

**ADVERSE DRUG REACTIONS ASSOCIATED WITH
ANTIRETROVIRAL THERAPY IN SOUTH AFRICA**

BY

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Submitted as the dissertation component in partial fulfilment for the degree of Master of Health Sciences in the school of Health Sciences, University of KwaZulu-Natal.

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PREFACE

This dissertation is presented in an article format. The findings of the study are presented in chapter 3, in manuscript format as required by the regulations of the University of KwaZulu-Natal. One manuscript will be submitted for publication in the *South African Medical Journal (SAMJ)*. The reference list is cited according to the instructions for authors as required by the SAMJ. A complete reference list is included at the end of every chapter and according to the reference style of the University of KwaZulu-Natal.

The dissertation consists of four chapters as follows:

- Chapter 1: provides an introduction to the study as well as the aims, objectives and a brief overview of the methodology.
- Chapter 2: highlights the literature review of adverse drug reactions relating to incidence and prevalence, HIV/AIDs, patient adherence, monitoring, cost implications and pharmacovigilance in South Africa.
- Chapter 3: consists of the results, discussion and conclusion written in a manuscript format.
- Chapter 4: provides the general conclusions, recommendations, limitations and strengths of the study.

ABSTRACT

Background and Aim

South Africa has one of the highest prevalence's of human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS) infected people in the world. HIV/AIDS patients face countless challenges, one of which is the risk of adverse drug reactions. This study aimed to describe the ADRs reported in South Africa with reference to the type of ADR, ARVs implicated, seriousness of the ADR and patient demographics associated with specific ADRs.

Methods

A retrospective quantitative study was carried out using ADR reports which were submitted to the National Department of Health during 01 January 2010 – 31 December 2014. Data, obtained electronically in the form of case study reports, was transcribed onto Microsoft Excel® (version 10) and analysed using SPSS® (version 19). A descriptive and inferential analysis was carried out to determine the strength of the relationships (Pearson Chi Square test) between different variables.

Results

A total of 2489 reports were analysed, of which the majority of ADRs reported were experienced by female patients (n=1511, 66.7%) as opposed to male patients (n=755, 33.3%). This study found evidence of a high degree of adverse drug reactions among patients on first-line ART with stavudine (n=1256, 50.46%), efavirenz (n=572, 22.98%), zidovudine (n=209, 8.40%), tenofovir (n=203, 8.16%) nevirapine (n=153, 6.15%) based regimens. The 10 most common ADRs reported with the use of ARVs were peripheral neuropathy (n=472, 19%), lipodystrophy (n=471, 18.9%), serious skin reactions (n=266, 10.7%), gynaecomastia (n=219, 8.8%), renal failure (n=140, 5.6%), dizziness (n=133, 5.3%), hyperlactatemia (n=118, 4.7%), psychosis/hallucinations (n=47, 1.9%), sleep disturbances (n=44, 1.8%) and vomiting (n=44, 1.8%). Peripheral neuropathy and lipodystrophy were the most common ADRs amongst the female patients who received stavudine treatment in the 30-44 year age group.

Discussion and Conclusion

Female patients were more likely to experience peripheral neuropathy, lipodystrophy, skin rash, anaemia and hyperlactatemia, while male patients were more prone to experience gynaecomastia and peripheral neuropathy. In addition, patients aged 30-44 years old reported

the most ADRs. Most reactions were caused due to the use of stavudine, efavirenz, zidovudine, nevirapine and tenofovir in the population groups identified in this study.

Keywords: Pharmacovigilance, antiretroviral therapy, human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS), adverse drug reactions

DECLARATION 1 – PLAGIARISM

I, **Sumeshni Birbal**, declare that:

1. The research reported in this thesis, except where otherwise indicated, is my original work.
2. The work described in this dissertation has not been submitted to UKZN or other tertiary institutions for purposes of obtaining an academic qualification, whether by myself or any other party.
3. This dissertation does not contain other persons' writing, unless specifically acknowledged as being sourced from other researchers. Where other written resources have been quoted, then:
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4. This dissertation does not contain text, graphics or tables copied and pasted from the Internet, unless specifically acknowledged, and the source being detailed in the thesis and in the reference sections.

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Date _____

This is to certify that the contents of this thesis are the original work of Ms Sumeshni Birbal and as the candidate's supervisor/co-supervisor, I have approved this thesis for submission.

1. Signed: _____ Name: **Dr. Frasia Oosthuizen** Date: _____
2. Signed: _____ Name: **Dr. Elizabeth Ojewole** Date: _____

DECLARATION 2 – ETHICS APPROVAL

A full ethical approval for the study was obtained from the Humanities and Social Sciences Research Ethics Committee of the University of KwaZulu-Natal (HSS/0916/015M) – (Annexure 1). Permission was obtained from the South African National Department of Health to use the adverse drug reaction case reports from their Pharmacovigilance centre (Annexure 2).

DECLARATION 3 – MANUSCRIPT PUBLICATION

1. My contribution to the project was as follows:

Sumeshni Birbal: Author – contributed to the project by performing all literature reviews, data and statistical analyses, interpretation of the results as well as manuscript preparation and writing of dissertation.

2. The contributions of others to the project were as follows:

Dr Frasia Oosthuizen: Supervisor – supervision of the concept of the study and writing of the dissertation and manuscript. Assisted in obtaining data sets upon which the study was based.

Dr Elizabeth Ojewole: Co-Supervisor – assisted with the overall writing of the manuscript and dissertation.

DEDICATION

Every challenging work needs self efforts as well as the blessings of God and the guidance of elders, especially those who are very close to our hearts. I dedicate this thesis and give special thanks to my parents and the Brijlal family, for their continuous love and support throughout my studies. I will always appreciate all that you have done.

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LIST OF ACRONYMS AND ABBREVIATIONS

ABC	Abacavir
AIDS	Acquired Immunodeficiency Syndrome
ADR	Adverse Drug Reaction
ART	Antiretroviral Therapy
ARV	Antiretroviral
ATV	Atazanavir
AZT	Zidovudine
CD4	Cluster of Differentiation 4
d4T	Stavudine
DDI	Didanosine
EFV	Efavirenz
HAART	Highly Active Antiretroviral Treatment
HCP	Healthcare Professional
HIV	Human Immunodeficiency Virus
IRIS	Immune Reconstitution Inflammatory Syndrome
KZN	KwaZulu-Natal
LPV/r	Lopinavir/ritonavir
NDoH	National Department of Health (South Africa)
NRTIs	Nucleoside Reverse Transcriptase Inhibitors
NNRTIs	Non-Nucleoside Reverse Transcriptase Inhibitors
NVP	Nevirapine
PIs	Protease Inhibitors
PN	Peripheral Neuropathy
PV	Pharmacovigilance
SA	South Africa
SAMJ	South African Medical Journal
SD	Standard deviation
TB	Tuberculosis

3TC	Lamivudine
TDF	Tenofovir
UK	United Kingdom
UKZN	University of KwaZulu-Natal
UNAIDs	Joint United Nations Programme on HIV/AIDs
USA	United States of America
WHO	World Health Organisation

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CHAPTER 1

INTRODUCTION

During the course of pharmacological therapy certain drugs can produce effects other than those that are desired or likely.^[1] These effects, which are known as adverse drug reactions (ADRs) raise concerns to both, the clinician and patient, adding to the cost of medical treatment, and increase in morbidity and mortality.^[1, 2] ADRs are between the fourth and sixth leading cause of death globally.^[1] The World Health Organization (WHO) defines pharmacovigilance (PV) as “the science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other possible drug-related problems.”^[3] This study aims to describe the ADRs reported in South Africa (SA) amongst patients using antiretrovirals (ARVs), with reference to the types and seriousness of ADRs reported, patient demographics associated with specific ADRs, and the types of ARVs mostly involved in ADRs.

1.1 Background and rationale for this study

ADRs have been creating headlines over the last 50 years and are one of the foremost causes of morbidity and mortality in healthcare.^[4] It is almost axiomatic that all drugs carry the potential to produce undesirable effects, in addition to the desired ones.^[4,5] In the last few decades, our country has seen a vast growth in the availability and consumption of medicines.^[6] Whilst most patients gain far more benefit than harm, a large proportion of patients experience the undesirable effects from the use of medicines which occurs at recommended doses and frequencies.^[7] For some, these adverse effects are severe enough to require hospitalization or may even result in death.^[7] ADRs have shown to diminish a person’s quality of life, leading to increased physician visits and hospitalizations.^[8]

The WHO defines an ADR as “any response to a drug which is noxious and unintended and which occurs at doses used in man for the prophylaxis, diagnosis or therapy of disease, or for the modification of physiological function”.^[3]

ADRs refer to the unwanted or dangerous effects that a drug may possess.^[9] The incidence and severity of ADRs are influenced by patient characteristics such as age, gender, body weight, coexisting diseases, ethnicity, genetic or geographic factors and by drug factors such as the type of drug, dosage, treatment duration, co-ingestion of other drugs, and route of administration.^[9]

ADRs can be grouped into categories/types such as those specified on the ADR reporting form (Annexure 4) which is used in South Africa. ADRs can be grouped as one of the following; haematological (e.g. neutropaenia, anaemia), dermatological (e.g. skin reactions), central nervous system (e.g. depression, epilepsy), metabolic (e.g. acidosis, diabetes, hyperkalaemia), reproductive (e.g. gynaecomastia, sexual dysfunction), gastrointestinal (e.g. nausea, vomiting, diarrhoea) bone disorders (e.g. osteopenia, osteoporosis), cardiovascular (e.g. arrhythmia, coronary angioblasty), hepatic (e.g. hepatitis, pancreatitis), neurological (e.g. peripheral neuropathy), renal (e.g. nephrotoxicity, renal failure) or other events .^[3] The seriousness of ADRs can vary and may result in persistent or significant disability/incapacity, hospitalization, a medically important or life-threatening condition, or even death.^[10] They commonly occur as a result of pharmacokinetic interactions (e.g. drug absorption, drug excretion, enzyme induction, enzyme inhibition) or pharmacodynamic interactions (drug-drug interactions, e.g. synergistic interactions, opposing interactions).^[11]

In addition, allergic reactions and combinations of incompatible medications can also lead to the development of ADRs.^[11,12] These occur due to the inability to know everything about a drug and its potential effects prior to it being marketed.^[13] Also, interactions between multiple medications are often not determined in the pre-market phase of drug testing.^[13] However, some ADRs are caused, or perpetuated, by human practices.^[13] These comprise patient non-compliance with medication regimens as well as prescription and dispensing errors. Even though these complications seem inexorable, there are ways to curtail their occurrence and diminish their prevalence, such as focusing attention and study on particular groups of people who suffer more frequently from drug allergies and medication interactions.^[11,13]

1.2 Research questions

This study focused on the following research questions:

- 1.2.1 What are the different types of ADRs reported in South Africa and associated with the use of ARVs?
- 1.2.2 Which ARVs result most often in ADRs?
- 1.2.3 What is the seriousness of the reported ADRs?
- 1.2.4 What are the demographics of the populations most at risk of developing ADRs?

1.3 Aims and objectives for this study

The aim of this study was to describe the ADRs reported in South Africa with reference to the types and seriousness of ADRs reported, patient demographics, and ARVs involved. To achieve this, the following specific objectives were outlined:

- 1.3.1 To identify the types of ADRs that have been reported in South Africa.
- 1.3.2 To identify the ARVs most involved in the reported ADRs mentioned above.
- 1.3.3 To determine the seriousness of reported ADRs based on the patient outcome.
- 1.3.4 To examine the patient demographics of the reported ADRs in relation to the type of ADR and ARVs implicated.

1.4 Significance of the study

In the United Kingdom (UK) and United States of America (USA), studies conducted to assess morbidity and mortality associated with ADRs have mainly been restricted to hospitalized patients, the occurrence of ADRs among in-patients, and the misuse of drugs that lead to the development of ADRs.^[11,13] Similarly, studies conducted in some parts of SA, have also been restricted to in-patients and patients that are admitted to hospitals for ADRs.^[14] Furthermore, studies to evaluate the most prevalent types of ADRs reported in SA and most common ARVs involved, have either been restricted to certain provinces or specified over a much shorter time frame.^[15]

In hope to endorse the rational and cost effective use of medicines, to ensure patient safety, and to minimize morbidity and mortality, studies have been conducted in different provinces of South Africa to help describe ADRs reported with reference to highly active antiretroviral treatment (HAART) patients, medication regimens, and reporting systems.^[10]

No studies have been conducted to quantify the types of ADRs experienced most frequently by specific patient population groups in South Africa. In addition, this study will add to the growing literature as it focuses on ADR reports from 01 January 2010 up to and including 31 December 2014. It will also highlight the types of ADRs reported, patient demographics and ARVs involved. Although many drugs have been tested, tried and used in developed countries, their safety profiles may not necessarily be applicable to other settings where the pattern,

incidence and severity of ADRs may differ because of local environmental and genetic influences.^[16] Further, scant data on the global burden of ADRs is available.^[17] Thus, the surveillance of medicine-related ADRs is a vital way to optimize patient safety.

The knowledge of the most prevalent ADRs, ARVs involved, and population groups most at risk of developing ADRs can help pave the way to ameliorate the incidence of ADRs experienced by specific populations in South Africa.^[18] This can assist with reinforcing the goals set out by the National Department of Health (NDoH) to help strengthen strategies to maximize patient safety, allow for easier patient monitoring, ensure the rational use of medicines, and reduce healthcare costs. Considering the impact ADRs have on a patient's quality of life, and morbidity and mortality rates in South Africa, a major stepping stone to achieving ways to detect or prevent ADRs before they proliferate would be to know which population groups are most susceptible to these harmful reactions and which ARVs are most likely to cause them.

1.5 Research methodology

1.5.1 Study design

A retrospective quantitative study of case reports was carried out on ADRs reported to the South African National Department of Health between 01 January 2010 and 31 December 2014.

1.5.2 Data source

All case reports submitted over the stipulated time frame (01 January 2010 – 31 December 2014), to the National Department of Health (South Africa), were included in the study. Data was received electronically in the form of case reports as a Microsoft Excel® document from the National Department of Health Pharmacovigilance centre. The inclusion criteria encompassed case reports that had an ADR reported with the use of ARVs and were submitted during 01 January 2010 – 31 December 2014. The exclusion criteria consisted of case reports that; were incomplete and had no ADR indicated which could be due to incomplete data capturing/reporting, as well as ADRs reported for medicines other than ARVs (anti-tuberculosis and anti-hypertensive medicines), ADR forms submitted for treatment failure, and reports received out of the stipulated time frame.

1.5.3 Data analysis

A total of 4286 ADR reports were received, of which 1797 were excluded from the study as per the inclusion and exclusion criteria. Therefore, the sample size (N) accumulated to 2489 reports for analysis. The data was in the form of case study reports which included the type of ADR reported (e.g. dermatological, metabolic, etc.), the patient outcome (resulting in death, life threatening, etc.), the ARVs that were involved, the patients' age, gender, weight, underlying disease, as well as their ARV regimen and possible causative agent. Data was coded using numbers and thereafter transcribed onto Microsoft Excel® (version 2010) using a data extraction sheet and analysed using SPSS® (version 19).

1.5.4 Data Management

The extraction sheet will be stored on a password protected computer in the supervisor's office and destroyed after 5 years. The original data sets that were obtained electronically from the NDoH PV centre will be permanently deleted.

1.5.5 Ethical approval

Full ethical approval for the study was obtained from the Humanities and Social Sciences Research Ethics Committee of the University of KwaZulu-Natal (HSS/0916/015M) 27 August 2015 – (Annexure 1), and permission to use the data sets was obtained from the South African National Department of Health – 24 March 2015 (Annexure 2). No patient hospital numbers, names/surnames/initials/ or date of birth/identification numbers were reported in the data sets, hence, patient confidentiality was maintained at all times.

1.6 Chapter summary

This chapter provided a background and rationale to the study, explaining ADRs. It also included the aims, objectives, research questions and a brief overview of the methodology.

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CHAPTER 2

LITERATURE REVIEW

2.1 Introduction

South Africa is home to approximately 52 million people.^[1] With more than 50% of the population living in poverty and many unemployed, government hospitals are over burdened in efforts to provide essential healthcare.^[1,2] The incidence of ADRs amongst this population increases exponentially.^[1,2]

ADRs impact profoundly on our healthcare system, contributing significantly to patient morbidity, mortality, hospital admissions, and healthcare costs.^[2,3] In attempt to closely monitor and help reduce the incidence of ADRs in the country, the National Department of Health has employed a Pharmacy and Therapeutics Pharmacovigilance committee to advise the Department of Health on issues relating to ADRs in order to promote the rational and cost-effective use of drugs in accordance with standard treatment guidelines.^[2] The objectives of this committee are to promote the safety of the patient, endorse the rational and cost effective use of drugs, inform healthcare institutions of policy and guideline changes, promote awareness of ADRs and the need to report all suspected ADRs.^[2]

Developing awareness of the potential risks of medicines, while also understanding the extent of their benefits, is critical to addressing the problem of drug-induced diseases.^[4] Failing to maintain constant vigilance when using medicines in patients can have devastating and even fatal consequences. This vigilance is required throughout the patient-practitioner relationship, i.e. when patients are being asked about their medicine use and medical history, when diagnosing a disease condition, and when prescribing, monitoring, and reassessing management.^[4]

When a new medicine is released into the market, there is still a substantial amount that is unknown about the safety of the medicinal product.^[5,6] The patients that are studied in the pre-marketing clinical trials of new medicines are usually limited to a small number and are studied for a short period of time.^[6] Hence, only the more common ADRs are detected during the clinical trials. Information about rare but serious ADRs, drug interactions, chronic toxicity, and risks in special patient groups (e.g. paediatric groups, geriatric groups, males, females, certain race groups, pregnant women) is often not available or incomplete at the time of marketing.^[5,6]

It seems clear from the presented evidence that ADRs have become a major global health problem that needs to be addressed at all levels of healthcare.^[7] The lack of awareness of size and severity of the problem are partially to blame for this silent epidemic.^[4] Furthermore, a large proportion of these ADRs can be prevented through more judicious medicine use.^[7] Knowledge of the most common ADRs and population groups that are prone to experiencing ADRs can help reinforce the goals set out by the National Department of Health to help strengthen strategies to maximize patient safety, ensure the rational use of medicines, and reduce healthcare costs.^[3]

2.2 Adverse drug reactions and HIV/AIDS

South Africa has one of the highest prevalence's of HIV-infected people in the world and is home to 17.9% of the reported 36.9 million people living with HIV/AIDS worldwide.^[8] According to reports from the joint-United Nations programme on HIV/AIDS (UNAIDS) and Statistics South Africa, Sub-Saharan Africa is the region worst affected by the HIV and AIDS epidemic.^[8] South Africa has the highest prevalence of HIV/AIDS compared to any other country in the world with 6.1 million people living with HIV, and 240,000 HIV related deaths recorded in 2012 alone.^[9] HIV prevalence varies markedly between provinces in SA with a soaring 40% HIV prevalence in KwaZulu-Natal (KZN) as compared to 18% in the Northern Cape and Western Cape.^[10] Statistics revealed that the annual number of deaths in South Africa from HIV/AIDS rose by a massive 93% between 1997 and 2006, and then decreased by 11% between 2006 and 2010.^[10]

South Africa has the largest ARV treatment rollout programme in the world, which achieved a 75% increase in antiretroviral therapy (ART) services between 2009 and 2011.^[10] By the end of October 2012, over two million people were receiving ART, surpassing SA's universal target (80%) in accordance with the 2010 WHO treatment guidelines (offering ART to people with a CD4 count less than 350 cells/mm³).^[10]

The Human Immunodeficiency Virus has transformed from life-threatening to a chronic condition for the majority of patients due to the universal use and ease of accessibility of ART amid HIV-infected patients'.^[11] ARV treatment works by providing suppression of a patients viral load and restoring their immune system. Nearly 6.6 million HIV/AIDS related deaths worldwide have been prevented as a result of ART. ^[9,11] In hope to improve morbidity and

mortality rates of HIV-infected individuals, the South African National Department of Health, together with the South African government and guidelines from the WHO, enforced and encouraged physicians to initiate HIV-infected patients on HAART combination therapy based on the patients' clinical staging as per WHO, viral load and CD4 count. HAART consists of 1st and 2nd line regimens.^[11]

Antiretroviral therapy consists of three ARVs that are capable of suppressing HIV replication when used in combination. The usual ARV regimen contains two nucleoside reverse transcriptase inhibitors (NRTIs) together with either a non-nucleoside reverse transcriptase inhibitor (NNRTI) or a protease inhibitor (PI). Orally administered NRTIs include tenofovir (TDF), lamivudine (3TC), abacavir (ABC), emtricitabine (FTC), stavudine (d4T), didanosine (DDI) and zidovudine (AZT). NNRTIs include efavirenz (EFV) and nevirapine (NVP), while protease inhibitors include lopinavir/ritonavir (LPV/r) and atazanavir (ATV).^[12] The following ARV regimens were available during the study period. First line regimens comprised of d4T/3TC/EFV, d4T/3TC/NVP, TDF/3TC/EFV, TDF/3TC/NVP, FTC/TDF/EFV, FTC/TDF/NVP, AZT/3TC/EFV, AZT/3TC/NVP, ABC/3TC/EFV, ABC/3TC/NVP. Second line regimens consisted of TDF/3TC and LPV/r, AZT/3TC and LPV/r or ABC/3TC and LPV/r.

Research has shown that ART increases the emotional and physical quality of life for people living with HIV/AIDS.^[13,14] Conversely, even with ART, HIV/AIDS patients face countless challenges. These patients remain at risk of ADRs and other complications, both short and long term.^[15]

Patients that are on ART are at increased risk of experiencing ADRs due to the effect of the disease, as well as the complex drug regimens that they take.^[15] Numerous patients have been reported to have toxicity concerns and on many occasions they are indisposed to start or adhere to treatment.^[16]

A retrospective review on ADRs reported in Mpumalanga (South Africa) from 2011 to 2013 depicted that a total of 1756 HIV-infected patients experienced an ADR whilst on ART.^[17] During May 2007 – May 2008, 3534 patients experienced ADRs in KwaZulu-Natal as a result of ART, where stavudine was implicated as the possible causative agent in 93% of these reports.^[17]

Thus, ADRs may rigorously jeopardize the confidence in the safety of ART, thereby altering patient adherence, increasing the risk for the emergence of drug resistance, and reducing treatment efficacy.^[18]

2.2.1 Adverse drug reactions commonly associated with antiretrovirals

The risk of ADRs arises due to the effect of disease on the immune system and the safety profiles of the multifaceted ARVs.^[16] There is a range of ADRs associated to ART that have been recognized, and may be short to long term and/or mild to severe, depending on the environment.^[19] ADRs in developing countries may diverge from those in developed countries because of high prevalence of conditions such as tuberculosis, poverty, malnutrition and patients presenting with an advanced stage of the disease.^[20,21]

A descriptive analysis conducted amongst HIV-infected patients receiving ART between January 2011 and December 2011 in Nigeria revealed a total of 1679 ADRs reported. Of these, 63.2% occurred in patients on zidovudine-based regimens, 8.2% due to stavudine and 19.3% due to tenofovir.^[22] The most common ADRs included peripheral neuropathy, skin rash, dizziness and pruritis. Peripheral neuropathy was mostly associated with stavudine and the tenofovir/efavirenz regimen, and anaemia with the zidovudine/lamivudine/nevirapine regimen.^[22]

An assessment of ADRs among HIV-infected individuals receiving ARVs in South Africa focused on 590 patients enrolled in the Medunsa National ARV Pharmacovigilance Surveillance System from February 2007 till July 2011.^[21] This study identified that 37% of patients had experienced at least one ADR when on the stavudine, efavirenz and lamivudine combination. Among patients that experienced ADRs, the majority were females (74%) in the age group of 38 to 44 years (39%).^[21] Similar to the Nigerian study, there was a high incidence of peripheral neuropathy (20% of all ADRs), followed by skin eruptions (15%). In addition, cough was also prevailing, accounting for 12% of the ADRs. Other ADRs accounting for 16% of the overall reports included dermatitis, oedema, acidosis and hypothyroidism.^[21]

ADRs experienced by patients admitted to a South African hospital based in a community with a high HIV/AIDS prevalence were examined through a 3-month prospective observational study.^[16] During data collection, 665 adults were admitted to the hospital. Among HIV-infected patients, those receiving ART were more likely to be admitted with an ADR than those not receiving ART.^[23]

During 2011 to 2013, Mpumalanga (South Africa) reported 1756 ADRs to the National Department of Health.^[17] The forms reported over this time frame were analysed and the 10 most frequent ADRs experienced were lipodystrophy, lipoatrophy, peripheral neuropathy, weight loss, breast enlargement and/or gynaecomastia, dizziness, rashes, vomiting, fat gain, and headache.^[17] The two most common ADRs were lipodystrophy (327 cases) and peripheral neuropathy (358 cases), associated mainly with stavudine-containing regimens.^[17] Whilst peripheral neuropathy is linked to almost all the NRTIs, it can be seen that d4T is the most commonly suspected drug. This is in keeping with other ART studies where a similar outcome had been established.^[20,21] This finding supports the World Health Organizations' recommendation to discontinue the use of d4T-based regimens in adolescents and adult patients due to the associated adverse effects.^[8] Other drugs implicated include efavirenz (53 cases), nevirapine (29 cases), lamivudine (4 cases), and zidovudine (22 cases).^[17]

A study conducted in KZN found that the use of stavudine and efavirenz in ARV patients contributed significantly to the development of gynaecomastia. In addition, stavudine caused peripheral neuropathy, lipodystrophy, lactic acidosis, and symptomatic hyperlactataemia. nevirapine and efavirenz were shown to contribute to skin reactions.^[24]

It is evident that peripheral neuropathy, lipodystrophy and neutropaenia are the principal ADRs reported globally and within some parts of Africa. Short term ADRs are an impending threat to successful initiation and compliance to ART. ADRs may be specific to a class of drugs. Efavirenz and nevirapine were known to cause skin rashes and hepatotoxicity, while zidovudine and stavudine were associated with peripheral neuropathy, lipodystrophy, anaemia, nausea, rashes, lipoatrophy and lactic acidosis.^[24]

2.2.2 Incidence and prevalence of adverse drug reactions

ADRs that are caused by immune and non-immune mechanisms are a major cause of morbidity and mortality worldwide.^[25] ADRs are the most widespread iatrogenic illness and are the fourth most common cause of death.^[26]

During 2013, the UK reported 31073 incidents of patients suffering serious adverse reactions to prescribed drugs.^[27] In addition, statistics showed that 1604 reported deaths were thought to be triggered by severe reactions to medicines.^[27] A further 6050 patients went to hospital with suspected ADRs but survived.^[27] These reactions can diminish a person's quality of life, leading

to increased physician visits, hospitalizations, and even death.^[3] ADRs can also result in increased healthcare costs which could put a strain on the over burdened healthcare system in South Africa.

In the USA, ADR deaths are higher among men than women and deaths due to ADRs are significantly more likely in persons older than 55 years.^[28] Rates were also found to be varied by ethnicity and race and were highest amongst blacks.^[28] In addition, more than 100 000 deaths were attributed annually to serious ADRs.^[29] Epidemiologic data suggests that specific factors can increase the risk of ADRs, such as the infection with HIV, age, race and gender.^[30]

A study conducted in Sub-Saharan Africa described the contribution of ADRs to patient morbidity, hospitalization and mortality.^[9] The findings of this study suggest that cardiovascular medicines and ARVs contributed the most to community-acquired ADRs, while medicines used for opportunistic infections (such as antiviral medicines, antibiotics and antifungals) were most generally implicated in hospital-acquired ADRs.^[9] In hospitalized patients, the overall incidence of serious ADRs was 6.7% and fatal ADRs was 0.32%, making these reactions the fourth and sixth leading cause of death, respectively.^[26]

In South Africa, a study conducted in the province of Mpumalanga, the number of ADRs reported from 2011 to 2013 was a total of 1057.^[17] Among these, 495 (28.9%) were recorded from males while 1057 (60.19%) were females.^[17] When these reports were categorised by age group, it was observed that the majority of ADRs were in the age group 31 to 40 years and with more reports in females (65.94%) than males (26.26%).^[17]

A large proportion of ADRs have been shown to be preventable through improved drug prescribing and monitoring.^[3]

2.3 Pharmacovigilance in South Africa

The World Health Organization defines pharmacovigilance (PV) as “the science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other possible drug-related problems”.^[32] The PV system incorporates timely and efficient identification, collection, assessment, and communication of medicine-related adverse reactions.^[32] A comprehensive PV system includes both active and passive surveillance methods, effective mechanisms to communicate medication safety information, and the

incorporation of PV systems and activities into all levels of the health system, from the facility to the national levels.^[32]

With augmented access to new fundamental medicines in South Africa, there is a greater need to promote and monitor the safety and efficacy of medicines.^[12] Besides the impact of ADRs on morbidity and mortality and the direct cost of managing these events, ADRs also have other associated costs in terms of the loss of confidence in the healthcare system, patient non-adherence to treatment which leads to the development of drug resistance and economic loss to the pharmaceutical industry.^[33] Although it is difficult to measure these costs, it is apparent that they may constitute a profound impact on the resources of the healthcare system.^[33]

South Africa uses a spontaneous reporting system in which healthcare providers are responsible for reporting suspected ADRs.^[18] After sufficient monitoring, laboratory tests and adherence counseling, an ADR report form is filled and submitted to the NDoH. This form indicates the patients' data, the ADR, current ARV regimen, viral load, CD4 count, concomitant diseases and medicine treatment.^[18] When a patient experiences an ADR, they would most likely be switched to another ARV regimen in which the drug in question will be substituted with another in its class.^[18]

Spontaneous reporting systems include both in-patient and out-patient reporting and can be used for reporting ADRs for large groups of patients.^[18] In addition, other advantages are that it can be used for reporting all types of medicines and is relatively inexpensive.^[18] However, underreporting seems to be the leading challenge with this system of reporting. Spontaneous reporting systems are currently being used in most parts of the world, including the UK, USA and India.^[34,35]

2.3.1 Importance of adverse drug reaction monitoring

ADR monitoring refers to the continuous periodical assessment of a patient's medical condition.^[36] The aim of ADR monitoring is to prevent untoward effects that could diminish a patient's quality of life, lead to death and have a negative effect on patient adherence.^[36] A patient monitoring system is a critical component of an integrated HIV care, ART and prevention programme.^[37]

An ADR monitoring system forms the backbone of clinical care, treatment and prevention.^[36] ADR monitoring serves two main functions: first, it enables effective clinical management of

patients; and second, it generates data used for programme monitoring and management, contributing to standardized indicators at the district, national and international levels.^[36]

Proper utilization of ART requires ongoing patient monitoring to assess therapeutic responses and to identify adverse events related to the chronic administration of these potentially toxic ARVs.^[37] Failure to respond to a recommended ART regimen is almost always a result of suboptimal adherence or viral resistance.^[37] Optimal adherence (i.e., taking all medication doses at the time intervals prescribed) to ART is important to help patients achieve and maintain virological suppression.^[37] Adherence can vary over time and can be impacted by factors such as depression, emotional stress, pill-burdens and lack of support.^[37]

Thus, ADRs impact negatively towards a patient's attitude regarding treatment.^[24] The identification of patients that are at risk to developing ADRs can help medical professionals make better decisions regarding drug management for diverse individuals.^[36] In addition, patients would have a much better treatment outcome and prognosis.^[36] Early detection of ADRs through monitoring can help prevent the unnecessary cost burden associated with managing the effects caused by these reactions.^[36]

Monitoring the safety and toxicity associated with ART remains a challenge facing the public health sector in South Africa.^[36] ADR monitoring is typically done using a spontaneous surveillance method.^[36] However, studies conducted globally have found that spontaneous reporting of ADRs to be an incompetent system as it leads to underestimation of the burden due to ADRs.^[22] Thus, more strong surveillance methods including structured surveillance PV systems, which monitor and assess the safety profile and the impact of ART needs to be ameliorated. A structured surveillance monitoring system tracks HIV infected patients who are on ART to assess ARV related morbidity and mortality over time.^[4] South Africa, a country which is heavily hit by the HIV epidemic, uses a spontaneous surveillance reporting system of HIV patients on ART to assess ART-related adverse effects.^[4]

ADRs contribute substantially to patient morbidity and hospitalization in South Africa, further increasing the burden and cost of managing patients in an overstretched healthcare system.^[3] In hope to prevent these dangerous reactions, knowledge of the most prevalent ADRs is greatly needed.^[3] To date, studies describing the types, as well as the most prevalent ADRs reported in South Africa, have not been conducted.

2.3.2 The impact of adverse drug reactions on patient adherence

Adherence to a medication regimen is defined as the extent to which patients take their medications as prescribed by their healthcare providers.^[38] Medication non-adherence is a growing concern to clinicians and healthcare systems due to escalating evidence that it is prevalent and associated with adverse outcomes and higher costs of care. To date, measurement of patient medication adherence and the use of interventions to improve adherence are rare in routine clinical practice.^[38]

Treatment adherence is generally regarded as an essential factor in achieving optimal outcomes across many disease states. Poor adherence to ART has the potential to impact on outcomes on multiple levels.^[38] Poor adherence to ART is commonly associated with a less effective viral load suppression, which risks the immediate health of the patient, but also risks creating permanent treatment resistance to that particular ARV or group of ARVs.^[38] This may have downstream effects on treatment costs as well as therapeutic options. The causes of poor adherence to ART are extremely diverse, and include complexity of therapeutic regimens (e.g. pill burden and dosing frequency), patient forgetfulness, poor health literacy, treatment side effects, patients with co-morbidities, poor patient-practitioner relationship, and limited access to ART as a result of formulary restrictions within the public sector.^[33]

In addition to the primary objective of reducing the risk of morbidity and mortality associated with ART, the secondary goal of ART is viral load suppression.^[12] Numerous effective therapeutic agents for viral load suppression in HIV/AIDS have been developed. Their efficacy, however, requires that patients with HIV/AIDS be adherent to their prescribed regimens. Effective use of ARVs requires not only good adherence to therapy but sustained adherence over time if viral load suppression is to be successful.^[3]

The importance to medication compliance especially for HIV-infected patients cannot be stressed enough. Poor adherence can lead to an increase in viral load and a decrease in CD4 counts which in turn sets the ground for the development of opportunistic infections such as; cryptococcal meningitis, oesophageal candidiasis, tuberculosis and many more.^[37] However, studies throughout the world have indicated that ADRs are associated with poor patient compliance as patients feel less inclined, motivated and confident about their treatment and are therefore dubious to continue taking their medicines as prescribed.^[38]

Currently, a much larger group of ARV drug combinations are being used to treat patients.^[9] The rate of ADRs amplifies exponentially after a patient is on four or more medications.^[9] Efforts to reduce polypharmacy are important but, for many patients, the number of medications cannot always be reduced without doing harm.

2.3.3 Adverse drug reactions and cost implications

ADRs are an imperative public health issue that threaten the safety of drug therapy and results in a considerable economic burden to the healthcare system.^[39] ADRs result in an increased number of physician visits, new treatment to treat the ADR, and possible hospitalization – all of which can put a strain on an overstretched healthcare system.^[39]

While estimates pertaining to the cost implicated by ADRs does not form part of the study's objectives, it is important to keep in mind that an estimate of the cost of drug-related morbidity and mortality is 136 billion US dollars annually, which is more than the total cost of cardiovascular or diabetic care in the USA.^[39] In addition, 1 out of 5 injuries or deaths per year to hospitalized patients may be as a result of an ADR.^[35] The severity and substantial costs of ADRs in hospital justify investments to prevent these events. Nonetheless, merely a segment of ADRs induce cost increases, suggesting that preclusion efforts should focus on this limited class of ADRs.^[39]

2.4 Chapter summary

This chapter comprised of a literature study based on ADRs and HIV/AIDS. This is related to the incidence and prevalence of these reactions, the common ADRs reported, ARVs implicated in these reactions, pharmacovigilance in South Africa, as well as cost implications relating to ADRs, and the importance of monitoring patients and the impact of this on patient adherence.

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CHAPTER 3

MANUSCRIPT FOR SUBMISSION AND PUBLICATION

3.1 Introduction

This chapter described the general findings and discussion of the results of the study and is represented in the form of a manuscript titled “Adverse drug reactions associated with antiretroviral therapy in South Africa”. This manuscript will be submitted to the “*South African Medical journal*” (SAMJ) for publication.

The journal instructions to the author can be viewed in Annexure 3 or with the following link:
<http://www.samj.org.za/index.php/samj/about/submissions>

3.2 Manuscript

Adverse drug reactions associated with antiretroviral therapy in South Africa

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ABSTRACT

Background and Aim

South Africa has one of the highest prevalence's of human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS) infected people in the world. HIV/AIDS patients face countless challenges, one of which is the risk of adverse drug reactions (ADRs). This study aimed to describe the ADRs reported in South Africa with reference to the type of ADR, ARVs implicated, seriousness of the ADR and patient demographics associated with specific ADRs.

Methods

A retrospective quantitative study was carried out using ADR reports which were submitted to the National Department of Health during 01 January 2010 – 31 December 2014. Data, obtained electronically in the form of case study reports, was transcribed onto Microsoft Excel[®] (version 10) and analysed using SPSS[®] (version 19). A descriptive and inferential analysis was carried out to determine the strength of the relationships (Pearson Chi Square test) between different variables.

Results

A total of 2489 reports were analysed, of which the majority of ADRs reported were experienced by female patients (n=1511, 66.7%) as opposed to male patients (n=755, 33.3%). This study found evidence of a high degree of adverse drug reactions among patients on first-line ART with stavudine (n=1256, 50.46%), efavirenz (n=572, 22.98%), zidovudine (n=209, 8.40%), tenofovir (n=203, 8.16%) nevirapine (n=153, 6.15%) based regimens. The 10 most common ADRs reported with the use of ARVs were peripheral neuropathy (n=472, 19%), lipodystrophy (n=471, 18.9%), serious skin reactions (n=266, 10.7%), gynaecomastia (n=219, 8.8%), renal failure (n=140, 5.6%), dizziness (n=133, 5.3%),

hyperlactatemia (n=118, 4.7%), psychosis/hallucinations (n=47, 1.9%), sleep disturbances (n=44, 1.8%) and vomiting (n=44, 1.8%). Peripheral neuropathy and lipodystrophy were the most common ADRs amongst the female patients who received stavudine treatment in the 30-44 year age group.

Discussion and Conclusion

Female patients were more likely to experience peripheral neuropathy, lipodystrophy, skin rash, anaemia and hyperlactatemia, while male patients were more prone to experience gynaecomastia and peripheral neuropathy. In addition, patients aged 30-44 years old reported the most ADRs. Most reactions were caused due to the use of stavudine, efavirenz, zidovudine, nevirapine and tenofovir in the population groups identified in this study.

Keywords: Pharmacovigilance, antiretroviral therapy, human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS), adverse drug reactions

Background and Introduction

South Africa (SA) has one of the highest prevalence of human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS) infected people in the world and is home to 17.9% of the reported 36.9 million people living with HIV/AIDS worldwide.^[1] Statistics reveals that the annual number of deaths in South Africa from HIV/AIDS rose by a massive 93% between 1997 and 2006, and then decreased by 11% between 2006 and 2010.^[2,3] Nearly 6.6 million HIV/AIDS related deaths worldwide have been prevented as a result of anti-retroviral therapy (ART).^[3] In hope to improve morbidity and mortality rates of HIV-infected patients, the National Department of Health (NDoH), together with the South African government and guidelines from the World Health Organisation (WHO), enforced and encouraged physicians to initiate HIV-infected patients on highly active antiretroviral treatment (HAART) combination therapy based on the patients' clinical staging as per WHO, viral load and CD4 count.^[4] HAART comprised of 1st and 2nd line regimens.^[4]

Antiretroviral therapy consists of three ARVs that are capable of suppressing HIV replication when used in combination. The usual ARV regimen contains two nucleoside reverse transcriptase inhibitors (NRTIs) together with either a non-nucleoside reverse transcriptase inhibitor (NNRTI) or a protease inhibitor (PI). Orally administered NRTIs include tenofovir (TDF), lamivudine (3TC), abacavir (ABC), emtricitabine (FTC), stavudine (d4T), didanosine (DDI) and zidovudine (AZT). NNRTIs include efavirenz (EFV) and nevirapine (NVP), while protease inhibitors include lopinavir/ritonavir (LPV/r) and atazanavir (ATV).^[12] The following ARV regimens were available during the study period. First line regimens comprised of d4T/3TC/EFV, d4T/3TC/NVP, TDF/3TC/EFV, TDF/3TC/NVP, FTC/TDF/EFV, FTC/TDF/NVP, AZT/3TC/EFV, AZT/3TC/NVP, ABC/3TC/EFV, ABC/3TC/NVP. Second line regimens consisted of TDF/3TC and LPV/r, AZT/3TC and LPV/r or ABC/3TC and LPV/r.

South Africa has the largest antiretroviral (ARV) treatment rollout programme in the world, which achieved a 75% increase in ART services between 2009 and 2011. By the end of October 2012, over two million people were receiving ART, surpassing SA's universal access target (80%) in accordance with the 2010 WHO treatment guidelines (offering ART to people with a CD4 count less than 350 cells/mm³).^[3] Research has shown that ART increases the emotional and physical quality of life for people living with HIV/AIDS.^[5,6] Conversely, even with ART, HIV/AIDS patients face countless challenges. These patients remain at risk of adverse drug reactions (ADRs) and other complications, both short and long term.^[7]

A retrospective review on ADRs reported in Mpumalanga (South Africa) from 2011 to 2013 depicted that a total of 1756 HIV-infected individuals experienced an ADR whilst on ART.^[8] During May 2007 – May 2008, 3534 patients experienced ADRs in KwaZulu-Natal (KZN) as a result of ART, where stavudine was implicated as the possible causative agent in 93% of these reports.^[9] Patients that are on ART are at increased risk of experiencing ADRs due to the effect of the disease, as well as the complex drug regimens that they take.^[7] Numerous patients have been reported to have toxicity concerns and on many occasions they are indisposed to start or adhere to treatment.^[10] Thus, ADRs may jeopardize the confidence in the safety of ART, thereby altering patient adherence, increasing the risk for the emergence of drug resistance, and reducing treatment efficacy.^[10,11]

The risk of ADRs arises due to the effect of disease on the immune system and the safety profiles of the multifaceted ARVs.^[11] There are a range of ADRs associated with ART that have been recognized, and may be short to long term and/or mild to severe, depending on the environment.^[11] ADRs in developing countries may diverge from those in developed countries because of high prevalence of conditions such as tuberculosis, poverty, malnutrition and patients presenting with an advanced stage of the disease.^[11] Besides the impact of ADRs on morbidity and mortality and the direct cost of managing these events, ADRs also have other associated costs in terms of the loss of confidence in the healthcare system, economic loss to the pharmaceutical industry, non-adherence to treatment, and development of drug resistance.^[11,12] Although it is challenging to measure these costs, it is apparent that they may constitute a profound impact on the resources of the healthcare system. The WHO defines pharmacovigilance (PV) as “the science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other possible drug-related problems.”^[13] The PV system safeguards the public through timely and efficient identification, assessment, collection, and communication of medicine-related adverse reactions.^[13] A comprehensive PV system includes both active and passive surveillance methods, effective mechanisms to communicate medication safety information, collaboration among a wide range of partners and organizations, and incorporation of PV activities into the various levels of the health system, from the facility to the national levels.^[13]

South Africa uses a spontaneous reporting system in which healthcare providers are responsible for reporting suspected ADRs.^[9] After sufficient monitoring, laboratory tests and adherence counseling, an ADR report form is filled and submitted to the NDoH.^[9] Although many drugs have been used and studied in developed countries, their safety profiles may not necessarily be applicable to other settings where the incidence, pattern, and severity of ADRs may differ because of local environmental and genetic influences.^[11,12] Further, scant data on the global burden of ADRs is available.^[11,13] Thus, the surveillance of medicine-related ADRs is a vital way to optimize patient safety.

It seems clear from the available evidence that ADRs have become a major global health problem that needs to be addressed at all levels of healthcare.^[11] The lack of awareness of the size and severity of the problem are partially to blame for this silent epidemic.^[13] Furthermore, a large proportion of these ADRs can be prevented through more judicious medicine use.^[14] Knowledge of the most prevalent ADRs, ARVs involved, and population groups at risk can help pave the way to ameliorate the incidence of ADRs experienced by specific populations in South Africa.

This can assist with reinforcing the goals set out by the NDoH to help strengthen strategies to maximize patient safety, allow for easier patient monitoring, ensure the rational use of medicines, and reduce healthcare costs.^[4] Considering the impact ADRs have on a patients quality of life, and morbidity and mortality rates in South Africa, a major stepping stone to achieving ways to detect or prevent ADRs before they proliferate would be to know which population groups are most susceptible to these harmful reactions and which ARVs are most likely to cause them.^[4]

No studies have been conducted to quantify the types of ADRs experienced most frequently by specific patient population groups in South Africa. In addition, this study will add to the growing literature as it focuses on ADR reports from 01 January 2010 up to and including 31 December 2014. It will also highlight the types of ADRs reported, patient demographics and ARVs involved.

The aim of this study was therefore to describe the ADRs reported in South Africa with reference to the type of ADR, ARVs implicated, seriousness of the ADR and patient demographics associated with specific ADRs.

Methods

Study sample

The study focused on ADRs reported in South Africa to the National Department of Health. All case reports submitted to the NDoH over the stipulated time frame (01 January 2010 – 31 December 2014), were included in the study. A total of 4286 ADR reports were received, of which 1797 were excluded from the study as per the inclusion and exclusion criteria. The inclusion criteria encompassed case reports that had an ADR reported with the use of ARVs and were submitted during 01 January 2010 – 31 December 2014. The exclusion criteria consisted of case reports that; 1) were incomplete and had no ADR or ARV indicated (which could be due to incomplete data capturing/reporting), 2) had ADRs associated with medicines other than ARVs (e.g. anti-tuberculosis and anti-hypertensive medicines), 3) were ADR forms submitted for ARV treatment failure, and 4) were received out of the stipulated time frame. Therefore, the sample size accumulated to 2489 reports for analysis. However, for each of the 2489 reports that were further analysed, not all information was received on the case reports for the following variables: 1) age, 2) gender, 3) ARV regimen and 4) patient outcome. These reports were still included in the study as they had an ADR and ARV reported. All of the results are based on information completed on the reporting forms by the healthcare providers and captured by the NDoH Pharmacovigilance centre – South Africa.

Full ethical approval for the study was obtained from the University of KwaZulu-Natal, and permission to use the data was sourced from the South African National Department of Health.

Sampling, data collection and analysis

A retrospective quantitative study was carried out. Data was obtained electronically from the National Department of Health which is situated in Pretoria, South Africa. The data was in the form of case study reports captured in Microsoft Office Excel® document format. Data included the type of ADR reported (e.g. dermatological, metabolic, etc.), the patient outcome (e.g. resulting in death, life threatening, etc.), the ARVs that were involved, the patient's age, gender, weight and underlying disease, as well as their ARV regimen. Data was coded using numbers and thereafter transcribed onto a Microsoft Excel® (version 2010) data extraction sheet and subsequently analysed using SPSS® (version 19).

Descriptive and inferential analyses were conducted. Descriptive analysis included information on frequencies, percentages, measures of central tendency (e.g. mean, median and mode), and measures of variability (e.g. range, standard deviation and variance). Inferential analysis was carried out to determine the strength of the relationships (Pearson Chi Square test) between different variables. A

difference between variables with a p-value of less than 0.05 was considered to be statistically significant. Close attention was paid to the most prevalent types of ADRs, anti-retroviral medicines involved, and patient demographics in order to identify if some populations are more at risk of developing ADRs.

Findings

Overview of patient demographics

A total of 2489 case reports were analysed, of which the majority of ADR reports submitted were ADRs experienced by female patients (n=1511, 66.7%) as compared to male patients (n=755, 33.3%) (Table 1). The mean weight of both males and females who experienced ADRs was $62.5 \pm 18.51\text{kg}$ (n=1796) and almost half of the patients were in the 30-44 year age group (n=1136, 49.9%). This was followed by 27% (n=615) of the patients in the 45-59 year age group and 12.9% (n=295) of patients aged 15-29 years. The 0-14 and ≥ 60 year old patients experienced the least amount of ADRs with 5.4% (n=121) and 4.9% (n=112) of ADRs having occurred in these groups, respectively (Table 1). The mean age was 39.06 ± 13.02 years old.

Analysis of ADRs and associated ARVs

The reported ADRs and their associated ARVs are described in Table 2. The 10 most commonly reported ADRs associated with the use of ARVs were peripheral neuropathy (n=472, 19%), lipodystrophy (n=471, 18.9%), serious skin reactions (n=266, 10.7%), gynaecomastia (n=219, 8.8%), renal failure (n=140, 5.6%), dizziness (n=133, 5.3%), hyperlactatemia (n=118, 4.7%), psychosis/hallucinations (n=47, 1.9%), sleep disturbances (n=44, 1.8%) and vomiting (n=44, 1.8%).

Stavudine was implicated in 50.46% (n=1256) of the reports and this was followed by efavirenz (n=572, 22.98%), zidovudine (n=209, 8.40%), tenofovir (n=203, 8.16%), nevirapine (n=153, 6.15%) and abacavir (n=120, 4.8%) (Table 2).

The total number of patients who experienced ADRs related to the use of stavudine was 1256. Of this, peripheral neuropathy and lipodystrophy accounted for 29.8% (n=374) and 32.4% (n=407) of the cases, respectively. Other common ADRs experienced by stavudine users were hyperlactatemia (n=87, 6.9%), gynaecomastia (n=68, 5.4%), lipoatrophy (n=23, 1.8%) and lactic acidosis (n=4, 0.3%). Skin reactions were mainly caused by nevirapine (n=97, 63.4%) and efavirenz (n=86, 15%). Patients being treated with efavirenz were more likely to experience gynaecomastia (n=131, 22.9%), as compared to tenofovir, that was found to mainly cause renal failure (n=100, 49.3%) (p=0.000). Tenofovir was also implicated in 8.9% (n=18) of the peripheral neuropathy cases as well as 8.4% (n=17) of the serious skin reaction reports. Zidovudine was commonly associated with ADRs like anaemia (n=49, 23.4%), peripheral neuropathy (n=31, 14.8%), lipodystrophy (n=25, 12%) and hyperlactatemia (n=22, 10.5%). Gastrointestinal disturbances, like vomiting, was commonly reported among patients who took stavudine (n=10, 0.8%), efavirenz (n=10, 1.7%) and tenofovir (n=8, 3.9%). Multiple ARVs were

responsible for 38 (1.53%) of the ADRs (Table 2).

Analysis of ARVs in relation to patient demographics

Stavudine caused statistically significant more ADRs in female patients (n=797, 52.7%) as opposed to male patients (n=338, 44.8%) (p=0.000). Efavirenz was also implicated with more ADRs in females (n=266, 17.6%) as opposed to males (n=259, 34.4%). In the 0-14 year age group, stavudine was responsible for the most amount of ADRs (n=97, 80.2%). In the 30-44 year age group, 49.3% (n=561) of patients developed ADRs associated with the use of stavudine, which was the highest occurrence for any ARV in any age group. Patients who were in the 15-29 (n=81, 27.5%), 30-44 (n=266, 23.4%) and 45-59 (n=147, 23.9%) year age groups experienced ADRs mostly attributed to the use of efavirenz. Nevirapine was associated with ADRs that occurred more in females (n=124, 8.2%) as opposed to males (n=27, 3.6%). Patients who were ≥ 60 years old mainly experienced ADRs caused by the use of stavudine, efavirenz and tenofovir (Table 3).

Analysis of ADRs in relation to patient demographics

Patients aged ≥ 60 years old were found statistically significant more likely to experience peripheral neuropathy (n=21, 18.8%) as opposed to those aged 0-14 years who mainly experienced lipodystrophy (n=47, 38.8%) (p=0.000). Peripheral neuropathy (n=283, 18.7%) and lipodystrophy (n=342, 22.6%) were the two most frequently reported ADRs among female patients. Skin rash was mainly prevalent among female patients in the 30-44 year age group. Gynaecomastia was the most commonly reported ADR among male patients (n=167, 22.1%) as opposed to anaemia which was the least reported ADR in male patients (n=15, 2%) (Table 1).

Analysis of the regimen duration prior to developing an ADR

The regimen duration prior to ADRs indicated how long patients were on that particular regimen until they elicited a sign or symptom indicative of an ADR. The regimen duration prior to the manifestation of ADRs was measured from the ARV start date to the report date. A total of 13 ARV regimens were identified in the ADR reports (n=1236). Amongst these regimens, 49.7% (n = 666) of the patients were on ARV regimen 1 (d4T/3TC/EFV) at the time of reporting. Other regimens implicated were 3TC/TDF/EFV (n=253, 20.5%) and 3TC/AZT/EFV (n=66, 5.3%). The mean regimen duration was 34.7 ± 27.2 months. The mode for this variable was 1 month (n=155), indicating that most patients presented with an ADR after 1 month of initiation on ARVs with any of the 3 regimens mentioned above.

Seriousness of the reported ADRs

Seriousness was measured by the patients' treatment outcome, as described in Table 4. Of the seven outcomes identified, majority of the patients (n=2196, 97.38%) required an intervention to prevent any significant impairment or disability, while 37 (1.64%) patients' symptoms were improved (Table 4).

Table 1: ADRs reported in relation to the patient demographics

<i>N=2489</i>							
ADR	<i>GENDER* n (%)</i>		<i>AGE GROUP (YEARS)** n (%)</i>				
	MALES n=755	FEMALES n=1511	0-14 n=122	15-29 n=295	30-44 n=1137	45-59 n=615	≥60 n=111
Peripheral Neuropathy	135 (17.9)	283 (18.7)	15 (12.4)	40 (13.6)	205 (18.3)	157 (25.5)	21 (18.8)
Lipodystrophy	97 (12.8)	342 (22.6)	47 (38.8)	42 (14.2)	229 (20.2)	106 (17.2)	13 (11.6)
Skin Rash	67 (8.9)	192 (12.7)	14 (11.6)	39 (13.2)	132 (11.6)	58 (9.4)	6 (5.4)
Gynaecomastia	167 (22.1)	44 (2.9)	6 (5)	24 (8.1)	115 (10.1)	42 (6.8)	16 (14.3)
Renal Failure	54 (7.2)	73 (4.8)	-	6 (2)	47 (4.1)	50 (8.1)	23 (20.5)
Hyperlactatemia	27 (3.6)	58 (3.8)	7 (5.8)	18 (6.1)	51 (4.5)	25 (4.1)	4 (3.6)
Anaemia	15 (2)	48 (3.2)	-	16 (5.4)	37 (3.3)	13 (2.1)	4 (3.6)
Other***	182 (24.1)	409 (27.1)	31 (25.6)	102 (34.6)	286 (25.2)	146 (23.7)	22 (19.6)
Multiple	11 (1.5)	62 (4.1)	2 (1.6)	8 (2.7)	35 (3.1)	18 (2.9)	2 (1.8)

***Gender was extracted for 2266 of the 2489 ADR case reports.**

****Age was extracted for 2280 of the 2489 ADR case reports.**

*****Includes ADRs that were listed under the category “other” on the ADR form (Annexure 4).**

Table 2: Analysis of the common ADRs reported in relation to the suspected causative ARVs

ADR TYPE	Total ADRs N=2489	Possible Causative ARVs n (%)							
		D4T n=1256 (50.46)	EFV n=572 (22.98)	AZT n=209 (8.40)	TDF n=203 (8.16)	NVP n=153 (6.15)	ABC n=12 (0.48)	Multiple ARVs n=38 (1.53)	Other ARVs n=46 (1.85)
<u>Reproductive system</u>									
Gynaecomastia	219(8.8)	68(5.4)	131(22.9)	7(3.3)	4(2)	2(1.3)	-	41(10.5)	3(6.5)
<u>CNS effects</u>									
Dizziness	133(5.3)	8(0.6)	97(17)	18(8.6)	4(2)	3(2)	-	1(2.6)	2(4.3)
Sleep disturbances	44(1.8)	3(0.2)	36(6.3)	1(0.5)	1(0.5)	2(1.3)	-	-	1(2.2)
Depression	2(0.08)	-	2(0.3)	-	-	-	-	-	-
Psychosis/Hallucinations	47(1.9)	-	44(7.7)	-	2(1)	1(0.7)	-	-	-
<u>Dermatological</u>									
Serious skin reactions	266(10.7)	36(2.9)	86(15)	11(5.3)	17(8.4)	97(63.4)	5(41.7)	3(7.9)	11(23.9)
Steven Johnson Syndrome	12(0.5)	1(0.1)	3(0.5)	1(0.5)	-	7(4.6)	-	-	-
<u>Haematological</u>									
Anaemia	76(3.1)	9(0.7)	7(1.2)	49(23.4)	3(1.5)	1(0.7)	1(8.3)	2(5.3)	4(8.7)
<u>Gastrointestinal</u>									
Nausea	4(0.2)	-	3(0.5)	-	1(0.5)	-	-	-	-
Vomiting	44(1.8)	10(0.8)	10(1.7)	6(2.9)	8(3.9)	1(0.7)	-	2(5.3)	7(15.2)
Diarrhoea	28(1.1)	7(0.6)	5(0.9)	2(1)	4(2)	1(0.7)	1(8.3)	2(5.3)	6(13)
<u>Hepatic</u>									
Hepatitis	13(0.5)	2(0.2)	1(0.2)	-	-	8(5.2)	1(8.3)	1(2.6)	-
Hepatic encephalopathy	1(0.04)	-	1(0.2)	-	-	-	-	-	-
<u>Metabolic</u>									
Lactic Acidosis	5(0.2)	4(0.3)	-	1(1)	-	-	-	-	-
Hyperlactatemia	118(4.7)	87(6.9)	-	22(10.5)	6(3)	-	1(8.3)	1(2.6)	1(2.2)
Lipodystrophy	471(18.9)	407(32.4)	21(3.7)	25(12)	6(3)	5(3.3)	1(8.3)	5(13.2)	1(2.2)
Lipoatrophy	28(1.1)	23(1.8)	2(0.3)	3(1.4)	-	-	-	-	-
Hypertension	3(0.1)	1(0.1)	1(0.2)	-	-	1(0.7)	-	-	-
Stroke	1(0.04)	-	-	-	1(0.5)	-	-	-	-
<u>Neurological</u>									
Peripheral Neuropathy	472(19)	374(29.8)	31(5.4)	31(14.8)	18(8.9)	4(2.6)	1(8.3)	9(23.7)	4(8.7)
<u>Renal</u>									
Renal Failure	140(5.6)	11(0.9)	22(3.8)	5(2.4)	100(49.3)	1(0.7)	-	1(2.6)	-
<u>Multiple</u>	155(6.2)	110(8.8)	30(5.2)	5(2.4)	5(2.5)	3(2)	-	2(5.3)	-
<u>Other*</u>	207(8.3)	95(7.6)	39(6.8)	22(10.5)	23(11.3)	16(10.5)	1(8.3)	5(13.2)	6(13)

***Includes ADRs that were listed under the category “other” on the ADR form (Annexure 4).**

Table 3: ARVs reported in relation to the patient demographics

<i>N=2489</i>							
<i>GENDER * n (%)</i>			<i>AGE GROUP (YEARS)** n (%)</i>				
ARV	MALES n=755	FEMALES n=1511	0-14 n=122	15-29 n=295	30-44 n=1137	45-59 n=615	≥60 n=111
Stavudine	338 (44.8)	797 (52.7)	97 (80.2)	120 (40.7)	561 (49.3)	318 (51.8)	55 (49.1)
Efavirenz	259 (34.4)	266 (17.6)	9 (7.4)	81 (27.5)	266 (23.4)	147 (23.9)	22 (19.6)
Nevirapine	27 (3.6)	124 (8.2)	1 (0.8)	37 (12.5)	81 (7.1)	16 (2.6)	2 (1.8)
Zidovudine	36 (4.8)	139 (9.2)	1 (0.8)	31 (10.5)	90 (7.9)	55 (9)	11 (9.8)
Tenofovir	63 (8.4)	126 (8.3)	-	13 (4.4)	94 (8.3)	56 (9.1)	21 (18.8)
Abacavir	5 (0.7)	6 (0.4)	7 (5.8)	-	1 (0.1)	3 (0.5)	-
Multiple	16 (2.1)	20 (1.3)	2 (1.6)	6 (2)	22 (1.9)	8 (1.3)	-
Other***	11 (1.3)	33 (2.2)	5 (4.1)	7 (2.4)	22 (1.9)	12 (1.8)	-

*Gender was extracted for 2266 of the 2489 ADR case reports.

**Age was extracted for 2280 of the 2489 ADR case reports.

***Includes ADRs caused by ARVs other than those listed above.

Table 4: Seriousness of the reported ADRs

<i>N=2489</i>	
<i>Seriousness of reported ADRs***</i> n=2255	<i>Frequency n (%)</i>
Required intervention	2196 (97.38)
Symptoms improved	37 (1.64)
Resulted in disability	1 (0.04)
Life-threatening	2 (0.09)
Patient monitored	9 (0.40)
Outcome pending	5 (0.22)
Patient demised	5 (0.22)

***Seriousness was extracted for 2255 of the 2489 ADR case reports.

Discussion

The majority of ADRs were seen among female patients as opposed to male patients. In addition, this study had a higher number of female patients receiving ARV treatment as opposed to male patients. Female patients were more likely to experience peripheral neuropathy, lipodystrophy, skin rash, anaemia and hyperlactatemia (Table 1). Male patients were more prone to experience gynaecomastia and peripheral neuropathy (Table 1). The outsized difference in ADRs between males and females have been reported in studies conducted globally and could be due to the body structure and weight differences in these population groups, and hence the variance in their ability to tolerate and metabolise drugs.^[7,15]

Peripheral neuropathy and lipodystrophy (mainly attributed to female patients on stavudine treatment in the 30-44 year age group), skin reactions and gynaecomastia (caused mainly by efavirenz in the same age group) reported in this study showed that the age group of 30-44 were at specific risk to these ADRs. The 45-59 year age group attained the second highest total number of ADRs and this comprised mainly of peripheral neuropathy, lipodystrophy, skin reactions and renal failure (Table 1). According to Statistics South Africa most patients receiving ARV treatment in SA during 01 January 2010 – 31 December 2014 were in the 30-44 year age group.^[3] This suggests that the high incidence of ADRs among patients in this group could be due to the high number of patients receiving ARV treatment and belonging to this particular age group at the time of reporting.

The 10 most commonly reported ADRs reported with the use of ARVs were peripheral neuropathy (n=472, 19%), lipodystrophy (n=471, 18.9%), serious skin reactions (n=266, 10.7%), gynaecomastia (n=219, 8.8%), renal failure (n=140, 5.6%), dizziness (n=133, 5.3%), hyperlactatemia (n=118, 4.7%), psychosis/hallucinations (n=47, 1.9%), sleep disturbances (n=44, 1.8%) and vomiting (n=44, 1.8%). A similar observation was made in other studies.^[11,14] Stavudine was seen to be the ARV having the strongest association to most of the commonly reported ADRs as compared to other ARVs (Table 2). Some experts believe that this is caused by stavudine damaging the mitochondria, causing a range of side effects faster than most drugs in its class.^[16]

Patients who were initiated on tenofovir-based regimens were more likely to experience renal failure. The high incidence of renal failure was striking and somewhat perplexing, however a study conducted among ARV patients in KZN also found a large proportion of patients, treated with tenofovir, experiencing renal failure.^[9] Females, aged 30-44 years old, who were treated with zidovudine, commonly experienced anaemia. Studies from African and Asian patients showed a large prevalence of

anaemia development after ART initiation with zidovudine-based regimens, specifically among female patients (Table 3).^[15] These findings concur with studies that have found this to be due to the fact that females have lower haemoglobin levels than males, hormonal imbalances and menstrual cycles.^[14,15]

A considerably high rate of patients required an intervention to prevent any significant impairment and/or disability (Table 4). Patients that required an intervention (either a change in regimen or supplementary drug) were mostly being treated with stavudine. Patients on stavudine-containing regimens presented an increased incidence of ADRs within 1 month of ARV initiation. These results coincide with other studies that have shown that stavudine causes ADRs quicker than any other ARV in its class.^[10,15]

Conclusion

In hope to endorse the rational and cost-effective use of medicines, to ensure patient safety, and to minimize morbidity and mortality rates, studies have been conducted in the different provinces of South Africa to help describe ADRs reported with reference to HIV-infected patients, ARV regimens, and reporting systems. However, no studies conducted have quantified the types of ADRs experienced most frequently by specific population groups in South Africa.

This study therefore showed that there are significant ADRs associated with the use of ARVs. The commonest ADRs reported were peripheral neuropathy, lipodystrophy, serious skin reactions, gynaecomastia and renal failure. In addition, female patients, aged 30-44 years old were found to be more susceptible to these reactions as opposed to males in the same age group. Most reactions were caused due to the use of stavudine, efavirenz, zidovudine, nevirapine and tenofovir in the population groups identified in this study. The results of this study can therefore assist in the treatment individualization of patients in order to enhance adherence and improve the success of ARV therapy in South Africa.

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CHAPTER 4

CONCLUSIONS

4.1 Introduction

This study was carried out to describe the ADRs reported in South Africa amongst patients using ARVs, with reference to the types and seriousness of ADRs reported, patient demographics associated with specific ADRs, and the types of ARVs mostly involved in ADRs. Although many drugs have been used and studied in developed countries, their safety profiles may not necessarily be applicable to other settings where the incidence, pattern, and severity of ADRs may differ because of local environmental and genetic influences. Further, there is scant information available on the burden of ADRs due to the use of ARVs among HIV-infected people in South Africa.

4.1.1 Strengths of the study methodology and design

Data collection was cost-effective as the data sets used in the study were obtained via email (from the NDoH PV centre) as a Microsoft Excel® document. The data was easy to analyse considering that it was quantitative and obtained in the form of an extraction sheet and made available electronically. This study comprised of a large sample size (N=2489). The study looked at case reports that were submitted from 01 January 2010- 31 December 2014, this allowed for a broader view of the case reports.

4.2 Conclusions drawn from the study findings

The aim of this study was to describe the ADRs reported in South Africa with reference to the types and seriousness of ADRs reported, patient demographics, and ARVs involved. To achieve this, the following specific objectives were outlined:

- To identify the types of ADRs that have been reported in South Africa.
- To identify the ARVs most involved in the reported ADRs mentioned above.
- To determine the seriousness of reported ADRs based on the patient outcome.
- To examine the patient demographics of the reported ADRs in relation to the type of ADR and ARVs implicated.

Conclusions drawn from the study findings based on each of the objectives

- The 10 most commonly reported ADRs associated with the use of ARVs were peripheral neuropathy (n=472, 19%), lipodystrophy (n=471, 18.9%), serious skin reactions (n=266,

10.7%), gynaecomastia (n=219, 8.8%), renal failure (n=140, 5.6%), dizziness (n=133, 5.3%), hyperlactatemia (n=118, 4.7%), psychosis/hallucinations (n=47, 1.9%), sleep disturbances (n=44, 1.8%) and vomiting (n=44, 1.8%).

- The most commonly reported ARVs associated with ADRs were stavudine (n=1256, 50.46%) and efavirenz (n=572, 22.98%). Following this was zidovudine (n=209, 8.40%), tenofovir (n=203, 8.16%), and nevirapine (n=153, 6.15%).
- Seriousness was measured by patient outcome. Of the seven outcomes identified, majority of the patients (n=2196, 97.38%) required an intervention to prevent any significant impairment or disability.
- Majority of ADR reports submitted were ADRs experienced by female patients (n=1511, 66.7%) as compared to male patients (n=755, 33.3%). Almost half of the patients were in the 30-44 year age group (n=1136, 49.9%). Stavudine caused more ADRs in female patients (n=797, 52.7%) than male patients (n=338, 44.8%). Efavirenz was also responsible for more ADRs in female patients (n=266, 17.6%) as compared to male patients (n=259, 34.4%). Peripheral neuropathy (n=21, 18.8%) and renal failure (n=23, 20.5%) were reported in patients aged ≥ 60 years as compared to patients in the 0-14 year age group in which lipodystrophy (n=47, 38.8%) was mostly reported.

4.3 Significance of the study

- Knowledge of the most prevalent ADRs, medicines involved, and population groups at risk can help pave the way to ameliorate the incidence of ADRs experienced by specific populations in South Africa. ADRs can have a detrimental effect on patient outcome, adherence, and management.
- The results of this study can assist in the treatment individualization of patients in order to enhance adherence and improve the success of ARV therapy in South Africa.
- This can also assist with reinforcing the goals set out by the National Department of Health to help strengthen strategies to maximize patient safety, allow for easier patient monitoring, ensure the rational use of medicines, and reduce healthcare costs.
- Considering the impact ADRs have on a patient's quality of life, and morbidity and mortality rates in South Africa, a major stepping stone to achieving ways to detect or prevent ADRs before they proliferate would be to know which population groups are most susceptible to these harmful reactions and which ARVs are most likely to cause them.

4.4 Limitations of the study

- Underreporting – many ADR reports were incomplete. This lack of information (age, gender, ADR, ARV, outcome) resulted in some patients' case reports being excluded from the study.
- Reported ADRs were restricted to those that were serious and required a change in drug regimen, therefore non-serious ADRs that did not require a change in regimen were not reported and not included in this study.
- The data obtained and used in this study was restricted to public-sector institutions; hence ADRs that could have occurred among patients from private-sector institutions were not taken into consideration.
- The use of complementary and/or herbal medicines by these patients was not considered in this study. Only medicines that patients were receiving from their relevant public-sector institutions were considered. Therefore, drug interactions amongst herbal/complementary medicines with ARVs were not considered in terms of possibly causing the ADR or influencing its outcome.

4.5 Recommendations

- This study was restricted to case reports received from public-sector institutions; hence ADRs were not included from private-sector institutions. ADR reports from both public-sector and private-sector can provide a greater insight and increase the generalisability when studying ADRs. Therefore, further studies should incorporate both sectors.
- Further studies on the topic should take into consideration herbal/complementary medicines that patients use to treat concomitant diseases and their possible drug-drug interaction(s) with ARVs as this could possibly influence the outcome of ADRs.
- The importance of the completion of ADR forms should be addressed on a direct level with all healthcare providers, as underreporting leads to lack of vital information supplied which can create hurdles during data analysis.

4.6 Chapter summary

The final chapter highlighted the conclusions drawn from the findings of the study, described the strengths and limitations of the study, as well as provided recommendations for future research.

ANNEXURE 1

Ethical clearance certificate obtained from the University of KwaZulu-Natal



Ms Sumeshni Birbal 209501662
School of Health Sciences
Westville Campus

Dear Ms Birbal

Protocol reference number: HSS/0916/015M
New project title: Adverse Drug Reactions Association with Anti-Retroviral Therapy in South Africa

Approval Notification – Amendment

This letter serves to notify you that your request for an amendment received on 27 August 2015 has now been approved as follows:

Change in Title and Objectives

Any alterations to the approved research protocol i.e. Questionnaire/Interview Schedule, Informed Consent Form; Title of the Project, Location of the Study must be reviewed and approved through an amendment /modification prior to its implementation. In case you have further queries, please quote the above reference number.

PLEASE NOTE: Research data should be securely stored in the discipline/department for a period of 5 years.

The ethical clearance certificate is only valid for period of 3 years from the date of issue. Thereafter Recertification must be applied for on an annual basis.

Best wishes for the successful completion of your research protocol.

Yours faithfully

Dr Shenuka Singh (Chair)
Humanities & Social Sciences Research Ethics Committee

Cc Supervisor: Dr F Oosthuizen
Cc Academic Leader Research: Prof J van Heerden
Cc School Administrator: Ms P Nene

ANNEXURE 2

Data user's agreement obtained from the National Department of Health



The User agrees that his/her signature indicates his/her agreement to comply with the above-stated requirements (Points 1-9)

Please complete this form

Data/Set/s for which Agreement is signed (Provide detail list):	Pharmacovigilance program ADRs database
Name (Print or Type):	SUMESHNI BIRBAL
Organisation/Department:	School of Health Sciences –University of KwaZulu–Natal
Position:	Masters Student
Purpose for which the data will be used (List attachment)	Data will be used as part of a study towards a Masters degree in Health Sciences, looking at the most prevalent Adverse Drug Reactions reported in South Africa, with reference to the type, seriousness, therapeutic drug(s) involved, underlying diseases and patient demographics.
Anticipated timeframe for completing the analysis/study/project for which data are requested	February 2015 – October 2015
Anticipated timeframe for sharing the results of the analysis/study/project with the National Department of Health	September 2015 – January 2016
Title (Mr/Mrs/Ms/Dr/Prof) :	Ms
Address:	Westville campus UKZN Varsity drive Durban 4000
City:	Durban
Province:	KwaZulu-Natal
Country:	South Africa
Telephone:	031 902 1930
Fax:	031 914 0043
E-mail:	sumeshni101@gmail.com
Signature:	
Date:	10/03/2015
Witness: Name	Rajan Birbal
Witness: Contact No	0746031991
Date:	10/03/2015

For Department of Health use only:

Approval by DOH Representative*:	
Date:	24/03/2015

The Data User's Agreement must be signed by the Chief Director for Health Information Management, Monitoring and Evaluation.

ANNEXURE 3

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- » Online Submissions
- » Author Guidelines
- » Copyright Notice
- » Privacy Statement

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Authors must declare all sources of support for the research and any association with a product or subject that may constitute conflict of interest.

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Provide evidence of Research Ethics Committee approval of the research where relevant.

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References to ethnic classification must indicate the rationale for this.

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Shorter items are more likely to be accepted for publication, owing to space constraints and reader preferences.

Research articles (previously 'Original articles') not exceeding 3 000 words, with up to 6 tables or illustrations, are usually observations or research of relevance to clinical medicine and related fields. *References should be limited to no more than 15.* Please provide a structured abstract not exceeding 250 words, with the following recommended headings: *Background, Objectives, Methods, Results, and Conclusion.*

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Guidelines must be endorsed by an appropriate body prior to consideration and all conflicts of interest expressed. A structured abstract not exceeding 250 words (recommended sub-headings: *Background, Recommendations, Conclusion*) is required. Sections and sub-sections must be numbered consecutively (e.g. 1. Introduction; 1.1 Definitions; 2. etc.) and summarised in a Table of Contents. References, appendices, figures and tables must be kept to a minimum.

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Scientific measurements must be expressed in SI units except: blood pressure (mmHg) and haemoglobin (g/dl). Litres is denoted with a lowercase 'l' e.g. 'ml' for millilitres). Units should

be preceded by a space (except for %), e.g. '40 kg' and '20 cm' but '50%'. Greater/smaller than signs (> and 40 years of age'. The same applies to \pm and $^{\circ}$, i.e. '35 \pm 6' and '19 $^{\circ}$ C'.

Numbers should be written as grouped per thousand-units, i.e. 4 000, 22 160...

Quotes should be placed in single quotation marks: i.e. The respondent stated: '...' Round **brackets** (parentheses) should be used, as opposed to square brackets, which are reserved for denoting concentrations or insertions in direct quotes.

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If tables or illustrations submitted have been published elsewhere, the author(s) should provide consent to republication obtained from the copyright holder.

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References must be kept to a maximum of 15. Authors must verify references from original sources. *Only complete, correctly formatted reference lists will be accepted.* Reference lists must be generated manually and **not** with the use of reference manager software. Citations should be inserted in the text as superscript numbers between square brackets, e.g. These regulations are endorsed by the World Health Organization,^[2] and others.^[3,4-6] All references should be listed at the end of the article in numerical order of appearance in the **Vancouver style** (not alphabetical order). Approved abbreviations of journal titles must be used; see the List of Journals in Index Medicus. Names and initials of all authors should be given; if there are more than six authors, the first three names should be given followed by et al. First and last page, volume and issue numbers should be given.

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Book references: Jeffcoate N. Principles of Gynaecology. 4th ed. London: Butterworth, 1975:96-101. *Chapter/section in a book:* Weinstein L, Swartz MN. Pathogenic Properties of Invading Microorganisms. In: Sodeman WA jun, Sodeman WA, eds. Pathologic Physiology: Mechanisms of Disease. Philadelphia: WB Saunders, 1974:457-472.

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8. An abstract has been included where applicable.
9. The research was approved by a Research Ethics Committee (if applicable)
10. Any conflict of interest (or competing interests) is indicated by the author(s).

Adverse drug reaction reporting form

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