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# THE INFLUENCE OF MENTAL ILLNESS ON PRESCRIBING PRACTICES OF ANTI-RETROVIRALS (ART)

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

**Johannesburg 2015**

## DECLARATION:

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

## PLAGIARISM DECLARATION OF WRITTEN WORK:

I, Dr Janice Buckley, as a postgraduate student registered for a MMed at the University of Witwatersrand declare the following:

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Signature:

Date: January 2015

## PUBLICATIONS AND PRESENTATIONS:

- Oral presentation
  25th Annual Psychiatry Research Day – Department of Neurosciences, Department of Psychiatry, University of Witwatersrand
  Johannesburg 12th June 2013

- Poster presentation
  2nd Annual Southern African HIV Clinicians Society Conference
  Cape Town 24th-27th September 2014

## ABSTRACT:

**Background:**

Evidence has shown that there is an increase in psychiatric co-morbidity amongst HIV-infected patients. However, there is limited data on prescribing of Antiretrovirals in this population, specifically in developing countries and South Africa. Furthermore, there are no guidelines as to which regimen should be prescribed for this group. The aim of this study was therefore to describe the ART regimen of patients attending the HIV Neuropsychiatric Clinic at Chris Hani Baragwanath Hospital and to ascertain if these patients were prescribed in accordance with the South African National Guidelines for Adults.

**Methods:**

A retrospective record review was conducted of all new adult patients with both HIV and a mental illness that attended the hospital's Neuropsychiatric Clinic from 1st April 2010 until 30th August 2012. The demographic information, clinical characteristics and psychotropic medication were examined and the prescribing practices of ART were reviewed to ascertain if these patients were following the National Guidelines for initiation of ART in the general adult population. If prescriptions were shown to deviate, the reasons for this were examined.

**Results:**

197 patient records met the criteria over the study period. 81% of the patients were prescribed the National Guidelines. Those not on these regimens were more likely to be male, have renal dysfunction, anaemia or, importantly, a diagnosis of HIV-associated

Neurocognitive Disorder. 77% of patients were started on a regimen containing Efavirenz, even with a concomitant mental illness.

**Conclusion:**

In conclusion, the majority of patients with both mental illness and HIV were prescribed the regimens suggested for the general population. However, there was a subset of patients that required more tailored care. This audit can form the basis of future research into the long-term outcomes of patients on regimens that deviate due to a diagnosis of HAND, as well as the use of Efavirenz in this population.

## ACKNOWLEDGEMENTS:

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# LIST OF ABREVIATIONS

| | |
|---|---|
| 3TC | Lamivudine |
| ART | Antiretroviral Treatment |
| APA | American Psychiatric Association |
| AZT | Zidovudine |
| ABC | Abacavir |
| AND | Asymptomatic Neurocognitive Disorder |
| BBB | Blood-Brain Barrier |
| CHBH | Chris Hani Baragwanath Hospital |
| CNS | Central Nervous System |
| CDC | Centres for Disease Control and Prevention |
| CPE | Central nervous system Penetration Effectiveness |
| D4T | Stavudine |
| EFV | Efavirenz |
| GMC | General Medical Condition |
| HIV | Human Immunodeficiency Virus |
| HAND | HIV-Associated Neurocognitive Disorder |
| HAD | HIV-Associated Dementia |
| IQR | Interquartile Range |
| IV | Independent Variables |
| LTFU | Lost To Follow Up |
| LPV/RTV | Lopinavir/Ritonavir |
| MDD | Major Depressive Disorder |
| MND | Mild Neurocognitive Disorder |
| NVP | Nevirapine |
| NNRTI | Non-Nucleoside Reverse Transcriptase Inhibitor |
| PTSD | Post-Traumatic Stress Disorder |
| STI | Sexually Transmitted Infection |
| SAS | Statistical Analysis Software |
| TDF | Tenofovir |
| TB | Tuberculosis |
| TNF | Tumour Necrosis Factor |
| UNAIDS | the Joint United Nations Programme on HIV/AIDS |
| USA | the United States of America |
| WHO | World Health Organisation |

# CHAPTER ONE: INTRODUCTION

The Human Immunodeficiency Virus (HIV) has had wide-reaching effects on medicine in South Africa, including in the discipline of Psychiatry. South Africa's prevalence rate of HIV as of 2012 is 12.2-17.9% (1) (2), while the world prevalence is 0.8% according to UNAIDS (3) and South Africa is ranked 4$^{th}$ globally in terms of HIV prevalence (3). It is currently estimated that 5, 51 million people are living with HIV in our country as of 2014 (4) and over the past few years, roll-out of antiretroviral medication has dramatically increased from 101 416 adults in 2005 to 1 058 399 adults in 2010 (2). All of these statistics can be translated into a large proportion of the population requiring treatment for HIV and the need for every doctor, no matter what area they work in, to have knowledge about how the virus affects their patient population.

As an increasing number of patients are gaining access to Anti-retroviral Treatment (ART) (4) and therefore could also be seeking help for psychiatric illnesses, there is a need to look closely at this specialised population with regards to their treatment, both biologically and psychologically. Currently, there are only recommendations from the World Health Organisation (WHO) on treatment of patients with co-morbid HIV infection and mental illness (5). As the medical community move into an era where evidence-based medicine is more commonly used to guide clinicians' decisions (6), it is important to evaluate how well current guidelines are being implemented so as to provide patients with optimal care in an ever-advancing and more complicated area of medicine.

Luthando Clinic is a centre for the care of mentally ill persons with HIV infection and neuropsychiatric disorders in Soweto Township within Johannesburg in South Africa. The unit was established in June 2008 and is the program of the Chris Hani Baragwanath Hospital (CHBH) and the University of Witwatersrand. It utilizes a multidisciplinary approach to the care of mentally ill persons with HIV infection and has adopted the National Guidelines for the prescribing of ART. As Luthando Clinic is one of the few neuropsychiatric units in South Africa, the opportunity exists to look at the prescribing practices of doctors at the Clinic and to determine if indeed the National Guidelines are being followed and the reasons for deviations, if any. It is hoped that the knowledge obtained from this clinical audit can help to improve and standardise care for this specialised group of patients.

The aim of this study is to describe the antiretroviral treatment prescribed to a group of HIV positive mentally ill patients attending the Luthando Clinic and to ascertain if prescriptions were in conflict with the National Guidelines for the general population and the reasons thereof. The hypothesis is that the prescribing of ART in mentally ill patients at Luthando Clinic is completely in accordance with National Guidelines for the general population**.**

The specific objectives of the study were to:

- Describe the demographic characteristics of the study population
- Describe the clinical characteristics
- Describe the antiretroviral and psychotropic medication prescribed
- Describe any deviations in the prescribing of ART from the National Guidelines
- Determine, if any, the factors associated with these deviations from the National Guidelines

# CHAPTER TWO: LITERATURE REVIEW

## 2.1 MENTAL HEALTH IN SOUTH AFRICA

South Africa is a large country with a population of 52 981 991 persons, as of 2013, according to Statistics SA (7). It is ranked as an upper-middle income country according to the World Bank and the 5th highest income per capita in Africa (8). However, it is only twenty years on from the legacy of apartheid which led to massive social inequality in the country, with 23% of the population being at the national poverty line (8). This has caused multiple social problems within the country and impacted on the health of the country's population, including the mental health, which was shown by the high rates of mental illness in the South African SASH study (9).

The WHO conducted a study in 2004 to examine the prevalence of mental illness in different areas of the world. The risk of any mental illness over a twelve month period was 4.7% for Africa, 9.1% for Asia and 26.3% for the USA (10). For specific illnesses, Africa had a prevalence of 3.3% for anxiety disorders, 0.8% for mood disorders and 0.8% for substance use disorders, compared to America's prevalence rates of 18.2%, 9.6% and 3.8% respectively (10). Since then, a nationwide study, known as the "SASH" study, was embarked on in South Africa to look at the prevalence rates of mental illness (9). It showed that the lifetime prevalence of any mental health disorder was 30.3%. The most prevalent class of lifetime disorders was anxiety disorders at 15.8%, followed by substance use disorders at 13.3% and mood disorders at 9.8%. However, the most prevalent individual lifetime disorder was alcohol abuse at 11.4%. In comparison to the WHO study, the twelve month prevalence risk of anxiety disorders was 8.1%, of substance use disorders was 5.8%

and mood disorders was 4.5%. This shows much higher rates of all three disorders within South Africa as compared to the overall risk in Africa. According to the SASH study, factors associated with an increased risk in mental disorders included being female, widowed, separated or divorced (9). Individuals with a low average income were at less of a risk of having these disorders. Interestingly, the study only found the lifetime prevalence of Post-Traumatic Stress Disorder to be 2.3% across all age groups. This is in contrast to research by Seedat et al, which showed that 22% of adolescents in Cape Town had a diagnosis of PTSD (11). One would expect high rates of PTSD in South Africa due to the high rates of crime, especially inter-partner violence (12).

Unfortunately the SASH study did not look at psychotic disorders and there is very little data on the prevalence of psychosis within South Africa. One study by Behr et al in 1996 looked at admissions to Chris Hani Baragwanath Hospital's Psychiatric Department. This study found that 38% of patients had a diagnosis of Schizophrenia and 10% had another psychotic disorder, although no further specification on diagnosis was given (13). Evidence internationally points to a consistent prevalence rate of about 1% for schizophrenia across different countries (14), which is obviously much lower than the 38% diagnosed at CHBH. However, this is a secondary level hospital draining psychiatric cases from the whole of Soweto and therefore shows a skewed prevalence and most likely not a true reflection of the average population. It is also looking at inpatient admissions rather than across the whole population.

From this, it can be seen that there is a paucity of literature on the mental wellness of South Africans in general, even though the prevalence of mental disorders is increasing globally and there is an increased understanding of the need to integrate mental health into the biological model of health in order to fully understand and treat patients (15) (16). Added to this context is the disproportionately large number of cases of HIV in South Africa, which further complicates the mental health of the population. Thus, it is an important area for further research to occur and information adding to our understanding of the psychopharmacology of ART and psychotropics is required as an increasing number of patients present with both HIV and psychiatric illness.

## 2.2 HIV AND MENTAL ILLNESS

With increased research into the effects of HIV/AIDS, it has become evident that there is an increase in psychiatric illness within this specific population as well (17) (18) (19) (20) (21). Both African and South African studies have also shown corresponding results with international studies (17) (22) (23). The Global Burden of Disease Survey estimated that by 2020, mental illness and HIV will both be in the top ten causes of morbidity in developing countries (16). The impact of mental illness on the outcome of patients living with HIV is now undisputed (24). It has been shown that patients with both mental illness and HIV have decreased adherence to their medication. Added to that, and possibly contributing to it, is the fact that they are living with the double burden of stigma, which leads to many social difficulties and can contribute to decreased access to care. Other areas of concern are that there is cognitive impairment due to viral infection of the brain, increased use of substances in this population and increase in depression and anxiety, which can increase disease progression (25). All these points highlight the importance of research and promotion of education in this developing area of medicine.

It has been established that HIV enters the Central Nervous System (CNS) early in the disease process and that the virus infects predominately macrophages and astrocytes within the brain which can then cause activation of an inflammatory cascade and the eventual death of neuronal tissue through cellular toxicity (26) (27). This leads to the neuropsychiatric manifestations, which can in turn lead to important social, functional and psychological sequelae which need to be attended to by the treating physician. It is also now understood that HIV affects mental health in different ways over time. In the early stages, there is the

psychological impact of the diagnosis. Later, there are the neuropsychiatric complications which include HIV-associated dementia and psychosis (28). However, all types of psychiatric illness can present and there is a need to understand the effects HIV has on these presentations.

HIV infection increases the risk of development of mood disorders, specifically depression and also anxiety disorders (22) (29). In one study from the USA, Major Depressive Disorder (MDD) was nearly twice as common in patients with HIV as in the general population (18). There was also at least double the prevalence of depressive, anxiety and substance abuse disorders in these patients, with 50% reporting substance abuse. Results from a study of a South African HIV clinic showed similar results with 35% of patients diagnosed with MDD, 15% with PTSD and 10% with alcohol abuse (30). Studies from other developing countries like India also show increased rates of anxiety in the early stages of disease, higher rates compared to the general population, as well as increased rates in those patients who are physically ill (31). This can make the diagnosis of depression difficult as many of the somatic complaints of depression and HIV overlap, such as fatigue and poor concentration, complicating the diagnosis for physicians who have less exposure to psychiatric illnesses. Importantly, new research has also shown that depression and anxiety may also accelerate the progression of the disease (28). One study looked at a cohort of patients with HIV and screened them for depression and PTSD (24). The results showed that individuals with a higher depressive score had lower CD4 counts than those individuals with high PTSD scores and those with both conditions. Those patients with higher depressive scores also were less likely to adhere to their ART medication. Thus this shows the importance of screening for

these common mental health concerns in all HIV-positive patients, as the mental illnesses are treatable.

Mania is more commonly seen in HIV infected patients than in the general population, if one compares studies done on this population versus the general population rate of approximately 1% of the population (14). One review suggested that the prevalence was 4-8% of the HIV-infected population (32). It may be seen in the context of a pre-existing Bipolar Mood Disorder as these patients can be at increased risk of acquiring HIV due to risk taking behaviour during the manic phase. However, there is evidence to suggest that it can be the presenting feature of HIV (33). The exact pathophysiology is unknown but it is thought to be linked to the neurotoxicity of the HIV infection (34). This secondary mania is more commonly seen at lower CD4 counts, appears to be more common in females and presents in a similar fashion to primary mania, except that the patients usually have more irritability than euphoria and more cognitive impairment (33) (35). Treatment of this mood disorder is obviously important because of the implications for the patient in terms of adherence as well as for others in terms of spread of the HIV infection.

The onset of psychosis during the course of the HIV infection has been recognised since the early history of the disease (36). There are many causes for the psychosis, which can be categorised into those patients with a primary psychiatric illness and HIV, those with psychosis secondary to the HIV and then medication-induced psychosis. Patients with schizophrenia may not appear to be at increased risk of HIV because they are often not in relationships and have poor social functioning. However, those who are sexually active are

at higher risk due to high-risk sexual behaviours related to poor impulse control, impaired judgement and the increased prevalence of substance abuse (37) (34). There are no studies within South Africa looking at the prevalence of HIV co-infection in schizophrenia, but one study from Kwa-Zulu Natal in 2003 showed a HIV prevalence rate of 26.5% of patients admitted to a psychiatric hospital (38). However, approximately half the sample had a diagnosis of schizophrenia spectrum disorder and a quarter had a diagnosis of organic psychosis, suggesting a high rate of HIV amongst these patients.

There are also a number of case reports and a few studies showing an increase in new-onset psychosis, which can include a maniform psychosis (39). Recent review of the literature revealed a prevalence of new onset psychosis in HIV of between 0.2 – 15.2% (40). Patients appear to present in a similar manner to patients with schizophrenia, although bizarre and systematised delusions appear uncommon (34). It is often difficult to establish the causal association between the HIV infection and the psychosis but research suggests that it may represent a late stage manifestation of the disease, related to CNS penetration (40). Early research on this topic showed that patients with new-onset psychosis and HIV showed greater global neurocognitive impairment, more stimulant and hypnotic abuse/dependence and a greater mortality rate (41). One study from Kwa-Zulu Natal looked at first episode psychosis and HIV infection prevalence rate and showed a point-prevalence rate of 23.8% amongst the patients admitted. Due to the difficulty in establishing the temporal relationship of the HIV to the psychosis, it was not possible in this study to determine whether the HIV infection had caused the psychotic illness, but does show a high percentage of new cases of psychosis have co-morbid HIV infection which may be of

significance. Medications used to treat HIV have also been associated with the development of psychiatric symptoms and this will be discussed later in the literature review.

Evidence also suggests that there is an increase in substance abuse amongst people living with HIV, which leads to decreased adherence to medication, poor physical health as well as an increase in mental health disorders such as depression (42) (43). The use of substances can also be a contributory factor in the acquiring of HIV due to high risk sexual behaviour and intravenous drug use and so may be confounding (44) (45) (46). This increase in mental illness can increase mortality in these patients as well as have a significant impact on quality of life (47). It also has other implications, including increased burden on resources and increased burden on the patients themselves with increased pill numbers and side effects to medication (43). The use of substances in this group will be discussed in more detail further on in the literature review.

Thus, over the past number of years, the importance of mental illness in the management of patients with HIV has become evident. As we have moved from an era of HIV being a life-threatening illness into a time where people live with the infection as a chronic illness, the role of psychiatry has become more important, both because of the high prevalence of mental illness amongst the population and because of the impact these illnesses have on the outcome of the disease process. More importantly, the treatment available, both medications and psychotherapeutic interventions, have been shown to be effective and to improve outcomes. It is thus important to have increased awareness of the use of

medications, especially ART, in this specialised population to provide the best care to patients.

## 2.3 GENDER, HIV AND MENTAL ILLNESS

At the onset of the HIV epidemic, there was a predominance of male patients infected with HIV (48), mainly because the epidemic was initially diagnosed in the USA. However, as the epidemic has evolved over the past thirty years, it has been observed that females are more at risk of acquiring HIV (1) for various reasons, both biological and psychosocial in nature. Literature from Africa has suggested that one out of ten women becomes HIV infected each year in Sub-Saharan Africa and that the number of women with HIV is 14% greater than the number of men (21). Statistics South Africa recently released the 2014 mid-year report for South Africa, which estimates that 18.5% of females in the reproductive age group of 15 – 49 years are infected with HIV, while approximately 15.5% of males in this age group have HIV (4). Another report showed a statistical difference between female infection rates (29%) compared to male infection rates (20%) in the 25 to 49 year age group and a 3.9 times higher prevalence of HIV in females aged 15 to 24 versus their male counterparts (1). The spread of HIV infection is mainly through heterosexual transmission (1), which differs from other areas of the world such as the USA, where homosexual transmission is greatest (48). Further added to this, clinical characteristics from a number of studies from South Africa show a female predominance at HIV clinics (49) (50) (51) and one study from Kwa-Zulu Natal showed that females admitted to a psychiatric hospital were statistically more likely to have HIV infection as a co-morbidity than males admitted to the institution (38). Thus, women are more at risk of acquiring HIV and this trend is seen in the female population with a dual diagnosis of HIV and mental illness as well (50).

From a biological perspective, women are more at risk of HIV infection for a number of reasons. Research suggests that females have a 2 to 4 percent increased risk of acquiring the virus when having unprotected sex compared to men because there is a larger surface area that is permeable to fluids in the female genital tract (21). Furthermore, semen from HIV-infected males has a higher concentration of HIV than female secretions which further increases the risk for females (21). There is also substantial evidence that the presence of sexually transmitted infections (STI) increases the risk of contracting HIV and in women, STI's are less likely to be diagnosed and treated because of the lack of obvious symptoms which then increases their risk of infection for HIV (21).

Other factors associated with the greater vulnerability of females for HIV infection are related to the role of gender-based violence. Studies both internationally and locally have shown that violence against women, most commonly inter-partner violence, is associated with a greater risk of HIV infection amongst women (52). A study from Soweto, South Africa, showed that the prevalence of gender-based violence against women was extremely common, with only 22% of females attending antenatal clinics within Soweto reporting having never experienced any form of abuse in their lifetime (12). Fifty five percent of women had experienced at least one incident of either sexual or physical abuse in their lifetime. Intimate partner violence was associated with increased risk of HIV infection amongst these women and it was also associated with increased risk of several other risk factors for acquiring HIV, including increased number of sexual partners, transactional sex and problem drinking. Women who felt more powerless in the relationship were also less likely to feel that they could negotiate safe sexual practices, such as condom usage. Thus

women are at greater risk of HIV infection for a number of reasons, which in South Africa specifically include social issues and violence.

The above research points to the fact that women, especially in Southern Africa, are more at risk of HIV infection. However, there is another factor to consider, which is that men are also less likely to test for HIV (53). A study from Soweto, South Africa, showed that two thirds of males had never tested for HIV and that condom usage amongst these males was poor (54). This is in comparison to an earlier study from the same area that showed that almost 65% of women had ever tested for HIV (53). Therefore more men are unaware of their status and are subsequently not accessing treatment at the clinics and are also transmitting the virus through sexual intercourse without the use of condoms.

Thus, there is increasing evidence that females are at greater risk of acquiring the HIV infection due to both biological and psychosocial reasons. With almost a third of women in the reproductive age group being infected with HIV (1), higher numbers of females are expected to attend HIV clinics and there also appears to be a trend towards them having increased co-morbidity of HIV and mental illness within South Africa.

## 2.4 GUIDELINES FOR PRESCRIBING ART IN THE GENERAL POPULATION

In deciding what ART to use in a patient, it is important to understand the general guidelines for all patients, both locally and internationally and what is recommended for patients' with co-morbid mental illness.

The WHO is a well-recognised and reputable organisation and many countries follow their guidelines for initiation of ART in adolescents and adults. It recommends starting ART:

- In all patients with severe disease (WHO Clinical Stage 3 or 4) or if the patient has a CD4 < 350 cells/$mm^3$
- In patients with a CD4 count >350 cells/$mm^3$ and <500 cells/$mm^3$ regardless of WHO Clinical staging
- In all patients, regardless of CD4 count or WHO clinical staging in the following situations:
    - Individuals with active TB disease
    - Individuals co-infected with HIV and Hepatitis B infection with evidence of chronic liver disease
    - Partners with HIV in serodiscordant relationships to reduce risk of transmission
- All pregnant and breast-feeding mothers should receive ART during the mother-to-child transmission period (55)

In South Africa, the National Guidelines for all adults and adolescents is slightly different to international guidelines and states that:

- Any person with CD4 count < 350 cells/$mm^3$ is eligible for ART
- Any person who has concurrent TB or a female who is pregnant or breastfeeding is eligible, regardless of CD4 count
- Any person with Cryptococcus or TB meningitis, regardless of CD4 count (but defer treatment for 4-6 weeks)
- Any person with WHO Stage 3 or 4 disease is eligible regardless of CD4 count

It is recommended that all new patients now start on a regimen of Tenofovir, Lamivudine (3TC) and either Nevirapine (NVP) or Efavirenz (EFV) as first line treatment, although EFV is strongly recommended, unless there are contraindications, due to the availability of fixed dose combination medication (56).

Internationally, both the CDC (Centres for Disease Control) and UNAID (Joint United Nations Programme on HIV/AIDS) do not have specific recommendations for treating patients with both HIV and a psychiatric illness. The CDC does warn on the potential neuropsychiatric side effects of EFV, including the increased risk of suicide, but does not give further recommendations on who should receive it (57). The American Psychiatric Association (APA) has developed recommendations for medications that can be used in conjunction with the ART (58). Here the focus is on being aware of the drug interactions between medications so that the care of patients is not compromised by adverse drug reactions or ineffectiveness of medications due to interactions. They also provide fact sheets on common mental illness co-

occurring with HIV on their website. The WHO has produced a recent set of treatment priorities, developed in 2010, which does include recommendations for patients with both HIV and mental illness. These recommendations include a focus on psychological support for patients and their families (5). There has been a shift internationally over the past few years towards increasing the awareness and the importance of mental health in all areas of medicine and humanitarian efforts, most likely due to the CDC report suggesting that mental illness will be one of the most common causes of disability in the coming years. Thus, the WHO has recently produced an action plan for mental health, which also includes the need to recognise the role of HIV in psychiatric illness and also integrate mental health services into HIV services, amongst other initiatives (15).

There are no current guidelines in South Africa on first line treatment for adults and adolescents who present with both HIV and psychiatric illness. The approach is that they would be considered as part of the general population and hence the general guidelines apply.

It is in this setting then that it appeared important to add to the pool of data on the prescribing of ART in patients with a dual diagnosis of HIV and mental illness, especially in South Africa where there is little literature on the subject. Further information is of benefit to clinicians who need to manage these complicated cases.

## 2.5 DEVIATIONS FROM THE GUIDELINES IN THE GENERAL POPULATION

In order to understand potential reasons for not prescribing the national guidelines for ART in adults with a co-morbid mental illness, it is first prudent to assess reasons for deviations in the general population without mental illness. There have only been a few studies that have looked at whether National Guidelines are being followed in a particular country and none of these have been done in South Africa. One comprehensive study from the United States of America (USA) looked at trends in prescribing of ART from 1992 until 2004 (59). Obviously over this period there were many changes in protocols for prescribing ART as a greater understanding of HIV developed. The prescribing practices were categorised as following the national guidelines, following alternative regimens which were acceptable practices, and other regimens, which deviated from the guidelines. For the group of patients that received medication that was seen as an alternative to the advised regimen at that point in time, the factors associated with these prescribing practices included age > 61 years, a CD4 between 201-350, a viral load between 20000–50000 copies/ml, black ethnicity, the area of the country in which the patient lived and the year of starting treatment. The group of patients that received medication that was termed “other”, were found to attend clinics where the size of patient load exceeded 50 patients and also depended on the area in which the patient lived. Those patients that were receiving four agents, which is also not part of the guidelines, were more likely to have CD4 <200, a viral load > 50000 copies/ml and live in a specific area within USA. In general, it was found that the greatest correlation between prescribing practices and the guidelines was for recommendations that informed on what to do to avoid harm, such as avoiding AZT in anaemia, rather than those recommendations that improved efficacy. A study in the United

Kingdom had similar findings that showed that the site of the clinic and the year of initiating treatment were important determinants of the choice of drugs at ART initiation (60). A Brazilian study showed that only 2% of patients were prescribed inappropriate regimens in a 2001 survey (61). However, there were alternative regimens that were considered acceptable that deviated from the National Guidelines and the range of those prescribed the actual recommended regimen varied between 17-57%, depending on the clinic surveyed.

Another interesting study from the USA looked at medical as well as non-medical factors that were associated with physicians' decisions to initiate ART (62). Medical factors included a viral load > 20000 copies/ml and evidence of an opportunistic infection. Sixty percent of doctors surveyed were following the prescription suggested by National Guidelines. However, physicians did admit that factors that were considered to affect compliance did influence the decision to start ART. The factors that strongly influenced against ART initiation included heavy alcohol use, current heroin use, homelessness and a history of previous hospitalisation for a psychiatric illness. The rationale may have been that poor compliance to ART has serious outcomes, with virological failure being an important consequence. However, recent studies have shown that physicians are not good at predicting who will be compliant on medication and further research has shown that patients from disadvantaged groups, such as those with mental illness or substance abuse, can have good compliance if provided with appropriate supportive structures.

Unfortunately there are no studies looking at prescribing practices of doctors when initiating patients on ART in South Africa. There are some studies looking at reasons for non-compliance, which may in turn influence decisions made on whether to initiate ART, as shown with the USA study, but this is speculative as there is no evidence to support it currently. Factors that were associated with a higher degree of compliance included living in an urban environment, lower depression scores, higher CD4 count at initiation, a better perception of health and a better physical environment with stronger social support (63).

Thus, it can be seen that there is little research into the choices around prescribing ART in the general population of patients with HIV. What was apparent from the study from the USA was that patients with a psychiatric illness, including substance abuse, may be more likely to be denied access to ART due to their co-morbidity. Therefore, studies are needed to look at the prescribing practices in this sub-group of patients to validate if this is an accurate reflection of practices and to then assess if the ART prescribed deviates from that prescribed to the general population of people living with HIV, especially now that there is mounting evidence to show that psychiatric illness occurs commonly as a co-morbidity with HIV.

## 2.6 DEVIATIONS FROM ART GUIDELINES IN PSYCHIATRIC POPULATION

While there are no comprehensive guidelines on management of mental illness and HIV, there are many areas of concern in terms of treatment for these patients. The main area of concern with a patient who is both HIV positive and has a mental illness is that multiple drugs are often used concurrently to treat both illnesses. This can lead to problematic drug interactions which can cause ineffectiveness of one or both sets of treatments. It is important for clinicians to be aware of these interactions and to prescribe accordingly. Many pharmacological studies have been done to look at various interactions between anti-retroviral agents and other medications. Of note, the protease inhibitors seem to have the most drug-drug interactions due to their action on the cytochrome P450 system in the liver (43) (64) (65). The other concern related to medications is that some of the antiretroviral agents can themselves cause psychiatric complications. This would include EFV, which is known to cause CNS side effects, including psychosis in some patients (66). Thus clinicians are faced with many complex considerations when they are treating a patient with HIV and co-morbid mental illness.

### 2.6.1 EFAVIRENZ AND MENTAL ILLNESS

Efavirenz is known to cause neuropsychiatric side effects in 25-70% of patients initiated on it (66). The most common reported side effects include abnormal/vivid dreams (20-50%), dizziness (20-66%), decreased concentration and insomnia (67). However, there have also been reports of risk of development of psychiatric decompensation (68) (69). It was for this reason that in the South African National Guidelines, it currently recommends that patients with a known psychiatric history are not initiated on EFV as a first line agent at the primary

health care level (56). These guidelines are currently under review though, because this policy may be detrimental to individuals with a dual diagnosis of HIV and mental illness.

The side effects of EFV usually begin within the first 1-3 days of initiation in up to 50% of patients (67). However, studies vary widely with the range between 10-74% (66). The peak incidence is at 7-14 days. Within 4 weeks, the majority of side effects have resolved, except in a small proportion of patients, where the side effects may continue for up to 2 years or longer (69). They are generally mild and well tolerated though. Rates of discontinuation differ between 2-11% depending on the study but in one large study, 24% of patients reported CNS side effects but only 6% discontinued due to these effects (67). The rates were not higher in the 7.9% of patients known with a history of a psychiatric disorder or in the 15.2% of patients who were on psychotropic medication at the time. While common, the actual grading of adverse events related to EFV appear to be mild in most studies (66). However, there are multiple case reports of psychiatric decompensation after initiation with EFV and it is suggested from reviews on EFV that this may be more common in people known with mental illness or substance abuse (69). These include the development of psychosis or mania in which EFV appears to play a role in the expression of these disorders. Luckily the majority of side effects are short-lived and even the severe adverse events appear to resolve within days of discontinuing the EFV. Interestingly, elevated serum levels of EFV did not correlate with CNS symptoms in one study done, but there is conflicting data on this (66).

In terms of the specific psychiatric complications associated with EFV, these include suicide, mood disorders and psychosis. The package insert for EFV does warn against an increased suicide risk but there have been no published reports on the prevalence of completed suicide associated with EFV use (67). On review of the literature, only one study showed an increased rate of suicidal ideation in the EFV arm of 0.5%, but this was not statistically significant (67). In other studies that have shown increased rates of suicidal ideation, there have been a number of limitations to the study design. There did seem to be a link between on-going significant CNS side effects and the risk of suicidality. However, a recent meta-analysis did show an increased risk of suicidal ideation amongst patients on an EFV-containing regimen versus other regimens (70). Therefore it is currently difficult to evaluate the role of EFV in precipitating suicidality and what the recommendations should be stemming from this research, but caution could be advised in patients with a history of suicide attempts.

In terms of mood symptoms, 25% of patients experience “mood changes” when initially started on EFV. The reason behind this is not known but a theory is that it is related to an increase in pro-inflammatory cytokines and therefore increased stress behaviour (67). Most commonly there is increased anxiety (16-35%) but usually the symptoms are mild (67) (69). Manic symptoms are also a concern with 7% of patients from one study developing mania (67). However, there were also reported increased rates of insomnia which may have confounded the diagnosis of mania. Another study showed rates of 3% which were equal to the rates in patients on protease inhibitors (67). Depression has been a major concern but the data so far is conflicting. Some studies show no statistically significant differences in rates of depression amongst those on EFV compared to other regimens. Another study

showed an increased risk of up to 8% and more worryingly, that these episodes were severe (67). Another study compared use of EFV with protease inhibitors and found that, while there were increased neuropsychiatric symptoms, including a trend towards more depressive symptoms, during the first six months of treatment, that there were no statistical differences (71). It is known however that patients with HIV alone have a greater risk of depression than the general population and therefore it is uncertain if this trend in increased depressive symptoms is due to confounding factors. There are only a very few case reports which suggest that there is an increased risk of developing psychosis when using EFV and therefore it is difficult at this stage to assess the risk in patients known with a mental disorder. Further research is urgently required in this area.

Thus there is much debate as to whether or not EFV should be used in patients known with mental illness due to the above factors. However, EFV has been proven to have superior ability to suppress the HIV virus when used as part of a 3 drug cocktail (66). It is a daily dosing and since 2006, there has been a combination pill which allows once daily single pill dosing. Therefore it provides for better adherence. Also, it has less effect on lipid profile, which is an important consideration in patients who are already on psychotropic medication known to cause metabolic side effects. HIV is known to invade the CNS early on in the disease process and there are reservoirs in the brain, even when patients are on ART. Therefore the ART the patient is on needs to be able to penetrate the blood-brain barrier in order to prevent neuropsychiatric complications of HIV. According to the latest CNS penetration effectiveness (CPE) scoring, EFV is a decent penetrator (72). There is no answer yet as to what is the best direction for patients with mental illness and HIV with regard to

Efavirenz use. The clinician, along with the patient or family, will need to weigh up the benefits and risks in each case to make a decision until further evidence is established.

### 2.6.2 NEUROPSYCHIATRIC SIDE EFFECTS OF OTHER ART

While Efavirenz has been shown to have the greatest number of neuropsychiatric effects, other ART medications do also have notable side effects. Most of the literature about these adverse events is in the form of case reports from the early days of ART roll-out with monotherapy. With the advent of combination therapy, it is now more difficult to pin point the exact medication causing the side effects. Generally, the adverse events described occurred soon after initiation with the offending agent or when there was an addition of further medication.

Interestingly, Zidovudine (AZT) was the first ART documented to have psychiatric side effects. In the early 1980's and 1990's, when it was used as monotherapy for HIV, there were a few case reports of patients developing mania and psychosis after commencing AZT, which then resolved within a few days of stopping the medication (73) (74). Importantly, the doses used where higher than doses used today and may have represented CNS neurotoxicity. All the patients in these case reports also had a family history of psychiatric illness and therefore there may be a genetic component to the risk of the psychiatric decompensation (69).

Nevirapine has also shown the potential to induce neuropsychiatric side effects in case reports. The literature suggests that it can cause delirium, abnormal affective states as well as psychosis in some patients (69). Unfortunately, because the sources were case reports, there is missing data that would be relevant in making the final link of causality to the NVP.

Another medication which is not as widely available in South Africa for adult patients, Abacavir (ABC), has a few case reports suggesting that it is linked to depressive symptoms, suicidal ideation and migraines (69). In a more recent case report, a patient presented with a maniform psychosis within a few weeks of being prescribed ART (75). However, this patient was started on four agents, including AZT, 3TC, NVP and ABC. On re-challenging the patient with only the AZT, 3TC and NVP though, there was no re-emergence of symptoms.

Thus, whilst EFV is known to have the greatest risk of neuropsychiatric side effects, it is also important to be aware of the associated risks with other ART in order to recognise these adverse events if they do occur.

### 2.6.3 CHOICE OF ART BASED ON CNS PENETRATION

An important factor in deciding on a regimen of ART in a patient with psychiatric illness would be the CNS penetration of the drugs. This would be an important consideration in patients who present with a mental illness which is felt to be due to the HIV infection rather than someone known with a psychiatric illness, who then contracts HIV. Currently it is not known whether these neuropsychiatric manifestations are due to direct injury by the virus

on the brain or due to a bystander injury. The theory of direct injury is that some of the HIV proteins, such as GP120 or the TAT protein, are directly toxic to brain tissue. The bystander theory suggests that HIV proteins, such as GP120, activate certain immune pathways, such as tumour necrosis factor (TNF) expression or activation of glutamate receptors, which leads to an immune cascade that damages neuronal tissues (26). There is currently much research into establishing the mechanism of injury to the brain by HIV, which will help doctors to better treat patients with both HIV and psychiatric illness. What is known is that different ART's have different penetrations into the CNS and that one would want a drug to be able to cross the blood-brain barrier in order to ensure effective treatment of the virus within the CNS. Letendre developed the CPE scale, which provides a rank of how effective agents are at penetrating the CNS (72). It is based on a drug's chemical properties, CSF concentration and effectiveness in clinical studies. Highly penetrating drugs receive a score of 4, high intermediate drugs 3, low intermediate drugs 2 and low penetrating drugs a 1 (72). Currently the National Guidelines for ART in South Africa includes TDF which has a score of 1, 3TC which scores 2 and either EFV with a score of 3, or NVP with a score of 4. Several studies have shown that increased CNS penetration improves the cognitive outcome of patients on ART, which is important for quality of life and also on ability to function in society (26). A recent study from South Africa showed that ART, no matter what the CPE score, improved or preserved cognitive outcome over one year (76). However, some newer studies are also suggesting that an increase in ability to cross the BBB may lead to increased risk of neurotoxicity (26). Further studies are needed to clarify these issues but in the meantime; clinicians need to be aware of these points when deciding on what medications they initiate their patients on.

### 2.6.4 CHOICE OF ART AND SUBSTANCE ABUSE

Another area of concern in patients with mental illness is the high concurrence of substance abuse (42). This further complicates treatment of these patients, as one needs to consider the effect the substance is having on the medication, as well as the patient's ability to adhere to the medication regimen. In the USA and other developed countries, a large proportion of the patients infected with HIV are also intravenous drug abusers (18). These patients can be initiated on programmes to stop the use of illicit drugs with agents such as Methadone. Numerous studies have now shown the drug interactions between Methadone and similar agents with the ART (18) (43) (65). Specifically with the non-nucleoside reverse transcriptase inhibitors (NNRTI) such as EFV, there is a decrease in the concentration of Methadone so that the dosages may need to be increased to prevent withdrawal symptoms. Thus the guidelines for the use of substitution therapy in patients on ART make recommendations for increase in dosing of the substitution therapy when used with certain ART, including EFV, NVP and AZT. There are also recommendations with regard to other medications, including some of those used in psychiatry such as anti-convulsants and benzodiazepines (65).

In South Africa there is not as high a percentage of intravenous drug users but there is a high degree of substance abuse, most notably alcohol and cannabis, but with methamphetamine abuse becoming more problematic (46) (77). There are no South African guidelines currently on substitution therapy and ART though. The SASH study showed a 12 month prevalence of any substance abuse disorder being 5.8%, which was six times greater than a similar study done in Nigeria (9). From a study done on the epidemiology of

substance abuse in South Africa, it was shown that the primary substance of abuse is alcohol (51%) followed by cannabis at 21% (78). The mean age of the patients with a primary alcohol abuse disorder was 36-41 years. In patients less than 20 years of age, the most common substance of abuse was cannabis, except in the Western Cape, where it was methamphetamines. Risk factors associated with substance abuse included male gender, white ethnicity and being single. Interestingly, 39% of participants were employed full time (78). The use of alcohol and cannabis was similarly the most commonly used substances in another developing country, India, which has a comparative pattern of HIV infection, being mostly heterosexual transmission of the infection (31). While these studies were not looking at patients with HIV specifically, what it does suggest is that substance abuse is a major concern in the general population and therefore needs to be screened for in this vulnerable population group as well. In a South African study looking at a HIV-infected group specifically, they showed a prevalence of alcohol abuse of 10%, which also suggests high risk (30). A later study done in 2009 on a similar population showed 192 participants out of 536 (36%) had alcohol abuse and a further 40 participants had substance abuse involving other drugs, showing much higher rates of these disorders than the previous study, as well as higher rates than the general population (50). While substance abuse can lead to decreased adherence to medication, in terms of public health, it can also lead to increased risky sexual behaviour which increases the likelihood of spread of HIV in this population. It is thus an important factor to consider in all patients presenting to their HIV clinic so that the co-morbid mental health disorder can be addressed.

### 2.6.5 ART CHOICE AND HIV-ASSOCIATED NEUROCOGNITIVE DISORDER

Evidence now shows that HIV infects the brain early on in the disease process and that the brain is a reservoir for the virus even during successful suppression, leading to neuropsychiatric sequelae. With the introduction in ART, there has been a decline in HIV-associated dementia (HAD) incidence but not in the prevalence and incidence of the milder forms of the disorder, all known collectively as HIV-associated Neurocognitive Disorder (HAND), namely Asymptomatic Neurocognitive Disorder (AND) and Mild Neurocognitive Disorder (MND) (27) (79). It has become evident that even the mild forms of this disorder lead to important consequences like decreased adherence, difficulty obtaining employment and shortened survival time (80). Thus diagnosing and managing HAND is an important part of the treatment of patients with HIV. However, there are limited studies both internationally and locally looking at the detection, treatment and follow-up of this group of patients. What has been researched are the risk factors for developing HAND. These can be divided into treatment factors, disease factors, co-morbidities and demographic factors. Current evidence suggests that the lower the nadir CD4 count, the greater the likelihood of HAND (81) (82). Other factors associated with the disease include presence of past HIV-related CNS illness and high plasma and CSF HIV RNA levels (81). Treatment factors include poor ART adherence, while co-morbid factors include Hepatitis C co-infection, other cerebrovascular risk factors and anaemia. Importantly, older age is associated with the development of HAND (82) (79). This is important because as more patients are being treated with ART and therefore living longer, the incidence of HAND is likely to increase and become more of a public health concern, in a similar fashion to dementia in the HIV-negative, aging population. There is less rigorous evidence that suggests that a lower CPE

index may contribute to increased incidence of HAND. Other factors such as co-morbid psychiatric illness, especially MDD, and neurological disorders such as Alzheimer's disease have also been linked to increased incidence of HAND (81). In a South African study that looked at clinical correlates with the disorder, it was found to be common, with 23% of a study population being diagnosed with HAND. Old age was also a significant risk factor. Other factors specific to the South African setting included PTSD and alcohol abuse (50). The Mind Exchange Working Group has recommended that all patients be screened for HAND, desirably before commencing ART, and that any patient at high risk for HAND be followed up every 6-12 months to ensure disease progression has not occurred (81). It is not known yet whether ART stops the disease progression of AND or MND to more severe forms of HAND or whether these disorders are reversible. The best treatment is also not yet known. What can be recommended presently is that patients with HAND be commenced on ART. There is some evidence that there is a modest improvement in neurocognitive performance after one year of successful ART treatment and that medication that had a greater penetrance into the CNS may cause a greater effect (26) (80). However, there are also other studies that suggest that ART with higher CPE scores may be associated with neurotoxicity and thus evidence is not conclusive at present (80) (76). A South African study by Cross et al did suggest that after one year of being initiated on ART following the National Guidelines, namely TDF, 3TC and EFV/NVP, that neuropsychological testing either improved or remained static, suggesting a protective effect in some individuals with HAND (76). It is important to always consider other causes of cognitive decline in patients before attributing it to HAND. This would include metabolic syndromes that can lead to vascular dementia, which would be important in patients on both ART and psychotropic medications that are known to cause metabolic syndrome. If a patient is on ART and still has cognitive

deterioration, it may be prudent to switch to a regimen which has a higher CPE index. There is no evidence to suggest that starting ART may prevent HAND and therefore it cannot currently be recommended that patients with normal cognitive functioning be started on ART prophylactically or that they are started on ART with a higher CPE index as prophylaxis (81). Thus, there are still many unanswered questions with regard to ART and HAND, which suggests that individualised care by an experienced physician may be the most appropriate care for these patients while the medical community awaits further evidence to guide prescribing practices.

### 2.6.6 ART CHOICE AND PSYCHOTROPIC MEDICATIONS

Finally, in terms of drug choices, one also has to look at what medications are chosen to treat the mental disorders in patients who are known with HIV. As stated earlier, it is known that HIV increases the likelihood of mental illness. The prevalence rates of depression in patients with HIV are 20-80%, depending on the study (29). Numerous studies have been done to look at the most effective antidepressants to use in this scenario. Currently there are no specific recommendations as to which drug to use but review of the studies does give important information about medication choice. The tricyclic antidepressants have been shown to be effective over numerous studies; however, there was a high drop-out rate due to adverse events related to the cholinergic effects (31) (32). The selective serotonin re-uptake inhibitors have been shown to be well tolerated and effective treatment for depression in HIV (31) (32). However, once again, drug interactions must be considered, with Fluoxetine being known to activate the cytochrome P450 system and therefore there

may be interactions, specifically with protease inhibitors and NNRTI's. From the literature, there have been case reports of serotonin syndrome linked to the use of Fluoxetine with ART, which underlies the importance of always checking on the possible drug interactions (34). More recent, smaller studies have shown the newer agents such as Venlafaxine are effective with possibly fewer side effects, which should be taken into consideration (32) (34). The serotonin-noradrenaline reuptake inhibitors may also be preferable due to the fact that they also act on pain symptoms, which can be also be a problem in patients with HIV. Mirtazapine has also had some successful small trials with the sedative effects helping with fatigue symptoms during the day (34). Thus the common depressive symptoms seen in HIV can be successfully treated with medication with careful consideration of side effects.

On the other spectrum of the mood disorders, patients can present with mania and may require a mood stabiliser. Previously it was believed that Valproate may cause the viral load to increase and so it was used with caution (83) (34). From there though, a more recent study then showed that it may actually help to eradicate viral reservoirs (84). However, from this proof-of-concept study, further research was done which then showed that Valproate did not deplete HIV reservoirs but it is beneficial in that it does not have significant drug interactions (85). Carbamazepine on the other hand has multiple drug interactions and should be avoided. It can cause induction of the liver CYP3A enzyme system and therefore decreased levels of some antiretrovirals such as Indinavir (34). Conversely, other ART, specifically Ritonavir, also inhibit the same enzyme system in the liver which can lead to decreased metabolism of Carbamazepine and therefore increased risk of toxicity (83). Lithium is often used in mania; however in patients with HIV there is some concern due to

the possibility of HIV nephropathy which would increase incidence of Lithium toxicity, especially when used in conjunction with Tenofovir which is also renally excreted. Early reports of its use in severely immunocompromised patients before HAART suggested that some patients seemed to have widely ranging levels of Lithium (86) and that the drug was poorly tolerated in late-stage illness due to side effects, including greater sensitivity to neurocognitive adverse effects (87). Thus it is used with caution and close monitoring, especially with Tenofovir.

In patients with psychosis, the newer atypical antipsychotics are preferred because there appears to be an increased risk of extra-pyramidal side effects with typical agents in patients with HIV infection (41) (37). The exact cause of this increased sensitivity is not known, but it may be due to the subcortical pathological changes that occur in HIV (87). While atypical antipsychotics are favoured, there is however an increasing concern about the effect of the metabolic syndrome on these patients in the long term, as patients are now living longer on ART. Both the atypical antipsychotics, most notably Olanzapine and Clozapine, and some of the ART medication, specifically the protease inhibitors, cause weight gain, dyslipidaemia and diabetes (86). Clozapine is also generally not recommended in these patients due to the risk of bone marrow suppression, which may confound an already compromised bone marrow due to the HIV infection itself. Olanzapine drug levels may also be significantly affected by concomitant use of protease inhibitors because the Ritonavir used to boost the protease inhibitors induces the CYP1A2 enzyme system, which can potentially lead to a decrease in the Olanzapine levels (88). It is important to note that there is a scarcity of literature on antipsychotic use in HIV infection, but that reviews on the topic suggest that

Risperidone appears to be effective and well tolerated (87). All the above factors need to be taken into consideration when choosing the psychiatric medication used in these patients.

From the above review of the relevant literature, it is evident that psychiatric illness and HIV are highly co-morbid diseases that impact on each other's treatment and outcome significantly. There is also a paucity of literature from South Africa on certain areas of this dual diagnosis dilemma that would benefit from further investigation. Specifically, there are limited recommendations on the use of ART and psychotropic medication together. Therefore, the aim of this study is to describe the antiretroviral treatment prescribed to a group of HIV positive mentally ill patients and to ascertain if prescriptions were in conflict with the National Guidelines for the general population and the reasons thereof. However, there may be deviations related to factors discussed above, which will provide valuable insight into the care of this specialised group of patients.

# CHAPTER THREE: METHODS

## 3.1 STUDY DESIGN

This study was a retrospective record review.

## 3.2 STUDY POPULATION

The study population consisted of all new adult patients with a dual diagnosis of HIV and a mental illness that attended the Luthando Clinic at Chris Hani Baragwanath Hospital from 1st April 2010 until 30th August 2012. The rationale behind the commencement date was because this was the date that the South African Government changed the National Guidelines for all adults to include TDF instead of Stavudine (D4T) as the first line treatment.

### 3.2.1 INCLUSION CRITERIA

- Patients had to have a positive diagnosis of HIV infection
- Patients had to be over the age of 18 and under 65 years of age
- They had to be ART naïve at time of referral to Luthando Clinic and started on ART during the study period
- There had to be psychiatric diagnosis that was based on the Diagnostic and Statistical Manual (DSM)-IV criteria

### 3.2.2 EXCLUSION CRITERIA

- Patients who were started on ART from another site before referral to Luthando Clinic, at any point in time
- Patients who were not started on ART during the study period

- There were no exclusion criteria based on the psychiatric diagnosis, associated medical illnesses or medications prescribed

### 3.2.3 SAMPLE SIZE

An estimated required sample size for adequate power was calculated to be 340. The expected sample size, based on patient records at Luthando Clinic, was 299 new patients during this study period. However, the actual sample size at the end of the data collection was 196 patients, after patients were excluded for various reasons.

## 3.3. DATA COLLECTION

The names and hospital numbers of all patients who attended the Luthando Clinic during the study period and were initiated on ART were accessed, using the Luthando database. Some of the information was available on the database itself. For the remaining required information, the files were accessed from the Luthando clinic filing system.

From this source, information on the following variables was obtained:

- Demographic characteristics: (Age, gender, marital status, employment status, social assistance status)
- Clinical characteristics: (CD4 count at first visit, viral load at first visit, WHO staging on initial assessment, alcohol use, medical co-morbidities such as Tuberculosis (TB), current psychiatric diagnosis using the DSM IV criteria for diagnosis)
- Psychotropic medication prescribed
- ART medication prescribed

- Compliance with National Guidelines for first-line treatment and reasons for prescriber-initiated deviations, if any

Those patients who were initiated on first-line Antiretroviral Treatment as recommended by the South African Government, namely TDF, 3TC and either EFV or NVP, were said to be prescribed medication following National Guidelines and therefore the prescription was compliant with Guidelines (henceforth to be known as the NG group). Those who were started on any other combination of Antiretroviral Treatment were said to have non-compliant prescriptions (henceforth to be known as the non-NG group) and thus the demographics, clinical characteristics and psychotropic medication were compared between these two groups.

The information was recorded on a data collection sheet (Appendix 1). From there, it was captured onto a Microsoft Office Excel data sheet and coded for the purposes of analysis.

## 3.4. DATA ANALYSIS

The quantitative analysis of the data comprised of three elements: calculation of descriptive statistics, simple bivariate tests of association and a multivariate logistic regression analysis.

Descriptive statistics: The first stage of the quantitative analysis was simply to summarise the data derived from the study, i.e. the demographic data and clinical data. Key descriptive statistics presented include frequencies (count and percentages) and summary statistics (means and standard deviations).

Bivariate analysis: The second stage of the analysis involved bivariate tests of association. Pearson's $X^2$ test or Fisher's exact test were used to assess the relationships between categorical independent variables (IVs) and deviations from the National Guidelines. T-tests (or the Wilcoxon rank sum test for skewed variables) were used to assess the relationships between the continuous IV's and deviations from the National Guidelines.

Multivariate analysis: The determination of factors associated with deviation from the National Guidelines was done by logistic regression, using the binary variable National Guidelines as the dependent variable (DV), and all the other variables as independent variables. Given the large number of IVs, univariate logistic regression was first performed with each IV separately. Those variables with no cases in one of the two National Guidelines groups, which would lead to quasi-complete separation of data points in the logistics regression analysis, were omitted. (Note also that the <=50 and 50-100 categories for CD4 count were combined to avoid having no patients in the group that was not prescribed National Guidelines for the 50-100 category.) Variables with a Wald statistic significant at $p<0.20$ were retained for multivariate analysis. The retained variables were:

- Gender
- Age category
- CD4 category
- Anaemia
- On TB treatment
- Diagnosis: HIV-associated Neurocognitive Disorder
- Psychiatric medication: None

Multiple logistic regressions were performed to determine the best-fit model using the independent variables from the univariate regression models. Independent variables that were not found to be significant at $p< 0.05$ were subsequently removed, and regression was again performed without the non-significant independent variables. Goodness-of-fit statistics (AIC and SC) were compared between models to determine whether the removal of non-significant variables improved model fit. The process of removing non-significant covariates continued until all covariates were significant at $p<0.05$. 95% confidence intervals (CI) were computed for the odds ratios (OR) in testing the measure of association.

Some of the independent variables retained from the univariate analysis were significantly associated with each other and so they could not be included in the multivariate model at the same time, in order to avoid the effects of multicollinearity. The combinations of variables which could not be used together were:

- CD4 category and On TB treatment
- Anaemia and On TB treatment
- On TB treatment and Anaemia, CD4 category

Accordingly several models were run, using suitable subsets of the nine variables retained from the univariate analysis.

All analyses were done using the Microsoft Office Excel 2010 and Statistical Analysis Software (SAS) (89).

The 95% confidence level was used throughout, unless specified otherwise.

## 3.5. ETHICAL CONSIDERATIONS

Authorisation to conduct the study was obtained from the management at Chris Hani Baragwanath Hospital and the Research Committee at CHBH. Permission was obtained from University of the Witwatersrand Human Research Ethics Committee (Clearance certificate number M111116). As the study was retrospective in nature, informed consent from study participants was not required. The patients' personal details remained anonymous and confidential and were not recorded on the data collection sheet. A separate register with the patient's name and a corresponding subject number was kept.

# CHAPTER FOUR: RESULTS

## 4.1 SAMPLE CHARACTERISTICS

During the study period of April 2010 until August 2012, there were 299 new patients attending the Luthando Clinic. However, once patients who were already initiated on ART elsewhere were excluded, the number decreased to 247 patients. On reviewing the records, a further 44 patients were excluded for not meeting the above requirements. Two patients were found to be HIV negative on repeat testing, three patients had no psychiatric diagnosis, 10 patients died before they were commenced on ART, 13 were lost to follow-up (LTFU) before they could be started on ART, 11 were not started on ART before the end of the study period and five were transferred to another site before they were started on ART. As this was a retrospective study, there were also administrative errors and five files could not be found and two files had incomplete documentation and therefore could not be included in the data analysis. The final analysis was thus based on 196 patients.

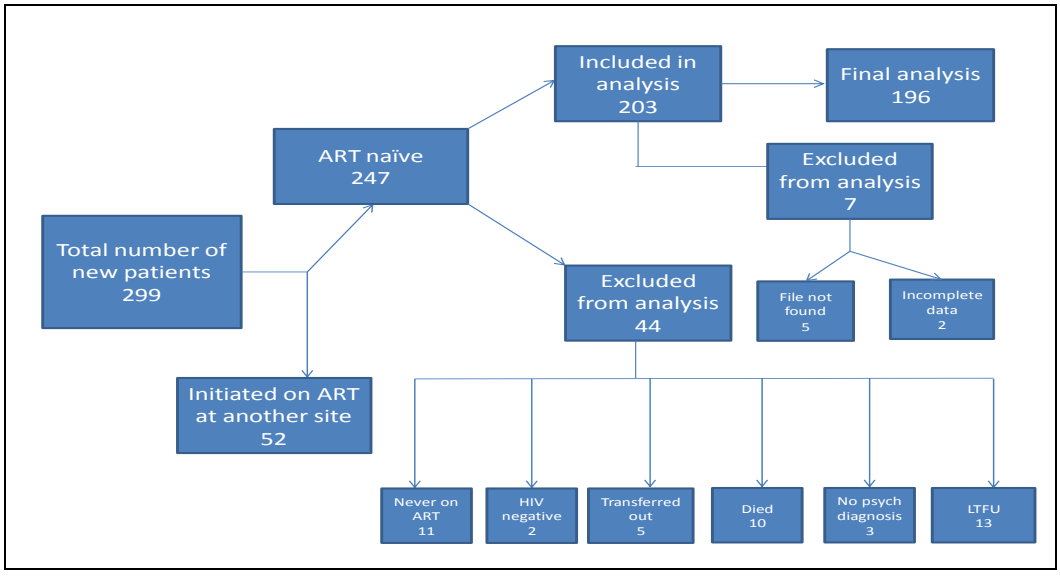



**Figure 4.1** Flow Chart outlining all new patients attending Luthando Clinic for the period of 1st April 2010 to 30th August 2012

## 4.2 DEMOGRAPHIC CHARACTERISTICS

After the 196 patient demographics were evaluated, the general population of patients attending the Luthando Clinic during the study period could be described. The median age of patients in this study was 36 years with an interquartile range (IQR) of 30.5-43.2. The majority of patients were female, with a total of 134 females out of the total of 196 (70%). Most patients were single (69%) and a further 18% were married. The unemployment rate was 153 patients out of the 196 total number (78%) and 48% of patients were receiving no social assistance in the form of government grants. Only 26% of patients were receiving a disability grant and 3% were eligible for a pension. Thus, in general, the population attending Luthando Clinic at this time can be summarised as being mostly female, single, unemployed and in their thirties.

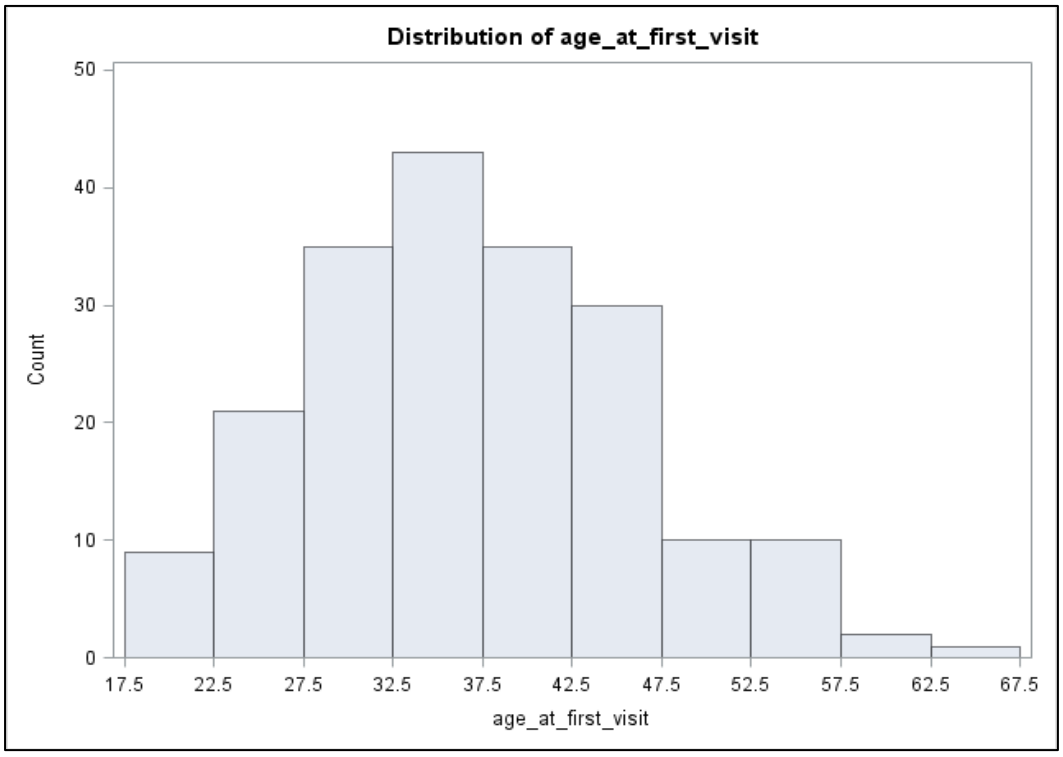



**Figure 4.2** Age distribution at first visit (years)

The data was then divided into patients that were initiated onto ART that followed the National Guidelines and those who were initiated on other regimens that deviated from the National Guidelines. When looking at these two groups, there was one aspect of the demographic characteristics in which they differed. This was that the age in years of the group not on the first-line recommended regimen was significantly higher than that of the other group (***T*** test 39.3 with IQR 33.2-45.5 versus 35.4 with IQR 29.8-42.1, $p < 0.019$) . The following table gives a more detailed breakdown of the results discussed above.

**Table 4.1** Demographic Characteristics of the Study Population with Comparison between those on an ART regimen following the South African National Guidelines and those in the non-NG group

| | | Overall | | ART regimen followed National Guidelines | | ART regimen did NOT follow National Guidelines | | p-value for $H_0$: no significant difference between groups |
|---|---|---|---|---|---|---|---|---|
| | | (n=196; 100%) | | (n=158; 80.6%) | | (n=38; 19.4%) | | |
| | | n | % | n | % | N | % | |
| Gender | Male | 58 | 29.6 | 42 | 26.6 | 16 | 42.1 | 0.075 |
| | Female | 138 | 70.4 | 116 | 73.4 | 22 | 57.9 | |
| Age in years (mean ± 95% CI); median (interquartile range) | | 37.0 ± 1.3y 36.2 (30.5 - 43.2) | | 36.3 ± 1.4 35.4 (29.8 - 42.1) | | 40.1 ± 3.0 39.3 (33.2 - 45.5) | | 0.019* (T-test) |
| Marital Status | Single | 136 | 69.4 | 110 | 69.6 | 26 | 68.4 | 0.25 |
| | Married | 36 | 18.4 | 31 | 19.6 | 5 | 13.2 | |
| | Separated | 3 | 1.5 | 3 | 1.9 | - | - | |
| | Divorced | 10 | 5.1 | 7 | 4.4 | 3 | 7.9 | |
| | Widowed | 5 | 2.6 | 3 | 1.9 | 2 | 5.3 | |
| | Steady Partner | 4 | 2.0 | 2 | 1.3 | 2 | 5.3 | |
| | Unknown | 2 | 1.0 | 2 | 1.3 | - | - | |
| Employment Status | Employed | 42 | 21.4 | 35 | 22.2 | 7 | 18.4 | 0.67 |
| | Unemployed | 153 | 78.1 | 122 | 77.2 | 31 | 81.6 | |
| | Unknown | 1 | 0.5 | 1 | 0.6 | - | - | |
| Social Assistance | Pension | 6 | 3.06 | 6 | 3.8 | - | - | 0.43 |
| | Child Support | 35 | 17.9 | 31 | 19.6 | 4 | 10.5 | |
| | Disability | 50 | 25.5 | 37 | 23.4 | 13 | 34.2 | |
| | Other | 10 | 5.1 | 8 | 5.1 | 2 | 5.3 | |
| | No Assistance | 93 | 47.5 | 74 | 46.8 | 19 | 50.0 | |
| | Unknown | 2 | 1.0 | 2 | 1.3 | - | - | |
| *= statistically significant | | | | | | | | |

## 4.3 CLINICAL CHARACTERISTICS

Overall, the median CD4 count for the entire group was 166cells/$mm^3$ (IQR 82-281), with the majority of patients (34%) having a CD4 count in the range of 201-350cells/$mm^3$, followed by 26% of patients having a CD4 between 101-200cells/$mm^3$. Those with the lowest CD4 count of <50cells/$mm^3$ made up 17% of patients, while those with the highest CD4 count of >350cells/$mm^3$ numbered 20 of the total population (10%). The frequency distribution of the CD4 counts is shown below.

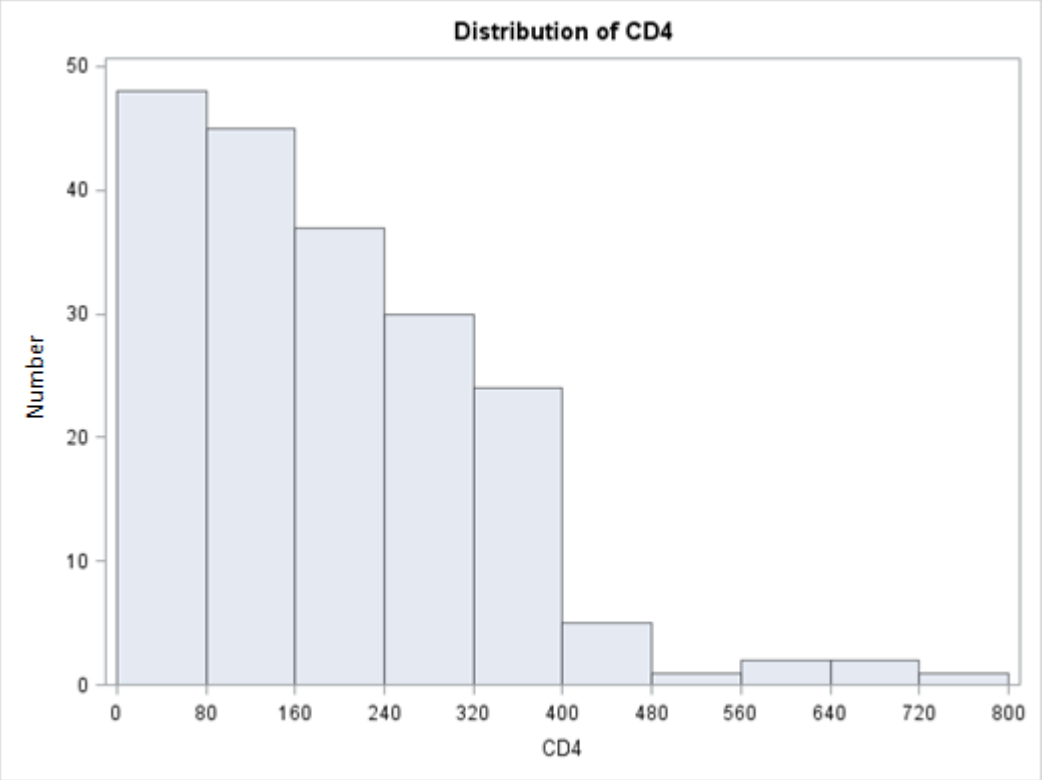



**Figure 4.3** Distribution of CD4 count across the entire Study Population (cells/$mm^3$)

The majority of patients were staged as Stage 4, according to the WHO guidelines, at the initial visit (n=96, 49%). The mean patient weight was 64.1 ± 2.1 kg. One quarter of the

patients were smokers and only 1% of the patients consumed levels of alcohol which corresponded to alcohol abuse, according to self-reports.

**Table 4.2** Clinical Characteristics of the Study Population with Comparison between the NG and the non-NG Groups

| | | Overall | | ART regimen followed National Guidelines | | ART regimen did NOT follow National Guidelines | | p-value for $H_0$: no significant difference between groups |
|---|---|---|---|---|---|---|---|---|
| | | (n=196; 100%) | | (n=158; 80.6%) | | (n=38; 19.4%) | | |
| | | N | % | N | % | N | % | |
| Smoker status | Smoker | 50 | 25.5 | 40 | 25.3 | 10 | 26.3 | 1.00 |
| | Non-smoker | 144 | 73.5 | 116 | 73.4 | 28 | 73.7 | |
| | Unknown | 2 | 1.0 | 2 | 1.3 | - | - | |
| Alcohol abuse | Alcohol abuse | 2 | 1.0 | 2 | 1.3 | - | - | 1.00 |
| | No alcohol abuse | 192 | 98.0 | 154 | 97.5 | 38 | 100.0 | |
| | Unknown | 2 | 1.0 | 2 | 1.3 | - | - | |
| Weight at first visit in kg (mean ± 95% CI); median (interquartile range) | | 64.1 ± 2.1<br>62.5 (54.0-72.0) | | 63.2 ± 2.3<br>61.0 (54.5-71.0) | | 67.6 ± 6.0<br>64.5 (54.0-75.0) | | 0.17 (t-test) |
| CD4 count in cells/$mm^3$ (mean ± 95% confidence interval); median (interquartile range) | | 191 ± 20<br>166 (82.0-281.0) | | 176 ± 18<br>163 (75.0-261.0) | | 255 ± 66<br>235 (109-373) | | 0.044* (Wilcoxon signed rank test) |
| Viral Load in copies/$mm^3$ | < 50 | 4 | 2.0 | 2 | 1.3 | 2 | 5.3 | 0.21 |
| | 50-1000 | 5 | 2.6 | 4 | 2.5 | 1 | 2.6 | |
| | > 1000 | 168 | 85.7 | 137 | 86.7 | 31 | 81.6 | |
| | Unknown | 19 | 9.7 | 15 | 9.5 | 4 | 10.5 | |
| WHO Disease Stage | 1 | 8 | 4.1 | 6 | 3.8 | 2 | 5.3 | 0.71 |
| | 2 | 43 | 21.9 | 33 | 20.9 | 10 | 26.3 | |
| | 3 | 49 | 25.0 | 42 | 26.6 | 7 | 18.4 | |
| | 4 | 96 | 49.0 | 77 | 48.7 | 19 | 50.0 | |
| *= statistically significant | | | | | | | | |

Of interest from the above tabled information is that four patients had a baseline viral load of less than 50 copies/mm$^3$. One would expect patients who are ART naïve to have much higher viral loads. When the total population was then divided into those patients who were prescribed ART that followed the National Guidelines and those who were not, there were only two areas in which there were statistically significant differences between the groups. The median CD4 count for those in the non-NG group (255cells/mm$^3$) was higher than that of those who were following Guidelines (176cells/mm$^3$), which had a significant difference and a p value of 0.044. Added to this, the non-NG group had a higher proportion of patients in the >350 CD4 count category. The graph below shows the distribution of CD4 counts across the two groups.

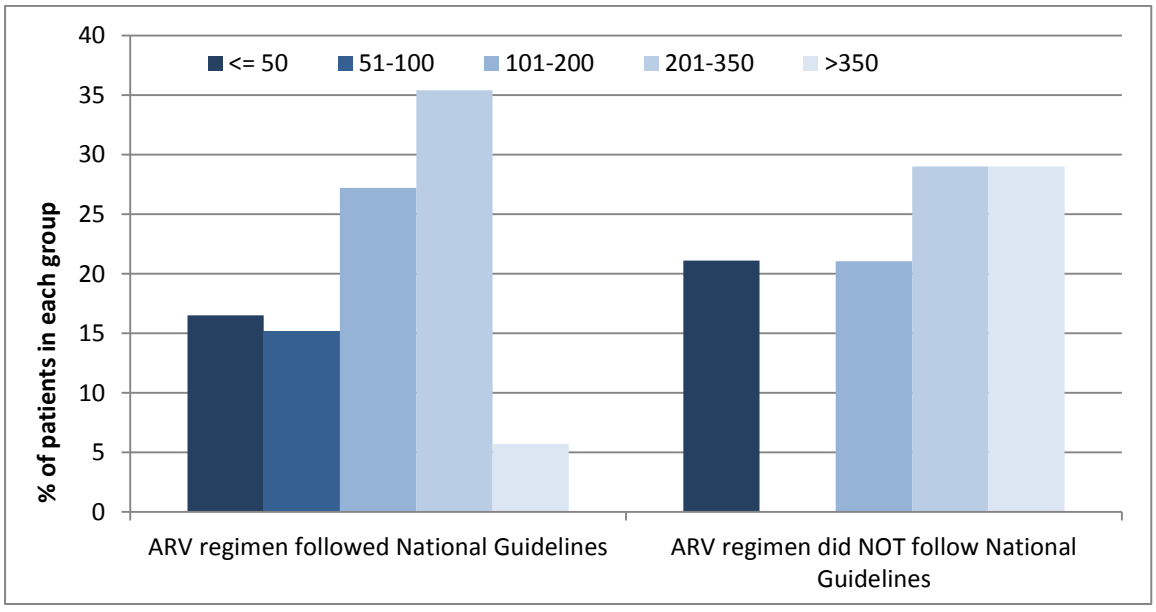



**Figure 4.4** Distribution of CD4 count (cells/mm$^3$) across the two Study Population Groups; the NG group and the non-NG group

In terms of medical co-morbidities, most of the patients had no other medical conditions (61%), while the most prominent medical condition amongst those who did have another diagnosis was TB, with 18% of patients being on TB treatment at the initial visit. Anaemia was the second most common disorder, with almost 11% of the study population being diagnosed with anaemia. There were only a small proportion of patients diagnosed with chronic Hepatitis B or C (2%). For only one condition, renal dysfunction, was there a significant difference between the two groups. All six cases of renal dysfunction were part of the non-NG group. However, it is important to note that the overall rate of renal dysfunction was low within the total sample.

The table below gives further information on all the medical conditions diagnosed in the study population.

**Table 4.3** Medical co-morbidities of the Study Population

| | | Overall | | ARV regimen followed National Guidelines | | ARV regimen did NOT follow National Guidelines | | p-value for $H_0$: no significant difference between groups |
|---|---|---|---|---|---|---|---|---|
| | | (n=196; 100%) | | (n=158; 80.6%) | | (n=38; 19.4%) | | |
| | | N | % | N | % | N | % | |
| Other medical conditions | None | 120 | 61.2 | 101 | 63.9 | 19 | 50.0 | 0.14 |
| | TB | 33 | 16.8 | 29 | 18.4 | 4 | 10.5 | 0.34 |
| | Anaemia | 21 | 10.7 | 14 | 8.9 | 7 | 18.4 | 0.14 |
| | Epilepsy | 10 | 5.1 | 10 | 6.3 | - | - | 0.21 |
| | Renal Dysfunction | 6 | 3.1 | - | - | 6 | 15.8 | < 0.0001 |
| | Neutropenia | 7 | 3.6 | 7 | 4.4% | - | - | 0.35 |
| | Meningitis | 3 | 1.5 | 2 | 1.3 | 1 | 2.6 | 0.48 |
| | Hypertension | 3 | 1.5 | 2 | 1.3 | 1 | 2.6 | 0.48 |
| | TB Meningitis | 3 | 1.5 | 2 | 1.3 | 1 | 2.6 | 0.48 |
| | Herpes Zoster | 3 | 1.5 | 3 | 1.9 | - | - | 1.00 |
| | Oral candida | 3 | 1.5 | 3 | 1.9 | - | - | 1.00 |
| | Neurosyphilis | 2 | 1.0 | 1 | 0.6 | 1 | 2.6 | 0.35 |
| | Diabetes Mellitus | 2 | 1.0 | 1 | 0.6 | 1 | 2.6 | 0.35 |
| | Hypothyroidism | 2 | 1.0 | 1 | 0.6 | 1 | 2.6 | 0.35 |
| | Hepatitis B | 2 | 1.0 | 1 | 0.6 | 1 | 2.6 | 0.35 |
| | Hepatitis C | 1 | 0.5 | 1 | 0.6 | - | - | 1.00 |
| | Stroke | 1 | 0.5 | - | - | 1 | 2.6 | 0.19 |
| | Cysticercosis | 1 | 0.5 | 1 | 0.6 | - | - | 1.00 |
| | Rheumatoid arthritis | 1 | 0.5 | 1 | 0.6 | - | - | 1.00 |
| | Systemic Lupus Erythematosus | 1 | 0.5 | 1 | 0.6 | - | - | 1.00 |
| | Salmonella sepsis | 1 | 0.5 | - | - | 1 | 2.6 | 0.19 |
| | Thrombocytopenia | 1 | 0.5 | - | - | 1 | 2.6 | 0.19 |
| | Huntington's Disease | 1 | 0.5 | - | - | 1 | 2.6 | 0.19 |
| | Chronic Diarrhoea | 1 | 0.5 | 1 | 0.6 | - | - | 1.00 |
| | Kaposi's sarcoma | 1 | 0.5 | 1 | 0.6 | - | - | 1.00 |
| | Polio | 1 | 0.5 | 1 | 0.6 | - | - | 1.00 |
| | Deep Vein Thrombosis | 1 | 0.5 | 1 | 0.6 | - | - | 1.00 |
| *= statistically significant | | | | | | | | |

### 4.3.1 PSYCHIATRIC DIAGNOSIS

The most common diagnosis in the total population was mood/psychosis secondary to HIV, with 79 patients out of the total study population having this diagnosis. Psychosis secondary to HIV was the next most common, with 40 patients having been diagnosed with this. The most common primary psychiatric disorder diagnosis was Bipolar Mood Disorder, but interestingly, this was only 27 patients out of the total study population, showing that secondary psychiatric disorders were more common. Only 15 patients were diagnosed with Major Depressive Disorder and no patients were given a diagnosis of Anxiety Disorder in this sample. HAND was diagnosed in 34 patients out of the total population. There were four patients who were diagnosed with psychosis/mood disorder or mood disorder secondary to a general medical condition (GMC). Unfortunately it was not always described in the files what the GMC was. One patient did have psychosis/mood disorder secondary to SLE documented in the file. The diagnoses are presented below, divided into primary and secondary psychiatric diagnosis. Note that percentages were not used since some patients had more than one diagnosis and therefore they would not sum to 100%.

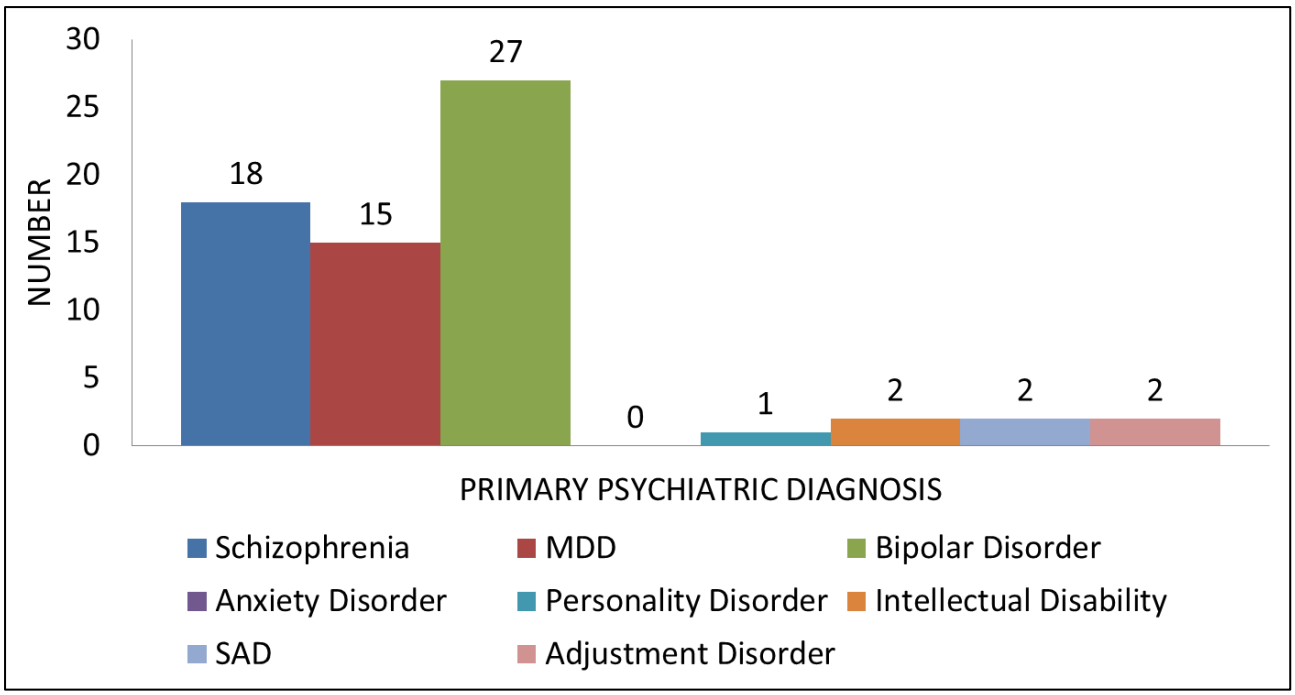



**Figure 4.5** Range of Primary Psychiatric Diagnoses In the Study Population

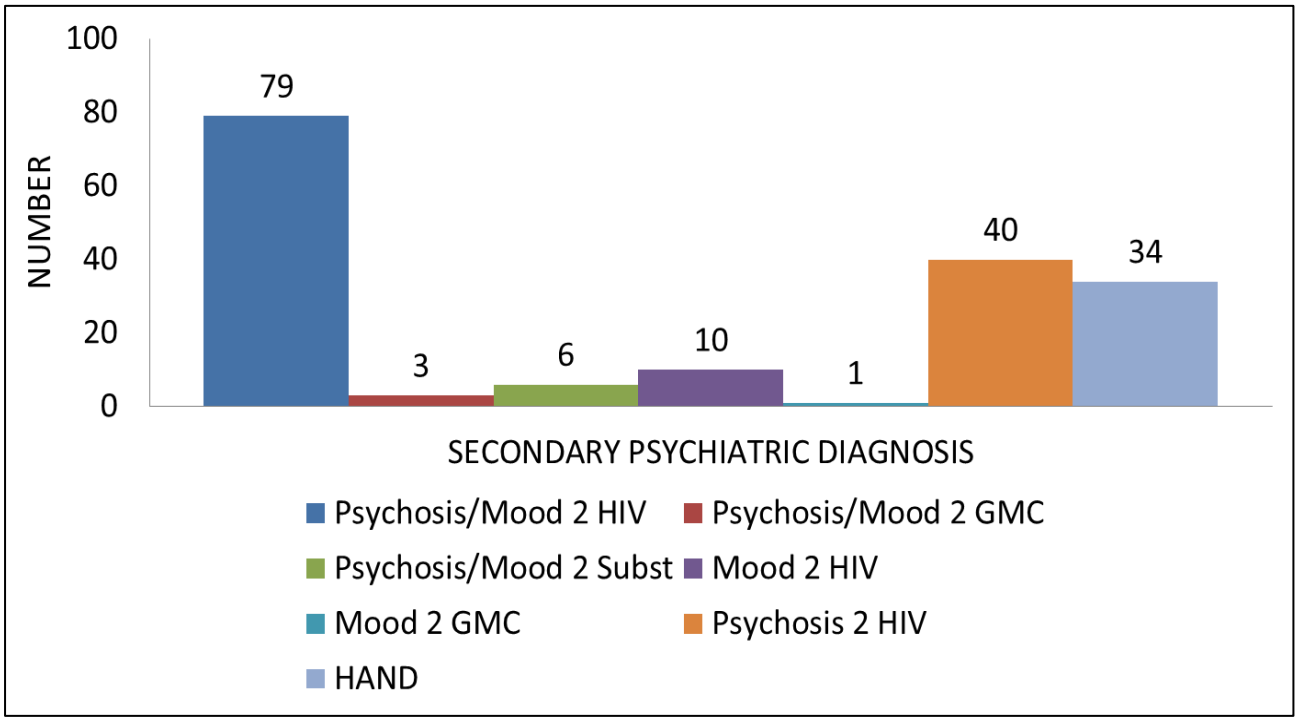



**Figure 4.6** Range of Secondary Psychiatric Diagnoses in the Study Population

When comparing the two groups, the most important finding was for the diagnosis of HAND. There was a significant difference ($p<0.001$), with 15 out of 158 patients prescribed the National Guidelines and 19 out of 38 of those not prescribed the National Guidelines being diagnosed with HAND, which showed that significantly more patients diagnosed with HAND were not prescribed ART that was suggested as first-line therapy.

### 4.3.2 PSYCHOTROPIC MEDICATION

The majority of patients in the study were on Risperidone (n=138, 70%) and then Valproate (n=85, 43%). There was also a high percentage of patients using Citalopram (n=32, 16%). In general, very few patients were prescribed typical antipsychotics with only one patient on a typical depot injection and 13 patients using Haloperidol (7% of the population). No patients were prescribed Clozapine during the study period and only five patients were started on Lithium (3% of study population). There was no significant difference between the two groups in terms of psychiatric medication prescribed.

## 4.4 ART MEDICATION

The ART regimens of 81% of the patients followed the National Guidelines, namely TDF, 3TC and either EFV or NVP, while those of 38 patients (19%) did not. In total, 77% of the patients were on ART regimes containing EFV. This comprised 82% of the patients in the National Guidelines group and 55% of those not following National Guidelines. Those patients started on a regimen other than the first line National Guidelines recommendations fell into another ten categories of combinations of ART. Therefore, as there were only 38 patients in

this group, there was insufficient power to perform any further analysis on each of these combinations.

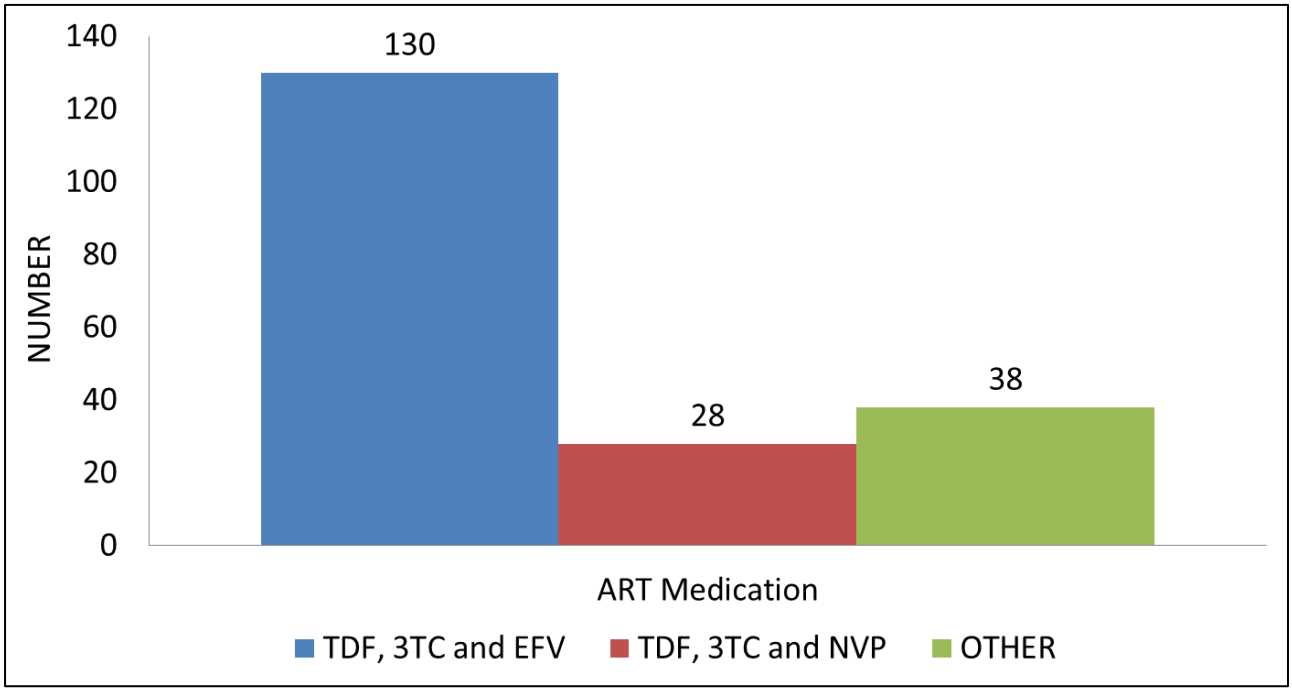



**Figure 4.7** ART Medication prescribed for the Study Population

## 4.5 FURTHER ANALYSIS

From the multiple logistic regression model looking at difference between the group of patients on prescriptions following National Guidelines and those not, males were 2.7 (1.1-6.5) times more likely to be in the non-NG treatment group than females, controlling for the other variables in the model. (Odds ratio=2.7; 95% CI 1.1-6.5)

The likelihood of being in the non-NG group increased with increasing CD4 count, compared to the <100cells/mm$^3$ CD4 count category (controlling for the other variables in the model).

It was 1.4 times more likely for the 101-200cells/mm$^3$ and 201-350cells/mm$^3$ CD4 categories to be in the group not following National Guidelines, and 12 times more likely for the >350cells/mm$^3$ CD4 category. (OR: 1.4 (0.41-4.6), 1.4 (0.45-4.4) and 12 (3.0-47) respectively). Patients with anaemia were 3.6 (1.1-12) times more likely to be in the non-NG treatment group than those without anaemia, controlling for the other variables in the model. The last variable to be shown to be important was patients with a diagnosis of HAND. They were 10.5 (4.1-27) times more likely to be in the non-NG treatment group than those without the condition, controlling for the other variables in the model. To illustrate the effect of these variables, the estimated probabilities are shown in the graphs below:

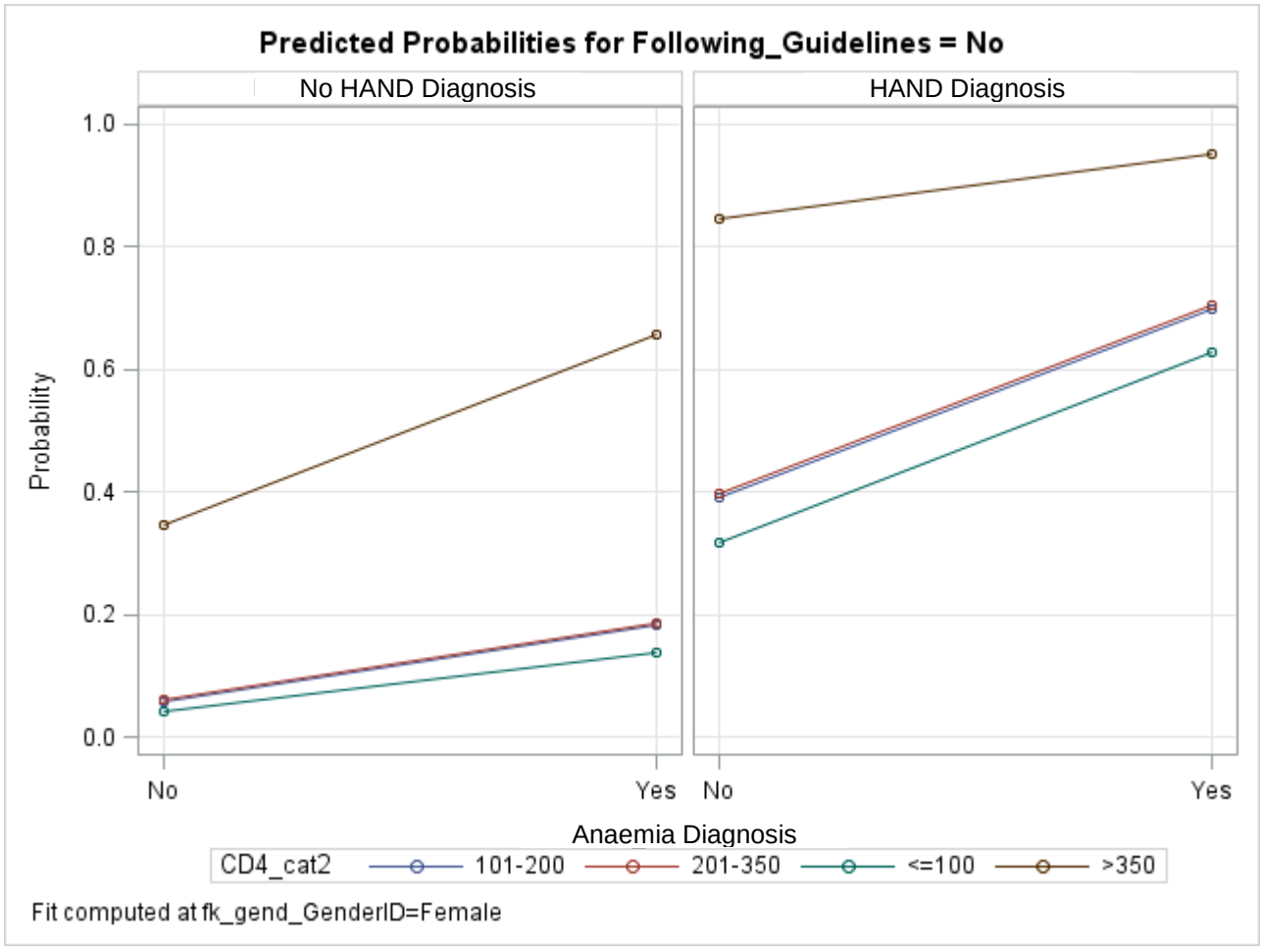



**Figure 4.8** Predicted Probabilities of the Patients Following the National Guidelines with respect to the diagnosis of HAND and anaemia and CD4 counts of patients

This graph demonstrates that patients with HAND and anaemia have a greater probability of being prescribed a regimen that does not follow the National Guidelines and that the probability is affected by the CD4 count as well, with those having a CD4 count >350cells/mm$^3$ having a greater probability of not being prescribed the first line adult regimen.

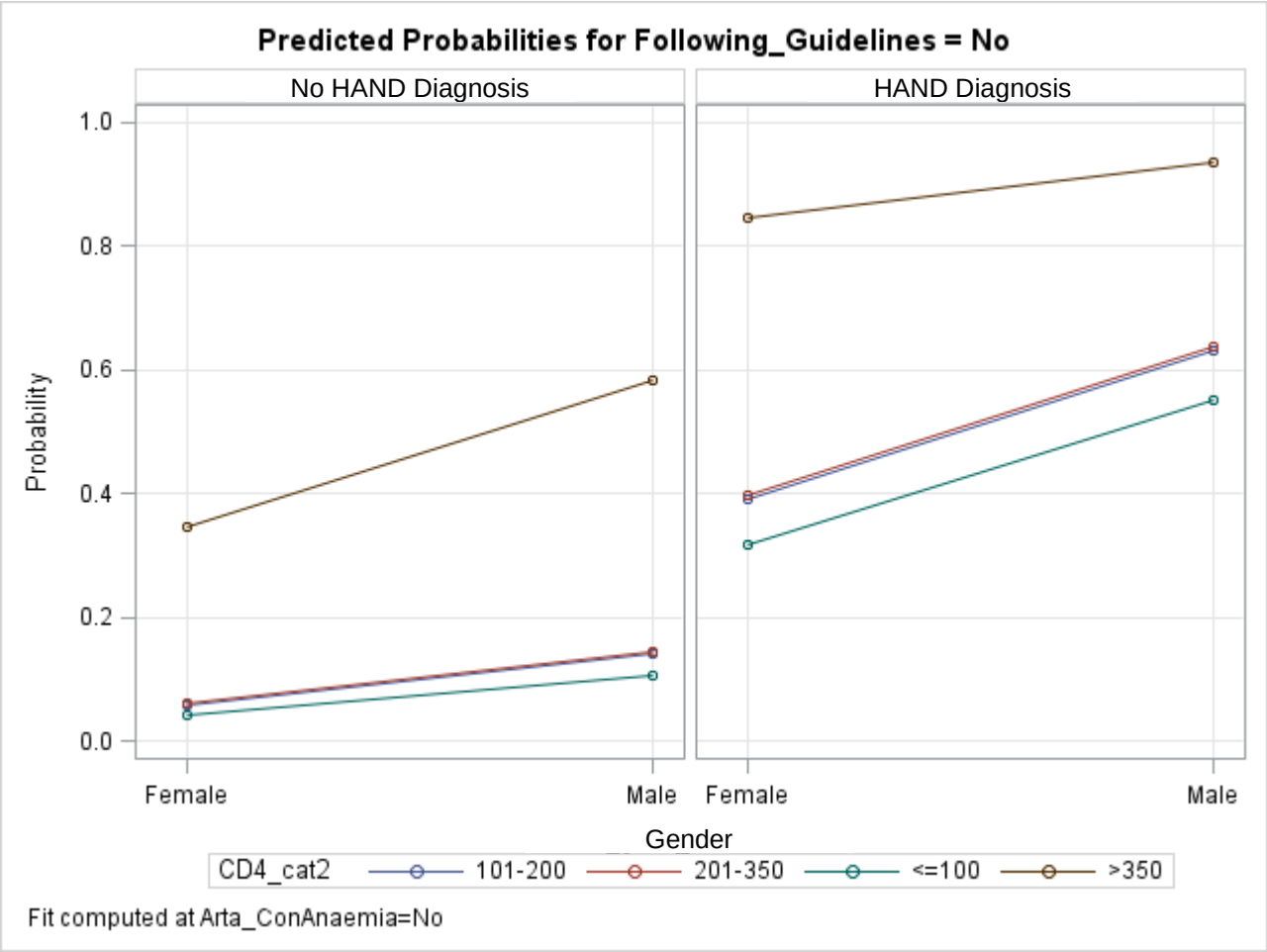



**Figure 4.9** Predicted Probabilities for the Patients following the National Guidelines with respect to the diagnosis of HAND, gender and the CD4 counts of the patients

This graph (Fig 4.9) shows that male patients with a diagnosis of HAND have a greater probability of being on a regimen other than that of the recommendations of National

Guidelines and that this probability is affected by the patient's CD4 count as well. Patients with a CD4 count of >350cells/$mm^3$, a diagnosis of HAND and being of male gender have the highest chance of not being prescribed the National Guideline recommendations.

# CHAPTER FIVE: DISCUSSION

This study has described the demographic and clinical characteristics of an out-patient population of patients with both HIV and mental illness. It has shown that there were a higher proportion of females attending the clinic than males, which is in keeping with other South African studies, but not overseas results (50) (90). It has demonstrated that patients at the clinic are still presenting late for treatment, with a median CD4 count of 166 cells/$mm^3$. There are also low levels of reported alcohol abuse, with only 1% of patients disclosing consumption of alcohol that met the definition for alcohol abuse. The most common diagnosis at the clinic was mood and psychosis secondary to HIV, suggesting that most patients were presenting with a psychiatric illness after being tested HIV positive and also pointing to the fact that HIV infection has important consequences in the brain. As hypothesised, most patients were initiated on a regimen that followed the National Guidelines (n=158, 81%). Interestingly, large proportions (77%) of patients were also initiated on EFV, even though they were presenting with psychiatric symptoms. Those that deviated from the National Guidelines were more likely to be male, have a higher nadir CD4 count, to have renal failure as a medical diagnosis and to have a psychiatric diagnosis of HAND. The meaning and implications of this will be discussed below.

## 5.1 DEMOGRAPHIC CHARACTERISTICS

The results of this study showed that the general population attending Luthando Clinic in Soweto, South Africa, can be described as middle-aged, female patients (70%). These results are in contrast to international studies from both developed and developing countries. The CDC in the USA reports that 79% of patients infected with HIV are male (90), which

corresponds with an Australian audit of a HIV clinic, which showed a 79% predominance of males at the clinic (91). Britain also has a larger number of male patients attending their clinics, with 54% being male (92). Interestingly, data from other developing countries such as China and India also shows a male predominance attending their HIV clinics, with the percentage of males being 59% attending clinics in a province in China (93) and 80% at clinics in a province in India (94). In contrast to this, studies from Southern Africa show a female predominance, with a study from Uganda having 64% of the study population being female (95). Recent studies from South Africa, mainly from Cape Town, also show more females attending HIV clinics, with a range of 70% to 78% of attendees being female (50) (51). However, an older study from the same region in Cape Town did show an increased number of males (61%) attending the clinics between 2002- 2005 (96), suggesting a changing demographic over the past ten years.

The reasons for this contrast between Africa and other countries can be hypothesised to be related to a number of factors. Firstly, the mode of transmission varies amongst these countries. South Africa is known to have mostly heterosexual transmission of HIV and, as discussed in the literature review, women are at greater risk of acquiring the infection because of biological factors. There are also psychosocial issues related to the increased risk for females, including high levels of inter-partner violence in South Africa, which increases the risk of transmission (52). Another factor to consider is that men may not be testing for HIV and therefore the prevalence may be biased towards those that know their status and may be under-representing males. In South Africa, women of reproductive age, the group known to have the highest incidence, are routinely offered HIV tests while they are

pregnant. There is often a high acceptance rate of the test because it is of benefit to their child, and so pregnant females are therefore more likely to test than other individuals. Men are known to have poorer health-seeking behaviour (97), and a study from Soweto, South Africa, showed that only 29% of males sampled had ever tested for HIV (54). The study participants were mostly young, Black males who were sexually active in the past six months. Thus, the predominance of females in this sample may be both because of their increased susceptibility to HIV infection (21), as well as psychosocial factors, including that men may not be testing and addressing their mental and physical health needs. It is in keeping with other studies from South Africa discussed above that also have large numbers of female attendees and thus adds to the literature that suggests that South Africa's demographics are different to other developed and developing countries, but possibly not to other countries within Africa.

Because there were a higher proportion of females in the study population as a whole, on further analysis of the group of patients who were prescribed ART that deviated from the National Guidelines, one would expect a higher number of females in this group as well. However, while there were more females, males made up 42% of the group, versus the group that were prescribed the National Guidelines, in which males made up less than 30%. This was not a statistically significant difference but is an interesting finding. The group not prescribed the National Guidelines was small; therefore it was not possible to look at factors within this group to shed light onto the characteristics that may have been affecting the increased proportion of men. However, 12 out of 16 men had a diagnosis of HAND versus 8 out of 21 females, which could be a contributing factor. When looking at international studies from both developed and developing countries focused on HAND, there does not

appear to be any significant difference between gender groups in terms of prevalence of HAND (98) (99). Interestingly though, a South African study showed that male gender was associated with an increased risk of HAND (100). This study had slightly more participants (283 in total) but again had a predominance of females at 74% of the group and still showed an increased number of men in the group with HAND. Thus, it was unclear why there is a predominance of males in this sample with the diagnosis of HAND and who then were prescribed ART regimens that deviated from the South African National Guidelines. It could be hypothesised that men are at greater risk for HAND in the South African population.

## 5.2 CLINICAL CHARACTERISTICS

When looking at the clinical characteristics of the study population, importantly, only 1% of the sample met the criteria for alcohol abuse and only 3% had a diagnosis of substance-induced psychosis. This is a very low number in comparison to both international and local studies. Internationally, most studies on substance use/abuse and HIV infection come from the USA. Studies from mostly out-patient clinics show a one year prevalence rate of 14% for alcohol abuse (101) and lifetime prevalence rates of substance use disorders ranging from 25% to 27% (47) (102). Studies from Cape Town also based on outpatients with both HIV and mental illness, showed rates of alcohol abuse ranging between 10 and 35% (30) (50). The reason for this deviation in the current study population was also not clear and needs to be investigated. One explanation could be that the screening for alcohol abuse is not standardised or sufficient enough and so patients are not being identified. If this were to be the case, it would be an important finding to come from the audit and would highlight the need for improved screening within the clinic setting. A South African study showed that the

AUDIT questionnaire had good specificity and sensitivity for detecting alcohol use disorders in a cohort of HIV positive out-patients (49) and so could be implemented to help improve diagnosis of this disorder in the Luthando Clinic population. It may also have been that information on other substance abuse was missing from file records and therefore not collected for this study. This could mean that patients were presenting with other substance abuse problems which were not accounted for and can be seen as a limitation to the study design. It also points to the fact that more research needs to be done in this important area in this study population, as lessons from developed countries have shown that substance abuse was a major issue. Alcohol abuse is known to increase the risk of HIV infection (44), and because it affects adherence, risky behaviour patterns and impacts on cognition (34). When looking at the two groups in the study, namely those prescribed the National Guidelines for ART versus those not prescribed these guidelines, there was no statistical difference between the two groups in terms of substance abuse. It is again important to note that the actual number of participants with this diagnosis was so small that there were only two participants in the group being prescribed the National Guidelines that met criteria for alcohol abuse. It would therefore be difficult to detect any meaningful differences between the groups.

Another interesting result was the association of anaemia with HAND and deviations in prescribing practices from the National Guidelines. Overall, 21 patients in the study were diagnosed with anaemia, with 9% being in the group that were prescribed ART in accordance with the National Guidelines and 18% being in the other group. The importance of anaemia in HIV is well established with numerous studies, both internationally and

locally, showing that patients with HIV are at increased risk of anaemia (103) and that anaemia itself is an independent risk factor for increased mortality amongst patients with HIV (104) (105). A study from India showed a prevalence of anaemia of 41%, with female gender being an increased risk factor (106), while a study from Nigeria showed that the prevalence of anaemia in a cohort of ART-naïve patients was 69%, but with male gender predicting increased risk (107). In South Africa, a study from a local clinic in Johannesburg showed a prevalence of anaemia in 53% of participants with HIV infection (108). Thus, the prevalence of anaemia of 10% in this study is quite low. The association of anaemia with male gender is in keeping with the Nigerian study but not with most other studies which show a female predominance (103) (106). The association between anaemia and HAND has not been evaluated in many studies. In an old study from the USA prior to ART, anaemia was a significant predictor of dementia in a male study sample (109) and in a study from Sub-Saharan Africa, there was a statistically significant risk of developing HAND if the patient's haemoglobin was less than 10g/dl (110). However, in a number of studies since then there has been no association between anaemia and HAND (82), including a study from South Africa (100). Thus, this finding from our study was difficult to interpret, especially as there were only a small proportion of patients that were diagnosed with anaemia. It may be a confounding factor related to the fact that the majority of patients were immunosuppressed, shown by the fact that the mean CD4 count in the group not being prescribed the National Guidelines was 255cells/$mm^3$. A consistent finding for factors related to the development of HAND is a low nadir CD4 count and so this could be a correlate related to that. The other hypothesis could be that it is related to the chronic inflammatory environment in the body due to the HIV infection. It is known that cytokines released during cell-mediated immune responses can lead to bone marrow suppression and

that as part of its defence mechanism against chronic inflammation; the body decreases the serum iron levels (111). This action is mostly macrophage mediated. While the pathogenesis of HAND is not yet fully understood, it is also believed to be linked to the infiltration by the HIV infection of macrophages in the CNS with the release of toxins causing chronic inflammation in the brain (26). Possibly the relationship between anaemia and HAND could be that they reflect similar pathogenesis in the peripheral system and central nervous system. However, further research is needed to ensure that this finding is of real significance and not merely due to chance.

From this study, it was shown that the majority of the patients attending the clinic had a diagnosis of mood and psychosis secondary to their HIV infection. A further 20% had a diagnosis of psychosis secondary to HIV. Interestingly, this does not seem to be a common presentation of patients in other developed countries, with most only having case reports of patients presenting with either acute psychosis or mania associated with delirium or end-stage disease (35) (41). Studies from other parts of Africa, specifically Uganda, seem to show a similar clinical presentation (33). In South Africa, this could be a more common presentation. There was one study from the Eastern Cape, looking at only the female population, which also demonstrated that the most common presentation was a maniform psychosis (112). In the current sample, this accounted for 40% of diagnoses in the clinic. With the limited data available, the neurobiological basis of this finding was difficult to ascertain. However, HIV infection is more prevalent in patients with severe mental illness and this is thought to be due to increased risk-taking behaviour during periods of relapse (34). Possibly these clinical features are because the patient population presented late, with

the median CD4 count in the study population being 166 cells/$mm^3$, which is classified as severe immunosuppression. There is literature to suggest that this clinical presentation is more common in late stage disease (35) (33) and that it may be due to neurotoxic effects of the virus on the brain (40). Another factor could be that there was a high rate of substance abuse leading to the psychiatric symptoms. This high rate of substance abuse was not detected in this study, but has been shown to be a factor in other studies from South Africa (30). Further research is required to look at the clinical presentation within South Africa as well as the rest of Africa and other developing countries, as a possible hypothesis may be that it could be linked to the clade of the virus or even socio-economic factors. Thus, the most common clinical presentation of patients at an out-patient clinic in Johannesburg, South Africa, was found to be a previous episode of maniform psychosis, which differs from international research.

The other interesting finding related to the types of diagnoses was that only approximately 8% of patients had a diagnosis of MDD and not a single patient was diagnosed with any type of anxiety disorder. This finding is in contrast to international studies with rates of depression exceeding 20% (29) and from a South African study which showed rates of 35% for depression and 15% for PTSD (30). The reason for this disparity was unknown but it could be speculated that patients may be more likely to present to a primary level psychiatric service with symptoms of depression associated with HIV rather than a tertiary level psychiatric clinic and therefore there is bias within the sample, with more severely ill patients presenting at Luthando Clinic.

From the data, it was shown that 77% of patients were started on a regimen containing EFV. This is an interesting finding because of the commonly held belief that patients with psychiatric symptoms should not be using this drug due to the increased rates of neuropsychiatric side effects. While there is theoretical evidence suggesting this (68), it would also seem to disadvantage this population by withholding a medication where the regimen is much simpler in terms of dosing, especially in a group who is on other medication to treat their mental illness already. Unfortunately as this was a retrospective review of only one time point, there is no information as to the outcome of prescribing EFV to this population. However, the study was done over a one and a half year period and so one would expect that if there had been multiple adverse events that the prescribing practice would have changed over time, which it did not appear to do.

There was one unexpected result in the clinical characteristics, which was that four patients had a viral load lower than detectable at baseline visit. Usually one would have an extremely high viral load prior to initiation of ART, especially in the study population, where the baseline CD4 was low. It is difficult to explain this result. It may be due to error in that the viral loads were taken after initiation but recorded as taken prior to initiation. The other possibility is that these patients could have been elite suppressors. Elite suppressors are patients who are able to control the virus without the use of ART, by an as yet unknown mechanism (113). However, this is extremely rare and so it would not be expected that there were four such patients in such a small sample size.

## 5.3 DEVIATIONS FROM NATIONAL GUIDELINES

There were some interesting indications that were shown when looking at the reasons for deviation from the National Guidelines. Firstly, 81% of patients were following the South African National Guidelines for initiation of ART in adults. This suggests that patients with mental illness can generally be started on the standard regimen and do not need to tailor their regimen due to drug interactions or drug side effect profile, which would be important information to make available to ART roll-out sites that may be unsure of management of these patients. However, there do appear to be subsets of patients that would need more personalised prescribing of medication and it would be important to refer these patients to specialised clinics.

From the group of patients who were not prescribed the South African National Guidelines, a proportion were also diagnosed with renal dysfunction and this result would be expected because the National Guidelines include TDF, which is contra-indicated in renal dysfunction. As the group not following National Guidelines was so small, analysis could not be carried out on variations within this group. It would appear though that the trend was towards those with renal dysfunction having lower nadir CD4 counts, with three out of the five patients having a CD4 count less than 50 cells/$mm^3$ and the other two patients having CD4 counts less than 300 cells/$mm^3$. One could speculate that these participants would have been more ill due to their severe immunosuppression and therefore had a higher risk of illness that could predispose to renal dysfunction, such as chronic diarrhoea. Thus this is an expected finding and confirms that the National Guidelines are being correctly followed, as patients with renal dysfunction are not being started on contra-indicated medications.

The most interesting finding was that those patients diagnosed with HAND were significantly more likely to be started on a regimen that did not follow the National Guidelines. As stated in the literature review, there is no conclusive evidence to suggest what the best regimen is for patients with this disorder. However, based on information available, it would seem prudent to attempt to use regimens that have a higher CPE index so that HIV within the brain is targeted. As is known, the lower the nadir CD4 and the higher the viral load at initiation, the greater the risk of developing HAND (81) (82). In the current study, patients were initiating late and so this would be an important factor to consider. Because HAND can have so many implications in terms of quality of life, adherence, obtaining employment and the increased risk of death (80), it would seem to be a reasonable indication for deviating from the National Guidelines for ART roll-out. However, one could also argue that there are reasons to continue to prescribe the recommended regimens for patients with the diagnosis of HAND. These would include that there is some conflicting evidence that regimens with a higher CPE index can increase the risk of neurotoxicity (81) (80), which then may have detrimental effects on the neurocognitive functioning of this already vulnerable population.

Looking at this dilemma in further detail, there is also the consideration of whether or not to use EFV in this population of patients. As stated, a large proportion of patients were started on EFV (77%), and this included 21 patients out of the 38 that were prescribed ART that deviated from the National Guidelines. EFV is known to have moderate penetration of the CNS, with a CPE score of 3 (72), and is also well known to have multiple neuropsychiatric

side effects (66). For this reason, it has been suggested that EFV should not be used in patients with HAND, as there are concerns that it may cause further decompensation in these patients (114). Of the 34 patients in this study with a diagnosis of HAND, 22 were prescribed EFV, which goes against these current recommendations. However, 12 patients were not started on the recommended first line regimen of either EFV or NVP when they were diagnosed with HAND and this could possibly be due to the fact that use of EFV is suggested to be linked to further neuropsychological deterioration. This finding is now quite controversial though, because more recent studies have suggested that EFV use is not contra-indicated in patients with HAND. A recent international study from Italy has shown no link between EFV use and neurocognitive impairment (115). There is also evidence from South Africa that use the National Guideline regimens, which includes either EFV or NVP, is associated with either a halt in the progression of neurocognitive decline or, more importantly, an improvement in functioning (76).

Therefore, at present, it is unclear what ART should be prescribed for patients with HAND. There is conflicting evidence for both the use of high CPE versus lower CPE index ART, as well as for the use of EFV in these patients. It would be important that this specific group be followed up regularly to look at the outcomes of the practice of deviating from National Guidelines and using EFV, as this would allow for recommendations to be put forward if it was found that these patients benefited from the interventions.

## 5.4 LIMITATIONS

As this was a retrospective study, there were limitations associated with the study design. One has to rely on the information being available in the files in order to include it in the data. Files were not found which decreased the sample size and two files had to be excluded because the information was not complete. It also meant that some information that could have been useful was not included because it was not available, such as a section on substance abuse other than alcohol. The information in the files was not collected with the intent of doing research on it, and was instead collected by various doctors at different levels of training while working in a busy clinic. This means that the collection of data was not standardised, relied upon clinician interruption and that decisions on what ART to start did not necessarily follow a standardised protocol. There were also errors and omissions in the files which led to the need to interrupt and handle the issue of missing data. As there was only one investigator, this did help as only one system was developed to handle this issue. This is the nature of a retrospective review and helps to plan for a future study that would be prospective.

The other major difficulty with the study was the sample size. Over 200 files were reviewed but a large number had to be excluded, which was not expected. A larger number of participants could possibly have included more male patients in the total population, which may have helped to determine if some of the findings related to gender in the study continued to be statistically significant with a larger group. While the group following National Guidelines was an acceptable size, it would have helped to have a larger sample size so that the group not following National Guidelines could be more substantial. As this

group was so small, it meant that analysis could not be done within the sub-groups of this population, which may have been helpful to look at factors associated with prescription of the various regimens.

Another limitation was that the psychiatric diagnoses were not based on assessments made by standardised objective tools, such as the Structured Clinical Interview for DSM-IV, but rather on the doctor's clinical impression. Again, as doctors were of different levels of experience, this could have led to inaccurate diagnoses, but also meant that patients often had a differential diagnosis list. Therefore, most patients had more than one diagnosis and this made analysis of the data more difficult to compare. It also had implications for the diagnosis of a substance abuse disorder and recording of substance use was not standardised and relied upon self-report by the patients. This may not have been the most reliable method of collecting this information and was an important point taken away from the audit.

Finally, in terms of external validity, this study specifically looked at a population of out-patient participants at a specialised HIV neuropsychiatric clinic and therefore would not be generalizable to other settings such as the in-patient population or patients attending a standard HIV clinic. The patients attending this clinic are expected to be more complicated than those attending a general clinic. However, some of the information obtained would be applicable to all patients in an out-patient setting and may be helpful in guiding decisions in these areas.

## CHAPTER SIX: CONCLUSION

This study has described the out-patient population of patients with both HIV and mental illness at Luthando Clinic in Johannesburg. It showed that there was a female predominance of patients attending the clinic and that patients were still presenting late for treatment as the median CD4 count was 166 cells/$mm^3$. It demonstrated that, while there are no guidelines for the treatment of patients with this dual diagnosis, most patients follow the South African National Guidelines for ART in adults. Interestingly, even though these participants were presenting with psychiatric symptoms, 77% of them were still initiated on an Efavirenz-containing regimen. Of those who did not follow the National Guidelines, the most common predictors for this included having renal dysfunction and a diagnosis of HAND. There appeared to be a low incidence of Depression and Substance Use Disorders amongst this population, with most patients being diagnosed with mood/psychosis secondary to the HIV infection. This may be due to the fact that this is a tertiary level psychiatric clinic.

## CHAPTER SEVEN: RECOMMENDATIONS

The information gained from the study adds to a paucity of literature on mental illness and HIV within South Africa and developing countries. While it may not answer any questions regarding this important area of research, it has allowed a more detailed inspection of this specific neuropsychiatric clinic in order to ask relevant questions going forward. Following on from this, it would be important to have a prospective study to look at different regimens of ART in patients with HAND in order to determine the most appropriate

treatment for this specific group and whether deviating from the National Guidelines is appropriate in these patients. Added to this, further information can be obtained regarding gender and HAND to assess whether there is a correlation between male gender and the diagnosis in the South African context. The link between anaemia and HAND could also be explored in more detail in a large, prospective study of this nature. It would also be helpful to have a longitudinal study looking at the outcome of patients with a dual diagnosis who are started on EFV because of the current concerns that this drug should be avoided in patients with psychiatric symptoms, which did not seem to be the practice at the clinic. Further research would also be helpful to look at clinical presentation of patients with HIV to ascertain if the diagnoses are significantly different to developed countries and if so, what the reasons are for this. This may specifically be helpful in terms of acute presentation in an in-patient setting but also at more generalizable out-patient clinics. There could also be more work looking at substance abuse rates so that recommendations can be designed for interventions that can be introduced if this is a significant problem.

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# APPENDICES:

## APPENDIX ONE: DATA COLLECTION SHEET

**DATA COLLECTION SHEET**

**Subject number**:_____

***Section 1: Demographic Characteristics***

1. **Age in years:**

_____

2. **Gender:**

| Male | Female | Unknown |
|---|---|---|
| 1 | 2 | 3 |

3. **Marital Status:**

| Single | Married | Divorced | Widow | Unknown |
|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 |

4. **Employment:**

| Yes | No | Unknown |
|---|---|---|
| 1 | 2 | 3 |

5. **Social Assistance:**

| Pension | Child Support | Disability | Other | No assistance | Unknown |
|---|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 | 6 |

***Section 2: Clinical Characteristics***

6. **TB Medical co-morbidity:**

| Yes | No | Unknown |
|---|---|---|
| 1 | 2 | 3 |

7. **Currently on TB medication:**

| Yes | No | Unknown |
|---|---|---|
| 1 | 2 | 3 |

**8. Other Medical co-morbidities:**

| Yes | No | Unknown |
|---|---|---|
| 1 | 2 | 3 |

**9. Alcohol Abuse:**

| Yes | No | Unknown |
|---|---|---|
| 1 | 2 | 3 |

**10. Smoking status:**

| Yes | No | Unknown |
|---|---|---|
| 1 | 2 | 3 |

**11. Weight at first visit in kilograms:**

**12. WHO staging:**

| Stage 1 | Stage 2 | Stage 3 | Stage 4 | Unknown |
|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 |

**13. CD4 Count on initiation of ART:**

| <50 | 51-100 | 101-200 | 201-350 | >350 | Unknown |
|---|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 | 6 |

**14. Viral Load on initiation of ART:**

| Lower than detectable | 50-1000 | >1000 | Unknown |
|---|---|---|---|
| 1 | 2 | 3 | 4 |

| | **Diagnosis** | **Yes** | **No** | **Unknown** |
|---|---|---|---|---|
| **15** | Psychosis/mood secondary to HIV | 1 | 2 | 3 |
| **16** | Psychosis/mood secondary to another GMC | 1 | 2 | 3 |
| **17** | Psychosis/mood secondary to substances | 1 | 2 | 3 |
| **18** | Schizophrenia | 1 | 2 | 3 |
| **19** | HIV-associated Neurocognitive | 1 | 2 | 3 |

| | | | | |
|---|---|---|---|---|
| | Disorder | | | |
| **20** | Major Depressive Disorder | 1 | 2 | 3 |
| **21** | Bipolar Mood Disorder | 1 | 2 | 3 |
| **22** | Anxiety Disorder | 1 | 2 | 3 |
| **23** | Personality Disorder | 1 | 2 | 3 |
| **24** | Intellectual Disability | 1 | 2 | 3 |
| **25** | Schizo-affective Disorder | 1 | 2 | 3 |

***Section 3: Psychotropic Medication***

| | **Psychotropic Medication** | **Prescribed** | | |
|---|---|---|---|---|
| | Mood Stabilisers: | Yes | No | Unknown |
| **26** | Sodium Valproate | 1 | 2 | 3 |
| **27** | Lithium | 1 | 2 | 3 |
| **28** | Carbamazepine | 1 | 2 | 3 |
| **29** | Lamotrigine | 1 | 2 | 3 |
| | Antipsychotics: | | | |
| **30** | Haloperidol | 1 | 2 | 3 |
| **31** | Risperidone | 1 | 2 | 3 |
| **32** | Risperdal Consta | 1 | 2 | 3 |
| **33** | Clozapine | 1 | 2 | 3 |
| **34** | Trifluoperazine | 1 | 2 | 3 |
| **35** | Olanzapine | 1 | 2 | 3 |
| **36** | Flupentixol | 1 | 2 | 3 |
| **37** | Amisulpiride | 1 | 2 | 3 |
| **38** | Aripiprazole | 1 | 2 | 3 |
| **39** | Chlorpromazine | 1 | 2 | 3 |
| **40** | Quetiapine | 1 | 2 | 3 |
| **41** | Zuclopenthixol | 1 | 2 | 3 |
| | Antidepressants: | | | |
| **42** | Citalopram | 1 | 2 | 3 |
| **43** | Fluoxetine | 1 | 2 | 3 |
| **44** | Mianserin | 1 | 2 | 3 |
| **45** | Venlafaxine | 1 | 2 | 3 |
| **46** | Amitriptyline | 1 | 2 | 3 |
| **47** | Benzodiazepine | 1 | 2 | 3 |
| | Stimulants: | | | |
| **48** | Methylphenidate | 1 | 2 | 3 |

***Section 4: Antiretroviral Treatment***

| | **Antiretroviral Regimen** | **Prescribed** | | |
|---|---|---|---|---|
| | | Yes | No | Unknown |

| | | | | |
|---|---|---|---|---|
| **49** | TDF, 3TC and NVP | 1 | 2 | 3 |
| **50** | TDF, 3TC and EFV | 1 | 2 | 3 |
| **51** | D4T, 3TC and NVP | 1 | 2 | 3 |
| **52** | AZT, 3TC and NVP | 1 | 2 | 3 |
| **53** | D4T, 3TC and EFV | 1 | 2 | 3 |
| **54** | ABC, 3TC and NVP | 1 | 2 | 3 |
| **55** | ABC, 3TC and EFV | 1 | 2 | 3 |
| **56** | ABC, 3TC and LPV/r | 1 | 2 | 3 |
| **57** | AZT, 3TC and EFV | 1 | 2 | 3 |
| **58** | TDF, 3TC and LPV/r | 1 | 2 | 3 |
| **59** | D4T, 3TC and LPV/r | 1 | 2 | 3 |
| **60** | AZT, 3TC and LPV/r | 1 | 2 | 3 |

**61. Currently on Regimen that follows South African National Guidelines for first line therapy in the general population:**

| Yes | No | Unknown |
|---|---|---|
| 1 | 2 | 3 |

## APPENDIX TWO: ETHICS CLEARANCE CERTIFICATE

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG
Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Dr J Buckley

CLEARANCE CERTIFICATE M111116

PROJECT A Clinical Audit of the Prescribing Practices of Doctors at Lutlando Neuropsychiatric Clinic

INVESTIGATORS Dr J Buckley

DEPARTMENT Department of Psychiatry

DATE CONSIDERED 25/11/2011

M111160DECISION OF THE COMMITTEE* Approved unconditionally

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

DATE CHAIRPERSON .....
(Professor PE Cleaton-Jones)

*Guidelines for written 'informed consent' attached where applicable
cc Supervisor : Dr Greg Jonsson

DECLARATION OF INVESTIGATOR(S)

To be completed in duplicate and ONE COPY returned to the Secretary at Room 10004, 10th Floor, Senate House, University.
I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. I agree to a completion of a yearly progress report.
PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES.

## APPENDIX THREE: CHANGE OF TITLE

Faculty of Health Sciences
Private Bag 3 Wits, 2050
Fax: 027117172119
Tel: 02711 7172076

Reference: Ms Thokozile Nhlapo
E-mail: thokozile.nhlapo@wits.ac.za

29 September 2014
Person No: 521196
TAA

Dr JA Buckley
59 Galway Raod
2193
South Africa

Dear Dr Buckley

**Master of Medicine: Change of title of research**

I am pleased to inform you that the following change in the title of your Research Report for the degree of **Master of Medicine** has been approved:

From:

To: **The influence of mental illness on prescribing practices of art**

Yours sincerely

Mrs Sandra Benn
Faculty Registrar
Faculty of Health Sciences