Awareness, attitudes, and experiences of patients taking antiretrovirals towards adverse drug reactions at a public health facility in KwaZulu-Natal

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AWARENESS, ATTITUDES AND EXPERIENCES OF PATIENTS TAKING ANTIRETROVIRALS TOWARDS ADVERSE DRUG REACTIONS AT A PUBLIC HEALTH FACILITY IN KWAZULU-NATAL

MALEBOGO TLAILA

2020

DECLARATION 1 – SUBMISSION OF DISSERTATION

This is to certify that the contents of this dissertation is the original research work of:

Student's Name: Malebogo Tlaila

Signed: [redacted]

Date: December 4, 2020

As the student's supervisor, I have approved this dissertation for submission.

Supervisor's Name: Dr Elizabeth Ojewole

Signed: [redacted]

Date: December 2020

DECLARATION 2 – PLAGIARISM

I, Malebogo Tlaila declare that:

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DECLARATION 3 – ETHICAL APPROVAL AND GATEKEEPER PERMISSION

This study – Awareness, attitudes and experiences of patients taking antiretrovirals towards adverse drug reactions at a public health facility in KwaZulu-Natal was approved by the Humanities and Social Sciences Research Ethics Committee (referenced HSS/2120/017M). A copy of the ethical approval letter can be found in Appendix C, page 73.

Gate keeper permission was obtained from the medical management of Clairwood Hospital. A copy of the approval letter (referenced "Research") can be found in Appendix E, page 75.

DECLARATION 4 – MANUSCRIPT PREPARED FOR JOURNAL SUBMISSION

Authors' contributions to the manuscript:

Malebogo Tlaila, as the student, conceptualized the research and performed all literature reviews, collected and captured the data and performed the interpretation of the results. She prepared the manuscript according to the format of the journal submission.

Dr Boikhutso Tlou performed the statistical data analysis and confirmed the interpretation of the results.

Dr Elizabeth Ojewole supervised the student and contributed to the overall research process, including the proposal, manuscript and dissertation writings.

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DEDICATION

I dedicate this dissertation to my God and guardian angels for seeing me through this challenging journey, for keeping me safe and in good health and for giving me the strength to persevere until the end. God, without You, I am nothing.

I also dedicate this study to my professional standing as a custodian of medicine. I take great pride in my profession and I am proud to know that I have added medicinal value to patients' lives. My goal is to see a healthcare system that functions holistically and takes patients' concerns to achieve a healthier relationship between patients and their intake of medicine.

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LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
AIDS	Acquired Immuno-deficiency Syndrome
ART	Antiretroviral Therapy
ARV	Antiretroviral
CKD	Chronic Kidney Disease
CYP 450	Cytochrome P-450
DDI	Drug–drug Interaction
DI	Drug Interaction
DDI	Drug Disease Interactions
DFI	Drug Food Interactions
DHI	Drug Herb Interactions
HIV	Human Immuno-deficiency Virus
MCC	Medicines Control Council
SAHPRA	South African Health Products Regulatory Authority
SJS	Steven Johnson Syndrome
TB	Tuberculosis
WHO	World Health Organisation

LIST OF DEFINITIONS

Definitions

The following terms are defined according to their relevant sources, in order to describe the focus of this study:

Adverse drug reactions:

Adverse drug reactions (ADRs) are defined as an injury caused by taking medication. It may occur following a single dose or a prolonged use of a drug or a combination of two or more drugs.

Attitudes:

Attitude is a settled way of thinking or feeling about something (Brown & Bussell, 2011)In this study, attitude refers to how people think ADRs occur and how they feel about them (Brown & Bussell, 2011).

Awareness:

Awareness is described as knowledge or perception of a situation or fact or a concern about and well-informed interest in a particular situation or development In this study, awareness is used as a description of knowledge about ADRs and the DDIs leading to these reactions when ARVs and other medication are taken (Bogolubova et al., 2018).

Drug–drug interactions:

Drug–drug interactions occur when a drug affects the activity of another drug when both are taken together (Gilligan et al., 2011).

Experience:

Experience is defined as practical contact with an observation of facts or events. It relates to how people respond to the facts in a practical manner (Van Hunsel et al., 2012).

ABSTRACT

Adverse drug reactions (ADRs) are undesirable side effects that occur even when a drug is administered at the proper dose and correctly for an appropriate indication. Given the high prevalence of Human Immuno-deficiency Virus (HIV) in South Africa, more than 3 million people are reported to be taking antiretrovirals (ARVs). Therefore, patients taking ARVs may also be taking other medicines due to other existing diseases such as diabetes, hypertension, and tuberculosis. The concurrent use of other medicines with ARVs may increase the potential of ADRs, snowballing to increased numbers of hospitalisations and contributing to mortality rates. The study investigated awareness, attitudes, and experiences of ADRs among patients taking ARVs. This was a descriptive cross-sectional study using a questionnaire that contained close-ended questions to which patients responded. The study was conducted at a selected public hospital in KwaZulu-Natal. Questionnaires were available in both English and isiZulu and were hand delivered to patients. Ethical approval was obtained prior to commencement of this study. The participants were recruited by a random systematic selection by choosing every second participant. Both verbal and written consents were obtained before handing out questionnaires for participation. Statistical Package for Social Sciences (SPSS®) version of 25 was used to capture and analyse data. Categorical measurements were summarised using frequencies and proportions. Out of 200 questionnaires, a total of 174 patients responded, which delivered an 87% response rate. Of the 174 respondents, 55% (n=96) were females and 45% (n=78) were males. About 8% (n=13) of respondents were aware of ADRs, 55% (n=94) of drug–drug interactions and 12% (n=20) had reported ADRs. About 13% (n=22) respondents reported having hypertension, 7% (n=4) respondents reported diabetes and 1% (n=2) respondents reported tuberculosis. Almost 65% (n=114) respondents took the fixed drug combination, 17% (n=30) respondents took lamivudine and zidovudine combination, and 2.3% (n=4) respondents took ritonavir and atazanavir combinations. About 5% (n=8) respondents experienced vomiting, 1.7% (n=3) of respondents experienced diarrhoea and 1.1% (n=2) respondents experienced rashes. Most patients on ARVs and anti-TB medicines can experience reduced hearing or deafness, particularly in patients using medicines such as Kanamycin. Most medicines metabolised by CYP450, such as rifampicin and lopinavir/ritonavir combination, where rifampicin lowers ritonavir blood serum levels therefore requiring a boost of ritonavir. Patients should therefore be made aware of ADRs of ARVs, particularly those that may arise due to drug-drug interactions among the patients that have co-existing diseases. Patients should also be counselled to report ADRs, to obtain the ADR form, complete it and ensure they submit the ADR reports the healthcare professionals as well as the pharmacovigilance centre. The awareness of ADRs among patients taking ARVs could be improved by providing quality training and in-depth counselling of the patients during their visit to the hospital in order to ensure optimal therapy and patients safety.

Keywords: antiretroviral, adverse drug reactions, drug–drug interactions, drug–disease interactions, awareness, attitudes, experiences

CHAPTER 1
INTRODUCTION TO THE STUDY

1.1 Introduction

Given the high prevalence of Human Immuno-deficiency Virus (HIV) in South Africa, more than 3 million people were reported to be using antiretrovirals (ARVs) in 2015. The figure escalated by about 20% within 4 years, signifying an increase in the use of ARVs by people living with HIV (Joint Uited Nations Programme on HIV/AIDS, 2019). South Africa has the highest rate of HIV positive people on antiretroviral therapy (ART) (Masenyetse et al., 2015). The test to treat strategy has been implemented worldwide to eliminate HIV by commencing positive patients on ARV medication, irrespective of patients' CD4 count or clinical stage (Davis et al., 2012; Miller et al., 2012; UNAIDS, 2019). A recent cohort study determined that the time to event models leading to adverse drug reaction (ADR) in HIV positive patients taking ART (37%) showed that patients had experienced at least one ADR (Masenyetse et al., 2015). Gastrointestinal, central nervous system (CNS) and dermatologic ADRs are seen in patients taking ARVs. Gastrointestinal reactions range from diarrhoea and nausea to hepatotoxicity. CNS reactions range from headaches and dizziness to neuropsychiatric disorders. Dermatologic reactions include rashes and skin changes. Steven Johnsons Syndrome (SJS) is an example of a severe dermatologic ADR due to the administration of Nevirapine (Patel et al., 2012). Since drug hypersensitivity reactions are a clinical problem for both health care and industry, one can only imagine where that leaves a patient who is completely unaware of ADRs (Pirmohamed et al., 2015). ADRs associated with the use of ARVs increase chances of worsening the patient's condition as seen with immune reconstitution inflammatory syndrome (Abah et al., 2019; Murphy et al., 2007). The study investigated patient's awareness, attitudes, and experiences of ADRs to antiretrovirals through a series of questions. Most studies have focused more on awareness of adverse drug reactions and reactions amongst healthcare professionals (Bogolubova et al., 2018) (Fadare et al., 2011), while a few studies have focused on patients awareness, attitudes and experiences (Sales et al., 2017). The study focused on patients and their awareness attitudes and experiences and compared its findings to literature that has already been published.

1.2 Background to the Study

The World Health Organisation (WHO) and other researchers define ADR as 'a response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis and therapy of disease, or modification of physiological function' (Davies et al., 2010)(Edwards & Aronson, 2000). Cao *et al*,2015 and other studies further state that ADRs are undesirable side effects that occur even when a drug is administered at the proper

dose and in the correct manner for an appropriate indication(Cao et al., 2015) (Maddison & Page, 2008)(Shatz & Weber, 2015).

ADRs are a major cause of iatrogenic morbidity, mortality and economic impact (Plumpton et al., 2016). Susceptibility to ADRs is influenced by age, gender, disease states, pregnancy, ethnicity and polypharmacy (Kaufman, 2016). Colliding epidemics of infectious non-communicable diseases, prevalent pharmacogenetic variants associated with increased risk of ADRs as well as the widespread concomitant use of traditional remedies potentially contribute to the burden of drug-related harm (Mouton et al., 2016).

ADRs are a major problem in clinical practice and drug development with a suggested estimate of 6.5%–6.7% of hospital admissions or acute hospitalisations due to them (Pirmohamed et al., 1998)(Walker et al., 2014)

1.2.1 Classification of adverse drug reactions

ADRs were initially classified as two major subtypes: Type A (augmented) and Type B (bizarre). More classifications were added as Type C (chronic), Type D (delayed), Type E (withdrawal) and Type F (unexpected failure of therapy). Type A ADRs are augmented, common and are predictable from the known pharmacology of the drug (Edwards & Aronson, 2000; Maddison & Page, 2008). Table 1.1 presents the summarised classifications of ADRs.

Type A reactions account for over 80% of all ADRs with the majority (70%–80%) caused by predictable, non-immunologic effects while Type B reactions are uncommon and unpredictable, dose-independent and affect a small portion of the population (Maddison & Page, 2008).

Table 1. Classification of adverse drug reactions

Type of reaction	**Mnemonic**	**Features**
A: Dose-related	Augmented	• Common • Predictable • Low morality • Related to drug pharmacology
B: Non-dose-related	Bizarre	• Uncommon • Unpredictable • High mortality • Not related to drug pharmacology

C: Dose-related and time-related	Chronic	• Uncommon • Related to cumulative dose
D: Time-related	Delayed	• Uncommon • Usually dose-related • Occurs or becomes apparent after prolonged drug usage
E: Withdrawal	End of use	• Uncommon • Occurs soon after withdrawal of the drug
F: Unexpected failure of therapy	Failure	• Common • Dose-related • Often cause by drug interactions

Source: Edwards and Aronson (2000)

1.2.2 Drug–drug iinteractions

Drug–drug interactions (DDIs) are one of the causes leading to ADRs (Bucşa et al., 2013). DDIs occur when one drug may alter the intended pharmacologic intensity and effects of another drug when given concurrently (Mutebi et al., 2013). Drug-related factors, such as polypharmacy, increase the likelihood of DDIs causing ADRs (Alomar, 2014). An adjustment of drug doses for infants and geriatrics is required due to their underdeveloped systems or the decreasing functionality of their organs, respectively.

Health education and counselling are tools that can be used to combat factors that affect DDIs and ADRs (Alomar, 2014). People are at risk are the elderly, especially those taking up to four or more medications (i.e. polypharmacy) have a 50% chance of experiencing DDIs (Bucşa et al., 2013).

1.2.3 The burden of adverse drug reactions related to HIV in South Africa

According to Mouton et al. (2016), limited data on the burden of serious ADRs in sub-Saharan Africa, which has a high prevalence of HIV, exists. However, through the expansion of HIV and tuberculosis (TB) treatment programmes, the understanding of the burden of ADRs is improving; approximately 12 medical admissions are due to ADRs and ADRs account for 16% of deaths among adult medical admissions in South Africa (Mehta et al., 2017). The nature and frequency of ADRs in South Africa differ significantly from other countries; the population structure, burden of disease and the risk profile of commonly used drugs influence this trend

(Mehta et al., 2017; Mouton et al., 2016).

1.3 Problem Statement

According to HIV/AIDS statistics reported for South Africa, KwaZulu-Natal Province (KZN) remains the highest rated province for HIV/AIDS cases in South Africa (National Department of Health, 2015). ARV medicines were made available to the South African public in 2004 for the treatment of HIV/AIDS and related cases (National Department of Health, 2003). ARV medicines are provided after people have undergone testing and counselling by appropriately trained health personnel and have been found to be HIV positive. Since 2004, the treatment regimens have changed due to adverse effects, drug interactions (DIs) and resistance to ART (Collins et al., 2016; Njuguna et al., 2013).

Studies in South Africa and other countries such as Switzerland have shown that ARVs have a number of well-recorded side effects, which result in patients' drug regimens having to be changed (Kovari et al., 2013; Mouton et al., 2015). Changes in drug regimens may lead to drug–drug interactions, causing ADRs as well as HIV/AIDS-related deaths due to the new drug treatments (Abo et al., 2015; Birbal et al., 2016; Mouton et al., 2015).

Patients taking ARVs may also be taking other medicines unavoidably because of their existing diseases such as diabetes, hypertension, and tuberculosis. When medicines are taking at the same time as ARVs, there is a possibility of DDIs. Several interactions between ARVs and other medicines have been reported to cause ADRs (Kovari et al., 2013; Rathbun & Liedtke, 2011; Tseng & Foisy, 2012).

It has also been reported that many patients do not know about ADRs, particularly those caused by DDIs (Mouton et al., 2015). In fact, patients cannot identify the drugs that interact with other drugs that can result in ADRs. Studies have also indicated that patients taking ARVs can suffer ADRs that are caused by DDIs (Kigen et al., 2011; Miller et al., 2012). Therefore, patients need to be aware of drugs that interact with others causing ADRs. It is imperative that patients who experience ADRs can report them as this will ensure the safety of medicine use, particularly in patients on ARV. Therefore, in order to add to the literature on ADRs of ARVs, particularly among patients in public health sectors of South Africa, this study focused on awareness, attitudes and experiences of ADRs among patients taking ARVs.

1.4 Research Questions

The main question in this study is "what are the awareness, attitudes and experiences due to adverse drug reactions due to antiretrovirals and non-antiretroviral medicines among patients at a public health facility in KZN"?

The specific questions were as follows:

1. To what extent are patients aware of ADRs to ARV and other non-ARV medicines?
2. What is the extent of patients' awareness of drug interactions that result in ADRs?
3. What are the experiences of patients regarding ADRs that result from their ARVs and other medicines?
4. What are the attitudes of patients towards ADRs resulting from ARVs and other medicines?

1.5 Aim and Objectives

1.5.1 Aim

To investigate the awareness , attitudes and experiences towards adverse drug reactions due to antiretrovirals among HIV patients at a public health facility in KZN.

1.5.2 Objectives

The study was guided by the following objectives:

1. To establish the awareness of patients regarding ADRs of ARVs and other medicines.
2. To determine the awareness of patients regarding drug interactions that result in ADRs among patients taking ARVs and other medicines.
3. To describe patients' experiences of ADRs of ARVs and other medicines.
4. To determine patients' attitudes towards ADRs of ARVs and other medicines.

1.6 Research Methodology

1.6.1 Study site and population

The study was conducted at a public district hospital in the eThekwini Municipality in KZN. The hospital has an HIV/AIDS clinic, which provides services to people who are referred from tertiary hospitals within their catchment area and to walk-ins. Nurses, doctors, counsellors, dieticians and pharmacists staff the clinic. Patients are initiated for ARV on site when they are seen by the doctors, nurses, and counsellors.

1.6.2 Study sample and size

The sample size was calculated from the total population of patients at the study facility. The following statistical parameters were used to determine sample size: a statistical power of 80%, effect size = 0.25, type 1 (α) error = 0.05 (this is the probability of falsely rejecting the null hypothesis of 5%), type 2 (β) error = 0.2 (this is the probability of falsely failing to reject the null hypothesis of 20%), statistical power (1- β) = 0.8 (80%). Based on the above statistical parameters, a minimum sample size of 180 was determined.

1.6.3 Inclusion and exclusion criteria

1.6.3.1 Inclusion criteria

All patients who fulfilled the following criteria were included:

- Patients who consented to participate
- Those who were 18 years and older
- Those who were collecting their own medication
- Those who were literate in isiZulu and/or English

1.6.3.2 Exclusion criteria

All patients who fell in the categories listed below were excluded:

- All patients who did not consent to participate
- Those who were below the age of 18 years
- Patients whose families, friends or supporters were collecting their medicines on their behalf
- Patients who were not literate in isiZulu and/or English

1.6.4 Data collection process

Data were collected through self-administered questionnaires. Three areas where patients could be informed about the study were identified as the main waiting room and two separate waiting rooms outside the nurses' rooms. Two nurses were informed and trained about the study, and then assisted with data collection. There is one main waiting room and two smaller waiting rooms leading to the nurses rooms. Patients seated and waiting for consultation in the nurse's rooms were selected. Upon entering the nurses room patients were introduced to the study and asked if they would like to participate in it.

1.6.5 Data analysis

The responses of the participants on the coded questionnaires were captured on Excel worksheet, and later transferred to Statistical Package for Social Sciences (SPSS®) version 25. The data was then analysed, and categorical measurements were summarised using frequency distribution tables and proportions.

1.6.6 Ethical considerations and confidentiality

An information leaflet clearly outlining the nature of the study and the consent of the participants to join the study was made available to all the participants. Participants had to clearly indicate if they were willing to be a part of the study by signing the consent form (Appendix B). Participation was completely voluntary, and no patients were coerced into participating in the study. Patient confidentiality was maintained throughout the study. No personal information was requested, and questionnaires were identified by numbers and not by

patient names. The study was approved by the Humanities and Social Sciences Research Ethics Committee (HSSREC) with a letter referenced HSS/2120/017M.

1.7 Thesis Overview

Chapter one describes the introduction, problem statement, methodology, design, and definitions used in the study. It also highlights the aims and objectives of the study. Chapter two provides a review of the literature that are relevant to this study. The findings emanating from the study were presented in Chapter three. The general conclusions of the study results are synthesized, and recommendations provided in Chapter 4.

References

1. Abah, I. O., Ncube, N. B. Q., Bradley, H. A., AgbaJi, O. O., & Kanki, P. (2019). Antiretroviral Therapy-associated Adverse Drug Reactions and their Effects on Virologic Failure- A Retrospective Cohort Study in Nigeria. *Current HIV Research*, *16*(6), 436–446. https://doi.org/10.2174/1389450120666190214144609
2. Abo, Y., Zannou Djimon, M., Messou, E., Balestre, E., Kouakou, M., Akakpo, J., Ahouada, C., de Rekeneire, N., Dabis, F., Lewden, C., & Minga, A. (2015). Severe morbidity after antiretroviral (ART) initiation: active surveillance in HIV care programs, the IeDEA West Africa collaboration. *BMC Infectious Diseases*, *15*(1), 176. https://doi.org/10.1186/s12879-015-0910-3
3. Alomar, M. J. (2014). Factors affecting the development of adverse drug reactions (Review article). *Saudi Pharmaceutical Journal*, *22*(2), 83–94. https://doi.org/10.1016/j.jsps.2013.02.003
4. Birbal, S., Dheda, M., Ojewole, E., & Oosthuizen, F. (2016). Adverse drug reactions associated with antiretroviral therapy in South Africa. *African Journal of AIDS Research*, *15*(3), 243–248. https://doi.org/10.2989/16085906.2016.1191519
5. Bogolubova, S., Padayachee, N., & Schellack, N. (2018). Knowledge, attitudes and practices of nurses and pharmacists towards adverse drug reaction reporting in the South African private hospital sector. *Health SA Gesondheid*, *23*, 1–9. https://doi.org/10.4102/hsag.v23i0.1064
6. Bucşa, C., Farcaş, A., Cazacu, I., Leucuta, D., Achimas-Cadariu, A., Mogosan, C., & Bojita, M. (2013). How many potential drug-drug interactions cause adverse drug reactions in hospitalized patients? *European Journal of Internal Medicine*, *24*(1), 27–33. https://doi.org/10.1016/j.ejim.2012.09.011
7. Cao, D.-S., Xiao, N., Li, Y.-J., Zeng, W.-B., Liang, Y.-Z., Lu, A.-P., Xu, Q.-S., & Chen, A. F. (2015). Integrating Multiple Evidence Sources to Predict Adverse Drug Reactions Based on a Systems Pharmacology Model. *CPT: Pharmacometrics & Systems Pharmacology*, *4*(9), 498–506. https://doi.org/10.1002/psp4.12002
8. Collins, S. E., Grant, P. M., & Shafer, R. W. (2016). Modifying Antiretroviral Therapy in Virologically Suppressed HIV-1-Infected Patients. *Drugs*, *76*(1), 75–

98. https://doi.org/10.1007/s40265-015-0515-6

9. Davies, E. C., Green, C. F., Mottram, D. R., & Pirmohamed, M. (2010). Interpreting adverse drug reaction (ADR) reports as hospital patient safety incidents. *British Journal of Clinical Pharmacology*, *70*(1), 102–108. https://doi.org/10.1111/j.1365-2125.2010.03671.x
10. Davis, J. L., Dowdy, D. W., den Boon, S., Walter, N. D., Katamba, A., & Cattamanchi, A. (2012). Test and Treat. In *JAIDS Journal of Acquired Immune Deficiency Syndromes* (Vol. 61, Issue 1, pp. e6–e8). https://doi.org/10.1097/qai.0b013e3182614bc5
11. Edwards, I. R., & Aronson, J. K. (2000). Adverse drug reactions: definitions, diagnosis, and management. *Lancet (London, England)*, *356*(9237), 1255–1259. https://doi.org/10.1016/S0140-6736(00)02799-9
12. Fadare, J. O., Enwere, O. O., Afolabi, A. O., Chedi, B. A. Z., & Musa, A. (2011). Knowledge, attitude and practice of adverse drug reaction reporting among healthcare workers in a tertiary centre in Northern Nigeria. *Tropical Journal of Pharmaceutical Research*, *10*(3), 235–242. https://doi.org/10.4314/tjpr.v10i3.4
13. Joint Uited Nations Programme on HIV/AIDS, 2019. (2019). *HIV and AIDS in South Africa*. 15. https://www.avert.org/professionals/hiv-around-world/sub-saharan-africa/south-africa
14. Kaufman, G. (2016). *Adverse drug reactions: classification, susceptibility and reporting*.
15. Kigen, G., Kimaiyo, S., Nyandiko, W., Faragher, B., Sang, E., Jakait, B., Owen, A., Back, D., Gibbons, S., Seden, K., & Khoo, S. H. (2011). Prevalence of potential drug-drug interactions involving antiretroviral drugs in a large kenyan cohort. *PLoS ONE*, *6*(2). https://doi.org/10.1371/journal.pone.0016800
16. Kovari, H., Sabin, C. A., Ledergerber, B., Ryom, L., Worm, S. W., Smith, C., Phillips, A., Reiss, P., Fontas, E., Petoumenos, K., De Wit, S., Morlat, P., Lundgren, J. D., & Weber, R. (2013). Antiretroviral drug-related liver mortality among HIV-positive persons in the absence of hepatitis B or C virus coinfection: The data collection on adverse events of anti-HIV drugs study. *Clinical Infectious Diseases*, *56*(6), 870–879. https://doi.org/10.1093/cid/cis919

17. Maddison, J. E., & Page, S. W. (2008). *Small Animal Clinical Pharmacology* (pp. 41–58).
18. Masenyetse, L. J., Manda, S. O., & Mwambi, H. G. (2015). An assessment of adverse drug reactions among HIV positive patients receiving antiretroviral treatment in South Africa. *AIDS Research and Therapy*, *12*, 6. https://doi.org/10.1186/s12981-015-0044-0
19. Mehta, U., Kalk, E., Boulle, A., Nkambule, P., Gouws, J., Cohen, K., Medicines, A., Council, C., & Unit, R. (2017). *Pharmacovigilance : A public health priority for South Africa*. *i*, 125–133.
20. Miller, V., Nwokike, J., & Stergachis, A. (2012). Pharmacovigilance and global HIV/AIDS. *Current Opinion in HIV and AIDS*, *7*(4), 299–304. https://doi.org/10.1097/COH.0b013e328354d8e7
21. Mouton, J. P., Mehta, U., Parrish, A. G., Wilson, D. P. K., Stewart, A., Njuguna, C. W., Kramer, N., Maartens, G., Blockman, M., & Cohen, K. (2015). Mortality from adverse drug reactions in adult medical inpatients at four hospitals in South Africa: A cross-sectional survey. *British Journal of Clinical Pharmacology*, *80*(4), 818–826. https://doi.org/10.1111/bcp.12567
22. Mouton, J. P., Njuguna, C., Kramer, N., Stewart, A., Mehta, U., Blockman, M., Waal, D., Parrish, A. G., Smidt, M. F., Wilson, D. P. K., Igumbor, E. U., Aynalem, G., Dheda, M., Maartens, G., & Cohen, K. (2016). *Adverse Drug Reactions Causing Admission to Medical Wards*. *95*(19), 1–10. https://doi.org/10.1097/MD.0000000000003437
23. Murphy, R. A., Sunpath, H., Kuritzkes, D. R., Venter, F., & Gandhi, R. T. (2007). Antiretroviral Therapy–Associated Toxicities in the Resource-Poor World: The Challenge of a Limited Formulary. *The Journal of Infectious Diseases*, *196*(s3), S449–S456. https://doi.org/10.1086/521112
24. Mutebi, A., Warholak, T. L., Hines, L. E., Plummer, R., & Malone, D. C. (2013). Assessing patients' information needs regarding drug-drug interactions. *Journal of the American Pharmacists Association*, *53*(1), 39–45. https://doi.org/10.1331/JAPhA.2013.12038
25. National Department of Health. (2003). *Operational Plan for Comprehensive HIV and Aids Care, Management and Treatment for South Africa*. *October*, 1–

40.

26. National Department of Health. (2015). *Hiv & aids 2014/15 data fact sheet 9-12*. *June*, 2014–2015.
27. Njuguna, C., Orrell, C., Kaplan, R., Bekker, L. G., Wood, R., & Lawn, S. D. (2013). Rates of Switching Antiretroviral Drugs in a Primary Care Service in South Africa before and after Introduction of Tenofovir. *PLoS ONE*, *8*(5), 1–7. https://doi.org/10.1371/journal.pone.0063596
28. Pate, P. P., Gandhi, A. M., Desai, C. K., Desai, M. K., & Dikshit, R. K. (2012). An analysis of drug induced Stevens-Johnson syndrome. In *Indian Journal of Medical Research* (Vol. 136, Issue 6, pp. 1051–1053).
29. Pirmohamed, M., Breckenridge, A. M., Kitteringham, N. R., & Park, B. K. (1998). Adverse drug reactions. *BMJ: British Medical Journal (International Edition)*, *316*(7140), 1295–1298.
30. Pirmohamed, M., Ostrov, D. a, & Park, B. K. (2015). New genetic findings lead the way to a better understanding of fundamental mechanisms of drug hypersensitivity. *The Journal of Allergy and Clinical Immunology*, *136*(2), 236–244. https://doi.org/10.1016/j.jaci.2015.06.022
31. Plumpton, C. O., Roberts, D., Pirmohamed, M., & Hughes, D. A. (2016). A Systematic Review of Economic Evaluations of Pharmacogenetic Testing for Prevention of Adverse Drug Reactions. *PharmacoEconomics*. https://doi.org/10.1007/s40273-016-0397-9
32. Rathbun, R. C., & Liedtke, M. D. (2011). Antiretroviral drug interactions: Overview of interactions involving new and investigational agents and the role of therapeutic drug monitoring for management. *Pharmaceutics*, *3*(4), 745–781. https://doi.org/10.3390/pharmaceutics3040745
33. Sales, I., Aljadhey, H., Albogami, Y., & Mahmoud, M. A. (2017). Public awareness and perception toward Adverse Drug Reactions reporting in Riyadh, Saudi Arabia. *Saudi Pharmaceutical Journal*, *25*(6), 868–872. https://doi.org/10.1016/j.jsps.2017.01.004
34. Shatz, S. ., & Weber, R. J. (2015). Adverse drug reactions. *Legal Medicine.*, 229–267. https://scholar.google.co.za/scholar?hl=en&as_sdt_0%2C5&as_vis=1&q=adv

erse+drug+reactions shatz&btnG=#d=gs_qabs&u=%3D_vb05Tb_LIQJ

35. Tseng, A., & Foisy, M. (2012). Important drug-drug interactions in HIV-infected persons on antiretroviral therapy: An update on new interactions between HIV and Non-HIV drugs. *Current Infectious Disease Reports*, *14*(1), 67–82. https://doi.org/10.1007/s11908-011-0229-1
36. Walker, L., Yip, V., Pirmohamed, M., & Padmanabhan, S. (2014). Chapter 20 – Adverse Drug Reactions. In *Handbook of Pharmacogenomics and Stratified Medicine* (pp. 405–435). https://doi.org/10.1016/B978-0-12-386882-4.00020-7

CHAPTER 2
LITERATURE REVIEW

2.1 Introduction

This chapter considers a variety of literature relevant to this study. Much of the literature was sourced on the PubMed search engine and the pertinent literature was reviewed. A review of studies conducted by the likes of Hamoudi et al. (2013), Mehta et al. (2017) and Mouton et al. (2016) indicates the need to examine the awareness, attitudes and experiences of patients related to ADRs and DDIs. According to a few studies by Joshi et al, (2015) and Mutebi et al, (2013) the use of ARV medication and other medicines is undeniable (Joshi et al., 2015)(Bucşa et al., 2013)(Mutebi et al., 2013). Awareness of Adverse drug reactions is discussed in a few studies encouraging the purpose of this study (Nehad, 2013) (Mutebi et al., 2013)(Teka et al., 2016).

2.2 Adverse Drug Reactions

Adverse drug reactions (ADRs) occur when medicine causes harm to a patient with no error taking place, the incident is explained as an ADR that could not have been prevented (Davies et al., 2010). Globally, morbidity due to adverse drug reactions accounts for 6.3%-6.7% of hospitalizations and mortality accounts for 0.08/100 000 - 0.12/100 000 deaths(Kaufman, 2016)(Masenyetse et al., 2015) (Shepherd et al., 2012). In developed countries, hospitalization accounts for 16.3%, mortality for 1.7% and preventable ADRs for 71.7% while in developing countries hospitalization, mortality and preventable ADRs account for 5.5%, 1.8% and 59.6%, respectively (Tarekegn et al., 2016). Honing into the developing and developed countries it was further reported that hospital admissions due to ADRs account for 4.2-30% in the USA and Canada, 5.7-18.8% in Australia, 2.5-10.6% in Europe, and 6.3% in South Africa(Sultana & Cutroneo, 2013)(U. Mehta et al., 2017)(Masenyetse et al., 2015). In South Africa mortality due to ADRs accounted for 2.5-18% (Mouton et al., 2015). Reporting of ADRs in Africa is in its developing stages with low numbers being reported. Africa has reported 103,499I cases in comparison to 11,824,804 cases reported in the rest of the world, the leading cases reported were ADRs due to antiretrovirals (Ampadu et al., 2016).

2.3. The burden of adverse drug reactions related to HIV in South Africa

HIV/AIDS continues to be among the most deadly diseases ravaging the world, especially in sub-Saharan Africa (World Health Organization, 2015). Globally, approximately 38 million people were living with HIV at the end of 2019 and 1.7 million people were being newly infected annually (Joint United Nations Programme on HIV/AIDS (UNAIDS), 2020).

According to WHO, about 2 million people living with HIV/AIDS died from illnesses related to Acquired Immune Deficiency Syndrome (AIDS) (World Health Organization, 2015).

Midyear population statistics for 2018 in South Africa estimated that 56.52 million people were living within the country (Joint United Nations Programme on HIV/AIDS (UNAIDS), 2020); approximately 7.96 million of these people (19.07%) were living with HIV (Statistics South Africa, 2019)(Joint Uited Nations Programme on HIV/AIDS, 2019). It has been further reported that more than 3 million people (42.5%) were using ARV medicines (Statistics South Africa, 2019).

According to Mouton et al. (2016), limited data exist on the burden of serious ADRs in sub-Saharan Africa, which has a high prevalence of HIV. However, through the expansion of HIV and TB treatment programmes the understanding of the burden of ADRs is improving; approximately 12 medical admissions due to ADRs account for 16% of deaths among adult medical admissions in South Africa (Mehta et al., 2017).

Mehta and colleagues explain that the nature and frequency of ADRs in South Africa differ significantly from other countries; the population structure, burden of disease and the risk profile of commonly used drugs influence this trend (Mehta et al., 2017; Mouton et al., 2016).

Adverse drug reactions such as gastrointestinal disorders, nervous system disorders and psychiatric disorders, are known to be caused by DDI's leading to hospitalization (Mirosevic Skvrce et al., 2011) (Bucşa et al., 2013).

2.3.1 Drug–drug interactions

Drug-drug interactions are one of the leading causes of ADRs (Bucşa et al., 2013). Drug-drug interactions occur when a drug alters the intended pharmacologic intensity and effects of another drug when given concurrently (Mutebi et al., 2013). Drug-related factors, such as polypharmacy, increase the likelihood of DDIs causing ADRs (Alomar, 2014). An adjustment of drug doses for infants and geriatrics is required due to their underdeveloped systems or the decreasing functionality of their organs, respectively.

Health education and counselling are tools that can be used to combat factors that affect DDIs and ADRs (Alomar, 2014). People who are at risk are the elderly, especially those taking up to four or more medications (polypharmacy); they have a 50% chance of experiencing DDIs (Bucşa et al., 2013).

Drug-drug interactions are one of the commonest causes of medication error in developed countries, and ARV medication is among the most therapeutically risky drugs for clinical significant DIs (Kigen et al., 2011). The complexity of DDIs is increased because of the ARV agents, particularly Protease Inhibitors, Non-Nucleotides Reverse Transcriptase Inhibitors and the CCR5 antagonists. Maraviroc, can cause or be affected by alterations in the activity of the CYP P450 enzyme system in the liver as well as by other mechanisms of drug metabolism (De

Maat et al., 2003; Kigen et al., 2011).

2.4 Awareness of Adverse Drug Interactions in Patients Taking Antiretrovirals

The failure of patients to maintain a sense of constant awareness when using medicines can be detrimental and could have potentially fatal consequences (U. C. Mehta, 2011). Becoming more informed and engaged, patients can decrease the likelihood of experiencing medication errors and so avoid DDIs (Mutebi et al., 2013).

A study in Ajiman, United Arab Emirates, reported that the participants had a fair knowledge of DIs and their types, however, most were unaware of the possible interactions between prescribed medications as well as how to manage and prevent DIs when they occurred (Nehad et al, 2013). Creating awareness about ADRs and DDIs is crucial in preventing drug-induced diseases and educating patients to minimise and manage them (Nehad et al., 2013)(Masenyetse et al., 2015)(Mutebi et al., 2013)(Teka et al., 2016).

2.4.1 Antiretrovirals and their adverse drug reactions

Despite the availability of ART and the simplification of treatment options, side effects continue to affect people living with HIV (Seth, 2008). In a study in south-west Nigeria, patients showed a considerable lack of awareness about the short- and long-term side effects of ARVs (Desalu et al., 2013).

According to Reust (2011), there are several interactions between ARVs and other medications that can result in sub-therapeutic or supra-therapeutic concentrations (Rathbun & Liedtke, 2011). ARVs are divided into four classes:

a. Non-nucleoside/non-nucleotide reverse transcriptase inhibitors (NNRTIs)
b. Nucleoside reverse transcriptase inhibitors (NRTIs)
c. Protease inhibitors (PIs)
d. Integrase strand transfer inhibitors (INSTI)

Non-nucleoside reverse transcriptase inhibitors and PIs are prone to DDIs, as they are both metabolised by cytochrome P450 (CYP450) (Reust, 2011); this is a system prone to pharmacokinetic interactions (Pau & Boyd, 2010).

a. Nucleoside and nucleotide reverse transcriptase inhibitors

NRTIs are the pillars of ART. Their adverse effects are associated with lactic acidosis and lipodostrophy (Reust, 2011). These adverse effects present to patients in the form of fatigue, nausea, vomiting, abdominal pains, diarrhoea and uneven fat distribution.

b. Non-nucleoside/nucleotide reverse transcriptase inhibitors

The combination of ART consists of one NNRTI and two NRTIs or PIs. NRTIs are associated

to neuropsychiatric disorders, rash and lipid disorders (Reust, 2011). Patients with co-morbid psychiatric disorders are contraindicated to use Efavirenz, due to its associated hepatotoxicity and resultant liver failure in women with a baseline CD4 cell count of more than 250 mm^3 and in men of more than 400 mm^3 (National Department of Health, 2015).

c. Protease inhibitors

PIs are metabolised by CYP450. They are prone to cause gastrointestinal effects, lipohypertrophy, glucose intolerance or diabetes mellitus and lipid disorders (Reust, 2011). They manifest themselves in the form of diarrhoea, abdominal pains, excessive thirst, frequent urination, constant hunger, and weight gain.

d. Integrase strand transfer inhibitors

Raltegravir is the first drug in this class to be approved for treatment in both treatment-naïve and treatment-experienced patients. Raltegravir, in comparison to Efavirenz, has fewer central nervous and neuropsychiatric problems (He et al., 2015). However, resistance to Raltegravir develops easily and this limits its long-term effectiveness. Common side effects experienced by patients are headache, nausea, vomiting, diarrhoea, insomnia, and fatigue.

2.4.1.1 Regimen combinations

An HIV regimen is composed of ARVs used to treat HIV infection. Regimens are grouped from first line therapy to specialist-initiated therapy. According to WHO, the antiretroviral regimen has been consolidated to accommodate most countries to have the same regimen and seen globally and in Zimbabwe and South Africa (Hirnschall et al., 2013)(Ministry of Health and Child Care, 2018)(South African National Department of Health, 2015).

2.4.1.2 Drug–drug interactions among antiretroviral classes

ARV medicine from the same class is generally avoided with the exception of approved NRTIs and Ritonavir boosting for other PIs (Foy et al., 2014). NNRTIs and PIs are metabolised by CYP450, causing interactions with these classes and other ART metabolised by CYP450 (Reust, 2011). PIs are primarily metabolised by CYP3A4 and are substrates for p-glycoprotein, while NNRTIs are substrates of CYP2B6 and/or CYP3A4 (Rathbun & Liedtke, 2011).

Regimens composed of both PIs and NNRTIs are generally avoided due to evident interactions. INSTI generally exhibits fewer interactions with other ART, as it is metabolized by uridine diphosphate glucuronosyltranferase 1A1 (UGT) (Rathbun & Liedtke, 2011).

2.4.1.3 Drug interactions between antiretrovirals and non-antiretrovirals

Various medications commonly used in primary care settings can exhibit an altered mechanism when used with ARV drugs (Rathbun & Liedtke, 2011). Many patients require additional medication to manage ARV associated adverse effects, such as hyperlipidemia and other co-morbidities (hypertension, diabetes mellitus and tuberculosis) (Pau & Boyd, 2010). DDIs and other medication can occur through various mechanisms. Medication such as Metformin and Isoniazid metabolised by CYP450 can potentially interact with PIs and NNRTIs (Ogu & Maxa, 2000; Rathbun & Liedtke, 2011).

2.4.1.4 Healthcare professionals' and traditional health practitioners' knowledge regarding drug–drug interactions and adverse drug reactions

Most studies have questioned whether healthcare professionals are knowledgeable about DDIs and can counsel patients appropriately when patients purchase medicinal products (Ansari, 2010)(Gilligan et al., 2011)(Harrington et al., 2011). Many drugs are introduced annually, thus making it impractical for physicians to rely on memory alone to avoid potential drug interactions (Ansari, 2010). Clinicians in resource-limited countries see high volumes of patients, have limited reference resources and thus find it difficult to avoid, detect and manage drug interactions (Pau & Boyd, 2010). However, as guardians of patients' health and safety, healthcare professionals have a responsibility to identify and prevent ADRs, making it essential that those who prescribe and dispense medications are educated and knowledgeable about DDIs, their potential to produce ADRs and the subsequent negative patient-related outcomes (Harrington et al., 2011).

One study states that physicians discuss what patients want to hear and not the actual or potential side effects patients may experience (Wylie et al., 2015). Informing patients about DDIs causing side effects and ADRs may result in doing more good than harm (Wells et al., 2013). Ethically, patients need to know the truth about the medication they are taking. Doctors are the first treatment initiators and therefore should inform patients about the possible side effects from the drugs they have been prescribed. Pharmacists can also ensure the safe, appropriate and effective use of medication and counsel patients on side effects when they dispense medication (Iancu et al., 2015).

DDIs during ART are common and often require dose modification to mitigate unwanted adverse events and sustain therapeutic concentrations (Rathbun & Liedtke, 2011). Awareness of the most commonly occurring DDIs should be raised to assist healthcare workers to prevent DDIs and ADRs (Bucşa et al., 2013). Although most HIV clinicians are aware of potential DDIs, many find themselves lacking the knowledge to recognise and manage interactions with confidence (Pau & Boyd, 2010).

Traditional health practitioners selected from two urban and rural areas in KZN were trained and encouraged to help reduce the risk of practices and to provide appropriate information and referral for their patients to consult doctors (Busia, 2010). Traditional healthcare providers should play a role in counselling patients appropriately about the potential of DDIs to cause the possibility of ADRs. People select the medicinal products of traditional healers, disregarding their doctor's advice on conventional medicines, and these products potentially lead to interactions with other pharmaceuticals. If doctors could become allies with traditional healers, the likelihood of DDIs could be reduced (Madamombe, 2006).

References

1. Alomar, M. J. (2014). Factors affecting the development of adverse drug reactions (Review article). *Saudi Pharmaceutical Journal*, *22*(2), 83–94. https://doi.org/10.1016/j.jsps.2013.02.003
2. Ampadu, H. H., Hoekman, J., de Bruin, M. L., Pal, S. N., Olsson, S., Sartori, D., Leufkens, H. G. M., & Dodoo, A. N. O. (2016). Adverse Drug Reaction Reporting in Africa and a Comparison of Individual Case Safety Report Characteristics Between Africa and the Rest of the World: Analyses of Spontaneous Reports in VigiBase®. *Drug Safety*, *39*(4), 335–345. https://doi.org/10.1007/s40264-015-0387-4
3. Ansari, J. A. (2010). Drug Interaction and Pharmacist. *Journal of Young Pharmacists : JYP*, *2*(3), 326–331. https://doi.org/10.4103/0975-1483.66807
4. Bucşa, C., Farcaş, A., Cazacu, I., Leucuta, D., Achimas-Cadariu, A., Mogosan, C., & Bojita, M. (2013). How many potential drug-drug interactions cause adverse drug reactions in hospitalized patients? *European Journal of Internal Medicine*, *24*(1), 27–33. https://doi.org/10.1016/j.ejim.2012.09.011
5. Busia, K. (2010). Regional Strategy on Promoting the Role of TM in Health Systems. *The African Health Monitor*, *14*, 40–46.
6. Davies, E. C., Green, C. F., Mottram, D. R., & Pirmohamed, M. (2010). Interpreting adverse drug reaction (ADR) reports as hospital patient safety incidents. *British Journal of Clinical Pharmacology*, *70*(1), 102–108. https://doi.org/10.1111/j.1365-2125.2010.03671.x
7. De Maat, M. M. R., Corine Ekhart, G., Huitema, A. D. R., Koks, C. H. W., Mulder, J. W., & Beijnen, J. H. (2003). Drug interactions between antiretroviral drugs and comedicated agents. *Clinical Pharmacokinetics*, *42*(3), 223–282. https://doi.org/10.2165/00003088-200342030-00002
8. Desalu, O. O., Onyedum, C. C., Adeoti, A. O., Ozoh, O. B., Fadare, J. O., Salawu, F. K., Danburam, A., Fawibe, A. E., & Adewole, O. O. (2013). Unmet needs in asthma treatment in a resource-limited setting: findings from the survey of adult asthma patients and their physicians in Nigeria. *The Pan African Medical Journal*, *16*(September), 20. https://doi.org/10.11604/pamj.2013.16.20.2798
9. Foy, M., Sperati, C. J., Lucas, G. M., & Estrella, M. M. (2014). Drug interactions and antiretroviral drug monitoring. *Current HIV/AIDS Reports*, *11*(3), 212–222. https://doi.org/10.1007/s11904-014-0212-1

10. Gilligan, A. M., Warholak, T. L., Murphy, J. E., Hines, L. E., & Malone, D. C. (2011). Pharmacy students' retention of knowledge of drug-drug interactions. *American Journal of Pharmaceutical Education*, *75*(6), 110. https://doi.org/10.5688/ajpe756110
11. Harrington, A. R., Warholak, T. L., Hines, L. E., Taylor, A. M., Sherrill, D., & Malone, D. C. (2011). Healthcare professional students' knowledge of drug-drug interactions. *American Journal of Pharmaceutical Education*, *75*(10), 199. https://doi.org/10.5688/ajpe7510199
12. He, Q., Johnston, J., Zeitlinger, J., City, K., & City, K. (2015). *HHS Public Access*. *33*(4), 395–401. https://doi.org/10.1038/nbt.3121.ChIP-nexus
13. Hirnschall, G., Harries, A. D., Easterbrook, P. J., Doherty, M. C., & Ball, A. (2013). The next generation of the World Health Organization's global antiretroviral guidance. *Journal of the International AIDS Society*, *16*, 1–7. https://doi.org/10.7448/IAS.16.1.18757
14. Iancu, M., Bucsa, C., Farcas, A., Leucuta, D., Dincu, A., Mogoșan, C., Dumitrașcu, D. L., & Bojita, M. (2015). Patient???s counselling and management of adverse drug reactions and drug interactions in the community pharmacy. *Farmacia*, *63*(1), 80–85.
15. Joint Uited Nations Programme on HIV/AIDS, 2019. (2019). *HIV and AIDS in South Africa*. 15. https://www.avert.org/professionals/hiv-around-world/sub-saharan-africa/south-africa
16. Joint United Nations Programme on HIV/AIDS (UNAIDS). (2020). *Fact sheet - latest global and regional statistics on the status of the AIDS epidemic*. UNAIDS. https://www.unaids.org/sites/default/files/media_asset/UNAIDS_FactSheet_en.pdf
17. Joshi, A., Shah, N., Mistry, M., & Gor, A. (2015). Evaluation of knowledge and perception toward adverse drug reactions among patients visiting tertiary-care teaching hospital. *National Journal of Physiology, Pharmacy and Pharmacology*, *5*(4), 280–284. https://doi.org/10.5455/njppp.2015.5.2502201543
18. Kaufman, G. (2016). *Adverse drug reactions: classification, susceptibility and reporting.*
19. Kigen, G., Kimaiyo, S., Nyandiko, W., Faragher, B., Sang, E., Jakait, B., Owen, A., Back, D., Gibbons, S., Seden, K., & Khoo, S. H. (2011). Prevalence of potential drug-drug interactions involving antiretroviral drugs in a large kenyan cohort. *PLoS ONE*, *6*(2). https://doi.org/10.1371/journal.pone.0016800
20. Madamombe, I. (2006). Traditional healers boost primary health care. *Africa Renewal Online*, *2006*(January), 10. http://www.un.org/africarenewal/magazine/january-

2006/traditional-healers-boost-primary-health-care

21. Masenyetse, L. J., Manda, S. O., & Mwambi, H. G. (2015). An assessment of adverse drug reactions among HIV positive patients receiving antiretroviral treatment in South Africa. *AIDS Research and Therapy*, *12*, 6. https://doi.org/10.1186/s12981-015-0044-0
22. Mehta, U. C. (2011). Pharmacovigilance : the devastating consequences of not thinking about adverse drug reactions. *Cme*, *29*(6), 247–251.
23. Mehta, U., Kalk, E., Boulle, A., Nkambule, P., Gouws, J., Cohen, K., Medicines, A., Council, C., & Unit, R. (2017). *Pharmacovigilance : A public health priority for South Africa*. *i*, 125–133.
24. Ministry of Health and Child Care. (2018). *Guidelines for Antiretroviral Therapy for the Prevention and Treatment of HIV in Zimbabwe*. *December*.
25. Mirosevic Skvrce, N., Macolic Sarinic, V., Mucalo, I., Krnic, D., Bozina, N., & Tomic, S. (2011). Adverse drug reactions caused by drug-drug interactions reported to Croatian Agency for Medicinal Products and Medical Devices: a retrospective observational study. *Croatian Medical Journal*, *52*(5), 604–614. https://doi.org/10.3325/cmj.2011.52.604
26. Mouton, J. P., Mehta, U., Parrish, A. G., Wilson, D. P. K., Stewart, A., Njuguna, C. W., Kramer, N., Maartens, G., Blockman, M., & Cohen, K. (2015). Mortality from adverse drug reactions in adult medical inpatients at four hospitals in South Africa: A cross-sectional survey. *British Journal of Clinical Pharmacology*, *80*(4), 818–826. https://doi.org/10.1111/bcp.12567
27. Mouton, J. P., Njuguna, C., Kramer, N., Stewart, A., Mehta, U., Blockman, M., Waal, D., Parrish, A. G., Smidt, M. F., Wilson, D. P. K., Igumbor, E. U., Aynalem, G., Dheda, M., Maartens, G., & Cohen, K. (2016). *Adverse Drug Reactions Causing Admission to Medical Wards*. *95*(19), 1–10. https://doi.org/10.1097/MD.0000000000003437
28. Mutebi, A., Warholak, T. L., Hines, L. E., Plummer, R., & Malone, D. C. (2013). Assessing patients' information needs regarding drug-drug interactions. *Journal of the American Pharmacists Association*, *53*(1), 39–45. https://doi.org/10.1331/JAPhA.2013.12038
29. Nehad, M. Hamoudi, Noor, Y. Al-Obaidi, Farman, M. K. (2013). *Drug Interaction Awareness among Public Attending GMCH Ajman/UAE*. www.jbiopharm.com
30. Ogu, C. C., & Maxa, J. L. (2000). Drug interactions due to cytochrome P450. *Proceedings (Baylor University. Medical Center)*, *13*(4), 421–423.

https://doi.org/10.1016/0090-6980(92)90063-Y

31. Pau, A. K., & Boyd, S. D. (2010). Recognition and management of significant drug interactions in HIV patients: challenges in using available data to guide therapy. *Clinical Pharmacology and Therapeutics*, *88*(5), 712–719. https://doi.org/10.1038/clpt.2010.130
32. Rathbun, R. C., & Liedtke, M. D. (2011). Antiretroviral drug interactions: Overview of interactions involving new and investigational agents and the role of therapeutic drug monitoring for management. *Pharmaceutics*, *3*(4), 745–781. https://doi.org/10.3390/pharmaceutics3040745
33. Reust, C. E. (2011). Common adverse effects of antiretroviral therapy for HIV disease. *American Family Physician*, *83*(12), 1443–1451. https://doi.org/d8785 [pii]
34. Seth, A. (2008). Pub Med Central CANADA. *Disabil Rehabil.*, *49*(2), 743–750. https://doi.org/10.1167/iovs.07-1072.Complement-Associated
35. Shepherd, G., Mohorn, P., Yacoub, K., & May, D. W. (2012). Adverse Drug Reaction Deaths Reported in United States Vital Statistics, 1999-2006. *Annals of Pharmacotherapy*, *46*(2), 169–175. https://doi.org/10.1345/aph.1P592
36. South African National Department of Health. (2015). *National Consolidated Guidelines for the Prevention of Mother-To-Child Transmission of HIV (PMTCT) and the Managment of HIV in Children, Adolescents and Adults*. *April*, 1–128.
37. Statistics South Africa. (2019). Mid-year population estimates 2019. *Mid-Year Population Estimates,2019*, *July*.
38. Sultana, J., & Cutroneo, P. M. (2013). *Clinical and economic burden of adverse drug reactions*. *June 2014*. https://doi.org/10.4103/0976-500X.120957
39. Tarekegn, M., Leanne, A., & Colin, C. (2016). Adverse-Drug-Reaction-Related Hospitalisations in Developed and Developing Countries : A Review of Prevalence and Contributing Factors. *Drug Safety*. https://doi.org/10.1007/s40264-016-0444-7
40. Teka, F., Teklay, G., Ayalew, E., & Teshome, T. (2016). Potential drug – drug interactions among elderly patients admitted to medical ward of Ayder Referral Hospital , Northern Ethiopia : a cross sectional study. *BMC Research Notes*, 1–8. https://doi.org/10.1186/s13104-016-2238-5
41. Wells, R. E., Israel, B., Medical, D., & Medical, H. (2013). *NIH Public Access*. *12*(3), 22–29. https://doi.org/10.1080/15265161.2011.652798.To
42. World Health Organization. (2015). Essential medicines and health products. *World Health Organization*, 1–2.

http://www.who.int/medicines/services/essmedicines_def/en/

43. Wylie, B. J., Singh, M. P., Coull, B. A., Quinn, A., Yeboah-, K., Sabin, L., Hamer, D. H., Singh, N., Macleod, W. B., Hospital, M. G., Road, N., Garha, P., Pradesh, M., Road, K., Garha, P., & Pradesh, M. (2015). *HHS Public Access*. *34*(3), 355–368. https://doi.org/10.3109/10641955.2015.1046604.Association

CHAPTER 3
MANUSCRIPT PREPARED FOR JOURNAL PUBLICATION

3.1 Introduction

This chapter presents the manuscript that was prepared and to be submitted to a peer reviewed journal for possible publication. The manuscript, Tlaila M, Ojewole E and Tlou B, "Awareness, attitudes and experiences of patients taking antiretrovirals towards adverse drug reactions at a public health facility in KwaZulu-Natal" was written in the format of the journal for submission. The manuscript is therefore presented according to the author's guidelines of the African Journal of Primary Healthcare and Family Medicine (PHCFM). Author guidelines may be found at https://phcfm.org/index.php/phcfm/pages/view/submission-guidelines.

3.2 Title page for the manuscript

Title: Awareness, attitudes and experiences of patients taking antiretrovirals towards adverse drug reactions at a public health facility in KwaZulu-Natal

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Awareness, attitudes, and experiences of patients taking antiretrovirals towards adverse drug reactions at a public health facility in KwaZulu-Natal

Abstract

Background: Adverse drug reactions (ADRs) are undesirable side effects that occur even when a drug is administered at the proper dose and correctly for an appropriate indication. Given the high prevalence of HIV in South Africa, more than 3 million people are reported to be taking antiretrovirals (ARVs). There is co-morbidity of diseases such as HIV/AIDS with other diseases including tuberculosis, diabetes, and hypertension, which inevitably may lead to polypharmacy, therefore increasing the risk of ADRs. Patients taking ARVs should be aware of the ADRs that may occur in ARV therapy.

Aim: This study aimed to investigate patients' awareness, attitudes, and experiences of ADRs that are precipitated by ARV therapy.

Setting: The study was conducted at a public hospital in KwaZulu-Natal, in South Africa.

Method: This was a descriptive cross-sectional study using a self-administered questionnaire which contained close-ended questions to which patients responded. Questionnaires were available in both English and isiZulu and were hand delivered to patients.

Results: Out of 200 questionnaires, a total of 174 patients responded, which delivered an 87% response rate. Of the 174 respondents, 55%(n=96) were females and 44%(n=78) were males. About 8%(n=13) of respondents were aware of ADRs, they were followed by 9% (n=15) who had experienced them, and only about 12%(n=20) had reported on them. About 8% (n=13) of respondents were aware of ADRs, 55% (n=94) of drug–drug interactions and 12% (n=20) had reported ADRs. About 13% (n=22) respondents reported hypertension, 7% (n=4) respondents reported they were diabetic, and 1% (n=2) respondents reported they had tuberculosis. Around 65% (n=114) respondents were taking the fixed drug combination, while 17% (n=30) were on the lamivudine and zidovudine combination and only 2.3% (n=4) respondents were on ritonavir and atazanavir combinations. About 5% (n=8) respondents experienced vomiting, 1.7% (n=3) of respondents experienced diarrhoea and 1.1% (n=2) respondents experienced a rash.

Conclusion: The awareness of ADRs among patients seemed exceptionally low and needs to be improved by conducting training and in-depth counselling of the patients at each visit to the hospital. Patients need to be aware that ADRs should be reported to their healthcare professionals about the side effects of drug interactions they experience.

Keywords: antiretrovirals, adverse drug reactions, drug–drug interactions, drug–disease interactions, awareness, attitudes, experiences

Introduction

According to HIV/AIDS statistics for South Africa, KwaZulu-Natal Province (KZN) remains the highest rated province for HIV/AIDS cases in South Africa (NDoH, 2015; Statistics South Africa, 2018). Despite the availability of ART and the simplification of treatment options, ADRs continue to affect people living with HIV (Seth, 2008). Adverse drug reactions (ADRs) are undesirable side effects that occur even when a drug is administered at the proper dose and correctly for an appropriate indication (Cao et al., 2015).

Since 2003, ART regimens have changed due to adverse effects, drug interactions and resistance to ARV therapy (Collins et al., 2016; Njuguna et al., 2013). Studies in South Africa and other countries such as Switzerland have shown that ARVs have several well-recorded side effects, which result in the drug regimens of patients having to be changed (Kovari et al., 2013; Mouton et al., 2015). Changes in drug regimens may lead to drug–drug interactions (DDIs), causing ADRs as well as HIV/AIDS-related deaths due to the drug treatments (Abo et al., 2015; Birbal et al., 2016; Mouton et al., 2015).

According to a study done in India it was reported that the awareness of ADRs in patients is limited (Joshi et al., 2015). A study in south-west Nigeria reported lack of awareness about the short- and long-term side effects, which are secondary unwanted effects from a drug and, different from ADRs which are unwanted or unintended reaction occurring during drug therapy (Desalu et al., 2013). It seems as though patients are more accustomed to the term side effects and not ADRs which may be the reason for the lack of awareness regarding ADRs. However, by examining patient records, studies in Saudi Arabia and South Africa have shown that patients have experienced ADRs (Mehta et al., 2017; Sales et al., 2017) although it may not have been reported by patients themselves but healthcare professionals.

In countries such as Sweden, Canada and Denmark systems are in place that enable patients to spontaneously report ADRs. Most countries in Africa, including South Africa, have a long way to go to achieve this type of support (Van Hunsel et al., 2012)(Maigetter et al., 2015). However, in some studies attitudes towards reporting ADRs have been demonstrated to be low irrespective of systems that are in place (Mehta et al., 2017)(Sales et al., 2017).

Aim and Objectives

This study aimed to investigate whether patients taking ARVs in a public health facility in KZN are aware of ADRs; and to determine the experiences and attitudes of patients towards these ADRs. The study was guided by the following objectives:

1. To establish the awareness of patients regarding ADRs of ARVs and other medicines.
2. To determine the awareness of patients regarding drug interactions that result in ADRs.
3. To describe patients' experiences of ADRs caused by their ARVs and other medicines.
4. To determine patients' attitudes towards ADRs caused by ARVs and other medicines.

Research Methods and Design

Study design

This study is a descriptive cross-sectional quantitative study using a questionnaire survey to obtain relevant information from participants. The self-designed structured questionnaire was used to collect quantitative data on awareness, attitudes and experiences of patients taking ARV and non-ARV medication.

Setting

The study was conducted at Clairwood Hospital, which is a district hospital in the eThekwini Municipality in KZN. The hospital has an HIV/AIDS clinic which provides services to people who are referred from tertiary hospitals within their catchment area and to walk-ins. Nurses, doctors, counsellors, dieticians, and pharmacists staff the clinic. Patients were initiated for ART on site when they have been seen by doctors, nurses, and counsellors.

Study Sample and Size

The sample size was calculated from the total population of patients at the study facility. The following statistical parameters were used to determine the sample size: a statistical power of 80%, effect size = 0.25, type 1 (α) error = 0.05 (this is the probability of falsely rejecting the null hypothesis of 5%), type 2 (β) error = 0.2 (this is the probability of falsely failing to reject the null hypothesis of 20%) and statistical power (1- β) = 0.8 (80%), calculated using Raosoft®, 2017. Based on the above statistical parameters, a minimum sample size of 180 was determined.

Inclusion and Exclusion Criteria

Inclusion criteria

All patients who fulfilled the following criteria were included:

- Those who consented to participate
- Those who were 18 years and older
- Those who were collecting their own medication
- Those who were literate in isiZulu and/or English

Exclusion criteria

All patients who fell in the categories listed below were excluded:

- All patients who did not consent
- Patients who were under the age of 18 years
- Patients whose families, friends or supporters were collecting their medicines on their behalf
- Patients who were not literate in English and IsiZulu

Data Collection Process

Data were collected using self-administered questionnaires. Three places where patients could be informed about the study were identified: the main waiting room and two separate waiting rooms outside the nurses' rooms. Two nurses assisted in collecting the data. One worked with the staff and the other worked with patients. The terms, such as ADR and DDI, were explained to patients because these terms could not be successfully translated into isiZulu.

A structured questionnaire was developed and administered to the participants, and consisted of four main sections:

A. Participants' socio-demographic characteristics
B. (i) Awareness of ADRs; and
   (ii) Awareness of drug interactions leading to ADRs
C. Experiences of ADRs caused by ARVs and other medicines
D. Attitudes towards ADRs caused by ARVs and other medicines.

***Data* Analysis**

Data were analysed using SPSS version 25. Frequency variables were established through data input. Valid percentages were calculated, and the report compiled.

Ethical Considerations and Confidentiality

A consent form clearly outlining the nature of the study and the enrolment for their approval to join the study was made available to all the participants. Participants had to indicate if they were willing to be a part of the study by signing a consent form. Participation was completely voluntary, and no patients were coerced into participating in the study. Patient confidentiality was maintained throughout the study. No personal information was requested, and questionnaires were identified by numbers and not by patient names. The study was approved by the Humanities and Social Sciences Research Ethics Committee with a reference number HSS/2120/017M.

Results

Socio-demographic characteristics of the participants

A total of 174 out of the 200 questionnaires issued out were completed and returned by the participants which gave a response rate of 87%. Of the 174 participants, 55.2% (*n*=96) were responded they were females and 44.8% (*n*=78) were males. The majority of the participants were in the age group 31–40 years. Regarding the participants' racial distribution in this study, 98.3% (n=171) responded they were blacks and 1.7% (*n*=3) were coloureds. Most of the participants 44.3% (*n* =77) responded that they had completed schooling at the primary school level and 25.3% (*n*=44) had completed Matric. Other levels of education reported by participants were as shown in Table 1.

TABLE 1

Socio-demographic characteristics of the participants (N = 174)

Variables	**Number of participants (*n*)**	**Percent (%)**
Age group		
21–30 years	37	21.3
31–40 years	68	39.1
41–50 years	48	27.6
Above 51 years	21	12.0
Total	174	100.0
Gender		
Male	78	44.8
Female	96	55.2
Total	174	100.0
Race		
Black	171	98.3
Coloured	3	1.7
Total	174	100.0
Level of education		
Primary school	77	44.3
Matric	44	25.3
Diploma	16	9.2
Bachelor	3	1.7
Certificate	32	18.4
No education	2	1.1

Total	174	100.0
Employment status		
Unemployed	84	48.3
Employed	87	50.0
Missing data*	03	1.7
Total	174	100.0
Diagnosis		
HIV	174	100
Diabetic	7	4.0
Hypertension	22	12.6
Tuberculosis	2	1.1
Cholesterol	7	4.0
Epilepsy	1	0.6

Key: ** indicates data was missing due to participants who did not report on employment status*

Awareness of participants regarding ADRs of ARVs

Of the 174 participants who were asked if they were aware of ADRs of ARVs, 98.8% (n=172) responded to the question (Table 2). Of those who responded to the question, only 13 (7.6%) participants said "Yes", they were aware of ADRs of ARVs. Of the 174 participants who were asked if they were aware of DIs causing ADRs, 97.7% (n=170) responded to the question. Of those participants, about 55% (n=94) agreed that they were aware of DIs causing the ADRs of ARVs (Table 2). In addition, participants were asked about the types of DIs causing ADRs, and all the 174 participants responded except for one participant who did not respond regarding drug-drug interactions (Table 2). About 32% (n=56) of participants agreed that they were aware of drug-herb interaction and other participants also reported awareness of other types of DIs as shown in Table 2.

Further, an alarmingly high proportion of participants (n= 153, 93.9%) were not aware of what causes ADRs. With regards to what causes ADRs, the participants were asked to choose between "taking other medication with ARV", "eating certain foods with ARV", "taking herbs with ARV" as well as "medication overdose". Of the 174 participants, only 9.2% (n=16) recognized ARV-herb interaction (AHI) due to taking herbs with ARV as a cause of ADR, and 2.3% (n=4) agreed to medicine overdose as causing ADR. This shows that majority of the participants could not identify causes of ADRs.

TABLE 2

Participants' awareness about ADRs and DIs of ARVs

	Frequency		**Percentage**	
	n	%	n	%
Statement	**Yes**		**No**	
	N	%	*N*	%
Are you aware of ADRs? (n=172)*	13	7.6	159	92.4
Are you aware of DIs? (n=170)*	94	55.3	76	44.7
Types of drug interactions				
Drug–drug interactions (n=173)*	26	15.0	147	84.5
Drug–food interactions (N=174)	16	9.2	158	90.8
Drug–herb interactions (N= 174)	56	32.2	117	67.2
Drug–disease interactions (N=174)	14	8.1	160	91.9

Key: ** indicates data was missing due to participants who did not respond to the question*

Attitudes and experiences of participants regarding ADRs of ARVs

Of the 174 participants in this study, about 95% (n=166) responded to the statement on "have you experienced any ADRs?". Of those who responded to the statement, 9% (n=15) reported that they had experienced ADRs. Some of the participants who experienced ADRs reported vomiting (n=8, 4.6%), and diarrhoea (n=3, 1.7%), both of which were the commonly reported gastrointestinal ADRs as seen in Table 3. About 12% (n=20) of the 167 participants who responded to "Have you reported an ADR?" agreed to have reported an ADR. This shows that many of the participants do not report the ADRs they experienced from their ARVs. The participants mainly reported to the nurses and very small proportion reported ADR to the pharmacists.

About 8% (n= 14) of the participants reported that they received counselling on ADR as shown in Table 3. The pharmacy department was mostly chosen as where ADRs can be reported by 7% (n=12) of the 172 participants who responded to the question (Table 3).

TABLE 3

Participants' attitudes and experiences regarding ADRs of ARVs.

Statements	**Yes**		**No**	
	N	%	*N*	%
Have you experienced an ADR? (n=166)*	15	9	151	91
Which ADR you experienced? (N=174)				

Kidney failure	1	0.6	173	99.4
Low CD4 count	1	0.6	173	99.4
Rash	2	1.1	172	98.9
Diarrhoea	3	1.7	171	98.3
Vomiting	8	4.6	166	95.4
Unexplainable weight gain	1	0.6	173	99.4
Dizziness	1	0.6	173	99.4
Have you reported an ADR? (n=167)*	20	12	147	88
How often?				
Weekly (n =173)*	0	0	173	100
Monthly (n=173)*	0	0	173	100
Few times a year (n=173)*	21	12.1	152	87.9
Never (n=173)*	3	1.7	170	98.3
To whom did you report it?				
Nurse (n=172)*	16	9.3	156	90.7
Doctor (n=173)*	10	5.8	163	94.2
Pharmacist (n=172)*	3	1.7	169	98.3
What happened after you reported? (n=173)**				
ADR form was completed	3	1.7	170	98.3
Counselling	14	8.1	159	91.9
Medication was changed	2	1.2	171	98.8
Nothing was done	2	1.2	171	98.8
Where do you think ADRs can be reported? (N=174)				
Pharmacy department (n=172)*	12	7.0	160	93.0
MCC** (N=173)*	2	1.2	171	98.8
Drug company (N=173)*	2	1.2	171	98.8
Department of Health (N=173)*	5	2.9	168	97.1

Key: ** indicates data was missing due to participants who did not respond to the question ; ** The medicine control council (MCC) has since changed name to South African Health and Products Regulatory Authority (SAHPRA).*

Discussion

Socio-demographic characteristics

The study included both males and females and most of the participants were aged 31–40 years. The majority of the participants were blacks (98.3%, n=171) and others were coloured (1.7%, n=3). There were no participants representing the racial groups as expected regarding race and ethnic distribution in

South Africa and this could be due to the site at which the study was conducted. Over 40% of participants had not completed their schooling and had dropped out of schooling while in primary school. About 25.3% (n=44) had matriculated, some had achieved certificates in courses conducted to further their education and a few had proceeded to get a diploma or a bachelor's degree. The drop out from schooling could be due to substance abuse, teenage pregnancy, financial constraints and other academic issues (Weybright et al., 2017). The study reported that almost an average number of the participants were unemployed. At the time the study was conducted, the unemployment rate was high at 29% in South Africa, according to the South African Labour Force Survey (Statistics South Africa, 2019). However, unemployment in the study was recorded at 48.3%. Based on the total number of the participants, it is understandable why the rate is higher than the national unemployment rate.

Awareness of adverse drug reactions in patients taking antiretrovirals

Notwithstanding co-morbidity resulting in polypharmacy leading to DDIs and ADRs, only a low proportion of participants (7.6%, n= 13) were aware of ADRs of ARVs in this study (Table 2). This result is similar to a study reported in Nigeria (Desalu et al., 2013) but in contrast to the findings in Saudi Arabia where higher proportion of participants were aware of ADRs (Sales et al., 2017). Lack of awareness regarding ADRs is a major concern. ARVs present with ADRs, such as Steven Johnson Syndrome (SJS), which is a severe skin reaction that requires immediate medical attention (Chateau et al., 2019). If patients are not aware that a minor rash may rapidly develop into a severe condition, they may not report the reaction or consider it important enough to report. This increase the concerns that the awareness among participants was low regarding the DIs of ARVs and non-ARVs.

Patients also lack awareness of non-ARV medicines that interact with ARVs. Awareness regarding ADRs or the lack thereof may result from the absence of counselling about the term "ADR". According to Joshi et al 2015, a "side effect" is a term commonly used with patients more than "ADRs", and suggested that the terms may be interchangeable (Joshi et al., 2015). The interchangeable use of the terms may therefore be a contributing factor to the lack of awareness regarding ADRs which further implicates the low level of awareness among the participants in this study. Interestingly, studies that used the term "side effects" in investigating awareness of ADRs still recorded low levels of awareness (Desalu et al., 2013; Sales et al., 2017). This shows that it is important to educate patients on the terms side effects and ADRs to increase awareness of the terms among the patients regarding their medications. Furthermore, a high proportion of participants were unaware of what causes ADRs. The lack of awareness of ADRs and the causes thereof may lead to increased hospitalisations and death of patients taking ARVs, which could be prevented (Mouton et al., 2015). It is therefore necessary to counsel patients on possible causes of ADRs to prevent fatalities, improve ART and ensure patients safety.

Patients' awareness of drug interactions causing adverse drug reactions

There were four types of DIs that the participants were asked to identify which of them they were aware of. Drug–herb interactions (DHI)_were the DIs most recognised by the participants, followed by drug-drug interactions (DDI). Although DHI was mostly recognized by the participants, however, the proportion of the participants who recognized the DHI was relatively low. This study finding is similar to the study reported by Nehad et al 2013, where participants in their study had reported low recognition of DHIs (Nehad et al., 2013). The patients on ARVs may present with co-morbidities, thus their drug intake may increase (Kovari et al., 2013). This may increase the likelihood of the co-administration of herbal medicines resulting in increased drug–herb interactions (Moreira et al., 2014). It is important that patients know about DHIs and be counselled on them to prevent ADRs.

Similar to the proportion of participants who recognized DHI, a relatively lower proportion of participants recognised DDIs. The potential of DDIs is common among elderly patients as they do experience DDIs when taking several medications (Teka et 2016). , To deal with the resulting ADRs due to DDIs, patients often take other medications without checking the problem of DDI when medicines are co-administered with their chronic medication (Bucşa et al., 2013) Healthcare professionals should do all they can to deal with ADRs due to polypharmacy (Ansari, 2010; Bucşa et al., 2013; Teka et al., 2016). The low awareness of the different types of DIs leading to ADRs requires that drug information and drug interaction centres be established to address the seriousness of DDIs and ADRs (Mutebi et al., 2013).

Drug–food interactions (DFI) occur when food and medicine interfere with each other (Bushra et al., 2011). A low percentage of participants (9.2%, n=16) were aware of DFIs. Drugs such as Abacavir are better taken on an empty stomach to increase absorption; when taken on a full stomach, absorption is reduced (Fadare et al., 2011). Patients need to be made aware of when to take their medicines with or without food. Patients with chronic kidney disease (CKD) are further compromised when taking drugs such as Tenofovir, because the drug are harmful to the kidneys and it will exacerbate the CKD (Muaed J.A. 2014). Thus, patients should be made aware that tenofovir needs to be changed to a suitable drug that will not further compromise the kidneys.

Patients may not be aware of relevant health terminologies and information known by the healthcare professionals. It is therefore it is necessary to improve the awareness of patients regarding different terminologies and information in health, particularly ADRs, DDIs, DHIs, DFIs as well as drug-disease interactions which may create a more medically conscious and health informed community.

Patients' experiences of adverse drug reactions

Only a small percentage of patients (9%) indicated that they have experienced ADRs. This may be due to patients being more aware of the term "side effects" than "adverse drug reactions" (Gupta et al., 2015). Studies in India, Nigeria and South Africa reported that the experience of ADRs and reporting is low among both the healthcare professionals and patients (Abah et al., 2019; Ampadu et al., 2016; Desai et al., 2011). These findings are similar to the results in this study. Further, retrospective studies

have investigated the most common types of ADRs experienced by patients on ART (Birbal et al., 2016). However, based on the findings of this study, the question stands as to whether patients are aware of experiencing ADRs or if they thought of the ADRs as common side effects that do not require reporting. Patients need to be told that they are experiencing ADRs and an explanation of what that means and how it will be managed must be presented to the patients. For example, if patients react to Nevirapine and experience SJS, they need to be told which drug caused the ADRs and how it will be changed so that they are aware and that their adherence to their drug regimens is not compromised.

Patient's attitudes towards adverse drug reactions and ADR reporting

The reporting of ADRs should not be left solely in the care of healthcare professionals including nurses, doctors, and pharmacists. Patients should be introduced to reporting ADRs and should be given access to the reporting system. Only 12% of patients in this study have reported ADRs. These reports were mainly made to nurses rather than doctors and the pharmacists. This is different to studies in Saudi Arabia and Nigeria which found that respondents reported their ADRs more to doctors than to nurses (Joshi et al., 2011; Sales et al., 2017). The reason why the participants mainly reported ADRs to the nurses and very small proportion reported to the pharmacists may be due to the fact that the patients collect medications from the nurses rather than the pharmacists.

There are numerous ways ADRs can be reported by patients, starting with informing a doctor, a nurse a pharmacist or spontaneous reporting. The study showed that majority of participants did not receive counselling about ADRs of ARVs after they have reported them. Patients are not aware of ADR reporting (Sales et al., 2017) and this remains a cause for concern.

It is undeniable that every year thousands of medications are introduced into the market (Nehad et al., 2013). Patients who are on prescribed medication such as ARVs have access to medication which has not been prescribed such as over the counter medication or herbal supplements.

Ingestion of one or multiple ARV medications may lead to undesirable side effects. Unavoidably, the ingestion of multiple medications due to co-morbidities increases the likelihood of patients experiencing undesirable effects that ultimately result in ADRs. Therefore, being aware of ADRs and their causes may help to minimise hospitalisations and unwarranted death.

Conclusion

This study revealed that participants' awareness of ADRs to ARVs and other medicines was low. The patients' attitudes towards reporting ADRs due to DDIs was poor, and not many patients reported experiences of ADRs regarding ARVs and other medicines. This may be due to lack of awareness regarding ADRs. It may also be due to the fact that participants could have been counselled using the term "side effects" more than "adverse drug reactions". This could have resulted in participants' lack of reporting ADRs they have experienced. Creating awareness about ADRs and what causes them through educating and counselling patients could be achieved by creating and placing educational

posters around healthcare facilities. Patients can read the posters while waiting to collect their medicines which could then create awareness for them . Reporting of ADRs by patients to health care professionals and spontaneous reporting should be taught and encouraged. This will help to reduce the increasing yearly rates of morbidity and mortality due to ADRs in patients taking ARVs and other medicines. This study revealed the need for ADRs reporting especially among patients, which will increase pharmacovigilance database that will further assist in monitoring the ADRs and side effects of medicines that were not previously reported during clinical trials.

References

1. Abah, I. O., Ncube, N. B. Q., Bradley, H. A., AgbaJi, O. O., & Kanki, P. (2019). Antiretroviral Therapy-associated Adverse Drug Reactions and their Effects on Virologic Failure- A Retrospective Cohort Study in Nigeria. *Current HIV Research*, *16*(6), 436–446. https://doi.org/10.2174/1389450120666190214144609
2. Abo, Y., Zannou Djimon, M., Messou, E., Balestre, E., Kouakou, M., Akakpo, J., Ahouada, C., de Rekeneire, N., Dabis, F., Lewden, C., & Minga, A. (2015). Severe morbidity after antiretroviral (ART) initiation: active surveillance in HIV care programs, the IeDEA West Africa collaboration. *BMC Infectious Diseases*, *15*(1), 176. https://doi.org/10.1186/s12879-015-0910-3
3. Ampadu, H. H., Hoekman, J., de Bruin, M. L., Pal, S. N., Olsson, S., Sartori, D., Leufkens, H. G. M., & Dodoo, A. N. O. (2016). Adverse Drug Reaction Reporting in Africa and a Comparison of Individual Case Safety Report Characteristics Between Africa and the Rest of the World: Analyses of Spontaneous Reports in VigiBase®. *Drug Safety*, *39*(4), 335–345. https://doi.org/10.1007/s40264-015-0387-4
4. Ansari, J. A. (2010). Drug Interaction and Pharmacist. *Journal of Young Pharmacists : JYP*, *2*(3), 326–331. https://doi.org/10.4103/0975-1483.66807
5. Birbal, S., Dheda, M., Ojewole, E., & Oosthuizen, F. (2016). Adverse drug reactions associated with antiretroviral therapy in South Africa. *African Journal of AIDS Research*, *15*(3), 243–248. https://doi.org/10.2989/16085906.2016.1191519
6. Cao, D.-S., Xiao, N., Li, Y.-J., Zeng, W.-B., Liang, Y.-Z., Lu, A.-P., Xu, Q.-S., & Chen, A. F. (2015). Integrating Multiple Evidence Sources to Predict Adverse Drug Reactions Based on a Systems Pharmacology Model. *CPT: Pharmacometrics & Systems Pharmacology*, *4*(9), 498–506. https://doi.org/10.1002/psp4.12002
7. Collins, S. E., Grant, P. M., & Shafer, R. W. (2016). Modifying Antiretroviral Therapy in Virologically Suppressed HIV-1-Infected Patients. *Drugs*, *76*(1), 75–98. https://doi.org/10.1007/s40265-015-0515-6
8. Desai, C. K., Iyer, G., Panchal, J., Shah, S., & Dikshit, R. K. (2011). An evaluation of knowledge, attitude, and practice of adverse drug reaction reporting among prescribers at a tertiary care hospital. *Perspect Clin Res*, *2*(4), 129–136. https://doi.org/10.4103/2229-3485.86883
9. Desalu, O. O., Onyedum, C. C., Adeoti, A. O., Ozoh, O. B., Fadare, J. O., Salawu, F. K., Danburam, A., Fawibe, A. E., & Adewole, O. O. (2013). Unmet needs in asthma treatment in a resource-limited setting: findings from the survey of adult asthma patients and their physicians in Nigeria. *The Pan African Medical Journal*, *16*(September), 20. https://doi.org/10.11604/pamj.2013.16.20.2798
10. Fadare, J. O., Enwere, O. O., Afolabi, A. O., Chedi, B. A. Z., & Musa, A. (2011). Knowledge,

attitude and practice of adverse drug reaction reporting among healthcare workers in a tertiary centre in Northern Nigeria. *Tropical Journal of Pharmaceutical Research*, *10*(3), 235–242. https://doi.org/10.4314/tjpr.v10i3.4

11. Gupta, S. K., Nayak, R. P., Shivaranjani, R., & Vidyarthi, S. K. (2015). A questionnaire study on the knowledge, attitude, and the practice of pharmacovigilance among the healthcare professionals in a teaching hospital in South India. *Perspectives in Clinical Research*, *6*(1), 45–52. https://doi.org/10.4103/2229-3485.148816
12. Joshi, A., Shah, N., Mistry, M., & Gor, A. (2015). Evaluation of knowledge and perception toward adverse drug reactions among patients visiting tertiary-care teaching hospital. *National Journal of Physiology, Pharmacy and Pharmacology*, *5*(4), 280–284. https://doi.org/10.5455/njppp.2015.5.2502201543
13. Kovari, H., Sabin, C. A., Ledergerber, B., Ryom, L., Worm, S. W., Smith, C., Phillips, A., Reiss, P., Fontas, E., Petoumenos, K., De Wit, S., Morlat, P., Lundgren, J. D., & Weber, R. (2013). Antiretroviral drug-related liver mortality among HIV-positive persons in the absence of hepatitis B or C virus coinfection: The data collection on adverse events of anti-HIV drugs study. *Clinical Infectious Diseases*, *56*(6), 870–879. https://doi.org/10.1093/cid/cis919
14. Maigetter, K., Pollock, A. M., Kadam, A., Ward, K., & Weiss, M. G. (2015). Pharmacovigilance in India, Uganda and South Africa with reference to WHO's minimum requirements. *Int J Health Policy Manag*, *4*(5), 295–305. https://doi.org/10.15171/ijhpm.2015.55
15. Mehta, U., Kalk, E., Boulle, A., Nkambule, P., Gouws, J., Cohen, K., Medicines, A., Council, C., & Unit, R. (2017). *Pharmacovigilance : A public health priority for South Africa*. *i*, 125–133.
16. Moreira, D. de L., Teixeira, S. S., Monteiro, M. H. D., De-Oliveira, A. C. A. X., & Paumgartten, F. J. R. (2014). Traditional use and safety of herbal medicines. *Brazilian Journal of Pharmacognosy*, *24*(2), 248–257. https://doi.org/10.1016/j.bjp.2014.03.006
17. Mouton, J. P., Mehta, U., Parrish, A. G., Wilson, D. P. K., Stewart, A., Njuguna, C. W., Kramer, N., Maartens, G., Blockman, M., & Cohen, K. (2015). Mortality from adverse drug reactions in adult medical inpatients at four hospitals in South Africa: A cross-sectional survey. *British Journal of Clinical Pharmacology*, *80*(4), 818–826. https://doi.org/10.1111/bcp.12567
18. Mutebi, A., Warholak, T. L., Hines, L. E., Plummer, R., & Malone, D. C. (2013). Assessing patients' information needs regarding drug-drug interactions. *Journal of the American Pharmacists Association*, *53*(1), 39–45. https://doi.org/10.1331/JAPhA.2013.12038
19. National Department of Health. (2015). *Hiv & aids 2014/15 data fact sheet 9-12*. *June*, 2014–2015.
20. Nehad, M. Hamoudi, Noor, Y. Al-Obaidi, Farman, M. K. (2013). *Drug Interaction Awareness among Public Attending GMCH Ajman/UAE*. www.jbiopharm.com

21. Njuguna, C., Orrell, C., Kaplan, R., Bekker, L. G., Wood, R., & Lawn, S. D. (2013). Rates of Switching Antiretroviral Drugs in a Primary Care Service in South Africa before and after Introduction of Tenofovir. *PLoS ONE*, *8*(5), 1–7. https://doi.org/10.1371/journal.pone.0063596
22. Sales, I., Aljadhey, H., Albogami, Y., & Mahmoud, M. A. (2017). Public awareness and perception toward Adverse Drug Reactions reporting in Riyadh, Saudi Arabia. *Saudi Pharmaceutical Journal*, *25*(6), 868–872. https://doi.org/10.1016/j.jsps.2017.01.004
23. Seth, A. (2008). Pub Med Central CANADA. *Disabil Rehabil.*, *49*(2), 743–750. https://doi.org/10.1167/iovs.07-1072.Complement-Associated
24. Statistics South Africa. (2019). Quarterly Labour Force Survey Quarter 2:2019. *Quarterly Labour Force Survey*, *PO211*(July), 1–70. https://www.statssa.gov.za/publications/P03022019.pdf
25. Stats SA Mid Year population estimates. (2018). *South African Stats SA Mid-year population estimates 2018*. *July*. www.statssa.gov.zainfo@statssa.gov.za
26. Teka, F., Teklay, G., Ayalew, E., & Teshome, T. (2016). Potential drug – drug interactions among elderly patients admitted to medical ward of Ayder Referral Hospital , Northern Ethiopia : a cross sectional study. *BMC Research Notes*, 1–8. https://doi.org/10.1186/s13104-016-2238-5
27. Van Hunsel, F., Härmark, L., Pal, S., Olsson, S., & Van Grootheest, K. (2012). Experiences with adverse drug reaction reporting by patients: An 11-country survey. *Drug Safety*, *35*(1), 45–60. https://doi.org/10.2165/11594320-000000000-00000

CHAPTER 4
SYNTHESIS AND CONCLUSIONS

4.1 Introduction

While several studies have assessed the knowledge and attitudes of health workers regarding ADRs, only few studies have investigated patients' knowledge and attitudes about ADRs particularly while taking ARVs. As at the time of writing this dissertation, there has been no study found in the literature on awareness, attitudes, and experiences of ADRs among patients taking ARVs, particularly among patients at a public health facility in KwaZulu-Natal. This dissertation aimed at determining patients' awareness, attitudes, and experiences of ADRs among patients taking ARVs. The study specifically targeted patients who were taking ARVs and possibly non-ARV medicines due to co-morbidities that exist among this category of patients. This chapter therefore reports on the findings that support the overall aim of the study conducted at the selected public hospital in eThekwini, KwaZulu-Natal, South Africa. The relevant key findings were discussed in the manuscript chapter (chapter 3) that was prepared and is to be submitted to a journal for publication. The synthesis chapter (chapter four) further shows the extent to which each objective was met by briefly presenting the main findings and conclusions. The significance and limitations of the study were highlighted, and recommendations for future research and practice were provided.

4.2 The study aim, objectives, and highlights of key findings

The aim of the study was to determine the awareness of, attitudes towards and experiences of adverse drug reactions due to antiretrovirals among patients taking ARVs at a public health facility in KZN.

4.2.1 The study objectives were:

1. To establish the awareness of patients regarding ADRs due to ARVs and other medicines.
2. To determine the awareness of patients regarding drug interactions that result in ADRs of ARVs and other medicines.
3. To describe patients' experiences of ADRs resulting from ARVs and other medicines.
4. To determine patients' attitudes towards ADRs to ARVs and other medicines.

4.2.2 The highlights of the key findings of the study

The socio demographic characteristic of the participants

The study reported on both males and females with the majority aged between 31–40 years. Although the male to female ratio was not 50%, the target was not far off with 44.8% (n=78) males and 55.2%

(n=96) females. Based on the site where the study was conducted, most participants were black 98.3% (n=171) and 1.7% (n=3) were coloured. Over 40% of participants (n=77)had not completed their schooling and had dropped out while in primary school; however, 25.3% (n=44) had matriculated.

According to the Labour Force Survey in South Africa, the unemployment rate was 29% during the period which this study was conducted (Statistics South Africa, 2019). However, in this study, unemployment was 49.1%. Based on the limited total number of participants, it is notably understandable why the rate is higher than the national rate of unemployment. The employed participants included those who are self-employed and/or working part-time jobs.

The patients taking ARVs in this study also had diabetes (4%), hypertension (12.6%), tuberculosis (1.1%), epilepsy (0.5%) and cholesterol (4%). This increases the possibility of numerous drugs being taken simultaneously and thus increases the potential of DDIs leading to ADRs.

Objective 1. To establish the awareness of patients regarding ADRs due to ARVs and other medicines.

Notwithstanding co-morbidity resulting in polypharmacy leading to DDIs and ADRs, a significantly low percentage of patients (8%) are aware of ADRs. In contrast, a study in Saudi Arabia reported a fair percentage of patients being aware of ADRs, while a study in Nigeria also reported a low percentage of awareness in patients (Desalu et al., 2013; Sales et al., 2017). Lack of awareness of ADRs is concerning.

The presence of ARVs with ADRs, such as SJS, increases concerns for awareness of ARV and DIs. Patients in this study lack awareness of non-ARV medicines that interact with ARV medications. Awareness regarding ADRs and the lack thereof may result from the absence of counselling and the knowledge of the terminology about ADRs. “Side effects” is a term commonly used with patients more so than “ADRs” which may be a contributing factor to the lack of awareness of ADRs (Joshi et al., 2015). Only a few patients were aware of what causes ADRs. The lack of awareness of patients regarding ADRs and the causes thereof may lead to increased hospitalisations and death which could have been prevented (Mouton et al., 2015). Awareness of what ADRs are but not being aware of what causes ADRs still remains a challenge. For instance, patients taking Nevirapine are aware that it can cause an ADR, but might not be aware that Nevirapine causes an SJS reaction.

Objective 2 To determine the awareness of patients regarding drug interactions that result in ADRs of ARVs and other medicines

DDIs can result in ADRs that require hospitalisation (Bucşa et al., 2013). DDIs are one of four types of drug interactions. Patients were asked to identify the type of drug interactions of which they were aware.

A low proportion of patients (15%) were aware of DDIs. It is common for patients to experience side effects when taking medication and to deal with those side effects without checking if they can be co-administered with their chronic medication (Ansari, 2010; Bucşa et al., 2013; Teka et al., 2016).

Drug–herb interactions were the highest recognised drug interactions by patients – 32% (n=55). People on ARVs who may present with co-morbidities increase their drug intake (Kovari et al., 2013). This increases the likelihood of herbal medicines being co-administered and results in increased drug–herb interactions (Moreira et al., 2014). In addition, most food groups consist of herbs such as garlic. Greater awareness of ADRs due to herbal medicine is required (Hamoudi et al., 2013).

Drug–food interactions occur when food and medicine interfere with each other. A low percentage of patients (9%, n=16) are aware of drug–food interactions. Drugs such as Abacavir are better taken on an empty stomach to increase absorption; when taken on a full stomach, absorption is reduced (Fadare et al., 2011). Increasing the awareness and better understanding of patients regarding how food interacts and interferes with the efficacy of their medication will assist in achieving therapeutic objectives.

Drug–disease interactions were the lowest recognised with only 8% (n=14) of patients demonstrating awareness. The awareness of the different types of DIs leading to a ADRs remains low, therefore DDI centres should be established to address the seriousness of DDIs and ADRs (Mutebi et al., 2013).

Objective 3 To describe patients' experiences of ADRs resulting from their ARVs and other medicines.

Only a small percentage of patients (9%) indicate that they have experienced ADRs. This may be owing to the fact that patients may be commonly aware of the term "side effects" over "ADRs" (Gupta et al., 2015). Studies in India, Nigeria and South Africa reported lack of awareness of ADRs and the reporting by both healthcare professionals and patients (Abah et al., 2019; Ampadu et al., 2016; Desai et al., 2011). Therefore, numerous patients may be experiencing ADRs more than that which is being reported. The most common types of ADRs experienced by patients on ART have been reported (Birbal et al., 2016). However, based on the findings of this study, the question stands as to whether patients are aware that they have experienced ADRs or whether they simply brush them off as common side effects that do not require further investigation or reporting.

Objective 4 To determine patients' attitudes towards ADRs of ARVs and other medicines.

Only 12% of patients have reported ADRs. There are numerous ways ADRs can be reported, such as informing a doctor, a nurse, a pharmacist, or spontaneous reporting by patients. Patients are not aware of ADR reporting systems that are in place let alone how to report ADRs individually (Sales et al.,

2017). Patients attitudes regarding reporting on ADRs of ARVs and other medication is low. It can be argued that patients do not see it necessary to report due to increased number side effects ARVs presented with (Van der Walt et al., 2013), therefore they probably feel it's expected and something they should be able to live with considering the nature of the immune compromising virus.

4.3 Significance of the study

This study has revealed lack of patients' awareness regarding ADRs of ARVs and other medicines. The attitudes towards and experiences of ADRs reporting among patients was poor suggesting the need to encourage ADR reporting among patients taking ARVs.

The study also showed the need for healthcare professionals to strengthen patient education regarding ADRs of ARVs, as well as ADR reporting.

There is also a need for development of antiretroviral stewardship policies that will guide the monitoring and counselling of patients taking ARVs, particularly in preventing ADRs, promoting patient's safety and optimizing ARV therapy.

The findings of the study will guide the planning of educational programmes for the patients, particularly to create awareness about ADRs of ARVs as well as ADRs due to DDIs among patients with coexisting disease conditions.

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4.4 Limitations

The study was conducted in one public healthcare facility within the eThekwini district, in the KZN province hence the study findings cannot be generalized to all patients taking ARVs in KZN and the whole of South Africa.

It was challenging to get patients to participate and consent due to the sensitivity of HIV as the disease condition being treated with ARVs. However, once confidentiality and anonymity were explained, patients were willing to give consent and participate in the study.

The use of questionnaires could have limited the interpretation of the study findings as the study relied on the information that the respondents provided which could have been subjected to recall bias and the information could have been exaggerated during the completion of the questionnaires

4.5 Recommendations

The lack of awareness regarding ADRs in patients makes it imperative to develop a platform to increase patients' awareness. Educating patients on the terms "ADRs" and "side effects" simultaneously is encouraged. It is important to make patients aware of how to report ADRs. Patients should be at liberty to express each ailment they experience when taking their ARV and non-ARV medication. Upon medication being introduced, especially for the first time, patients should be thoroughly counselled on

the side effects and ADRs they may experience when ingesting the medication. Upon follow-up visits, patients should be encouraged to express any new experiences which they experienced during the duration of the treatment. Patients should be made aware of spontaneous reporting systems that are in place. These should be made accessible and facilitate reporting irrespective of their educational level and language constraints of patients.

Healthcare professionals should be reminded on the importance of counselling patients each time they consult them and monitor patients' adherence to medication. The pharmacists could establish antiretroviral use monitoring whereby follow-up protocol is designed for checking how patients are progressing since their last appointment, identify any misunderstandings to their treatments and make further assessments during patients' visits to the health facilities.

Similar studies should be conducted across other health districts in South Africa in order to understand the status of ADRs awareness and ADRs reporting among patients ARVs. Such studies may be extended to both private and public healthcare facilities. The risk of the possible DDIs among patients who are taking ARVs as well as other medicines due to their co-existing diseases could be investigated.

4.6 Overall Conclusion

This study revealed that participants awareness of ADRs to ARVs and other medicines were low. The participants attitudes towards reporting ADRs due to DDIs was poor, as not many participants reported experiences of ADRs regarding ARVs and other medicines. The poor awareness and reporting of ADRs may be due to low spontaneous reporting of ADRs by participants. Participants responses were low regarding awareness of ADRs reporting and how they can actively participate in reporting ADRs. It seems as though they rely on healthcare professionals to complete the ADR forms and hand them in. Furthermore, side effects and ADRs were used interchangeably, which could have caused confusion thereby acting as barriers to ADR reporting. Creating awareness about ADRs and what causes them through educating and counselling patients could be achieved by creating and placing educational posters around healthcare facilities. Patients can read the posters while waiting to collect their medicines which could then create awareness for them .Reporting of ADRs by patients to health care professionals and spontaneous reporting should be taught and encouraged. This will help to reduce the increasing yearly rates of morbidity and mortality due to ADRs in patients taking ARVs and other medicines. This study has revealed the need of ADRs reporting especially by patients, which will increase pharmacovigilance database that will further assist in monitoring the ADRs and side effects of medicines that were previously not reported during clinical trials. An in-depth investigation of ADRs of ARVs among patients is recommended to get a better understanding of how patients can handle ADRs and ADR reporting.

References

1. Abah, I. O., Ncube, N. B. Q., Bradley, H. A., AgbaJi, O. O., & Kanki, P. (2019). Antiretroviral Therapy-associated Adverse Drug Reactions and their Effects on Virologic Failure- A Retrospective Cohort Study in Nigeria. *Current HIV Research*, *16*(6), 436–446. https://doi.org/10.2174/1389450120666190214144609
2. Ampadu, H. H., Hoekman, J., de Bruin, M. L., Pal, S. N., Olsson, S., Sartori, D., Leufkens, H. G. M., & Dodoo, A. N. O. (2016). Adverse Drug Reaction Reporting in Africa and a Comparison of Individual Case Safety Report Characteristics Between Africa and the Rest of the World: Analyses of Spontaneous Reports in VigiBase®. *Drug Safety*, *39*(4), 335–345. https://doi.org/10.1007/s40264-015-0387-4
3. Ansari, J. A. (2010). Drug Interaction and Pharmacist. *Journal of Young Pharmacists : JYP*, *2*(3), 326–331. https://doi.org/10.4103/0975-1483.66807
4. Birbal, S., Dheda, M., Ojewole, E., & Oosthuizen, F. (2016). Adverse drug reactions associated with antiretroviral therapy in South Africa. *African Journal of AIDS Research*, *15*(3), 243–248. https://doi.org/10.2989/16085906.2016.1191519
5. Bucşa, C., Farcaş, A., Cazacu, I., Leucuta, D., Achimas-Cadariu, A., Mogosan, C., & Bojita, M. (2013). How many potential drug-drug interactions cause adverse drug reactions in hospitalized patients? *European Journal of Internal Medicine*, *24*(1), 27–33. https://doi.org/10.1016/j.ejim.2012.09.011
6. Desai, C. K., Iyer, G., Panchal, J., Shah, S., & Dikshit, R. K. (2011). An evaluation of knowledge, attitude, and practice of adverse drug reaction reporting among prescribers at a tertiary care hospital. *Perspect Clin Res*, *2*(4), 129–136. https://doi.org/10.4103/2229-3485.86883
7. Desalu, O. O., Onyedum, C. C., Adeoti, A. O., Ozoh, O. B., Fadare, J. O., Salawu, F. K., Danburam, A., Fawibe, A. E., & Adewole, O. O. (2013). Unmet needs in asthma treatment in a resource-limited setting: findings from the survey of adult asthma patients and their physicians in Nigeria. *The Pan African Medical Journal*, *16*(September), 20. https://doi.org/10.11604/pamj.2013.16.20.2798
8. Fadare, J. O., Enwere, O. O., Afolabi, A. O., Chedi, B. A. Z., & Musa, A. (2011). Knowledge, attitude and practice of adverse drug reaction reporting among healthcare workers in a tertiary centre in Northern Nigeria. *Tropical Journal of Pharmaceutical Research*, *10*(3), 235–242. https://doi.org/10.4314/tjpr.v10i3.4
9. Gupta, S. K., Nayak, R. P., Shivaranjani, R., & Vidyarthi, S. K. (2015). A questionnaire study on the knowledge, attitude, and the practice of pharmacovigilance among the healthcare professionals in a teaching hospital in South India. *Perspectives in Clinical Research*, *6*(1), 45–52. https://doi.org/10.4103/2229-3485.148816

10. Joshi, A., Shah, N., Mistry, M., & Gor, A. (2015). Evaluation of knowledge and perception toward adverse drug reactions among patients visiting tertiary-care teaching hospital. *National Journal of Physiology, Pharmacy and Pharmacology*, *5*(4), 280–284. https://doi.org/10.5455/njppp.2015.5.2502201543
11. Kovari, H., Sabin, C. A., Ledergerber, B., Ryom, L., Worm, S. W., Smith, C., Phillips, A., Reiss, P., Fontas, E., Petoumenos, K., De Wit, S., Morlat, P., Lundgren, J. D., & Weber, R. (2013). Antiretroviral drug-related liver mortality among HIV-positive persons in the absence of hepatitis B or C virus coinfection: The data collection on adverse events of anti-HIV drugs study. *Clinical Infectious Diseases*, *56*(6), 870–879. https://doi.org/10.1093/cid/cis919
12. Moreira, D. de L., Teixeira, S. S., Monteiro, M. H. D., De-Oliveira, A. C. A. X., & Paumgartten, F. J. R. (2014). Traditional use and safety of herbal medicines. *Brazilian Journal of Pharmacognosy*, *24*(2), 248–257. https://doi.org/10.1016/j.bjp.2014.03.006
13. Mouton, J. P., Mehta, U., Parrish, A. G., Wilson, D. P. K., Stewart, A., Njuguna, C. W., Kramer, N., Maartens, G., Blockman, M., & Cohen, K. (2015). Mortality from adverse drug reactions in adult medical inpatients at four hospitals in South Africa: A cross-sectional survey. *British Journal of Clinical Pharmacology*, *80*(4), 818–826. https://doi.org/10.1111/bcp.12567
14. Mutebi, A., Warholak, T. L., Hines, L. E., Plummer, R., & Malone, D. C. (2013). Assessing patients' information needs regarding drug-drug interactions. *Journal of the American Pharmacists Association*, *53*(1), 39–45. https://doi.org/10.1331/JAPhA.2013.12038
15. Nehad, M. Hamoudi, Noor, Y. Al-Obaidi, Farman, M. K. (2013). *Drug Interaction Awareness among Public Attending GMCH Ajman/UAE*. www.jbiopharm.com
16. Sales, I., Aljadhey, H., Albogami, Y., & Mahmoud, M. A. (2017). Public awareness and perception toward Adverse Drug Reactions reporting in Riyadh, Saudi Arabia. *Saudi Pharmaceutical Journal*, *25*(6), 868–872. https://doi.org/10.1016/j.jsps.2017.01.004
17. Statistics South Africa. (2019). Quarterly Labour Force Survey Quarter 2:2019. *Quarterly Labour Force Survey*, *PO211*(July), 1–70. https://www.statssa.gov.za/publications/P03022019.pdf
18. Teka, F., Teklay, G., Ayalew, E., & Teshome, T. (2016). Potential drug – drug interactions among elderly patients admitted to medical ward of Ayder Referral Hospital , Northern
19.
20. Ethiopia : a cross sectional study. *BMC Research Notes*, 1–8. https://doi.org/10.1186/s13104-016-2238-5
21. Van der Walt, M., Lancaster, J., Odendaal, R., Davis, J. G., Shean, K., & Farley, J. (2013). Serious Treatment Related Adverse Drug Reactions amongst Anti-Retroviral Naïve MDR-TB Patients. *PLoS ONE*, *8*(4). https://doi.org/10.1371/journal.pone.0058817

BIBLIOGRAPHY

1. Abah, I. O., Ncube, N. B. Q., Bradley, H. A., AgbaJi, O. O., & Kanki, P. (2019). Antiretroviral Therapy-associated Adverse Drug Reactions and their Effects on Virologic Failure- A Retrospective Cohort Study in Nigeria. *Current HIV Research*, *16*(6), 436–446. https://doi.org/10.2174/1389450120666190214144609
2. Abo, Y., Zannou Djimon, M., Messou, E., Balestre, E., Kouakou, M., Akakpo, J., Ahouada, C., de Rekeneire, N., Dabis, F., Lewden, C., & Minga, A. (2015). Severe morbidity after antiretroviral (ART) initiation: active surveillance in HIV care programs, the IeDEA West Africa collaboration. *BMC Infectious Diseases*, *15*(1), 176. https://doi.org/10.1186/s12879-015-0910-3
3. Alomar, M. J. (2014). Factors affecting the development of adverse drug reactions (Review article). *Saudi Pharmaceutical Journal*, *22*(2), 83–94. https://doi.org/10.1016/j.jsps.2013.02.003
4. Ampadu, H. H., Hoekman, J., de Bruin, M. L., Pal, S. N., Olsson, S., Sartori, D., Leufkens, H. G. M., & Dodoo, A. N. O. (2016). Adverse Drug Reaction Reporting in Africa and a Comparison of Individual Case Safety Report Characteristics Between Africa and the Rest of the World: Analyses of Spontaneous Reports in VigiBase®. *Drug Safety*, *39*(4), 335–345. https://doi.org/10.1007/s40264-015-0387-4
5. Ansari, J. A. (2010). Drug Interaction and Pharmacist. *Journal of Young Pharmacists : JYP*, *2*(3), 326–331. https://doi.org/10.4103/0975-1483.66807
6. Birbal, S., Dheda, M., Ojewole, E., & Oosthuizen, F. (2016). Adverse drug reactions associated with antiretroviral therapy in South Africa. *African Journal of AIDS Research*, *15*(3), 243–248. https://doi.org/10.2989/16085906.2016.1191519
7. Bogolubova, S., Padayachee, N., & Schellack, N. (2018). Knowledge, attitudes and practices of nurses and pharmacists towards adverse drug reaction reporting in the South African private hospital sector. *Health SA Gesondheid*, *23*, 1–9. https://doi.org/10.4102/hsag.v23i0.1064
8. Brown, M. T., & Bussell, J. K. (2011). Medication Adherence: WHO Cares? *Mayo Clinic Proceedings*, *86*(4), 304–314. https://doi.org/10.4065/mcp.2010.0575
9. Bucşa, C., Farcaş, A., Cazacu, I., Leucuta, D., Achimas-Cadariu, A., Mogosan, C., & Bojita, M. (2013). How many potential drug-drug interactions cause adverse drug reactions in hospitalized patients? *European Journal of Internal Medicine*, *24*(1), 27–33. https://doi.org/10.1016/j.ejim.2012.09.011
10. Busia, K. (2010). Regional Strategy on Promoting the Role of TM in Health Systems. *The African Health Monitor*, *14*, 40–46.
11. Cao, D.-S., Xiao, N., Li, Y.-J., Zeng, W.-B., Liang, Y.-Z., Lu, A.-P., Xu, Q.-S., & Chen, A. F. (2015). Integrating Multiple Evidence Sources to Predict Adverse Drug Reactions Based on a

Systems Pharmacology Model. *CPT: Pharmacometrics & Systems Pharmacology*, *4*(9), 498–506. https://doi.org/10.1002/psp4.12002

12. Collins, S. E., Grant, P. M., & Shafer, R. W. (2016). Modifying Antiretroviral Therapy in Virologically Suppressed HIV-1-Infected Patients. *Drugs*, *76*(1), 75–98. https://doi.org/10.1007/s40265-015-0515-6
13. Davies, E. C., Green, C. F., Mottram, D. R., & Pirmohamed, M. (2010). Interpreting adverse drug reaction (ADR) reports as hospital patient safety incidents. *British Journal of Clinical Pharmacology*, *70*(1), 102–108. https://doi.org/10.1111/j.1365-2125.2010.03671.x
14. Davis, J. L., Dowdy, D. W., den Boon, S., Walter, N. D., Katamba, A., & Cattamanchi, A. (2012). Test and Treat. In *JAIDS Journal of Acquired Immune Deficiency Syndromes* (Vol. 61, Issue 1, pp. e6–e8). https://doi.org/10.1097/qai.0b013e3182614bc5
15. De Maat, M. M. R., Corine Ekhart, G., Huitema, A. D. R., Koks, C. H. W., Mulder, J. W., & Beijnen, J. H. (2003). Drug interactions between antiretroviral drugs and comedicated agents. *Clinical Pharmacokinetics*, *42*(3), 223–282. https://doi.org/10.2165/00003088-200342030-00002
16. Desai, C. K., Iyer, G., Panchal, J., Shah, S., & Dikshit, R. K. (2011). An evaluation of knowledge, attitude, and practice of adverse drug reaction reporting among prescribers at a tertiary care hospital. *Perspect Clin Res*, *2*(4), 129–136. https://doi.org/10.4103/2229-3485.86883
17. Desalu, O. O., Onyedum, C. C., Adeoti, A. O., Ozoh, O. B., Fadare, J. O., Salawu, F. K., Danburam, A., Fawibe, A. E., & Adewole, O. O. (2013). Unmet needs in asthma treatment in a resource-limited setting: findings from the survey of adult asthma patients and their physicians in Nigeria. *The Pan African Medical Journal*, *16*(September), 20. https://doi.org/10.11604/pamj.2013.16.20.2798
18. Edwards, I. R., & Aronson, J. K. (2000). Adverse drug reactions: definitions, diagnosis, and management. *Lancet (London, England)*, *356*(9237), 1255–1259. https://doi.org/10.1016/S0140-6736(00)02799-9
19. Fadare, J. O., Enwere, O. O., Afolabi, A. O., Chedi, B. A. Z., & Musa, A. (2011). Knowledge, attitude and practice of adverse drug reaction reporting among healthcare workers in a tertiary centre in Northern Nigeria. *Tropical Journal of Pharmaceutical Research*, *10*(3), 235–242. https://doi.org/10.4314/tjpr.v10i3.4
20. Foy, M., Sperati, C. J., Lucas, G. M., & Estrella, M. M. (2014). Drug interactions and antiretroviral drug monitoring. *Current HIV/AIDS Reports*, *11*(3), 212–222. https://doi.org/10.1007/s11904-014-0212-1
21. Gilligan, A. M., Warholak, T. L., Murphy, J. E., Hines, L. E., & Malone, D. C. (2011). Pharmacy students' retention of knowledge of drug-drug interactions. *American Journal of Pharmaceutical Education*, *75*(6), 110. https://doi.org/10.5688/ajpe756110

22. Gupta, S. K., Nayak, R. P., Shivaranjani, R., & Vidyarthi, S. K. (2015). A questionnaire study on the knowledge, attitude, and the practice of pharmacovigilance among the healthcare professionals in a teaching hospital in South India. *Perspectives in Clinical Research*, *6*(1), 45–52. https://doi.org/10.4103/2229-3485.148816
23. Harrington, A. R., Warholak, T. L., Hines, L. E., Taylor, A. M., Sherrill, D., & Malone, D. C. (2011). Healthcare professional students' knowledge of drug-drug interactions. *American Journal of Pharmaceutical Education*, *75*(10), 199. https://doi.org/10.5688/ajpe7510199
24. He, Q., Johnston, J., Zeitlinger, J., City, K., & City, K. (2015). *HHS Public Access*. *33*(4), 395–401. https://doi.org/10.1038/nbt.3121.ChIP-nexus
25. Hirnschall, G., Harries, A. D., Easterbrook, P. J., Doherty, M. C., & Ball, A. (2013). The next generation of the World Health Organization's global antiretroviral guidance. *Journal of the International AIDS Society*, *16*, 1–7. https://doi.org/10.7448/IAS.16.1.18757
26. Iancu, M., Bucsa, C., Farcas, A., Leucuta, D., Dincu, A., Mogoșan, C., Dumitrașcu, D. L., & Bojita, M. (2015). Patient???s counselling and management of adverse drug reactions and drug interactions in the community pharmacy. *Farmacia*, *63*(1), 80–85.
27. Joint Uited Nations Programme on HIV/AIDS, 2019. (2019). *HIV and AIDS in South Africa*. 15. https://www.avert.org/professionals/hiv-around-world/sub-saharan-africa/south-africa
28. Joint United Nations Programme on HIV/AIDS (UNAIDS). (2020). *Fact sheet - latest global and regional statistics on the status of the AIDS epidemic*. UNAIDS. https://www.unaids.org/sites/default/files/media_asset/UNAIDS_FactSheet_en.pdf
29. Joshi, A., Shah, N., Mistry, M., & Gor, A. (2015). Evaluation of knowledge and perception toward adverse drug reactions among patients visiting tertiary-care teaching hospital. *National Journal of Physiology, Pharmacy and Pharmacology*, *5*(4), 280–284. https://doi.org/10.5455/njppp.2015.5.2502201543
30. Kaufman, G. (2016). *Adverse drug reactions: classification, susceptibility and reporting.*
31. Kigen, G., Kimaiyo, S., Nyandiko, W., Faragher, B., Sang, E., Jakait, B., Owen, A., Back, D., Gibbons, S., Seden, K., & Khoo, S. H. (2011). Prevalence of potential drug-drug interactions involving antiretroviral drugs in a large kenyan cohort. *PLoS ONE*, *6*(2). https://doi.org/10.1371/journal.pone.0016800
32. Kovari, H., Sabin, C. A., Ledergerber, B., Ryom, L., Worm, S. W., Smith, C., Phillips, A., Reiss, P., Fontas, E., Petoumenos, K., De Wit, S., Morlat, P., Lundgren, J. D., & Weber, R. (2013). Antiretroviral drug-related liver mortality among HIV-positive persons in the absence of hepatitis B or C virus coinfection: The data collection on adverse events of anti-HIV drugs study. *Clinical Infectious Diseases*, *56*(6), 870–879. https://doi.org/10.1093/cid/cis919
33. Madamombe, I. (2006). Traditional healers boost primary health care. *Africa Renewal Online*, *2006*(January), 10. http://www.un.org/africarenewal/magazine/january-2006/traditional-healers-boost-primary-health-care

34. Maddison, J. E., & Page, S. W. (2008). *Small Animal Clinical Pharmacology* (pp. 41–58).
35. Maigetter, K., Pollock, A. M., Kadam, A., Ward, K., & Weiss, M. G. (2015). Pharmacovigilance in India, Uganda and South Africa with reference to WHO's minimum requirements. *Int J Health Policy Manag*, *4*(5), 295–305. https://doi.org/10.15171/ijhpm.2015.55
36. Masenyetse, L. J., Manda, S. O., & Mwambi, H. G. (2015). An assessment of adverse drug reactions among HIV positive patients receiving antiretroviral treatment in South Africa. *AIDS Research and Therapy*, *12*, 6. https://doi.org/10.1186/s12981-015-0044-0
37. Mehta, U. C. (2011). Pharmacovigilance : the devastating consequences of not thinking about adverse drug reactions. *Cme*, *29*(6), 247–251.
38. Mehta, U., Kalk, E., Boulle, A., Nkambule, P., Gouws, J., Cohen, K., Medicines, A., Council, C., & Unit, R. (2017). *Pharmacovigilance : A public health priority for South Africa*. *i*, 125–133.
39. Miller, V., Nwokike, J., & Stergachis, A. (2012). Pharmacovigilance and global HIV/AIDS. *Current Opinion in HIV and AIDS*, *7*(4), 299–304. https://doi.org/10.1097/COH.0b013e328354d8e7
40. Ministry of Health and Child Care. (2018). *Guidelines for Antiretroviral Therapy for the Prevention and Treatment of HIV in Zimbabwe*. *December*.
41. Mirosevic Skvrce, N., Macolic Sarinic, V., Mucalo, I., Krnic, D., Bozina, N., & Tomic, S. (2011). Adverse drug reactions caused by drug-drug interactions reported to Croatian Agency for Medicinal Products and Medical Devices: a retrospective observational study. *Croatian Medical Journal*, *52*(5), 604–614. https://doi.org/10.3325/cmj.2011.52.604
42. Moreira, D. de L., Teixeira, S. S., Monteiro, M. H. D., De-Oliveira, A. C. A. X., & Paumgartten, F. J. R. (2014). Traditional use and safety of herbal medicines. *Brazilian Journal of Pharmacognosy*, *24*(2), 248–257. https://doi.org/10.1016/j.bjp.2014.03.006
43. Mouton, J. P., Mehta, U., Parrish, A. G., Wilson, D. P. K., Stewart, A., Njuguna, C. W., Kramer, N., Maartens, G., Blockman, M., & Cohen, K. (2015). Mortality from adverse drug reactions in adult medical inpatients at four hospitals in South Africa: A cross-sectional survey. *British Journal of Clinical Pharmacology*, *80*(4), 818–826. https://doi.org/10.1111/bcp.12567
44. Mouton, J. P., Njuguna, C., Kramer, N., Stewart, A., Mehta, U., Blockman, M., Waal, D., Parrish, A. G., Smidt, M. F., Wilson, D. P. K., Igumbor, E. U., Aynalem, G., Dheda, M., Maartens, G., & Cohen, K. (2016). *Adverse Drug Reactions Causing Admission to Medical Wards*. *95*(19), 1–10. https://doi.org/10.1097/MD.0000000000003437
45. Murphy, R. A., Sunpath, H., Kuritzkes, D. R., Venter, F., & Gandhi, R. T. (2007). Antiretroviral Therapy–Associated Toxicities in the Resource-Poor World: The Challenge of a Limited Formulary. *The Journal of Infectious Diseases*, *196*(s3), S449–S456. https://doi.org/10.1086/521112

46. Mutebi, A., Warholak, T. L., Hines, L. E., Plummer, R., & Malone, D. C. (2013). Assessing patients' information needs regarding drug-drug interactions. *Journal of the American Pharmacists Association*, *53*(1), 39–45. https://doi.org/10.1331/JAPhA.2013.12038
47. National Department of Health. (2003). *Operational Plan for Comprehensive HIV and Aids Care, Management and Treatment for South Africa*. *October*, 1–40.
48. National Department of Health. (2015). *Hiv & aids 2014/15 data fact sheet 9-12*. *June*, 2014–2015.
49. Nehad, M. Hamoudi, Noor, Y. Al-Obaidi, Farman, M. K. (2013). *Drug Interaction Awareness among Public Attending GMCH Ajman/UAE*. www.jbiopharm.com
50. Njuguna, C., Orrell, C., Kaplan, R., Bekker, L. G., Wood, R., & Lawn, S. D. (2013). Rates of Switching Antiretroviral Drugs in a Primary Care Service in South Africa before and after Introduction of Tenofovir. *PLoS ONE*, *8*(5), 1–7. https://doi.org/10.1371/journal.pone.0063596
51. Ogu, C. C., & Maxa, J. L. (2000). Drug interactions due to cytochrome P450. *Proceedings (Baylor University. Medical Center)*, *13*(4), 421–423. https://doi.org/10.1016/0090-6980(92)90063-Y
52. Pate, P. P., Gandhi, A. M., Desai, C. K., Desai, M. K., & Dikshit, R. K. (2012). An analysis of drug induced Stevens-Johnson syndrome. In *Indian Journal of Medical Research* (Vol. 136, Issue 6, pp. 1051–1053).
53. Pau, A. K., & Boyd, S. D. (2010). Recognition and management of significant drug interactions in HIV patients: challenges in using available data to guide therapy. *Clinical Pharmacology and Therapeutics*, *88*(5), 712–719. https://doi.org/10.1038/clpt.2010.130
54. Pirmohamed, M., Breckenridge, A. M., Kitteringham, N. R., & Park, B. K. (1998). Adverse drug reactions. *BMJ: British Medical Journal (International Edition)*, *316*(7140), 1295–1298.
55. Pirmohamed, M., Ostrov, D. a, & Park, B. K. (2015). New genetic findings lead the way to a better understanding of fundamental mechanisms of drug hypersensitivity. *The Journal of Allergy and Clinical Immunology*, *136*(2), 236–244. https://doi.org/10.1016/j.jaci.2015.06.022
56. Plumpton, C. O., Roberts, D., Pirmohamed, M., & Hughes, D. A. (2016). A Systematic Review of Economic Evaluations of Pharmacogenetic Testing for Prevention of Adverse Drug Reactions. *PharmacoEconomics*. https://doi.org/10.1007/s40273-016-0397-9
57. Rathbun, R. C., & Liedtke, M. D. (2011). Antiretroviral drug interactions: Overview of interactions involving new and investigational agents and the role of therapeutic drug monitoring for management. *Pharmaceutics*, *3*(4), 745–781. https://doi.org/10.3390/pharmaceutics3040745
58. Reust, C. E. (2011). Common adverse effects of antiretroviral therapy for HIV disease. *American Family Physician*, *83*(12), 1443–1451. https://doi.org/d8785 [pii]
59. Sales, I., Aljadhey, H., Albogami, Y., & Mahmoud, M. A. (2017). Public awareness and perception toward Adverse Drug Reactions reporting in Riyadh, Saudi Arabia. *Saudi*

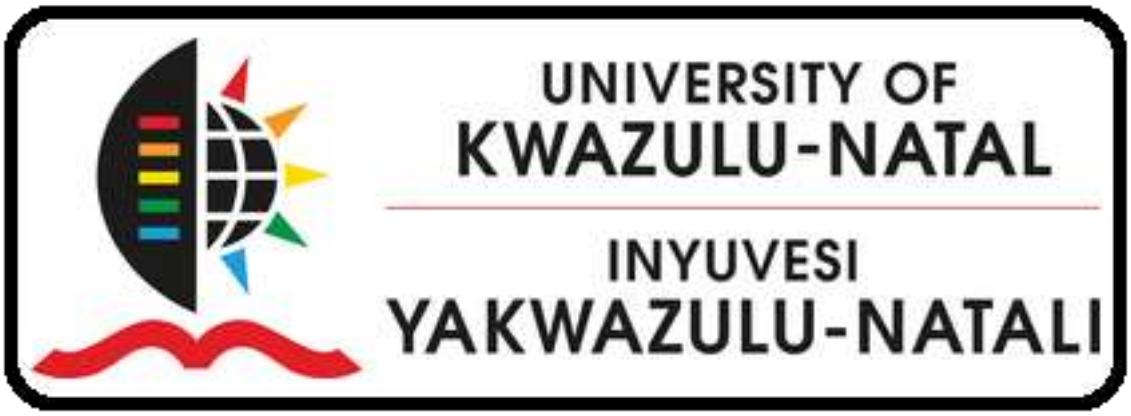
Pharmaceutical Journal, *25*(6), 868–872. https://doi.org/10.1016/j.jsps.2017.01.004

60. Seth, A. (2008). Pub Med Central CANADA. *Disabil Rehabil.*, *49*(2), 743–750. https://doi.org/10.1167/iovs.07-1072.Complement-Associated
61. Shatz, S. ., & Weber, R. J. (2015). Adverse drug reactions. *Legal Medicine.*, 229–267. https://scholar.google.co.za/scholar?hl=en&as_sdt_0%2C5&as_vis=1&q=adverse+drug+reactions shatz&btnG=#d=gs_qabs&u=%3D_vb05Tb_LIQJ
62. Shepherd, G., Mohorn, P., Yacoub, K., & May, D. W. (2012). Adverse Drug Reaction Deaths Reported in United States Vital Statistics, 1999-2006. *Annals of Pharmacotherapy*, *46*(2), 169–175. https://doi.org/10.1345/aph.1P592
63. South African National Department of Health. (2015). *National Consolidated Guidelines for the Prevention of Mother-To-Child Transmission of HIV (PMTCT) and the Managment of HIV in Children, Adolescents and Adults*. *April*, 1–128.
64. Statistics South Africa. (2019a). Mid-year population estimates 2019. *Mid-Year Population Estimates,2019*, *July*.
65. Statistics South Africa. (2019b). Quarterly Labour Force Survey Quarter 2:2019. *Quarterly Labour Force Survey*, *PO211*(July), 1–70. https://www.statssa.gov.za/publications/P03022019.pdf
66. Stats SA Mid Year population estimates. (2018). *South African Stats SA Mid-year population estimates 2018*. *July*. www.statssa.gov.zainfo@statssa.gov.za
67. Sultana, J., & Cutroneo, P. M. (2013). *Clinical and economic burden of adverse drug reactions*. *June 2014*. https://doi.org/10.4103/0976-500X.120957
68. Tarekegn, M., Leanne, A., & Colin, C. (2016). Adverse-Drug-Reaction-Related Hospitalisations in Developed and Developing Countries : A Review of Prevalence and Contributing Factors. *Drug Safety*. https://doi.org/10.1007/s40264-016-0444-7
69. Teka, F., Teklay, G., Ayalew, E., & Teshome, T. (2016). Potential drug – drug interactions among elderly patients admitted to medical ward of Ayder Referral Hospital , Northern Ethiopia : a cross sectional study. *BMC Research Notes*, 1–8. https://doi.org/10.1186/s13104-016-2238-5
70. Tseng, A., & Foisy, M. (2012). Important drug-drug interactions in HIV-infected persons on antiretroviral therapy: An update on new interactions between HIV and Non-HIV drugs. *Current Infectious Disease Reports*, *14*(1), 67–82. https://doi.org/10.1007/s11908-011-0229-1
71. Van der Walt, M., Lancaster, J., Odendaal, R., Davis, J. G., Shean, K., & Farley, J. (2013). Serious Treatment Related Adverse Drug Reactions amongst Anti-Retroviral Naïve MDR-TB Patients. *PLoS ONE*, *8*(4). https://doi.org/10.1371/journal.pone.0058817
72. Van Hunsel, F., Härmark, L., Pal, S., Olsson, S., & Van Grootheest, K. (2012). Experiences with adverse drug reaction reporting by patients: An 11-country survey. *Drug Safety*, *35*(1), 45–60. https://doi.org/10.2165/11594320-000000000-00000

73. Walker, L., Yip, V., Pirmohamed, M., & Padmanabhan, S. (2014). Chapter 20 – Adverse Drug Reactions. In *Handbook of Pharmacogenomics and Stratified Medicine* (pp. 405–435). https://doi.org/10.1016/B978-0-12-386882-4.00020-7
74. Wells, R. E., Israel, B., Medical, D., & Medical, H. (2013). *NIH Public Access*. *12*(3), 22–29. https://doi.org/10.1080/15265161.2011.652798.To
75. World Health Organization. (2015). Essential medicines and health products. *World Health Organization*, 1–2. http://www.who.int/medicines/services/essmedicines_def/en/
76. Wylie, B. J., Singh, M. P., Coull, B. A., Quinn, A., Yeboah-, K., Sabin, L., Hamer, D. H., Singh, N., Macleod, W. B., Hospital, M. G., Road, N., Garha, P., Pradesh, M., Road, K., Garha, P., & Pradesh, M. (2015). *HHS Public Access*. *34*(3), 355–368. https://doi.org/10.3109/10641955.2015.1046604.Association

APPENDICES

Appendix A: Questionnaire



Questionnaire

Awareness, attitudes, and experiences of patients taking antiretroviral towards adverse drug reactions at public health facility in KwaZulu-Natal

This study is aimed to create awareness about adverse drug reactions and drug interactions amongst patients taking antiretroviral therapy and other medication.

Researchers name: Malebogo Tlaila	Code: _____

A. Participants' characteristics

1. Age (in years)

1. > 20 ☐ 2. 21-30 ☐ 3. 31-40☐ 4. 41-50☐ 5. Above 51 ☐

2. Gender

1. Male ☐ 2. Female ☐

3.Race

1. Black ☐

2. White ☐

3. Coloured ☐

4. Indian ☐

5. Other (Please specify)

_____

3. Weight (kg)

1. 40-60 ☐ 2. 61-80☐ 3. 81-99 ☐ 4.Above 100 ☐

5. Level of education achieved

1. Primary School ☐

2. Matric ☐

3. Diploma ☐

4. Bachelor ☐

5. Certificate ☐

6. No education ☐

7. Other (Please specify)

_____

6. Employment status

1. Unemployed ☐
2. Self-employed ☐
3. Fully employed ☐

7. If answered employed to question 6 above, Please indicate occupation

1. Street vendor ☐

2. Domestic worker ☐

3. Gardner ☐

4. Teacher ☐

5. Nurse ☐

6. Other (Please specify)

_____

8. If unemployed, please indicate other sources of income

1. No skill ☐

2. Semi-skilled ☐

3. Skilled ☐

4. Other (Please specify)

_____

9. Disease- conditions you are being treated

9.1 HIV/AIDS ☐

9.2 Diabetes ☐

9.3 Hypertension ☐

9.4 Tuberculosis ☐

9.5 Cholesterol ☐

9.6 Other (Please Specify)

_____

10. Can you identify the medication you are on?

1. Yes ☐

2. No ☐

11. If yes to question 10 above, please indicate the type of medication you are taking

11.a) Antiretroviral Medication	**Please Tick**
1 FDC/Atroiza/®Odiomune® (Efavirenz 600mg |+ Emtricitabine 200mg + Tenofovir 300mg)	
2 Dumiva® Abacavir 300 mg + Lamivudine 150 mg	
3. Lamzid®/Duranavir® Lamivudine 150 mg + Zidovudine 300 mg	
4. Aluvia® 200/50mg	
5. Efavirenz 600 mg	
6.Nevirapine 200mg	

7. Tenofovir 300 mg	
8. Ritonavir 100mg	
9. Atazanavir 150 mg	
10. Zidovudine 300 mg	

11. b) Tuberculosis (TB) Medication	
1. Rifafour®	
2. Rifinah®	
3. Rifampicin	
4. Pyrazinamide	
5. Ethionamide	
6.Other (Please specify):	

11. c) Diabetic Medication	
1. Metformin	
2. Glimepiride	
3. Glibenclamide	
4. Other (Please specify):	

11. d) Hypertension Medication	
1.Hydrochlorothiazide	
2. Furosemide	
3. Enalapril	
4. Amlodipine	

5. Atenolol	
6.Other (Please Specify)	

11. d) Cholesterol Medication	
1. Simvastatin	
2. Atorvastatin	
3. Bezafibrate	
4. Other (Please specify):	

12. Has the antiretroviral medication you are taking been changed since you have been taking them?

1. Yes ☐

2. No ☐

3. Not sure ☐

13. If yes to question 10 above, who changed the antiretroviral medication?

1. Doctor ☐

2. Nurse ☐

3. Other (Please specify)

_____

14. Please reason indicate reason for changing the antiretroviral medication (You can tick more than one)

14.1 Treatment failure ☐

14.2 Side effects ☐

14.3 Drug–drug interactions ☐

14.4 Drug-Food interactions ☐

14.5 Drug-Herb interactions ☐

14.6 Adverse drug reaction ☐

14.7 Other (Please Specify)

_____

15. Has other medication, besides antiretroviral been changed?

Yes ☐

No ☐

16. If yes to question 15 above, please indicate reason for change (You can tick more than one)

Treatment failure ☐

Side Effects ☐

Drug–drug interactions ☐

Drug-Food interactions ☐

Drug-Food interactions ☐

Adverse Drug reaction ☐

Other (Please specify)

_____

B. i. Awareness of adverse drug reactions:

17. Are you aware what ADR is?

Yes ☐

No ☐

18. If yes to question 17 above, indicate whether you agree, disagree or are not sure about this statement:

Statement	Agree	Disagree	No Sure

An adverse drug reaction is an injury caused by taking a medication. It may occur following a single dose or prolonged administration of a drug or a combination of two or more drugs.			

19. Have you ever been counselled on ADR

Yes ☐

No ☐

20. If yes to question 19 above, please indicate who counselled you

Doctor ☐

Nurse ☐

Pharmacist ☐

Other (Please specify)

_____

21. Are you aware what causes ADR?

Yes ☐

No ☐

22. If yes to the question 21 above, please indicate what causes ADR:

Taking other medication with ARV

Eating food that interacts with ARV

Taking herbs that interact with ARV

Medication overdose

Other diseases

Other (Please Specify):_____

23. Please indicate if the following signs are results of adverse drug reaction

Vomiting		Peripheral neuropathy	
Diarrhoea		Uneven fat distribution	
Nausea		Hypertension	
Depression		Stroke	
Hallucinations		Renal failure	
Dizziness		Hepatitis	
Sleep disturbances		Anaemia	
Breaset development		Lactic Acidosis	

B. ii. Awareness of drug interactions leading to ADRs:

24. Are you aware of drug interactions?

Yes ☐

No ☐

25. If yes to question 24 above, please indicate if you agree, disagree or not sure about this statement:

Statement	Agree	Disagree	Not sure
Drug interaction occurs in a situation in which a substance affects the activity of a drug when both are taken together.			

26. Which of the following types of drug interactions are you aware of? (You can choose more than one)

Drug–drug interactions ☐

Drug-food interactions ☐

Drug-herb Interaction ☐

Drug-disease interaction ☐

Other (Please specify)

_____

27. Are you aware that the following drug combinations can cause drug interaction? (You can pick more than one)

	Rifafour®	Rifinah®	Rifampicin	Pyrazinamide	Ethionamide	Metformin	Glimepiride
Atrozia®							
Dumiva®							
Lamzid®							
Aluvia®							
Efavirenz							
Nevirapine							
Tenovofir							
Ritonavir							
Atazanavir							
Zidovudine							
Rifafour®							
Rifinah®							
Rifampicin							
Pyrazinamide							
Ethionamide							
Metformin							
Glimepiride							
Hydrochlorothiazide							
Furosemide							
Enalapril							
Amlodipine							
Atenolol							

Simvastatin							
Atorvastatin							
Bezafibrate							

28. Are you aware if the following food can interact with your antiretroviral medication? (Tick on the interaction you are aware of)

	Grapefruit	Alcohol	Banana	Caffeine	Dairy Products
Atrozia®					
Dumiva®					
Lamzid®					
Aluvia®					
Efavirenz					
Nevirapine					
Tenovofir					
Ritonavir					
Atazanavir					
Zidovudine					
Rifafour®					
Rifinah®					
Rifampicin					
Pyrazinamide					
Ethionamide					
Metformin					
Glimepiride					
Hydrochlorothiazide					
Furosemide					
Enalapril					
Amlodipine					
Atenolol					
Simvastatin					
Atorvastatin					
Bezafibrate					

Other (Please Specify): _____

29. Are you aware if the following herbs can cause drug interactions? (Tick on the interaction you are aware of)

Drug/Herb	Garlic	Ginger	African Potato	Sutherlandia (umnwele)	St. John's Wort
Atrozia®					
Dumiva®					
Lamzid®					
Aluvia®					
Efavirenz					
Nevirapine					
Tenovofir					
Ritonavir					
Atazanavir					
Zidovudine					
Rifafour®					
Rifinah®					
Rifampicin					
Pyrazinamide					
Ethionamide					
Metformin					
Glimepiride					
Hydrochlorothiazide					
Furosemide					
Enalapril					
Amlodipine					
Atenolol					
Simvastatin					
Atorvastatin					
Bezafibrate					

Other (Please Specify): _____

30. How often have you experienced adverse drug reactions?

a. Weekly ☐

b. Monthly ☐

c. A few times a year☐

d. Never

C. Experiences of adverse drug reactions regarding ARVs and other medicines

31. Have you experienced ADR?

Yes ☐

No ☐

32. If yes to question above 31, indicate which of the following you have experienced?

Kidney failure ☐

Inadequate blood supply ☐

Rash ☐

Unexplained weight gain ☐

Diarrhoea ☐

Vomiting ☐

Other (Please Specify)

_____

33. Have you ever been hospitalized due to ADR?

Yes ☐

No ☐

34. Has your antiretroviral medicine been changed due to ADR?

Yes ☐

No ☐

35. If yes to above, who changed it:

Doctor ☐

Nurse ☐

Family ☐

Friends ☐

Other (Please specify): _____

D. Attitudes towards adverse drug reactions regarding ARVs and other medicines

36. Have you reported adverse drug reactions?

Yes ☐

No ☐

37. If yes to question 35 above, how often have you reported adverse drug reactions?

Weekly ☐

Monthly ☐

A few times a year ☐

Never ☐

38. How did you report it?

Told the Nurse ☐

Doctor ☐

Pharmacist ☐

Family ☐

Friends ☐

Ignored the reaction ☐

Other (Please specify)

_____

39. What was done after reporting it?

Completed an adverse drug reaction form ☐

Received counselling ☐

Medicines changed ☐

Nothing was done ☐

Other (Please specify)

_____

40. I feel that the completed adverse drug reaction form can be submitted to:

(You can choose more than one)

Pharmacy Department ☐

Medicines Control Council ☐

Drug Company ☐

National Department of Health ☐

Other (Please Specify)

_____

Appendix B: Participant Information Leaflet and Consent Form

Participant Information Letter

Awareness and attitudes of patients towards possible drug–drug interactions and adverse drug reactions at a selected public health facility in KwaZulu-Natal

Hello! I would like to ask some of your time to read through this consent form requesting you to participate in our study.

My name is Malebogo Tlaila. I am postgraduate student at the University of KwaZulu-Natal; Department of Pharmacy situated in Varsity drive Durban, 4091. You can freely contact me on tlailamalebogo@yahoo.com or my supervisor Dr E. Ojewole on Ojewolee@ukzn.ac.za in relation to this research study.

You are invited to consider participating in a study that involves research about awareness, experiences and attitudes towards adverse drug reactions (ADRSs)

The aim of the study is to evaluate the participants' awareness and attitudes towards possible drug–drug interactions and adverse drug reactions.. The study is expected to enrol more than one hundred and eighty (180) participants from health care facilities in the eThekwini district, Clairwood Hospital, KwaZulu-Natal. It will involve questionnaires that you will be requested to answer honestly . The time requested to complete the questionnaire is 10 minutes. The study is not funded and is pursued for study purposes.

The study will involve questions that may make you feel uncomfortable to answer; however, your honest response will help benefit the output of the study to give suitable recommendations.

This study has been ethically reviewed and approved by the UKZN Humanities and Social Sciences Ethics Committee (awaiting approval number).

In the event of any problems, questions or concerns you may contact the researcher at tlailamalebogo@yahoo.com or the UKZN Humanities and Social Research Ethics Committee (HSSREC), contact details as follows:

HUMANITIES & SOCIAL SCIENCES RESEARCH ETHICS ADMINISTRATION

Research Office, Westville Campus
Govan Mbeki Building
Private Bag X 54001
Durban
4000
KwaZulu-Natal, SOUTH AFRICA

Tel: 27 31 2604557- Fax: 27 31 2604609

Email: HSSREC@ukzn.ac.za

Consent form

Date:

Hello! I hope that you are feeling well today. I would like to ask some of your time to read through this consent form requesting you to participate in our study.

My name is Malebogo Tlaila. I am postgraduate student at the University of KwaZulu-Natal; Department of Pharmacy situated in Varsity drive Durban, 4091. You can freely contact me on tlailamalebogo@yahoo.com in relation to this research project.

You are invited to consider participating in a study that involves research about awareness and attitudes towards side effects and how people manage them.

The aim of the study is to evaluate the participants' awareness and attitudes towards possible drug–drug interactions and adverse drug reactions. Here onwards the term drug–drug interactions was interchangeably used with the term side effects. The study is expected to enrol more than three hundred participants from health care facilities in the eThekwini district. It will involve self-administered questionnaires that you will be requested to honestly answer. The time requested to complete the questionnaire is 10 minutes. The study is not funded and is pursued for study purposes.

The study will involve questions that may make you feel uncomfortable to answer; however, your honest response will help benefit the output of the study to give suitable recommendations.

This study has been ethically reviewed and approved by the UKZN Humanities and Social Sciences Research Ethics Committee (awaiting approval number).

In the event of any problems, questions or concerns you may contact the researcher on tlailamalebogo@yahoo.com or the UKZN Humanities and Social Sciences Research Ethics Committee (HSSREC), contact details as follows:

HUMANITIES & SOCIAL SCIENCES RESEARCH ETHICS ADMINISTRATION

Research Office, Westville Campus
Govan Mbeki Building
Private Bag X 54001
Durban
4000

KwaZulu-Natal, SOUTH AFRICA

Tel: 27 31 2604557- Fax: 27 31 2604609

Email: HSSREC@ukzn.ac.za

Your participation is completely voluntary and you have the write to withdraw from the study at any point. There will be no penalty for sudden withdrawal from the study. Questionnaires that have been withdrawn from shall be considered incomplete and voided out from the study.

The information given will be highly confidential and at no time will you be requested to identify yourself. Data collected will be safely stored at the School of Pharmacy. Electronic data will safely be stored in a secure database that will only be accessed by the researcher. The data will be discarded after 5 years.

	Please tick box
I confirm that I understand the information sheet for the study above	
I understand that my participation is voluntary and that I can withdraw at any time without giving reason	
I agree that my data gathered in this study can be stored and may be used for future research.	

_____ _____

Signature of participant Date

_____ _____

Signature of Researcher Date

_____ _____

Signature of translator Date

Appendix C: Ethical Approval

UNIVERSITY OF KWAZULU-NATAL
INYUVESI YAKWAZULU-NATALI

23 July 2018

Mrs Malebogo Tlaila 215062088
School of Health Sciences-Pharmacy
Pietermaritzburg Campus

Dear Mrs Tlaila

Protocol reference number: HSS/2120/017M
Project Title: Awareness, attitudes and experience of patients taking antiretroviral towards adverse drug reactions at a public health facility in KwaZulu-Natal

Full Approval – Expedited Application

In response to your application received 1 November 2017, the Humanities & Social Sciences Research Ethics Committee has considered the abovementioned application and the protocol has been granted **FULL APPROVAL.**

Any alteration/s to the approved research protocol i.e. Questionnaire/Interview Schedule, Informed Consent Form, Title of the Project, Location of the Study, Research Approach and Methods must be reviewed and approved through the 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 a period of 3 years from the date of issue. Thereafter Recertification must be applied for on an annual basis.

I take this opportunity of wishing you everything of the best with your study.

Yours faithfully

[redacted]

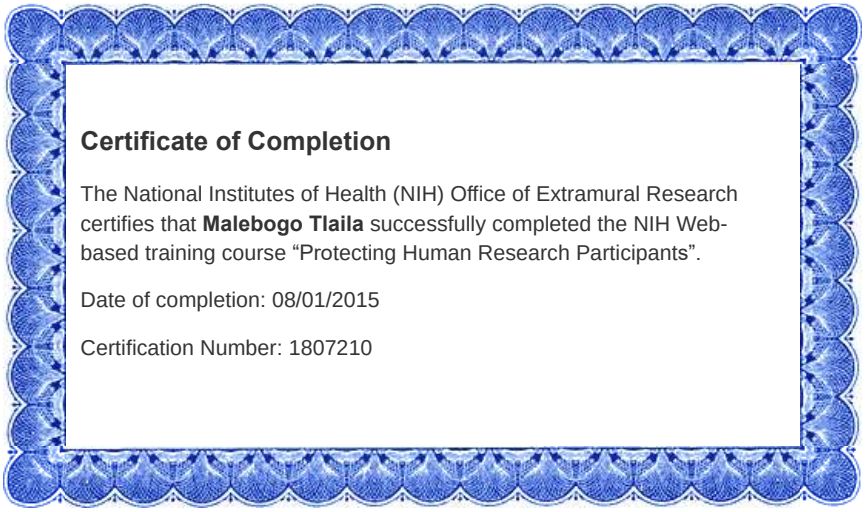
Dr Shamila Naidoo (Deputy Chair)
Humanities & Social Sciences Research Ethics Committe

/pm

cc Supervisor: Dr Elizabeth Ojewole
cc. Academic Leader Research: Professor P Naidoo
cc. School Administrator: Ms P Nene

Humanities & Social Sciences Research Ethics Committee
Dr Shenuka Singh (Chair)
Westville Campus, Govan Mbeki Building
Postal Address: Private Bag X54001, Durban 4000
Telephone: +27 (0) 31 260 3587/8350/4557 Facsimile: +27 (0) 31 260 4609 Email: [redacted]
Website: www.ukzn.ac.za

Appendix D: Protecting Human Subject Participants



Certificate of Completion

The National Institutes of Health (NIH) Office of Extramural Research certifies that **Malebogo Tlaila** successfully completed the NIH Web-based training course “Protecting Human Research Participants”.

Date of completion: 08/01/2015

Certification Number: 1807210

Appendix E: Gatekeepers Approval Letter

health
Department:
Health
PROVINCE OF KWAZULU-NATAL

CLAIRWOOD HOSPITAL
Medical department

Postal address: private bag x01 Mobeni, 4060
Physical address: 11 Higginson Highway, Mobeni, 4060
Tel: 031 451 5179/81 fax: 031 4622682
Email: Bujisaw.Mabaso2@kznhealth.gov.za

Reference: Research
Enquiries: Dr BG Mabaso
Date: 03 May 2018

Malebogo Tlaila
UKZN
School of Health Sciences
Discipline of Pharmaceutical Sciences
Howard College

Re: Permission to conduct research at Clairwood hospital

Dear Ms Tlaila

Clairwood hospital is hereby granting you authority to conduct research with a title "Awareness, attitudes and experience of patients taking antiretroviral towards adverse drug reactions at a public health facility in KwaZulu-Natal". This permission is subject to approval by ethics committee prior to commencement of your study.

Kind Regards

[redacted]

Dr Mabaso BG
Manager: Medical Services
Clairwood Hospital

Fighting Disease, Fighting Poverty, Giving Hope

Appendix F: TURNITIN Receipt for Chapter 1

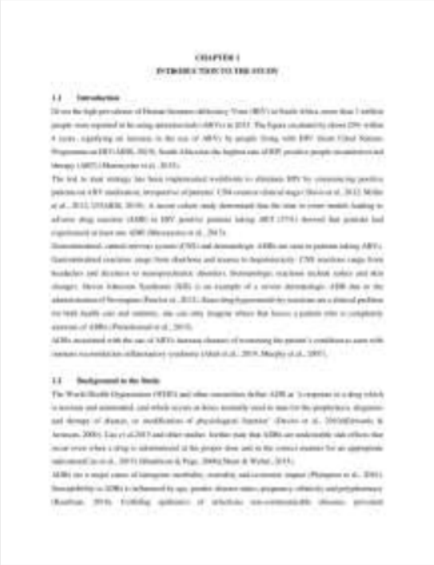
turnitin

Digital Receipt

This receipt acknowledges that Turnitin received your paper. Below you will find the receipt information regarding your submission.

The first page of your submissions is displayed below.

Submission author:	Malebogo Tlaila
Assignment title:	ADRofARV/AAE Chp1
Submission title:	Chapter 1: Introduction to the study
File name:	CHAPTER_1.docx
File size:	66.98K
Page count:	6
Word count:	2,111
Character count:	11,550
Submission date:	30-Nov-2020 02:09PM (UTC+0200)
Submission ID:	1459090978



Appendix G: TURNITIN Receipt Chapter 2

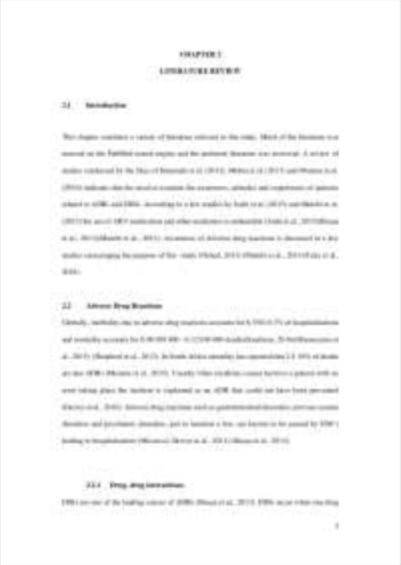
turnitin

Digital Receipt

This receipt acknowledges that Turnitin received your paper. Below you will find the receipt information regarding your submission.

The first page of your submissions is displayed below.

Submission author:	Malebogo Tlaila
Assignment title:	ADRofARV/AAE Chp2
Submission title:	Chapter 2: Literature Review
File name:	CHAPTER_2.docx
File size:	73.77K
Page count:	8
Word count:	2,069
Character count:	11,880
Submission date:	30-Nov-2020 02:10PM (UTC+0200)
Submission ID:	1459091900



Appendix H: TURNITIN Receipt for Chapter 3

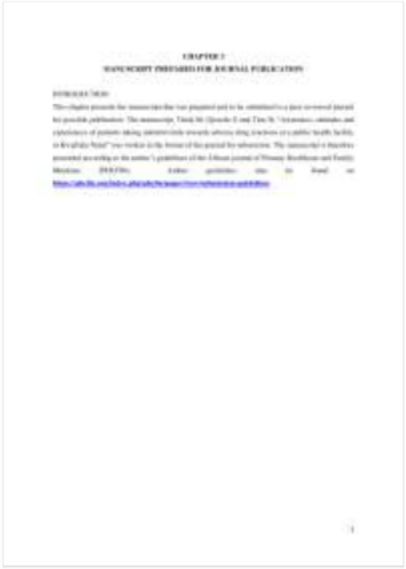
turnitin

Digital Receipt

This receipt acknowledges that Turnitin received your paper. Below you will find the receipt information regarding your submission.

The first page of your submissions is displayed below.

Submission author:	Malebogo Tlaila
Assignment title:	ADRofARV/AAE Chp3
Submission title:	Chapter 3: Manuscript Prepared for…
File name:	CHAPTER_3.docx
File size:	82.2K
Page count:	13
Word count:	3,627
Character count:	19,391
Submission date:	30-Nov-2020 02:12PM (UTC+0200)
Submission ID:	1459092754



Appendix I: TURNITIN Receipt for Chapter 4

turnitin

Digital Receipt

This receipt acknowledges that Turnitin received your paper. Below you will find the receipt information regarding your submission.

The first page of your submissions is displayed below.

Submission author:	Malebogo Tlaila
Assignment title:	ADRofARV/AAE Chp4
Submission title:	Chapter 4: Synthesis and Conclusions
File name:	CHAPTER_4.docx
File size:	49.49K
Page count:	6
Word count:	2,044
Character count:	11,067
Submission date:	30-Nov-2020 02:14PM (UTC+0200)
Submission ID:	1459093291