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LONG-TERM OUTCOMES OF PSYCHIATRIC PATIENTS INITIATED ON ANTI-RETROVIRAL THERAPY (ART) AT LUTHANDO CLINIC IN 2008-2010

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A research report submitted to the Faculty of Health Sciences, University of Witwatersrand, Johannesburg in partial fulfilment for the degree of MMed Psychiatry.

Johannesburg 2018

DECLARATION

I, Nokuthula Audrey Mdaka, declare that this research report is my own work. It is being submitted for the degree of MMed Psychiatry at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other university.

……17 January 2019

DEDICATION

This work is dedicated to my late parents, Kula, my husband (Kwezi), two daughters (Bulumko and Ayabonga), my siblings, Rea and my extended family. Thank you for all your limitless support and sacrifices.

PRESENTATIONS ARISING FROM THIS RESEARCH REPORT

University of the Witwatersrand, Department of Psychiatry, Annual Research Day, 2017, Johannesburg.

ABSTRACT

BACKGROUND

The Luthando Neuropsychiatric Clinic (Luthando Clinic) is a HIV and neuropsychiatry unit situated at the Chris Hani Baragwanath Academic Hospital (CHBAH) located at the South-Western Township of Johannesburg (SOWETO). The centre provides care for psychiatric patients who are also diagnosed with HIV, using a multidisciplinary integrated model of care. [1] Previous research at the Luthando Clinic has focused on short-term treatment outcomes.[1,2] The aim of this study was to determine the long-term (four-year) outcomes of psychiatric patients initiated on ART between 1 June 2008 and 31 December 2010 at the Luthando Clinic.

METHODS

A retrospective record review using patient files was conducted to examine follow-up and clinical outcomes. The primary outcome of the study was to determine follow-up outcomes (retained in care, loss to follow up, transferred to other centres, those who died) four years after initiation of ART. Retention in care was further explored as a secondary outcome. Clinical data of the patients who were retained in integrated care at four years after ART initiation were then collected and compared to baseline data (at ART initiation) to determine clinical outcomes.

RESULTS

Of the 291 patients initiated on ART at the clinic, 49.8% remained in integrated care at the end of the four-year follow-up period, 24.1% were lost to follow-up, 19.9% were transferred to other treatment centres and 6.2% had died. For those who remained in integrated care, there was a statistically significant increase in the CD4 count from baseline to the four-year follow-up period of 350 cells/mm^3 ($p<0.0001$), and 71.8% ($p<0.0001$) of the patients had suppressed viral load values at the end of the four-year follow-up period.

CONCLUSION

The psychiatric patients with HIV who were retained in integrated care at the Luthando Clinic were able to achieve favourable long-term outcomes, as evidenced by the significant improvement in their clinical parameters.

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LIST OF ABBREVIATIONS

ABC	Abacavir
AIDS	Acquired Immune Deficiency Syndrome
ART	Antiretroviral Treatment/Therapy
AUDIT	Alcohol Use Disorders Identification Test
AZT	Zidovudine
BMI	Body Mass Index
CDC	Centers for Disease Control and Prevention
CD4	Cluster of differentiation 4 lymphocyte
CHBAH	Chris Hani Baragwanath Academic Hospital
CIDI	Composite International Diagnostic Interview
CMD	Common Mental Disorder
CNS	Central Nervous System
DART	Development of Antiretroviral Therapy in Africa Trial
DDI	Didanosine
D4T	Stavudine
DSM IV-TR	Diagnostic and Statistical Manual of Mental Disorders Text Revision
EFV	Efavirenz
GMC	General Medical Condition
HAD	HIV-Associated Dementia
HAND	HIV-Associated Neurocognitive Disorder

HIV	Human Immunodeficiency Virus
HIV/AIDS	Human Immunodeficiency Virus/Acquired Immune Deficiency Syndrome
HRQOL	Health-Related Quality of Life
IHDS	International HIV Dementia Scale
INH	Isoniazid
IQR	Interquartile Range
LAI	Long-Acting Injection
LPV/r	Lopinavir/Ritonavir
LTFU	Loss To Follow-up
MDD	Major Depressive Disorder
MND	Minor Neurocognitive disorders
NNRTI	Non-Nucleoside Reverse Transcriptase Inhibitor
NRTI	Nucleoside Reverse Transcriptase Inhibitor
NVP	Nevirapine
OI	Opportunistic Infection
PI	Protease Inhibitor
PLWHIV	People Living With HIV
PTSD	Post Traumatic Stress Disorder
SA	South Africa
SASH	South African Stress and Health Study
SMD	Severe Mental Disorder

SMI	Severe/Serious Mental Illness
SNRI	Selective Nor-epinephrine Reuptake Inhibitor
SOWETO	South-Western Township
SSRI	Selective Serotonin Reuptake Inhibitor
TB	Tuberculosis
TCA	Tricyclic Antidepressant
TDF	Tenofovir
3TC	Lamivudine
VL	Viral Load
WHO	World Health Organization

CHAPTER ONE: INTRODUCTION

1.1 BACKGROUND

According to the World Health Organization (WHO), approximately 35 million people were estimated to be living with HIV and 1.5 million people had died from HIV-related illnesses globally by the end of 2014.[3] South Africa (SA) has one of the highest HIV prevalence rates with an estimation of 18% of the general population being infected.[3] This prevalence has been shown to be higher in certain vulnerable groups, one of which comprises those with severe mental illness (SMI). The relationship between mental illness and HIV can be bidirectional, as studies have also shown that people living with HIV (PLWHIV) are at a greater risk of developing mental illness due to the indirect and direct effects of the virus on the Central Nervous System (CNS).[4,5] Additionally, those with mental illness have a greater risk of contracting HIV, which is related to factors such as increased vulnerability to sexual abuse and increased high-risk sexual behaviours in the psychiatric population.[4,5]

Since the introduction of the antiretroviral therapy (ART) programme in South Africa in 2004, mortality due to HIV/AIDS (Human Immunodeficiency Virus/Acquired Immune Deficiency Syndrome)-related illnesses has declined and the number of people living with HIV accessing ART has increased.[6] The WHO has long recommended the integration of mental health services into HIV/AIDS treatment programmes.[7] Studies have shown that integrated care is the most effective means of promoting adherence in patients with SMI. This model works through adequate stabilisation of the individual's mental health symptoms and the integration of mental health into a comprehensive treatment plan.[8] Despite this

knowledge, the integration of mental health and HIV care has been a slow process in SA with few centres offering this type of care.

The Luthando Neuropsychiatric Clinic is situated in Chris Hani Baragwanath Academic Hospital (CHBAH) in the South-Western Township (SOWETO) in Johannesburg, SA. It was established in 2008 as a joint venture with the CHBAH Department of Psychiatry and the University of the Witwatersrand. The clinic aimed to provide integrated care for psychiatric patients with neuropsychiatric illnesses and HIV by means of a multidisciplinary team.[1]

CHBAH is the largest hospital in Africa and serves the community of SOWETO and surrounding areas.[9] The psychiatric department has an outpatient department and a 150-bed inpatient department. Patients are referred to Luthando Clinic from the psychiatric department as inpatients or outpatients. In addition, the clinic accepts referrals from other clinical departments in the hospital, surrounding community clinics, transfers from other ART sites, other psychiatric hospitals (Tara H. Moross Hospital and Sterkfontein Hospital) and Mother Theresa Home. Prior to ART initiation, patients receive a full medical workup, psychiatric assessment and adherence counselling. Other services available at the clinic include occupational therapy groups and support groups.

Previous research at Luthando Clinic has focused on short-term Loss To Follow-Up (LTFU) and other clinical outcomes.[1,2] There are currently no studies in previous literature examining long-term retention in care and clinical outcomes in HIV-infected mentally ill patients initiated on ART in South Africa. This study aimed to determine the long-term (four-year) outcomes of psychiatric patients initiated on ART between 2008 and 2010 at Luthando Clinic.

1.2 AIMS

To assess long-term (four-year) follow-up and clinical outcomes in psychiatric patients initiated on ART between 2008 and 2010 at Luthando Clinic.

1.3 STUDY OBJECTIVES

- The primary objective of the study was to assess the long-term follow-up outcomes (retention in care, death, LTFU, transferred out) four years after the date of ART initiation in HIV-positive psychiatric patients at the Luthando Clinic who were initiated on ART during the period between 1 June 2008 and 31 December 2010.

- The secondary objectives of the study included:

    - To describe demographic and clinical data and comparing baseline and follow-up data of the patients who were retained in care at the end of the four year follow up period.

    - To describe the following baseline (pre-ART initiation) clinical characteristics of those retained in care at four years after ART initiation.

        - Psychiatric diagnosis

        - Substance use history

        - Pharmacotherapy (non-ART pharmacotherapy which included psychotropic medication, TB medication and ART at initiation)

        - CD4 count, viral load, BMI, pregnancy status, International HIV Dementia Scale (IHDS) score, WHO HIV clinical stage, OI (Oppportunistic Infections)

        - Admission status

    - To describe and compare the clinical and immunological measures of those retained in care (BMI, development of OI, CD4 count) at baseline and at four years after initiation of ART.

    - To describe the adverse effects of ART, ART regimen changes, admissions (medical and psychiatric) and treatment interruption during the four-year follow-up period of those retained in care.

- To assess virologic suppression at six months and at four years after ART initiation in those who remained in care.

CHAPTER TWO: LITERATURE REVIEW

2.1 BURDEN OF MENTAL ILLNESS IN SOUTH AFRICA

Mental illness contributes significantly to the burden of diseases worldwide, with neuropsychiatric disorders comprising five of the ten leading causes of disability and early mortality globally.[10] In SA, it is estimated that one in three people present with mental illness. According to the South African Stress and Health Study (SASH) conducted between 2002 and 2004, the lifetime prevalence for any mental illness was 30.3% and anxiety disorders were the most prevalent presentation.[11] The burden of mental illness in SA is an ongoing challenge and is often complicated by the comorbid presence of HIV and other chronic illnesses which directly and indirectly impact significantly on health care costs.[12] Studies done in sub-Saharan Africa have shown that integrating mental health care services into primary community- and tertiary-based services is the most cost-effective intervention.[7,12]

2.2 HIV AND MENTAL ILLNESS

2.2.1 Prevalence of HIV in psychiatric patients

The prevalence of HIV in people living with severe mental illness (SMI) in South Africa has been reported to be as high as 26.5%, which is much higher than the prevalence reported in the general population.[13] This prevalence of HIV in the psychiatric population varies in literature. In a study conducted at Weskoppies Psychiatric Hospital in Gauteng, the prevalence of HIV in patients admitted in the psychiatric unit was 11%.[14] Although this percentage was lower than that reported in the general population, it was higher than the previous prevalence of 9% reported in an earlier study at Weskoppies Hospital.[15] Other studies conducted in the sub-Saharan region have reported a higher prevalence of HIV in the psychiatric population. In a cross-sectional study by Lundberg *et al.* conducted in Uganda, the prevalence of HIV in psychiatric patients discharged from psychiatric units was 11.3% overall, which was higher than the 8% prevalence reported in the general population of Uganda.[16] In this study, the prevalence was twice as high in female participants and there were no associations between HIV

infection and the different psychiatric diagnoses. In SA, other studies have reported a higher HIV prevalence among the psychiatric population. In a KwaZulu-Natal study, Collins *et al.* reported a prevalence of 26.5% in psychiatric patients.[13] This high prevalence suggests that people with "severe mental illness" may be at greater risk of contracting HIV.

The factors that contribute to this high prevalence have been described in literature and include socioeconomic factors, comorbid substance use and factors related to psychopathology of the SMI.[17] In a study by Abayomi *et al.*, the HIV risk behaviour in persons with SMI in a psychiatric hospital was evaluated using an HIV risk questionnaire and 48% of the participants reported a history of high-risk sexual behaviour.[18] Increased vulnerability to sexual abuse may also contribute to the high prevalence of HIV infection in this population.[19] Alcohol use is known to increase sexual risk behaviours through various mechanisms including impairing judgement and decision-making, especially in the intoxication phase resulting in high-risk sexual behaviour.[19,20,21] In a Cape Town study on patrons attending a shebeen, more men than women reported hazardous alcohol use associated with high-risk sexual behaviours.[22] A study by Singh *et al.* examining the seroprevalence and HIV-associated factors among adults with SMI concluded that since psychiatric patients were a vulnerable group, HIV testing and HIV treatment programmes should be implemented in a way that caters for this population's specific needs.[23]

2.2.2 Mental illness in people living with HIV

The relationship between HIV and mental illness has been described as a complex and bidirectional interaction.[24] The virus can directly invade the central nervous system (CNS) resulting in neuropsychiatric manifestations and CNS opportunistic infections.[25] Antiretroviral drugs are also known to cause neuropsychiatric side effects.[26] The psychological impact of HIV diagnosis through stigma, discrimination, poverty and loss of partner can also indirectly result in mental illnesses such as anxiety and depressive disorders.[27,28]

In literature, mental disorders are often described as “common mental disorders” and “severe mental disorders” or “serious mental illnesses” based on the severity and prevalence thereof.[4] Common mental disorders (CMD) refer to disorders that are highly prevalent in the general population; these include anxiety, depressive and substance use disorders.[4] These disorders are also common among people living with HIV (PLWHIV). In SA, studies have reported prevalence rates of between 26% and 38% among PLWHIV.[29] Severe mental disorders (SMD) or severe mental Illness (SMI) are disorders that occur less commonly in the general population and lead to significant impairment in cognitive, occupational and social functioning.[4,30] These disorders include schizophrenia, bipolar disorder and major depressive disorder with psychotic features.[4,30] In other literature, SMI is further classified into primary and secondary SMI.[4] Primary SMI refers to SMI that is present prior to HIV diagnosis and secondary SMI refers to SMI diagnosis which is related to the HIV infection and occurs as a consequence of the HIV infection. The prevalence of SMI in PLWHIV is estimated at 15%.[4,30]

The most prevalent CMD in PLWHIV include depressive disorders, anxiety disorders, Post Traumatic Stress Disorder (PTSD) and substance use disorders.[31] Depressive disorders are the most commonly reported CMD in literature with prevalence estimated to be twice as high compared to that reported in the general population.[31,32] In a cross-sectional study by Myer *et al.* conducted in the Western Cape, the prevalence of CMD was evaluated using psychiatric screening tools. Depressive disorders were the most prevalent CMD at 14%, followed by alcohol use and PTSD at 7% and 5% respectively.[31] In another study by Freeman *et al.*, the prevalence of mental illness in PLWHIV was examined in a sample of 900 patients across five provinces in SA, and 43.7% of the participants were diagnosed with a mental illness using the Composite International Diagnostic Interview (CIDI).[33] The findings of this study were similar to the findings by Myer *et al.* in that depressive disorders were the most prevalent CMD followed by substance use disorders.[33] CMD may impact negatively on ART treatment

outcomes. In a prospective study by Cichowitz *et al.,* 33%, 49% and 33% of the HIV-infected patients screened positive for depression, anxiety and alcohol use respectively at ART initiation. Retention in care and viral suppression were then evaluated six months after ART initiation.[34] Overall, 67.6% remained in care, but those with depression, anxiety disorders and alcohol use disorders were less likely to be retained in care.[34]

In terms of SMI in PLWHIV, mania and psychosis are the commonest psychiatric complications of HIV infection reported in literature.[35,36] Both these psychiatric manifestations of HIV may occur on the back of a pre-existing mental illness, as part of a substance-related disorder, secondary to an opportunistic infection or as an adverse effect of ART.[35,36] New onset psychosis without mania in PLWHIV occurs less commonly as compared to mania, with varying rates reported in literature.[37] In a review by Nebhinani and Mattoo, the prevalence of new onset psychosis among PLWHIV was estimated to be between 0.23% and 15.2%. In this review, psychosis was also associated with medical conditions, substance use and with the neuropsychiatric adverse effects of ART.[35] First episode mania or bipolar disorder is also common among PLWHIV. The prevalence of bipolar disorder among PLWHIV has been reported to be up to five times higher than in the general population.[36,38,39] A study by Nakimuli-Mpungu *et al.* compared the presentation of first episode mania in HIV-positive and HIV-negative patients admitted in a psychiatric hospital in Uganda. Overall 141 patients were admitted with a first episode of mania, 55% of whom were HIV positive and 79% of which were diagnosed with HIV-related mania. HIV-related mania was also associated with more severe HIV infection and cognitive impairment.[36] In HIV-infected individuals, the prevalence of bipolar disorder or mania has been shown to be higher in those with an AIDS (Acquired Immune Deficiency Syndrome)-defining illness as compared to those without.[39] Mania in HIV-positive patients also occurs commonly in those with CD4 counts below 250 cells/mm^3, and is thus associated with more progressive and advanced HIV infection.[39,40] In a study by Ellen *et al.,* the 17-month prevalence of mania in HIV-positive

patients with AIDS was 8%, whilst in those without AIDS it was reported at 1.4%.[38]

It is evident that mental illness is commonly comorbid in PLWHIV and that several factors contribute to the causality of these illnesses. Treatment programmes for PLWHIV should focus on integrating the screening of mental illness among PLWHIV and the management of comorbid psychiatric illness. Freeman *et al.* recommended that HIV/AIDS treatment programmes should include the assessment and appropriate management of mental illness, support for further research of the relationship between mental illness and HIV/AIDS and, lastly, the promotion of advocacy highlighting the importance of mental health in PLWHIV.[41]

2.2.3 Severe mental illness and antiretroviral treatment

According to the SA Department of Health National Antiretroviral Treatment Guidelines regarding ART initiation during the study period between 2008 and 2010, patients who were eligible for ART were those with CD4 counts of less than 200 cells/mm3 and those with a WHO stage IV AIDS-defining illness. [42] Eligible patients also had to express willingness and readiness to adhere to the ART regimen.[42] The first line ART regimen recommended comprised three drugs, two Nucleoside Reverse Transcriptase Inhibitors (NRTI) and one Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI). The first line regimen was comprised of Stavudine (D4T), Lamivudine (3TC) and Efavirenz (EFV) or Nevirapine (NVP), whilst the second line was comprised of Zidovudine (AZT), Didanosine (DDI) and Lopinavir/Ritonavir (LPV/r).[42] In the 2010 National ART initiation guidelines the NRTI Tenofovir (TDF) was introduced to replace D4T.[43]

Initially, clinicians were sceptical to prescribe ART in the psychiatric population due to reasons of assumed poor adherence.[1] Literature has however shown that psychiatric patients are able to adhere to ART.[1] In a study by Himmelhoch *et al.,* 4989 patients were assessed at ART initiation and 9% were classified as having a mental illness. The patients with a

mental illness were more likely to remain on ART in the first two years of ART initiation.[44]

Although there are several published ART guidelines with recommendations on the co-management of HIV and mental illness, there are currently no specific guidelines on first line ART regimens for psychiatric patients with HIV.[4,45] That being said, there are several factors that need to be considered when selecting an ART regimen for people with mental illness. Since patients with SMI and HIV can be on multiple medications to treat both conditions and other conditions such as opportunistic infections, the pharmacokinetic and pharmacodynamic drug interactions are of concern when prescribing ART in this population.[46] Antiretroviral drugs, psychotropic medication and some of the drugs used to treat opportunistic infections are metabolised by the hepatic cytochrome P450 enzyme system. The co-administration of these drugs can therefore result in drug toxicity or a decrease in the effectiveness of the drugs.[46,47]

People living with HIV are also known to be more vulnerable to the adverse effects of psychotropic medication.[46,47] Potential drug to drug interactions may lead to increased concentration of psychotropic medication resulting in the worsening of adverse effects.[46,47] Antiretroviral drugs can also cause neuropsychiatric adverse effects.[48] The NNRTI EFV is the drug most commonly associated with neuropsychiatric adverse effects.[49] It estimated that up to 50% of patients on EFV experience neuropsychiatric adverse effects.[50] Other drugs implicated include the NRTI class with ABC and AZT in particular, though the integrase inhibitors are rarely implicated.[48] These neuropsychiatric adverse effects may result in the worsening of a pre-existing mental illness.[19] The neuropsychiatric adverse effects of ART vary and are often mild and transient and usually resolve spontaneously within six weeks.[50,51] Gaida *et al.* recommended that since the neuropsychiatric effects of EFV are often mild and transient, patients who develop these effects should rather be monitored closely instead of switching to another ART.[52] Other guidelines also recommend that severe adverse effects such

as psychosis and depressive disorders should rather be treated first prior to considering switching to another NRTI such as NVP.[51] The adverse effects of ART may impact negatively on adherence and should therefore be considered when initiating ART in this population.

Substance use is common among the psychiatric population and among PLWHIV. The presence of substance use in PLWHIV may further complicate the choice of the ART regimen. Alcohol use in particular has been reported be high among PLWHIV in SA.[53] Alcohol use not only impacts negatively on ART adherence and increases high-risk sexual behaviour, but also interacts with ART through various mechanisms.[54] Alcohol, like the ART drugs is also metabolised by the cytochrome hepatic enzyme system. Alcohol toxicity can therefore impair liver function and ART metabolism resulting in ineffective ART therapy or ART toxicity.[55] Alcohol use may also compound some of the ART and psychotropic adverse effects and interact with some of the drugs used to treat opportunistic infections (OI).[47,54,56]

Another factor to consider is the presence of HIV-Associated Neurocognitive Disorder (HAND). The presence of cognitive deficits in PLWHIV may impact negatively on ART adherence, therefore ART regimens in these patients need to be tailored accordingly. Despite the increased roll out of ART, HAND remains prevalent in the sub-Saharan region. It is estimated that up to 60% of PLWHIV have some form of cognitive decline.[57,58] There has been a change in the pattern of HAND post ART roll out, with a decreased prevalence of severe HAND and an increased prevalence of the milder forms of HAND.[59] One of the factors contributing to the high prevalence of the latter is thought to be related to the neurotoxic effects of some of the ART drugs.[60,61] Since HAND interferes with social and occupational functioning, this may result in poor adherence in PLWHIV. The screening for HAND prior to ART initiation and during ART treatment is therefore important. In those with comorbid HAND,

simple drug regimens and ongoing adherence support will also need to be considered in order to improve adherence and treatment outcomes.

2.3 INTEGRATION OF CARE

The complexity of the interaction between HIV and mental illness highlights the need for a comprehensive and integrated model of care. According to the World Health Organization (WHO), integrated care is defined as: “The management and delivery of health services so that clients have a continuum of preventative and curative services according to their needs over time and across different levels of the health system”.[62] This model of care involves the integration or co-management of two or more chronic illnesses by the same health care provider or team. The WHO has long recommended the integration of mental illness interventions in the global HIV/AIDS initiatives. The integration of the psychosocial needs of PLWHIV in all HIV treatment programmes has also been highlighted by the organisation.[63] The integration of mental health services into a comprehensive ART treatment plan has been shown to be one of the most cost-effective means of promoting adherence in patients with SMD and HIV.[12] This approach allows for a holistic model of care and also reduces the stigma associated with mental illness and HIV. In fragmented care, patients would receive care for the various conditions from different clinics; for example, the patient would attend a psychiatric clinic, ART clinic and TB clinic separately. This may have cost implications for the individual resulting in poor adherence.

Chuah *et al.* described different models of integrated care as “single facility”, “multi-facility” and “integration through care-coordination via the use of case managers”.[64] The single-facility model allows the patient to receive care from one facility by a multidisciplinary team of health care professionals. In the multi-facility model, integration of services occurs through established referral systems between facilities or health care providers who provide separate services. Integration through care-coordination via the use of case managers involves the use of a non-physician, such as a nurse or social

worker acting as a case manager responsible for developing an integrated treatment care plan and facilitating referrals. This model requires intensive training of the case manager who is a non-physician. The advantage of the model is that it promotes continuity of care within the community.[64]

The Luthando Clinic is one example of single-facility model of integrated care where patients receive care for both their psychiatric illness and HIV and HIV-related disorders in one centre. This type of integrated model is reported to improve communication among the health care providers. Less physical barriers to adherence have been reported in those managed in this type of care model.[65] There are however several challenges related to costs pertaining to this model of care. Due to financial and human resource constraints, the health systems of low-income countries may not cope with implementing this model of care.[64]

Joska proposed a model of integration of mental health care that targets high-risk patients who require mental health care, as well as the provision of training and screening tools for detecting mental illnesses.[65] Integrated care of HIV and SMI has shown to improve overall treatment outcomes of both conditions through the management of substance use disorders, improving psychosocial circumstances, better retention in psychiatric care and adherence to medication.[12] A study by Hoang *et al.* examining virologic response to ART at five HIV clinics found that patients who attended HIV clinics which offered integrated services were more likely to achieve viral suppression.[66]

2.4 MEASURES OF LONG-TERM OUTCOME IN HIV TREATMENT

There are several measures that are considered important in assessing the long-term outcomes of HIV treatment programmes. These include clinical parameters, immunological parameters, follow-up outcomes and overall quality of life.

In PLWHIV on ART, commonly used measures of long-term outcome, disease progression and response to treatment can be grouped into clinical

measures and laboratory immunological measures. Routine BMI measurements, presence of opportunistic infections and adverse events form part of the clinical parameters.[67] Laboratory parameters include the CD4 count and viral load (VL). Additional clinical markers include regimen change and hospital admissions.[68,69] Other literature included retention in care, adherence as well as functional ability and employment status as other measures of long- and short-term outcomes.[69,70] Other measures of outcome used specifically in the psychiatric population without HIV infection include clinical and functional outcome measures which involve the use of symptom rating scales and measures of occupational and social functioning.[71] These measures of long-term outcome can also differ according to researchers; for example, in certain studies symptom control might have been the goal, whilst in others it may have been social functioning and community stability.[71] In some literature, quality of life or risk reduction were used as measures of long-term outcome in both psychiatric and HIV populations.[71,72] In research, hospitalisation is commonly used as an outcome measure in the psychiatric population.[71] Health-Related Quality of Life (HRQOL) for PLWHIV has become increasingly important, with the goals of therapy now including improvement of HRQOL in addition to the reduction of symptoms, suppression of the virus and extension of survival.[73] This outcome includes the assessment of the impact of HIV or other illnesses on physical, mental and social functioning using subjective and objective rating tools.[73]

2.4.1 "Follow-up outcomes" as a measure of long-term outcome

"Follow-up outcomes" include those lost to follow-up, those who have died, those who were transferred out to other treatment sites and those who remained in care.[74]

Success in HIV treatment programmes requires individuals to adhere to long-term ART treatment. Adherence is therefore a good measure of long-term treatment outcome. Poor adherence is associated with poorer treatment outcomes of continuing viral replication with possible viral

resistance, treatment failure, progression to AIDS and death.[70] Despite this knowledge, ART adherence remains a challenge. In 2007, a systematic review of ART programmes in the general population in sub-Saharan Africa reported that only 60% of those initiated on ART remained on treatment by the end of the second year. This estimate was also reported to decline over time.[74] Medication adherence may be defined as the extent to which a patient takes a medication in the way intended by a health care provider [75] Other authors define adherence as taking at least 95% of the prescribed medication.[76] However, additional studies have shown that up to 80% adherence is sufficient to achieve successful virologic suppression.[77] There are several measures of adherence and retention in care that have been described in literature including objective and subjective measures.[78,79] The subjective measures used in the psychiatric population and in ART programs include the use of self-report questionnaires whilst objective measures include the use of pill count, electronic monitoring caps, missed clinic appointments and immunological and virologic markers and drug levels.[78,79] In a study conducted at an adult HIV clinic in Johannesburg examining markers of poor adherence among PLWHIV on ART, self-report, VL and the number of missed appointments were used as measures of adherence. This study found that VL measurement was the most reliable measure of adherence.[79] There is evidence supporting the association between regular clinic attendance for medication refills as an important measure of adherence.[80] In a study by Kunutsor *et al.*, clinic attendance was associated with ART adherence. The authors of this study concluded that the monitoring of clinic attendance may be an objective and effective measure of adherence.[80] Adherence in psychiatric patients and PLWHIV is influenced by multiple factors related to the patient, the nature of the illness, treatment regimen prescribed, health care system factors and environmental factors.[78,81] Barriers to adherence can be grouped into patient, health care provider, condition, treatment and socioeconomic factors. Predictors of good adherence include social stability and support, the individual's beliefs and knowledge about the illness and treatment, a

trusting patient-provider relationship and the provision of an ART relationship suitable for the patient's lifestyle.[81]

The term "attrition" in care is defined as the discontinuation of ART and encompasses those who are lost to follow-up, those who stop ART while in care and those who have died while on ART.[82] The phrase "loss to follow-up" describes individuals who have discontinued care for six months (180 days) or more since the last clinic visit.[83] It is estimated that 20 to 40% of patients are lost to follow-up in ART treatment programmes in sub-Saharan countries.[84] Loss to follow-up also impacts negatively on the immunological and virologic benefits of ART and increases AIDS-related mortality. In order to improve adherence, one would need to understand the factors that contribute to LTFU. Some of the predictors of LTFU that have been described in literature include low CD4 count, poor nutritional status, advanced clinical staging, TB co-infection, adverse drug reactions and younger age.[85] In a previous study conducted at the Luthando Clinic over a 14-month period of follow-up, 24.8% of patients were classified as lost to follow-up.[2] This rate of LTFU was similar to that reported in studies among PLWHIV in the general population.[74] Another outcome that impacts negatively on the rate of retention in care is the rate of patients who are transferred to other treatment sites.[84] Relocation to another place of residence was the main reason for transferring to another treatment site reported in literature.[86] Nglazi *et al.* examined the characteristics of patients who were transferring out of an ART clinic to another. In this study, patients who transferred to other treatment sites had not achieved viral suppression prior to the transfer.[87] This finding suggests that transfer to other treatment sites may be associated with poorer treatment outcomes. Mortality further contributes to attrition, as the mortality rate amongst PLWHIV with a comorbid mental illness has been reported to be increased as compared to the general population.[88,89] In a study by De Lorenzo *et al.*, there was a higher mortality rate reported in patients with a comorbid psychiatric diagnosis. This mortality rate was further increased in those who could not access psychiatric care.[89]

Severe mental illness (SMI) in PLWHIV may impact negatively on ART initiation and adherence.[90] Nachega *et al.* conducted a cohort study of 773 patients who were initiated on ART between January 2005 and July 2009 and aimed to measure the association between SMI at initiation of ART and subsequent retention in care in HIV-infected Ugandan adults. This study found that SMI at the time of ART initiation is associated with worse retention in HIV care, specifically over the first 12 months. The rate of retention at 12 months after ART initiation for those with SMI was estimated at 47% versus 65% in those without SMI, with the difference noted specifically in the first six months.[91] Other studies have reported retention in care rates in the psychiatric population that were similar to those of PLWHIV in the general population. In a study by Karstaedt *et al.*, 64% of the patients remained in care at the end of the follow-up period of 96 weeks. The findings of this study suggested that patients with a comorbid mental illness were able to remain in care at similar rates to PLWHIV in the general population. These patients were also able to achieve good virologic and immunological outcomes at follow-up.[92] A cross-sectional retrospective review by Joska *et al.* also demonstrated that adherence amongst those with SMI could be equal to that of PLWHIV without SMI, as psychiatric patients were already experienced in taking medication daily.[93]

2.4.2 Clinical measures of long-term outcome

2.4.2.1 CD4 count and viral load

CD4 count and viral load (VL) are known to be good measures of short-term and long-term immunological outcome. In the Development of Antiretroviral Therapy in Africa Trial (DART), it was shown that patients who had routine laboratory monitoring had better survival rates and less disease progression compared to those who were only monitored clinically.[94] Another study showed that those who had both the CD4 count and viral loads monitored routinely had less AIDS-related illnesses.[95]

The CD4 count, which is expressed as the number of CD4 cells/mm^3 is useful not only to make decisions about ART initiation, but also as a

measure of clinical outcome and disease progression. In a resource-limited setting, the addition of CD4 count monitoring to clinical monitoring has been shown to be more cost effective than additional viral load monitoring.[95] Previously, ART initiation was based on the CD4 count and WHO HIV staging. However, the WHO currently recommends that ART should be initiated in all HIV-positive people irrespective of the CD4 count.[96] According to ART initiation guidelines, CD4 count measurements should be repeated six months after initiation then yearly thereafter.[97] The average expected improvement in CD4 count ranges from 75-100 mm^3 in the first three months, rapidly increasing in the early months of initiation, followed by a more gradual increase thereafter of approximately 50-100 cells/mm^3/year.[98] Decline in CD4 count might be a sign of immunological failure particularly when associated with increasing VL.[99] Literature has shown that individuals initiated on ART at higher CD4 counts (more than 350 cells/mm3) have better treatment outcomes compared to those initiated on values below 200 copies/ml.[99] CD4 count is thought to be a marker of prognosis at low values, however, when high, CD4 count has little prognostic value, as patients with high CD4 counts can have high viral loads.[100] The occurrence of opportunistic infections (OI) during ART treatment could also be an indicator of immunological and virologic failure.[100,101] Severe mental illness at ART initiation and during ART treatment is associated with poorer CD4 outcomes. It has previously been shown that patients on ART with chronic untreated depressive symptoms had slower CD4 count improvement when compared to those without depressive symptoms.[102]

Due to financial constraints in sub-Saharan African countries and cost of VL measurement, CD4 count measurement is generally used to decide on ART initiation and VL measurement at initiation is not recommended.[103,104] According to the SA National ART initiation guidelines, VL measurement should be done six months after ART initiation and yearly thereafter according to the response.[97] In well-resourced settings, regular VL measurements are mainly used to monitor for treatment failure.[105] Regular

VL monitoring is also useful in identifying adherence issues early, therefore limiting the development of treatment resistance.[106] Although full suppression is expected at six months, studies have shown a varied response, with the percentage of patients who achieved undetectable VL by 12 months averaging only at 45%.[100,107] In resource-limited countries, it is currently recommended that six-monthly CD4 count monitoring should be eliminated in patients who have had an undetectable VL for 12 months with a CD4 count of more than 350 cells/mm^3.[107] Viral load monitoring was shown in literature to be a better measure of outcome.[107,108]

The WHO defines treatment success as a decline in VL to values less than 50 copies/ml within six months of ART initiation and sustained thereafter. [109] In order to define viral suppression as per the WHO guidelines, one would have to collect VL values yearly following the initial value done six months after ART initiation. When treatment failure is suspected, two consecutive measurements that are at least three months apart should be done.[110] According to the WHO, treatment failure is defined as a VL measurement above 1000 copies/mL on two consecutive measures three months apart in a setting of adequate adherence counselling. [98,109] This definition is usually applied in ART guidelines of low to middle-income countries. The threshold at which patients should be considered as failing treatment is still under debate. There has been some suggestion that the cut-off value used by the WHO is a misrepresentation of viral failure.[109,110] Several authors have suggested that the cut-off value for virologic failure should therefore be lowered.[109,110] In a four-year prospective cohort evaluating outcomes of patients with sustained viral suppression compared with those with episodes of viremia, it was found that the majority of the patients with viremia achieved suppression when VL measurement was repeated. It was reported that in those with intermediate viremia (1000-10000 copies/ml) and high viremia (more than 10000 copies/ml), only 39.6% and 19.1% of patients respectively needed to be switched to a second line ART regimen. [110] Studies done in high-income countries have shown that PLWHIV with VL values far below 1000 copies/ml already had mutations

suggestive of resistance to their current ART regimen.[110,111] If there is ongoing virologic failure, it results in regimen switching, which is a measure of poor virologic outcome.

Mental illness at the time of ART initiation and during ART treatment is known to be associated with poor immunological and virologic responses. In a study by Pence *et al*, those with a comorbid psychiatric diagnosis had a slower rate of virologic suppression and higher rate of virologic failure compared to those without a comorbid psychiatric diagnosis.[111] Depressive symptoms in PLWHIV have also been associated with poor adherence to ART, which in turn would have a negative effect on immunological and virologic response.[112] In a study by Cichowitz *et al.,* patients who screened positive for depression, anxiety disorders and alcohol use at ART initiation achieved poor viral suppression compared to those without mental illness at ART initiation.[34]

2.4.2.2 Body mass index (BMI)

Body mass index, which is measured in kilograms/m^2 has been proven to be a strong and independent predictor of mortality in those with HIV when recorded at baseline within three months of HIV diagnosis.[113] In a study examining the relationship between pre-ART BMI and AIDS-related deaths, it was found that being underweight prior to ART initiation doubled the risk of AIDS-related death. Low BMI at ART initiation was a predictor of early mortality whilst increased BMI was seen as a protective factor.[114] Those with low BMI (below 18 kg/m^2) have also been shown to have increased risk of developing opportunistic infections such as Tuberculosis (TB).[113] In resource-limited settings where CD4 count and VL measurements may be a challenge, BMI has been used as a tool to decide on ART initiation and to measure treatment failure.[114]

Although increase in BMI is associated with good prognostic outcome in HIV, it is also an indicator of some of the ART and psychotropic metabolic adverse effects.[115] These adverse effects are particularly important in the psychiatric population as some of the psychotropic medications also have

metabolic adverse effects that need to be considered when initiating these patients on ART. Second generation antipsychotics and some mood stabilizers are known to cause metabolic side effects and when combined with protease inhibitors these side effects may potentially be worsened.[115] Thus, the goal is to have a BMI within the normal range of 18,5-25. Baseline measurement of BMI and continuous monitoring at every visit is mandatory for monitoring ART response and also for monitoring adverse effects of ART.

2.4.3 Hospital admissions

Despite increased access to ART treatment in SA, a substantial number of PLWHIV still experience severe HIV-associated illnesses leading to hospitalisation.[116] Psychiatric admissions are also common in those with SMI and can be used as a measure of outcome.[117] Hospital admissions could reflect poor adherence, the presence of opportunistic infections, relapse from their mental illness, or immunological and virologic failure. Hospital admissions have been used in literature as an outcome measure as they are relatively easy to measure and a reliable measure of outcome.[118] In patients with schizophrenia, poor adherence has been shown to be associated with multiple hospital admissions.[119] Factors contributing to hospitalization as an outcome measure include treatment adherence, adverse events and insight about the illness.[120] The frequency of hospital admissions has been shown to decline with time on ART in patients with favourable virologic and immunological outcomes.[120] Despite the potential value of hospitalisation as a performance measure for mental health services, the relationship between it and other outcome measures is not well studied. Mental illness in PLWHIV is associated with increased risk of both psychiatric and non-psychiatric admissions.[121,122]

2.5 SUMMARY OF LITERATURE REVIEW

There is a clear bidirectional relationship between mental illness and HIV, which can negatively impact on overall treatment outcomes. Recent

literature has shown that people with SMI and HIV can have similar treatment outcomes to PLWHIV without SMI when care is integrated into a comprehensive treatment model. Concurrent treatment of both illnesses has been shown to improve overall treatment outcomes through improving treatment adherence for both illnesses. Antiretroviral treatment outcomes have been well studied in PLWHIV in the general population, though little is known about the long-term outcomes of psychiatric patients who are on ART. Previous studies in this population have mostly assessed the prevalence of comorbidity and short-term treatment outcomes. Outcomes used to measure treatment success include retention in care, hospital admissions, and clinical and laboratory parameters. These outcomes are similar to those used to measure long-term outcomes in the psychiatric population. It is also evident from the literature above that retention in care is associated with better treatment outcomes. This study aimed to study the long-term treatment outcomes in psychiatric patients with HIV at the Luthando Clinic.

CHAPTER THREE: METHODOLOGY

3.1 STUDY DESIGN, SAMPLE, SIZE AND POPULATION

This study was conducted at CHBAH at the Luthando Neuropsychiatric Clinic and was a retrospective record review. The study population included ART naïve psychiatric patients between the ages of 18 and 65 years who were initiated on ART at the clinic from 1 June 2008 to 31 December 2010 as inpatients or outpatients.

A list of all patients who attended the clinic between 1 June 2008 and 31 December 2010 was compiled from the clinic's database; the total number of these patients was 526. From the files reviewed, all the patients who were on ART at the time of the first visit and those who were not initiated on ART during the study period were then excluded from the study population. The total number of patients who were ART naïve and were initiated on ART during this period was 291. The study was then divided into two parts. In the first part, all these files were reviewed and categorised into "lost to follow-up", "died" "transferred out" and "retained in care" groups. In the second part of the study, those who were lost to follow-up, transferred out and those who died were excluded from further analysis. Baseline data and follow-up data at the end of the four-year follow-up period were only collected on the 145 patients who were retained in care at the end of the four-year follow-up period.

3.2 POSTGRADUATE COMMITTEE AND ETHICS APPROVAL

The research proposal was submitted to the University of the Witwatersrand's Human and Research Ethics Committee (HREC) and permission to conduct the study was granted unconditionally (ethics clearance number: M150862). Permission to conduct the study at CHBAH was also obtained from the CHBAH Research Committee, permission to access files from the Psychiatric Department and Medicom database was granted. Since the study was a retrospective record review informed consent was not necessary. The patient names, file numbers and other personal identification information were not recorded on the data sheet,

patients thus remained anonymous. There were no clinical interventions done on the participants.

3.3 INCLUSION AND EXCLUSION CRITERIA

In the first part of the study, to determine the “follow-up outcomes” we included the following patients:

- Psychiatric patients who were HIV positive and were ART naïve at first presentation to the Luthando Neuropsychiatry Clinic.
- Those who were initiated on ART during the period 1 June 2008 to 31 December 2010, as inpatients or outpatients.
- Those who were between the ages 18 and 65 years.

In the first part of the study we excluded the following patients:

- Those transferred from other ART initiation sites already on ART.
- Those who presented during the period between 1 June 2008 and 31 December 2010 and were ART naïve but were not initiated on ART.

For the second part of the study, further data was only collected on those who fulfilled the inclusion and exclusion criteria for the first part of the study and on those who remained in care for the full four years following ART initiation.

3.4 DATA COLLECTION

A data collection sheet was used to manually record all data collected from each of the files used. Each form was numbered and a sticker with the corresponding number was placed on the corresponding file so as to not use the hospital file number and other patient identifying data. Information from each file was then recorded manually on each form and later transferred onto an electronic spreadsheet to be used for data analysis.

Each Luthando Neuropsychiatric Clinic file consists of four documents, namely: the initial referral form to the clinic, the core demographics and baseline record form, the ART assessment form and the HIV care and ART clinic visit form. These sheets also contained other data such as the date of

visit, basic demographic details, admissions to hospital, TB diagnosis, information on patient adherence, current symptoms, weight, height, results of urine pregnancy test and vital signs. This information is recorded on each clinic visit.

In cases where information from the Luthando Neuropsychiatric Clinic file was incomplete, the patient's file was retrieved from the Psychiatric Outpatient Department. The Medicom Database, which is a computerised system at CHBAH that holds patient information about admissions to the hospital was also used to confirm the number and type of hospital admissions.

Operational Definitions:

Loss to follow-up: Defined as those who discontinued care for six months (180 days) or more since last clinic visit at four years after initiation of ART.

Retention in care: Defined as those who are currently in care at the Luthando Clinic at the end of the four-year follow-up period.

Virologic Suppression: Viral load in our study was collected at six months after ART initiation and at the end of the four-year follow-up period. Virologic suppression was then defined as viral load declines to less than 50 copies/ml or less than the detectable limit within six months of commencing ART or at the end of the four-year follow-up period.

Virologic failure: This study only measured the number of patients who achieved VL values above 1000 copies/ml at six months after ART initiation and at four years after ART initiation.

3.5 OUTCOMES

3.5.1 Primary outcome- Follow up outcomes

The primary outcome was to determine the long-term follow up outcomes (retention in care, death, LTFU, transferred out) at four years after ART initiation in patients who were initiated on ART during the period between 1

June 2008 and 31 December. The date of the last visit was obtained from the last completed HIV care and ART clinic visit form.

Files were grouped into four categories, namely: those retained in care, LTFU, those who died, and those who were transferred to other treatment centres before the end of the study period. Only the baseline and follow-up data of those retained in care was then collected.

3.5.2 Secondary outcomes- Patients retained in care: baseline and follow up data

A descriptive and comparative study was conducted on those patients retained in care at four years, describing their demographic and clinical data and comparing baseline and follow-up data for these patients.

The following data was collected on those who were retained in care at four years:

3.5.2.1 Demographics

3.5.2.2 Psychiatric diagnosis

Psychiatric diagnoses were classified according to the DSM IV-TR multi-axial diagnostic formulation based on the clinical assessment in the patient record. [123] The Axis I diagnoses were then grouped into primary psychiatric diagnosis and those due to a general medical condition (GMC) and substances. Primary psychiatric diagnoses were those disorders that were pre-existing prior to the diagnosis of HIV and included schizophrenia, schizoaffective disorder, major depressive disorders, bipolar disorder I and II, anxiety and personality disorders. Anxiety disorders and the Axis II personality disorders were grouped together as per the Luthando Clinic file. Psychiatric diagnoses due to GMC included HIV-related psychiatric diagnoses, other GMC and substance-related disorders. Substance-induced psychiatric diagnoses were also grouped into one category. When patients had a differential diagnosis, all the conditions were recorded. Only the diagnosis recorded on the initial visit at Luthando Neuropsychiatric Clinic was recorded.

3.5.2.3 Other medical diagnoses (in addition to HIV and opportunistic infections)

Included the diagnosis of epilepsy, hypertension, hyperlipideamia and other medical illnesses excluding OI.

3.5.2.4 Substance use history

Substance use history was obtained from the CHBAH psychiatry file as it was mostly not recorded in the Luthando file. The substances recorded in the Luthando file were alcohol and nicotine. A urine drug screen was also not routinely done on ART initiation. This category was classified into “yes” or “no”, based on history of any substance use at any point in the clinical record and the substances were not specified.

3.5.2.5 Non-ART pharmacotherapy (including psychotropics, TB and other medication)

ART at initiation was recorded, as well as non-ART medication which included psychotropic medication, TB medication, TB prophylaxis (INH) and other OI prophylaxis (clotrimazole, fluconazole and dapsone). Psychotropic medication was divided further into antipsychotics, mood stabilizers, antidepressants and other psychotropic medication. In each category, the individual drugs were specified. The category of other psychotropic medication included benzodiazepines, anticholinergic agents and methylphenidate.

3.5.2.6 WHO HIV clinical stage at ART initiation

The WHO clinical stage was not determined by the researcher. The researcher recorded the WHO clinical stage as it was recorded in the Luthando patient file.

3.5.2.7 ART regimen on initiation and regimen change (over four-year follow up period) and reasons for change

3.5.2.8 Other clinical parameters

- CD4 count, VL, weight/height/BMI and presence of OI
- International HIV Dementia Scale (IHDS) score. The IHDS was collected as it was recorded in the file.

- Pregnancy status

3.5.2.9 Hospital admissions-admission status on initiation and subsequent admissions over four-year follow up period

3.5.3 Outcome at follow-up

These outcomes were recorded at the end of the study period, which was four years after ART initiation.

The following data were retrospectively collected for the patients who were retained in care at the end of the follow-up period:

- Viral load six months after initiation.
- CD4 count and VL at the four-year follow-up end point.
- Body mass index at four years post initiation
- Treatment interruption during the four-year follow-up period.
- OI at any point during the four-year study period after ART initiation.

ART regimen changes and reasons for change were recorded from the Luthando file. The list of reasons used was based on the existing list on the follow-up sheet inside the file. In those with multiple reasons for regime change, all the reasons were recorded in no particular order.

Data on hospital admissions was obtained from the CHBAH Psychiatry Outpatient Department file, Luthando Clinic file and Medicom Database. Admissions were not always recorded correctly in the files, thus all the admissions were confirmed using Medicom. The number of admissions was stated with the type of admission, whether medical or psychiatric.

3.6 STATISTICAL ANALYSIS

Data analysis was carried out using SAS version 9.4 for Windows. The 5% significance level was used.

Descriptive analysis of the data was carried out as follows: Categorical variables were summarised by frequency and percentage tabulation, and illustrated by means of bar charts. Continuous variables were described by the mean, standard deviation, median, interquartile range and histogram.

Comparison between baseline and four-year follow-up data for CD4 count, VL and BMI were conducted by the paired t-test (or its non-parametric equivalent, the Wilcoxon matched pairs test, if the requirements of the paired t-test were not met). McNemar's test for paired categorical data was used to compare the presence/absence of opportunistic infections at baseline and follow-up.

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CHAPTER FOUR: RESULTS

4.1 SAMPLE CHARACTERISTICS AND PRIMARY OUTCOME

During the study period between 1 July 2008 and 31 December 2010, 526 new patients were seen at the Luthando Clinic, of which 373 were ART naïve. (Figure 4.1) Of the 373 patients, 291 patients were initiated on ART during the study period. There were 77 patients who were seen but were not initiated on ART as they were not eligible for ART initiation according to the National ART initiation guidelines and were therefore excluded from further analysis. A further five files were excluded from the analysis as three files could not be traced and two files had incomplete data.

Four years after ART initiation, of the 291 new ART naïve patients initiated on ART, 58 (19.9%) were transferred out, 70 (24.1%) were lost to follow-up, 18 (6.2%) had died and 145 (49.8%) of the patients remained in care at the Luthando Clinic. (Figure 4.2) The final data analysis concerns only the 145 patients who were retained in care four years after ART initiation.

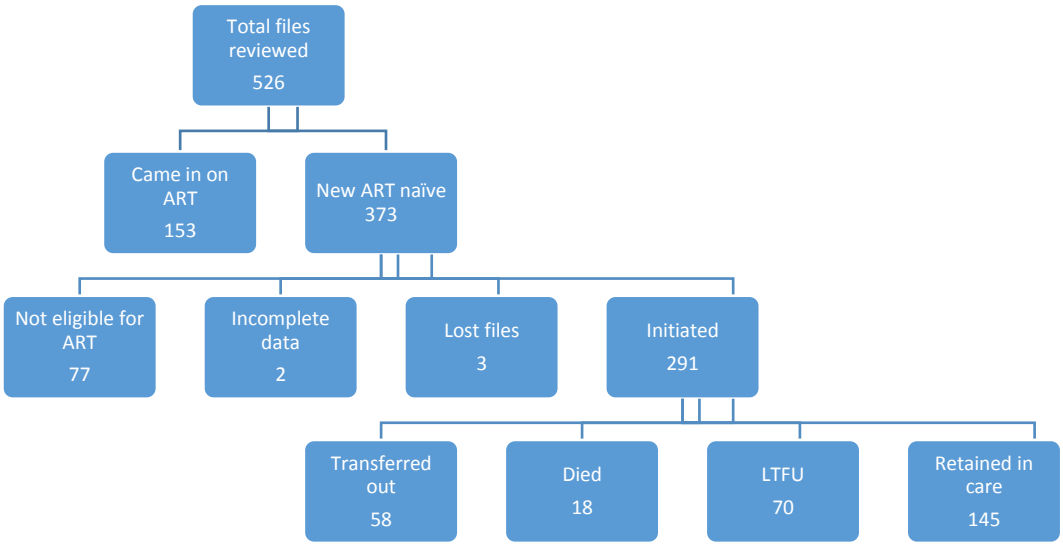

Figure 4.1 Flow chart detailing sample characteristics of patients at the Luthando Clinic for the period 1 July 2008 to 31 December 2010

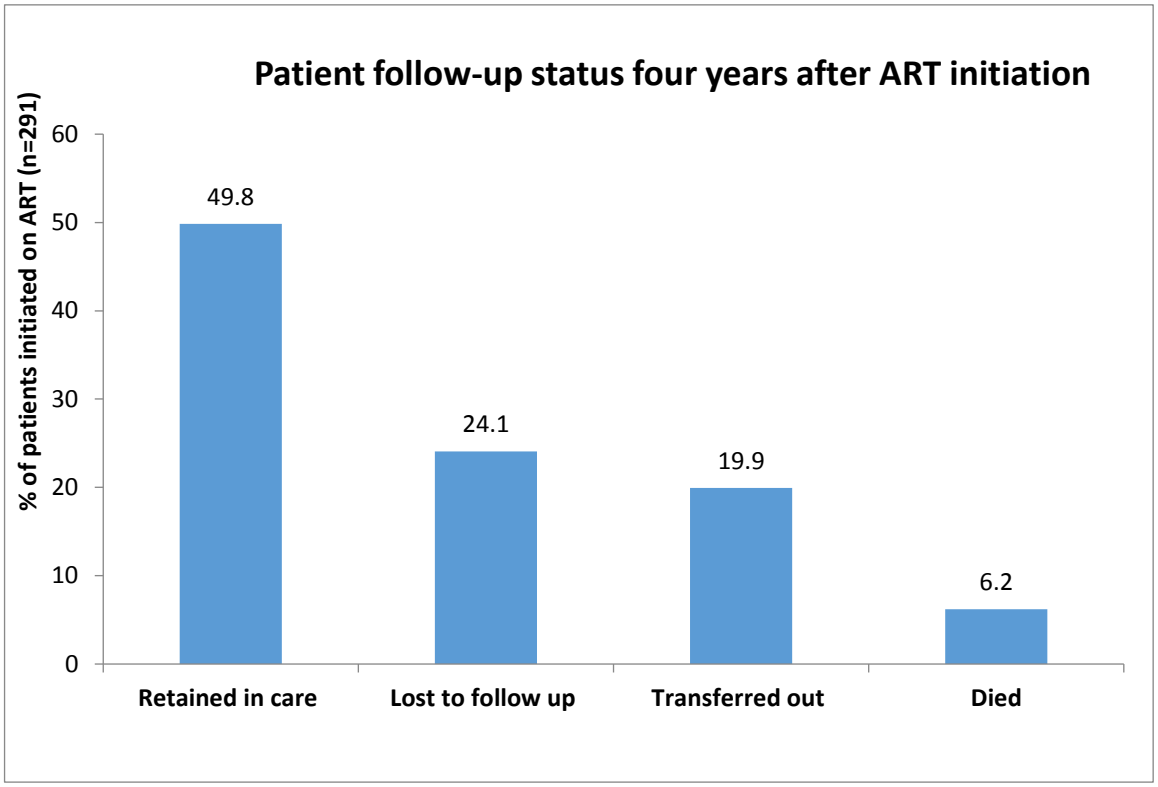

Figure 4.2 Patient follow up status four years after ART initiation

4.2 SECONDARY OUTCOMES: PATIENTS RETAINED IN CARE

4.2.1 Demographic Characteristics

The baseline demographic characteristics at ART initiation of the patients who were retained in care at the end of the four-year follow-up period were described (Table 4.1). The median age was 35 years with an Interquatial Range (IQR) of 31-42 years; 73.8% (n=107) of the study group were females. The majority of the patients, 61.4% (n=89) were single and 17.2% were married. The unemployment rate was 84.1% (n=122) and the median number of years of schooling was 8 years with an in IQR of 5-10.

Table 4.1 Demographic details of participants (retained in care) at baseline

		Median	N	%	IQR
Age (years)		35			31-42
Years of education		8			5-10
Gender	Female		107	73.8	
	Male		38	26.2	
Relationship Status	Single		89	61.4	
	Married		25	17.2	
	Living together		12	8.3	
	Divorced		7	4.8	
	Widowed		7	4.8	
	Separated		4	2.8	
	Unknown		1	0.68	
Employment	Employment		23	15.9	
	Unemployed		122	84.1	

4.2.2 Clinical Characteristics

4.2.2.1 Psychiatric diagnosis

Psychiatric diagnoses were classified according to the DSM IV-TR multi-axial diagnostic formulation. The Axis I diagnoses were then grouped into primary psychiatric diagnosis and those due to GMC and substances. Some patients had more than one diagnoses and it was not stated which diagnosis the clinician considered as the main one, hence all the differential diagnoses were recorded.

Psychiatric disorders due to another medical condition and substance-related disorders accounted for most of the psychiatric disorders (n=93 ,64.1%). The most common psychiatric diagnosis due to a medical condition was that of a mood disorder with psychotic features due to HIV (n=39, 26.9%). This was followed by the diagnosis of psychotic disorder due to HIV (n=21, 14.5%) and mood disorder due to HIV (n=9, 6.2%) respectively. When the medical condition was not specified, the diagnosis was captured as a disorder due to GMC (mood disorder with psychotic features due to GMC, mood disorder due to GMC, psychotic disorder due to GMC). In this category the diagnosis of mood disorder with psychotic features due to GMC was the most common (n=6, 4.1%), followed by the diagnosis of psychotic disorder due to GMC (n=4, 2.8%) and that of mood disorder due to GMC (n=2, 1.4%) respectively. In terms of the diagnosis of HAND, eight (5.5%) of the patients were diagnosed with HAND at ART initiation. In terms of substance related disorders at the time of ART initiation, four (2.8%) patients were diagnosed with substance induced mood disorder with psychotic features.

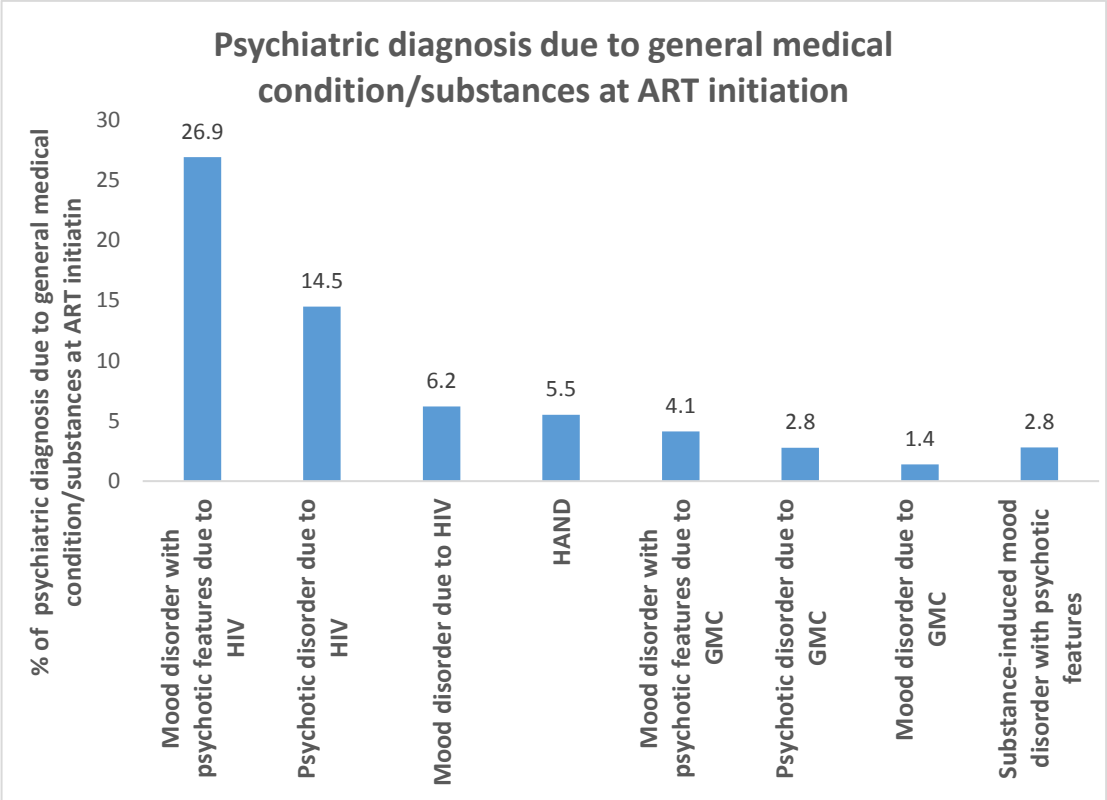

Figure 4.3 Psychiatric diagnosis due to general medical condition/substances at ART initiation

In terms of primary psychiatric disorders (n=63, 43%), the most common diagnosis was bipolar I disorder with a prevalence of 20% (n=29) followed by major depressive disorder at 11.7% (n=17).

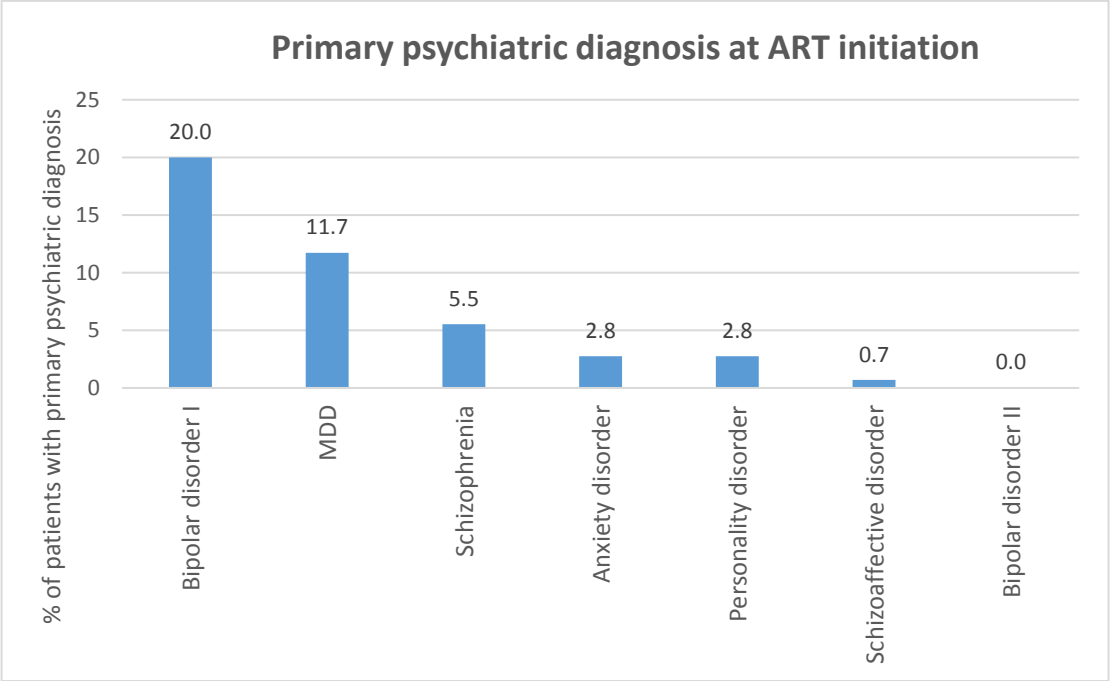

Figure 4.4 Primary psychiatric diagnosis at ART initiation

4.2.2.2 Other medical diagnoses (in addition to HIV and opportunistic infections)

In this category (n=17, 11.7%) patients had an additional medical diagnosis. Hypertension was the most common diagnosis (n=8, 47.1%) followed by epilepsy (n=6) and hyperlipidaemia (n=1). There were no patients with the diagnosis of diabetes mellitus and asthma.

4.2.2.3 Substance use history

At the time of ART initiation 22.8% (n=33) patients reported a history of substance use.

4.2.2.4 Non-ART pharmacotherapy (including psychotropics, TB and other medication)

Psychotropic medications were divided into antipsychotics, mood stabilizers, antidepressants and other psychotropic medication. In total, 118 patients (81.4%) were prescribed antipsychotics, some of whom were prescribed more than one antipsychotic. The most commonly used antipsychotic among patients retained in care, was Risperidone (n=86, 59.3%). Antidepressants were divided into classes and the different

medications under each class were not specified. Twenty six (17.9%) patients were prescribed antidepressants, with the most commonly prescribed class being the Selective Serotonin Reuptake Inhibitor (SSRI) group (n=24, 16.6%). Fifty patients (34.5%) were prescribed mood stabilizers with the most commonly used mood stabilizer was sodium valproate (n=46, 31.7%). Some patients were prescribed more than one mood stabilizer, as there were 53 scripts in total in total for the various mood stabilizers. Other psychotropic medications commonly used in psychiatry were also recorded, with 3.4% benzodiazepines and 2.8% anticholinergics prescribed.

Thirteen (9%) patients were on TB treatment and one was on INH TB prophylaxis. Of the 13 who were diagnosed with TB, 61.5% (n=8) were on the TB intensive phase treatment (Rifampicin, Isoniazid, Pyrazinamide, Ethambutol), whilst 38.4% (n=5) were on TB continuation phase treatment (Rifampicin and Isoniazid). Some patients were also prescribed prophylaxis for other OI, with 53.1% (n=77) and 1.4%(n=2) patients on Cotrimazole and Fluconazole respectively.

Table 4.2 Psychotropic medication at ART initiation

		N	%
Antipsychotics	Risperidone	86	59.3
	Haloperidol	14	9.7
	Olanzapine	7	4.8
	Trifluoperazine	6	4.1
	Chlorpromazine	5	3.4
	Aripiprazole	3	2.1
	Clozapine	1	0.7
	Risperidone long acting injection	1	0.7
	Quetiapine	0	0.0
	Flupenthixol Decanoate	0	0.0
	Zuclopenthixol Decanoate	0	0.0
	Other	1	0.7
	None	27	18.6
Antidepressants	SSRI	24	16.6
	TCA (Tricyclic Antidepressants)	1	0.7
	SNRI (Serotonin-norepinephrine reuptake inhibitor)	1	0.7
	Other	0	0.0
	None	119	82.1
Mood stabilizers	Sodium valproate	46	31.7
	Carbamazepine	1	0.7
	Lithium	3	2.1
	Lamotrigine	3	2.1
	Gabapentin	0	0.0
	None	95	65.5
Other psychotropic medication	Benzodiazepine	5	3.4
	Anticholinergic drugs	4	2.8
	Methylphenidate	0	0.0
	Other	0	0.0

4.2.2.5 WHO HIV clinical stage at ART initiation

At ART initiation the majority of the patients were classified as WHO HIV stage IV (n=93, 64.1%).

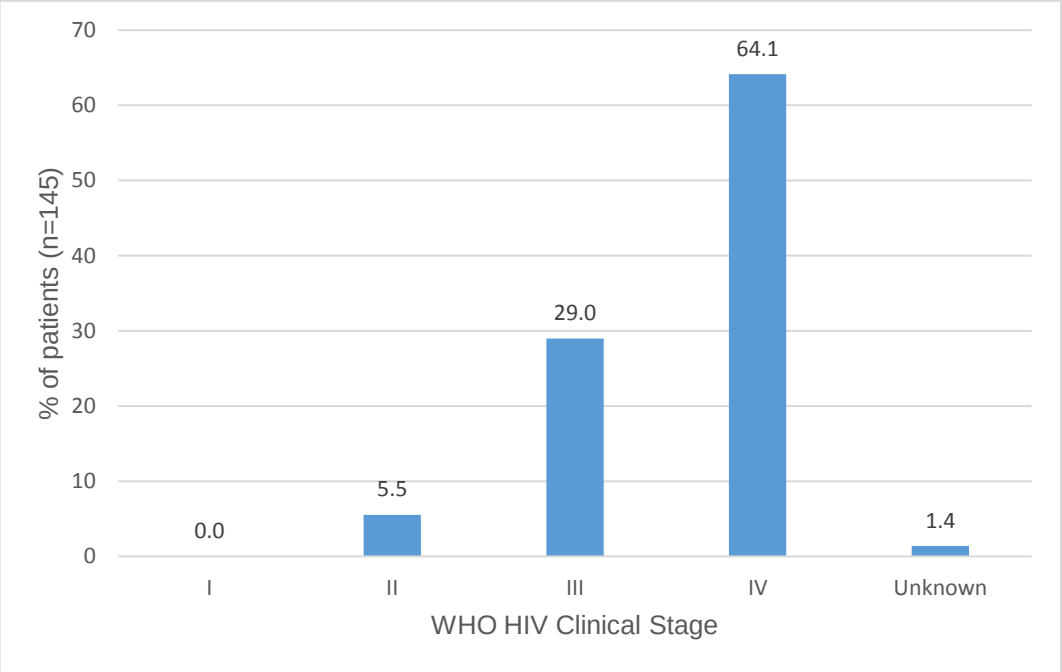

Figure 4.5 WHO HIV Stage at ART initiation

4.2.2.6 Antiretroviral treatment regimen at initiation and regimen change (over four-year follow up period) and reasons for change

The most commonly used NRTIs were 3TC (n=139, 95.9%) and D4T (n=97, 66.9%). Fewer patients were on a TDF containing regimen (n=42, 29%). The most commonly used NNRTI was EFV (n=71, 49%) followed by NVP (n=63, 43.4%). Nine patients (6.2%) were initiated on a second line regimen with LPV/r.

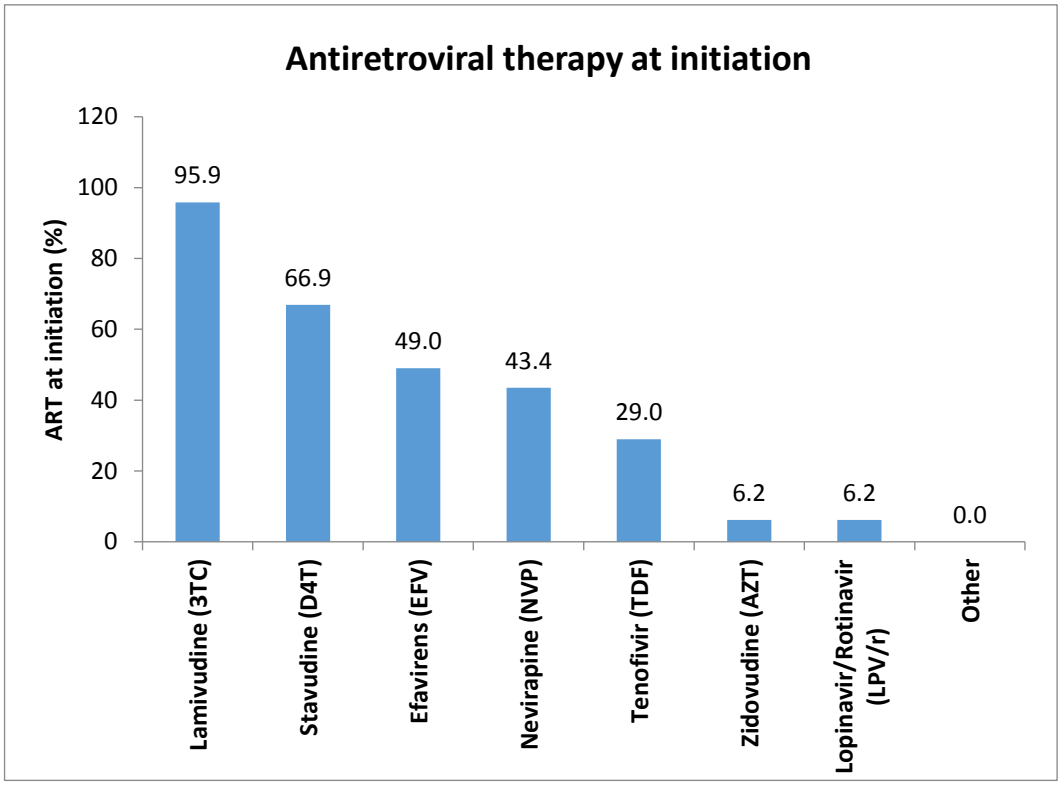

Figure 4.6 ART medication at initiation

After ART initiation, 72.4% (n=105) of the patients had a regimen change during the four-year period. The most common reason for regimen change was adverse effects (n=76, 72.4%), followed by treatment failure (n=24, 22.9%). The specific adverse effects were not recorded. Of the patients who had regimen change due to adverse effects 18 (23.6%) defaulted ART during the four-year follow-up period and 54 (71%) achieved viral suppression at the end of the four-year follow-up period. Those who had regimen change due to reasons of treatment failure ten (41.6%) interrupted ART treatment during the four-year follow-up period and 11 (45.8%) achieved viral suppression at the end of the four-year follow-up period.

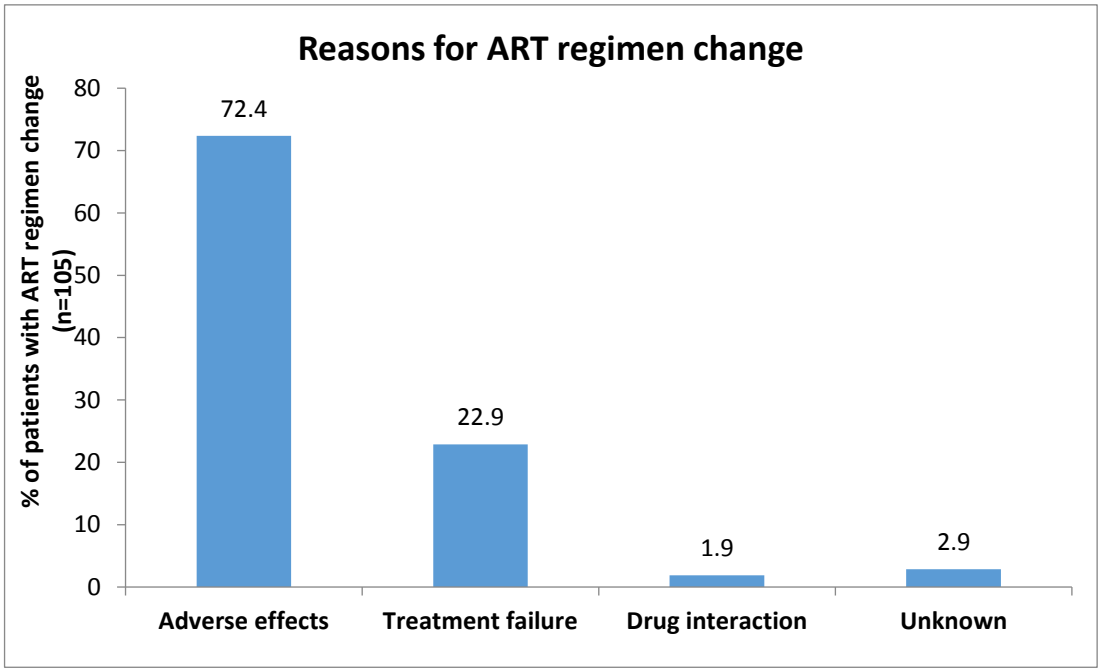

Figure 4.7 Reasons for ART regimen change

4.2.2.7 Other clinical parameters: Pregnancy status

At ART initiation three (2.8%) of the female patients were pregnant.

4.2.2.8 Other clinical parameters: IHDS score

The IHDS score was collected at ART initiation only. At ART initiation, the IHDS was recorded in 15 (10.3%) patients, ten (66.6%) of the 15 patients who had an IHDS score recorded had scores of ten or less points.

4.2.3 Hospital admissions- admission status on initiation and subsequent admissions over four-year follow up period

Patients were initiated on ART as both inpatients and outpatients, with 49.7% initiated as outpatients. During the four-year follow-up period, 39 (26.9%) of the patients had one or more admissions. Psychiatric admission was the most common reason for admission (n=26, 66.7%) and (n=6,15.4%) of the patients had both medical and psychiatric admissions during the four-year follow-up period.

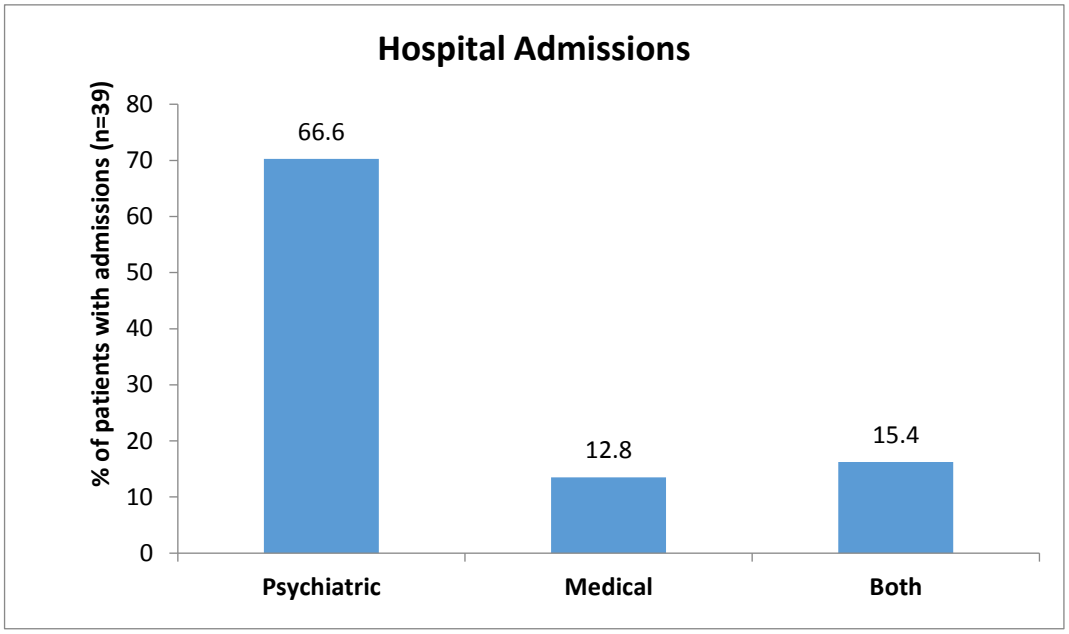

Figure 4.8 Hospital admissions during four-year follow-up period

4.3 COMPARISON BETWEEN BASELINE AND FOUR-YEAR FOLLOW-UP CLINICAL DATA FOR THOSE RETAINED IN CARE

4.3.1 CD4 count

The median CD4 count was 157 (IQR 87-254) and 490 (IQR 380-625) at baseline and four years after ART initiation respectively. There was a statistically significant increase in the median CD4 count from baseline, with the CD4 levels increasing by an average of 350 (95% CI: 310-391) from baseline to follow-up (paired t-test; p<0.0001).

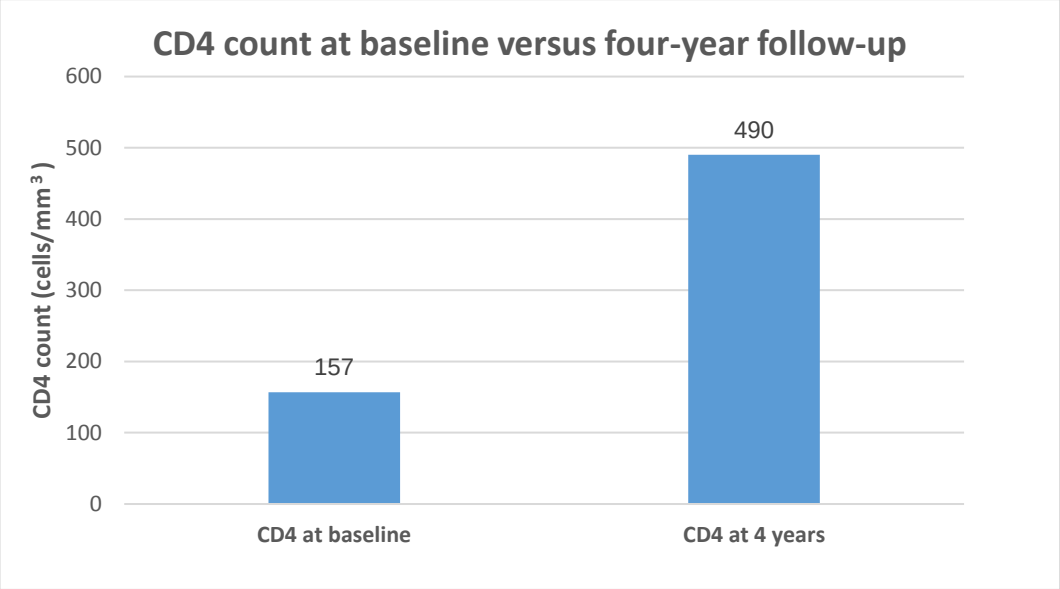

Figure 4.9 Median CD4 count comparison at baseline and at four years after ART initiation

4.3.2 Viral load and viral suppression

4.3.2.1 Viral load at baseline, six months and at four years after ART initiation

The median VL at ART initiation was 38000 copies/ml (IQR 6662-120000). One patient had a non-detectable VL value at ART initiation, which was non-detectable throughout the four-year follow-up period. VL was only recorded in 131 patients.

The median VL at six months after ART initiation was 50 copies/ml (IQR 25-294). At six months, 54.3% (n=75) of the patients achieved viral suppression

using a cut-off value of 50 copies/ml. The VL was not recorded for seven of the patients. At six months after ART initiation, 61.6% (n= 85) of the patients had a VL of less than 100 and 88.4% (n=122) had viral loads less than 1000 copies/ml, 16 (11.6%) had values above 1000 copies/ml.

4.3.2.2 Treatment interruptions and viral suppression

At the four-year follow-up period after ART initiation, 71.8% (n=102) of the patients were virally suppressed using a cut-off value of less than 50 copies/ml, with a median VL of 25 copies/ml (IQR 25-100). VL results were available in 142 patients. There was a significant improvement in the number of patients who achieved viral suppression from baseline (at ART initiation) to the end of the four-year follow-up period (McNemar's test $p<0.0001$). Viral load decreased by a median of 35000 copies/ml (IQR 5500-120000) from baseline (at ART initiation) to the end of the four-year follow-up period (Wilcoxon matched pairs test; $p<0.0001$). There were no suppressed patients at six months who were unsuppressed at the four-year follow-up period.

Of those patients retained in care at the four-year follow-up, 72.5% (n=103) had a VL value of less than 100 copies/ml, and 89.4% (n=127) had a VL less than 1000 copies/ml. Fifteen (10.6%) patients had VL of more than 1000 copies/ml at four years.

During the four-year follow-up period, 26.9 % (n=39) of the study group had interrupted treatment at some point but subsequently remained in care at the end of the four-year period. It was not recorded whether the patients interrupted both the ART and psychotropic medications, while the reasons for treatment interruption were also not recorded. Of the patients who interrupted treatment during the follow-up period, 33.3% (n=13) had unsuppressed VL values at the end of the four-year follow-up period and the median VL for these patients was 4158.7 copies/ml.

4.3.3 Body mass index

The median BMI count at ART initiation was 22.2 kg/m^2 (IQR 18.5-27.4 kg/m^2) and 25.9 kg/m^2 (IQR 21.8-31.2 kg/m^2) at four-year follow-up. The BMI increased by an average of 3.0 kg/m^2 (95% CI: 2.2-3.8 kg/m^2) from baseline to follow-up (n=127; paired t-test; p<0.0001). BMI values were not recorded for all the patients at baseline and at four-year follow-up.

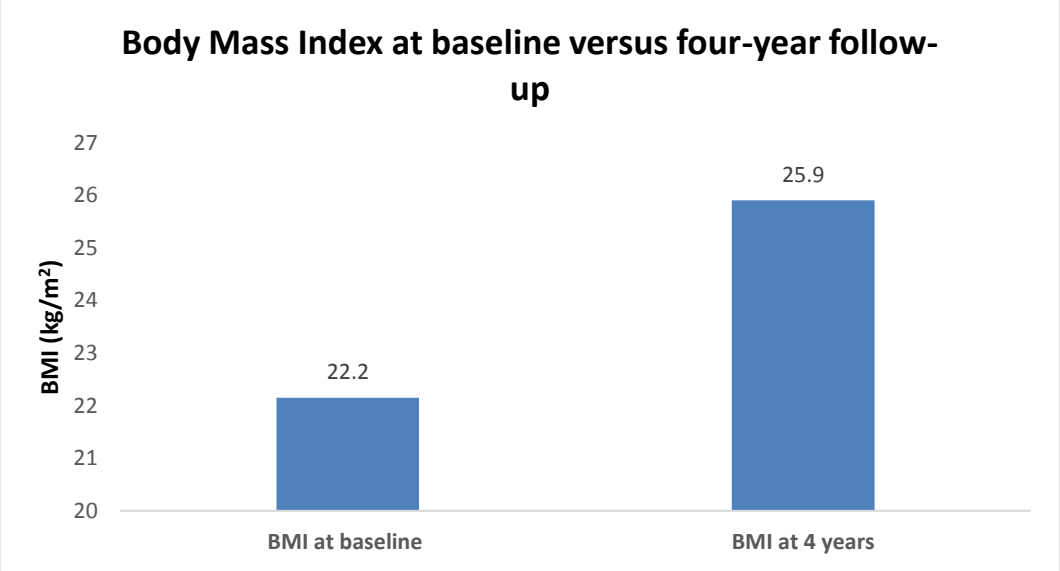

Figure 4.10 Body Mass Index at baseline and four years after ART initiation

4.3.4 Opportunistic infections

With regard to OI, 41(28.3%) patients had OI at ART initiation. It was not recorded if patients had more than one OI at ART initiation. The most common OI at ART initiation was candidiasis (n=20, 13.8%), followed by TB (n=13, 9%), syphilis (n=3, 2.1%) and meningitis (n=2, 1.4%) respectively. There was a significant decline in the prevalence of OI from baseline to follow-up (McNemar's test: p=0.0007), with 17 patients (11.7%) having OI during the four-year follow-up period after ART initiation. The most common OI during the four-year follow-up period was TB (n=14) followed by oral candidiasis (n=3). Of the patients who had infections at baseline, 37 (90.2%) did not have OI during the follow-up period, while 13 patients (12.5%) who did not have infections at baseline had infections during the follow-up period. In terms of viral suppression, 43.8% (n=7) of the patients with OI had

not achieved viral suppression whilst 56.3% (n=9) were virally suppressed during the end of the four-year follow-up period. VL results were available for 16 patients who had OIs during the four-year follow-up period. The mean CD4 count of the patients who had OI during the four-year follow-up period after ART initiation was 605 cells/mm^3 at the end of the four-year follow-up period. Of the patients who had OI after ART initiation 14 (82.3%) had regimen change, main reason for regimen change was that of adverse drug reactions (n=9, 64.3%) followed by treatment failure (n=3, 21.4%) and drug interactions (n=2, 14.3%). During the four-year follow up period three of the patients were admitted with OI to hospital, of these patients two were admitted for psychiatric reasons.

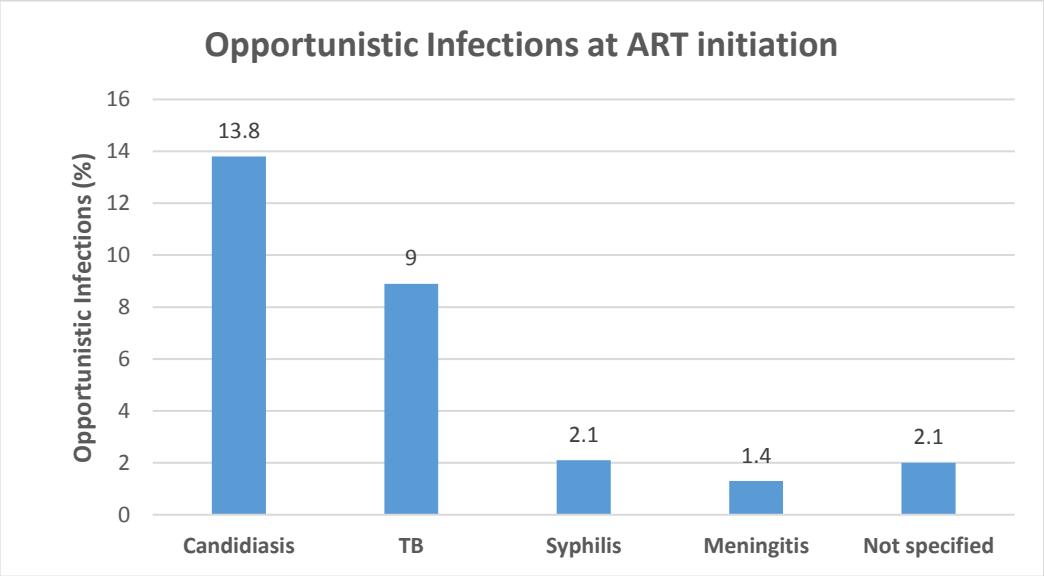

Figure 4.11 Opportunistic Infections at ART initiation

Table 4.3 Comparison of clinical data at baseline (ART initiation) and at four-year follow-up period

	N	Initiation	N	6 months	N	4-year follow-up	p-values (initiation/four-year follow-up)
CD4 Count (cells/mm^3) Median (IQR)	145	157 (87-254)			145	490 (380-625)	p<0.0001* (paired t-test)
Viral Load (copies/ml) Median (IQR)	131	38000 (6662-120000)	138	50 (25-294)	142	25 (25-100)	p<0.0001* (Wilcoxon matched pairs test)
BMI (kg/m^2) Median (IQR)	128	22.2 (18.5-27.4)			127	25.9 (21.8-31.2)	p<0.0001* (paired t-test)
OI (%)	41	28.3			17	11.7	p<0.0007* (McNemar's test)
Viral suppression (%)			75	54.3	102	71.8	p<0.0001 (McNemar's test)

*-statistically significant

CHAPTER FIVE: DISCUSSION

5.1 FOLLOW-UP OUTCOMES

The aim of this study was to determine follow-up outcomes, with particular interest in also determining retention in care, which was then also explored further as a secondary outcome. From the findings of this study, 49.8% of patients remained in care at the end of the four-year follow-up period, though this retention rate could have been influenced by several factors. As a specialist clinic, Luthando Clinic generally caters for patients who are in need of tertiary level integrated care. These are the patients who would be difficult to manage in a primary health care setting, particularly at treatment initiation. Once patients are stable, they are occasionally discharged to follow-up at their local clinics after initiation. Other factors that could have influenced our retention in care rate include the duration of follow-up, loss to follow-up (LTFU) and mortality during the follow-up period.

The rate of retention in care in PLWHIV with comorbid SMI varies in literature. In a study done in Uganda comparing the long-term outcomes of PLWHIV with SMI and those without SMI at baseline, the retention in care rate in patients with SMI was 47% 12 months after ART initiation compared to 65% in patients without SMI. This retention in care rate was similar to that of this current study, however the follow-up period was shorter.[91] Karstaedt *et al.* conducted a retrospective cohort at CHBAH, describing retention in care and other clinical outcomes in 53 patients on ART with comorbid SMI. In this cohort, 64% of the patients were retained in care at 96 weeks after ART initiation. Although the patients in this cohort were not managed in an integrated care ART programme, they were able to achieve a retention in care rate similar to that of PLWHIV without a psychiatric diagnosis.[92] Previous literature has shown that psychiatric patients with HIV are able to achieve adherence rates similar to that of PLWHIV in the general population.[93] A retrospective study by Himmelhoch *et al.* found that psychiatric patients on ART managed in an integrated HIV care programme were also less likely to discontinue ART compared to non-psychiatric

patients on ART.[44] The rate of retention in care in PLWHIV in the general population and the duration of the follow-up period at which retention in care is reported also varies. Most studies have reported retention in care rate at 6, 12 and 24 months. In a sub-Saharan systematic review by Rosen *et al.*, the retention in care rate over 6, 12, and 24 months was 79%, 75% and 61.6% respectively.[84] In another sub-Saharan systematic review by Fox and Rosen, retention in care at 12, 24 and 36 months was estimated at 80%, 76.8% and 72.37% respectively.[74] In both reviews, retention in care rate was also reported to decline over the follow-up period. The retention in care rate in this current study could have also been influenced by the length of our follow-up period of four years after ART initiation.

In the current study, 19.9% of the patients were transferred out to other treatment centres. These patients could represent the number of patients still in care even though they are in other sites. Additional studies have reported lower rates of patients transferred to other treatment facilities. In one retrospective longitudinal study conducted in Ethiopia on non-psychiatric patients, only 9% of patients were transferred to other treatment centres at 12 months after ART; this percentage increased to 12% at 24 months after ART initiation.[70] The high rate of patients transferred to other treatment sites in this current study could have negatively influenced the retention in care rate. There are several reasons for transferring patients to other treatment centres that have been reported in literature. These include relocation to another area and convenience for the patient in terms of distance.[86] A retrospective cohort conducted in non-psychiatric PLWHIV in a South African township examining the characteristics of patients who transferred to other treatment sites found that females were most likely to be transferred to another treatment site. This cohort also found that those who were transferred were more likely to have VL values of more than 1000 copies/ml and had not collected ART for more than 12 weeks before the transfer date.[87] It was beyond the scope of the current research study to examine the reasons for transfer out or to compare patients retained in care with those who were transferred to other treatment sites.

LTFU and mortality rates at the end of the four-year follow-up period further contributed to the retention in care rate. The rate of LTFU in the current study over the four-year period was 24.1%. This rate was similar to that of another study done at the Luthando Clinic over a 14-month period.[2] This rate varies in literature in PLWHIV in the general population. In a retrospective review by Assefa *et al.* evaluating outcomes of an antiretroviral programme in Ethiopia in non-psychiatric patients, the rate of LTFU was similar to that of our study, with 24.1% of the patients being LTFU. The Ethiopian study was however over a 24-month follow-up period after ART initiation and LTFU was also reported at 6 and 12 months after initiation at 15% and 20% respectively. The LTFU rate was shown to increase over the follow-up period.[70] Factors associated with LTFU have been reported in literature.[124,125] In a previous study done at the Luthando Clinic, the main factor associated with LTFU according to patients was lack of transport.[2] Adverse effects of the medication were the least reported barriers to treatment.[2] This was similar to the findings of a study by Miller *et al*, where reasons for non-adherence included transport costs, time needed for treatment and logistical reasons as the main barriers to adherence.[125]

The mortality rate in this study was 6.2%, though the causes of death were not recorded. This rate may possibly have been higher if some patients who died were misclassified as being LTFU. Mortality rates also vary across literature on PLWHIV in the general population. There are studies that have reported rates comparable to that of our study.[70,126,127] In one retrospective study done in India examining mortality risks among non-psychiatric PLWHIV on ART over a five-year follow-up period, the mortality rate was 9%. Factors associated with the high mortality rate included the diagnosis of TB and poor adherence.[126] The highest death rate has been reported to occur in the first six months after ART initiation and TB is reported as the main contributor of mortality.[70,127]

5.2 DEMOGRAPHIC CHARACTERISTICS

According to the demographic profile of the study population, the majority of the participants were female. In addition, most participants were in their thirties and were unemployed at ART initiation. These findings were similar to the population described in a study done at Weskoppies Psychiatric Hospital in Gauteng, SA.[14] Gender distribution in PLWHIV varies in literature, with studies done in developed countries having reported higher prevalence of HIV in men.[128] Historically, HIV infection was reported to dominate in males, however in sub-Saharan Africa, HIV predominantly affects women. [128,129] According to the CDC, in 2017 it was estimated that one in four PLWHIV in the United States were women, whilst studies done in SA have shown a female predominance.[130] The discrepancy of gender distribution in developed and developing countries could be accounted for by the differences in the mode of HIV transmission. In SA, transmission is mostly heterosexual, whilst in developed countries intravenous drug use is reported to be the main contributor of HIV transmission.[129,130] There are several factors that contribute to the high prevalence of HIV in women in the sub-Saharan region. These include biological factors and certain psycho-social factors which may increase the vulnerability to HIV infection in women.[131,132] The biological factors are related to the anatomy of the female genitalia. Through the large surface area of mucous membranes exposed and the larger volume of the viral content in semen transferred to females during sexual intercourse, the risk of HIV transmission in women is increased.[132] The psycho-social factors reported in literature include poverty, unemployment and gender-based violence.[131,133,134] Other factors contributing to the high prevalence of HIV infection in women include the presence of SMI. In a study conducted in Uganda examining the HIV prevalence in psychiatric patients, it was found that women with SMI were at increased risk of acquiring HIV.[16] In another study done in a psychiatric hospital in KwaZulu-Natal, female patients admitted were more likely to have comorbid HIV diagnosis than their male counterpart.[13] These findings were similar to those of another study conducted in Gauteng. [14,15] Females

are thus at risk of acquiring HIV due to multiple factors and there is also an association between mental illness and HIV infection in female psychiatric patients. Another factor to be considered is that in SA, all pregnant women are routinely tested for HIV, which could further contribute to the high prevalence of HIV infection reported in women.[135]

The median age in this current study was 35 years, which was similar to that of a study done in a psychiatric hospital in KwaZulu-Natal and to the Weskoppies study.[13,14] Previous literature has shown that the prevalence of new HIV infections is higher in the lower age group of 24-34 years, with more women in this age bracket being infected more than men, and peaks between 30 and 34 years.[130]

5.3 PSYCHIATRIC CHARACTERISTICS

5.3.1 Psychiatric diagnosis

At ART initiation, the Axis I DSM IV-TR diagnosis of a psychiatric disorder due to HIV, other GMC, and substances accounted for the majority of psychiatric diagnoses, compared to the primary Axis I DSM IV-TR psychiatric disorders.

The most common diagnosis in this study was that of a mood disorder with psychotic features due to HIV, with 26.9% of patients having this diagnosis. A further 14.5% were diagnosed with a psychotic disorder due to HIV, 6.2% with mood disorder due to HIV and 5.5% with HAND, contributing collectively to the Axis I diagnosis of psychiatric disorders due to HIV. These findings were similar to those of a study conducted by Uys on female psychiatric patients.[136] In the study by Uys, 53% of the patients had an Axis I diagnosis of a psychiatric disorder due to HIV, the most common diagnosis being that of a mood disorder with psychotic symptoms due to HIV.[136] In the study by Uys, mood disorders due to HIV were classified into manic and depressive episodes. Although the majority of the patients in this current study had a diagnosis of a mood disorder with psychotic features due to HIV, it was not specified whether the presentation was that of depression or mania. In a retrospective clinical audit of patients admitted to the psychiatric

ward at Helen Joseph Hospital, the majority of the patients who tested positive for HIV were diagnosed with a psychotic disorder due to HIV.[137] The reported prevalence of a mood disorder with psychotic features due to HIV was lower in the above study compared to this current study. The CHBAH cohort by Karstaedt *et al.* reported similar findings, with 67% of the patients with SMI having the diagnosis of a psychotic disorder due to HIV.[92] In this current study, psychiatric diagnosis was only collected at ART initiation, it would have been useful to know if the psychiatric diagnosis secondary to HIV changed during the course of the follow-up period. In a retrospective review by Karstaedt *et al*. of HIV-positive patients on ART with a mental illness, the majority of the patients discontinued their psychotropic drugs at the end of the follow-up period. This finding suggested that successful ART treatment was also associated with an improvement of psychiatric diagnoses secondary to HIV.[92]

Although it was not specifically noted whether the 26.9% of the patients diagnosed with a mood disorder with psychotic features due to HIV presented with mania or depression, it was likely that the majority of the patients presented with a maniform psychosis, based on the finding that mood stabilizers were prescribed about twice more frequently than antidepressants. Furthermore 20 % of the patients in this study were diagnosed with bipolar disorder. Previous literature has estimated that the prevalence of bipolar disorder in PLWHIV may be five times higher than in the general population.[138,139] Mania can occur as part of a co-existing primary diagnosis of bipolar disorder or due to secondary CNS complication of HIV.[38,39] The presence of secondary mania in PLWHIV can therefore be used as an indicator for clinical progression of HIV infection and also as an indicator to initiate ART in poorly resourced settings.[38,39] In a comparative cross-sectional comparative study in HIV negative and positive patients admitted in a psychiatric hospital in Uganda, patients presenting with secondary mania presented with advanced HIV infection. The majority of these patients were classified as Stage III and IV WHO HIV staging and had CD4 counts below 350 cells/mm^3. The manic episodes of these patients

were also associated with psychotic symptoms and neurocognitive decline.[40] The above findings suggest that maniform psychosis in PLWHIV is associated more with advanced and progressive HIV infection. New onset psychosis without mania in PLWHIV occurs less commonly as compared to mania, with varying rates reported in literature.[37] Similarly to mania, the causes of psychosis in PLWHIV are multi-factorial. Psychosis may occur with CNS OI, underlying HAND, HIV mania, substance use and as side effects of some ART.[140]

In this current study 5.5% of the patients were recorded as being diagnosed with HAND as per the clinical diagnosis at ART initiation. This recorded prevalence was low compared to that reported in literature.[57,59] According to literature, HAND remains highly prevalent. It is estimated that 30-60% HIV-infected patients have HAND.[57] Although the roll-out of ART has decreased the prevalence of HAD (HIV-Associated Dementia) the prevalence of the milder forms HAND remains high.[57] According to the National ART Initiation Guidelines at the time of this study patients who were eligible for ART initiation included those with CD4 count values of less than 200 copies/mm^3 and those with a stage IV AIDS-defining illness.[42] This would indicate that patients were only initiated on ART at advanced stages of the illness. The majority of the patients were also documented as being classified as WHO HIV clinical stage IV with a median CD4 count of 157 cells/mm^3 at ART initiation. Since HAND is an AIDS defining illness, with these poor immunological parameters a higher prevalence of HAND would be expected.[56,58] Several factors may have contributed to the recorded low prevalence of HAND in this study. Mania and psychosis in PLWHIV may present as part of HAND, and as such patients in this study may have been diagnosed with a mood or psychotic disorder due to HIV rather than HAND. This may have further contributed to the low prevalence of HAND in this study.[35,36]

Several neuropsychological brief screening tools have been developed for clinical use.[141] These include the HIV dementia scale, the IHDS and Montreal cognitive assessment.[141] In this current study, the IHDS score

was only recorded in 10.3% of the patients at ART initiation, this may have further contributed to an underestimation of the prevalence of HAND. Of these patients, 66.6% had IHDS scores recorded of 10 or less points, cutoff value which is suggestive of HAND.[142] The IHDS is quick screening tool that relatively easy to perform for any health care provider in resource limited treatment centres. The tool has a few limitations in that it can be used it patients with MND (Minor Neurocognitive Disorder) and cannot differentiate the different stages of HAND. Comprehensive neuropsychological assessments are thus recommended in those who are at risk of HAND on IHDS to correctly diagnose HAND. [141,142,143] Joska *et al.* assessed the validity of the IHDS in a South African population on HIV-negative and HIV-positive individuals.[143] Cognitive assessments were done using the IHDS and a neuropsychological test battery. According to the findings of this study, HIV-positive patients demonstrated greater cognitive decline. The IHDS had a 45% sensitivity and 79% specificity at a cutoff score of 10 and individual neuropsychological tests differentiated well between the HAND categories.[143] The presence of HAND is associated with poor adherence and subsequent poorer outcomes. Screening for HAND should therefore be an ongoing process from ART initiation and throughout ART treatment. In this current study the IHDS score was not collected during the four-year follow up period, but it may have been useful to see if there was better screening for HAND during their follow up visits. It would have also been useful to compare the prevalence of HAND at ART initiation and during the four-year follow up period after patients were initiated on ART.

In this current study, primary Axis I DSM IV-TR psychiatric diagnosis accounted for 43% of the psychiatric diagnoses at ART initiation, with bipolar I disorder and major depressive disorder being the most common diagnoses in this category. Previous literature has reported higher prevalence of HIV in patients with bipolar I disorder; this could be related to the increase in high-risk sexual behaviour which might be part of the symptomology of the disorder.[144,145] The prevalence of bipolar I disorder in

this study was 20%, which was in keeping with other studies that reported similar prevalence in those with HIV.[146]

In terms of other diagnoses known to be common in PLWHIV, 2.8% of the patients were diagnosed with an anxiety disorder and 11.7% were diagnosed with a major depressive disorder. The prevalence of anxiety disorders was low compared to the prevalence reported in other sub-Saharan and international studies.[29,34] Patients who are referred to Luthando Clinic have severe mental disorders that need to be managed in a tertiary level setting, which would explain the low rates of anxiety disorders in this current study. The prevalence of minor depressive episodes in PLWHIV has been reported as up to 25% with some studies reporting even higher rates, whilst major depressive episodes have been reported in 5 to 10% of PLWHIV.[34] The latter finding is in keeping with the findings of the current study. In a study conducted in SA where the validity of the Patient Health Questionaire-9 (PHQ-9) was examined, 11.8% of PLWHIV met criteria for a major depressive episode, similarly to the findings of this current study.[147]

According to the findings of the current study, the prevalence of substance use history was 22.8%. Substance use was not routinely screened for at ART initiation and during ART follow-up reviews using objective substance use screening methods such as the use of urine drug tests and the Alcohol Use Disorders Identification Test (AUDIT). Despite the findings of substance use history, as well as 2.8% patients having a diagnosis of substance induced psychiatric disorders, no patients at all had a diagnosis in their files of any type of substance use disorder. There have been various studies conducted comparing self-report methods and objective methods such as biological measures for the screening of substances. In one study on trauma patients without head injury, self-report methods were found to be inadequate for screening for substance use. In this study, 12.8% of patients who had denied alcohol use in their self-report were identified as having an alcohol use disorder when using the AUDIT. Another 53.8% were identified

through urine drug screen for other illicit drugs.[148] The use of other objective screening tools is therefore recommended when screening for substance use.

5.3.2 Psychotropic medication at ART initiation

In terms of psychotropic medication, the majority of the patients were on an antipsychotic medication, with 59.3% being on Risperidone. A further 34.5% of the patients were on a mood stabilizer whilst antidepressants were only prescribed in 17.9% of the patients. This corresponded to the most prevalent diagnoses of a mood disorder with psychotic features due to HIV, bipolar disorder I and psychotic disorder due to HIV. Mood stabilizers were prescribed in twice as many patients compared to antidepressants. Although mood disorders due to HIV in this study were not specified into depressive or manic type, these findings suggest that the presentation was more often maniform than depressed presentation. In another SA study by Uys conducted in the Eastern Cape, SA in a study population of HIV-infected female psychiatric patients, antipsychotics were prescribed in 84% of the patients and the antipsychotic commonly prescribed was Haloperidol.[136] A study by Janse van Rensburg and Bracken also found Haloperidol was used often versus this current study where it was only used in 9.7% patients.[137]

Risperidone has been used effectively to treat mania in PLWHIV without a mood stabilizer. In this current study, Risperidone was prescribed in 59.3% patients. PLWHIV are more vulnerable to the extrapyramidal side effects of antipsychotic medication and potential drug to drug effects.[45] The older class of antipsychotic medication, the first generation antipsychotics are associated with an increased risk of extrapyramidal side effects in PLWHIH compared to the newer class, the second generation antipsychotics.[45]The second generation antipsychotics, are therefore recommended as first line over the first generation antipsychotics in PLWHIV.[45] This group of drugs however has potential adverse effects related to drug to drug interactions and metabolic adverse effects in combination with some ART.[46,47]

Antipsychotic Long-Acting Injections (LAIs) was only prescribed in one patient. In the public sector in SA, majority of the LAIs available are the first generation antipsychotics, this may have impacted on the use of LAIs due to the side effect profile.[149] In a review by Nebhinani and Mattoo, Risperidone followed by Clozapine and Olanzapine were recommended for the treatment of psychotic disorders due to HIV.[35] The mood stabilizer most commonly used in the study was sodium valproate and was prescribed to 31.7% of the patients. The mood stabilizer, Lithium was only prescribed in 2.1% of the patients. There have been concerns with regard to the combination of Lithium and the NNRTI TDF as both drugs are excreted by the kidneys and can therefore cause renal dysfunction.[150] It is unknown if this may have impacted on the limited use of Lithium in this study. Safety of Lithium use in PLWHIV has however been reported in literature. In a randomised placebo-controlled trial by Decloedt *et al.* evaluating renal safety of Lithium in HIV-infected patients who were prescribed TDF in combination with Lithium, it was found over a 24-week period that the combination of Lithium and TDF did not result in renal toxicity when compared to the placebo group.[151]

5.4 BASELINE AND FOUR-YEAR CLINICAL OUTCOMES

5.4.1 CD4 count at ART initiation and four-year follow-up period

At ART initiation, the median CD4 count in our study was 157 cells/mm^3 and 64.1% of the patients were classified WHO clinical stage IV. This meant that the majority patients were initiated on ART late when the disease had progressed to AIDS. Research has demonstrated that the most rapid improvement in CD4 count values is usually seen in the first six months after ART initiation.[98,152] There was a significant increase in the median CD4 count to a median of 490 cells/mm^3 at the end of the four-year follow-up period. On average, CD4 count increased by 350 cells/mm^3 in this study. In a Nigerian retrospective cohort examining the long-term outcomes of patients on ART in the general population, the median CD4 count was 147 cells/mm^3 at ART initiation, and 487 cells/mm^3 at 72 months after ART

initiation. The greatest increase in CD4 count was observed in the first six months after ART initiation.[152] These baseline and follow-up CD4 results were similar to this current study and highlights that a psychiatric population can achieve similar immunological outcomes as PLWHIV in the general population on ART. In a cohort by Nachega *et al.* examining the association between mental illness in PLWHIV and retention in care, it was also found that there were no differences in the baseline median CD4 count of patients with SMI and those without SMI at ART initiation.[91] Other studies reported similar findings. In a study by Freeman *et al.* examining the prevalence of mental illness in PLWHIV and the association between SMI and certain variables, they found no significant differences in the CD4 count of depressed and non-depressed patients. In the above study, there was a rather significant association between the presence of mental illness and WHO HIV clinical staging, with 68.8% of the patients with a SMI classified as WHO HIV stage IV.[33]

5.4.2 Viral load

In this study, VL was collected at ART initiation, six months after initiation and at the end of the four-year follow-up period. Viral suppression was defined as VL values of less than 50 copies/ ml or less than the detectable limit within six months after ART initiation, or at four years after ART initiation.

The mean VL at ART initiation was 38000 copies/ ml. At ART initiation, one patient had a non-detectable VL, which was an unexpected finding as one would expect high VL at ART initiation. There are possible explanations for this finding. This patient could be an “elite suppressor” or “elite controller”. Elite suppressors or controllers are patients who can naturally control their VL without ART.[153] Another possible explanation could have been the incorrect recording of VL at six months after ART initiation as the baseline VL. At six months after ART initiation, 54.3% of the patients had achieved initial viral suppression; this rate increased to 71.8% at the end of the four-year follow-up period. In a retrospective analysis comparing treatment

outcomes of psychiatric patients and non-psychiatric patients on ART, where viral suppression was defined as VL values of 200 copies/ml or less, 65.9% of the patients with SMI achieved viral suppression compared to 74.4% in those without SMI. In this analysis, psychiatric patients were less likely to achieve viralogical suppression compared to non-psychiatric patients at 12 months after ART initiation.[154] In another study on psychiatric patients, the VL cut-off value was 400 copies/ml and the rate of viral suppression at 24 weeks was 83% and 85% at 96 weeks. [92] Studies examining long-term outcomes on PLWHIV in the general population have reported higher rates of viral suppression. In a cohort done in Nigeria where viral suppression was defined as one VL value below 400 copies/ml after initiation, 69.3% of the patients had achieved viral suppression six months after ART initiation; this suppression rate increased to 75% 42 months post ART initiation, which is similar to this current study.[152] The strict definition of viral suppression used in this current study (less than 50 copies/ml) might account for the lower suppression rate at six months after ART initiation when compared to the Nigerian cohort. Some literature that used the same criteria of virologic suppression reported higher rates of viral suppression in non-psychiatric populations compared to our study.

Several studies have also reported an association between baseline CD4 count and subsequent viral suppression. In a study done in Nigeria looking at long-term treatment outcomes in non-psychiatric patients, it was found that low CD4 counts at ART initiation were associated with poorer viral suppression at six months.[152] In the above study, in patients initiated with CD4 counts less than 100 cells/mm^3, 65.4% achieved initial viral suppression compared to 70.7% in those who initiated ART at values above 100 cells/mm^3. This poor initial viral suppression rate could be associated with more advanced HIV illness with low CD4 count values at ART initiation.[152] In this current study, the relationship between CD4 count values at ART initiation and initial VL suppression at six months after ART initiation was not explored. Other factors associated with poor initial virological suppression in PLWHIV in the general population reported in

literature include TB diagnosis at ART initiation, poor adherence and male gender.[155]

In this current study virological failure was not studied as per the WHO definition of two values above 1000 copies/ml three months apart. The study only measured the number of patients who achieved VL values above 1000 copies/ml at six months after ART initiation and at four years after ART initiation. Overall, 11.6% and 10.6% of the patients had a VL of above 1000 copies/ml or above at six months after ART initiation and at the four-year follow-up period respectively. Therefore, despite the low initial VL suppression, the majority of patients had VL less than 1000 copies/ml, which may suggest that most of the patients were not failing treatment according to the WHO ART guidelines definition of virological failure. Studies done in PLWHIV in the general population have reported higher rates of virological failure. In a Nigerian retrospective review in non-psychiatric patients, virologic failure was defined as two consecutive VL values above 1000 copies/ml six months after ART initiation. In this review 24.4% met the criteria for virological failure, and the rate was seen to be the highest at month six.[152] The WHO definition of virological failure is however not applied in high-income areas where cut-off values above 50 copies/ml are used. [109,110] In a recent cohort conducted in SA, the risk for virological failure increased by up to five-fold in patients with VL levels between 400 and 999 copies/ml.[111] Findings from this cohort suggested that the current WHO definition of virological failure may fail to identify a large proportion of patients who might already be failing treatment, thus delaying the switch to a second line ART regimen. It has been recommended that cut-off values of 80 copies/ml be used to define virologic failure in all ART guidelines irrespective of resources.[110] Previous studies have reported better virological suppression on PI-boosted second line ART regimens even with moderate adherence. [156] In a study by Shuter *et al.*, patients on LPV/r-boosted second line regimens achieved better virological suppression at lower adherence rates compared to those on NNRTI-based regimens with moderate levels of adherence.[156] In a study by Bulage *et al.*, second and

third line ART regimens were found to be protective against virological non-suppression.[155]

In terms of the relationship between the presence of psychiatric illness and virologic response in patients on ART, previous literature has shown an association. In a study by Pence *et al.*, patients in an HIV clinic were screened for mental illness using different psychiatric screening tools, and patients who had a higher predicted risk of a psychiatric illness took longer to achieve virological suppression. Overall, virological failure was higher in these patients as well.[111] In a study by Moore *et al.*, HIV-infected patients with a comorbid bipolar disorder showed slower rates of viral suppression and faster rate of virologic failure compared to those without bipolar disorder.[139] This finding was found to be related to poor adherence to both ART and psychotropic medication.[139] Poor viral suppression in both the psychiatric and general population on ART can thus be related to poor adherence to medication. The presence of mental illness at ART initiation and during ART treatment can therefore impact negatively on treatment adherence as well as immunological and virological outcomes.

5.4.3 Opportunistic infections

It is well documented that poor clinical, immunological and virologic parameters at ART initiation are associated with OI.[157] In this current study, 28.3% of the patients had OI at ART initiation. At ART initiation, the majority (64.1%) of the patients were also classified as stage IV. According to the WHO HIV clinical staging, stage IV is characterized by certain severe OI, various malignancies and HIV encephalopathy.[158] Since the majority of the patients were classified as stage IV at ART initiation a higher prevalence of OI at ART initiation would be expected. The WHO HIV clinical stage was not determined by the researcher, it was therefore unclear how these patients were classified as stage IV. Psychiatric disorders due to HIV are associated with more advanced immunosuppression and the majority of the patients in this study were diagnosed with the latter, these patients may have been classified as stage IV. Considering that the median CD4 count

in this current study was less than 200 cells/mm^3, coupled with advanced HIV clinical staging, higher rates of OI and HAND at ART initiation were expected when comparing to other literature on PLWHIV in the general population.[159] In a retrospective review conducted in Ethiopia's Hiwott Fana Academic Hospital, the prevalence of OI and associated factors was studied over a four-month period after ART initiation. The prevalence of OI was 48% and the most prevalent OI in this study were TB, herpes zoster and candidiasis at 21.3%, 11.2% and 9.5% respectively.[116] Much the same as this current study, the majority of the patients had baseline CD4 counts less than 200 cells/mm^3 at ART initiation.[116] Factors associated with OI included initial CD4 count values of below 200 cells/mm^3 and advanced WHO clinical staging.[116] In this current study, candidiasis was the most prevalent OI followed by TB and syphilis at 13.8%, 9% and 2.1% respectively. Candidiasis has also been documented as the most prevalent OI in non-psychiatric PLWHIV.[159] The relationship between syphilis, HIV and mental illness has been demonstrated in previous literature.[160,161] The clinical presentation of neurosyphilis may include psychiatric symptoms of a neurocognitive disorder, psychosis, personality changes and mood changes.[160,162] In this current study there were no patients diagnosed with neurosyphilis. In a study assessing the screening, prevalence and diagnostic profile of syphilis in psychiatric patients. The prevalence of syphilis was 11.7% which was much higher than the prevalence in this current study.[162] The above study also demonstrated a significant association between syphilis and high-risk sexual behavior and HIV-infection.[162]

There was a significant decline of OI during the four-follow up period, with 11.7% having OI. These patients were diagnosed with an OI at any point during the four-year follow-up period after ART initiation. At the end of the four-year period, 56.3% of these patients achieved viral suppression, the viral suppression rate was much lower than the overall viral suppression rate in this study. The mean CD4 count was however 605 cells/mm^3. The possible explanation for this finding could be that the OI may have been

diagnosed soon after ART initiation prior to viral suppression. The presence of SMI in PLWHIV may also contribute to OI, the relationship between OI and mental illness is however not well studied.[163] It has been reported that people who are co-infected with HIV and TB have high rates of SMI as compared to those with HIV only.[164] The presence of a SMI in PLWHIV may be associated with the presence of OI by decreasing immunity or impacting negatively on ART adherence by direct or indirect mechanisms.[164,165] The low rates of OI at the follow-up period could have been due to under-reporting as patients could have been diagnosed and treated at their local clinic. The majority of the patients who were diagnosed with OI after ART initiation also had ART regimen change, the most common reason for ART regimen change in this group was that of adverse effects followed by treatment failure and drug interactions respectively. Since ART, psychotropic medication and some of the drugs used to treat opportunistic infections are metabolised by the hepatic cytochrome P450 enzyme system, the co-administering of these drugs can result in drug toxicity, adverse drug reactions and a decrease in the effectiveness of the ART or psychotropic drugs.[46,47]

5.4.4 Body mass index

Body mass index has been shown to be a strong and independent predictor of survival in those with HIV when recorded at baseline, within three months of HIV diagnosis.[113] In this study, the median BMI at ART initiation was 22.2kg/m^2, which was within normal limits of BMI. This normal BMI could have been influenced by the use of psychotropic medication, which is known to cause weight gain. Literature on PLWHIV in the general population has shown lower BMIs at ART initiation of less than 18,5 kg/m^2.[166] Low BMI at ART initiation is associated with poorer outcomes, high prevalence of OI and increased mortality.[114] Wasting is a common clinical feature of HIV. It has been shown that in sub-Saharan Africa, wasting at ART initiation was one of the main factors contributing to mortality.[167,168] In the US, several studies have reported better outcomes on patients who were overweight at ART initiation. This has been debated however as some literature has

reported that obesity was not a protective against HIV-related mortality, as these patients were more likely to develop adverse events related to obesity.[169] Body mass index is expected to increase in those who were underweight at ART initiation. In this current study, BMI increased by an average of 3.0 kg/m^2 from baseline to follow-up.

5.4.5 Antiretroviral treatment regimen initiated and regimen change

Most of the patients in this study were on the first line ART regimen as per the National Guidelines during the period between 2008 and 2010. These patients were initiated on ART as inpatients and outpatients. There were some deviations from regimens prescribed for PLWHIV in the general population. In our study, 43.4% of our patients were prescribed NVP. This was more than expected as NVP is generally recommended for pregnant patients and only 2.8% of patients were pregnant at ART initiation.[42,43] The ART guidelines during this period also discouraged the use of EFV in psychiatric patients, due to its neuropsychiatric adverse effects, which could have accounted for the high use of NVP in this population.[42,43] However, in spite of these recommendations, in this study EFV was prescribed to 49% of the patients. Risk factors for developing EFV-associated neuropsychiatric adverse effects that have been reported in literature. These include HIV disease progression as well as genetic polymorphism in certain population groups.[52] The use of EFV in PLWHIV with comorbid mental illness remains controversial. Literature has reported that EFV is generally well tolerated and that the neuropsychiatric adverse effects commonly occur within the first few weeks of treatment and are usually self-remitting. [51,170,171] In a cohort by Karstaedt *et al.*, 66% of patients with SMI were initiated on an EFV-based regimen and of these patients only four were later switched to Ritonavir/Lopinavir, the reasons for which were unclear. In this cohort, the use of EFV in PLWHIV with a comorbid mental illness was demonstrated to be safe and was not associated with the deterioration of the mental illness.[92] In a review published in 2015, the use of EFV in psychiatric patients was not contraindicated unless there was worsening of an existing

psychiatric illness, or if there was a new psychiatric illness coinciding with the initiation of EFV.[52]

The most commonly prescribed NRTIs in this study were D4T and 3TC. This was in keeping with the ART initiation guidelines during this period. The South African National Guidelines published in 2010 recommended the withdrawal of D4T from the first-line ART regimen.[43] The use of TDF was introduced in these guidelines to replace D4T as part of the first line regimen.[43] This would explain the low rates of TDF use in this population during the study period relative to other NRTIs. This change in the National Guidelines could have also contributed to the high percentage of patients who switched ART regimens.

Overall, 72.4% of the patients had ART regimen change in this study. It was however not specified if patients changed to full second line therapy, or if they only had certain drugs substituted. The rate of ART regimen change of this current study was higher than that reported in other studies in the general population.[172,173] Reasons for regimen change reported in literature include adverse drug effects, treatment failure, pregnancy, comorbid OI and psychiatric diagnosis as well as other side effects depending on ART used.[173] Adverse effects were reported as the main reason for ART regimen change in this current study. These adverse effects were however not specified. In a retrospective study conducted in Ethiopia, the reasons and risk factors for ART regimen change were assessed, 47.7% had regimen change. Drug toxicities were reported as the main reason for regimen change. Other reasons reported included treatment failure, TB diagnosis and pregnancy. Predictors for ART regimen change included TB co-infection and patients on EFV-based and non-D4T regimens had a lower risk of ART regimen change.[172] In a SA retrospective cohort study conducted in patients initiated on ART from 2002 to 2011, the rates of drug substitution and regimen change in patients on TDF, AZT and D4T-based regimens were compared. In this cohort TDF was the best tolerated drug and was associated with least drug substitution. The D4T-based regimen

was associated with a four-fold increase in drug substitution and 74.1% of these patients had regimen change due to reasons of adverse effects.[174] All three regimens however demonstrated similar rates of viral suppression. In this current study 71.8% achieved viral suppression at the end of the four-year follow-up period, this rate was similar to the overall rate of viral suppression in the study described above. In another SA cohort study done over four years on patients initiated on ART between 2004 and 2007, the main drug substituted was D4T. The use of D4T in that study was associated with increased morbidity and mortality due to life-threatening lactic acidosis and symptomatic hyperlactataemia.[175] In this current study, 72.4% had ART regimen change for reasons of adverse effects. Of the patients who had regimen change due to adverse effects, 71% were virally suppressed at the end of four years, this rate was similar to that of the entire sample.

5.4.6 Treatment interruption

In this study, the number of patients who interrupted treatment at some point during the four-year period but were still in care at the end of the period was documented. It was found that 26.9% of the participants interrupted treatment during the course of the study period. It was not assessed if non-adherence was to medication only or clinic appointments only, or whether there was a combination of both. It was also not recorded whether these patients interrupted ART, psychotropic medications, or both. The reasons for treatment interruption were also not recorded in this study. Previous literature has reported that socio-economic problems are one of the main contributors to poor adherence in PLWHIV in the general population and in the psychiatric population.[75,78,176] Other factors associated with non-adherence in PLWHIV reported in literature include stigma, discrimination, adverse effects of medication and substance use.[176,177] In a descriptive qualitative study conducted in Cape Town on PLWHIV without an SMI, the barriers to ART adherence described included financial constraints, lack of transport, stigma and discrimination, ART adverse effects, substance use and forgetfulness.[178] These barriers were similar to those described in

literature on psychiatric patients who are HIV negative.[78] In this current study there was an association between treatment interruption and virological non-suppression. It was found that 33.3% of the patients who interrupted treatment during the four-year follow-up period had unsuppressed VL values at the end of the four-year follow-up period with a median VL of 4158.7 copies/ml and 17.9% of these patients were diagnosed with OI during the four-year follow-up period, VL non-suppression in this group was three times more than the overall rate of non-suppression in this study. Treatment interruption was therefore associated with poorer viral suppression. There is sufficient evidence in previous literature demonstrating that poor adherence is associated with poorer treatment outcomes of continuing viral replication with possible viral resistance, treatment failure and progression to AIDS and death.[70]

5.4.7 Hospitalisation

During the four-year follow-up period, 26.9% of the patients had one or more hospital admissions, with psychiatric admissions being the most common reason for admission. In a retrospective review by Joska examining the prevalence and correlates of attendance at a six-month HIV clinic visit in psychiatric patients diagnosed with HIV, the participants had a median of one psychiatric admission and the length of hospital stay averaged at 46 days. This study also found that the patients who were readmitted during the six-month period were less likely to return to their six-month clinic appointment.[93] Medical admissions also contribute to admissions in this population, and it is estimated that up to two thirds of hospital admissions for PLWHIV in the general population are due to medical illnesses.[121] This rate has been seen to decline with the advent of ART. It is possible that medical admissions were misrepresented in our results as the patients could have been admitted in other hospitals and may not have reported this at their follow-up appointments at Luthando Clinic. Factors associated with both medical and psychiatric admissions in this population include late ART initiation, poor adherence to ART, ART resistance and presence of OI.[179,180] In this current study, the relationship between hospital admissions

and VL was not investigated. This association would have been beneficial to study in this population as previous literature in PLWHIV in the general population has shown that virologic and immunological success was associated with a decline in hospital admissions.[180]

5.5 LIMITATIONS

Since this study was a retrospective record review, there were certain limitations related to the nature of the study. The study relied on information being accurately and completely recorded in the patients' clinical records and electronic database by previous clinicians. This was mostly observed to be inconsistent, with the poor recording of the IHDS score and poor documentation of substance use history at ART initiation. Another important clinical variable that was not consistently recorded at the six-month and four-year follow-up period was the VL, the results were therefore given as a percentage of only those who had results recorded. This may have impacted on the findings as the final results were not based on the entire study population. The data on the electronic database was at times incorrectly recorded or not updated efficiently. In those cases, the original Luthando Clinic file and the psychiatry outpatient clinic file would be retrieved to obtain the missing data or verify the information.

Another major limitation of the study was that its findings could not be generalised to other treatment centres, as Luthando Clinic is a tertiary unit where patients are managed by a multidisciplinary team.

The sample size of our study was a further limitation. Although the total number of files reviewed was 595, the total number of files that could be used to collect baseline and follow-up data was small. A significant number of the patients were excluded from the sample size as they were already on ART when they came in or were not eligible for ART according to the National ART initiation guidelines.

There was also no control group of patients who were HIV positive without SMI to compare clinical outcomes. We could therefore only compare our group with findings from other studies looking at treatment outcomes in PLWHIV in the general population.

Another limitation of this study was that psychiatric diagnoses were not based on a standardised objective tool, but were rather based on the

clinicians' clinical impressions at the time of ART initiation. The use of other standardised objective tools such as those used for substance use, cognitive impairment screening and psychotic and mood disorder rating scales could have assisted in having a more reliable and objective assessment of the patients' diagnosis at ART initiation. Most of the patients also had a differential diagnosis, which further affected recording of the psychiatric diagnoses and analysis. The psychiatric diagnoses were not recorded on follow-up and it is not known if this diagnosis changed over time when the patients were reviewed by other clinicians after ART initiation.

The exclusion of those who were transferred to other treatment centres, from the analysis of clinical data also created a selection bias as the patients who were transferred were also essentially also retained in care but in another treatment site. Finally, the factors or criteria which may have influenced the decision to retain patients at Luthando Clinic or to transfer to another treatment centre were not clearly documented in the patient file. It was therefore unclear which type of patient would fall under each category. The patients who remained in care at Luthando may have been more unwell both psychiatrically and due to HIV, and therefore selected to remain at an integrated treatment care unit. This may have impacted negatively on clinical outcomes.

In spite of these limitations, the study yielded results of clinical significance to this population and for future research.

CHAPTER SIX: CONCLUSION

The aim of this study was to determine the long-term outcomes of psychiatric patients initiated on ART at Luthando Clinic between 2008 and 2010. According to literature, there are no previous studies examining long-term ART outcomes in a psychiatric population managed in a tertiary integrated treatment centre. Previous literature has demonstrated that integrated care model has cost implications and may be difficult to implement in developing countries. According to the findings of this study, although retention in care was relatively low compared to that of ART programmes in the general population, psychiatric patients with comorbid HIV were able to achieve successful treatment outcomes when retained in care. This was supported by our findings of significant improvements in immunological and virologic parameters. These outcomes were however not compared with HIV-positive psychiatric patients who were not receiving integrated care. It was therefore difficult to conclude that psychiatric patients who received integrated HIV care achieved better outcomes.

CHAPTER SEVEN: FURTHER RECOMMENDATIONS

The findings of this study contribute to the literature on the psychiatric population with comorbid HIV-infection in the sub-Saharan region. Although the rate of retention in care in this study was low, we obtained useful information with regard to the long-term treatment outcomes of the participants who remained in care, while certain areas where further research is still required were indicated. This study highlighted that psychiatric patients were able to achieve favourable treatment outcomes when managed in an integrated facility. The integration of HIV care in the population should therefore be considered in this population balanced with the costs and challenges involved in delivering this type of care.

Clinicians should be continuously motivated to accurately and completely record patients' clinical data. The use of brief screening tools should also be integrated in the management of people living with HIV and should be encouraged at every encounter with a patient. Further research should focus on outcomes of those retained in integrated care compared with those referred to local community clinics, to determine the profile of patients who would benefit from an integrated care approach. It would also be important to consider other factors which may impact on LTFU such as distance from Luthando Clinic and financial contraints as this may impact on the outcomes of the patients retained in care. This would also be helpful in terms of formalising the criteria for retention in integrated care at the Luthando Clinic.

In terms of the socio-demographic profile of our study population, the female predominance of the Luthando population suggests that interventions focused on women's mental and physical health issues should be implemented. Screening tools specific to women such as regular Pap smears could be included as part of a comprehensive treatment plan. This could also include the provision of contraception at the clinic. Socio-economic intervention in this population should also be a point of focus as most of our study population were unemployed, single and with a low level of education.

Another area that could be studied further is the comparison of treatment outcomes in those initiated on ART as inpatients and those initiated as outpatients. The relationship between severe mental illness and ART treatment, factors related to poor retention in care and poor viral suppression need to be studied further so as to improve outcomes in this group. Further research should also focus on the factors associated with treatment interruption in psychiatric patients with HIV infection. The relationship between treatment interruption and virologic suppression in this population is another area that should be targeted in future research. Other outcomes of clinical importance that need to be studied further in this population entail the relationship between cognitive impairment, substance use and adherence.

This study not only highlights the need for further research in psychiatric patients with comorbid HIV infection, but also the need for integrated care for the dual diagnosis of mental illness and HIV. Further research in this population will assist in motivating for more funding for the integration of HIV and psychiatric care in PLWHIV.

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APPENDICES

APPENDIX ONE: DATA SOURCE SHEET

1. Outcomes (at four years after ART initiation)

a. Follow-up outcomes (all initiated between 2008 and 2010)

Loss to follow-up	0
Dead	1
Transferred out	2
Retained in care	3
Unknown	4

DATA OF THOSE RETAINED IN CARE

2. DEMOGRAPHICS (Baseline at ART initiation)

a. Age ☐

b. Gender

Male	0
Female	1
Unknown	2

c. Marital status

Single	0
Married	1
Divorced	2
Widow	3
Separated	4
Living together	5

Unknown	6

d. Employment Status

Employed	0
Unemployed	1
Self employed	2
Other	3
Unknown	4

e. Years of education ☐

3. PSYCHIATRIC DIAGNOSIS (at ART initiation):

a. Primary		
Schizophrenia	Yes	No
Schizoaffetive disorder	Yes	No
Major Depressive disorder	Yes	No
Bipolar disorder I	Yes	No
Bipolar disorder II	Yes	No
Anxiety disorder	Yes	No
Personality disorder	Yes	No
None	Yes	No
Other	Yes	No

b. Due to GMC/Substances		
Psychotic disorder due to HIV	Yes	No
Psychotic disorder due to GMC	Yes	No
Mood disorder due to HIV	Yes	No
Mood disorder due to GMC	Yes	No
Mood disorder with psychotic features due to HIV	Yes	No
Mood disorder with psychotic features due to GMC	Yes	No
HAND	Yes	No
Substance induced mood disorder with psychotic disorder	Yes	No
None	Yes	No
Other	Yes	No

4. MEDICAL DIAGNOSIS (in addition to HIV) at ART initiation

Yes	0
No	1
Unknown	2

5. If yes to 4 specify,

Diabetes Mellitus	0
Hypertension	1
Epilepsy	2

Asthma	3
Hyperlipidaemia	4
Other	5

6. SUBSTANCE USE HISTORY (at ART initiation):

Yes	0
No	1
Unknown	2

7. PHARMACOTHERAPY (at ART initiation)

a. Anti-psychotics			**b.Anti-depressants**		
Trifluoperazine	Yes	No	Tricyclic antidepressants	Yes	No
Chlorpromazine	Yes	No	SSRI	Yes	No
Haloperidol	Yes	No	SNRI	Yes	No
Risperidone	Yes	No	Other	Yes	No
Olanzapine	Yes	No	None	Yes	No
Clozapine	Yes	No			
Quetiapine	Yes	No			
Aripiprazole	Yes	No			
Risperidone LAI	Yes	No			

Flupenthixol decanoate	Yes	No
Zuclopenthixol decanoate	Yes	No
Other	Yes	No
None	Yes	No

c. Mood stabilizers		
Sodium valproate	Yes	No
Carbamazepine	Yes	No
Lithium	Yes	No
Lamotrigine	Yes	No
Gabapentin	Yes	No
Other	Yes	No
None	Yes	No
d. Other Psychotropics		
Benzodiazepines	Yes	No
Anticholinergic	Yes	No
Methylphenidate	Yes	No
None	Yes	No

Other	Yes	No

8. BASELINE CLINICAL PARAMETERS (at ART initiation)

a. CD4 count

b. Viral load (if available)

c. Weight (kg)

d. Height (m)

e. Body mass index (kg/m^2)

f. Pregnant (at ART initiation)

Yes	0
No	1
Unknown	2

g. IHDS (baseline)

h. WHO Stage

I	0
II	1
III	2
IV	3
Unknown	4

i. Opportunistic infections (at ART initiation)

Yes	0
No	1
Unknown	2

j. If yes to i, specify

TB	0
Candida	1
Cryptococcus	2
Toxoplasmosis	3
Meningitis	4
STIs	5
Syphilis	6
Not specified	7

k. Admission status (at ART initiation)

Inpatient	0
Outpatient	1
Unknown	2

l. Date of ART initiation

m. ART Regimen initiated

Stavudine	Yes	No
Tenofovir	Yes	No
Zidovudine	Yes	No
Lamivudine	Yes	No
Efavirenz	Yes	No
Nevirapine	Yes	No
Lopinavir/Ritonavir	Yes	No

Other	Yes	No

n. Other medications:

INH	Yes	No
Cotrimazole	Yes	No
Fluconazole	Yes	No
Dapsone	Yes	No
Other	Yes	No
Not specified	Yes	No

9. CLINICAL OUTCOMES (at four-year follow-up period)

i. CD4 count (within 18 months before 4 year follow-up) ☐

ii. Viral load (6 months after ART initiation) ☐

iii. Viral load (within 18 months before 4 year follow-up) ☐

iv. Date of last viral load ☐

v. ART regimen change

Yes	0
No	1

vi. If yes to v specify reason for change

Adverse effects	0
Treatment failure	1
Drug interaction	2
Patient request	3
Unknown	4

vii.Weight

viii.BMI

ix.Admissions

Yes	0
No	1
Unknown	2

x.If yes to ix, how many

xi.If yes to ix, specify

Medical	0
Psychiatric	1
Both	2
Not specified	3

xii.Opportunistic infections (at four-year follow-up period)

Yes	0
No	1

xiii.If Yes to xii specify

TB	0
Candida	1
Cryptococcus	2
Toxoplasmosis	3
Meningitis	4

STIs	5
Syphilis	6
Other	7

APPENDIX TWO: ETHICS CLEARANCE CERTIFICATE

R14/49 Dr Nokuthula Mdaka

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M150862

NAME: (Principal Investigator)	Dr Nokuthula Mdaka
DEPARTMENT:	Psychiatry Chris Hani Baragwanath Academic Hospital
PROJECT TITLE:	Long Term Outcomes of Psychiatry Patients Initiated on Anti-Retroviral (ART) at Luthando Clinic in 2008-2010
DATE CONSIDERED:	28/08/2015
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr Yvette Nel and Dr Gregory Jonsson

APPROVED BY: _____

Professor P Gleaton-Jones, Chairperson, HREC (Medical)

DATE OF APPROVAL: 02/09/2015

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Secretary in Room 10004, 10th floor, Senate House, University.

I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. I **agree to submit a yearly progress report.**

_____ _____

Principal Investigator Signature Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES