.821
Reference	4	8	3	10	2	7	0.821
Nihilistic	1	2	0	0	0	0	0.999
Mean number of different types of delusions (SD)	1.7 (1.00)		2.1 (0.98)		2.5 (0.90)		0.001
Any hallucinations present	47	90	27	93	25	83	0.529
Types of hallucinations							
Visual	31	60	13	45	8	27	0.015
Auditory	44	85	27	93	24	80	0.372
Tactile	14	27	3	10	2	7	0.043
Olfactory	5	10	1	3	1	3	0.539

	Late HIV N=52		Early HIV N=29		HIV-Negative N=30		p-value
Somatic	2	4	0	0	1	3	0.796
Gustatory	1	2	0	0	0	0	0.999
Mean number of different types of hallucinations (SD)	1.87 (1.04)		1.52 (0.78)		1.20 (0.89)		0.001
Symptom fluctuation	27	52	3	10	3	10	<0.001
Episode/s of disorientation noted during admission	31	60	6	21	5	17	<0.001
Sleep abnormality	42	81	20	69	20	67	0.276
Memory impairment on history	24	49	1	3	2	7	<0.001

5.3.9 Sub-group analysis of psychiatric symptomatology

The analysis of psychiatric symptoms was repeated, limited to Xhosa-speaking patients to control for possible cultural or language factors that may be biasing the results (Appendix E). In this analysis, there were 42 patients in the late HIV-positive group, 26 in the early HIV-positive group and 17 in the HIV-negative group. The relatively small sample size accounts for the reduction in significance for some parameters, but there were no data to suggest that language or culture may be biasing any of the findings. The analysis was also repeated by selection group, and was limited to patients with first presentation of manic or psychotic symptoms because patients in the HIV-negative group, and to a lesser extent in the early HIV group, were significantly more likely to have had a previous psychiatric episode. It was possible that the symptoms of a first episode psychosis or mania, irrespective of cause, may differ from the presentation in subsequent episodes. The numbers in the second analysis were small, with 37 patients being in the late group, 11 in the early group and 12 in the HIV-negative group (Appendix F). There do not, however, appear to be any factors in this analysis that might be driving the differences between groups.

5.3.10 Psychotropic medication

Most of the patients in the study were on haloperidol (N=72, or 65%), followed by chlorpromazine (N=28, or 25%). There was a trend towards increasing doses of neuroleptics across groups (p for trend =0.001): the mean equivalent doses of chlorpromazine were 86.7mg (SD=109.8) for patients with late HIV disease, 117.2mg (SD=113.7) for patients with early HIV disease and 210.6mg (SD=263.9) for HIV-negative patients (p=0.0061). Sodium valproate was the most commonly used mood stabiliser (N=26, or 29%), followed by lithium (N=24, or 22%). Carbamazepine was used in two HIV-negative patients. Benzodiazepines were used regularly in 27 patients (30%) and fluoxetine was the most commonly used anti-depressant (N=14, or 14%). A table of the psychotropic use is presented in Appendix G.

5.3.11 Movement abnormalities

Movement abnormalities (Table 5.8) were significantly more common in patients with late HIV (N=22, or 42%) compared to patients with early HIV (N=8, or 28%) or those who were HIV negative (N=3, or 10%) (p= 0.007, p for trend =0.002). This is reflected in the mean times recorded for the 10 metre step test, which were significantly slower in the late HIV-positive group, followed by the early HIV-positive group and then the HIV-negative group. The mean times were 10.2 seconds (SD=2.46), 9.6 seconds (SD=2.00) and 8.7 seconds (SD=1.62) respectively (p= 0.022, p for trend = 0.003). Extrapyramidal side-effects were documented in 23 patients (21%) at some stage during their admission. With regard to the formal measures of movement abnormalities, the most common abnormal movement was akathisia as measured by the Simpson Angus Rating Scale (SARS) with a trend across mean scores from a higher score in the late HIV group to a lower score in HIV-negative group. The mean SARS score for patients in the late HIV group was 3.63 (SD=5.55), for those in the early HIV group, it was 1.86 (SD=2.00), and for those who were HIV-negative, it was 1.77 (SD=2.16). The prevalence of abnormalities as measured by the AIMS and the Barnes was relatively low with no significant difference between groups (p=0.792 and 0.439 respectively). Two patients with late HIV developed neuroleptic malignant syndrome.

Table 5-8 Movement abnormalities, by selection group

	Late HIV N=52	Early HIV N=29	HIV-Negative N=30	p-value
	N %	N %	N %	
Catatonia	6 12	1 3	2 7	0.554
Movement abnormality noted at any time during admission	22 42	8 28	3 10	0.007
10m step test: mean time (seconds) (SD)	10.2 (2.46)	9.6 (2.00)	8.7 (1.67)	0.022
Mean number of steps (SD)	17.1 (3.29)	16.6 (2.38)	15.7 (1.95)	0.065
AIMS				
Mean (SD)	0.77 (2.53)	0.28 (0.92)	0.3 (0.99)	0.405
Median AIMS	0	0	0	0.792
AIMS total >=1 (%)	8 (15)	3 (10)	4 (13)	0.936
Barnes				
Mean (SD) (SD)	0.54 (1.69)	0.10 (0.41)	0.10 (0.40)	0.167
Median Barnes	0	0	0	0.439
SARS				
Mean (SD) [without item 2]	3.63 (5.55)	1.86 (2.00)	1.77 (2.16)	0.070
Median SARS	1.5	1	1	0.396

5.3.12 Measures of delirium

Patients with late HIV had significantly higher mean scores on both the Delirium Rating Scale (DRS) and the Delirium Rating Scale-98-revised (DRS-98), with a trend towards the increased prevalence across the means of the scales from HIV negative to the late HIV group (Table 5.9). The significance was maintained when the items describing the presence of a physical disorder were removed. The mean DRS score for patients with late HIV was 17.92 (SD= 5.85), while it was 12.38 (SD= 4.77) for those with early HIV and 10.13 (SD= 4.21) for those who were HIV negative ($p < 0.001$). There was a trend across means with respect to a number of parameters in which patients in the late HIV group had higher mean scores than those in the early group, who scored higher than those in the HIV-negative group. Late HIV positive patients were more likely to have a shorter onset

of symptoms ($p<0.001$ on the DRS and $p=0.007$ in the DRS-98) and more symptom fluctuation ($p<0.001$ in both scales). They were significantly more cognitively impaired on the general measure used by the DRS ($p< 0.001$), and more specifically with respect to orientation and attention on the DRS-98 ($p<0.001$). They were more impaired with respect to the language abnormalities and long-term memory (for both $p=0.014$), but not as significantly different with respect to short-term memory ($p= 0.074$). HIV-positive patients with advanced disease were more likely to have psychomotor retardation ($p=0.03$) or a change in psychomotor behaviour ($p=0.004$). There were no significant differences in the occurrence of perceptual disturbances or delusions ($p=0.997$ and $p=0.559$ respectively on the DRS-98). Neither scale distinguished between one or more hallucinations or delusions.

Table 5-9 Delirium scales, by selection group

	Late HIV N=29	Early HIV N=52	HIV-negative N=30	p-value
Delirium Rating Scale				
Mean (SD)	17.92 (5.85)	12.38 (4.77)	10.13 (4.21)	<0.001
Median DRS (IQR)	18 (5.5-9.0)	12 (8.5-10.0)	10 (8.0-10.0)	<0.001
Temporal onset of symptoms	2.08	1.41	0.87	<0.001
Perceptual disturbances	2.56	2.62	2.60	0.961
Hallucination type	1.71	1.41	1.37	0.210
Delusions	2.42	2.14	1.90	0.031
Psychomotor behaviour	2.02	1.66	1.20	0.004
Cognitive status	1.62	0.31	0.50	<0.001
Physical disorder *	1.96	1.17	0	<0.001
Sleep-wake cycle disturbance	1.21	0.83	0.80	0.048
Lability of mood	1.15	0.76	0.90	0.174
Variability of symptoms	1.19	0.07	0	<0.001
* Mean recalculated without physical disorder	15.96	11.20	10.13	<0.001
Delirium Rating Scale–98				
Mean (SD)	21.31 (7.03)	15.62 (5.67)	13.77 (5.59)	<0.001
Median (IQR)	20.5 (6.0-11.5)	15 (10.0-12.0)	14 (8.0-13.0)	<0.001
Sleep-wake cycle disturbance	1.17	0.93	0.97	0.426
Perceptual disturbances	2.50	2.52	2.50	0.997
Delusions	2.90	2.93	3.00	0.559
Lability of affect	1.13	0.72	1.00	0.188
Language	0.65	0.21	0.13	0.014
Thought process abnormal	0.96	1.07	0.70	0.312
Motor agitation	1.62	1.31	1.20	0.230
Motor retardation	0.69	0.31	0.20	0.030
Orientation	0.85	0.38	0.10	<0.001
Attention	1.46	0.66	0.87	<0.001
Short-term memory	0.62	0.24	0.33	0.074
Long-term memory	0.65	0.17	0.33	0.014
Visuo-spatial ability	0.98	0.83	0.57	0.105
Temporal onset	1.48	1.10	0.83	0.007
Fluctuation of severity	0.52	0.10	0.07	<0.001
Physical disorder *	1.96	1.20	0	<0.001
* Mean recalculated without physical disorder	19.38	14.43	13.77	<0.001

5.3.13 The Young Mania Rating Scale

The Young Mania Rating Scale (YMRS) was used to rate the severity of mania in patients presenting with manic symptoms (N=77) (Table 5.10). There was a trend towards increased mean scores across groups with late HIV positive group having a higher mean score of 40.47 (SD 6.55) on the YMRS compared to those with early HIV disease, whose mean score was 35.28 (SD=8.19) and the HIV-negative patients with a mean score of 32.30 (SD=6.33). The means of the scales were recalculated after removing the item concerning increased sexual interest and personal appearance because of the potential bias in these questions as discussed in the methodology section. Item 8 was removed because all the patients scored full points for this item as they were all psychotic. This reduced the standard deviations across the groups. On the amended scale, patients with late HIV disease scored a mean of 30.12 (SD= 6.44) as opposed to those with early HIV disease who scored 24.90 (SD=7.58) and 21.70 (SD=6.18) ($p< 0.001$). With respect to the sub-tests in the scale, patients with advanced disease had higher mean scores for irritability, with a trend across mean scores across the early HIV group and HIV-negative group ($p<0.001$). There was a similar trend across means for aggressive-disruptive behaviour ($p=0.001$). HIV-negative patients had higher mean scores on the psychomotor activity sub-test compared to HIV-positive patients where the early HIV positive and late HIV-positive groups were similar ($p=0.005$). The HIV-positive groups had similar mean scores for thought disorder, which were significantly higher than the HIV- negative patients ($p=0.029$).

Table 5-10 Young Mania Rating Scale results, by selection group

Mean YMRS	Late HIV N=33	Early HIV N=21	HIV-Negative N=23	p-value
Elevated mood	2.36	2.43	2.70	0.607
Increased motor activity-energy	3.12	2.62	5.27	0.005
Sexual interest	0.97	0.52	0.48	0.366
Sleep	2.61	2.38	2.61	0.672
Irritability	6.18	4.10	3.57	<0.001
Speech	4.88	4.19	3.12	0.222
Language-thought disorder	2.64	2.67	1.70	0.029
Content	8	8	8	----
Disruptive-aggressive behaviour	6.12	4.95	3.74	0.001
Appearance	0.91	0.95	0.61	0.621
Insight	2.91	2.48	2.57	0.430
Total: Mean (SD)	40.73 (6.55)	35.28 (8.19)	32.30 (6.33)	<0.001
Total: Median (IQR)	40(37-47)	36 (28-39)	32 (28-37)	<0.001
Total: Mean without sexual interest, content and appearance (SD)	30.12 (6.44)	24.90 (7.58)	21.70 (6.18)	<0.001
Total: Median without sexual interest, content and appearance (IQR)	32 (27-35.5)	27 (19.5-31)	24 (18-28)	<0.001

5.3.14 Cognitive assessment and activities of daily living

Patients with late HIV had a much lower mean score [mean 6.85 (SD=2.86), median 7.75)] on the International HIV Dementia Scale (IHDS) than patients with early HIV [mean 8.90 (SD=1.63), median= 7.75 or HIV patients (p< 0.001) (Table 5.11). The early HIV-positive group had a slightly higher mean score (8.90) than the HIV-negative group (8.53) but this was not significant and the medians were identical [median=9.5 (IQR 8.5–10 for the early HIV group and 8–10 for the HIV-negative group)]. The patients with late HIV had lower scores than the other two groups on all sub-tests of the scale including motor speed (p=0.010), psychomotor speed (p=0.005), and memory recall (p=0.002). There was a trend towards a lower score from the HIV-negative group to towards the late HIV group (p=0.010) with respect to the motor-speed sub-test.

The original HIV Dementia Scale (HDS) was not as useful as patients across all three groups struggled with the anti-saccadic eye movement tests, the language-based psychomotor speed sub-test and the construction task and results were inconsistent.

Table 5-11 HIV Dementia Scales, by selection group

	Late HIV N=52	Early HIV N=29	HIV-negative N=30	p-value
International HIV Dementia Scale				
Mean (SD)	6.85 (2.86)	8.90 (1.63)	8.53 (2.28)	<0.001
Median (IQR)	7.75 (5.5-9.0)	9.5 (8.5-10.0)	9.5 (8.0-10.0)	<0.001
Motor-speed	1.74	2.03	2.38	0.010
Psychomotor speed	2.82	3.66	3.41	0.005
Memory recall	2.29	3.21	2.74	0.002
HIV Dementia Scale				
Mean (SD)	8.74 (4.76)	11.55 (3.84)	10.57 (3.51)	0.014
Median	7.5 (6.0-11.5)	11 (10.0-12.0)	10.5 (8.0-13.0)	0.006
Memory-registration	3.44	4.00	3.90	0.003
Attention	1.36	2.34	2.24	0.039
Psychomotor speed	1.14	1.48	1.00	0.642
Memory-recall	2.29	3.21	2.74	0.002
Construction	0.51	0.52	0.69	0.639

5.3.15 Activities of daily living

Overall, 51 patients (46%) had impairment in their basic activities of daily living (BADLS) and 85 patients (76%) had impairment in their advanced (instrumental) activities of daily living (AADLS) (Table 5.12). With respect to BADLS, 16 patients in the late HIV-positive group (31%) had intact BADLS as opposed to 15 in the early HIV group (54%) and 20 in the HIV-negative group (77%), with a trend towards increasing prevalence of BADLS across the groups (p for trend=0.001). Severe impairment in BADLS occurred in 19 patients with late HIV (37%), six with early HIV (22%) and four patients who were HIV negative (13%) (p=0.026). Patients across all three groups were similarly impaired with respect to AADLS (p=0.902).

Table 5-12 Activities of Daily Living Scales, by selection group

	Late HIV N=52		Early HIV N=29		HIV-negative N=30		p-value
Basic ADLS	N	%	N	%	N	%	
Intact	16	31	15	54	20	77	0.026
Mild/moderate impairment	17	33	7	25	6	20	
Severe impairment	19	37	6	21	4	13	
Advanced (instrumental) ADLS							
Intact impairment	12	23	6	22	8	28	0.902
Mild/moderate impairment	10	19	7	26	7	24	
Severe impairment	30	58	14	52	14	48	

5.3.16 Neurocognitive evaluation

Patients with late HIV had poor scores with a trend towards lower means across groups with respect to the Rey Complex Figure Copy Test (p=0.009) (Table 5.13). This test evaluates visuo-constructional ability and visual memory as well as executive functioning relating to planning, problem solving abilities and motor abilities. The differences across the groups with respect to the Grooved Pegboard Test were not significant, although patients with advanced disease had slower mean scores and there was a trend towards lower mean scores across the groups (0.239). The Trail Making Test, Part A, which tests visual attention, visual scanning, neglect, sequencing and cognitive flexibility, was marginally significant with a trend for lower means across groups from the HIV-negative group to the late HIV group (p=0.059). None of the other tests were significantly different, although successive finger tapping, a test of fine-motor speed suggested a trend towards slower responses from the HIV-negative to the late HIV group (dominant hand, p=0.146). On the overall rating of cognitive impairment, taking into account those who were unable to attempt the tests due to severity of illness rather than language and education, there were 22 patients in the late HIV-positive group (43%) as opposed to four patients in the early HIV- positive group (14%) and four patients in the HIV negative group (14%) with moderate to severe cognitive impairment (p=0.004).

Table 5-13 Neurocognitive evaluation results, by selection group

	Late HIV N=52			Early HIV N=29			HIV-negative N=30			p-value
	N	Mean	SD	N	Mean	SD	N	Mean	SD	
Successive Finger Tapping, dominant hand (seconds)	45	13.24	5.54	28	11.37	4.40	28	11.11	4.83	0.146
Successive Finger Tapping, non-dominant hand (seconds)	47	12.56	4.05	28	11.01	3.18	28	11.51	5.57	0.293
Grooved Pegboard Test, dominant hand (seconds)	46	126.1	51.2	28	115.7	36.5	27	107.7	43.5	0.239
Grooved Pegboard Test, non- dominant hand (seconds)	46	141.4	49.7	28	134.7	59.2	26	122.4	61.5	0.381
Digit Span, forwards (scaled score)	48	7.23	1.70	28	8.00	1.9	28	7.54	2.03	0.220
Rey Complex Figure, copy	47	20.3	8.8	26	26.5	7.4	27	24.6	8.7	0.009
Rey Complex Figure, initial	43	11.4	6.5	27	13.9	5.5	24	14.2	7.1	0.136
Rey Complex Figures, delayed	37	11.3	6.6	24	13.8	5.4	24	13.5	7.2	0.261
Trail Making Test A (seconds)	38	122.3	60.4	24	113.5	45.4	23	90.2	35.4	0.059

	Late HIV N=52			Early HIV N=29			HIV-negative N=30			p-value
	N	N= Yes	%	N	N= yes	%	N	N= yes	%	
Mental Control I, counting backwards from 20 (N,%=Yes)	46	40	87	27	25	93	28	25	89	0.917
Mental Control II, reciting the alphabet (N,%=Yes)	47	28	60	27	23	82	28	21	75	0.121
Global assessment of cognition		N	%		N	%		N	%	
Normal to mild impairment		29	47		25	86		24	86	0.004
Moderate to severe impairment		22	43		4	14		4	14	

The matched neuropsychological control group with late HIV but no mental disorder consisted of 25 patients matched of gender, education, race and age. The mean CD4+ count for this group was 149 cells/mm^3 (IQR 114-192.5). When compared to this group, patients with late stage HIV and psychosis/mania scored significantly worse with respect to all the neuropsychological tests apart from the Digit Forwards Test and the Mental Control Test (counting backwards from 20) (appendix L). The differences were also significant, but less so, for the patients with mild HIV. Interestingly, although the HIV-negative patients with psychosis or mania had the best scores when compared to the other two selection groups, their scores were significantly worse than the patients with late HIV disease but no mental disorder. They were more impaired on most of the neuropsychological measures, particularly those related to fine motor speed, manual dexterity complex visual motor coordination, visuo-constructional ability, visual memory and executive function. The differences were not significant for measures of attention, verbal memory, attention and concentration and working memory.

5.3.17 Summary

In summary, patients with advanced HIV disease had a significantly higher prevalence of depressive symptoms, mood lability, behavioural disturbance and symptom fluctuation. This group also had a significantly increased prevalence of episodes of disorientation, the occurrence of more than one hallucination, movement abnormalities and cognitive impairment. There was trend towards an increasing prevalence of the symptoms across the three groups. Patients with advanced disease were, however, more likely to have more than one delusion than the other two groups. Sub-group analyses of psychiatric symptomatology controlling for language and previous admissions, demonstrated that these factors did not appear to be biasing the results in any significant manner. Overall, most patients in the study were on haloperidol and there was a trend towards increasing doses of neuroleptics across groups with the lowest dose (equivalents dose of chlorpromazine equals 86.7 mg) for patients with late HIV disease. Despite the lower doses of neuroleptics in this group, they were more likely to have movement abnormalities, particularly extra-pyramidal side-effects and had reduced motor speed on formal measures such as the IHDS. Patients with advanced disease had higher mean scores for delirium on both the DRS and the DRS-98 and there was a trend across means with respect to a number of parameters within the sub-tests, many of which were significant. Patients with mania were compared across groups and it was found that patients with late HIV had higher mean scores on the YMRS than those with early HIV or HIV-negative patients. Patients in the late HIV group had higher mean scores for irritability and aggressive-disruptive behaviour whereas HIV-negative patients had higher mean scores for psychomotor activity. HIV-positive patients had significantly higher mean scores for thought disorder than those who were HIV negative.

With regard to cognition, patients with late HIV had significantly impaired cognition with respect to motor speed, psychomotor speed and memory recall as measured on the IHDS and there was a trend affect across groups with the HIV-negative group being least affected. All three groups demonstrated impairment with advanced activities of daily living but were differentiated with respect to basic activities of daily living with more patients with advanced HIV having moderate or severe impairment in this regard.

On neurocognitive evaluation patients with late HIV had poor scores with a trend towards lower means across groups with respect to tests of visual constructional ability, visual memory and executive functioning. Although the differences with respect to tests of manual dexterity, motor co-ordination, fine-motor speed and cognitive flexibility (Grooved Pegboard and Trail-Making Test A) were not significant, there was a trend towards increasing impairment across groups from the HIV-negative group to the late HIV group. On the overall rating of cognitive impairment, more patients in the late HIV-positive group had moderate to severe cognitive impairment as compared to those with early HIV and the HIV negative patients.

5.4 A description of the Latent Class Analysis

The best-solution in the Latent Class Analysis (LCA) was a model with one latent variable with two levels, which are hereafter called class 1 and class 2 (df=2024, χ^2 = 1934). The latent variable was best described by 12 items, which were distilled from the 30 originally considered. There were 72 patients in class 1 and 39 in class 2. The assignment probabilities for the LCA are attached in Appendix H.

The clinical features characterising classes 1 and 2 consisted of cognitive symptoms and impairment in motor function, depressive symptomatology, multiple hallucinations and delusions, and symptom fluctuation. The cognitive symptoms comprised disorientation, thought-process abnormalities, attentional deficits and impaired registration. The motor symptoms were in the form of motor-speed deficits, catatonia and movement abnormalities. Psychomotor speed, which encompasses both cognitive and motor function, was also an important clinical characteristic distinguishing the two classes. Table 5.14 describes the clusters of psychiatric symptoms that constitute the latent classes.

Table 5-14 Description of Latent Class Analysis

Clinical Feature	Class 1 [a] 65% of participants N=72	Class 2 [a] 35% of participants N=39
Multiple hallucinations	0.3316	0.7197
Multiple delusions	0.7735	0.4194
Depression	0.4052	0.6357
Movement abnormalities	0.1183	0.6259
Catatonia	0.0273	0.1799
Moderately severe–severe motor speed deficit: [IHDS, item 2 = 0 or 1(on a scale of 0–4)]	0.1509	0.5661
Moderately severe–severe psychomotor speed deficit: [IHDS, item 3 <4 (on a scale of 0–4)]	0.2894	0.6695
Severe thought process problem (thought disorder): [DRS–98, item 6 = 3 (on a scale of 0–3)]	0.0000	0.2044
Severe attention deficit: [DRS–98, item 10 = 3 (on a scale of 0–3)]	0.0136	0.2816
Moderately severe–severe inpairment in registration: [HDS item 1 <4 [(on a scale of 0–4)]	0.0543	0.3858
Disorientation	0.1309	0.8328
Fluctuation	0.0885	0.6806

[a] Decimals are the proportions of people in each class with these symptoms

With respect to the cognitive symptoms, disorientation was the most prevalent symptom in class 2, with 83% of patients having episodes of disorientation at some time during their admission as opposed to 13% of patients in class 2. Severe impairment in attention had a prevalence of 28% in class 2, as opposed to 1% in class 1, and 39% of patients in class 2. In class 1, 5% had moderate to severe impairment in registration. Although severe thought-process abnormalities (thought disorder) were relatively rare, they occurred in 20% of patients in class 2 and no patients in class 1. Moderate to severe psychomotor speed deficits, as measured by the IHDS, were displayed by 67% of patients

in class 2 as opposed to 29% in class 1. Motor disorders were more common in class 2 with 63% of patients exhibiting movement abnormalities at some stage during their admission, compared with 12% of patients in class 1. Moderate to severe motor-speed deficits as measured by the IHDS occurred in 56% of patients in class 1 and 15% in class 2. Catatonia, although relatively rare, was more prevalent in class 2, with 18% of patients having catatonic symptoms as opposed to 3% in class 1. Depressive symptomatology was documented in 64% of patients in class 2 and 41% of patients in class 1. Multiple hallucinations occurred in 77% of patients in class 1 compared to 33% in class 1. The opposite was true for multiple delusions, with 77% of patients in class 1 having multiple delusions and 42% of patients in class 2. Symptom fluctuation occurred in 68% of patients in class 2, as opposed to 9% in class 1.

5.5 Analysis of the underlying (latent) classes of psychiatric symptoms

5.5.1 HIV characteristics of the latent classes

Class 1 comprised 21 patients with late HIV, 25 patients with early HIV and 26 HIV-negative patients (Table 5.15). Class 2 comprised 31 patients with late disease, four with early disease, and four HIV-negative patients. Class 1 therefore compromised most of the patients from the early HIV-positive and HIV-negative groups and 40% of the patients with late HIV disease. The remaining 60% of this group made up the majority of patients in Class 2. With respect to the HIV-positive patients in each class, the median CD4+ count in class 1 was 256.5 cells/mm^3 (IQR 148–425) as opposed to 66.0 cells/mm^3 (IQR 32–126) in class 2 ($p< 0.001$). When the analysis was limited to individuals with late HIV and first admission, the median CD4+ count in class 1 was 109.0 cells/mm^3 as opposed to 47.5 cells/mm^3 in class 2. The median viral load in class 1 was lower than in class 2 (log 4.58 vs. 4.83 copies/ml), but the difference was not significant ($p= 0.160$).

Table 5-15 HIV disease characteristics, by latent class

		Class 1 N=72		Class 2 N=39		p-value
		N	%	N	%	
HIV-negative		26	36	4	10	0.003
WHO stage:	1	16	35	4	11	<0.001
	2	12	26	1	3	
	3	13	28	11	31	
	4	5	11	19	54	
Early HIV		25	35	4	10	
Late HIV		21	29	31	80	<0.001
		Median	**IQR**	**Median**	**IQR**	
Median CD4+ count		256.5	148–425	66	32–126	<0.001
Median HIV viral load (log, copies/ml)		4.58	3.70–5.79	4.83	4.30–5.63	0.160

5.5.2 Demographic characteristics

Latent classes 1 and 2 were similar with respect to median age [30 (IQR= 25–38) years and 29 (IQR=24–33) years respectively], educational qualifications, and family income (Table 5.16). The racial differences between the classes were similar to those found in the analysis by selection group, in that 36 patients in class 2 were black (92%) as opposed to 55 in class 1 (76%). Three patients in class 2 were coloured (85) as opposed to 15 in class 1 (21%). The differences between the classes did not extend to the language groups as they did in the former analysis because the number of Afrikaans-speaking patients in class two is very small (N=3, or 8%). The differences between the classes with respect to employment status is marginally significant, with only five patients in class 2 having a disability grant (13%) as opposed to 24 in class 1 (35%), and 27 patients in class 2 being unemployed (71%) as opposed to 36 (52%) in class 1.

Table 5-16 Socio-demographic characteristics, by latent class

	Class 1 N=72		Class 2 N=39		p-value
	N	%	N	%	
Female	53	73	32	82	0.357
Education					
None/illiterate	1	1	0		0.410
Grades 1–7	21	29	16	41	
Grades 8–11	31	43	18	46	
Grade 12 (completed schooling)	9	13	4	10	
Technical education/college	9	13	1	3	
University	1	1	0		
Employment					
Employed	9	13	6	16	0.053
Unemployed	36	52	27	71	
Unemployed on grant	24	35	5	13	
Race					
Black	55	76	36	92	0.001
Coloured	15	21	3	8	
Other	2	3	0	0	
Language					
English	4	5	1	3	0.449
Afrikaans	12	17	3	8	
Xhosa	53	76	34	87	
Other	1	1	1	3	
Income (in Rand):					
1–499	8	15	4	19	0.677
500–999	16	30	8	38	
1000–1999	14	26	3	14	
2000–4999	9	17	5	24	
5000+	6	11	1	5	

5.5.3 Medical findings among HIV-positive patients

The high medical morbidity in class 2 reflects a high proportion of patients in the class with advanced HIV. Table 5.17 describes the medical morbidity of HIV-positive patients by class. Patients in class 2 had higher rates of tuberculosis (N=24, or 69% vs. N=13 or 29%) ($p< 0.001$).Tuberculosis was therefore analysed by class to establish whether the high prevalence of tuberculosis was driving any of the findings. Overall, 14 patients in class 1 (20%) and 24 patients in class 2 (62%) had had tuberculosis in the two years preceding the study ($p < 0.001$). When the analysis is restricted to only those patients with advanced HIV disease, however, there is no significant difference between the classes as 13 patients in class 1 (62%) and 24 patients in class 2 had had tuberculosis (77%) in the preceding 2 years ($p=0.350$).

Table 5-17 Medical findings, among HIV-positive patients, by latent class

Medical findings	Class 1 N=46		Class 2 N=35	
	N	%	N	%
Pulmonary tuberculosis in previous 24 months	13	29	24	69
Pulmonary tuberculosis > 24 months ago	3	7	0	0
Extrapulmonary TB (excluding central nervous system as they were excluded from the study)	3	7	3	9
Oral candidiasis	13	29	19	54
Oesophageal candida	2	4	1	3
Oral hairy leukoplakia	6	13	8	23
Weight loss <10 kg	7	15	6	17
Weigh loss >10 kg	5	11	7	20
Severe gingivitis	9	20	7	20
Fungal infection of nails or skin	6	13	5	14
Sexually transmitted disease other than syphilis	3	7	5	14
Primary syphilis	1	2	0	0
Secondary syphilis	2	4	2	6
Papular pruritic eruptions	14	31	13	37
Seborrhoeic dermatitis	5	11	1	3
Generalised lymphadenopathy	28	61	24	69
Cytomegalovirus retinitis	1	2	2	6
Peripheral neuropathy	4	9	6	17
Oral ulcers	1	2	3	9
Drug induced hepatitis	0	0	2	6
Anaemia	10	22	12	34
Leucopenia	0	0	3	9
Pancytopenia	1	2	0	0
Probable Kaposi Sarcoma	1	2	1	3
Herpes zoster	2	4	3	9

5.5.4 Psychiatric history and symptomatology

The comparison of psychiatric symptoms by latent class excluded those symptoms used to define the latent classes as inclusion of these variables would be meaningless. With respect to personal and past psychiatric history, as described in Table 5.18, 39 patients in class 1 (54%) had a past psychiatric history (excluding those occurring after stigmata of AIDS had developed), as opposed to five patients in class 2 (3%) (p<0.001). The differences with respect to the family history of psychiatric illness were marginally significant with 17 patients in class 1 (26%) and three patients in class 2 (9%) having a positive family psychiatric history (p=0.065).

Table 5-18 Personal and family history, by selection group

	Class 1 N=72		Class 2 N=39		p-value
	N	%	N	%	
All previous admissions	43	61	7	18	<0.001
Previous admissions excluding those occurring after stigmata of AIDS had developed	39	54	5	13	<0.001
Family history of psychiatric illness	17	26	3	9	0.065

Psychiatric symptomatology analysed by latent class is described in Table 5.19. Although patients in class 2 tended to experience a shorter duration of symptoms, the difference was not significant (p=0.205). Manic symptoms were common in both groups occurring in 49 patients in class 1 (68%) and 23 patients in class 2 (59%) (p=0.406). There was no significant difference between classes with respect to the co-occurrence of depressive and manic symptoms (p= 0.815), suicidal ideation (p=0.554), suicidal intent (p=0.999) and aggressive behaviour (p= 0.999). Behavioural disturbance was prevalent in both groups and there was a marginally significant difference between the two groups with 58 patients in class 1 (81%) and 37 patients in class 2 (95%) having episodes of behavioural disturbance (p=0.049). Delusions were highly prevalent in both groups, with nearly all the patients having at least one delusion (p=0.999). Persecutory delusions occurred in 66

patients in class 1 (92%) and 34 of patients in class 2 (87%) (p=0.513). Grandiose delusions were also common, being more prevalent in class 1 with 42 patients (58%) having grandiose delusions as opposed to 13 patients in class 2 (33%) (p=0.017). Patients in class 1 were also more likely to have religious delusions with 23 patients (32%) experiencing them as opposed to six patients (15%) in class 2 (p=0.072). The patients in class 1 were more likely to have multiple delusions with a mean of 2.3 delusions as opposed to patients in class 2 who had a mean of 1.6 delusions (p<0.001). There was no significant difference between the classes with respect to other delusions.

Hallucinations of any type were more common in class 2, but not significantly so, with 37 patients in class 2 (95%) having hallucinations as opposed to 62 in class 1 (82%) (p=0.209). Visual hallucinations and tactile hallucinations were significantly more likely to occur in patients in class 2, with 26 patients in this class (67%) having visual hallucinations as opposed to 26 in class 1 (36%) (p=0.003). In class 2, 12 patients had tactile hallucinations (31%) as opposed to seven in class 1 (10%) (p=0.008). Patients in class 2 had a mean of 2.05 hallucinations, as opposed to those in class 1 with a mean of 1.34 (p < 0.001). With respect to cognition, 21 patients in class 2 (57%) reported problems with the memory as opposed to seven in class 1 (10%) (p < 0.001). A total of 49 patients in class 1 (68%) reported sleep difficulties as opposed to 33 in class 2 (45%) (p= 0.072).

Table 5-19 Psychiatric symptoms, by latent class[a]

	Class 1 N=72		Class 2 N=39		p-value
	N	%	N	%	
Duration of symptoms					
Days	7	10	8	22	0.205
Weeks	28	39	17	46	
Months	30	42	11	30	
Years	6	8	1	3	
Affective symptoms					
Manic symptoms	49	68	23	59	0.406
Depressive and manic symptoms	16	22	10	26	0.815
Lability	37	52	28	72	0.045
Irritability	55	76	26	67	0.275
Suicidal ideation	29	40	18	46	0.554
Suicidal intent	20	28	10	26	0.999
Behavioural disturbance	58	81	37	95	0.049
Aggression	40	56	22	56	0.999
Any delusions present	71	99	38	97	0.049
Types of delusion					
Persecutory	66	92	34	87	0.513
Grandiose	42	58	13	33	0.017
Religious	23	32	6	15	0.072
Somatic	8	11	4	10	0.999
Erotomanic	2	3	1	3	0.999
Jealousy	4	6	0	0	0.295
Guilt	7	10	2	5	0.490
Reference	7	10	2	5	0.490
Nihilistic	1	0	1	0	0.999
Mean number of different types of delusions (SD)	2.3	(0.93)	1.6	(1.04)	<0.001
Any hallucinations present	62	82	37	95	0.209
Types of hallucination					
Visual	26	36	26	67	0.003
Auditory	60	83	35	90	0.412
Tactile	7	10	12	31	0.008
Olfactory	3	4	4	10	0.239
Somatic	1	1	2	5	0.282
Gustatory	0	1	2	5	0.351

	Class 1 N=72		Class 2 N=39		p-value
Mean number of different types of hallucinations (SD)	1.35	(0.89)	2.05	(0.92)	<0.001
Sleep disturbance	49	68	33	45	0.072
Memory impairment on history	7	10	21	57	<0.001

[a] Depressive symptoms, fluctuation and disorientation were omitted from the table as they are variables used to define the latent classes and their inclusion would therefore be meaningless

5.5.5 Movement abnormalities

The 10 metre step test was done more slowly in patients in class 2, with a mean time of 10.4 seconds as opposed to 9.2 seconds in class 1 (p=0.016) (Table 5.20). There was a higher prevalence of movement abnormalities in scores in patients in class 2 as recorded by the formal measures. The mean AIMS score for patients in class was 0.97 (SD 0.46), which was marginally significant when compared to a mean score of 0.26 (SD=0.10) for patients in class 1 (p=0.056). Although not significant, patients in class 2 also had higher mean scores on the Barnes [0.59 (SD=0.06) vs. 0.59 (SD=0.30), p= 0.070]. The difference between the mean SARS scores was highly significant with a mean score of 4.56 (0.97) in class 1 as opposed to 1.64 (SD=0.24) in class 2 (p<0.001).

Table 5-20 Movement abnormalities, by latent class [a]

	Class 1 N=72	Class 2 N=39	p-value
10m step test: mean time (seconds) (SD)	9.2 (1.9)	10.4 (2.5)	0.016
mean number of steps (SD)	16.39 (2.13)	17.5 (3.72)	0.061
AIMS			
Mean (SD)	0.26 (0.10)	0.97 (0.46)	0.056
Median AIMS	0	0	0.553
AIMS total >=1 (%)	9 (13)	6 (15)	0.773
Barnes			
Mean (SD)	0.15 (0.06)	0.59 (0.30)	0.070
Median Barnes	0	0	0.391
SARS			
Mean (SD) [without item 2]	1.64 (0.24)	4.56 (0.97)	<0.001
Median SARS	1	3	0.002

[a] Catatonia and movement abnormality noted at any time during admission were omitted from the table as they are variables used to define the latent classes and their inclusion would therefore be meaningless

5.5.6 Sub-group analyses

There were no changes in the findings after restricting the latent class analysis to Xhosa-speaking patients, apart from some reduction in the significance of the difference between the two groups with a decrease in numbers in each class (Appendix I). Limiting the analysis to patients with first presentation of a psychiatric illness, also had no impact on the findings apart from some reduction in significance (Appendix J). As patients with advanced HIV disease constituted 80% of the patients in class 2, a third sub-group analysis was therefore conducted, limited to patients with advanced HIV disease (late HIV-positive) (Appendix K). Patients in class 2 were more immuno-compromised compared to those in class 1 with a mean CD4+ count of 52 cells/mm^3 in class 2 as opposed to a mean CD4+ count of 143 cells/mm^3 in class 1 (p=0.008). There was no significant difference between the groups with respect to the prevalence of manic symptoms (p= 0.392), the co-occurrence of depressive and manic symptoms (p= 0.747), or suicidal ideation and intent (p=0.778 and p= 0.741 respectively). The differences between the classes with respect to delusions and hallucinations were maintained with patients in class 1 having a mean of two different types of delusions as opposed to the mean of 1.5 in class 2 (p=0.034). Patients in class 2, however, had a mean of 2.2 different types of hallucinations as opposed to the mean of 1.3 in class 1 (p=0.005). Visual and tactile hallucinations were also more common in patients with advanced HIV in class 2 (p= 0.051 and 0.027 respectively). There was also a significant difference in reports of memory impairment, with 62% of late stage patients in class 2 reporting memory impairment as opposed to 33% of late stage patients in class 1. There were no significant differences in behavioural disturbance (p=0.999), lability (p=0.999), irritability (p=0.353) or symptom duration (p=0.693).

5.5.7 Measurements of delirium

As described in Table 5.21, patients in class 2 had higher scores on the Delirium Rating Scale (DRS) (mean=19.36, SD=5.04) compared to those in class 1 (mean=11.67, SD=4.89) ($p<0.001$). This significance remained after the mean was recalculated without item seven which specifies the presence of an underlying physical disorder. The median DRS score for patients in class one was 11 (IQR 9-15) which was very similar to those of patients with early HIV [12 (IQR 10-15)] and the HIV-negative patients [10 (IQR 7-13)] when analysed by selection group. The median score for patients in class two was 19 (IQR15-23) which was similar to that found in the late HIV group with the median was 18 (IQR 14.5-22). The differences between the two classes were significant across all the sub-tests from the DRS, particularly those of temporal onset of symptoms, psychomotor behaviour, cognitive status and symptom variability (all of which were $p< 0.001$). The mean score on the DRS-98 was calculated without the items specifying thought-process abnormalities and attention, as they were used to define the latent classes, as well as the item for the presence of a physical disorder. The mean score for patients in class 1 was 11.2 (SD=3.87) and for those in class 2, it was 17.8 (SD= 4.5) ($p<0.001$). The differences between the two classes were significant on all sub-tests apart from delusions ($p=0.851$) and short-term memory ($p=0.137$).

Table 5-21 Delirium scales, by latent class [a]

	Class 1 N=72	Class 2 N=39	p-value
Delirium Rating Scale			
Mean (SD)	11.67 (5.04)	19.36 (4.89)	<0.001
Median DRS (IQR)	11 (9–15)	19 (15–23)	<0.001
Temporal onset of symptoms	1.22	2.23	<0.001
Perceptual disturbances	2.44	2.85	0.046
Hallucination type	1.39	1.82	0.023
Delusions	2.03	2.54	0.003
Psychomotor behaviour	1.38	2.31	<0.001
Cognitive status	0.39	2.05	<0.001
Physical disorder	0.97	1.69	<0.001
Sleep-wake cycle disturb	0.82	1.33	0.002
Lability of mood	0.83	1.26	0.025
Variability of symptoms	0.19	1.28	<0.001
Mean recalculated without physical disorder	10.69	17.67	<0.001
Delirium–98, Severity Scale [a]			
Mean without physical disorder (SD)	11.2 (3.87)	17.8 (4.5)	<0.001
Median (IQR)	11 (9–14)	17 (15–21)	<0.001
Sleep-wake cycle disturb	0.89	1.36	0.008
Perceptual disturbances	2.34	2.79	0.041
Delusions	2.93	2.95	0.851
Lability of affect	0.85	1.26	0.033
Language	0.14	0.87	<0.001
Motor agitation	1.19	1.85	0.003
Motor retardation	0.28	0.79	0.003
Orientation	0.24	1.05	<0.001
Short-term memory	0.36	0.59	0.137
Long-term memory	0.26	0.77	<0.001
Visuo-spatial ability	0.65	1.15	0.003
Temporal onset	0.94	1.69	<0.001
Fluctuation of severity	0.08	0.64	<0.001
Physical disorder	0.99	1.69	<0.001

[a] Thought process abnormalities and attention were omitted from the table as they are variables used to define the latent classes and their inclusion would therefore be meaningless

5.5.8 Evaluation of mania

In contrast to the YMRS findings analysed by selection group which showed significant differences, most of the differences between the two latent classes were not significant (Table 5.22). The mean score (excluding items: sexual interest, content and appearance for reasons described above) was 28.15 (SD= 5.88) in class 2 and 25.18 (SD=8.13) in class 1 but this difference was not significant. The only sub-test for which there was a significant difference was that patients in class 2 were more likely to be destructive and aggressive than those in class 1 (p=0.02). Patients in class 2 were less likely to have an elevated mood than those in class 1, with the difference between the classes being marginally significant (p=0.065).

Table 5-22 Young Mania Rating Scale results, by latent class

Mean YMRS score	Class 1 N=52	Class 2 N=26	p-value
Elevated mood	2.67	2.12	0.065
Increased motor activity-energy	2.73	2.96	0.200
Sexual interest	0.59	0.92	0.336
Sleep	2.65	2.34	0.205
Irritability	4.51	5.46	0.096
Speech	4.38	3.38	0.999
Language-thought disorder	2.24	2.62	0.280
Content	8	8	--
Disruptive-aggressive behaviour	4.62	6.0	0.021
Appearance	0.88	0.73	0.632
Insight	2.55	2.96	0.190
Total: Mean (SD)	35.8 (8.37)	38.5 (6.32)	0.156
Total Median	36	38.5	0.161
Total: Mean without sexual interest, content and appearance (SD)	25.18 (8.13)	28.15 (5.88)	0.102
Total: Median without sexual interest, content and appearance	25	28	0.100

5.5.9 Cognitive testing and activities of daily living

As described in Table 5.23, patients in class 2 scored poorly on cognitive measures, with a mean score 6.16 (SD=3.09) on the International HIV Dementia Scale (IHDS) as opposed to patients in class 1 who had a mean score of 8.77 (SD=1.67) ($p< 0.001$). There was a significant difference in the memory recall item with patients in class 2 having lower scores than those in class 1 ($p=0.005$). The motor-speed item and the psychomotor speed sub-set in the scale were used to define the latent classes and were therefore not included. Similarly, the memory registration item in the Original HIV Dementia Scale (OHDS) was not included. With respect to the OHDS, patients in class 2 had significantly lower mean scores, scoring 7.47 (SD=4.30) compared to the 11.34 (SD=3.75) by patients in class 1 ($p< 0.001$). Patients in class 2 scored significantly worse in both the advanced and basic measures of activities of daily living (Table 5.24). In class 2, 11 patients (28%) had intact basic activities of daily living and three (8%) ($p=0.002$) had intact advanced activities of daily living as opposed to 40 (56%) and 23 (33%) ($p=0.002$) respectively in class 1.

Table 5-23 HIV Dementia Scales, by latent class[a]

	Class 1 N=72	Class 2 N= 39	p-value
International HIV Dementia Scale (IHDS)			
Mean (SD)	8.77 (1.67)	6.16 (3.09)	<0.001
Median	9	6.5	<0.001
Memory recall	2.88	2.23	0.005
HIV Dementia Scale (HDS)			
Mean (SD)	11.35 (3.75)	7.47 (4.30)	<0.001
Median	11	7	<0.001
Attention	2.83	0.89	<0.001
Psychomotor speed	1.49	0.66	0.041
Memory-recall	2.89	2.24	0.005
Construction	0.64	0.41	0.174

[a] Motor speed, psychomotor speed (from the International HDS) and memory-registration (from the original HDS) were omitted from the table as they are variables used to define the latent classes and their inclusion would therefore be meaningless

Table 5-24 Activities of Daily Living (ADL) Scales, by latent class

	Class 1 N=52		Class 2 N=29		p-value
Basic ADLS	N	%	N	%	
Intact	40	56	11	28	0.002
Mild/moderate impairment	20	28	10	26	
Severe impairment	11	15	18	46	
Advanced (instrumental) ADLS					
Intact impairment	23	33	3	8	0.002
Mild/moderate impairment	17	25	7	18	
Severe impairment	29	42	29	74	

5.5.10 Formal neurocognitive testing

The neurocognitive findings were more striking when analysed with respect to latent class as compared to the analysis by selection groups (Table 5.25). Patients in class 2 performed poorly on several measures compared to those in class 1. The Non-Dominant Hand Grooved Pegboard Test was marginally significant (p=0.063) and the differences with respect to the digit span forwards test were significant (p=0.007). There were also significant differences for the Rey Complex Figure Copy Task (p=0.002), the Timed Trail Making Test A (p=0.003) and the Mental Control Scale I and II Tests (p=0.008 and p=0.025 respectively). These results therefore indicate that patients in class 2 performed significantly worse with respect to manual dexterity, visual-motor co-ordination, attention, concentration and verbal memory, visuo-constructional ability, visual memory, planning and problem solving, visual attention and scanning, sequencing and cognitive flexibility. On the overall rating of cognitive impairment, taking into account those who were unable to attempt the tests due to severity of illness rather than language and education, there were 17 patients in class 2 (45%) as opposed to 13 patients (19%) in Class 1 with moderate to severe cognitive impairment (p=0.006).

Table 5-25 Neurocognitive evaluation results, by latent class

	Class 1 N=72			Class 2 N=39			p-value
	N	**Mean**	**SD**	**N**	**Mean**	**SD**	
Successive Finger Tapping, dominant hand (seconds)	69	11.67	4.83	32	13.10	5.60	0.191
Successive Finger Tapping, non-dominant hand (seconds)	69	11.44	3.77	34	12.68	5.25	0.173
Grooved Pegboard Test, dominant hand (seconds)	68	112.65	40.17	34	130.00	54.25	0.073
Grooved Pegboard Test, non-dominant hand (seconds)	67	127.34	50.69	33	149.31	62.80	0.063
Digit Span, forwards (scaled score)	67	7.8	1.89	37	6.86	1.84	0.007
Rey Complex Figure, copy	65	25.03	8.05	35	19.46	9.06	0.002
Rey Complex Figure, initial	64	13.25	6.52	30	11.9	6.35	0.348
Rey Complex Figures, delayed	60	13.15	6.56	25	11.44	6.40	0.274
Trail Making Test A (seconds)	61	98.76	36.76	24	142.71	69.33	0.003
	N	**N= yes**	**%**	**N**	**N= Yes**	**%**	
Mental Control , counting backwards from 20 (N,%=Yes)	66	63	95	35	27	77	0.008
Mental Control, reciting the alphabet (N,%=Yes)	67	52	78	36	20	56	0.025
Global assessment of cognition		**N**	**%**		**N**	**%**	
Normal to mild impairment		57	81		21	55	0.006
Moderate to severe impairment		13	19		17	45	

5.5.11 Psychiatric diagnosis based on the MINI-Plus

The MINI-Plus was administered to 69 out of a possible 72 patients in class 1 and to 26 out of 39 patients in class 2. In those patients for whom it was not possible to administer the MINI-Plus, the diagnosis was reached from the collateral information and semi-structured interviews with patients using the DSM-IV criteria. The purpose of making DSM-related diagnoses was to determine which diagnoses, other than those due to a medical condition, would have been made if it was not assumed that HIV was aetiologically related to the clinical presentation. The diagnoses determined in this manner are described in Table 5.26. The frequency of the diagnosis of bipolar disorder was very similar. Including patients with elevated or euphoric mania, a mixed affective state, or irritable mania, 48 patients in class 1 (67%) and 25 patients in class 2 (64%) had symptoms fitting into the bipolar disorder category. As indicated in Table 5.19, there is no significant difference in the presence of irritability between the two classes (p= 0.275). However, 15% (N=6) of patients in class 2 presented with irritability dominating the clinical picture as opposed to 1% (N=1) in class 1 (p=0.007). The higher prevalence of depressive symptoms in class 2 is reflected in the categorical diagnoses with 12 patients in class 2 (31%) and 14 patients in class 1 (19%) being diagnosed with a major depressive episode, although the difference was not significant (p=0.240). There were no patients in class 2 with schizophrenia, schizophreniform disorder or schizoaffective disorder while there were 10 patients with one of these diagnoses in class 1 (p=0.014).

Table 5-26 Psychiatric diagnoses based on MINI-Plus, by latent class

	Class 1 N=72		Class 2 N=39		
MINI-Plus diagnoses					
Classic elevated or euphoric mania	32		8		
Mixed affective state	13		7		
Irritable mania	1		4		
Major depressive episode	14		5		
Schizophrenia	5		0		
Schizoaffective disorder	1		0		
Psychotic disorder NOS	0		1		
Schizophreniform disorder	3		0		
Other pathology from the MINI-Plus					
Panic attacks	8		3		
Generalised social phobia	2		1		
Post traumatic stress disorder	3		3		
Agoraphobia	1		1		
Combining MINI & DSM-IV	**N**	**%**	**N**	**%**	**p-value**
Classic elevated or euphoric mania	33	46	10	26	0.043
Mixed affective state	14	19	9	23	0.413
Irritable mania	1	1	6	15	0.007
Major depressive episode	14	19	12	31	0.240
Schizophrenia	5	7	0	0	0.109
Schizoaffective disorder	2	1	0	0	0.540
Psychotic disorder NOS	0	0	2	5	0.121
Schizophreniform disorder	3	4	0	0	0.551

5.5.12 Summary

The Latent Class Analysis revealed two classes described by the following variables: multiple hallucinations, depressive symptomatology, movement abnormalities, catatonia, moderately severe to severe motor-speed deficits and psychomotor-speed deficits, severe thought disorder, attentional deficits, moderately severe impairment in registration, disorientation and symptom fluctuation. These variables were more prevalent in class 2. Multiple delusions were more prevalent in class 1. Class 1 comprised most of the patients with early HIV and the HIV-negative patients and 40% of the patients with late HIV. The remaining 60% of this group made up the majority of patients in class 2. When the analysis was limited to patients with late HIV and first admission, the patients in class 2 were more immuno-compromised. The two classes were similar with respect to demographics apart from fewer patients in class 2 having disability grants. Patients in class 2 had higher medical co-morbidity in keeping with their advanced HIV status. A sub-group analysis restricted to patients with tuberculosis did not suggest that tuberculosis itself was driving any differences between the classes. Patients in class 2 were less likely to have a family history of psychiatric illness and significantly less likely to have reported a past psychiatric history compared to patients in class 1. Manic symptoms were common in both groups and grandiose and religious delusions were more prevalent in class 1 while visual and tactile hallucinations when more prevalent in class 2.

Patients in class 2 had higher mean scores on measures of delirium and had impaired cognition and activities of daily living when compared to patients in class 1. Patients in class 2 were more likely to have a short onset of symptoms, more severe psychotic symptoms and increased mood lability. They were also more likely to have more disruption in their sleep wake cycle, increased psychomotor retardation, disorientation and symptom fluctuation as compared to those in latent class 1. DSM-IV diagnoses were examined by class to determine how patients' symptoms in different clusters related to primary diagnostic categories. Most of the patients were diagnosed with a mood disorder with psychotic features with no patients in class 2 being diagnosed with schizophrenia, schizophreniform disorder or schizoaffective disorder.

5.6 Possible misclassification of patients in the Latent Class Analysis

There were five patients in class 2 with a past psychiatric history. One patient had a borderline intelligence with atypical symptoms and severe akathisia, one had severe tardive dyskinesia as well as severe thought disorder which interfered with cognitive and motor tasks. Of the remaining three patients, two were reported to have a recent change in their symptoms on collateral history with more behavioural disturbance, mood lability and symptom fluctuation. Details with respect to the previous history of the fifth patient were unknown.

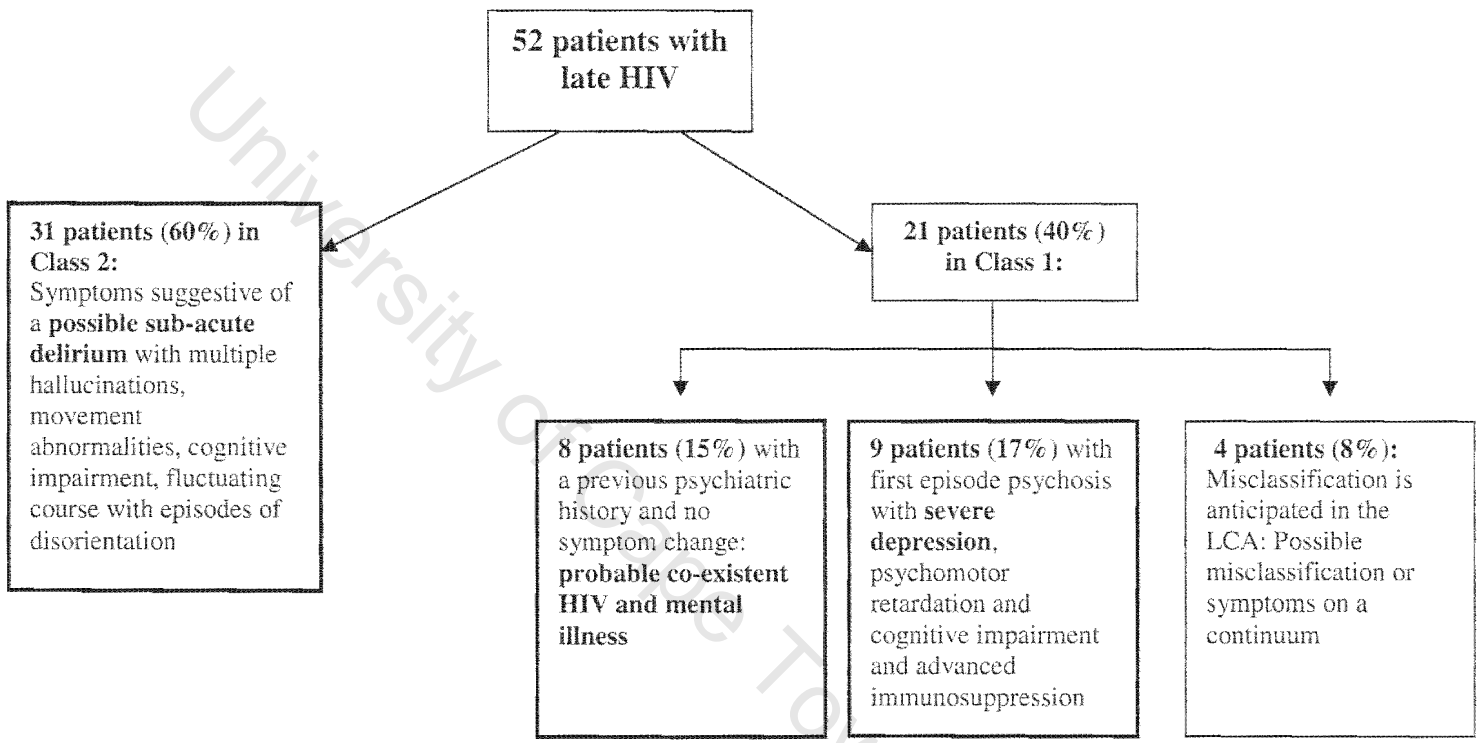
There were four patients in class 2 with early HIV disease and four who were HIV-negative. There was one patient in each group with borderline normal intelligence (This is the same patient as described with respect to previous past history above). At the time of the evaluation of these two patients, there was considerable debate as to whether they should be included in the sample. However it was decided to keep them in the sample as patients with borderline intelligence commonly present to psychiatric admission wards in Cape Town. Of the remaining three patients in the HIV-positive group, two had mixed affective states with marked fluctuation in symptoms and the third was probably a miss-classification as she had a CD4+ count of 277 cells/mm^3. Of the remaining three patients in the HIV-negative group, one patient was catatonic, alternating from catatonic stupor to an agitated catatonic excitement. One patient had severe tardive dyskinesia which severely interfered with cognitive testing with respect to psychomotor and motor tasks (This patient also had a past psychiatric history as discussed above). The third patient was initially presumed to be HIV-positive as he had lost more than 10 kg in weight and was presenting with psychotic symptoms of the first time.

There were 21 patients in latent class one with late HIV disease. Of these, eight had previous psychiatric histories which began prior to them developing symptoms of immunosuppression. None of these patients had a history of any change in their psychiatric symptomatology.

Of the remaining thirteen patients, nine patients (70%) had severe depression with severe psychomotor retardation and eight of them (62%) had suicidal ideation. Of the remaining four patients, two died shortly after the evaluation was concluded. The median CD4+ count of this group was 89 cells/mm^3 (IQR 57-171) which is similar to the median CD4+ count in class two (66 cells/mm^3). The median viral load was log 5.15 copies/ml (IQR 4.28- 5.66) which is higher than the median viral load for class two which was log 4.83 copies/ml. Of those patients who had magnetic resonance imaging (section 5.7 below), six (60%) had periventricular white matter changes and 7 (70%) had white matter changes.

In summary, the late HIV group was comprised of three main subgroups. The largest sub-group was comprised of patients in class 2 with symptoms suggestive of a sub-acute delirium. These patients had a high prevalence of multiple hallucinations, movement abnormalities, cognitive impairment, a fluctuating course, episodes of disorientation and advanced immunosuppression. The second subgroup was comprised of patients presenting with first episode psychosis characterised by severe depression, psychomotor retardation, cognitive impairment and advanced immunosuppression. The third subgroup was comprised of patients in Class 1 with probable co-existent HIV and mental illness who had experienced no change in their psychiatric symptomatology (figure 5.2).

Figure 5-2 Classification of patients with late HIV



5.7 Neuro-imaging and other laboratory findings

5.7.1 Neuro-imaging

Overall, 73 patients had CT scans (brain) and 42 patients had MRI's (brain), which was restricted to patients with late HIV disease as described in Tables 5.27 and 5.28. Only eight HIV-negative patients had CT scans done. With respect to relevant abnormal findings, 32 patients (74%) with late HIV, 11 patients (50%) with early HIV and three patients (38%) who were HIV negative had atrophy on CT scan (p=0.001). There was a trend across groups with an increasing prevalence of atrophy from the HIV-negative to the late group (p for trend=0.015). Seven patients in the late group and three in the early group had old calcified neurocysterceri, which were considered to be of no clinical relevance.

With regard to MRI findings, patients in class 2 were more likely to have atrophy than in class 1, although this did not reach significance, with 10 patients (63%) in class 1 and 22 patients (85%) in class 2 had atrophy on MRI (p=0.142). White matter changes were identified as high signal foci in the white matter on flair imaging. Patients in class 1 were more likely to have white matter changes with 12 patients (75%) in class 1 and 13 patients (50%) in class 2, having white matter changes. With regard to periventricular white matter changes only, changes were observed in 11 patients (69%) in class 1 and 9 patients (35%) in class 2 (p=0.055). Examples of MRI findings with respect to atrophy, white matter changes and, more specifically, periventricular white matter changes are presented in Figures 5-3 and 5-4.

Table 5-27 CT scan results by selection group

	Late HIV N=43		Early HIV N=22		HIV-negative N=8		p-value
	N	%	N	%	N	%	
Normal (excluding neurocystercosis)	11	26	11	50	5	63	0.047
Atrophy	32	74	11	50	3	38	0.047
Neurocysticercosis	7	16	3	15	0	0	0.693

Table 5-28 Neuroimaging by latent class

	Class 1		Class 2		p-value
	N	%	N	%	
CT scan	**40**		**33**		
Normal (excluding neurocystercosis)	22	55	5	15	0.001
Atrophy	18	45	28	85	0.001
Neurocysticercosis	3	15	7	16	0.693
MRI	**16**		**26**		
Normal	2	12.5	3	12	0.999
Atrophy	10	63	22	85	0.142
White matter changes	12	75	13	50	0.195
Periventricular white matter changes	11	69	9	35	0.055
Subcortical changes	2	13	3	12	0.999
Marrow signal of the clivus of cervical spine reduced	4	25	5	20	0.711

Figure 5-3 **MRI (flair) image illustrating severe atrophy and diffuse deep and sub-cortical and periventricular white matter changes (a)**

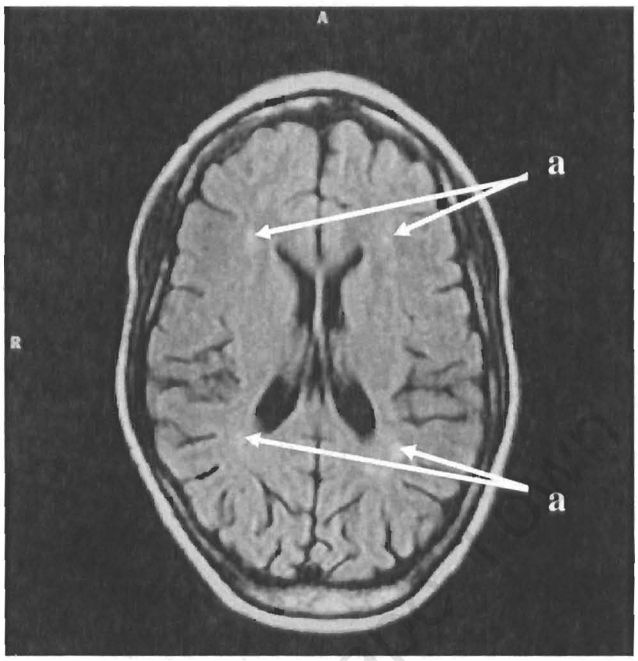
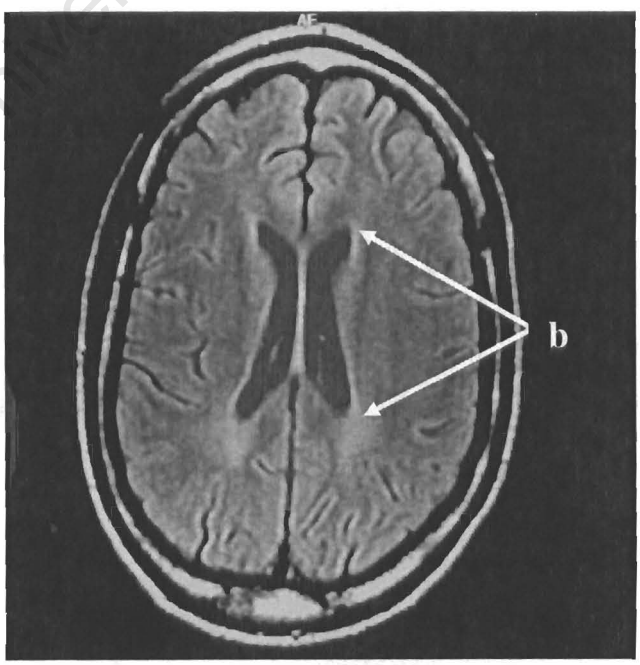


Figure 5-4 **Figure MRI (flair) image illustrating moderate cortical atrophy and diffuse periventricular white matter changes (b)**



5.7.2 Electro-encephalograms

The occurrence of possible seizures was queried in three patients. None of the patients had a pre-existing history of seizures. The first patient had a generalised tonic-clonic seizure, after he had been discharged from hospital, a few minutes before his death. With the second patient, seizures were queried after she had short-lived episodes of bizarre behaviour. The EEG showed non-specific slowing and there were no other features of seizures. The third patient had a history of two episodes of possible seizure-like activity subsequent to the development of the psychotic symptoms. These occurred in the community and were never confirmed. There was no evidence clinically or on investigations, subsequent to her admission, of any seizures. A total of 23 patients had EEG examinations (14 in the late HIV group, five in the early HIV group and four in the HIV-negative group). Only three were abnormal, all of which were reported as having non-specific slowing. All three patients had late HIV disease (p=0.743), one was in class 1 and two were in class 2 (p= 0.560).

5.7.3 Cerebrospinal fluid results, thyroid function and vitamin studies

It was only possible to measure the cerebrospinal fluid (CSF) viral load in 14 patients. The CSF viral load in the late group was slightly higher than that in the early group [mean=log 3.81 (SD=0.38) copies/ml as opposed to mean=log 3.30 (SD=0.31) copies/ml (p=0.202)]. Overall, the mean difference between the (log) viral load in the serum and the (log) viral load in the cerebrospinal fluid (CSF) was log 1.18 (SD 0.75) copies/ml. With regard to other CSF findings, most patients had normal CSF findings and those that were abnormal had non-specific findings. With respect to selection groups, 39 patients with late HIV (76%) had normal CSF measurements as opposed to 15 patients with early HIV (60%). Only eight HIV-negative patients had CSF evaluated. Patients in Class 2 [N=30 (79%)] were more likely to have normal CSF findings than those in Class 1 [N=29 (63%)] (p=0.151). With respect to the abnormal CSF results, the most common abnormality was an elevated CSF protein, often associated with a mild lymphocytosis or pleocytosis but the numbers were too small for formal analysis. With respect to thyroid function tests, two patients had low thyroid stimulating hormone levels, but both had

normal T3 and T4 levels. Folate deficiency was found in one patient and another patient was found to have low vitamin B12 levels.

5.8 Cohort study

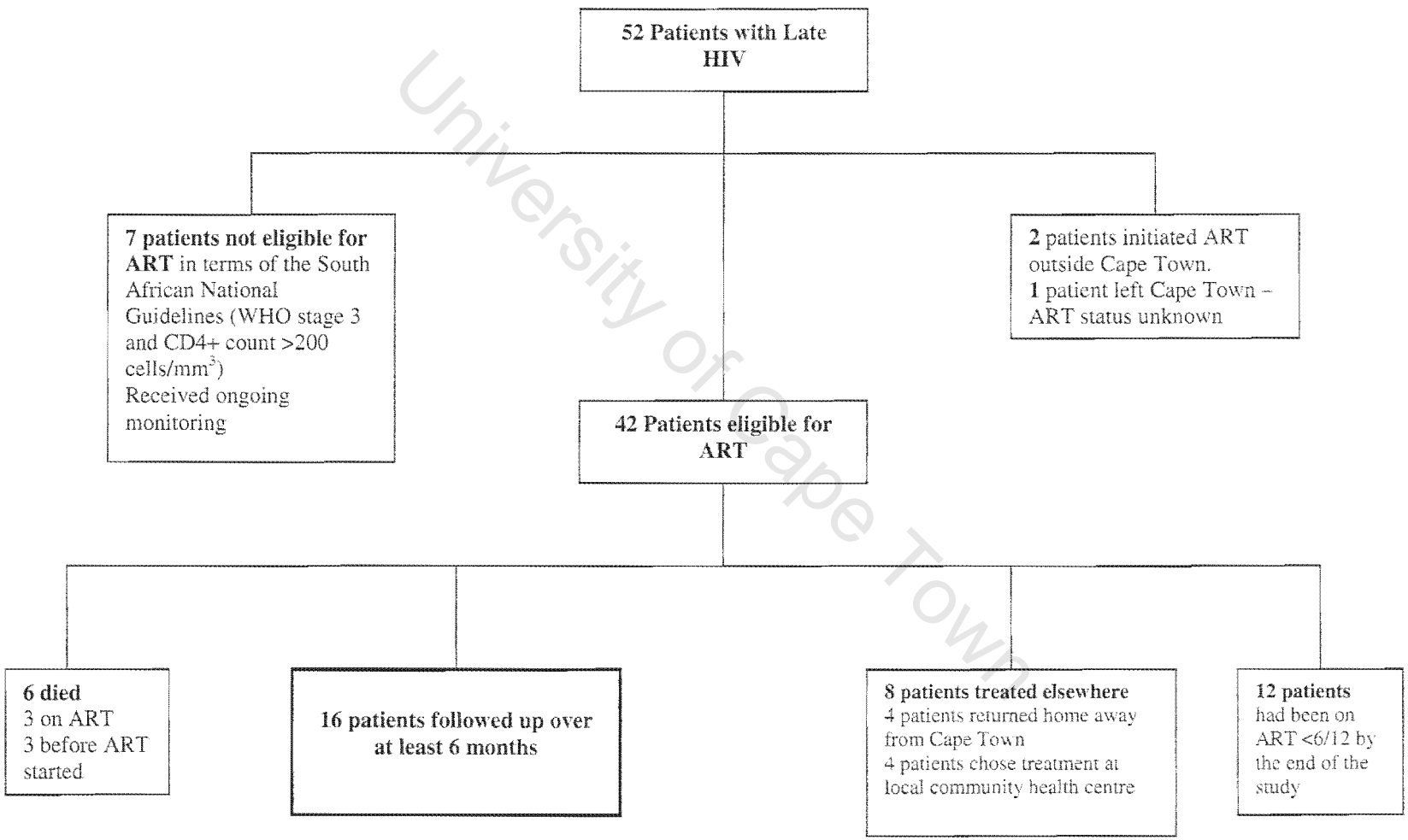
5.8.1 Process of sample selection

A summary of procedures followed in the cohort study is tabulated in Figure 5.5. A total of 52 patients were identified as having late HIV disease WHO stage 3 or 4, or a CD4+ count less than 200 cells/mm^3. Of these, seven were not eligible for ART in terms of the South African National guidelines as they had WHO stage 3 disease and CD4+ counts were less than 200 cells/mm^3. It is common practice for people to come to Cape Town seeking medical assistance and then return home once treatment is initiated. Three patients returned home to have ART initiated there. Of the 42 remaining patients who had ART initiated at the Desmond Tutu HIV Centre, eight patients chose to be treated closer to home once they were doing well. Six patients died during the course of the study, three before ART could be initiated and three who had recently initiated treatment. A summary of the patients who died is outlined in Table 5.29. Of the six patients who died, three were in class 1 and three in class 2. The cause of death was unknown in three patients with septicaemia being the probable cause in two patients and extra-pulmonary tuberculosis in the last patient. Of the remaining 28 patients, 12 patients had been on ART for less than six months by the time the study ended. The remaining 16 patients were followed up over a period of at least six months.

Table 5-29 Summary of patient deaths

Class	Clinical Stage	CD4+ count	Viral load (log, copies/ ml)	Psychiatric symptoms	Duration of ART	Probable cause of death
1						
1	3	21	4.97	Both depressive and manic symptoms, bizarre behaviour. No fluctuation or episodes of disorientation	14 days	Unknown
2	4	43	5.91	Depressive and manic symptoms. Irritable with fluctuation but no episodes of disorientation	9 days	Psychosis resolved. Died 2 weeks later from probable septicaemia
3	4	487	3.04	Psychotic depression. No fluctuation or disorientation. Became physically ill a week after psychosis settled	None	Extrapulmonary TB
2						
1	4	43	4.32	Irritable with depressive symptoms, labile with fluctuation and episodes of disorientation	None	Sudden death. Cause unknown. Normal neuroimaging
2	4	52	4.59	Labile with depressive symptoms. Fluctuation and episodes of disorientation	18 days	Psychosis resolved. Septicaemia. Intravenous antibiotics not given
3	4	33	4.53	Persecutory delusions and auditory hallucinations with prominent cognitive impairment. Later developed myoclonus	None	MRI excluded Progressive multifocal leucoencephalopathy (PML). Died the day before she was due to commence ART. Cause unknown

Figure 5-5 Follow-up of patients treated with antiretroviral medication



5.8.2 Choice of antiretroviral treatment

As discussed in Chapter 3, (Methodology), patients were treated with ART at the Desmond Tutu HIV Centre. Patients were started on a non-nucleoside reverse transcriptase inhibitor (NNRTI)-containing regimen for their first line treatment: nevirapine or efavirenz plus stavudine and lamivudine. Nevirapine was the drug of choice due to the concerns outlined in Chapter 3 regarding efavirenz use in psychotic patients. Kaletra with additional ritonavir was initially used for patients with tuberculosis but this was soon changed to efaverinz (with appropriate contraceptive advice due to its teratogenicity) as the large pill burden led to problems with adherence. By the end of the study, 15 patients were on efavirenz-containing regimens with no patients experiencing exacerbation of psychotic or manic symptoms. Nevirapine-based regimens were used in 14 patients long-term and eight patients received kaletra with additional ritonivir-based regimens.

5.8.3 Description of Sample

The description of the cohort and the progress over six months is documented in Table 5.30. Of the 16 patients, 15 were female, none had a family history of psychiatric illness, and one had a past psychiatric history. With respect to the latent class analysis, five patients were in class 1 and eleven in class 2. The patients' progress was formally documented monthly and most of the patients' psychiatric and physical symptoms began to settle once they had been on ART for about eight weeks, although many of them began to improve before then. At the eight-week visit, nine patients showed clear improvement or symptom resolution. At the 12-week visit, a further six patients had improved and one patient took between 16–20 weeks to improve.

Table 5-30 Description of cohort and progress over six months

Class	Age	Clinical features on admission	Course	Clinical features at 6 months
1				
1	23	Acute onset of disruptive behaviour. Prominent auditory hallucinations persecutory delusions and delusions of reference	Recovered very well and had an uncomplicated course	Very good physical and psychiatric health. Euthymic apsychotic. Excellent adherence
2	24	Acute onset of psychotic and depressed symptoms, preceded by a manic episode a month previously. Marked EPSE	Developed a pancytopenia, responded well to ART	Excellent adherence. Well
3	46	Fearful, aggressive, depressed with persecutory delusions. Marked psychomotor slowing	Responded very well to ART and to fluoxetine	Very well. Normal cognitively but still slow motorically. Excellent adherence
4	41	Sub-acute presentation of manic and psychotic symptoms. Agitated and labile. Marked fluctuation in behaviour	Symptoms resolved quickly. Ongoing depression and struggled with adherence	Depression improved with additional support and fluoxetine and euthymic. Adherence then improved.
5	33	Acute presentation of manic symptoms with mood lability, irritability and aggression	Initially had poor insight but this improved Subsequently developed pulmonary TB	Euthymic and apsychotic. Insightful with excellent adherence
2				
1	29	Acute onset of manic and psychotic behaviour. Euphoric and labile. Marked fluctuation	Developed diarrhoea, herpes zoster and PTB. Adherence which improved after further counselling and support	Insight improved. Still struggling at times with adherence
2	29	Acute onset of psychotic symptoms. Marked fluctuation. Initially agitated and then psychomotor retarded	Subsequently developed a bronchopneumonia and PTB	Functioning well. Adherence excellent. Memory improved
3	22	Gradual onset of cognitive slowing, visual and tactile hallucinations with persecutory delusions	Symptoms resolved when on ART for 2 months	Well. Very good adherence. No cognitive slowing, restarting grade 12.
4	24	Gradual onset of depressive & psychotic symptoms. Marked lability and fluctuation. Severe EPSE on low doses of haloperidol	Only started to settle after being on ART for 2-3months	Very well. Engaging, motivated. Excellent adherence

Class	Age	Clinical features on admission	Course	Clinical features at 6 months
2				
5	31	Presented after trying to hang herself. Fluctuating psychotic and affective illness (depressive and manic). Marked EPSE. Cachectic	Pulmonary TB which complicated the initiation of ART. Began to settle after 3 months on ART	Adherence excellent. Went home shortly after 6 months on ART. Gained 16 kg
6	22	Acute onset of psychosis and depression. Cognitive impairment. Severe akathisia. Labile, terrified, overwhelming delusions of guilt and persecution. Cachectic	Immune reconstitution problems. CMV retinitis. Hepatits- had to be taken off nevirapine and changed to efaverinz. Gained 20kg	Very well. No cognitive problems. Very good adherence. **At 1 year:** Very well. Looking for employment. Adherence maintained.
7	25	Acute onset of depressive and psychotic symptomatology. Prominent hallucinations and delusions. Marked fluctuation. Became catatonic. Cachectic	Immune reconstitution problems. CMV retinitis which resulted in a retinal detachment in her right eye. Also developed disseminated TB. Gained 20kg	Very well. **At 1 year:** Feels completely recovered. Has returned to university and is managing well. Was interviewed on television about her experience of having HIV-related neuropsychiatric disease.
8	30	Several months of cognitive symptoms and depressed mood.Tried to stab his wife. Psychosis and cognitive impairment. Severe functional impairment with episodic severe aggression.	Slow improvement, symptoms began to improve after 2 months on ART. Psychotropics: poorly tolerated and poor response.	Much improved. Mild frontal lobe symptoms. Impulsive with limited insight. Euthymic and apsychotic. Gained 19 kg. **At 2 years**: working, fully functional, socially appropriate. On no psychotropics
9	25	Acute onset of psychotic symptoms with lability. Fluctuation: irritable & intermittently aggressive.	Psychotic symptoms resolved. Did very well physically. Gained 17 kg	Very well physically. Struggling to come to terms with living with HIV. Apsychotic but mild depression related to HIV status. Excellent adherence.
10	30	Acute onset of depressive and psychotic symptoms. Marked fluctuation with short lived episodes of behavioural disturbance.	Extrapulmonary TB. Symptoms responded well to sodium valproate.	Adherence excellent. Functioning very well. Cognition normal
11	24	Gradual presentation of depressive and psychotic symptoms. Marked fluctuation with episodes of disorientation	Completed TB treatment. Psychiatric symptoms settled after 2 months on ART	Feeling well and functioning normally. Adherence very good

5.8.4 Adherence

Initially, adherence was ensured by the nursing staff in the hospitals to which patients had been admitted. Treatment partners assisted with adherence maximisation after the patients were discharged from hospital. At six-month review, two patients had had problems with adherence. With respect to one patient, adherence was negatively impacted by depressive symptomatology and improved after the patient started fluoxetine. Another patient had more intensive adherence counselling and her adherence subsequently improved with additional support from her family.

5.8.5 Findings at six month assessment

Overall, patients did extremely well and, by six months, had returned to very good levels of functioning. Continued improvement from six months to a year was noted in the three patients who were followed up for more than a year. No patients were acutely mentally ill at six months. Table 5.31 describes relevant formal measures, laboratory findings and medication at baseline and at six months. The baseline Delirium Rating Scale-98 ranged from seven to twenty nine. At six months, all 16 patients scored zero. Physically, the patients improved dramatically, many of them gaining more then 10 kg in weight and were unrecognisable when compared to their initial physical appearances. Many of them returned to the previous levels of functioning, with one patient returning to university. After she left the study, this patient was interviewed on national television as part of a discussion of the mental health consequences of HIV. She spoke about her experiences of having had an affective psychosis, during which time she became catatonic as well as her subsequent recovery.

Table 5-31 Formal measures, laboratory findings and medication

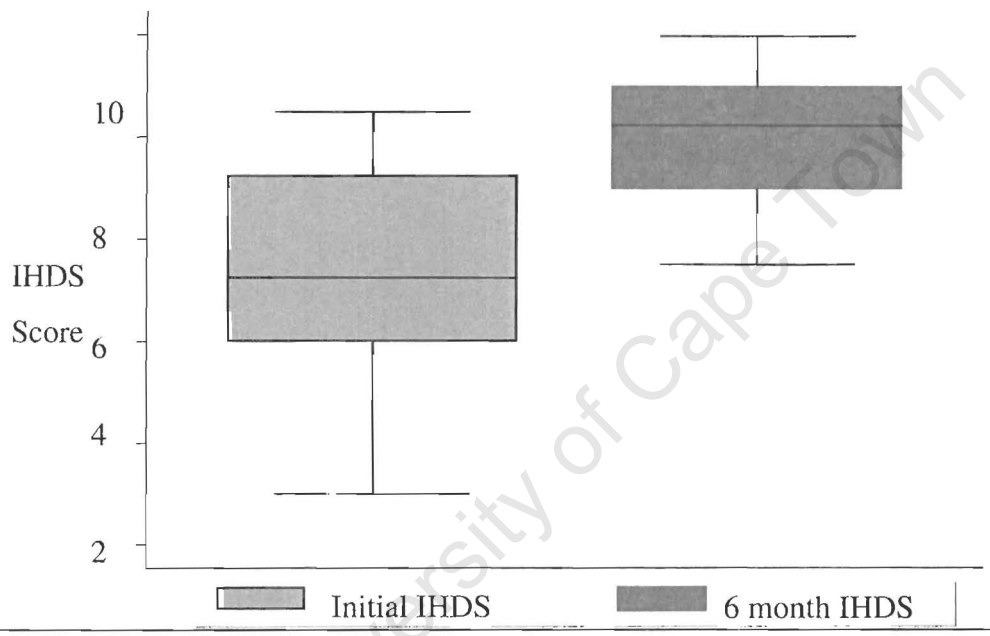
Class	Initial DRS-98	Initial IHDS (max=12)	6 month IHDS (max=12)	Initial CD4+ count (cells/mm^3)	6 month CD4+ count (cells/mm^3)	Initial viral load (copies/ml)	6 month viral load (copies/ml)	Initial Medication	Psychotropics at 6 months
1									
1	18	6.5	9	57	140	nr [a]	ldl [b]	Haloperidol 0.5 mg po BD	Haloperidol stopped at 6 month visit
2	7	10.5	10.5	89	444	Log 5.65	ldl	Haloperidol 0.5 mg po BD Amitriptyline 100 mg po nocte	None
3	19	6	8	73	168	Log 5.08	ldl	Fluoxetine 20 mg daily Haloperidol 0.5 mg po BD	None
4	18	9.5	11	129	nr	Log 4.72	ldl	Haloperidol 1 mg po BD	Fluoxetine
5	18	5.5	7.5	188	nr	Log 4.15	ldl	Lithium carbonate. Haloperidol 1.5 mg BD	Lithium carbonate
2									
1	18	9	10	17	175	Log 5.7	Log 2.85	Chlorpromazine 100 mg po nocte. TB treatment	None
2	29	9	11.5	78	140	Log4.32	ldl	Haloperidol 0.5 mg am and 2.5 mg po nocte, TB treatment	None
3	24	6	11	208	415	Log 5.36	ldl	Haloperidol 2 mg po nocte	None
4	16	8	10	164	403	Log 4.15	ldl	Fluoxetine 20mg alternate days. Chlorpromazine 50 mg po am and 100 mg nocte	None

Class	Initial DRS-98	Initial IHDS (max=12)	6 month IHDS (max=12)	Initial CD4+ count (cells/mm^3)	6 month CD4+ count (cells/mm^3)	Initial viral load (copies/ml)	6 month viral load (copies/ml)	Initial Medication		Psychotropics at 6 months
2										
5	22	6.5	9	28	169	Log 5.45	ldl	Haloperidol Reduced to after she developed severe EPSEs. Sodium valproate	5-10mg day. 1.5 mg daily	Sodium valproate
6	21	9	9.5	11	321	Log 5.04	ldl	Haloperidol	2 mg BD	None
7	24	10	11	34	371	Log 4.83	ldl	Haloperidol Lorazepam, valproate	5 mg stat dose. sodium	Sodium valproate stopped at 6 month visit
8	16	6.5	9	28	189	Log 5.36	ldl	Haloperidol Fluoxetine	1.5 mg BD, 20 mg daily	Clozapine 12.5 mg po BD
9	27	3	11	130	401	Log 5.57	ldl	Haloperidol Citalopram TB treatment	0.5 mg po BD, 20 mg po BD	None
10	22	4	12	14	nr	Log 5.81	ldl	Haloperidol Sodium valproate	0.5 mg BD,	Sodium valproate
11	12	10	11	15	nr	Log 4.61	ldl	Haloperidol	2 mg po nocte	None

[a] nr = not recorded; [b] ldl = lower than detectable limited

When comparing baseline scores with those at six months, there was a significant improvement in the International HIV Dementia Scale (IHDS) scores (maximum score =12). The baseline mean IHDS score (N=16) was 7.45 (SD= 2.26) and the score at six months was 10.06 (SD=1.28) p<0.001) (Figure 5.6). The IHDS score remained unchanged in one patient (10.5) who had no cognitive impairment at baseline.

Figure 5-6 Box Plot of International HIV Dementia Scale at baseline and six months



There was significant improvement with respect to most of the formal neuropsychological measures as described in Table 5.32. The baseline mean successive finger tapping score, (non-dominant hand) was 11.7 (SD=4.13) seconds and the six month score was 9.58 (SD=2.19) seconds (p= 0.041) indicating completion of the task in a shorter period of time, whereas the difference with respect to the dominant hand was not significant. The differences with respect to the Grooved Pegboard Test, both dominant and non-dominant hands were significant with the time taken for the task reducing from a mean of 120.17 (SD=28.61) seconds at baseline for the dominant hand test to 87.67 (SD=28.61) seconds at six months (p=0.002). The non-dominant mean time at baseline was 136.27 (SD=19.65) seconds and 91.73 (SD=20.71) seconds at six months

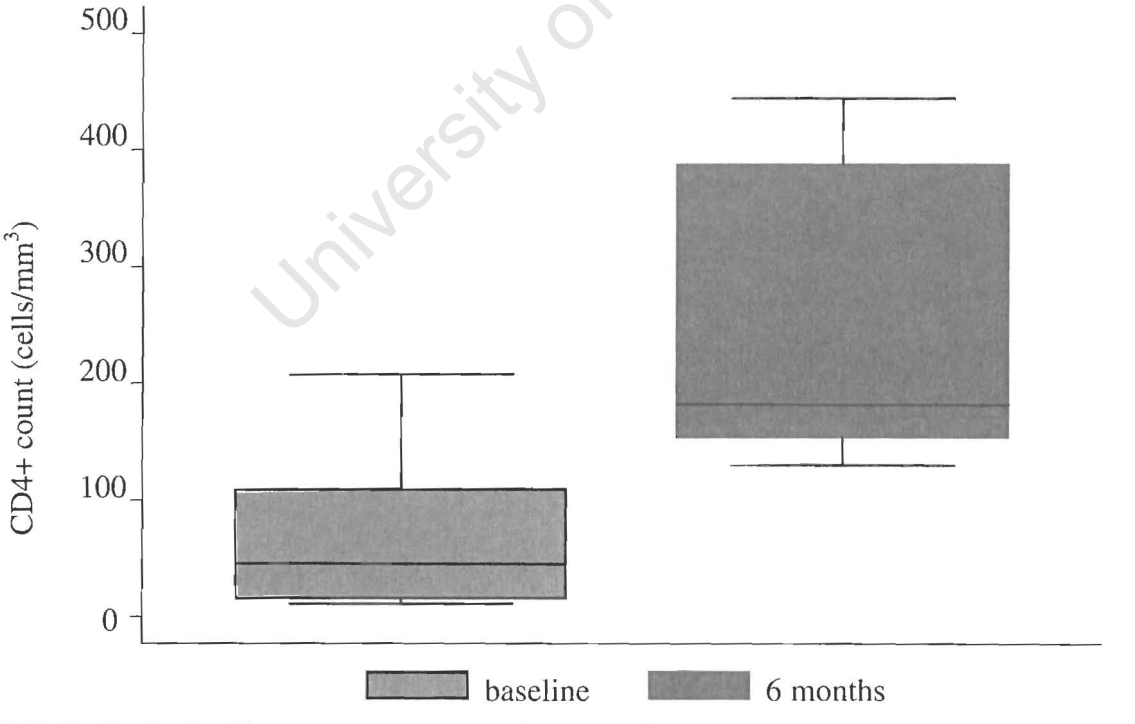
(p=0.001). There were also significant improvements with respect to the Trail Making Test–A (p= 0.011), and the copy and initial drawing of the Rey Complex Figure (p=0.029 and p=0.036 respectively). When the patients who were seen at six month follow-up were compared to the HIV-positive control group with no mental illness (appendix L), there were no significant differences between the groups apart from one measure of visual memory, constructional ability and executive functioning (p=0.037). The patients at six month follow up were slower with respect to fine-motor speed, but this was marginally significant (p=0.053).

Table 5-32 Neurocognitive evaluation at baseline and at 6 months

	N	Initial evaluation		Six month evaluation		p-value
		Mean	SD	Mean	SD	
Successive Finger Tapping, dominant hand (seconds)	13	12.37	6.8	10.02	2.84	0.254
Successive Finger Tapping, non-dominant hand (seconds)	13	11.7	4.13	9.58	2.19	0.041
Grooved Pegboard Test, dominant hand (seconds)	12	120.17	28.61	87.67	28.61	0.002
Grooved Pegboard Test, non- dominant hand (seconds)	12	136.27	19.65	91.73	20.71	0.001
Digit Span, forwards (scaled score)	12	7.75	1.91	6.67	1.56	0.047
Rey Complex Figure, copy	13	22.69	7.59	26.84	4.52	0.029
Rey Complex Figure, initial	12	13.16	8.16	19.17	13.99	0.0359
Rey Complex Figures, delayed	10	13.70	6.57	16.70	5.89	0.0617

The mean CD4+ count (N=12) was 66.5 cells/mm^3 (SD=62.5) at baseline and 255.4 cells/mm^3 at six months (SD=123.9) p< 0.001) (Figure 5.7). With respect to viral load measurement, as discussed in the chapter 4 (Methodology), a viral load of < log 2.60 is considered to be adequate viral suppression [lower than detectable limit (ldl)]). Therefore, for the purposes of comparison, it was assumed that the viral load was log 2.60 when recorded by the laboratory as ldl. The mean baseline viral load (N=15) was log 5.05 (SD=log 0.57) compared to the 2.62 (SD=0.06) at six months (p<0.001). With respect to psychotropic medication at six months, nine patients were not taking any psychotropic medication and two patients had their psychotropic medication stopped at six months. Decisions with respect to treatment duration were individualised. Mood stabilisers were more likely to be continued beyond six months with the plan to stop them once patients had been on ART for a year, provided that they were well.

Figure 5-7 Box Plot of CD4+ counts at baseline and 6 months



Chapter 6. Discussion

6.1 Introduction

Over the past ten years, there has been an increase in the number of HIV-positive patients presenting at the University of Cape Town linked psychiatric facilities with psychotic and mood symptoms. These patients posed a number of clinical challenges in that they presented with atypical features, comprising a mixture of affective and psychotic symptoms, which appeared to fluctuate over the course of their admissions. Furthermore, they had cognitive impairment and poor psychiatric and medical prognoses with high morbidity and mortality. Although acute medical illnesses, other than HIV itself, were excluded in these patients, their clinical features suggested the existence of a sub-acute delirium. Patients appeared to be resistant to treatment and often developed prohibitive side-effects which prevented dose increases. Their hospital stays were longer than most other patients and re-admission rates were high. Management was complicated by co-existing medical problems and HIV-positive patients with mania and psychosis had limited access to antiretroviral treatment. There was limited information available as to which special investigations would be appropriate in our local context and practice varied greatly between facilities. As the epidemic grew, there was a growing urgency to clarify the diagnostic features of HIV-positive patients presenting with psychotic and manic symptoms so that patients could receive appropriate treatment for AIDS-related neuropsychiatric diseases. This chapter summarises the arguments and results presented in this thesis thus far. Each of the 12 latent variables, as well as the findings by latent class, are discussed with reference to the available literature within the framework of the broader arguments in the thesis. Strengths and limitations of this study are discussed as well as suggestions with respect to possible future avenues of enquiry in this field.

The central hypothesis of the thesis was that HIV psychosis and mania are not distinct clinical entities, but rather overlapping manifestations of the neuropathophysiological consequences of HIV infection on the central nervous system in patients vulnerable to the inflammatory activation of neurotoxic processes resulting in psychotic and affective symptoms. The specific hypotheses are that patients with HIV-associated psychosis and

mania have clinical features indicative of a sub-acute delirium, and that many of them have associated cognitive impairment. It was also hypothesised that HIV-associated mania and psychosis are AIDS-defining features and should be indications for antiretroviral treatment.

6.2 Diagnostic validity of HIV-associated psychosis and mania

The atypical presentation of HIV-positive psychotic and manic patients highlights one of psychiatry's most serious challenges: the lack of diagnostic validity in psychiatric diagnoses within the categorical models which frame our understanding of psychiatric disorders. In order to develop the methodology to describe HIV-related neuropsychiatric features, a critical examination of the clinical and neurobiological evidence with respect to diagnostic validity in psychiatry was conducted in Chapter two. This focused in particular on the possible conceptualisation of HIV psychosis and mania within the context of other psychiatric disorders manifesting with psychotic, mood and fluctuating symptoms. The appraisal was conducted with four questions in mind: are the current diagnostic systems valid in that they described discrete diagnostic entities? If there are problems with diagnostic validity in primary psychiatric disorders presenting with psychotic or manic symptoms, is there a model available that may improve the diagnostic validity? How are HIV-associated psychosis and mania conceptualised within this new model? What methodological approaches would be useful to address the challenges surrounding the examination of HIV-associated psychosis and mania as diagnostic entities?

Disorders presenting with psychotic and manic symptoms are characterised by waxing and waning heterogeneous symptoms and a lack of natural boundaries between disorders. Treatment responses are non-specific and there are overlapping genetic and psychosocial mediators of disease. Although categorical systems have historically distinguished between primary and secondary psychiatric disorders, they are both secondary to underlying neuropathophysiological processes, some of which overlap. The main difference between them is that the aetiological agent or process involved in the

generation of secondary symptomatology is more readily identifiable. The diagnosis of a psychosis or mania due to general medical condition is difficult as there is often an overlap in symptomatology between delirium, psychosis and dementia. The onset of symptoms over the age of 35 years, the absence of a personal or family history, atypical features and the temporal association with the onset or change in the underlying medical illness have been suggested as indicators of secondary psychosis or mania (12). There is a large overlap in symptomatology between psychosis, mania and delirium including distractibility, hallucinations, delusions, sleep changes, agitation, disinhibition, affective symptoms and cognitive symptoms (12;40;43). Furthermore, patients with Lewy Body dementia, a neurodegenerative disease involving the cortex and sub-cortical structures, can present with symptoms very similar to those of a delirium (52). The phenomenological distinction between psychosis and delirium becomes particularly difficult in the context of the repeated acute medical illnesses superimposed on a chronic neuropathological entity such as HIV. There is also considerable overlapping symptomatology between HIV-associated dementia and HIV-associated psychosis and mania (70).

Neurobiological evidence supports an overlap in the neurophysiology of disorders manifesting with psychotic and manic symptoms. There are data supporting shared susceptibility to primary and secondary psychotic disorders with respect to an overlap in genetic susceptibility to behavioural disturbance in Alzheimer's disease, HIV-associated dementia, multiple sclerosis and schizophrenia (82). There is increasing recognition of the importance of inflammation and immunological pathways in the pathophysiology of psychosis and mania which may explain the intermittent nature of many psychotic and affective disorders (87). Some of the cytokines and other pro-inflammatory modifiers implicated in schizophrenia are activated by the infection of the central nervous system by HIV (82). After HIV breaches the blood-brain barrier, the development of subsequent neuropsychiatric and neurological sequelae appears to be dependent on the activation of pro-inflammatory pathways resulting in neurotoxic damage which may be offset by anti-apoptotic mechanisms, possibly through the regulation of calcium homeostasis (83).

Conceptualisation of psychiatric disorders can be improved through the use of specific methodological approaches such as phenomenological studies crossing traditional categorical boundaries which will enable the identification of correlations between symptoms clusters and underlying neurobiological processes. Cluster analytic methods can facilitate the identification of cross-category latent variables and thereby assist in establishing clinically valid and stable diagnostic phenotypes. The relationship between these phenotypes, or underlying endophenotypes, and possible neurophysiological mechanisms and genetic determinants of susceptibility or resilience, can be investigated. In terms of this model, the extent to which an underlying genetic vulnerability expresses itself in the form of the disorder is dependent on a number of co-factors, both biological and psychosocial. A number of "hits" are therefore required for the disease to manifest. The data are suggesting that some "hits" may be mediated through inflammatory pathways as appears to be the case with respect to HIV psychosis and mania. It is therefore the interaction between the various constituents of these pathways and between the pathways themselves that ultimately confer protection or pathology to psychosis or mania in an HIV-positive person. Common symptoms may therefore result from shared and different "hits", conferring vulnerability in some contexts but not in others.

6.3 Systematic review

A systematic review, in all languages, of HIV-associated psychosis and mania was described in Chapter three. Increased prevalence in psychotic and manic symptoms has been reported in HIV-positive patients. The systematic review addressed four main questions: what evidence is there that HIV-associated mania and psychosis exist? If they do exist, what features characterise their clinical presentation? Are they distinct entities, and if not, how are they related to each other? What is their relationship to HIV staging and their role in indicating the need for antiretroviral treatment? The review included 58 studies, of which 52 were case reports, letters or case series. The remaining six studies reported comparisons between patients with HIV psychosis or mania and another condition. The studies reflect the evolution of understanding with respect to HIV from isolated case reports in the 1980s to a large study from Uganda in 2006. Most of the

sample sizes were small and there was variability with respect to the definition of HIV-associated mania or psychosis. Terminology to describe symptomatology and diagnoses was often loosely applied and information was often incomplete. This particularly applied to the case reports and case series, where symptoms of interest were discussed rather than all possible symptoms. The findings with respect to the case reports and case series documented in Table 3.1 may therefore have limitations with respect to the accuracy with which they reflect symptom frequency. The studies reviewed were all subject to some extent to redundancy with respect to methodology. HIV-positive patients with psychotic or manic symptoms were defined as having HIV-consequent symptoms by virtue of their selection and then examined using definitions, instruments and methodological approaches that had either informed the initial group selection or were directly derived from it.

The systematic review confirmed that the increased prevalence of manic and psychotic symptoms in HIV-positive patients occurs late in the disease when patients have advanced immunosuppression and low CD4+ counts. In the studies that focused on manic symptoms, irritability and psychotic symptoms were reported as being prominent and in those focusing on psychosis, affective symptoms were described as being prominent. Persecutory and grandiose delusions were common and electroencephalogram (EEG) findings were non-specific. There was also evidence that psychotic or manic symptoms may be the presenting symptoms which lead to the diagnosis of AIDS. A single small neuroradiological study in HIV-associated mania and another small study in HIV-associated psychosis were described. Cerebral atrophy was documented in 26% of the patients with HIV-associated mania and 33% of the patients with HIV-associated psychosis. HIV- associated mania and psychosis were also both associated with impaired cognition and poor tolerability of psychotropic agents. This evidence suggests that HIV psychosis and mania do exist but not as mutually exclusive entities. It is more likely that they represent overlapping manifestations of the underlying neuropathophysiological consequences of HIV disease in the central nervous system. Patients with HIV-associated psychosis and mania had a poor prognosis and there was evidence that antiretroviral treatment may be protective against developing symptoms as well as in treatment. This

suggests that, as with HIV-associated dementia, HIV-associated psychosis and mania should possibly be considered as AIDS-defining phenomena and should therefore be indications for the commencement of antiretroviral therapy.

6.4 Results

6.4.1 Sociodemographic information and sexual behaviour

The median age across the three selection groups in the sample varied from 29 to 34 years and replicates previous findings in the literature. The mean age in the case reports and case series described in the systematic review in Chapter three, was 34 years and the mean age for the comparative studies was between 33 and 37 years (134). A study in Uganda reported a mean age for the HIV-negative of 25 years, as opposed to 34 years in this study (6). Possible reasons for this, as discussed in chapter three, may relate to the establishment of HIV prevention programmes in Uganda in the 1990s. There was no difference in this study between groups with respect to education with approximately one third of patients having had primary school education or less. The findings from this study with respect to other associated demographic parameters are similar to those found by Nakimuli-Mpungu *et al.* in Uganda and reflect differences between sociodemographics of the HIV pandemic in the developing world as opposed to epidemics within sub- populations found in the developed world (6). For example, most of the patients in this and Nakimuli-Mpungu *et al's* study were female, whereas most of the patients in the studies from the developed world were male. Furthermore, studies from the developed world report a high prevalence of intravenous drug use in their samples, whereas this was rare in this sample, even among the excluded patients. Most of the patients in the sample were heterosexual as opposed the high prevalence of HIV found in homosexual men reported in studies from the developed world (62;94;131;134).

In keeping with the epidemiology of HIV in South Africa, the patients in this study were predominantly black, Xhosa-speaking and poor. Employment rates were low in the sample, with less than 20% of the patients employed and 50% of the HIV-positive patients' families living on less than R 1000 per month. The HIV-negative group was

also poor, with 43% living on less than R1000 per month. When analysed according to latent class, patients in class 2 were significantly less likely to be on a disability grant which may reflect the difficulty that HIV-positive patients with serious mental illness have in accessing social support. Overall, most patients (80%) did not use condoms or used them inconsistently and 42% reported having had five or more sexual partners. There was no difference between groups with respect to the number of sexual partners or condom use.

6.4.2 Medical findings

Medical findings reported in the patients with late HIV reflect the high medical morbidity in this population. Patients in this study were more immunocompromised than those described in the Ugandan study with the overall median CD4+ count among the HIV-positive patients, being 176 cells/mm^3 as opposed to a median of 272 cells/mm^3 (6). In this study, patients in Class 2 had advanced immunosupression with a median CD4+ count 66 cells/mm^3. The high prevalence of tuberculosis is consistent with findings in the literature and reflects the high prevalence of this disease in the Western Cape province of South Africa where the tuberculosis epidemic is superimposed on the HIV epidemic with devastating consequences for affected people (6;270). Sub-group analyses, however, suggest that tuberculosis itself was not driving any of the data in the study.

6.4.3 Personal and family history

The absence of a personal or family psychiatric history, as described in Chapters 2 and 3, has frequently been used as part of the definition of having HIV-consequent mania or psychosis. The findings in this study were interesting in this regard. Patients with late HIV were far less likely to have had a previous episode of psychosis or mania than patients with early HIV or HIV-negative patients. This finding was replicated in the latent class analysis in which patients in class 1 were far more likely to have had a previous episode than those in class 2. This is consistent with previous studies and suggests that HIV-consequent mania and psychosis are associated with late stage HIV disease (131;134). Overall, a positive family psychiatric history was reported in 18% of patients and in 30% of the HIV-negative patients. This is low when compared to some other studies where rates of 80–90% have been reported in patients presumed to have primary

psychosis or mania (6;134). One study reported a rate of 7.7% amongst psychotic patients (131). It is possible that underreporting with respect to family history occurred in this study as many of the patients were living far from their families of origin as it is a common occurrence in South Africa for people to move to the cities in search of work or medical care. Although it was possible to get collateral information concerning the patient's symptomatology and recent history, caregivers were often unaware of the patient's family history or more distant past history. Comparisons between the groups were therefore more useful than the overall numbers. In this regard, a family's psychiatric history was only marginally significant, both with respect to analysis by selection group and by latent class. This supports the possibility that patients with a high genetic vulnerability to psychosis or mania may develop primary disorders, whereas those with a moderate degree of vulnerability, together with abnormal inflammatory reponses to HIV infection, developed symptoms in the presence of additional central nervous system damage secondary to the neurotoxic consequences of HIV.

6.4.4 Duration of symptoms and length of hospital stays

Although the symptom duration prior to admission to hospital was reported to be weeks or months in most patients, patients with late HIV had a higher frequency of presenting with an acute history over days and there was trend across groups towards longer hospital admission. Delirious patients are usually described as presenting with symptoms over a matter of hours rather than days, and in this respect, the patients in this study differ from patients with acute delirium. There was no difference in the duration of admission across groups, which was contrary to the experience of clinicians in Cape Town prior to the study where patients with advanced HIV usually had long hospital stays and frequent re-admissions. These findings are also different from those described by Nakimuli-Mpungu *et al.* (6) in which HIV-positive patients were reported as having shorter hospital stays (6). This difference may be due to local health-system related issues and different selection criteria for the two studies.

With respect to this study, there are a number of possible explanations as to why the patients with advanced HIV did not have the protracted hospital stays previously

experienced. The first is that patients in this study received intensive physical and psychiatric evaluation and probably had more rapid intervention with respect to complications than with the previous standard of care. As discussed in Chapter four, staff at all the sites received in-service training with respect to the diagnosis and management of patients with neuropsychiatric HIV, including advice that very low-dose neuroleptics should be used wherever possible. The greatest factor in shortening the length of hospital admission was probably that most of the patients in this group were treated with antiretroviral medication. Another possibility is the selection bias with respect to the HIV-negative group. As mentioned in Chapter four, patients were not tested for HIV for the purposes of the study, but for clinical reasons. HIV-negative patients were therefore tested because clinicians thought that they might be HIV-positive. This was usually because they were not responding to treatment, had atypical features or were physically ill, which resulted in longer hospital stays. This is supported by the fact that the mean hospital stay for all patients in the admission wards in the psychiatric facilities in which the study was conducted was approximately 20-30 days during the time of the study. This was considerably shorter than for all the groups in this study, whose mean admission lengths varied from 51-58 days.

6.4.5 Clinical features compared across selection groups

All the patients had at least one psychotic symptom. This is a reflection of the pressure on mental health service in Cape Town, where the threshold for admission to psychiatric facilities is very high. Patients who are not behaviourally disturbed or psychotic, and even those who are mildly psychotic, are not admitted because of the shortage of beds. Both psychotic and mood symptoms were prominent, in keeping with previous studies (6;94). Manic symptoms were more prevalent in the HIV-negative group. In a sub-analysis of the severity of mania, patients with late HIV had more severe manic symptoms, were more irritable and more behaviourally disturbed with a trend across groups for these variables. The increased severity of mania and disruptive aggressive behaviour is consistent with the findings of Nakimuli-Mpungu *et al.*, but their mean scores for mania on the Young Mania Rating Scale were higher (6). This may be due to differences in the application of the scale as well as the patients in this study being

reluctant to disclose information concerning sexual behaviour and the difficulties rating the appearance of patients, as discussed in Chapter four. The increased irritability is consistent with findings from a number of other studies (134). HIV-positive manic patients were more thought disordered than HIV-negative patients which is consistent with Nakimuli-Mpungu *et al.*'s findings, but HIV-negative patients were more likely to have increased motor activity compared to the HIV-positive patients. This is contrary to finding by Nakimuli-Mpungu *et al.* (6) who also found significant differences in speech which were not replicated in this study.

Symptoms of depression were significantly more common in the late HIV group with a trend towards increased prevalence across groups. This is in keeping with the findings of Sewell *et al.* (94) who reported depressed symptoms in 55% of patients in their study on HIV psychosis. The other comparative studies did not report specific findings with respect to depressive symptomatology and three of them had mania as an inclusion criterion, which would have excluded depressed patients apart from those presenting with a mixed- affective state. Patients with late HIV had an increased prevalence of lability, behavioural disturbance and, although not significant, were more likely to have suicidal ideation and intent than other groups.

Delusions and hallucinations were very common across all three groups. HIV-negative patients had higher prevalence of grandiose and religious delusions and they were more likely to have multiple delusions with a trend across groups. The reverse was found for hallucinations as patients with late HIV were more likely to experience multiple hallucinations, as well as being more likely to have visual and tactile hallucinations with a trend across groups to the HIV-negative group. The findings with respect to the higher prevalence of visual and tactile hallucinations are consistent with previous studies (6;94;131). Patients with late HIV were more likely to have symptom fluctuation and episodes of disorientation during admission. These differences were highly significant and did not appear to follow a trend across groups. To my knowledge, no other studies have specifically looked at the mean number of different types of hallucinations, fluctuation or disorientation. With respect to movement abnormalities, patients with late

HIV had a much higher frequency of movement abnormalities, particularly extra-pyramidal side-effects (which also followed a trend across groups), which is consistent with findings in other studies (94).

Patients with late HIV had higher mean and median scores on both delirium rating scales. The differences across groups were highly significant with a trend towards increased scores on many of the subtests, as well as the overall means. The scales confirmed the findings from the clinical interviews with respect to shorter onset of symptoms, impaired cognition, orientation, symptom fluctuation and behavioural disturbance, which were all more prevalent in patients with late HIV. Patients with late HIV were more likely to have cognitive impairment, including impaired motor speed, psychomotor speed and memory recall. With regard to the formal neurocognitive evaluation by selection group, patients with late HIV were significantly more impaired with respect to visuo-constructional ability, visual memory and executive functioning relating to planning, problem solving and motor abilities compared to the other groups. They also had a higher prevalence of impairments with respect to visual attention and scanning, neglect, sequencing and cognitive flexibility although this was marginally significant. Although the other tests were not significant, there was a trend towards lower or slower scores for tests of fine-motor speed and co-ordination. Overall, most patients had impaired advanced activities of daily living with no significant differences across groups, but there was a trend towards worsening basic activities of daily living, with late HIV having the most impairment.

6.4.6 Latent class analysis

A series of Latent Class Models was developed in this study whereby many different combinations of manifest variables, numbers of latent variables and numbers of latent classes within each variable were examined through the construction of separate models. Overall, 24 variables were initially considered. The best-fit model was found to be one with one latent variable comprised of two classes which were predicted by 12 items. There were 72 patients in class 1 and 39 patients in class 2. Most of the patients in class 2 had late HIV disease as opposed to class 1 which was comprised of most of the patients

from the HIV-negative and early HIV group and 40% of the patients from the late HIV group. The following variables were more prevalent in class 2: multiple hallucinations, depressive symptomatology, movement abnormalities, catatonia, moderately severe to severe motor-speed deficits and psychomotor-speed deficits, severe thought disorder, attentional deficits, moderately severe impairment in registration, disorientation and symptom fluctuation. Multiple delusions were more prevalent in class 1. When the analysis was limited to patients with late HIV and first admission, the patients in class 2 were more immuno-compromised. The high proportion of patients with late HIV disease (80%) in latent class 2 resulted in many similarities between class 2 and the late HIV-positive selection group.

The two classes were similar with respect to demographics, apart from fewer patients in class 2 having disability grants. Patients in class 2 had higher medical co-morbidity, in keeping with their advanced HIV status. Sub-group analyses restricted to patients with tuberculosis, first presentation of disease and Xhosa-speaking individuals, suggested that these factors were not driving any differences between the classes. Patients in class 2 were less likely to have a family history of psychiatric illness and significantly less likely to have had a past psychiatric history compared to patients in class 1. Manic symptoms were common in both groups and grandiose and religious delusions were more prevalent in patients in class 1 while visual and tactile hallucinations were more prevalent in patients in class 2. Patients in the two classes were similar with respect to the severity of manic symptomatology. Patients in class 1 were more likely to have elevated or euphoric mania and patients in class 2 were significantly more likely to be behaviourally disturbed. Irritability scores were higher in patients in class 2 but this did not reach significance.

6.4.7 Multiple hallucinations and delusions

When considering the findings from both the latent class analysis and the analysis by selection group, a number of themes emerge. In keeping with the literature with respect to the higher prevalence of visual and tactile hallucinations in patients with secondary psychosis, the findings that patients in latent class 2, most of whom have late HIV, are more likely to have multiple hallucinations, and that there is a trend across groups in the

selection group analysis, is not unexpected. The opposite finding with respect to multiple delusions is interesting. It is difficult to interpret as, to my knowledge, the number of different types of delusions in patients with secondary psychosis or delirium has not been documented previously. It is unlikely that this difference is due to the increased prevalence of cognitive impairment as delusions occur in patients with HIV-associated dementia and cortical dementias such as Alzheimer's disease and most patients with Alzheimer's disease who have hallucinations also have delusions (271-273).

6.4.8 Movement abnormalities

Patients in class 2 had a higher prevalence of movement abnormalities, characterised by slowness and extra-pyramidal symptoms, particularly akathisia. This occurred despite the significantly lower doses of neuroleptics used in patients with advanced HIV. This is consistent with previous studies that have reported sensitivity to neuroleptics, particularly extra-pyramidal symptoms in patients with advanced HIV (94).

Although catatonia was rare, it was far more prevalent in class 2, compared to class 1, as were deficits in motor speed and psychomotor speed. Two patients with late HIV developed neuroleptic malignant syndrome. This is also consistent with the literature which indicates an increased prevalence of catatonia and neuroleptic malignant syndrome in patients with advanced HIV (37;157;177;180;205). Catatonia, dehydration, agitation, acute disorganisation, the co-administration of other medications, extra-pyramidal side-effects, the diagnosis of an affective disorder, as well as an underlying medical disease of the central nervous system, are all risk factors for the development of neuroleptic malignant syndrome (274;275). As many of these factors are often present in patients with HIV-affective psychoses, patients with the symptoms are at high risk of developing neuroleptic malignant syndrome. The importance of movement abnormalities in this latent class analysis is consistent with the evidence that HIV neuropsychiatric disease particularly affects sub-cortical areas.

6.4.9 Delirium

Patients in class 2 had significantly higher mean scores on measures of delirium, as well as most of the sub-tests compared to those in class 1. The overall median scores of 19 (DRS) and 23 (DRS-98) for patients in class 2 were very close to that of patients with late HIV in the analysis by selection group and patients with early HIV or those who were HIV-negative had very similar scores to patients in class 1 (DRS median score =11 and DRS-98=14.5). Although studies have reported a wide range of cutoffs in the DRS and DRS-98, delirious patients scored between 20-23 on the DRS in a number of studies (54;240), whereas lower cutoffs of ten have been used in geriatrics patients (51). With respect to the DRS-98, a cut off of 17.75 has been used (237). Although the scores of the HIV-negative patients and patients with early HIV were very similar, they were both higher than those described in patients without delirium in previous studies. However, as discussed in Chapter 4, the severity of disease of the patients in the control groups in previous studies indicated mild to moderate illness, whereas this study was conducted in patients with severe symptoms. This would account for the higher scores in these two groups. Overall, the data with regard to the delirium scales in the study suggest that patients in class 2 had many symptoms previously reported in delirious patients. The sub-test findings in the delirium scales confirm that patients in latent class 2 were more likely to have a short onset of symptoms, cognitive impairment, psychomotor behaviour abnormalities and symptom fluctuation. This is in keeping with Meagher *et al.*'s findings that patients with hyperactive delirium had higher scores for psychotic symptoms, mood lability, sleep-wake disturbances, agitation and symptom variability (48). Although the onset of symptoms was more acute for patients in class 2 than those in class 1, many patients in latent class 2 had sub-acute presentations. In this respect, although patients in this latent class had high scores on the Delirium Rating Scale, the findings differ from studies of acute delirium where patients typically presented with symptoms that developed over hours or days (12;58).

Rosen *et al.* (51) reported a 32% false-positive rate using the DRS in geriatric patients with organic mental disorders, especially for those who had higher scores on the Brief Psychiatric Rating Scale (BPRS). It has been suggested that the patients in the study were

miss-assigned and that they should have been labeled as being delirious (52).This is indicative of the difficulty with respect to diagnostic validity in patients with affective and psychotic symptoms and underlying medical diseases. Apart from having a longer temporal onset of symptoms compared to patients described in the literature with acute delirium, the patients in the study also differed in other respects. They were younger than most of patients described in the literature with delirium and most of them were not in acute medical settings but rather in psychiatric facilities (52). Any possible medical contributor to their symptoms, other than HIV, had been carefully excluded. Furthermore, their symptoms took much longer to resolve than is usually the case in acute delirium (58). They also had prominent psychotic and affective symptoms, often with well-formed delusions. Auditory hallucinations are relatively uncommon in patients with acute delirium, having been reported in four to fifteen percent of patients as opposed to visual hallucinations that have been reported in 30–70% (43). It has been suggested that the core deficits of delirium consist of cognitive deficits in the form of impaired attention and disorientation, disorganised thinking, language disturbance and sleep-wake cycle disturbance, with other symptoms varying depending on the aetiology of the delirium (43). In this study, patients in latent class 2 had significantly higher scores on all these parameters compared to patients in latent class 1. Overall therefore, the patients in this study had many symptoms in keeping with primary psychiatric disorders as well as many in keeping with the clinical features of a sub-acute delirium.

6.4.10 Cognitive impairment

Patients in latent class 2 had more cognitive impairment with significantly more impairment compared to latent class 1 with respect to impaired motor speed, psychomotor speed and memory recall on the IHDS. In formal neuropsychological testing, there was significant impairment in patients in class 2 compared to those in class 1 with respect to recall, manual dexterity, visuo-motor co-ordination, attention, concentration and verbal memory. Visuo-constructional ability, visual memory, planning and problem solving, visual attention and scanning, sequencing and cognitive flexibility were also more impaired in patients in class 2. This is consistent with the literature in respect of HIV-associated dementia (HIV-D), where early features of HIV-D have been

reported as being mental slowing, psychomotor retardation and fine-motor difficulties (197;276). The differences between class 2 and class 1 were more significant than those found when comparisons were conducted across selection groups. There was a trend towards more severe impairment across the classes with the late HIV group being most impaired with respect to motor tasks and some measures of executive functioning, such as the Trail Making Test A. This may indicate Minor Neurocognitive Disorder in the patients with early disease as opposed to the more serious cognitive impairment suggestive of early HIV-associated dementia seen in the patients with late stage disease. In other measures of executive functioning, such as the Rey Complex Figure, which also evaluates visual memory and constructional ability, the HIV-negative group and the group with early HIV had very similar scores. In fact, patients with early HIV had higher mean scores on the IHDS than did the patients in the HIV-negative group, although the median scores were the same.

The trends across groups with respect to movement abnormalities indicate an increasing susceptibility to extra-pyramidal side-effects and the development of bradyphrenia in the group with early HIV which worsens as the disease progresses. Patients in latent class 2 were also more impaired with respect to both basic and advanced activities of daily living than those in class 1 whereas the differences across groups were not as significant. Compared to patients with late stage HIV but no mental disorder, patients with late HIV and psychosis/mania scored significantly worse with respect to the same parameters described above with a trend across the early HIV and HIV-negative groups. Interestingly, although the HIV-negative patients with psychosis or mania had the best scores when compared to the other two selection groups, their scores were significantly worse than the patients with late HIV disease but no mental disorder. They were more impaired on most of the neuropsychological measures, particularly those related to fine-motor speed, manual dexterity, complex visual-motor co-ordination, visuo-constructional ability, visual memory and executive function. The differences were not significant for measures of attention, verbal memory, concentration and working memory.

As discussed in Chapter 2, chronic cognitive deficits have been described in patients with bipolar disorder and schizophrenia (25;26;277). With respect to bipolar disorder, patients with acute disease have been reported to have widespread cognitive abnormalities, including impairment in attention and executive functioning, as well as some memory impairment. Impairment is worse in bipolar patients with psychosis. Impaired verbal fluency has been reported in patients with bipolar depression. Impairments in executive function and visual memory may persist in asymptomatic patients with bipolar disorder (26). Cognitive dysfunction is a core feature of schizophrenia with widespread cognitive impairment including impairment in executive functioning, verbal learning, praxis, attention, information processing and motor function. In acute psychosis, these deficits are more apparent (277-279). The cognitive performances of the HIV-negative patients in this study reflect these deficits. All HIV-negative patients in this study were acutely psychotic and many had severe affective symptoms, including mania and depression. Most of them were on classical neuroleptics, all of which could negatively impact their cognitive performances. Neuroleptic medication has been shown to impair visuo-motor and motor functioning, particularly fine-motor functioning, as well as tasks that require sustained attention (280;281)

The findings in the study with respect to cognitive impairment are consistent with studies presented in the systematic review (6;94;131;134). Slowing on Grooved Pegboard has been reported to be a good screening tool for cognitive impairment in HIV-positive patients (134;282). Patients in latent class 2 took longer to perform the Grooved Pegboard Test indicating impairment in manual dexterity, but the differences were marginally significant. The findings for other tests of motor speed, such as Successive Finger Tapping, were also not significant between latent classes. There was impairment in fine-motor function in all selection groups although it was worse in the HIV-positive patients with late disease, despite them being on lower doses of neuroleptics.

The International HIV Dementia Scale distinguished cognitive impairment between the latent classes and across selection groups with the results being highly significant. The cut-off score for the diagnosis of cognitive impairment of 10 was reported by Sacktor *et*

al. in Uganda (211). This was higher than that achieved by the HIV-negative group in this study, whose mean score was 8.53 (SD=2.28) with a median of 9.5, which was the same as the median for the early HIV group. This is consistent with the literature discussed above with respect to cognitive impairment in patients with primary psychiatric disorders on classical neuroleptics (25;26;277). In Sacktor *et al.'s* (211) study, patient with mild dementia had a mean IHDS score of 9.3 and those with severe dementia had a mean score of 7.0. The mean score of patients with late HIV in this study was 6.85 and the mean score for patients in class 2 was 6.16. These findings suggest that while the IHDS distinguished between the groups (and classes), a cut-off of 10 would be too high for this patient sample.

The movements required in the tests of psychomotor speed and motor speed on the IHDS differ from those used in the formal neuropsychological testing. The motor tests in the formal neuropsychological testing require the co-ordination of finer movements than are required for the IHDS. The movements tested in the IHDS could be adequately performed by patients with mild slowing, as is commonly found in patients on classical neuroleptics, but not by patients with more severe motor impairments. Formal neuropsychological testing was therefore not as useful in distinguishing between groups and classes. In this respect, the IHDS was found to be very useful. This is reflected in the fact that the registration item from the HIV Dementia Scale (HDS) and the psychomotor speed and motor speed items from the IHDS form three of the clinical items that are described in the latent class analysis.

The clinical features suggestive of a sub-acute delirium, such as impaired attention and disorientation, would have impaired functioning on neuropsychological testing. However, patients were not tested when clinically disorientated. Furthermore, as described above, the cognitive deficits found in patients in class 2 are consistent with the literature with respect to HIV-D. There is also overlap in symptomatology between a sub-acute delirium and HIV-associated dementia, with the diagnostic criteria for HIV-associated dementia including dysfunction in attention or concentration as well as language deficits (70). As occurs in Lewy Body Dementia, the precise distinction between symptoms attributable to

delirium and those attributable to an underlying dementia may not be possible (52). The deficits demonstrated by the patients in class 2 extend beyond those attributable purely to a sub-acute delirium in that they exhibited other deficits such as psychomotor and motor-speed impairment and deficits in executive functioning. Overall, the data in this study are suggesting that patients in class 2 had neuropsychological features in keeping with early HIV-associated dementia.

6.4.11 DSM-IV diagnoses

If DSM-IV criteria, excluding those of psychosis or mania due to a general medical condition, had been used to make the diagnosis, most patients would have had the diagnosis of Bipolar Affective Disorder with similar frequencies in both classes. The difference between the classes was that patients in class 1 had a higher prevalence of euphoric mania whereas those in class 2 had a higher prevalence of irritable mania. The frequency of mixed affective states was similar in both classes. The diagnosis of major depressive episode was more prevalent in class 2. Interestingly, there were no patients with schizophrenia, schizoaffective disorder or schizophreniform disorder in class 2. Some early case reports described HIV-positive patients with symptoms indistinguishable from those of schizophreniform psychoses and suggested that the psychosis may be HIV consequent (145;146;152). The data from this study are consistent with more recent comparative studies which documented prominent psychotic symptoms in manic patients and prominent affective symptoms in psychotic patients, suggesting that HIV-consequent disease is more commonly an affective psychosis (6;94;134).

6.4.12 Misclassification with respect to latent class

The real determinants of psychosis and mania in HIV-positive patients are far more complex than can be described in this study. There are unmeasured and unknown determinants of the latent classes, which may be clinical, neurobiological or psychosocial. Misclassification is therefore expected as the study has used 12 symptoms to describe extremely complex phenomena. Furthermore, although HIV psychosis and mania occur predominantly in late stage HIV, it is likely that there is a continuum of symptom severity and time of presentation. In this respect, it was interesting to examine the patients who are expected to have been in a different latent class. Of the 21 patients in

class 1 with late HIV disease, eight had previous psychiatric histories and had not experienced any change in the pattern of their symptoms. Of the remaining 13 patients, there appeared to be a sub-group comprising nine patients who had severe depression and severe psychomotor retardation, cognitive impairment on the IHDS and a high prevalence of suicidal ideation. With respect to immuno-suppression, these patients' CD4+ counts were similar to those of patients in latent class 2 rather than latent class 1, and their median viral load was higher than the median viral load for patients in class 2. These patients also had a high prevalence of white matter change on MRI. There were two patients in this sub-group in the cohort study and they both responded very well to antiretroviral therapy. It is therefore possible that there is a less common HIV-consequent phenomenon, which presents with severe psychomotor retardation and depression, white matter changes on MRI and severe immuno-suppression.

Both patients included in the sample with borderline intelligence were latent class 2. As described earlier, there was considerable debate when these patients were screened as to whether they should be included or not. They were included because it is common to see patients in psychiatric facilities in Cape Town with borderline intelligence and although omitting them from the study would have increased the homogeneity, and therefore possibly improved some of the statistical significance in the study, the inclusion of these patients has added to the studies clinical utility. It is useful to know that patients with borderline intelligence may be misclassified and clinician should be cognisant of this when evaluating these patients. As HIV psychosis and mania were not used to stage the patients, it is possible that some of the patients were misclassified and should have been in latent class 2. This is consistent with the findings of other studies that have demonstrated that HIV-patients can present with psychotic or manic symptoms as the first indication of immuno-suppression. There appears to be at least one such patient who was otherwise staged as having early HIV but had a CD4+ count of 277 cells/mm^3. As 68% of patients in class 2 had fluctuation as opposed to 9% in class 1, the presence of fluctuation in symptoms such as occurred in two patients with mixed affective states and the patients with catatonia could result in the patients being in class 2. Severe movement disorders such as tardive dyskinesia can have an impact on both psychomotor and motor

tasks, resulting in the patient being assigned to class 2 as occurred with one patient in this study. With respect to the five patients in latent class 2 with a previous psychiatric history, it was interesting that two patients had a recent alteration in symptoms whereby they had become more behaviourally disturbed, more labile and had developed symptom fluctuation. The neuropathophysiological consequences of HIV appeared to be impacting on these patients as opposed to the eight patients in latent class 1 who appeared to have co-existing mental illness and late stage HIV without HIV- consequent neuropsychiatric complications.

6.4.13 Neuroimaging, cerebrospinal fluid and electroencephalogram findings

Cerebral atrophy was common in patients in the late HIV-positive group with a trend across groups. With respect to class, atrophy was significantly more prevalent in patients in class 2 compared to those in class 1. Magnetic resonance imaging was performed on patients with late HIV disease and patients in class 2 were also more likely to have atrophy but this was not significant. Of interest, was that white matter changes in general were more common in patients in class 1, particularly in those patients with high viral loads, as well as those with severe depression and psychomotor retardation. Mijch *et al.* (62) reported atrophy in 26% of HIV-positive patients with mania and the same percentage of patients was reported as having white matter changes. Sewell *et al.* (94) found no difference in neuroradiology findings between matched psychotic and apsychotic HIV-positive patients. Cerebral atrophy and diffuse white matter disease, including periventricular white matter disease, are the most common clinical findings in HIV-associated dementia (283). These changes are non-specific and the field is unresolved as to the significance of white matter changes as the correlation with HIV-associated dementia is poor (284). Small localised areas of white matter disease, which remain unchanged over time and are thought to represent gliosis caused by the primary HIV infection of the central nervous system, have been reported in the approximately one third of HIV-positive asymptomatic patients (285).

Progressive brain atrophy characterises late stage HIV infection and central atrophy predominates over cortical atrophy (207). In general, there is a correlation between

cognitive impairment and loss of volume in areas such as the basal ganglia and caudate nucleus (284). White matter lesions also occur in patients with HIV-associated dementia and are thought to be associated with demyelination and vacuolation, having a poorly circumscribed appearance which coalesces as the disease progresses. These white matter changes usually begin periventricularly, involving other sub-cortical structures later in the disease (207). Functional neuroimaging such as magnetic resonance spectroscopy (MRS) has been more useful in providing information with regard to the neuropathogenesis of HIV and have demonstrated that the extent of white matter and basal ganglia pathology on MRS correlates with the onset and severity of cognitive impairment (284). A high prevalence of neurocysticercosis on CT scan is consistent with the high prevalence of the disease in the Eastern Cape of South Africa, where the family homes of many the patients in the study are located (286). There was no significant difference in the prevalence of neurocysticercosis between patients in latent class 1 and latent class 2 and in all the scans where it was positive, the cysticerci were calcified. With regard to the two patients who were excluded from the study because of progressive multifocal leucoencephalopathy, MRI findings were useful in confirming the diagnosis for which there was strong clinical evidence. With respect to the patients included in the study, the MRI findings were non-specific and had no impact on clinical decisions. CT scans were very helpful in identifying space occupying lesions such as cerebral toxoplasmosis and cerebral tuberculomas in patients who were excluded from the study.

Patients with early HIV were more likely to have abnormal CSF findings, including raised protein and lymphocytes, but the numbers were small, particularly in the HIV-negative group, and the findings were not significant. CSF viral loads were only possible in 14 patients and they were all in latent class 1 and a formal analysis was therefore not done. These non-specific CSF findings are consistent with the literature where the significance of raised protein and pleocytosis or lymphocytosis in the CSF of HIV-positive patients, without other neurological complications, is unresolved (287). Interestingly, patients with advanced HIV disease and low CD4+ counts have been reported as having a high CSF: plasma viral load ratio and a low prevalence of CSF pleocytosis (210). Although the number of patients in the study with CSF viral loads was

too small for formal analysis, patients in class 2 were less likely to have CSF pleocytosis than those in class 1. Some studies have reported a correlation between a high CSF viral load and subsequent HIV-associated dementia, but HIV-associated dementia can occur in patients with low CSF viral loads (287). On reviewing the patient records after the latent class analysis, it was found that patients in latent class 2 were more likely to have had lumbar punctures prior to referral to the study as the physicians were concerned about the possibility of a delirium. As lumbar punctures were only performed in the study for clinical indications, CSF viral loads could not be determined on those patients who had already had lumbar punctures performed. There was no significant difference in CSF viral loads between the patients with early HIV and those with late HIV and the CSF viral loads were lower than the plasma viral loads. Most patients had normal CSF findings and there was a slightly increased prevalence of abnormal findings in patients with early HIV. The findings were non-specific and comprised increased protein, lymphocytosis and pleocytosis. This is in keeping with CSF studies in HIV where non-specific changes can occur early or late in the disease (288). The only abnormal EEG's were in three patients with late HIV disease and the findings were non-specific.

6.4.14 Cohort study

Overall, 42 patients were eligible for antiretroviral therapy (ART) and 16 patients were followed up for at least six months. Of the six patients who died, three were in each class, three died prior to receiving ART and the other three within the first month of treatment. Most of the patients began the antiretroviral treatment as inpatients. As most of the patients were initially unable to participate in the ART readiness programme, the treatment partner system was established whereby the treatment partner went through education and counselling sessions and took responsibility for the administration of ART in a directly observed therapy system (DOT). Patients participated in the counselling and treatment readiness programmes once they were able to do so. A multi-disciplinary team comprising HIV clinicians (nurses and doctors), psychiatrists and psychologists worked together to develop an antiretroviral treatment programme appropriate for patients with serious mental illness. This system worked well and adherence was good provided that the patients received adequate support. The results with respect to the 16 patients who

were followed up over six months were very encouraging. There were dramatic improvements in their physical and psychiatric health. With regard to viral suppression, 15 out of the 16 patients had viral loads lower than the detectable limit and there were highly significant improvements in their CD4+ cell counts. There were also highly significant improvements in the patients' cognitive function. When the patients were seen at six month follow-up, their neuropsychological findings were similar to those of the HIV-positive control group with no mental illness. The two patients who were assessed again after one year showed ongoing improvement. This is consistent with the literature in which ongoing improvements in cognition have been demonstrated to occur for every year after the initiation of antiretroviral treatment (289). No patients were acutely mentally ill at six-month review and nine patients were on no psychotropics at that time with another two patients having their psychiatric medication discontinued at that visit. The intention was to reduce the medication of the remaining patients and to stop it after they had been on antiretroviral treatment for a year. As no guidelines exist with respect to the duration of psychiatric medication following a good response to antiretroviral treatment, treatment was individualised according to the clinical scenario.

As discussed in chapter 4, a randomized double blind trial comparing patients receiving psychotropics only with those receiving psychotropics and ART is not ethically possible. However, the results of the cohort study within the context of the larger study and the literature review, suggest that HIV psychosis and mania respond to ART.

Both the neuropsychiatric sequaelae and teratogenicity of efavirenz is well-documented and it was therefore avoided as most of the patients were female in the reproductive age group and all of the patients with psychotic (119;120;290). When patients were unable to take nevirapine, and subsequently did not manage with a high pill burden of alternative regimens, efavirenz was initiated with some trepidation but none of the 15 patients on efavirenz experienced worsening of psychotic symptoms. It is possible that the neuroleptic medication the patients were taking were protective in this regard. Although this is a small number of patients, it is to my knowledge the first time that efavirenz has been given to a group of psychotic patients and the findings are encouraging. Limiting the pill burden is an important component in maximising adherence in HIV-positive

patients and efavirenz has good central nervous system penetration and can be used in patients on treatment for tuberculosis, thus making it an important first line antiretroviral. Considering that the neuropathogenesis of neuropsychiatric symptoms are diverse and complex, it is possible that the neurophysiological mechanism of the neuropsychiatric side-effects of efavirenz differ in some respects to HIV-consequent neuropsychiatric symptoms. These data suggest that the consequence of treating these patients with efavirenz is to address the primary aetiological source of a symptomatology without a synergistic worsening of their psychotic symptoms as had been initially anticipated. Patients' responses to antiretroviral treatment in the study are consistent with respect to the literature concerning central nervous system penetration of antiretroviral drugs. The main antiretrovirals used in this study (stavudine, lamivudine, nevirapine and efavirenz) have all been demonstrated to have consistent penetration into the central nervous system and have been recommended as appropriate candidates for neuroprotective antiretroviral treatment regimens (291).

6.5 Neurobiology

As discussed in Chapter 2, HIV infects the central nervous system early in the disease and initiates and pro-inflammatory and other neurotoxic processes, including the dysregulation of cholinergic and dopaminergic systems (83;93). Dopamine and acetylcholine dysregulation are also implicated in the neuropathophysiology of delirium (43;58;292). Some interesting parallels can be drawn between HIV-associated mania and psychosis and Lewy Body dementia (LBD). As discussed in Chapter two, LBD is characterised by, amongst other symptoms, progressive cognitive decline with deficits of attention, executive function and visuo-spatial ability, fluctuating cognition, recurrent visual hallucinations and spontaneous features of parkinsonism and severe neuroleptic sensitivity (59;60). Both HIV psychosis or mania and LBD are progressive diseases with symptom fluctuation and a poor prognosis. Lewy Body dementia, HIV infection of the central nervous system and delirium all have sub-cortical involvement and there is evidence of the dysregulation of cholinergic and dopaminergic systems. Acetylcholine depletion has been described in all three disorders and while both HIV and LBD are

associated with dopamine depletion in the basal ganglia, increased dopamine availability has been implicated in HIV. Factors such as response to atypical anti-psychotics in patients with LBD, indicate a complex neurotransmitter dysregulation (93;100;293). These common neurophysiological and neuroanatomical abnormalities may explain the overlap in symtomatology described above. Diverse aetiological agents ranging from an acute delirium in a patient with burns to the neurodegenerative consequences of Lewy Body dementia and the neuroinflammatory and pro-apoptotic processes in HIV, while differing in many respects, may therefore share common final pathways in the neurophysiological processes underpinning some of their symptomatology. The increased availability of dopamine in HIV-associated psychosis and mania and delirium may also explain some of the overlapping features they share with primary psychiatric disorders characterised by psychosis. As discussed in Chapter 2, there is increasing recognition of the role of inflammatory processes in the activation of the neuropathogenesis of primary psychiatric disorders, HIV-related diseases of the central nervous system, Lewy Body dementia and delirium. This may also explain the intermittent nature of many psychotic and affective disorders, as well as the more pronounced fluctuations seen in patients with delirium, Lewy Body dementia and HIV psychosis and mania (88). A pre-existing psychiatric history does not appear to put patients at risk of developing HIV-consequent psychosis or mania and suggests that there may be different mediators in the two groups. For example, it is possible that some of the neuroinflammatory mechanisms operating in HIV differ from those implicated in primary psychiatric illnesses. The susceptibility to psychotic symptoms therefore appears to be more than a sample threshold effect with a number of complex neurophysiological and neuroinflammatory processes manifesting with overlapping symptoms

6.6 Implications for clinical practice

6.6.1 Clinical features suggestive of HIV consequent neuropsychiatric disease

In countries such as South Africa where the prevalence of HIV is high, HIV should be considered as a possible aetiological factor in patients presenting for the first time with psychotic or manic symptoms, particularly if patients have clinical or laboratory findings suggestive of immuno-suppression. HIV may also be playing an aetiological role in the exacerbation or alteration of symptoms in patients with previous episodes of mental illness. With respect to patients who have a past psychiatric history, distinguishing between the onset of symptoms before or after stigmata of immuno-suppression have developed, is useful in indicating the likelihood of HIV playing a role in symptomatology. Many patients in this study, however, were unaware of their HIV status prior to admission with a psychiatric illness and their psychiatric symptoms led to the diagnosis of AIDS so this distinction may not always be possible. HIV-consequent disease is more likely if patients present with multiple hallucinations, movement abnormalities including neuroleptic sensitivity, sub-cortical cognitive impairment, deficits in attention and the fluctuating course with episodes of disorientation. The International HIV Dementia Scale is a useful screen for cognitive impairment but the cutoff should probably be lower in patients with psychiatric disorders. Patients with mixed affective states and mental handicap may have many of the symptoms and in this respect may be false positives. Patients with severe or resistant psychotic depression with marked psychomotor retardation and cognitive impairment should also be considered as possibly having HIV-consequent disease. HIV-consequent disease is associated with advanced immuno-suppression and laboratory investigations such as a low CD4+ count (< 200 cell/mm^3) are useful in making the diagnosis. It is important to conduct a careful physical assessment of these patients, with appropriate investigations such as chest x-rays, lumbar punctures and CT scans (if available), to exclude any other medical complications other than HIV itself, as well as to determine patients' HIV stages accurately.

6.6.2 Psychiatric medication

Atypical neuroleptics are less likely to cause extrapyramidal side-effects and other movement abnormalities and have been reported as being well tolerated in HIV-positive patients with psychosis (202). If possible, it would be preferable to use these agents rather than the classical neuroleptics such as haloperidol that have high extrapyramidal side-effect profiles. In developing countries where atypical anti-psychotics may not be available, haloperidol may still be the best choice. Low potency agents such as chlorpromazine may be preferable from an extrapyramidal point of view, but the high prevalence of anti-cholinergic side effects may be problematic in that acetylcholine is thought to play a major role in delirium and anti-cholinergics have been shown to either cause or exacerbate the symptoms of delirium. Furthermore, low potency neuroleptics frequently have increased histamine activity, which can lead to sedation. Patients with advanced HIV and psychosis or mania therefore demonstrate similar sensitivities to neuroleptics as have been documented in other forms of dementia, particularly Lewy Body dementia (66;294).

With respect to mood stabilisers, carbamazepine should be avoided in patients on antiretrovirals as it induces their metabolism and can thereby promote the development of resistance (119). There is evidence to suggest that lithium may be neuroprotective (295-297). There was initial concern with respect to sodium valproate as in vitro studies demonstrated that it accelerated viral replication (298;299). This does not appear to be the case in vivo and sodium valproate is now a source of interest with respect to neuroprotection, use as an augmentation treatment in HIV–associated dementia and may have a potential role to play in treating latent HIV infection (299-304).

6.6.3 The role of antiretroviral treatment in HIV psychosis and mania

The findings of the cohort study suggest that HIV psychosis and mania respond well both physically and psychiatrically to antiretrovirals and that patients returned to good levels of functioning. As with all antiretroviral treatment programmes, adequate support and an appropriate treatment readiness programme is essential. Many psychotic or manic patients may need to have their treatment initiated in hospital where adherence can be maximised and where the treatment partner is involved in treatment readiness counselling. Although there has been some criticism of the use of directly observed therapy (DOT) for patients with AIDS, it may have a role to play in some patients until they are well enough to assume responsibility for their own treatment (305;306). In others, such as those with premorbid psychiatric illnesses that impair insight and judgement or in patients with mental handicap, DOT may have to be used in the long term. In this study, antiretroviral agents were true psychotropic agents in that they addressed the primary aetiological mediator of psychosis or mania. Antiretrovirals are therefore predictive validators with respect to the diagnostic validity of HIV-affective psychosis.

6.6.4 Guidelines with respect to the findings of this study

With respect to achieving the implementation objectives of the study, the findings presented in this thesis will be summarised and presented as practical guidelines for the identification of clinical features suggestive of HIV-consequent psychosis and mania and recommendations with regard to appropriate investigations. Recommendations for the management of these patients, including the co-administration of antiretrovirals and psychotropics will be made. This will include information that has been formulated in conjunction with the Medicines Information Centre at the University of Cape Town with respect to psychotropic treatments in HIV-positive patients, including those on antiretroviral therapy that does not form part of this thesis. This study has formed the basis of an HIV mental health service, funded by the Western Cape Provincial Department of Health to provide an ongoing HIV mental health service. A formal report will be submitted, following the completion of this thesis, to the provincial HIV and

Mental Health directorates motivating for antiretroviral treatment to be made available to patients with HIV-consequent neuropsychiatric disease.

6.7 Limitations

6.7.1 Patient selection

This study has a number of limitations. The sample was not randomly selected for both practical and ethical reasons. The study was conducted in a hospital setting within the context of an overburdened mental health service. As the threshold of symptom severity for admission to medical and psychiatric facilities in Cape Town is very high, all the patients in the study were psychotic. The patients in the study therefore had severe psychiatric illness and it is possible that clinical characteristics may differ in patients with less severe illness. Furthermore, although the prevalence of HIV in South Africa is highest in poor communities, affluent patients use private health providers and were not assessed in this study. It is also possible that very poor patients living in rural areas with limited access to health services were not well accessed as the study was based in an urban centre.

6.7.2 Local HIV-related issues

Some unavoidable limitations in the study arise from the nature of the HIV epidemic in South Africa, as well as from HIV-testing practices in Cape Town. With respect to the former, the prevalence of HIV is highest in black communities and this is reflected in the study although a sub-group analysis demonstrated that this was not driving the data. There is also considerable confusion in the community with regard to HIV, its prevention and treatment. The stigma of being HIV-positive is considerable and, as a result, many people are reluctant to be tested. Prior to antiretroviral treatment becoming available, many clinicians felt powerless when managing HIV disease and adopted a passive approach to HIV-positive patients. For instance, patients would not be ventilated or be given other expensive interventions, and many patients were simply sent home to die. Although antiretroviral treatment has recently become available in South Africa, this passive attitude remains to some extent. The HIV epidemic is forcing mental health

practitioners to engage with patients who are physically ill and there is considerable anxiety and a consequent reluctance on the part of psychiatrists and other mental health practitioners to do this which in turn influences HIV testing. There is considerable variability across different hospitals and between different consultant psychiatrists with respect to the enthusiasm for HIV testing. In many wards, patients are tested only if the staff suspected that they may be HIV positive. This introduces an unavoidable sampling bias into the study, particularly amongst the HIV-negative group who probably had an atypical presentation or some other reason why they were tested for HIV. It is therefore possible that the differences between the HIV-positive patients, particularly those with late stage disease, and the HIV-negative patients, would be more pronounced when applied to all HIV-negative psychotic and manic patients. This may also apply, but probably to a lesser extent, to patients who have early HIV disease. It will be less problematic in this group because many HIV-positive patients who are well, have subtle stigmata of HIV disease, such as generalised lymphadenopathy or pruritic eruptions. Routine testing for HIV for the purposes of the study was ethically unacceptable and this limitation was therefore unavoidable.

6.7.3 Multi-cultural multi-linguistic sample with low education levels

The study was conducted in a multicultural setting and patients in the sample spoke three different languages. Methodological issues with respect to language and culture were addressed as far a possible and sub-group analyses indicated that language was not driving differences in the neuropsychiatric data. The heterogeneity of the patient sample also improves the generalisability of the data. Patients in the sample were not randomly selected and, apart from the HIV-positive controls for the neuropsychology tests, were not matched. It was not possible to use random selection as this would have meant that some patients would not have had access to antiretroviral treatment. Despite the groups not being matched, sub-analyses for possible confounders caused by these factors suggested that this did not impact the findings in the study. With respect to the neuropsychology, there were no local neuropsychological norms available and the detailed neuropsychological assessments were conducted in English, which was a second language for most of the patients in the study. A number of problems relating to language

and education affected the findings. In order to address these problems, the neuropsychological battery was amended where possible and the results interpreted within the context of these limitations. The HIV-negative patients with psychosis on the one hand and the HIV-positive patients with late stage disease and no mental illness on the other, served as controls for the two main variables in this study: HIV disease and psychosis and mania which compensated to some extent for the absence of local neuropsychological norms. The neuropsychological findings are useful in the context of comparing groups rather than viewing them in isolation.

6.7.4 Determining baseline measurements

A number of patients were too ill to be assessed when they were first admitted to hospital and referred to the study. Assessments were conducted as soon as possible but this time frame varied depending on symptom severity. This also applied to the neuropsychological testing where some patients were unable to do be tested initially. The true baseline cognitive functioning of these patients with respect to the neuropsychological assessment and a screening test such as the International HIV Dementia Scale, could therefore not be recorded. This particularly applied to patients with advanced HIV disease, some of whom could not have baseline neuropsychological assessments conducted as they improved only after antiretroviral treatment had been initiated. This problem of underreporting profoundly severe symptoms was unavoidable. To minimise this problem, the neuropsychologist rated patients using a global rating score which took into account patients who performed poorly as a result of impaired functioning rather than education and language factors.

6.7.5 Missing data

There are some missing data in the study, particularly with respect to some aspects of the demographic information, which patients were unable to give and about which collateral informants were unaware. Furthermore, retrospective recall bias may have influenced the reports of past and family histories of psychiatric illness. The other area where data are missing is in the neuropsychological assessments as described above as well as in the

patients where it was not possible to conduct a MINI-Plus assessment as described in the methodology and results chapters.

Although it was possible to conduct MRI studies on the patients with advanced HIV, it was not possible to do so with respect to the other groups and functional imaging was not possible for financial reasons. Given the literature with respect to MRI as discussed above, it is unlikely that structural imaging would have contributed any significant information, but functional imaging such as magnetic resonance spectroscopy may have been more useful. It would have been preferable to have had more CSF viral load results but this was not possible given that most patients had had lumbar punctures prior to referral to the study.

6.7.6 Multiple comparisons

Although this is one of the largest studies in this field to date, and more patients were recruited than was necessary in terms of the sample size power calculation, multiple comparisons were made within the context of a modest sample size. This increases the chances of Type1 error. To reduce the overall number of statistical comparisons, global comparisons were preferred to two-way comparisons, and no corrections for multiple statistical comparisons were used.

6.7.7 General limitations

Many of the limitations of the study relate to intractable problems in the field. The patients in the study were psychotic and were therefore unable to give full accounts of the histories and demographic information. Using multiple sources of information and serial evaluations compensated for many of these problems. With respect to the health systems difficulties encountered in this study, Cape Town has a relatively good health system compared to other provinces in South Africa and South Africa has a relatively good health care system relative to many other sub-Saharan countries. It is likely that these problems will remain a reality in the resource-poor health systems environment in sub-Saharan Africa.

6.8 Strengths of the study

6.8.1 Conceptual framework

The methodology adopted in the study has attempted to circumvent the redundancy present in many previous studies with respect to diagnostic validity of psychotic and affective disorders. HIV mania and psychosis were not assumed to be mutually exclusive entities and diagnostic constructs derived from categorical models such as the DSM-IV were not used for selection into groups. Presumptions with respect to the role of the previous psychiatric history or family history of psychiatric disorders were also not made.

6.8.2 Systematic Review

To my knowledge, the systematic review presented in this thesis is the first systematic review in this field and this is the first study of HIV psychosis and mania to use cluster analytic methods to identify possible latent variables.

6.8.3 Capturing clinical information

As there was paucity of literature in this field, there was a risk of viewing the clinical features through the lens of previous descriptions and thereby missing symptom clusters that had not previously been identified. Careful attention was given to the instruments used in this study so that there was adequate breadth and depth of field with respect to capturing clinical information. For example, the number of different types of hallucinations and delusions were recorded and this was found to be highly significant across selection groups and between the latent classes. Furthermore, the prevalence of depression was high in patients with advanced HIV and as well as in latent class 2, which, to my knowledge, has not previously been documented in the literature as being an important feature of HIV psychosis. A comprehensive combination of formal neuropsychiatric instruments and semi-structured interviews covering diagnosis, movement abnormalities, delirium scores, severity of mania and cognitive assessments maximised the quality and quantity of data collection.

Several sources were used to gain as much information as possible and serial assessments were conducted in order to document the symptoms over the course of the patients'

admissions. Extensive records with respect to qualitative information were also kept. Although this approach was labour-intensive, it facilitated thorough patient assessments. Assessments were done by psychiatrists, psychologists, HIV clinicians and other specialist healthcare professionals. This was necessary as the assessments were complex and having specialist field workers improved the quality of the data. Attention was given to the ethical aspects of the study, as well as to the factors that culture, language and education were playing in confounding the findings. Instruments were translated and back-translated to ensure colloquial use of language. In addition, all neuropsychiatric assessments were conducted in the patients' first language. Methodological challenges such as the resistance of physicians or psychiatrists to look after the patients in the study and access to the study sample were overcome. Information with respect to patients excluded from the study was recorded and detailed physical examinations were conducted, often on more than one occasion, to ensure that patients had no cause for this symptomatology other than HIV alone or a primary psychiatric illness.

6.8.4 Sample size, patient selection and laboratory findings

To my knowledge, this study is one of the largest studies with respect to HIV psychosis and mania, with only one other study having more than 50 patients (6). To my knowledge, it is also the largest study of neuropsychological findings in HIV-positive patients with psychosis and mania to date and the only study to have compared neuropsychological findings in HIV-negative psychotic patients, psychotic patients with early HIV disease, psychotic patients with late HIV disease and patients with late HIV disease but no mental illness. In addition, to my knowledge, it is the largest study of neuroimaging and cerebrospinal fluid findings in HIV-positive patients with psychosis and mania to date and it is the only study to date that has reported serum and CSF viral loads in this patient population.

6.8.5 Cohort study

The cohort study, whereby a mechanism for the administration of antiretrovirals to patients with severe psychosis and mania was formulated, the antiretrovirals administered and the patients followed up with respect to neuropsychiatric, physical and neuropsychological findings over at least six months, is to my knowledge the first study of its kind. It is informative with respect to the administration of ART in patients with impaired adherence capacities as well as providing evidence that HIV-associated mania and psychosis should be indications of ART.

6.8.6 Statistical analysis

This study is, to my knowledge, the first to use cluster analytic methods in examining HIV psychosis and mania. Conservative cutpoints were used to maximise the generalisability of the data. Furthermore, Fisher's Exact Tests, which are more appropriate for small sample sizes and global comparisons rather than two way comparisons, were used to reduce the overall number of statistical comparisons.

6.9 Conclusions

The evidence presented in this study suggests that the disorders described in the literature as HIV psychosis and mania are not discrete entities. They are better conceptualised as overlapping clinical manifestations of HIV-related neuropsychiatric disease. Furthermore, the findings suggest that the patients with advanced HIV disease consisted of three groups. The largest group constituted most of the patients in class 2. These patients had symptoms in keeping with a sub-acute delirium and advanced immunosuppression consistent with an AIDS-defining phenomenon. Patients in this group had a high prevalence of multiple hallucinations, severe thought disorders, movement abnormalities, attentional deficits, disorientation, sub-cortical cognitive impairment and symptom fluctuation. They were more likely to have had an acute onset of symptoms, were more immuno-suppressed and more functionally impaired than patients in class 1. They were much less likely to have had a previous admission and, if

they did have a past history, may have experienced a change in symptomatology. Family history was not useful in distinguishing these patients from the other groups.

The second group comprised nine patients who were in class 1 but had advanced HIV accompanied by severe depression and severe psychomotor retardation, high viral loads and a high prevalence of suicidal ideation and cognitive impairment. They were also more likely to have white matter changes on MRI. These patients may represent a less common HIV-consequent phenomenon. Previous studies have focused on psychosis and mania, but depression was also prominent in patients in latent class 2 and appears to be an important clinical feature. The third group consisted of patients with a previous psychiatric history who had no change in symptomatology and were in latent class 1. This group probably had co-existent primary psychiatric illnesses with advanced HIV but without HIV-consequent neuropsychiatric involvement. Some symptoms appear to be on a continuum with less prominent symptoms in patients with early HIV whereas others are characteristic of patients with late disease and have a low prevalence in early HIV and HIV-negative patients. It is likely that patients can present with less severe symptoms than were documented in the study which was conducted among psychiatric inpatients with severe mental illness. The results of the cohort study found that patients responded very well to antiretroviral treatment and that very good adherence could be maintained provided that there was adequate social support.

With respect to the specific hypotheses posed at the beginning of this thesis, the findings of this study support the hypothesis that some patients with HIV-associated psychosis and mania have clinical features in keeping with a sub-acute delirium. They appear to be a sub-group of patients who do not fluctuate but have profound psychomotor retardation and psychotic depression. Both these groups of patients are associated with sub-cortical impairment which appear to be AIDS-defining phenomena and respond well to antiretroviral treatment.

With respect to the maximisation of diagnostic validity of HIV-associated mania and psychosis as described in 3.1.2, the above-mentioned clinical features suggest a defined

clinical syndrome. There is an increased prevalence of the syndrome in HIV-positive patients who often do not have a past psychiatric history. The investigative evidence in the form of low CD4+ counts, high viral loads and atrophy on neuroimaging, together with neurobiological evidence of HIV infection of the central nervous system, suggest that these symptoms are HIV consequent. The temporal relationship between HIV and the onset of symptoms is difficult to determine due to the delay between infection and immuno-suppression. The late age of symptom onset is also not useful as HIV commonly occurs in young people. The clinical features of a sub-acute delirium in class 2 and a possible second group in class 1 with severe psychomotor retardation and psychotic depression, respond to antiretroviral treatment, thereby providing a powerful predictive diagnostic validator for HIV-consequent psychotic disorders.

Lewy Body dementia, acute delirium and HIV-associated psychosis and mania have many symptoms in common, shared anatomical involvement of sub-cortical structures and dysregulation of acetylcholine and dopamine which appear to be mediated through pro- inflammatory mechanisms. It is therefore likely that patients with these disorders share some genetic susceptibility with respect to central nervous system inflammation and neurotransmitter modulation. Patients with schizophrenia or bipolar affective disorder may have vulnerability to other pro-inflammatory pathways and mediators of disease. In patients with primary psychiatric disorders, multiple "hits" may result in threshold effects whereby symptoms become manifest. With respect to HIV psychosis and mania, however, it may be activation of specific vulnerable pro-inflammatory and neurotoxic pathways that results in the manifestation of neuropsychiatric HIV disease. It is therefore likely that psychiatric symptoms such as mood, psychotic and cognitive symptoms, as well as disorientation and symptom fluctuation, represent final common pathways for multiple diverse and complex neurophysiological processes.

The findings of this study suggest many possible future avenues of inquiry. An exploration of common genetic susceptibility in acute delirium, HIV psychosis and mania and Lewy Body dementia, correlating with possible endophenotypes and symptom clusters, may help in the understanding of the neurophysiological bases of some

psychiatric symptoms and assist in improving diagnostic validity in psychiatric disorders characterised by affective and psychotic symptoms. Phenomenological studies across diagnostic boundaries analysed by cluster analytic methods may enable the identification of symptom clusters such as fluctuation, visual hallucinations and disorientation and correlate them with underlying neurobiological processes. The clinically validity and stability of the diagnostic phenotypes found in this study could then be assessed. Larger studies, including a larger cohort study of antiretroviral treatment in patients with HIV psychosis and mania can be studied prospectively would be very useful. It would also be interesting to use MRI volumetric analysis to examine cerebral atrophy in more detail and to clarify the significance of white matter changes on MRI. The extent to which findings of this study are replicated could be then examined, as well as whether a possible sub-group with severe depression can be more clearly delineated. Examination of factors relating to the predictive and prognostic role of functional neuroimaging and CSF viral loads could also be further explored further. On a local level, with the overwhelming health service needs, creative evidence-based approaches are necessary to maximise patient care. Healthcare professionals in South Africa have an important role to play in patient advocacy in HIV. There is a profound moral imperative in this regard: poor disadvantaged patients who have the misfortune of having HIV affect their brains have just as much right to treatment as any other HIV-infected person and it is the responsibility of health care providers to develop mechanisms whereby this can be achieved. South Africans must be given access to antiretroviral treatment. The alternative is unimaginable.

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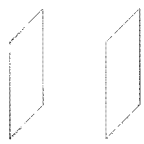
Appendix A

HIV Dementia Scale (212)

		Max	Score
1.	**Memory- Registration** Give four words to recall (e.g. dog, hat, green, peach)- One second to say each Then ask the patient all 4 after you said them.	4	
2.	**Attention** Anti-saccadic eye movements: 20 (twenty commands) (Ask the patient to focus on the examiner's nose and then to look to and from the examiner's moving index finger and nose. Use alternating hands. Examiner's hands held at patient's shoulder width and height. When patient comfortable looking at the moving finger, he/she is then asked to look at the stationary finger. Practice until patient familiar with task. Then ask patient to perform 20 serial anti-saccades. Error: patient looks at moving finger) Scoring: ≤ 3 errors = 4, 4 errors = 3, 5 errors = 2, 6 errors = 1, > 6 errors = 0	4	
3.	**Psychomotor Speed** Ask the patient to write the alphabet in upper case letters horizontally across a page and record time..... seconds. Scoring: ≤ 21 sec = 6, 21.1-24 sec = 5, 24.1-27 sec = 4, 27.1-30 sec = 3, 30.1-33 sec = 2, 33.1-36 sec = 1, > 36 sec=0.	6	
4.	**Memory-Recall** Ask for four words from registration above. Scoring: One point for each correct answer. For words not recalled give a semantic clue (e.g. animal for dog, piece of clothing for hat, fruit for peach). Give ½ point for each correct answer after prompting	4	
5.	**Construction** Copy the cube below: record the time.....seconds (sec). < 25 sec = 2, 25-35 sec = 1, > 35 sec = 0	2	



TOTAL SCORE:...../20

Appendix B

International HIV Dementia Scale (21I)

1. **Memory-Registration:** Give four words to recall (e.g., in English use dog, hat, bean, red) _____

2. **Motor-Speed:** Have the patient tap the first two fingers of the non-dominant hand as wide and as quickly as possible _____
   4 => 15 in 5 seconds
   3 = 11-14 in 5 seconds
   2 = 7-10 in 5 seconds
   1 = 3-6 in 5 seconds
   0 = 0-2 in 5 seconds

3. **Psychomotor Speed:** Have the patient perform the following movements with the non-dominant hand as quickly as possible. _____
   Demonstrate and have the patient perform twice for practice.
   a) Clench the hand in fist on flat surface
   b) Put hand flat on surface with the palm down
   c) Put hand perpendicular on flat surface on the side of the 5th digit
   4 = 4 sequences in 10 seconds
   3 = 3 sequences in 10 seconds
   2 = 2 sequences in 10 seconds
   1 = 1 sequence in 10 seconds
   0 = unable to perform

4. **Memory-Recall:** As the patient to recall the four words. For words not recalled prompt with a semantic clue as follows: animal (dog); piece of clothing (hat); vegetable (bean); colour (red) _____
   Give 1 point for each word spontaneously recalled
   Give 0.5 points for each correct answer after prompting
   Maximum = 4 points

5. **Total International HIV Dementia Scale Score** _____
   This is the sum of the scores on items 2-4 only.
   The maximum possible score is 12.

Appendix C. Delirium Rating Scale (DRS) (54)

Item 1: Temporal onset of symptoms

This item addresses the time course over which symptoms a pear; the maximum rating is for the most abrupt onset of symptoms-a common pattern for delirium. Dementia is usually more gradual in onset. Other psychiatric disorders, such as affective disorders, might be scored with 1 or 2 points on this item. Sometimes delirium can be chronic (e.g., in geriatric nursing home patients), and unfortunately only 1 or 2 points would be assessed in that situation.

0. No significant change from longstanding behaviour, essentially a chronic or chronic-recurrent disorder
1. Gradual onset of symptoms, occurring within a 6-month period
2. Acute change in behaviour or personality occurring over a month
3. Abrupt change in behaviour, usually occurring over a 1- to 3-day period

Item 2: Perceptual disturbances

This item rates most highly the extreme inability to perceive differences between internal and external reality, while intermittent misperceptions such as illusions are given 2 points. Depersonalization and derealisation can be seen in other organic mental disorders like temporal lobe epilepsy, in severe depression, and in borderline personality disorder and thus are given only 1 point.

0. None evident by history or observation
1. Feelings of depersonalization or derealisation
2. Visual illusions or misperceptions including macropsia, micropsia; e.g., may urinate in wastebasket or mistake bedclothes for something else
3. Evidence that the patient is markedly confused about external reality; e.g., not discriminating between dreams and reality

Item 3: Hallucination type

The presence of any type of hallucination is rated. Auditory hallucinations alone are rated with less weight because of their common occurrence in primary psychiatric disorders. Visual hallucinations are generally associated with organic mental syndromes, although not exclusively, and are given 2 points. Tactile hallucinations are classically described in delirium, particularly due to anti-cholinergic toxicity, and are given the most points.

0. Hallucinations not present
1. Auditory hallucinations only
2. Visual hallucinations present by patient's history or inferred by observation, with or without auditory hallucinations
3. Tactile, olfactory, or gustatory hallucinations present with or without visual or auditory hallucinations

Item 4: Delusions

Delusions can be present in many different psychiatric disorders, but tend to be better organized and more fixed in non-delirious disorders and thus are given less weight. Chronic fixed delusions are probably most prevalent in schizophrenic disorders. New delusions may indicate affective and schizophrenic disorders, dementia, or substance

intoxication but should also alert the clinician to possible delirium and are given 2 points. Poorly formed delusions, often of a paranoid nature, are typical of delirium

0. Not present
1. Delusions are systematized, i.e., well-organized and persistent
2. Delusions are new and not part of a pre-existing primary psychiatric disorder
3. Delusions are not well circumscribed; are transient, poorly organized, and mostly in response to misperceived environmental cues; e.g., are paranoid and involve persons who are in reality caregivers, loved ones, hospital staff, etc.

Item 5: Psychomotor behaviour

This item describes degrees of severity of altered psychomotor behavior. Maximum points can be given for severe agitation or severe withdrawal to reflect either the hyperactive or the hypoactive variant of delirium.

0. No significant retardation or agitation
1. Mild restlessness, tremulousness, or anxiety evident by observation and a change from patient's usual behavior
2. Moderate agitation with pacing, removing i.v.'s, etc.
3. Severe agitation, needs to be restrained, may be combative; or has significant withdrawal from the environment, but not due to major depression or schizophrenic catatonia

Item 6: Cognitive status during formal testing

Information from the cognitive portion of a routine mental status examination is needed to rate this item. The maximum rating of 4 points is given for severe cognitive deficits while only 1 point is given for mild inattention which could be attributed to pain and fatigue seen in medically ill persons. Two points are given for a relatively isolated cognitive deficit, such as memory impairment, which could be due to dementia or organic amnestic syndrome as well as to early delirium.

0. No cognitive deficits, or deficits which can be alternatively explained by lack of education or prior mental retardation
1. Very mild cognitive deficits which might be attributed to inattention due to acute pain, fatigue, depression, or anxiety associated with having a medical illness
2. Cognitive deficit largely in one major area tested, e.g., memory, but otherwise intact
3. Significant cognitive deficits which are diffuse, i.e., affecting many different areas tested; must include periods of disorientation to time or place at least once each 24-hr period; registration and/or recall are abnormal; concentration is reduced
4. Severe cognitive deficits, including motor or verbal perseverations, confabulations, disorientation to person, remote and recent memory deficits, and inability to cooperate with formal mental status testing

Item 7: Physical disorder

Maximum points are given when a specific lesion or physiological disturbance can be temporally associated with the altered behaviour. Dementias are often not found to have a specific underlying medical cause, while delirium usually has at least one identifiable physical cause

0. None present or active
1. Presence of any physical disorder which might affect mental state
2. Specific drug, infection, metabolic, central nervous system lesion, or other medical problem which can be temporally implicated in causing the altered behaviour or mental status

Item 8: Sleep-wake cycle disturbance

Disruption of the sleep-wake cycle is typical in delirium, with demented persons generally having significant sleep disturbances much later in their course. Severe delirium is on a continuum with stupor and coma, and persons with a resolving coma are likely to be delirious temporarily.

0. Not present; awake and alert during the day, and sleeps without significant disruption at night
1. Occasional drowsiness during day and mild sleep continuity disturbance at night; may have nightmares but can readily distinguish from reality
2. Frequent napping and unable to sleep at night, constituting a significant disruption of or a reversal of the usual sleep-wake cycle
3. Drowsiness prominent, difficulty staying alert during interview, loss of self-control over alertness and somnolence
4. Drifts into stuporous or comatose periods

Item 9: Lability of mood

Rapid shifts in mood can occur in various organic mental syndromes, perhaps due to a disinhibition of one's normal control. The patient may be aware of this lack of emotional control and may behave inappropriately relative to the situation or to his/her thinking state, e.g., crying for no apparent reason. Delirious patients may score points on any of these items depending upon the severity of the delirium and upon how their underlying psychological state "colours" their delirious presentation. Patients with borderline personality disorder might score 1 or 2 points on this item.

0. Not present; mood stable
1. Affect/mood somewhat altered and changes over the course of hours; patient states that mood changes are not under self-control
2. Significant mood changes which are inappropriate to situation, including fear, anger, or tearfulness; rapid shifts of emotion, even over several minutes
3. Severe disinhibition of emotions, including temper outbursts, uncontrolled inappropriate laughter, or crying

Item 10: Variability of symptoms

The hallmark of delirium is the waxing and waning of symptoms, which is given 4 points on this item. Demented as well as delirious patients, who become more confused at night when environmental cues are decreased, could score 2 points.

0. Symptoms stable and mostly present during daytime
2. Symptoms worsen at night
4. Fluctuating intensity of symptoms, such that they wax and wane during a 24-hr period

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Appendix D. Delirium Rating Scale- revised 98 (237)

1. Sleep-wake cycle disturbance

Rate sleep-wake pattern using all sources of information, including from family, caregivers, nurses' reports, and patient. Try to distinguish sleep from resting with eyes closed.

0. Not present
1. Mild sleep continuity disturbance at night or occasional drowsiness during the day
2. Moderate disorganization of sleep-wake cycle (e.g., falling asleep during conversations, napping during the day or several brief awakenings during the night with confusion/behavioural changes or very little night-time sleep)
3. Severe disruption of sleep-wake cycle (e.g., day-night reversal of sleep-wake cycle or severe circadian fragmentation with multiple periods of sleep and wakefulness or severe sleeplessness.)

2. Perceptual disturbances and hallucinations

Illusions and hallucinations can be of any sensory modality. Misperceptions are "simple" if they are uncomplicated, such as a sound, noise, color, spot, or flashes and ''complex'' if they are multidimensional, such as voices, music, people, animals, or scenes. Rate if reported by patient or caregiver, or inferred by observation.

0. Not present
1. Mild perceptual disturbances (e.g., feelings of derealization or depersonalization; or patient may not be able to discriminate dreams from reality)
2. Illusions present
3. Hallucinations present

3. Delusions

Delusions can be of any type, but are most often persecutory. Rate if reported by patient, family or caregiver. Rate as delusional if ideas are unlikely to be true yet are believed by the patient who cannot be dissuaded by logic. Delusional ideas cannot be explained otherwise by the patient's usual cultural or religious background.

0. Not present
1. Mildly suspicious, hypervigilant, or preoccupied
2. Unusual or overvalued ideation that does not reach delusional proportions or could be plausible
3. Delusional

4. Lability of affect

Rate the patient's affect as the outward presentation of emotions and not as a description of what the patient feels.

0. Not present
1. Affect somewhat altered or incongruent to situation; changes over the course of hours; emotions are mostly under self-control
2. Affect is often inappropriate to the situation and intermittently changes over the course of minutes; emotions are not consistently under self-control, though they respond to redirection by others
3. Severe and consistent disinhibition of emotions; affect changes rapidly, is inappropriate to context, and does not respond to redirection by others

5. Language

Rate abnormalities of spoken, written or sign language that cannot be otherwise attributed to dialect or stuttering. Assess fluency, grammar, comprehension, semantic content and naming. Test comprehension and naming nonverbally if necessary by having patient follow commands or point.

0. Normal language
1. Mild impairment including word-finding difficulty or problems with naming or fluency
2. Moderate impairment including comprehension difficulties or deficits in meaningful communication (semantic content)
3. Severe impairment including nonsensical semantic content, word salad, muteness, or severely reduced comprehension

6. Thought process abnormalities

Rate abnormalities of thinking processes based on verbal or written output. If a patient does not speak or write, do not rate this item.

0. Normal thought processes
1. Tangential or circumstantial
2. Associations loosely connected occasionally, but largely comprehensible
3. Associations loosely connected most of the time

7. Motor agitation

Rate by observation, including from other sources of observation such as by visitors, family and clinical staff. Do not include dyskinesia, tics, or chorea.

0. No restlessness or agitation
1. Mild restlessness of gross motor movements or mild fidgetiness
2. Moderate motor agitation including dramatic movements of the extremities, pacing, fidgeting, removing intravenous lines, etc.
3. Severe motor agitation, such as combativeness or a need for restraints or seclusion

8. Motor retardation

Rate movements by direct observation or from other sources of observation such as family, visitors, or clinical staff. Do not rate components of retardation that are caused by parkinsonian symptoms. Do not rate drowsiness or sleep.

0. No slowness of voluntary movements
1. Mildly reduced frequency, spontaneity or speed of motor movements, to the degree that may interfere somewhat with the assessment.
2. Moderately reduced frequency, spontaneity or speed of motor movements to the degree that it interferes with participation in activities or self-care
3. Severe motor retardation with few spontaneous movements.

9. Orientation

Patients who cannot speak can be given a visual or auditory presentation of multiple choice answers. Allow patient to be wrong by up to 7 days instead of 2 days for patients hospitalized more than 3 weeks. Disorientation to person means not recognizing familiar persons and may be intact even if the person has naming difficulty but recognizes the person. Disorientation to person is most severe when one doesn't know one's own identity and is rare. Disorientation to person usually occurs after disorientation to time and/or place.

0. Oriented to person, place and time
1. Disoriented to time (e.g., by more than 2 days or wrong month or wrong year) or to place (e.g., name of building, city, state), but not both
2. Disoriented to time and place
3. Disoriented to person

10. Attention

Patients with sensory deficits or who are intubated or whose hand movements are constrained should be tested using an alternate modality besides writing. Attention can be assessed during the interview (e.g., verbal perseverations, distractibility, and difficulty with set shifting) and/or through use of specific tests, e.g., digit span.

0. Alert and attentive
1. Mildly distractible or mild difficulty sustaining attention, but able to refocus with cueing. On formal testing makes only minor errors and is not significantly slow in responses
2. Moderate inattention with difficulty focusing and sustaining attention. On formal testing, makes numerous errors and either requires prodding to focus or finish the task
3. Severe difficulty focusing and/or sustaining attention, with many incorrect or incomplete responses or inability to follow instructions. Distractible by other noises or events in the environment

11. Short-term memory

Defined as recall of information (e.g., 3 items presented either verbally or visually) after a delay of about 2 to 3 minutes. When formally tested, information must be registered adequately before recall is tested. The number of trials to register as well as effect of cueing can be noted on scoresheet. Patient should not be allowed to rehearse during the delay period and should be distracted during that time. Patient may speak or nonverbally communicate to the examiner the identity of the correct items. Short-term deficits noticed during the course of the interview can be used also.

0. Short-term memory intact
1. Recalls 2/3 items; may be able to recall third item after category cueing
2. Recalls 1/3 items; may be able to recall other items after category cueing
3. Recalls 0/3 items

12. Long-term memory

Can be assessed formally or through interviewing for recall of past personal (e.g., past medical history or information or experiences that can be corroborated from another source) or general information that is culturally relevant. When formally tested, use a verbal and/or visual modality for 3 items that are adequately registered and recalled after at least 5 minutes. The patient should not be allowed to rehearse during the delay period during formal testing. Make allowances for patients with less than 8 years of education or who are mentally retarded regarding general information questions. Rating of the severity of deficits may involve a judgment about all the ways long-term memory is assessed, including recent and/or remote long-term memory ability informally tested during the interview as well as any formal testing of recent long-term memory using 3 items.

0. No significant long-term memory deficits
1. Recalls 2/3 items and/or has minor difficulty recalling details of other long-term information
2. Recalls 1/3 items and/or has moderate difficulty recalling other long-term information
3. Recalls 0/3 items and/or has severe difficulty recalling other long-term information

13. Visuospatial ability

Assess informally and formally. Consider patient's difficulty navigating one's way around living areas or environment (e.g., getting lost). Test formally by drawing or copying a design, by arranging puzzle pieces, or by drawing a map and identifying major cities, etc. Take into account any visual impairments that may affect performance.

0. No impairment
1. Mild impairment such that overall design and most details or pieces are correct; and/or little difficulty navigating in his/her surroundings
2. Moderate impairment with distorted appreciation of overall design and/or several errors of details or pieces; and/or needing repeated redirection to keep from getting lost in a newer environment despite, trouble locating familiar objects in immediate environment
3. Severe impairment on formal testing; and/or repeated wandering or getting lost in environment

14. Temporal onset of symptoms

Rate the acuteness of onset of the initial symptoms of the disorder or episode being currently assessed, not their total duration. Distinguish the onset of symptoms attributable to delirium when it occurs concurrently with a different pre-existing psychiatric disorder. For example, if a patient with major depression is rated during a delirium episode due to an overdose, then rate the onset of the delirium symptoms.

0. No significant change from usual or longstanding baseline behaviour
1. Gradual onset of symptoms, occurring over a period of several weeks to a month
2. Acute change in behaviour or personality occurring over days to a week
3. Abrupt change in behaviour occurring over a period of several hours to a day

15. Fluctuation of symptom severity

Rate the waxing and waning of an individual or cluster of symptom(s) over the time frame being rated. Usually applies to cognition, affect, intensity of hallucinations, thought disorder, language disturbance. Take into consideration that perceptual disturbances usually occur intermittently, but might cluster in period of greater intensity when other symptoms fluctuate in severity.

0. No symptom fluctuation
1. Symptom intensity fluctuates in severity over hours
2. Symptom intensity fluctuates in severity over minutes

16. Physical disorder

Rate the degree to which a physiological, medical or pharmacological problem can be specifically attributed to have caused the symptoms being assessed. Many patients have such problems but they may or may not have causal relationship to the symptoms being rated.

0. None present or active
1. Presence of any physical disorder that might affect mental state
2. Drug, infection, metabolic disorder, CNS lesion or other medical problem that specifically can be implicated in causing the altered behaviour or mental state

Appendix E. Psychiatric symptoms, by selection group, limited to Xhosa-speaking individuals (N= 88)

	Late HIV N=42 (%)	Early HIV N=26 (%)	HIV-negative N=17 (%)	p-value
Duration of symptoms:	9 (21)	2 (8)	3 (18)	0.063
Days				
Weeks	23 (55)	13 (50)	5 (29)	
Months	10 (21)	8 (31)	6 (35)	
Years	0	3 (12)	3 (18)	
Depressive symptoms	28 (64)	10 (37)	4 (24)	0.008
Manic symptoms	25 (57)	17 (63)	13 (76)	0.382
Depressive/Manic symptoms	10 (23)	5 (19)	3 (18)	0.941
Suicidal ideation	10 (23)	12 (44)	4 (24)	0.143
Suicidal intent	20 (45)	13 (48)	5 (29)	0.471
Fluctuation	26 (59)	3 (11)	1 (6)	<0.001
Behavioural disturbance	42 (95)	22 (81)	15 (88)	0.123
Violence and/or aggression	22 (50)	17 (63)	11 (65)	0.490
Delusions (any)	42 (95)	27 (100)	17 (100)	0.690
Persecutory	38 (86)	26 (96)	16 (94)	0.488
Erotomanic	1 (2)	0	0	0.999
Religious	7 (16)	7 (26)	5 (25)	0.378
Somatic	3 (7)	1 (4)	1 (6)	0.999
Grandiose	17 (39)	13 (48)	11 (65)	0.180
Jealousy	0	1 (4)	1 (6)	0.247
Reference	3 (7)	3 (11)	2 (12)	0.693
Nihilism	1 (2)	0	0	0.999
Mean number of different types	1.7	2.0	2.3	0.077
Hallucinations (any)	41 (93)	25 (93)	16 (94)	0.999
Visual	28 (64)	12 (44)	4 (24)	0.017
Auditory	39 (89)	25 (93)	15 (88)	0.811
Tactile	13 (30)	3 (11)	1 (6)	0.069
Olfactory	5 (11)	0	0	0.115
Somatic	2 (5)	0	0	0.690
Gustatory	1 (2)	0	0	0.999
Mean number of different types	2.0	1.4	1.2	0.003
Memory change	21 (50)	1 (4)	0	<0.001
Catatonia	4 (9)	1 (4)	2 (12)	0.669
Episodes/s of disorientation	27 (61)	6 (22)	4 (24)	0.001

	Late HIV N=42 (%)	Early HIV N=26 (%)	HIV-negative N=17 (%)	p-value
Movement abnormality	18 (41)	7 (26)	2 (12)	0.074
Lability	33 (75)	11 (41)	7 (41)	0.005
Irritability	32 (73)	20 (74)	12 (71)	0.999

Appendix F. Psychiatric symptoms, by selection group, limited to individuals with first presentation (N=61)

	Late HIV N=37 (%)	Early HIV N=12 (%)	HIV-negative N=12 (%)	p-value
Duration of symptoms:	9 (26)	1 (8)	2 (17)	0.017
Days				
Weeks	19 (54)	5 (42)	2 (17)	
Months	7 (20)	5 (42)	5 (42)	
Years	0	1 (8)	3 (5)	
Depressive symptoms	26 (70)	5 (42)	4 (33)	0.043
Manic symptoms	17 (46)	4 (33)	7 (58)	0.451
Depressive/Manic symptoms	7 (19)	1 (8)	3 (25)	0.585
Suicidal intent	11 (30)	7 (58)	4 (33)	0.223
Suicidal ideation	20 (54)	8 (67)	5 (42)	0.451
Fluctuation	22 (59)	0	3 (25)	<0.001
Behavioural disturbance	35 (95)	7 (58)	9 (75)	0.008
Violence and/or aggression	17 (46)	6 (50)	4 (33)	0.767
Delusions (any)	37 (100)	12 (100)	12 (100)	0.999
Persecutory	33 (89)	12 (100)	10 (83)	0.419
Erotomanic	1 (2)	0	1 (8)	0.636
Religious	5 (14)	3 (25)	6 (50)	0.027
Somatic	3 (8)	1 (8)	3 (25)	0.279
Grandiose	9 (24)	4 (33)	6 (50)	0.266
Jealousy	0	0	2 (17)	0.072
Guilt	4 (11)	3 (25)	1 (8)	0.554
Reference	3 (8)	3 (25)	1 (8)	0.279
Nihilism	1 (3)	0	0	0.999
Mean number of different types	1.6	2.3	2.7	0.005
Hallucinations (any)	35 (95)	12 (100)	10 (83)	0.332
Visual	24 (65)	4 (33)	4 (33)	0.067
Auditory	32 (86)	12 (100)	10 (83)	0.539
Tactile	11 (30)	2 (17)	1 (8)	0.330
Olfactory	4 (11)	0	1 (8)	0.812
Somatic	2 (5)	0	1 (8)	0.999
Gustatory	0	0	0	-----
Mean number of different types	2.0	1.5	1.4	0.127
Memory change	21 (60)	1 (8)	2 (17)	0.001

	Late HIV N=37 (%)	Early HIV N=12 (%)	HIV-negative N=12 (%)	p-value
Catatonia	6 (16)	0	1 (8)	0.407
Episodes of disorientation	27 (73)	3 (25)	3 (25)	0.001
Movement abnormality	17 (46)	3 (25)	2 (17)	0.150
Lability	27 (73)	2 (17)	6 (50)	0.002
Irritability	25 (67)	7 (58)	10 (83)	0.465

Appendix G. Summary of Psychotropic Medications

Psychotropic Drug	No of Patients (N=111) (%)
Neuroleptics	
Haloperidol	72 (65)
Chlorpromazine	21(19)
Zuclopenthixol (long acting intramuscular injection)	11 (10)
Clozapine	7 (6)
Sulpiride	4
Flupenthixol (long acting intramuscular injection)	3
Risperidone	2
Fluphenazine decanoate	2
Other psychotropic agents	
Lithium carbonate	24 (22)
Sodium valproate	32 (29)
Carbamazepine	2
Fluoxetine	14 (13)
Citalopram	1
Lorazepam	26 (23)
Diazepam	8 (7)

Appendix H. Assignment probabilities for Latent Class Analysis, by patient

Patient Number	Probability of being in Class 1	Probability of being in Class 2
1	0.9747	0.0253
2	0.3093	0.6907
3	0.998	0.002
4	0.0002	0.9998
5	0.9992	0.0008
6	0.0014	0.9986
7	0.9996	0.0004
8	0.0143	0.9857
9	0.9998	0.0002
10	0.9938	0.0062
11	0.9979	0.0021
12	0.9998	0.0002
13	0	1
14	0.0014	0.9986
15	0.9817	0.0183
16	0.0037	0.9963
17	0.0037	0.9963
18	0.9946	0.0054
19	0	1
20	0.9898	0.0102
21	0.1154	0.8846
22	0.9998	0.0002
23	0	1
24	0.7638	0.2362
25	0.9893	0.0107
26	0.0022	0.9978
27	0.9385	0.0615
28	0	1
29	0.9441	0.0559
30	0	1
31	0.0297	0.9703
32	0.8971	0.1029
33	0.1184	0.8816
34	0.0865	0.9135
35	0.206	0.794
36	0.8086	0.1914
37	0.9996	0.0004
38	0	1
39	0.998	0.002
40	0.7276	0.2724
41	0.9266	0.0734

Patient Number	Probability of being in Class 1	Probability of being in Class 2
42	0.9817	0.0183
43	0.0466	0.9534
44	0.9992	0.0008
45	0.0002	0.9998
46	0.9026	0.0974
47	0.0065	0.9935
48	0.9725	0.0275
49	0.9946	0.0054
50	0.996	0.004
51	0	1
52	0.0219	0.9781
53	0.9998	0.0002
54	0.9992	0.0008
55	0.8866	0.1134
56	0.256	0.744
57	0.9998	0.0002
58	0	1
59	0.9992	0.0008
60	0.3722	0.6278
61	0.9969	0.0031
62	0.6193	0.3807
63	0.1913	0.8087
64	0.9281	0.0719
65	0.9737	0.0263
66	0	1
67	0.0008	0.9992
68	0.9843	0.0157
69	0.3655	0.6345
70	0.9385	0.0615
71	0.7218	0.2782
72	0.9948	0.0052
73	0	1
74	0.0123	0.9877
75	0.012	0.988
76	0.9266	0.0734
77	0.9154	0.0846
78	0.0063	0.9937
79	0.9998	0.0002
80	0.9992	0.0008
81	0.9992	0.0008
82	0.996	0.004
83	0.9738	0.0262
84	0.0024	0.9976
85	0.9996	0.0004

Patient Number	Probability of being in Class 1	Probability of being in Class 2
86	0.9998	0.0002
87	0.9979	0.0021
88	0.9982	0.0018
89	0.1928	0.8072
90	0.9998	0.0002
91	0.9992	0.0008
92	0.9979	0.0021
93	0.9257	0.0743
94	0.975	0.025
95	0.9998	0.0002
96	0.987	0.013
97	0.9996	0.0004
98	0.9992	0.0008
99	0.9988	0.0012
100	0	1
101	0.9998	0.0002
102	0.9946	0.0054
103	0.9893	0.0107
104	0.9996	0.0004
105	0.0041	0.9959
106	0.9992	0.0008
107	0.9992	0.0008
108	0.9998	0.0002
109	0.9992	0.0008
110	0.9998	0.0002
111	0.9996	0.0004

Appendix I. Psychiatric symptoms, by latent class, limited to Xhosa speaking individuals (N=88)

	Class 1 N=54 (%)	Class 2 N=34 (%)	p-value
Duration of symptoms: Days	6 (11)	8 (25)	0.290
Weeks	25 (47)	16 (50)	
Months	17 (32)	7 (22)	
Years	5 (9)	1 (3)	
Manic symptoms	35 (65)	20 (59)	0.653
Depressive/Manic symptoms	10 (19)	8 (24)	0.596
Suicidal ideation	23 (43)	15 (44)	0.999
Suicidal intent	18 (33)	8 (24)	0.350
Behavioural disturbance	46 (85)	33 (97)	0.145
Violence and/or aggression	32 (59)	18 (53)	0.660
Delusions (any)	53 (98)	33 (97)	0.999
Persecutory	51 (94)	29 (85)	0.252
Erotomanic	0	1 (3)	0.386
Religious	15 (28)	4 (12)	0.110
Somatic	3 (5)	2 (6)	0.999
Grandiose	30 (56)	11 (32)	0.048
Jealousy	2 (4)	0	0.520
Guilt	7 (13)	2 (6)	0.473
Reference	7 (13)	1 (3)	0.145
Nihilism	1 (2)	0	0.999
Mean number of different types	2.2	1.5	0.001
Hallucinations (any)	50 (93)	32 (94)	0.999
Visual	21 (39)	23 (68)	0.015
Auditory	49 (91)	30 (88)	0.730
Tactile	6 (11)	11 (32)	0.025
Olfactory	1 (2)	4 (12)	0.071
Somatic	0	2 (6)	0.147
Gustatory	0	1 (3)	0.386
Mean number of different types	1.4	2.1	0.001
Memory change	6 (11)	16 (50)	<0.001
Lability	26 (48)	25 (74)	0.026
Irritability	41 (76)	23 (68)	0.464

Appendix J. Psychiatric symptoms, by latent class, limited to patients with first presentation (N=61)

	Class 1 N=29 (%)	Class 2 N=32 (%)	p-value
Duration of symptoms: Days	5 (17)	7 (23)	0.193
Weeks	11 (38)	15 (50)	
Months	9 (31)	8 (27)	
Years	4 (14)	0	
Manic symptoms	11 (38)	17 (53)	0.306
Depressive/Manic symptoms	4 (14)	7 (22)	0.514
Suicidal intent	14 (48)	8 (25)	0.068
Suicidal ideation	18 (62)	15 (47)	0.306
Behavioural disturbance	21 (72)	30 (94)	0.037
Violence and/or aggression	9 (31)	18 (56)	0.071
Delusions (any)	29 (100)	32 (100)	0.999
Persecutory	27 (93)	28 (88)	0.674
Erotomanic	1 (3)	1 (3)	0.999
Religious	8 (28)	6 (19)	0.545
Somatic	3 (10)	4 (13)	0.999
Grandiose	10 (34)	9 (28)	0.782
Jealousy	2 (7)	0	0.222
Guilt	6 (21)	2 (6)	0.135
Reference	5 (17)	2 (6)	0.241
Nihilism	1 (3)	0	0.475
Mean number of different types	2.3	1.6	0.019
Hallucinations (any)	27 (93)	30 (94)	0.999
Visual	11 (38)	21 (66)	0.041
Auditory	26 (90)	28 (88)	0.999
Tactile	4 (14)	10 (31)	0.134
Olfactory	1 (3)	4 (13)	0.357
Somatic	1 (3)	2 (6)	0.999
Mean number of different types	1.5	2.0	0.027
Memory change	5 (17)	19 (63)	<0.001
Irritability	19 (66)	23 (72)	0.782

Appendix K. Psychiatric Symptoms by latent class, limited to patients with Late HIV disease (N=52)

	Class 1 N=21 (%)	Class 2 N=31 (%)	p-value
Median CD4+ cell count	**143**	**52**	**0.008**
Duration of symptoms: Days	3 (14)	7 (24)	0.693
Weeks	12 (57)	14 (48)	
Months	6 (29)	8 (28)	
Years	--	--	
Manic symptoms	14 (67)	16 (52)	0.392
Depressive/Manic symptoms	6 (29)	7 (23)	0.747
Suicidal intent	4 (19)	8 (26)	0.741
Suicidal ideation	11 (52)	14 (45)	0.778
Behavioural disturbance	20 (95)	29 (94)	0.999
Violence and/or aggression	10 (48)	17 (55)	0.778
Delusions (any)	20 (95)	30 (97)	0.999
Persecutory	20 (95)	26 (84)	0.382
Erotomanic	0	1 (3)	0.999
Religious	3 (14)	4 (13)	0.999
Somatic	2 (10)	3 (10)	0.999
Grandiose	11 (52)	8 (25)	0.078
Jealousy	1 (5)	0	0.404
Guilt	2 (10)	2 (7)	0.999
Reference	3 (14)	1 (3)	0.291
Nihilism	1 (5)	0	0.404
Mean number of different types	2.0	1.5	0.034
Hallucinations (any)	18 (86)	29 (94)	0.383
Visual	9 (43)	22 (71)	0.051
Auditory	17 (81)	27 (87)	0.700
Tactile	2 (10)	12 (39)	0.027
Olfactory	1 (5)	4 (13)	0.637
Somatic	0	2 (6)	0.509
Gustatory	0	1 (3)	0.999
Mean number of different types	1.3	2.2	0.005
Memory change	7 (33)	18 (62)	0.085
Lability	15 (71)	22 (71)	0.999
Irritability	17 (81)	21 (68)	0.353

Appendix L. Neuropsychological Assessment of patients with no mental illness, [4] compared with the selection groups and six month follow up results [5]

	Late HIV without any mental disorder N=25	p-value for comparison with Late HIV and mania /psychosis N=52	p-value for comparison with early HIV and mania /psychosis N=28	p-value for comparison with HIV-negative and mania /psychosis N=30	p-value for comparison with six month cohort post ART
Mean Successive Finger Tapping, dominant hand (seconds)	N=24 8.43 (2.00)	<0.001	0.014	0.014	0.063
Mean Successive Finger Tapping, non-dominant hand (seconds)(SD)	N=25 8.39 (1.48)	<0.001	<0.001	0.009	0.052
Mean Grooved Pegboard Test, dominant hand (seconds) (SD)	N=25 80.02 (34.74)	<0.001	<0.001	0.015	0.491
Mean Grooved Pegboard Test, non-dominant hand (seconds) (SD)	N=25 83.12 (19.61)	<0.001	<0.001	0.004	0.241
Mean Digit Span, forwards (scaled score)(SD)	N=25 7.72 (1.65)	0.242	0.572	0.727	0.074

[4] matched with patients with late HIV
[5] The patient scores for this analysis are described in Tables 5-13 and 5-32 in chapter 5

	Late HIV without any mental disorder N=25	p-value for comparison with Late HIV and mania /psychosis N=52	p-value for comparison with early HIV and mania /psychosis N=28	p-value for comparison with HIV-negative and mania /psychosis N=30	p-value for comparison with six month cohort post ART
Mean Rey Complex Figure, copy (SD)	N=25 30.96 (6.00)	<0.001	0.035	0.004	0.037
Mean Rey Complex Figure, initial (SD)	N=25 19.64 (6.49)	<0.001	0.001	0.007	0.851
Mean Rey Complex Figures, delayed (SD)	N=24 19.71 (6.31)	<0.001	0.001	0.003	0.252
Mean Trail Making Test A (seconds)(SD)	N=21 66.27 (27.86)	<0.001	< 0.001	0.018	0.243
Mental Control I, counting backwards from 20 (N,%=Yes)	25 (100%)	0.084	0.491	0.238	Not recorded
Mental Control II, reciting the alphabet (N,%=Yes)	19 (76%)	0.200	0.492	1.00	Not recorded