QUALITY OF ADVERSE EVENT REPORTS IN KENYA AND SAFETY SIGNALS FOR ANTIRETROVIRAL THERAPY RELATED ARRHYTHMIAS

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DEDICATION

I dedicate this thesis to all the pharmacovigilantes who are committed to making the pharmaceutical sector a safe sanctuary for consumers in an ever increasingly treacherous world.

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ABBREVIATIONS AND ACRONYMS

3TC	Lamivudine
ABC	Abacavir
ACEI	Angiotensin Converting Enzyme Inhibitor
ACF	Autocorrelation Function
ADR	Adverse Drug Reaction
AE	Adverse Event
AIDS	Acquired Immunodeficiency Syndrome
APV	Amprenavir
ART	Antiretroviral therapy
ARV	Antiretroviral
ATC	Anatomical Therapeutic Chemical
ATV	Atazanavir
AV	Atrio-ventricular
AZT	Zidovudine
BAN	British Adopted Name
BCPNN	Bayesian Confidence Propagation Neural Network
BMI	Body Mass Index
CIOMS	Council for International Organizations of Medical Sciences
CPA	Change Point Analysis
CVD	Cardiovascular disease
CVS	Cardiovascular
CYP	Cytochrome P 450

d4T	Stavudine
DAEN	Australian Database of Adverse Event Notifications
ddC	Zalcitabine
ddI	Didanosine
DDI	Drug-Drug Interaction
DLV	Delavirdine
DRV	Darunavir
DTG	Dolutegrevir
EBGM	Empirical Bayesian Geometric Mean
ECG	Electrocardiogram
EFV	Efavirenz
EMA	European Medicines Agency
ENF	Enfuvirtide
ETR	Etravirine
FAERS	Food and Drug Administration Adverse Event Reporting System
FDA	Food and Drug Administration
FDCs	Fixed Drug Combinations
FPV	Fosamprenavir
FTC	Emtricitabine
GLS	Generalized Least Squares
HAART	Highly Active Antiretroviral Therapy
HAART	Highly Active Antiretroviral Therapy
HIV	Human Immunodeficiency Virus

HLGTs	High Level Grouped Terms
HLTS	High Level Terms
IC	Information Component
ICH	International Conference for Harmonisation
ICSR	Individual Case Safety Report
IDV	Indinavir
IHD	Ischaemic Heart Disease
KS	Kaposi's sarcoma
LLTs	Lowest Level Terms
LMICs	Low and Middle Income Countries
LPV	Lopinavir
LPV/r	Lopinavir/ritonavir
MedDRA	Medical Dictionary for Regulatory Affairs
MGPS	Multi-item Gamma Poisson Shrinker
MI	Myocardial Infarction
MoH	Ministry of Health
NASCOP	National AIDS and STI Control Programme
NFV	Nelfinavir
NRTIs	Nucleoside Reverse Transcriptase Inhibitors
NVP	Nevirapine
PEPFAR	President's Emergency Plan for AIDS Relief
P-gp	P-glycoprotein 1
PI	Protease Inhibitors

PLWH	People Living with HIV
PPB	Pharmacy and Poisons Board
PREVALEAT	PREmature VAscular LEsions and Antiretroviral Therapy
PRR	Proportional Reporting Ratio
PTs	Preferred Terms
PV	Pharmacovigilance
r	Ritonavir
RAL	Raltegravir
ROR	Reporting Odds Ratio
RR	Relative Reporting
RTV	Ritonavir
SMQs	Standardised MedDRA Queries
SOC	System Organ Class
SQV	Saquinavir
TDF	Tenofovir Disoproxil Fumarate
UK	United Kingdom
USAN	United States Adopted Name
WHO-UMC	World Health Organization-Uppsala Monitoring Centre

DEFINITION OF TERMS

Adverse drug reaction is a noxious and unintended reaction that occurs at a dose used for the treatment, diagnosis and prevention of a disease, disorder or syndrome.

Adverse event is any unexpected medical occurrence resulting from a drug that occurs in a patient or clinical investigation subject. It does not necessarily have a causal relationship with the product. Serious adverse events are those that result in death, hospitalisation or significant disability.

Anatomical Therapeutic Chemical classification is a drug classification system maintained by the World Health Organisation. According to this system, medicines are classified according to the organ or system on which they act; their therapeutic category; pharmacological actions; and chemical properties.

Antiretrovirals (ARVs) are a group of medications used in the management of infection by retroviruses. When used to treat HIV, they inhibit different steps in the HIV replication process. Antiretrovirals are usually used in a combination of two to four drugs known as Highly Active Anti-Retroviral Therapy (HAART).

Arrhythmogenic right ventricular dysplasia is a form of myocardial heart disease where the walls of the right ventricle are replaced by fibrous tissue. Patients present with arrhythmia and are at an increased risk of cardiac arrest and death.

Cardiac arrhythmias refer to a group of conditions in which the regular heartbeat is disrupted resulting in a heartbeat that is either irregular (flutter or fibrillation), too fast (tachycardia), or too slow (bradycardia). These conditions are caused by a disruption of your normal cardiac electrical system.

Cardiac failure is a chronic condition characterized by the inability of the heart to pump sufficient amounts of blood flow to meet the body's needs.

Cardiomyopathy is an acquired or hereditary disease of the myocardium in which the heart muscle is progressively weakened and can eventually result in heart failure.

Cardiovascular disease refers to conditions generally affecting the heart or blood vessels. These include coronary artery disease, congestive heart disease, arrhythmias, hypertension, stroke, peripheral artery disease and cardiac arrest.

Data mining is the process of getting useful information from large data sets. It may involve the use of quantitative and qualitative procedures.

Disproportionality analysis is an approach to signal detection premised on the comparison of reporting proportions between a given drug of interest and all other drugs in a spontaneous reports database.

Drug-drug interaction refers to pharmacodynamics and pharmacokinetic changes in drug properties when it is co-administered with another drug, usually due to the effects of the second drug.

Dyslipidaemia refers to abnormal plasma lipid levels mostly involving High Density Lipoproteins, triglycerides, or Low-Density Lipoproteins. Dyslipidaemia may be genetic or the result of secondary factors.

Food and Drug Administration Adverse Event Reporting System (FAERS) is the spontaneous adverse events database in the United States of America.

High Level Grouped Terms is a level in the MedDRA hierarchy in which related High Level Terms (HLTs) are grouped together based on aetiology, anatomy, pathology, physiology or function.

High Level Terms (HLTs) refers to a level of MedDRA hierarchy in which related Preferred Terms (PTs) are grouped together. This grouping is based on anatomy, pathology, physiology, aetiology or function.

Hypertension refers to a condition of elevated blood pressure usually above a systolic pressure of 140 mm/Hg and a diastolic pressure above 90 mm/Hg

Individual Case Safety Report is a pharmacovigilance report that details an adverse event relating to an individual patient.

Ischaemic heart disease is a condition that results from the narrowing of heart vessels due to accumulation of atherosclerotic plaque within the vessels resulting in inadequate perfusion of the cardiac muscles. Ischaemic heart disease is also referred to as coronary artery disease.

Lowest Level Terms (LLTs) refers to about 70,000 terms in the MedDRA hierarchy which reflect how an observation is actually reported in medical practise. These are the most specific terms in the hierarchy.

MedDRA refers to a standardised medical terminology used to facilitate sharing of regulatory information internationally for medical products for human use. It was developed by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) in order to provide a uniform dictionary for use in the registration, documentation and monitoring of medical products.

Paroxysmal arrhythmia refers to a form of episodic arrhythmia that starts and ends abruptly.

Pharmacovigilance is the science to enhance patient care and patient safety regarding the use of medicines by collecting, monitoring, assessing, and evaluating information from healthcare providers and patients.

Preferred Term (PT) refers to a description that is deemed to be the most clinically appropriate way of expressing a concept in a clinical record and it varies with language and dialect.

Signal refers to reported information on a possible causal relationship between a drug an adverse event which was previously unknown and undocumented.

Spontaneous adverse event reports are reports submitted voluntarily by patients or healthcare providers that pertain to negative events occurring during routine drug therapy. The reports are usually in manual or electronic form and are submitted to organisations responsible for collecting reports of adverse effects, usually national pharmacovigilance centres.

Standard MedDRA Query is a group of MedDRA terms usually at the Preferred Term (PT) level that relate to a defined medical condition or area of interest.

Torsade de pointes is a form of polymorphic ventricular tachycardia in patients with a long QT interval. It is a life-threatening condition and is usually characterized by rapid, irregular QRS complexes.

Ventricular arrhythmia refers to abnormal heartbeats that originate from the ventricles.

VigiBase is a global spontaneous adverse reports database maintained jointly by the World Health Organisation and the Uppsala Monitoring Centre (WHO-UMC).

ABSTRACT

Background The body responsible for monitoring drug safety in Kenya is the Pharmacy and Poisons Board (PPB). One of the methods for tracking the safety of medicines is through information submitted in spontaneous adverse event reports. These reports are technically known as individual case safety reports (ICSRs) and are submitted by health care workers, drug consumers and other interested parties such as lawyers and lobby groups. In order for potential signals of new adverse reactions to be effectively detected, these reports must contain all the relevant patient and drug information as well as a description of the adverse event. One of the potential areas for signal detection is the relationship between antiretroviral therapy and cardiovascular diseases (CVDs). Cardiovascular diseases are some of the major causes of death and morbidity among Human Immunodeficiency Virus (HIV) patients. While various studies have been done to assess the relationship between antiretroviral therapy (ART) and cardiovascular diseases, few have utilized pharmacovigilance databases to evaluate this link. Disproportionality analysis is one of the methods for detecting potential new signals using spontaneous reports databases.

Objective: The objective of the study was to identify the trend of quality of Kenyan individual case safety reports (ICSRs) submitted to the World Health Organizations's (WHO) global spontaneous adverse events database, VigiBase. The study also sought to identify safety signals for cardiac arrhythmias associated with the use of antiretroviral drugs in HIV patients. Moreover, the study aimed to evaluate for potential drug-drug interactions between antiretroviral (ARV) drugs and some selected cardiovascular (CVS) agents.

Methods: The study was divided into two parts. The first part encompassed a time series analysis of the completeness score of Kenyan adverse events reports on VigiBase. The average quarterly scores were subjected to interrupted generalized linear regression analysis using R programming software. The second part involved an exploratory analysis of cardiac arrhythmias associated with the use of antiretroviral drugs as well as an evaluation of possible drug interactions between ARVs and selected cardiovascular agents. Disproportionality analysis of the Food and Drug Administration Adverse Event Reporting System (FAERS) database was used to identify signals between antiretroviral drugs and arrhythmia. Data for disproportionality analysis was retrieved through customized queries using the AERSMine platform. Assessment of potential drug-drug interactions was done by customizing the search terms to include the Boolean operator "AND". Addition of this operator enabled the data

mining tool to capture only the adverse events reported with the concomitant use of the drugs under evaluation.

Results: A total of 11,270 Kenyan individual case safety reports (ICSRs) were retrieved from VigiBase. Reports from Nairobi (15.4%), Uasin Gishu (11%), Migori (10.5%), Kisumu (7.4%) and Kiambu (6.2%) constituted the highest proportion of the database. Most of the reports involved antiretroviral drugs (79%), anti-tuberculosis medications (6.6%), antibiotics (5.5%) and anticancer medications (2.2%). There was an initial drop in the quality of reports during early reporting period followed by a big improvement with the completeness score peaking at around 0.66 by the end of 2014. This was followed by a period of declining quality which later took an upward trajectory. The highest score recorded was 0.74 which was achieved in the last quarter of 2017. Interrupted time series analysis of the quality revealed a major change point in the fourth quarter of 2012. In the period following this event, the average quarterly completeness scores increased by 0.055 ± 0.017 ($p = 0.003$). A total of 11, 919, 342 reports in the FAERS database were evaluated. A strong association was found between some ARV drugs and cardiac arrhythmia. The strongest signals identified were for foetal and neonatal arrhythmias, tachyarrhythmia and ventricular arrhythmias. With regard to bradycardia and bradyarrhythmia in HIV patients on ARVs, the signals were only significant for zalcitabine, lopinavir/ritonavir and nelfinavir. The strongest signal for tachyarrhythmias was recorded in delavirdine (>4). Protease inhibitors produced relatively strong signals for torsade de pointes with indinavir, saquinavir, nelfinavir and fosemprenavir all having signals of more than two. Efavirenz, nelfinavir and raltegravir also exhibited a strong signal for ventricular arrhythmia. For all the ARVs in which sinus node dysfunction was reported, the signal was more than 2. Potentially toxic drug-drug interactions between protease inhibitors, non-nucleoside reverse transcriptase inhibitors (NNRTIs) and selected cardiovascular agents were also observed. The adverse events that exhibited the strongest signals with regard to these suspected interactions include sinus tachycardia and QT interval prolongation.

Conclusion and recommendations: The quality of Kenyan adverse event reports has stagnated at a score of about 70%. Continued pharmacovigilance training of health care workers and consumers is therefore required to achieve further improvement in the quality of reporting. The study also established that some antiretroviral drugs may have arrhythmic adverse events. These potential signals require further investigation using more rigorous research methods such as cohort event monitoring.

CHAPTER ONE: INTRODUCTION

1.1 BACKGROUND

Highly active antiretroviral therapy (HAART), used to manage Human Immunodeficiency Virus (HIV), tends to cause a broad range of adverse effects in HIV patients (1). Some of the most common adverse effects include fatigue; headache; and gastrointestinal disturbances such as nausea, vomiting, bloating and diarrhoea. Other less common but more serious adverse effects include hypersensitivity reactions associated with nevirapine and efavirenz; anaemia linked to chronic zidovudine use; stavudine associated peripheral neuropathy; and dyslipidaemias associated with protease inhibitors such as lopinavir and ritonavir. Additional serious adverse effects include hepatotoxicity, lactic acidosis, hyperlactatemia, hyperglycaemia, and haematological and bone disorders (1–4).

Despite the challenge of the sometimes-debilitating adverse effects, recent advances in medical research have led to the development of highly effective antiretroviral (ARV) drugs with fewer adverse effects and more friendly dosage forms, such as fixed dose combinations (FDCs), which have enhanced compliance and viral suppression. Furthermore, programs such as the President's Emergency Plan for AIDS Relief (PEPFAR) have led to widespread and consistent access to ARVs for patients throughout the world. The convergence of these factors has consequently resulted in a major reduction in Acquired Immunodeficiency Syndrome (AIDS)-related morbidity and deaths (5–7). Corresponding with this decrease however, has been a notable increase in mortality and health conditions that are not directly related to HIV. Of particular concern are cardiovascular diseases (CVDs) (5, 8). CVDs are now some of the leading causes of death among HIV patients (6, 7, 9, 10). Some of the postulated mechanisms for these include ARV drug induced metabolic changes; HIV-accelerated systemic immune activation that is postulated to promote atherosclerosis; as well as the high prevalence of risk factors for the development of CVDs in HIV patients (5, 6 ,9–13).

The body responsible for the monitoring of adverse effects of marketed drugs in Kenya is the Pharmacy and Poisons Board (PPB). It was established by an Act of Parliament (14). In addition to this Act, there are other supporting and subsidiary legislation, rules, regulations and guidelines that regulate the pharmaceutical industry in the country. The Department of Pharmacovigilance at the Board was established in 2004, primarily to ensure the post marketing quality, safety and efficacy of pharmaceutical products in the country through the early detection, assessment, understanding and prevention of adverse effects or any other possible

drug-related problems (15). Since 2010, the Board has maintained a database of all spontaneous reports of drug adverse effects from all over the country. This data, which is stored in VigiBase, was utilised in this study. The World Health Organization-Uppsala Monitoring Centre (WHO-UMC) has given PPB access to the data for purposes of analysis as well as signal detection.

1.2 PROBLEM STATEMENT

Spontaneous adverse effect reports to VigiBase and other databases are in the form of individual case safety reports (ICSRs). These reports must be of good quality in order for new potential signals of a new adverse reaction to be detected. The data should be sufficient to allow for a full assessment of the relationship between the drug and the event (16). Analysis of the causal relationship between a drug and an adverse event is usually a complex, multi stakeholder approach often requiring the application of different approaches. However, a corresponding element to all these approaches is that the assessment is made easier when more information is available in a report. Conclusions of these evaluations are also more likely to be correct if the information provided is complete and relevant (17). Nonetheless, despite the seemingly indispensable importance of completeness of ICSRs, this aspect of pharmacovigilance reporting remains a lingering challenge especially for the nascent pharmacovigilance practices in the low- and middle-income countries of Africa, Asia and much of South America. This could be attributed to systemic weaknesses of the individual national pharmacovigilance systems such as inadequate funding, lack of proper capacity building frameworks at the national pharmacovigilance (PV) centres as well as lack of structures to enable continuous stakeholder training and coaching on adverse events reporting tools and techniques (18).

While the problem of inadequate reporting persists in the aforementioned areas, data on the quality of reporting remains scanty or even non-existent, and policy makers often have to rely on anecdotal evidence to make strategic decisions and issue policy directives to guide the practice of pharmacovigilance in these areas. Kenya has not been spared in as far as lack of credible data is concerned. No research has been undertaken to critically assess the completeness of ICSRs submitted to the national PV centre at the Pharmacy and Poisons Board as well as examine possible determinants for the quality of these reports. Furthermore, there has not been a comprehensive analysis of the spontaneous reports to determine various data characteristics such as reporter qualifications, regional reporting patterns and severity of the adverse effects.

The Kenyan adverse events (AEs) database contains multiple reports concerning ARV associated adverse drug reactions (ADRs). While various studies have been done to assess the relationship between antiretroviral therapy (ART) and cardiovascular diseases, few have utilized pharmacovigilance databases to evaluate this link. Moreover, data on signals relating ARVs to CVD is scanty (4). This data is crucial for proper planning of strategies to prevent as well as deal with CVDs, if and when they occur. Disproportionality analysis is one of the ways by which predictive factors for AEs can be established through the detection of potential new signals in the adverse effects database.

This study therefore sought to address the gap with regards to the use of data mining of safety report databases as a tool to assess cardiovascular system (CVS) adverse events of antiretroviral drugs by carrying out a disproportionality analysis of the Food and Drug Administration Adverse Event Reporting System (FAERS). The study also sought to provide data on the quality of ICSRs submitted to the PPB database by determining the trend with regard to completeness scores of ICSRs submitted to the Board since 2010.

1.3 RESEARCH QUESTIONS

This study sought to answer the following questions:

i. What is the trend of quality of Kenyan individual case safety report (ICSRs) submitted to VigiBase?
ii. Are there potentially new safety signals with regard to antiretroviral drugs and cardiac arrhythmias that can be identified from the spontaneous reports database?
iii. Are there drug interactions between ARVs and cardiovascular agents that can be identified using these data?

1.4 STUDY OBJECTIVES

1.4.1 General objective

The broad objective of this study was to assess the trend of quality of Kenyan adverse event reports as well as to determine if there were potentially new safety signals with respect to antiretroviral drugs and cardiac arrhythmias in HIV patients.

1.4.2 Specific objectives

The specific objectives were to:

i. Describe the trend of the completeness scores of Kenyan adverse effects data in VigiBase.
ii. Identify potential new safety signals with respect to antiretroviral drugs and cardiac arrhythmias.
iii. Identify safety signals for possible drug-drug interactions between antiretroviral drugs and selected cardiovascular agents.

1.5 STUDY JUSTIFICATION

Information on the quality of spontaneous reports as well as the attributes of submitted data such as reporter characteristics and regional reporting patterns is vital for monitoring the effectiveness of pharmacovigilance efforts in the country. Moreover, this information provides important feedback as to whether strategies to promote adverse effect reporting especially in the rural facilities are working. Disproportionality analysis on the other hand is an important tool for signal detection. While various studies evaluating the safety profile of antiretroviral drugs have been carried out in various parts of the world, data on studies that have specifically utilised data mining of pharmacovigilance databases to identify safety issues with regard to ARVs is scanty. It was therefore of utmost importance that this study be undertaken. This study used data from the FAERS database that contained more than eleven million adverse event reports. The size of this database provides a very good platform for data mining as well as signal detection. Additionally, the growing threat of cardiovascular diseases among HIV patients makes the evaluation of safety signals for ARV associated CVD a particularly crucial research area.

The findings of this study will be shared with the Pharmacovigilance department at the Pharmacy and Poisons Board and HIV program stakeholders at the Ministry of Health (MOH) including the National AIDS and STI Control Programme (NASCOP). The findings will hopefully provide an informed basis for the formulation and implementation of interventions to improve the quality of adverse event reporting in the country. Information on potential new signals identified will also be shared with the Board and the Ministry of Health. Such data may be useful in highlighting the need to identify and promptly manage CVS adverse events in HIV patients.

CHAPTER TWO: LITERATURE REVIEW

2.1 STATUS OF PHARMACOVIGILANCE IN KENYA

Since the establishment of the Pharmacovigilance department at the PPB in 2004, significant progress has been made. The National Pharmacovigilance System in Kenya was formally launched in June 2009 with a focus on spontaneous reporting of adverse drug reactions (ADRs) and poor quality drugs. The system has since been rolled out to the whole country, with over 10, 0000 health care workers trained on various aspects of pharmacovigilance. Additionally, over 8000 ADRs and 4000 poor quality medicines reports have been submitted in the national pharmacovigilance database (19). The main purpose of these reports is fourfold. Firstly, the reports provide crucial information that aids in the early detection of new ADRs and drug interactions. Secondly, the reports help in the detection of increases in the frequency of known ADRs. Thirdly, the reports provide data that can be utilised in the systematic identification of risk factors and mechanisms underlying the ADRs. These reports also enable the estimation of quantitative aspects of benefit/risk analysis and dissemination of information needed to improve drug prescribing and regulation to the relevant stakeholders (15). Importantly, there are on-going efforts to further enhance pharmacovigilance reporting in the country. Reporting by patients and consumers is especially being targeted with strategies such as public awareness campaigns and consumer education seminars being rolled out.

2.2 QUALITY OF PHARMACOVIGILANCE REPORTS

2.2.1 World Health Organization guidelines on quality of Individual Case Safety Reports

Reports of suspected ADRs to the national PV database are done in the form of individual case safety reports (ICSRs). The value of these reports is directly proportional to the amount of clinically relevant information they contain (20). The importance of the quality of data in ICSR databases cannot be overstated. Poor quality data could lead to wrong or delayed conclusions about a patient or a safety signal, resulting in poor quality of care and possible patient harm (17). Towards this end, the Uppsala Monitoring Centre (UMC) is continuously devising strategies to further ameliorate the quality of ICRS data inputted into its ADR database, VigiBase. Data quality improvement encompasses both the aspects of data input and output. Consequently, the UMC has taken an active role in promoting the international ICSR standard exchange format known as the International Conference on Harmonization E2B (ICH E2B). The ICH E2B format includes all the important data fields that allow for an in-depth medical

analysis of the data. Additionally, the UMC has, together with its partners developed Vigiflow which is an ICSR management tool that allowscountries entering the WHO Programme to use the ICH E2B format (17).

The ICH E2B format sets out a basic yardstick for all ICSRs uploaded into VigiBase in a bid to promote the quality of inputted data. As such, the minimum administrative information needed for the processing and identification of an ICSR in VigiBase includes a sender's unique case identification number; a worldwide unique case identification number; and a sender identifier. This information is vital for the correct report identification as well as for picking out duplicate reports in the database. Moreover, the date of receipt of most recent information is also required to enable the follow-up and verification. In addition to the administrative information, ICH E2B lists the minimum information needed for a valid ICSR. These include an identifiable patient and reporter, one reaction/event, and one suspect drug (17).

2.2.2 Assessment of quality of Individual Case Safety Reports

As part of its continuous efforts to improve the quality of data reports, UMC has developed the VigiGrade completeness score. This is a multidimensional measure of the quality of information contained in ICSRs. It exposes problems of missing data in reports received from national pharmacovigilance centres with an aim to help countries improve data collection, management and transmission onto VigiBase (17, 22). A number of fields have been selected for their usefulness in the case assessment process and a score is given to each field. The individual field scores are weighted and combined into a single score for the whole report.

The VigiGrade completeness score (*C*) starts at 1 for perfect ICSRs with complete information on time-to-onset, age, sex, indication, outcome, report type, dose, country, primary reporter and comments. While the completeness score is calculated for each report, the score is usually given as an average number for all reports submitted from one country over a given time period. For each missing dimension, a penalty is subtracted with the size of the penalty dictated by clinical relevance as shown in Table 1 (21, 23, 24). It is important to note , however, that VigiGrade does not provide any insight as to whether the information provided in the report establishes causality between the drug and adverse event (20).

VigiGrade is primarily used as a means of feedback to national PV centres with regard to the data quality of their submitted reports. However, the tool has also proven to be an indicator of

a true signal. It has therefore been incorporated as one of the parameters included in the VigiRank method used by UMC in signal detection (22).

Table 1: Dimensions of VigiGrade completeness score and its computation*

Dimensions	Description	Considerations	Penalty
Time to onset of adverse event	Time from start of treatment to the adverse event	Temporal sequence of events leading to adverse event	Between 10% to 50% depending on ambiguity
Drug indication	Condition being treated	Proper description of condition that allows mapping to standard terminologies such as MedDRA and ICD	30% penalty for missing information
Outcome of event	How the adverse event was resolved	Whether information about the outcome was clearly provided	30% penalty if outcome data is missing
Sex of the patient	Patient gender	whether information on patients' gender was provided	30% penalty if data on gender was not provided
Age of the patient	Patient's age	Whether age or age group of the patient is specified	30% penalty if age is not given and 10% penalty if only the age group is specified
Dose of the suspected drug(s)	Total daily dose of the suspected drug	Whether the total daily dose can be calculated from the dosage information given	10% penalty if no proper dosage data is given to enable estimation of the total daily dose
Country of origin	Country in which the event was reported	Whether the country of origin of report is indicated	10% penalty if this information is not indicated
Primary reporter	Cadre of health worker	Interpretation of events may differ between different cadres	10% if cadre of reporter is not given
Report type	Whether it's a spontaneous report, report from study or otherwise	Whether this information is provided	10% penalty if information not filled
Comments	Free text information	Whether additional information is relevant and helpful	10% penalty for irrelevant comments

**(Adapted from the Agency for Medicinal Products and Medical Devices of Croatia (HALMED))*

2.3 DATA MINING IN PHARMACOVIGILANCE

2.3.1 Databases used for signal detection

There are various sources of pharmacovigilance data that can be used for evaluation of potential new safety signals. Some of the most fertile grounds for data mining are spontaneous reports databases. These include the WHO managed VigiBase; EudraVigilance, a spontaneous reports database run by the European Medicines Agency (EMA) that handles reports from the European Economic Area member states; and the Food and Drug Administration's Adverse Event Reporting System (FAERS) that manages adverse event reports from the United States of America (19, 25–27). Others include the Canadian Canada Vigilance adverse reaction online database and the Australian Database of Adverse Event Notifications (DAEN) (28, 29).

Apart from the spontaneous reports databases, there are other less utilised databases that store useful drug safety information that could be evaluated for signals. Examples include prescription event monitoring databases and electronic health records databases such as records of healthcare insurance claims (24). It is important to note however that while some of these databases such as FAERS and Canada Vigilance are freely accessible, others like VigiBase have restricted access and require permission from national pharmacovigilance centres for access to their data to be granted.

2.3.2 Data mining methods used in signal detection

According to the Council for International Organizations of Medical Sciences (CIOMS VIII), a drug safety signal refers to "*Information that arises from one or multiple sources (including observations and experiments), which suggests a new potentially causal association, or a new aspect of a known association, between an intervention and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify verificatory action*" (19, 30). Data mining methods therefore seek to exploit mathematical and statistical techniques to assess large databases of adverse events with the principle object of uncovering potentially significant drug-event relationships and generating hypotheses. Nevertheless, while useful in signal detection and hypothesis generation, these methods cannot be used to establish causality (19, 26).

There are diverse methods that can be applied in data mining, specifically with regard to spontaneous report databases. The most commonly used methods are pegged on the concept of disproportionality. These methods are collectively referred to as disproportionality analysis and

utilise measures of disproportionality/algorithms to assess associations between drugs and a given event. Disproportionality analysis refers to approaches to signal detection premised on the comparison of reporting proportions between a given drug of interest and all other drugs in a spontaneous reports database (25). The data construct that underlies disproportionality analysis is based on a contingency table as shown in Table 2 (24). Some of the more commonly applied measures of disproportionality used during data mining of spontaneous reports databases include the Proportional Reporting Ratio (PRR), Reporting Odds Ratio (ROR), Relative Reporting (RR) and the Information Component (IC).

Table 2: Adverse reports data for disproportionality analysis

	Reports for event of interest	**Reports for all other events**	**Total**
Reports for drug of interest	A	B	A+B
Reports for all other drugs	C	D	C+D
Total	A+C	B+D	A+B+C+D

PRR=A(C+D)/C(A+B); ROR=AD/CB; RR=A(A+B+C+D)/(A+C)(A+B);

IC=Log2[A(A+B+C+D)/(A+C)(A+D)].

Generally, measures of disproportionality values greater than 2 indicate that a drug-adverse event combination is twice as likely as all other combinations and is therefore significant enough to warrants further investigation (31). While these algorithms are quite straightforward, there are instances when it may be necessary to adjust for the variability resulting from the small number of the expected/observed reports of the drug-event pair. This requires the use of more complex statistical procedures such as the Empirical Bayesian Geometric Mean (EBGM), the Multi-item Gamma Poisson Shrinker (MGPS) and the Bayesian Confidence Propagation Neural Network (BCPNN) (19, 26, 27).

There are other non-disproportionality-based methods that can be used in data mining. One of them is Change-Point Analysis (CPA) that is used to assess changes in the slope in the time series of a database. Significant changes or shifts in the slope could be indicative of important changes in the reporting patterns that may require further investigation. Text mining could also be utilised especially for data that is in the form of narratives and/or contains a description of the event. Finally, visualization tools such as heat maps and sector maps have also found utility in the data mining process (26).

2.3.3 Benefits of mining spontaneous reports databases

The use of spontaneous reports databases as a source of data for signal detecting is advantageous in many ways. Firstly, the coverage of spontaneous reports is practically

universal. Spontaneous reports databases therefore have the potential to monitor drug use in all patients using a particular drug. Secondly, spontaneous reporting offers one of the cheapest means for drug safety surveillance, providing a sustainable method of tracking adverse events and ensuring that reporting is not hindered by financial challenges. This promotes consistency in reporting rates (32). Moreover, data mining using spontaneous reports databases promotes efficiency because they enable automation of the data mining procedures in addition to allowing the application of standardized techniques for whole datasets (26). Spontaneous databases can also be used to identify potential drug-drug interactions (33, 34).

2.3.4 Biases associated with spontaneous reports databases

In spite of the strengths associated with spontaneous report databases, it has been argued that spontaneous data contain inherent weaknesses that render disproportionality analysis a poor method for comparing the safety profile of two drugs. Further, it has been claimed that disproportionality analysis is only practical as tool for hypotheses generation and even then, these hypotheses must be subjected to more rigorous assessment before they can be applied to guide policy directives or even steer clinical decisions (25). To support these assertions, a number of flaws in the data contained in spontaneous reports databases have been pointed out.

One of the major weaknesses of spontaneous report databases is reporting bias. Reporting bias could lead to the over reporting or under reporting of adverse events related to a given product. One of the postulated reasons for reporting bias is the Weber effect whereby the reporting of adverse effects for a drug peaks at the second year following marketing authorization and then declines in the subsequent years. Other peculiarities that could lead to reporting bias include activities by the regulatory authorities such as issuing an alert for a given adverse event; increased media attention towards a product; or the approval of a new indication for a given drug (25, 32, 35). A study by Moore et al (36) in the UK fittingly describes reporting bias. The study was initiated after the suspension of the neuroleptic sertindole from the UK market because it appeared to have ten times the PRR of other drugs in the same class with regard to proportional reporting of sudden death and fatal arrhythmias. It was discovered that the requirement for mandatory electrocardiogram monitoring for sertindole as well as “Dear doctor letters” accompanying this directive led to higher adverse events reporting for sertindole compared to other similar drugs such as olanzapine and risperidone. When this bias was unmasked, the decision to suspend the drug was rescinded.

Confounding could also affect the credibility of findings of disproportionality analysis of a spontaneous reports database. This is especially so if comparisons are made for drugs with varying indications. Apart from indications, disparities in background rates of events for populations using dissimilar products could also introduce confounding into disproportionality analysis. One of the ways by which confounding could be handled is by adjusting the results obtained by factors such as concomitant medications and age using logistic regression. Alternatively, confounding could be curbed by restricting disproportionality analysis to products within the same therapeutic class (25).

In addition to reporting bias and confounding, the lack of a known incidence denominator that results in the assumption of equal reporting rates between two drugs under evaluation could also result in erroneous conclusions (25). Challenges related to duplication of reports submitted to spontaneous reports databases, incorrect, vague and missing information further damages the reliability of spontaneous databases as a credible source of signal detection data (26).

2.4 CARDIOVASCULAR DISEASE AND HIV

2.4.1 HIV associated cardiovascular disease

Cardiovascular disease is one of the major causes of death and mortality among people living with HIV (PLWH). Many studies show that the risk of ischaemic heart disease (IHD) among this cohort is about 1.5 to 2 times higher than in the HIV negative population (8, 9). While anti-retroviral drugs have been implicated in heart disease, the human immunodeficiency virus/acquired immunodeficiency syndrome have also been found to be a major contributor of cardiovascular disease in this cohort. In a South African study by Sliwa et al (37), it was established that HIV associated cardiomyopathy is the most common manifestation of cardiovascular disease related to HIV; accounting for about 38% of all newly diagnosed CVDs in HIV patients. The pathophysiology of cardiomyopathy in HIV is largely unknown. Several mechanisms have however been suggested (37– 41). Direct HIV infestation of the cardiac myocytes; autoimmune reactions; as well as cardiac infiltration by other HIV associated pathogens such as *Toxoplasmosis gondii* have been proposed to explain cardiac derangement in HIV. Other postulated mechanisms include endocrine dysfunction, myocarditis, malnutrition and low CD4 count (below 100 cells/ml).

According to the study, other common presentations of cardiovascular disease in HIV patients are pericarditis (12.5%), valve disease (11.2%) and hypertension (7.1%). The most frequent

causes of pericarditis are mycobacterial and bacterial infection in HIV. Lymphomas, Kaposi's sarcoma (KS), fungal and viral infections have also been implicated. A majority of the causes (45%) are however idiopathic (39, 41). In addition to these heart diseases, HIV infection has been associated with an increased risk of coronary artery disease (CAD) (42). This is due to HIV associated chronic immune activation that promotes arteriosclerosis.

Electrocardiographic (ECG) abnormalities have also been widely reported in HIV patients (43). The most common ECG derangement in HIV is Q-T interval prolongation (44, 45). This defect increases the chance of sudden death in HIV patients by almost 5 times. Hepatitis C co-infected HIV patients are especially susceptible to ECG anomalies (44). Other ECG abnormalities are sinus tachycardia, T-wave inversion and ventricular and atrial ectopics (46). The pathophysiology of these defects is not well understood. According to Okoye et al (46) however, low BMI in HIV patients that leads to cachectic processes in the heart is one of the main causes of ECG abnormalities. It is hypothesized that sinus tachycardia is the result of beta-receptor stimulation by HIV associated gp 120 proteins. Emotions and dehydration has also been suggested as possible causes. S-T wave changes and T-wave inversion are suspected to be caused by HIV related cardiomyopathy and pericarditis.

HIV has been associated cardiac neoplasms (41). Non-Hodgkin lymphoma is the most common of these. Others are endocardial papillary fibroelastoma and herpes virus 8 associated primary effusion lymphoma. Minimal KS involvement in the heart among HIV patients has also been seen. HIV has also been associated pulmonary hypertension, with about 1 in 200 HIV patients presenting with the condition. While a majority of these are idiopathic, HIV related inflammatory processes in the heart may be a contributing factor. Pulmonary hypertension in HIV patients has a poor prognosis, with a median survival period of 6 months (41, 47).

2.4.2 Association between antiretroviral therapy and cardiovascular disease

ART related cardiovascular dysfunction has been widely reported. The first generation protease inhibitors (PIs) such as lopinavir cause CVDs (9). It is postulated that CVD events arise as a result of the dyslipidaemias associated with this class of ARVs. Newer PIs have also been associated with heart disease. In the PREVALEAT (PREmature VAscular LEsions and Antiretroviral Therapy) II study, Maggi et al (48) established that ART naive HIV patients started on a darunavir based regimen had a higher risk developing carotid atherosclerosis compared with those started on atazanavir or efavirenz based regimens. The study however involved patients with less than 200 CD4 cells/ml and follow up was limited to only 12 months.

In the Data Collection on Adverse Events of Anti-HIV Drugs study (49), darunavir was associated with a 59% increase in the risk of CVD with over 5 years of exposure. While this rate is comparatively similar to that of older PIs, indinavir and lopinavir, it did not appear to be associated with dyslipidaemia. Findings by Moller et al (50) also support this association. The study by Moller et al found out that in patients exposed to PIs for more than six years, the incidence of myocardial infarction (MI) increased from 1.53/1000 person years to 6.01/1000 person years. An association between PIs and MI could still be established even after adjustments were made for serum lipid levels and concomitant drugs which were possible confounders. An analysis of pooled data from 19 clinical trials did not show any association between darunavir and an increased risk of CVD (9). Of note though is that these studies were sponsored by the product manufacturers.

Abacavir and didanosine, both nucleoside reverse transcriptase inhibitors (NRTIs), have also been associated with MI (9, 51). These claims have however been refuted (52), and further research is needed for conclusive findings to made concerning the CVD effects of this class of ARVs. Other cardiovascular events associated with ARVs include systemic arterial hypertension (53) and arrhythmias caused by the prophylactic trimethoprim-sulfamethoxazole, an ART adjuvant used in the prevention of opportunistic infections (54). Most of these studies are not conclusive and further research is required to investigate the relationship between ARVs and cardiovascular events in HIV patients.

2.4.3 Cardiovascular dysfunction resulting from antiretroviral drug-drug interactions in HIV patients

In addition to individual actions by ARVs that precipitate cardiac disease, drug-drug interactions between ARVs and other concomitant medications is also a major cause of heart function derangement. The most widely reported dysfunction is bradycardia resulting from co-administration of certain ARVs and antihypertensive drugs. A case study reported by Puech et al in 2011 (55) involved a 51 year old patient on multiple drugs. They included the anti-hypertensives lacidipine, metoprolol and ramipril; a thyroid hormone replacement drug levothyroxine; an antiplatelet acetylsalicylic acid; and a lipid lowering drug, rosuvastatin. The patient was stable. However, about 48 hours after he was put on HIV post-exposure prophylaxis, the patient came down with severe bradycardia (20-25 bpm) and hypotension (50/20 mmHg). The post exposure regimen included emtricitabine (FTC), lopinavir/ritonavir (LPV/r) and tenofovir (TDF). Investigations revealed complete atrioventricular (AV) block.

Upon treatment with isoprenaline, regular sinus rhythm was restored. Diagnostic tests such as electrolytes, cardiac enzymes and complete haemogram turned out normal. LPV/r, lacidipine, ramipril and metoprolol were immediately stopped. On the fourth day, raltegravir (RAL) was prescribed and started. On the seventh day, lacidipine and ramipril were re-instated while metoprolol was re-started on the ninth day.

Analyses of the blood showed higher than normal lopinavir concentrations in plasma. Further, after genetic analyses, it was established that the patient was a low expressor of P-glycoprotein 1 (P-gp) and an intermediate metaboliser for CYP2D6. The patient however exhibited a normal CYP3A4 metabolism. After extensive case analysis, it was proposed that concomitant use of LPV/r, metoprolol and lacidipine was responsible for the hypotension and bradycardia experienced by the patient. Metoprolol is chiefly metabolised by CYP 2D6. CYP 3A4 metabolism of metoprolol is minimal. It was hypothesized that ritonavir inhibition of CYP3A4 may have led to an increase in the plasma concentration of metoprolol. This is because the proportion of metoprolol metabolism by CYP3A4 could be enhanced due to the fact that the patient was an intermediate metaboliser for CYP2D6. Additionally, lacidipine is primarily cleared through CYP3A4. Inhibition of CYP3A4 and P-gp by ritonavir would therefore lead to increased plasma concentrations of lacidipine resulting in marked hypotension.

Inhibition of CYP isoforms by PIs including ritonavir, indinavir (IDV) and nelfinavir (NFV) is well known. And while ritonavir has a greater tendency for interactions such as the one described by Puech et al, significant interactions involving nelfinavir have also been reported. Rossi et al (56) reported a case of a HIV patient on extended-release nifedipine who developed symptomatic orthostasis and AV block after being started on an ART regimen that included nelfinavir. Upon withdrawal of the ARVs, the ECG abnormalities were resolved in 24 hours. When a nelfinavir re-challenge was instituted, the patient again developed orthostatic symptoms. The patient was later switched to an efavirenz based ART regimen with no recurrence of symptoms. However, subsequent concurrent administration of a ritonavir and indinavir based ART regimen with nifedipine again resulted in orthostatic symptoms. These were effectively controlled by stopping atenolol and reducing the dose of nifedipine by 50%. A similar case of the nifedipine-LPV/r interaction is described by Baeza et al (57) in a patient with renal failure. With the co-administration of nifedipine and ritonavir, CYP3A4 is inhibited by ritonavir leading to a high nifedipine exposure. This consequently leads to hypotension and renal failure. Patients with some degree of renal disease are especially susceptible. IDV/r has

also been shown to increase exposure and response to both amlodipine and diltiazem (58). To avoid potentially serious interactions involving ARVs therefore, it is important to avoid concomitant administration of drugs that have a high propensity for interaction. Alternatively, where co-administration cannot be avoided, low dose initiation and vigilant titration to response should be applied (58).

2.4.4 Prevention and management of cardiovascular disease in HIV patients

In addition to proper ARV drug selection, there are several strategies that can be applied to prevent the development or advancement of heart disease in HIV patients. Proper diabetes control in co-morbid patients is essential. For patients with pre-existing hypertension, blood pressure control is important to forestall progress to heart failure. The use of lipid lowering agents such as statins and fibrates in patients with a high risk of cardiovascular disease; as well as early treatment of atherogenic dyslipidaemia has also been recommended (39). The early commencement of beta-blockers and ACE-Is therapy to prevent the progress of CVD into severe systolic dysfunction is also encouraged. In end stage HIV associated cardiovascular disease, cardiac transplantation is advocated. The conventional therapy for treatment of heart disease can also be applied in the management of cardiovascular disease in HIV patients (59).

2.5 CONCEPTUAL FRAMEWORK

Disproportionality analysis for the purpose of identification of potential new signals with regards to ARVs was carried out according to the Council of International Organizations of Medical Sciences (CIOMS) Working Group VIII guidelines. The main source of safety data for this study was WHO's VigiBase and the American Food and Drug Administration Adverse Event Reporting System (FAERS) database. Other major pharmacovigilance databases that can be used as a source of data for disproportionality analysis include the European Medicines Agency's Eudravigilance and Canada's Canadavigilance. VigiBase was used to source data for Kenyan adverse event reports while FAERS was the source of safety data for the disproportionality analysis. The study sought to assess whether there was a relationship between ARVs and cardiac arrhythmias among patients on the highly active antiretroviral therapy. Some of the outcomes of interest were the safety signals for foetal and neonatal arrhythmias, tachyarrhythmia and bradyarrhythmia in adults as well as sinus node disorders. This was done by mining adverse events data from FAERS and subjecting it to disproportionality analysis. Measures of disproportionality including the proportional reporting

ratio (PRR), information component (IC) and the Yates Chi Square (χ 2) were calculated to identify any potential safety signals.

Significant safety issues identified are ideally supposed to be subjected to further assessment. Further action after the investigations could include forwarding the recommendations to the relevant drug safety committee at the PPB. It will then be the responsibility of this committee to decide on any risk communication directives as well as other relevant courses of action (24). The conceptual framework for this study is presented in Figure 1.

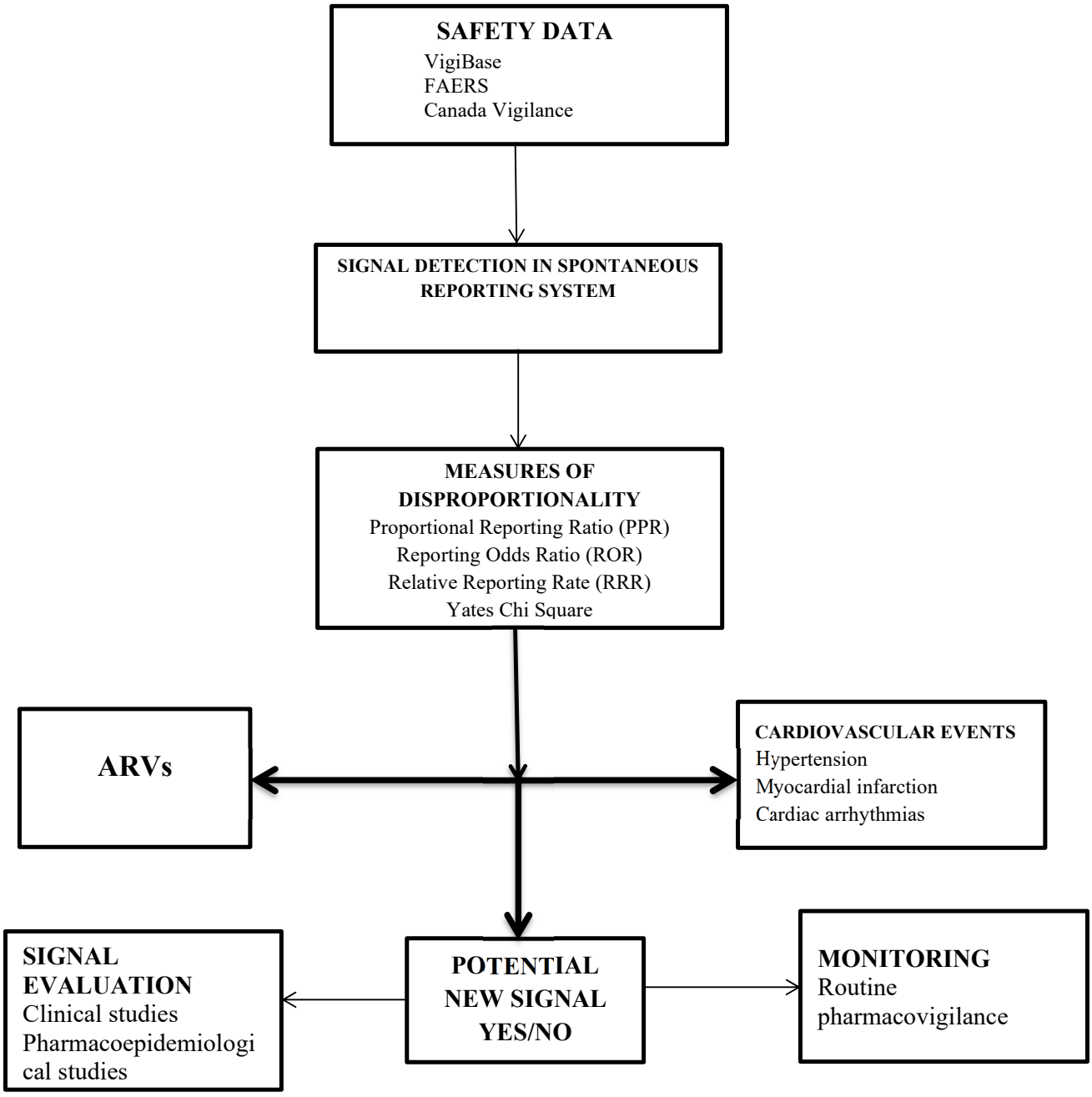


Figure 1: Conceptual map of the steps of signal detection and evaluation of the cardiovascular risks of ARVs

CHAPTER THREE: MATERIALS AND METHODS

The study was divided into two parts namely:

i. Time series analysis of the quality of Kenyan Individual Case Safety Reports (ICSRs) submitted to VigiBase since May 2010.
ii. Disproportionality analysis of the Federal Drug Administration Adverse Event Reporting System (FAERS) database for identification of possible signals between antiretroviral drugs and cardiovascular diseases.

3.1 TIME SERIES ANALYSIS

3.1.1 Study design and study population

The time series assessment was a retrospective longitudinal desktop review of Kenyan ICSRs on VigiBase. The analysis included all adverse event reports submitted to VigiBase between May 2010 and August 2018. No cases were excluded.

3.1.2 Study setting

Information on the quality of Kenyan ICSRs was obtained from VigiBase through the Pharmacy and Poisons Board. The data was in the form of completeness scores ranging from 0 to 1. The data was extracted from VigiBase in diverse dates of June 2019.

3.1.3 Data analysis

Data analysis was performed using R version 3.4.4 software. A total of 11, 270 Kenyan reports were obtained from VigiBase. These include all the reports submitted to the WHO from May 2010 to August 2018. The quality data of Kenyan ICSRs was divided into quarters. The quarterly means of the scores were then computed. In some instances, no reports were submitted for whole quarters. In order to have a complete dataset therefore, missing data was imputed from previous quarters. This was the case for the last quarter of 2010 and the first quarter of 2016. For quarters in which no data was submitted to Vigibase, the quarterly mean was imputed using the Hot-Deck imputation method. This involves randomly choosing the missing value from a given set of related and similar variables.

A time series of the quarterly mean scores was plotted against time periods. A regression line was also fitted into the plot. The graphical output provided a visual idea of the trend of quality of the reports over time. The time series was then decomposed into its constituent components,

which were the trend, random, seasonal and random effects components using the "*decompose* ()" function in R software. The decomposed time series data was then plotted against time periods to obtain trend and seasonal plots.

Interrupted time series analysis using the generalized least squares (GLS) regression method was then conducted on the time series data. GLS regression was used due to the assumption of heteroscedasticity of the residuals. The aim of this analysis was to identify key points at which there was a significant shift in the quality of adverse event reporting. Changes in reporting could either be significant increases or considerable decreases in the completeness scores of the ICSRs submitted to VigiBase by the Pharmacy and Poisons Board.

The change point was identified by establishing the model that best described an event in the timeline. The R command *model a=gls (x~time + event b + inter c)* was used to generate models to describe the change point. The general equation for analysis of times series data by GLS modeling as follows:

Equation 1: General equation for analysis of time series data

$$Y_t = \beta_0 + \beta_1 T_t + \beta_2 X_t + \beta_3 X_t T_t + \varepsilon_t$$

Whereby:

Y_t is the aggregated outcome variable measured at each equally-spaced time-point t;

T_t is a continuous variable indicating time in quarterly periods since the event of interest;

X_t is a dummy variable representing the intervention (pre-intervention periods=0, otherwise=1);

$X_t T_t$ is an interaction term;

β_0 is the starting level of the outcome variable;

β_1 is the slope of the outcome variable until the introduction of the intervention.

β_2 is the change in the level of the outcome that occurs in the period immediately after an event;

β_3 is the difference between pre- and post-event slopes;

The sum of β_1 and β_3 is the slope after the occurrence of the event of interest;

Ɛt is the random error which is random variability not explained by the model;

If β_2 was statistically significant, then the event of interest caused a change immediately after its occurrence leading to an almost immediate increase or decrease in the levels of the outcome variable. If β_3 was statistically significant, then the intervention caused a change in the outcome variable over a longer period of time.

Both linear and quadratic models were tested. Thereafter, a parsimonious model was obtained through backward stepwise modeling.

3.2 DISPROPORTIONALITY ANALYSIS

3.2.1 Study design and study population

Disproportionality analysis involved a retrospective longitudinal desktop review of all adverse events data submitted to the Food and Drug Administration Adverse Event Reporting System (FAERS) between January 2004 and December 2018.

3.2.2 Study setting

The disproportionality analysis was conducted using data obtained from the Food and Drug Administration Adverse Event Reporting System (FAERS) database.

3.2.3 Data retrieval

Data from the FDA's Adverse Events Reporting System (FAERS) was used to assess arrhythmic adverse events of ARVs as well as well as evaluate for interaction between antiretroviral drugs and selected cardiovascular agents drugs. A total of 25 ARVs were analysed encompassing 6 different classes of antiretroviral drugs used in management of HIV. Additionally, 18 different regimens were assessed. These regimens are the first, second- and third-line combinations currently being used in adult patients in Kenya.

The information was retrieved using the AERSMine data mining tool. AERSMine is computer software is developed at Division of Biomedical Informatics, Cincinnati Children's Hospital Medical Center (BMI CCHMC), Cincinnati, United States of America (60). The tool is accessible on https://research.cchmc.org/aers/home. The version of the software used was Version 2019-03-11. The data used in the analysis was for the period from the first quarter of 2004 to the fourth quarter of 2018. This consisted of a total of 11, 191, 342 reports. The data was retrieved on diverse dates of April and May 2019.

Both customised and standardised MedDRA queries were used to retrieve data for the analysis. *"Standardised MedDRA Queries (SMQs) are groupings of MedDRA terms, ordinarily at the Preferred Term (PT) level that relate to a defined medical condition or area of interest. The only Lowest Level Terms (LLTs) represented in an SMQ are those that link to a PT used in the SMQ; all others are excluded"* (61).

SMQs help in identifying and retrieving potentially relevant ICSRs from MedDRA based databases. SMQs are not in a standard format. Some contain a mixture of very specific terms and less specific terms that describe the overall clinical syndrome associated with a particular adverse event and drug exposure. Others are a straightforward collection of terms while some are designed to accommodate combinations of terms from more than one group. In order to accommodate all these different aspects therefore, SMQs have unique design features (61).

These standardised queries are algorithms that have been designed by a team of professionals. The algorithms are also hierarchical in nature (62).

The queries used in the study were either narrow or broad. The narrow scope refers to instances when a user may need to identify cases that are highly likely to represent the condition of interest. Application of a narrow scope leads to higher specificity. The broad scope on the other hand may be applied when a user seeks to identify all possible cases, including some that may prove to be of little or no interest on closer inspection. This results in greater search sensitivity.

In generating SMQs for this study, the *Introductory Guide for Standardised MedDRA Queries (SMQs) Version 16.1* (63) guidelines were used to define the specific cardiovascular adverse events of interest. The AEs analysed included cardiac arrhythmias and QT prolongation (Torsade de pointes). For the SMQs, both narrow and broad search strategies were used and these are provided in Table 3. Additionally, a customised search strategy was applied for some of the SMQs using High Level Grouped Terms (HLGTs) High Level Terms (HLTs) and Preferred Terms (PTs). Parenthesis and Boolean operators including 'AND', 'OR', and 'NOT' were also used. The inclusion and exclusion criteria were also be applied as per the guidelines. The HLTs and PTs used were obtained from the MedDRA Web-Based Browser version 3.0. Queries were modified depending on the output of the search. For all the adverse events, a mixture of SMQs and customised queries was used.

Table 3: Standardised search strategies for arrhythmic adverse events

Adverse Event	Broad query	Narrow query
Cardiac arrhythmias	1. Cardiac arrhythmias (HLGT) 2. Conduction defects (SMQ) 3. Disorders of sinus node function (SMQ)	1 a) Bradycardia (PT) OR Bradyarrhythmias (PT) OR Central bradycardia **(PT)** b) Cardiac arrest (PT) OR Cardiac death (PT) OR Cardiopulmonary arrest 2. Conduction defects (SMQ) 3. Disorders of sinus node function (SMQ)
Torsade de pointes	Ventricular arrhythmias and cardiac arrests (HLT) OR Cardiac conduction disorders	Torsade de pointes (PT) OR Conduction disorder (PT) OR Long QT syndrome (PT)

The customised search strategies used in the study are listed in Table 4.

Table 4: Customised queries used to retrieve data from AERSMine

Adverse event	Customised query
Cardiac arrhythmias	1. "cardiac arrhythmias" OR "ventricular arrhythmias and cardiac arrest" OR "supraventricular arrhythmias" OR "arrhythmia" OR "ventricular arrhythmia" OR "tachyarrhythmia" OR "sinus arrhythmia" OR "bradyarrhythmia" OR "arrhythmia supraventricular" OR "nodal arrhythmia" OR "foetal arrhythmia" OR "ventricular tachyarrhythmia" OR "supraventricular tachyarrhythmia" OR "paroxysmal arrhythmia" OR "arrhythmia neonatal" OR "reperfusion arrhythmia" OR "arrhythmogenic right ventricular dysplasia" OR "foetal tachyarrhythmia" 2. "bradycardia" OR "sinus bradycardia" OR "bradycardia neonatal" OR "bradycardia foetal" 3. "cardiac arrest" OR "cardiac arrest neonatal" "cardiopulmonary failure" OR "sudden cardiac death" OR "cardiac death" 4. "conduction disorder" OR "cardiac conduction disorders" OR "defect conduction intraventricular" OR "atrial conduction time prolongation" OR "atrioventricular conduction time shortened" 5. "sinus node dysfunction" OR "sinus tachycardia"
Torsade de pointes	"torsade de pointes" OR "electrocardiogram qt prolonged" OR "long qt syndrome" OR "electrocardiogram qt corrected interval prolonged" OR "electrocardiogram qt interval abnormal" OR "electrocardiogram qt shortened" OR "electrocardiogram qt interval" OR "electrocardiogram qt corrected interval shortened"

3.2.4 Measures of disproportionality for identification of safety signals

Different measures of disproportionality were used to evaluate for an association between ARVs and cardiac arrhythmias. These include the proportional reporting ratio (PRR), the Yates Chi Square, and the information component (IC). The threshold for a significant signal was set as follows: PRR of ≥2.0, IC of ≥2.0 and Yates Chi-squared test (χ 2) of ≥4.0. The level of significance was set at 5%. The IC was obtained using the AERSMine data mining tool. The following resource was used for the purpose of PRR and (χ 2) calculations: *http://openvigil.pharmacology.uni-kiel.de/contingency-table-calculator.php#* The results were presented in both graphical and tabular formats.

3.2.5 Evaluation of potential safety signals for arrhythmias with the concomitant use antiretroviral drugs and selected cardiovascular agents

3.2.5.1 Criteria used to select drugs with possible interactions

Protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs) are mostly metabolised by the Cytochrome P450 3A4 enzymes. Drugs that undergo biotransformation through the same system are therefore likely to have potential interactions with these ARVs. To assess for these possible interactions, ten cardiovascular agents from different classes commonly used in the Kenyan health care set up were selected. The drugs selected shared a metabolic pathway with some ARVs and therefore had potential for drug-drug interactions. Kenya National Guidelines for Cardiovascular Diseases Management (2018 Edition) (64) was used to identify some of the popularly applied agents. These include amlodipine, nifedipine, diltiazem, verapamil, atenolol, carvedilol, metoprolol, losartan, amiodarone and digoxin. Each of these were tested against seven ARVs including efavirenz, nevirapine, etravirine, atazanavir, ritonavir, darunavir and lopinavir/ritonavir. In total seventy drug combinations were evaluated for potential safety signals with respect to cardiovascular rhythm disorders. Only arrhythmic adverse events resulting from possible drug-drug interactions were evaluated.

3.2.5.2 Assessment for potential safety signals resulting from possible drug-drug interaction

Evaluation of potential drug-drug interactions was done by customizing the search terms to include the Boolean operator "AND". Addition of this operator enabled the data mining tool to capture only the adverse events reported with the concomitant use of the drugs under evaluation. For example, in order to assess the adverse events associated with the co-use of amlodipine and ritonavir, the search term in the 'Drugs' field of AERSMine was "'Amlodipine' AND 'Ritonavir'". The search term in the 'Adverse events' field was the customized query described in Section 3.2.3.

Potential safety signals were first evaluated using the Information Component (IC). Further assessment of the unknown adverse events with an IC of more than 1 was carried out using the Openvigil 2*2 contingency table tool to determine the proportional reporting ratio (PRR) and the Yates Chi Square (χ 2). This was done to further validate the observed associations in AERSMine between the drugs and the adverse events. The cut off for significant safety signals that warrant further investigation was as presented in Section 3.2.4.

3.2.6 Data quality and cleaning

AERSMine contains information from FAERS that is already cleaned and validated. No further cleaning was therefore necessary. The data was downloaded from AERSMine and exported to either Excel files or STATA (13.1) for analysis. Files were regularly backed up in email and external storage to avoid data loss.

3.3 DATA APPROVAL AND ETHICAL CONSIDERATIONS

Ethical approval for this study was sought from and granted by the Kenyatta National Hospital/University of Nairobi Ethics and Research Committee (KNH/UoN-ERC). The letter of ethical approval as appended in Appendix A (reference number P887/12/2018). Informed consent was not sought from patients because any identifier information is made inaccessible upon the entry of ICSR data into VigiBase through the use of a unique adverse event registration number. Additionally, the necessary approval was obtained from the Pharmacy and Poisons Board in order to ensure proper data management as well as guarantee that measures are put in place to protect confidential information. This approval letter is attached in Appendix B.

CHAPTER FOUR: RESULTS

The results are presented in three major sections. A description of adverse event reporting patterns and a time series assessment of the quality of Kenyan adverse event reports is given in the initial part of the chapter. The second part involves results of the disproportionality analysis of data obtained from the Food and Drug Administration Adverse Event Reporting System (FAERS) for evaluation of potential safety signals between cardiac arrhythmias and antiretroviral drugs. In the final section, results of the assessment of interaction effects between ARVs and selected cardiovascular agents are presented.

4.1 PATTERN OF ADVERSE EVENT REPORTING IN KENYA

4.1.1 Socio-demographic characteristics of the patients

A total of 11, 270 Kenyan reports were analysed. A majority of the adverse events in the country were reported among women (63.4%). Reports relating to male patients accounted for only about a third (33%) of the Kenyan pharmacovigilance database as shown in Figure 2.

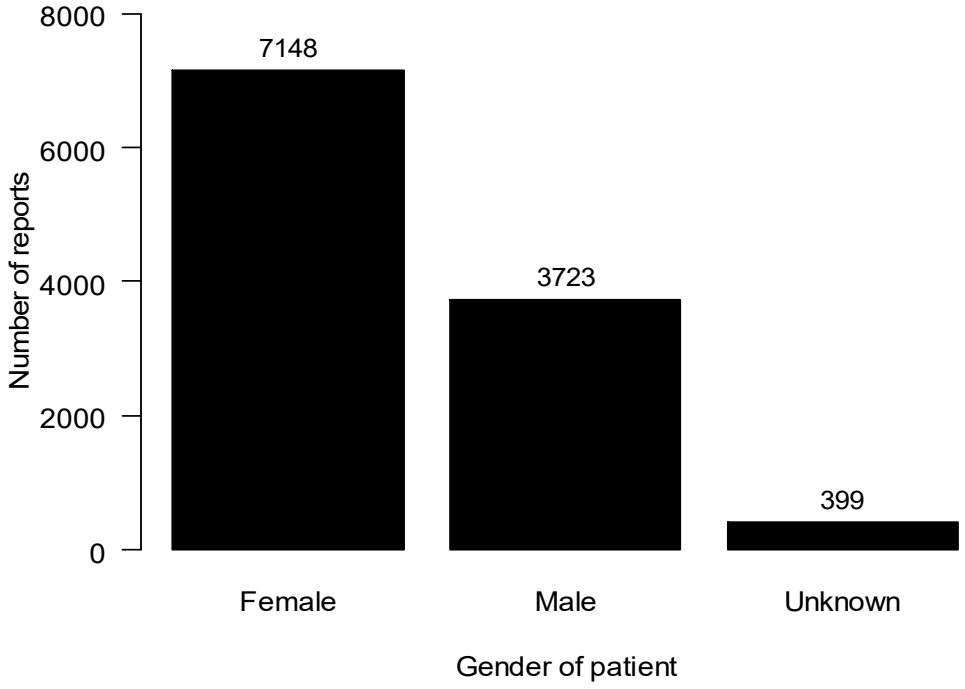


Figure 2: Adverse event reports submitted for each gender

More than 70% of all the reports in the Kenyan database involved adult patients. Children (3.3%) and adolescents (2.2%) had the second and third highest proportion of reports respectively. There were very few adverse event reports involving for the elderly (1.2%) and neonates (0.4%) as shown in Figure 3.

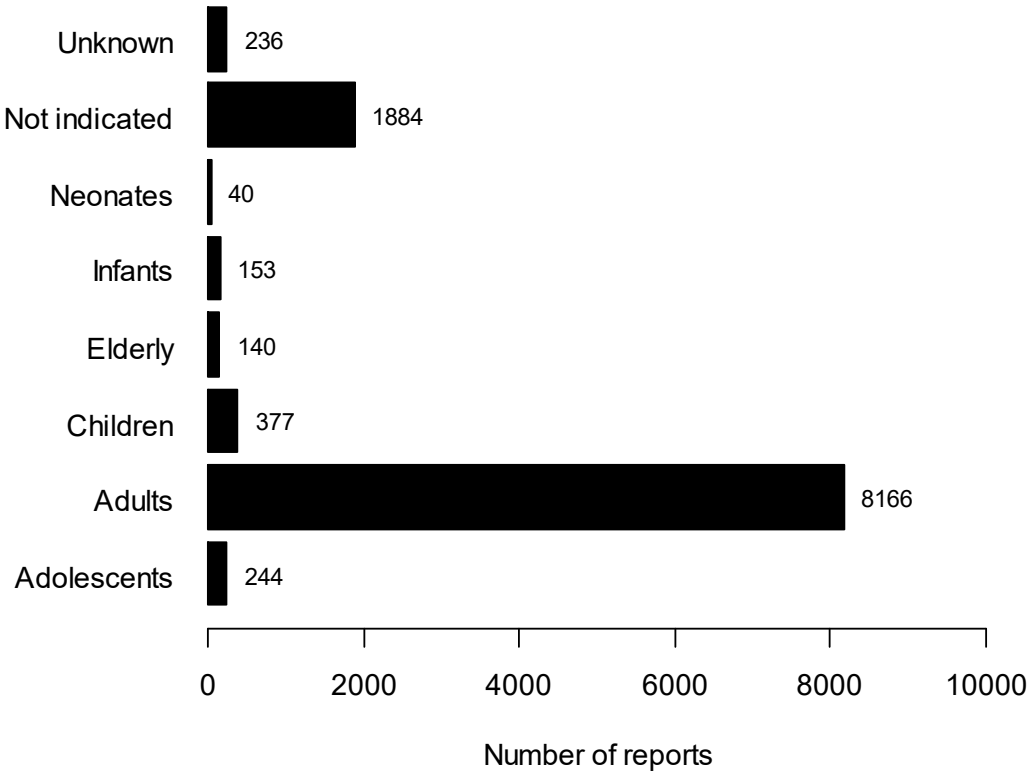


Figure 3: Adverse event reports categorized by age of patients

4.1.2 Reporters of adverse events

Most of the adverse events were reported by healthcare professionals. These included pharmacists and physicians. Other healthcare professionals including nurses and clinical officers were responsible for the largest number of reports in the database (66.5%) as shown in Figure 4. Notably, the pharmacovigilance database also contained reports submitted by consumers and non-health care professionals. These reports were however very few (0.3%).

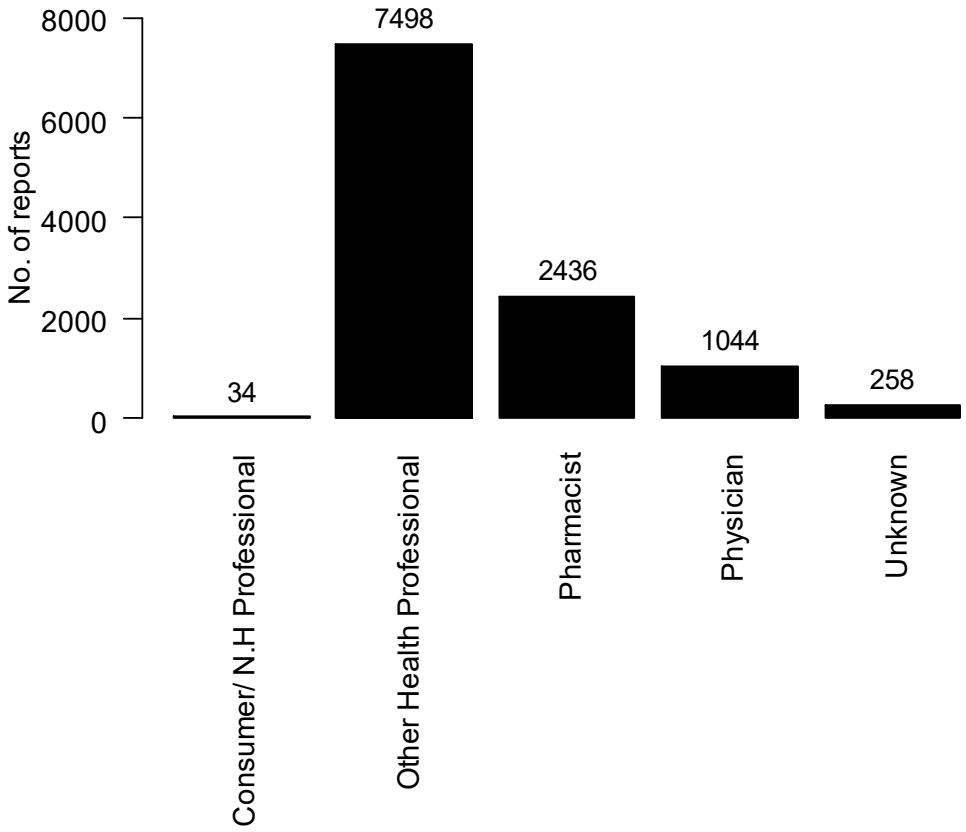


Figure 4: Classification of reporters of adverse events

4.1.3 Reports by county of origin

Reports from Nairobi (15.4%), Uasin Gishu (11%), Migori (10.5%), Kisumu (7.4%) and Kiambu (6.2%) constituted the highest proportion of reports submitted to the pharmacovigilance database in the country. It was also notable that adverse event reports from the top eleven counties constituted about 75% of all the reports in the database. There were no submissions from Marsabit, Lamu, West Pokot, Tana River and Wajir counties. A breakdown of reporting rates from the top eleven counties is shown in Figure 5.

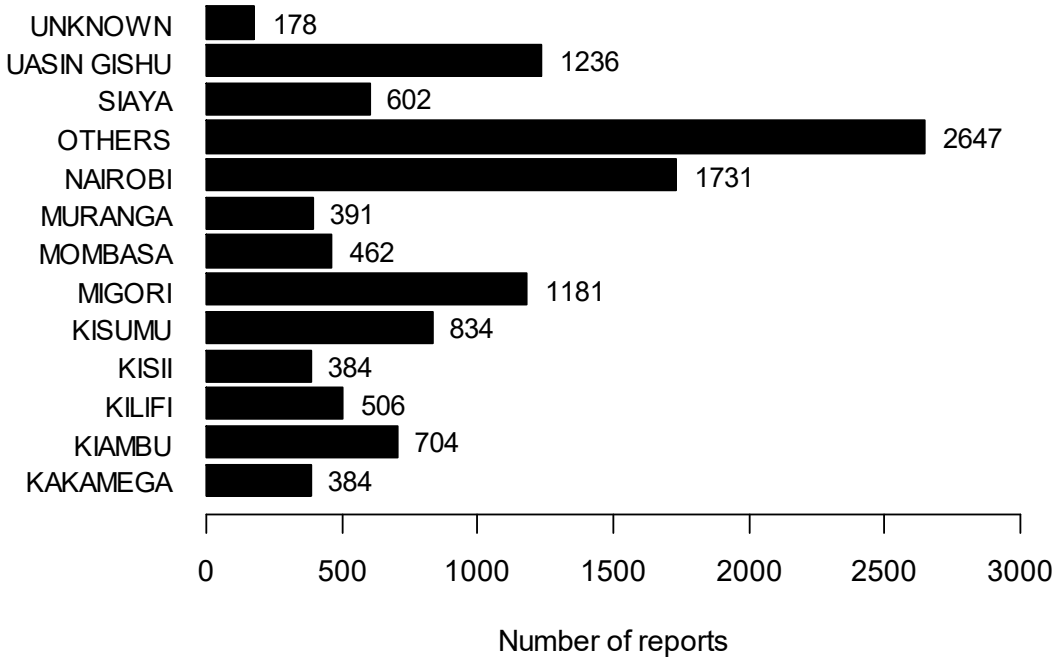


Figure 5: Summary of reporting rates from the top counties

4.1.4 Classes of drugs cited in the adverse event reports

Antiretroviral drugs (79%) comprised the bulk of the drugs cited in the database as shown in Figure 6. Anti-TB drugs (6.6%), antibiotics (5.5%) and anticancer medications (2.2%) were also included in a sizable proportion of the adverse event reports. Only 1.3% of the reports involved vaccines.

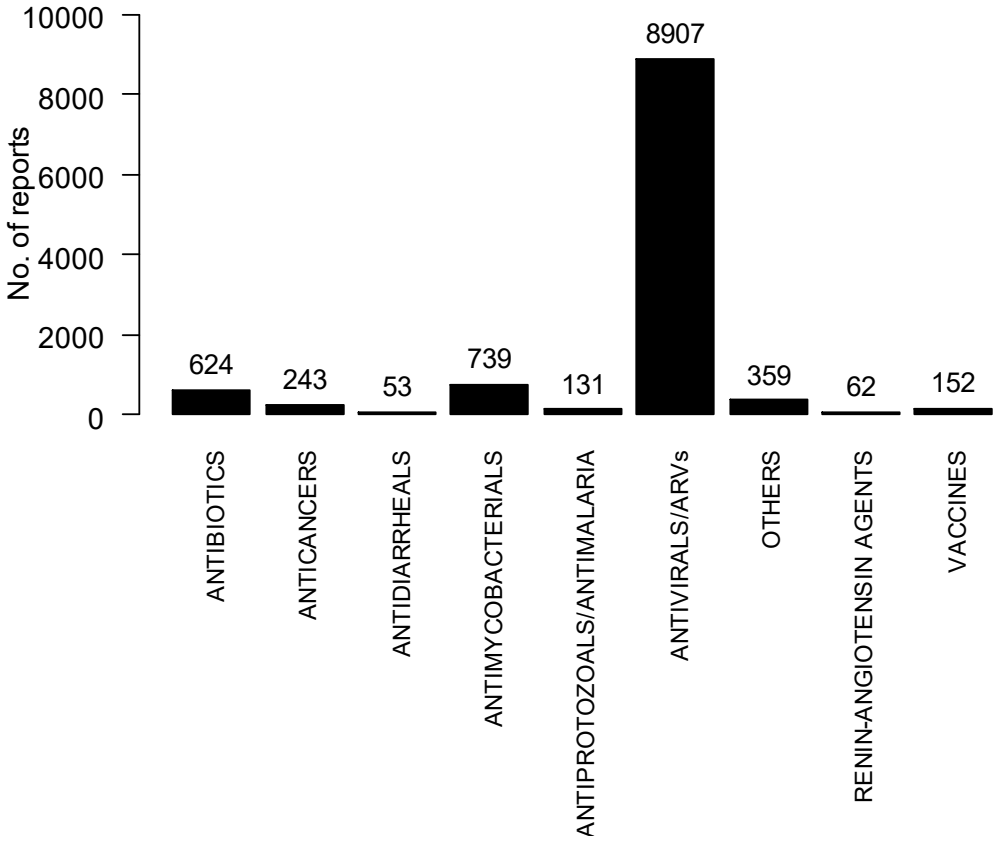


Figure 6: Classes of drugs cited in the adverse event reports

4.1.5 Classification of the reported adverse events by seriousness

Most of the adverse events (86.8%) were categorized as not serious. This means that they did not result in prolonged hospitalization, disability, congenital anomalies or death of the patient. There was however a sizable number of serious adverse events. About 7% of these resulted in prolonged hospitalization while about 0.9% of the patients were either disabled or suffered a congenital malformation. It was notable that 1.1% of the patients were reported to have died as a result of drug related adverse events as shown in Figure 7.

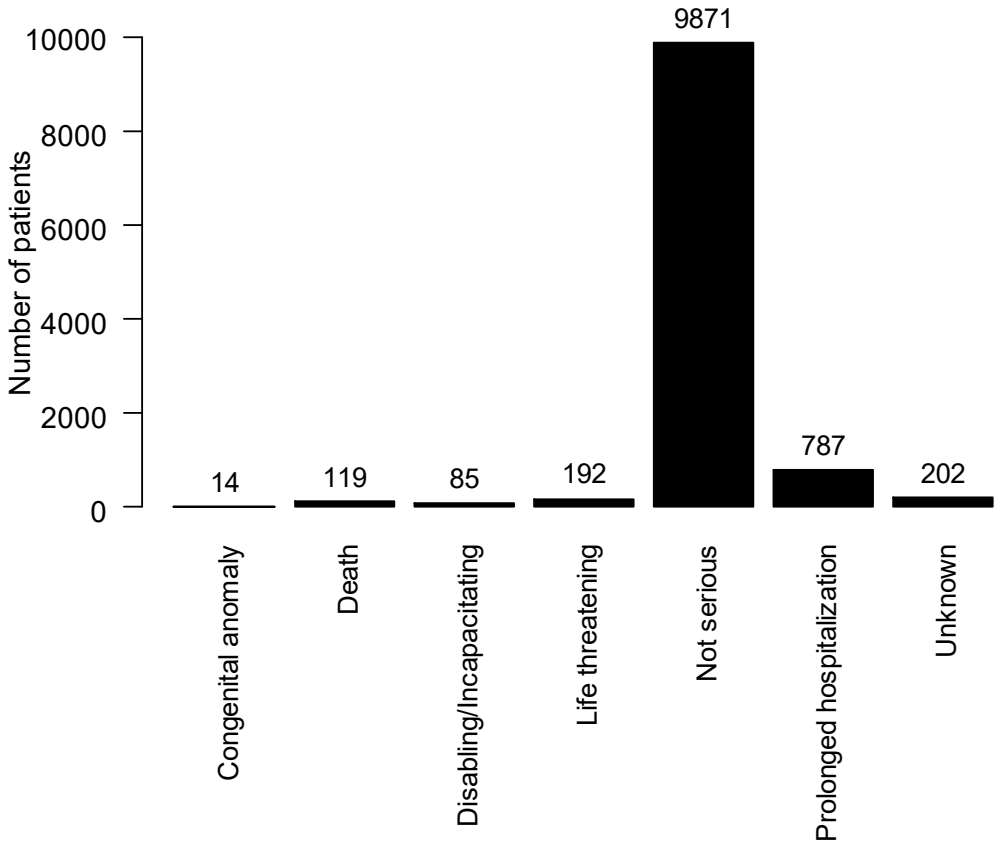


Figure 7: Outcomes of the reported adverse events

4.2 TIME SERIES OF THE QUALITY OF KENYAN INDIVIDUAL CASE SAFETY REPORTS (ICSRS)

The quarterly means of the completeness scores were plotted against the quarterly time periods to obtain a time series graph as shown in Figure 8. A regression line was then fitted into the time series. The regression line shows a linear increase in the completeness score of Kenyan ICSRs since the first reports were submitted to VigiBase in 2010.

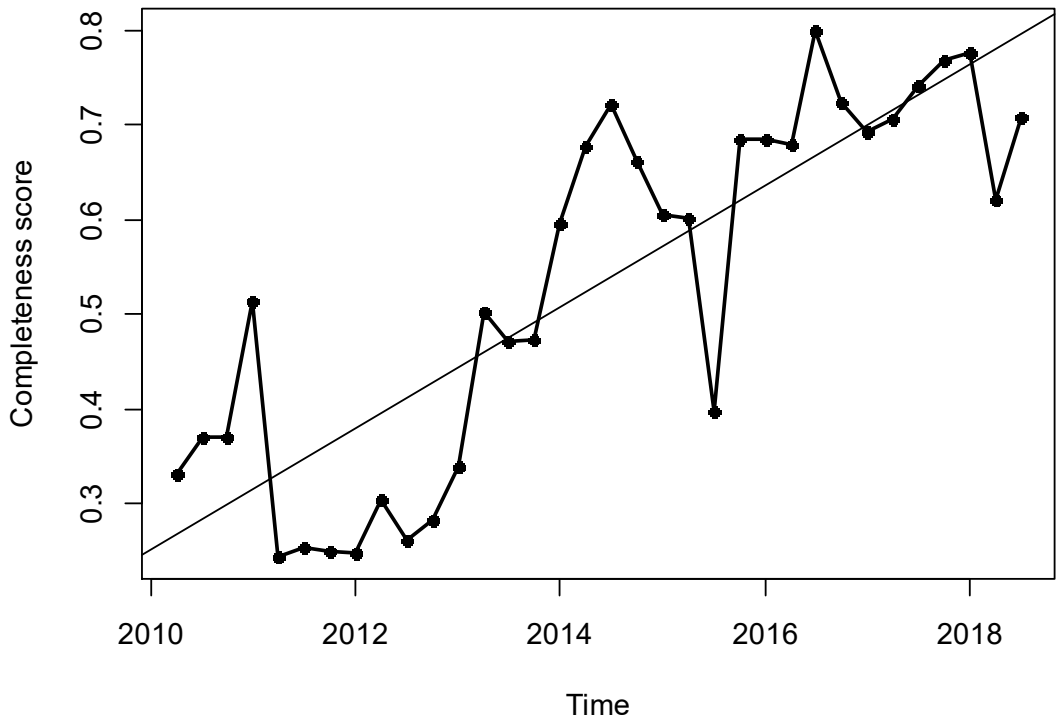


Figure 8: Time series of the completeness score of Kenyan adverse event reports

4.3 TREND OF QUALITY OF INDIVIDUAL CASE SAFETY REPORTS

The five-point moving average of the quarterly completeness score mean showed an initial drop in the quality of ICSRs during the formative reporting period. This was followed by a big improvement in the quality of the reports with the completeness score peaking at around 0.66 by the end of 2014. The first half of 2015 was marked by a brief period of declining quality which however took an upward trajectory from the third quarter, eventually peaking at a high of 0.74 in the last quarter of 2017 as shown in Table 5.

Table 5: Trend of quality of Kenyan adverse event reports

	Quarter 1	Quarter 2	Quarter 3	Quarter 4
2010	-	-	-	0.3849091
2011	0.359461	0.3299311	0.2815724	0.2557264
2012	0.2643401	0.2696391	0.2852741	0.3215899
2013	0.3726029	0.4224379	0.4781585	0.5320251
2014	0.585422	0.6406589	0.6656369	0.657457
2015	0.6072705	0.5694344	0.5822365	0.601847
2016	0.6619419	0.7173773	0.7233536	0.7276714
2017	0.7237594	0.7220685	0.7383032	0.7382914
2018	0.7232931	-	-	-

4.4 SEASONAL VARIATIONS IN THE QUALITY OF INDIVIDUAL CASE SAFETY REPORTS

The decomposition showed that there was a small seasonal variation in the quality of ICSRs. Reports submitted during the first and second quarters had the highest quality with respective seasonal indices of 0.017 and 0.003. This means that with a median score of about 0.6, the quality of the ICSRs in these quarters were 1.7% and 0.3% higher than the average. The lowest score was recorded in the third quarter with a seasonal index of -0.017 and a median score of about 0.45. Reports submitted in this quarter had a completeness score that was 2% lower than the average. The quality of reports submitted in the fourth quarter was 0.3% lower than the average. The seasonal indices are provided in Appendix D. Figure 9 presents a box plot of the completeness scores for each quarter over the duration of the study.

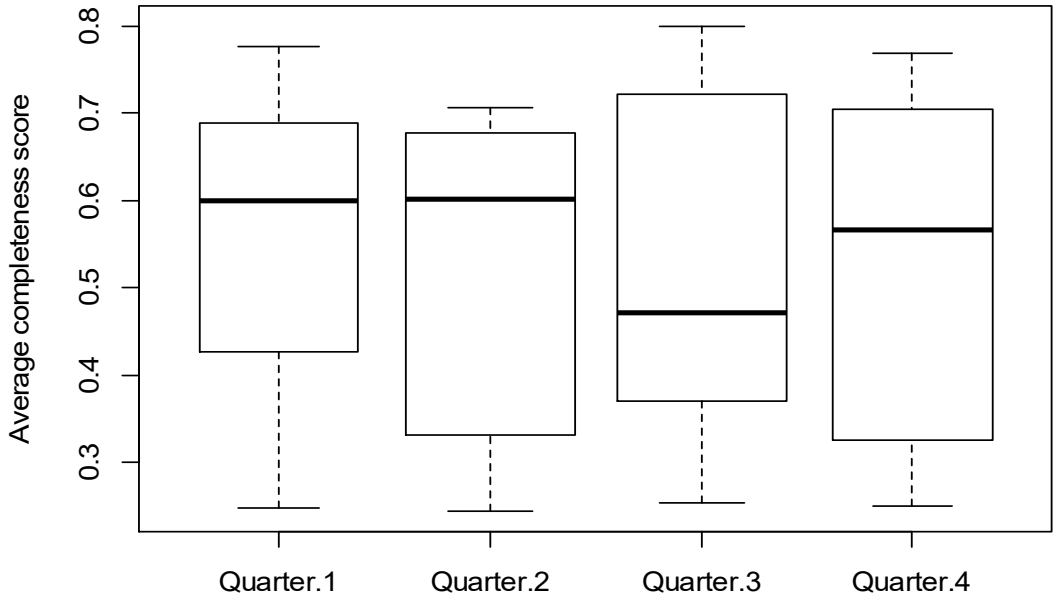


Figure 9: Variation in average completeness scores of reports per quarter

4.5 SEGMENTED REGRESSION ANALYSIS OF THE QUALITY OF KENYAN ADVERSE EVENT REPORTS

The five-point moving average is presented in Figure 10. Segmented regression analysis was carried out using the generalized least square method in order to assess for any events that may have led to a drastic change in the completeness score of the adverse event reports.

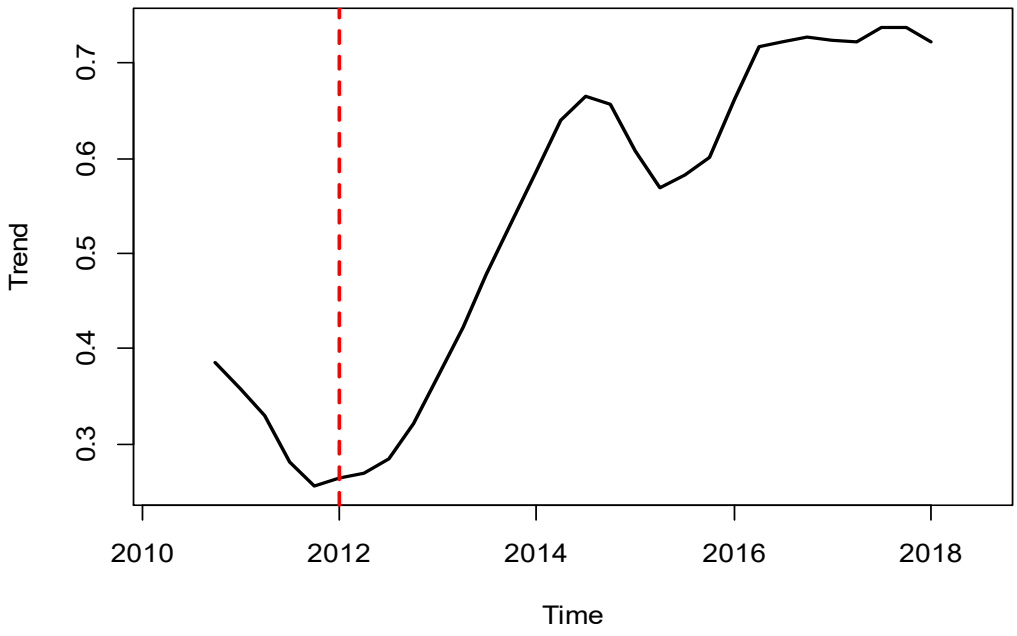


Figure 10: Five point moving average plot of trend of quality of adverse event reports

Both linear and quadratic models were tested in order to determine the period in which the significant event occurred that led to a major change in the quality of adverse event reports. It was established that the change point occurred during the fourth quarter of 2012. This event was best described using a quadratic regression model as represented in Table 6. Starting with a completeness score of 0.364 ± 0.055, there was an insignificant decline in the scores by 0.002 ($p = 0.824$) points per quarter until the change point in the fourth quarter of 2012. Immediately after the first quarter of 2012, there was a significant decline in quality by a further 0.444 ± 0.215 ($p = 0.048$). Report quality however gradually improved over time after the fourth quarter of 2012 with the completeness scores exhibiting a significant quarterly increase of 0.055 ± 0.017 ($p = 0.003$). The quadratic nature of the time series was evidenced by a statistically significant quarterly decline in the score by 0.001 ($p = 0.052$) per quarter that followed this rise in report quality.

Table 6: Segmented regression analysis of Kenyan adverse event reports

Full segmented regression model (intervention in Quarter 4, 2012)				
	Coefficient	**Standard error**	**t-statistic**	**p-value**
Intercept (β_0)	0.364	0.055	6.681	**< 0.001**
Time from quarter 2 2010 (β_1)	-0.002	0.009	-0.224	0.824
Event in quarter 4 2012(β_2)	-0.444	0.215	-2.062	**0.048**
Time after event (β_3)	0.055	0.017	3.262	**0.003**
Time after event squared (β_3^2)	-0.001	0.000	-2.030	**0.052**
Most parsimonious segmented regression model				
Intercept (β_0)	0.354	0.029	12.027	**< 0.001**
Event in quarter 4 2012(β_2)	-0.459	0.200	-2.296	**0.029**
Time after event (β_3)	0.055	0.017	3.351	**0.002**
Time^2 (β_3^2)	-0.001	< 0.001	-2.624	**0.014**

Residual standard error: 8.12; AIC: -32.192; BIC: -25.186; logLik: 21.096

4.6 IDENTIIFICATION OF SIGNALS FOR RHYTHM DISORDERS IN PATIENTS ON ANTIRETROVIRAL THERAPY

The data used in the analysis consisted of all adverse event reports submitted to FAERS from the first quarter of 2004 to the fourth quarter of 2018. This consisted of a total of 11, 191, 342 reports. The data was retrieved on diverse dates of April and May 2019 using a customised query as presented in Chapter three. The measure of disproportionality presented in this section is the Information Component (IC). IC was preferred over other measures such as the Relative Reporting Risk (RRR) in order to minimise the occurrence of false positives.

4.6.1 Proportion of reports for each drug in the Food and Drug Administration Adverse Event Reporting System (FAERS)

Ritonavir had the highest number of reports (65,143) followed by tenofovir (58,434) and lamivudine (54,519) as shown in Table 7. Very few reports were submitted for zalcitabine and delavirdine while there were only two unique patient reports related to with ibalizumab use. The drugs that had high numbers of unique patient reports also had a high number of adverse events reported. The number of reports and the number of adverse events differed because some adverse events were reported more than once. Lamivudine had the highest number of reported adverse events (2,330). Ritonavir (1,987), zidovudine (1,787), lopinavir/ritonavir (1,703) and tenofovir (1,689) were the other drugs with the most adverse events reported. Ibalizumab, with only four adverse events, had the least number of reported events.

All the adverse event reports related to ARVs constituted about 3.6% of the total reports in the FAERS database. Ritonavir, tenofovir and lamivudine made up for 0.5% each. Reports for most of the other drugs accounted for less than 0.1% of the database.

Table 7: Summary of adverse event reports related to antiretroviral drugs submitted to FAERS, 2004-2018.

Drug	Unique patient reports	Total adverse events reported	Unique reports as a proportion of total reports in database (%)
Ritonavir (RTV)	65143	1987	0.5
Tenofovir disoproxil fumarate (TDF)	58434	1689	0.5
Lamivudine (3TC)	54519	2330	0.5
Emtricitabine (FTC)	43534	1351	0.4
Zidovudine (AZT)	26259	1787	0.2
Efavirenz (EFV)	22139	1268	0.2
Abacavir (ABC)	21985	1460	0.2
Lopinavir/ritonavir (LPV/r)	20454	1703	0.2
Atazanavir (ATV)	16491	1123	0.1
Raltegravir (RAL)	16194	1395	0.1
Darunavir (DRV)	15329	967	0.1
Nevirapine (NVP)	14473	1151	0.1
Stavudine (d4T)	9089	1241	0.1
Dolutegrevir (DTG)	8154	634	0.1
Didanosine (ddI)	7971	1187	0.1
Etravirine (ETR)	4987	616	< 0.1
Nelfinavir (NFV)	4537	1034	< 0.1
Enfuvirtide (ENF)	4378	724	< 0.1
Saquinavir (SQV)	3121	823	< 0.1
Fosamprenavir (FPV)	2747	600	< 0.1
Indinavir (IDV)	2331	715	< 0.1
Amprenavir (APV)	1569	522	< 0.1
Zalcitabine (ddC)	354	308	< 0.1
Delavirdine (DLV)	320	123	< 0.1
Ibalizumab	2	4	< 0.1

4.6.2 Frequency of cardiovascular adverse events for each drug

When the adverse events were analysed using the System Organ Class (SOC) classification, nelfinavir and zalcitabine were found to have the highest proportion of reported cardiovascular adverse events. CVS adverse events constituted 22.1% and 21.8% of all reported events for the two drugs respectively. Delavirdine (16.6%), zidovudine (15.5%), saquinavir (14.3%), abacavir (13.5%), didanosine (12.6%), lopinavir/ritonavir (12.1%), amprenavir (11.7%), and stavudine (11.3%) also had a high number of cardiovascular events reported as compared to

other systems. Out of the four adverse events reported for ibalizumab, none involved the cardiovascular system. Some of the most commonly reported cardiovascular adverse events include coronary artery disease, arrhythmia, bradycardia, atrial and septal defects, patent ductus arteriosus and cardiac malposition. The proportion of reports involving the CVS with respect to all reports for each drug is shown in Figure 11.

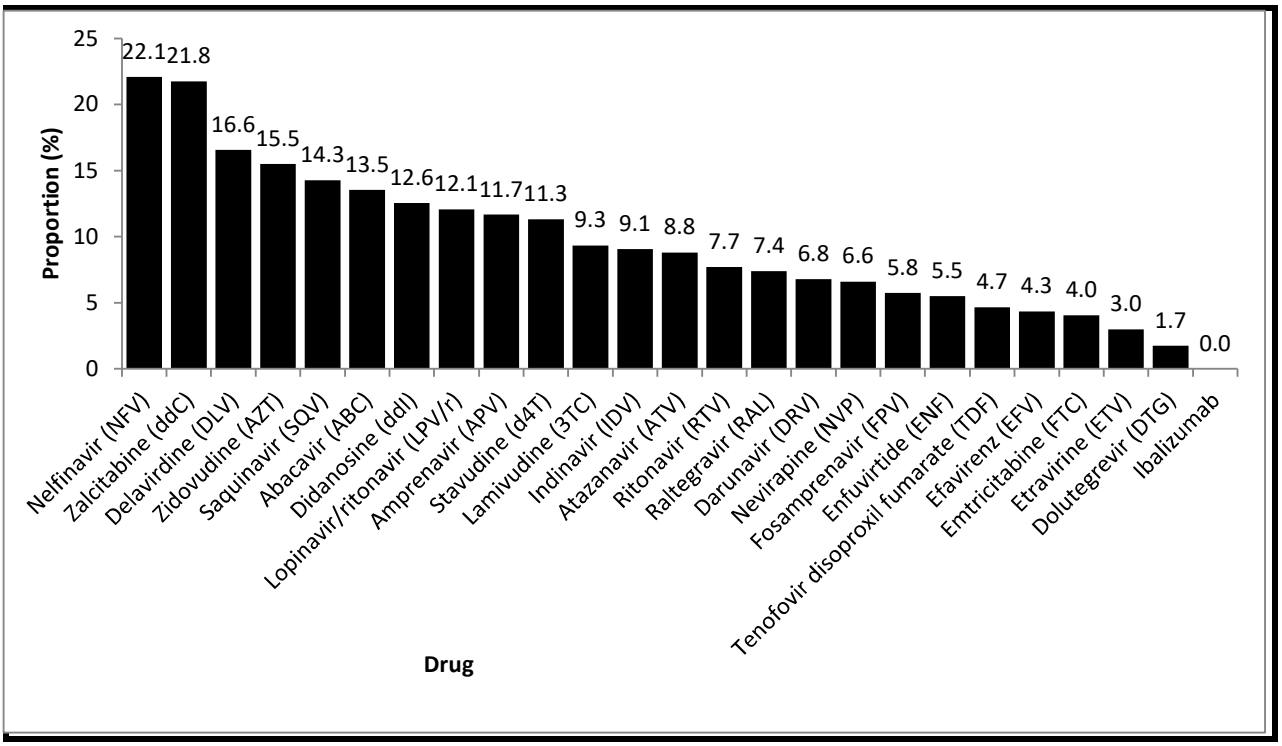


Figure 11: Cardiovascular adverse events as a proportion of the total adverse events reported for each drug

4.6.3 Proportion of reports for specific adult regimens in FAERS

FAERS data was analysed by specific drug combinations that are currently being used in Kenya. The first line regimen consisting of zidovudine, lamivudine and lopinavir/ritonavir (AZT/3TC/LPV/r) had the highest number of patient reports (4,587) as shown in Table 8. Other first line regimens with notably high reporting rates include ABC/3TC/DTG (3,022), AZT/3TC/EFV (2,577), ABC/3TC/ATV/r (1,843), ABC/3TC/LPV/r (1,640), ABC/3TC/EFV (1,339) and AZT/3TC/ATV/r (1,307). Notably, these regimens were some of the earliest applied in the management of HIV and continue to be widely used to date. High reporting rates

of adverse events may therefore be expected. Among the first line agents, the combination of tenofovir, lamivudine and efavirenz (TDF/3TC/EFV) had only a paltry seven reports submitted. A majority of the second and third line regimens had fewer than a thousand reported cases. No report was submitted for the second line combination of TDF/3TC/RAL/DRV/r. Some of the adverse events reported were expected for the particular regimens. These include atrio-ventricular block and cardiomyopathy with ABC/3TC/ATV/r as well as palpitations with ETV/3TC/DRV/r. Notably, zidovudine based regimens had more reported events compared to tenofovir based regimens.

Table 8: Summary of adverse event reports relating to selected antiretroviral regimens submitted to FAERS, 2004-2018.

Regimen	Unique patient reports	Total adverse events reported	Unique patient reports as a proportion of total reports in the database (%)
First line regimens			
AZT+3TC+LPV/r	4587	754	0.04
ABC+3TC+DTG	3022	332	0.03
AZT+3TC+EFV	2577	593	0.02
ABC+3TC+ATV/r	1843	464	0.02
ABC+3TC+LPV/r	1640	515	0.01
ABC+3TC+EFV	1339	431	0.01
AZT+3TC+ATV/r	1307	434	0.01
AZT+3TC+DTG	83	86	< 0.01
TDF+3TC+ATV/r	32	21	< 0.01
TDF+3TC+LPV/r	26	29	< 0.01
TDF+3TC+DTG	23	32	< 0.01
TDF+3TC+EFV	7	7	< 0.01
Second line regimens			
AZT+3TC+DRV/r+RAL	296	110	< 0.01
AZT+3TC+ATV/r	1307	434	0.01
TDF+3TC+ATV/r	32	21	< 0.01
TDF+3TC+DRV/r+RAL	0	0	< 0.01
Third line regimens			
ETV+3TC+DRV/r	831	267	0.01
DTG+3TC+DRV/r	341	197	< 0.01
DTG+AZT+3TC+DRV/r	17	35	< 0.01
DTG+TDF+3TC+DRV/r	14	3	< 0.01
DTG+TDF+3TC	23	32	< 0.01
DTG+AZT+3TC	83	86	< 0.01

4.6.4 Frequency of cardiovascular adverse events for each adult regimen

Proportionally, CVS adverse events comprised a major fraction of the total reports for DTG/TDF/3TC/DRV/r (42.9%), DTG/AZT/3TC/DRV/r (35.3%) and TDF/3TC/DTG (26.1%). This finding is significant in the Kenyan/African context because the use of dolutegravir has recently been up scaled. This implies that clinicians should be vigilant for cardiovascular events in patients on dolutegravir based regimens. Third line regimens had the highest proportion of cardiovascular adverse events. Some regimens including TDF/3TC/RAL/DRV/r, TDF/3TC/LPV/r, TDF/3TC/ATV/r and TDF/3TC/EFV did not have a single reported CVS adverse event as shown in Figure 12.

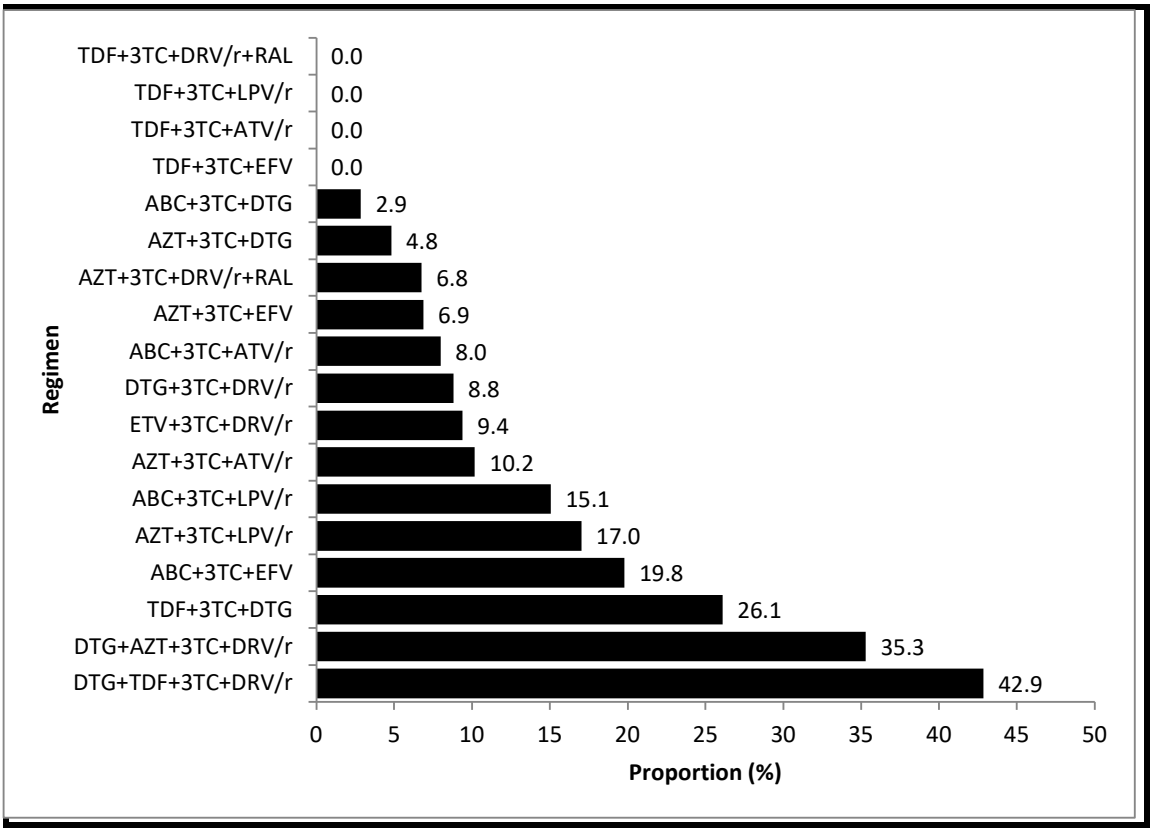
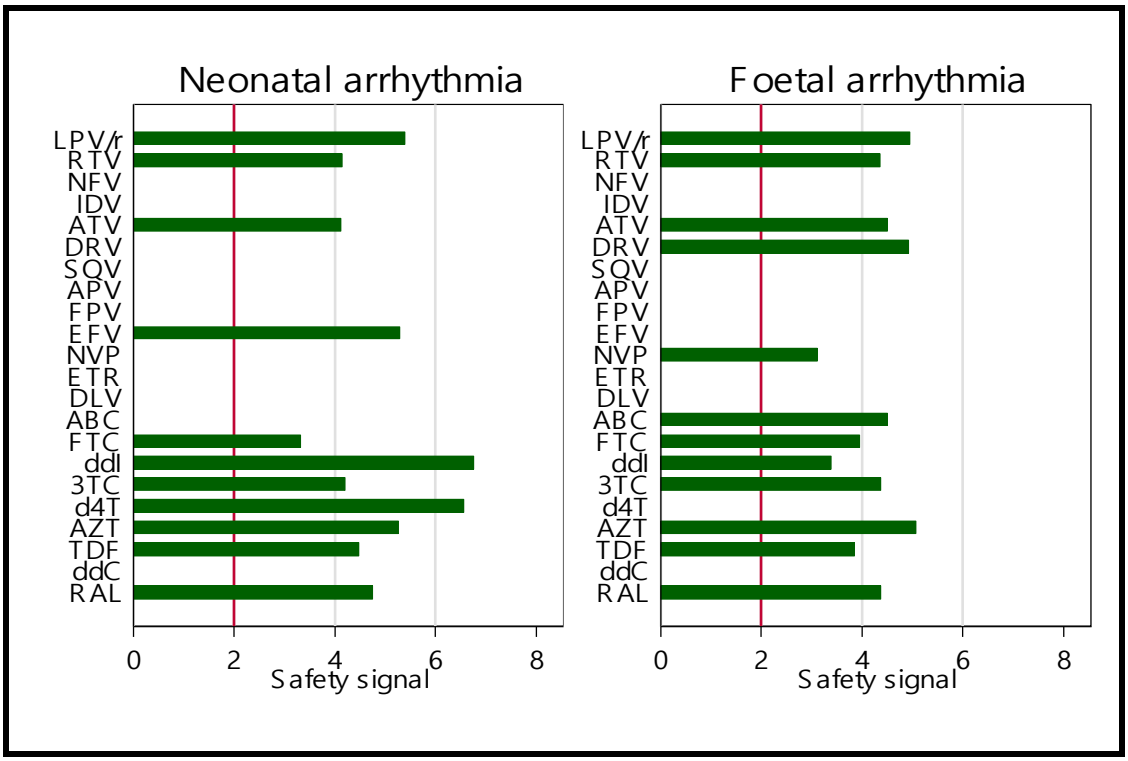


Figure 12: Cardiovascular adverse events as a proportion of the total adverse events reported for each regimen

4.6.5 Signals for cardiac arrhythmias in neonates and the foetus exposed to antiretroviral drugs

Among neonates and the developing foetus, arrhythmia was the most commonly reported cardiovascular rhythm disorder with exposure to ARVs. For all the drugs in which this adverse

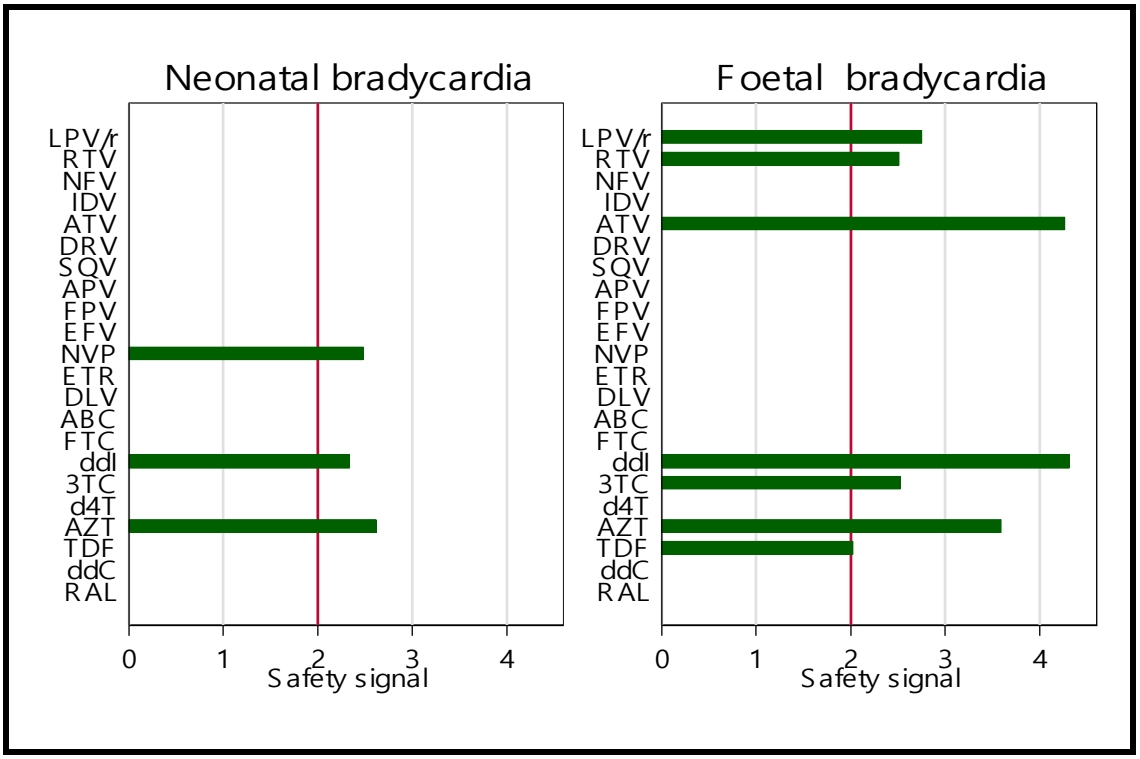
event was described, the safety signal was significant as shown in Figure 13. A signal is considered significant to warrant further investigations if the signal strength is two or more. Almost all nucleoside reverse transcriptase inhibitors (NRTIs) were linked with either neonatal or foetal arrhythmia. Neonatal arrhythmia with didanosine and stavudine use had the strongest safety signals. Amongst non-nucleoside reverse transcriptase inhibitors (NNRTIs), neonatal and foetal arrhythmias were reported for efavirenz and nevirapine respectively.



Ritonavir (RTV), Tenofovir disoproxil fumarate (TDF), Lamivudine (3TC), Emtricitabine (FTC), Zidovudine (AZT), Efavirenz (EFV), Abacavir (ABC), Lopinavir/ritonavir (LPV/r), Atazanavir (ATV), Raltegravir (RAL), Darunavir (DRV), Nevirapine (NVP), Stavudine (d4T), Didanosine (ddI), Etravirine (ETV), Nelfinavir (NFV), Saquinavir (SQV), Fosamprenavir (FPV), Indinavir (IDV), Amprenavir (APV), Zalcitabine (ddC), Delavirdine (DLV)

Figure 13: Safety signal for neonatal and foetal arrhythmias with various antiretroviral drugs

Neonatal bradycardia was only reported for nevirapine, didanosine and zidovudine. In all the cases, the safety signal was significant. Foetal bradycardia was more commonly reported with the strongest signals being recorded for atazanavir and didanosine. The safety signals for neonatal bradycardia were conspicuously weaker than those of foetal bradycardia as shown in Figure 14.

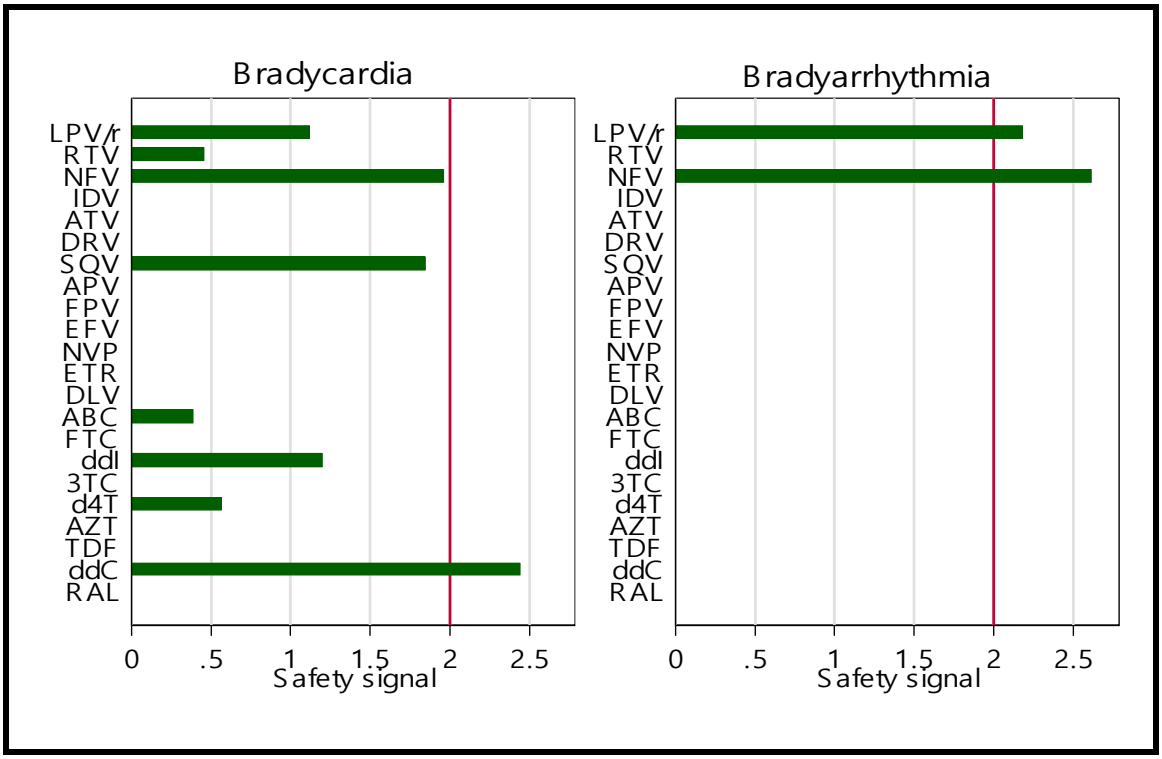


Ritonavir (RTV), Tenofovir disoproxil fumarate (TDF), Lamivudine (3TC), Emtricitabine (FTC), Zidovudine (AZT), Efavirenz (EFV), Abacavir (ABC), Lopinavir/ritonavir (LPV/r), Atazanavir (ATV), Raltegravir (RAL), Darunavir (DRV), Nevirapine (NVP), Stavudine (d4T), Didanosine (ddI), Etravirine (ETV), Nelfinavir (NFV), Saquinavir (SQV), Fosamprenavir (FPV), Indinavir (IDV), Amprenavir (APV), Zalcitabine (ddC), Delavirdine (DLV)

Figure 14: Safety signals for neonatal and foetal bradycardia; with various antiretroviral drugs

4.6.6 Signals for bradyarrhythmia in HIV patients on antiretroviral therapy

Although many reports were recorded concerning bradycardia and bradyarrhythmia in HIV patients on ARVs, the adverse signals were only significant for zalcitabine, lopinavir/ritonavir and nelfinavir as shown in Figure 15. The most affected classes of the antiretrovirals were particularly protease inhibitors and to a lesser extent, nucleoside reverse transcriptase inhibitors.

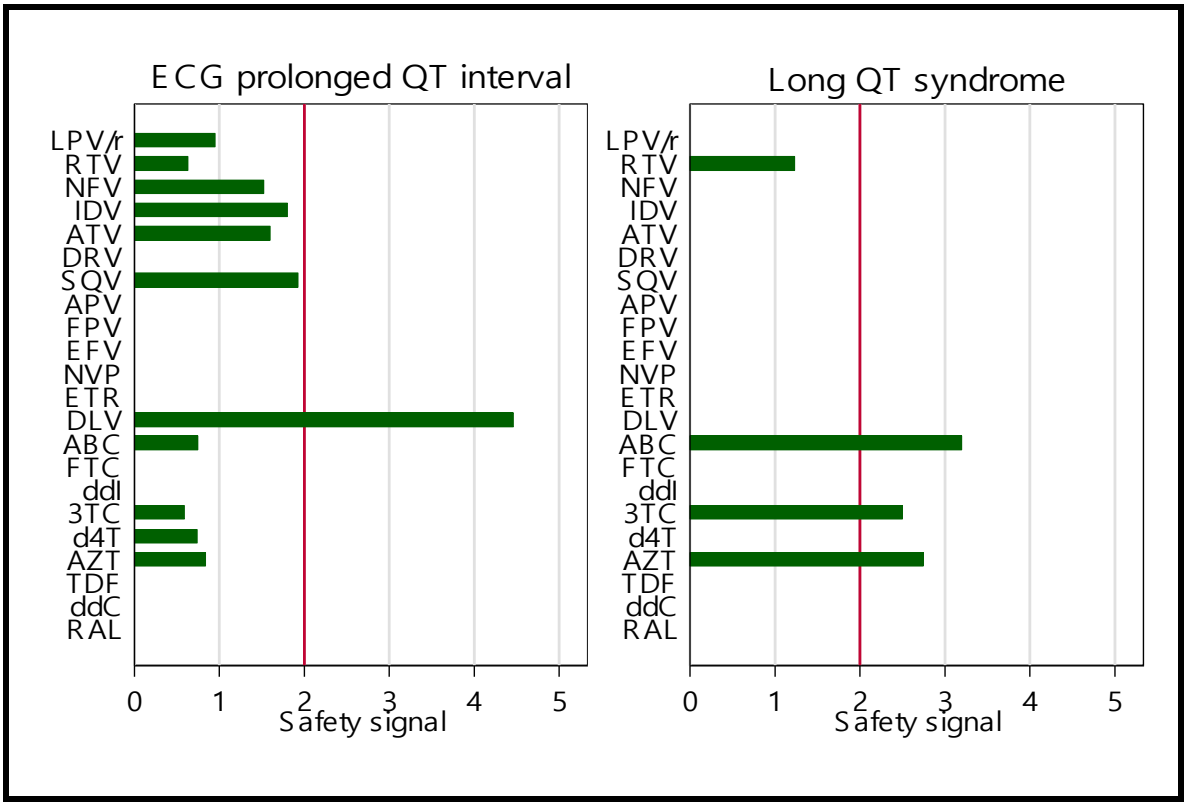


Ritonavir (RTV), Tenofovir disoproxil fumarate (TDF), Lamivudine (3TC), Emtricitabine (FTC), Zidovudine (AZT), Efavirenz (EFV), Abacavir (ABC), Lopinavir/ritonavir (LPV/r), Atazanavir (ATV), Raltegravir (RAL), Darunavir (DRV), Nevirapine (NVP), Stavudine (d4T), Didanosine (ddI), Etravirine (ETV), Nelfinavir (NFV), Saquinavir (SQV), Fosamprenavir (FPV), Indinavir (IDV), Amprenavir (APV), Zalcitabine (ddC), Delavirdine (DLV)

Figure 15: Safety signals for bradyarrhythmia with various antiretroviral drugs

4.6.7 Signals for tachyarrhythmias in HIV patients on antiretroviral therapy

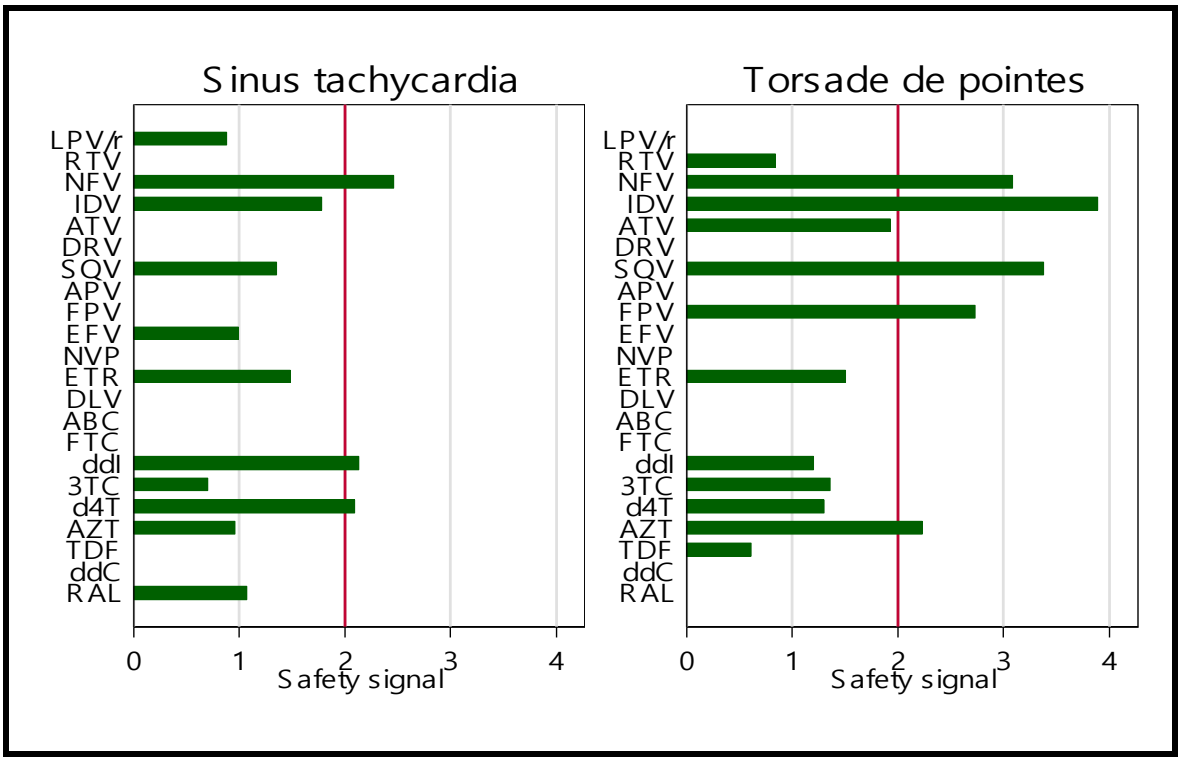
Protease inhibitors and nucleoside reverse transcriptase inhibitors were implicated in reports for QT interval prolongation. Most of the signals were however quite weak. The strongest signal for this disorder was recorded in delavirdine. Signals for abacavir, zidovudine and emtricitabine were also significantly high as shown in Figure 16.



Ritonavir (RTV), Tenofovir disoproxil fumarate (TDF), Lamivudine (3TC), Emtricitabine (FTC), Zidovudine (AZT), Efavirenz (EFV), Abacavir (ABC), Lopinavir/ritonavir (LPV/r), Atazanavir (ATV), Raltegravir (RAL), Darunavir (DRV), Nevirapine (NVP), Stavudine (d4T), Didanosine (ddI), Etravirine (ETV), Nelfinavir (NFV), Saquinavir (SQV), Fosamprenavir (FPV), Indinavir (IDV), Amprenavir (APV), Zalcitabine (ddC), Delavirdine (DLV)

Figure 16: Safety signals for QT interval disorders with various antiretroviral drugs

The strongest signals for sinus tachycardia were observed with the use of nelfinavir, didanosine and stavudine. Torsade de pointes was reported predominantly in patients taking protease inhibitors and nucleoside reverse transcriptase inhibitors (NRTIs). With regard to NRTIs, only zidovodine exhibited a safety signal of two or above with the rest having weak signals. Protease inhibitors produced relatively stronger signals for torsade de pointes with indinavir, saquinavir, nelfinavir amd fosemprenavir all having signals of more than two as shown in Figure 17.

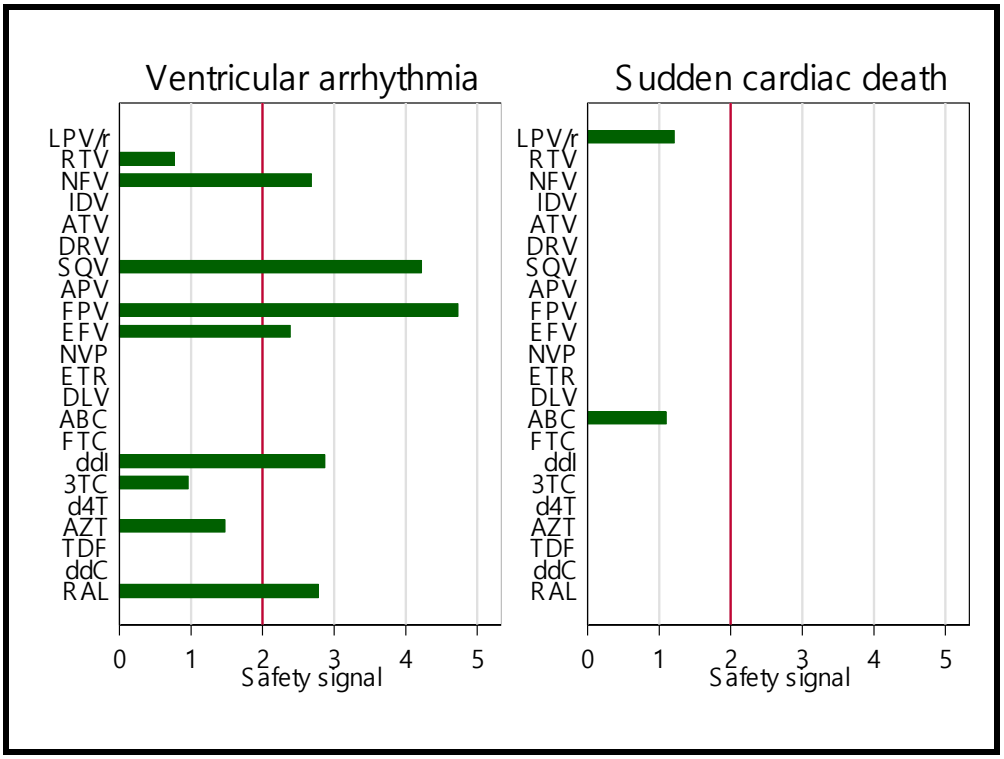


Ritonavir (RTV), Tenofovir disoproxil fumarate (TDF), Lamivudine (3TC), Emtricitabine (FTC), Zidovudine (AZT), Efavirenz (EFV), Abacavir (ABC), Lopinavir/ritonavir (LPV/r), Atazanavir (ATV), Raltegravir (RAL), Darunavir (DRV), Nevirapine (NVP), Stavudine (d4T), Didanosine (ddI), Etravirine (ETV), Nelfinavir (NFV), Saquinavir (SQV), Fosamprenavir (FPV), Indinavir (IDV), Amprenavir (APV), Zalcitabine (ddC), Delavirdine (DLV)

Figure 17: Safety signals for sinus tachycardia and torsade de pointes with various antiretroviral drugs

4.6.8 Signals for ventricular arrhythmias and sudden cardiac death in HIV patients on antiretroviral therapy

Ventricular arrhythmia carries a very high risk of sudden cardiac death. The strongest signals for ventricular arrhythmia were reported with protease inhibitors. Fosemprenavir and saquinavir had the strongest signals for the disorder. Efavirenz, nelfinavir and raltegravir also exhibited a strong signal for ventricular arrhythmia. These findings are shown in Figure 18. Sudden cardiac death was reported in patients on lopinavir/ritonavir and abacavir. The signals between the drugs and the adverse event was however quite weak as none of the drug-adverse event relationships had a signal of more than 2.

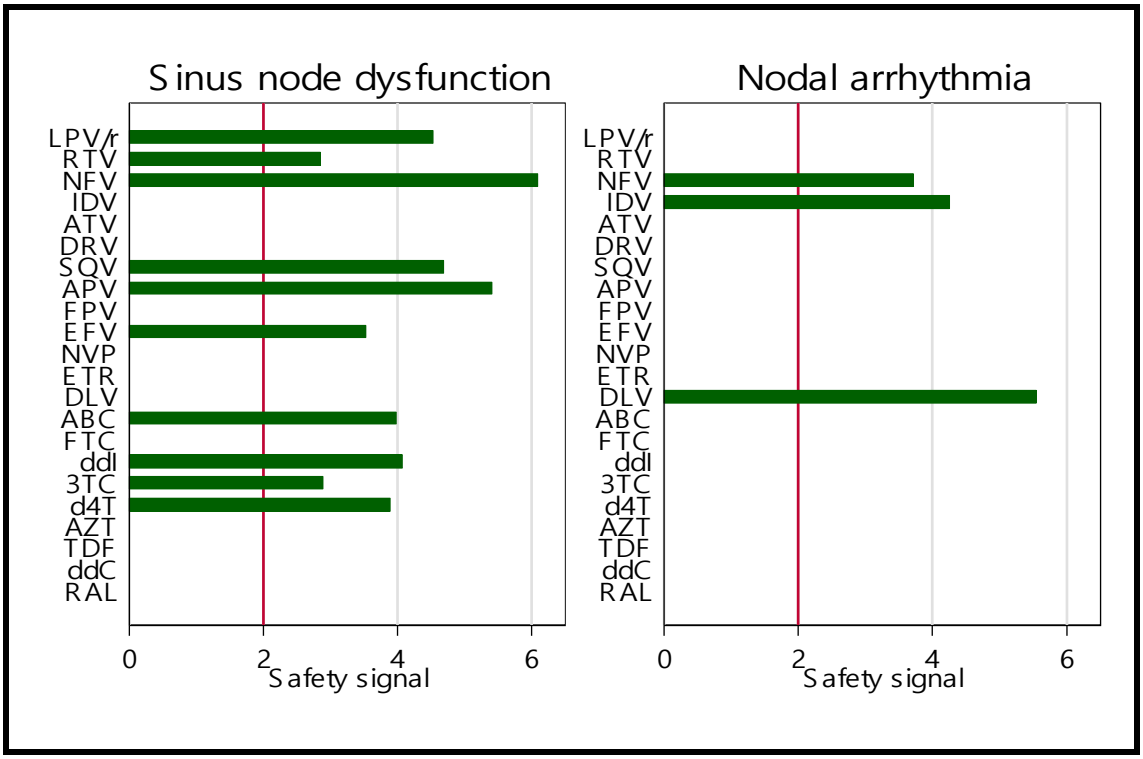


Ritonavir (RTV), Tenofovir disoproxil fumarate (TDF), Lamivudine (3TC), Emtricitabine (FTC), Zidovudine (AZT), Efavirenz (EFV), Abacavir (ABC), Lopinavir/ritonavir (LPV/r), Atazanavir (ATV), Raltegravir (RAL), Darunavir (DRV), Nevirapine (NVP), Stavudine (d4T), Didanosine (ddI), Etravirine (ETV), Nelfinavir (NFV), Saquinavir (SQV), Fosamprenavir (FPV), Indinavir (IDV), Amprenavir (APV), Zalcitabine (ddC), Delavirdine (DLV)

Figure 18: Safety signals for ventricular arrhythmias with various antiretroviral drugs

4.6.9 Signals for sinus node disorders in HIV patients on antiretroviral therapy

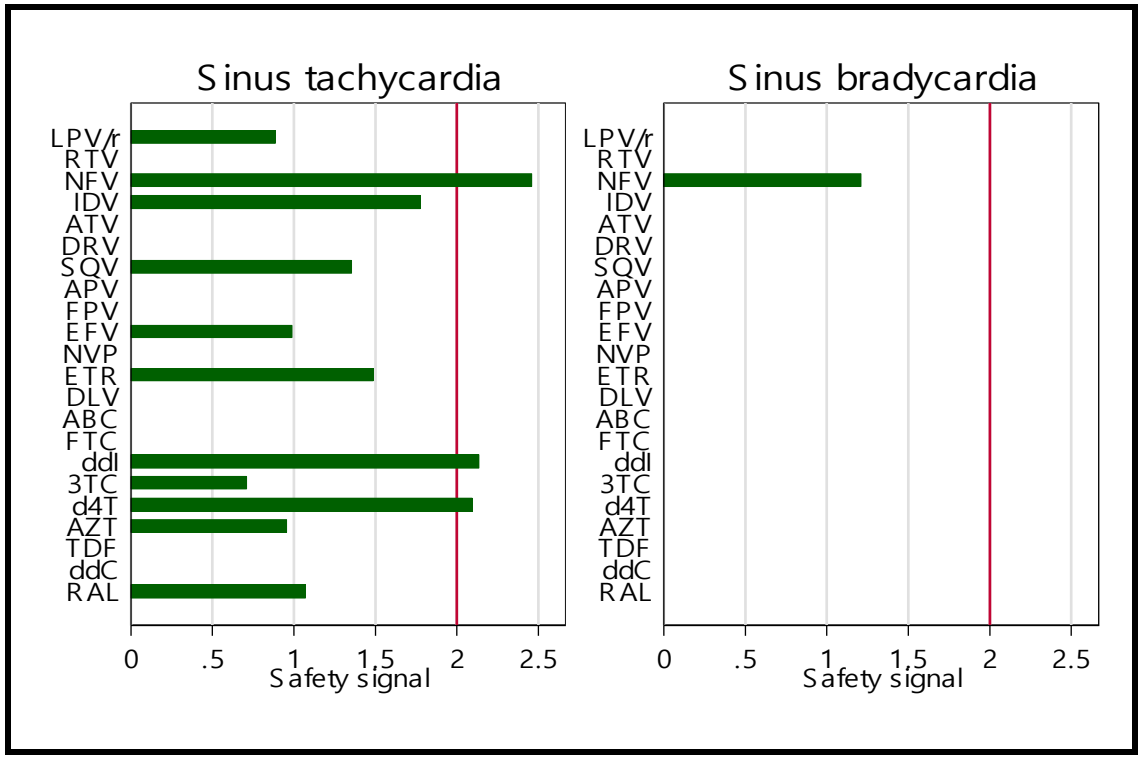
Sinus node dysfunction and sinus tachycardia were the most commonly reported adverse events involving the sinus node among patients on antiretroviral drugs. Other sinus node disorders documented included sinus bradycardia, sinus tachycardia and nodal arrhythmia. Sinus node dysfunction was reported mainly for protease inhibitors and nucleoside reverse transcriptase inhibitors. Nelfinavir associated sinus node dysfunction had the strongest signal of about 6, followed by nelfinavir and amprenavir. For all the ARVs in which this adverse event was reported, the signal was above 2 meaning that further investigations are warranted to confirm a definitive link between the drugs and sinus node dysfunction. Nodal arrhythmia was only recorded for patients on nelfinavir, indinavir and delavirdine. The signal for the association between nodal arrhythmia and the drugs was also quite strong as shown in Figure 19.



Ritonavir (RTV), Tenofovir disoproxil fumarate (TDF), Lamivudine (3TC), Emtricitabine (FTC), Zidovudine (AZT), Efavirenz (EFV), Abacavir (ABC), Lopinavir/ritonavir (LPV/r), Atazanavir (ATV), Raltegravir (RAL), Darunavir (DRV), Nevirapine (NVP), Stavudine (d4T), Didanosine (ddI), Etravirine (ETV), Nelfinavir (NFV), Saquinavir (SQV), Fosamprenavir (FPV), Indinavir (IDV), Amprenavir (APV), Zalcitabine (ddC), Delavirdine (DLV)

Figure 19: Safety signals for sinus node disorders with various antiretroviral drugs

With regard to rate disorders involving the sinus node, sinus tachycardia was the most commonly reported arrhythmia. The strongest signals for sinus tachycardia were recorded with the use of nelfinavir, didanosine and stavudine. All the other drugs exhibited a weak link with sinus tachycardia. They all had a safety signal of less than 2. Sinus bradycardia was only reported with the use of nelfinavir. The link was also quite weak with a safety signal of about 1.3 as shown in Figure 20.



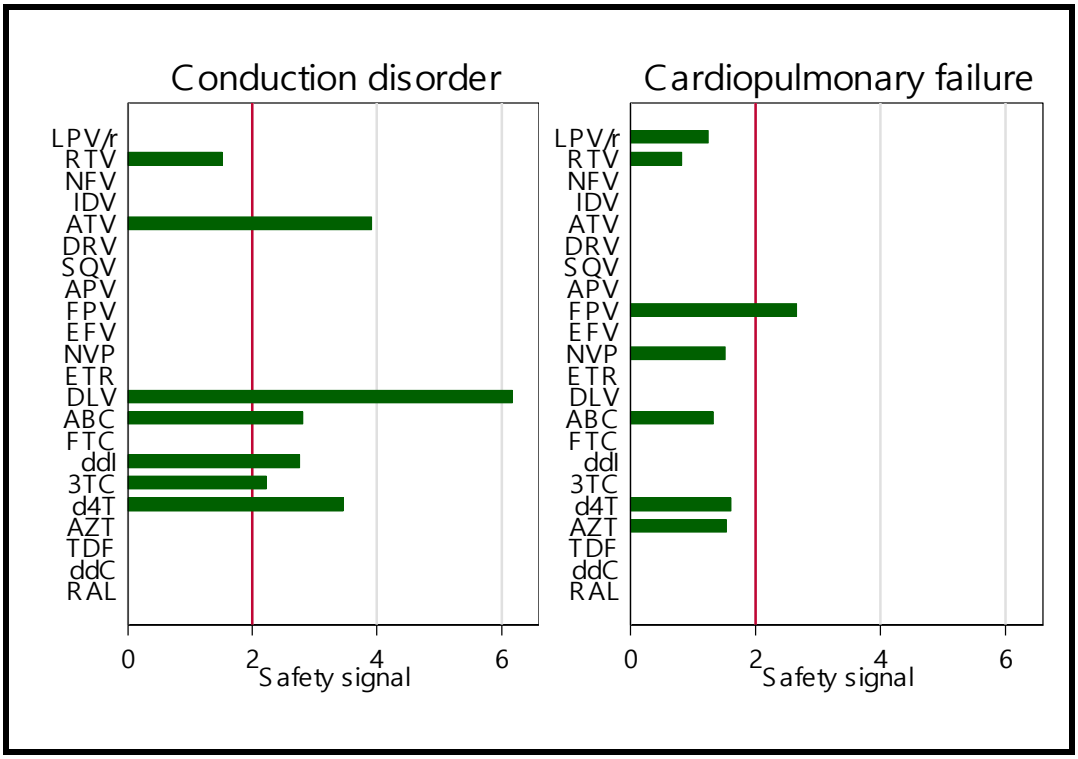
Ritonavir (RTV), Tenofovir disoproxil fumarate (TDF), Lamivudine (3TC), Emtricitabine (FTC), Zidovudine (AZT), Efavirenz (EFV), Abacavir (ABC), Lopinavir/ritonavir (LPV/r), Atazanavir (ATV), Raltegravir (RAL), Darunavir (DRV), Nevirapine (NVP), Stavudine (d4T), Didanosine (ddI), Etravirine (ETV), Nelfinavir (NFV), Saquinavir (SQV), Fosamprenavir (FPV), Indinavir (IDV), Amprenavir (APV), Zalcitabine (ddC), Delavirdine (DLV)

Figure 20: Safety signals for rate disorders of the sinus node and with antiretroviral drugs

4.6.10 Safety signals for unspecified arrhythmias in HIV patients on antiretroviral therapy

Unspecified cardiovascular rhythm disorders refer to reported cardiac arrhythmias where the site or type was not indicated in the report. The unspecified adverse events reported include arrhythmia, conduction disorder, cardiopulmonary failure and paroxysmal arrhythmia.

Cardiopulmonary failure was mainly reported with the use of PIs and NRTIs. However, only fosemprenavir exhibited a fairly strong signal with the adverse event as shown in Figure 10. Delavirdine had the strongest signal with regards to conduction disorder. It had a safety signal of more than 6 and is therefore a strong candidate for further analysis to determine causality. Most of the drugs for which conduction disorder was reported had a safety signal of more than 2 with the exception of ritonavir as shown in Figure 21.



Ritonavir (RTV), Tenofovir disoproxil fumarate (TDF), Lamivudine (3TC), Emtricitabine (FTC), Zidovudine (AZT), Efavirenz (EFV), Abacavir (ABC), Lopinavir/ritonavir (LPV/r), Atazanavir (ATV), Raltegravir (RAL), Darunavir (DRV), Nevirapine (NVP), Stavudine (d4T), Didanosine (ddI), Etravirine (ETV), Nelfinavir (NFV), Saquinavir (SQV), Fosamprenavir (FPV), Indinavir (IDV), Amprenavir (APV), Zalcitabine (ddC), Delavirdine (DLV)

Figure 21: Safety signals for unspecified arrhythmia and conduction disorder with various antiretroviral drugs

4.6.11 Summary of safety signals for cardiac arrhythmias and antiretroviral drugs

Foetal and neonatal arrhythmogenic adverse events were more strongly associated with NRTIs and PIs than with any other group of ARVs. Foetal and neonatal arrhythmias were the most commonly reported cardiac arrhythmias in neonates and the foetus while neonatal cardiac arrest was the least reported. Among NRTIs, zidovudine had more reported adverse events compared to tenofovir. There were no recorded arrhythmic events in the cohort with respect to zalcitabine and abacavir. The same was true for nelfinavir, indinavir, saquinavir, amprenavir and fosemprenavir among PIs. Arrhythmic disorders involving the heart rate were majorly reported in patients on PIs as were ventricular and sinus node disorders. Generally, more types of cardiac arrhythmias were reported in patients on PIs than on any other group of antiretroviral drugs. A summary of the arrhythmogenic adverse events reported with the use of various ARVs is given in Table 9.

Table 9: Summary of signals for cardiac arrhythmias with antiretroviral drugs

	NRTIs	NNRTIs	PIs	Others
Foetal and neonatal arrhythmias				
Foetal arrhythmia	AZT>ABC>3TC>FTC>TDF>ddI	NVP	LPV/r>DRV>ATV>RTV	RAL
Foetal bradycardia	ddI>AZT>3TC>TDF	-	ATV>LPV/r>RTV	-
Neonatal arrhythmia	ddI>d4T>AZT>TDF>FTC	EFV	LPV/r>RTV>ATV	RAL
Neonatal bradycardia	AZT>ddI	NVP	-	-
Neonatal cardiac arrest	AZT	-	-	RAL
Slow heart rhythm				
Bradycardia	ddC	-	-	-
Bradyarrhythmia	-	-	NFV>LPV/r	-
ECG QT corrected interval prolongation	d4T	DLV	SQV>ATV>NFV	-
ECG QT interval prolongation	-	DLV	-	-
Long QT syndrome	ABC>AZT>3TC	-	-	-
Increased heart rate				
Sinus tachycardia	ddI	-	NFV	-
Torsade de pointes	AZT	-	IDV>SQV>NFV>FPV	-
Atrial and ventricular arrhythmias				
Atrial conduction time prolongation	-	-	RTV	-
Arrhythmogenic right ventricular dysplasia	-	-	LPV/r>RTV	-
Torsade de pointes	AZT	-	IDV>SQV>NFV>FPV	-
Ventricular arrhythmia	ddI	EFV	FPV>SQV>NFV	RAL
Sinus node disorders				
Nodal arrhythmia	-	DLV	IDV>NFV	-
Sinus tachycardia	ddI	-	NFV	-
Sinus node dysfunction	ddI>ABC>d4T>3TC	EFV	NFV>APV>SQV>LPV/r>RTV	-
Unspecified arrhythmias				
Cardiopulmonary failure	-	-	FPV	-
Conduction disorder	d4T>ABC>ddI>3TC	DLV	ATV	-
Paroxysmal arrhythmia	-	EFV	-	-

4.6.12 Arrhythmias reported with the use of common Kenya adult antiretroviral regimens

Guidelines on Use of Antiretroviral Drugs for Treating and Preventing HIV Infection in Kenya (2018 Edition) (65) were used to identify adult regimens used in the country (≥ 15 years or ≥ 35 kg). There were seven regimens in which cardiovascular rhythm disorders had been reported. Foetal bradycardia associated with AZT/3TC/ATV/r had the strongest safety signal (6.24). It was followed by foetal arrhythmias reported with the use of ABC/3TC/ATV/r with a signal of 5.51. Other arrhythmias reported with these regimens included bradycardia, sinus arrhythmia and sinus tachycardia as shown in Table 10. Notably, all the regimens in which arrhythmias were reported as potential new safety signals had protease inhibitors as part of the antiretroviral regimen.

Table 10: Signals for arrhythmias reported with use of selected antiretroviral regimens

Adverse event	AZT/3TC/ATV/r	AZT/3TC/LPV/r	ABC/3TC/LPV/r	ABC/3TC/ATV/r	AZT/3TC/DTG/DRV/r	AZT/3TC/RAL/DRV/r	ETV/3TC/DRV/r
Foetal arrhythmias							
Foetal arrhythmia	-	1.03	-1.11	**5.51**	-	-	-
Foetal bradycardia	**6.24**	-	-	-	-	-	-
Slow heart rhythm							
Bradycardia	-	-0.83	-0.42	-	**5.24**	**2.70**	-
Sinus bradycardia	-	-	0.23	-	-	-	-
Increased heart rate							
Sinus tachycardia	-	-	-	-	-	-	**4.07**
Sinus node disorders							
Sinus arrhythmia	**5.07**	-	-	-	-	-	-
Sinus bradycardia	-	-	0.23	-	-	-	-
Sinus tachycardia	-	-	-	-	-	-	**4.07**
Unspecified arrhythmias							
Cardiopulmonary failure	-	-	-	-	-	-	**4.07**
Sudden cardiac death	-	-	**2.34**	-	-	-	-

4.7 IDENTIFICATION OF POTENTIAL DRUG INTERACTIONS BETWEEN ANTIRETROVIRAL DRUGS AND SELECTED CARDIOVASCULAR AGENTS

Nineteen arrhythmic adverse events were found to have been reported for the seventy drug combinations evaluated. Five of these adverse events were labeled as 'known' and therefore were not evaluated further. These include sudden cardiac death, conduction disorder, ECG QT prolongation, ventricular arrhythmias and bradycardia. In a majority of the instances, there was an increased risk of the reported adverse events when the antiretroviral drugs were used together with the cardiovascular agents compared to when the CVS drugs were excluded.

4.7.1 Preliminary assessment using the Information Component (IC)

Out of the ten cardiovascular agents evaluated for interaction effects with atazanavir, there were no reported cardiac arrhythmias with the joint use of losartan and atazanavir. Most of the reported arrhythmic adverse events had a safety signal of less than 1. Concomitant use of atazanavir with amlodipine exhibited a strong signal with regard to conduction disorders. However, there was less risk of conduction disorders when atazanavir was combined with amlodipine compared to when used alone. There was a strong signal with regard to the joint use of atazanavir with verapamil and presence of QT prolongation and ventricular arrhythmia in HIV patients. The signal was higher when the ARV was used together with the CVS agents as shown in Table 11. The three are all known adverse events associated with the concomitant use of these drugs.

Five types of cardiac arrhythmias were found to have a strong safety signal with regard to the concomitant use of ritonavir and some of the cardiovascular agent assessed. Conduction disorder reported in patients jointly on amlodipine and ritonavir exhibited the strongest signal. QT interval prolongation was also strongly linked with the simultaneous use of ritonavir and verapamil. Other adverse events for which there were strong signals with the drugs of interest were atrial conduction time prolongation, bradycardia, ventricular arrhythmia and cardiopulmonary failure. Bradycardia and ventricular arrhythmia are known adverse events associated with the joint use of verapamil and ritonavir.

Table 11: Drug combinations for which safety signals for cardiac arrhythmias were ≥ 1

Drug combination	Type of arrhythmia	Signal strength (IC)		
		ARV drug	CVS agent	Combination
Combinations involving PIs				
Atazanavir/verapamil	QT prolongation	1.61	1.84	**2.84**
Atazanavir/verapamil	Ventricular arrhythmia	1.05	2.57	**2.16**
Atazanavir/amlodipine	Conduction disorder	3.91	1.13	**3.05**
Ritonavir/verapamil	Bradycardia	0.46	3.09	**0.95**
Ritonavir/verapamil	QT prolongation	0.63	1.84	**2.17**
Ritonavir/verapamil	Ventricular arrhythmia	0.78	2.57	**1.91**
Ritonavir/diltiazem	QT prolongation	0.63	1.17	**1.07**
Ritonavir/amlodipine	Conduction disorder	1.51	1.13	**2.73**
Ritonavir/bisoprolol	Cardiopulmonary failure	0.82	1.73	**1.49**
Lopinavir/ritonavir/diltiazem	QT prolongation	0.96	1.17	**1.80**
Lopinavir/ritonavir/verapamil	QT prolongation	0.96	1.84	**1.98**
Lopinavir/ritonavir/atenolol	Sinus tachycardia	0.89	1.09	**1.18**
Lopinavir/ritonavir/carvedilol	Sinus tachycardia	0.89	0.96	**2.21**
Darunavir/carvedilol	QT prolongation	0.28	0.87	**0.99**
Darunavir/carvedilol	Sinus tachycardia	0.38	1.29	**2.02**
Combinations involving NNRTIs				
Efavirenz/atenolol	Sinus tachycardia	0.99	1.09	**1.01**
Efavirenz/carvedilol	Sinus tachycardia	0.99	0.96	**2.14**
Nevirapine/amlodipine	Sinus tachycardia	0.23	0.88	**1.77**
Etravirine/carvedilol	Sinus tachycardia	1.49	0.96	**2.40**

When interactions between lopinavir/ritonavir and the selected cardiovascular drugs were assessed for arrhythmic adverse events, only two reported events had a safety signal of more than 1. These include QT interval prolongation and sinus tachycardia. QT interval prolongation was reported in patients on lopinavir/ritonavir and diltiazem as well as those on both lopinavir/ritonavir and verapamil. Sinus tachycardia was documented in patients concomitantly on lopinavir/ritonavir and atenolol as well as those jointly on lopinavir/ritonavir and carvedilol. Sinus tachycardia resulting from the co-use of lopinavir/ritonavir and carvedilol exhibited the strongest signal of 2.21. There were no reports recorded for patients on both losartan and lopinavir/ritonavir.

Five types of cardiac arrhythmias were reported in patients concomitantly on darunavir and the selected cardiovascular agents under assessment. There were weak signals between most of the adverse events and the drugs. The strongest safety signal with regard to cardiac arrhythmias was found with the co-administration of carvedilol and darunavir with sinus tachycardia and QT interval prolongation being reported. They had safety signals of 2.02 and 0.99 respectively

as shown in Table 11. There were no reports recorded for patients concomitantly using darunavir and either losartan or digoxin.

Sinus tachycardia was the arrhythmias most strongly linked to the concomitant use of efavirenz and the cardiovascular agents under evaluation. The adverse event was reported in patients on atenolol/efavirenz and carvedilol/efavirenz combinations with a safety signal of 1.01 and 2.14 respectively as shown in Table 11. All the other reported arrhythmic adverse events exhibited weak signals to the drugs under consideration with most having a safety signal of less than 0. No cardiac arrhythmias were reported in patients using both efavirenz and either nifedipine or verapamil.

Two types of cardiac arrhythmias were reported in patients on nevirapine and the cardiovascular drugs under evaluation. These were sinus tachycardia and cardiac arrest. Out of these, co-use of nevirapine and amlodipine exhibited the strongest signals with sinus tachycardia. It had a safety signal of 1.77. No arrhythmogenic adverse event reports were made with the concomitant use of nevirapine and nifedipine, verapamil, losartan, bisoprolol or amiodarone.

There was a weak link between cardiac arrhythmias and the concomitant use of etravirine and the cardiovascular drugs under assessment with most arrhythmias exhibiting a safety signal of less than 1. The strongest signal was found to be between sinus tachycardia and etravirine/carvedilol combination with a safety signal of 2.40 as shown in Table 11. No arrhythmias were reported with the use of atravirine with amlodipine, nifedipine, verapamil or losartan.

4.7.2 Further assessment of identified safety signals using other measures of disproportionality

Reported arrhythmic adverse events with a safety signal of I or more were further evaluated using other measures of disproportionality. These included Proportional Reporting Ratio (PRR) and the Yates Chi Square (χ 2).

The signal between ritonavir/amlodipine and conduction disorder was found to be the strongest with a PRR of about 60. This is far above the set cut-off point of 2 to differentiate background noise and potentially new safety signals. All the other three adverse events also had strong links with the respective drugs. They all had a PRR value of more than 15. All the p-values were less than 0.001 further confirming the strength of the signals. When the PRR was log

transformed to minimise the false positives and stabilise the extreme PRR values, the $\log_2$ PRR values remained significant with values above 4 as shown in Table 12.

Table 12: Measures of disproportionality for potentially new safety signals associated with the co-use of antiretroviral drugs and selected cardiovascular agents

Drug combination	PRR (C.I)	Log2 PRR	Chi squared Yates (χ 2)	p-value (non-exact)
Cardiopulmonary failure				
RTV/bisoprolol	42.342 (20.261 ; 88.488)	5.404	242.302	**< 0.001**
Conduction disorder				
RTV/amlodipine	62.776 (35.653 ; 110.533)	5.972	663.906	**< 0.001**
QT prolongation				
RTV/diltiazem	19.492 (9.416 ; 40.350)	4.285	105.166	**< 0.001**
RTV/verapamil	50.782 (29.622 ; 87.055)	5.666	537.581	**< 0.001**
LPV/r/diltiazem	88.501 (42.541 ; 184.114)	6.468	435.940	**< 0.001**
LPV/r/verapamil	218.303 (117.441 ; 405.788)	7.770	1091.338	**< 0.001**
DRV/carvedilol	20.516 (8.682 ; 48.483)	4.359	74.453	**< 0.001**
Sinus tachycardia				
LPV/r/atenolol	42.035 (17.821 ; 99.149)	5.394	161.455	**< 0.001**
LPV/r/carvedilol	107.758 (53.510 ; 217.001)	6.752	637.725	**< 0.001**
DRV/carvedilol	52.663 (25.601 ; 108.332)	5.719	305.120	**< 0.001**
EFV/atenolol	33.572 (14.179 ; 79.486)	5.069	127.188	**< 0.001**
EFV/carvedilol	94.652 (46.762 ; 191.587)	6.565	558.598	**< 0.001**
NVP/amlodipine	51.309 (23.530 ; 111.883)	5.681	247.922	**< 0.001**
ETR/carvedilol	212.251 (109.943 ; 409.763)	7.730	1268.645	**< 0.001**

The assessed associations also exhibited very high χ 2 values of more than 100. Generally, χ 2 values greater than 4 indicate statistical significance with $p \leq 0.05$. These statistically significant χ 2 values show that there is a more than 95% chance that the observed numbers are really different from the expected numbers. There is therefore a very strong safety signal with regard to the drug-adverse events evaluated.

With regard to lopinavir/ritonavir, all the interactions with a safety signal of more than 1 had very high proportional reporting ratios of more than 40. They also had very high χ 2 values with lopinavir/ritonavir/verapamil combination having a χ 2 value of about 1100 as shown in Table 12. The measures of disproportionality were significant with $p< 0.001$ pointing to very strong signal between the drugs and the reported adverse events. QT interval prolongation and sinus tachycardia associated with darunavir/carvedilol co-use had significant PRRs of about 20 and 50 respectively ($p< 0.001$). This point to very strong safety signals between the adverse events and the drugs.

The PRRs for sinus tachycardia associated with both efavirenz/atenolol and efavirenz/carvedilol were above 30 with p values less than 0.001 pointing to a strong signal between sinus tachycardia and the drug combinations. The PRR for sinus tachycardia associated with the joint use of nevirapine and amlodipine was found to be about 50. The χ 2 value was about 250 and the values were statistically significant ($p< 0.001$). When the link between sinus tachycardia and the concomitant use of etravirine and carvedilol was assessed using other measures of disproportionality, a strong and statistically significant signal between the joint use of the two drugs and sinus tachycardia was established. These measures of disproportionality are shown in Table 12.

4.7.3 Summary of potentially new safety signals for interactions between non-nucleoside reverse transcriptase inhibitors, protease inhibitors and selected cardiovascular agents

Concomitant use of protease inhibitors and selected cardiovascular agents was strongly linked with triggering QT interval prolongation, sinus tachycardia, cardiopulmonary failure and conduction disorders in HIV patients. The most commonly implicated drugs were Lopinavir/riotonavir and ritonavir for the ARVs and beta blockers and calcium channel blockers among the cardiovascular drugs. Among the arrhythmic adverse events, joint use of non-nucleoside reverse transcriptase inhibitors and selected cardiovascular drugs was only reported to induce sinus tachycardia among HIV patients. Efavirenz, nevirapine and etravirine were implicated among the NNRTIs while atenolol, carvedilol and amlodipine had the strongest signals among the cardiovascular drugs. A synopsis of the potential new signals related to the concomitant use of PIs and NNRTIs and selected cardiovascular drugs is given in Table 13.

Table 13: Summary of potentially new safety signals associated with the concomitant use of NNRTIs, PIs and selected cardiovascular

Protease inhibitors	Non-nucleoside reverse transcriptase inhibitors
QT interval prolongation	
Ritonavir + diltiazem	-
Ritonavir + verapamil	-
Lopinavir/ritonavit + diltiazem	-
Lopinavir/ritonavir + diltiazem	-
Darunavir + Carvedilol	-
Sinus tachycardia	
Lopinavir/ritonavit + atenonol	Efavirenz + atenolol
Lopinavir/ritonavir + carvedilol	Efavirenz + carvedilol
Darunavir + carvedilol	Etravirine + carvedilol
-	Nevirapine + amlodipine
Cardiopulmonary failure	
Ritonavir + bisoprolol	-
Conduction disorder	
Ritonavir + amlodipine	-

CHAPTER FIVE: DISCUSSION OF RESULTS

5.1 TIME SERIES OF THE QUALITY OF KENYAN ADVERSE EVENT REPORTS

A total of 11, 270 reports were evaluated during the time series assessment of the quality of Kenyan individual case safety reports (ICSRs). Most of the reports were submitted from counties with big referral hospitals. Counties with large urban areas also recorded a high reporting due to the high concentration of health care workers in these areas. A majority of the adverse events reported involved antiretroviral and antimycobacterial drugs because pharmacovigilance reporting efforts were initially concentrated in the HIV and TB programs. Quarterly means of the completeness score were used to study the trend of quality of the reports. From the assessment, the first adverse event reports were submitted to VigiBase in May 2010. This is despite the Pharmacovigilance Department at the Kenya Pharmacy and Poisons Board having being established in 2004 and the consequent launch of the National Pharmacovigilance Reporting System in June 2009 (15). The reason for this lag is that most of the Kenyan pharmacovigilance reports are filled manually at the user points and the reports submitted to PPB. The reports are then compiled at the National Pharmacovigilance Centre and submitted electronically to VigiBase. There is therefore no real time submission of reports to the WHO database. For the same reason, there were no submitted reports in some quarters including the fourth quarter of 2010 and the first quarter of 2016.

There was little seasonal variability in the completeness scores meaning that the quality of reporting was fairly constant throughout the year. There was however a conspicuous upward improvement in the quality of pharmacovigilance reports in the country. From a low of about 0.3 in 2010, the quarterly mean score increased gradually peaking at about 0.8. This could be the result of sustained pharmacovigilance training of health care workers carried out since 2009(66). The quality of the ICSRs appears to have stagnated at around 0.7. More robust strategies need to be employed to further improve the quality of reports. The recent launch of the Guidelines for the Establishment of Qualified Persons for Pharmacovigilance (67) is one of the approaches that the regulator is taking to bolster the level pharmacovigilance reporting in the country.

Segmented time series analysis revealed that a significant event occurred in the last quarter of 2012 that resulted in a major improvement in the quality of ICSRs. While this study could not

conclusively determine what was behind this change point, it can be speculated that there was a major drive to sensitive health care workers on detection and reporting of adverse drug reactions around this period.

5.2 DISPROPORTIONALITY ANALYSIS TO EVALUATE FOR POSSIBLE LINKS BETWEEN ANTIRETROVIRAL DRUGS AND CARDIAC ARRHYTHMIAS

Ritonavir (0.5%), tenofovir disoproxil fumarate (0.5%), lamivudine (0.5%), emtricitabine (0.4%) and zidovudine (0.2%) were the ARVs most cited in reports in the Food and Drug Administration Adverse Event Reporting System (FAERS). These findings mirror those of Haggar et al (68) who in a study published in 2016 found out that nucleoside and nucleotide reverse transcriptase inhibitors are some the major products listed in African ICSRs submitted to VigiBase. This is probably due their widespread use in HIV management. Nelfinavir (22.1%) and zalcatabine (21.8%) had the highest proportion of cardiovascular adverse events reported. Cardiovascular adverse events accounted for above 10% of AEs reported for many other ARVs in contrast to other studies that demonstrate only very few cardiovascular events linked to antiretrovirals (69,70).

Several antiretroviral drugs gave very strong signals for an association with foetal and neonatal cardiac arrhythmias. Nucleoside reverse transcriptase inhibitors (NRTIs) and protease inhibitors (PIs) exhibited especially strong signals for these adverse events. No prior study was found that could offer an adequate explanation linking these ARVs and foetal and neonatal arrhythmias. It has however been suggested that in-utero exposure to ARVs may have deleterious clinical effects on the cardiac structure and function. This could occur even in children where mother to child transmission has been successfully inhibited and children are therefore born free of the HIV virus. The structural and functional changes described include reductions in the left ventricular mass and septal wall thickness and resulting in an increased afterload. Additionally, foetal and neonatal exposure to highly active antiretroviral therapy (HAART) has been linked to deficient myocardial development similar to that seen in anthracycline cardiotoxicity (47). These structural and functional abnormalities could explain the strong signal for an association between ARVs and arrhythmias in neonates and the developing foetus. However, two different 5-year prospective studies seeking to assess the association between zidovudine and foetal and neonatal cardiotoxicity found no such link (71).

Various other types of cardiac arrhythmias were found to be strongly associated with ARVs with potential to be flagged as new safety signals. These included QT interval disorders, sinus node dysfunction as well as unspecified arrhythmias. Various studies support these findings. Ritonavir boosted protease inhibitors such as lopinavir/ritonavir and atazanavir/ritonavir combinations may cause QT interval prolongation. Among all the PIs, QT interval prolongation has most strongly been associated with saquinavir/ritonavir combination. Efavirenz has also been previously linked with these adverse event (39).

Nevertheless, it has been postulated that apart from HAART, arrhythmias in HIV patients can occur as a symptom of other myocardial diseases such as heart failure and myocarditis (72). Such co-morbidities in HIV patients are therefore potential confounders when evaluating for an association between HAART and cardiac arrhythmias. Additionally, HIV-related immunosuppression and traditional CVD risk factors such as obesity and smoking have been associated with an increased risk of atrial fibrillation, atrial flutter, sinus tachycardia and QT interval prolongation among HIV patients (44,46,73). Cardiac arrhythmias have been observed as a secondary manifestation of a malignancy. In HIV patients, a high viral load and systolic and diastolic left ventricular impairment have been linked to sudden cardiac death (73).

When protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs) were assessed for interaction effects when used together with selected cardiovascular agents, the strongest safety signals were seen when the ARVs were co-administered with calcium channel blockers and beta blockers. Significant arrhythmogenic adverse events reported with these combinations included QT interval prolongation, sinus tachycardia, conduction disorder and cardiopulmonary failure. These findings are consistent with some previous studies assessing interactions between ARVs and cardiovascular agents. The PI nelfinavir has been linked to ECG abnormalities when used concomitantly with nifedipine (56). Indinavir has been shown to increase the blood plasma levels of amlodipine and diltiazem resulting in increased effects of the antihypertensive drugs (58). A case study presented by Puech et al (55) concluded that interactions between lopinavir/ritonavir, metoprolol and lacidipine were responsible for severe bradycardia experienced by a patient presented in the study.

The reported CVS adverse events may be the result of pharmacokinetic interactions between the co-administered drugs. Some of the adverse events from possible drug interactions were expected. These include sudden cardiac death, conduction disorder, ECG QT prolongation, ventricular arrhythmias and bradycardia. PIs and NNRTIs are metabolized majorly by

cytochrome P450 3A4 (CYP 3A4) enzymes. Most calcium channel blockers including nifedipine, amlodipine, diltiazem and verapamil as well as beta blockers such as atenolol and metoprolol are also bio transformed using this pathway. NNRTIs including efavirenz and nevirapine are CYP inducers. They induce metabolism of concomitant drugs and reduce their effectiveness. Protease inhibitors on the other hand mainly inhibit CYP and can therefore increase the effects of concomitant drugs leading to toxicity (74–76).

5.3 LIMITATIONS OF THE STUDY

The major limitations of this study are due to weaknesses inherent in using spontaneous report databases such as FAERS as a source of data for disproportionality analysis. As set out in the literature review, one of the major deficiencies of such databases is reporting bias due to factors such as the Weber effect. Confounding factors such as age of patients and comorbid conditions are also a major issue when spontaneous report databases are used as a source of data. This can however be controlled by stratification or logistic regression. Moreover, lack of a known incidence denominator, duplication of reports and missing information further weaken the credibility of spontaneous reports databases as a reliable data mining source (25,26,32,35,36).

The spontaneous reports database used in the study (FAERS) contains primarily American adverse event reports. Ideally, VigiBase which contains global spontaneous reports data should have been used. Limited access to VigiBase prevented this. It is however important to note that FAERS data also contains reports from other countries since pharmaceutical companies domiciled in America are bound to submit adverse events reported in user countries to FAERS. Additionally, FAERS data is also submitted to VigiBase and it is notable that American adverse event reports form the largest proportion of ICSRs in WHO's VigiBase (77).

The identified limitations are however not material enough to interfere with the validity of the findings of this research.

CHAPTER SIX: CONCLUSION AND RECOMMENDATIONS

6.1 CONCLUSION

While the quality of adverse event reporting has improved since 2010, it has stagnated at around 70%. New policy guidelines such as the new requirement for marketing authorization holders (MAHs) to have a qualified person for pharmacovigilance (QPPV) as well as continued sensitization of health workers and consumers may however aid in further improving the standard of adverse event reporting in the country.

Disproportionality analysis revealed a very strong signal for an association between some antiretroviral drugs and cardiac arrhythmias. This was especially with regard to foetal and neonatal arrhythmias. While not conclusive, these findings form a basis for hypothesis generation in future studies. There were also notable interaction effects between some of the ARVs and selected cardiovascular agents especially those metabolized by cytochrome P450 3A4 enzymes.

6.2 RECOMMENDATIONS FOR POLICY AND PRACTISE

There is a need for the implementation of the new pharmacovigilance reporting guidelines to be enforced. Continuous health worker training on adverse events detection and reporting should also be sustained. There is also a need to intensify public sensitisation on identification of adverse events and the importance of submitting such reports to the regulator.

Health practitioners working with HIV patients should be on the look-out for cardiovascular adverse events relating to ARVs in this cohort. This is especially so with regard to pregnant women; neonates; as well as patients with prior cardiovascular diseases and on concomitant cardiovascular agents.

6.3 RECOMMENDATIONS FOR RESEARCH

More robust studies such as cohort event monitoring and case controls are needed to confirm the observed safety signals for the association between antiretroviral therapy and cardiac arrhythmias. Apart from cardiac arrhythmias, other cardiovascular adverse events may also be evaluated.

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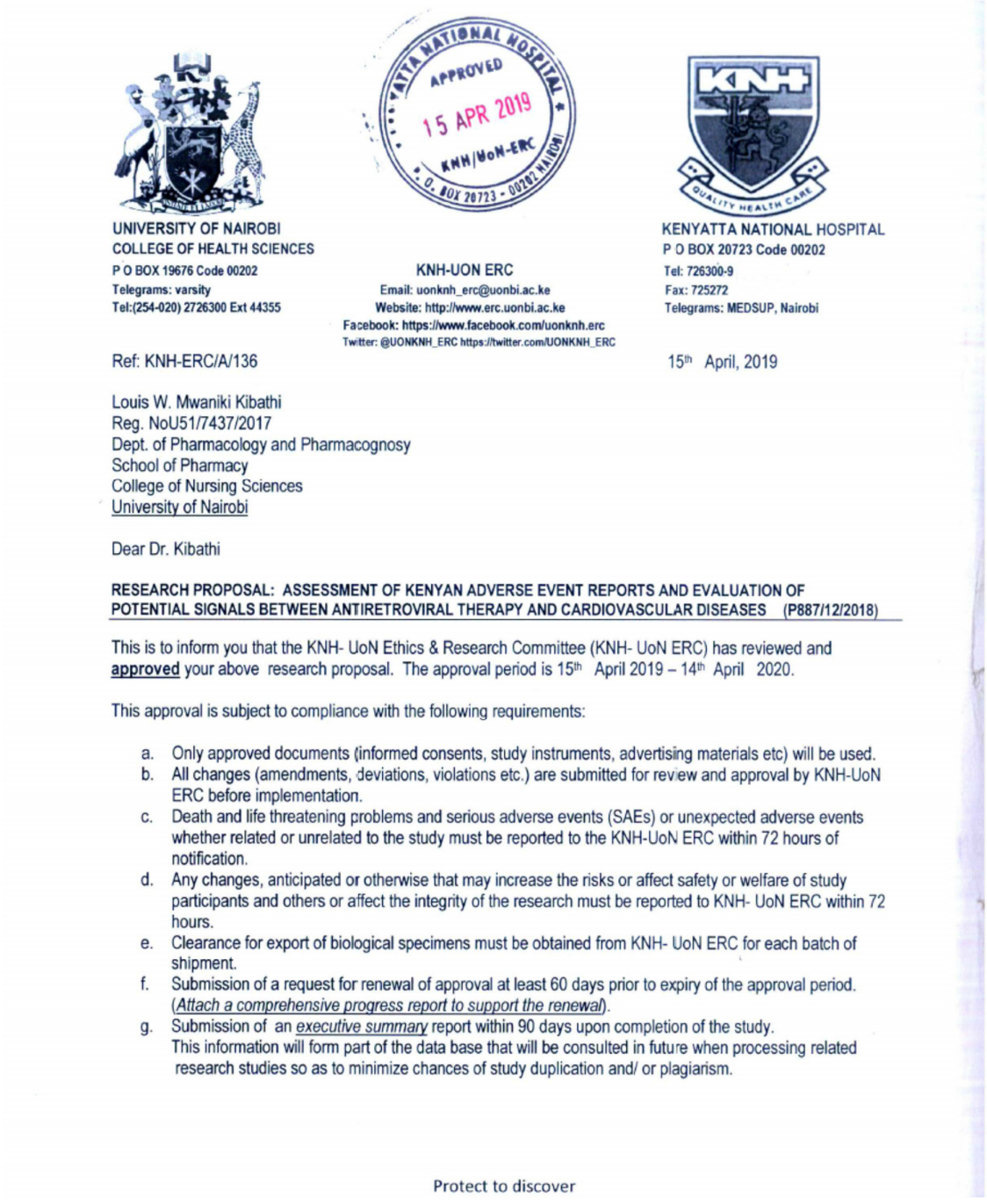
APPENDICES

Appendix A: Ethical approval from the Kenyatta National Hospital/University of Nairobi Ethics and Research Committee (KNH/UoN-ERC)



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Fax: 725272
Telegrams: MEDSUP, Nairobi

Ref: KNH-ERC/A/136

15th April, 2019

Louis W. Mwaniki Kibathi
Reg. NoU51/7437/2017
Dept. of Pharmacology and Pharmacognosy
School of Pharmacy
College of Nursing Sciences
University of Nairobi

Dear Dr. Kibathi

RESEARCH PROPOSAL: ASSESSMENT OF KENYAN ADVERSE EVENT REPORTS AND EVALUATION OF POTENTIAL SIGNALS BETWEEN ANTIRETROVIRAL THERAPY AND CARDIOVASCULAR DISEASES (P887/12/2018)

This is to inform you that the KNH- UoN Ethics & Research Committee (KNH- UoN ERC) has reviewed and **approved** your above research proposal. The approval period is 15th April 2019 – 14th April 2020.

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 serious 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. Clearance for export of biological specimens must be obtained from KNH- UoN ERC for each batch of shipment.
f. 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*).
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.

Protect to discover

For more details consult the KNH- UoN ERC website **http://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 Director, CS, KNH
The Chairperson, KNH- UoN ERC
The Assistant Director, Health Information, KNH
The Dean, School of Pharmacy, UoN
The Chair, Dept. of Pharmacology and Pharmacognosy,UON
Supervisors: Prof. Faith A.Okalebo, Dr. Timothy Kuria Kamanu

Appendix B: Approval to conduct the study by the Pharmacy and Poisons Board

MINISTRY OF HEALTH
PHARMACY AND POISONS BOARD

Telegram: "MINHEALTH" Nairobi
Telephone: 020-2716905/6, 020-3562107
Cellphone: 0733-884411/0720 608811
Fax: 2713409
Email: admin@pharmacyboardkenya.org
Website: www.pharmacyboardkenya.org

Pharmacy & Poisons Board Hse
Along Lenana Road
P. O. Box 27663-00506
NAIROBI

When replying please quote our ref No:
PPB/BSA/HR/INT/O18/19

6th May, 2019

Louis M. Kibathi
Thru'
Dept. of Pharmacology and Pharmacognosy
School of Pharmacy
University of Nairobi
Reg. No.: U51/7473//2017
NAIROBI

Dear Madam,

RE: RESEARCH THESIS IN MPHARM. PHARMACOEPIDEMIOLOGY AND PHARMACOVIGILANCE

Reference is made to your letter dated 12th April, 2019 to Pharmacy and Poisons Board.

The Board has reviewed your proposal entitled: ***"Assessment of Kenya Adverse Events reports and evaluation of potential signals between antiretrovirals therapy and cardiovascular diseases"***

Your proposal has been reviewed and the *Board* has approved your request to carry out the study, before commencement of the data collection process you are required to;

- sign and adhere to the conditions of the stipulated student ***confidentiality agreement*** enclosed herein
- provide ***the approval from*** the Ethics Review Committee

You are further advised to confirm the references figures quoted under Literature review on the status of pharmacovigilance as some data does not reflect a true picture of what is currently available; eg the figure provided for poor quality reports is almost 3 times higher than what is available in the PPB database.

Kindly note that for purposes of publication this is the proposed list of names from PPB. The team will work closely with you in the course of your work.

1. Chief Executive Officer: Dr Fred M. Siyoi
2. Head of Pharmacovigilance: Dr Christabel Khaemba
3. Pharmacovigilance Regulatory officer: Dr Martha Mandale

Mr. Keter will be included on the list of acknowledgements

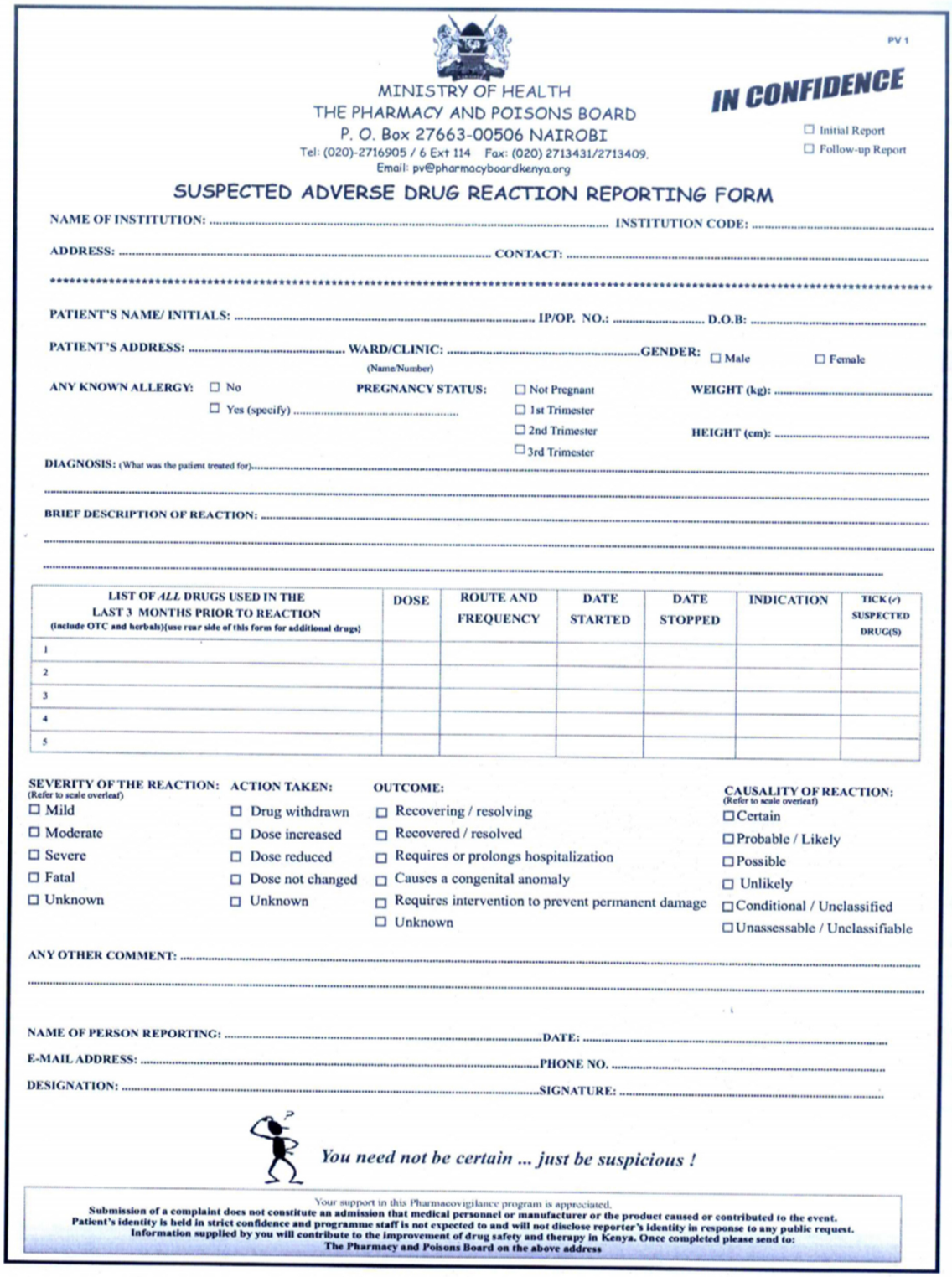
Be informed that Pharmacy & Poisons Board shall terminate your study should any of the stated conditions in the student confidentiality agreement be violated.

You are further required to provide a copy of your final project work for information and future reference to the Medicines Information and Pharmacovigilance Directorate.

Yours faithfully,

Dr. F. M. Siyoi
CHIEF EXECUTIVE OFFICER
CK/eo

Appendix C: Suspected 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: ..... (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. 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 D: Seasonal indices of completeness scores of Kenyan individual safety case reports

	Quarter 1	Quarter 2	Quarter 3	Quarter 4
2010	-	0.003195419	-0.017515027	-0.003024344
2011	0.017343953	0.003195419	-0.017515027	-0.003024344
2012	0.017343953	0.003195419	-0.017515027	-0.003024344
2013	0.017343953	0.003195419	-0.017515027	-0.003024344
2014	0.017343953	0.003195419	-0.017515027	-0.003024344
2015	0.017343953	0.003195419	-0.017515027	-0.003024344
2016	0.017343953	0.003195419	-0.017515027	-0.003024344
2017	0.017343953	0.003195419	-0.017515027	-0.003024344
2018	0.017343953	0.003195419	-0.017515027	-

Appendix E: Trend, seasonal and random components of the complete scores of kenyan adverse event reports