EVALUATING NEUROPSYCHIATRIC SYMPTOMOLOGY IN HIV-POSITIVE PATIENTS ON EFAVIRENZ IN PUBLIC-SECTOR CLINICS AND PSYCHIATRIC HOSPITALS

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I, Razia Gaida student number 207060291, hereby declare that the above mentioned thesis is my own work and that it has not previously been submitted for assessment to another University or for another qualification.

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ABSTRACT

Background: South Africa has the highest number of people living with human immunodeficiency virus (HIV) infection in the world. In 2014, an estimated 10.2% of the population was HIV-positive which amounted to 5.51 million people. Efavirenz forms part of the triple therapy backbone used in South Africa and is part of the first-line treatment for HIV. Efavirenz has been strongly associated with causing neuropsychiatric side effects in at least 50.0% of patients to whom it is prescribed. These side effects cause hesitation amongst healthcare professionals to prescribe this agent to patients with active mental illnesses.

Aim: The aim of the study was to evaluate the neuropsychiatric side effects of efavirenz in HIV-positive psychiatric and non-psychiatric patients and to determine whether this drug may be recommended for use in an HIV-positive psychiatric patient population.

Method: The study was divided into two parts, namely a quantitative portion and a qualitative portion. The quantitative study was a prospective drug utilisation study, while the qualitative portion consisted of semi-structured interviews carried out with healthcare professionals working with people living with HIV/AIDS (PLWHA). The study included five municipal clinics in the Nelson Mandela Metropole as well as two public-sector psychiatric facilities in the Eastern Cape where medical records were reviewed to obtain the information required. Patients were followed in both instances for a period of 24 weeks with follow-up assessments carried out at two, four, 12 and 24 week intervals. In terms of the qualitative study, nurses at the clinics and doctors at the hospitals were contacted and appointments for interviews were made. The interviews were recorded using a voice recorder and were transcribed and analysed using theoretical framework analysis.

Results: The review of 126 medical records at the clinics revealed that no patient had suffered from or complained of a neuropsychiatric side effect. This may indicate that patients were not suffering from clinically significant side effects, side effects were not being adequately recorded by healthcare staff, or the healthcare staff were not questioning patients regarding side effects. A total of 26 hospitalised patients were followed for 24 weeks in the psychiatric facilities. Almost half of the patients using efavirenz experienced an improvement in symptoms to the extent that they were

discharged from the facility. The majority of patients (66.7%) not on an efavirenz-containing regimen did not improve to the point of discharge. Healthcare staff were vague when providing a definition of neuropsychiatric side effects. There were conflicting ideas on whether or not efavirenz should be used in patients with an active psychiatric illness.

Conclusions: Further studies need to be performed in public-sector institutions to obtain a clearer picture of the side effects experienced by patients using efavirenz. Healthcare staff need to be encouraged to keep complete records to allow for meaningful analysis. The further integration of mental health services into existing HIV programmes is essential for holistic treatment. Patients in psychiatric hospitals demonstrated that even patients with psychiatric disorders on efavirenz can experience positive outcomes and stabilisation of psychiatric symptoms, which may indicate that these may not have due to efavirenz use. Further elucidation concerning the use of efavirenz in patients with psychiatric disorders, a description of the neuropsychiatric side effects, as well as management strategies must be provided in subsequent HIV guidelines.

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GLOSSARY

3TC – Lamivudine
ABC – Abacavir
AIDS – Acquired Immune Deficiency Syndrome
ART – Antiretroviral Treatment
ARV – Antiretroviral
AZT – Zidovudine
d4T – Stavudine
CIDI – Composite International Diagnostic Interview
CNS – Central nervous system
DSM – Diagnostic and Statistical Manual
DUR – Drug utilisation review
EFV – Efavirenz
FDC – Fixed dose combination
FTC – Emtricitabine
HIV – Human immunodeficiency virus
LSD – Lysergic acid diethylamide
MINI – Mini-International Neuropsychiatric Interview
NRTI – Non-nucleoside reverse transcriptase inhibitor
NNRTI – Non-nucleoside reverse transcriptase inhibitor
NVP – Nevirapine
PCP – Phencyclidine hydrochloride
PI – Protease inhibitor
PLWHA – People living with HIV/AIDS
PTSD – Post-traumatic stress disorder
SA – South Africa
SIV – Simian immunodeficiency virus
SSA – sub-Saharan Africa
TB – Tuberculosis
TDF – Tenofovir
THC – Tetrahydrocannabinol

WHO – World Health Organisation

AUTHORS' CONTRIBUTIONS (MANUSCRIPT 1)

The contribution of each author for the manuscript entitled 'Efavirenz: a review of the epidemiology, severity and management of neuropsychiatric side-effects' is stipulated in the table below:

Author	Contribution
Razia Gaida	Conceptualisation of the study Literature review Interpretation of the results Writing of the manuscript
Ilse Truter	Conceptualisation of the study and the manuscript Supervision in the writing of the manuscripts Critical revision of the manuscript for intellectual content Editing and proofreading of the final manuscript
Christoffel Grobler	Conceptualisation of the study and the manuscript Supervision in the writing of the manuscripts Critical revision of the manuscript for intellectual content Editing and proofreading of the final manuscript

The following statement provided by the co-authors confirms their individual roles in the study and their permission that the manuscript may form part of this dissertation:

I declare that I have approved the above-mentioned manuscript and that my role in this study, as indicated above, is indicative of my actual contributions and I hereby give my consent that the manuscript may be published as part of the PhD study of Razia Gaida.

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The contribution of each author for the manuscript entitled 'Perspectives of healthcare professionals of the neuropsychiatric side effects associated with efavirenz and its management' is stipulated in the table below:

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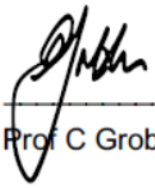
Prof I Truter



Prof C Grobler

CHAPTER 1

INTRODUCTION

1.1 INTRODUCTION

> *'I said to myself, I want to live as long as I can. I decided I'm not going to let this kill me. So I started going to the clinic. I take my treatment…every day and I'm looking forward to a longer life. I'm 36 years old now. It was 10 years ago when I tested positive. Look at me, I'm still here.'*
>
> (Anonymous, 2010)

The human immunodeficiency virus (HIV) affects the lives of everyone, whether infected or not. The roll-out of antiretroviral treatment (ART) has not only increased the life expectancy of people living with HIV/acquired immune deficiency syndrome (AIDS) (PLWHA), but has also improved their quality of life. In spite of this there are still many challenges facing PLWHA.

This first chapter provides a summary of HIV as a global problem, then focusing on sub-Saharan Africa (SSA) as the region with the highest burden of HIV. The incidence of HIV in patients with psychiatric conditions and the challenges facing treatment adherence is explored. The chapter then closes with a proposal for determining the incidence and severity of neuropsychiatric side effects caused by efavirenz in patients with a psychiatric condition and those without.

1.2 HIV GLOBALLY

The UNAIDS Gap Report (2014: 3) stated that there were 35 million PLWHA worldwide. Of these, 3.2 million were children and 2.1 million were adolescents. Of the 35 million infected people, 4.2 million were over the age of 50 years (The Gap Report 2014: 3). Furthermore, 70.0% of the total infections were in SSA.

1.3 HIV IN SUB-SAHARAN AFRICA

SSA is the most affected global region in terms of HIV infections (WHO, 2014). In 2013, there were 24.7 million PLWHA in SSA (WHO, 2014).

According to the UNAIDS Global Report on AIDS (2010: 10), slightly more than half of all PLWHA were women and girls. In SSA there were more women than men living with HIV, and young women between the ages of 15 and 24 years were more likely to be infected with HIV than men (UNAIDS, 2010: 10). This statistic was reiterated in The Gap Report (2014: 7) which stated that 59.0% of PLWHA in SSA were women. The consequences of gender inequalities in terms of low socioeconomic and political status, unequal access to education and fear of violence, add to the vulnerability of women and girls being infected with HIV (UNAIDS, 2010: 130). Women and girls generally do not have the capacity to negotiate safer sex, to access the health services they need or to make use of empowerment opportunities (UNAIDS, 2010: 130).

The global HIV community tends to focus on the prevalence of HIV amongst adults aged 15 to 49 years (Negin and Cumming, 2010: 851). This means that the population over the age of 50 years is not usually considered which produces an information gap. Negin and Cumming (2010: 847) aimed to extrapolate data obtained from UNAIDS, World Population Prospects and Demographic and Health Surveys in an attempt to quantify the prevalence of HIV amongst older adults in SSA. Extrapolation of the data showed that, in 2007, approximately 3 million people over the age of 50 years were living with HIV in SSA (Negin and Cumming, 2010: 848). This figure represents 14.3% of the 21 million people aged 15 years and older who are living with HIV in SSA (Negin and Cumming, 2010: 848).

1.4 HIV IN SOUTH AFRICA

South Africa (SA) has the highest number of PLWHA in the world. In 2013, an estimated 10.0% of the population was HIV positive which amounted to 5.26 million people (Statistics South Africa, 2013: 4). This increased to 10.2% in 2014 which amounted to 5.51 million people (Statistics South Africa, 2014: 2). For adults between the ages of 15 and 49 years, an estimated 15.9% was HIV positive in 2013 (Statistics South Africa, 2013: 2). This value showed an increase in 2014 to 16.8% of adults between the ages of 15 and 49 years being HIV positive (Statistics South Africa, 2014: 2). These statistics indicate that HIV in SA is a growing problem.

The gender distribution of PLWHA in SA reflects the general situation in SSA with greater vulnerability amongst women. It was found that there was no significant gender

difference in HIV prevalence amongst adults aged 25 years and older, indicating that HIV can only be gendered amongst younger people (Shisana, Rehle, Simbayi, Zuma, Jooste, Pillay-van-Wyk, Mbelle, van Zyl, Parker, Zungu, Pezi and the SABSSM III Implementation team, 2009: 30; Shisana, *et al.,* 2010: 43).

In some societies in SA women tend to be economically dependent on men, making it difficult to protect themselves against HIV (Shisana, Rice, Zungu and Zuma, 2010: 43). Poor access to education combined with low employment rates result in inequalities leading to inadequate access to basic resources including HIV-preventative information (Gilbert and Selikow, 2011: 328). This socioeconomic disadvantage has been found to be associated with unsafe sexual behaviours and experiences for females (Gilbert and Selikow, 2011: 328). Economic dependency may also result in women engaging in 'transactional sex' which refers to exchanging sex for material gain (Gilbert and Selikow, 2011: 328).

The role of multiple and concurrent sexual partners is recognised as being a significant risk factor for heterosexual HIV transmission. When groups of people are linked in a sexual network, a new infection has the potential to spread rapidly through that network due to higher viral loads in the early stage of HIV infection (Shisana, *et al.,* 2009: 41). Multiple partnerships are four to seven times more common in males than in females (Shisana, *et al.,* 2009: 41). For males, the idea of multiple sexual partners affirms self-worth and validates 'manhood' amongst peers and women (Gilbert and Selikow, 2011: 329; Leclerc-Madlala, 2008: 9). Shisana and colleagues (2009: 41) found that the proportion of males between the ages of 15 years and 24 years who have had multiple sexual partners increased from 23.0% in 2002 to 27.2% in 2005 to 30.8% in 2008. The corresponding female values are 8.8% for 2002 and 6.0% for 2005 and 2008. For older adults, values were consistently higher for males than females by at least a factor of five, but proportions remained relatively constant over the three-year time period. However, with increased incidences of transactional sex, more young women are involved in having multiple partners (Gilbert and Selikow, 2011: 329). Transactional sex is noted as a key driver in the HIV epidemic in SA. Women are aware that their bodies are a valued resource and that they may use it to their advantage. This has resulted in many young urban women seeking multiple partners (Leclerc-Madlala, 2008: 6).

1.5 HIV IN PATIENTS WITH PSYCHIATRIC ILLNESS

A survey undertaken in South Africa showed that a 12-month prevalence of mental disorders amounted to 16.5% of a population of 4351 participants (Williams, Herman, Stein, Heeringa, Jackson, Moomal and Kessler, 2008: 213-214). Diagnoses were made using the DSM-IV/Composite International Diagnostic Interview (CIDI). Major depressive disorder, agoraphobia and alcohol abuse were the three most prevalent disorders. Approximately 26.6% of the respondents were classified as having a serious disorder, 31.1% as having a moderate disorder and 42.7% as having a mild disorder (Williams, *et al.,* 2008: 214). The study found no significant difference between males and females in terms of the prevalence of a mental disorder, however, female patients were more likely to suffer from a mood or anxiety disorder and male patients were more likely to suffer from a substance abuse disorder (Williams, *et al.,* 2008: 214).

In 2008 in South Africa, the prevalence of HIV was 16.9% in people between the ages of 15 and 49 years and the widespread roll-out of antiretrovirals (ARVs) was not yet in place (Freeman, Nkomo, Kafaar and Kelly, 2008: 490). A total of 43.7% of patients with HIV had a mental disorder (n=897). Freeman and colleagues (2008: 493) showed that amongst HIV-positive patients, mild depressive disorder was the most common mental disorder in both males (28.1%) and females (30.5%). This was followed by major depressive disorder and alcohol abuse in both males and females (Freeman, *et al.,* 2008: 493). These results were similar to those obtained in the general population by Williams and colleagues (2008: 214). Male patients were more likely to develop mental disorders than female patients, as were unemployed people compared to those employed. Patients with children were more likely to experience a mental disorder compared to those without (Freeman, *et al.,* 2008: 494). A strong relationship was found between stage of illness and depression with the incidence of depression increasing with advancing illness (Freeman, *et al.,* 2008: 494).

Another study conducted in 2008 included 465 patients and found a mental disorder prevalence of 19.0% (Myer, Smit, le Roux, Parker, Stein and Seedat, 2008: 152). The measuring instrument for psychiatric diagnoses used by Freeman and colleagues (2008) was the CIDI which was part of the WHO World Mental Health Survey, whereas Myer and colleagues (2008: 149) made use of the Mini-International Neuropsychiatric

Interview (MINI) to diagnose psychiatric disorders. The MINI has been used as the gold standard in cross-cultural studies globally. Myer and colleagues (2008: 152) showed that 14.0% of the participants had experienced major depression in the last 12 months and 5.0% had suffered from post-traumatic stress disorder (PTSD). The samples used in each study may play a role in the differing prevalence of mental disorders. Myer and colleagues (2008: 148) recruited patients from primary level public care facilities in Cape Town, while Freeman and colleagues (2008: 491) recruited participants from 18 different public clinics or non-government organisations aimed at PLWHA spanning across five provinces.

A study (Collins, Berkman, Mestry and Pillai, 2009: 864-865) conducted at a psychiatric institution in the KwaZulu-Natal province of SA showed that of 151 patients admitted, 40 patients (26.5%) tested HIV-positive with females being almost twice as likely to be HIV-positive than males (odds ratio 2.03). Amongst the various racial groups, black patients were more likely to be infected than others (odds ratio 6.29). However, there was no difference in HIV prevalence between psychiatric diagnostic groups, marital status, employment status or substance abuse (Collins, *et al.,* 2009: 865). The HIV prevalence amongst people with serious mental illness largely matched that of the general population (Collins, *et al.,* 2009: 866). Conversely, American studies (Blank, Himelhoch, Balaji, Metzger, Dixon, Rose, Oraka, Davis-Vogel, Thompson and Heffelfinger, 2014: 2377; Beyer, Taylor, Gersing and Krishnan, 2007: 33) report that the HIV prevalence amongst people with severe mental illness is four times higher than that of the general population. However, Collins and colleagues (2009: 866) suggest that the HIV prevalence amongst psychiatric patients in the United States of America reflects the prevalence of HIV only amongst the poor and socially marginalised parts of the general population.

It has been seen that mental disorders persist for at least six months in PLWHA (Olley, Seedat and Stein, 2006: 482). A total of 149 HIV-positive patients were recruited at an outpatient clinic in Cape Town. Patients were interviewed using the MINI. The average duration of diagnosis was 5.8 months±4.1 months and 98.7% of the patients were not receiving ART. Only 43.6% of the total population returned for the follow-up visit after six months. At baseline, 56.0% of patients had at least one psychiatric disorder and at six months 48.0% had at least one psychiatric disorder (Olley, *et al.,* 2006: 481). At

both baseline and follow-up, depression and PTSD were the most prevalent disorders. The study concluded that psychiatric evaluation needs to be a continuous process in PLWHA.

Adherence of patients with a psychiatric illness is also a concern. A study conducted in Cape Town retrospectively reviewed medical records of patients attending three public sector psychiatric facilities (Joska, Obayemi Jr, Cararra and Sorsdahl, 2014: 1493). There were 100 patients included in the final analysis, 85.0% of whom were female. Only 37 patients from this sample attended a six-month follow-up assessment following discharge from the psychiatric facility. One significant indicator of patients not returning for follow-up to clinics, was shown to be more than one re-admission to the psychiatric facility (Joska, *et al.,* 2014: 1496). The study does, however, acknowledge that patients may not be attending follow-up visits due to socioeconomic factors (Joska, *et al.,* 2014: 1497). If patients are unable to afford transport to clinics or food, they will forego medical treatment. An Australian study concurred with these results, showing that patients with mental illnesses exhibited poor adherence to ART (Sternhell and Corr, 2002: 530). However, the reasons for non-adherence differed in that scepticism concerning the effectiveness of ART, knowledge of the disease and past use of psychotropic medication played significant roles in adherence behaviour (Sternhell and Corr, 2002: 531).

It can be seen that PLWHA suffer from psychiatric disorders as much as the general South African population with the seemingly most common disorder being depression in varying severities. Depression could be seen as an emotional response to the illness, as could PTSD, which is also commonly reported in HIV-positive patients (Olley, *et al.,* 2006: 482).

There are at least five distinct mental health problems that are relevant to PLWHA. These are: cognitive impairment and dementia due to viral infection of the brain; depression and anxiety due to the impact of the infection on the person's life; alcohol and drug use; the psychiatric side effects of some ARVs; and the social difficulties faced as a result of stigma and discrimination (Freeman, Patel, Collins and Bertolote, 2005: 1). It is important to consider HIV-associated psychiatric illness as a possibility in all clinical presentations where patients exhibit stigmata of AIDS or are simply HIV-positive (Saunders, 2006: 431). Some common clinical presentations of mental illness

in PLWHA include depression, anxiety disorders, mania and psychoses and HIV-associated dementia (Saunders, 2006: 431-433).

1.5.1 Depression

Depression is a common complication of HIV that can occur at any time during the illness (Penzak, Reddy and Grimsley, 2002: 376; Saunders, 2006: 431). Depression shares some symptoms with HIV infection such as loss of weight, loss of appetite, lethargy and poor sleeping patterns. It may therefore be more prudent to consider features such as poor self-esteem, tearfulness and deterioration in supportive relationships in order to diagnose a PLWHA with depression (Badkoobehi, Chana and Everall, 2006: 86; Saunders, 2006: 431). Depression can have a significant impact on PLWHA and is associated with disease progression and mortality (Starace, Ammassari, Trotta, Murri, De Longis, Izzo, Scalzini, d'Arminio Monforte, Wu and Antinori, 2002: 137). Depression is also one of the primary causes for non-adherence to ART (Starace, *et al.,* 2002: 137; Saunders, 2006: 431). Depression in PLWHA can be managed with selective serotonin-reuptake inhibitors such as citalopram, escitalopram and sertraline (Brogan and Lux, 2009: 109; Ferrando, 2009: 236).

1.5.2 Anxiety

Anxiety disorders in PLWHA are not uncommon and may be co-morbid with other psychiatric problems (Saunders, 2006: 432). A study conducted on a sample of females showed that HIV-positive females showed higher levels of anxiety than HIV-negative females, however not significantly higher (Morrison, Petitto, Ten Have, Gettes, Chiappini, Weber, Brinker-Spence, Bauer, Douglas and Evans, 2002: 794). Another study performed using a sample of males showed a lifetime prevalence of 15.0% of generalised anxiety in HIV-positive males compared to 8.8% in HIV-negative males (Dew, Becker, Sanchez, Caldararo, Lopez, Wess, Dorst and Banks, 1997: 401). Benzodiazepines should be avoided in PLWHA due to potential drug interactions and accumulation in the case of hepatic failure. Buspirone may be used as alternative treatment for anxiety disorders or alternatively selective serotonin-reuptake inhibitors. No trials have, however, been published concerning the use of selective serotonin-reuptake inhibitors (Brogan and Lux, 2009: 110; Ferrando, 2009: 237)

1.5.3 Mania and psychoses

Mania and psychoses are not as common as depression, but are important as they are AIDS defining illnesses and possibly indications of ART adverse effects (Saunders, 2006: 431). Most patients who present with HIV-related psychosis also have features of cognitive impairment and, if left untreated, will develop HIV-associated dementia (Saunders, 2006: 431). The first-line agents for treating mania, lithium, valproic acid and carbamazepine, need to be approached with caution due to the neurotoxicity and nephrotoxicity of lithium, the ability of carbamazepine to cause blood dyscrasias and possibly reduce the serum levels of protease inhibitors and valproic acid's potential ability to stimulate the replication of HIV-1 (Brogan and Lux, 2009: 110; Ferrando, 2009: 238). The ability of valproic acid to stimulate replication of HIV-1 has been demonstrated *in vitro*, but not *in vivo* (Brogan and Lux, 2009: 110). Lamotrigine can be used as an alternative, however lamotrigine has to be titrated up slowly in order to decrease the risk of Steven-Johnson's syndrome (Brogan and Lux, 2009: 110; Ferrando, 2009: 238). Ferrando (2009: 238) states that clozapine has been successfully used in manic HIV-positive patients, but Brogan and Lux (2009: 110) state that it should be avoided in HIV-positive patients due to adverse effects and interaction with ritonavir. Ferrando (2009: 238) recommends the use of risperidone and Brogan and Lux (2009: 110) recommend the use of quetiapine.

1.5.4 HIV-associated dementia

Dementia associated with HIV is common of advanced disease and affects more than 50.0% of all HIV patients (Ances and Ellis, 2007: 86). HIV-associated dementia is an AIDS-defining complication (Saunders, 2006: 432). Disabling dementia due to HIV is recognised when a patient's cognitive abilities decline over a period of weeks or months with decreased cognitive and operative agility, motor dysfunction and behavioural disturbances (Saunders, 2006: 432; Ances and Ellis, 2007: 88). HIV-associated dementia responds to ART (Saunders, 2006: 432; Ances and Ellis, 2007: 90).

1.6 PROBLEM DEFINITION

Many of the articles referenced above indicate that the side effects of efavirenz are mild and transient. Patients with active mental illness tend to be excluded from the

efavirenz treatment group. This could be due to the warnings concerning the potential neuropsychiatric side effects associated with efavirenz as stated in the South African Guidelines (2010: 26) and the package insert of efavirenz (Adco-efavirenz, 2007). However, the package insert does not directly contraindicate the use of efavirenz in patients with active mental illness, but rather issues a warning stating that it may cause serious nervous system and psychiatric side effects (Adco-efavirenz, 2007). As efavirenz is available in a single tablet combination, if it were used in patients with active mental illness, it would reduce the pill burden in this patient group and possibly improve compliance. Denying PLWHA access to efavirenz may be at the cost of effective virological control. Jonsson and colleagues (2013: 159, 161) state that withholding efavirenz therapy for fear of worsening psychosis or depression is not warranted. The argument in favour of this statement is that efavirenz has a more favourable side effect profile, a lower pill burden and fewer interactions with medication frequently used to treat psychiatric disorders (Jonsson, *et al.,* 2013: 161).

1.7 PRIMARY AIM AND OBJECTIVES

The primary aim of the study is to evaluate the neuropsychiatric side effects of efavirenz in HIV-positive psychiatric and non-psychiatric patients and to determine whether this drug may be used in PLWHA.

The objectives of the study are to:

- determine whether patients are being screened for a history of psychiatric disorders before initiating efavirenz in public-sector clinics;
- determine the incidence of efavirenz-induced neuropsychiatric side effects in patients in public-sector clinics and hospitals;
- determine whether efavirenz may be used in patients with a current psychiatric illness;
- determine how neuropsychiatric symptoms are identified and managed in these public facilities; and
- determine the attitude of prescribers toward prescribing efavirenz to patients with a current psychiatric disorder.

1.8 SUMMARY OF THE FOLLOWING CHAPTERS

The following chapters will discuss HIV the disease and its transmission and life-cycle as well as the treatment thereof. Thereafter, Chapter 3 focuses on an overview of the literature. The literature review is presented in the form of two articles. The first provides a summary of the neuropsychiatric side effects of efavirenz and recommends management strategies as proven by the literature. The second focuses on various trials investigating the incidence of neuropsychiatric side effects of efavirenz and the implications thereof. Chapter 4 is a synopsis of the methodologies used in the study. The next chapter discusses the results of the current study. The results are presented in the form of three articles. The first focuses on the incidence, severity and management of neuropsychiatric side effects amongst treatment-naïve HIV-positive patients at public-sector clinics. The second article describes the outcomes of hospitalised psychiatric patients using efavirenz. The final article analyses the perspectives of healthcare professionals concerning the neuropsychiatric side effects associated with efavirenz and the management thereof. The conclusion chapter, Chapter 6, provides a summary of the major findings of the study together with recommendations based on these conclusions.

CHAPTER 2

HIV AND ITS TREATMENT

2.1 INTRODUCTION

There are two identified strains of HIV, namely HIV-1 and HIV-2. HIV-2 is less frequently associated with the development of immunodeficiency and AIDS as compared to HIV-1 (Nowak and Handford, 2004). There are three groups of HIV-1 with the M group being responsible for the epidemic. Within the M group, HIV-1 is further divided into 10 distinct subtypes or clades designated A to J (Nowak and Handford, 2004). These varied genetic compositions pose a challenge to the development of vaccines which would need to protect against each clade.

2.2 DISEASE CHARACTERISTICS

HIV is a disease that gradually attacks the immune system (WHO, 2016). HIV destroys T-helper cells which is a type of white blood cell, also referred to as a CD4 cell. These CD4 cells assist the immune system in fighting off disease (AIDS.gov, 2015). If HIV is left untreated, it will decrease the total number of CD4 cells in the body making it easier for infections or cancers to flourish (AIDS.gov, 2015). These infections are known as opportunistic infections (AIDS.gov, 2015). HIV can only be diagnosed by being tested for the virus. Commonly used HIV tests detect antibodies produced by the immune system to the virus present in the bloodstream (WHO, 2016). Some patients may experience mild influenza-like symptoms two weeks after being infected (Centre for Disease Control, 2015). During this time, a HIV-test may not show as positive, but the infected person is highly infectious at this stage (Centre for Disease Control, 2015). If HIV is left untreated, the immune system may be severely damaged after 10 to 15 years and AIDS may develop. AIDS is a syndrome caused by HIV. AIDS occurs when HIV has destroyed the immune system to the extent where it is too weak to fight off infections. There are three stages of HIV summarised in Table 2.1.

Table 2.1: Stages of HIV*

Stage	Symptoms
I (Acute HIV infection)	- Influenza-like symptoms (fever, headache and rash)
II (Chronic HIV infection)	- HIV continues to multiply in the body - No symptoms may manifest, but the patient is still infectious
III (AIDS)	- One or more opportunistic infections - CD4 count is below 200cells/mm^3

*Source: AIDSinfo. HIV overview: stages of HIV infection. 2016. Available at https://aidsinfo.nih.gov/education-materials/fact-sheets/19/46/the-stages-of-hiv-infection [Date accessed: 22/02/2016].

2.3 TRANSMISSION AND INFECTION

HIV is spread through certain body fluids. These fluids include; blood, semen, pre-seminal fluid, rectal fluids, vaginal fluids and breast milk (AIDS.gov, 2015). In order for infection to occur, these body fluids need to come into direct contact with mucous membranes or damaged tissue or be injected into the bloodstream for transmission to occur. The mucous membranes include those found inside the rectum, vagina, penis and mouth. Importantly, HIV cannot be spread by air or water, mosquitoes or other insects, saliva, tears or sweat that is not mixed with the blood of an HIV-positive person, handshakes, hugging, toilets, sharing of dishes or drinking glasses (AIDS.gov, 2015).

Once it enters the bloodstream, HIV can infect multiple cells, including brain cells, but the main target is the CD4 lymphocyte or CD4 cell. The process through which the virus goes to replicate is broken down into the following steps (AIDS.gov, 2015):

- Binding and fusion: the virus binds to the specific CD4 receptor and co-receptor on the surface of the CD4 cell. Once this binding occurs, the HIV is able to enter the cell and release its genetic material.
- Reverse transcription: a special enzyme called reverse transcriptase alters the genetic material of the virus so that it may be integrated into the host DNA.

- Integration: the new genetic material of the virus enters the nucleus of the host's CD4 cell and uses the enzyme integrase to become incorporated into the host's genetic material where it may remain inactive for several years.
- Transcription: when the host cell becomes activated, HIV uses the host's enzymes to create more of its own genetic material. It also creates more specialised genetic material which allows it to make longer proteins.
- Assembly: the enzyme protease cuts the longer viral proteins into individual proteins. When these individual proteins come together with the viral genetic material, a new virus is formed.
- Budding: this is the final stage of HIV replication. The virus pushes out of the CD4 host cell, taking with it part of the cell's membrane. This membrane covers the virus and contains all of the necessary structures to bind to a new CD4 cell and its receptors and begin the process again.

The medication used in the treatment of HIV serves to interrupt various steps in the replication process of HIV.

2.4 DRUGS USED FOR THE MANAGEMENT OF HIV

HIV cannot be cured; however, there are several major classes of drugs used in the management of PLWHA. When compliant with these agents, patients may live many years with the virus (Centre for Disease Control, 2015). There are five classes of drugs used for the management of HIV. These include entry inhibitors, fusion inhibitors, integrase inhibitors, protease inhibitors and reverse transcriptase inhibitors (nucleoside reverse transcriptase inhibitors and non-nucleoside reverse transcriptase inhibitors) (Meintjes, Black, Conradie, Cox, Dlamini, Fabian, Maartens, Manzini, Mathe, Menezes, Moorhouse, Moosa, Nash, Orrell, Pakade, Venter and Wilson (The Southern African HIV Clinicians Society), 2014: 122).

2.4.1 Entry inhibitors

Entry inhibitors interfere with the ability of the virus to bind to the receptors of the cell of the host it tries to enter. If the virus cannot enter the cell, it cannot infect the cell (National Institute of Health, 2013). There is only one currently approved entry inhibitor called maraviroc.

2.4.2 Fusion inhibitors

Fusion inhibitors interfere with the ability of the virus to fuse with the host cellular membrane, preventing the HIV from entering the cell. Fusion inhibitors are a type of entry inhibitor (National Institute of Health, 2013). There is only one fusion inhibitor available and that is enfuvirtide.

2.4.3 Integrase inhibitors

Integrase inhibitors bind to the HIV protein integrase and prevent the incorporation of the HIV RNA with the CD4 cellular DNA (National Institute of Health, 2013). Examples of integrase inhibitors are dolutegravir, elvitegravir and raltegravir.

2.4.4 Protease inhibitors

Protease is a HIV protein responsible for cleaving long chains of HIV proteins into smaller individual proteins. Inhibition of this enzyme by protease inhibitors will prevent the cleavage of viral proteins and result in immature, non-infectious viral particles. Protease inhibitors are generally reserved for second-line therapy. Examples of protease inhibitors include amprenavir, indinavir, lopinavir, nelfinavir, ritonavir and saquinavir (Rossiter, 2012: 341).

2.4.5 Reverse transcriptase inhibitors

Reverse transcriptase inhibitors interfere with the conversion of HIV RNA to DNA inside the infected CD4 cell through the inhibition of the HIV reverse transcriptase enzyme. There are two types of reverse transcriptase inhibitors, namely; nucleoside reverse transcriptase inhibitors and non-nucleoside reverse transcriptase inhibitors.

2.4.5.1 Nucleoside reverse transcriptase inhibitors

Nucleoside reverse transcriptase analogues act as false substrates for the enzyme reverse transcriptase and result in the termination of the DNA chain. Currently available nucleoside reverse transcriptase inhibitors include abacavir, didanosine, emtricitabine, lamivudine, stavudine and zidovudine (Rossiter, 2012: 334).

2.4.5.2 Non-nucleoside reverse transcriptase inhibitors

Non-nucleoside reverse transcriptase inhibitors inhibit the activity of HIV reverse transcriptase directly. This results in the suppression of HIV replication. The non-nucleoside reverse transcriptase inhibitors currently available include efavirenz, etravirine and nevirapine (Rossiter, 2012: 339).

2.5 MANAGEMENT OF HIV IN SOUTH AFRICA

Treatment of HIV in SA has been scaled up between 2009 and 2011. By 2013, there were an estimated 6.4 million PLWHA in SA and 2.3 million (35.9%) were on ARVs (Simelela and Venter, 2014: 251). In SA, the most recently published HIV treatment guidelines (National Consolidated Guidelines for the Prevention of Mother-to-Child Transmission of HIV (PMTCT) and the Management of HIV in Children, Adolescents and Adults. 2015: 72) indicate that patients who test HIV-positive with a CD4 count of 500cells/mm^3 must be started on ART. However, as of the 1st of September 2016, a circular released by the National Department of Health stated that SA was to adopt a 'test and treat' strategy, according to which patients testing HIV-positive are started on ART regardless of their CD4 count (Department of Health, 2016). Patients with tuberculosis (TB) must be initiated on ART irrespective of CD4 cell count and patients who are in the WHO clinical stages 3 or 4 of HIV must be initiated on treatment, irrespective of CD4 cell count. It is important that patients adhere to ART as the interruption of treatment can result in drug resistance (Avert). If patients present with psychosis due to underlying psychiatric disorders, the psychiatric disorder needs to be stabilised and the patient immediately referred to a public-sector clinic for initiation of ART (Jonsson and Joska, 2009: 22).

The standardised national ART regimens for adults and adolescents is summarised in Table 2.2. A change in access to ARVs between mid-2004 and mid-2011 was investigated (Johnson, 2012: 22) and it was found that the number of patients receiving ARVs had increased from 47500 in mid-2004 to 1.79 million in mid-2011. The majority of these patients in mid-2011 were women aged 15 years and older. Men accounted for 31.0% of patients and children under the age of 15 years comprised the remaining 8.0% of patients (Johnson, 2012: 23). The lower rate of men being initiated on therapy could be due to gender differences in health seeking behaviour and

perceptions. The higher rate of women being initiated on therapy may be due to higher rates of HIV diagnosis through antenatal screening (Johnson, 2012: 25). KwaZulu-Natal and Gauteng were the two provinces with the largest number of patients, together accounting for 56.0% of patients receiving ARVs. The Eastern Cape constituted 187000 (10.4%) of patients receiving ARVs in South Africa.

2.5.1 Efavirenz

Efavirenz is part of a class of drugs called non-nucleoside reverse transcriptase inhibitors (NNRTIs) (MedlinePlus, 2015) and is part of the first-line treatment for HIV. It is a non-competitive inhibitor of the reverse transcriptase enzyme of HIV and possesses a long half-life of 40 hours to 55 hours (Piscitelli, 2000). Efavirenz binds directly to the enzyme and blocks the activities of DNA-RNA polymerase, resulting in the destruction of the catalytic site of the enzyme (Cavalcante, Capistrano, Cavalcante, Vasconcelos, Macedo, Sousa, Woods and Fonteles, 2010: 740). Efavirenz is metabolised via the cytochrome P450 (CYP450) enzyme system and is metabolised by CYP2B6 and 3A4 *in vitro* (Gourevitch and Friedland, 2000: 431). Efavirenz is both an inducer and inhibitor of CYP3A4 (Gourevitch and Friedland, 2000: 431).

Table 2.2: Standardised national antiretroviral therapy regimens for adults and adolescents*

Standardised first-line antiretroviral therapy regimens for adults and adolescents in South Africa		
Patient group	**Regimen**	**Recommendations**
Adolescents >15 years and weighing >40kg Adults All TB co-infection All hepatitis B virus co-infection	Tenofovir + lamivudine (or emtricitabine) + efavirenz to be provided as a fixed dose combination	Replace efavirenz with nevirapine in patients with significant psychiatric comorbidity or intolerance to efavirenz and where the neuropsychiatric toxicity of efavirenz may impair daily functioning, e.g. shift workers
Adults and adolescents on stavudine	Change stavudine to tenofovir (no patient should be on stavudine)	Switch to tenofovir if virally suppressed and the patient has normal creatinine clearance, even if stavudine is well tolerated. If the viral load is >1 000 copies/mL, manage as treatment failure and consider switching to second line
Adolescents <15 years or weight <40 kg	Abacavir + lamivudine + efavirenz	If adolescent weight <40 kg, align with paediatric regimen
Contraindication	**Substitution drug**	**Comments**
Contraindications to efavirenz: Significant psychiatric comorbidity Intolerance to efavirenz Impairment of daily function	Tenofovir + emtricitabine (or lamivudine) + nevirapine or lopinavir/ritonavir	If CD4 <250 (females) and <400 (males), give nevirapine 200 mg daily for 2 weeks, then 200 mg twice daily CD4 ≥250 (females) and ≥400 (males), use lopinavir/ritonavir (two tablets 12 hourly)
Contraindications to tenofovir: Creatinine clearance of <50ml/min	Abacavir + lamivudine + efavirenz (or nevirapine)	Renal disease or the use of other nephrotoxic drugs, e.g. aminoglycosides Multi-drug-resistant TB treatment
TB - tuberculosis.		

*Source: National Consolidated Guidelines for the Prevention of Mother-to-child Transmission of HIV (PMTCT) and the Management of HIV in Children, Adolescents and Adults. 2015: 73.

2.5.2 Neuropsychiatric side effects of efavirenz

Almost half of patients initiated on efavirenz experience neuropsychiatric side effects (Gutierrez-Valencia, Viciana, Palacios, Ruiz-Valderas, Lozano, Terron, Rivero and Lopez-Cortes, 2009: 149; Kenedi and Goforth, 2011: 1803; Lochet, Pyriere, Lotthe, Mauboussin, Delmas and Reynes, 2003: 62). The most commonly reported side effects include dizziness, insomnia, headache, abnormal dreams and impaired concentration (Arendt, de Nocker, von Giesen and Nolting, 2007: 148; Kenedi and Goforth, 2011: 1803; Nelson, Stellbrink, Podzamczer, Banhegyi, Gazzard, Hill, van Delft, Vingerhoets, Stark and Marks, 2011: 337; MedlinePlus, 2015). These side effects occur most commonly in the first days of treatment and generally resolve within the first four to six weeks (Gutierrez-Valencia, *et al*., 2009: 155).

The spectrum of neuropsychiatric side effects experienced by patients on efavirenz therapy and baseline predictors was specifically investigated (Blanch, Martinez, Rousaud, Blanco, Garcia-Viejo, Peri, Mallolas, De Lazzari, De Pablo and Gatell, 2001: 337). The most frequently reported symptoms were dizziness, light-headedness and feeling disengaged from reality (Blanch, *et al*., 2001: 339). There was a high incidence of major side effects in the first two weeks of therapy and, in spite of this; most patients were able to maintain efavirenz therapy. Another study (Journot, Chene, De Castro, Rancinan, Cassuto, Allard, Vilde, Sobel, Garre, Molina and the ALIZE study group, 2006: 1792) aimed to determine whether or not efavirenz was associated with a higher risk of depressive disorders. There were 177 patients, 30 of whom exhibited depressive disorders, four of which were attempted suicides. In spite of this, statistical analysis showed that efavirenz was not a factor in the onset of these depressive episodes. Rather, a younger age and a history of depressive symptoms proved more significant risk factors (Journot, *et al.,* 2006: 1796-1797). Other studies reported a range of neuropsychiatric side effects similar to that of Blanch and colleagues (2001) in addition to sleep disturbances, drunkenness and mood changes (Lochet, *et al.,* 2003: 63; Fumaz, Munoz-Moreno, Molto, Negredo, Ferrer, Sirera, Perez-Alvarez, Gomez, Burger and Clotet, 2005: 562; Gutierrez, Navarro, Padilla, Anton, Masia, Borras and Martin-Hidalgo, 2005: 1651; Hoffman, Fielding, Charalambous, Sulkowski, Innes, Thio, Chaisson, Churchyard and Grant, 2008; Gutierrez-Valencia, *et al.,* 2009: 152).

The long-term effect of efavirenz was determined in patients receiving efavirenz for an average of 14.50 months (Lochet, *et al.,* 2003: 62, 63). Most of the neuropsychiatric adverse events appeared during the first month of treatment and continued for at least three months afterwards (Lochet, *et al*., 2003: 63). A total of 10.3% of patients reported suicidal ideations whereas none had these feelings before the initiation of efavirenz. This symptom was associated with other depressive symptoms such as demoralisation and cognitive disorders (Lochet, *et al*., 2003: 65). Other long term studies such as those conducted by Fumaz and colleagues (2005: 563), Rihs and colleagues (2006: 547) and Clifford and colleagues (2009: 345), demonstrated that the neuropsychiatric symptoms may persist for up to two to three years after the initiation of efavirenz therapy. Both these studies stated that the side effects noted to persist were dizziness, sleep disturbances, abnormal dreams and light-headedness. This may prompt patients to stop adhering to medication over a period of time.

The severity of neuropsychiatric adverse reactions may influence the adherence of patients to efavirenz therapy which would have a negative impact on treatment efficacy. Although the study conducted by Lochet and colleagues (2003: 65) reported feelings of suicide, Kenedi and Goforth (2011: 1815) stated that there was no clear evidence of a systematically increased risk of suicide or violent behaviour when administering efavirenz, and patients with mental illness or substance abuse histories should not be routinely excluded from receiving efavirenz containing regimens.

The Clinical Guidelines for the Management of HIV and AIDS in Adults and Adolescents in South Africa (2010: 26) state that the recommended safety monitoring for the CNS side effects of efavirenz such as dizziness, distractedness, vivid dreams, dysphoria and depression is ‘clinical’. The term ‘clinical’ is left open to interpretation with no specific symptoms that should be taken into account when considering a diagnosis being listed. According to the South African Guidelines, efavirenz should be avoided in patients with untreated depression and patients receiving psychoactive drugs (2010: 32). The Guidelines further state that efavirenz may be replaced with nevirapine if the patient is experiencing severe dizziness due to efavirenz that cannot be resolved (2010: 20). The 2013 version of the South Africa ART Guidelines (2013: 7) expressly states that efavirenz should be replaced with nevirapine in patients with psychiatric co-morbidities while the 2014 Guidelines (Meintjes, *et al.*, 2014: 123) state

that efavirenz may cause central nervous system symptoms such as vivid dreams, problems with concentration, dizziness, confusion, mood disturbances and psychosis. The efavirenz package insert does not state that efavirenz is contraindicated in psychiatric patients (Adco-Efavirenz, 2007). The insert does mention that efavirenz can cause neuropsychiatric side effects; however, the incidence is classified as rare and includes only anxiety, apathy, emotional lability, euphoria, hallucinations and depression (Adco-Efavirenz, 2007).

2.5.2.1 Comparison studies

Some studies aimed to compare the incidence of neuropsychiatric side effects with efavirenz compared to other ARVs. One study compared efavirenz and nevirapine initial treatment as part of triple therapy (Nunez, Soriano, Martin-Carbonero, Barrios, Barreiro, Blanco, Garcia-Benayas and Gonzalez-Lahoz, 2002: 186). CNS symptoms such as light-headedness, insomnia and restlessness only occurred in the efavirenz group. Four of 12 patients on efavirenz discontinued the medication, but in other patients the symptoms were transient or mild (Nunez, *et al*., 2002: 190).

Another study compared patients using efavirenz with those using protease inhibitors as part of their ART (Hawkins, Geist, Young, Giblin, Mercier, Thornton, Haubrich, 2005: 187). Patients had to have been on their current regimen for at least four weeks to be included in the study (Hawkins, *et al*., 2005: 188).. Efavirenz therapy was associated with increased neuropsychiatric impairment compared to patients receiving a protease inhibitor during the first four weeks of treatment. However, assessment of patients using either efavirenz or a protease inhibitor beyond the first four weeks of treatment showed little difference in neuropsychiatric symptoms. Neurologic symptoms caused by efavirenz tended to disappear after four weeks, but other symptoms may persist for up to a year and may even present at a later point in time (Hawkins, *et al*., 2005: 190, 195). The study therefore suggested that ongoing psychological of patients of efavirenz be made a part of the general follow-up assessments.

A study by Nelson and colleagues (2011: 336) evaluated whether 12 weeks of once daily etravirine with nucleoside reverse transcriptase inhibitors (NRTIs) would be associated with fewer neuropsychiatric adverse events than efavirenz with two NRTIs.

The duration of the trial was 48 weeks, with the primary analysis of neuropsychiatric side effects at week 12. Patients were randomised to either etravirine or efavirenz with two investigator-selected NRTIs (either tenofovir/emtricitabine, abacavir/lamivudine or zidovudine/lamivudine). Patients attended study visits at week two, six and 12. There were 10 patients in the etravirine arm and eight in the efavirenz who discontinued therapy after 12 weeks (Nelson, *et al*., 2011: 337). Clinical and laboratory abnormalities were classified using the Division of AIDS grading system. This system classifies adverse events as either grade 1 (mild), grade 2 (moderate), grade 3 (severe) or grade 4 (life-threatening). At the primary analysis, the percentage with treatment-induced grade 1 to 4 drug-related neuropsychiatric adverse events was 16.5% in the etravirine arm and 46.2% in the efavirenz arm (Nelson, *et al.,* 2011: 337). The most common adverse event of the nervous system was dizziness, reported in three patients (4.0%) in the etravirine arm and 15 patients (19.0%) in the efavirenz arm. The most common psychiatric adverse events were sleep disorder (abnormal dreams, nightmares, sleep disorders or insomnia) which was observed in seven patients (9.0%) in the etravirine arm and 25 patients (32.0%) in the efavirenz arm (Nelson, *et al*., 2011: 337). Although there was a statistically significant benefit for etravirine over efavirenz for neuropsychiatric adverse events, most of these adverse events were grade 1 (mild) or grade 2 (moderate) in intensity.

Orkin and colleagues (2012: 115) also considered efavirenz and etravirine by means of a randomised trial. Efavirenz consistently showed more association with neuropsychiatric side effects than etravirine. The specific symptoms considered were sleep, attention, dizziness, mood and tiredness. However, at week 48 of the follow up there was no significant difference between patient arms with regards to the HIV-Patient Symptoms Profile questionnaire that was used. This study supports the notion that the neurological component of neuropsychiatric side effects caused by efavirenz are short-lived (Orkin, *et al.,* 2012: 117).

Lennox and colleagues (2009: 800) compared 566 treatment naïve HIV-positive patients who were treated with either raltegravir- (n=281) and efavirenz-based (n=282) regimens as initial therapy. The incidence of CNS effects was higher in the efavirenz group than the raltegravir which was shown by an analysis after eight weeks that at least one CNS-related adverse effect had occurred in 18.0% (n=50) of patients on

efavirenz compared to 10.0% (n=29) of patients on raltegravir (Lennox, *et al.,* 2009: 801). The specific clinical events of any severity affecting more than 10.0% of patients in either the raltegravir or efavirenz arms were dizziness, headache and abnormal dreams.

The studies mentioned above agree that neuropsychiatric side effects are more common with efavirenz therapy than with other ARVs. These effects may present themselves within the first month of therapy and disappear after six weeks. The side effects tend to be mild and do not always necessitate the discontinuation of efavirenz. However, the studies note that there have been incidences of delayed onset of neuropsychiatric effects associated with efavirenz, which means that patient monitoring needs to be a continuous process. Interestingly, there has been one German study that indicated no increased susceptibility to neuropsychiatric side effects with efavirenz (von Giesen, Koller, de Nocker, Haslinger and Arendt, 2003: 387). The study compared efavirenz with nevirapine and reported that although there was an incidence of neuropsychiatric side effects within the first few weeks of therapy, the risk was not higher with efavirenz as opposed to nevirapine (von Giesen, *et al.,* 2003: 387-388).

2.5.3 Epidemiology of efavirenz-induced neuropsychiatric side effects

The three main risk factors for the development of neuropsychiatric symptoms in PLWHA are: pre-existing mental disorders, HIV disease progression and ART. The plasma levels of efavirenz are thought to play a role in the development of neuropsychiatric adverse events (Gutierrez-Valencia, *et al.,* 2009: 155; Gazzard, *et al*., 2010: 68). Other risk factors include genetic polymorphisms in certain populations and gender differences in the incidence of neuropsychiatric side effects. These risk factors will be discussed in this section.

2.5.3.1 Plasma levels

Gutierrez-Valencia and colleagues (2009: 155) aimed to determine whether initiating efavirenz in a stepwise dosing schedule would result in fewer neuropsychiatric side effects than normal dosing. The rationale was that the plasma levels obtained through the stepwise dosing of efavirenz would be lower than when initiating the normal

efavirenz dose and therefore result in lower incidences of neuropsychiatric adverse events. The study concluded that the stepwise dosing of efavirenz over two weeks decreased the incidence and severity of neuropsychiatric side effects while maintaining the same virological efficacy as the standard dosing schedule (Gutierrez-Valencia, *et al.,* 2009: 155).

Another study examined whether monitoring plasma levels of efavirenz would serve as a predictor for the emergence of neuropsychiatric adverse events (Gutierrez, Navarro, Padilla, Anton, Masia, Borras and Martin-Hidalgo, 2005: 1649). More than half of the participants reported neuropsychiatric adverse events during long-term efavirenz therapy and 25.0% developed delayed CNS toxicity which led to discontinuation of efavirenz. All discontinuations included patients who were on efavirenz for longer than one year which indicates a delayed neurotoxic effect of efavirenz (Gutierrez, *et al*., 2005: 1652). Patients experiencing neuropsychiatric symptoms during efavirenz therapy usually had drug plasma concentrations of more than 2.74µg/ml. Patients with efavirenz concentrations below this value seemed to have a lower risk for developing CNS-related adverse events during long-term efavirenz therapy (Gutierrez, *et al*., 2005: 1652). An earlier study produced similar results (Marzolini, Telenti, Decosterd, Greub, Biollaz and Buclin, 2001: 74). However, in this study, the neuropsychiatric side effects were associated with slightly higher plasma levels of efavirenz of 4µg/ml (Marzolini, *et al*., 2001: 73).

2.5.3.2 Genetic polymorphism

Efavirenz is predominantly metabolised by the CYP450 enzyme system. The specific enzyme within the system being the most important for the metabolism of efavirenz is CYP2B6 (Mukonzo, Okwera, Nakasujja, Luzze, Sebwufu, Ogwal-Okeng, Waako, Gustafsson, Aklillu, 2013: 2; Mukonzo, Owen, Ogwal-Okeng, Kuteesa, Nanzigu, Sewankambo, Thabane, Gustafsson, Ross and Aklillu, 2014: 1; Naidoo, Chetty and Chetty, 2014: 380). This enzyme is highly polymorphic and it has been shown that these polymorphisms play a role in the variability of efavirenz concentrations (Naidoo, *et al*., 2014: 381). Functionally deficient alleles such as CYP2B6*6, *18 and *22 may result in significantly higher plasma levels of efavirenz in patients receiving a standard dose (600mg daily) due to decreased metabolism of efavirenz. The frequency of these deficient alleles varies amongst populations (Naidoo, *et al*., 2014: 381). These

polymorphisms have been shown to be more common in patients of African descent and such patients should be monitored more closely as they are more likely to experience higher plasma levels of efavirenz and be susceptible to neuropsychiatric side effects. This means that the standard dose of efavirenz may not be suitable for all patients (Naidoo, *et al*., 2014: 386).

A Ugandan study found that high plasma levels of efavirenz was the main predictor for the development of neuropsychiatric side effects (Mukonzo, *et al*., 2013: 7). The plasma concentrations were predicted by CYP2B6 genotypes. Although the results were not statistically significant, it was shown that there was a tendency for CYP2B6*6 genotype to be associated with a higher incidence of sleep disorders and hallucinations (Mukonzo, *et al*., 2013: 7). Another Ugandan based study stated that although there is evidence of inter-ethnic efavirenz pharmacokinetic variability, dosing of the medication in sub-Saharan Africa is based on studies conducted among Caucasians (Mukonzo, *et al*., 2014: 6). The study recommended a dose decrease from 600mg daily to 450mg daily based upon a general genetic make-up amongst Ugandans in general and a 50.0% dose decrease (300mg daily) to those with a CYP2B6*6 allele variation (Mukonzo, *et al*., 2014: 6). Patients with the CYP2B6*6 allele variation are more susceptible to neuropsychiatric adverse effects due to the decreased metabolism of efavirenz which results in increased CNS exposure.

Another African study conducted by Ngaimisi and colleagues (2013: 2) focused on differences in efavirenz pharmacogenetics and pharmacokinetics between Ethiopians and Tanzanians. The major findings showed that geographic differences and CYP2B6*6 are significant predictors of efavirenz plasma and intracellular concentrations (Ngaimisi, *et al*., 2013: 7). The genetic variations were higher amongst Tanzanians than Ethiopians, therefore efavirenz plasma and intracellular concentrations were higher in Tanzanians than in Ethiopians. Neuropsychiatric symptoms were observed more frequently in Tanzanian patients (Ngaimisi, *et al*., 2013: 7). Ethiopian patients experience fewer neuropsychiatric side effects and none of the patients discontinued treatment (Ngaimisi, *et al*., 2013: 7). The findings of this study demonstrated that the results obtained from one geographic region may not necessarily be extrapolated to others (Ngaimisi, *et al*., 2013: 7). However, genetic variations may not be the only explanation for the differences observed in efavirenz

pharmacokinetics. Environmental factors may also play a role (Ngaimisi, *et al*., 2013: 7).

In order to determine if this phenomenon existed amongst South Africans, 80 black South African patients were recruited from an ARV clinic in Johannesburg (Gounden, van Niekerk, Snyman and George, 2010: 2). The patients were ARV naïve and were initiated on efavirenz at the time of the study. It was showed that 23.0% of the patients possessed an allelic variant of CYP2B TT and were, as a result, poor metabolisers of efavirenz. However, the study states that there is no evidence to suggest that genotyping and measurement of efavirenz plasma concentrations would improve therapeutic outcomes (Gounden, *et al.,* 2010: 8). In spite of the presence of these allelic variants, after four weeks, no patient reported to be experiencing any neuropsychiatric side effect (Gounden, *et al.,* 2010: 7).

2.5.4 Management of neuropsychiatric side effects

The Clinical Guidelines for the Management of HIV and AIDS in Adults and Adolescents in South Africa (2010: 32) does not discuss the management of neuropsychiatric side effects caused by efavirenz in depth. Instances have shown that efavirenz is generally discontinued if patients are unable to tolerate the side effects, but it is not specified whether it should be substituted by another ARV agent or whether the efavirenz is reinstated once the side effects have abated. The Clinical Guidelines (2010: 32) state that a diagnosis of an acute psychotic episode should be managed according to the National Treatment Guidelines.

Turjanski and Lloyd (2005: 60) recommend that neuropsychiatric side effects caused by efavirenz be treated according to the severity. Mild symptoms can be monitored and treated pharmacologically if necessary, whereas more severe symptoms may warrant the discontinuation of efavirenz. Again, no suggestion is made of an alternative drug. Treisman and Kaplin (2002: 1211) suggest that patients with a history of depression should receive antidepressant therapy before the initiation of ART or the antidepressants should be initiated concurrently (Treisman and Kaplin, 2002: 1210). If depression occurs after the initiation of efavirenz and does not resolve spontaneously, alternative ART may need to be considered or aggressive antidepressant treatment. However, no specific drug is suggested.

Nevirapine may be substituted for efavirenz if the neuropsychiatric side effects are found to be intolerable to the patient. However, there are safety concerns with nevirapine in terms of hepatic toxicity (Schouten, Krambrink, Ribaudo, Kmack, Webb, Shikuma, Kuritzkes and Gulick, 2010: 787). Schouten and colleagues (2010: 787) aimed to assess the safety and efficacy of substituting nevirapine for efavirenz. A total of 765 patients were randomised to efavirenz and two nucleoside reverse transcriptase inhibitors or three nucleoside reverse transcriptase inhibitors. Of the total, 70 patients substituted nevirapine for efavirenz with 47 patients requiring this substitution this due to intolerable neuropsychiatric side effects (Schouten, *et al.,* 2010: 789). Most of these substitutions took place within the first 24 weeks of therapy. The study showed that a history of psychiatric disorder was a statistically significant predictor of nevirapine substitution. After switching to nevirapine, most patients experienced resolution of CNS symptoms (n=97; 87.0%). Within 32 weeks of nevirapine substitution, 15 patients discontinued nevirapine due to adverse effects such as skin abnormalities, hepatotoxicity and virologic failure (Schouten, *et al.,* 2010: 789). This study showed that switching to nevirapine will result in resolution of efavirenz-induced neuropsychiatric side effects, but liver functioning needs to be monitored in patients who receive nevirapine (Schouten, *et al.,* 2010: 790).

Jonsson and Joska (2009: 23) state that antipsychotic agents are safe to use in PLWHA and may be used to manage an acute psychotic episode. However, these agents should always be used at the lowest possible dose for the shortest duration possible (Jonsson and Joska, 2009: 23). Generally typical antipsychotic agents, such as haloperidol or chlorpromazine, are used in resource-limited settings. The patients should be monitored for extrapyramidal symptoms. If risperidone, an atypical antipsychotic, is available it may be used at a dose of 1mg to 4mg daily (Jonsson and Joska, 2009: 24). The atypical antipsychotics are recommended rather than typical antipsychotics as they are better tolerated, however this does not mean that they are without side effects. Atypical antipsychotics are associated with long-term metabolic effects and the potential for drug interactions (Jonsson and Joska, 2009: 24).

2.6 EFAVIRENZ USE IN PREGNANCY OR WOMEN OF CHILD-BEARING POTENTIAL

Female patients who test HIV-positive whilst pregnant are eligible for ART irrespective of CD4 count and WHO clinical stage (South African Antiretroviral Treatment Guidelines, 2013: 5). The 2010 South African guidelines state that efavirenz should be avoided during the first trimester of pregnancy due to a risk of congenital abnormalities (Clinical Guidelines for the Management of HIV and AIDS in Adults and Adolescents, 2010: 26) however, according to the 2013 ART guidelines, efavirenz is the recommended ART for pregnant women at their first antenatal visit at any stage of gestation in spite of concerns of its teratogenicity (South African Antiretroviral Treatment Guidelines, 2013: 12). Efavirenz is only contraindicated in pregnancy in the case of active psychosis (South African Antiretroviral Treatment Guidelines, 2013: 12).

As pregnant women are excluded from clinical trials, the teratogenicity concerns of efavirenz arose following malformations occurring in foetuses of pregnant monkeys with plasma concentrations of efavirenz similar to that obtained in humans (Adco-Efavirenz package insert, 2007; Chersich, Urban, Venter, Wessels, Krause, Gray, Luchters and Viljoen, 2006). Data concerning the teratogenicity of efavirenz in humans can only be obtained through prospective cohort studies or retrospective observational studies. A review by Belden and Squires (2008: 427) suggests that efavirenz should be avoided in pregnant female patients, and nevirapine or a protease-inhibitor based regimen be used instead, as does a review by Rakhmanina and van den Anker (2010: 99) which state that prospective reports have shown birth defects in 13/407 live births when initiating efavirenz during the first trimester and 2/37 live births when there is exposure to efavirenz during the second and third trimesters. These defects include neural tube defects, anophthalmia, severe oblique facial clefts and amniotic banding. A review by Stek (2009: 72) however, showed that 407 prospectively reported first trimester exposures to efavirenz reported no birth defects.

A South African study (Bera, McCausland, Nonkwelo, Mgudlwa, Chacko and Majeke, 2010: 284) based in the Eastern Cape aimed to determine the prevalence and type of birth defects in women taking efavirenz during pregnancy. The study was prospective and followed a cohort of pregnant women. A total of 623 women were initiated on an efavirenz-based regimen during pregnancy (Bera, *et al.,* 2010: 285). Birth defects

occurred in 16 (2.6%) of the 623 live births. The defects included arachnoid cyst, unconfirmed pulmonary stenosis, postaxial polydactyly, facial asymmetry and overlapping fingers, bilateral club feet, congenital naevus and umbilical hernia (Bera, *et al.,* 2010: 286). There were 195 women who conceived whilst on an efavirenz-based regimen with all of these pregnancies being unplanned. In 55 of these women, efavirenz was substituted for nevirapine. Birth defects were observed in five of the 184 live births and in one of four stillbirths which gives a birth defect prevalence of 3.3%. The birth defects were Trisomy 18, arthrogryposis multiplex congenital, oesophageal atresia, postaxial polydactyly of fingers and preaxial polydactyly with syndactyly of toes (Bera, *et al.,* 2010: 286). Of the 33 women who conceived whilst on a nevirapine-based regimen, the prevalence of birth defects amounted to 3.0% (Bera, *et al.,* 2010: 287). There was no significant difference in the prevalence of birth defects following conception with efavirenz compared to nevirapine (Bera, *et al.,* 2010: 287) nor was there any difference in the prevalence of birth defects of women who were exposed to efavirenz in the first trimester compared to the second and third trimesters. The study suggests that altering efavirenz therapy would not significantly decrease the risk of birth defects neither does the use of efavirenz during the second and third trimesters of pregnancy.

The 2014 South African Guidelines however, now state that efavirenz may be used in pregnant women (Meintjes, *et al.*, 2014: 131). Women should be given the explanation that teratogenicity studies were in fact performed in animals and human studies have not shown an increased risk of congenital abnormalities (Meintjes, *et al.*, 2014: 131). The WHO also recommends that efavirenz be used in women of child-bearing potential and throughout pregnancy (WHO, 2012: 14).

2.7 SUBSTANCE ABUSE AND EFAVIRENZ

Substance abuse is associated with progression of HIV disease even when taking into consideration non-adherence. Moosa (2013: 63) is of the opinion that substance abuse is a more significant barrier to adherence than mental illness. It is important that clinicians know whether or not patients are substance abusers in order to counsel patients on possible interactions with ARVs (Gruber and McCance-Katz, 2010: 152). Commonly considered substances by studies include ethanol, cocaine, lysergic acid diethylamide (LSD), opiates, phencyclidine hydrochloride (PCP) and

tetrahydrocannabinol (THC). Each of these substances will be discussed in this section.

2.7.1 Ethanol

Ethanol metabolism occurs primarily via alcohol dehydrogenase and subsequently aldehyde dehydrogenase. The acute ingestion of ethanol results in the inhibition of the enzymes CYP2D6 and 2C19, while the long term use of ethanol can induce the activity of CYP2E1 and CYP3A4. Therefore, long term use of ethanol can result in chronic medications like NNRTIs to become sub-therapeutic (Antoniou and Lin-in Tseng, 2002: 1 609; Wynn, Cozza, Zapor, Wortmann and Armstrong, 2005: 80).

2.7.2 Cocaine

Intravenous drug use is a major risk factor for the transmission of HIV. The metabolism of cocaine to its metabolite norcocaine, takes place via the CYP3A4 enzyme (Antoniou and Lin-in Tseng, 2002: 1604; Gruber and McCance-Katz, 2010: 153). Efavirenz is an inhibitor of this enzyme and the concomitant use may result in an overdose of cocaine which is potentially fatal (Antoniou and Lin-in Tseng, 2002: 1 604; Wynn, *et al*., 2005: 81). Cocaine is also known to cause alterations in different lymphocytes such as helper T cells, suppressor T cells and natural killer cells, which may then affect the pathobiology of HIV (Xu, Flick, Mitchell, Knowles and Ault, 1999: 464). Cocaine can also enhance the replication of HIV (Gruber and McCance-Katz, 2010: 153; Xu, *et al*., 1999: 464).

2.7.3 Lysergic acid diethylamide

LSD is a powerful hallucinogenic drug of which the metabolism is incompletely understood. Therefore, patients using LSD concurrently with ARVs need to be counselled on the possibility of unknown interactions (Antoniou and Lin-in Tseng, 2002: 1601; Wynn, *et al*., 2005: 82).

2.7.4 Opiates

Heroin addiction reduces adherence to ART therefore heroin addiction needs to be treated (Gruber and McCance-Katz, 2010: 154). Methadone is a long-acting μ-opioid receptor agonist and is helpful in patients with an opioid addiction. Methadone can

also be used in heroin addicts who suffer from chronic pain. There is some disagreement on the enzymes involved in the metabolism of methadone. One study states that methadone is metabolised by CYP2B6 and 2C19, with mixed opinions on the involvement of CYP3A4 and minor involvement of CYP2C8 and 2D6 (Gruber and McCance-Katz, 2010: 155), another indicates that the metabolism of methadone is primarily metabolised by CYP3A4 and 2D6 with 2C possibly playing a role as well (Gourevitch and Friedland, 2000: 430). Yet another study states that the metabolism of methadone is by CYP3A4 with minor contributions from CYP2D6, 2C9, 2E1 and 1A2 (Wynn, *et al.,* 2005: 82) and another indicating that metabolism is primarily by CYP3A4 with contributions by 2D6, 2C19 and 2B6 (Antoniou and Lin-in Tseng, 2002: 1601). However, the studies concur that the concurrent administration of efavirenz and methadone will result in opiate-withdrawal symptoms.

Buprenorphine is a mixed μ agonist/antagonist whose primary metabolism occurs via CYP3A4 with subsequent conjugation of metabolites. Efavirenz, being an inhibitor of CYP3A4, may cause buprenorphine overdose (Wynn, *et al*., 2005: 83). However, because buprenorphine and its metabolite norbuprenorphine are further metabolised by glucuronidation, the likelihood of clinically significant interactions is reduced by reducing the competition with other drugs at the CYP450 enzyme system (Gruber and McCance-Katz, 2010: 155).

2.7.5 Phenylcyclidine hydrochloride

The metabolism of PCP is mainly through the activity of CYP3A4, therefore the concurrent use of efavirenz, an inhibitor of the enzyme, can lead to toxic plasma levels of PCP. PCP may also inhibit the activity of CYP2B6. As efavirenz is a substrate of CYP2B6, co-administration of PCP could lead to increased plasma levels of efavirenz (Antoniou and Lin-in Tseng, 2002: 1600; Wynn, *et al*., 2005: 383).

2.7.6 Tetrahydrocannabinol

The primary means of metabolism for THC is CYP3A4, therefore efavirenz administration may result in toxicity of THC due to the inhibitory activity of efavirenz on CYP3A4 (Wynn, *et al*., 2005: 84). No conclusive data have been obtained as to the potential risks associated with HIV infection and THC use in a therapeutic mode (Abrams, Hilton, Leiser, Shade, Elbeik, Aweeka, Benowitz, Bredt, Kosel, Aberg,

Deeks, Mitchell, Mulligan, Bacchetti, McCune and Schambelan, 2003: 264; Cabral, 2006: 286; Gruber and McCance-Katz, 2010: 154). The studies involving THC are performed using government-issued marijuana of known content and potency and do not take into consideration marijuana obtained from other sources.

2.8 TB CO-INFECTION

HIV with a TB co-infection results in patients requiring a large number of different medications. This increases the likelihood of drug interactions and side effects that a patient may experience. The combination of rifampicin and efavirenz may result in the slight decrease in plasma concentrations of efavirenz in Caucasian populations, which means that the dose of efavirenz should be increased from 600mg daily to 800mg daily (Lopez-Cortes, Ruiz-Valderas, Viciana, Alarcon-Gonzalez, Gomez-Mateos, Leon-Jimenez, Sarasa-Nacenta, Lopez-Pua and Pachon, 2002: 689; Burman, 2008: 93; Gengiah, Gray, Naidoo and Karim, 2011: 4). However, it has been shown that genetic variations in certain patient populations such as Africans and Asians have more of an effect on the plasma concentration of efavirenz than the co-administration of rifampicin (Uttayamakul, Likanonsakul, Manosuthi, Wichukchinda, Kalambaheti, Nakayama, Shioda and Khusmith, 2010: 8). Indeed, these patient populations have been successfully managed on efavirenz 600mg daily (Gengiah, *et al.,* 2011: 4). A South African study was conducted in 2011 (Orrell, Cohen, Conradie, Zeinecker, Ive, Sanne and Wood: 8) that showed that the dose escalation of efavirenz to 800mg daily is not necessary in a South African population. However, the incidence of neuropsychiatric side effects in patients with the CYP2B6 genetic variation, which is relatively common in Africa, South-East Asia and the Caribbean, still needs to be determined (Lawn, Meintjies, McIlleron, Harries and Wood, 2013: 5).

Concerning the side effects associated with efavirenz in TB co-infected patients, studies have shown that side effects experienced are minimal. A randomised trial conducted by Swaminathan and colleagues (2011: 716) reported that a nevirapine-containing regimen was inferior to an efavirenz-containing regimen. The relative risk of treatment failure with nevirapine was shown to be 1.28 compared to efavirenz. Of 122 patients, there were 10 virological failures and five deaths in the nevirapine arm compared to just five virological failures and no deaths in the efavirenz arm (Swaminathan, *et al.,* 2011: 718). One patient in the efavirenz arm discontinued

therapy due to psychosis and two patients in the nevirapine arm switched to efavirenz due to Stevens-Johnson syndrome. A study conducted by Manosuthi and colleagues (2008: 296) also reported that the incidence of adverse events associated with nevirapine was higher and resulted in eight patients (n = 111) discontinuing therapy due to adverse events compared to none in the efavirenz group (n = 77).

A meta-analysis by Jiang and colleagues (2014: 134) also found that efavirenz was favoured over nevirapine to be prescribed to HIV-positive patients with TB co-infection. The review showed that higher rates of discontinuation were associated with nevirapine than efavirenz, but efavirenz still holds the risk of neuropsychiatric side effects for patients with a history of psychiatric disorders (Jiang, Zhang, Chen, Yang, Deng and Ruan, 2014: 134). The South African Antiretroviral Treatment Guidelines (2013: 14) state that an efavirenz-based regimen is the preferred regimen for patients who are HIV-positive with a TB co-infection.

2.9 CONCLUSION

There are a variety of agents available for the management of HIV. Since the introduction of ART, the lifespan of HIV-positive patients has increased dramatically. As indicated, different patient factors such as substance abuse, psychiatric illness, pregnancy, TB co-infection and even ethnicity may make treatment more complicated. Efavirenz forms part of the first-line treatment of HIV in SA and its viability in these various groups of patients must be cemented in the guidelines.

CHAPTER 3

REVIEWS OF THE LITERATURE

3.1 INTRODUCTION

Before the research process begins, an overview of the current opinions and evidence concerning the use of efavirenz and the neuropsychiatric side effects caused by efavirenz needs to be reviewed. This literature chapter considers the neuropsychiatric side effects caused by efavirenz, its severity and management. A review of clinical trials involving efavirenz with the neuropsychiatric side effects recorded and the consequences of these side effects being the primary outcome of these trials was performed. Trials comparing the incidence and severity of the neuropsychiatric side effects caused by efavirenz and those caused by other ARVs such as nevirapine, protease inhibitors, raltegravir and emtricitabine were also considered. These are the agents that can be used in place of efavirenz in the case of intolerable neuropsychiatric side effects or failure of the regimen to suppress the viral load to undetectable levels. A brief overview concerning the place of efavirenz in the guidelines of various countries with differing incomes is provided.

These reviews were used to prepare two articles, one of which was published in the South African Journal of Psychiatry (Gaida, Truter and Grobler, 2015) and the other in Expert Review of Anti-infective Therapy (Gaida, Truter, Grobler, Kotze and Godman, 2016). These two articles will provide the core content of this chapter.

3.2 GAIDA, R., TRUTER, I. AND GROBLER, C. 2015. EFAVIRENZ: A REVIEW OF THE EPIDEMIOLOGY, SEVERITY AND MANAGEMENT OF NEUROPSYCHIATRIC SIDE EFFECTS. *SOUTH AFRICAN JOURNAL OF PSYCHIATRY*, 21(3): 94-97.

Efavirenz: A review of the epidemiology, severity and management of neuropsychiatric side-effects

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South Africa has the highest proportion of HIV-positive people in the world. HIV cannot be cured; however, there are several major classes of drugs used in its management. Efavirenz is one such agent of the class non-nucleoside reverse transcriptase inhibitors which inhibits the replication of the virus. Efavirenz is associated with causing neuropsychiatric side-effects (NPSEs), with almost 50% of patients experiencing at least one NPSE while on treatment. The NPSEs tend to occur within the first few days of initiation of therapy and resolve spontaneously within the first 4 - 6 weeks, with the most commonly reported being dizziness, insomnia, headache, abnormal dreams and impaired concentration. The plasma level of efavirenz and genetic polymorphisms are thought to play a role in the development of such NPSEs. NPSEs need to be treated according to severity. If necessary, efavirenz may be replaced with nevirapine or lopinavir/ritonavir. It should be remembered that nevirapine may also produce some severe side-effects such as skin abnormalities and hepatotoxicity. The monitoring of patients receiving efavirenz therapy should be ongoing, with those with a history of mental illness requiring closer monitoring than others.

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South Africa (SA) has the highest proportion of HIV-positive people in the world. In 2013, an estimated 10% of the population was HIV-positive, which amounted to 5.26 million people.[1] For adults between the ages of 15 and 49 years, an estimated 15.90% were HIV-positive.[1] However, SA has made positive changes in managing the HIV epidemic. The number of people on antiretroviral therapy (ART) has increased, and there have been fewer AIDS-related deaths from 2005 to 2011.[2]

Antiretrovirals used in the management of HIV

HIV cannot be cured; however, there are several major classes of drugs used in its management. The five classes of drugs used for the management of HIV are entry inhibitors, fusion inhibitors, integrase inhibitors, protease inhibitors and reverse transcriptase inhibitors (nucleoside reverse transcriptase inhibitors and non-nucleoside reverse transcriptase inhibitors).[3] These agents act through various mechanisms to stop the replication of HIV. The recommended regimens for the management of HIV in SA are summarised in Table 1.[4]

Efavirenz is a non-nucleoside reverse transcriptase inhibitor that produces its antiretroviral activity by binding directly to the enzyme reverse transcriptase, thus inhibiting replication of the virus.[5] Efavirenz possesses a long half-life of 40 - 55 hours[6] and is predominantly metabolised in the liver by the CYP450 enzyme system. The specific isoform within the system most important for the metabolism of efavirenz is CYP2B6.[7-9]

Almost 50% of patients on efavirenz experience at least one NPSE.[10-12] In spite of this, efavirenz is part of the first-line regimen of HIV management in SA. The NPSEs tend to occur within the first few days after initiation of therapy and then resolve spontaneously within the first 4 - 6 weeks.[10] The most commonly reported NPSEs are dizziness, insomnia, headache, abnormal dreams and impaired concentration.[11,13,14] An increased risk of suicidality has been a concern with efavirenz; however, there is conflicting opinion regarding this.[11,12,15] In light of this, patients with an active psychiatric illness being considered for efavirenz therapy should be evaluated in terms of suicide risk, and these patients should be closely monitored after the initiation of therapy.

HIV infection is now regarded as a 'chronic' condition;[16] therefore, it is important to understand the long-term effects of efavirenz. Studies[12,17,18] have been done to assess the long-term effects and have shown that NPSEs may persist for up to 2 - 3 years following initiation of efavirenz. Dizziness, sleep disturbances, abnormal dreams and light-headedness were the persisting symptoms.[12,17,18] The 2010 *Clinical Guidelines for the Management of HIV and AIDS in Adults and Adolescents in South Africa*[19] stated that the recommended safety monitoring for the NPSEs of efavirenz is 'clinical'. The term 'clinical' is left open to interpretation with no specific symptoms that should be taken into account when considering a diagnosis being listed. This indicates that it is the responsibility of the clinician to determine whether or not side-effects constitute a clinical change in the patient's condition and what management strategies need to be implemented. These *Guidelines* also advise that efavirenz should be

Table 1. Standardised first-line antiretroviral therapy regimens for adults and adolescents in SA[4]

Patient group	Regimen	Recommendations
Adolescents >15 years and weighing >40 kg Adults All TB co-infection All hepatitis B virus co-infection	Tenofovir + lamivudine (or emtricitabine) + efavirenz to be provided as a fixed-dose combination	Replace efavirenz with nevirapine in patients with significant psychiatric comorbidity or intolerance to efavirenz and where the neuropsychiatric toxicity of efavirenz may impair daily functioning, e.g. shift workers
Adults and adolescents on stavudine	Change stavudine to tenofovir (no patient should be on stavudine)	Switch to tenofovir if virally suppressed and the patient has normal creatinine clearance, even if stavudine is well tolerated. If the viral load is >1 000 copies/mL, manage as treatment failure and consider switching to second line
Adolescents <15 years or weight <40 kg	Abacavir + lamivudine + efavirenz	If adolescent weight <40 kg, align with paediatric regimen
Contraindication	**Substitution drug**	**Comments**
Contraindications to efavirenz: Significant psychiatric comorbidity Intolerance to efavirenz Impairment of daily function	Tenofovir + emtricitabine (or lamivudine) + nevirapine or lopinavir/ritonavir	If CD4 <250 cells/mm^3 (females) and <400 cells/mm^3 (males), give nevirapine 200 mg daily for 2 weeks, then 200 mg twice daily If CD4 ≥250 cells/mm^3 (females) and ≥400 cells/mm^3 (males), use lopinavir/ritonavir (two tablets 12 hourly)
Contraindications to tenofovir: Creatinine clearance of <50 mL/min	Abacavir + lamivudine + efavirenz (or nevirapine)	Renal disease or the use of other nephrotoxic drugs, e.g. aminoglycosides Multidrug-resistant TB treatment

TB = tuberculosis.

avoided in patients with untreated depression and patients receiving psychoactive drugs.[19] The 2014 *Guidelines*[4] warn that efavirenz may cause persistent central nervous system toxicity such as abnormal dreams, depression or mental confusion, and that these side-effects are more likely to occur in patients with current or previous depression or other mental disorder or if the efavirenz is taken during the day.[4] The efavirenz package insert does not state that efavirenz is contraindicated in psychiatric patients.[20] It does, however, mention that efavirenz can cause NPSEs, although the incidence is stated as rare and includes only the following symptoms: anxiety, apathy, emotional lability, euphoria, hallucinations and depression.[20]

Epidemiology of neuropsychiatric effects

The three main risk factors for the development of NPSEs in HIV-positive patients are: pre-existing mental conditions, HIV disease progression and ART. The plasma level of efavirenz is thought to play a role in the development of NPSEs, as are genetic polymorphisms in certain population groups.[10,21]

Plasma level

The plasma level of efavirenz seems to have a place in predicting the incidence of NPSEs since the stepwise dosing of efavirenz is shown to decrease both the incidence and severity of NPSEs.[10] However, studies[22,23] attempting to determine the exact plasma level above which patients are at risk of developing these NPSEs have produced inconsistent data.

Genetic polymorphisms

Efavirenz is predominantly metabolised by the CYP450 enzyme system, specifically by the CYP2B6 isoform.[7-9] This enzyme is highly susceptible to polymorphism and these polymorphs play a role in the variability of efavirenz plasma concentrations.[9] Functionally deficient alleles may result in higher plasma levels of efavirenz in patients receiving a standard dose of 600 mg daily because of decreased metabolism of efavirenz.[9] The frequency of these deficient alleles varies among populations, but has been shown to be more common in patients of African descent.[9] Such patients should therefore be monitored more closely as they are more likely to experience a higher plasma level of efavirenz and be susceptible to NPSEs. In an SA context, there are patients who possess the allelic variations, but there is no evidence to suggest that patients would benefit from routine genotyping and measurement of efavirenz plasma levels in terms of therapeutic outcomes.[24] Therefore the current doses are sufficient.

Comparative studies between efavirenz and other antiretrovirals

Studies have been conducted comparing the incidence of NPSEs caused by efavirenz and other antiretroviral agents. Efavirenz has been compared with nevirapine, protease inhibitors, etravirine and raltegravir.[25-27] All of these studies[25-27] analysed have shown that the virological efficacy of efavirenz is not inferior to any other regimen. Although efavirenz demonstrated a higher incidence of NPSEs in all cases, the symptoms tended to be mild and necessitated discontinuation in only small numbers of patients. However, the studies[17,27] noted that there were incidences of delayed onset of NPSEs associated with efavirenz, which refer to patients who develop these NPSEs approximately 1 year after efavirenz has been initiated. This means that patient monitoring needs to be a continuous process. One study[25] stated that the only side-effects that did resolve were the neurological side-effects as the psychiatric side-effects were not generally identified and addressed by physicians. It was suggested that the psychiatric status of patients initiated on efavirenz be closely

monitored for at least the first 6 months to 1 year of treatment.[25] Specific patients who should be monitored are those with early neurological side-effects, as well as those with a history of psychiatric disorders or substance abuse. For patients who are in hospital environments, daily mental status evaluations should be performed. For patients in outpatient settings, evaluations should be performed at every visit for at least 1 year after the initiation of efavirenz.

Severity of NPSEs

The severity of NPSEs may negatively influence the adherence of patients to efavirenz therapy. Studies generally show that the symptoms are mild and do not warrant the discontinuation of efavirenz.[10,14,22,28] It has, however, been stated that if the side-effects persist, patient adherence may decline over time regardless of whether or not the NPSEs are mild to moderate in severity.[17,25,28] Ongoing patient counselling and monitoring is thus imperative for patients using efavirenz, as it is for all patients on ART.

Management of NPSEs

The *Clinical Guidelines for the Management of HIV and AIDS in Adults and Adolescents in South Africa*[19] do not discuss the management of NPSEs caused by efavirenz in depth. Studies[21,25] show that efavirenz is discontinued in patients who are unable to tolerate the side-effects. It is not indicated whether or not another antiretroviral agent is substituted in its place or if efavirenz is reinstated once the side-effects have resolved. The *Clinical Guidelines*[19] state that an acute psychotic episode should be managed according to the *Standard Treatment Guidelines*,[29] which recommend that an acute psychotic episode be managed with 2 - 5 mg of haloperidol administered intramuscularly, to be repeated in 60 minutes if required. If the response to haloperidol is poor, a benzodiazepine such as lorazepam may be administered intramuscularly at a dose of 1 - 4 mg.[29]

The NPSEs caused by efavirenz should be treated according to severity.[30] Mild symptoms can be monitored and treated pharmacologically if necessary, whereas more severe symptoms may warrant the discontinuation of efavirenz and the addition of an alternative antiretroviral agent. Patients with a history of depression should receive antidepressant therapy before the initiation of ART or concurrently.[31] If depression occurs after the initiation of efavirenz and does not resolve spontaneously, alternative ART (as ART is always a combination of three agents) or aggressive antidepressant treatment may need to be considered. Depression may be treated with selective serotonin reuptake inhibitors such as citalopram, escitalopram or fluoxetine.[32,33] If a patient experiences acute psychosis, antipsychotic agents are safe to use.[34] These agents should always be used at the lowest possible dose for the shortest duration possible. Generally, typical antipsychotic agents such as haloperidol or chlorpromazine are used in resource-limited settings. The patients should be monitored for extrapyramidal symptoms. If risperidone, an atypical antipsychotic, is available, it may be used at a dose of 1 - 4 mg daily.[34] Atypical antipsychotics are recommended over typical antipsychotics as they are better tolerated, but this does not mean that they are without side-effects. Atypical antipsychotics are associated with long-term metabolic effects and the potential for drug interactions.[34] Patients who have been experiencing NPSEs with efavirenz for years may be treated symptomatically if necessary. The patient may still be on efavirenz because the patient finds the side-effects tolerable. Indeed, one of the studies that demonstrated delayed onset or persistence of NPSEs indicates that the long-term effects may be mild and tolerated well by patients.[17]

Nevirapine may be substituted for efavirenz if the patient finds the NPSEs intolerable. Research has shown that this substitution will result in the resolution of NPSEs.[35] However, there are safety concerns with nevirapine in terms of skin abnormalities and hepatitis, which is a life-threatening reaction.[35] Patients being initiated on nevirapine need to be reviewed during the first 2 weeks, as recommended by the *Guidelines*.[4] The other alternative as indicated by the *Guidelines* is lopinavir/ritonavir. However, there are significant drug interactions between ritonavir and psychotropic drugs such as clozapine, carbamazepine, and sedatives and hypnotics such as diazepam, midazolam and zolpidem.[36] This would result in further problems in managing the psychiatric patient and the benefits should be weighed against the potential risks before initiating this agent. Other options would be the integrase-inhibitor raltegravir[36] or the non-nucleoside reverse transcriptase inhibitor rilpivirine.[37] Virological failure is more prevalent with rilpivirine than efavirenz, but the side-effect profile of rilpivirine is superior to efavirenz, specifically in terms of NPSEs.[37]

Currently, clinical practice does not favour the prescribing of efavirenz to patients with pre-existing psychiatric conditions, which may compromise the quality of virological control. It is interesting to note that the *Guidelines* state that efavirenz is contraindicated in patients with an active psychiatric illness and nevirapine or lopinavir/ritonavir should be considered instead.[4] Considering that NPSEs of efavirenz are not generally severe enough to warrant the discontinuation of the medicine, there is cause for reconsideration of this matter. Improved compliance may be possible with use of the fixed-dose combination in patients with an active psychiatric illness in order to reduce an already extensive pill burden, as well as improved virological control.

Declaration. We declare that we have no financial or personal relationships which may have inappropriately influenced us in writing this paper.

References

1. Statistics South Africa. Mid-year population estimate. 2013. http://www.statssa.gov.za/publications/P0302/P03022013.pdf (accessed 13 February 2015).
2. AIDS Foundation South Africa. http://www.aids.org.za/hivaids-in-south-africa/ (accessed 12 September 2013).
3. Avert: AVERTing HIV and AIDS. http://www.avert.org/hiv-and-aids-treatment-care.htm (accessed 13 February 2015).
4. National Consolidated Guidelines for the Prevention of Mother-to-child Transmission of HIV (PMTCT) and the Management of HIV in Children, Adolescents and Adults. 2014. Pretoria: National Department of Health, 2014.
5. Cavalcante GIT, Capistrano VLM, Cavalcante FSD, et al. Implications of efavirenz for neuropsychiatry: A review. Int J Neurosci 2010;120(12):739-745. [http://dx.doi.org/10.3109/00207454.2010.520541]
6. Piscitelli SC. Space out drug discontinuations prior to 'drug holiday'? Medscape. 2000. http://www.medscape.com/viewarticle/413306 (accessed 1 September 2014).
7. Mukonzo JK, Okwera A, Nakasujja N, et al. Influence of efavirenz pharmacokinetics and pharmacogenetics on neuropsychological disorders in Ugandan HIV-positive patients with or without tuberculosis: A prospective cohort study. BMC Infect Dis 2013;13(261):1-11. [http://dx.doi.org/10.1186/1471-2334-13-261]
8. Mukonzo JK, Owen JS, Ogwal-Okeng J, et al. Pharmacogenetic-based efavirenz dose modification: Suggestions for an African population and the different CYP2B6 genotypes. Plos One 2014;9(1):1-9. [http://dx.doi.org/10.1371/journal.pone.0086919]
9. Naidoo P, Chetty VV, Chetty M. Impact of CYP polymorphisms, ethnicity and sex differences in metabolism on dosing strategies: The case of efavirenz. Eur J Clin Pharmacol 2014;70(4):379-389. [http://dx.doi.org/10.1007/s00228-013-1634-1]

10. Gutierrez-Valencia A, Viciana P, Palacios R, et al. Stepped-dose versus full dose efavirenz for HIV infection and neuropsychiatric adverse events: A randomized trial. Ann Intern Med 2011;151(3):149-156. [http://dx.doi.org/10.7326/0003-4819-151-3-200908040-00127]
11. Kenedi CA, Goforth HW. A systematic review of the psychiatric side-effects of efavirenz. AIDS Behav 2011;15(8):1803-1808. [http://dx.doi.org/10.1007/s10461-011-9939-5]
12. Lochet P, Peyriere H, Lotthe A, Mauboussin JM, Delmas B, Reynes J. Long-term assessment of neuropsychiatric adverse reactions associated with efavirenz. HIV Med 2003;4(1):62-66. [http://dx.doi.org/10.1046/j.1468-1293.2003.00136.x]
13. Arendt G, de Nocker D, von Giesen H, Nolting T. Neuropsychiatric side effects of efavirenz therapy. Expert Opin Drug Saf 2007;6(2):147-154. [http://dx.doi.org/10.1517/14740338.6.2.147]
14. Nelson M, Stellbrink H, Podzamczer D, et al. A comparison of neuropsychiatric adverse events during 12 weeks of treatment with etravirine and efavirenz in a treatment-naive, HIV-1-infected population. AIDS 2011;25(3):335-340. [http://dx.doi.org/10.1097/QAD.0b013e3283416873]
15. Journot V, Chene G, de Castro N, et al. Use of efavirenz is not associated with a higher risk of depressive disorders: A substudy of the randomized clinical trial ALIZE-ANRS 099. Clin Infect Dis 2006;42(12):1790-1799. [http://dx.doi.org/10.1086/504323]
16. Deeks SG, Lewin SR, Havlir DV. The end of AIDS: HIV infection as a chronic disease. Lancet 2013;382(9903):1525-1533. [http://dx.doi.org/10.1016/S0140-6736(13)61809-7]
17. Fumaz CR, Munoz-Moreno JA, Molto J, et al. Long-term neuropsychiatric disorders on efavirenz-based approaches: quality of life, psychological issues, and adherence. J Acq Immun Def Synd 2005;38(5):560-565. [http://dx.doi.org/10.1097/01.qai.0000147523.41993.47]
18. Clifford DB, Evans S, Yang Y, Acosta EP, Ribaudo H, Gulick RM. Long-term impact of efavirenz on neuropsychological performance and symptoms in HIV-infected individuals (ACTG5097s). HIV Clin Trials 2009;10(6):343-355.
19. Clinical Guidelines for the Management of HIV and AIDS in Adults and Adolescents. Pretoria: National Department of Health, 2010.
20. Adco-Efavirenz package insert. Midrand (Gauteng): Adcock Ingram, 2007.
21. Gazzard B, Balkin A, Hill A. Analysis of neuropsychiatric adverse events during clinical trials of efavirenz in antiretroviral-naïve patients: A systematic review. AIDS Rev 2010;12(2):67-75.
22. Marzolini C, Telenti A, Decosterd LA, Greub G, Biollaz J, Buclin T. Efavirenz plasma levels can predict treatment failure and central nervous system side effects in HIV-1 infected patients. AIDS 2001;15(1):71-75. [http://dx.doi.org/10.1097/00002030-200101050-00011]
23. Hawkins T, Geist C, Young B, et al. Comparison of neuropsychiatric side effects in an observational cohort of efavirenz- and protease inhibitor-treated patients. HIV Clin Trials 2005;6(4):187-196.
24. Gounden V, van Niekerk C, Snyman T, George JA. Presence of CYP2B6 516G> T polymorphism, increased plasma efavirenz concentrations and early neuropsychiatric side effects in South African HIV-infected patients. AIDS Res Ther 2010;7(32):1-9. [http://dx.doi.org/10.1186/1742-6405-7-32]
25. Lennox JL, DeJesus E, Lazzarin A, et al. Safety and efficacy of raltegravir-based versus efavirenz-based combination therapy in treatment-naïve patients with HIV-1 infection: A multicentre, double-blind, randomised controlled trial. Lancet 2009;374(9692):796-806. [http://dx.doi.org/10.1016/s0140-6736(09)60918-1]
26. Orkin C, Nelson M, Katlama C, et al. Changes in patient-reported neuropsychiatric outcomes during the SENSE trial: First-line treatment with two nucleoside analogues plus etravirine or efavirenz. Health Outcomes Res Med 2012;3(3):113-119. [http://dx.doi.org/10.1016/j.ehrm.2012.06.002]
27. Gutierrez F, Navarro A, Padillo S, et al. Prediction of neuropsychiatric adverse events associated with long-term efavirenz therapy, using plasma drug level monitoring. Clin Infect Dis 2005;41(11):1648-1653. [http://dx.doi.org/10.1086/497835]
28. Rihs TA, Begley K, Smith DE, et al. Efavirenz and chronic neuropsychiatric symptoms: A cross-sectional case control study. HIV Med 2006;7(8):544-548. [http://dx.doi.org/10.1111/j.1468-1293.2006.00419.x]
29. Standard Treatment Guidelines and Essential Medicines List for South Africa: Hospital Level Adults. Pretoria: National Department of Health, 2012.
30. Turjanski N, Llyod GG. Psychiatric side effects of medications: Recent developments. Adv Psychiatr Treat 2005;11:58-70. [http://dx.doi.org/10.1192/apt.11.1.58]
31. Treisman GJ, Kaplin AI. Neurologic and psychiatric complications of antiretroviral agents. AIDS 2002;16(9):1201-1215. [http://dx.doi.org/10.1097/00002030-200206140-00002]
32. Brogan K, Lux J. Management of common psychiatric conditions in the HIV-positive population. Curr HIV/AIDS Rep 2009;6(2):108-115. [http://dx.doi.org/10.1007/s11904-009-0016-x]
33. Ferrando SJ. Psychopharmacologic treatment of patients with HIV/AIDS. Curr Psychiatry Rep 2009;11(3):235-242. [http://dx.doi.org/10.1007/s11920-009-0036-7]
34. Jonsson G, Joska JA. Assessment and treatment of psychosis in people living with HIV/AIDS. S Afr J HIV Med 2009;10(3):20-27.
35. Schouten JT, Krambrink A, Ribaudo HJ, et al. Substitution of nevirapine because of efavirenz toxicity in AIDS Clinical Trials Group A5095. Clin Infect Dis 2010;50(5):787-791. [http://dx.doi.org/10.1086/650539]
36. Rossiter D, ed. South African Medicines Formulary. 10th ed. Cape Town: Health and Medical Publishing Group, 2012.
37. Claydon P, ed. HIV Treatment Bulletin + South. HIV i-Base 2012;5(1):1-42.

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REVIEW

A review of trials investigating efavirenz-induced neuropsychiatric side effects and the implications

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ABSTRACT

Efavirenz is part of the first-line treatment for HIV patients including those in South Africa with approximately 50% experiencing neuropsychiatric side effects. A systematic review of papers reporting neuropsychiatric side effects with efavirenz published between January 2001 and December 2014 was performed, to provide guidance. 13 articles were reviewed. Patient ages ranged between 37 to 41 years, with a high percentage males. Scales used to measure incidence and severity of side effects were varied; with disease severity or stage not reported. Patients with psychoses were excluded. Most commonly reported side effects were a reduction in sleep quality, depression, dizziness and anxiety. These were generally mild and not warranting discontinuation of efavirenz. It is difficult to directly compare the studies. Standardised methods need to be introduced and all patient groups represented including the elderly, children, patients with active symptomatic illness and more women especially among the African population.

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Introduction

Efavirenz (EFV) is part of the first-line treatment for human immune-deficiency virus (HIV) in countries such as South Africa [1]. It is used as part of triple therapy involving three separate drugs as well as fixed-dose combinations. However, it has been shown in published studies that almost half of the patients initiated on EFV will experience some form of neuropsychiatric side effect [2,3]. These side effects are said to occur most commonly within the first few days of treatment and resolve within the first 4–6 weeks of treatment [4]. However, it has been found that such symptoms may persist longer than initially thought [5–7]. The symptoms may persist for up to 2 years after initiation, although they may not be severe enough to warrant the discontinuation of EFV [6]. The aim of this review was to provide an overview of the neuropsychiatric side effects caused by EFV in order to determine the severity as well as their use in particular patient populations including psychiatric patients to provide future guidance.

Methods

We undertook a systematic review of studies concerning HIV-positive patients on EFV reporting experiencing neuropsychiatric side effects. All primary studies published from January 2001 to December 2014 were included.

The inclusion criteria were that patients had to be over the age of 18 years and were HIV positive; the study had to follow patients who were using EFV either short term or long term and could be retrospective, prospective, cross-sectional, or comparison studies. The primary outcome must indicate the incidence of neuropsychiatric side effects with a secondary outcome being the number of discontinuations due to these side effects. The electronic databases searched included; Biomed Central, EBSCOhost, Emerald, ISI web of knowledge, JSTOR, PubMed Central, SAGE, ScienceDirect, and SpringerLink. The search terms used were EFV, HIV-positive, neuropsychiatric, and side effects to find primary studies. A broad search was done initially using the keywords EFV, HIV-positive, and side effects. The keywords were then refined (EFV, HIV, and neuropsychiatric side effects) to identify more specific studies. Articles that contained these keywords in the title or abstract were extracted and their relevance was determined. Review articles as well as those including children under the age of 18 years and patients with comorbidities were excluded.

Those that were considered relevant were read in entirety by the principal researcher (RG) to determine potential inclusion. The articles included and excluded are outlined in Figure 1. The search was limited to English language full-text articles published in journals accessible via the Nelson Mandela Metropolitan University database.

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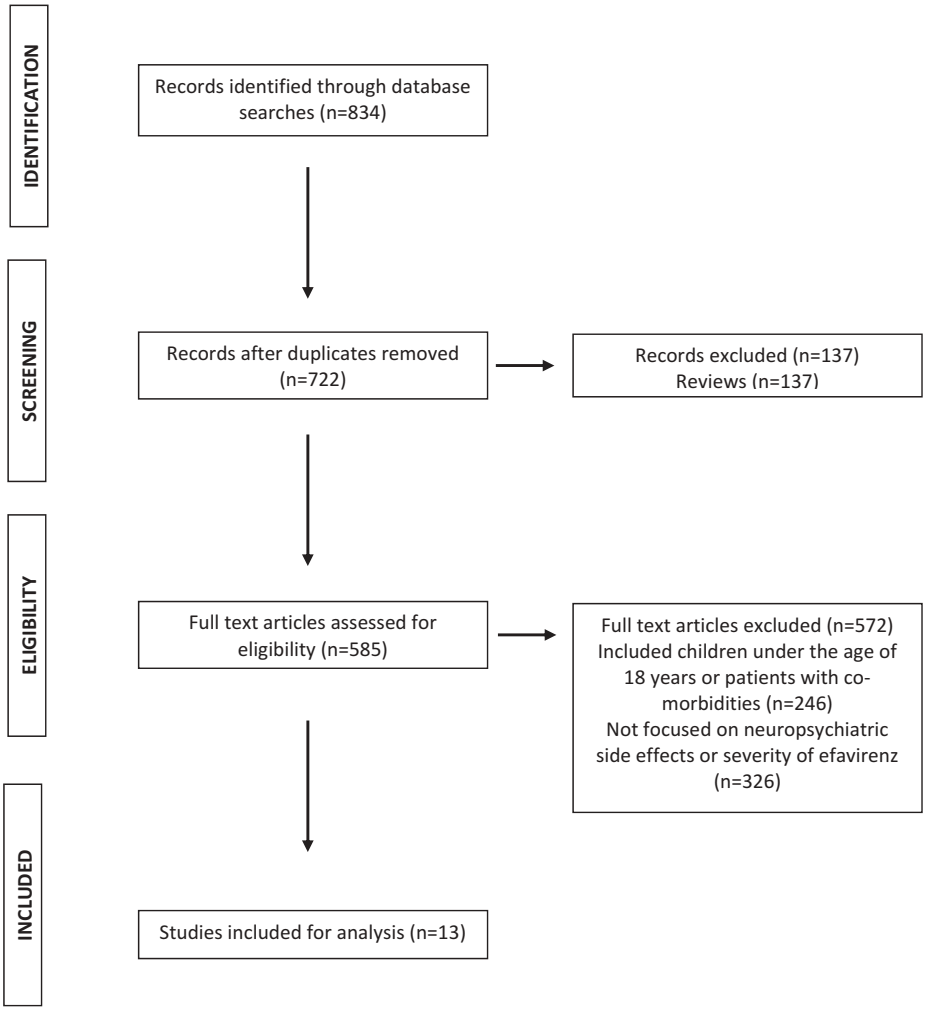

Figure 1. Articles included and excluded in the systematic review.

Results

Overview of studies

Of the studies analyzed, two were randomized controlled trials, one was double-blind, but not randomized, four were cross-sectional cohort studies, four were prospective cohorts, one a retrospective analysis, and another a longitudinal study. Four studies randomized patients to either EFV or another regimen. The other studies included patients who were already receiving EFV or a different regimen and were compared against each other. Five of the studies were conducted in Europe (Spain and France), four in the United States of America (USA), and one each in Australia, South Africa, and the United Kingdom. Details of the studies are summarized in Table 1.

Patient populations

Patients were recruited mostly from outpatient clinics (five studies). Two of the studies were a subset of a larger clinical trial. One study made use of a workplace HIV-program to recruit patients and another recruited patients from the investigators' private practices. Most of the studies showed the patient population was at least 70% male with some studies showing as high as 90% male dominance. The average age of the patients across all of the studies was 37–41 years.

The inclusion criteria varied widely between studies. All participants had to be aged 18 years or older; however, the duration of EFV therapy varied from initiation up to at least 1 year of therapy. Fumaz and colleagues [6] were considering the long-term side effects experienced with EFV and stated that the patient had to be on an EFV -containing regimen for at least 1 year in order to be included. Clifford and colleagues [5] followed consenting patients for 184 weeks after being randomized to EFV. Other studies considered the immediate effects and focused on patients who had just been initiated on EFV or were using EFV for 3–6 months.

The standard dose of EFV is 600 mg daily generally taken at bedtime [8]. Only four studies explicitly stated the dose of EFV being received by the patients. One study made use of three 200 mg tablets that had to be taken together at bedtime while others made use of single 600 mg tablets and one study [4] randomized patients to stepped dose of EFV or EFV 600 mg daily. Although the standard dose of EFV is 600 mg daily, it is dosed based on the weight of the patient. Patients weighing less than 40 kg received 400 mg of EFV at bedtime as opposed to 600 mg, which may impact on the incidence and/or the severity of side effects experienced.

Table 1. Demographics of studies.

Authors, publication year and country	Type of study	Setting	Follow-up period	Number of patients/controls	Average age of patients	Male patients (%)	Duration of efavirenz treatment
Blanch et al. [9] (Spain)	Open-label, prospective, observational study	HIV hospital outpatients	12 weeks	31/–	41 ± 10 years	71	12 weeks
Clifford et al. [5] (USA)	Substudy of randomized, double-blind, controlled trial (A5095)	Multicenter academic clinical trial units	24 weeks	283/–	Median age – 37 years (efavirenz group), 38 years (non-efavirenz group)	82 (efavirenz group), 80 (non-efavirenz group)	184 weeks
Clifford et al. [10] (USA)	Substudy of A5095. Prospective, comparative, placebo-controlled study	Substudy	184 weeks	Efavirenz only – 86, various regimens – 37, late long-term efavirenz – 21, non-efavirenz only – 33, total – 177	Efavirenz only – 39.2 years, various regimens – 37.4 years, late long-term efavirenz – 40 years, non-efavirenz only – 40.5 years	Efavirenz-only – 85, various regimens – 70, late long-term efavirenz – 81, non-efavirenz only – 81	24 weeks
Fumaz et al. [6] (Spain)	Cross-sectional comparative study	Hospital	Cross-sectional study	Efavirenz – 60, protease inhibitor – 60	Efavirenz – 41.4 ± 8.05 years, protease inhibitor – 39.2 ±7.7 years	Efavirenz – 75%, PI – 70	Average time 91.1 ± 39.5 weeks for efavirenz patients and 119.9 ± 67.4 weeks for the PI patients
Gutierrez et al. [11] (Spain)	Longitudinal study	Hospital	18 months	17/–	Median age – 40 years	82.4	Median time was 18 months (range 6–27 months)
Gutierrez-Valencia et al. [4] (Spain)	Randomized, double-blind, controlled trial	Investigators' clinical practice	24 weeks	108 patients (full dose group – 50, stepped dose group – 58)	39 years	Full dose group – 80, stepped dose group – 77.6	24 weeks
Hawkins T et al. [7] (USA)	Cross-sectional questionnaire-based cohort	Not indicated	Cross-sectional	77 protease inhibitor group and 75 efavirenz group	43 ± 7.4 PI group and 40 ± 8.1 years efavirenz group	95 protease inhibitor group and 92 efavirenz group	345 ± 250 days for patients on efavirenz and 582 ± 445 days for patients on PIs
Hoffman et al. [12] (South Africa)	Prospective cohort	Workplace	Included patients started on highly active antiretroviral therapy (HAART) over 3 years (2002–2005) and followed up until November 2006	853/–	Median age – 40 years	98	378 days
Leutscher et al. [13] (Denmark)	Prospective cohort	University hospital outpatient HIV clinic	Patients initiated on therapy from January 2000 until December 2009 were included and followed up until December 2010	276 (168 on efavirenz)/–	Median age – 39 years	Efavirenz group – 71, non-efavirenz group – 53	Patients were on efavirenz between 1 and 11 years
Lochet et al. [14] (France)	Cross-sectional study	HIV outpatients at hospitals	Cross sectional	174/–	Median age – 40 years	78.2	Median duration – 14.5 months (range 3–43.5 months)
Nelson et al. [15] (UK)	Double-blind placebo controlled trial	Clinical trial	48 weeks (primary assessment of neuropsychiatric symptoms at 12 weeks)	157/–	38 years	81	
Rihs et al. [16] (Australia)	Single-center, cross-sectional case controlled	Outpatient HIV clinic	Cross sectional	32/32	Efavirenz group – 43 ± 10 years Control – 44 ± 10 years	Efavirenz – 97 Control – 97	Average duration – 14 ± 5 months in the efavirenz group and 24 ± 14 months in the control group
Ward and Curtin [17] (USA)	Retrospective analysis	HIV-specialty private practice	3 years	40/–	Median age 41 years	97.5	Average of 27 months on efavirenz (range 3–69 months)

Measuring protocols

In terms of the instruments used to measure the neuropsychiatric side effects caused by EFV, there was some diversity. The instruments used are summarized in Table 2. The only common scales were the Symptom Checklist-90-Revised and the Medical Outcome Study for HIV-positive patients scale which were used by two studies.

Seven of the studies used clinicians to interview participants concerning side effects, whereas four studies allowed patients to answer questionnaires themselves. The exception was the study conducted by Fumaz and colleagues [6] who used a combination of both. Further details are provided in Table 2.

Side effects

The most commonly reported side effects included sleep quality (nine studies), depression (eight studies), dizziness (seven studies), and anxiety (seven studies). Some other notable problems reported included impaired concentration (five studies), abnormal dreams (four studies), and light-headedness (four studies). More serious side effects such as suicidal ideation and paranoia were each reported just once. Studies tend to demonstrate that the symptoms are prominent in the first few weeks of therapy and then decline in severity, with the exception of the study by Fumaz and colleagues [6] who showed that symptoms may persist for up to a mean of 2 years. Several studies [7,11,13,18] also suggested that side effects can persist for up to 1 year after the initiation of EFV and recommend that patient monitoring continue past the first few weeks of therapy. Hawkins and colleagues [7] showed that the side effects of EFV can persist up to a year after the initiation of treatment. However, the side effects present after 1 year of therapy are not severe and are tolerated by patients. Gutierrez and colleagues [11] showed that patients who discontinued EFV were using the mediation for a range of 16–34 months. Detailed information is provided in Table 3. The package insert of EFV does mention that the drug can cause neuropsychiatric side effects; however, the incidence is stated as rare and includes only anxiety, apathy, emotional lability, euphoria, hallucinations, and depression [8].

Severity of side effects

The severity of the side effects was recorded by five studies. Different scales were used to evaluate severity. Gutierrez and colleagues [11] utilized the World Health Organisation (WHO) severity scale, Hoffman and colleagues [12] allowed providers to grade the severity of clinical side effects, Nelson and colleagues [15] made use of the Division of AIDS Grading Table, and Rihs and colleagues [16] used the Depression Anxiety and Stress Scale to measure the severity of anxiety, depression, and stress. Gutierrez-Valencia and colleagues [4] did not state which scale was used to evaluate the severity of the side effects.

Almost all of the studies reported patients discontinuing EFV treatment due to intolerable neuropsychiatric side effects (NPSEs); however, this occurred in the minority of patients. Generally, though patients experienced mild symptoms as expressed by the various scales. However, it is worthy to note that some patients may experience intolerable side effects and require the discontinuation of EFV. Nelson and colleagues [15] divided side effects caused by EFV into neurological and psychiatric. A total of 33.4% of patients on EFV were reported to have demonstrated at least one grade one to four neurologic side effect and 39% of patients using EFV reported at least one grade one to four psychiatric side effect. In both cases, these values were higher when compared to the group of patients receiving etravirine (20.2% neurologic side effect and 11% psychiatric side effects). Rihs and colleagues [16] demonstrated that patients prescribed EFV had experienced severe to extremely severe anxiety, depression, and stress, although they were all small groups of patients. Gutierrez-Valencia and colleagues [4] separated patients into a stepped dose and a full dose EFV group and explored a variety of side effects. They reported a higher number of patients (n = 6) from the full dose group experiencing severe side effects at day 30 of the follow-up compared to the stepped dose group (n = 2).

The studies all showed that these side effects were transient in nature and not severe enough to warrant the discontinuation of EFV in the majority of patients. However, if the side-effects persist, as shown by Fumaz [6], Hawkins [7], Rihs [16], and Leutscher [13], patient adherence to EFV may decline even if the side effects are mild or moderate in severity.

Discussion

Due to the varied nature of the measuring instruments used, it is difficult to directly compare these trials in a systematic review. However, in spite of the varying nature of these studies, there are some common findings. All published studies included in the review showed that the side effects caused by EFV can be tolerated by most patients and that these side effects tend to be transient in nature. There has not been any significant evidence of EFV causing suicidal ideation or paranoia in patients. In fact, a study by Napoli [19] and colleagues employed a technique to identify associations between drugs and adverse reactions. The results showed that EFV was not associated with an increased risk of suicidality. Similarly, a study conducted by Smith and colleagues [20] showed that there was no higher rate of completed suicide in patients using EFV. However, Mollan and colleagues [21] found that there is an increased risk of idealized, attempted, or completed suicide with EFV. Only one of the studies in this review mentioned suicide. This means that this particular side effect was not detected or not significant amongst the participants of the other studies. The neuropsychiatric symptoms have, however, been shown to persist for several years after the initiation of therapy and appropriate caution should therefore be taken. Continuing patient monitoring and counseling needs to be conducted in order to identify late-emergent side effects.

Patients with a history of psychoses, active psychoses, or depression were included in only one study [9]. Blanch and colleagues [9] referred participating patients to be interviewed

Table 2. Statistical methods and outcomes.

Primary author	Evaluation methods	Statistical methods	Primary outcome	Secondary outcome
Blanch [9]	100-point Karnofsky scale (clinician administered) Psychological and physical 10-point self-report scale (self-administered) Structured clinical interview of the clinical version of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) (psychiatrist administered) Validated Spanish adaptations of the Symptom Check List-90-Revised (SCL-90-R) Medical Outcome Study for HIV-positive patients (MOS-HIV)	Univariate repeated-measures. ANOVA followed up with univariate simple contrast effects test Friedman test Wilcoxon signed – rank tests – Bonferroni adjustment Univariate and multivariate regression analyses	Four patients discontinued efavirenz due to neuropsychiatric side effects Patients who completed the follow-up demonstrated a decrease in SCL-90-R total score and in several subscales of interpersonal sensitivity, depression, and anxiety No changes in MOS-HIV	Having fewer years of education Having fewer baseline central nervous system symptoms Reporting better baseline physical status Having higher baseline scores in the Health Transition subscale of the MOS-HIV and in the somatization subscale of the SCL-90-R (associated with more neuropsychiatric side effects)
Clifford [5]	Trail making tests (series A and B) and the digital symbol substitution test	Nonparametric tests Generalized estimation equation modeling Wei–Johnson test Spearman correlation efficient	All components improved Higher levels of efavirenz were associated with slightly lower responses Efavirenz-related central nervous system scores increased Median change of bad dream scores and anxiety increased while global depression score decreased	Neurocognitive performance was maintained without decline over the 3 years of the study. This provides some reassurance that chronic neurotoxicity is unlikely in many patients
Clifford [10]	Trail making tests (series A and B) Digit symbol test Pittsburgh sleep quality index State-trait anxiety inventory for adults Center for epidemiologic studies depression scale Specially designed questionnaire	Wilcoxon signed rank tests Wilcoxon rank sum tests	Efavirenz-related symptoms were higher than baseline at final assessment. Bad dreams' detected a mean increase Anxiety increased When efavirenz-only patients are compared with those never receiving efavirenz, there is no statistically significant difference in changes over the study period.	None recorded
Fumaz [6]	MOS-HIV questionnaire Profile of mood state	Kolmogorov–Smirnov test Mann–Whitney nonparametric test χ^2 test Fisher exact test Spearman nonparametric test	54% of efavirenz patients reported at least one neuropsychiatric disorder within the 4 weeks before the visit Dizziness (21.7%), sadness (36.78%), mood changes (26.7%), irritability (30%), light-headedness (28.3%), nervousness (30%), impaired concentration (26.7%), abnormal dreams (48.3%), somnolence (15%)	Mean efavirenz levels showed no significant differences between those with and without neuropsychiatric disorders 60% of efavirenz patients reported adherence and 55% of protease inhibitor patients
Gutierrez [11]	Semi-structured interview (included questions exploring common presumptive efavirenz-related side effects) WHO toxicity scale Simplified medication adherence questionnaire	Student's *t*-test Receiver operating characteristic values Contingency tables Multivariate analysis Logistic regression	Four patients discontinued due to side effects Adherence to efavirenz therapy was >90% for 16 of 17 patients Ten patients reported neuropsychiatric side effects during the observation period, mostly sleep disturbances Others include dizziness (6), insomnia or abnormal dreaming (5), impaired concentration and attention span (2), depression (2), obsessive disorder (1), drowsiness (1), irritability (1), and light-headedness (1) Efavirenz plasma levels were higher for patients with neuropsychiatric side effects	Patients having plasma levels of more than 2.74 µg/ml were 5.68 times more likely to experience central nervous system toxicity

(*Continued*)

Table 2. (Continued).

Primary author	Evaluation methods	Statistical methods	Primary outcome	Secondary outcome
Gutierrez-Valencia [4]	11 questions on common efavirenz-related neuropsychiatric side effects (dizziness, feelings of drunkenness, headache, impaired concentration, mood disorders, anxiety, and depression) Validated 13-item protocol that measured subjective sleep quality, somnolence, insomnia, and nightmares	-χ^2 test Student's *t*-test Mann–Whitney–Wilcoxon test	During the first week, 55.5% developed efavirenz-related neuropsychiatric side effects [these were more frequent in the full dose group (66%) than the stepped dose group (46.5%)] Incidences of dizziness (66% vs. 32.8%), feeling of hangover (45.8% vs. 20.7%), impaired concentration (22.9% vs. 8.9%) and hallucinations (6.1% vs. 0%) were higher and more severe in the full dose compared to stepped dose group	None recorded
Hawkins [7]	SCL-90-R	Univariate analysis Student's *t*-test χ^2 test Multivariate analyses	In the first 6 months, worse scores were seen in 39 of the 75 patients receiving efavirenz The efavirenz group had higher scores for somatization, anxiety, obsessive-compulsive disorder, the Global Severity Index, and the Positive Symptom Distress Index with trends for higher scores in paranoid ideation and depression After 12 months, the efavirenz group had lower scores than the protease inhibitor treated group for somatization, interpersonal sensitivity, Global Severity Index, and Positive Symptom Total	Efavirenz -related neuropsychiatric symptoms can last up to 200 days after the initiation of treatment Severity of the side effects decline over time in efavirenz-treated patients compared to patients treated with a protease inhibitor-based regimen
Hoffman [12]	Structured visit forms and results from routine and acute laboratory testing Special side-event reporting form	Pre-HAART person-years at risk were calculated from the first clinical evaluation or 1 year before the initiation of HAART Person-years at risk on HAART were calculated from the time of HAART initiation to the earliest of the following: time of event, change or discontinuation of HAART, date of last clinical, or laboratory encounter in the database or 1 year of follow-up on HAART	CNS effects with efavirenz – 187 patients 37/100 person years, 95% confidence interval 32–43	Subjects on co-trimoxazole had higher rate of central nervous system symptoms
Leutscher [13]	Review of medical records	χ^2 test	54% (n = 90) of patients in the efavirenz group (n = 168) discontinued efavirenz Overall, 51% of patients discontinued efavirenz throughout the study A small percentage of the 90 patients (n = 17%) discontinued efavirenz during the first month of therapy, 32% discontinued between 1 and 12 months and the remaining 51% discontinued after more than 1 year Neuropsychiatric disturbances was the most common reason for discontinuation among both patients discontinuing the initial efavirenz-based regimen as well as those discontinuing efavirenz as part of a second-line regimen Among the first-line treatment patients, 50% discontinued after 1 year of therapy	Other reasons for discontinuation of efavirenz were pregnancy, treatment failure, or noncompliance Once efavirenz was discontinued, there was resolution of the neuropsychiatric side effects in 61% of patients in the first-line efavirenz group No differences in gender distribution, country of origin, history of HIV transmission or viral load, or CD4 counts

(*Continued*)

Table 2. (Continued).

Primary author	Evaluation methods	Statistical methods	Primary outcome	Secondary outcome
Lochet [14]	SENSIO questionnaire	None indicated	Neuropsychiatric side effects occurred mainly in the first month of treatment Sleep disturbances and dizziness occurred mostly at the beginning of efavirenz treatment Neuropsychiatric side effects which persisted or worsened include anxiety, behavioral troubles, sadness, and cognitive disorders Late neuropsychiatric side effects included abnormal dreams, nocturnal waking, memory disorders, concentration difficulty, morning tiredness, and daytime drowsiness	None recorded
Nelson [15]	Division of AIDS grading table	Logistic regression	13 of the 79 patients in the etravirine arm and 36 of the 78 patients in the efavirenz arm showed at least one grade one to four drug-related treatment-emergent neuropsychiatric side effect Four of 79 patients in the etravirine arm and 13 of 78 in the efavirenz arm showed at least one grade two to four drug-related treatment-emergent neuropsychiatric side effect	Change in HIV-RNA to week 12 was $-2.9\log_{10}$ in both treatment arms Median rise in CD4 cell counts was 146 cells/μl in the etravirine arm and 121 cells/μl in the efavirenz arm
Rihs [16]	Depression anxiety and stress scale-cognitive failures questionnaire	Paired *t*-tests Wilcoxon's signed rank test χ^2 tests Fisher's exact tests	Higher stress scores in the efavirenz group 19% reported severe to extremely severe levels of stress – 19% of patients treated with efavirenz reported severe to extremely severe levels of anxiety This group reported unusual dreams	No significant differences were found between the groups concerning cognitive impairment, fatigue, dizziness, derealization, or depersonalization
Ward [17]	No formal measuring tool used	Paired student's *t*-test	14 patients reported full recovery after switching The other six patients reported significant improvement in symptoms Three of the six patients had a history of depression before starting efavirenz	None recorded

Table 3. Side effects recorded.

Primary Author	Side effects and consequences
Blanch [9]	Depression, anxiety, dizziness, light-headedness, and feeling disengaged from reality. There were nine patients who dropped out of the study, four of whom did so due to intolerable NPSEs. Efavirenz was effective in decreasing viral load and improved the psychological distress level. Patients who maintained efavirenz treatment showed a decrease in interpersonal sensitivity during the first 4 weeks and a decrease in depression up to the first 3 months. The study found no association between NPSEs and personal psychiatric history
Clifford [5]	The significant increase in the NPSEs seen during the first week of treatment declined toward baseline levels during the study, but remained higher than baseline levels at the final visit. These side effects were not significantly associated with efavirenz trough levels measured at the final visit. Changes in the global sleep score over the study were not significant although the 'bad dreams' question detected a mean increase after 184 weeks. There was a statistically significant decrease in depression symptoms over the course of the study. The symptoms of anxiety increased by a median of four points as measured by the State Anxiety Index. There were 31 patients who discontinued treatment, 11 did so due to NPSEs
Clifford [10]	Sleep quality scores changed little over time. Patients who were not receiving efavirenz had significantly poorer sleep quality at week 4 as compared to the efavirenz group. All participants experienced anxiety throughout the study. Changes in depressed mood were similar in both groups.
Fumaz [6]	Patients on efavirenz reported higher prevalence of dizziness, sadness, mood changes, irritability, light-headedness, nervousness, impaired concentration, abnormal dreams, and somnolence. Other side effects included fatigue, headaches, euphoria, difficulty sleeping. There was no correlation between the plasma levels of efavirenz and the presence of NPSEs. There were no significant differences in quality of life between patients on efavirenz and those not on efavirenz
Gutierrez [11]	Overall, 10 patients of the 17 experienced NPSEs, mostly sleep disturbances. CNS effects included dizziness, insomnia or abnormal dreams, impaired concentration and attention span, depression, drowsiness, irritability, and light-headedness. In 6 of the 10 patients, NPSEs were mild. In the other four cases, CNS toxicity was moderate or severe leading to the discontinuation of efavirenz. This occurred at months 6, 8, 11, and 13 of the study. Plasma levels of efavirenz were found to be higher in patients experiencing NPSEs
Gutierrez-Valencia [4]	There were 12 patients who discontinued the study due to adverse effects. Five of these patients were in the stepped-dose group and seven in the full-dose group. Dizziness, feelings of drunkenness, impaired concentration and hallucinations, sleep disorders, and nightmares were the most commonly recorded side effects. Other side effects included headache, mood disorders, disorientation, anxiety, and depression. Throughout the second week of the study, the incidence of NPSEs was similar in both groups, although the more severe NPSEs occurred in the full-dose group
Hawkins [7]	Somatization, obsessive–compulsive disorder, anxiety, depression, and paranoid ideation were side effects more commonly seen in patients using efavirenz for less than 6 months. However, as treatment duration increased (199–365 days), even though the scores in the measuring instruments used for patients using efavirenz were higher than PI using patients, it was not statistically significant
Hoffman [12]	For dizziness, insomnia, bizarre dreams, or hallucinations, efavirenz was thought to be the responsible agent. The neurocerebellar toxicity affected 22% of patients at 2 weeks
Leutscher [13]	Of the 168 patients who started efavirenz, 90 later discontinued during the follow-up period. Of these 90 patients, 15 discontinued within the first month of treatment, 29 between month 1 and month 12 and the remaining 46 patients after 1 year. NPSEs are stated as the main reason for efavirenz discontinuation but no specific side effects were mentioned. A history of mental illness was reported in the same proportion of patients who continued efavirenz as those who discontinued
Lochet [14]	Abnormal dreams, sleep disorders, memory disorders, restlessness, daytime drowsiness, impaired concentration, sadness, irritability, agitation, emotional instability, suicidal ideation, aggressiveness, headaches, feelings of drunkeness, euphoria, hallucinations, anxiety, behavioral troubles, sadness, and cognitive disorders. At the time of the study, 23 (13.2%) of patients claimed to have frequent or very frequent suicidal ideation. Among these 23 patients, 18 (10.3%) did not report having this feeling before initiating efavirenz treatment, four patients did and one did not answer. There were 11 patients who discontinued efavirenz due to NPSEs
Nelson [15]	The most common side effect of the nervous system was dizziness (19% in efavirenz arm and 4% in the etravirine arm). The most common psychiatric disorders were sleep disorder (abnormal dreams, insomnia, nightmares, and sleep disorders) (9% of patients in the etravirine arm and 32% in the efavirenz arm). There were no deaths in the study
Rihs [16]	Patients on efavirenz experienced higher levels of depression, anxiety, and bad dreams, but not regarding the quality of sleep. There were no differences between the groups in terms of cognitive impairment, feelings of derealization, dizziness, or light-headedness
Ward [17]	Mental cloudiness, decreased memory, drunken sensations, difficulty concentrating, agitation, depression, fatigue, sleep difficulty, and vivid dreams were experienced by patients on efavirenz before the switch to nevirapine was made

NPSE: neuropsychiatric side effects; PI: protease inhibitors.

by a psychiatrist. It was found that only 54.8% of their patients had a psychiatric disorder, but 83.9% reported at least one psychiatric symptom at baseline, 71% reported some form of psychiatric symptom after the initiation of EFV, and 13% dropped out of the study due to psychiatric side effects. The package insert of EFV does not state that EFV is contraindicated in patients with a psychiatric disorder [8]. As mentioned, the South African National consolidated Guidelines [1] state that an alternative may be used in place of EFV where the patient has significant psychiatric comorbidity. However, the CD4 count has an impact on the alternative chosen. If a female patient has a CD4 count of less than 250 and a male patient has a CD4 count of less than 400, nevirapine may be used as an alternative. If the CD4 count of the female patient is equal to or more than 250 and the male patient has a CD4 count of 400 or more, the lopinavir/ritonavir combination should be used instead. It must be remembered that nevirapine has the potential to cause significant hepatotoxicity as well as skin abnormalities [1]. However, there are significant drug interactions between ritonavir and psychotropic drugs such as clozapine, carbamazepine, and sedatives and hypnotics such as diazepam, midazolam, and zolpidem [8]. Also of note, a retrospective analysis that compared a large group of patients receiving EFV to a large group of patients receiving nevirapine showed that there were no significant differences between them in terms of treatment withdrawal. This further supports the idea that the neuropsychiatric side effects caused by EFV are not severe enough to warrant its discontinuation in the majority of patients [22].

Even though EFV is no longer used as part of the first-line treatment in the United States of America [23] or the United Kingdom [24], it still forms part of the treatment backbone in South Africa which has the largest HIV epidemic in the world [25]. Several other countries in Africa with an HIV prevalence of more than 10% use EFV as part of the recommended first-line treatment of naïve patients [25]. Agents used as first-line

treatment in the United States of America and the United Kingdom are reserved for second- or third-line use in the African countries mentioned below. This demonstrates the importance of a thorough understanding of EFV as is it still widely used in developing countries. The various regimens are summarized in Table 4.

The Malawian [28], South African [1], and United Kingdom Guidelines [23] state that if a patient has a history of, or current, mental illness that patient should not be given EFV. The guidelines published in the United States of America [23] acknowledge that EFV causes a myriad of NPSEs, some of which may be severe, but do not state that EFV should not be given to such patients or that therapy should be switched to an alternative agent. The 2010 HIV Treatment Guidelines of Swaziland [30] suggest that patients with mental illness, even such severe conditions such as schizophrenia or schizoaffective disorder, should not be discriminated against in terms of antiretroviral treatment (ART). These patients should be assessed individually and appropriate decisions made using the screening tools provided in the guideline. Both the 2010 and 2015 treatment Guidelines of Swaziland [30,31] also warn that EFV is associated with mental health disturbances such as bad dreams and being in an altered state of mind; thus, patients should be encouraged to take EFV before bedtime.

The 2010 WHO ART Guidelines [32] recommend the use of two nucleoside reverse transcriptase inhibitors in combination with one non-nucleoside reverse transcriptase inhibitor. This is a global recommendation, and takes into account the cost and accessibility of the medication to those countries that are classified as low or middle income by the World Bank. According to the 2015 World Bank classification of economies [33], Malawi and Zimbabwe were classified as low income countries and Swaziland and Lesotho are both ranked as lower-middle income countries. Botswana, Namibia and South Africa on the other hand, were classified as upper-middle income countries as of July 2015. All seven of these countries however, follow the 2010 WHO [32] recommendations regarding ART. African countries face a myriad of problems, of which HIV is only one. These challenges may restrict the allocation of funds to the upgrading of ART regimens to include more expensive agents.

There have been suggestions that the plasma level of EFV may be a risk factor for the development of neuropsychiatric side effects; however, there has not been a consensus concerning the threshold concentration [11,35]. Given that studies have shown that genetic variations, particularly of the enzyme CYP2B6, in patients affect the plasma levels of EFV [18,36], studies need to be conducted in a broader range of countries to determine region-specific guidelines for EFV dosing. These polymorphisms have been shown to be more common in patients of African descent and such patients should be monitored more closely as they are more likely to experience higher plasma levels of EFV and be susceptible to neuropsychiatric side effects [36]. This is particularly important as only one of the studies included patients from South Africa [12]. This indicates that there is a need for further safety and pharmacovigilance studies in Africa to determine the clinical importance of this variation. This is endorsed by recent reports which showed that a nevirapine safety signal was detected in Namibia using their adverse reporting database – VigiFlow® – after shifting the initiation of nevirapine to patients with higher CD4 counts than previously recommended. This resulted in the Ministry of Health in Namibia halting this move and returning to the previous recommendations [37]. This is important as the majority of people with HIV live in low- and middle-income countries, particularly sub-Saharan Africa, and HIV disproportionately affects young women in these countries [38,39]. This compares with the high proportion of men in the published studies from Europe and the USA.

All of the studies included in this review had a majority male population and there was an average age range of 37–41 years. This implies a knowledge gap in special populations such as older patients, pediatrics, and patients with a psychiatric illness as these factors will impact the treatment chosen. Such patients need to be included in studies in addition to

Table 4. First-line ART regimens for treatment-naïve patients of various countries.

Country	Date of guidelines	Recommended first-line treatment for treatment-naïve patients
Botswana [26]	2012	Tenofovir + lamivudine + efavirenz (preferably as a single dose combination)
Lesotho [27]	2014	Tenofovir + lamivudine + efavirenz (preferably as a single dose combination)
Malawi [28]	2014	Tenofovir + lamivudine + efavirenz
Namibia [29]	2010	Tenofovir + lamivudine + nevirapine (if the CD4 count in women is >350 cells/μl, or if the CD4 count in men is >400 cells/μl and the man is classified as WHO stage 3 or 4, efavirenz should be used instead of nevirapine)
South Africa [1]	2014	Tenofovir + lamivudine + efavirenz (preferably as a single dose combination)
Swaziland [30]	2010	Tenofovir + lamivudine + efavirenz
United States of America [23]	2015	Abacavir + lamivudine + dolutegravir **OR** Tenofovir + emtricitabine + dolutegravir **OR** Tenofovir + emtricitabine + elvitegravir/cobicistat **OR** Tenofovir + emtricitabine + raltegravir (a suitable regimen is to be chosen based on laboratory investigation results as stated in the full guideline)
United Kingdom [24]	2015	Tenofovir + emtricitabine + atazanivir/ritonavir **OR** Darunavir/ritonavir **OR** Dolutegravir **OR** Elvitegravir/cobicistat **OR** Raltegravir **OR** Rilpivirine as preferred agents **OR** Efavirenz as an alternative agent **Alternative regimen** Abacavir + lamivudine + any of the above
Zimbabwe [34]	2013	Tenofovir + lamivudine + efavirenz (preferably as a single dose combination)

including more women and patients in Africa in order to obtain a complete picture and representative sample. Consequently, it is difficult to provide additional guidance on the use of EFV especially in patients in Africa apart from that already documented.

None of the studies indicated the WHO stage of HIV. However, this has not been considered as a possible risk factor in the development of neuropsychiatric side effects of EFV. Determining risk factors for side effects may assist with discerning possible causes of the problem. The location and sample population has also shown to be of importance in studies concerning EFV and has to be taken into account when generalizing results.

Limitations

There were only small numbers of female patients in the studies compared to males, with only limited follow-up. In addition, since only one of the studies was conducted in an Africa setting, the results may not be generalizable to all countries and settings due to the varied nature of EFV metabolism in patients of African descent. We are also aware that the methodologies of the included studies are varied and do not allow for direct comparisons, and that the small number of studies sourced due to our strict methodology, which limited included studies to English language full-text articles published in journals accessible via the Nelson Mandela Metropolitan University database, does serve as a limitation to this study. However, we do not believe that the inclusion of more studies would have significantly altered the conclusions of our findings.

Conclusion

Standardized methods for measuring outcomes need to be determined. Similar studies need to be conducted in more countries to represent the various populations and their differences across continents. Given that the highest burden of HIV lies in Africa and that EFV still features as part of preferred first-line treatment in all of the African Guidelines considered in this study (Table 4), it follows that comprehension of the side effects caused by EFV in African countries amongst African populations with limited resources is a necessity. In the studies included in this systematic review, the neuropsychiatric side effects of EFV do not appear severe enough to warrant discontinuation of the medication, even if they may persist longer or emerge later than initially thought. However in clinical practice, if EFV adversely affects the quality of life of the patient impacting on issues such as persistence, an alternative regimen may be considered. Continuous pharmacovigilance, adherence counseling, and support are important to these, and other patients, as EFV will form part of a lifelong regimen.

Expert commentary

HIV is a multifaceted condition, particularly among African regions where often patients need to make the choice between food and medication. Providing patients with medication that is effective, would cause limited side effects and is simple to take is the aim of any health-care program. The introduction of the fixed dose combination has improved adherence to ART. The systematic review confirmed that EFV does cause neuropsychiatric side effects in an appreciable number of patients, which include changes in sleep quality, dizziness, anxiety, and depression; however, the side effects seen are generally mild and do not typically warrant discontinuation. They can though be severe in some patients, leading to discontinuation and switching to other treatments. Having said this, currently EFV forms a major part of HIV treatment in sub-Saharan Africa, which is likely to remain. Its utilization would even appreciably increase in South Africa if the 'test and treat' option, that is if a patient tests HIV-positive, ART is started regardless of the CD4 count, was introduced, which South Africa is currently considering as a future treatment strategy. The situation in southern Africa enhances the argument that EFV is still a medicine that requires more understanding among different African settings, given the likely increases in its utilization as well as concerns with the make-up and the different genetic variations between HIV populations in Africa versus Western countries. In the meantime, patients will need to be appropriately screened before initiating EFV. They will also need to be continuously monitored for side effects and current adherence given the prevalence of side effects with EFV.

Five-year view

Africa has the highest burden of HIV in the world. Given the various social aspects contributing to the spread of the disease, it is unlikely that this situation will change significantly over the next 5 years. The cost of medication will become even more of a determining factor in treatment decision-making. Adherence to treatment currently is, and will always be, a concern in patients expected to take lifelong treatment. Advances in medicine may result in a vaccine against HIV being developed and rolled out over the next 5 years. There may also be improvements in technology, leading to resistance testing in all patients testing HIV-positive before being initiated on treatment. However, for these advances to be implemented in countries with high HIV burden and limited resources, cost will be continue to a major factor leading to continued use of treatments such as EFV. It is hoped that more studies are conducted among HIV patients in Africa given the different patient patterns to Western countries and different genetic variations. This will help to further guide treatment choices.

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Key issues

- The neuropsychiatric side effects caused by efavirenz may persist longer than the first 4–6 weeks of treatment as initially thought.
- These side effects are not generally severe enough to warrant the discontinuation of EFV.
- Older patients, pediatric patients and patients with active symptomatic mental illness need to be included in studies to obtain a representative sample. Similarly, for Africa there needs to be more women included in studies monitoring the side effects of treatments for HIV.
- Patients need to be provided with continuous adherence education to enhance the effectiveness of treatment.

References

1. National consolidated guidelines for the prevention of mother-to-child transmission of HIV (PMTCT) and the management of HIV in children, adolescents and adults. Pretoria: The National Department of Health; 2015. p. 119.
2. Kenedi CA, Goforth HW. A systematic review of the psychiatric side-effects of efavirenz. AIDS Behav. 2011;15(8):1803–1808.
3. Muñoz-Moreno JA, Fumaz CR, Ferrer MJ, et al. Neuropsychiatric symptoms associated with efavirenz: prevalence, correlates, and management. A neurobehavioral review. AIDS Rev. 2009;11 (2):103–109.
4. Gutierrez-Valencia A, Viciana P, Palacios R, et al. Stepped-dose versus full dose efavirenz for HIV infection and neuropsychiatric adverse events: a randomized trial. Ann Intern Med. 2009;151 (3):149–156.
5. Clifford DB, Evans S, Yang Y, et al. Long-term impact of efavirenz on neuropsychological performance and symptoms in HIV-infected individuals (ACTG 5097s). HIV Clin Trials. 2009;10(6):343–355.
6. Fumaz CR, Munoz-Moreno JA, Molto J, et al. Long-term neuropsychiatric disorders on efavirenz-based approaches: quality of life, psychological issues, and adherence. J Acq Immun Def Synd. 2005;38(5):560–565.
7. Hawkins T, Geist C, Young B, et al. Comparison of neuropsychiatric side effects in an observational cohort of efavirenz- and protease inhibitor-treated patients. HIV Clin Trials. 2005;6(4):187–196.
8. Adco-Efavirenz [package insert]. Midrand (Gauteng): Adcock Ingram; 2007.
9. Blanch J, Martinez E, Rousaud A, et al. Preliminary data of a prospective study on neuropsychiatric side effects after initiation of efavirenz. J Acq Immun Def Synd. 2001;27(4):336–343.
10. Clifford DB, Evans S, Yang Y, et al. Impact of efavirenz on neuropsychological performance and symptoms in HIV-infected individuals. Ann Intern Med. 2005;143(10):714–721.
11. Gutierrez F, Navarro A, Padillo S, et al. Prediction of neuropsychiatric adverse events associated with long-term efavirenz therapy, using plasma drug level monitoring. Clin Infect Dis. 2005;41 (11):1648–1653.
12. Hoffman CJ, Fielding KL, Charalambous S, et al. Antiretroviral therapy using zidovudine, lamivudine, and efavirenz in South Africa: tolerability and clinical events. AIDS. 2008;2(1):670–674.
13. Leutscher PDC, Stecher C, Storgaard M, et al. Discontinuation of efavirenz therapy in HIV patients due to neuropsychiatric adverse effects. Scand J Infect Dis. 2013;45(8):645–651.
14. Lochet P, Peyrière H, Lotthé A, et al. Long-term assessment of neuropsychiatric adverse reactions associated with efavirenz. HIV Med. 2003;4(1):62–66.
15. Nelson M, Stellbrink H, Podzamczer D, et al. A comparison of neuropsychiatric adverse events during 12 weeks of treatment with etravirine and efavirenz in a treatment-naive, HIV-1-infected population. AIDS. 2011;25(3):335–340.
16. Rihs TA, Begley K, Smith DE, et al. Efavirenz and chronic neuropsychiatric symptoms: a cross-sectional case control study. HIV Med. 2006;7(8):544–548.
17. Ward DJ, Curtin JM. Switch from efavirenz to nevirapine associated with resolution of efavirenz-related neuropsychiatric adverse events and improvement in lipid profiles. AIDS Patient Care STDs. 2006;20(8):542–548.
18. Naidoo P, Chetty VV, Chetty M. Impact of CYP polymorphisms, ethnicity, and sex differences in metabolism on dosing strategies: the case of efavirenz. Eur J Clin Pharmacol. 2014;70(4):379–389.
19. Napoli AA, Wood JJ, Coumbis JJ, et al. No evident association between efavirenz use and suicidality was identified from a disproportionality analysis using the FAERS database. J Int AIDS Soc. 2014;17:19214.
20. Smith C, Ryom L, d'Arminio Monforte A, et al. Lack of association between use of efavirenz and death from suicide: evidence from the D:A:D study. J Int AIDS Soc. 2014;17(4suppl3):19512.
21. Mollan KR, Smurzynski M, Eron JJ, et al. Association between efavirenz as initial therapy for HIV-1 infection and increased risk for suicidal ideation or attempted or completed suicide: an analysis of trial data. Ann Intern Med. 2014;161(1):1–10.
22. Von Giesen HJ, Köller H, De Nocker D, et al. Long-term safety and efficacy of NNRTI within the central nervous system. HIV Clin Trials. 2003;4(6):382–390.
23. Guidelines for the use of antiretroviral agents in HIV-1 infected adults and adolescents. Panel on antiretroviral guidelines for adult and adolescents. Department of Health and Human Services; 2015.
24. British HIV Association guidelines for the treatment of HIV-1-positive adults with antiretroviral therapy. British HIV Association; 2015.
25. Unicef. Eastern and Southern Africa HIV and AIDS. [cited 2015 Dec 27]. Available from: http://www.unicef.org/esaro/5482_HIV_AIDS.html.
26. Botswana national HIV and AIDS treatment guidelines. Gaborone: Ministry of Health; 2012. p. 197. Available from: http://www.med.upenn.edu/botswana/user_documents/BotsNatHIV-AIDSTreatGuideWEB22-05-2012.pdf
27. National guidelines on the use of antiretroviral therapy for HIV prevention and treatment. Lesotho: Ministry of Health; 2014. p. 140. Available from: http://www.emtct-iatt.org/wp-content/uploads/2015/02/National-ART-Guidelines_Final_16-June-20142.pdf
28. Clinical management of HIV in children and adults. Malawi: Ministry of Health; 2014. p. 105. Available from: http://www.emtct-iatt.org/wp-content/uploads/2015/09/Malawi-HIV-Guidelines-2014.pdf
29. National guidelines for antiretroviral therapy. Republic of Namibia Ministry of Health and Social Services; 2010. p. 90. Available from: http://www.who.int/hiv/pub/guidelines/namibia_art.pdf
30. National comprehensive HIV package of care for adults and adolescents in Swaziland. Kingdom of Swaziland: Ministry of Health; 2010. p. 174. Available from: http://www.who.int/hiv/pub/guidelines/swaziland_art.pdf
31. National comprehensive HIV package of care for adults and adolescents in Swaziland. Kingdom of Swaziland: Ministry of Health; 2015. 165p.
32. Antiretroviral therapy for HIV infection in adults and adolescents recommendations for a public health approach. World Health Organisation: Austria; 2010. 156p.
33. The World Bank Data: Country and Lending Groups. 2015. Available form: http://data.worldbank.org/about/country-and-lending-groups
34. Guidelines for antiretroviral therapy for the prevention and treatment of HIV in Zimbabwe. Harare: The National Medicine and Therapeutics Policy Advisory Committee and The AIDS and TB Directorate, Ministry of Health and Child Care; 2013. p. 88. Available from: http://www.nac.org.zw/sites/default/files/2013%20Zimbabwe%20ARV%20Guidelines%20%20Main%20Document%20(1).pdf

35. Marzolini C, Telenti A, Decosterd LA, et al. Efavirenz plasma levels can predict treatment failure and central nervous system side effects in HIV-1 infected patients. AIDS. 2001;15(1):71–75.
36. Ngaimisi E, Habtewold A, Minzi O, et al. Importance of ethnicity, CYP2B6 and ABCB1 genotype for efavirenz pharmacokinetics and treatment outcomes: a parallel-group prospective cohort study in two sub-Saharan African populations. PLoS ONE. 2013;8(7):e67946.
37. Massele A, Burger J, Katende-Kyenda NL, et al. Outcome of the first medicines utilization research in Africa group meeting to promote sustainable and rational medicine use in Africa. Expert Rev Pharmacoecon Outcomes Res. 2015;15(6):885–888.
38. AVERT. HIV and AIDS in sub-Saharan Africa regional overview. [cited 2015 Aug 20]. Available from: http://www.avert.org/professionals/hiv-around-world/sub-saharan-africa/overview.
39. Leclerc-Madlala S. Age-disparate and intergenerational sex in southern Africa: the dynamics of hypervulnerability. AIDS (London, England). 2008;22(Suppl 4):S17–25.

3.4 CHAPTER SUMMARY

The aim of the literature review was to attain an idea of the global and local incidence and severity of neuropsychiatric side effects and if there was sufficient evidence to determine whether it could safely be used in PLWHA who have active psychiatric disorders. A search was done using the databases available through the NMMU using the terms ‘efavirenz’, ‘neuropsychiatric’, ‘side effects’, ‘incidence’ and ‘management’ in various combinations.

As can be seen from the above articles, numerous studies have been done comparing the incidence of neuropsychiatric side effects between efavirenz and other agents. In all cases, efavirenz proved to be associated with a higher incidence of these side effects as compared to nevirapine, protease inhibitors or integrase inhibitors. However, efavirenz also proved to have superior virological activity and less severe side effects such as the hepatotoxicity or Stevens-Johnson Syndrome associated with nevirapine. In addition, the studies showed that the neuropsychiatric side effects were mild and in the majority of cases did not warrant the discontinuation of efavirenz. The side effects did not persist and would spontaneously resolve, although there was a concern about the risk of these side effects persisting or that they may manifest at a later point during treatment. As ART is a commitment to lifelong treatment, this is an important factor in continuing compliance. Patient counselling and monitoring are imperative to detect side effects and to promote compliance.

The management strategies outlined for these neuropsychiatric side effects are pharmacological in nature and treated according to severity. It is possible that certain conditions such as depression may not be due to efavirenz, but rather an emotional reaction to being diagnosed with HIV. If the side effects are intolerable, the patient may be switched to nevirapine. This would necessitate monitoring for skin reactions and hepatitis, which may be life-threatening. Another option would be to substitute lopinavir/ritonavir, though this particular agent is known for its numerous drug interactions with psychotropic medication such as clozapine, carbamazepine and sedative hypnotics due to its inhibition of the CYP450 enzyme system.

Given that efavirenz is part of the first-line treatment in numerous countries in SSA including SA and, more importantly, part of the fixed dose combination (FDC) which

serves to reduce the pill burden in patients with co-morbidities, it is important that clarification of its role in a variety of patients is established. Mental health and HIV are highly integrated conditions and further studies on how they impact each other are crucial to provide patients with complete and effective care.

CHAPTER 4

METHODOLOGY

4.1 INTRODUCTION

The study was divided into two parts, namely a quantitative portion and a qualitative portion. The quantitative study was a prospective (should this be changed to retrospective?) drug utilisation study. The qualitative study involved semi-structured interviews verbally administered to healthcare professionals recruited at each of the study sites. This chapter outlines the research design, study sites, data collection and analysis for both the quantitative and qualitative portion of the study.

4.2 RESEARCH DESIGN

Epidemiology was defined by the WHO as 'the study of the distribution and determinants of health-related states and events in the population, and the application of this study to the control of health problems' (WHO, 2003: 8). Epidemiological studies thus investigate the distribution and historical changes in the frequency of disease and the causes of these (Rohrig, du Prel, Wachtlin and Blettner, 2009: 265). There are two types of epidemiological studies; observational and experimental. Experimental studies are defined by the absence or presence of an ongoing intervention whereas observational studies simply observe and assess the strength of a causal relationship (Song and Chung, 2010: 2). Observational studies are further subdivided into cohort and case-control studies. Cohort studies compare similar populations but who have been exposed to certain factors. Populations are then followed until the outcome or disease of interest occurs (Song and Chung, 2010: 2). Cohort studies identify the exposure before the outcome and can be prospective or retrospective in nature. Case-control studies compare people who have been diagnosed with a particular disease and those who have not (Checkoway, Pearce and Kriebel, 2007: 635). Case-control studies identify the outcome before the exposure (Song and Chung, 2010: 4). The current study was an observational cohort study. There was no intervention by the researcher and the exposure, efavirenz, was identified before the outcome.

4.3 LITERATURE REVIEW

An extensive literature review was conducted during the period January 2014 until March 2016. The literature review was performed to obtain knowledge about the neuropsychiatric side effects caused by efavirenz, drug utilisation and the chosen methods of data collection. The appropriate books, internet websites and journal articles were consulted. Electronic information, including local and international journal articles were obtained through the use of PubMed®, ScienceDirect®, EBSCOHost® and the library search engine of the Nelson Mandela Metropolitan University (NMMU).

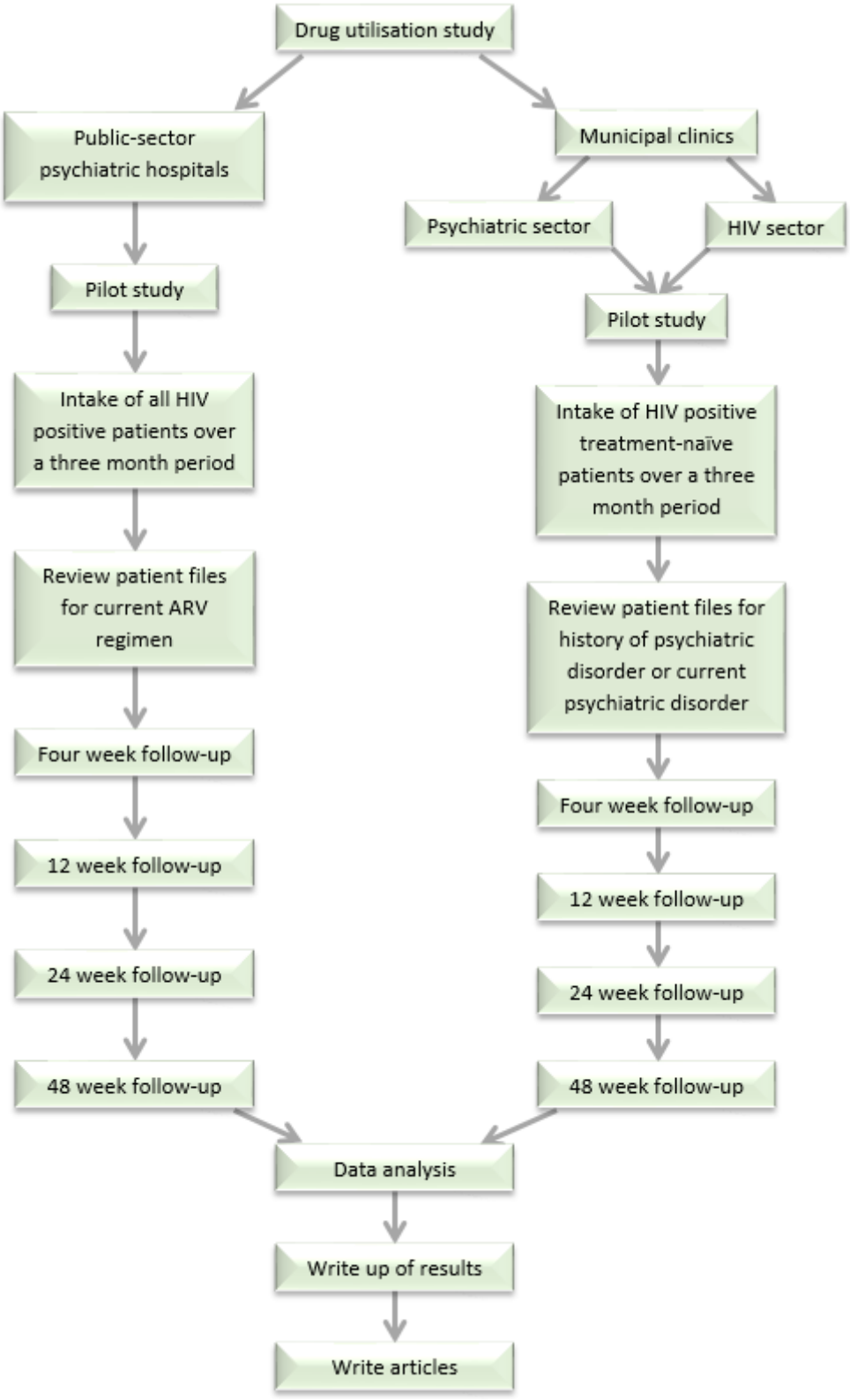
4.4 DRUG UTILISATION STUDY

Drug utilisation research, as defined by the WHO, refers to 'the marketing, distribution, prescription, and use of drugs in a society, with special emphasis on the resulting medical social and economic consequences' (WHO, 2003: 8). The aim of drug utilisation research is to facilitate the rational use of medicines in a population. This research is conducted to determine the pattern of medicine use, the quality of use, the determinants of use and the outcomes of said usage (WHO, 2003: 8,9). The drug utilisation study followed HIV positive treatment-naïve patients started on ART. Figure 4.1 provides an overview of the drug utilisation study.

4.4.1 Study sites and population

The study included five municipal clinics in the Nelson Mandela Metropolitan area that had HIV as well as psychiatric clinics and two public-sector psychiatric hospitals. Clinics are the primary sites for HIV-testing and dispensing of ARVs. The clinics chosen were large, well-known clinics in the Nelson Mandela Metropolitan area and selection was based on monthly new patient density as well as demographic diversity.

Figure 4.1: Flowchart of drug utilisation study



For the purposes of this study, the term ‘patient’ is used to denote the medical record belonging to that patient. The minimum number of patients from the public-sector clinics to be included was 150 and the maximum 200 as these numbers would allow for significant differences to be detected. After obtaining ethical approval from the NMMU, the Eastern Cape Department of Health and the respective clinic and hospital managers (Appendix H and Appendix I), the baseline data collection form was piloted (see Appendix D and F for baseline screening data collection tools). Thereafter, patient intake commenced. All treatment-naïve HIV-positive patients aged 18 years or older who attended the clinics over a three-month period were included in the study. Patients were selected sequentially provided the inclusion criteria were filled. The inclusion criteria for public-sector clinic patients required that all patients be aged 18 years or older, be diagnosed as HIV-positive, be ART treatment naïve, attend the clinic within the three-month intake period, a positive or negative TB diagnosis and be prescribed efavirenz or nevirapine as first-line treatment. Exclusion criteria for public-sector clinics are all HIV-positive patients already on ART at the initiation of the study and all patients younger than 18 years.

In the hospitals, all HIV-positive patients admitted to psychiatric wards within the three-month period were included in the study. This means that patients were already diagnosed as HIV positive for a period of time and were either receiving efavirenz or nevirapine as the NNRTI of choice, or were not yet initiated on ART. The intake period was to ensure that sufficient patient numbers of at least 100 would be obtained to detect statistically significant differences.

Patients prescribed nevirapine as first-line treatment were included in the study to serve as a point of comparison for those prescribed efavirenz. Patients with TB were included in the study.

The inclusion criteria for the public-sector psychiatric hospitals required that patients be aged 18 years or older, diagnosed as HIV-positive, patients may or may not already be using ART and be admitted to the hospital within the three-month inclusion period. The exclusion criterion for the public-sector psychiatric hospitals was patients younger than 18 years.

At the public-sector hospitals, formal appointments were made with all available psychiatrists for interview purposes. The doctors were given informed consent forms before the interviews took place. Once consent was given, the interview was conducted. The interviews were recorded using an application designed to act as a voice recorder. The interviews were subsequently transcribed within 24 hours after the interview. The interviews were recorded using an application designed to record telephonic conversations and subsequently transcribed within the next 24 hours.

4.4.2 Data collection

4.4.2.1 Clinics

Following doctor/nurse-patient consultation, the patient files were reviewed to determine whether the patients were screened for a history of or current psychiatric disorder. The benefits of screening patient folders rather than conducting patient interviews were language, time, patient understanding of the disease, understanding of the questions being asked and being able to effectively communicate and receive an answer. The WHO (2003: 23) recommends patient files as the main source of data for drug use evaluation.

At baseline, the patient age, gender, weight, date of HIV diagnosis and dose of efavirenz were recorded. Other information such as the ARV regimen, any co-morbidities and resulting medication, particularly CNS medication, the patient may be receiving and viral load were recorded (see Appendix D). Thereafter, patient files were followed-up at four, 12, and 24 week periods (see Appendix E for follow-up assessment data collection tool). A large number of patients experienced efavirenz-induced side effects within the first month of therapy and these persist for about three months (Blanch, *et al*., 2001: 339; Lochet, *et al.,* 2003: 63; Gutierrez-Valencia, *et al*., 2009: 155). One study (Nelson, et al., 2011: 337) comparing efavirenz to another therapy extended over a 48-week period with follow-up assessments conducted at four weeks, 12 weeks, 24 weeks and at endpoint. Another comparison study (Hawkins, et al., 2005: 190, 195) with efavirenz and protease inhibitors was conducted over a 24-week period and showed that symptoms may persist for more than a year after the initiation of treatment. New neuropsychiatric symptoms may present as late as 10 months after the initiation of efavirenz therapy, which justifies the extent of the

proposed follow-up period (Zaccarelli, Soldani, Liuzzi, Sette, Grisetti, Trotta, Perno, Antinori, 2002). The follow-up assessments would indicate any neuropsychiatric side effects of efavirenz such as dizziness, insomnia, headache, abnormal dreams and impaired concentration (Arendt, *et al.,* 2007: 1803; Nelson, *et al*., 2011: 337) as well as how the side effects were managed. Any other medications initiated within the follow-up period were recorded, as well as changes in the patient's weight, CD4 count and viral load. Patients found to default medication were excluded from the study as plasma levels of efavirenz could be erratic.

Upon visiting the clinics, the nurses responsible for the HIV sector were requested to provide a list of newly initiated HIV-positive patients. The data capturers then provided access to the medical records of the patients to allow for data collection. All patients were followed-up for 24 weeks.

4.4.2.2 Hospitals

In the case of the public-sector psychiatric hospitals, patient files were screened at baseline (see Appendix F for baseline screening data collection tool) to determine how the psychiatric symptoms were managed and whether treatment-naïve patients were prescribed efavirenz or not. The follow-up assessment (see Appendix G for follow-up assessment data collection tool) points were the same as those for the clinic, as well as the information recorded during the follow-up assessments.

The nurse in charge of each ward was requested to provide a list of HIV-positive patients in the ward. The medical records were subsequently obtained from each ward for data collection. Each patient was followed up to the point of discharge or until 24 weeks were completed.

4.4.3 Data analysis

After collection, data were captured onto Microsoft Excel® and analysed. The data were subject to general descriptive statistics, measures of central tendency (mean, median and mode), frequency distribution and standard deviation. The data were cross-tabulated and the Chi-square test was performed. Due to the small sample sizes of the hospital population, Fisher's exact test was used to determine significance.

4.5 QUALITATIVE STUDY

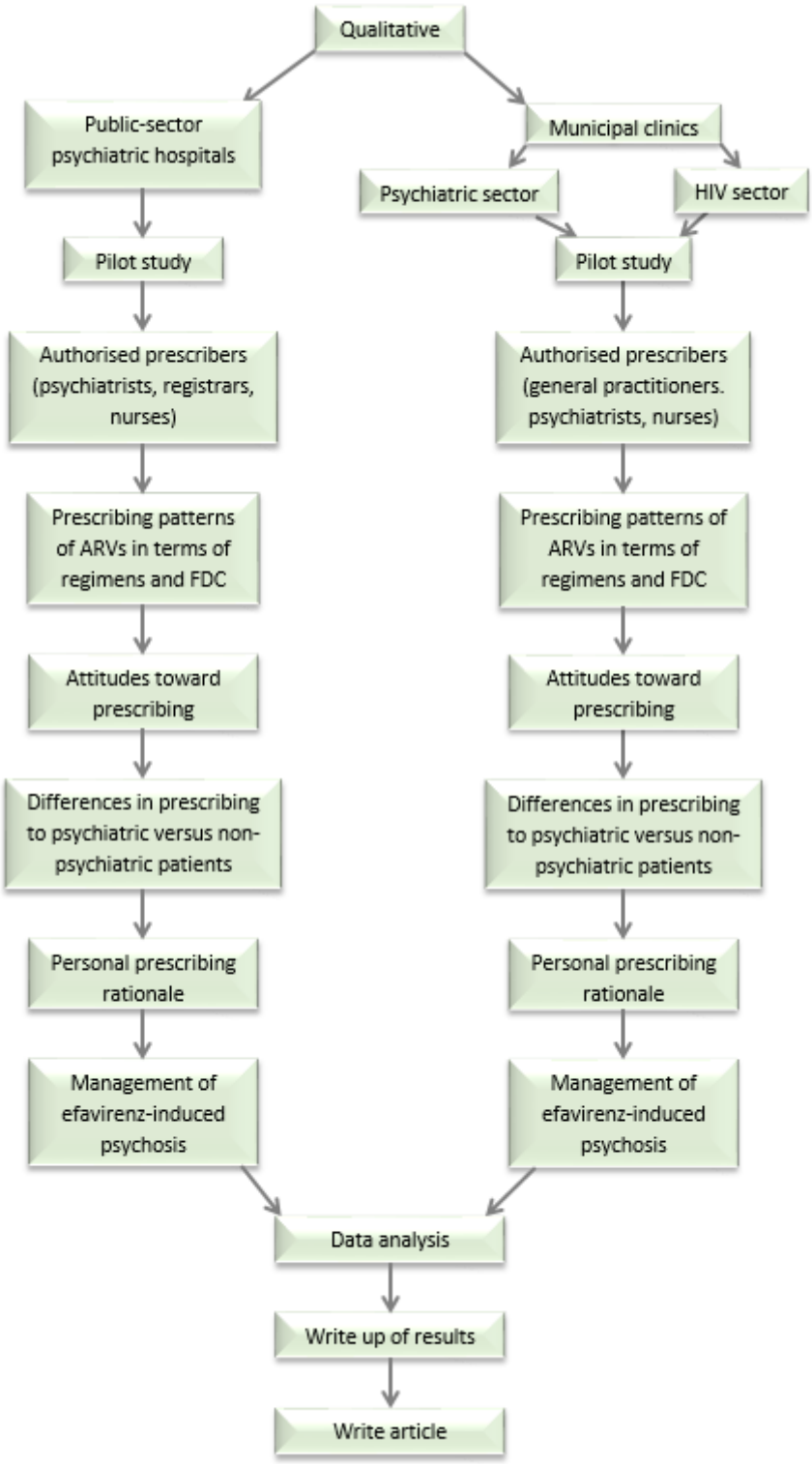
A qualitative research design is a means to explore and understand the meaning individuals or groups ascribe to a particular social or human problem (Banyard and Grayson, 2008: 45; Cresswell, 2009: 4). Qualitative research allows the researcher to gain new insights into a particular phenomenon, to develop new concepts or theoretical perspectives regarding that phenomenon and to discover problems that exist within that phenomenon. Qualitative research is a form of social inquiry that focuses on the way people interpret and make sense of their experiences and the world in which they live (Holloway & Wheeler, 2010: 3). The qualitative approach allows the researcher to test the validity of certain assumptions, claims, theories or generalisations within a real-world context (Leedy and Ormrod, 2005: 134). Choosing a qualitative method would allow the researcher to determine the attitudes and experiences of prescribers and nurses toward the prescribing and side effects experienced with efavirenz and particularly then in patients with a psychiatric disorder. The qualitative study was exploratory and descriptive in nature. Figure 4.2 provides an overview of the qualitative study.

The goal of an exploratory study is to explore a relatively unknown research area. Exploratory research aims at assessing the full nature of a phenomenon and implies that a problem about which little is known will be investigated. The purpose is to develop and clarify ideas, in order to obtain a rich familiarity with a phenomenon (Struwig & Stead, 2001:7). Exploratory research is useful when a new area or topic is investigated, which applies to this study. In South Africa, there is little to no information available concerning the attitudes of prescribers and healthcare workers towards the use of efavirenz in general and in patients with psychiatric disorders. An exploratory study would allow for the views and opinions of nurses and doctors involved with such patients to be explored which could be used to generate new knowledge and provide insight into and understanding of practical experiences.

In contrast to exploratory research characterised by its flexibility, descriptive studies attempt to provide a complete and accurate description of the situation (Struwig and Stead, 2001: 8). Through descriptive studies, researchers discover new meanings, determine what exists, determine the frequency with which something occurs, and categorise information. Accordingly, this approach was used to describe the

experiences of healthcare professionals when using efavirenz in patients with or without an active psychiatric disorder.

Figure 4.2: Flowchart of qualitative study



4.5.1 Study sample

Criterion-based, non-probability, purposive sampling was used in selecting the study sample. Purposive sampling is concerned with providing a sample of information-rich participants (Struwig and Stead, 2001: 122). Polit and Hungler (1993: 237) describe purposive sampling as a sampling method based on the researcher's judgement of the subjects that are typical or representative of the phenomenon being studied. Therefore, in order to participate in the study, the participants had to meet the following criteria:

- be professional nurses working in the wellness centre of the public-sector clinic; or
- be a qualified general practitioner, registrar or psychiatrist working either in the clinics or at the public-sector psychiatric hospitals included as sites for the study.

4.5.2 Data collection

Semi-structured interviews were used as the data collection method. The participants were informed that the purpose of the interview was to obtain information on their experiences. They were assured of the ethical issues and their rights during the interview. The researcher explained that the conversation would be digitally recorded, and transcribed later. An indication was given as to how long the interview would last, because taking too long could result in the participants losing interest.

The researcher's contact information was made available, should the need arise for the participant to contact the researcher to communicate specific issues, such as a decision to withdraw one's participation in the study. The participant was allowed to clarify any doubt about the interview by asking questions.

The process of entry into the selected clinics was made by contacting the manager of each of these clinics and explaining that all of the ethical approvals had been obtained as well as providing said managers with copies of the relevant documentation for record-keeping purposes. The nurse in charge at the wellness centre was then contacted to enquire which day and time would best suit them for interviews. On arrival at the clinics the researcher presented to the nurse in charge and was taken to the

individual consulting rooms of each of the nurses to conduct the interviews. At the psychiatric hospitals, the Clinical Manager was contacted and permission was sought via him or her from the Chief Executive Officer. Individual appointments were made with the doctors at the hospitals. Upon arrival at the hospital, the researcher would present to the Clinical Manager who would then inform the prospective interviewee of the researcher's presence and a quiet room in the medical offices would be allocated for the interview. Doctors at one of the hospitals were contacted and interviewed telephonically rather than face-to-face due to logistical challenges. A request to alter the methodology of the study was first submitted to the Faculty Postgraduate Study Committee at NMMU, approval was granted and the change was implemented. The informed consent letter (Appendix J) was emailed to the doctors, however only one doctor completed the form and returned it to the researcher. Subsequent to this, an appointment was made to conduct the interview. The other interviewees preferred to provide verbal consent and the interview was conducted immediately after.

Following each interview, the digital recording was transferred onto the researcher's laptop, as well as onto a flash disc. The interviews were relaxed and informal; and they lasted between seven and 15 minutes; and the data recorded were transcribed verbatim later.

4.5.2.1 Semi-structured interviews

The purpose of this portion of the study was to conduct individual interviews with healthcare professionals directly involved in the treatment and management of patients on efavirenz. Individual interviews were preferable to holding focus group sessions as, with health care professionals, schedules may differ and finding convenient times for focus groups may be challenging.

Semi-structured interviews were conducted with authorised prescribers in the clinics and hospitals and voice-recorded using an audio recording device and was transcribed within 24 hours of conducting the interview. Semi-structured interviews allow for probing and the clarification of answers (Nieuwenhuis, 2007: 87). Structured interviews include detailed predetermined questions and do not always allow for probing (Nieuwenhuis, 2007: 87).

The questionnaire (Appendix K) was piloted to determine whether or not the questions operate properly and to establish the researcher's ability to conduct an interview (Johnson and Christensen, 2008: 189). Three interviews were conducted prior to the formal study. Informed consent was obtained prior to the data collection. The pilot studies were not included in the final results.

After providing informed consent (Appendix J), the prescribers were asked about prescribing patterns in HIV-positive treatment-naïve patients and the difference between prescribing to patients with a current psychiatric disorder compared to those without, as well as their rationale behind this. They were questioned concerning their attitudes towards ART such as how effective, in their opinion, the current regimens were, whether patients were appropriately screened before ART was prescribed and initiated and whether they would prescribe efavirenz to a patient with a current psychiatric disorder. Their estimate of the rate of efavirenz-induced neuropsychiatric side effects, the clinical significance of these symptoms, the provisions for such patients in terms of alternative treatment and the management of psychiatric symptoms was also investigated. The prescribers were also asked whether they would re-challenge a patient with efavirenz once side effects were no longer problematic. The interviews were conducted subsequently to the prospective study to prevent bias in prescribing patterns.

4.5.2.2 Advantages and disadvantages of interviews

The best research strategy for conducting a descriptive, general interest study is by making use of sample surveys (Mouton and Marais, 1988: 50). Questionnaires may be introspective or extrospective. They are considered introspective if the interviewee is answering questions about themselves and extrospective if answering questions about someone else. The questionnaire in this study is introspective (Behr, 1983: 150-151).

Questionnaire surveys are relatively simple to administer and there is reliable data collection. Further, face-to-face interviews may also take advantage of social cues such as facial expression, tone of voice and body language (Opdenakker, 2006). In face-to-face interviews, the interviewer and interviewee can react off each other. There is instant response from the interviewee and no extended reflection before answering

questions (Opdenakker, 2006). However, face-to-face interviews become challenging when the person to be interviewed is a distance from the researcher and traveling time and costs need to be taken into consideration when intending to conduct this kind of interview. Telephonic interviews would have the advantage due to the wider access to participants however, this would come at the cost of the social cues afforded by face-to-face interviews. Face-to-face interviews may also be time consuming and time restraints my influence the responses given by the interviewee. Prompting from the researcher may result in biased answers if the interviewee does not understand the question, furthermore, as the interviewees are aware that they are participating in research, bias may arise (Malhotra, 1999: 178).

4.5.3 Data analysis

The data obtained from the semi-structured interviews were transcribed by the researcher. The transcribed data were then analysed using conventional content analysis in order to prevent imposing pre-conceived ideas on the data (Hsieh and Shannon, 2005: 1 279, 1 280). An independent coder went through the data and liaised with the researcher to discuss themes and categories in order to reach a consensus. The researcher used the eight steps, as described by Tesch (in Cresswell, 2009: 186) for analysing the data, as follows:

The researcher:

- Made sense of the whole by reading all the transcripts carefully and making short notes. The researcher made transcripts of the digital-recorder interviews.
- Chose one transcript at a time, went through it, and tried to make sense of its contents; then she wrote notes in the margin.
- Made a list of all the topics, clustered similar ones together, and formed them into columns that could be arranged as major topics, unique topics and left-overs.
- Took the list and went back to the data. She then abbreviated the topics as codes next to the appropriate segments of the text, in order to see whether new categories and codes emerged.
- Found the most descriptive wording for the topics, and turned them into categories. The researcher reduced the total list of categories by grouping

topics that related to one another. Lines were drawn between the topics to show any interrelationships.

- Made a final decision on the abbreviations for each category named, and then alphabetised those codes.
- Assembled the data material belonging into each category in one place, and performed a preliminary analysis.
- If necessary, recoded the existing data. An independent coder was provided with the transcripts for coding.

After coding the data, and developing themes, the researcher and the independent coder discussed themes and categories in order for consensus to be reached. Both the researcher and the independent coder agreed that data saturation had been reached, and that there was no need for further interviews to be conducted. The themes, sub-themes and categories portrayed the storyline in a meaningful and descriptive way.

4.5.4 Trustworthiness

Trustworthiness means achieving methodological soundness and adequacy. Guba's model (in Krefting, 1991: 214) identifies the following four criteria for trustworthiness that are also relevant to qualitative studies. The criteria are truth value, transferability, consistency and neutrality. These are discussed in further detail below.

4.5.4.1 Truth value

Truth value attempts to establish confidence in the truth of the findings (Krefting, 1991: 215). Truth value is based on the criterion of credibility, which is the correct interpretation of the experiences of the participants (Guba in Krefting, 1991:217). Truth value was achieved by exploring and describing the experiences and opinions of authorised prescribers and registered professionals. Credibility is usually obtained from the discovery of human experiences as they are lived and perceived by the informants or the participants. The credibility is therefore subject-orientated and not determined before the data collection takes place (Krefting, 1991: 215). Strategies to ensure credibility include the authority of the researcher, field experiences, interviewing technique, member checking, peer examination, reflexivity and structural

coherence (Krefting, 1991: 215). The researcher's attempt to establish the credibility of this research by applying these strategies is set out in Table 4.1.

4.5.4.2 Transferability

Transferability, or applicability, refers to the extent to which findings can be applied to other contexts or settings or other groups (Krefting, 1991: 216). The purpose of this study, as it is with other qualitative studies, is not to generalise findings, but to gain deeper insight into the research phenomenon. A nominated sample and dense description were strategies used to ensure applicability as outlined in Table 4.1.

4.5.4.3 Consistency

Consistency, or dependability, considers whether the findings would be consistent if the enquiry is replicated with the same subjects or in a similar context (Krefting, 1991: 216). Dense description, or a detailed methodology and literature control, will be provided in order to maintain clarity and allow for repeatability of the study. The methodology will be structured in such a way that another researcher will be able to replicate the study. This dense description is further explained in Table 4.1.

4.5.4.4 Neutrality

Neutrality, or confirmability, is the freedom of bias in the research procedure and results (Krefting, 1991: 216). Neutrality does not refer to the neutrality of the researcher, but rather the neutrality of the data. It refers to the degree to which the findings are a function only of the participants and conditions of the research and is not due to other biases, motivations and perspectives (Krefting, 1991: 216). Reflexivity and triangulation were strategies employed to ensure neutrality. The application of these strategies is described in Table 4.1.

4.6 ETHICAL CONSIDERATIONS

Before the commencement of data collection, ethical approval (H14-HEA-PHA-001) was obtained from the Research Ethics Committee - HUMAN (REC-H) at the Nelson Mandela Metropolitan University (NMMU) (Appendix C). The requirement for written consent from individual patients was waived given that patients were not directly

involved in the data collection process. Ethical approval was also requested from the Department of Health (Appendix C). Permission was requested from the relevant clinic and hospital managers for authorisation to review patient files (Appendix H and I). Informed consent forms were drawn up for prescribers to sign upon agreeing to be interviewed (Appendix J). No patient was linked to data and confidentiality was maintained at all times. The researcher declared that the study was conducted in accordance with the Declaration of Helsinki, 2013.

Table 4.1: Criteria to ensure trustworthiness

Criteria to ensure trustworthiness	Strategy	Criteria	Application
Truth value	Credibility	Prolonged engagement	• Contact was made with the participants, in order to build rapport with them. • The researcher has gained insight into the context in which the participants experience utilising efavirenz and the associated side effects thereof in patients with or without psychiatric disorders in a practical context.
		Reflexivity	• Objectivity was maintained throughout the research study, as far as possible.

Criteria to ensure trustworthiness	Strategy	Criteria	Application
		Triangulation	• The data were collected from participants familiar with HIV and its treatment by working with such patients and treatment on a daily basis. • The data were verified by the literature control. • The researcher and an independent coder, experienced in qualitative research, analysed the data. • Participants from various cultures and ages were interviewed. • Participants were interviewed at different times in various clinics and hospitals, to avoid limiting the experiences of the participants to one site only. • Examples of sources that were used by the researcher are as follows: the literature control was done through the use of books, journals, internet searches, etc.
		Peer examination	• Independent checking of the data was done by experts in qualitative methodology.
		Structural coherence	• The researcher and independent coder ensured that there were no inconsistencies between the data and the interpretation thereof. • The participants' experiences using efavirenz and the associated side effects thereof in patients with or without psychiatric disorders comprised the main focus of the study.
Applicability	Transferability	Choose a sample	• A purposive, criterion-based sample was drawn from the available participants. • The researcher set sample criteria.

Criteria to ensure trustworthiness	Strategy	Criteria	Application
		Dense description	• A detailed description of the research methodology, including literature control, was provided to maintain clarity. • These data provided information on the repeatability of the study. • The dense description was written in such a manner that another researcher would be able to follow the proceedings of the study.
Consistency	Dependability	Dense description	• As discussed above
		Triangulation	• As discussed above
		Peer examination	• As discussed above
Neutrality	Confirmability	Triangulation	• As discussed above
		Reflexivity	• As discussed above

4.7 LIMITATIONS

The patients included from the clinics were treatment-naïve, therefore only the relatively short term effect of efavirenz was considered. Patients recruited from the outpatient clinics may have been non-adherent to treatment as they themselves were responsible for taking their ARVs. Defaulters were excluded from the study as the plasma levels of efavirenz would be unreliable. Because patients were not interviewed, some psychosocial factors which could influence the incidence of efavirenz-induced neuropsychiatric side effects may not have been considered.

CHAPTER 5

RESULTS

5.1 INTRODUCTION

This chapter presents the five scientific papers that were generated from the research conducted. Upon submission of the thesis, three of the five papers had been published in peer-reviewed journals. The first two papers were reviews of the literature and were included in Chapter 4 of this thesis. The third, fourth and fifth papers describe the results obtained from the review of medical records at the five public-sector clinics, the results of the HIV-positive psychiatric patients at two public-sector psychiatric hospitals as well as the interviews conducted with nurses and doctors concerning their views of the neuropsychiatric side effects associated with the use of efavirenz. In addition to the publications, two abstracts from this research were thus far accepted for presentation at scientific gatherings. This consisted of one podium presentation at the first Medicines Utilisation Research in Africa (MURIA) conference (Gaborone, 2015) and the second, a poster presented at the second MURIA conference (Gaborone, 2016).

5.2 PUBLISHED ARTICLES

1. Gaida, R., Truter, I. and Grobler, C. 2015. Efavirenz: a review of the epidemiology, severity and management of neuropsychiatric side effects. *South African Journal of Psychiatry*, 21(3): 94-97.

2. Gaida, R., Truter, I., Grobler, C., Kotze, T. and Godman, B. 2016. A review of trials investigating efavirenz-induced neuropsychiatric side effects and the implications. *Expert Review of Anti-infective Therapy*, 14(4): 377-388.

3. Gaida, R., Truter, I. and Grobler, C. 2016. Incidence of neuropsychiatric side effects of efavirenz in HIV-positive treatment-naïve patients in public-sector clinics in the Eastern Cape. *Southern African Journal of HIV Medicine*, [online] 17(1), 6 pages. Available at http://www.sajhivmed.org.za/index.php/hivmed/article/view/452 [Date accessed: 19/10/2016].

5.3 ABSTRACTS PRESENTED AT SCIENTIFIC MEETINGS

1. Gaida, R., Truter, I., Grobler, C. and Kotze, T. A systematic review of efavirenz and neuropsychiatric side effects. Oral presentation at the 1st annual meeting of the MURIA group, July 27 to 29, 2015, Gaborone, Botswana.

2. Gaida, R., Truter, I. and Grobler, C. Incidence of neuropsychiatric side effects in HIV-positive treatment-naïve patients in public-sector clinics in the Eastern Cape Poster presentation at the 2nd annual meeting of the MURIA group, July 25 to 27, 2016, Gaborone, Botswana.

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AOSIS

Page 1 of 6 Original Research

Incidence of neuropsychiatric side effects of efavirenz in HIV-positive treatment-naïve patients in public-sector clinics in the Eastern Cape

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Background: It is acknowledged that almost half of patients initiated on efavirenz will experience at least one neuropsychiatric side effect.

Objectives: The aim was to determine the incidence and severity of neuropsychiatric side effects associated with efavirenz use in five public-sector primary healthcare clinics in the Eastern Cape.

Method: The study was a prospective drug utilisation study. A total of 126 medical records were reviewed to obtain the required information. After baseline assessment, follow-up reviews were conducted at 4 weeks, 12 weeks and 24 weeks from 2014 to 2015.

Results: The participant group was of 74.60% female (n = 94), and the average age was 37.57±10.60 years. There were no neuropsychiatric side effects recorded for any patient. After the full follow-up period, there were a total of 49 non-adherent patients and one patient had demised. A non-adherent patient was defined as a patient who did not return to the clinic for follow-up assessment and medication refills 30 days or more after the appointed date. Some patients (n = 11) had sent a third party to the clinic to collect their antiretroviral therapy (ART). The clinic pharmacy would at times dispense a two-month supply of medication resulting in the patient presenting only every two months.

Conclusion: Further pharmacovigilance studies need to be conducted to determine the true incidence of these side effects. Healthcare staff must be encouraged to keep complete records to ensure meaningful patient assessments. Patients being initiated on ART need to personally attend the clinic monthly for, at least, the first 6 months of treatment. Clinic staff should receive regular training concerning ART including changes made to guidelines as well as reminders of side effects experienced.

Introduction

In 2013, an estimated 10% of the South African population was HIV-positive which amounted to 5.26 million people.[1] This increased to 10.2% in 2014 which amounted to 5.51 million people.[2] Efavirenz forms part of the first-line treatment of HIV in South Africa and is used as part of the fixed-dose combination of triple therapy.

It is acknowledged that almost half of patients initiated on efavirenz will experience at least one neuropsychiatric side effect.[3,4,5] Commonly reported side effects include dizziness, insomnia, headache, abnormal dreams and impaired concentration.[4,6,7] These side effects tend to occur within the first few weeks of treatment and spontaneously resolve within that time.[3] It has also been shown that these side effects may persist longer than a few weeks after the initiation of efavirenz.[5] They may in fact persist for up to 2 years and this may influence the long-term adherence to efavirenz.[8,9] The plasma levels of efavirenz as well as genetic polymorphisms in certain populations are thought to be the cause of these neuropsychiatric side effects.[3,10,11]

There have been several studies[7,12,13,14,15] comparing efavirenz with various other treatments such as nevirapine, protease inhibitors, etravirine and raltegravir. In all instances, efavirenz was seen to induce neuropsychiatric side effects more frequently than these other treatments. The side effects presented most commonly during the first few weeks of treatment and resolved spontaneously after 6 weeks. However, the studies did note that there were instances of late-emergent side effects and recommend that monitoring be an ongoing process.

Efavirenz is effective in reducing viral load in HIV-positive patients. This was shown by Gulick et al.[16] who compared a regimen containing three nucleoside reverse-transcriptase inhibitors (abacavir, lamivudine and zidovudine) with efavirenz-containing regimens. The results of the study showed that efavirenz-containing regimens were virologically superior to those without. Another study[17] showed that efavirenz treatment resulted in an increase in CD4 cell count and was associated with fewer hypersensitivity reactions and hepatitis than nevirapine. These could be the reasons for efavirenz being selected as part of the first-line treatment for HIV in South Africa.[7] However, in light of the problems caused by efavirenz, patient adherence may be affected and treatment interrupted which is undesirable for conditions such as HIV where consistent long-term therapy is required. The South African Guidelines[18] do acknowledge the neuropsychiatric side effects caused by efavirenz and indicate that previous or current depression or other mental disorders would increase the likelihood of these side effects occurring. The guidelines do not however provide guidance as to how to manage these side effects once they manifest.

Before efavirenz is initiated, patients need to be screened for a history of, or a current mental illness, as such patients may be at a higher risk of developing neuropsychiatric side effects. A South African study conducted in 2008[19] showed that the prevalence of HIV in people between the ages of 15 and 49 years at the time was 16.9% and that of this population, 43.7% had some kind of mental disorder. The study showed that mild depressive disorder was the most common amongst males (28.1%) and females (30.5%). This was followed by major depressive disorder and alcohol abuse in both sexes.[20] Another study,[21] conducted in that same year, included 465 HIV-positive patients and found a mental disorder prevalence of 19%.

The aim of this study was to determine the incidence and severity of neuropsychiatric side effects associated with efavirenz use in HIV-positive patients in a public-sector primary healthcare setting.

Research design

Study setting and population

The study was designed as a prospective drug utilisation study. Five public-sector primary healthcare clinics in the Eastern Cape were used as locations for the study. Each of these sites had both an HIV clinic as well as a psychiatric clinic which ensured that patients would be treated at the same facility and not referred.

Patients themselves were not directly involved in the study, and there was no patient contact. Instead, the medical records were reviewed to obtain the required information. Patients were chosen through purposive sampling. The patient files were evaluated to determine whether or not patients met the inclusion criteria. All of the patients who met the outlined criteria were included. Patients who were 18 years or older and diagnosed HIV-positive were included in the study. All of the selected patients were treatment-naïve upon initiation of antiretroviral therapy (ART) and were prescribed efavirenz as part of the triple therapy regimen. Patients with current or previous tuberculosis (TB) infection were also included as were pregnant women. Patients who were previously non-adherent (missed 30 days or more of treatment) and subsequently restarted on ART were excluded. The total sample amounted to 126. For the purposes of this study, the term 'patient' will refer to a patient file or medical record. The data capturers at each of the clinics were contacted to obtain access to files. Data capturers are administrative staff at the clinics who electronically capture information concerning HIV-positive patients recorded by nurses. Patients were enrolled between July 2014 and November 2014 and were selected based on the inclusion criteria.

Ethical consideration

The study was granted ethics approval by the Nelson Mandela Metropolitan University Research Ethics Committee (Human) (reference number: H14-HEA-PHA-001) as well as the Eastern Cape Department of Health and was conducted according to the principles outlined in the Declaration of Helsinki.[20] The necessary permissions were obtained from the management of each individual clinic.

Measurements, outcomes and follow-up procedures

In the public-sector of South Africa, HIV medical records are standardised across the country and contain a number of questions to be asked by the healthcare professional to obtain a baseline picture of the patient's condition. This form was used to obtain the baseline information required for the study. A self-developed data collection tool was used to extract the required information. The information required included age, gender, weight, date of HIV diagnosis, CD4 count at antiretrovirals (ARV) initiation, TB infection, pregnancy status, World Health Organization (WHO) stage, whether the patient was a substance abuser and a history of, or current, psychiatric condition. The primary outcome was the incidence and severity of neuropsychiatric side effects associated with efavirenz use as well as the subsequent management of the patient. After the baseline information was obtained, follow-up was conducted at 4, 12 and 24 weeks. In standard practice, patients receive counselling before the HIV test is performed. The healthcare workers explain the significance of a positive result or provide counselling to encourage the continuation of safe practices if the result is negative. For those who test HIV-positive, the patient is counselled to provide an understanding of what measures need to be taken in order to ensure their future well-being. Healthy living, disclosure of status and, if the patient qualifies for ART, the medication and the importance of adherence is discussed with the patient. Once the patient is considered 'ART-ready', the patient is initiated on treatment. The time lapse between testing and the initiation of treatment varies between patients. After ART has been initiated,

patients present at the clinic on a monthly basis for follow-up assessments and to collect medication. At each visit, the patient would be seen by the wellness clinic nurses for the clinical assessment and the information would be recorded in the file. At the 4-, 12- and 24-week follow-ups, the file was reviewed by the researcher using the data collection tool.

Statistical analysis

The data was captured in Microsoft Excel® and analysed using descriptive statistics.

Results

Subjects at baseline

A total of 126 patients were followed through the 24-week study period. The participant group was 74.60% female (n = 94). The average age was 37.57±10.60 years with females being, on average, younger (35.66±9.83 years) than males (43.19±10.91 years). The difference was seen to be statistically significant ($p < 0.05$). The baseline data are summarised in Table 1.

There were 14 (14.89%) female patients who were pregnant at the start of the study, five of whom were in the first trimester, four in the second semester and two in the third trimester. The trimester was not indicated for three patients. All of these women were initiated on efavirenz before the National Department of Health had published an updated guideline[7] stating that efavirenz could be prescribed to pregnant women regardless of trimester.

TABLE 1: Baseline data of patients.

Variable	Female†	Male‡
Average age ± standard deviation	35.66±9.83 years	43.19±10.91 years
Date of diagnosis		
Before 2008	12	2
2008–2010	5	3
2011–2014	76	27
Not indicated	1	0
CD4 count		
> 350 cells/mm^3	7	3
350–200 cells/mm^3	29	7
< 200 cells/mm^3	17	7
Not indicated	41	15
World Health Organization (WHO) stage		
Stage 1	46	10
Stage 2	17	6
Stage 3	19	10
Stage 4	4	1
Not indicated	8	5
Pregnant	14	-
Antiretroviral (ARV) regimen		
Fixed-dose combination (tenofovir, emtricitabine and efavirenz)	91	31
Zidovudine, lamivudine and efavirenz	1	-
Abacavir, lamivudine and efavirenz	2	1
History of psychiatric illness	1	-
Current psychiatric illness	1	-
Substance abuser	1	-
Alcohol abuser	5	1
Previous TB infection	13	9
Current TB infection	15	6

†, n = 94; ‡, n = 32.

Patients were also screened for a history of psychiatric disorders. This was done by means of a single 'yes' or 'no' question on the standardised medical record asking if the patient had a history of psychiatric illness. One patient had a current symptomatic mental illness and one patient had a history of depression.

Patients were treatment-naïve before the initiation of the efavirenz-containing regimen. The majority of patients (96.83%; n = 112) received efavirenz in the form of the fixed-dose combination (FDC) tablet. Two patients were not receiving the FDC, one was receiving efavirenz in combination with lamivudine and abacavir, and the other efavirenz in combination with lamivudine and zidovudine. All patients, except one, were receiving efavirenz 600 mg daily. That patient was switched to a lower dose of 400 mg of efavirenz due to weight loss resulting in a total body weight of less than 40 kg. Just over half (53.17%; n = 67) of the study population was diagnosed with HIV in 2014. There were 14 patients (11.11%) diagnosed as HIV-positive before 2008 but were initiated on ART only in 2014. This could be due to the CD4 count remaining above the specified threshold of 350 cells/mm^3 which, according to the South African Guidelines[7] at that time, was the point at which the patient must be initiated on ART.

The majority of patients (44.40%; n = 56) were classified as being in clinical stage 1 of the WHO staging and 23.0% (n = 29) being classified as stage 3. Of the patients classified as being stage 3, 62.07% (n = 18) were suffering from a concurrent TB infection.

More than half (55.56%) of the patients had a CD4 count of less than 350 cells/mm^3. This is in keeping with the previous guidelines[22] which stated that patients with a CD4 count of 350 cells/mm^3 or less regardless of the clinical stage must be started on ART. The guidelines have since changed to state that patients with a CD4 count of 500 cells/mm^3 or less must be started on ART regardless of the clinical stage.[18] There were 10 patients who were initiated on ART with a CD4 count of more than 350 cells/mm^3. There were three patients in this group with active TB infection at baseline and another three who were pregnant at baseline. Pregnant patients and those with TB must be initiated on life-long ART regardless of the CD4 count.[18]

Substance abuse was not well documented. The standardised medical record includes a 'yes' or 'no' question querying if the patient is a current 'drug abuser'. There were 59 (46.83%) patients for whom no response was documented. Alcohol abuse is also in the form of a 'yes' or 'no' question asking if the patient is a current alcohol abuser and is questioned separately from substance abuse. There were 60 (47.62%) patients for whom no response concerning alcohol abuse was documented. Only one patient admitted to being a substance abuser and six patients admitted to abusing alcohol.

TABLE 2: Characteristics of non-adherent patients.

Variable	Non-adherent patients†
Male	14 (28.57%)
Average age±standard deviation	36.86±10.58 years
Baseline CD4 count	
> 350 cells/mm^3	6
350–200 cells/mm^3	23
< 200 cells/mm^3	16
Not indicated	25
Pregnant	5
Alcohol abuser	4
Comorbidities	14
TB	6
WHO stage when recorded non-adherent	
1	11
2	4
3	8
4	5
Not indicated	21

†, n = 49.

Not many patients were seen to have comorbidities. There were 13 (10.32%) patients each with hypertension and asthma, five (3.97%) patients with diabetes and two (1.59%) patients with epilepsy. Three patients suffered from diabetes and hypertension, one patient suffered from hypertension and asthma, and one patient suffered from hypertension, asthma and epilepsy in addition to HIV.

Follow-up

There were no neuropsychiatric side effects recorded in the medical records for any patient. One patient reported experiencing a headache; however, this was accompanied by other influenza symptoms and was therefore unlikely to have been caused by efavirenz.

There were non-adherent patients (defined as a patient who did not return to the clinic for follow-up assessment and medication refills 30 days or more after the appointed date) at each follow-up, and this number increased throughout the follow-up period. There were 27 (21.43%), 39 (30.95%) and 49 (38.89%) non-adherent patients after 4, 12 and 24 weeks, respectively. At each follow-up point, there were more female non-adherent patients than male non-adherent patients. After 24 weeks, there were 35 (73.47%; n = 49) female non-adherent patients as compared with 14 (28.57%; n = 49) male non-adherent patients; however, this was not found to be statistically significant. There were nine patients transferred to different facilities over the follow-up period. Some patients (n = 11) sent a third party to the clinic to collect their ART for the month and did not personally present themselves. The clinic pharmacy would also, at times, dispense a 2-month supply of medication resulting in the patient presenting only every 2 months. By the end of the 24-week follow-up, one patient had demised and the cause of death was unknown.

Considering the non-adherent patients more closely (Table 2), six patients were diagnosed with TB co-infection, two were diagnosed as being hypertensive and three were diagnosed as being asthmatic. One patient had both hypertension and asthma. Although patients with comorbidities were prescribed medication for their chronic or infectious diseases, adherence to the medication cannot be guaranteed. Of the 49 non-adherent patients, more than half (56%; n = 28) were between the ages of 18 and 35 years. As CD4 cell counts are checked only 12 months after initiation of ART, there were no new results available during the follow-up period.

Discussion

According to the literature, at least half of the patients who are initiated on efavirenz will experience at least one neuropsychiatric side effect. The clinic records show zero incidence of neuropsychiatric side effects. This could mean that patients were not reporting side effects, clinic staff were not enquiring about side effects or the side effects were not being recorded in the medical records. There were instances of information not being documented in the medical records. This included information such as previous TB infection, whether or not the patient was a substance abuser or whether the patient had a history of a psychiatric disorder.

The questions contained in the standardised medical record for HIV patients were not extensive. A history of psychiatric illness is an important factor in determining the ARV regimen, but only a single 'yes' or 'no' question is devoted to this topic asking the patient if they have a history of psychiatric illness. The patient may not be willing to divulge information concerning a previous mental illness, may not recognise it in themselves or it may not be asked by the healthcare worker. This section should be reviewed, and follow-up questions could be asked in order to determine a history, or current feelings, of depression. It is known that mental illness, particularly depression, serves as a barrier towards adherence.[23] The 'yes' or 'no' questions with regard to substance and alcohol abuse may elicit a feeling of shame and the patient may therefore answer in the negative. The South African Guidelines[18] are not expansive in terms of preparing the patient for ART. It states that the patient must be screened for nutritional status, comorbidities and possible drug interactions and any mental health and substance abuse issues must be addressed.[18] Further elucidation is not provided concerning the specific questions to be asked or clinical assessments to be done. The way these issues are addressed seems to be at the discretion of individual provinces or facilities. The 2010 HIV Guidelines of Swaziland[24] dedicate a chapter to mental health and substance abuse. It states that these are underdiagnosed conditions and not properly managed. It recommends that healthcare workers at the primary care level conduct a basic mental health screen and refer patients who appear to have any issues or are at risk of suicide. The Swaziland guidelines[24] stress that mental illness may affect adherence to ART and is an important issue to consider before initiating treatment. An extensive list of questions is provided to assist healthcare workers in detecting various mental illnesses such as anxiety, depression and suicide risk. In order to provide more comprehensive mental illness screening in South Africa, a similar tool could be adopted.

Some patients did not return to the clinic each month. Patients should be encouraged to personally present themselves at the clinics on a monthly basis for assessment and collection of ART. Third parties should not be allowed to collect medication on behalf of the patient, especially during the first 6 months of therapy when side effects may manifest and this in itself may present barriers to adherence. This also denies the patient any adherence counselling that may be done at these visits. Kranzer et al.[25] found that the rate of non-adherence to ART was highest during the first 6 months of treatment and thereafter declined. It can be understood that the clinics dispense a 2-month supply to patients in order to reduce the patient burden on the dispensary. However, to encourage new patients to come to the clinic, only 1-month supply of medication should be dispensed for at least the first 6 months of treatment in order to ensure retention of the patient.

A study[26] conducted with patients across South Africa showed an adherence of only 40% after an average of 29 months of treatment. A study focused in the Eastern Cape[27] showed 37.5% poor compliance to treatment, but no patient discontinued treatment. Another study[28] set in Cape Town showed only 12.8% non-adherence of a cohort of 242 patients. This shows that adherence varies between provinces in South Africa. It was interesting to note that in this study there were more female non-adherent patients than male non-adherent patients. However, even though the number of female non-adherent patients exceeded the number of male non-adherent patients, the percentage of male non-adherent patients (43.75%) was higher. Kranzer et al.[25] stated that male patients were at higher risk of being non-adherent, whereas female non-adherent patients were more likely to subsequently restart therapy. A retrospective analysis[29] carried out in South Africa stated that gender was not a predictive factor in terms of non-adherence which shows that there are conflicting ideas surrounding gender as a risk factor for non-adherence to ART. It was also noteworthy that the majority (20.41%; $n = 10$) of patients who were non-adherent by the end of the 24-week follow-up period had initial CD4 counts of below 150 cells/mm^3.

Studies[30,31] have been conducted in South Africa to determine the reasons behind non-adherence to ART. Reasons put forth by patients include transport costs, not obtaining time off from work to attend the clinic, transfers between clinics being difficult to complete and resulted in lost paperwork as well as other administration problems.[30,31] Suggestions have been made to provide patients with vouchers for transport, providing transport to and from the clinic, extending clinic hours for patients who work or providing mobile clinic services in order to decrease the distance patients need to travel to reach the clinic.[30,31] A study conducted in rural Rwanda[32] showed that by providing nutritional support, healthcare worker visits to patients' homes to supervise treatment and a transportation allowance resulted in a 92.3% retention rate. This study showed that high retention rates can be achieved in resource-limited settings.

It was noted that overall the standardised medical record sheet used by the public-sector clinics is not sufficient. The form only allows the most elementary screening of co-morbid conditions that would affect the choice of ART prescribed to the patient. Complex conditions such as psychiatric illnesses as well as substance abuse disorders cannot be comprehensively determined by means of single questions. This calls for more integrated healthcare services with psychiatric services performing a more thorough screening of a patient's mental state. Patients need to be adequately screened to determine those at risk for developing side effects to prevent future hospitalisation. These medical records need to be re-evaluated and a more integrated healthcare service provided to patients.

Conclusion

Record-keeping at the public-sector clinics is not currently optimal. Healthcare staff must be encouraged to keep complete records in order to ensure meaningful patient assessments with more attention being paid to mental illness, neuropsychiatric side effects, substance abuse and emotional well-being of the patients. Patients being initiated on ART need to personally attend the clinic for monthly assessments at least for the first 6 months of treatment in order to increase the likelihood of retention in care. Suggestions made by other studies to retain patients should be taken into consideration. These included home visits by healthcare workers, extended clinic hours and mobile clinics as well as providing patients with transport or remuneration for transport to attend the clinics. The medical information sheet used to obtain the patient's medical history should be re-examined and improvements made where necessary. Clinic staff should receive regular training concerning ART including changes made to guidelines as well as reminders of side effects experienced and suggestions for questions to be asked when the patient attends follow-up sessions.

Limitations

The small sample size serves as a limitation to the study as well as the fact that the patients were contained in a single district within the province. The inclusion of patients stretching across a broader location would be desirable. The record-keeping at these facilities has not proven optimal, and improvement in this regard would serve to improve future studies.

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Competing interests

The authors declare that they have no financial or personal relationships which may have inappropriately influenced them in writing this article.

Authors' contributions

All authors contributed towards the conceptualisation and design of the study. R.G. was responsible for the acquisition of the data, data analysis and interpretation of the data.

I.T. and C.G. were responsible for critically revising for intellectual content, proofreading and editing of the final manuscript.

References

1. Statistics South Africa. Mid-year population estimates. Pretoria: Statistics South Africa; 2013. Statistical release P0302.
2. Statistics South Africa. Mid-year population estimates. Pretoria: Statistics South Africa; 2014. Statistical release P0302.
3. Gutierrez-Valencia A, Viciana P, Palacios R, et al. Stepped-dose versus full dose efavirenz for HIV infection and neuropsychiatric adverse events: A randomized trial. Ann Intern Med. 2011;151(3):149–156. http://dx.doi.org/10.7326/0003-4819-151-3-200908040-00127
4. Kenedi CA, Goforth HW. A systematic review of the psychiatric side-effects of efavirenz. AIDS Behav. 2011;15(8):1803–1808. http://dx.doi.org/10.1007/s10461-011-9939-5
5. Lochet P, Peyriere H, Lotthe A, Mauboussin JM, Delmas B, Reynes J. Long-term assessment of neuropsychiatric adverse reactions associated with efavirenz. HIV Med. 2003;4(1):62–66. http://dx.doi.org/10.1046/j.1468-1293.2003.00136.x
6. Arendt G, de Nocker D, von Giesen H. Neuropsychiatric side effects of efavirenz therapy. Expert Opin Drug Saf. 2007;6(2):147–154. http://dx.doi.org/10.1517/14740338.6.2.147
7. Nelson M, Stellbrink H, Podzamczer D, et al. A comparison of neuropsychiatric adverse events during 12 weeks of treatment with etravirine and efavirenz in a treatment-naive, HIV-1-infected population. AIDS. 2011;25(3):335–340. http://dx.doi.org/10.1097/QAD.0b013e3283416873
8. Rihs TA, Begley K, Smith DE, et al. Efavirenz and chronic neuropsychiatric symptoms: A cross-sectional case control study. HIV Med. 2006;7(8):544–548. http://dx.doi.org/10.1111/j.1468-1293.2006.00419.x
9. Clifford DB, Evans S, Yang Y, et al. Long-term impact of efavirenz on neuropsychological performance and symptoms in HIV-infected individuals (ACTG5097s). HIV Clin Trials. 2009;10(6):343–355. http://dx.doi.org/10.1310/hct1006-343
10. Mukonzo JK, Okwera A, Nakasujja N, et al. Influence of efavirenz pharmacokinetics and pharmacogenetics on neuropsychological disorders in Ugandan HIV-positive patients with or without tuberculosis: A prospective cohort study. BMC Infect Dis. 2013;13(261):1–11. http://dx.doi.org/10.1186/1471-2334-13-261
11. Mukonzo JK, Owen JS, Ogwal-Okeng J, et al. Pharmacogenetic-based efavirenz dose modification: Suggestions for an African population and the different CYP2B6 genotypes. Plos One. 2014;9(1):1–9. http://dx.doi.org/10.1371/journal.pone.0086919
12. Nunez M, Soriano V, Martin-Carbonero L, et al. SENC (Spanish efavirenz vs. nevirapine comparison) trial: A randomised, open-label study in HIV-infected naïve individuals. HIV Clin Trials. 2002;3(3):186–194. http://dx.doi.org/10.1310/0CJ5-2ABQ-CB00-6MR6
13. Hawkins T, Geist C, Young B, et al. Comparison of neuropsychiatric side effects in an observational cohort of efavirenz- and protease inhibitor-treated patients. HIV Clin Trials. 2005;6(4):187–196. http://dx.doi.org/10.1310/92VR-FP24-J8GA-B49Q
14. Orkin C, Nelson M, Katlama C, et al. Changes in patient-reported neuropsychiatric outcomes during the SENSE trial: First-line treatment with two nucleoside analogues plus etravirine or efavirenz. Health Outcomes Res Med. 2012;3(3):113–119. http://dx.doi.org/10.1016/j.ehrm.2012.06.002
15. Lennox JL, DeJesus E, Lazzarin A, et al. Safety and efficacy of raltegravir-based versus efavirenz-based combination therapy in treatment-naïve patients with HIV-1 infection: A multicentre, double-blind, randomised controlled trial. Lancet. 2009;374(9692):796–806. http://dx.doi.org/10.1016/S0140-6736(09)60918-1
16. Gulick RM, Ribaudo HJ, Shikuma CM, et al. Triple-nucleoside regimens versus efavirenz-containing regimens for the initial treatment of HIV-1 infection. N Engl J Med. 2004;350(18):1850–1861. http://dx.doi.org/10.1056/NEJMoa031772
17. Patel AK, Pujari S, Patel K, et al. Nevirapine versus efavirenz based antiretroviral treatment in naïve Indian patients: Comparison of effectiveness in clinical cohort. J Assoc Physicians India. 2006;54:915–918
18. National Department of Health. National consolidated guidelines for the prevention of mother-to-child transmission of HIV (PMTCT) and the management of HIV in children, adolescents and adults. Pretoria: National Department of Health; 2015.
19. Freeman M, Nkomo N, Kafaar Z, et al. Mental disorder in people living with HIV/AIDS in South Africa. S Afr J Psychol. 2008;11(3):235–242. http://dx.doi.org/10.1177/008124630803800304
20. World medical association declaration of Helsinki: Ethical principles for medical research involving human subjects. 59th WMA General Assembly, Seoul, Republic of Korea, October 2008 [cited n.d]; 1–5. Available from: http://www.wma.net/en/30publications/10policies/b3/17c.pdf
21. Myer L, Smit J, le Roux L, et al. Common mental disorders among HIV-infected individuals in South Africa: Prevalence, predictors and validation of brief psychiatric rating scales. AIDS Patient Care. 2008;22(2):147–158.
22. National Department of Health. The South African antiretroviral treatment guidelines. Pretoria: National Department of Health; 2013.
23. Kagee A. Adherence to antiretroviral therapy in the context of the national roll-out in South Africa: Defining a research agenda for psychology. S Afr J Psychol. 2008;38(2):413–428. http://dx.doi.org/10.1177/008124630803800211
24. Ministry of Health. National Comprehensive HIV Package of Care. Kingdom of Swaziland; World Health Organization, Geneva, Switzerland. 2010.
25. Kranzer K, Lewis JJ, Ford N, et al. Treatment interruption in a primary care antiretroviral therapy programme in South Africa: Cohort analysis of trends and risk factors. J Acquir Immune Defic Syndr. 2010;55(3):17–23. http://dx.doi.org/10.1097/QAI.0b013e3181f275fd
26. Van Dyk A. Treatment adherence following national antiretroviral rollout in South Africa. Afr J AIDS Res. 2010;9(3):235–247. http://dx.doi.org/10.2989/16085906.2010.530177
27. Bhat VG, Ramburuth M, Singh M, et al. Factors associated with poor adherence to anti-retroviral therapy in patients attending a rural health centre in South Africa. Eur J Clin Microbiol Infect Dis. 2010;29(8):947–953. http://dx.doi.org/10.1007/s10096-010-0949-4
28. Orrell C, Bangsberg DR, Badri M, Wood R. Adherence is not a barrier to successful antiretroviral therapy in South Africa. AIDS. 2003;17(9):1369–1375. http://dx.doi.org/10.1097/00002030-200306130-00011
29. Dalal RP, MacPhail C, Mqhayi M, et al. Characteristics and outcomes of adult patients lost to follow-up at an antiretroviral treatment clinic in Johannesburg, South Africa. J Acquir Immune Defic Syndr. 2008;47(1):101–107. http://dx.doi.org/10.1097/QAI.0b013e31815b833a
30. Miller CM, Ketlhapile M, Rybasack-Smith H, Rosen S. Why are antiretroviral treatment patients lost to follow-up? A qualitative study from South Africa. Trop Med Int Health. 2010;15(suppl1):48–54. http://dx.doi.org/10.1111/j.1365-3156.2010.02514.x
31. Govindasamy D, Ford N, Kranzer K. Risk factors, barriers and facilitators for linkage to antiretroviral therapy care: A systematic review. AIDS. 2012;26(16):2059–2067. http://dx.doi.org/10.1097/QAD.0b013e3283578b9b
32. Rich ML, Miller AC, Niyigena PRN, et al. Excellent clinical outcomes and high retention in care among adults in a community-based HIV treatment program in rural Rwanda. J Acquir Immune Defic Syndr. 2012;59(3):e35–e42. http://dx.doi.org/10.1097/QAI.0b013e31824476c4

5.3.2.1 Proof of submission

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Outcomes of HIV-positive Patients in two Public-sector Psychiatric Facilities in the Eastern Cape Using an Efavirenz-containing Regimen

Short title: Outcomes of psychiatric in-patients on efavirenz

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Abstract

Background: The effects and outcomes with efavirenz in patients diagnosed with active psychiatric disorders has not been well studied.

Objective: This study aimed to determine the outcomes of HIV-positive patients with an active symptomatic mental illness admitted to a public-sector psychiatric facility who were using an efavirenz-containing regimen.

Method: A prospective drug utilisation study was conducted. Two public-sector psychiatric hospitals in the Eastern Cape were approved as study sites. Patients who were 18 years or older and diagnosed as HIV-positive were included in the study. Follow-up assessments were conducted at four, 12 and 24 weeks. The patients were seen by the doctors at the hospital during ward rounds and notes on their progress and medication changes were recorded in their medical records. The files were then reviewed by the researcher using the data collection tool.

Results: A total of 37 patients were enrolled, but only 26 were followed for the full follow-up period. A total of 43.2% were female patients and the average age was 39.38±8.76 years. At baseline, 32.4% patients were diagnosed with schizophrenia. A total of 80.8% of patients experienced an improvement in psychiatric symptoms after 24 weeks. Of these, 42.9% were on an efavirenz-containing regimen.

Conclusion: The majority of patients demonstrated an improvement in their psychiatric condition to the extent that they were discharged from the facilities. Half of these patients were using an efavirenz-containing regimen. This shows that patients with psychiatric disorders on efavirenz can experience good outcomes and stabilisation of the psychiatric symptoms.

Keywords: drug utilisation, HIV-positive, efavirenz, neuropsychiatric, psychiatric, side effects

1. INTRODUCTION

Soon after the human immunodeficiency virus (HIV) is contracted it infects the cerebrospinal fluid[1]. HIV-related cognitive decline is associated with a high viral load and low CD4 count[1,2]. The virus crosses the blood-brain-barrier using the macrophages it infects. Inside the brain, the virus infects the glial cells from which it secretes neurotoxins that lead to neuronal damage and cell death[2]. The clinical manifestation of neurological disorders is dependent on the extent of this neuronal damage. These neurocognitive deficits do not manifest in all HIV-positive patients which suggests that peripheral triggers may be involved[2].

With the introduction of antiretroviral therapy (ART), the life expectancy of people living with HIV has increased and it has made it more likely that the neuropsychiatric manifestations of HIV infection will arise[2]. However, there are a variety of risk factors such as neurotoxicity from the virus itself and cellular products, the effects of ART on the nervous system, substance abuse, previous neurological conditions, age, the psychological consequences of living with HIV and HIV itself that play a role in the psychiatric status of HIV-positive patients[1,3]. The most commonly diagnosed neurological disorders are minor cognitive and motor disorders and associated HIV-dementia while the most common psychiatric manifestations are depressive disorders[2]. An Italian study[4] aimed to determine the prevalence of HIV-associated neurocognitive disorders (HAND) in HIV-positive patients who appeared asymptomatic. Of the 146 patients enrolled, 129 (88.4%) were on ART and just less than 60.0% were on that regimen for longer than one year. The study found that the use of efavirenz increased the risk (odds ratio = 4.00) of HAND in patients[4].

It is well established that efavirenz is associated with inducing neuropsychiatric side effects soon after the initiation of ART[5-7]. The most commonly reported symptoms are dizziness, insomnia, headache, abnormal dreams and impaired concentration[6,8,9], symptoms similar to those of various psychiatric conditions. The reason that clinicians are hesitant to prescribe efavirenz to patients with active psychiatric conditions is likely due to warnings published in national guidelines. In South Africa, the guidelines[10] state that efavirenz is contraindicated in patients with an active psychiatric condition and nevirapine or lopinavir/ritonavir should be used

instead. In contrast, the package insert[11] of efavirenz does not contraindicate its use in patients with active psychiatric conditions, but warns clinicians to be cautious and to stop treatment if severe symptoms manifest.

Efavirenz has been proven to be less likely to cause virological failure than lopinavir/ritonavir[12] and virologically superior to nevirapine[13]. By withholding efavirenz therapy, clinicians may be compromising virological control. Due to the inhibition of enzyme activity, lopinavir/ritonavir has the potential to interact with a variety of drugs, particularly those metabolised by the CYP3A4 and CYP2D6 enzymes of the CYP450 system[14]. These include agents such as amitriptyline, buspirone, carbamazepine, paroxetine and risperidone all of which are used in the treatment of psychiatric conditions[15]. The doses of these agents will require alteration if co-administered with lopinavir/ritonavir. Nevirapine may also be used in the instance of efavirenz toxicity. It must be remembered that nevirapine carries the risk of hepatotoxicity as well as severe skin reactions[16].

1.1 HIV and psychiatric conditions

Freeman and colleagues[17] interviewed a sample of 900 HIV-positive patients and found that 43.7% had a diagnosable mental illness with the most prevalent mental disorder being mild depressive disorder in both males (28.1%) and females (30.5%), followed by major depressive disorder and alcohol abuse in both males and females. Another South African study conducted in 2008[18] included 465 HIV-positive patients and found a mental disorder prevalence of 19.0%. Myer and colleagues[18] showed that 14.0% of the participants had experienced major depression in the last 12 months and 5.0% had suffered from post-traumatic stress disorder. A study in the South African province of KwaZulu Natal[19] examined the HIV seroprevalence of patients admitted to a psychiatric hospital and showed that 26.5% of 151 patients tested HIV-positive. The study[19] did not however, find any significant difference in HIV seroprevalence amongst the various psychiatric conditions.

In 2006[8], a review showed that the most commonly observed affective disorder in HIV-positive patients was bipolar I and bipolar II disorder followed by depression. In the United States, Johns Hopkins Moore HIV Clinic found a 54.0% prevalence of axis

I disorders in newly diagnosed HIV-positive patients[20]. Depression made up 20.0% of this total and adjustment disorder 18.0%. Almost three quarter of the population (n=74.0%) were found to be substance abusers[20]. HIV infection tends to occur with repeated high risk behaviour. Patients with psychiatric disorders are more likely to engage to such high risk behaviour on a chronic basis. Another study[21] conducted in the United States aimed to determine the HIV prevalence amongst the psychiatric population. A retrospective review was conducted of medical records of patients assessed at the Duke University Medical Centre. The review was restricted to only outpatients to prevent inclusion of severely ill mental patients[21]. The study found that psychiatric outpatients exhibited a higher prevalence of HIV than the general population of the medical centre site. Psychiatric patients presented with a 1.2% prevalence whereas the general population prevalence was recorded to be 0.3% to 0.4%[21]. These results were confirmed by Blank and colleagues[22] who also found that the HIV prevalence amongst patients receiving treatment for mental illness was four times higher than that of the general population in a study conducted in Baltimore in the United States.

While some patients present with psychiatric disorders before the initiation of ART, most likely due to the adjustment disorder upon receiving the diagnosis of an incurable condition, other problems may arise only after ART has been initiated. In South Africa, a study[23] was conducted to determine the spectrum of central nervous system (CNS) disorders in HIV-positive patients during the first year of ART. Patients exhibiting signs or symptoms of psychiatric disorder were recruited over a 12 month period. At the end of the recruitment period a total of 75 patients who presented with neurological deterioration were enrolled. The estimated person time at risk for the first year of ART was 3222 patient years taking into account patients lost to care. At the time of neurological deterioration, 44 patients were receiving tuberculosis (TB) treatment. The four most common causes of deterioration were recorded to be CNS TB, cryptococcal meningitis, intracerebral space occupying lesions and psychosis[23]. After following these patients for six months, 17 had passed on and 15 were lost to follow up. This particular population in Cape Town has an especially high prevalence of TB and significant immunosuppression at ART initiation which accounts for the 60.0% of deterioration occurring due to TB and cryptococcal meningitis[23]. This presents a unique problem of HIV-positive patients in a high TB setting and puts

additional strain on the healthcare facility in an already resource constrained environment.

The adherence of patients with a psychiatric illness is of concern. A study conducted in Cape Town[24] retrospectively reviewed medical records of patients attending three public-sector psychiatric facilities. There were 100 patients included in the final analysis, 85.0% of whom were female. Only 37 patients from the study sample attended a six month follow-up assessment following discharge from the psychiatric facility. One significant indicator of patients not returning was shown to be more than one re-admission to the psychiatric facility[24]. However, the study does acknowledge that patients may not be attending follow-up visits due to socioeconomic factors[24].

1.2 HIV and substance abuse

Illicit drugs target a wide range of systems within the body, the immune system being one of those affected[25,26]. While the neuropsychological and neuropathological aspects of HIV are understood, those of drugs of abuse are not[27]. Populations who use these illicit substances on a recreational basis are at higher risk of being infected with HIV due to unsafe sexual practice[26]. Furthermore, not only do these drugs pose a hazard in terms of interactions with ART[28,29], there is also the concern of increased non-adherence to ART amongst substance abusers[30].

Whether CNS disease is more prevalent in HIV-positive patients who are substance abusers is a debated topic given that substance abuse itself can cause immune suppression, breakdown of the blood brain barrier, microglial activation and neuronal injury[31]. Various drugs of abuse exert their own effects on the brain. The use of these illicit drugs results in mood altering effects due to a release of dopamine. However, with repeated use of the drug, the responsiveness of the brain decreases and higher doses of the illicit substance are required to produce an effect[31]. Abuse of opioids has the potential to disrupt the natural opioid system whose receptors are most prevalent in the basal ganglia and various cells such as neurons, glial cells and microglia. Personality disorder is also commonly seen in substance abusers, sometimes before substance abuse begins[31].

Given that the effects of efavirenz in patients with an active psychiatric disorder has not been well studied, this study aimed to determine the outcomes of HIV-positive patients with an active symptomatic mental illness admitted to a public-sector psychiatric facility who were using an efavirenz-containing regimen. Patients were recruited between July 2014 and February 2015 and each patient was followed for a period of 24 weeks.

2. METHODS

2.1 Design and setting

The study was designed as a prospective drug utilisation study. Two public-sector psychiatric hospitals in the Eastern Cape were approved as study sites. One of these facilities was a short-term facility and the other was able to admit patients for a longer period of time.

2.2 Participants

The patients themselves were not directly involved in the study. The medical records were reviewed to obtain the required information. For the purposes of this study, the term ‘patient’ will refer to a patient file or medical record. Patients who were 18 years or older and diagnosed as HIV-positive were included in the study. Patients did not have to be on an efavirenz-containing regimen to be included. Patients were enrolled between July 2014 and February 2015 and were selected according to the inclusion criteria. The total sample amounted to 37 patients.

2.3 Measurements, outcomes and follow-up procedures

A self-developed data collection tool was piloted and changes made before baseline information was obtained. The baseline information included gender, age, weight, duration of HIV infection, primary psychiatric diagnosis, psychiatric medication, ART, a history of TB, head injuries, neurological disorders or substance abuse and any other chronic conditions. After the baseline information was obtained, follow-up assessments were conducted at four, 12 and 24 weeks. The patients were seen by

the doctors at the hospital during ward rounds and notes on their progress and medication changes were recorded in their medical records. The file was then reviewed by the researcher using the data collection tool. The information collected included changes in medication, side effects recorded as well as patient psychiatric symptom progression.

2.4 Ethics

The study was granted ethics approval by the university (H14-HEA-PHA-001) as well as the Eastern Cape Department of Health. The necessary permissions were obtained from the management of each individual hospital.

3. RESULTS

3.1 Subjects at baseline

A total of 37 patients were followed for 24 weeks. There were 16 (43.2%) female patients with an average age of 39.38±8.76 years with the majority (n=24; 64.9%) being between the ages of 39 and 50 years. Male patients formed the remaining 56.8% (n=21) of the patient population with an average age of 38.10±6.25 years and the majority being between the ages of 39 and 50 years. The various baseline diagnoses are summarised in Table 1.

Table 1. Psychiatric diagnosis at baseline.

Diagnosis	Female patients (n=16)	Male patients (n=21)
Bipolar disorder	3	5
Cognitive disorder	-	1
Dementia	1	2
Mild mental retardation	1	-
Psychosis secondary to a general medical condition (HIV)	9	3
Schizophrenia	2	10

Ten patients (27.0%) were aware of their HIV-positive status for one to five years upon admission, with nine patients (24.3%) having a CD4 count of more than 350 cells/mm^3.

This information was not available for 20 patients. The various ART regimens used by the hospitals are outlined in Table 2. Upon admission there were 17 patients (45.9%) using an efavirenz-containing regimen and 20 patients who were not. These patients were instead using nevirapine (n=13) or a protease inhibitor (n=6) while one patient was not on ART at the time of the study.

Table 2. ART regimens.

Regimen	Number of patients (n=37)
Fixed dose combination (efavirenz, emtricitabine and tenofovir)	11
Efavirenz, lamivudine and tenofovir	5
Efavirenz, lamivudine and zidovudine	1
Lamivudine, nevirapine and tenofovir	9
Lamivudine, nevirapine and zidovudine	4
Lamivudine, lopinavir/ritonavir and tenofovir	2
Lamivudine, lopinavir/ritonavir and stavudine	1
Lamivudine, lopinavir/ritonavir and zidovudine	3
None	1

There were 11 patients (29.7%) who had a prior TB infection and 22 (59.4%) with a history of substance use. The most commonly reported substances were alcohol (n=14; 63.6%) followed by marijuana (n=12; 54.6%) and nicotine (n=4; 18.1%). A total of four patients suffered from epilepsy, one had a previous head injury and one patient had a history of meningitis. In addition to ART, patients were receiving a variety of psychiatric medications, often in combination. The various psychiatric medications prescribed is outlined in Table 3. As can be seen risperidone and sodium valproate were the two most commonly used agents in these hospitals.

Table 3. Psychiatric medication used in HIV-positive patients.

Drug classes	Number of patients
Antiepileptics	15
Atypical antipsychotics	24
Benzodiazepines	7
Other (lithium)	2
Selective serotonin-reuptake inhibitors	2
Tricyclic antidepressants	1
Typical antipsychotics	12

3.2 Follow-up

There were 26 patients followed for the full 24-week period. During the follow-up period, two patients had absconded, four patients had been transferred to another facility, one had been down-referred to the local clinic, one patient was granted a leave of absence for six months, two patients had no information available in the medical records and one patient had committed suicide. Of the 26 patients followed for the full 24-week period, 42.9% experienced stabilisation of psychiatric symptoms whilst on efavirenz. The psychiatric symptoms had stabilised and patients were deemed fit to be discharged.

As the patients' mental status improved and they were no longer overtly psychotic, the psychiatric diagnosis was, at times, altered upon subsequent patient evaluation. Therefore, the diagnoses after the follow-up period are summarised in Table 4. 0861103195

Table 4. Psychiatric diagnosis after follow-up.

Diagnosis	Female patients (n=11)	Male patients (n=15)
Bipolar disorder	2	6
Dementia	-	1
Intellectual disability	1	-
Mild neurocognitive disorder	-	1
Psychosis secondary to a general medical condition (HIV)	6	3
Schizophrenia	2	4

There were 21 (80.8%) patients who experienced an improvement in psychiatric symptoms after 24 weeks. Of these, nine (42.9%) patients were on an efavirenz-

containing regimen. Only two patients who showed no improvement after 24 weeks were on an efavirenz-containing regimen. One patient was switched from efavirenz to nevirapine however, in spite of the change in regimen, the patient did not show an improvement after 24 weeks. This may imply that the psychiatric symptoms may not have been due to efavirenz.

The average admission period in hospital for patients who were discharged was 13±10 weeks. The large standard deviation is due to three patients who had longer hospital stays. One for 20 weeks, one for 28 weeks and one for 36 weeks. The two facilities included in the study differed in that one was a long-term facility and the other a short-term facility. The patient with a 36-week stay was admitted to the short-term facility and was subsequently transferred to a long-term facility. A total of 11 patients (42.3%) were discharged by the end of 24 weeks. Of these 11 patients, five were discharged still using an efavirenz-containing regimen. The remaining six patients were all using nevirapine as part of the triple therapy regimen. A comparison between patients using efavirenz-containing regimens and those not is provided in Table 5 below.

Table 5. Comparison between patients using efavirenz-containing regimens and those using other regimens.

Outcome	**Patients on efavirenz (n=16)**	**Patients not on efavirenz (n=21)**
Patients remaining at the hospital for 24 weeks (p=0.1449)	43.8%	66.7%
Improvement in patient condition at last follow-up point (p=0.2703)	56.3%	71.4%
Substance use (p=0.2535)	68.8%	52.4%

Considering the small sample sizes, Fisher's exact test was applied to the above results. The test showed that for all categories the differences were not statistically significant with p-values being above 0.05 for all three categories.

There were just two patients not discharged from the short-term facility by the end of the 24 weeks. Both of these patients were diagnosed as having psychosis secondary to a general medical condition that was HIV. Neither of these patients was on an efavirenz-containing regimen. Of the 13 patients still present at the long-term facility at the end of the follow-up period, four were diagnosed with schizophrenia, two as

having dementia, six with bipolar mood disorder, one with mild neurocognitive disorder and one as having psychosis secondary to a general medical condition that was HIV.

4. DISCUSSION

Of the 26 patients followed for the full 24-week period, 42.9% experienced stabilisation of psychiatric symptoms whilst on efavirenz. The psychiatric symptoms had stabilised and patients were deemed fit to be discharged.

There was one patient in this study who committed suicide while still in hospital. The patient was admitted less than four weeks before the incident and was receiving a combination of tenofovir, lamivudine and nevirapine. The patient was a known defaulter of ART with a history of a TB infection, the treatment of which was also defaulted. Neither the CD4 count nor the duration of the HIV infection of the patient was available. The diagnosis was made as psychosis secondary to a general medical condition that was HIV. It is likely that the patient may have had an existing psychiatric condition before being initiated on ART.

When assessing a patient, the clinician needs to take into account various causes of the psychiatric symptoms. As shown by this study, other psychiatric conditions such as bipolar mood disorder and schizophrenia may co-exist with HIV. It remains unclear whether these psychiatric disorders are incidental or if they are brought about by HIV or its medication[1]. HIV infection itself may be associated with psychotic symptoms with new-onset psychosis occurring in 10.0% to 15.0% of HIV-positive patients[32]. These patients tend to be those with late-stage disease and those suffering from HIV-associated dementia. This would lead to the diagnosis of psychosis secondary to the general medical condition that is HIV often seen in this study. It is noted that some of these patients were initiated on ART at the primary health care facilities and not at the psychiatric hospitals themselves. This indicates a need for mental health services to be further integrated into the HIV services provided at primary health care level.

Interactions between ART and drugs of abuse are not well understood. The study showed that alcohol was the most commonly used substance by this patient population. The metabolism of alcohol occurs primarily via alcohol dehydrogenase and

subsequently aldehyde dehydrogenase. The acute ingestion of alcohol results in the inhibition of the enzymes CYP2D6 and 2C19, while the long term use of alcohol can induce the activity of CYP2E1 and CYP3A4. Therefore, long term use of alcohol can result in chronic medications like NNRTIs to become subtherapeutic[28,29]. If efavirenz is being used by a patient who is chronic user of alcohol, plasma levels of efavirenz may decrease. This could result in HIV in the CNS to proliferate, thereby increasing the risk of the patient developing HAND or HIV-associated dementia. The primary means of metabolism for marijuana or tetrahydrocannabinol (THC) is CYP3A4, therefore efavirenz administration may result in THC toxicity due to the inhibitory activity of efavirenz on CYP3A4[29]. Given that more than half of the population of the current study were marijuana users, furthermore in uncontrolled doses and of uncertain quality, it is possible that an interaction with efavirenz occurred and resulted in psychotic symptoms. Considering that patients who are HIV-positive are abusing various substances, further research into the interactions with ART would be enlightening. Illicit drugs are themselves damaging to the CNS. Combined with an HIV infection, the resulting damage to the CNS can be imagined to be substantial. The prevalence of HIV has also been shown to be higher in the psychiatric population.

5. CONCLUSION

The majority of patients demonstrated an improvement in their psychiatric condition to the extent that they were discharged from the facilities. More than half of the cohort were users of marijuana. Half of the total population were using an efavirenz-containing regimen which shows that patients with psychiatric disorders on efavirenz can experience stabilisation of the acute psychiatric symptoms.

In patients with pre-existing mental disorders, it seems as though those attending primary health care facilities are not being adequately screened for psychiatric disorders. This indicates a need for mental health services to be further integrated into the HIV services provided at primary health care level. Improved screening tools are needed to adequately detect patients at risk as well as further studies investigating the readmission rate of patients with an active mental illness on efavirenz-containing regimens are needed.

Given that efavirenz is part of the fixed dose combination, it is unlikely that its use will decrease, particularly in resource limited settings such as sub-Saharan Africa. It is therefore important to determine the effect of efavirenz in patients with psychiatric disorders both at initiation of ART and during treatment. This would serve to reduce pill burden and improve patient compliance. Integration of services at primary healthcare facilities will enable holistic care of the patient and possibly prevent future hospitalisation.

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LIST OF ABBREVIATIONS

ART- antiretroviral therapy
CNS – central nervous system
HAND – HIV-associated neurological disorder
HIV – Human immunodeficiency virus
TB – tuberculosis
THC - tetrahydrocannabinol

CONFLICT OF INTEREST

The authors state that they have no conflict of interests to declare.

REFERENCES

1. Badkoobehi H, Chana G and Everall IP. Psychiatric aspects of HIV. Psychiatry 2006;5(3): 85-88.

2. Dube B, Benton T, Cruess DG and Evans DL. Neuropsychiatric manifestations of HIV infection and AIDS. J Psychiatry Neurosci 2005;30(4): 237-246.

3. Hill L and Lee KC. Pharmacotherapy considerations in patients with HIV and psychiatric disorders: focus on antidepressants and antipsychotics. Ann Pharmacother 2013;47(1): 75-89.

4. Ciccarelli N, Fabbiani M, Di Giambenedetto S, Fanti I, et al. Efavirenz associated with cognitive disorders in otherwise asymptomatic HIV-infected patients. Neurology 2011;76(16): 1403-1409.

5. Gutierrez-Valencia A, Viciana P, Palacios R, et al. Stepped-dose versus full dose efavirenz for HIV infection and neuropsychiatric adverse events: a randomized trial. Ann Intern Med. 2009;151(3): 149-156.

6. Kenedi CA and Goforth HW. A systematic review of the psychiatric side-effects of efavirenz. AIDS Behav. 2011;15(8): 1803-1808.

7. Lochet P, Peyriere H, Lotthe A, et al. Long-term assessment of neuropsychiatric adverse reactions associated with efavirenz. HIV Med. 2003;4(1): 62-66.

8. Arendt G. Affective disorders in patients with HIV infection: Impact of antiretroviral therapy. CNS Drugs 2006; 20(6): 507-518.

9. Nelson M, Stellbrink H, Podzamczer D, et al. A comparison of neuropsychiatric adverse events during 12 weeks of treatment with etravirine and efavirenz in a treatment-naive, HIV-1-infected population. AIDS. 2011;25(3): 335-340.

10. National Consolidated Guidelines for the Prevention of Mother-to-Child Transmission of HIV (PMTCT) and the Management of HIV in Children, Adolescents and Adults. National Department of Health: Pretoria; 2014.

11. Adco-Efavirenz® [package insert]. 2007. Midrand (Gauteng): Adcock Ingram.

12. Riddler SA, Haubrich R DiRienzo AG, et al. Class-sparing regimens for initial treatment of HIV-1 infection. N Engl J Med 2008; 358(20): 2095-2106.

13. Nachega JB, Hislop M, Dowdy DW, et al. Efavirenz versus nevirapine in treatment of HIV infection: clinical and virological outcomes in Southern African adults. AIDS 2008; 18(22).

14. Cvetkovic RS and Goa KL. Lopinavir/ritonavir: a review of its use in the management of HIV infection. Drugs 2003; 63(8): 769-802.

15. Ogu CC and Maxa JL. Drug interactions due to cytochrome P450. Proc (Bayl Univ Med Cent) 2000; 13(4): 421-423.

16. Schouten JT, Krambrink A, Ribaudo HJ, et al. Substitution of nevirapine because of efavirez toxicity in AIDS clinical trials group A5095. Clin Infect Dis 2010; 50(5): 787-791.

17. Freeman M, Nkomo N, Kafaar Z, et al. Mental disorder in people living with HIV/AIDS in South Africa. S Afr J Psychol 2008;38(3): 489-500.

18. Myer L, Smit J, le Roux L, et al. Common mental disorders among HIV-infected individuals in South Africa: prevalence, predictors and validation of brief psychiatric rating scales. AIDS Patient Care 2008;22(2): 147-158.

19. Collins PY, Berkman A, Mestry K and Pillai A. HIV prevalence among men and women admitted to a South African public psychiatric hospital. AIDS Care 2009;21(7): 863-867.

20. Angelino F. Impact of psychiatric disorders on the HIV epidemic. Top HIV Med 2008; 16(2): 99-103.

21. Beyer JL, Taylor L, Gersing KR, Ranga K and Krishnan R. Prevalence of HIV infection in a general psychiatric outpatient population. Psychosomatics 2007; 48(1): 31-37.

22. Blank MB, Himelhoch SS, Balaji AB, et al. A multisite study of the prevalence of HIV with rapid testing in mental health settings. Am J Public Health 2014; 104(12): 2377-2384.

23. Asselman V, Thienemann F, Pepper DJ, et al. Central nervous system disorders after starting antiretroviral therapy in South Africa. AIDS 2010; 24(18).

24. Joska JA, Obayemi A, Cararra H, et al. Severe mental illness and retention in anti-retroviral care: a retrospective study. AIDS Behav 2014;18(8): 1492-1500.

25. Burdo TH, Katner SN, Taffe MA, et al. Neuroimmunity, drugs of abuse and neuroAIDS. J Neuroimmune Pharmacol 2006;1(1): 41-49.

26. Cabral GA. Drugs of abuse, immune modulation, and AIDS. J Neuroimmune Pharmacol 2006;1(3): 280-295.

27. Bell JE, Arango J and Anthony IC. Neurobiology of multiple insults: HIV-1 associated brain disorders in those who use illicit drugs. J Neuroimmune Pharmacol 2006;1(2): 182-191.

28. Antoniou T and Lin-in Tseng A. Interactions between recreational drugs and antiretroviral agents. Ann Pharmacother 2002;36(10): 1598-1613.

29. Wynn GH, Cozza KL, Zapor MJ, et al. Antiretrovirals, part III: antiretrovirals and drugs of abuse. Psychosomatics 2005;46(1): 79-87.

30. Chander G, Himelhoch S and Moore RD. Substance abuse and psychiatric disorders in HIV-positive patients: epidemiology and impact on antiretroviral therapy. Drugs 2006;66(6): 769-789.

31. Bell JE, Arango J and Anthony IC. Neurobiology of multiple insults: HIV-1-associated brain disorders in those who use illicit drugs. J Neuroimmune Pharmacol 2006; 1(2): 182-191.

32. Owe-Larsson B, Sall L, Salamon E and Allgulander C. HIV infection and psychiatric illness. Afr J Psychiatry 2009;12(2): 115-128.

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Perspectives of healthcare professionals of the neuropsychiatric side effects associated with efavirenz and its management

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ABSTRACT

Background: The use of efavirenz in patients with mental illness has not been conclusively established. The aim of the study was to determine the experiences of healthcare professionals with efavirenz, the associated neuropsychiatric side effects and the management thereof.

Methods: A qualitative, descriptive, exploratory design was used to understand the phenomenon under study and to share the experiences of the participants. Semi-structured interviews were conducted, recorded using a voice recorder and transcribed. The data was analysed using thematic framework analysis and coded by the researcher as well as an independent coder.

Results: The main finding was that there were mixed feelings concerning the use of efavirenz in patients with active mental illnesses. Participants required clarity on the subject.

Conclusions: The study concluded that expansion of National Guidelines to include descriptions of the side effects caused by antiretrovirals (ARVs) and management strategies thereof would empower healthcare professionals to make informed decisions regarding patient care.

Keywords: efavirenz, healthcare professionals, neuropsychiatric, side effects

1. Introduction

Literature strongly associates efavirenz with the incidence of neuropsychiatric side effects (Lochet et al, 2003, p. 62; Gutierrez-Valencia et al, 2009, p. 149; Kenedi & Goforth, 2011, p. 1803). According to literature, at least 50.0% of patients initiated on efavirenz therapy will experience at least one neuropsychiatric side effect (Lochet et al, 2003, p. 62; Gutierrez-Valencia et al, 2009, p. 149; Kenedi and Goforth, 2011, p. 1803). These side effects usually occur within the first few weeks of treatment and will resolve spontaneously during that time (Blanch et al, 2001, p. 339; Gutierrez-Valencia et al, 2009, p. 155). Yet, it is possible for these neuropsychiatric side effects to start manifesting at a later stage in the patient's treatment (Lochet et al, 2003, p. 62, 63, Fumaz et al, 2005, p. 563).

However, the human immunodeficiency virus (HIV) itself is able to cause neurocognitive decline (Badkoobehi, Chana & Everall, 2006, p. 85). The virus achieves this by infecting the cerebral spinal fluid shortly after it enters its human host (Badkoobehi, Chana & Everall, 2006, p. 85). Viral activity inside the brain results in neuronal damage and ultimately cell death (Dube, Benton, Cruess & Evans, 2005, p. 238). The clinical manifestation of neurological disorders is dependent on the extent of the neuronal damage (Dube, Benton, Cruess & Evans, 2005, p. 238). With ageing, HIV-associated neurocognitive disorders are more likely to manifest due to the decreased functionality of the central nervous system (CNS) barriers (Apostolova et al, 2015, para. 10). This is a significant consideration given that the introduction of antiretroviral therapy (ART) has increased the lifespan of HIV-positive patients. Efavirenz is able to suppress the HI viral load in the CNS (Tashima et al, 1999, p. 864). This is a desirable effect of an antiretroviral as the CNS serves as an important viral reservoir (Apostolova et al, 2015, para. 10). However, due to the propensity of efavirenz to cause neuropsychiatric side effects, clinicians are hesitant to prescribe this agent to patients at risk of, or those having, an active mental illness.

In 2008 in South Africa, the prevalence of HIV was 16.9% in people between the ages of 15 and 49 years (Freeman, Nkomo, Kafaar & Kelly, 2008, p. 490). In 2015 the overall HIV prevalence in South Africa was 11.2% translating to a total of 6.19 million persons living with HIV. For the same age group, 15 to 49 years, 16.6% were HIV-

positive (Statistics SA, 2015, p. 1). Kagee and colleagues (2016, para. 4) aimed to determine the prevalence of mental disorders amongst South Africans seeking HIV testing. A total of 485 patients were screened. The most prevalent disorder was major depressive disorder (14.2%) followed by a generalised anxiety disorder (5.0%) and posttraumatic stress disorder (4.9%). Alcohol use disorder was found to be prevalent in 19.8% of the population screened (Kagee, Saal, de Villiers, Sefatsa & Bantjes, 2016, para. 12). This study demonstrates the necessity for more integrated mental health services within the voluntary counselling and testing sphere.

There is no conclusive evidence on the use of efavirenz in patients with an active mental illness. The package insert (Adco-efavirenz®, 2007) of efavirenz does not contraindicate the use of efavirenz in patients with an active psychiatric condition but, rather warns against its use if a patient manifests severe psychiatric symptoms. The National Consolidated Guidelines in South Africa (2014, p. 72, 77) state that efavirenz must not be used in patients with psychiatric illness and warn that it may cause persistent CNS-related side effects. The management strategy suggested is that efavirenz be substituted with nevirapine. If nevirapine cannot be tolerated, then a boosted protease inhibitor such as the combination of lopinavir and ritonavir should be used instead (National Consolidated Guidelines for the Prevention of Mother-to-Child Transmission (PMTCT) of HIV and the Management of HIV in Children, Adolescents and Adults 2014, p. 77).

Efavirenz has shown to be less likely to cause virological failure as compared to lopinavir/ritonavir (Riddler et al, 2008, p. 2103) and virologically superior to nevirapine (Nachega et al, 2008, p. 6). By withholding efavirenz therapy, clinicians may be compromising virological control. Due to the inhibition of activity of enzymes in the CYP450 enzyme system, lopinavir/ritonavir has the potential to interact with a variety of drugs, particularly those metabolised by the CYP3A4 and CYP2D6 enzymes (Cvetkovic & Goa, 2003). These include agents such as amitriptyline, buspirone, carbamazepine, paroxetine and risperidone all of which are used in the treatment of psychiatric conditions (Ogu & Maxa, 2000, p. 422). The doses of these agents will require adjustment if co-administered with lopinavir/ritonavir. Nevirapine may also be used in the instance of efavirenz toxicity. Nevirapine does, however, carry the risk of hepatotoxicity as well as severe skin reactions (Schouten et al, 2010, p. 4).

HIV not only affects patients biologically, there is a psychological component as well. An Indian review (Srinivasan, 2014, para. 4) stated that poor Indian families required extra assistance when caring for a sick family member. Assistance implies visits to the home from healthcare workers, food parcels and advice to the family caring for the patient. This reminds us that HIV is a disease that affects the whole family and not just the individual. In South Africa, some patients may be in similar situations and would benefit from such support. HIV also threatens other aspects of a patient's life such as the way they perceive their life, goals and relationships (Srinivasan, 2014, para. 4). A small study (n=6) (Ramovha, Khoza, Lebese & Shilubane, 2012, p. 4) done at a public-sector psychiatric hospital in the Limpopo province of South Africa, found feelings of depression, hopelessness, anxiety and fear amongst the HIV-positive participants. Some expressed suicidal feelings and said that they did not feel that the staff maintained confidentiality concerning their HIV status particularly in the ward environment of the hospital (Ramovha et al, 2012, p. 4). Patients need to be able to trust healthcare workers for a relationship is to be built between them.

A study in the United Kingdom (Gellaitry, Cooper, Davis, Fisher, Date Leake & Horne, 2005, p. 368) used a questionnaire survey to determine the patient perception of the information they receive concerning ART. The study showed that 42.0% of patients were not completely satisfied with the information they received (Gellaitry et al, 2005, p. 370). If patients were unsatisfied with the information, they were less likely to agree to treatment (Gellaitry et al, 2005, p. 372). The researchers accept that the population largely comprised of homosexual males and that other populations may feel differently. However, it does indicate that healthcare workers need to be knowledgeable about ART in order to fully convince patients of the importance of treatment.

The aim of the study was to determine the experiences of healthcare professionals regarding efavirenz, the associated neuropsychiatric side effects and the management thereof.

2. Material and Methods

A qualitative, descriptive, exploratory design was used to understand the phenomenon under study and to share the experiences of the participants. The qualitative approach

allows the researcher to test the validity of certain assumptions, claims or theories within a real-world context (Leedy & Ormrod, 2005, p. 134).

Criterion-based, non-probability, purposive sampling was used in selecting the study sample. Purposive sampling is concerned with providing a sample of information-rich participants (Struwig & Stead, 2001, p. 122). In order to participate in the study, participants had to be professional nurses working in the wellness centre of the public-sector clinic or a qualified general medical practitioner, registrar or psychiatrist working either in the clinics or at the public-sector psychiatric institutions which were included as study sites. In public-sector clinics, professional nurses are responsible for a significant portion of the work involving the provision of ART to HIV-positive patients, due to the lack of other qualified healthcare professionals such as pharmacists and medical practitioners.

A total of 14 semi-structured interviews were conducted with consenting participants. This group consisted of five nurses and nine doctors. The participants recruited were involved in working with HIV-positive patients as well as patients with active psychiatric conditions. Subsequent to ensuring the relevant permissions were obtained, the researcher telephonically contacted potential participants to inquire as to their interest in participating. If the response was positive, interviews were booked and were conducted at the participant's place of work. All interviews, except two, were conducted face-to-face. The two interviews were conducted telephonically due to logistic challenges. A request was made from the Nelson Mandela Metropolitan University Human Research Ethics Committee to approve the change in methodology before the telephonic interviews were conducted. One of the participants contacted telephonically provided written informed consent, while the other provided verbal consent.

The interview schedule was self-developed keeping the aim of the study in mind in order to learn their opinion on the issues surrounding efavirenz through their experiences. The interview schedule was piloted with three participants to determine appropriateness and ease of understanding. A total of 10 semi-structured questions were used to obtain relevant data. The questions focused on defining neuropsychiatric side effects associated with efavirenz and how these were managed. Any comments

made by the participant during the interview that the researcher found compelling and pertinent were probed with follow-up questions. The interviews ended with asking for recommendations that could be made concerning the National HIV/AIDS Guidelines in assisting healthcare professionals by providing clarity as to the use of efavirenz in psychiatric patients and dealing with these side effects. The interviews were conducted in English due to it being a language the researcher and participants were able to fluently converse in. The interviews were recorded using a voice recorder and were later transcribed. The data were analysed using a thematic framework analysis. As reliability in qualitative studies are important, the researcher made a conscious effort to set aside pre-existing conceptions and expectations when analysing the data.

The data was coded by the researcher as well as an independent coder to ensure neutrality. The final codes and themes presented in this paper had consensus between the coders. Literature was used to support the study findings. Every theme and sub-theme identified was substantiated by quotations from the raw data. This provided valuable data regarding the experiences of healthcare professionals with the use of efavirenz and the neuropsychiatric side effects associated with its use.

Prior to commencement of the study, permission was obtained from the Nelson Mandela Metropolitan University Human Research Ethics Committee [H14-HEA-PHA-001] and the Eastern Cape Department of Health. Before any interviews were conducted, the participants provided written consent by completing an informed consent form. No financial incentive was provided to participants for interviews.

2.1 Trustworthiness

Trustworthiness means achieving methodological soundness and adequacy. According to Guba's model (in Krefting, 1991, p. 214) truth value, transferability, consistency and neutrality ensure trustworthiness in a qualitative study. Truth value in this study was achieved by spending sufficient time with participants to build a rapport before the interview, reflexivity, triangulation, peer examination and structural coherence (the experiences of the participants in using efavirenz and the associated side effects thereof remained the main focus of the study). Transferability refers to the extent to which the findings can be applied to other groups, contexts or settings and

was ensured by purposive sampling and provided a dense description of the context, participants and findings. Consistency is achieved by the same strategies used to ensure trustworthiness, in addition to the co-coding procedure in which the data was coded by both the researcher and an independent coder. The concept of neutrality, or the freedom of bias in the research procedure and results is ensured by triangulation and maintaining objectivity throughout the study as far as possible. Neutrality refers to the neutrality of the data, not of the researcher.

3. Results and Discussion

The study sought to determine the experiences of healthcare professionals with the neuropsychiatric side effects associated with the use of efavirenz. The following themes and sub-themes, pertinent to this article, in that they related to the experiences and opinions of the healthcare professionals, are presented below.

3.1 Theme 1 – Knowledge of screening of patients with HIV for a history of psychiatric disorders prior to commencing efavirenz

3.1.1 Sub-theme 1.1 Effectiveness of screening for a history of psychiatric disorder prior to initiating efavirenz

A history of a psychiatric disorder increases the risk of developing neuropsychiatric side effects associated with efavirenz therapy (Schouten et al, 2010, p. 789). Almost half of patients, without any history of a psychiatric disorder, initiated on efavirenz will experience neuropsychiatric side effects (Gutierrez-Valencia et al, 2009, p. 149; Kenedi & Goforth, 2011, p. 1803; Lochet et al, 2003, p. 62). The most commonly reported side effects include dizziness, insomnia, headache, abnormal dreams and impaired concentration (Arendt, de Nocker, von Giesen & Nolting, 2007, p. 148; Kenedi & Goforth, 2011, p. 1803; Nelson et al, 2011, p. 337; MedlinePlus, 2015). These side effects occur most commonly in the first days of treatment and generally resolve within the first four to six weeks (Gutierrez-Valencia et al., 2009, p. 155). This underlines the importance of baseline screening before the initiation of efavirenz. The screening for a history of psychiatric disorders is done by means of a single ‘yes’ or ‘no’ question on the record card before ART is initiated (Gaida, Truter & Grobler, 2016,

para. 23). Screening for psychiatric disorders is essential in order to identify patients who are at possible risk of developing neuropsychiatric side effects if put on efavirenz.

'*…insomnia uhm, psychosis depression anything causing you know mood symptoms, mania uhm ya.*' [Interview 11]
'…a side effect that you can get from uh interaction of uh neurotransmitters from a circuit point of view and also the the receptors involved psychiatrically like the dopamine receptors and the noradrenaline and adrenaline receptors.' [Interview 8]

Healthcare staff working with HIV-positive patients could provide, at most, a vague definition of a neuropsychiatric side effect. Participants were able to give examples of side effects, but not explain the term itself.

'*…a neuropsychiatric is when the nerve…the nerve of a psychiatric patient has been affected and that's why the patient is having a neuropsychiatric side effect.'*
[Interview 3]

The side effects mentioned above tended to be more psychiatric in nature than neurologic, which could indicate that these are the side effects seen more commonly or those that prove the most problematic. The HIV pandemic has placed a significant burden on the public healthcare system. A system that was already suffering from a shortage of staff and resources cannot be expected to cope with the ever increasing necessity of dedicating staff to the counselling and testing of HIV status, ordering, storing and dispensing of treatment as well as the follow-up assessments and care of these patients. Investment in the recruitment of sufficient numbers of trained personnel such as nurses and pharmacists is vital to the proper functioning of public health care.

'…it is uh psychotic symptoms, mood symptoms, cognitive symptoms…' [Interview 13]

'…causes uhm psychiatric symptoms…' [Interview 12]

'…they complain about eh bad dreams some dizziness ne headaches.' [Interview 7]

'*it's when um someone is have experiencing hallucinations even if it's visual or auditory hallucination bad dreams… you will relate it to mental illness whatever*.' [Interview 5]

The importance of screening for a history of psychiatric disorders may not be realised by healthcare staff, given the ambiguous definitions they have provided of neuropsychiatric side effects. Of concern is that, vulnerable patients could be commenced on efavirenz treatment and develop severe side effects resulting in referral to a psychiatric institution for further management. Clearly, screening for psychiatric disorders needs to be expanded in South Africa. The HIV Guidelines of Swaziland (2010, p. 8, 10) recommends several follow-up questions to assess the mood of the patient and detect symptoms of depression. This emphasises the notion that patients need to be treated holistically and calls for integrated services within clinics. Certainly a centralised electronic data capturing system would prove useful in ensuring that every clinician who comes into contact with the patient has access to a complete medical history.

3.2 Theme 2. Participants described the side effects of efavirenz

3.2.1 Sub-theme 2.1 Participants had diverse knowledge regarding the possibility of neurological side effects of efavirenz

The commonly reported side effects caused by efavirenz such as dizziness, headache, insomnia, abnormal dreams and impaired concentration include both neurological and psychiatric symptoms. The side effects reported by participants vary in nature, some quoting only psychiatric side effects and others a combination:

'*…the reaction you got after you took maybe a medication which induces you know those side effects of neurological it's like it could be related to your mentality would be disturbed…*' [Interview 4]

'*…they will be having that dizziness…that blurred vision at night then what is also going to happen they will others they will have they will see some things that they are afraid of [visual hallucinations]…*' [Interview 6]

'*…they complain about eh bad dreams some dizziness ne headaches.*' [Interview 7]

'*…can expect um psychosis some patients can become psychotic after taking efavirenz.*' [Interview 8]

Considering that the above responses were provided by qualified professional nurses or doctors, the vocabulary used when explaining various medical phenomena was non-scientific to the point that it was doubtful they are fully aware of the effects of the medication.

'…it be danger the patient in danger because if a car can just bump the patient so if it comes to that point ya I'll stop it.' [Interview 7]

Although simple terms may be used with patients, healthcare professionals need to be clear on the concept they are explaining. A lack of understanding on the part of the healthcare professional can result in incorrect information being relayed and a subsequent lack of understanding in the patient.

3.3 Theme 3. Use of efavirenz in patients with current psychiatric illness

3.3.1 Sub-theme 3.1 Participants comment on whether efavirenz may be used in patients with current psychiatric illness

Efavirenz is not specifically contraindicated in patients with active mental disorders (Adco-efavirenz® 2007). The National Consolidated Guidelines (2014, p. 77) in South Africa warn that efavirenz may cause persistent central nervous system toxicity such as abnormal dreams, depression or mental confusion. The risk factors for these side effects are cited as depression or other mental disorder either previous or at baseline (National Consolidated Guidelines for the prevention of mother-to-child transmission of HIV (PMTCT) and the management of HIV in children, adolescents and adults, 2014, p. 77).

'*…if they can tolerate it… no problem prescribing…efavirenz to them.*' [Interview 11]

'*…somebody who's got risk like to have a mental illness… for such a patient…I wouldn't want to put on on efavirenz because that patient is already predisposed you know.*' [Interview 13]

'*We don't we don't we don't do it.*' [Interview 6]

'*I don't recommend it*.' [Interview 9]

There are conflicting opinions regarding whether or not to prescribe efavirenz to a patient with a symptomatic mental illness. This is due to inconclusive evidence provided by the literature and guidelines.

'*…no one can really say whether efavirenz is actually contraindicated… people really just do what they want…'* [Interview 11]

'*I don't have an idea really we don't initiate actually the patient come from the HIV clinics here…*' [Interview 9]

It must be remembered that the majority of ART is initiated by nursing sisters in primary healthcare facilities in South Africa therefore, clarity in guidelines as well as comprehensive screening tools are essential for ensuring that patients receive appropriate treatment.

3.3.2 Sub-theme 3.2 Identification and management of neuropsychiatric symptoms in patients with HIV taking efavirenz

The neuropsychiatric side effects associated with efavirenz may be treated according to its severity (Turjansky & Lloyd, 2005, p. 60). Mild symptoms can be monitored and treated pharmacologically if necessary, whereas more severe symptoms may warrant the discontinuation of efavirenz.

'*…impair the patient's functioning, you know.*' [Interview 13]

'*…influencing their function or affecting their function then I would stop.'* [Interview 11]

Healthcare workers demonstrated an awareness of the more severe side effects that significantly impaired the quality of life of the patient. The suggested management of these side effects by participants was to discontinue efavirenz treatment and replace it with a viable alternative. The National Consolidated Guidelines (2014, p. 77) state that efavirenz may be replaced with either nevirapine or the lopinavir/ritonavir combination in the case of intolerable side effects. However, there was a shift in the responsibility as to who manages the patient's HIV:

'*…we have to involve the uh um the patient uh doctors who managed the HIV you must refer back to them…*' [Interview 9]

'*…normally we don't fiddle with that we just treat them psychiatrically.*' [Interview 9]

It would appear as though clinicians in specialist facilities are unwilling to treat patients holistically and will treat just the condition they consider their responsibility. This results in these clinicians not being familiar with HIV in practice and having, at best, a theoretical knowledge of the condition:

'*I don't have an idea really we don't initiate actually the patient come from the HIV clinics here*.' [Interview 9]

'*I'm not actually…ya knowledgeable (laughs) I must go and read up.*' [Interview 11]

'*…wouldn't be confident but I don't have much information.*' [Interview 13]

'*But I must say, I have very limited experience…*' [Interview 14]

Patients presenting with acute psychosis are managed using antipsychotic agents:

'*…appropriate antipsychotics trying to get the patient, you know, psychiatrically stable again.*' [Interview 1]

'*…often you have to put the patient on a low dose of an antipsychotic.*' [Interview 13]

Jonsson and Joska (2009, p. 23) indicate that it is safe to use antipsychotic agents in HIV-positive patients who present with acute psychosis. These agents should always be used at the lowest possible dose for the shortest duration possible. Interestingly, the idea that efavirenz, when used as part of the fixed dose combination (FDC), induced fewer neuropsychiatric side effects as compared to efavirenz when used as individual therapy. It could be that efavirenz, when used as part of the FDC, does not reach the same levels in the CNS as when efavirenz is used as a single agent:

'*FDC here that contains efavirenz and we don't really, you know, see many um you know efavirenz-related psychiatric symptoms.*' [Interview 1]

'*…most patients that I have seen they'll present it [neuropsychiatric side effects] in the six months of initiation of efavirenz. But but that is uh that applies to when efavirenz is used as a single drug, not as part of the uh combination fixed dose combination.*' [Interview 13]

3.4 Theme 4. Participants commented on whether the National Treatment Guidelines for HIV and AIDS are sufficient to assist practitioners in all aspects of disease management

3.4.1 Sub-theme 4.1 National Treatment Guidelines covers all possible aspects of treatment

While the National Guidelines (2014, p. 76-78) focus on some adverse effects of antiretrovirals (ARVs), the information is superficial. Certain conditions such as fat redistribution syndrome, bone density reduction and renal tubular dysfunction due to tenofovir and abacavir hypersensitivity reaction are discussed in more detail. As most HIV-positive patients are diagnosed and initiated on treatment in primary healthcare facilities the staff, particularly nurses, in these facilities view the guidelines as a definitive document. Therefore, further elucidation on the major side effects caused by each agent and management strategies thereof would prove useful.

'*I think there is room for improvement.*' [Interview 1]

'*…think improvements can be made…*' [Interview 2]

'*There's uh room to make uh improvement.*' [Interview 8]

Clarity concerning the identification and management of neuropsychiatric side effects would give healthcare staff more confidence when faced with such challenges:

'*…bit scared when dealing with a neuropsychiatric [side effect]…*' [Interview 12]

3.4.2 Sub-theme 4.2 Participants provided possible improvements for the guidelines

'*…especially side effects and there should perhaps be, even just an addendum, attached for further enquiry.*' [Interview 12]

'*…HIV and HIV associated neurocognitive disorders I couldn't rely on only national guidelines…*' [Interview 2]

'*…basically it's not a holistic approach…*' [Interview 4]

'*…identifying the patients uh who are who are vulnerable to these uh uh side effects in the first place.*' [Interview 8]

Further studies concerning the effects of efavirenz and mental illness in HIV-positive patients are necessary to provide the kind of information participants are suggesting. The standardised medical record card needs to be re-evaluated and follow-up questions probing into the mental status of the patient must be included.

4. Conclusions

A lack of understanding of basic definitions can undermine an entire system. The inability of many participants to provide a clear definition of a neuropsychiatric side effect in medical language indicates a lack of appreciation of the importance of this particular phenomenon.

Participants indicated mixed feelings regarding the use of efavirenz in patients with an active mental illness. Most of the participants expressed confusion as to whether or not efavirenz may be used. Though, clinicians in psychiatric hospitals indicated that they had not encountered patients who needed to be switched to alternative therapy due to the neuropsychiatric side effects caused by efavirenz. Other participants mentioned that the use of the FDC has reduced the incidence of neuropsychiatric side effects compared to efavirenz being used as a single agent. This was an interesting fact to note as the reasons behind this have not been established.

The place of efavirenz in the treatment of patients with mental illnesses needs to be more clearly defined. Even though efavirenz is no longer being used in developed countries such as the United States, it has a wide presence in Africa as part of the recommended first-line treatment of HIV. Participants in this study made the desire for more information clear.

5. Recommendations

The employment of sufficiently trained staff in wellness clinics is essential in ensuring that a comprehensive medical history is taken from patients and that the appropriate medication is prescribed. Further integration of mental health services into the wellness programme at primary healthcare facilities is critical in order to effectively screen for patients who had a history of, or who are currently suffering from, mental disorders and treat them appropriately.

Further studies focusing on the incidence of psychiatric relapse in these patients would provide valuable information. The National ART Guidelines of South Africa need to be expanded to include side effects caused by all agents and suggestions for management strategies. This will serve to further empower healthcare staff with knowledge and will translate to better patient care and outcomes.

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References

Adco-Efavirenz® [package insert]. (2007). Midrand (Gauteng): Adcock Ingram.

Apostolova, N., Funes, H.A., Blas-Garcia, A., Galindo, M.J., Alvarez, A. & Esplugues, J.V. (2015). Efavirenz and the CNS: what we already know and questions that need to be answered. J Antimicrob Chemother, 70(10), 2693-708. https://doi.org/10.1093/jac/dkv183

Arendt, G., de Nocker, D., von Giesen, H. & Nolting, T. (2007). Neuropsychiatric side effects of efavirenz therapy. Expert Opin Drug Saf, 6(2), 147-154. https://doi.org/10.1517/14740338.6.2.147

Badkoobehi, H., Chana, G. & Everall, I.P. (2006). Psychiatric aspects of HIV and AIDS. Psychiatry, 5(3), 85-88. https://doi.org/10.1383/psyt.2006.5.3.85

Cvetkovic, R.S., & Goa, K.L. (2003). Lopinavir/ritonavir: a review of its use in the management of HIV infection [Abstract]. Drugs, 63(8), 769-802.

Dube, B., Benton, T., Cruess, D.G. & Evans, D.L. (2005). Neuropsychiatric manifestations of HIV infection and AIDS. J Psychiatry Neurosci, 30(4), 237-246

Freeman, M., Nkomo, N., Kafaar, Z. & Kelly, K. (2008). Mental disorder in people living with HIV/AIDS in South Africa. S Afr J Psychol, 38(3), 489-500. https://doi.org/10.1080/09540120701426482

Fumaz, C.R, Munoz-Moreno, J.A., Molto, J., Negredo, E. Ferrer, M.J., Sirera, G., Perez-Alvierrez, N., Gomez, G., Burger, D. & Clotet, B. (2005). Long-term neuropsychiatric disorders on efavirenz-based approaches: quality of life, psychological issues, and adherence. J Acquir Immune Defic Syndr, 38(5), 560-565. https://doi.org/10.1097/01.qai.0000147523.41993.47

Gaida, R., Truter, I. & Grober, C. (2016). Incidence of neuropsychiatric side effects of efavirenz in HIV-positive treatment-naïve patients in public-sector clinics in the Eastern Cape. S Afr J HIV Med, 17(1). https://doi.org/10.4102/hivmed.v17i1.452

Gellaitry, G., Cooper, V., Davis, C., Fisher, M., Leake Date, H. & Horne, R. (2005). Patients' perception of information about HAART: impact on treatment decisions. AIDS Care, 17(3), 367-376. https://doi.org/10.1080/09540120512331314367

Gutierrez-Valencia, A., Viciana, P., Palacios, R., Ruiz-Valderas, R., Lozano, F., Terron, A., Rivero, A. & Lopez-Cortes, L.F. (2011). Stepped-dose versus full dose efavirenz for HIV infection and neuropsychiatric adverse events: a randomized trial. Ann Intern Med, 151(3): 149-156. https://doi.org/10.7326/0003-4819-151-3-200908040-00127

Jonsson, G. & Joska, J.A. (2009). Assessment and treatment of psychosis in people living with HIV/AIDS. S Afr J HIV Med, 10(3): 20-27. https://doi.org/10.4102/hivmed.v10i3.279

Kagee, A., Saal, W., de Villiers, L, Sefatsa, M. & Bantjes, J. (2016). The prevalence of common mental disorders among South Africans seeking HIV testing. AIDS Behav. https://doi.org/10.1007/s10461-016-1428-4

Kenedi, C.A. & Goforth, H.W. (2011). A systematic review of the psychiatric side-effects of efavirenz. AIDS Behav, 15(8), 1803-1808. https://doi.org/10.1007/s10461-011-9939-5

Krefting, L. (1991). Rigor in qualitative research: the assessment of trustworthiness. Am J Occup Ther, 45(3): 214-222.

Leedy. P.D & Ormrod, J.E. (2005). 8th Edition. Practical research planning and design. USA: Pearson Merrill Prentice Hall.

Lochet, P., Peyriere, H., Lotthe, A., Mauboussin, J.M., Delmas, B. & Reynes, J. (2003). Long-term assessment of neuropsychiatric adverse reactions associated with efavirenz. HIV Med, 4(1), 62-66. https://doi.org/10.1046/j.1468-1293.2003.00136.x

Nachega, J.B., Hislop, M., Dowdy, D.W., Gallant, J.E., Chaisson, R.E., Regensberg, L. & Maartens, G. (2008). Efavirenz versus nevirapine-based initial treatment of HIV infection: clinical and virological outcomes in southern African adults. AIDS, 18(22), 2117-2125. https://doi.org/10.1097/qad.0b013e328310407e

National comprehensive HIV package of care for adults and adolescents in Swaziland. (2010). Kingdom of Swaziland: Ministry of Health.

National Consolidated Guidelines for the Prevention of Mother-to-child Transmission of HIV (PMTCT) and the Management of HIV in Children, Adolescents and Adults. (2014). Pretoria: National Department of Health, 2014.

Nelson, M., Stellbrink, H., Podzamczer, D., Banhegyi, D., Gazzards, B., Hill, A., von Delft, Y., Vingerhoets, J., Stark, T. & Marks, S. (2011). A comparison of neuropsychiatric adverse events during 12 weeks of treatment with etravirine and efavirenz in a treatment-naive, HIV-1-infected population. AIDS, 25(3), 335-340. https://doi.org/10.1097/qad.0b013e3283416873

Ogu, C.C. & Maxa, J.L. Drug interactions due to cytochrome P450. (2000). Baylor University Medical Centre Proceedings,13(4), 421-423.

Ramovha, R., Khoza, L.B., Lebese, R.T. & Shilubane, H.N. (2012). The psychological experience of HIV and AIDS by newly diagnosed infected patients at hospital A of Vehembe District, Limpopo Province. J AIDS Clin Res, S1, 1-6. https://doi.org/10.4172/2155-6113.s1-006

Riddler, S.A., Haubrich, R., DiRienzo, A.G., Peeples, L., Powderly, W.G., Klingman, K.L., Garren, K.W., George, T., Rooney, J.F., Brizz, B., Lalloo, U.G., Murphy, R.L., Swindells, S., Havlir, D. & Mellors, J.W. (2008). Class-sparing regimens for initial

treatment of HIV-1 infection. N Engl J Med, 358(20), 2095-2106. https://doi.org/10.1056/nejmoa074609

Schouten, J.T., Krambrink, A., Ribaudo, H.J., Kmack, A., Webb, N., Shikuma, C., Kuritzkes, D.R. & Gulick, R.M. (2010). Substitution of nevirapine because of efavirenz toxicity in AIDS Clinical Trials Group A5095. Clin Infect Dis, 50(5), 787-791. https://doi.org/10.1086/650539

Srinivasan, S. (2014). Psychosocial problems faced by HIV/AIDS patients. Journal of Research, Extension and Development, 2(8).

Statistics South Africa. (2015). Mid-year population estimates. (pp 1-20). South Africa: Pretoria.

Tashima, K.T., Caliendo, A.M., Ahmad, M., Gormley, J.M., Fiske, W.D., Brennan, J.M. & Flanigan, T.P. (1999). Cerebrospinal fluid human immunodeficiency virus type 1 (HIV-1) suppression and efavirenz drug concentrations in HIV-1-infected patients receiving combination therapy. J Infect Dis, 180(3), 862-64. https://doi.org/10.1086/314945

Turjanski, N. & Llyod, G.G. (2005). Psychiatric side effects of medications: recent developments. Adv Psychiatr Treat. 11, 58-70. https://doi.org/10.1192/apt.11.1.58

5.4 CHAPTER SUMMARY

The primary aim of this study was to determine the incidence of neuropsychiatric side effects associated with the use of efavirenz and whether this agent could be successfully used in PLWHA who have active psychiatric conditions. The required data was collected from five public-sector clinics and two public-sector psychiatric hospitals in the Eastern Cape. The specific clinics were chosen on the basis of ethnic diversity and the presence of both wellness and psychiatric services in each facility. The psychiatric hospitals were chosen based on location and the number of patients required. Healthcare professionals based at the sites included in the study were requested to be interviewed to gauge their opinions on the use of efavirenz and the potential problems associated with its use. The inclusion of more sites would have added precision to the final outcome.

A review of the medical records was performed at the clinics in order to determine the incidence and severity of the neuropsychiatric side effects associated with the use of efavirenz. The patients were followed from baseline up to 24 weeks after the initiation of treatment. It was found that no neuropsychiatric side effects were recorded for any patient during this time period. This indicated that either there were no neuropsychiatric side effects to report, patients were not being questioned concerned these side effects, the side effects were not clinically significant, or they were not being recorded in the files.

Patients on efavirenz at the psychiatric hospitals were followed for 24 weeks from admission to determine whether or not there was an improvement in the psychiatric symptoms. The results showed that a total of 80.8% of patients experienced an improvement in psychiatric symptoms after 24 weeks to the extent that they were deemed fit enough to be discharged from the individual facilities. Of these, 42.9% were on an efavirenz-containing regimen. This shows that patients exhibiting acute psychiatric symptoms may not necessarily need to be switched from efavirenz to another agent.

Healthcare professionals employed at the sites included in the study were personally contacted by the researcher to request an interview. Those who agreed provided an appointment. The interviews were recorded on a voice recording device and were

transcribed. Coding was done by the researcher as well as an independent coder to ensure neutrality in the results. Analysis of the data showed that, at best, healthcare workers could provide only a vague definition of neuropsychiatric side effects. A lack of understanding of the phenomenon itself may undermine the importance of screening for psychiatric disorders in patients before efavirenz is prescribed. Knowledge of the nurses in primary healthcare facilities was equivocal whereas the knowledge and opinions of the clinicians at the psychiatric institutions was theoretical. There was a perceived split in the responsibility of the patients' conditions. The clinics were perceived to be responsible for managing the HIV, whereas the hospital clinicians considered themselves responsible for treating the psychiatric manifestations. Treatment of the patient needs to be holistic, with clinicians having a better understanding of HIV and its treatment. There were conflicting opinions concerning the use of efavirenz in patients with an active psychiatric illness. This is a direct result of inconclusive evidence provided by the literature and unclear directions in the National Guidelines. Participants expressed that description of the neuropsychiatric side effects caused by efavirenz as well as strategies on managing these side effects would prove useful in providing proper patient care. Regular training of staff at both clinic and hospital level would assist in ensuring that healthcare professionals are equipped with sufficient knowledge and confidence to provide effective patient care.

CHAPTER 6

CONCLUSIONS

6.1 INTRODUCTION

This chapter summarises the major findings from the five public-sector clinics and two public-sector psychiatric hospitals concerning the use of efavirenz. The chapter will describe the incidence of neuropsychiatric side effects associated with efavirenz as found in the public-sector clinics and outline how these were managed. The chapter will also focus on the outcomes of PLWHA with active psychiatric conditions who were on efavirenz as part of the triple therapy regimen. Lastly, the chapter will outline the perspectives of healthcare professionals concerning their experiences of efavirenz use in patients with or without psychiatric conditions. The chapter will close by providing recommendations as to the way forward with efavirenz.

6.2 LIMITATIONS

The study was performed across a limited geographic area. Including facilities across a broader area would have allowed for more generalisable results. The patients included in the clinic review were treatment-naïve before initiation of ART, therefore only a relatively short duration of efavirenz therapy was considered. Due to there being no direct patient involvement, data collection relied on the information documented by healthcare staff in both the clinics and hospitals.

6.3 SUMMARY OF MAJOR FINDINGS

6.3.1 Clinics

A cohort of 126 patients were followed in the five public-sector clinics included in the study. The patients were followed from initiation of ART until 24 weeks of treatment. Follow-up visits were made after two, four, 12 and 24 weeks. Female patients formed the majority of the group (74.6%; n=94) and this group was, on average, younger (35.66±9.83 years) than their male counterparts (43.19±10.91 years).

Patients initiated on ART at the clinics are screened for a history of psychiatric disorders to determine the appropriateness of efavirenz treatment. This screening is

done by means of a single ‘yes’ or ‘no’ question. One patient had a history of mental illness and another was suffering from a mental illness at the time of the study and was receiving the appropriate treatment. The majority of patients were receiving efavirenz in the form of the FDC.

Upon follow-up it was found that there was a zero incidence of neuropsychiatric side effects. One patient reported experiencing a headache, but as this was accompanied by other influenza symptoms, it was unlikely that it was due to the efavirenz. The number of non-adherent patients was 27 (21.4%), 39 (30.9%) and 49 (38.9%) at four, 12 and 24 weeks respectively. During the follow-up period, few patients (n=11) sent third parties to collect treatment on behalf of the patients. At the end of the follow-up period one patient had demised, but the cause of death was unknown.

6.3.2 Hospitals

A total of 37 patients were included in the study, but only 26 were followed for the complete 24 weeks. There were 16 (43.2%) female patients with the overall average age being 39.38±8.76 years. The most common diagnosis (n=12) was psychosis secondary to HIV implying that the HIV itself induced the psychotic episode. Schizophrenia (n=12) was also commonly seen as was bipolar disorder (n=8). There were a total of 17 (45.9%) patients using efavirenz as the NNRTI backbone and 13 using nevirapine (35.1%). Six patients were using the combination of lopinavir and ritonavir and one patient was not on ART.

There were 11 patients (29.7%) with a prior TB infection and 22 (59.4%) had a history of substance abuse. The most commonly abused substances were alcohol (n=14; 63.6%) followed by marijuana (n=12; 54.6%) and nicotine (n=4; 18.1%). A total of four patients suffered from epilepsy, one had a previous head injury and one patient had a history of meningitis. In addition to ART, patients were receiving a variety of psychiatric medication, often in combination, with risperidone and sodium valproate being the most commonly prescribed agents at the hospital.

By the end of the 24-week period, one patient had committed suicide while in hospital. This patient was not on an efavirenz-containing regimen and the suicidality could be attributed to the psychiatric disorder itself. The patient was diagnosed as being

psychotic secondary to HIV infection. There were 21 (80.8%) patients who experienced an improvement in psychiatric symptoms after 24 weeks. Of these, nine (42.9%) patients were on an efavirenz-containing regimen. One patient was switched from efavirenz to nevirapine, but this did not result in an improvement in the overall condition of the patient.

6.3.3 Perspectives of healthcare professionals concerning the use of efavirenz

Healthcare professionals were elusive when asked to define neuropsychiatric side effects. A lack of understanding of the phenomenon itself may result in healthcare workers underestimating the importance of screening for psychiatric disorders before initiating patients on ART. There were conflicting opinions concerning the use of efavirenz in PLWHA with psychiatric disorders. This is due to the inconclusive evidence in literature and vague guidelines.

Patients are initiated on ART at primary healthcare facilities by nurses. When admitted to a psychiatric facility, clinicians are willing to treat only the psychiatric symptoms of these patients. Patients need to be considered as a whole in order for effective therapy to be achieved.

Participants felt that there was room for improvement in the National HIV Guidelines and expressed the desire for more in depth description of the neuropsychiatric side effects caused by efavirenz and suggested management strategies.

6.4 RECOMMENDATIONS

The following recommendations stem from the findings of the study. Taking into account the limitations of the study, the following recommendations concerning documentation, clinical practice and healthcare services were formulated.

6.4.1 Recommendation 1

The standardised medical record used for the screening of newly diagnosed HIV-positive patients needs to be re-evaluated and revision considered. A single ‘yes’ or ‘no’ question for the screening of as complex a condition such as a psychiatric disorder is insufficient. Follow-up questions need to be added to gauge the patients’ current mental state as the diagnosis of a condition like HIV is likely to have an impact on the

mental health of the individual. Adapting questions from the Diagnostic and Statistical manual of Mental Disorders version 5 may be considered.

6.4.2 Recommendation 2

PLWHA initiated on ART for the first time need to be encouraged to visit the clinic personally on a monthly basis for at least the first six months of treatment to ensure compliance. This will allow for pill counts and ongoing counselling.

6.4.3 Recommendation 3

Maintaining complete medical records are essential to ensure optimal patient care. Besides being good clinical practice, due to a shortage of staff in the public-sector, it cannot be guaranteed that a patient will always be seen by the same physician or nurse. It is therefore critical that complete notes be available in the medical records. Comprehensive notes will also allow for complete data collection when research is conducted at the facility.

6.4.4 Recommendation 4

Patients suffering from acute psychosis on efavirenz should first be stabilised in terms of the psychosis. If, upon monitoring, the patient does not relapse, the efavirenz may be continued if the patient is able to tolerate it. The introduction of the FDC has reduced the pill burden for PLWHA and to an even greater extent for those with co-morbidities. Lower pill burdens encourage compliance amongst patients and this is particularly important for those with mental disorders. Further studies concerning the readmission of patients on efavirenz to psychiatric institutions would be beneficial in determining whether or not the patient can tolerate efavirenz long-term.

6.4.5 Recommendation 5

Mental health services need to be further integrated into HIV wellness programmes. The diagnosis of an incurable illness such as HIV will have an impact on the mental health of a patient and psychological assistance will assist patients in accepting their condition and adapting to a new way of life. Integration of mental health services may also assist in detecting patients with a mental illness at baseline and allow them to be referred to a psychologist or psychiatrist for further evaluation. Existing staff in the HIV

clinics should be trained to perform basic mental health assessments before the initiation of ART or the standardised medical records should incorporate more comprehensive psychological screening.

6.4.6 Recommendation 6

Further elucidation in the guidelines outlining the neuropsychiatric side effects of efavirenz and management strategies would prove useful to all levels of healthcare professionals in the public-sector. Regular training of healthcare staff informing them of updates to guidelines and reiteration of the side effects caused by the various ARVs will ensure that patients are being treated by individuals who are confident in their knowledge.

6.5 CHAPTER SUMMARY

The conclusions and recommendations made by this study were drawn from the findings. These recommendations may assist in improving the quality of care received by PLWHA. PLWHA are attempting to cope with the acceptance of a lifelong, incurable disease. Incorporation of mental health services to a greater extent within the HIV programmes will serve to assist PLWHA in adjusting to their new circumstances. Encouraging PLWHA to attend clinics will enable healthcare workers to provide necessary counselling and support to these patients. Given that HIV forms the largest burden of disease in South Africa, the proper education of all levels of healthcare workers concerning HIV and AIDS will empower them in caring for PLWHA, thus ensuring that these patients receive optimal care.

REFERENCES

Abrams, D.I., Hilton, J.F., Leiser, R.J., Shade, S.B., Elbeik, T.A., Aweeka, F.T., Benowitz, N.L., Bredt, B.M., Kosel, B., Aberg, J.A., Deeks, S.G., Mitchell, T.F., Mulligan, K., Bacchetti, P., McCune, J.M. and Schambelan, M. 2003. Short-term effects of cannabinoids in patients with HIV-1 infection: a randomized, placebo-controlled clinical trial. *Annals of Internal Medicine,* 139(4): 258-266.

Adco-Efavirenz [package insert]. Midrand (Gauteng): Adcock Ingram; 2007.

AIDS.gov. What is HIV/AIDS? 2015. Available at https://www.aids.gov/hiv-aids-basics/hiv-aids-101/what-is-hiv-aids/ [Date accessed: 22/02/2016].

AIDS Foundation South Africa. Testing and Treatment. Available at http://www.aids.org.za/testing-and-treatment/ [Date accessed 2/10/2016].

AIDSinfo. HIV overview: stages of HIV infection. 2016. Available at https://aidsinfo.nih.gov/education-materials/fact-sheets/19/46/the-stages-of-hiv-infection [Date accessed: 22/02/2016].

Ances, B.M. and Ellis, R.J. 2007. Dementia and neurocognitive disorders due to HIV-1 infection. *Seminars in Neurology,* 27(1): 86-92.

Anonymous. 2010. HIV and hope: one woman's story. Available at http://www.southafrica.info/services/health/ntombi.htm#.VrnFG1h94U0 [Date accessed: 9/2/2016].

Antoniou, T. and Lin-in Tseng, A. 2002. Interactions between recreational drugs and antiretroviral agents. *The Annals of Pharmacotherapy,* 36(10): 1598-1613.

AOSIS Publishing. AOSIS publishing house style for authors. Available at http://aosis.co.za/documents/20151118.AOSIS_Publishing_house_style_for_journal_and_book_authors.pdf [Date accessed: 20/07/2016].

Arendt, G., de Nocker, D., von Giesen, H. and Nolting, T. 2007. Neuropsychiatric side effects of efavirenz therapy. *Expert Opinion on Drug Safety*, 6(2): 147-154.

Author information pack. Health SA Gesondheid. Available at https://www.elsevier.com/journals/health-sa-gesondheid/1025-9848/guide-for-authors [Date accessed: 25/10/2016].

Badkoobehi, H., Chana, G. and Everall, I.P. 2006. Psychiatric aspects of HIV and AIDS. *Psychiatry,* 5(3): 85-88.

Banyard, P. and Grayson, A. 2008. Introducing psychological research. Third Edition. New York: Palgrave Macmillan.

Behr, A.L. 1983. Empirical research methods for the human sciences. Durban/Pretoria: Butterworths.

Belden, K.A. and Squires, K.E. 2008. HIV infection in women: do sex and gender matter? *Current Infectious Disease Reports*, 10(5): 423-431.

Bera, E., McCausland, K., Nonkwelo, R., Mgudlwa, B., Chacko, S. and Majeke, B. 2010. Birth defects following exposure to efavirenz-based antiretroviral therapy during pregnancy: a study at a regional South African hospital. *AIDS,* 24(2): 283-289.

Beyer, J.L., Taylor, L., Gersing, K.R. and Krishnan, K.R.R. 2007. Prevalence of HIV infection in a general psychiatric outpatient population. *Psychosomatics,* 48(1): 31-37.

Blanch, J., Martinez, E., Rousaud, A., Blanco, J., Garcia-Viejo, M., Peri, J., Mallolas, J., De Lazzari, E., De Pablo, J. and Gatell, J.M. 2001. Preliminary data of a prospective study on neuropsychiatric side effects after initiation of efavirenz. *Journal of Acquired Immune Deficiency Syndromes*, 27(4): 336-343.

Blank, M.B., Himelhoch, S.S., Balaji, A.B., Metzger, D.S., Dixon, L.B., Rose, C.E., Oraka, E., Davis-Vogel, A., Thompson, W.W., Heffelfinger, J.D. 2014. A multisite study of the prevalence of HIV with rapid testing in mental health settings. *American Journal of Public Health,* 104(12): 2377-2384.

Brogan, K. and Lux, J. 2009. Management of common psychiatric conditions in the HIV-positive population. *Current HIV/AIDS Reports,* 6(2): 108-115.

Burman, W.J. 2008. Treatment of HIV-related tuberculosis - unresolved issues. *Respirology*, 13(suppl3): 88-99.

Cabral, G.A. 2006. Drugs of abuse, immune modulation, and AIDS. *Journal of Neuroimmune Pharmacology,* 1(3): 280-295.

Cavalcante, G.I.T., Capistrano, V.L.M., Cavalcante, F.S.D., Vasconcelos, S.M.M., Macedo, D.S., Sousa, F.C.F., Woods, D.J. and Fonteles, M.M.F. 2010. Implications of efavirenz for neuropsychiatry: a review. *International Journal of Neuroscience,* 120(12): 739-745.

Centres for Disease Control and Prevention. About HIV/AIDS. 2015. Available at http://www.cdc.gov/hiv/basics/whatishiv.html [Date accessed: 22/02/2016].

Checkoway, H., Pearce, N. and Kriebel, D. 2007. Selecting appropriate study designs to address specific research questions in occupational epidemiology. *Occupational and Environmental Medicine*, 64(9): 633-638.

Chersich, M.F., Urban, M.F., Venter, F.W.D., Wessels, T., Krause, A., Gray, G.E., Luchters, S. and Viljoen, D.L. 2006. Efavirenz use during pregnancy and for women of child-bearing potential. *AIDS Research and Therapy,* [online] 3(11), 6 pages. Available at https://aidsrestherapy.biomedcentral.com/articles/10.1186/1742-6405-3-11 [Date accessed: 19/10/2016].

Clifford, D.B., Evans, S., Yang, Y., Acosta, E.P., Ribaudo, H. and Gulick, R.M. 2009. Long-term impact of efavirenz on neuropsychological performance and symptoms in HIV-infected individuals (ACTG5097s). *HIV Clinical Trials*, 10(6): 343-355.

Clinical guidelines for the management of HIV and AIDS in adults and adolescents. 2010. Republic of South Africa: Department of Health.

Collins, P.Y., Berkman, A., Mestry, K. and Pillai, A. 2009. HIV prevalence among men and women admitted to a South African public psychiatric hospital. *AIDS Care,* 21(7): 863-867.

Cresswell, J.W. 2009. Research design: qualitative, quantitative, and mixed method approaches. 3rd ed. California: Sage Publications.

Declaration of Helsinki – Ethical principles for medical research involving human subjects. 2013. World Medical Association. 1-8.

Department of Health. 2016. Implementation of the universal test and treat strategy for HIV positive patients and differentiated care for stable patients. Pretoria: National Department of Heatlh.

Dew, M.A., Becker, J.T., Sanchez, J., Caldararo, R., Lopez, O.L., Wess, J., Dorst, S.K. and Banks, G. 1997. Prevalence and predictors of depressive, anxiety and substance use disorders in HIV-infected and uninfected men: a longitudinal evaluation. *Psychological Medicine*, 27(2): 395-409.

Ferrando, S.J. 2009. Psychopharmacologic treatment of patients with HIV/AIDS. *Current Psychiatry Reports,* 11(3): 235-242.

Freeman, M., Patel, V., Collins, P.Y. and Bertolote, J. 2005. Integrating mental health in global initiatives for HIV/AIDS. *The British Journal of Psychiatry*, [online] 187(1), 3 pages. Available at http://bjp.rcpsych.org/content/187/1/1 [Date accessed: 19/10/2016].

Freeman, M., Nkomo, N., Kafaar, Z. and Kelly, K. 2008. Mental disorder in people living with HIV/AIDS in South Africa. *South African Journal of Psychology,* 38(3): 489-500.

Fumaz, C.R, Munoz-Moreno, J.A., Molto, J., Negredo, E. Ferrer, M.J., Sirera, G., Perez-Alvarez, N., Gomez, G., Burger, D. and Clotet, B. 2005. Long-term neuropsychiatric disorders on efavirenz-based approaches: quality of life, psychological issues, and adherence. *Journal of Acquired Immune Deficiency Syndromes,* 38(5): 560-565.

Gaida, R., Truter, I. and Grobler, C. 2015. Efavirenz: a review of the epidemiology, severity and management of neuropsychiatric side effects. *South African Journal of Psychiatry*, 21(3): 94-97.

Gazzard, B., Balkin, A., and Hill, A. 2010. Analysis of neuropsychiatric adverse events during clinical trials of efavirenz in antiretroviral-naïve patients: a systematic review. *AIDS Reviews,* 12(2): 67-75.

Gengiah, T.N., Gray, A.L., Naidoo, K. and Karim, Q.A. 2011. Initiating antiretrovirals during tuberculosis treatment: a drug safety review. *Expert Opinion in Drug Safety,* 10(4): 559-574.

Gilbert, L., and Selikow, T. 2011. 'The epidemic in this country has the face of a woman': gender and HIV/AIDS in South Africa. *African Journal of AIDS Research,* 10(supp): 325-334.

Gounden, V., van Niekerk, C., Snyman, T. and George, J.A. 2010. Presence of CYP2B6 516G> T polymorphism, increased plasma efavirenz concentrations and early neuropsychiatric side effects in South African HIV-infected patients. *AIDS Research and Therapy,* [online] 7(32), 9 pages. Available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2933581/ [Date accessed: 19/10/2016].

Gourevitch, M.N. and Friedland, G.H. 2000. Interactions between methadone and medications used to treat HIV infection: a review. *The Mount Sinai Journal of Medicine,* 67(5-6): 429-436.

Gruber, V.A. and McCance-Katz, E.F. 2010. Methadone, buprenorphine, and street drug interactions with antiretroviral medications. *Current HIV/AIDS Report*, 7(3): 152-160.

Gutierrez, F., Navarro, A., Padilla, S., Anton, R., Masia, M., Borras, J. and Martin-Hidalgo, A. 2005. Prediction of neuropsychiatric adverse events associated with long-term efavirenz therapy, using plasma drug level monitoring. *Clinical Infectious Diseases*, 41(11): 1648-1653.

Gutierrez-Valencia, A., Viciana, P., Palacios, R., Ruiz-Valderas, R., Lozano, F., Terron, A., Rivero, A. and Lopez-Cortes, L.F. 2009. Stepped-dose versus full-dose efavirenz for HIV infection and neuropsychiatric adverse events: a randomized trial. *Annals of Internal Medicine*, 151(3): 149-156.

Hawkins, T., Geist, C., Young, B., Giblin, A., Mercier, R.C., Thornton, K. and Haubrich, R. 2005. Comparison of neuropsychiatric side effects in an observational cohort of efavirenz- and protease inhibitor-treated patients. *HIV Clinical Trials,* 6(4): 187-196.

Hoffman, C.J., Fielding, K.L., Charalambous, S., Sulkowski, M.S., Innes, C., Thio, C.L., Chaisson, R.E., Churchyard, G.J. and Grant, A.D. 2008. Antiretroviral therapy using zidovudine, lamivudine, and efavirenz in South Africa: tolerability and clinical events. *AIDS,* 22(1): 67-74.

Hsieh, H. and Shannon, S.E. 2005. Three approaches to qualitative content analysis. *Qualitative Health Research*, 15(9): 1277-1288.

Instructions for Authors. Reviews on Recent Clinical Trials. Available at http://benthamscience.com/journals/reviews-on-recent-clinical-trials/author-guidelines/#top [Date accessed: 11/11/2016]

Instructions for Authors. Expert Review of Anti-Infective Therapy. Available at http://www.tandfonline.com/action/authorSubmission?journalCode=ierz20&page=instructions#Guidelines [Date accessed: 20/07/2016].

Jiang, H., Zhang, M., Chen, H., Yang, Y., Deng, M. and Ruan, B. 2014. Nevirapine versus efavirenz for patients co-infected with HIV and tuberculosis: a systematic review and meta-analysis. *International Journal of Infectious Diseases,* 25: 130-135.

Johnson, L.F. 2012. Access to antiretroviral treatment in South Africa, 2004-2011. *The Southern African Journal of HIV Medicine*, 13(1): 22-27.

Jonsson, G., Davies, N., Freeman, C., Joska, J., Pahad, S., Thom, R., Thompson, K., Woollett, N., Furin, J. and Meintjes, G. 2013. Management of mental health disorders in HIV-positive patients by the Southern African HIV Clinicians Society. *The Southern African Journal of HIV Medicine*, 14(4): 155-165.

Jonsson, G. and Joska, J.A. 2009. Assessment and treatment of psychosis in people living with HIV/AIDS. *The Southern African Journal of HIV Medicine,* 10(3): 20-27.

Joska, J.A., Obayemi Jr., A., Cararra, H., Sorsdahl, K. 2014. Severe mental illness and retention in anti-retroviral care: a retrospective study. *AIDS Behaviour,* 18(8): 1492-1500.

Journot, V., Chene, G., De Castro, N., Rancinan, C., Cassuto, J., Allard, C., Vilde, J., Sobel, A., Garre, M., Molina, J. and the ALIZE Study Group. 2006. Use of efavirenz is not associated with a higher risk of depressive disorders: a substudy of the randomized clinical trial ALIZE-ANRS 099. *Clinical Infectious Diseases,* 42(12): 1790-1799.

Julg, B. and Bogner, J.R. 2008. Atripla™ – HIV therapy in one pill. *Therapeutics and Clinical Risk Management,* 4(4): 573-577.

Kenedi, C.A. and Goforth, H.W. 2011. A systematic review of the psychiatric side-effects of efavirenz. *AIDS Behaviour*, 15(8): 1803-1808.

Krefting, L. 1991. Rigor in qualitative research: the assessment of trustworthiness. *The American Journal of Occupational Therapy,* 45(3): 214-222.

Lawn, S.D., Meintjes, G., McIlleron, H., Harries, A.D. and Wood, R. 2013. Management of HIV-associated tuberculosis in resource-limited settings: a state-of-the-art review. *BMC Medicine,* [online] 11(253), 16 pages. Available at https://www.ncbi.nlm.nih.gov/pubmed/24295487 [Date accessed: 19/10/2016].

Leclerc-Madlala, S. 2008. Multiple and concurrent partnering in South Africa: the ethnographic perspective. [Powerpoint presentation]. Available at http://www.aidstar-one.com/sites/default/files/PEPFAR_Washington.pdf [Date accessed: 23/05/2014].

Leedy. P.D and Ormrod, J.E. 2005. 8th ed. Practical research planning and design. Boston: Pearson Merrill Prentice Hall.

Lennox, J.L., DeJesus, E., Lazzarin, A., Pollard, R.B., Madruga, J.V.R., Berger, D.S., Zhao, J., Xu, X., Williams-Diaz, A., Rodgers, A.J., Barnard, R.J.O., Miller, M.D., DiNubile, M.J., Nguyen, B., Leavitt, R., Sklar, P. 2009. Safety and efficacy of raltegravir-based versus efavirenz-based combination therapy in treatment-naïve patients with HIV-1 infection: a multicentre, double-blind, randomised controlled trial. *Lancet*, 374(9692): 796-806.

Lochet, P., Peyriere, H., Lotthe, A., Mauboussin, J.M., Delmas, B. and Reynes, J. 2003. Long-term assessment of neuropsychiatric adverse reactions associated with efavirenz. *HIV Medicine*, 4(1): 62-66.

Lopez-Cortes, L.F., Ruiz-Valderas, R., Viciana, P., Alarcon-Gonzalez, A., Gomez-Mateos, J., Leon-Jimenez, E., Sarasa-Nacenta, M., Lopez-Pua, Y. and Pachon, J. 2002. Pharmacokinetic interactions between efavirenz and rifampicin in HIV-infected patients with tuberculosis. *Clinical Pharmacokinetics,* 41(9): 681-690.

Malhotra, N.K., 1999. Research Design. *Marketing Research: An Applied Orientation.* 3rd edition. New Jersey: Prentice-Hall Inc.: 178.

Management of drug-resistant tuberculosis: policy guidelines. 2011. Republic South Africa: Department of Health.

Manosuthi, W., Mankatitham, W., Lueangniyomkul, A., Chimsuntorn, S. and Sungkanuparph, S. 2008. Standard-dose efavirenz vs. standard-dose nevirapine in antiretroviral regimens among HIV-1 and tuberculosis co-infected patients who received rifampicin. *HIV Medicine*, 9(5): 294-299.

Marzolini, C., Telenti, A., Decosterd, L.A., Greub, G., Biollaz, J. and Buclin, T. 2001. Efavirenz plasma levels can predict treatment failure and central nervous system side effects in HIV-1-infected patients. *AIDS*, 15(1): 71-75.

MedlinePlus: Efavirenz. Available at http://www.nlm.nih.gov/medlineplus/druginfo/meds/a699004.html. [Date accessed: 14/04/2015].

Meintjes, G., Black, J., Conradie, F., Cox, V., Dlamini, S., Fabian, J., Maartens, G., Manzini, T., Mathe, M., Menezes, C., Moorhouse, M., Moosa, Y., Nash, J., Orrell, C., Pakade, Y., Venter, F. and Wilson, D. (The Southern African HIV Clinicians Society). 2014. Adult antiretroviral therapy guidelines 2014. *The Southern African Journal of HIV Medicine*, 15(4): 121-143.

Moosa, M.Y.H. 2013. Provider-initiated HIV counselling and testing (PICT) in the mentally ill. *South African Journal of Psychiatry*, 19(3): 60-64.

Morrison, M.F., Petitto, J.M., Ten Have, T., Gettes, D.R., Chiappini, M.S., Weber, A.L., Brinker-Spence, P., Bauer, R.M., Douglas, S.D. and Evans, D.L. 2002. Depressive and anxiety disorders in women with HIV infection. *American Journal of Psychiatry*, 159(5): 789-796.

Mouton, J. and Marais, H.C. 1988. Basic concepts in the methodology of social sciences. *HSRC Studies in Research Methodology*. Pretoria: Human Sciences Research Council.

Mukonzo, J.K., Okwera, A., Nakasujja, N., Luzze, H., Sebuwufu, D., Ogwal-Okeng, J., Waako, P., Gustafsson, L.L. and Aklillu, E. 2013. Influence of efavirenz pharmacokinetics and pharmacogenetics on neuropsychological disorders in Ugandan HIV-positive patients with or without tuberculosis: a prospective cohort study. *BMC Infectious Diseases*, [online] 13(261), 11 pages. Available at https://www.ncbi.nlm.nih.gov/pubmed/23734829 [Date accessed: 19/10/2016].

Mukonzo, J.K., Owen, J.S., Ogwal-Okeng, J., Kuteesa, R.B., Nanzigu, S., Sewankambo, N., Thabane, L., Gustafsson, L.L., Ross, C. and Aklillu, E. 2014. Pharmacogenetic-based efavirenz dose modification: suggestions for an African population and the different CYP2B6 genotypes. *Plos One*, [online] 9(1), 9 pages. Available at https://www.ncbi.nlm.nih.gov/pubmed/24497997 [Date accessed: 19/10/2016].

Myer, L., Smit, J., le Roux, L., Parker, S., Stein, D.J. and Seedat, S. 2008. Common mental disorders among HIV-infected individuals in South Africa: prevalence, predictors, and validation of brief psychiatric rating scales. *AIDS Patient Care,* 22(2): 147-158.

Naidoo, P., Chetty, V.V. and Chetty, M. 2014. Impact of CYP polymorphisms, ethnicity and sex differences in metabolism on dosing strategies: the case of efavirenz. *European Journal of Clinical Pharmacology,* 70(4): 379-389.

National Consolidated Guidelines for the Prevention of Mother-to-child Transmission of HIV (PMTCT) and the Management of HIV in Children, Adolescents and Adults. 2014. Pretoria: National Department of Health.

National Institute of Health. 2013. Types of HIV/AIDS antiretroviral drugs. Available at http://www.niaid.nih.gov/topics/HIVAIDS/Understanding/Treatment/pages/arvdrugclasses.aspx [Date accessed: 26/05/2014].

Negin, J. and Cumming, R.G. 2010. HIV infection in older adults in sub-Saharan Africa: extrapolating prevalence from existing data. *Bulletin of the World Health Organisation,* 88(11): 847-853.

Nelson, M., Stellbrink, H., Podzamczer, D., Banhegyi, D., Gazzard, B., Hill, A., von Delft, Y., Vingerhoets, J., Stark, T. and Marks, S. 2011. A comparison of neuropsychiatric adverse events during 12 weeks of treatment with etravirine and efavirenz in a treatment-naive, HIV-1-infected population. *AIDS*, 25(3): 335-340.

Ngaimisi, E., Habtewold, A., Minzi, O., Makonnen, E., Mugusi, S., Amogne, W., Yimer, G., Riedel, K., Janabi, M., Aderaye, G., Mugusi, F., Bertilsson, L., Aklillu, E. and Burhenne, J. 2013. Importance of ethnicity, CYP2B6 and ABCB1 genotype for efavirenz pharmacokinetics and treatment outcomes: a parallel-group prospective cohort study in two sub-Saharan Africa populations. *Plos One*, [online] 8(7), 14 pages. Available at http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0067946 [Date accessed: 19/10/2016].

Nieuwenhuis, J. 2007. Qualitative research designs and data gathering techniques. In Maree, K. (ed), *First Steps in Research: revised edition*: 70-92. Pretoria: Van Schaik.

Nowak, T.J. and Handford, A.G. 3rd ed. 2004. Diseases of Immunity. In: Pathophysiology: concepts and applications for health care professionals. New York: McGraw Hill.

Nunez, M., Soriano, V., Martin-Carbonero, L., Barrios, A., Barreiro, P., Blanco, F., Garcia-Benayas, T. and Gonzalez-Lahoz, J. 2002. SENC (Spanish efavirenz vs. nevirapine comparison) trial: a randomized, open-label study in HIV-infected naïve individuals. *HIV Clinical Trials*, 3(3): 186-194.

Olley, B.O., Seedat, S. and Stein, D.J. 2006. Persistence of psychiatric disorders in a cohort of HIV/AIDS patients in South Africa: a 6-month follow-up study. *Journal of Psychosomatic Research,* 61(4): 479-484.

Opdenakker, R. 2006. Advantages and disadvantages of four interview techniques in qualitative research. *Forum: Qualitative Social Research,* 7(4). Available at http://www.qualitative-research.net/index.php/fqs/article/view/175/391 [Date accessed: 8/2/2016].

Orkin, C., Nelson, M., Katlama, C., Morlat, P., Furrer, H., van Delft, Y., Janssen, M., Hill, A. and Marks, S. 2012. Changes in patient-reported neuropsychiatric outcomes during the SENSE trial: first-line treatment with two nucleoside analogues plus etravirine or efavirenz. *Health Outcomes Research in Medicine,* 3(3): 113-119.

Orrell, C., Cohen, K., Conradie, F., Zeinecker, J., Ive, P., Sanne, I. and Wood, R. 2011. Efavirenz and rifampicin in the South African context: is there a need to dose increase efavirenz with concurrent rifampicin therapy? *Antiviral Therapy,* 16(4): 527-534.

Penzak, S.R., Reddy, Y.S. and Grimsley, S.R. 2000. Depression in patients with HIV infection. *American Journal of Health-System Pharmacy*, 57(4): 376-386.

Piscitelli, S.C. 2000. Space out drug discontinuations prior to ‘drug holiday’? Medscape. Available at http://www.medscape.com/viewarticle/413306 [Date accessed: 01/09/2014].

Polit, D.F. and Hungler, B.P. 2001. Fifth Edition. Essentials of Nursing Research. Methods, Appraisal and Utilisation. Philadelphia: J.B. Lippincott Company.

Rakhmanina, N.Y. and van den Anker, J.N. 2010. Efavirenz in the therapy of HIV infection. *Expert Opinion on Drug Metabolism & Toxicology,* 6(1): 95-103.

Rihs, T.A., Begley, K., Smith, D.E., Sarangapany, J., Callaghan, A., Kelly, M., Post, J.J. and Gold, J. 2006. Efavirenz and chronic neuropsychiatric symptoms: a cross-sectional case control study. *HIV Medicine,* 7(8): 544-548.

Rohrig, B., du Prel, J., Wachtlin, D. and Blettner, M. 2009. Types of study in medical research. *Deutsches Arzteblatt International*, 106(15): 262-268.

Rossiter, D. (ed.) 2012. South African Medicines Formulary. 10th ed. Cape Town: Health and Medical Publishing Group.

Saunders, J. 2006. HIV and mental health. *Continuing Medical Education Journal*, 24(8): 431-434.

Schouten, J.T., Krambrink, A., Ribaudo, H.J., Kmack, A., Webb, N., Shikuma, C., Kuritzkes, D.R. and Gulick, R.M. 2010. Substitution of nevirapine because of efavirenz toxicity in AIDS Clinical Trials Group A5095. *Clinical Infectious Diseases,* 50(5): 787-791.

Shisana, O., Rehle, T., Simbayi, L.C., Zuma, K., Jooste, S., Pillay-van-Wyk, V., Mbelle, N., van Zyl, J., Parker, W., Zungu, N.P. Pezi, S. and the SABSSM III Implementation Team. 2009. South African national HIV prevalence, incidence, behaviour and communication survey 2008: a turning tide among teenagers? Cape Town: HSRC Press.

Shisana, O., Rice, K., Zungu, N. and Zuma, K. 2010. Gender and poverty in South Africa in the era of HIV/AIDS: a quantitative study. *Journal of Women's Health,* 19(1): 39-49.

Simelela, N.P. and Venter, W.D.F. 2014. A brief history of South Africa's response to AIDS. *South African Medicine Journal,* 104(3 suppl 1): 249-251.

Song, J.W. and Chung, K.C. 2010. Observational studies: cohort and case-control studies. *Plastic Reconstruction Surgery*, 126(6): 2234-2242.

Starace, F., Ammassari, A., Trotta, M.P., Murri, R., De Longis, P., Izzo, C., Scalzini, A., d'Arminio Monforte, A., Wu, A.W. and Antinori, A. for the AdICoNA and the NeuroICoNA Study Groups. 2002. Depression is a risk factor for suboptimal adherence to highly active antiretroviral therapy. *Journal of Acquired Immune Deficiency Syndromes*, 31(supp3): 136-139.

Statistics South Africa. 2013. Mid-year population estimate, Pretoria: Statistics South Africa.

Statistics South Africa. 2014. Mid-year population estimates, Pretoria: Statistics South Africa.

Stek, A.M. 2009. Antiretroviral medications during pregnancy for therapy or prophylaxis. *Current HIV/AIDS Reports*, 6(2): 68-76.

Sternhell, P.S. and Corr, M.J. 2002. Psychiatric morbidity and adherence to antiretroviral medication in patients with HIV/AIDS. *Australian and New Zealand Journal of Psychiatry,* 36(4): 528-533.

Structure and style of your original research article. Southern African Journal of HIV Medicine. Available at http://www.sajhivmed.org.za/index.php/hivmed/pages/view/original [Date accessed: 20/07/2016].

Struwig, F.W. and Stead, G.B. 2001. Planning, designing and reporting research. Cape Town: Pearson Education.

Submission guidelines. South African Journal of Psychiatry. Journal Information. Available at http://www.sajp.org.za/index.php/sajp/pages/view/journalinformation#part_3 [Date accessed: 20/07/2016].

Swaminathan, S., Padmapriyadarsini, C., Venkatesan, P., Narendran, G., Kumar, S.R., Iliayas, S., Menon, P.A., Selvaraju, S., Pooranagangadevi, N.P., Bhavani, P.K., Ponnuraja, C., Dilip, M. and Ramachandran, R. 2011. Efficacy and safety of once-daily nevirapine- or efavirenz-based antiretroviral therapy in HIV-associated tuberculosis: a randomized clinical trial. *Clinical Infectious Diseases,* 53(7): 716-724.

The Gap Report. 2014. People living with HIV. Available at http://www.unaids.org/sites/default/files/media_asset/01_PeoplelivingwithHIV.pdf [Date accessed: 7/04/2015].

The South African Antiretroviral Treatment Guidelines. 2013. Republic of South Africa: Department of Health.

Treisman, G.J. and Kaplin, A.I. 2002. Neurologic and psychiatric complications of antiretroviral agents. *AIDS,* 16(9): 1201-1215.

Turjanski, N. and Llyod, G.G. 2005. Psychiatric side-effects of medications: recent developments. *Advances in Psychiatric Treatment: Journal of Continuing Professional Development.* 11(1): 58-70.

UNAIDS Report on the Global AIDS Epidemic. 2010. Available at http://www.unaids.org/documents/20101123_GlobalReport_em.pdf [Date accessed: 22/05/2014].

Unicef. South Africa, HIV and AIDS: Gender-based violence. Available at http://www.unicef.org/southafrica/hiv_aids_729.html [Date accessed: 17/09/2013].

Uttayamakul, S., Likanonsakul, S., Manosuthi, W., Wichukchinda, N., Kalambaheti, T., Nakayama, E.E., Shioda, T. and Khusmith, S. 2010. Effects of CYP2B6 G516T polymorphisms on plasma efavirenz and nevirapine levels when co-administered with rifampicin in HIV/TB co-infected Thai adults. *AIDS Research and Therapy,* [online] 7(8), 10 pages. Available at https://www.ncbi.nlm.nih.gov/pubmed/20338069 [Date accessed: 19/10/2016].

Von Giesen, H.J., Koller, H., de Nocker, D., Haslinger, B.A. and Arendt, G. 2003. Long-term safety and efficacy of NNRTI within the central nervous system. *HIV Clinical Trials,* 4(6): 382-390.

WHO International Working Group for Drug Statistics Methodology, WHO Collaborating Centre for Drug Statistics Methodology, WHO Collaborating Centre for Drug Utilisation Research and Clinical Pharmacological Services. 2003. Introduction to Drug Utilisation Research. Oslo: WHO Library Cataloguing-in-Publication Data. Available at http://apps.who.int/medicinedocs/pdf/s4876e/s4876e.pdf [Date accessed: 8/02/2016].

WHO. 2012. Technical Update on Treatment Optimization. Use of efavirenz during pregnancy: a public health perspective. Geneva: WHO Document Production Services. Available at http://apps.who.int/iris/bitstream/10665/70920/1/9789241503792_eng.pdf?ua=1 [Date accessed: 13/04/2015].

WHO. 2014. HIV/AIDS Fact Sheet. Available at www.who.int/mediacentre/factsheets/fs360/en/ [Date accessed 07/04/2015].

WHO. 2016. HIV/AIDS Fact Sheet. Available at http://www.who.int/mediacentre/factsheets/fs360/en/ [Date accessed December 2016].

Williams, D.R., Herman, A., Stein, D.J., Heeringa, S.G., Jackson, P.B., Moomal, H. and Kessler, R.C. 2008. Twelve-month mental disorders in South Africa: prevalence, service use and demographic correlates in the population-based South African Stress and Health Study. *Psychology Medicine,* 38(2): 211-220.

Wynn, G.H., Cozza, K.L., Zapor, M.J., Wortmann, G.W. and Armstrong, S.C. 2005. Antiretrovirals, part III: antiretrovirals and drugs of abuse. *Psychosomatics*, 46(1): 79-87.

Zaccarelli, M., Soldani, F., Liuzzi, G., Sette, P., Grisetti, S., Trotta, M.P., Perno, C.F., Antinori, A. 2002. CNS side effects as main risk factor for efavirenz failure and transient HIV-RNA elevation. Presented at: 9th Conference on retroviruses and opportunistic infections; Seattle, Washington. Abstract 720-T.

APPENDIX A: AUTHOR GUIDELINES FOR JOURNALS TO WHICH THE PAPERS WERE SUBMITTED FOR PUBLICATION

APPENDIX A1: SOUTH AFRICAN JOURNAL OF PSYCHIATRY

(Submission guidelines. South African Journal of Psychiatry. Available at http://www.sajp.org.za/index.php/sajp/pages/view/journal-information#part_3 [Date accessed: 20/07/2016])

Manuscript formatting

The entire manuscript must be neatly prepared, spell-checked, and adhere to the following formatting requirements:

- Those of the type of article you are submitting
- The AOSIS house style guide
- The Vancouver referencing style

Original articles

An original article provides an overview of innovative research in a particular field within or related to the focus and scope of the journal, presented according to a clear and well-structured format (3000 words with a maximum of 15 references). When presenting your article in English. Please use British English, that is, according to the Oxford English Dictionary. Avoid Americanisms (e.g. use ‘s’ and not ‘z’ spellings). Consult the Oxford English Dictionary when in doubt and remember to set your version of Microsoft Word to UK English.

- Language: Manuscripts must be written in British English.
- Line numbers: Insert continuous line numbers.
- Font type: Palatino
- Symbols font type: Times New Roman
- General font size: 12pt
- Line spacing: 1.5
- Headings: Ensure that formatting for headings is consistent in the manuscript.
    - First headings: normal case, bold and 14pt

- Second headings: normal case, underlined and 14pt
- Third headings: normal case, bold and 12pt
- Fourth headings: normal case, bold, running-in text and separated by a colon.

Our publication system supports a limited range of formats for text and graphics. Text files can be submitted in the following formats only:

- Microsoft Word (.doc): We cannot accept Word 2007 DOCX files. If you have created your manuscript using Word 2007, you must save the document as a Word 2003 file before submission.
- Rich Text Format (RTF) documents uploaded during Step 2 of the submission process. Users of other word processing packages should save or convert their files to RTF before uploading. Many free tools are available that will make this process easier.

Your manuscript must adhere to the AOSIS house style.

Structure and style

Page 1

The format of the compulsory cover letter forms part of your submission and is on the first page of your manuscript and should always be in English. Refer to the **new submissions checklist**.

Page 2 and onwards

Title

The article's full title should contain a maximum of 95 characters (including spaces).

Abstract

The abstract, written in English, should be no longer than 250 words and must be written in the past tense. The abstract should give a succinct account of the objectives, methods, results and significance of the matter. The structured abstract for an Original

Research article should consist of six paragraphs labelled Background, Aim, Setting, Methods, Results and Conclusion.

- Background: Summarise the social value (importance, relevance) and scientific value (knowledge gap) that your study addresses.
- Aim: State the overall aim of the study.
- Setting: State the setting for the study.
- Methods: Clearly express the basic design of the study, and name or briefly describe the methods used without going into excessive detail.
- Results: State the main findings.
- Conclusion: State your conclusion and any key implications or recommendations.

Do not cite references and do not use abbreviations excessively in the abstract.

The following headings serve as a guide for presenting your research in a well-structured original article. As an author you should include all first-level headings, but subsequent headings (second- and third-level headings) can be changed.

Introduction (first-level heading)

The introduction must contain your argument for the social and scientific value of the study, as well as the aim and objectives:

- Social value: The first part of the introduction should make a clear and logical argument for the importance or relevance of the study. Your argument should be supported by use of evidence from the literature.
- Scientific value: The second part of the introduction should make a clear and logical argument for the originality of the study. This should include a summary of what is already known about the research question or specific topic, and should clarify the knowledge gap that this study will address. Your argument should be supported by use of evidence from the literature.
- Conceptual framework: In some research articles it will also be important to describe the underlying theoretical basis for the research and how these theories are linked together in a conceptual framework. The theoretical

evidence used to construct the conceptual framework should be referenced from the literature.

- Aim and objectives: The introduction should conclude with a clear summary of the aim and objectives of this study.

Research methods and design (first-level heading)

The methods should include:

- Study design (second-level heading): An outline of the type of study design.
- Setting (second-level heading): A description of the setting for the study; for example, the type of community from which the participants came or the nature of the health system and services in which the study is conducted.
- Study population and sampling strategy (second-level heading): Describe the study population and any inclusion or exclusion criteria. Describe the intended sample size and your sample size calculation or justification. Describe the sampling strategy used. Describe in practical terms how this was implemented.
- Intervention (if appropriate) (second-level heading): If there were intervention and comparison groups, describe the intervention in detail and what happened to the comparison groups.
- Data collection (second-level heading): Define the data collection tools that were used and their validity. Describe in practical terms how data were collected and any key issues involved, e.g. language barriers.
- Data analysis (second-level heading): Describe how data were captured, checked and cleaned. Describe the analysis process, for example, the statistical tests used or steps followed in qualitative data analysis.
- Ethical considerations (second-level heading): Approval must have been obtained for all studies from the author's institution or other relevant ethics committee and the institution’s name and permit numbers should be stated here.

Results (first-level heading)

Present the results of your study in a logical sequence that addresses the aim and objectives of your study. Use tables and figures as required to present your findings. Use quotations as required to establish your interpretation of qualitative data.

All units should conform to the SI convention and be abbreviated accordingly. Metric units and their international symbols are used throughout, as is the decimal point (not the decimal comma).

Discussion (first-level heading)

The discussion section should address the following four elements:

- Key findings: Summarise the key findings without reiterating details of the results.
- Discussion of key findings: Explain how the key findings relate to previous research or to existing knowledge, practice or policy.
- Strengths and limitations: Describe the strengths and limitations of your methods and what the reader should take into account when interpreting your results.
- Implications or recommendations: State the implications of your study or recommendations for future research (questions that remain unanswered), policy or practice. Make sure that the recommendations flow directly from your findings.

Conclusion (first-level heading)

Provide a brief conclusion that summarises the results and their meaning or significance in relation to each objective of the study.

Acknowledgements (first-level heading)

If, through your study, you received any significant help in conceiving, designing or carrying out the work, or received materials from someone who did you a favour by supplying them, you must acknowledge their assistance and the service or material

provided. Authors should always acknowledge outside reviewers of their drafts and any sources of funding that supported the research.

Competing interests (second-level heading)

A competing interest exists when your interpretation of data or presentation of information may be influenced by your personal or financial relationship with other people or organisations that can potentially prevent you from executing and publishing unbiased research. Authors should disclose any financial competing interests but also any non-financial competing interests that may cause them embarrassment were they to become public after the publication of the manuscript.

Where an author has no such competing interests, the listing will read as follows: ‘The authors declare that they have no financial or personal relationship(s) that may have inappropriately influenced them in writing this article.’

Authors' contributions (second-level heading)

This section is necessary to give appropriate credit to each author, and to the authors' applicable institution. The individual contributions of authors should be specified with their affiliation at the time of the study and completion of the work. An ‘author’ is generally considered to be someone who has made substantive intellectual contributions to a published study. Contributions made by each of the authors listed can follow the example below (please note the use of authors’ initials):

J.K. (University of Pretoria) was the project leader, L.M.N. (University of KwaZulu-Natal) and A.B. (Stellenbosch University) were responsible for experimental and project design. L.M.N. performed most of the experiments. P.R. (Cape Peninsula University of Technology) made conceptual contributions and S.T. (University of Cape Town), U.V. (University of Cape Town) and C.D. (University of Cape Town) performed some of the experiments. S.M. (Cape Peninsula University of Technology) and V.C. (Cape Peninsula University of Technology) prepared the samples and calculations were performed by C.S. (Cape Peninsula University of Technology).

References (first-level heading)

Begin the reference list on a separate page, and give no more than 15 references in all. The journal uses the Vancouver referencing style. Note: No other style will be permitted.

APPENDIX A2: EXPERT REVIEW OF ANTI-INFECTIVE THERAPY

(Instructions for Authors. Expert Review of Anti-Infective Therapy. Available at http://www.tandfonline.com/action/authorSubmission?journalCode=ierz20&page=instructions#Guidelines [Date accessed: 20/07/2016])

About the journal

Expert Review of Anti-infective Therapy is an international, peer-reviewed journal publishing high-quality, review articles, original research, editorials and drug evaluation articles on anti-infective therapy. Please see the journal's Aims & Scope for information about its focus and peer-review policy. Please note that this journal only publishes manuscripts in English.

Peer review

Taylor & Francis is committed to peer-review integrity and upholding the highest standards of review. Once your paper has been assessed for suitability by the editor, it will then be double blind peer-reviewed by independent, anonymous expert referees. Find out more about what to expect during peer review and read our guidance on publishing ethics.

Preparing your paper

All authors submitting to medicine, biomedicine, health sciences, allied and public health journals should conform to the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, prepared by the International Committee of Medical Journal Editors (ICMJE).

Original Research: Expert Review

Prior publication: Expert Reviews will only consider work that has not been previously published in full. Abstract, poster or oral presentations do not constitute prior publication, but should be mentioned in the covering letter and details included as a footnote on the manuscript title page

Covering letter

All manuscripts must be accompanied by a covering letter and an electronic version of the Disclosure Form signed by the principal author(s). The covering letter should include all of the following information:

The name and contact details (telephone, fax, postal and email addresses) of the corresponding author who will deal with the comments from reviewers and approve final proofs.

A statement that the contribution represents original work that has not been previously published or simultaneously submitted for publication elsewhere.

A statement that the manuscript has been read and approved by all the authors, and that all the conditions as previously stated by the ICMJE have been met. The body providing explicit ethical approval of the work reported should also be stated.

A statement of financial or other relationships of a declarable nature (i.e., commercial associations that might lead to a conflict of interest), including disclosure of sources of support in the form of sponsorship, grants, materials (drugs) or equipment, and editorial or manuscript support. In case there are no disclosures of a declarable nature, or acknowledgements for financial or editorial support, this should be clearly stated. The authors' preference for publication with either UK or US spellings.

General

Manuscripts submitted should be in English and written for an international, general medicine readership. Where national or regional issues are discussed, the international context should also be considered. When a licensed drug or device is being discussed outside its licensed indication, this must be made clear to the reader.

All complete submissions will be acknowledged by the Editorial Office upon receipt. Please note that manuscripts without a covering letter or a Disclosure Form will not be considered to be 'complete' submissions.

Every article must contain

Title page: All articles should have a concise, informative title that contains no brand names. In addition to the title itself, the title page should also have the name(s) and initials of all the authors and their institutional affiliation(s). The name of the corresponding author and their mailing address should be given in full, including email, telephone and fax numbers. Should any of the material contained in the paper have been previously presented at a meeting, the full name, location and inclusive dates of the meeting should also appear on the title page. Authors are to avoid using Trade names in their titles, and are encouraged to have non-promotional titles for their articles.

Abstract

The second page should contain a brief, structured abstract of the paper (no more than 200 words) summarizing the main facts, findings and principal conclusions.

Suggested headings:

Background (including the reason for the study);

Research design and methods (including study population and setting, study blinding, comparators, dosage, treatment regimens and durations, efficacy and safety issues); Main outcome measures;

Results (both efficacy results and adverse events should be given);

Conclusions (qualified by any key limitations).

No references are to be cited in the Abstract. Please bear in mind that the Abstract needs to accurately reflect the content of the article and that the aim of the Abstract is to draw in the interested reader.

Keywords

4–6 keywords, listed in alphabetical order, are required to assist indexers in cross-referencing. The keywords will encompass the therapeutic area, mechanism(s) of action, key compounds and so on.

Body of the article

This should include the following sections: introduction; patients and methods; results; discussion; conclusions.

Introduction

This should state the clinical relevance and background to the study, its rationale and purpose.

Patients and methods

This should contain details of the study population and setting, subject selection (inclusion/exclusion criteria), methods of randomization and blinding, and efficacy and safety measures. The study design and statistical methodology should be described, with justification for the choice of analysis and sample size given; CONSORT guidelines should be considered where appropriate. All materials should be identified precisely, with drugs referred to by their generic names (proprietary names, if required, should be given in parentheses along with the company name and country of the manufacturer), and with dose and routes of administration. The ethical approval procedure followed and the name of the ethics committee should be stated. Indicate how adverse events were determined (and by whom) and indicate if/how compliance was measured. (Authors are reminded to ensure that they follow the ICMJE requirements when dealing with privacy and informed consent from patients see Section II.E.1.of the ICMJE requirements document).

Results

Use should be made of tables and figures to help with the clear presentation of results data. The sample size of each data point should be shown, with p-values and

confidence intervals quoted for significant findings. Any data not included in the analysis (including patients withdrawn from the study) should be detailed. Details of data on efficacy and adverse events should be provided in a balanced fashion.

Discussion

This will essentially be a discussion of the results and experimental data collected. The section should include implications of the findings and their limitations, with reference to all other relevant studies and the possibilities these suggest for future research. In addition, the discussion affords authors the opportunity to discuss the developments that are likely to be important in the future and the avenues of research likely to become exciting as further studies yield more detailed results.

Conclusions

This section must summarize the paper, with a concise statement of the clinical implications of the study results. Ensure that extrapolations are reasonable and that conclusions are justified by the data presented. Indicate if the study design can be generalized to a broader patient population.

References

Full references to relevant material cited in the text should be provided. References should be comprehensive, accurate and up-to-date: wherever possible, please use primary references, and as far as possible, avoid the use of unpublished references (such as ‘Data on file’ or ‘Poster’). Reference to unpublished data should be kept to a minimum and authors must obtain a signed letter of permission from cited persons to use unpublished results or personal communications in the manuscript.

Acknowledgements

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preparation must also be acknowledged in this section. Finally, if any trial registration information and/or a trial registration number are available for the study, this should also be mentioned in the acknowledgements section.

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Spacing and headings

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A structured abstract should cover (in the following order):

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Introduction: Authors are required to describe the significance of the topic under discussion;

Areas covered: Authors are required to describe the research discussed and the literature search undertaken;

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Please use SI units (non-italicized).

Appendix A3: Southern African Journal of HIV Medicine

(Structure and style of your original research article. Southern African Journal of HIV Medicine. Available at http://www.sajhivmed.org.za/index.php/hivmed/pages/view/original [Date accessed: 20/07/2016])

We ask our authors to ensure that they submit original work that:

- have been honestly carried out according to rigorous scientific standards that has not been obtained fraudulently or dishonestly, or fabricated or falsified
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- present sufficient detail and reference to public sources of information in order to permit peers to repeat the work if needed
- report data accurately and never 'fudged', with any problematic data also treated accordingly
- cite all relevant references; it is the duty of the author to check the references that are cited very carefully to ensure that the details are accurate and in the correct format
- declare any (potential) conflicts of interest
- do not claim originality if others have already reported similar work in part or as a whole
- give credit to the work and findings of others that have led to your findings or influenced them in some way
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Appendix A4: Reviews on Recent Clinical Trials

(Instructions for Authors. Reviews on Recent Clinical Trials. Available at http://benthamscience.com/journals/reviews-on-recent-clinical-trials/author-guidelines/#top [Date accessed: 11/11/2016])

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- Title
- Title page
- Structured Abstract
- Graphical Abstract
- Keywords
- Text Organization
- Conclusion

- List of Abbreviations (if any)
- Conflict of Interest
- Acknowledgements
- References
- Appendices
- Figures/Illustrations (if any)
- Chemical Structures (if any)
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- Background
- Objective
- Method
- Results
- Conclusion
-

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Conference Proceedings:

Harris AH, Ed. Economics and health: 1997. In: Proceedings of the 19th Australian Conference of Health Economists; 1997 Sep 13-14; Sydney, Australia. Kensington, N.S.W.: School of Health Services Management, University of New South Wales 1998.
Anderson JC. Current status of chorion villus biopsy. In: Tudenhope D, Chenoweth J, Eds. In: Proceedings of the 4th Congress of the Australian Perinatal Society; 1986: Brisbane, Queensland: Australian Perinatal Society 1987; pp. 190-6.

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Aylin P, Bottle A, Jarman B, Elliott, P. Paediatric cardiac surgical mortality in England after Bristol: descriptive analysis of hospital episode statistics 1991-2002. BMJ [serial on the Internet]. 2004 Oct 9; [cited: 15 October 2004]; 329: [about 10 screens]. Available from: bmj.bmjjournals.com/cgi/content/full/329/7470/825

Patent:

Larsen CE, Trip R, Johnson CR. Methods for procedures related to the electrophysiology of the heart. US Patent 5529067, 1995.

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Appendix A5: Health SA Gesondheid

(Author information pack. Health SA Gesondheid. Available at https://www.elsevier.com/journals/health-sa-gesondheid/1025-9848/guide-for-authors [Date accessed: 25/10/2016])

INTRODUCTION

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Submission checklist

You can use this list to carry out a final check of your submission before you send it to the journal for review. Please check the relevant section in this Guide for Authors for more details.

Ensure that the following items are present:

One author has been designated as the corresponding author with contact details:

• E-mail address

• Full postal address

All necessary files have been uploaded:

Manuscript:

• Include keywords

• All figures (include relevant captions)

• All tables (including titles, description, footnotes)

• Ensure all figure and table citations in the text match the files provided

• Indicate clearly if colour should be used for any figures in print Graphical Abstracts / Highlights files (where applicable) Supplemental files (where applicable)

Further considerations:

• Manuscript has been 'spell checked' and 'grammar checked'

• All references mentioned in the Reference List are cited in the text, and vice versa

• Permission has been obtained for use of copyrighted material from other sources (including the Internet)

• Relevant declarations of interest have been made

• Journal policies detailed in this guide have been reviewed

• Referee suggestions and contact details provided, based on journal requirements

For further information, visit our Support Centre.

Article Types Health SA Gesondheid publishes:

Original Articles

Should report relevant original research not published before, in the following format:

• Word limit: 5000 words (excluding the abstract and references).

• Abstract: structured up to 250 words to include a Background, Methods, Results and Conclusions.

• References:40 or less.

• Tables and figures: no more than 7 Tables/Figure

Review Articles

Review topics should be related to clinical aspects interdisciplinary health sciences and should reflect trends and progress or a synthesis of data in the following format:

• Word limit: 4000 words (excluding the abstract and references).

• References: 40 or less.

• Abstract: Up to 150 words, unstructured.

• Tables/Figures: Data in the text should not be repeated extensively in tables or figures.

Editorials

Editorials are solicited by the HSAG EIC or editorial board members in the following format:

• Word limit: 1200 words.

• Tables/Figures: A maximum of 1 figure or table.

• References: 10 or less.

• Ensure that there is a clear message in the conclusion.

Article structure

Subdivision - numbered sections

Divide your article into clearly defined and numbered sections. Subsections should be numbered 1.1 (then 1.1.1, 1.1.2, ...), 1.2, etc. (the abstract is not included in section numbering). Use this numbering also for internal cross-referencing: do not just refer to 'the text'. Any subsection may be given a brief heading. Each heading should appear on its own separate line.

Introduction

State the objectives of the work and provide an adequate background, avoiding a detailed literature survey or a summary of the results. The introduction should include the following:

• Research problem statement

• Purpose (aims) and objectives

• Definitions of key concepts

Material and methods

Provide sufficient detail to allow the work to be reproduced. Methods already published should be indicated by a reference: only relevant modifications should be described.

Theory/calculation

A Theory section should extend, not repeat, the background to the article already dealt with in the Introduction and lay the foundation for further work. In contrast, a Calculation section represents a practical development from a theoretical basis.

Results and Findings

Results should be clear and concise.

Discussion

This should explore the significance of the results of the work, not repeat them. A combined Results and Discussion section is often appropriate. Avoid extensive citations and discussion of published literature.

Conclusions, Limitations & Recommendations for Future Research

The main conclusions of the study may be presented in a short Conclusions section, which may stand alone or form a subsection of a Discussion or Results and Discussion section. Appendices If there is more than one appendix, they should be identified as A, B, etc. Formulae and equations in appendices should be given separate numbering: Eq. (A.1), Eq. (A.2), etc.; in a subsequent appendix, Eq. (B.1) and so on. Similarly, for tables and figures: Table A.1; Fig. A.1, etc.

Essential title page information

• *Title*. Concise and informative. Titles are often used in information-retrieval systems. Avoid abbreviations and formulae where possible.

• *Author names and affiliations*. Please clearly indicate the given name(s) and family name(s) of each author and check that all names are accurately spelled. Present the authors' affiliation addresses (where the actual work was done) below the names. Indicate all affiliations with a lowercase superscript letter immediately after the author's name and in front of the appropriate address. Provide the full postal address of each

affiliation, including the country name and, if available, the e-mail address of each author.

• *Corresponding author.* Clearly indicate who will handle correspondence at all stages of refereeing and publication, also post-publication. Ensure that the e-mail address is given and that contact details are kept up to date by the corresponding author.

• *Present/permanent address.* If an author has moved since the work described in the article was done, or was visiting at the time, a 'Present address' (or 'Permanent address') may be indicated as a footnote to that author's name. The address at which the author actually did the work must be retained as the main, affiliation address. Superscript Arabic numerals are used for such footnotes.

Abstract

A concise and factual abstract of no more than 250 words is required. The abstract should state briefly the background, purpose of the research, methodology, the principal results and major conclusions. An abstract is often presented separately from the article, so it must be able to stand alone. For this reason, References should be avoided, but if essential, then cite the author(s) and year(s). Also, nonstandard or uncommon abbreviations should be avoided, but if essential they must be defined at their first mention in the abstract itself.

Keywords

Immediately after the abstract, provide a maximum of 6 keywords, using American spelling and avoiding general and plural terms and multiple concepts (avoid, for example, 'and', 'of'). Be sparing with abbreviations: only abbreviations firmly established in the field may be eligible. These keywords will be used for indexing purposes.

Abbreviations

Define abbreviations that are not standard in this field in a footnote to be placed on the first page of the article. Such abbreviations that are unavoidable in the abstract must be defined at their first mention there, as well as in the footnote. Ensure consistency of abbreviations throughout the article.

Acknowledgements

Collate acknowledgements in a separate section at the end of the article before the references and do not, therefore, include them on the title page, as a footnote to the title or otherwise. List here those individuals who provided help during the research (e.g., providing language help, writing assistance or proof reading the article, etc.).

Formatting of funding sources

List funding sources in this standard way to facilitate compliance to funder's requirements:

Funding: This work was supported by the National Institutes of Health [grant numbers xxxx, yyyy]; the Bill & Melinda Gates Foundation, Seattle, WA [grant number zzzz]; and the United States Institutes of Peace [grant number aaaa].

It is not necessary to include detailed descriptions on the program or type of grants and awards. When funding is from a block grant or other resources available to a university, college, or other research institution, submit the name of the institute or organization that provided the funding.
If no funding has been provided for the research, please include the following sentence:

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Units

Follow internationally accepted rules and conventions: use the international system of units (SI). If other units are mentioned, please give their equivalent in SI.

Math formulae

Please submit math equations as editable text and not as images. Present simple formulae in line with normal text where possible and use the solidus (/) instead of a horizontal line for small fractional terms, e.g., X/Y. In principle, variables are to be presented in italics. Powers of e are often more conveniently denoted by exp. Number

consecutively any equations that have to be displayed separately from the text (if referred to explicitly in the text).

Footnotes

Footnotes should be used sparingly. Number them consecutively throughout the article. Many word processors can build footnotes into the text, and this feature may be used. Otherwise, please indicate the position of footnotes in the text and list the footnotes themselves separately at the end of the article. Do not include footnotes in the Reference list.

References

Citation in text

Please ensure that every reference cited in the text is also present in the reference list (and vice versa). Any references cited in the abstract must be given in full. Unpublished results and personal communications are not recommended in the reference list, but may be mentioned in the text. If these references are included in the reference list, they should follow the standard reference style of the journal and should include a substitution of the publication date with either 'Unpublished results' or 'Personal communication'. Citation of a reference as 'in press' implies that the item has been accepted for publication.

Reference links

Increased discoverability of research and high quality peer review are ensured by online links to the sources cited. In order to allow us to create links to abstracting and indexing services, such as Scopus, CrossRef and PubMed, please ensure that data provided in the references are correct. Please note that incorrect surnames, journal/book titles, publication year and pagination may prevent link creation. When copying references, please be careful as they may already contain errors. Use of the DOI is encouraged.

A DOI can be used to cite and link to electronic articles where an article is in-press and full citation details are not yet known, but the article is available online. A DOI is guaranteed never to change, so you can use it as a permanent link to any electronic article. An example of a citation using DOI for an article not yet in an issue is: VanDecar

J.C., Russo R.M., James D.E., Ambeh W.B., Franke M. (2003). Aseismic continuation of the Lesser Antilles slab beneath northeastern Venezuela. Journal of Geophysical Research, http://dx.doi.org/10.1029/2001JB000884i. Please note the format of such citations should be in the same style as all other references in the paper.

Web references

As a minimum, the full URL should be given and the date when the reference was last accessed. Any further information, if known (DOI, author names, dates, reference to a source publication, etc.), should also be given. Web references can be listed separately (e.g., after the reference list) under a different heading if desired, or can be included in the reference list.

References in a special issue

Please ensure that the words 'this issue' are added to any references in the list (and any citations in the text) to other articles in the same Special Issue.

Reference style

Text: Citations in the text should follow the referencing style used by the American Psychological Association. You are referred to the Publication Manual of the American Psychological Association, Sixth Edition, ISBN 978-1-4338-0561-5, copies of which may be ordered online or APA Order Dept., P.O.B. 2710, Hyattsville, MD 20784, USA or APA, 3 Henrietta Street, London, WC3E 8LU, UK. List: references should be arranged first alphabetically and then further sorted chronologically if necessary. More than one reference from the same author(s) in the same year must be identified by the letters 'a', 'b', 'c', etc., placed after the year of publication.

Examples:

Reference to a journal publication: Van der Geer, J., Hanraads, J. A. J., & Lupton, R. A. (2010). The art of writing a scientific article. Journal of Scientific Communications, 163, 51–59. Reference to a book: Strunk, W., Jr., & White, E. B. (2000). The elements of style. (4th ed.). New York: Longman, (Chapter 4).

Reference to a chapter in an edited book: Mettam, G. R., & Adams, L. B. (2009). How to prepare an electronic version of your article. In B. S. Jones, & R. Z. Smith (Eds.), Introduction to the electronic age (pp. 281–304). New York: E-Publishing Inc.

Reference to a website: Cancer Research UK. Cancer statistics reports for the UK. (2003). http://www.cancerresearchuk.org/ aboutcancer/statistics/cancerstatsreport/ Accessed 13.03.03.

Journal abbreviations source

Journal names should be abbreviated according to the List of Title Word Abbreviations.

APPENDIX B: PERMISSION FROM EXPERT REVIEW OF ANTI-INFECTIVES

Holland, Dean <Dean.Holland@informa.com>

Fri 6/24, 3:11 PM

Gaida, Razia, (Mrs) (s207060291); +2 more

Dear Razia,

Following on from my previous email, I have investigated this myself and I am happy to state that you are able to include your article in your final thesis. As stated here:http://authorservices.taylorandfrancis.com/copyright-and-you/.

Thank you for submitting your paper to us and best of luck with your thesis.

Kind regards,

Dean Holland

Commissioning Editor, Expert Reviews

Taylor & Francis | 5 Howick Place | London | SW1P 1WG

Tel: +44 (0)20 337 73955 | Fax: +44 (0)20 7017 7667

Dean.Holland@informa.com | http://www.tandfonline.com

APPENDIX C: ETHICAL APPROVAL DOCUMENTS

APPENDIX C1: ETHICS APPROVAL FROM NMMU

• PO Box 77000 • Nelson Mandela Metropolitan University
• Port Elizabeth • 6031 • South Africa • www.nmmu.ac.za

Nelson Mandela Metropolitan University
for tomorrow

Vice-Chairperson: Research Ethics Committee (Human)
Tel: +27 (0)41 504-2235

Ref: [H14-HEA-PHA-001 Approval]

Contact person: Mrs U Spies

15 April 2014

Prof I Truter
NMMU
Faculty of Health Sciences
Department of Pharmacy
12-03-51
South Campus

Dear Prof Truter

EVALUATING NEUROPSYCHIATRIC SYMPTOMOLOGY IN HIV-POSITIVE PATIENTS ON EFAVIRENX IN PUBLIC SECTOR CLINICS AND PSYCHIATRIC HOSPITALS IN THE EASTERN CAPE

PRP: Prof I Truter
PI: Ms R Gaida

Your above-entitled application for ethics approval served at Research Ethics Committee (Human).

We take pleasure in informing you that the application was approved by the Committee.

The ethics clearance reference number is **H14-HEA-PHA-001** and is valid for three years. Please inform the REC-H, via your faculty representative, if any changes (particularly in the methodology) occur during this time. An annual affirmation to the effect that the protocols in use are still those for which approval was granted, will be required from you. You will be reminded timeously of this responsibility, and will receive the necessary documentation well in advance of any deadline.

We wish you well with the project. Please inform your co-investigators of the outcome, and convey our best wishes.

Yours sincerely

CB Cilliers

Prof CB Cilliers
Chairperson: Research Ethics Committee (Human)

cc: Department of Research Capacity Development
Faculty Officer: Health Sciences

APPENDIX C2: EASTERN CAPE DEPARTMENT OF HEALTH ETHICS APPROVAL

Eastern Cape Department of Health

Enquiries: Zonwabele Merile
Tel No: 040 608 0830
Date: 05th May 2014
e-mail address: zonwabele.merile@impilo.ecprov.gov.za
Fax No: 043 642 1409

Dear Ms Razia Gaida 041 504 2131

Re: Evaluating neuropsychiatric symptomology in HIV-positive patients on efavirenx in public sector clinics and psychiatric hospitals in the Eastern Cape

The Department of Health would like to inform you that your application for conducting a research on the abovementioned topic has been approved based on the following conditions:

1. During your study, you will follow the submitted protocol with ethical approval and can only deviate from it after having a written approval from the Department of Health in writing.
2. You are advised to ensure, observe and respect the rights and culture of your research participants and maintain confidentiality of their identities and shall remove or not collect any information which can be used to link the participants.
3. The Department of Health expects you to provide a progress on your study every 3 months (from date you received this letter) in writing.
4. At the end of your study, you will be expected to send a full written report with your findings and implementable recommendations to the Epidemiological Research & Surveillance Management. You may be invited to the department to come and present your research findings with your implementable recommendations.
5. Your results on the Eastern Cape will not be presented anywhere unless you have shared them with the Department of Health as indicated above.

Your compliance in this regard will be highly appreciated.

DEPUTY DIRECTOR: EPIDEMIOLOGICAL RESEARCH & SURVEILLANCE MANAGEMENT

APPENDIX D: BASELINE DATA COLLECTION FORM (CLINIC)

Date:_____

1. Gender

☐ Female

☐ Male

2. Age

3. Weight

4. Date of HIV diagnosis

5. CD4 count at ART initiation

6. WHO stage at ART initiation

7. Pregnant

☐ Yes, indicate trimester

☐ No

8. Prescribed HIV treatment regimen

9. Patient screened for history of psychiatric disorder?

☐ Yes, note any comments or referrals

☐ No

☐ Not documented

10. Screening performed by

☐ Nurse

☐ General practitioner

☐ Other, specify

11. Current substance use?

☐ Yes, which substance?

☐ No

☐ Not documented

12. Alcohol use

☐ Yes

☐ No

13. Previous TB infection?

☐ Yes, type of TB and date of diagnosis and outcome of treatment

☐ No

14. Concurrent TB infection?

☐ Yes, type of TB?

☐ No

15. Other concurrent medical conditions at presentation?

APPENDIX E: FOLLOW-UP OF PATIENT SYMPTOMS AFTER THE INITIATION OF EFAVIRENZ (CLINIC)

Date:_____

1. Follow-up period

☐ Four weeks

☐ Twelve weeks

☐ Twenty-four weeks

☐ Forty-eight weeks

2. Symptoms presented

3. Severity if indicated in file

4. Weight

5. Efavirenz discontinued?

☐ Yes, with which drug was efavirenz replaced?

☐ No, how is the patient being managed?

6. Were the neuropsychiatric side effects resolved?

7. Are there any new side effects?

8. Date and result of any CD4 counts done

APPENDIX F: BASELINE PATIENT SCREENING DATA COLLECTION FORM (HOSPITAL)

Date:_____

1. Gender

☐ Female

☐ Male

2. Age

3. Weight

4. Duration of HIV infection, if indicated

5. Current CD4 count

6. Current viral load

7. Prescribed HIV regimen

8. Primary psychiatric diagnosis

9. Comments in file, if any

10. Past or current TB infection?

☐ Current

☐ Past

☐ None

11. Prescribed TB regimen

12. Past substance use?

☐ Yes, which substance/s

☐ No

☐ Not documented

13. Past head injury?

☐ Yes

☐ No

14. History of epilepsy, meningitis or other neurological disorder?

☐ Yes, specify

☐ No

15. Other chronic medical conditions?

16. Other medication used?

APPENDIX G: FOLLOW-UP OF PATIENT SYMPTOMS (HOSPITAL)

Date_____

1. Follow-up period

☐ Four weeks

☐ Twelve weeks

☐ Twenty-four weeks

☐ Forty-eight weeks

2. Primary psychiatric diagnosis

3. Patient discharged?

☐ Yes

☐ No

3.1 If yes, date of discharge?

3.2 Total admission period?

3.3 Mental status upon discharge?

3.4 Diagnosis upon discharge?

3.5 Medication upon discharge?

4. Psychiatric symptom progression

5. Adverse events

6. Side effects which are possibly related to HIV treatment?

7. Was the ARV regimen changed?

8. Were there any changes to the psychiatric medication?

9. Was there any improvement to the patient's condition?

APPENDIX H: LETTER TO CLINIC MANAGEMENT

Faculty of Health Sciences, Department of Pharmacy
Tel. 076335589
razia.gaida@live.nmmu.ac.za
Date: 22/05/2014

REC-H reference number: H14-HEA-PHA-001
Contact person: Razia Gaida

Dear Sir/Madam

I am a postgraduate student at the Nelson Mandela Metropolitan University conducting a research project in fulfilment of my PhD.

The topic of my research is 'Evaluating neuropsychiatric symptomology in HIV-positive patients on efavirenz in public-sector clinics and public-sector psychiatric hospitals'. The aim of the study is to determine the incidence of efavirenz-induced neuropsychiatric side effects, the severity and management thereof in these patient populations. I request your permission to conduct research in the HIV and psychiatric sectors of the following clinics:

- Central CHC;
- Chatty Clinic;
- Kwazakele CHC;
- Motherwell CHC; and
- Zwide CHC

There will be no patient contact involved, only reviewing of medical files. The patient files will not be removed from the premises. Patient confidentiality will be maintained at all times.

I have obtained ethics approval from the Human Research Ethics Committee of the Nelson Mandela Metropolitan University as well as from the Eastern Cape Department of Health. I would appreciate your co-operation and assistance. If you have any queries please feel free to contact me at the above contact details.

Razia Gaida

APPENDIX I: LETTER TO HOSPITAL MANAGEMENT

Faculty of Health Sciences, Department of Pharmacy
Tel. 076335589
razia.gaida@live.nmmu.ac.za
Date:_____

REC-H reference number: H14-HEA-PHA-001
Contact person: Razia Gaida

Dear Sir/Madam

I am a postgraduate student at the Nelson Mandela Metropolitan University conducting a research project in fulfilment of my PhD.

The topic of my research is 'Evaluating neuropsychiatric symptomology in HIV-positive patients on efavirenz in public-sector clinics and public-sector psychiatric hospitals'. The aim of the study is to determine the incidence of efavirenz-induced neuropsychiatric side effects and the severity and management thereof in these patient populations. I request your permission to conduct research in this public-sector psychiatric hospital. There will be no patient contact involved, only reviewing of medical files. The files will not be removed from the premises and patient confidentiality will be maintained at all times.

I have obtained ethics approval from the Human Research Ethics Committee of the Nelson Mandela Metropolitan University as well as the ECDoH. I would appreciate your co-operation and assistance. If you have any queries please feel free to contact me at the above details.

Razia Gaida

APPENDIX J: INFORMED CONSENT

Faculty of Health Sciences, Department of Pharmacy
Tel. 076335589
razia.gaida@live.nmmu.ac.za
Date:_____

Contact person: Razia Gaida

NMMU REC-H Ref: H14-HEA-PHA-001

Dear Sir/Madam

You are being asked to participate in a research study. The title of the study is 'Evaluating neuropsychiatric symptomology in HIV-positive patients with or without mental illness on efavirenz in three public-sector clinics and two public-sector psychiatric hospitals'. The study aims to determine the incidence of efavirenz-induced neuropsychiatric effects and the severity and management thereof in the different patient populations.

In order to participate, you are required to provide written consent that must include:

- Your name and surname
- The date
- Your signature

Your participation will involve a verbal interview conducted personally by the researcher. This interview will be voice recorded and subsequently transcribed. It is important that you understand that participation in this study is completely voluntary.

If you agree to participate, you are free to withdraw at any time during the study without any penalty incurred to you. If you wish to withdraw please notify the researcher so that your participation may be ended in an orderly manner.

It is important to remember that participation in this study will not benefit you in any way. Participation in this study will not incur any additional costs to you as the participant.

This research may be presented at scientific conferences or in scientific publications, but your identity will remain confidential at all times. No information will be able to be tracked back to you.

This study has been approved by the Research Ethics Committee (Human) of the Nelson Mandela Metropolitan University in Port Elizabeth.

If you have any questions, please feel free to contact the researcher using the following details:

Telephone: 076 633 5589

E-mail: razia.gaida@live.nmmu.ac.za

If you have any questions regarding your rights and welfare as a participant, please feel free to contact the Research Ethics Committee (Human) of the Nelson Mandela Metropolitan University, using the following details:

Telephone: (041) 504 3140

This informed consent statement has been prepared in compliance with current statutory guidelines.

If you understand and accept the conditions and are willing to participate please sign your name and signature below.

_____ _____

Participant's name and surname Participant's signature

Yours sincerely,

_____ _____

Razia Gaida Date

Researcher

APPENDIX K: INTERVIEW

1. Qualification

☐ General medical practitioner

☐ Registered Nurse

☐ Psychiatrist

☐ Other, specify:_____

2. In your opinion, how would you define ‘neuropsychiatric side effects’ of anti-retroviral drugs?

3. In your experience, approximately how long after efavirenz is initiated would neuropsychiatric symptoms appear?

4. Are the symptoms generally severe enough to warrant discontinuation of efavirenz?

5. With what symptoms, in your opinion, would a patient need to present in order for efavirenz to be discontinued?

6. When a patient is diagnosed with severe efavirenz-induced neuropsychiatric symptoms, what would you recommend for the management of the patient?

7. Once neuropsychiatric symptoms have been stabilised, would you reinstate efavirenz?

8. What is your opinion about prescribing efavirenz to a patient with an active psychiatric condition?

9. In your opinion, do patients who are switched to nevirapine due to an intolerable neuropsychiatric effect of efavirenz tolerate treatment better i.e. with fewer neuropsychiatric side effects?

10. Are side effects less or resolved when patients have been switched to nevirapine?

11. In general, do you prefer efavirenz or nevirapine as first-line treatment? Why?

12. Do you feel that the national treatment guidelines for HIV and AIDS is sufficient in assisting management of the condition and all its aspects? Where do you think improvements could be made? Please elaborate.

APPENDIX L: EDITOR'S LETTER

One Stop Solution
24 Firenze Gardens
Warbler Road
Cotswold Ext
Port Elizabeth
6045

www.onestopsolution.co.za

TO WHOM IT MAY CONCERN

I, Michelle van Niekerk, declare that I have done the language editing of Razia Gaida's (s207060291) research paper entitled:

EVALUATING NEUROPSYCHIATRIC SYMPTOMOLOGY IN HIV-POSITIVE PATIENTS ON EFAVIRENZ IN PUBLIC-SECTOR CLINICS AND PSYCHIATRIC HOSPITALS

Submitted for the Degree of Philosophiae Doctor in the Faculty of Health Sciences at the Nelson Mandela Metropolitan University.

Any other queries related to the language and technical editing of this dissertation can be directed to me at 083 652 9826

Signed at Port Elizabeth on 05 November 2016

Mrs M van Niekerk