Assessment of the Prevalence of Central Nervous System Adverse Reactions in adult patients taking Efavirenz based regimens at Mbagathi District Hospital's comprehensive Care Centre

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DECLARATION

This thesis is my original work and has not been presented for a degree in any other university.

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DEDICATION

I dedicate this thesis to my parents Eng Wambura and Mrs. Wambura, to my husband Cedric, to my sisters Roseline, Christine, Elizabeth, Carol and Angela and my brothers Fredrick, Leonard, Johnnie and Ronald for their support and encouragement during this study.

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LIST OF ABBREVIATIONS AND ACRONYMS

AE	Adverse event
AIDS	Acquired Immune Deficiency Syndrome
AOR	Adjusted odds ratio
ART	Antiretroviral Therapy
ARV	Antiretroviral
ADR	Adverse Drug Reaction
ATV	Atazanavir
AZT	Zidovudine
BMI	Body Mass Index
CCC	Comprehensive Care Centre
CD4	T helper cells that carry the CD4 glycoprotein on their surface
CI	Confidence interval
CNS	Central Nervous System
CYP	Cytochrome P
D4T	Stavudine
DR	Doctor
DNA	Deoxyribonucleic acid
EEG	Electroencephalogram

EFV	Efavirenz
ERC	Ethical Review Committee
3TC	Lamivudine
GI	Gastrointestinal
HAART	Highly Active Antiretroviral Therapy
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HIV 1	Human Immunodeficiency Virus Type 1
IBM	International Business Machines
IRS	Immune Reconstitution Syndrome
JKUAT	Jomo Kenyatta University of Agriculture and Technology
KEMRI	Kenya Medical Research Institute
MDH	Mbagathi District Hospital
MOH	Ministry of Health
MS	Microsoft
MSF	Médecins Sans Frontières
MSH	Management Sciences for Health
NRTI	Nucleoside Reverse Transcriptase Inhibitor
NNRTI	Non Nucleoside Reverse Transcriptase Inhibitor

NVP	Nevirapine
OR	Odds ratio
PI	Protease inhibitor
PPB	Pharmacy and Poisons Board
RR	Relative risk
SSC	Scientific Steering Committee
SPSS	Statistical Package for Social Science
TB	Tuberculosis
TDF	Tenofovir
WHO	World Health Organization

DEFINITION OF TERMS USED IN THE STUDY

Adverse drug reaction A response to a drug which is noxious, unintended and which occurs at doses normally used in humans for the therapy, prophylaxis or diagnosis of a disease.

Adverse drug event Any medical occurrence that may present during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with this treatment.

Age The measure of time elapsed since a person's birth.

Anxiety A state of uneasiness and apprehension, as about future uncertainties.

ART The treatment that suppresses or stops the replication of Human Immunodeficiency Virus.

CD4 count A measure of the number of helper T cells that carry the CD4 glycoprotein on their cell surface and that help B cells produce certain antibodies.

Depression A mood disorder that can take different forms, but is typically characterized by feelings of sadness, helplessness and worthlessness.

Gender	It is the category to which an individual is assigned on the basis of sexual orientation.
Hallucination	False or distorted sensory experiences that appear to be real perceptions.
Insomnia	Chronic inability to fall asleep or to enjoy uninterrupted sleep.
Pharmacovigilance	The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug related problems.
Side effect	Any unintended effect of a pharmaceutical product occurring at doses normally used in humans which is related to the pharmacological properties of the drug.
Skin rash	A condition whereby there is temporary eruption on the skin.
Treatment naïve adult	Human Immunodeficiency Virus-infected individuals who have never been exposed to antiretroviral drugs.
Vertigo	A sensation of dizziness or abnormal motion resulting from a disorder of the sense of balance.

ABSTRACT

In Mbagathi District Hospital's Comprehensive Care Centre a large number of patients are on treatment with the antiretroviral drug TDF+3TC+EFV which is known to cause Central Nervous System Adverse Drug Reactions, but currently no detailed data exists in Mbagathi District Hospital and in Kenya on the prevalence of such adverse effects following the use of the antiretroviral drug Efavirenz. The documented literature that exists is from other countries and may differ from what is experienced in the hospitals and in Kenya due to genetic and socio demographic factors. This study was carried out to determine the prevalence of reported CNS adverse reactions in adult patients taking Efavirenz based regimens, the number of reported CNS ADRs, the Efavirenz based regimen that had the most CNS ADRs, the CD4 counts in the affected patients and the duration of treatment with Efavirenz when most of the adverse reactions occurred. The study was cross sectional with a sample size of 420 HIV positive patients on Efavirenz based regimens. Analysis of the results indicated that the prevalence of CNS adverse drug reactions was 48.6%. The number of reported reactions was 8 and of these the most reported were vertigo (23.8%), nightmares (13.6%) and drowsiness (9.5%). The Efavirenz based regimen that had the highest number of CNS ADRs was TDF/3TC/EFV (190 cases), AZT/3TC/EFV (8 cases) and D4T/3TC/EFV (6 cases) whereas the CD4 count that had the highest number of reports ranged between 200-299 (54.2%), 100-199 (50.7%) > 399 (48.5%), 300-399 (46.1%) and < 100 (41.8%). The respondents who experienced the CNS ADRs stated that they occurred within the first two weeks, were mild, resolved and the medication use was continued. Multivariate analysis identified the factors associated with occurrence of ADRs during treatment and they included gender, nutritional status, concomitant medical conditions and concurrent use of other medications. Binary logistic regression with removal at **$p<0.05$** retained two factors in the final analysis which were health status and concurrent use of other medications during treatment whereby a patient with a BMI of normal ($p= 0.039$) was 2.02 times more likely to experience a CNS ADR compared to one with BMI of underweight,

whereas an overweight patient (p=0.011) was 2.48 times more likely to experience a CNS ADR compared to an underweight patient. Similarly, a patient on other medication(s) during treatment was 1.74 times more likely to experience a CNS ADR compared to one not using any other medication (p=0.012). In conclusion, CNS ADRs were found to be prevalent in adult patients taking Efavirenz based regimens in Mbagathi District Hospital's CCC. Clinicians should recognize high risk patients and start therapy at the lowest effective dose in susceptible patients and also know the patients drug-drug potential interactions

CHAPTER ONE

INTRODUCTION

1.0 Background information

Human Immunodeficiency Virus- 1 is the main cause of the global HIV pandemic and is much more infective than HIV-2 and it is further sub-divided into different groups; M, N and O with different geographical distribution. Nine sub-types (A to D, F to H, J and K) are currently recognized for group M. The commonest clades in Kenya are A and D while in eastern and southern Africa subtype C is the commonest, and also accounts for over 50% of all HIV 1 infection globally. The WHO clinical staging system for HIV/AIDS uses a set of clinical parameters to classify HIV infection into 4 stages reflecting disease severity and prognosis, MOH(2011) (Table1.1).

Table 1.1: World Health Organization clinical staging of Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome in adults and adolescents

Clinical stage 1
1. Asymptomatic 2. Persistent generalized lymphadenopathy (PGL)
Clinical stage 2
1. Moderate unexplained weight loss (<10% of presumed or measured body weight) 2. Minor mucocutaneous manifestations (seborrheic dermatitis, popular pruritic eruptions, fungal nail infections, recurrent oral ulcerations, angular cheilitis) 3. Herpes zoster 4. Recurrent upper respiratory tract infections (sinusitis, tonsillitis, bronchitis, otitis media, pharyngitis)

Clinical stage 3
1. Unexplained severe weight loss (over 10% of presumed or measured body weight) 2. Unexplained chronic diarrhoea for longer than one month 3. Unexplained persistent fever (intermittent or constant for longer than one month) 4. Persistent oral candidiasis 5. Oral hairy leukoplakia 6. Pulmonary tuberculosis 7. Severe bacterial infections (e.g. pneumonia, empyema, pyomyositis, bone or joint infection, meningitis, bacteraemia) 8. Acute necrotizing ulcerative stomatitis, gingivitis or periodontitis 9. Unexplained anaemia (below 8 g/dl), neutropenia (below 0.5 x 109/l) and/or chronic thrombocytopenia (below 50 x109 /l)
Clinical stage 4
Conditions where a presumptive diagnosis can be made using clinical signs or simple investigations: 1. HIV wasting syndrome 2. Pneumocystis jiroveci pneumonia (PCP) 3. Recurrent severe bacterial pneumonia (≥ 2 episodes within 1 year) 4. Cryptococcal meningitis 5. Toxoplasmosis of the brain 6. Chronic orolabial, genital or ano-rectal herpes simplex infection for >1 month 7. Kaposi sarcoma (KS) 8. HIV encephalopathy 9. Extra pulmonary tuberculosis (EPTB)

Source: MOH (2011)

The recommended first-line antiretroviral regimens in treatment of HIV naive adults and adolescents are: TDF + 3TC + EFV / NVP OR AZT + 3TC + NVP / EFV, MOH (2011) (Appendix 1).

Efavirenz, a non-nucleoside reverse transcriptase inhibitor has been an important component in the treatment of HIV infection for 10 years and has contributed significantly to the evolution of highly active antiretroviral therapy, Maggilio (2009). It acts by attaching to and blocking the HIV enzyme reverse transcriptase. The blocking of the reverse transcriptase enzyme prevents HIV from multiplying thus reducing the amount of HIV in the body, MOH (20l1).

It has been demonstrated that NVP and EFV are able to cross the blood–brain barrier and arrive at the central nervous system causing important adverse effects, Streck *et al*., (2008) thus the commonest side-effects of Efavirenz involve the brain. Fifty four percent of patients on Efavirenz had at least one neuropsychiatric disorder within the 4 weeks before the visit. Patients in the Efavirenz group reported a significantly higher prevalence of dizziness, sadness, mood changes, irritability, lightheadedness, nervousness, impaired concentration, abnormal dreams, and somnolence, Fumaz *et al*., (2005).

Adverse drug reactions predict hazards from future administration and warrant prevention or specific treatment, alteration of the dosage regimen or withdrawal of the product. Timing, the pattern of illness, the results of investigations, and rechallenge can help attribute causality to a suspected adverse drug reaction, Ralph and Jeffrey (2000).

New adverse drug reactions are often discovered when drugs are used in larger or in different populations than those studied during initial clinical trials. This typically occurs within 3 years of entering the market. Therefore, documentation and reporting becomes a crucial element in clarifying the side effect profile of a drug, VA centre for medication safety (2006). There are two types of ADRs; A and B, Ralph and Jeffrey (2000); PPB (2009).

Type A adverse reactions are due to an exaggerated response to the expected action of the drug. They are predictable from their pharmacology and although the incidence of such reactions is high, mortality is low.

Type B adverse reactions are bizarre reactions unrelated to the conventional pharmacology of the drug and occur only in susceptible individuals. It is not always the active drug itself, but may be the tablet excipients that are responsible for the observed ADR. Type B ADRs have a low incidence, but when they do occur they tend to be more serious.

1.1 Statement of the problem

• Efavirenz CNS drug toxicity may be distressing thus adversely affecting quality of the patient's life. It can affect the confidence of the patient's in the safety of the drugs and thus alter adherence to therapy thus reducing the treatment efficacy and increasing the risk of treatment failure, Sivadasan *et al*., (2009).

• Currently no detailed data exists in Mbagathi District Hospital and in Kenya on the prevalence of such central nervous system adverse effects related to the use of Efavirenz.

1.2 Justification

1 The results obtained will provide data on Efavirenz related CNS ADRs reported within the hospital and in Kenya.

2 The results will be used to inform policy making decisions in the hospital.

3 The results will promote understanding on adverse drug reactions to the health care workers.

4 The results can be used in developing a hypothesis for future studies.

5 The spectrum of adverse effects related to HAART in developing countries may differ from that in developed countries because of the high prevalence of conditions such as anemia, malnutrition, and tuberculosis and frequent initial presentation with advanced HIV disease Subbaraman *et al*., (2007).

6 The information collected will provide tools for the effective management of individual patients and the ultimate purpose of ADR reporting and monitoring is to reduce risks associated with drug prescribing and administration and improve patient care, safety and treatment outcome.

1.3 Objectives

1.3.1 General objective

To determine the prevalence of Central Nervous System adverse reactions in adult patients taking Efavirenz based regimens at Mbagathi district hospital's Comprehensive Care Clinic.

1.3.2 Specific objectives

1) To determine the number of reported Central Nervous System adverse reactions in adult patients.

2) To determine which Efavirenz based regimen had the most Central Nervous System adverse reactions.

3) To determine the CD4 counts in patients with Central Nervous System adverse reactions.

4) To determine the duration of treatment with Efavirenz within which the adverse reactions occurred.

1.4 Research Questions

1) What was the number of reported CNS adverse reactions in adult patients?

2) Which Efavirez based regimen had the most CNS adverse reactions?

3) What was the CD4 count in the patients with CNS adverse reactions?

4) What was the duration of treatment with Efavirenz when the adverse reactions occurred?

1.5 Scope

The study was carried out at Mbagathi district hospital's comprehensive care centre in Nairobi. The hospital is located in Dagoretti district, Golf Course location (Appendix 2) and has a bed capacity of 200 and a cot capacity of 10 (www.ehealth.or.ke). The hospital serves a large catchment area and has well trained and experienced clinicians making it the most ideal site to carry out the study. It has one of the oldest CCC facilities dating back to the year 2003 when MSF Belgium started providing antiretroviral treatment at the level of the outpatient consultations, MSF (2008).

MSF introduced ART as part of a comprehensive care package to ensure access to good quality medical and psycho-social services for People Living With HIV and to remove any financial barriers to care by providing services free at the point of delivery. The GOK started its own ART service in Mbagathi hospital soon afterwards, and integration of the two programmes into one Comprehensive Care Centre under a single management system began in 2005, MSF(2008).The Mbagathi District Hospital's HIV clinic has become a model, successfully combining capacity, quality and access to services and a wide-ranging training programme that has improved both staff and patient knowledge about what can and should be done in caring for HIV-positive people, MSF (2008).

The antiretroviral drugs used at the hospital's CCC by the respondents in the study in combination with Efavirenz are discussed below;

1.5.1 Efavirenz

Efavirenz 600 mg tablet is indicated for the treatment of HIV-1 infection in combination with other antiretroviral agents. Studies in humans and *in vitro* studies using human liver microsomes have demonstrated that Efavirenz is principally metabolized by the cytochrome P450 system to hydroxylated metabolites with subsequent glucuronidation

of these hydroxylated metabolites. Major new findings of a present study were that CYP2A6-mediated Efavirenz 7-hydroxylation accounts for ~23% of Efavirenz metabolism; CYP2A6 is a partial contributor toward Efavirenz 8-hydroxylation; Efavirenz is metabolized sequentially to novel dihydroxylated metabolite(s), via CYP2B6-mediated 7- and 8-hydroxyefavirenz hydroxylation as intermediary; and 8, 14-dihydroxyefavirenz is formed *in vivo* but not *in vitro*, suggesting novel metabolic reactions, Ogburn *et al*., (2010).

Efavirenz dosing in adults is 600 mg once daily at bedtime on an empty stomach or with a low fat meal. Dosing is not established for children age <3 years, or of weight <10 kg , MOH (2011).

The manufacturer currently recommends that Efavirenz be taken before going to bed, since the feelings of dizziness and anxiety are likely to be most intense in the hours leading up to the peak in drug levels, usually about four hours after dosing though some patients prefer to take Efavirenz in the morning, to avoid bad dreams, disturbed sleep, and morning drowsiness attributed to the drug, Sustiva (1998).

Fifty-three percent (531/1008) of patients receiving Efavirenz in controlled trials reported central nervous system symptoms compared to 25% (156/635) of patients receiving control regimens. These symptoms began during the first or second day of therapy and generally resolved after the first 2-4 weeks of therapy. After 4 weeks of therapy, the prevalence of nervous system symptoms of at least moderate severity ranged from 5% to 9% in patients treated with regimens containing Efavirenz and from 3% to 5% in patients treated with a control regimen, Sustiva (1998).

Adverse reactions of Efavirenz include; lipodystrophy, gynecomastia, hepatotoxicity, rash and central nervous system toxicity.

1.5.2 Tenofovir

Tenofovir disoproxil fumarate is a bio available pro drug of tenofovir, a potent nucleotide analogue reverse-transcriptase inhibitor with activity against HIV and hepatitis B virus. It is administered as a single 300-mg tablet once daily. It was approved for the treatment of HIV infection on the basis of data from clinical trials demonstrating activity in treatment experienced patients, and it was subsequently shown to be effective when used as a component of initial therapy, Gallant and Deresinski (2003).

1.5.3 Lamivudine

Lamivudine tablets 150 mg is used in antiretroviral combination therapy for the treatment of HIV infection. It belongs to a class of HIV drugs called nucleoside reverse transcriptase inhibitors which block the HIV enzyme reverse transcriptase thus preventing the virus from multiplying. The usual daily dose for adults and adolescents over 12 years of age is 300 mg. This can be taken either as one 150 mg tablet twice a day approximately 12 hours apart or 300 mg once a day. The tablets can be taken with or without food, Lamivudine (2007).

Lamivudine tablets must always be taken in combination with other antiretroviral medication. Short-term adverse reactions to combination antiretroviral therapy are common. After you start taking Lamivudine tablets 150 mg headache, nausea and vomiting, abdominal pain, diarrhoea and fatigue may occur: these reactions are usually mild and disappear within a few weeks even if treatment is continued. Commonly reported side effects are fatigue, headache, insomnia, nausea, abdominal pain, diarrhoea and hair loss, Lamivudine (2007).

1.5.4 Zidovudine

It belongs to a group of antiviral medicines, also known as antiretrovirals, called NRTIs. These are used to treat HIV infection. It inhibits the activity of reverse transcriptase and blocks the production of DNA and new viruses and thus reduces the amount of HIV

virus in the body, and keeps it at a low level and thus increases CD4 cell counts that play an important role in maintaining a healthy immune system to help fight infection, Zidovudine (2006).

The usual dose of Zidovudine 300 mg tablets for adults and adolescents from over 12 years of age is twice a day one tablet of 300 mg zidovudine. Each dose of Zidovudine 300 mg tablets should be taken approximately 12 hours apart. Short-term adverse reactions to combination antiretroviral therapy are common and these include headache, insomnia, nausea and vomiting, abdominal pain or cramps, diarrhoea, fatigue, and malaise may occur; these reactions are usually mild and disappear within a few weeks even if treatment is continued, Zidovudine (2006).

Common long-term adverse reactions include hyper-pigmentation. Rare and very rare long-term adverse reactions include lactic acidosis, hepatic steatosis, pancreatitis, liver failure and muscle toxicity. It can be taken with or without food. The tablets should always be taken in combination with other antiretroviral medication, Zidovudine (2006).

1.6 Limitations of the study

• Participants may have experienced recall bias. .

• Some patients may not have disclosed their actual social behavioral characteristic with regards to alcohol, smoking and narcotic drug use.

• The quality of data obtained from the patient's files was dependent on the clinician who reviewed the patient at the time and entered their data.

• The study was conducted at a single center and therefore the results may not be generalisable to other settings but the sample size used was relatively large and the socio demographic characteristics of the participants in this study and the issues relevant to their care are comparable to those of other patients treated at many urban centers and rural centers.

• Loss of information may have occurred by excluding from analysis files with missing data.

• The study was of a cross sectional nature therefore the results obtained could not be used to establish incidence and relative risk but only possible significant associations.

1.7 Study hypothesis

Central Nervous System adverse drug reactions are not experienced in adult patients taking Efavirenz based regimens at Mbagathi District Hospital's Comprehensive Care Centre.

CHAPTER TWO

LITERATURE REVIEW

2.0 Introduction

Efavirenz is known by its efficacy and easy treatment compliance due to its once daily dosing. However, it has been observed that in more than 50% of patients receiving Efavirenz neurological adverse symptoms which are very specific of this NNRTI are reported as the drug is able to cross the blood–brain barrier and get into the central nervous system (CNS), causing important adverse effects related to their presence within this tissue , Streck *et al*., (2008).

In a study carried out, 54% percent of patients reported that they had at least one neuropsychiatric disorder within the 4 weeks before the return visit to the clinic. The results of the study indicated that patients in the Efavirenz group reported a significantly higher prevalence of dizziness, sadness, mood changes, irritability, lightheadedness, nervousness, impaired concentration, abnormal dreams, and somnolence compared to those in the PI group, Fumaz *et al*., (2005). These adverse effects are very frequent during the first week of therapy, Adkins and Noble (1998); Treisman and Kaplin (2002); Gutiérrez *et al*., (2005) and some neuropsychiatry disorders may persist in patients chronically treated with Efavirenz, Fumaz *et al*., (2005), Rihs *et al*., (2006).

Post-marketing data and case reports have highlighted the potential for serious psychiatric complications including depression, psychosis, amnesia, extreme excitability, aggressive behavior, post-traumatic stress disorder symptoms, and suicidal ideation, Peyriere *et al*., (2001), Puzantian (2002), Moreno *et al*., (2003). In a French study involving self-reports from 327 patients, a history of multiple episodes of depression was associated with a higher rate of discontinuation of therapy. In the same study, women had a higher rate of developing adverse effects and discontinuing therapy, Spire *et al*., (2004).

Efavirenz related neurologic adverse effects especially insomnia may be explained by alterations in sleep architecture. Electroencephalogram monitoring may be a helpful tool to detect sleep abnormalities in patients complaining of insomnia while receiving Efavirenz, especially for those with few therapeutic alternatives to Efavirenz. The observance that plasma Efavirenz levels correlate with reductions in sleep efficiency opens a door to investigate whether adjusting Efavirenz dosages could ameliorate sleep disturbances without compromising the drug's virologic efficacy, Gallego *et al*., (2004).

In a study carried out to determine whether Efavirenz plasma concentration monitoring could predict treatment failure and central nervous system tolerability, blood samples were obtained from 130 HIV-infected patients receiving Efavirenz in combination with other antiretroviral agents for more than 3 months. An evaluation of CNS side-effects was performed and the viral load, CD4 cell count and other clinical and laboratory data were assessed. CNS toxicity was approximately three times more frequent in patients with high Efavirenz levels (> 4000 μg/l) compared with patients with Efavirenz levels between 1000–4000 μg/l, Marzolini *et al*., (2001). In a similar study, patients achieving higher plasma levels were observed to be at increased risk of experiencing neuropsychiatric adverse events, Gutiérrez *et al*., (2005).

Understanding how genetic variation affects EFV metabolism and influences CNS adverse effects becomes more important as HIV incidence and use of antiretrovirals increases worldwide. Studies to date have consistently found the CYP2B6 G516T mutation to be associated with higher plasma EFV concentrations. This genotype could prove to be a significant development in the identification of individuals at risk of high plasma concentrations of EFV, and those who may be more at risk to develop CNS side effects, King and Aberg (2008). Genetic variation could be a contributory factor to the adverse effects seen as some people will metabolize Efavirenz slower than others. This variation is common among people with a black African heritage and it may increase the risk of side-effects, Haas *et al*., (2004).

2.1 Theoretical review

Independent variables thought to influence the development of CNS ADRs in patients using Efavirenz in this study included CD4 count, patient BMI, duration of treatment with Efavirenz, socio-demographic factors (age, gender, marital status, employment status and parity), socio-behavioral characteristics, coexisting medical conditions and concomitant medication use are discussed below;

2.1.1 CD4 count effect on development of Efavirenz related Central Nervous System Adverse Drug Reactions

Low CD4 cell count at treatment initiation is a risk factor for multiple adverse effects, including Stavudine induced peripheral neuropathy, lipodystrophy, and lactic acidosis, Zidovudine induced myelosuppression, Didanosine induced pancreatitis and IRS. In addition**,** initiation of antiretroviral therapy at advanced stages of AIDS has implications beyond the obvious risk of morbidity and mortality. The high burden of opportunistic infection in patients with low CD4 cell counts increases overlapping toxicities between HAART and opportunistic infection treatments .Therefore, earlier HAART initiation, before the development of a low CD4 cell count and opportunistic infection, may reduce the incidence of adverse effects, Subbaraman *et al*., (2007).

A retrospective cohort study carried out on 2650 patients followed up for 2456 person-years in Nigeria on the incidence, type and risk factors of adverse drug reactions to antiretroviral therapy, established that there was no significant association between CD4 cell count and clinical stage with the development of ADRs, Eluwa *et al.,* (2012).

The results from Eluwa *et al.,* (2012) study differed with the results of Subbaraman *et al*., (2007) study which concluded that low CD4 cell count at treatment initiation is a risk factor for multiple adverse effects, including Stavudine induced peripheral neuropathy, lipodystrophy, lactic acidosis, Zidovudine induced myelosuppression and Didanosine induced pancreatitis but there was no mention of it's effect on CNS adverse effects, Subarraman *et al*., (2007).

2.1.2 Patient body mass index effect on development of Efavirenz related Central Nervous System Adverse Drug Reactions

In a study carried out in Brazil involving 41 subjects on 'the plasma concentrations of Efavirenz are associated with body weight in HIV-positive individual', it was established that there was a significant and inverse correlation between Efavirenz concentrations, body weight (P=0.013) and body mass index (P=0.001), Poeta *et al*., (2011). These results differed with those of a different study where 10% of patients had persistent CNS side-effects and the description of CNS adverse effects included light-headedness, feeling faint, dizzy, drunk and 'out of control' or restless feeling. A few of the patients had nightmares / disturbing dreams and impaired concentration. The study demonstrated that CNS side-effects were more frequent in patients with high drug levels. Among the covariates tested to explain the pharmacokinetic variability of Efavirenz it was established that neither sex, age or body mass index influenced Efavirenz plasma levels, Marzolini *et al*., (2001).

2.1.3 Duration of treatment with Efavirenz

In a cross sectional comparative study comparing 60 patients on an Efavirenz based approach (EFV group) and 60 patients on a protease inhibitor-containing regimen (PI group) for at least 1 year, Fumaz *et al*., (2005), 54% percent of patients in the Efavirenz group and 27% in the PI group reported that they had at least one neuropsychiatric disorder within the 4 weeks before the visit. Patients in the Efavirenz group reported a significantly higher prevalence of dizziness, sadness, mood changes, irritability, lightheadedness, nervousness, impaired concentration, abnormal dreams, and somnolence.

In another study 73.6% of the patients experienced at least one Efavirenz related neuropsychiatric symptom during the first twelve weeks of starting ART. Commonest symptoms experienced were sleep disorders 60.5% (n=124) and hallucinations 30.7% (n=63). Neuropsychiatric symptoms during HAART were significantly predicted by Efavirenz plasma concentrations consistently. These were the results obtained from the

prospective study carried out on 197 treatment naïve Ugandan HIV patients, of whom 138 were TB co-infected, enrolled on Efavirenz based HAART, Mukonzo *et al*., (2013). In a retrospective study involving 403 patients in Ethiopia, the time to occurrence of rash, hepatotoxicity, most GI, and CNS adverse effects was early after starting treatment at a mean interval of 2 weeks, Teklay *et al*., (2013). Lipodystrophy, anemia and peripheral neuropathy were among the long term adverse effects observed with a mean time occurrence of 2, 1.6, and 0.5 years respectively.

In the study on 'the Individualization of antiretroviral therapy', it was established that two thirds or more of patients initiating Efavirenz will experience some degree of CNS side effects, which can be characterized by the full spectrum of minor sleep disturbances and vivid dreams through to major depression and anxiety. Most patients reported amelioration of these symptoms by 2–4 weeks of treatment, Pavlos and Phillips (2012).

The results from the studies above are in line with those of a comparative study involving HIV-1 infected patients included between February 2000 and June 2001 from 65 study sites in Europe, South Africa, Canada, United States, Argentina, Brazil, Australia and Thailand. 825 AEs were observed and most of the AEs occurred during the first 6 weeks of treatment, Kappelhoff *et al*., (2005).

2.1.4 Socio-demographic factors influencing development of the Central Nervous System Adverse Drug Reactions

In the cross-sectional case control study 'Efavirenz and chronic neuropsychiatric symptoms' EFV treated patients reported higher levels of severe stress and anxiety as well as a higher rate of unusual dreams than patients not treated with EFV which may have be an expression of persisting CNS side effects in patients who remain on EFV for a prolonged period, Rihs *et al*., (2006). The study also established that there were no significant differences between the two groups in terms of the following characteristics: age, sex, viral load, CD4 cell count, time in months since HIV positive diagnosis and total months on antiretrovirals.

In a study which sought to identify the characteristics that placed patients at an elevated risk of discontinuation on Efavirenz treatment, the data came from self administered questionnaires distributed by French AIDS community association, Spire *et al*., (2004). Information was collected on socio demographic characteristics, addictive behaviours, treatment regimens, EFV history and depression.

Patients remaining on EFV for more than six months were compared with those who had stopped taking it. Of the 828 patients who completed the questionnaire, 175 had taken EFV for at least six months, and 152 had discontinued it and of these 327 patients (median age=42), 23% were women, 46% were unemployed, 38% had a steady sexual partner and 24% reported a history of multiple depressive episodes. Logistic regression showed that the factors independently associated with EFV discontinuation were female gender (OR [95%CI] =2.2[1.2–3.8]), unemployment (1.8[1.1–2.8]), a steady sexual partner (1.7[1–2.5]) and multiple episodes of depression (2.6[1.5–4.5]). Results from this study suggested that female gender, unemployment, steady sexual partner and prior depression history were risk factors for toxicity induced by Efavirenz.

A study carried out in Brazil involving 41 subjects having a mean age and weight of 45.4 years and 70.9 kg, respectively had Efavirenz plasma concentration of 2.20±2.17 mg/L. Most plasma concentrations (73%) were within the therapeutic window (1–4 mg/L); 17% were below and 10% above the limits. It established that there was no significant association between Efavirenz concentration and age, CD4 cell count, time on antiretroviral treatment and gender. However, there was significant and inverse correlation between Efavirenz concentrations and body weight (P=0.013) and body mass index (P=0.001), Poeta *et al*., (2011).

In a cross sectional survey where patients included were those attending the Comprehensive Care Centre on a monthly basis, data was collected from 354 respondents using an investigator- administered questionnaire study carried out to establish the prevalence, detection and management of adverse drug reactions in the Comprehensive Care Centre of Kiambu District Hospital.

In the above study, chi-square measurement was used to assess whether there was association between the various demographic variables like age, occupation, education level and occurrence/reporting of the symptoms of various ADRs. A significant association was noted between age and weight both at P<0.001. Other significant associations observed were with marital status P=0.016, occupation P<0.001, religion P<0.001 and education P<0.001 Nderitu, (2012).

In a cross sectional study carried out in three hospitals in Ethiopia from February to April, 2009, the study population consisted of 155 TB/HIV co-infected and 465 non-co-infected HIV patients. Common mental disorders were assessed through face to face interviews by trained clinical nurses whereas risk factors for common mental disorders were assessed using a structured questionnaire. The results from the study indicated that individuals who had no source of income [OR = 1.7, (95%CI: 1.1, 2.8)] and day labourers [OR = 2.4, 95%CI: 1.2, 5.1)] were more likely to have common mental disorders as compared to individuals who had a source of income and government employees respectively, Amare *et al*., (2010).

2.1.5 Socio-behavioral characteristics

According to an observational cohort study which evaluated the short term incidence of adverse events and treatment interruptions in patients using EFV, the results showed that intravenous drug users had higher treatment discontinuation rates due to intolerance of side effects than non intravenous drug users (22.6 vs. 6.6%), Hirschel *et al*., (2002).

2.1.6 Concomitant medical conditions

Concurrent tuberculosis was found to be the only influential risk factor for development of ADRs identified by multivariate logistic regression in a study on 400 patients on ‘Adverse drug reactions to antiretroviral therapy: an experience of spontaneous reporting and intensive monitoring’ from ART centre in India, Modayil *et al*., (2010).

In the study ‘evaluating neuropsychiatric side effects in patients able to tolerate an EFV containing regimen for more than 4 weeks while still experiencing neuropsychological side effects’, the charts of 110 patients were screened. Fifty patients (50%) had a history

of depression; of these, 56% were currently depressed. Relative risk for current depression was significantly higher for patients with any history of depression than for patients without such a history (RR, 31.2; 95% CI, 6.81Y142.6, P G 0.0001), Boly *et al*., (2006).

2.1.7 Concurrent use of other medications

The results from a study established that nine cases of neuropsychiatric intolerance occurred early after a switch from an antiretroviral regimen without TDF to an EFV and TDF containing regimen. Initially, the nine HIV-1 infected patients were treated with an EFV containing regimen for a median duration of 31 months without any EFV related central nervous system effects. Moderate to severe neuropsychiatric events occurred immediately (<48 hours) after TDF initiation in five patients and 2 weeks to 24 months after the switch in the remaining four patients. Although the exact mechanism of these symptoms remains hypothetical, neuropsychiatric disorders could be either a consequence of an unexplained interaction between EFV and TDF or an infrequent TDF related side effect, Allavena *et al*., (2006).

The CYP2B6 G516T mutation is associated with significantly reduced function of the 2B6 enzyme which primarily metabolizes Efavirenz. A case was reported of a 33-year-old HIV-infected woman patient who presented at Cantonal Hospital of Muensterlingen, Switzerland with sudden and severe neuropsychiatric symptoms during therapy with Efavirenz. The patient was homozygous for this mutation and it was postulated that slow hepatic metabolism was primarily responsible for the excessively high plasma Efavirenz levels. Furthermore, a drug interaction with Fluconazole might have contributed to the accumulation of Efavirenz because Fluconazole has been shown to prolong the elimination half-life of Efavirenz. However, under normal circumstances, no dose adjustment is recommended when Efavirenz and Fluconazole are given concomitantly, Hasse *et al*., (2005).

In a cross sectional study involving 339 patients, it was established that there were decreased plasma concentrations for both Efavirenz and Nevirapine when given with Rifampicin confirming the findings of formal interaction studies, Stohr *et al*., (2008).

2.2 Critique of existing literature

In the study on 'Adverse effects of highly active antiretroviral therapy in developing countries' Subbaraman *et al*., (2007), the results obtained were based on the review of current knowledge about toxicities related to HAART in resource limited settings. Similarly, the studies carried out on 'Neurologic and psychiatric complications of antiretroviral agents' Treisman and Kaplin (2002) on 'Individualization of antiretroviral therapy' Pavlos and Phillips (2012) and 'Clinical impact of patient population differences and genomic variation in Efavirenz therapy,' King and Aberg (2008) these were all editorial reviews of other studies that had been done.

In the cross-sectional comparative study performed at the outpatient HIV clinic of a university hospital where interviews were conducted from October 2002 through May 2003, Fumaz *et al*., (2005), the study had a total of 120 HIV infected subjects who met the inclusion criteria and were recruited to the study. In the study, Patients who had previously discontinued Efavirenz because of moderate and severe adverse events and who might have had Efavirenz plasma levels greater than the upper limit of the therapeutic interval were not included in the study resulting in loss of data from an important pool of subjects. Other limitations of the study were its cross sectional nature and the small sample size. One advantage is the absence of previous history of depression, schizophrenia, or other psychotic or personality disorders and not be taking psychiatric medication at the time of recruitment to the study.

In the single centre cross-sectional study carried out where a cohort of patients who had been treated with EFV600 mg once a day as part of their combination antiretroviral regimen for at least 6 months were compared with a matched cohort who were stable on non EFV combination antiretroviral therapy for a minimum duration of 6 months, the

EFV treated patients reported higher levels of severe stress and anxiety as well as a higher rate of unusual dreams than patients not treated with EFV, Rihs *et al*., (2006). Patients with severe cognitive or psychiatric impairment, with evidence of past or present drug or alcohol dependence or with a diagnosis of AIDS dementia complex were excluded from the study. Measures were taken once by means of a set of self-administered questionnaires. Limitations to this study were its cross-sectional nature and its small sample size. The study involved a total of 82 participants and should have incorporated a larger sample size. Another limitation is that there may also have been a potential for reporting bias in the self administered questionnaires where the subjects taking EFV may have been more likely to report symptoms than the subjects in the control group.

In the study involving 828 patients to identify the characteristics that placed patients at an elevated risk of discontinuation, data for this cross-sectional study came from self-administered questionnaires distributed by French AIDS community associations and collected information about sociodemographic characteristics, addictive behaviours, treatment regimens, EFV history and depression, the limitations to the study were its cross sectional nature and the self administered questionnaires which could have resulted in reporting bias, Spire *et al*., (2004).

In the study where a total of 26 HIV infected patients receiving a triple antiretroviral combination including Efavirenz (600 mg once a day at bedtime) for >12 weeks were selected in a prospective and nonrandomized fashion, one disadvantage of the study is that it involved a small sample size meaning that the results would not be accurately generalisable to other populations, Gallego *et al*., (2004).

In the retrospective cohort analysis of prescription events conducted in three public hospitals in Nigeria between May 2009 and May 2010 on Adverse drug reactions to antiretroviral therapy, Eluwa *et al*., (2012), the strengths included the large sample size and the median percentage of missing variables was 0% confirming that the data was of

good quality. The limitations included the fact that the ADR screening tool was structured thus did not allow details of unknown ADRs to be captured and the study included patients who had initiated ART before active surveillance of the ADRs had commenced thus leaving out information from this segment of patients.

The study involving 130 patients in Switzerland between January 1999 to June 2000 on 'Efavirenz plasma levels can predict treatment failure and central nervous system side effects in HIV-1 infected patients,' Marzolini *et al*., (2001) had one of its strengths in the fact that it recorded the use of concomitant medications at the time of sample collection. Limitations included the small sample size and no mention of the exclusion of patients having psychiatric illness prior to initiation of HAART, from the study.

In the prospective study carried out in southern Brazil on 'Plasma concentrations of Efavirenz are associated with body weight in HIV positive individuals' from July 2009 to March 2010 involving 41 patients, the sample size was small and should have been much larger to be able to draw conclusions about the potential factors associated with Efavirenz plasma concentrations and secondly the results on adherence relied on patients self reports which could have been influenced by reporting bias, Poeta *et al*., (2011).

In the prospective cohort study carried out in Uganda between 2008 and 2009 involving 197 subjects whereby the influence of Efavirenz pharmacokinetics and pharmacogenetics on neuropsychological disorders in Uganda HIV positive patients with or without tuberculosis was studied, the sample size should have incorporated a larger number of participants and there is no mention of a history of existing mental illness in the participants being in the exclusion criteria, Mukonzo *et al*., (2013).

In the retrospective review of patient medical records between 2009 and 2011, sampling 403 patient medical records to establish the adverse effects and regimen switch among patients on antiretroviral treatment in a resource limited setting in Ethiopia using structured data abstraction format some of the strengths of the study were that it had a

big sample size but the limitations included ; poor ADR recording and reporting, being a retrospective study differentiation between ART related ADRs and AIDs related outcomes occurring in untreated patients was difficult and the quality of data obtained in the study was dependent on the clinician entering the data in the patients records ,Teklay *et al*., (2013).

In the prospective study involving 1216 HIV-1-infected patients included between February 2000 and June 2001 from 65 study sites in Europe, South Africa, Canada, United States, Argentina, Brazil, Australia and Thailand on 'Are adverse events of Nevirapine and Efavirenz related to plasma concentrations,' Kappelhoff *et al*., (2005), the study had its strengths in its large sample size and its prospective nature whereas one of the limitations was that there was no mention of use of concomitant medications being part of the exclusion criteria in study participants.

In a cross sectional survey where patients included were those attending the Comprehensive Care Centre on a monthly basis and data was collected from 354 respondents using an investigator- administered questionnaire, the study was carried out to establish the prevalence, detection and management of adverse drug reactions in Kiambu District Hospital, Nderitu, (2012). The sample size in the study was fairly large meaning that the results obtained could be generalized to other populations. The limitations in the study were that it was a cross sectional study, the assessment should have included the use of concomitant medications and concurrent medical conditions and finally the survey should have taken part over a longer duration of time to be able to improve on the randomness in the sampling.

In the cross sectional study carried out in three hospitals in Ethiopia from February to April, 2009 where the study population consisted of 155 TB/HIV co-infected and 465 non-co-infected HIV patients, the common mental disorders were assessed through face to face interviews by trained clinical nurses, Amare *et al*., (2010). The strengths of the study were that it had a large sample size and sampling was carried out in three different

hospitals meaning that the results obtained could be easily generalized to other populations.

In the study 'Evaluating neuropsychiatric side effects in patients able to tolerate an EFV-containing regimen for more than 4 weeks while still experiencing neuropsychological side effects,' Boly *et al*., (2006) where the charts of 110 patients were screened from 6 participating private practices in the San Francisco Bay area, the use of concurrent medication in the study participants was documented. Limitations to the study were the fact that it was a retrospective review of patient's charts to diagnose past depression meaning the results obtained were dependent on the clinician who entered the data at the time.

In the prospective study involving 9 patients in which it was concluded that the exact mechanism of the neuropsychiatric symptoms remains hypothetical, and that they could be either a consequence of an unexplained interaction between EFV and TDF or an infrequent TDF-related side effect, Allavena *et al*., (2006), the sample size was very small.

In the case reported of a 33-year-old HIV-infected woman patient who presented at Cantonal Hospital of Muensterlingen, Switzerland with sudden and severe neuropsychiatric symptoms during therapy with Efavirenz, Hasse *et al*., (2005) further studies would have to be carried out on a larger study population to be able to give more accurate associations.

In the cross sectional study involving 339 patients, it was established that there were decreased plasma concentrations for both Efavirenz and Nevirapine when given with Rifampicin confirming the findings of formal interaction studies, Stohr *et al*., (2008). This study had a relatively large sample size that could be generalized to other populations but its cross sectional nature meant that the results could not be used to establish incidence and relative risk.

CHAPTER THREE

METHODOLOGY

3.0 Study design

The study design was cross sectional in nature whereby exposure (Efavirenz) and outcome (development of a CNS adverse reaction) were assessed simultaneously at one point in time in individuals of a well defined population (HIV positive patients on an Efavirenz based regimen).

3.1 Target population

The study population comprised of adult HIV positive male and female patients on an Efavirenz based regimen between January 2002 and December 2012 at Mbagathi District Hospital. As of December 2012 the hospital's CCC had 3854 and 334 cumulative active adult and children patients on HAART respectively. The total number of adult patients on an efavirenz based regimens were 1861 of whom 20 are on D4T/3TC/EFV, 77 on AZT/3TC/EFV and 1764 on TDF/3TC/EFV.

Upon registration of a new patient at the CCC, a thorough medical history and physical examination of the patient is undertaken by a registered clinical officer to capture any existing medical conditions and or opportunistic infections .The patient's CD4 count is also determined so as to be able to stage the patient in line with the clinical staging spelled out in national treatment guidelines and determine whether they are qualified for starting ART. The CD4 count was determined by collecting a blood sample from the vein in the arm then subjecting this sample to flow cytometry and the results expressed as cells per cubic millimeter of blood. Upon every repeat visit by the patient, history taking is carried out and captured in the patients file.

3.1.1 Inclusion/Exclusion criteria

Inclusion criteria

Adult patients on an Efavirenz based regimen who gave their consent to take part in the study

Exclusion criteria

1. Pregnant women due to its teratogenic effect, MOH (2011)
2. Adults on non Efavirenz based regimens
3. Children
4. Patients with documented CNS illness prior to starting Efavirenz
5. Patients who did not give their consent to take part in the study

3.2 Sampling technique

Stratified random sampling was used to select the files of patients on an Efavirenz based regimen between the period January 2002 and December 2012. In this technique, each member of the population had an equal chance of being selected as a subject. The 1861 files of patients on an Efavirenz based regimen were put aside and arranged in smaller groups/ strata according to the Efavirenz based regimens as follows; AZT/3TC/EFV,77 files, D4T/3TC/EFV, 20 files and TDF/3TC/EFV, 1764 Files. Each group was assigned numbers based on the total number of files in the strata. A table of random numbers was then generated for each stratum based on number of files required per strata (determined through probability to size sampling) in Table 3.1 above to give the sample size of 424. The file numbers not included in the table were excluded from the study. The patients whose files were selected were interviewed on the date of their routine clinic appointment date using a structured questionnaire after being taken through the informed consent form and consenting to take part in the study.

3.2.1 Sample size determination

The calculated sample size was 385 using the, Kothari (2003) formula.

$$n = \frac{z^2pq}{d^2}$$

Whereby;

n= study sample size

z= the value corresponding to the 95% confidence interval

p= proportion of patients who have experienced an Adverse Drug Reaction, Kenedi and Goforth (2011).

q=1-p

d= leve l of precision of the mean estimate i.e. the acceptable error margin (0.05)

$$n = \frac{1.96^2 \times 0.50 \times 0.50}{(0.05)^2} = \frac{3.8416 \times 0.50 \times 0.50}{0.0025} = 385$$

The calculated sample size was 385. However a 10% non-response was factored to adjust the sample size upwards.

$$\frac{10}{100} \times 385 = 39$$

The required sample size was therefore 385 + 39 = 424. The sampling frame of 1861(from the total number of adult patients on an Efavirenz based regimen) was distributed in three categories. Probability Proportional to Size (PPS) sampling was used

to determine the number of files to be reviewed. The regimen based sample selection was as shown in the **(Table 3.1)**

Table 3.1: Population sample size of the target population per drug regimen

Drug regimen	Target population	Sample population
AZT/3TC/EFV	77	$\frac{77}{1861} \times 424 = 18$
D4T/3TC/EFV	20	$\frac{20}{1861} \times 424 = 5$
TDF/3TC/EFV	1764	$\frac{1764}{1861} \times 424 = 402$

Key:

AZT/3TC/EFV - Zidovudine/Lamivudine/Efavirenz

D4T/3TC/EFV - Stavudine/Lamivudine/Efavirenz

TDF/3TC/EFV - Tenofovir/ Lamivudine/Efavirenz

3.3 Data collection instruments

The instruments used in the study included the patient's files, the CCC pharmacy MSH dispensing tool, the Pharmacovigilance suspected adverse reaction reporting form (Appendix 3) and a structured questionnaire (Appendix 4).

3.4 Data collection procedure

Desk review of the selected patient's files was carried out to determine whether the patient had any mental illness prior to starting ARV medication. The files were also used to confirm the patient's regimen, age, weight, height, CD4 count, concomitant medical condition(s) and medication use. The Pharmacovigilance forms and the CCC pharmacy MSH dispensing tool were used to confirm the case reports and the regimens used,

where available. The 424 patients whose files were selected and who consented to take part in the study after being taken through the informed consent form (Appendix 5&6) were interviewed in the CCC by a registered clinical officer on the day of their routine clinic appointment.

3.5 Data processing and analysis

The data from the questionnaires was coded and double entered into a computer database designed using MS-Excel application. File back-up was regularly done to avoid any loss or tampering. Data cleaning and validation was performed in order to achieve a clean dataset that was exported into a Statistical Package format (SPSS) for analysis. All the questionnaires were stored in a lockable drawer for confidentiality purposes. Data analysis was conducted using IBM SPSS version 21 statistical software. The development of a CNS adverse reaction was analyzed as a composite outcome whereby development of any one CNS adverse reaction was captured and compiled to be used in determining the final prevalence of CNS adverse reactions in patients taking an Efavirenz based regimen. Descriptive statistics such as proportions were used to summarize categorical variables while measures of central tendency such as mean, Standard deviation, median and ranges were used for the continuous variables. Pearson's Chi-square or Fisher exact tests were used to test for the strength of association between categorical variables. All Independent variables (Age, gender, CD4 count etc) were associated with the dependent variable (CNS adverse reaction) to determine which ones had a significant association. Odds Ratio (OR) and 95% Confidence Interval (CI) were used to estimate the strength of association between independent variables and the dependent variable. The threshold for statistical significance was set at $p<0.05$. All independent variables identified to significantly associate with dependent variable (CNS adverse reaction) at bivariate analysis were considered together in a multivariate analysis using binary logistic adjusted odds ratio (AOR) with corresponding 95% Confidence Interval (CI) was used to estimate the strength of association between the retained independent predictors and occurrence of CNS adverse reaction.

3.6 Ethical considerations

Approval to carry out the study was obtained from;

- Mbagathi District Hospital CCC in-charge (Appendix 7)
- KEMRI SSC (Appendix 8)
- KEMRI ERC (Appendix 9)
- The hospital's medical superintendent
- The respondents

CHAPTER FOUR

RESULTS AND DISCUSSION

4.0 Results

Central Nervous System ADRs were found to be prevalent amongst adult patients taking Efavirenz based regimens at Mbagathi District Hospital's CCC at 48.6 %.

4.0.1 Study participants

A total of 424 adults met the inclusion criteria, gave their consent to participate and were recruited to the study. Out of the 424, 4 respondents had incomplete data in their files and were removed from the study leaving 420 respondents. The analysis results are discussed below.

4.0.1.1Demographic and socio-economic characteristics of the respondents

The demographic and socio-economic characteristics of the respondents are indicated in Table 4.1.There was a higher proportion of females (59.3%) compared to males (40.7%) who participated in the study. Twenty nine point seven percent(29.7%) of the respondents were aged more than 45 years, 45.5% were between 35- 44 years, 15.2% were between 30-34 years and a small percentage were less than 29 years (9.5%). The highest proportion of respondents were married (56.9%) followed by single (23.6%) and divorced (0.7%). Analysis on the number of children per household revealed that most of the households had 1 – 2 children. Most of the respondents were self employed (51.9%) with a small proportion being unemployed (17.1%).

Table 4.1: Demographic and socio-economic characteristics of the respondents

Variables	n=420	%
Gender		
Male	171	40.7
Female	249	59.3
Age in years		
<25	11	2.6
25 – 29	29	6.9
30 – 34	64	15.2
35 – 39	91	21.7
40 – 44	100	23.8
45 – 49	66	15.7
>50	59	14.0
Marital status		
Married	239	56.9
Single	99	23.6
Separated	26	6.2
Divorced	3	0.7
Widowed	53	12.6
Number of children		
None	38	9.0
1 – 2	195	46.4
3 – 4	132	31.4
5 or more	55	13.1
Employment status		
Employed	130	31.0
Self employed	218	51.9
Unemployed	72	17.1

Key:

< - Less than

> - Greater than

% - Percentage of respondents

n - Total number of respondents

4.0.1.2 Health status of the respondents

A relatively small proportion of the respondents were underweight (11.4%) while 31.9% were overweight. Most of the respondents (22.9%) had their CD4 count in the range of 200-299, 21.2% were between 300-399 and 23.6% >399 cells/mm3.Tuberculosis was the most reported medical condition (33.1%) prior to starting of ARV's. Other medical conditions were reported by less than 5.0% of the remaining respondents (Table 4.2).

Table 4.2: Health status of the respondents

Variables	**n=420**	**%**
Nutritional status		
Underweight (<18.50 kg/m2)	48	11.4
Normal (18.5 - 24.99 kg/m2)	238	56.7
Overweight (>24.99 kg/m2)	134	31.9
CD4 count in cells/mm3		
<100	67	16.0
100-199	69	16.4
200-299	96	22.9
300-399	89	21.2
>399	99	23.6
Any medical condition experienced prior to starting ARV medication		
Tuberculosis	139	33.1
Pneumonia	18	4.3
Meningitis	11	2.6
Herpes zoster	4	1.0
Anaemia	1	0.2
Diabetes	1	0.2
Kaposi's sarcoma	1	0.2
None	260	61.9

Key:

< - Less than

> - Greater than

% - Percentage of respondents

n - Total number of respondents

4.0.1.3 Efavirenz based treatment regimens used by the respondents

Majority of respondents were on TDF/3TC/EFV (92.1%), 5% on AZT/3TC/EFV and 2.9% on D4T/3TC/EFV. Majority of the respondents (98.3%) indicated that they took their medication at night while 92.4% took their medication after a meal (Table 4.3).

Table 4.3: E**favirenz based treatment regimens used by the respondents**

Variables	**n=420**	**%**
Efavirenz based regimen taken		
TDF+3TC+EFV	387	92.1
AZT+3TC+EFV	21	5.0
D4T+3TC+EFV	12	2.9
Time of day when medication is taken		
Morning	7	1.7
Night	413	98.3
Medication is taken before or after a meal		
Before	32	7.6
After	388	92.4

Key:

AZT/3TC/EFV - Zidovudine/Lamivudine/Efavirenz

D4T/3TC/EFV - Stavudine/Lamivudine/Efavirenz

TDF/3TC/EFV - Tenofovir/ Lamivudine/Efavirenz

n - Total number of respondents

% - Percentage of respondents

4.0.1.4 Socio-behavioral characteristics of the respondents

A relatively small proportion of the respondents stated that they used alcohol (6.4%) and smoked 2.1% while none (0.0%) abused narcotic drugs (Table 4.4).

Table 4.4: Socio-behavioral characteristics of the respondents

Variables	n=420	%
Alcohol intake history		
Yes	27	6.4
No	393	93.6
Smoking history		
Yes	9	2.1
No	411	97.9
Narcotic drug abuse history		
Yes	0	0.0
No	420	100.0

Key:

n - Total number of respondents

% - Percentage of respondents

4.0.1.5 Concomitant medical conditions and concurrent use of other medication among the respondents

The most reported concomitant medical condition was\tuberculosis (17.9%) and hypertension (6.9%). Occurrence of other specific concomitant medical conditions accounted for less than 2.0%. The most reported concurrently used medication(s) were; Anti tuberculosis (17.9%), and Anti-hypertensive drugs (6.7%) (Table 4.5)

Table 4.5: Concomitant medical conditions and concurrent use of other medications among the respondents

Variables	n=420	%
Concomitant medical condition(s)		
Tuberculosis	75	17.9
Hypertension	29	6.9
Asthma	8	1.9
Diabetes	4	1.0
Allergies	2	0.5
Herpes Zoster	2	0.5
Meningitis	2	0.5
Anaemia	1	0.2
Goiter	1	0.2
Kaposi's sarcoma	1	0.2
Ulcers	1	0.2
None	300	71.4
Concurrent use of other medication(s)		
Anti-TB's	75	17.9
Anti-hypertensive's	28	6.7
Contraceptives	8	1.9
Salbutamol tablets	4	1.0
Hypoglycemics	4	1.0
Acyclovir tablets	2	0.5
Cetrizine tablets	2	0.5
Salbutamol inhaler	2	0.5
Carbimazole tablets	1	0.2
Fluconazole tablets	1	0.2
Omeprazole tablets	1	0.2
Simbicort inhaler	1	0.2
Vincristine injection	1	0.2
None	296	70.5

Key:

n - Total number of respondents

% - Percentage of respondents

Tb - Tuberculosis

4.0.1.6 Central Nervous System Adverse Drug Reactions experienced by the respondents

The most commonly reported CNS Adverse Drug Reactions included; vertigo (dizziness) (25.5%), nightmares (13.6%), and somnolence (drowsiness) (9.5%). Overall occurrence of CNS ADRs was 48.6%. All the respondents experienced ADRs within the first two weeks, all being mild, resolved and the medication use continued (Table 4.6).

Table 4.6: Central Nervous System Adverse Drug Reactions experienced by the respondents

Variables	**n=420**	**%**
Any suspected CNS adverse drug reaction(s) experienced		
Vertigo (dizziness)	107	25.5
Nightmares	57	13.6
Somnolence (drowsiness)	40	9.5
Drunk feeling	16	3.8
Hallucinations	6	1.4
Insomnia	4	1.0
Confusion	1	0.2
Sleep talking	1	0.2
None	216	51.4
Duration of treatment with Efavirenz in years when the reaction occurred		
<=2 weeks	201	100.0
Not applicable	215	
Non response	4	
Severity of the reaction experienced		
Mild, resolved and the medication use continued	201	100.0
Not applicable	215	
Non response	4	

Key:

< - Less than

n - Total number of respondents

% - Percentage of respondents

4.0.2 Bivariate analysis

Occurrence of CNS ADRs was analyzed in relation to (i) Demographic and socio-economic characteristics, (ii) Health status, (iii) Efavirenz based treatment, (iv) Socio-behavioral characteristics and (v) Concomitant medical condition and concurrent use of medication among the respondents.

4.0.2.1 Central Nervous System Adverse Drug Reactions experienced in relation to demographic and socio-economic characteristics of the respondents

Bivariate analysis indicated that gender was significantly associated with the occurrence of CNS ADRs among the respondents and female gender was significantly associated with the occurrence of ADRs (53.0%) compared to male gender (42.1%), (OR=1.55; 95% CI: 1.05 – 2.30; p=0.028) (Table 4.7). Age, marital status, employment status and number of children had a p value greater than 0.05 and thus were not significantly associated with the occurrence of CNS ADRs.

Table 4.7: Central Nervous System Adverse Drug Reactions experienced in relation to demographic and socio-economic characteristics of the respondents

Variables	ADRs present (n=204) N	%	ADRs absent (n=216) N	%	OR	95% CI Lower	Upper	P value
Patients gender								
Female	132	53.0	117	47.0	1.55	1.05	2.30	**0.028***
Male	72	42.1	99	57.9	1.00			
Age in years								
<25	7	63.6	4	36.4	1.58	0.42	5.98	0.500
25 – 29	18	62.1	11	37.9	1.48	0.60	3.66	0.399
30 – 34	29	45.3	35	54.7	0.75	0.37	1.52	0.423
35 – 39	45	49.5	46	50.5	0.88	0.46	1.70	0.711
40 – 44	42	42.0	58	58.0	0.65	0.34	1.25	0.199
45 – 49	32	48.5	34	51.5	0.85	0.42	1.72	0.651
50 or more	31	52.5	28	47.5	1.00			
Marital status								
Married	118	49.4	121	50.6	1.08	0.65	1.78	0.777
Single	47	47.5	52	52.5	1.00	0.55	1.79	0.991
Separated/ divorced/ widowed	39	47.6	43	52.4	1.00			
Employment status								
Employed	69	53.1	61	46.9	1.34	0.75	2.38	0.325
Self employed	102	46.8	116	53.2	1.04	0.61	1.77	0.888
Unemployed	33	45.8	39	54.2	1.00			
Number of children								
None	23	60.5	15	39.5	1.98	0.85	4.59	0.111
1 – 2	99	50.8	96	49.2	1.33	0.73	2.43	0.351
3 – 4	58	43.9	74	56.1	1.01	0.54	1.91	0.970
5 or more	24	43.6	31	56.4	1.00			

***implies variables with significance**

Key:

< - Less than

% - Percentage of respondents

n - Total number of respondents

N - Number of respondents

P - Level of significance

CI - Confidence interval

OR - Odds ratio

ADR - Adverse drug reaction

4.0.2.2 Central Nervous System Adverse Drug Reactions experienced in relation to health status of the respondents

Analysis of health status of the respondents indicated that the Body mass Index (BMI) of the patients was associated with the development of CNS ADRs compared to CD4 count and medical condition experienced prior to starting ARV medication. Under BMI, normal body weight was found to be significantly associated with an increased number of respondents experiencing ADRs (48.7%) compared to underweight (31.3%), (OR=2.09; 95% CI: 1.08 – 4.05; p=0.029). Similarly, Overweight was significantly associated with an increased number of respondents experiencing ADRs (54.5%) compared to underweight (31.3%), (OR=2.63; 95% CI: 1.31 – 5.29; p=0.007).

The CD4 count range that had the highest number of respondents experiencing a CNS ADR was between 200 – 299 where 52 out of 204 respondents (25.5%) experienced a CNS ADR, >399 where 48 out of 204 respondents (23.5%) experienced a CNS ADR, 300 – 399 where 41 out of 204 respondents (20.1%) experienced a CNS ADR,100– 199 where 35 out of 204 respondents (17.2%) experienced a CNS ADR and < 100 had the lowest number with 28 out of 204 respondents (13.7%) experiencing a CNS ADR. Bivariate analysis determined that the respondents CD4 counts were not significantly associated with the development of a CNS ADR as none had a p value of less than 0.05 (Table 4.8).

Table 4.8: Central Nervous System Adverse Drug Reactions experienced in relation to health status of the respondents

Variables	ADRs present (n=204) N	%	ADRs absent (n=216) N	%	OR	95% CI Lower	Upper	P value
BMI								
Overweight (>24.99 kg/m^2)	73	54.5	61	45.5	2.63	1.31	5.29	**0.007***
Normal (18.5 - 24.99 kg/m^2)	116	48.7	122	51.3	2.09	1.08	4.05	**0.029***
underweight (<18.50 kg/m^2)	15	31.3	33	68.8	1.00			
CD4 count in cells/mm3								
<100	28	41.8	39	58.2	0.76	0.41	1.43	0.396
100-199	35	50.7	34	49.3	1.09	0.59	2.02	0.775
200-299	52	54.2	44	45.8	1.26	0.72	2.20	0.428
300-399	41	46.1	48	53.9	0.91	0.51	1.61	0.740
>399	48	48.5	51	51.5	1.00			
Any medical condition experienced prior to starting ARV medication								
Present	79	49.4	81	50.6	1.05	0.71	1.56	0.796
Absent	125	48.1	135	51.9	1.00			

***implies variables with significance**

Key:

> - More than

< - Less than

% - Percentage of respondents

n - Total number of respondents

N - Number of respondents

P - Level of significance

CI - Confidence interval

CD4 - T helper cells that carry the CD4 glycoprotein on their surface

ARV - Antiretroviral

ADR - Adverse drug reaction

BMI - Body mass index

OR - Odds ratio

4.0.2.3 Central Nervous System Adverse Drug Reactions experienced in relation to Efavirenz based treatment among the respondents

Analysis of the occurrence of CNS ADRs among the respondents indicated that none of the factors namely; Efavirenz based regimen taken, time of day when medication is taken and whether medication is taken before or after a meal was significantly associated with occurrence of CNS ADRs during treatment among the respondents.

Tenofovir/Lamivudine/Efavirenz was the Efavirenz based regimen that had the highest number of respondents in total experiencing a CNS ADR where 190 out of the 204 respondents (93.1%) who experienced a CNS ADR being on this regimen. Zidovudine/Lamivudine/Efavirenz had 8 out of 204 respondents (3.9 %) and Stavudine/Lamivudine/Efavirenz had the least with only 6 out of the 204 respondents (2.9%) that experienced a CNS ADR (Table 4.9).

Table 4.9: Central Nervous System Adverse Drug Reactions experienced in relation to Efavirenz based treatment regimen among the respondents

Variables	ADRs present (n=204)		ADRs absent (n=216)		OR	95% CI		P value
	N	%	N	%		Lower	Upper	
Efavirenz based regimen taken								
TDF+3TC+EFV	190	49.1	197	50.9	0.96	0.31	3.04	0.951
AZT+3TC+EFV	8	38.1	13	61.9	0.62	0.15	2.58	0.507
D4T+3TC+EFV	6	50.0	6	50.0	1.00			
Time of day when medication is taken								
Morning	5	71.4	2	28.6	2.69	0.52	14.01	0.222
Night	199	48.2	214	51.8	1.00			
Medication taken before or after meal								
Before	12	37.5	20	62.5	0.61	0.29	1.29	0.192
After	192	49.5	196	50.5	1.00			

Key:

% - Percentage of respondents

n - Total number of respondents

N - Number of respondents

P - Level of significance

CI - Confidence interval

OR - Odds ratio

ADR - Adverse drug reaction

AZT/3TC/EFV - Zidovudine/Lamivudine/Efavirenz

D4T/3TC/EFV - Stavudine/Lamivudine/Efavirenz

TDF/3TC/EFV - Tenofovir/ Lamivudine/Efavirenz

4.0.2.4 Central Nervous System Adverse Drug Reactions experienced in relation to socio-behavioral characteristics of the respondents

Analysis of the occurrence of CNS ADRs in relation to socio-behavioral characteristics among the respondents indicated that neither alcohol intake nor smoking history was significantly associated with occurrence of CNS ADRs during treatment among the respondents (Table 4.10).

Table 4.10: Central Nervous System Adverse Drug Reactions experienced in relation to socio-behavioral characteristics of the respondents

	ADRs present (n=204)		ADRs absent (n=216)		95% CI			
Variables	**N**	**%**	**N**	**%**	**OR**	**Lower**	**Upper**	**P value**
Alcohol intake history								
Yes	16	59.3	11	40.7	1.59	0.72	3.50	0.251
No	188	47.8	205	52.2	1.00			
Smoking history								
Yes	2	22.2	7	77.8	0.30	0.06	1.44	0.177
No	202	49.1	209	50.9	1.00			

Key:

% - Percentage of respondents

n - Total number of respondents

N - Number of respondents

P - Level of significance

CI - Confidence interval

ADR - Adverse drug reaction

OR - Odds ratio

4.0.2.5 Central Nervous System Adverse Drug Reactions experienced in relation to concurrent medical conditions and concomitant use of other medications among the respondents

Concomitant medical condition(s) and concurrent use of other medication(s) were significantly associated with the occurrence of CNS ADRs during treatment among the study respondents (Table 4.11). The presence of a concomitant medical condition was significantly associated with increased number of respondents experiencing ADRs (57.5%) compared to the absence of none (45.0%), (OR=1.65; 95% CI: 1.08 – 2.54; p=0.021). Concurrent use of other medication was also significantly associated with increased number of respondents experiencing ADRs (58.9%) compared to non-use of other medication (44.3%), (OR=1.80; 95% CI: 1.18 – 2.76; p=0.006).

Table 4.11: Central Nervous System Adverse Drug Reactions experienced in relation to concomitant medical conditions and concurrent use of other medications among the respondents

	ADRs present (n=204)		ADRs absent (n=216)			95% CI		
Variables	**N**	**%**	**N**	**%**	**OR**	**Lower**	**Upper**	**P value**
Presence of any concomitant medical condition(s)								
Present	69	57.5	51	42.5	1.65	1.08	2.54	**0.021***
Absent	135	45.0	165	55.0	1.00			
Concurrent use of other medication(s)								
Using	73	58.9	51	41.1	1.80	1.18	2.76	**0.006***
Not using	131	44.3	165	55.7	1.00			

***implies variables with significance**

Key:

% - Percentage of respondents

n - Total number of respondents

N - Number of respondents

P - Level of significance

ADR- Adverse drug reaction

CI - Confidence interval

OR - Odds ratio

4.0.3 Multivariate analysis

Multivariate analysis was performed to identify factors associated with the occurrence of CNS ADRs during treatment. Four factors that were associated with the occurrence of CNS ADRs during treatment at $p<0.05$ during bivariate analysis were considered together in a multivariate analysis. They included; (1) Gender, (2) BMI, (3) Presence of concomitant medical condition(s) and (4) Concurrent use of other medication(s) during Efavirenz treatment. Upon fitting the factors using Binary logistic regression and specifying *'backward conditional'* method with removal at $P<0.05$, two factors were retained in the final analysis (Table 4.12).

Adjusting for other factors, there was increased risk of occurrence of CNS ADRs among patients with BMI ranging between 18.5 – 24.99 kg/m^2 (normal) compared to those with BMI< 18.5 kg/m^2 (underweight) (AOR=2.02; 95% CI: 1.04 – 3.93; p=0.039). A patient with a BMI ranging between 18.5 – 24.99 kg/m^2 (normal) was 2.02 times more likely to experience a CNS ADR compared to one with a BMI<18.5 (underweight). Similarly, a BMI>24.99 kg/m^2 (overweight) was significantly associated with occurrence of a CNS ADR among the patients compared to BMI<18.5 (underweight) (AOR=2.48; 95% CI: 1.23 – 5.02; p=0.011). A patient with BMI> 24.99 kg/m^2 (overweight) was 2.48 times more likely to experience CNS ADRs compared to one with BMI<18.5 (underweight).

Concurrent use of other medication(s) during treatment was significantly associated with occurrence of CNS ADRs among the patients (AOR=1.74; 95% CI: 1.13 – 2.67; p=0.012). A patient on other medication(s) during treatment was 1.74 times more likely to experience a CNS ADR compared to one not on other medication.

Table 4.12: Factors associated with the occurrence of Central Nervous System Adverse Drug Reactions among the respondents at multivariate analysis

Variables	AOR	95% CI Lower	95% CI Upper	P value
Full model				
Patients gender				
Female	1.44	0.96	2.16	0.079
Male	1.00			
BMI				
Overweight (>24.99 kgs/m2)	2.32	1.14	4.71	**0.020***
Normal (18.5 - 24.99 kgs/m2)	2.04	1.05	3.97	**0.037***
Underweight (<18.50 kg/m2)	1.00			
Any concomitant medical condition(s)				
Present	0.63	0.16	2.55	0.522
Absent	1.00			
Concurrent use of other medication(s)				
Using	2.61	0.66	10.40	0.174
Not using	1.00			
Reduced model				
BMI				
Overweight (>24.99 kg/m2)	2.48	1.23	5.02	**0.011***
Normal (18.5 - 24.99 kg/m2)	2.02	1.04	3.93	**0.039***
Underweight (<18.50 kg/m2)	1.00			
Concurrent use of other medication(s)				
Using	1.74	1.13	2.67	**0.012***
Not using	1.00			

***implies variables with significance**

Key:

% - Percentage of respondents
P - Level of significance
CI - Confidence interval
AOR – Adjusted odds ratio
BMI – Body mass index
> - More than

< - Less than

4.1 Discussion

4.1.1 Prevalence of Central Nervous System Adverse Drug Reactions

The prevalence of CNS ADRs in the study was 48.6% which compared well with the prevalence obtained in other studies which gave a prevalence of 50%, Treisman and Kaplin (2002); Kenedi and Goforth (2011) which were carried out in the USA. In a cross-sectional comparative study performed at the outpatient HIV clinic of a university hospital in Spain, interviews were conducted from October 2002 through May 2003. Fifty four percent of he patients reported that they had at least 1 neuropsychiatric disorder within the 4 weeks before the visit, Fumaz *et al*., (2005).

4.1.2 Types of Central Nervous System Adverse Drug Reactions experienced

The total number of CNS ADRs reported was 8 and examples of the reported CNS ADRs included vertigo (dizziness) (25.5%), nightmares (13.6%), and somnolence (drowsiness) (9.5%). Insomnia accounted for 1% of the CNS ADRs experienced. Occurrence of other ADRs experienced during treatment accounted for less than 2.0%. The most commonly experienced adverse reaction amongst the respondents was dizziness accounting for 25.5% with the least reported adverse reaction being confusion and sleep talking. Out of the 420 respondents, 216 (51.4%) did not experience any adverse reaction while on treatment with Efavirenz. The results obtained in this study differed with those obtained in a cross-sectional study conducted as a retrospective review in Ethiopia on 403 patient medical records at the ART clinic of Jimma University Specialized Hospital to assess adverse effects associated with antiretroviral therapy. The central nervous system (CNS) side effects observed were nightmares (24.6%), dizziness (15.6%) and insomnia (20.5%) Teklay *et al*., (2013).

4.1.3 Efavirenz based regimens used by the respondents

Tenofovir/Lamivudine/Efavirenz was the Efavirenz based regimen that had the highest number of respondents in total experiencing a CNS ADR where 190 out of the 204 respondents in total (93.1%) who experienced a CNS ADR were on this regimen.

Zidovudine/Lamivudne/Efavirenz had 8 out of the 204 respondents (3.9%) that experienced a CNS ADR and Stavudine/Lamivudine/Efavirenz had 6 out of the 204 respondents (2.9%) that experienced a CNS ADR but none of these regimens was significantly associated with the occurrence of CNS ADRs during treatment among the respondents. Tenofovir/Lamivudine/Efavirenz had the highest number of respondents experiencing a CNS ADR secondary to the fact that it was the regimen most commonly used by the respondents but CNS ADRs experienced per Efavirenz regimen used indicated that Stavudine/ Lamivudine/Efavirenz had the highest number at 50 % followed by Tenofovir/Lamivudine/Efavirenz (49.1%) and Zidovudine/Lamivudine/Efavirenz (38%).

4.1.4 CD4 count in patient's experiencing Central Nervous System Adverse Drug Reactions

Analysis of the CD4 counts in the respondents who experienced a CNS ADR indicated that majority had their CD4 counts > 399 (23.6%), 200-299 (22.9%) and 300-399 (21.2%) cells/mm^3.This study did not establish any significant association between the patients CD4 count and the occurrence of CNS ADRs which compared well with results obtained from a retrospective cohort study carried out on 2650 patients followed up for 2456 person-years in Nigeria, Eluwa *et al*., (2012) on 'the incidence, type and risk factors of adverse drug reactions to antiretroviral therapy' which established that there was no significant association between CD4 cell count and development of an ADR. The strengths of the Nigerian study were that it involved a large study population together with the fact that it was conducted in three public hospitals.

4.1.5 Time to occurrence of the Central Nervous System Adverse Drug Reactions

The respondents in this study who experienced the CNS ADRs stated that they occurred within the 1st two weeks of initiation of treatment with an Efavirenz based regimen but the effects experienced were mild, resolved and the medication (Efavirenz based

regimen) use was continued. A small number of the respondents who experienced the CNS ADRs stated that they occurred when the medication was taken before a meal i.e. on an empty stomach and they therefore had to switch the timing of medication intake to after meals following which the severity of the adverse effects diminished. The duration to occurrence of the CNS ADRs compares well with the results in a study where 54% of patients in the EFV group and 27% in the PI group reported that they had at least 1 neuropsychiatric disorder within the 4 weeks before the visit, Fumaz *et al*., (2005). In the Teklay *et al*., (2013) study, the time occurrence of adverse effects, rash, hepatotoxicity, most GI, and CNS adverse effects occurred early after starting treatment at mean interval of 2 weeks. Lipodystrophy, anemia and peripheral neuropathy were among the long term adverse effects observed with mean time occurrence of 2, 1.6, and 0.5 years respectively. This is an indication that CNS ADRs occur earlier on during treatment compared to other ADRs like anaemia, lipodystrophy and peripheral neuropathy which occur later on during treatment. In the study carried out by Kappelholff *et al*. (2005), CNS and psychiatric events emerged more frequently during the first 6 weeks of treatment than after 6 weeks (45.7% vs 12.1%).

4.1.6 Demographic and socio-economic characteristics of the respondents

The results in this study indicated that a higher proportion of females (59.3%) took part compared to males (40.7%) secondary to the fact that the clinic has more female patients enrolled than males. Age of the respondents, marital status, employment status and number of children were not found to be significantly associated with the development of CNS ADRs amongst the respondents. Bivariate analysis indicated that gender, was significantly associated with the occurrence of CNS ADRs during treatment with an Efavirenz based regimen among the respondents with females being significantly associated with more cases of CNS ADRs (53.0%) compared to males (42.1%), ($p=0.028$).

However, upon carrying out multivariate analysis using binary logistic regression with removal at $P<0.05$, gender was not retained in the final analysis and thus was not found

to be significantly associated with the occurrence of CNS ADRs in adult patients taking Efavirenz based regimens. This differed with the results obtained in the study carried out by Spire *et al*., (2004) where patients remaining on Efavirenz for more than six months were compared with those who had stopped taking it. Of the 828 patients who completed the questionnaire 327 patients (23%) were women. Logistic regression showed that the factors independently associated with EFV discontinuation were female gender. The results in Spire *et al*., (2004) study compared well with that obtained in two other studies which indicated that female gender is a predictor of development certain ADRs like rash, Mazhude *et al*., (2002) and hepatotoxicity, Kappelholff *et al*., (2005) in patients using Nevirapine based regimens but unlike Nevirapine induced hepatotoxicity, female gender is not a predictor for the development of Efavirenz induced CNS ADRs.

4.1.7 Health status of the respondents

In this study tuberculosis was the most reported medical condition (33.1%) experienced prior to starting ARV medication followed by pneumonia (4.3%) and meningitis (2.6%) with other medical conditions accounting for less than 5.0%. A large number of respondents (61.9%) indicated that they did not experience any medical condition prior to starting the ARV's. Any medical condition experienced prior to starting ARV medication and CD4 counts and any were not found to be significantly associated with the development of CNS ADRs amongst the respondents.

Body mass index of the respondents was calculated by dividing their weight in kilograms by their height in meters squared. The results obtained in this study indicated that body mass index was significantly associated with occurrence of CNS ADRs during HIV treatment among the respondents following both bivariate and multivariate analysis. Normal BMI (p=0.029) was significantly associated with increased number of respondents experiencing ADRs (48.7%) compared to those having a BMI of underweight (31.3%). Similarly, a BMI of overweight (p = 0.007) was significantly

associated with increased number of respondents experiencing CNS ADRs (54.5%) compared to those having a BMI of underweight (31.3%). These results differed with those obtained in a study carried out at an outpatient HIV clinic university hospital in Switzerland on 130 patients which demonstrated that CNS side-effects were more frequent in patients with high drug levels and among the covariates tested to explain the pharmacokinetic variability of Efavirenz, neither sex, age or body mass index influenced Efavirenz plasma levels, Marzolini *et al*., (2001). More research needs to be carried out to establish the role of BMI in the development of CNS ADRs especially in patients with normal BMI and overweight BMI.

4.1.8 Socio-behavioral characteristics of the respondents

Analysis of socio-behavioral characteristics among the respondents revealed that a relatively small proportion (6.4%) used alcohol, 2.1% smoked cigarettes whereas none (0.0%) used narcotic drug(s). Neither alcohol use nor smoking was found to be significantly associated with the occurrence of CNS ADRs among the respondents. The validity of the responses given in regards to alcohol, smoking and narcotic drug intake may not have been a true picture because of the fear of victimization and thus establishing the actual number that had ever used or were using a narcotic drug was expected to be a challenge as any respondent using one would probably not be willing to disclose this information for personal reasons.

In a separate study, the results obtained noted that the use of alcohol and marijuana was high but no association was found between their use and the incidence of depression or treatment discontinuation. An observational cohort study carried out on 191 patients in Switzerland, Hirschel *et al*., (2002) which evaluated the short term incidence of adverse events and treatment interruptions of patients using EFV established that intravenous drug users had higher treatment discontinuation rates due to intolerance of side effects than non intravenous drug users (22.6 vs. 6.6%). Further studies need to be carried out in our setting to establish whether there is an association between intravenous drug use and development of CNS ADRs in HIV infected patients using Efavirenz based regimens.

4.1.9 Concomitant medical conditions and concurrent use of other medications

Analysis of concomitant medical conditions indicated that the most reported conditions were tuberculosis (17.9%), and hypertension (6.9%). Presence of other concomitant medical conditions accounted for less than 2.0%.The most reported medication(s) concurrently used were anti TB's (17.9%), and anti-hypertensive's (6.7%). Presence of concomitant medical conditions and concurrent use of other medication were significantly associated with the occurrence of a CNS ADR during treatment among the study respondents.57.5% with concomitant medical conditions experienced CNS ADRs compared to those that lacked any concomitant medical condition (45.0%) giving a p value of 0.021. Concurrent use of other medication(s) was also significantly associated with increased number of respondents experiencing ADRs (58.9%) compared to non use of other medication (44.3%) with a p value of 0.006.

CHAPTER FIVE

SUMMARY, CONCLUSIONS AND RECOMMENDATIONS

5.0 Summary

Multivariate analysis using binary logistic regression with removal at **P<0.05** retained two factors in the final analysis which were a BMI of normal and overweight and concurrent use of other medication. There was an increased risk for occurrence of a CNS ADR among patients with normal BMI (p=0.039) compared to those who were underweight. A patient with a normal BMI was 2.02 times more likely to experience a CNS ADR compared to an underweight patient. Similarly an overweight patient (p=0.011) was 2.48 times more likely to experience a CNS ADR compared to one who was underweight.

Concurrent use of other medication(s) during treatment was significantly (p=0.012) associated with the occurrence of CNS ADRs among patients. A patient on other medications during treatment was 1.74 times more likely to experience a CNS ADR compared to one not using any other medication. Concurrent tuberculosis was the only influential risk factor for development of ADRs identified by multivariate logistic regression according to a study carried out on 400 patients on 'Adverse drug reactions to antiretroviral therapy: an experience of spontaneous reporting and intensive monitoring from an ART centre in India' Modayil *et al*., (2010). Though the results in the study were not specific to CNS ADRs, they indicated that there was an association between having a concomitant medical condition and development of an ADR in patients using ARVs which could be further explained by drug-drug interactions.

5.1 Conclusions

1) Central Nervous System ADRs were prevalent amongst adult patients taking Efavirenz based regimens at Mbagathi District Hospital's CCC at 48.6 % with

dizziness being the most commonly reported ADR amongst the 8 reported adverse drug reactions.

2) TDF/3TC/EFV was the regimen with the most reported CNS ADRs.
3) The CD4 count range with the highest number of patients experiencing an ADR was between 200 and 299.
4) The CNS ADRs experienced by the respondents occurred within the 1st two weeks, were mild and medication use was continued.
5) Body mass index and concomitant use of other medication were the only two independent variables were found to be significant in the occurrence of CNS adverse drug reactions.
6) The alternate hypothesis 'Central Nervous System adverse drug reactions are experienced in adult patients taking Efavirenz based regimens at Mbagathi District Hospital's Comprehensive Care Centre' was thus true as CNS ADRs were found to be present amongst the respondents.

5.2 Recommendations

The clinicians should adopt the following in preventive measures for ADRs

1. Recognize high risk patients and start therapy at the lowest effective dose in susceptible patients.

2. Note variables influencing drug levels and know the patients drug-drug potential interactions as many patients who have HIV/AIDS also suffer from other chronic diseases e.g diabetes, asthma and hypertension.

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APPENDICES

Appendix 1: Recommended regimens for adults and adolescents

FIRST LINE REGIMEN	SECOND LINE REGIMEN
TDF + 3TC + EFV or NVP	AZT + 3TC + LPV/r or ATV/r*
AZT + 3TC + EFV or NVP	TDF + 3TC + LPV/r or ATV/r*
d4T + 3TC + EFV or NVP	TDF + 3TC + LPV/r or ATV/r*

Source: (MOH, 2011)

*ATV/r is a suitable substitute when LPV/r is not tolerated

Key:

AZT+3TC+EFVor NVP – Zidovudine + Lamivudine + Efavirenz or Nevirapine

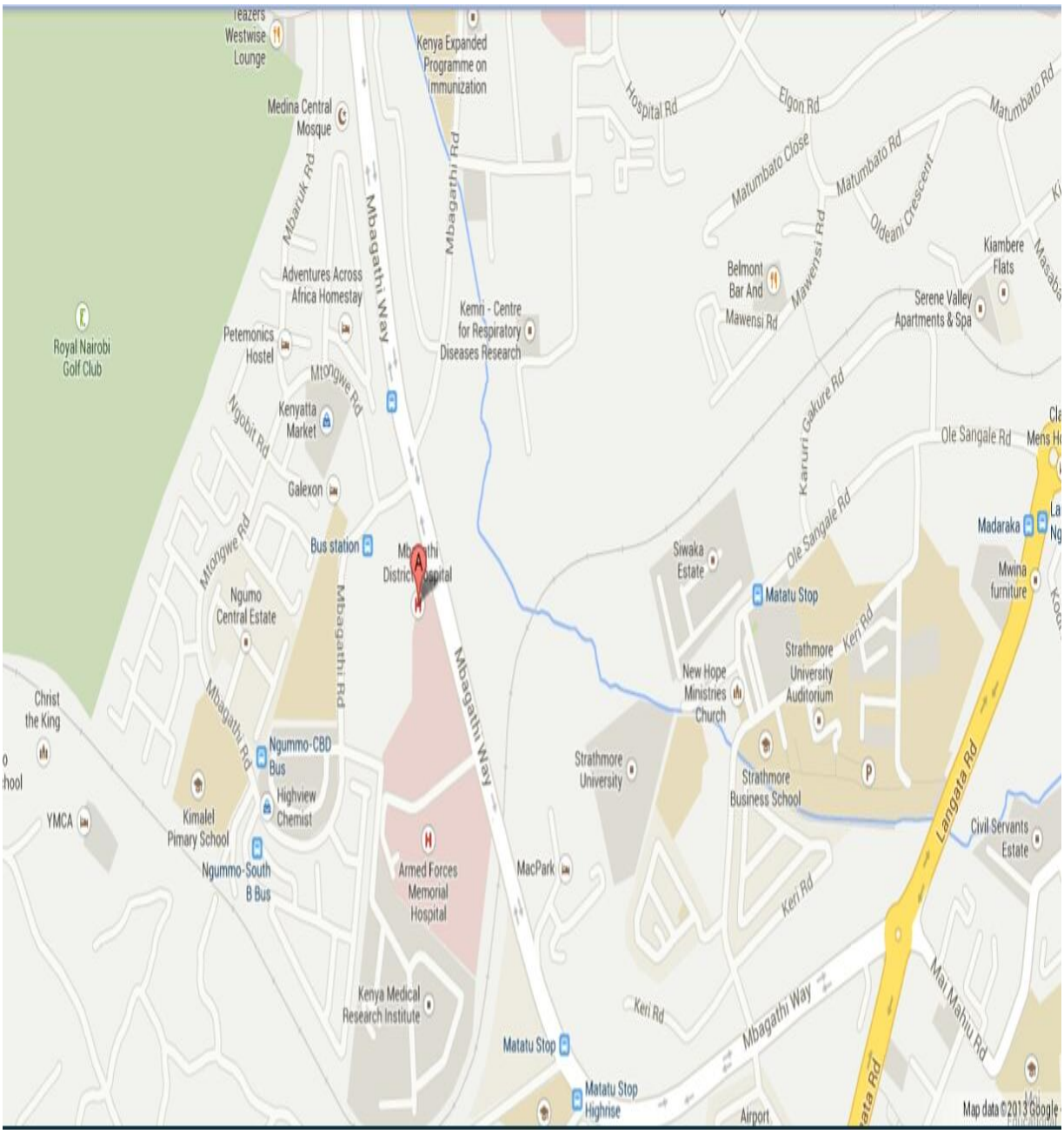
D4T+3TC+EFVor NVP – Stavudine + Lamivudine + Efavirenz or Nevirapine

TDF+3TC+EFVor NVP – Tenofovir + Lamivudine +Efavirenz or Nevirapine

AZT+3TC+LPV/r or ATV/r- Zidovudine + Lamivudine + Lopinavir/ritonavir or Atazanavir/ritonavir

TDF+3TC+LPV/r or ATV/r- Tenofovir + Lamivudine + Lopinavir/ritonavir or Atazanavir/ritonavir

Appendix 2: Map of Mbagathi District Hospital Location



Source: https://www.google.co.ke/maps

Appendix 3: Pharmacovigilance Adverse Drug Reaction reporting form

PV 1

MINISTRY OF HEALTH
THE PHARMACY AND POISONS BOARD
P. O. Box 27663-00506 NAIROBI
Tel: (020)-2716905 / 6 Ext 114 Fax: (020) 2713431/2713409.
Email: pv@pharmacyboardkenya.org

IN CONFIDENCE

☐ Initial Report
☐ Follow-up Report

SUSPECTED ADVERSE DRUG REACTION REPORTING FORM

NAME OF INSTITUTION: ..... **INSTITUTION CODE:** .....

ADDRESS: ..... **CONTACT:** .....

****

PATIENT'S NAME/ INITIALS: ..... **IP/OP. NO.:** ..... **D.O.B:** .....

PATIENT'S ADDRESS: ..... **WARD/CLINIC:** ..... **GENDER:** ☐ Male ☐ Female
(Name/Number)

ANY KNOWN ALLERGY: ☐ No ☐ Yes (specify) .....

PREGNANCY STATUS: ☐ Not Pregnant ☐ 1st Trimester ☐ 2nd Trimester ☐ 3rd Trimester

WEIGHT (kg): .....

HEIGHT (cm): .....

DIAGNOSIS: (What was the patient treated for)..... .....

BRIEF DESCRIPTION OF REACTION: ....

LIST OF *ALL* DRUGS USED IN THE LAST 3 MONTHS PRIOR TO REACTION (include OTC and herbals)[use rear side of this form for additional drugs]	DOSE	ROUTE AND FREQUENCY	DATE STARTED	DATE STOPPED	INDICATION	TICK (✓) SUSPECTED DRUG(S)
1						
2						
3						
4						
5						

SEVERITY OF THE REACTION: (Refer to scale overleaf)
☐ Mild
☐ Moderate
☐ Severe
☐ Fatal
☐ Unknown

ACTION TAKEN:
☐ Drug withdrawn
☐ Dose increased
☐ Dose reduced
☐ Dose not changed
☐ Unknown

OUTCOME:
☐ Recovering / resolving
☐ Recovered / resolved
☐ Requires or prolongs hospitalization
☐ Causes a congenital anomaly
☐ Requires intervention to prevent permanent damage
☐ Unknown

CAUSALITY OF REACTION: (Refer to scale overleaf)
☐ Certain
☐ Probable / Likely
☐ Possible
☐ Unlikely
☐ Conditional / Unclassified
☐ Unassessable / Unclassifiable

ANY OTHER COMMENT: ....

NAME OF PERSON REPORTING: ..... **DATE:** .....

E-MAIL ADDRESS: ..... **PHONE NO.** .....

DESIGNATION: ..... **SIGNATURE:** .....

You need not be certain ... just be suspicious !

Your support in this Pharmacovigilance program is appreciated.
Submission of a complaint does not constitute an admission that medical personnel or manufacturer or the product caused or contributed to the event.
Patient's identity is held in strict confidence and programme staff is not expected to and will not disclose reporter's identity in response to any public request.
Information supplied by you will contribute to the improvement of drug safety and therapy in Kenya. Once completed please send to:
The Pharmacy and Poisons Board on the above address

Appendix 3 continued

EXPLANATORY NOTES

CONFIDENTIALITY
All information collected in this form, identities of the reporter and patient, will remain confidential

WHAT TO REPORT
An Adverse Drug Reaction (ADR) is defined as a reaction that is noxious and unintended, and occurs at doses normally used in man for prophylaxis, diagnosis or treatment of a disease, or for modification of physiological function.

Report all suspected adverse experiences with medications,
especially those where the patient outcome is:

- Death
- Life-threatening (real risk of dying)
- Hospitalization (initial or prolonged)
- Disability (significant, persistent or permanent)
- Congenital anomaly
- Required intervention to prevent permanent impairment or damage

Report even if:

- You are not certain if the drug caused the reaction
- You do not have all the details

WHO CAN REPORT
All healthcare professionals (clinicians, dentists, nurses, pharmacists, physiotherapists, community health workers etc) are encouraged to report. Patients (or their next of kin) may also report.

WHAT HAPPENS TO THE SUBMITTED INFORMATION
All information submitted is handled in strict confidence. The Pharmacy and Poisons Board will assess causality and statistical analysis on each form. Data will periodically be used for review and suggest any interventions that may be required to the Ministry of Health. Data will also be submitted periodically to the Uppsala Monitoring Centre - the WHO Collaborating Center for International Drug Monitoring in Sweden.

SUBMISSION OF INITIAL OR FOLLOW-UP REPORTS
It is important to tick the appropriate box on the top-right corner of the front page to indicate whether the report is an initial (original) report or is a follow-up (subsequent) report.
It is very important that follow-up reports are identified and linked to the original report.

WHERE TO REPORT
After completing this form, please forward the same to your Pharmacy Department for onward submission, or mail directly, to:

THE PHARMACY AND POISONS BOARD
Lenana Road.
P. O. Box 27663-00506 NAIROBI
Tel: (020)-2716905 / 6 Ext 114 Fax: (020)-2713431/2713409
E-mail: pv@pharmacyboardkenya.org

Please use the space provided below for any further information. You may attach more pages to this form if required.

.....
.....
.....

LIST OF ALL DRUGS USED IN THE LAST 3 MONTHS PRIOR TO REACTION (include OTC and herbals)	DOSE	ROUTE AND FREQUENCY	DATE STARTED	DATE STOPPED	INDICATION	TICK (✓) SUSPECTED DRUG(S)
6						
7						
8						
9						
10						

Criteria for Assessment of Severity of an ADR

Mild	• The ADR requires no change in treatment with the suspected drug • The ADR requires that the suspected drug be withheld, discontinued or otherwise changed. No antidote or other treatment is required • No increase in length of stay.
Moderate	• The ADR requires that the suspected drug be withheld, discontinued or otherwise changed, and/or an antidote or other treatment is required. • Increases length of stay by at least one day • The ADR is the reason for admission.
Severe	• The ADR requires intensive medical care • The ADR causes permanent harm to the patient
Fatal	• The ADR either directly or indirectly leads to the death of the patient

WHO-UMC Causality Assessment Scale

Causality Term	Assessment
Certain	• Event of laboratory test abnormality, with plausible time relationship to drug intake • Cannot be explained by disease or other drugs • Response to withdrawal plausible (pharmacologically, pathologically) • Event definitive pharmacologically or phenomenologically *(i.e an objective and specific medical disorder or a recognized pharmacological phenomenon)* • Rechallenge satisfactory , if necessary.
Probable / Likely	• Event or laboratory tests abnormality, with reasonable time relationship to drug intake • Unlikely to be attributed to disease or other drugs • Response to withdrawal clinically reasonable • Rechallenge not required
Possible	• Event or laboratory tests abnormality, with reasonable time relationship to drug intake • Could also be explained by disease or other drugs • Information on drugs withdrawal lacking or unclear
Unlikely	• Event or laboratory tests abnormality, with a time to drug intake that makes a relationship improbable (but not impossible) • Disease or other drugs provide plausible explanations
Conditional/ Unclassified	• Event or laboratory test abnormality • More data for proper, assessment needed or • Additional data under examination
Unassessable/ unclassifiable	• Report suggesting an adverse reaction • Cannot be judged because of insufficient or contradictory information • Data cannot be supplemented or verified.

Your support in this Pharmacovigilance program is appreciated.
Submission of a report does not constitute an admission that medical personnel or manufacturer or the product caused or contributed to the event.
Patient's identity is held in strict confidence and programme staff is not expected to and will not disclose reporter's identity in response to any public request.
Information supplied by you will contribute to the improvement of drug safety and therapy in Kenya.
Once completed please send to: The Pharmacy and Poisons Board on the above address

Appendix 4: Questionnaire of patients on Efavirez based regimens

Date…….

A) Serial number……

B) Patients gender ……....

1) Male 2) Female

C) Age in years ……..

D) Marital status……

1) Married 2) Single 3) Separated 4) Divorced 5) Widowed

E) Employment status…….

1) Employed 2) Self employed 3) Unemployed

F) Number of children (parity)…….

G) Weight in kilograms ……..

H) Height in centimeters……..

I) Body Mass Index ……

J) Any medical condition experienced prior to starting ARV medication……..

1) None

2) Other (List) ……

K) Efavirenz based regimen taken……

1) TDF+3TC+EFV

2) AZT+3TC+EFV

3) D4T+3TC+EFV

L) Duration of treatment with Efavirenz in years ……..

1) <1 2) 1 – 3 3) 4 – 6 4) 7 – 9 5) > 10

Appendix 4 continued

M) Time of day when medication is taken ……

1) Morning 2) Night

N) Medication is taken before or after a meal ……

1) Before 2) After

O) Any Suspected CNS Adverse Drug reaction(s) experienced during treatment……..

1) None

2) Confusion

3) Insomnia

4) Somnolence (Drowsiness)

5) Impaired concentration

6) Vertigo (Dizziness)

7) Hallucinations

8) Psychosis

9) Other (List) …….

If yes,

Duration of treatment with Efavirenz in years when the reaction occurred……..

1) <1 2) 1 – 3 3) 4 – 6 4) 7 – 9 5) > 10

P) CD4 count in cells/mm³ ……

1) 0 -99 2) 100 – 199 3) 200 – 299 4) 300 – 399 5) > 400

Q) Alcohol intake history ……

1) Yes 2) No

Appendix 4 continued

R) Narcotic drug abuse history ……

1) Yes 2) No

S) Smoking history ……

1) Yes 2) No

T) Any concomitant medical condition(s)……..

1) None

2) Hypertension

3) Diabetes

4) Tuberculosis

5) Depression

6) Others (List)……..

U) Concurrent use of other medication(s)……

1) None

2) Antihypertensives

3) Hypoglycemics

4) Anti TB's

5) Others (List)……

Appendix 5: Informed Consent

TITLE: Assessment of the prevalence of central nervous system adverse reactions in adult patients taking Efavirenz based regimens in Mbagathi District Hospital's comprehensive care centre.

INVESTIGATORS AND THEIR AFFILIATIONS

CATHERINE AWINO WAMBURA

MPH student

ITROMID

INTRODUCTION

I am a master of Public health student who wants to undertake a study on the effects (if any) of the drug Efavirenz on adult patients taking Antiretrovirals.

The study is purely research based and your participation is voluntary.

PURPOSE

The research will be carried out to determine if the drug Efavirenz has had any effect on you or on your normal daily activities after intake.

PROCEDURES

The study will involve using data from selected files of patients on efavirenz based regimens between the period January 2002 and December 2012, the pharamcovigilance reporting form and the CCC pharmacy Management Sciences for Health dispensing tool. A short oral interview in the form of a questionnaire will be carried out by a registered clinical officer in patients whose files are selected. If you give your consent, you will be taken through the interview which will only take a few minutes of your time. The

Appendix 5 continued

collected data will then be compiled, coded and stored in a password protected computer system.

BENEFITS

The results from the study will be presented back to the clinic and used to improve the quality of services and patient care at the clinic.

RISKS

The study will not cause any risks to the study participants.

CONFIDENTIALITY

The study participant's identities will not be disclosed and the questionnaire will not contain the name or CCC number of any of the participants but instead a random serial number will be assigned to each questionnaire. The compiled data will be coded and kept in a password protected computer system.

CONTACT OF PRINICIPAL INVESTIGATOR

In case of any questions about the study you can contact me, **Catherine Wambura**

on the mobile number **0715272055**.

CONTACT OF KEMRI/ERC

In case of any questions about your rights of participation in this study you can get in touch with Kenya Medical Research Institute (KEMRI) Ethical Review Committee (ERC) using the following contacts;

Telephone number: 254 20 272 6781

Appendix 5 continued

Postal address : Box 54840-00200 Nairobi

Email address : erc@kemri.org

Website : www.kemri.org

Physical address : Kenya Medical Research Institute, off Mbagathi way Nairobi

COMPENSATION

The interviews will be carried out on the patient's scheduled appointment day and therefore transport reimbursements will not be made.

STORAGE OF COLLECTED DATA

The completed questionnaires will be kept in the CCC pharmacy in a cabinet only accessible to pharmacy staff. The compiled data from the questionnaires will then be coded and kept in a password protected computer system as it awaits analysis.

CONSENT AND SIGNATURE OPTIONS

I have been taken through the informed consent document and I hereby agree to voluntarily participate in the study.

Signature: .....

OR

Thumb print:.....

Appendix 6: Utafiti

MADA : Tathmini ya kubainisha kiwango cha madhara kwenye mishipa kuu ya mwili wa mtu mzima, baada ya kutumia madawa aina ya Efavirenz katika hospitali ya wilaya ya Mbagathi kwenye kituo cha kutoa huduma za kina kwa watu wanao ugua ugonjwa wa ukimwi.

MTAFITI

CATHERINE AWINO WAMBURA
Shahada ya Uzamili katika afya ya umma
ITROMID

DIBAJI

Mimi ni mwanafunzi anaye somea shahada ya uzamili katika afya ya umma na nina nuia kufanya utafiti kuhusu madhara yanayohusika na matumizi ya madawa ya Efavirenz yanayopatikana katika kundi la madawa ya ARVs, ambayo hutumiwa kuongeza kinga ya mwili dhidi ya kuongezeka kwa virusi vya Ukimwi mwilini. Somo hili ni kwa minajili ya utafiti pekee yake na kuhusika kwako ni kwa hiari yako tu.

LENGO LA UTAFITI

Utafiti huu unanuia kubainisha iwapo dawa aina ya Efavirenz huwa na madhara yeyote kwako wewe mtumiaji au katika shughuli zako za kila siku baada ya matumizi.

Appendix 6 continued

TARATIBU

Utafiti huu utawezeshwa kufanywa kwa kutumia takwimu zilizotolewa kwenye mafaili ya wagonjwa wanaotumia madawa ya aina ya Efavirenz kwa muda wa kipindi baina ya mwezi wa Januari 2002 na Disemba 2012, fomu za kuripotia umakini wa utumiaji wa madawa, na pia chombo cha kusimamia upeanaji wa madawa katika kliniki zinazotoa huduma za kina .Wale wagonjwa ambao faili zao zitachaguliwa, watafanyiwa mahojiano mafupi kwa njia ya dodosi na afisa wa kliniki. Ukipeana idhini, utafanyiwa mahojiano ambayo yatachukua muda wako mfupi. Takwimu zitakazokusanywa zitapewa nambari za kipekee, na kuhifadhiwa katika mfumo wa kompyuta uliyolindwa vilivyo.

FAIDA

Matokeo ya utafiti huu yatawasilishwa katika kliniki na yatatumiwa kuboresha huduma kwa wagonjwa kwenye kliniki.

HATARI

Utafiti huu hautazua hatari zozote kwa wote watakao shiriki katika mahojiano haya.

USIRI

Utambulisho wa washirika hautafichuliwa, na pia dodoso itakayotumiwa haitakua na majina ya washirika wowote, au nambari zao za kipekee, wanazopewa katika kliniki za kutoa huduma kina. Badala yake, nambari za mfululizo, ambazo hazitakua na mpangilio wowote wa kipekee, zitapewa kila dodoso/kidadisi. Takwimu zitakazokusanywa zitapewa nambari za kipekee na kuhifadhiwa katika mfumo wa kompyuta uliolindwa vilivyo.

Appendix 6 continued

ANWANI YA MAWASILIANO YA MTAFITI MKUU

Panapo ibuka maswali yoyote kuhusu utafiti huu, unaweza wasiliana nami, mtafiti mkuu, **Catherine Wambura** kwa kutumia nambari za simu rununu 0715272055.

AMWANI ZA KEMRI/ERC

Panapo ibuka maswali yoyote kuhusu haki zako kama mhusika katika utafiti huu, unaweza wasiliana na taasisi ya utafiti wa matibabu ya Kenya (KEMRI), kamati ya kutathmini maadili (Ethical Review Committee - ERC), kwa kutumia anwani zifuatazo;

Nambari za simu: **254 20 272 6781**
Anwani ya posta: Sanduku ya Barua **54840-00200 Nairobi**
Barua pepe: **erc@kemri.org**
Tovuti: **www.kemri.org**

Anwani maelezo: Kenya Medical Research Institute, kando ya barabara ya Mbagathi, Nairobi

FIDIA

Mahojiano yatafanywa siku ambayo mgonjwa anatarajiwa au alikua amepangiwa kukuja kliniki kama kawaida, na kwa hivyo, malipo ya nauli hayatazingatiwa au kufanywa.

KUHIFADHIWA KWA TAKWIMU ZILIZOKUSANYWA

Dodosi au vidadisi vilivyojazwa na kumalizwa vitawekwa kwenye droo inayopatikana katika jengo la hifadhi ya madawa ya kliniki, inayotoa huduma ya kina (CCC). Droo hii itaweza kufikiwa au kufunguliwa tu na mafamasia wanaofanya kazi katika jengo hilo la kuhifadhi madawa. Takwimu zilizokusanywa kwenye dodosi au vidadisi, vitapewa nambari au herufi spesheli, na kuhifadhiwa ndani ya kompyuta zilizolindwa na nenosiri au vitambulisho vya siri.

IDHINI NA SAHIHI

Nimeweza kufahamishwa yote yaliyomo kwenye hati hii ya idhini elezo, na nakubali kuhusika katika utafiti huu kwa hiari yangu.

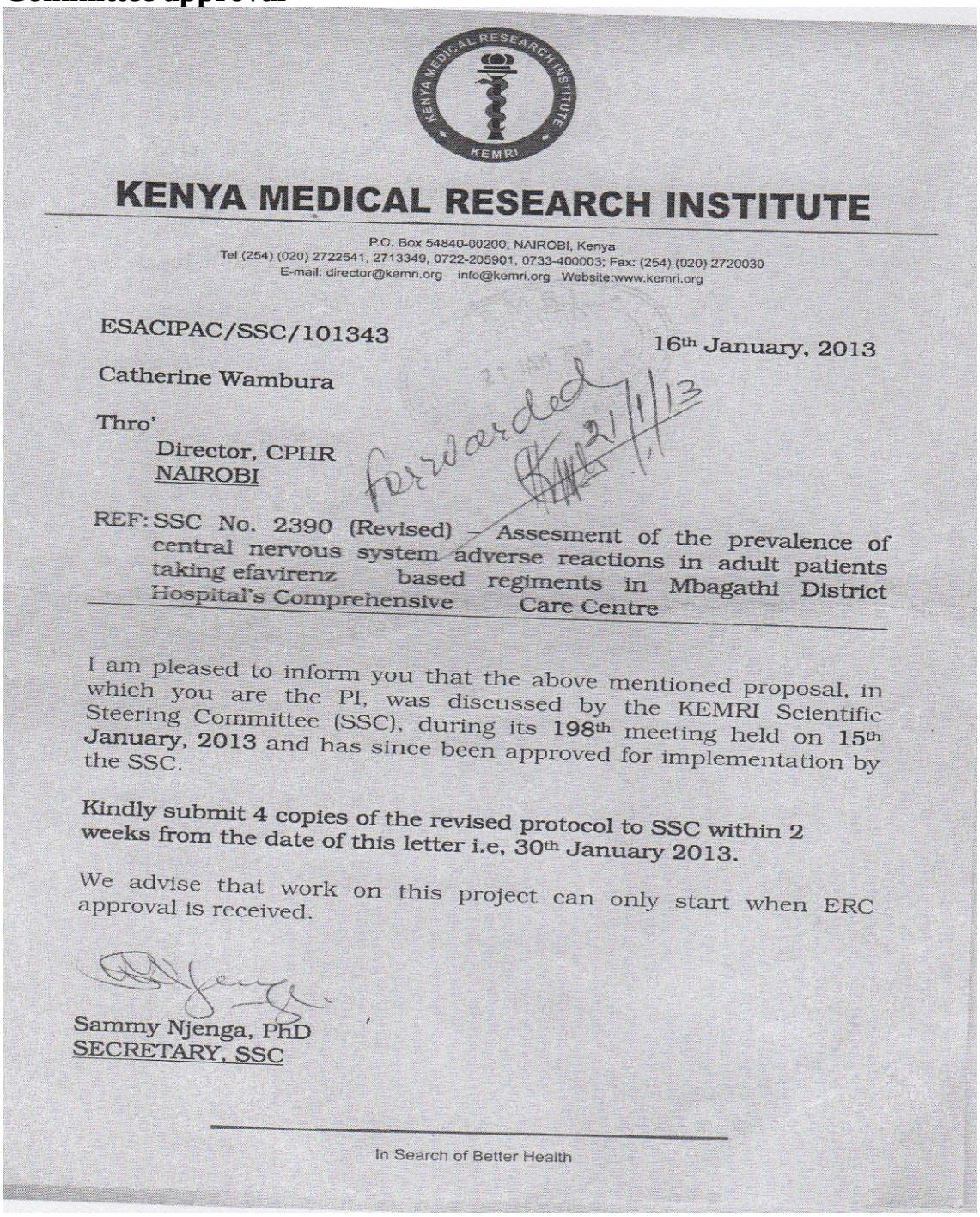
Sahihi: ……

AMA

Alama ya kidole gumba:

…….

Appendix7: Kenya Medical Research Institute Scientific Steering Committee approval



KENYA MEDICAL RESEARCH INSTITUTE

P.O. Box 54840-00200, NAIROBI, Kenya
Tel (254) (020) 2722541, 2713349, 0722-205901, 0733-400003; Fax: (254) (020) 2720030
E-mail: director@kemri.org info@kemri.org Website:www.kemri.org

ESACIPAC/SSC/101343

16th January, 2013

Catherine Wambura

Thro'
Director, CPHR
NAIROBI

forwarded 21/1/13

REF: SSC No. 2390 (Revised) – Assesment of the prevalence of central nervous system adverse reactions in adult patients taking efavirenz based regiments in Mbagathi District Hospital's Comprehensive Care Centre

I am pleased to inform you that the above mentioned proposal, in which you are the PI, was discussed by the KEMRI Scientific Steering Committee (SSC), during its 198th meeting held on 15th January, 2013 and has since been approved for implementation by the SSC.

Kindly submit 4 copies of the revised protocol to SSC within 2 weeks from the date of this letter i.e, 30th January 2013.

We advise that work on this project can only start when ERC approval is received.

Sammy Njenga, PhD
SECRETARY, SSC

In Search of Better Health

Appendix 8: Mbagathi District Hospital approval

MINISTRY OF MEDICAL SERVICES

Tel: 2724712, 2725791, 0721 311 808
Email: mdhnairobi@yahoo.co.uk
Our Ref.medsup/rsc/27/03/1-13

Mbagathi District Hospital
P.O. Box 20725- 00202
Nairobi

27th March 2013

Catherine Wambura
Jomo Kenyatta University of Agriculture and Technology
ITROMID
P. O. Box 54840-00200
Nairobi.

Dear Madam,

RE: RESEARCH AUTHORIZATION

This is in reference to your application for authority to carry out research on "Assessment of the prevalence of central nervous system adverse reactions in adult patients taking efavirenz based regimens in Mbagathi District Hospital's Comprehensive Care Centre".

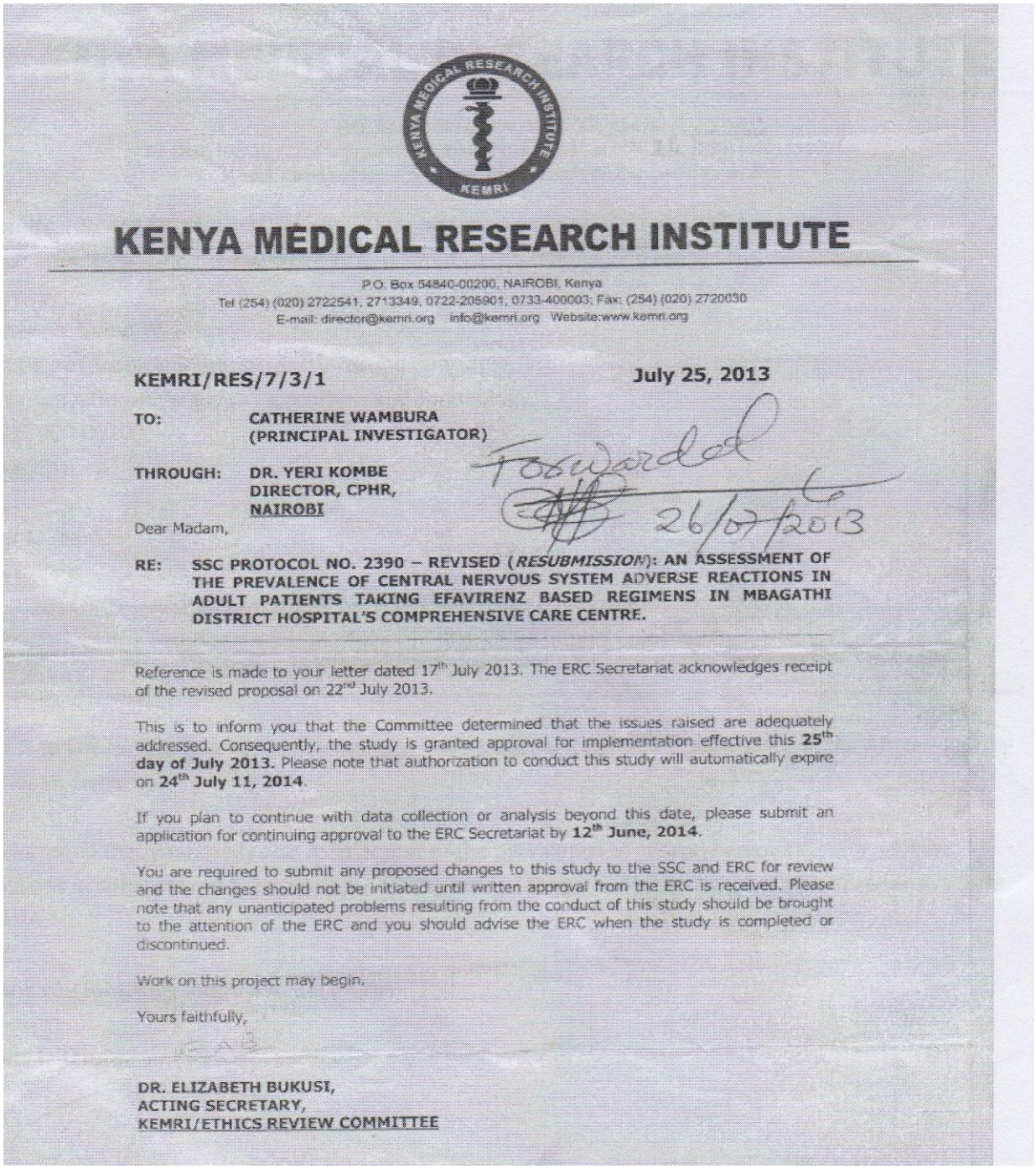
I am pleased to inform you that your request to undertake the research in the hospital has been granted.

On completion of the research you are expected to submit one hard copy and one soft copy of the research report / thesis to this office.

for **Hospital Research Committee**
Mbagathi District Hospital

MBAGATHI DISTRICT HOSPITAL
27 MAR 2013
P.O. BOX 20725

Appendix 9: Kenya Medical Research Institute Ethical Review Committee approval



KENYA MEDICAL RESEARCH INSTITUTE

P.O. Box 54840-00200, NAIROBI, Kenya
Tel (254) (020) 2722541, 2713349, 0722-205901, 0733-400003; Fax: (254) (020) 2720030
E-mail: director@kemri.org info@kemri.org Website:www.kemri.org

KEMRI/RES/7/3/1 **July 25, 2013**

TO: **CATHERINE WAMBURA**
(PRINCIPAL INVESTIGATOR)

THROUGH: **DR. YERI KOMBE**
DIRECTOR, CPHR,
NAIROBI

Forwarded
26/07/2013

Dear Madam,

RE: **SSC PROTOCOL NO. 2390 – REVISED (*RESUBMISSION*): AN ASSESSMENT OF THE PREVALENCE OF CENTRAL NERVOUS SYSTEM ADVERSE REACTIONS IN ADULT PATIENTS TAKING EFAVIRENZ BASED REGIMENS IN MBAGATHI DISTRICT HOSPITAL'S COMPREHENSIVE CARE CENTRE.**

Reference is made to your letter dated 17th July 2013. The ERC Secretariat acknowledges receipt of the revised proposal on 22nd July 2013.

This is to inform you that the Committee determined that the issues raised are adequately addressed. Consequently, the study is granted approval for implementation effective this **25th day of July 2013.** Please note that authorization to conduct this study will automatically expire on **24th July 11, 2014**.

If you plan to continue with data collection or analysis beyond this date, please submit an application for continuing approval to the ERC Secretariat by **12th June, 2014**.

You are required to submit any proposed changes to this study to the SSC and ERC for review and the changes should not be initiated until written approval from the ERC is received. Please note that any unanticipated problems resulting from the conduct of this study should be brought to the attention of the ERC and you should advise the ERC when the study is completed or discontinued.

Work on this project may begin.

Yours faithfully,

DR. ELIZABETH BUKUSI,
ACTING SECRETARY,
KEMRI/ETHICS REVIEW COMMITTEE