ANALYSIS OF INDIVIDUAL CASE SAFETY REPORTS ON ADVERSE DRUG REACTIONS TO ANTIRETROVIRAL THERAPY FROM THE SPONTANEOUS REPORTING DATABASE IN KENYA

BY

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DEDICATION

I dedicate this work to my loving husband, Hillary for his love, encouragement and support during my studies and also to my mother, Mrs.StellaLubanga for being the pillar of success throughout my life.

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ABBREVIATIONS AND ACRONYMS

3TC	Lamivudine
ABC	Abacavir
ADR	Adverse drug reaction
AIDS	Acquired immune deficiency syndrome
ART	Antiretroviral therapy
ARV	Antiretroviral drugs
ATZ	Atazanavir
AZT	Zidovudine
CD4	T-lymphocyte cell bearing CD4 receptor
D4T	Stavudine
ddI	Didanosine
DNA	Deoxyribonucleic acid
EFV	Efavirenz
ENF	Enfurvitide
FTC	Emtricitabine
HIV	Human immunodeficiency virus
ICSRs	Individual case safety reports
KNH	Kenyatta National Hospital
LPV/r	Lopinavir/ritonavir
MSH	Management Sciences for Health
NASCOP	National AIDS and STI Control Programme
NNRTI	Non-nucleoside reverse-transcriptase inhibitor
NRTIs	Nucleoside reverse transcriptase inhibitors
NVP	Nevirapine

PIs	Protease inhibitors
PPB	Pharmacy and Poisons Board
PV-ERS	Pharmacovigilance Electronic Reporting System
RAL	Raltegravir
RNA	Ribonucleic acid
RTV	Ritonavir
SIV	Simian immunodeficiency virus
SJS	Stevens-Johnson syndrome
TDF	Tenofovir
TEN	Toxic epidermal necrolysis
UNAIDS	Joint United Nations Programme on HIV/AIDS
UON	University of Nairobi
USAID	United States Agency for International Development
WHO	World Health Organization

ABSTRACT

Introduction: There were 35 million people living with Human immunodeficiency virus (HIV) in the World at the end of 2013. Kenya's estimated HIV prevalence is 6% among people aged 15-49 years.There are 41.7% of adults on antiretroviral drugs (ARVs). Despite these drugs reducing morbidity and mortality, they have also resulted in adverse drug reactions (ADRs) which have affected patients' adherence. Some of the documented reactions include hepatoxicity, mitochondrial toxicity, peripheral neuropathy, hypersensititvity reactions, anaemia andlipodystrophy syndrome among others.

The Pharmacy and Poisons Board (PPB) in Kenya established a pharmacovigilance system in 2004 where adverse reactions spontaneously reported by health professionals are monitored. The individual case safety reports (ICSRs) generated from these cases arethen forwarded by PPB to the World Health Organization Collaborating Centre for International Drug Monitoring, Uppsala for detection of safety signals.

Objective: The objective of the study was to analyse the individual case safety reports for severity, outcomes and risk factors associated with adverse drug reactions (ADRs)due to antiretroviral therapy (ART)from the spontaneous reporting database in Kenya from January 2014 to December 2014.

Methodology: The study was a retrospective cross-sectional survey thatanalyzed 850 ICSRs on ART-related ADRs reported between January 2014 and December 2014 from the National Pharmacovigilance System at the PPB in Kenya. Data was collected and 729 ICSRs that were included in the study were analysed using IBM SPSS statistics version 21 software.

Results: There were more females (63.4%) reporting ADRs compared to the males (35.0%). The mean age of the cases was 40 (SD $\pm$ 14) years. Majority of the reported ADRs were associated with the integumentary system (62.6%) with lipodystrophyaccounting for 42.1% as the most commonly reported ADR. Stavudinewas suspected to cause most of the ADRs and was reported in 44.7% of all the cases. Most of the suspected ADRs reported were mild (44.4%) and moderate (40.0%) with 85.5% of the cases having the offending drug withdrawn. Complete recovery was reported in 11.9% of the cases. Age and sex were reported to be associated with specific ADRs while having allergies and Stevens Johnson Syndrome (SJS) were found to be independent predictors of severity. Older age and having more than one ADR was found to increase the risk of having an undesirable outcome or no recovery.

Conclusion: This study found that most of the patients were on stavudine (D4T) based regimens. This may explain why lipodystrophy, was the most commonly reported ADRs as it has been associated with D4T-based regimens. Concomitant cotrimoxazole was found to be an independent predictor of skin rashes and SJS. The findings in this study emphasize the need for close monitoring and follow up of all patients especially children and the elderly on ART and concomitant cotrimoxazole.

CHAPTER ONE

INTRODUCTION

1.1 Prevalence of HIV in the World

There were 35 million people living with Human immunodeficiency virus (HIV) in the World at the end of 2013 (1). Sub-Saharan Africa accounted for 71% of the HIV epidemic in the world with 24.7 million people living with HIV(1).

The National HIV and AIDS working group estimated the HIV prevalence in Kenya to be 6% among people aged 15-49 years(2). Besides, the estimated HIV prevalence was as high as 25.7% in Homabay County and as low as 0.2% in Wajir County with 65% of new infections nationally being contributed by nine out of the forty seven counties(2).

1.2 Access to antiretroviral therapy

There were 12.9 million people receiving antiretroviral therapy in the World at the end of 2013. This is estimated to haveaverted 7.6 million deaths globally and 4.8 million deaths in Sub-Saharan Africa(1).Currently, 41.7% of the adult population living with HIV in Kenya are onantiretroviraldrugs (ARVs). This has led to a decrease in Acquired immune deficiency syndrome (AIDS) related deaths by 60% between 2005 and 2013(2).

1.3 Management of HIV

Antiretroviral therapy (ART) is used in the prevention and treatment of people infected or at risk of being infected with the HIV. They reduce the viral load and rate of viral mutation. Management of the HIV infection requires a prolonged period of follow-up and monitoring of the HIV infected individuals on antiretroviral drugs (ARVs). Antiretroviral therapy

consistsof various combinations of at least three ARV drugs from more than one class.There are 5 classes of ARV drugs including nucleoside reverse transcriptase inhibitors (NRTIs) which prematurely terminate DNA chainformation as the enzyme reverse transcriptase copies viral RNA into DNA. Drugs in this class arezidovudine (AZT), didanosine (ddI), lamivudine (3TC), abacavir (ABC), tenofovir (TDF) and emtricitabine (FTC).Non-nucleoside reverse transcriptase inhibitors (NNRTIs) inhibit reverse transcriptase enzyme terminating the formation of viral DNA from viral RNA. They includenevirapine (NVP) and efavirenz (EFV).Protease inhibitors(PIs) inhibit the protease enzyme preventing the formation of viral proteins. Examples of drugs in this class are lopinavir/ritonavir(LPV/r), ritonavir (RTV) and atazanavir(ATZ).Entry inhibitors prevent entry of HIV into the host cell. Drugs include the fusion inhibitor enfurvitide (ENF) and the CCR5 antagonist maraviroc.HIV integrase inhibitors block integrase enzyme preventing the incorporation of the viral DNA into the host cell DNA. They areraltegravir (RAL) and elvitegravir.

Despite positive outcomes such as reduction in morbidity and mortality, ARVs have been known to cause adverse drug reactions (ADRs). These ADRs may interfere with adherence to ART which may result in poor treatment outcomes in patientsincluding resistance (3,4)

1.4 Adverse reactions associated with antiretroviral therapy

The adverse reactions associated with the various ARVs are generally class-based. Those that associated with NRTIs include peripheral neuropathy, lipodystrophy, pancreatitis, hepatitis, hypersensitivity, lactic acidosis, dyslipidemia, anaemia and renal toxicity. The ADRs associated with NNRTIs include Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), fever, severe nausea, neuropsychiatricchanges (depression and confusion), hepatotoxicity, hyperlipidaemia, gynaecomastia.The major adverse reactions associated with PIs include lipodystrophy, hyperglycemia, gastrointestinal intolerance, nausea, vomiting,

diarrhoea, hyperlipidaemia, elevated serum transaminases, possible increased bleedingepisodes in patients withhaemophilia, PR interval prolongation and QT interval prolongation and torsades pointes(5,6).

The WHO/Forum for Collaborative Research Joint Meeting held in Geneva Switzerland 2008 identified the most common ARV-related ADRs in Southeast Asia, South America and Africa in 40 publications from 1999-2007. The most predominant adverse reactions reported in South America were gastrointestinal, haematologic toxicities and neuropathy. In Southeast Asia they were lipodystrophy, rash and hepatitis and in Africa they were neuropathy, neutropenia and lipodystrophy(7).A study in Ghana, found that anaemia and diarrhoea were the most common ADRs reported (8).The commonest ADRs reported in Nigeria were pain (30%) and skin rash (18%)(9). In comparison, the most frequently reported ADRs in Ethiopia were rash (30%), nausea (28%) and nightmares (24.6%) (10).A study in Uganda reported that peripheral neuropathy occurred in 36% of the patients followed by rash (6%) and hypersensitivity reactions (2%) (11). In Tanzania, a study reported that the most reported ADRs were anaemia, hepatoxicity, skin rash and peripheral neuropathy (12). A study in Kenya reported that 11.3% of the study participants developed peripheral neuropathy (13). Adverse drug reactions associated with ART may lead to problems with adherence, switching of regimens and discontinuation of therapy(9,11–18).Therefore, there is need to closely monitor patients on ART in a process known as pharmacovigilance.

1.5 Spontaneous reporting

It is a method that involves monitoring of suspected adverse drug reactions where individual case safety reports are voluntarily submitted from health professionals and pharmaceutical manufacturers to the national regulatory authority(22). These spontaneous reports can be used for the identification and evaluation of information on possible causal relationship

between an unknown adverse event and a drug, also known as a safety signal. Signals may result in various regulatory actions. The regulatory actions may involve product withdrawal or removal from the market.In Kenya, Pharmacy and Poisons Board (PPB) and National AIDS and STI Control Programme (NASCOP) have sentinel sites where adverse reactions due to ART are reported by health professionals to the PPB. These reports are submitted both electronically and manually using the yellow form.

1.6Problem statement

The management of HIV infected persons in Kenya follows set treatment guidelines but patients, including pregnant women, children, those with various comorbitiesare still susceptible to adverse drug reactions.Efforts have been made towards monitoring of these adverse effects all over the world to ensure patient safety while maximizing on patient access to ART.

In Kenya, therehave been significant safety concerns raised about serious ADRs with both short term and long term effects.There is also insufficient nationwide documentation on severity, outcomes and risks associated with these adverse drug reactions since studies on the same have not been carried out on the National pharmacovigilance database.

There is therefore need to analyse thisdata to determine the burden of ADRs associated with antiretroviral drugs in order to improve the management of patients on ART, while maximizing clinical benefits and ensuring their safety.

1.7 Research question

What factors are associated with the occurrence, severity and outcomes of ADRs to ART from the spontaneous database in Kenya from January 2014 to December 2014?

1.8Objectives

General objective

To analyse the individual case safety reports for severity, outcomes and risk factors associated with ADRs due to ART from the spontaneous reporting database in Kenya from January 2014 to December 2014.

Specific objectives

1. To describethe severity of the adverse drug reactions associated with ART in Kenya.
2. To determine the outcome of adverse drug reactions attributed to ART in Kenya.
3. To identify the risk factors associated with severity and outcomes of ART related ADRs in Kenya.

CHAPTER TWO

LITERATURE REVIEW

2.1 Adverse reactions associated with ART

2.1.1 Peripheral neuropathy

This is the most frequent occurring toxicity in patients receiving ART. It presents as pain, numbness and burning sensation in the feet. It occurs in the majority of patients receiving NRTIs. Studies conducted in Malawi and Cameroonfound that the most common ADRamong patients who received nevirapinewas peripheral neuropathy with a prevalence of 56% and 28.5% respectively(20,21). Similar studies conducted in Kenya and Uganda observed that 20.7% and 36% developed peripheral neuropathy during the study period (12,22). There are factors that contribute to development of peripheral neuropathy in these patients. They include low CD4 cell count (<100 cells/mm^3), a prior history of an AIDS defining illness or neoplasm, a history of peripheral neuropathy, use of neurotoxic agents such as high alcohol consumption and nutritional deficiencies such as low serum hydroxocobalamin levels(25).

2.1.2 Lipodystrophy syndrome

Lipodystophy occurs as a result of altered subcutaneous fat distribution on the limbs and face. There is a significant increase in build upof fat around the abdominal area, under the skin (lipoma), in the breasts and on the back of the neck and shoulders(buffalo hump).Lipodystrophy syndrome occurs when triglycerides blood levels are elevated upto 8-9 times the normal. Cholesterol levels are also elevated. The PIs and NRTIs are known to cause these metabolic effects resulting in enhanced morbidity and mortality from atherosclerosis(26).Post marketing adverse events reported to the Food and Drug

Administration (FDA) associated abnormal fat distribution with protease inhibitors (17). A study conducted in India observed that 14.5 percent of patients developed lipodystrophy(27).In Canada, another study reported that 50 percent of the study participants in the HIV/AIDS treatment database developed lipodystrophy(28).

2.1.3 Anaemia

Anaemia is a common occurrence particularly in individuals with advanced HIV disease. This can be aggravated by AZT treatment within few weeks of therapy which is associated with myelosuppression and an increased risk of developing anaemia. Other risk factors include low CD4 cell count, pre-existing anaemia and increased treatment duration (29–32). Studies conducted in Ethiopia and Cameroon reported that anaemia occurred in 4.8% and 3.8% of the study participants respectively (21,31). A cohort study of HIV-infected adults in Côte d'Ivoire reported an incidence of neutropenia, anaemia and thrombocytopenia within the first six months of taking AZT and cotrimoxazole(34).

2.1.4 Hypersensitivity

A hypersensitivity reaction is an undesirable immune-mediated response to a foreign agent. It may be drug induced presenting with symptoms such as fever, skin rash, fatigue, nausea, vomiting, diarrhoea, or cough. Hypersensitivity reactions have been observed with abacavir. Non-nucleoside reverse transcriptase inhibitors also cause hypersensitivity reactions although less frequently. Some PIs may cause skin rashes. Abacavir hypersensitivity reactions may occur in less than 5% of all patients within the first six weeks of therapy (35–38). Severe skin rashes have been found to occur in 7.3% of patients on nevirapine within the first four weeks of treatment. This includes patients who develop SJS (less than 10% skin detachment) and toxic epidermal necrolysis (more than 30% skin detachment) (39).

2.1.5 Hepatotoxicity

Hepatotoxicity is characterised by elevations in liver enzymes in serum. Risk factors include Hepatitis B and/or Hepatitis C virus co-infection (increases risk upto 10-25%), old age, alcohol use, cirrhosis, substance abuse and other hepatotoxic medications such as anti-tuberculosis therapy. Mechanisms of ART-related heptotoxicity with NRTI are mainly mitochondrial toxicity and hypersensitivity reactions.The NNRTIs, particularly nevirapine are associated with hypersensitivity and direct drug–related toxicity. However PIs have been shown to have minimal liver toxicity of between 1-9.5% (40). A study in Spain reported that hepatotoxicity developed in 12.5% of the patients on nevirapine(41). A multicenter study conducted in Netherlands and Belguim on patients on PIs reported that 9% developed liver enzyme elevation within 48 weeks of follow up (42).

2.1.6 Central nervous effects

Efavirenz is known to cause adverse effects on the central nervous system. In controlled trials, 53% of patients reported central nervous system symptoms compared to 25% who received control regimens. These symptoms included dizziness (28.1%), insomnia (16.3%), impaired concentration (8.3%), somnolence (7.0%), abnormal dreams (6.2%), severe depression(2.4%) and hallucinations (1.2%). These symptoms were severe in 2% of patients, and as a result, 2.1% of patients discontinued therapy (43).These symptoms usually begin during the first or second day of therapy and generally resolve after the first 2-4 weeks of therapy(5). In contrast, another study in Cameroon reported that 9.9% of patients experienced headaches, dizziness, tinnitus and insomnia (24).A similar study in India found that 32.3% of those who received efavirenz, developed central nervous system symptoms in form of insomnia, dizziness and nightmares (44).

2.1.7 Gastrointestinal adverse effects

Several studies have reported that the most frequently observed ADRs were gastrointestinal complaints, mainly diarrhoea, vomiting and abdominal complaints. These effects were reported in patients on PIs, nevirapine and abacavir containing regimens(21,36,43,44).

A prospective cohort study conducted in Kenya reported that 21% of children on ART developed gastrointestinal effects including nausea and vomiting. These symptoms subsided in 79% of the children after one month of therapy (32).

2.1.8 Nephrotoxicity

ART-induced kidney injury may result in acute and chronic kidney disease.Many studies have reported tenofovirto be the most common cause of acute tubular toxicity(43,45–47). Among protease inhibitors, indinavirhas also been shown to cause crystal deposition in the kidney that may result in renal failure(50). The NRTIs such as abacavir and didanosinerarely cause nephropathy although there have been a few cases reported (49,50).

2.2 Origin of Pharmacovigilance

Pharmacovigilance is the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug related problem(53). The International Drug Monitoring Programme came into being in 1968 after the 16th World Health Assembly adopted a resolution (WHA 16.36).This resolution was the first step in emphasizing the need for early action in immediate dissemination of information on ADRs to medicines. This move came after the thalidomide disaster in 1961. Mothers who had taken thalidomide for morning sickness during pregnancy gave birth to babies without limbs(54). In Kenya, thalidomide was banned in 1960's (Gazette no. L. N. 36/1963).

The World Health Organization (WHO) programme consists of the WHO Collaborating Centre for International Drug Monitoring, Uppsala and the Pharmacovigilance department of WHO, Geneva. It mainly coordinates 118 National Pharmacovigilance Centres in the World.The World Global individual case safety reports database, VigiBase at the Uppsala Monitoring Centre (UMC) contains 10 million adverse drug reaction reports from around the world.Recently, the Uppsala Monitoring Centre have launched vigiRank, a novel method for screening ICSRsin databases for new safety signals with minimal false leads(55).

2.3 The National Pharmacovigilance System of Kenya

The Division of Medicine Information and Pharmacovigilance within the PPBbegan monitoring and reporting ADRs in 2004.It was accredited by the Ministry of Health to be the National Pharmacovigilance Centre. The National Pharmacovigilance System was later officially launched on June 9, 2009.The PPB together with other stakeholders then developed guidelines for the National Pharmacovigilance System in Kenya in 2009. This was to assist health professionals to participate in continuous surveillance of safety and efficacy of all pharmaceutical products used in Kenya(56).Kenya was later awarded the 98th full membership to the WHO Programme for International Drug Monitoring on 4th May 2010(57).

A new digital system was launched by PPB on April 23, 2013 with financial and technical support from Management Sciences for Health (MSH) and United States Agency for International Development (USAID). This system ensures that adverse reaction reports are enteredinto the pharmacovigilance data management system, VigiFlow through an application that can be downloaded on a smart phone or a computer(58).The individual case safety reports (ICSRs)arising from ADRs are voluntarily submitted by health professionals and pharmaceutical manufacturers to the national regulatory authority, PPB. These ADRs

are reported both manually and electronically using the yellow forms for suspected ADRs. This information is then transmitted directly by PPB to the UMC via the VigiBase.

2.4 Pharmacovigilance of antiretroviral drugs

The ARVs have been proven to reduce morbidity and mortality. They are used as a combination of drugs sometimes resulting in immediate and delayed toxicities. This is what informs decisions on treatment choices and switching of drug regimens when need arises. These adverse drug reactions have greatly affected patient adherence to ART, resulting in opportunistic complications and HIV drug resistance.

World Health Organization defines adverse drug reaction as a response which is noxious and unintended, and which occurs at doses normally used in humans for the prophylaxis, diagnosis, or therapy of disease, or modification of physiological function(59).Studies have been conductedin different countries to establish an estimated incidence of ADRs caused by ART as demonstrated in Table 1.1.The PPB reported that the majority of the spontaneously reported ADRs from 2010 to 2014 were ARVs related. They contributed to 85 percent of all ADR reports submitted to the Uppsala database since PV reporting started in 2010 (60). There is a challenge in developing countries because of a high prevalence of comorbid conditions such as tuberculosis, anaemia, malnutrition, concomitant alternative medicines and frequent initial presentation with advanced HIV disease(61).It is therefore very important to monitor the ART as this may affect patient adherence leading to treatment failure.

Table 1.1: Estimated incidence of ADR based on reports submitted per country(8,24,11,27,62)

Country	ADR (%)
Cameroon	19.5
Ghana	9.4
India	71.1
Kenya	65
Uganda	40

2.4.1 Gender differences in antiretroviral therapy-related adverse reactions

There have been no known mechanisms to explain the differences in adverse reactions to antiretroviral drugs. It is postulated that factors such as hormonal changes in women at puberty, during menstrual cycles, and at menopause and their effect on the metabolism of drugs may play a major role. Other factors include the gender differences in fat composition and its effect on drug distribution as well as genetics in relation to drug metabolizing enzymes(63).A study in Kenya reported that HIV infected women were ten times more likely than men to develop peripheral neuropathy within the first year of ART (13).

2.5Justification of the study

There is no study that has been carried out on the National pharmacovigilance database at PPB to determine the burden of ART-related ADRs and the gaps in the reporting system. There is therefore need to study and document this information to facilitate development of measures targeted to minimize the potential negative impact of ART-related ADRs in Kenya and also improve the quality of reporting.

CHAPTER THREE

METHODOLOGY

3.1 Study design

The study design wasa retrospective cross-sectional surveyanalyzingapproximately 850 ICSRs on ART-related ADRs reported between January 2014 and December 2014 from the spontaneous reporting system in Kenya.

3.2 Study site

The study was carried out at the PPB, located on Lenana Road, Nairobi. Pharmacy and Poisons Board is the Drug Regulatory Authority which was established in 1957 under the Pharmacy and Poisons Act, Chapter 244 of the Laws of Kenya.Adverse drug reactions are reported by health professionals using the suspected adverse drug reaction reporting form (PV 1-the yellow form) and the Pharmacovigilance Electronic Reporting System (PV-ERS). The filled forms are sent to PPB and then forwarded to WHO Uppsala Monitoring Centre through VigiBase, the WHO global ICSR database.All ICSRs on patients who were on ART from January 2014 to December 2014 were included in this study.

3.3 Study population

The target population for this studycomprised of all the cases who received ART and were captured by ICSRs in the database from January 2014 to December 2014 in Kenya.

Inclusion criteria and exclusion criteria

The ICSRsincluded in this studywereof all cases who were HIV infected and on ART and those on post exposure prophylaxis. Only complete ICSRs were included in the study.

3.4 Sample size determination and sampling technique

The sample size for the study was 850 ICSRs on ADRs attributed to antiretroviral drugs submitted spontaneously to PPB between January 2014 and December 2014. This sample size was used because very large sample sizes are required to detect rare ADRs. Therefore, the universal sampling method was used, whereby all cases available during the study period were sampled. Those reports which met the inclusion criteria were selected and analysed.

3.5 Data collection procedures and instruments

A pre-designed modified data collection form (Appendix 1) adapted from the suspected adverse drug reaction reporting form (yellow form) was used to collect data. The information on patients' demographics, ADR description, suspected drug details, concomitant medicines, severity of the reaction, outcome of the reaction and the qualification of the reporter was collected. Data was abstracted retrospectively from both computerized and filed manual ADR reports. A confidentiality agreement form (Appendix 7) was signed between the researcher and PPB before data collection. An authorizing officer's electronic password was used to retrieve the reports from the electronic database. The manual ADR reports were re-filed back after data collection.Therefore, reports retrieved from the database remained at PPB.

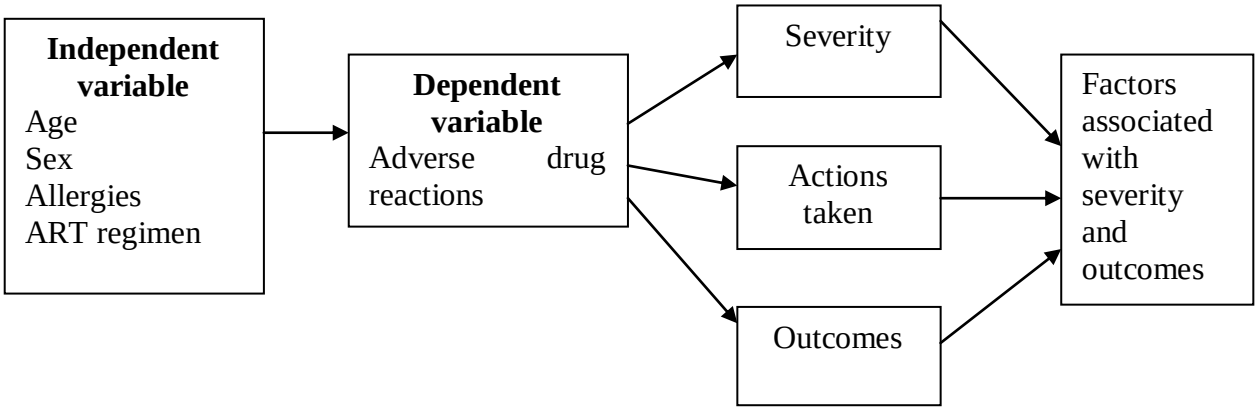
3.6 Data quality control

During data entry into an Excel spreadsheet, data was keyed inand then counterchecked electronically for double entry and any other mistakes. Each cell of the spreadsheet had one piece of information. This data was backed up in a database which had well defined restricted fields that accepted either text only or numerical values only. During data analysis, data fields were sorted out statistical summaries such as means and standard errors were carried out to check for any discrepancies.

3.7 Variables

The outcomes of interest in this study were severity of ADRs, recovery, inpatient hospitalization or prolongation of existing hospitalization, disability, congenital abnormalities and death. The dependent variable was ADR while the independent variables were age, sex, allergies and ART regimens.

3.8 Conceptual framework



This study investigated the above mentioned variables in order to identify the factors associated with severity and outcomes of ADRs due to ART.

3.9 Data analysis

Data analysis was performed using the IBM SPSS statistics version 21 software. Descriptive data analysis was carried out on all variables. The continuous variables were expressed as mean and standard deviation while the categorical variables were reported as proportions and percentages. Bivariate analysis and logistic regression were conducted on the data to identify the risk factors associated with the severity and outcome of the ART-related ADRs. The association between the severity and outcomes of ADRs with specific variables such as patients' age, sex, allergies and ART regimens, number of ADRs was assessed at 95% confidence interval. P values of 0.05 or less were considered as statistically significant.

4.0Ethical considerations

The ethical approval to carry out this study was obtained from the Kenyatta National Hospital (KNH) University of Nairobi (UON)-Ethics and Research Committeeas per the letter referenced KNH-ERC/A/194 dated 27th April 2015. The permission to collect data was then sought and obtained from the Registrar, PPB.Codes and serial numbers were used to conceal patient and reporter identity during data collection. The data collectionforms were kept under lock and key by the researcher during the study period.

CHAPTER FOUR

RESULTS

4.1 Baseline characteristics of individual case safety reports

The distribution of ICSRs on ART related ADRs received at the PPB has been shown in Figure 4.1. One hundred and twenty one (121) cases were excluded from the analysis as ART regimen and description of ADR were not indicated.

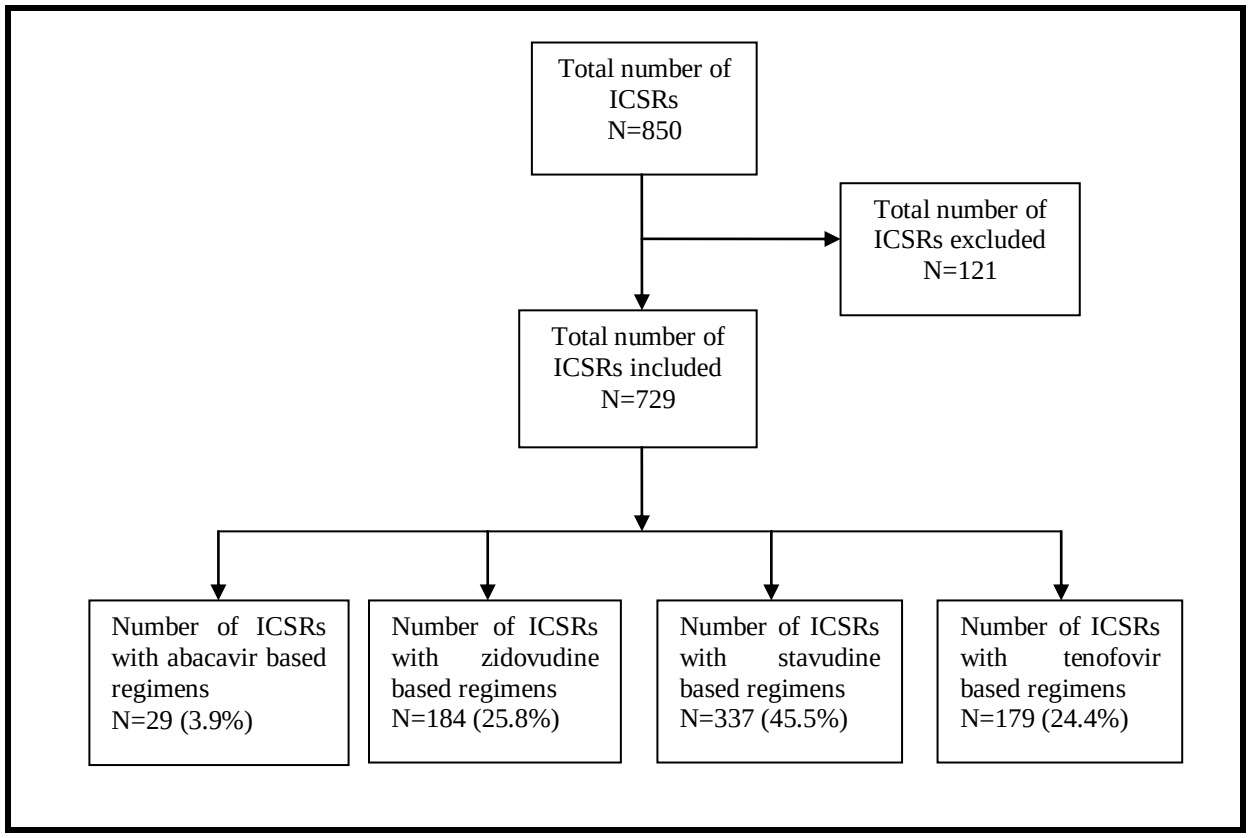


Figure 4.1: Distribution of individual case safety reports (ICSRs) by regimen

The baseline characteristics of the 729 ICSRs included in the study are summarized in Table 4.1. There were more females (63.4%) compared to the males (35.0%). The mean age of the cases was 40 (SD $\pm$ 14) years. Most of the cases were between ages 30-44years (36.9%). Cases who were reported to have had no known allergieswere 97.8%. A significant number of them (70.1%) were on NVP based regimensfollowed by D4T based and EFVbased

regimens at 45.5% and 26.7% respectively. Only 23 (3.2%) caseswere on LPV/rbased regimens. The median duration between the regimen start date and date of report was 37.9 (IQR: 4.8-63.8) months.

Table 4.1: Baseline characteristics of cases with ICSRs on ART (N = 729)

Variable	n (%)
Age group in years	
0-14	36 (4.9)
15-29	71 (9.7)
30-44	269 (36.9)
45-59	169 (23.2)
60-74	39 (5.3)
75-89	3 (0.4)
Not indicated	142 (19.5)
Sex	
Male	257 (35.3)
Female	460 (63.1)
Not indicated	12 (1.6)
Allergies	
No	713 (97.8)
Yes	16 (2.2)
Regimen	
NRTI backbone	
Abacavir based	29 (3.9)
Zidovudine based	184 (25.8)
Stavudine based	337 (45.5)
Tenofovir based	179 (24.4)
NNRTI backbone	
Nevirapine based	511 (70.1)
Efavirenz based	195 (26.7)
PI backbone	
Lopinavir/ritonavir based	23 (3.2)

4.2 Types and sites of ADRs reported in the cases

As shown in Figure 4.2, most ADRs occurred in the integumentary system (62.6%), followed by the central nervous system (18.3%) and cardiovascular system (6.8%). The endocrine and the gastrointestinal system had similar number of ADRs at 3.9% and 3.8% respectively. The least common adverse drug reactions involved the musculoskeletal system (0.1%).

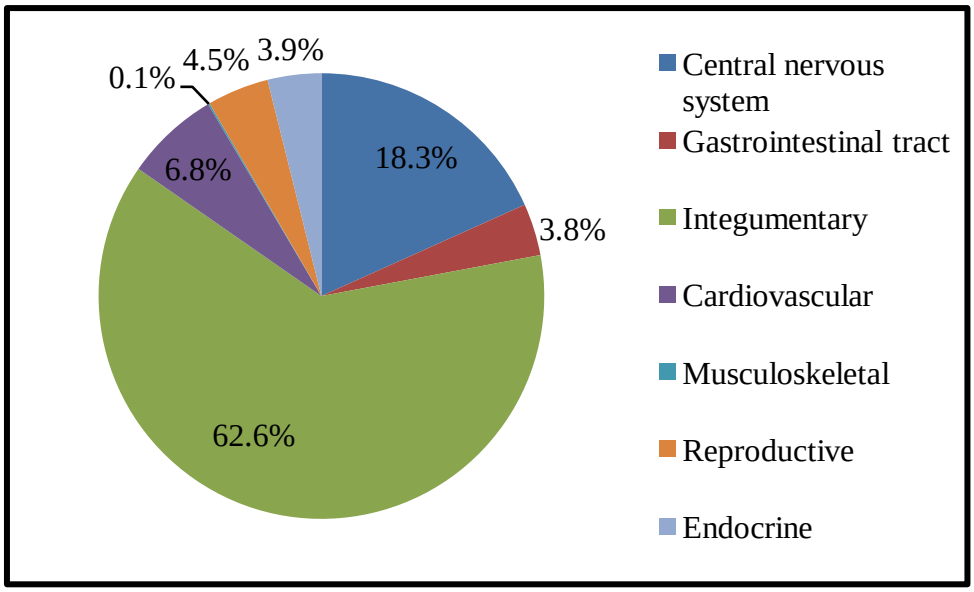


Figure 4.2: Sites of ADRs reported in the cases

There were many ADRs reported from the cases as presented in Table 4.2. Majority of the reported ADRs were associated with the integumentary system (62.6%). Out of this, lipodystrophy and skin rash accounted for 42.1% and 17.3% respectively. This was followed by peripheral neuropathy (14.1%) and anaemia (7.1%). The least reported ADRs were depression, nightmares, arthralgia and galactorrhoea each at 0.1%. There were no reported cases of cough, lactic acidosis, malaise and pancreatitis.

Table 4.2: Types of ADRs from ICSRs (N=729)

Adverse drug reaction by organ system	n (%)
Central and peripheral nervous system	
Dizziness	27 (3.7)
Headaches	8 (1.1)
Psychosis	7 (1.0)
Insomnia	5 (0.7)
Hallucination	3 (0.4)
Depression	1 (0.1)
Nightmares	1 (0.1)
Peripheral neuropathy	103 (14.1)
Gastrointestinal tract system	
Oral ulcers	4 (0.5)
Loss of appetite	4 (0.5)
Vomiting	7 (1.0)
Diarrhoea	13 (1.8)
Nausea	4 (0.5)
Integumentary system	
Discolouration of nails	4 (0.5)
Lipodystrophy	307 (42.1)
Lipoatrophy	66 (9.1)
Skin rash	126 (17.3)
Skin hypersensitivity	12 (1.6)
Steven Johnson Syndrome	14 (1.9)
Toxic epidermal necrolysis	2 (0.3)
Cardiovascular/Respiratory system	
Anaemia	52 (7.1)
Leucopenia	6 (0.8)
Cough	0 (0.0)
Musculoskeletal system	
Arthralgia	1 (0.1)
Reproductive system	
Gynaecomastia	34 (4.7)
Erectile dysfunction	3 (0.4)
Galactorrhea	1 (0.1)
Endocrine system	
Nephrotoxicity	21 (2.9)
Hepatotoxicity	12 (1.6)
Pancreatitis	0 (0.0)
Others	
Lactic acidosis	0 (0.0)
Malaise	0 (0.0)

4.3Types of concomitant drugs used by cases on ART

There were 399 (54.7%)cases who were also on concomitant medicines in addition totheir respective ART regimens. Approximately 51.6% of these cases were on cotrimoxazole. Thedistribution of the cases on concomitant medicines has been summarized in Table 4.3. The table shows that 4.8% of all the cases were on multivitamins while 1.8% were on anti-tuberculosis drugs.

Table 4.3: The distribution of cases on concomitant drugs (N=729)

Medication	n(%)
Cotrimoxazole	376 (51.6)
Hydrochlorthiazide	5 (0.7)
Nifedipine	5 (0.7
Paracetamol	2 (0.3)
Dapsone	9 (1.2)
Enalapril	2 (0.3)
Metformin	2 (0.3)
Pyridoxine	2 (0.3)
Multivitamins	35 (4.8)
Chlorpromazine	8 (1.1)
Benzhexol	2 (0.3)
Albendazole	1 (0.1)
Anti-tuberculosis drugs*	13 (1.8)

**include Rifampicin, Isoniazid, Pyrizinamide, Ethambutol*

4.4Identification of suspected drugs in the cases

The suspected drugs responsible for ADRs among the caseshas been summarised in Table 4.4. Stavudinewas suspected to cause most of the ADRs reported at 44.7% of all the cases. It was followed by AZT at 17.4% and closely by NVP at 16.7%. The drug that was least suspected to cause ADRs was LPV/r at 1.1%. In some cases, a single subject would have more than one drug being reported as suspect for the presenting ADR. Nine reports out of the 729 did not have suspected drugs indicated on them.

There were some concomitant drugs in addition to the ARVs that were suspected of causing ADRs, of these, cotrimoxazole accounted for 3.1% of all the reported cases (Table 4.4). Omeprazole and nifedipine were each reported in 0.1% of the cases. These medicines were reported in cases where the reporter was not able to distinguish whether the ADR was caused by ART alone or by the concomitant drugs due to their similar ADR profiles.

Table 4.4: Identification of suspected drugs in the cases(N=729)

Suspected drug	n (%)
Zidovudine	127 (17.4)
Nevirapine	122 (16.7)
Stavudine	326 (44.7)
Efavirenz	118 (16.2)
Lamivudine	35 (4.8)
Tenofovir	47 (6.4)
Abacavir	11 (1.5)
Lopinavir/ritonavir	8 (1.1)
Cotrimoxazole	23 (3.1)
Omeprazole	1 (0.1)
Nifedipine	1(0.1)

4.5The number of ADRs among cases

Out of the 729 ICSRs, 617 (84.6%) indicated that the patients had suffered only 1 ADR as illustrated in Figure 4.3. Those who reported to have had 2, 3, and 4 ADRs were 106 (14.5%), 5 (0.7%) and 1 (0.1%) respectively.

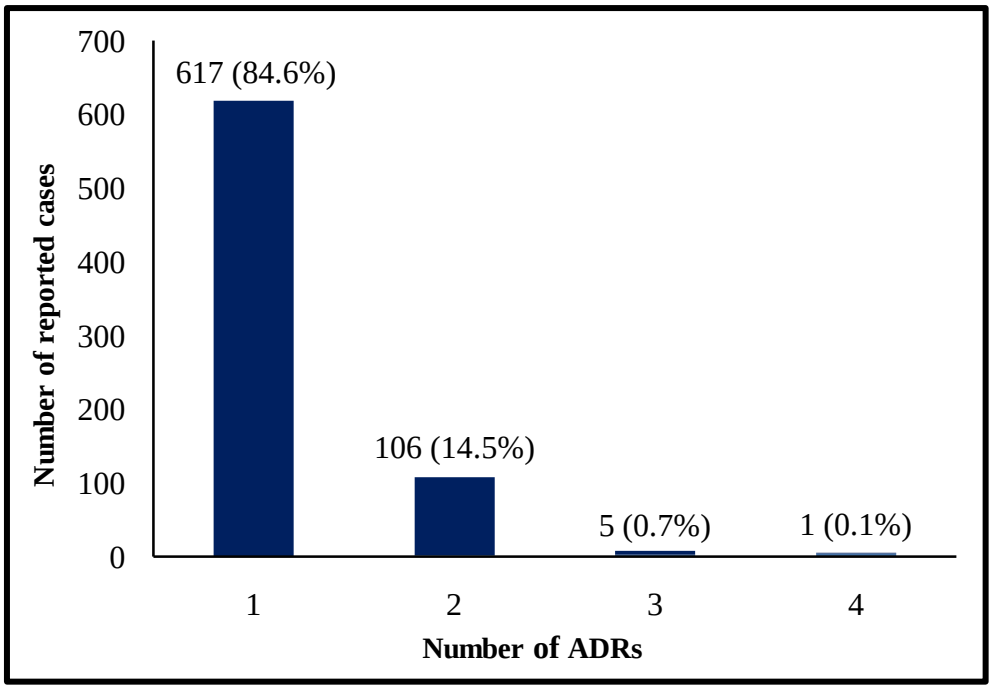


Figure 4.3: The number of ADRs reported per case

4.6 ADRs and ART regimens used by the cases

The distribution ofsuspected ADRs was associated with the different ART regimens the cases were on at the time of reporting as indicated in Appendix 3.The ADRs included anaemia reported mainly in cases on AZT-based regimens with the highest on AZT/3TC/NVP (75%) followed by those on AZT/3TC/EFV (17.3%) and AZT/3TC/LPV/r (3.8%).There was strong evidence ($p< 0.0001$) to indicate that anaemia was associated with ART regimen. Leucopenia($p = 0.003$) and discolouration of nails ($p = 0.031$) were onlyreported in AZT-based regimens. The gastrointestinal tract ADRs such as diarrhoea, nausea and vomiting were most common with TDF-based regimen followed by AZT-based regimen. Diarrhoea was reported inalmost half of the cases (46.2%)on TDF/3TC/EFV compared to 23.1%in those on AZT/3TC/LPV/r.

On the other hand, oral ulcers were common in NVP-based regimens. The central nervous system ADRs were commonly reported in cases on EFV-based regimens with depression,

dizziness, hallucinations,headaches, insomnia and psychosis beingmostly observed in cases on TDF/3TC/EFV. There was also strong evidence that among ADRs associated with the nervous system, dizziness (P<0.0001), peripheral neuropathy (p<0.0001) and psychosis (p = 0.002), were associated with ART regimen. The ADRs involving the integumentary system were reported across all the regimens. Lipodystrophy and lipoatrophy were common with D4T-based regimens in combination with NVP (74.3% and 69.7% respectively), while skin rash and SJS were commonly reported in cases on TDF-based regimens also in combination with NVP (31% and 35.7% respectively). Nephrotoxicity was mostly reported in TDF-based regimens (61.9%).

Gynaecomastiaand erectile dysfunction were common in EFV-based regimens in 21 (61.8%) and 1 (33.3%) cases respectivelywho were on the TDF/3TC/EFV and8 (23.5%) and 1 (33.3%) respectively on AZT/3TC/EFV. On the other hand, hepatotoxicity, described in terms of deranged liver functions and/or presence of jaundice was reported more in cases on AZT/3TC/NVP (50%) followed by TDF/3TC/EFV (25%).

4.7 Severity of ADRs reported in the cases

Most of the suspected ADRs reported were mild in 315 (44.4%) cases and moderate in 284 (40.0%) cases. Fatal reactions were observed in only 4 (0.6%) of the cases as shown in Figure4.4. Severe cases were about 94 (13.2%) while about 13 (1.8%) cases were indicated as unknown. The latter may have resulted from lack of knowledge among the reporters on how to assess severity despite a clear outline of the same at the back of the yellow ADR reporting form.

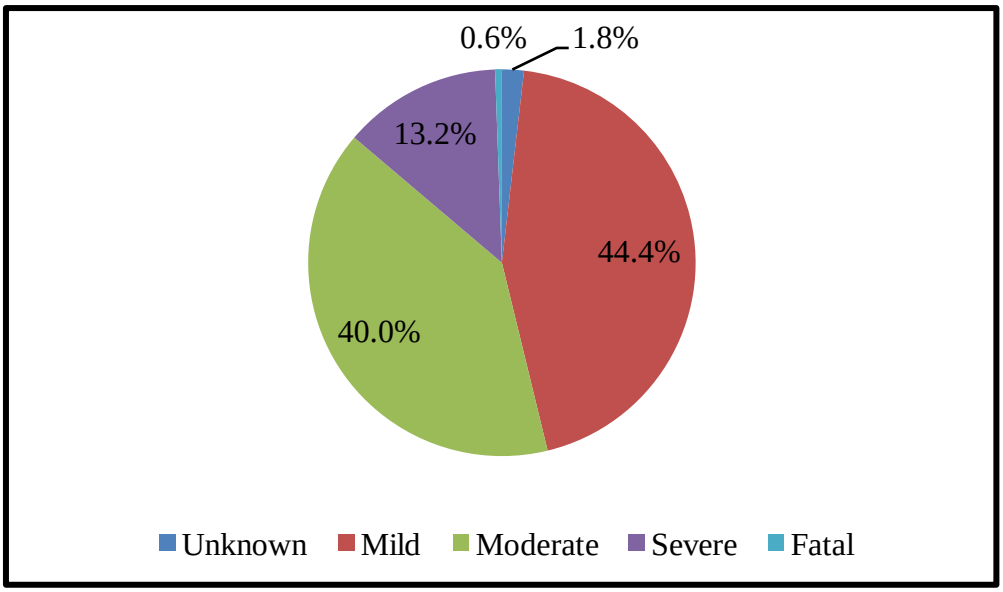


Figure 4.4: Severity of reported ADRs in the ICSRs

4.8Actions takento manage theADRs reported in the cases

The interventions that were taken in the cases of the suspected ADRs included withdrawal of the offending drug in 619 (85.5%) cases as shown in Figure 4.5.Eighty sevencases (12%)were maintained on the doses they were on at the onset of the ADR. One case report (0.1%) indicated a reduction in dose as action taken in a 35 year old female on TDF/3TC/EFV, a fixed dose combination regimen which cannot be reduced. There were no details available on how this was done as the Kenya ART treatment guidelines does not also state management of ADRs in adults by dose reduction. The action taken was not indicated in 17 (2.3%) of the reported cases.

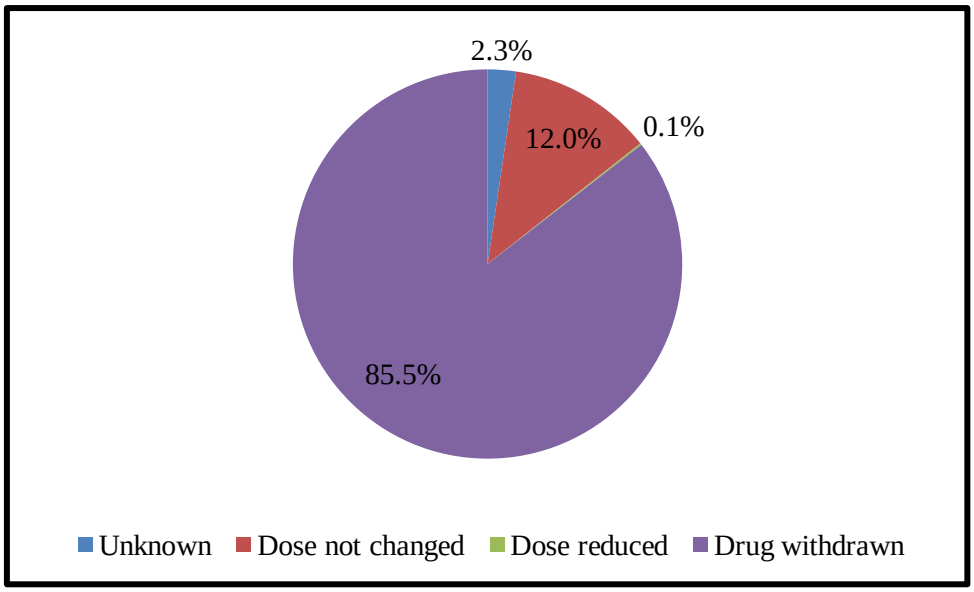


Figure 4.5:Actions taken to manage the ADRs reported in ICSRs

4.9 Outcomes of reported ADRs in the cases

Complete recovery was reported in 84 (11.9%) cases while the reporters felt that about 11 (13.5%) cases required intervention to prevent permanent damage as shown in Figure 4.6. Approximately 8 (1.1%) cases required hospitalization with 11 (1.6%) reported as not recovered. Four cases (36.4%) out of those who had not recovered at the time of reporting died due to an ADR. The outcome in most of the reported cases (34.6%) was indicated as unknown. Unfortunately there was also no description of any pharmacological intervention that was prescribed for most of the cases who were hospitalized. A few of the reports indicated that some of the cases who had anaemia were transfused in addition to having their ART regimens switched.

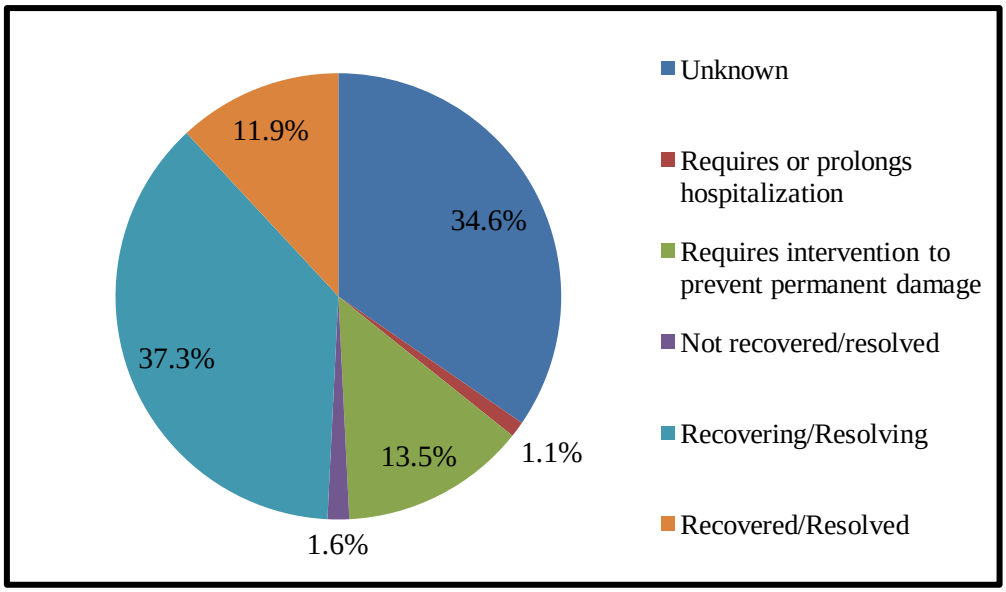


Figure 4.6: Outcomes of reported ADRs in the study cases

4.10Factors associated with severity of ADRs reported in ICSRs

The factors that were associated with ADRs have been shown in Appendix 5. There was strong evidence that being older than 15 years was associated with lipodystrophy ($p < 0.0001$), skin rash ($p < 0.0001$), peripheral neuropathy ($p<0.0001$) and nephrotoxicity ($p = 0.011$). There was also strong evidence that the male sex was associated with gynaecomastia ($p<0.0001$). There was weak evidence that sex was associated withlipodystrophy ($p = 0.05$) and skin rash ($p = 0.035$).In addition, there was strong evidence that indicated that cases with allergies were also more likely to develop SJS ($p = 0.002$). This may be explained by the fact that ARVs may have exacerbated the ADRs.

Severity was indicated in only 716 ICSRs out of the 729 included in this study. The remaining 13 were indicated as unknown or had missing data on severity. Bivariate analysis was then conducted on variables to determine the factors associated with severity of the reported ADRs.Findings indicated that there was strong evidence that ART regimen ($p =$

0.002), presenceof allergies (p = 0.003) and SJS (p<0.0001) were associated with severity of ADRs as indicated in Tables4.5 and 4.6.

Table 4.5: Bivariate analysis of factors associated with severity of ADRs (N=716)

Variable	Mild-Moderate n (%)	Severe-Fatal n (%)	Pvalue
Age group in years			
Not indicated	117 (83.6)	23 (16.4)	0.427
<15 years	32 (88.9)	4 (11.1)	
15-29 years	56 (78.9)	15 (21.1)	
30-44 years	227 (86.3)	36 (13.7)	
45-59 years	131 (79.9)	33 (20.1)	
60 - 74 years	34 (87.2)	5 (12.8)	
75-89 years	2 (66.7)	1 (33.3)	
Sex			
Male	216 (86.1)	35 (13.9)	0.301
Female	372 (82.1)	81 (17.9)	
Not indicated	11 (91.7)	1 (8.3)	
Allergies			
No	590 (84.3)	110 (15.7)	0.003
Yes	9 (56.2)	7 (43.8)	
Regimen			
ABC/3TC/EFV	5 (100.0)	0 (0.0)	0.002
ABC/3TC/LPV/r	4 (100.0)	0 (0.0)	
ABC/3TC/NVP	16 (80.0)	4 (20.0)	
AZT/3TC/EFV	27 (64.3)	15 (35.7)	
AZT/3TC/LPV/r	10 (83.3)	2 (16.7)	
AZT/3TC/NPV	104 (81.9)	23 (18.1)	
D4T/3TC/EFV	32 (94.1)	2 (5.9)	
D4T/3TC/LPV/r	1 (100.0)	0 (0.0)	
D4T/3TC/NVP	264 (89.5)	31 (10.5)	
TDF/3TC/ LPV/r	5 (83.3)	1 (16.7)	
TDF/3TC/EFV	85 (76.6)	26 (23.4)	
TDF/3TC/NVP	46 (78.0)	13 (22.0)	
Number of ADRs			
1	506 (83.8)	98 (16.2)	0.712
2	87 (82.1)	19 (17.9)	
3	5 (100.0)	0 (0.0)	
4	1 (100.0)	0 (0.0)	

Table 4.6: Frequency distribution of ART-related ADRs by severity (N=716)

Variable	Mild-Moderate n (%)	Severe-Fatal n (%)	P value
Lipodystrophy			
No	342 (82.2)	74 (17.8)	0.217
Yes	257(85.7)	43 (14.3)	
Skin rash			
No	493(83.4)	98 (16.6)	0.704
Yes	106(84.8)	19 (15.2)	
Peripheral neuropathy			
No	511(83.2)	103 (16.8)	0.440
Yes	88 (86.3)	14 (13.7)	
Anaemia			
No	559 (84.1)	106 (15.9)	0.295
Yes	40 (78.4)	11 (21.6)	
Dizziness			
No	576 (83.5)	114 (16.5)	0.500
Yes	23 (88.5)	3 (11.5)	
Gynaecomastia			
No	571 (83.6)	112 (16.4)	0.850
Yes	28 (84.8)	5 (15.2)	
Nephrotoxicity			
No	582 (83.7)	113 (16.3)	0.733
Yes	17 (81.0)	4 (19.0)	
S J S*			
No	594 (84.6)	108 (15.4)	<0.0001
Yes	5 (35.7)	9 (64.3)	
Diarrhoea			
No	588 (83.6)	115 (16.4)	0.925
Yes	11 (84.6)	2 (15.4)	

**N/B Stevens-Johnson Syndrome*

Further analysis using logistic regression was then carried out. It was found that with adjusting for regimen, cases with allergies (adjusted odds ratio (OR)3.517; 95% CI: 1.216-10.171; p = 0.020) and SJS (adjusted OR 8.989; 95% CI: 2.898 - 27.877; p = 0.000) were three times and about nine times respectively more likely to have a severe ADR as shown in Table 4.7.

Table 4.7: Multivariate analysis of factors associated with severity of ADRs

Variable	Coefficient	Standard error of coefficient	Adjusted OR (95% C.I.)	P value
Regimen	-0.021	0.041	0.979 (0.904 -1.061)	0.609
Allergies	1.258	0.542	3.517 (1.216 -10.171)	0.020
S J S*	2.196	0.577	8.989 (2.898 - 27.877)	0.000

**N/B Stevens-Johnson Syndrome*

4.11ADRs and use of concomitant drugs

Bivariate analysis of ADRs and use of concomitant drugs found that there was strong evidence indicating that cotimoxazole was associated with lipodystrophy($p < 0.0001$), skin rash($p < 0.0001$)and SJS($p<0.0001$). Omeprazole and nifedipine were both associated with skin rash ($p = 0.029$)as shown on Table 4.8. The full details on other adverse drug reactions segregated by concomitant medicines can be seen in Appendix 4.

Table 4.8: Adverse drug reactions segregated by concomitant medicines (N=729)

Adverse drug reaction		Cotrimoxazole No n(%)	Cotrimoxazole Yes n (%)	Cotrimoxazole P value	Omeprazole No n (%)	Omeprazole Yes n(%)	Omeprazole P value	Nifedipine No n (%)	Nifedipine Yes n (%)	Nifedipine P value
Lipodystrophy	N	399 (56.50)	23 (100.0)	<0.0001	421 (57.8)	1 (100.0)	0.393	421 (57.8)	1 (100.0)	0.393
	Y	307 (43.5)	0 (0.0)		307 (42.2)	0 (0.0)		307 (42.2)	0 (0.0)	
Skin rash	N	596 (84.4)	7 (30.4)	<0.0001	603 (82.8)	0 (0.0)	0.029	603 (82.8)	0 (0.0)	0.029
	Y	110 (15.6)	16 (69.6)		125 (17.2)	1 (100.0)		125 (17.2)	1 (100.0)	
Peripheral neuropathy	N	603 (85.4)	23 (100.0)	0.048	625 (85.9)	1 (100.0)	0.685	625 (85.9)	1 (100.0)	0.685
	Y	103 (14.6)	0 (0.0)		103 (14.1)	0 (0.0)		103 (14.1)	0 (0.0)	
S J S*	N	696 (98.6)	19 (82.6)	<0.0001	714 (98.1)	1 (100.0)	0.889	714 (98.1)	1 (100.0)	0.889
	Y	10 (1.4)	4 (17.4)		14 (1.9)	0 (0.0)		14 (1.9)	0 (0.0)	

**N/B Stevens-Johnson Syndrome*

When logistic regression was conducted, findings indicated that patients who were on concomitant cotrimoxazole were 28 times more likely to develop skin rash (adjusted OR 28.412; 95% CI: 8.142 - 99.150; p = 0.000) and 78 times more likely to have SJS (adjusted OR 78.133; 95% CI: 15.428 - 395.687; p = 0.000) as shown on Table 4.9.

Table 4.9: Multivariate analysis of significant adverse drug reactions and cotrimoxazole

Adverse drug reaction	Coefficient	Standard Error of coefficient	Adjusted OR (95% C.I.)	P value
Skin rash	3.347	0.638	28.412 (8.142 - 99.150)	0.000
S J S*	4.358	0.828	78.133 (15.428 - 395.687)	0.000

**N/B Stevens-Johnson Syndrome*

4.12 Factors associated with outcomes of ADRs in the reported cases

Bivariate analysis for factors associated with outcomes of ADRS was conducted on various variables as shown in Table 4.10. Findings indicated that age (p <0.0001), sex(p = 0.025), ART regimen(p <0.0001), and number of ADRs (p = 0.017) were associated with outcomes as shown in Table 4.10. Approximately 244 ICSRs had either outcome indicated as unknown or not indicated at all.

Table 4.10: Bivariate analysis of factors associated with outcome (N=485)

Variable	Not recovered n (%)	Recovered/Recovering n (%)	P value
Age group in years			
Not indicated	11 (9.1)	110 (90.9)	<0.0001
<15 years	4 (16.0)	21 (84.0)	
15-29 years	5 (11.9)	37 (88.1)	
30-44 years	60 (33.7)	118 (66.3)	
45-59 years	31 (32.6)	64 (67.4)	
60 - 74 years	3 (13.0)	20 (87.0)	
75-89 years	0 (0.0)	1 (100.0)	
Sex			
Male	34 (19.2)	143 (80.8)	0.025
Female	75 (25.1)	224 (74.9)	
Not indicated	5 (55.6)	4 (44.4)	
Allergies			
No	111 (23.5)	362 (76.5)	0.902
Yes	3 (25.0)	9 (75.0)	
Regimen			
ABC/3TC/EFV	0 (0.0)	3 (100.0)	<0.0001
ABC/3TC/LPV/r	0 (0.0)	2 (100.0)	
ABC/3TC/NVP	0 (0.0)	13 (100.0)	
AZT/3TC/EFV	3 (15.0)	17 (85.0)	
AZT/3TC/LPV/r	3 (37.5)	5 (62.5)	
AZT/3TC/NPV	15 (17.4)	71 (82.6)	
D4T/3TC/EFV	7 (50.0)	7 (50.0)	
D4T/3TC/LPV/r	1 (100.0)	0 (0.0)	
D4T/3TC/NVP	71 (31.4)	155 (68.6)	
TDF/3TC/LPV/r	0 (0.0)	2 (100.0)	
TDF/3TC/EFV	8 (10.5)	68 (89.5)	
TDF/3TC/NVP	6 (17.6)	28 (82.4)	
No. of ADRs			
1	106 (25.8)	305 (74.2)	0.017
2	8 (11.4)	62 (88.6)	
3	0 (0.0)	4 (100.0)	
Severity			
Mild-Moderate	87 (22.0)	308 (78.0)	0.517
Severe-Fatal	21 (25.3)	62 (74.7)	

Multivariate analysis was then conducted and it showed an association between age, sex and number of ADRs with the outcome as shown onTable 4.11. Older age and having more than one ADR increased the risk of having an undesirable outcome or not recovering.

Table 4.11: Multivariate analysis for independent predictors of outcomes

Variable	Coefficient	Standard Error of coefficient	Adjusted OR (95% C.I.)	P value
Age	-0.293	0.078	0.746 (0.641- 0.869)	0.000
Sex	-0.424	0.221	0.655 (0.425- 1.010)	0.055
Number of ADRs	0.893	0.381	2.442 (1.156- 5.156)	0.019

CHAPTER FIVE

DISCUSSION, CONCLUSION AND RECOMMENDATIONS

5.1 Discussion

This study analysed factors associated with the occurrence, severity and outcomes of ART-related ADRs in the spontaneous database in Kenya from January 2014 to December 2014. The major findings were that lipodystophy was the most common ADR reported. In addition, stavudine was found to cause most of the ADRs.

Lipodystrophy and Stavudine

Lipodystrophy was found to be the most common ART-related ADR (42.1%). This may be due to the fact that most patients were on D4T-based regimens. A similar study in Kenya found lipodystrophy to be responsible for 43.1% of ADRs while another reported 14.3% (64,65). Stavudine was responsible for approximately 44.7% of all the reported ADRs. This finding is comparable to a study in Canada where 50% of the study participants developed lipodystrophy(28) but contrasts one conducted in India where the prevalence was found to be 14.5% (27). A study conducted in Switzerland found an association between stavudine and lipodystrophy(66).

Despite these findings from various studies and the recommendation of switching from D4T to TDF for all patients on first line treatment by the WHO, there are still some patients in Kenya on D4T-based regimens. Stavudineuse should be stopped completely despite the large stocks that were procured in the country.

Outcomes and ADRs

This study showed that age, sex and number of ADRs were independent predictors of

outcomes. It found that older age, males and having more than one ADR increased the risk of having undesirable outcomes including no recovery. This study finding concurs with a similar study in Italy (67). The reason for this may be due to age related organ changes and multiple chronic illness. This is a clear indicator that this category of patients require close monitoring and follow up as they take their medicines and during management of ART-related ADRs.

The highest number of cases who did not recover were 71 (31.4%) on D4T/3TC/NVP regimen followed by 15 (17.4%) on AZT/3TC/NVP.Patients on D4T and AZT should be monitored closely as they also reported severe to fatal reactions. This may explain why most of the reported cases did not recover.

Cotrimoxazole and severity of ADRs

Concomitant cotrimoxazole was found to be an independent predictor of skin rash and SJS.This concurs with studies that found cotrimoxazole to be responsible for these reactions(68,69). This study reported cotrimoxazoleto be responsible for 3.1% of all ADRs contrary to a study in Nigeria (61.1%) (70). This big difference may be explained by the fact that many ICSRs (48.4%) did not capture concomitant cotrimoxazoleand yet in Kenya, it is prescribed to all HIV infected persons. The cases that had developed skin rashes and SJS had to be switched to dapsone in addition to a change in their ART regimen where the reporter was unable to distinguish between the suspect drugs causing the ADR.

Withdrawal and switching of ART regimens

Most of the reported cases (85.5%) had the offending drug withdrawn and switched to other regimens.This resulted in a positive outcome where half of the cases were reported to either have recovered or were recovering.A study in Malawi reported that D4T was switched to

another regimen in 18.8% of the study participants (71). A similar study in South Africa found that D4T was associated with the highest risk of switching regimen. Out of those requiring a switch in their regimen, 51.8% was due to lipodystrophy. Thirty patients accounting for about 51.7% had their regimens switched from AZT due to anaemia while 11 (68.8%) switched from TDF to other regimens due to nephrotoxicity(72). Another study in Ethiopia reported that out of 257 (62.8%) patients who had required regimen switching, about 30% was due to adverse reactions(10).

The findings in this study on withdrawal and switching of regimen, clearly demonstrate how positive treatment outcomes can still be achieved in patients when appropriate management of ADRs is done.

5.2 Conclusion

This is the first study conductedin Kenya to show the burden of ART-related morbidity and mortality in adults and children on ARVs.This study found that most of the patients were on D4T-based regimens with lipodystrophy as the most common ADR reported. Concomitant cotrimoxazole was found to be an independent predictor of skin rashes and SJS. This study also found that older age and having more than one ADR increased the risk of having undesirable outcomes including no recovery. Withdrawal and switching of regimen in 85.5% of the reported cases may have resulted in about half of them reportingrecovery.

The findings in this study emphasize the need for close monitoring and follow up of all patients especially the children and the elderly on ART and concomitant cotrimoxazole in HIV infected persons.

5.3 Recommendations

All patients, especially children and the elderly on ART and concomitant cotrimoxazole should be closely monitored to minimize the rate of mortality and morbidity associated with the medicines. The PPB should device mechanisms of following up on reported cases whose ICSRs are incomplete. In addition, they should also carry out periodic analysis of the spontaneous database.

The findings in this study can be used to inform policy on management of ART-related ADRs in Kenya. Further sensitization and training on reporting of ADRs should be done to the healthcare workers to enhance the rate of reporting and improve the quality of reports generated. The suspected ADR reporting form should also be modified to include provision for details of management of the ADRs so that this information may be correlated with outcomes.

Further research can be conducted to investigate the mortality rate associated with lipodystophy as the most commonly reported ADR associated with stavudine. This is in order to determine whether it should be phased out completely from the treatment guidelines in Kenya as recommended by WHO in 2010.

5.4 Study limitations

This study had a large sample size robust enough to detect ADRs. However, with spontaneous reporting, it was difficult to verify what was reported. There was also no documentation of any clinical investigations done in most of the reported cases. This limited our analysis to severity and outcomes of ADRs. A second limitation is that some reports were illegible, incomplete and in most of them, interventions used to manage the ADRs was

not described. This may contribute to an underestimation of the significance of the reported ADRs.

5.5 Information dissemination plan

The information obtained from this study will be shared with PPB and disseminated through publications, sensitization of healthcare workers in scientific conferences and conducting continuous medical education sessions.

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APPENDICES

Appendix 1: Data collection form

PATIENT BIODATA

Patient study number.....

Date of Birth .....

Age in years (At time of ADR reporting).....

Gender (Female/Male).....

Location (County).....

MEDICATION HISTORY

Report date.....

Date started on ARVs.....

ART regimen.....

Other drugs.....

Suspected drug(s).....

Description of ADR reaction.....

Severity of reaction (tick where appropriate):

Mild ( )

Moderate ( )

Severe ( )

Fatal ( )

Unknown ( )

Action taken (tick where appropriate):

Drug withdrawn ( )

Dose reduced ( )

Dose not changed ( )

Unknown ( )

Outcome (tick where appropriate):

Recovering/resolving ( )

Recovered/resolved ( )

Requires or prolongs hospitalization ( )

Causes a congenital anomaly ( )

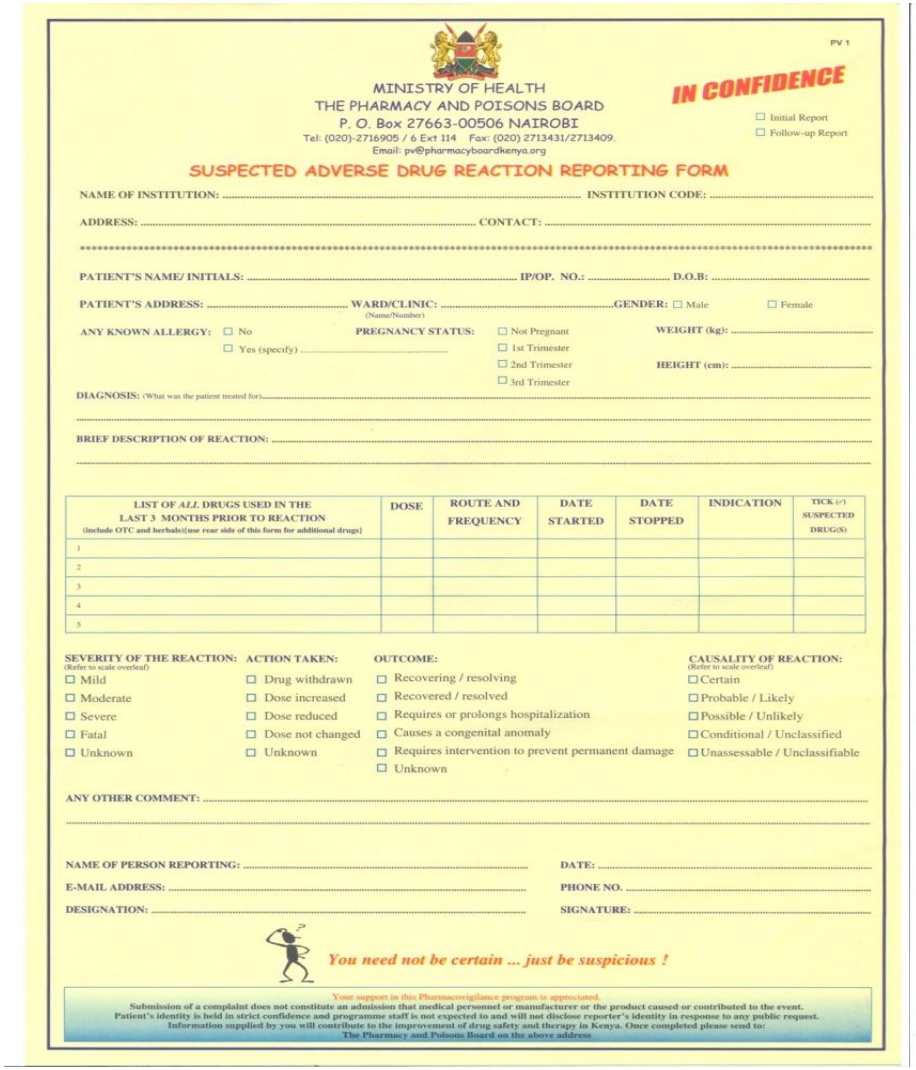
Requires intervention to prevent permanent damage ( )

Not recovered/not resolved ( )

Unknown ( )

Reporter (designation).....

Appendix 2: Yellow 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: ..... (Name/Number) GENDER: ☐ Male ☐ Female

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: .....

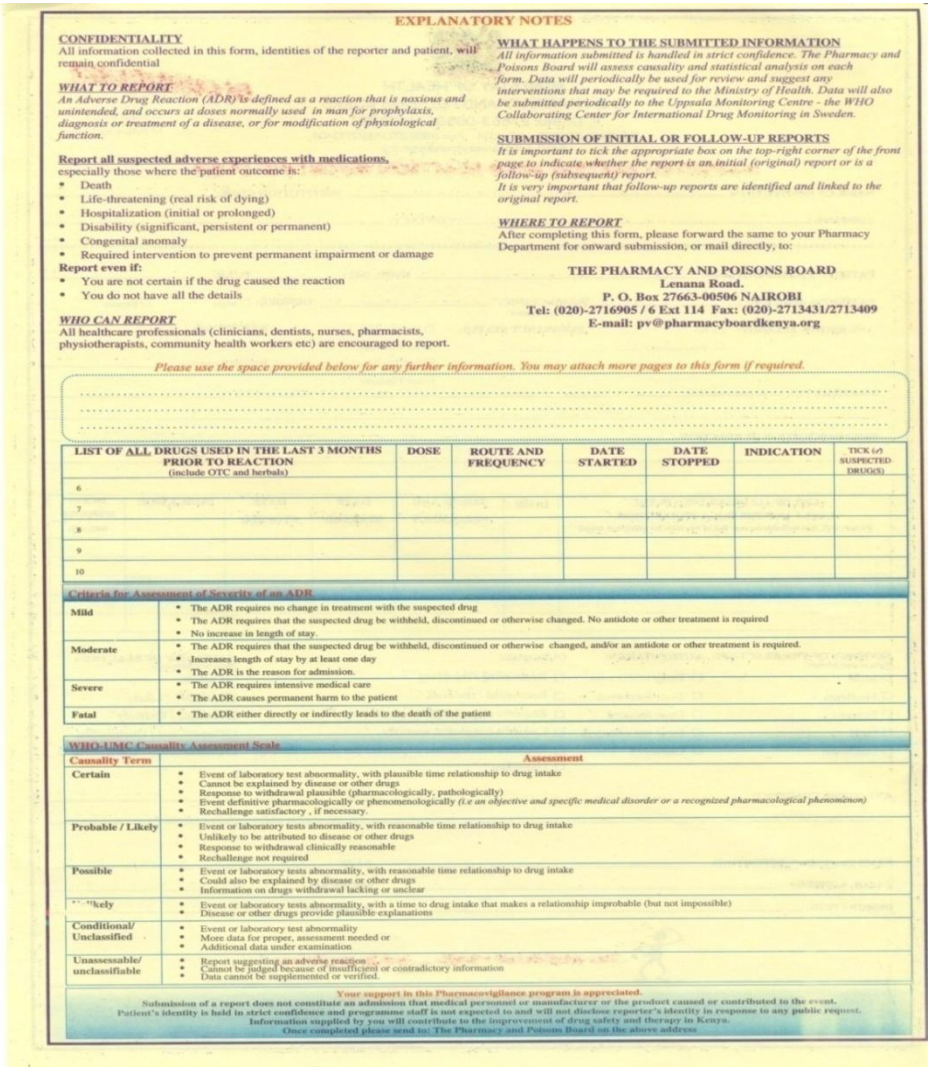
NAME OF PERSON REPORTING: ..... DATE: .....

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



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.

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
"kely	• 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 3: Frequency distribution of suspected ADRs by ART regimens, N=729, percentage in parenthesis

	ABC/ 3TC/ EFV	ABC/ 3TC/ LPV/r	ABC/ 3TC/ NVP	AZT/ 3TC/ EFV	AZT/ 3TC/ LPV/r	AZT/ 3TC/ NPV	D4T/ 3TC/ EFV	D4T/ 3TC/ LPV/r	D4T/ 3TC/ NVP	TDF/ 3TC/ LPV/r	TDF/ 3TC/ EFV	TDF/ 3TC/ NVP	P value
Anaemia	1 (1.9)	0 (0)	1 (1.9)	9 (17.3)	2 (3.8)	39 (75)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	<0.0001
Cough	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	-
Depression	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (100)	0 (0)	0.907
Diarrhoea	0 (0)	0 (0)	1 (7.7)	0 (0)	3 (23.1)	1 (7.7)	0 (0)	0 (0)	0 (0)	2 (15.4)	6 (46.2)	0 (0)	<0.0001
Dizziness	0 (0)	0 (0)	1 (3.7)	3 (11.1)	0 (0)	5 (18.5)	0 (0)	0 (0)	0 (0)	0 (0)	18 (66.7)	0 (0)	<0.0001
Hallucination	0 (0)	0 (0)	0 (0)	1 (33.3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (66.7)	0 (0)	0.419
Headaches	0 (0)	0 (0)	1 (12.5)	0 (0)	0 (0)	4 (50)	0 (0)	0 (0)	0 (0)	0 (0)	2 (25)	1 (12.5)	0.310
Hepatotoxicity	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	6 (50)	0 (0)	0 (0)	2 (16.7)	0 (0)	3 (25)	1 (8.3)	0.379
Insomnia	0 (0)	0 (0)	0 (0)	1 (20)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	4 (80)	0 (0)	0.580
Lactic acidosis	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	-
Lipodystrophy	1 (0.3)	0 (0)	0 (0)	15 (4.9)	1 (0.3)	30 (9.8)	22 (7.2)	1 (0.3)	228 (74.3)	1 (0.3)	4 (1.3)	4 (1.3)	<0.0001
Loss of appetite	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (25)	0 (0)	0 (0)	0 (0)	0 (0)	3 (75)	0 (0)	0.364
Malaise	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	-
Nausea	0 (0)	0 (0)	0 (0)	0 (0)	1 (25)	1 (25)	0 (0)	0 (0)	0 (0)	0 (0)	1 (25)	1 (25)	0.098
Nightmares	0 (0)	0 (0)	0 (0)	1 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0.142
Nephrotoxicity	0 (0)	0 (0)	0 (0)	1 (4.8)	0 (0)	2 (9.5)	2 (9.5)	0 (0)	3 (14.3)	2 (9.5)	8 (38.1)	3 (14.3)	<0.0001
Pancreatitis	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	-
Peripheral neuropathy	0 (0)	0 (0)	0 (0)	5 (4.9)	0 (0)	6 (5.8)	7 (6.8)	0 (0)	80 (77.7)	1 (1)	1 (1)	3 (2.9)	<0.0001
Psychosis	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (14.3)	0 (0)	0 (0)	0 (0)	6 (85.7)	0 (0)	0.002
Skin Rash	2 (1.6)	3 (2.4)	15 (11.9)	0 (0)	0 (0)	29 (23)	0 (0)	0 (0)	2 (1.6)	0 (0)	36 (28.6)	39 (31)	<0.0001
S .J. S	0 (0)	0 (0)	2 (14.3)	0 (0)	0 (0)	4 (28.6)	0 (0)	0 (0)	0 (0)	0 (0)	3 (21.4)	5 (35.7)	0.002
Toxic epidermal necrolysis	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0.592
Vomiting	0 (0)	0 (0)	1 (14.3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	3 (42.9)	3 (42.9)	0.022
Gynaecomastia	1 (2.9)	0 (0)	0 (0)	8 (23.5)	1 (2.9)	0 (0)	3 (8.8)	0 (0)	0 (0)	0 (0)	21 (61.8)	0 (0)	<0.0001
Skin Hypersensitivity	0 (0)	0 (0)	0 (0)	1 (8.3)	2 (16.7)	3 (25)	0 (0)	0 (0)	0 (0)	0 (0)	4 (33.3)	2 (16.7)	0.005
Lipoatrophy	1 (1.5)	0 (0)	0 (0)	3 (4.5)	0 (0)	10 (15.2)	4 (6.1)	0 (0)	46 (69.7)	0 (0)	1 (1.5)	1 (1.5)	0.001
Erectile Dysfunction	0 (0)	0 (0)	0 (0)	1 (33.3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (33.3)	1 (33.3)	0 (0)	<0.0001
Arthralgia	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (100)	0 (0)	0.907
Galactorrhea	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (100)	0 (0)	0.907
Discolouration Of Nails	0 (0)	0 (0)	0 (0)	1 (25)	1 (25)	2 (50)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0.031
Leucopenia	0 (0)	0 (0)	0 (0)	0 (0)	1 (16.7)	5 (83.3)	0 (0)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0.003
Oral ulcers	0 (0)	1 (25)	1 (25)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (50%)	<0.0001

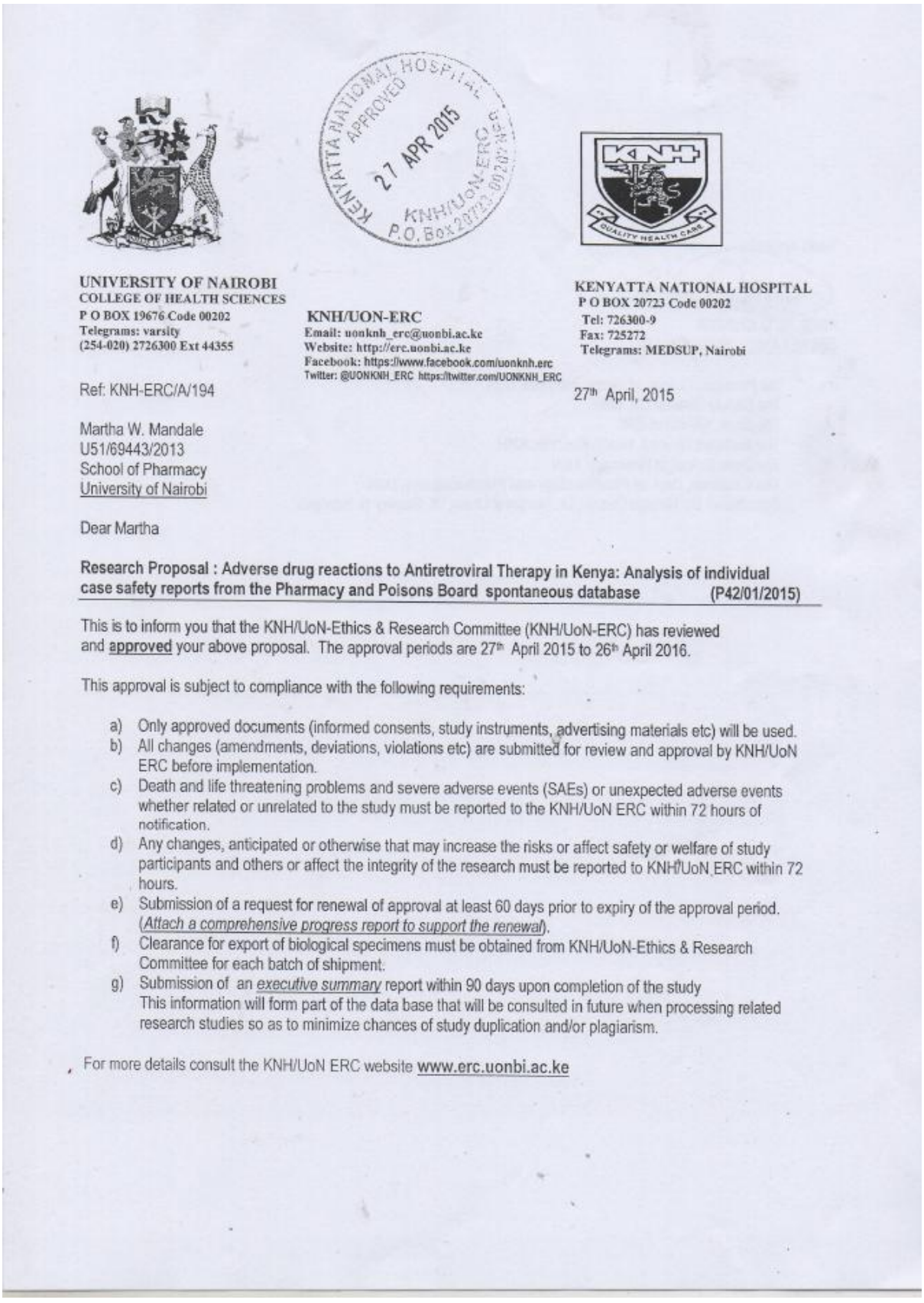
Appendix 4: Adverse drug reactions by concomitant medicines

Adverse drug reaction		Cotrimoxazole			Omeprazole			Nifedipine		
		No N (%)	Yes N (%)	P value	No N (%)	Yes N (%)	P value	No N (%)	Yes N (%)	P value
Lipodystrophy	N	399 (56.50)	23 (100.0)	<0.0001	421 (57.8)	1 (100.0)	0.393	421 (57.8)	1 (100.0)	0.393
	Y	307 (43.5)	0 (0.0)		307 (42.2)	0 (0.0)		307 (42.2)	0 (0.0)	
Skin rash	N	596 (84.4)	7 (30.4)	<0.0001	603 (82.8)	0 (0.0)	0.029	603 (82.8)	0 (0.0)	0.029
	Y	110 (15.6)	16 (69.6)		125 (17.2)	1 (100.0)		125 (17.2)	1 (100.0)	
Peripheral neuropathy	N	603 (85.4)	23 (100.0)	0.048	625 (85.9)	1 (100.0)	0.685	625 (85.9)	1 (100.0)	0.685
	Y	103 (14.6)	0 (0.0)		103 (14.1)	0 (0.0)		103 (14.1)	0 (0.0)	
Anaemia	N	655 (92.8)	22 (95.7)	0.598	676 (92.9)	1 (100.0)	0.782	676 (92.9)	1 (100.0)	0.782
	Y	51 (7.2)	1 (4.3)		52 (7.1)	0 (0.0)		52 (7.1)	0 (0.0)	
Dizziness	N	679 (96.2)	23 (100.0)	0.339	701 (96.3)	1 (100.0)	0.844	701 (96.3)	1 (100.0)	0.844
	Y	27 (3.8)	0 (0.0)		27 (3.7)	0 (0.0)		27 (3.7)	0 (0.0)	
Gynaecomastia	N	672 (95.2)	23 (100.0)	0.281	694 (95.3)	1 (100.0)	0.825	694 (95.3)	1 (100.0)	0.825
	Y	34 (4.8)	0 (0.0)		34 (4.7)	0 (0.0)		34 (4.7)	0 (0.0)	
Nephrotoxicity	N	686 (97.2)	22 (95.7)	0.669	707 (97.1)	1 (100.0)	0.863	707 (97.1)	1 (100.0)	0.863
	Y	20 (2.8)	1 (4.3)		21 (2.9)	0 (0.0)		21 (2.9)	0 (0.0)	
S J S	N	696 (98.6)	19 (82.6)	<0.0001	714 (98.1)	1 (100.0)	0.889	714 (98.1)	1 (100.0)	0.889
	Y	10 (1.4)	4 (17.4)		14 (1.9)	0 (0.0)		14 (1.9)	0 (0.0)	
Diarrhoea	N	693 (98.2)	23 (100.0)	0.511	715 (98.2)	1 (100.0)	0.893	715 (98.2)	1 (100.0)	0.893
	Y	13 (1.8)	0 (0.0)		13 (1.8)	0 (0.0)		13 (1.8)	0 (0.0)	

Appendix 5: Predictors of ADRs

Variable		Lipodystrophy	Skin rash	Peripheral neuropathy	Anaemia	Dizziness	Gynaecomastia	Nephrotoxicity	SJS	Diarrhoea
Age in years	Not indicated	46.5%	4.9%	28.9%	5.6%	2.8%	2.1%	2.1%	1.4%	.7%
	<15	2.8%	61.1%	5.6%	16.7%	0.0%	2.8%	0.0%	5.6%	2.8%
	15-29	18.3%	35.2%	2.8%	7.0%	9.9%	5.6%	2.8%	5.6%	1.4%
	30-44	49.4%	17.5%	9.3%	7.8%	3.3%	4.1%	1.9%	1.5%	2.2%
	45-59	47.3%	11.8%	14.2%	5.3%	3.0%	6.5%	3.6%	1.2%	.6%
	60-74	35.9%	10.3%	20.5%	5.1%	5.1%	10.3%	12.8%	0.0%	7.7%
	75-89	0.0%	33.3%	33.3%	33.3%	0.0%	0.0%	0.0%	0.0%	0.0%
	P value	**<0.0001**	**<0.0001**	**<0.0001**	**0.134**	**0.127**	**0.330**	**0.011**	**0.147**	**0.098**
Sex	Male	39.7%	12.5%	12.1%	7.8%	2.3%	12.5%	3.1%	3.1%	.8%
	Female	42.6%	19.8%	15.7%	7.0%	4.6%	.4%	2.8%	1.3%	2.4%
	Not indicated	75.0%	25.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
	P value	**0.050**	**0.035**	**0.153**	**0.575**	**0.250**	**<0.0001**	**0.815**	**0.212**	**0.263**
Allergies	No	42.4%	17.4%	14.3%	7.0%	3.6%	4.6%	2.8%	1.7%	1.8%
	Yes	31.3%	12.5%	6.3%	12.5%	6.3%	6.3%	6.3%	12.5%	0.0%
	P value	**0.374**	**0.609**	**0.360**	**0.399**	**0.586**	**0.761**	**0.415**	**0.002**	**0.586**
Regimen	ABC/3TC/EFV	20.0%	40.0%	0.0%	20.0%	0.0%	20.0%	0.0%	0.0%	0.0%
	ABC/3TC/LPV/r	0.0%	75.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
	ABC/3TC/NVP	0.0%	75.0%	0.0%	5.0%	5.0%	0.0%	0.0%	10.0%	5.0%
	AZT/3TC/EFV	34.9%	0.0%	11.6%	20.9%	7.0%	18.6%	2.3%	0.0%	0.0%
	AZT/3TC/LPV/r	8.3%	0.0%	0.0%	16.7%	0.0%	8.3%	0.0%	0.0%	25.0%
	AZT/3TC/NPV	23.3%	22.5%	4.7%	30.2%	3.9%	0.0%	1.6%	3.1%	.8%
	D4T/3TC/EFV	64.7%	0.0%	20.6%	0.0%	0.0%	8.8%	5.9%	0.0%	0.0%
	D4T/3TC/LPV/r	100.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
	D4T/3TC/NVP	75.5%	.7%	26.5%	0.0%	0.0%	0.0%	1.0%	0.0%	0.0%
	TDF/3TC/ LPV/r	16.7%	0.0%	16.7%	0.0%	0.0%	0.0%	33.3%	0.0%	33.3%
	TDF/3TC/EFV	3.5%	31.9%	.9%	0.0%	15.9%	18.6%	7.1%	2.7%	5.3%
	TDF/3TC/NVP	6.7%	65.0%	5.0%	0.0%	0.0%	0.0%	5.0%	8.3%	0.0%
	P value	**<0.0001**	**<0.0001**	**<0.0001**	**<0.0001**	**<0.0001**	**<0.0001**	**<0.0001**	**0.002**	**<0.0001**

Appendix 6: Letter of ethical approval



KENYATTA NATIONAL HOSPITAL APPROVED 27 APR 2015 KNH/UON-ERC P.O. Box 20723-00202

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Ref: KNH-ERC/A/194

27th April, 2015

Martha W. Mandale
U51/69443/2013
School of Pharmacy
University of Nairobi

Dear Martha

Research Proposal : Adverse drug reactions to Antiretroviral Therapy in Kenya: Analysis of individual case safety reports from the Pharmacy and Poisons Board spontaneous database (P42/01/2015)

This is to inform you that the KNH/UoN-Ethics & Research Committee (KNH/UoN-ERC) has reviewed and **approved** your above proposal. The approval periods are 27th April 2015 to 26th April 2016.

This approval is subject to compliance with the following requirements:

a) Only approved documents (informed consents, study instruments, advertising materials etc) will be used.
b) All changes (amendments, deviations, violations etc) are submitted for review and approval by KNH/UoN ERC before implementation.
c) Death and life threatening problems and severe adverse events (SAEs) or unexpected adverse events whether related or unrelated to the study must be reported to the KNH/UoN ERC within 72 hours of notification.
d) Any changes, anticipated or otherwise that may increase the risks or affect safety or welfare of study participants and others or affect the integrity of the research must be reported to KNH/UoN ERC within 72 hours.
e) Submission of a request for renewal of approval at least 60 days prior to expiry of the approval period. (*Attach a comprehensive progress report to support the renewal*).
f) Clearance for export of biological specimens must be obtained from KNH/UoN-Ethics & Research Committee for each batch of shipment.
g) Submission of an *executive summary* report within 90 days upon completion of the study This information will form part of the data base that will be consulted in future when processing related research studies so as to minimize chances of study duplication and/or plagiarism.

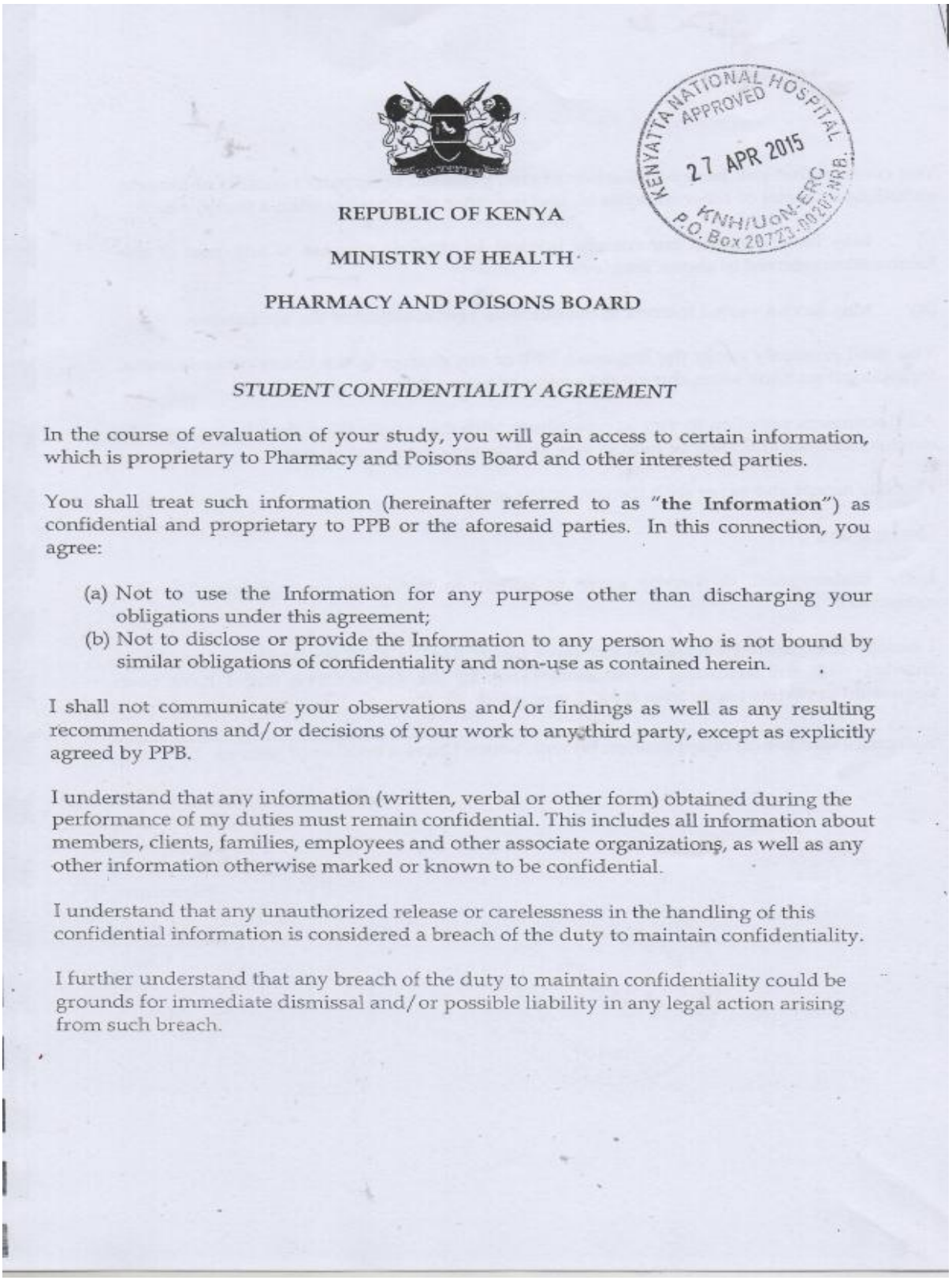
For more details consult the KNH/UoN ERC website **www.erc.uonbi.ac.ke**

Yours sincerely,

PROF. M. L. CHINDIA
SECRETARY, KNH/UON-ERC

c.c. The Principal, College of Health Sciences, UoN
The Deputy Director CS, KNH
The Chair, KNH/UoN-ERC
The Assistant Director, Health Records, KNH
The Dean,School of Pharmacy, UoN
The Chairman, Dept. of Pharmacology and Pharmacognosy, UoN
Supervisor: Dr. George Osanjo, Dr. Margaret Oluka, Dr. Stanley N. Ndwigah

Appendix 7: Student confidentiality agreement form



KENYATTA NATIONAL HOSPITAL APPROVED 27 APR 2015 KNH/UON-ERC P.O. Box 20723-00202 NAIROBI

REPUBLIC OF KENYA

MINISTRY OF HEALTH

PHARMACY AND POISONS BOARD

STUDENT CONFIDENTIALITY AGREEMENT

In the course of evaluation of your study, you will gain access to certain information, which is proprietary to Pharmacy and Poisons Board and other interested parties.

You shall treat such information (hereinafter referred to as "**the Information**") as confidential and proprietary to PPB or the aforesaid parties. In this connection, you agree:

(a) Not to use the Information for any purpose other than discharging your obligations under this agreement;
(b) Not to disclose or provide the Information to any person who is not bound by similar obligations of confidentiality and non-use as contained herein.

I shall not communicate your observations and/or findings as well as any resulting recommendations and/or decisions of your work to any third party, except as explicitly agreed by PPB.

I understand that any information (written, verbal or other form) obtained during the performance of my duties must remain confidential. This includes all information about members, clients, families, employees and other associate organizations, as well as any other information otherwise marked or known to be confidential.

I understand that any unauthorized release or carelessness in the handling of this confidential information is considered a breach of the duty to maintain confidentiality.

I further understand that any breach of the duty to maintain confidentiality could be grounds for immediate dismissal and/or possible liability in any legal action arising from such breach.

You confirm that you have no situation of real, potential or apparent conflict of interest including financial or other interests in, and/or other relationship with, a party, which:

(i) May have a vested commercial interest in obtaining access to any part of the Information referred to above; and/or

(ii) May have a vested interest in the outcome of evaluation of the application.

You shall promptly notify the Registrar, PPB of any change in the above circumstances, including if an issue arises during the course of your work.

All documents supplied to you in connection with this application shall be accepted in strict confidence and shall be held in safe and secure custody at all times.

I hereby accept and agree with the conditions and

Declaration:

I, the undersigned, do hereby agree to adhere to the provisions contained in this agreement.

I hereby declare that I have/do not have (*delete what is NOT applicable*) a Conflict of Interest with the following application(s)/any of the applications that I have been requested to review (*delete what is NOT applicable*)

Reference number (s) of application (s) with which I have a conflict of interest

MARTHA WERE MANDALE
(Student Name)

(Signature)

29/05/2015
(Date)

KENYATTA NATIONAL HOSPITAL APPROVED 27 APR 2015 KNH/UoN-ERC P.O. Box 20723-00202 NAIROBI