

https://dspace.org/

Investigating the prevalence and management of potential drug--drug interactions among HIV patients on treatment for comorbid illnesses: a mixed methods approach

Munshi, Aaminah

2020
https://hdl.handle.net/10539/31716

Downloaded from a DSpace repository. https://dspace.org/

Investigating the prevalence and management of potential drug-drug interactions among HIV patients on treatment for comorbid illnesses: A mixed methods approach

---

Aaminah Munshi



UNIVERSITY OF THE
WITWATERSRAND,
JOHANNESBURG

Supervisors:
Rubina Shaikh, Neelaveni Padayachee
& Belinda Strydom

A dissertation submitted to the School of Therapeutic Sciences, Faculty of Health Sciences, University of the Witwatersrand in fulfillment of the requirements for the degree of Master of Pharmacy

Johannesburg, 2020

DECLARATION

I, Aaminah Munshi declare that this dissertation is my own unaided work. It is being submitted for the degree of Master of Pharmacy at the University of the Witwatersrand, Johannesburg. It has not been submitted for any other degree or examination at any other University.



_____

Aaminah Munshi

July 2020
Date

RESEARCH OUTPUTS

Podium Presentations

Aaminah Munshi, Rubina Shaikh, Neelaveni Padayachee, Belinda Strydom. Drug-Drug Interactions among HIV patients with comorbid illnesses. Podium Presentation for the School of Therapeutic Sciences Biennial Research Day, 10 September 2019, Johannesburg (Abstract in Appendix A1).

Drafts of research submitted for publication

Review Article

Aaminah Munshi; Rubina P Shaikh; Neelaveni Padayachee; Belinda Strydom. The role of pharmacists in the management of drug-drug interactions: A focus on HIV and Comorbidities. *(aimed to be published) Hosp Pract.* (Abstract in Appendix A2).

Hospital practice is a MEDLINE-indexed, peer-reviewed medical journal with an impact factor of 0.970.

Research Papers

Aaminah Munshi; Rubina P Shaikh[1]; Neelaveni Padayachee[1]; Belinda Strydom.[2] Potential drug-drug interactions among HIV patients with comorbid illnesses- A retrospective study conducted at an HIV Clinic in Gauteng, South Africa. *(aimed to be published) Hosp Pract.* (Abstract in Appendix A3)

Aaminah Munshi; Nabeelah Bemath[1]; Rubina P Shaikh[1]; Neelaveni Padayachee[1]; Belinda Strydom.[2] Qualitative exploration of drug-drug interactions and its management among pharmacists and pharmacy personnel. *(aimed to be published*) *Qual Health Res.* (Abstract in Appendix A4)

Qualitative Health Research is a peer- reviewed journal with an impact factor of 3.380.

ABSTRACT

The high burden of comorbid conditions and diseases in HIV-infected patients increases the risk for drug-related problems such as drug-drug interactions (DDIs). These DDIs can result in worsening of symptoms and/or mortality. This study aimed to determine the prevalence of potential DDIs (pDDIs) among HIV patients that are on treatment for both HIV and other comorbidities. DDI management strategies were also investigated as a way to evaluate reasons for high DDI prevalence and suggestions for future improvement. The study was conducted at the Themba Lethu HIV Clinic (TLC) in Johannesburg. A mixed methods research design was employed to achieve the objectives of this study. Within the quantitative phase, 645 electronic patient files were analysed over a 3-year period. pDDIs were identified and categorised through Lexicomp®. A total of 5,584 pDDIs were found. Different DDI categories were identified, ranging from category A which corresponds to no evidence of a DDI, category B, minor interaction with limited clinical concern, category C, moderate interaction, category D, major interaction and category X, contraindicated interactions. Category A and B in general are of academic, but not of clinical concern whereas C, D, or X require attention. The most common pDDI rating found was Category C, 63.94%. The second highest pDDI category identified was Category D, 25.58%. The lowest prevalence of pDDIs was recorded for category X, 0.23%. The odds for pDDI exposure were associated with a higher number of comorbidities and the prevalence of pDDIs increased significantly among patients over the age of 50.

The qualitative phase included three focus groups wherein the perceptions of pharmacists and pharmacy personnel on DDI management strategies were determined. The group members were made up of 9 pharmacists; 1 intern; 3 post basic pharmacist assistants; 2 basic pharmacist assistants and 1 learner basic pharmacist assistant. The material used during the focus group addressed DDIs and its management. Demographic questionnaires were handed out to the participants at the beginning of each session. The focus group recordings were subjected to an inductive and essentialist thematic analysis wherein the

identification, analysis and reporting of themes or patterns occurred. Three themes emerged from the analysis; Potential risk factors that contribute towards DDIs, Perceived barriers in the detection and management of DDIs and Recommendations/ Strategies to manage DDIs. All of the participants were aware of the prevalence of DDIs among prescriptions, 56.25% mentioned they encounter DDIs at least once a week and 81.25% had no training in the management of DDIs. Results have indicated that pharmacy personnel would like to provide pharmaceutical care such as the detection and management of pDDIs but have difficulty finding time for it. Factors such as high patient ratios, prescribing errors, polypharmacy, poor communication with patients and clinic hopping were perceived as contributing factors to drug interactions. Some of the barriers that prevent the identification and management of pDDIs reported were the attitude of pharmacy personnel, pharmacist-prescriber relationships, resource-related constraints and lack of knowledge. Such barriers result in negative therapeutic outcomes. To overcome these barriers, it was recommended that pharmacy personnel attend training programmes to help identify and manage DDIs. Patient education was also highlighted as a significant factor in reducing the risk of certain DDIs and increasing patient adherence. In addition, participants expressed that the use of an electronic patient database that alerts pDDIs will to a large extent reduce possible medical complications and consequences. Lastly, the use of multidisciplinary teams for HIV patients was recommended.

Improvement in drug safety is essential in terms of patient morbidity/mortality and in economic terms. Most DDIs are avoidable and can be identified by applying principles of clinical pharmacology and good clinical practice. Although, moderate DDIs featured the highest which suggests that the DDIs were not severe, being able to identify these is critical for patient care. Drug-drug Interactions are directly linked to adverse drug reactions (ADRs), both of which lead to hospital admissions. These findings fortify the need for increased vigilance of drug therapy by healthcare professionals in the prevention of drug related problems.

ACKNOWLEDGEMENTS

In completion of this dissertation I would like to firstly thank The All Mighty, The All Powerful, who has made this journey possible.

A special thanks goes to my supervisors Rubina Shaikh, Neelaveni Padayachee and Belinda Strydom for their continuous support, guidance and expertise throughout the research process.

To my family and friends, I greatly appreciate the love, support, encouragement and patience that you continuously shower me with.

Finally, thank you to all who chose to participate in this research.

TABLE OF CONTENTS

CHAPTER 1

INTRODUCTION AND MOTIVATION FOR STUDY

1.1 Background to the study _____ 1

1.2 Rationale for study _____ 3

1.3 Aim _____ 4

1.4 Study Objectives _____ 4

1.5 Synopsis of the Dissertation _____ 4

CHAPTER 2

THE ROLE OF PHARMACISTS IN THE MANAGEMENT OF DRUG-DRUG INTERACTIONS: A FOCUS ON HIV AND COMORBIDITIES

2.1 Introduction _____ 6

Search strategies _____ 7

2.2 Pharmacovigilance _____ 8

2.2.1 Current pharmacovigilance activities in South Africa _____ 8

2.2.2 Pharmacovigilance and HIV _____ 11

2.3 The NCD epidemic _____ 12

2.4 Drug-Drug Interactions among HIV patients _____ 13

- *Decentralized care* _____ 14
- *Lack of monitoring in resource-poor settings* _____ 14
- *Comorbidities and polypharmacy in an aging population* _____ 14

2.5 Management of drug-drug interactions _____ 17

2.5.1 Multidisciplinary care _____ 17

2.5.2 Patient-Professional relationship _____ 19

2.5.3 Integration of care _____ 19

2.5.4 The role of a pharmacist _____ 20

2.6 Conclusion _____ 21

CHAPTER 3

METHODOLOGY

3.1 Phase 1 25

3.1.1 Study site 25

3.1.2 Participants 25

3.1.3 Sample size 26

3.1.4 Data collection 26

3.1.5 Data collection tools 26

3.1.5.1 Screening of prescriptions for pDDIs 26

3.1.5.2 Determining the prevalence of DDIs 27

3.1.6 Data analysis 27

3.2 Phase 2 28

3.2.1 Study site 28

3.2.2 Sample and sample size 28

3.2.3 Data collection 28

3.2.4 Data collection tools 29

3.2.5 Data analysis 29

3.2.5.1 Familiarization with the data 29

3.2.5.2 Generating initial codes 29

3.2.5.3/ 3.2.5.4 Search for/ Review themes 30

3.2.5.5 Defining and naming themes 30

3.2.5.6 Producing the report 30

3.2.6 Self-reflexivity 30

3.2.7 Ethics 31

CHAPTER 4

RESULTS

4.1: Phase 1- Determining the prevalence of pDDIs between ARVs and agents used to treat cardiovascular, respiratory, epileptic, endocrine and psychotic conditions. 32

4.1.1 General characteristics of study participants 32

4.1.2 Comorbidities 33

4.1.3 Drug-Drug Interactions 35

4.1.4 pDDI-associated risk factors investigated 38

4.1.4.1 Diseases affiliated with pDDIs 38

4.1.4.2 Number of comorbidities associated with pDDIs 38

4.1.4.3 The impact of gender 38

4.1.4.4 The impact of age 39

4.2: Phase 2- Exploring the perceptions of pharmacists and pharmacy personnel on DDI management strategies. 40

4.2.1 Potential risk factors that contribute towards DDIs 41

4.2.1.1 Patient ratios 41

4.2.1.2 Prescribing errors 42

4.2.1.3 Polypharmacy 43

4.2.1.4 Poor communication with patients 44

4.2.1.5 Clinic Hopping 45

4.2.2 Perceived barriers in the detection and management of DDIs 46

4.2.2.1 Insufficient knowledge 46

4.2.2.2 Attitude of pharmacy personnel 47

4.2.2.3 Pharmacist- Prescriber relationship 48

4.2.3 Recommendations/ Strategies to manage DDIs 50

4.2.3.1 Patient education/ counselling 50

4.2.3.2 Electronic systems 51

4.2.3.3 Training of pharmacy personnel 52

4.2.3.4 Multidisciplinary teams for HIV patients 53

CHAPTER 5

DISCUSSION

5.1 Section A ____ 55
Purpose of the research ____ 55
5.2 Section B ____ 56
5.2.1 Quantitative data ____ 56
5.2.2 Qualitative findings ____ 59
5.2.2.1: Theme 1- Potential risk factors that contribute towards DDIs ____ 60
5.2.2.2: Theme 2- Perceived barriers in the detection and management of DDIs ____ 61
5.2.2.3: Theme 3- Recommendations/ Strategies to manage DDIs ____ 62
5.3 Section C: Integration of quantitative and qualitative results ____ 63

CHAPTER 6

STRENGTHS AND LIMITATIONS

6.1 Strengths ____ 68
6.2 Limitations ____ 68

CHAPTER 7

FUTURE RECOMMENDATIONS ____ 70

CHAPTER 8

CONCLUSION ____ 72
REFERENCES ____ 73

APPENDICES

Abstract of podium presentation: 88

Appendix A1 89

Appendix A2 90

Appendix A3 91

Appendix A4 92

Appendix B2 95

Patient Data Collection Sheet 95

Appendix B3 96

Risk Rating Categories as Presented by Lexicomp for Each Drug-Drug Interaction adapted from Dirin et al. 96

Appendix B4 97

Prescription data: Drugs, NCDs, DDIs (Identification and classification of potential DDIs using Lexicomp software). 97

Appendix B5 98

Participant Information Sheet 98

Appendix B6 103

Focus group demographic details questionnaire 103

Appendix B7 104

Questions adapted from Anthierens et al. 104

Appendix B8 105

Ethics clearance 105

Appendix B9 106

Plagiarism report 106

LIST OF TABLES

Table 2.1: Inclusion and Exclusion criteria for search analysis 7

Table 2.2: Common DDIs between ARVs and agents used for chronic illnesses.[37] 16

Table 2.3: Professionals constituting a multidisciplinary team.[49] 18

Table 3.1: Inclusion and Exclusion Criteria for the study sample. 25

Table 4.1.1: Demographic variables and nature of pDDIs 33

Table 4.1.2: Most prevalent identified pDDIs, their risk ratings and potential adverse outcomes 37

Table 4.1.3: Chronic diseases and pDDIs (total number of scripts n = 5938) 38

Table 4.1.4: Exposure to pDDIs stratified with respect to patients' age groups 39

Table 4.2.1: Identified themes and subthemes emerging from focus groups 40

LIST OF FIGURES

Figure 2.1: Adverse Drug Reaction (ADR) communication channels in South Africa (adapted from Maigetter et al., 2015).[27] _____ 9

*Figure 2.2: Basic Pharmacovigilance activities in South Africa*_____ 10

Figure 3.1: An overview of the study design[63]_____ 24

*Figure 4.1.1: Patients presenting with comorbidities within each age group*___ 34

*Figure 4.1.2: % of patients presenting with different multi-morbidity cohorts.*__ 34

*Figure 4.1.3: Risk rating categories of potential drug-drug interactions over the years 2015-2017*_____ 35

*Figure 4.1.4: Risk ratings of the identified potential drug-drug Interactions between ARVs and NCDs*_____ 36

Figure 4.1.5: Distribution of potential drug-drug interactions among the different age bands. _____ 39

LIST OF EQUATIONS

Equation 3.1: Sample size calculation used to determine sample population of the study. [65] _____ *26*

Equation 3.2: Prevalence calculation used to determine the prevalence of pDDIs. [67] _____ *27*

LIST OF ABBREVIATIONS

Adverse drug events - ADEs

Adverse drug reactions - ADRs

Antiretroviral therapy – ART

Antiretroviral – ARV

Calcium channel blockers - CCB

Cardiovascular diseases – CVD

Confidence Intervals - CI

Cytochrome P450 - CYP450

Drug-Drug Interactions – DDIs

Healthcare professionals – HCPs

Hypertension - HTN

Low middle-income countries – LMICs

Medicines Control Council – MCC

Myocardial Infarction – MI

National Adverse Drug Event Monitoring Centre – NADEMC

Non-communicable diseases – NCDs

National Department of Health – NDOH

Non-nucleoside reverse transcriptase inhibitors - NNRTIs

National Pharmacovigilance Centre for Public Health Programmes - NPC

Over the counter- OTC

Pharmaceutical and Therapeutics Committees - PTC’s

Pharmacovigilance – PV

Potential Drug-Drug Interactions- pDDIs

Protease Inhibitors – PIs

Right To Care – RTC

South African Health Products Regulatory Agency - SAHPRA

St Luke's/Roosevelt – SLR

Targeted Spontaneous Reporting System - TSR

Themba Lethu HIV Clinic - TLC

Uppsala Monitoring Centre - UMC

World Health Organization – WHO

CHAPTER 1
INTRODUCTION AND MOTIVATION FOR STUDY

1.1 Background to the study

South Africa has the highest profile HIV epidemic in the world with over 7.1 million (12.7%) of the total population living with the disease.[1] Antiretroviral therapy (ART) increases the quality of life both physically and emotionally in HIV infected patients, which has led to a greater number of patients accessing antiretrovirals (ARVs).[2-3] As the life expectancy of ARV recipients increases, the aging population begin to suffer from an increased occurrence of chronic diseases including non-communicable diseases (NCDs). Factors which have been associated with the high prevalence of NCDs in HIV infected patients include inflammation by HIV, opportunistic infections or treatment thereof and traditional risk factors such as obesity and high blood pressure.[4] According to the Department of Health, by 2025, around 12,3-million South Africans will be on chronic medication for HIV and other NCDs.[5] Of note, the NCD escalation is noticeably higher in developing countries. A study conducted in South Africa in 2016 revealed that 20% of HIV-infected patients on ARVs within a primary health care clinic, were concurrently on treatment for another chronic disease.[6]

Common comorbidities that HIV patients are diagnosed with include mental disorders, heart disease, diabetes and tuberculosis (TB), furthermore, these patients are susceptible to opportunistic infections or toxicity from long-term use of ARVs. The high burden of comorbid conditions and diseases in HIV-infected patients increases the risk for drug-related issues such as polypharmacy and drug-drug interactions(DDIs).[3-4] Several ARVs display repressive and/or inciting effects on cytochrome P450 isoenzymes, enzymes responsible for the metabolism of many medications used in treatment of comorbidities in the aging HIV population.[7] The simultaneous use of these ARVs and medications used to treat comorbidities can lead to DDIs which results in worsening of symptoms and/or mortality.[3] A DDI is a change of the effect of a drug when administered with another drug. There are two types of DDIs, pharmacodynamics interactions and pharmacokinetic interactions. Pharmacodynamic interactions result in one drug altering the tissue sensitivity to another drug by having an agonistic or antagonistic effect. Pharmacokinetic interactions consist of one drug

adjusting the absorption, distribution, protein binding, metabolism, or excretion of another drug causing a change in the amount of accessible drug at the receptor sites. These alterations can be identified by poor clinical outcomes or changes in drug concentrations.[8]

A pharmacist is responsible for the detection and prevention of potential DDIs (pDDIs) and the monitoring of patients at high risk for these pDDIs. Pharmacists are able to reduce DDIs with the correct systems in place. However, there are certain factors that prevent pharmacists from being able to detect, evaluate, or avoid drug interactions. These include time restrictions, inadequate computer systems for screening and group classification of drugs rather than the ideal individual drug classification system used by most computer programmes. The process of detecting DDIs is further complicated when patients use multiple physicians and pharmacies. Patients may be self-medicating with over-the-counter (OTC) products or taking medications that are not recorded on the patient's records within their respective pharmacies due to pharmacy hopping. The patient may even take medication prescribed for other patients, without being aware of the potential risks of DDIs. The ability to detect a DDI is also affected by the timing and dose of medication ingestion. If too much of a drug is taken or the medications are taken in the wrong sequence, potential for an interaction increases.[9] The role of a pharmacist is critical in the prevention, detection and reporting of DDIs to ensure better therapeutic outcomes.[10] The risk of most drug interactions can be minimised by accurate management such as prescribing an alternative non-interacting drug, monitoring with clinical screening tests (blood pressure, glucose), specialised laboratory investigations (INR, liver function tests) and monitoring clinical symptoms (dizziness, muscle aches). If other interventions are unsuccessful, the target interacting drug can be stopped temporarily and thus, drug combinations do not have to be avoided. The interaction is deemed managed if the presenting symptoms are treated or if the dosage and administration is adjusted.[11]

We are at a stage in time wherein HIV patients may experience mortality or a decline in quality of life, not from the virus itself, but from a preventable NCD that may be a consequence of HIV-related immunosuppression, ARV drug toxicities, or HIV-related inflammation.[12] The need to monitor patients on ARV treatment is further confounded in developing countries due to the use of traditional and/or alternative therapies,

insufficient healthcare professionals (HCPs), abuse of prescription-only medicines and the risk of medication interactions that could increase the toxicity profile of HIV patients.[13] Therefore, a robust pharmacovigilance (PV) system is required to avoid such challenges associated with ARV therapy, this system can aid in achieving comprehensive, safe and effective healthcare.[14]

1.2 Rationale for study

The medical management of HIV patients diagnosed with NCDs is complex. These patients are at an increased risk of experiencing adverse drug effects that can be attributed to the safety profile of concomitant ARVs and treatments for chronic diseases as well as their compromised immune systems. The simultaneous use of ART with other chronic treatments increases the risk of clinically significant DDIs, which can lead to drug toxicity, poorer ARV adherence, loss of efficacy of the co-administered medication or virologic breakthrough.[12] By increasing awareness of frequent DDIs and the use of DDI screening systems, one can avoid co-administration of potentially harmful combinations in HIV patients.

This study aimed to highlight the need for a DDI monitoring system by determining the prevalence and management of pDDIs between ARV agents and other chronic medications. The pDDIs between ARVs and drugs used to treat comorbid conditions such as cardiovascular, psychiatric, endocrine, epileptic and respiratory related problems were investigated in an HIV clinic located within a university-affiliated teaching hospital. These five conditions were selected for the study as the clinic reported several patients diagnosed with HIV and the specified comorbidities. Drugs such as Simvastatin, Amitriptyline, Valproate, Phenytoin, Salbutamol and Metformin had moderately significant clinical drug interactions when administered with HIV medication.[15] Measures are thus required to manage these DDIs.

1.3 Aim

The aim of this study is to determine the prevalence and management of pDDIs between ARVs and chronic medication in HIV infected patients within an HIV clinic situated in Gauteng.

1.4 Study Objectives

1. To determine the prevalence of pDDIs between ARVs and agents used to treat cardiovascular, respiratory, epileptic , endocrine and psychotic conditions.
2. To classify the severity of the pDDIs.
3. To explore the perceptions of pharmacists and pharmacy personnel on DDI management strategies.

1.5 Synopsis of the Dissertation

Chapter One of this dissertation provides a background to the study. It outlines the high prevalence of NCDs among HIV patients and the risk of pDDIs among these patients. A summary of the aim and objectives is included within the chapter.

Chapter Two provides a comprehensive literature review, focusing on the role of PV with regards to HIV and the comorbidities patients face. Furthermore, the occurrence of DDIs, its management, the use of a multidisciplinary team and the role of a pharmacist in such cases is discussed.

Chapter Three of this dissertation provides a summary of the study design. The methodology used for both phase 1 and 2 (quantitative and qualitative) of the study is outlined.

Chapter Four includes the results of the study. The quantitative data was presented as graphs and tables indicating the prevalence of pDDIs, its associations and the most common pDDIs identified. The qualitative data explores participants experience towards potential interactions and its management thereof, through the use of quotations.

Chapter Five of this dissertation analyses the results mentioned in chapter four. Both quantitative and qualitative data are discussed independently. Thereafter, integration of both data sets occurs.

Chapter Six highlights the strengths and limitations of the study.

Chapter Seven of this dissertation presents recommendations for future work.

Chapter Eight concludes the study.

CHAPTER 2
THE ROLE OF PHARMACISTS IN THE MANAGEMENT OF DRUG-DRUG INTERACTIONS: A FOCUS ON HIV AND COMORBIDITIES

"Since rational use of medicines requires that the patients receive 'medicines appropriate to their clinical needs', active/ more effective involvement of pharmacists in pharmacovigilance systems will improve the rational use of medicines" [16]

2.1 Introduction

The rise of the HIV epidemic has led to an increase in NCDs including chronic pulmonary disease, cancer and heart disease resulting from the interaction of multiple risk factors, such as nutrition, smoking, physical activity and genes. Furthermore, both the HIV virus itself and the treatment used for the infection may interact with traditional risk factors and give rise to NCDs. There is insufficient evidence available on the challenges of NCDs among HIV patients in low middle-income countries (LMICs). Many of these challenges compromise the provision of public health interventions and quality clinical care. Thus, overcoming such challenges includes improvement in the assessment of NCD risk factors, engagement in care and the integration of health data systems. This can be done through an effective PV system.[17]

The World Health Organization (WHO) defines PV as "the science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other drug-related problem".[18] PV targets the safe and effective use of medicine. Pharmacists are vital in a healthcare system for their drug expertise and special training. They play an essential role in healthcare systems to help preserve the rational and safe use of medicines. Given their training, pharmacists can employ PV systems to monitor the performance of drugs and identify pDDIs and adverse drug reactions (ADRs) earlier thereby reducing high healthcare costs.[16] This review focuses firstly on the role of PV in developing countries, specifically with regards to the HIV/AIDS epidemic and the comorbidities patients face. Secondly the link between ARV treatment and other comorbidities is covered and lastly, the occurrence of DDIs, its management and the role of a pharmacist in such cases is discussed.

Search strategies

Electronic databases (PubMed, Cochrane Library and International Pharmaceutical Abstracts) were searched for the period from 1 January 1995 to 31 May 2019 to identify relevant South African and international literature. Furthermore, the references sections of the returned publications and review articles were screened for additional hits. 15 articles were returned and 51 were included in the review. The inclusion and exclusion criteria are seen in Table 2.1 below:

Table 2.1: Inclusion and Exclusion criteria for search analysis

Inclusion Criteria	Exclusion Criteria
1. All searches included English language literature. 2. Articles addressing PV and its impact on HIV and NCDs on patients. 3. Articles reporting pDDIs and its management were assessed. 4. Articles addressing the impact of HIV globally and the different methods of treating HIV patients including a multidisciplinary approach were analysed. 3. Literature addressing the role of a pharmacist in healthcare were addressed.	1. Studies with non- English abstracts were assessed for inclusion on the basis of the abstract. 2. Studies addressing ADRs were excluded. A detailed review of these kinds of services was recently published.[19]

Lists of titles and abstracts of papers from the searches were analysed by the researcher and then compared using the inclusion/exclusion list. To the best of the researcher's knowledge, there have only been a scarce amount of studies that have focused on the prevalence and management of DDIs in the overall treatment of HIV patients in South Africa.

Search terms included: pharmacists; clinical pharmacy; HIV; ARV therapy; Multidisciplinary teams; DDIs; DDI management; PV and public health.

2.2 Pharmacovigilance

Medications are unavoidable and are generally used to improve the health of a target population. Medicines are essential not only because of their capability to cure and prevent disease but also because the confidence a countries population has in their health policies affects their reliance in the availability of medicines that are safe and efficient. There is a possibility of some risk of harm in all medicines, therefore, the identification of these risks and unexpected outcomes help strengthen the relationship between patient care, safety, and medicine use. This is the role of PV.[20,21]

In 1961, the Thalidomide disaster wherein thousands of congenitally deformed infants were born due to maternal Thalidomide use during pregnancy, served as a catalyst that led to the launch of the Uppsala Monitoring Centre (UMC). The purpose of the UMC was to use information collected on adverse effects of medicines and to ensure drug safety, through identifying the possible risk factors associated with medication use in order to avoid/minimize harm.[22,23] UMC has been instrumental in the development of PV.[24] Systems were put into place for the compilation and evaluation of individual ADR case histories. Ultimately, the information gained from these reports are aimed at protecting patients and the public from drug-related harm and improving patient-therapy outcomes. Currently, UMC is responsible for collecting reports and information on ADRs and supporting member countries in their PV activities.[24] These international reports contribute to the work of national drug regulatory authorities, enhance the safety profile of medicines and assist in the avoidance of further disasters.

2.2.1 Current pharmacovigilance activities in South Africa

In South Africa, PV initiatives are largely determined by three key participants; the regulators and the pharmaceutical industry, public health programmes and HCPs.[25] The Medicines Control Council (MCC) which has now been replaced by the South African Health Products Regulatory Agency (SAHPRA) is the statutory body that is responsible for the safety, efficacy and quality of all medicines used by the South African public. SAHPRA applies standards stipulated by the Medicines and Related Substances Act (Act 101 of 1965) which clearly stipulates that “any new or existing quality, safety or effectiveness concerns related to any medicine or scheduled

substance, including but not limited to ADRs, and the risk management activities associated with these concerns, must be reported to SAHPRA within a stipulated time frame".[25] The National Adverse Drug Event Monitoring Centre (NADEMC), a unit of the MCC, was established in 1987 to bridge the gap between the MCC and UMC and is responsible for promoting ADR monitoring as illustrated in Figure 2.1 below. NADEMC collects and reviews submitted ADR reports from HCPs.[26]

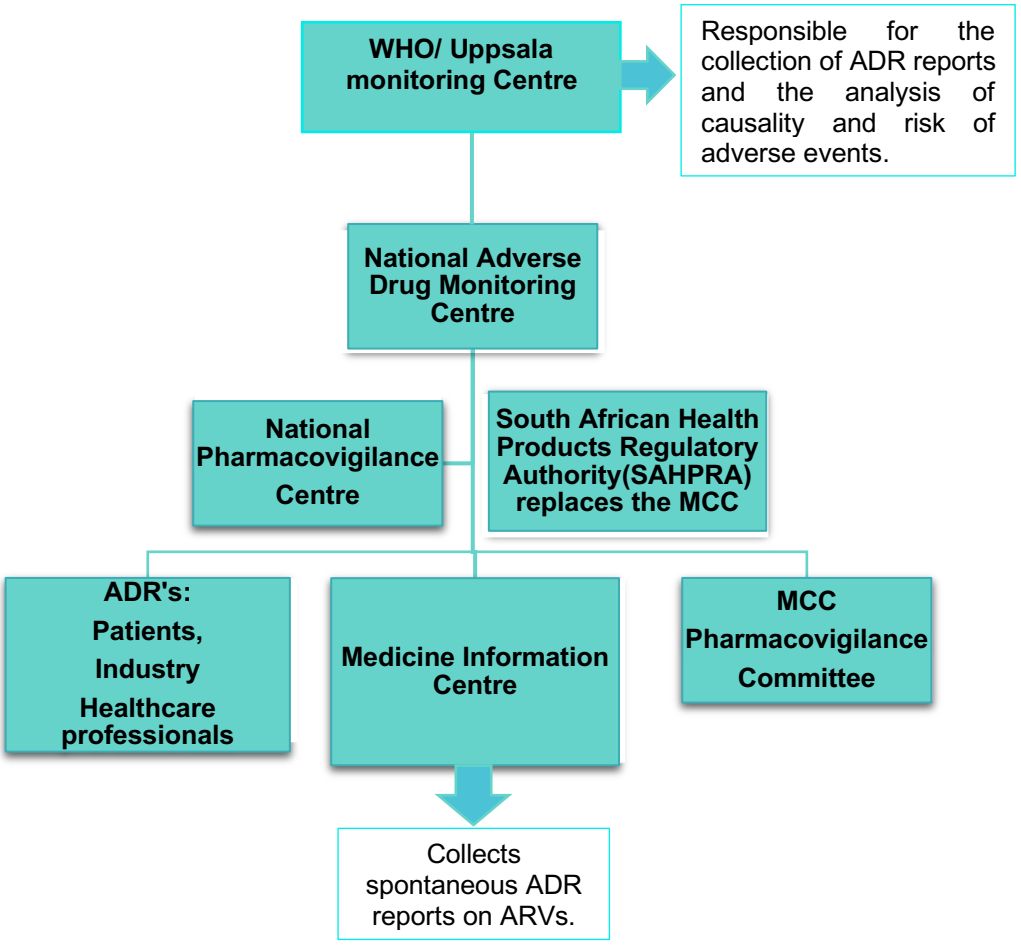


Figure 2.1: Adverse Drug Reaction (ADR) communication channels in South Africa (adapted from Maigetter et al., 2015). [27]

Figure 2.2: Adverse Drug Reaction (ADR) communication channels in South Africa (adapted from Maigetter et al., 2015). [27]

In 1992 nal Drug Monitoring Programme. Combined effects between PV and the related activities of disease surveillance and health system strengthening has led to PV becoming recognised as a critical public health discipline in South Africa, requiring integration into all aspects of healthcare.[25] As depicted in Figure 2.2 below, in 2004, PV was enhanced with the release of the South African ART programme and the development of the National Pharmacovigilance Centre for Public Health Programmes (NPC) within

the National Department of Health (NDOH). The NPC's main focus is on public health PV and the monitoring of patient safety within important treatment programmes, namely TB and HIV.[26] Active surveillance systems investigating the effects of HIV and TB medicines has resulted in positive public health interventions.[21] PV is rapidly evolving, however, attention should be paid to medications used to treat NCDs such as diabetes, hypertension (HTN), inflammatory and cardiovascular conditions as these are the other major contributors of drug-related hospitalisations.[21] There are hospital committees within South Africa known as Pharmaceutical and Therapeutics Committees (PTC's). PTCs address "problems of drug selection, procurement, distribution and use."[28] They are accountable for the management of ADRs and medication errors, evaluation of clinical use of drugs and the management of the formulary. PTC's allow for public organizations to combine all the information collected and then submit it to national centres. PTC's also serve as a source of feedback on ADR management at a clinical level.[28]

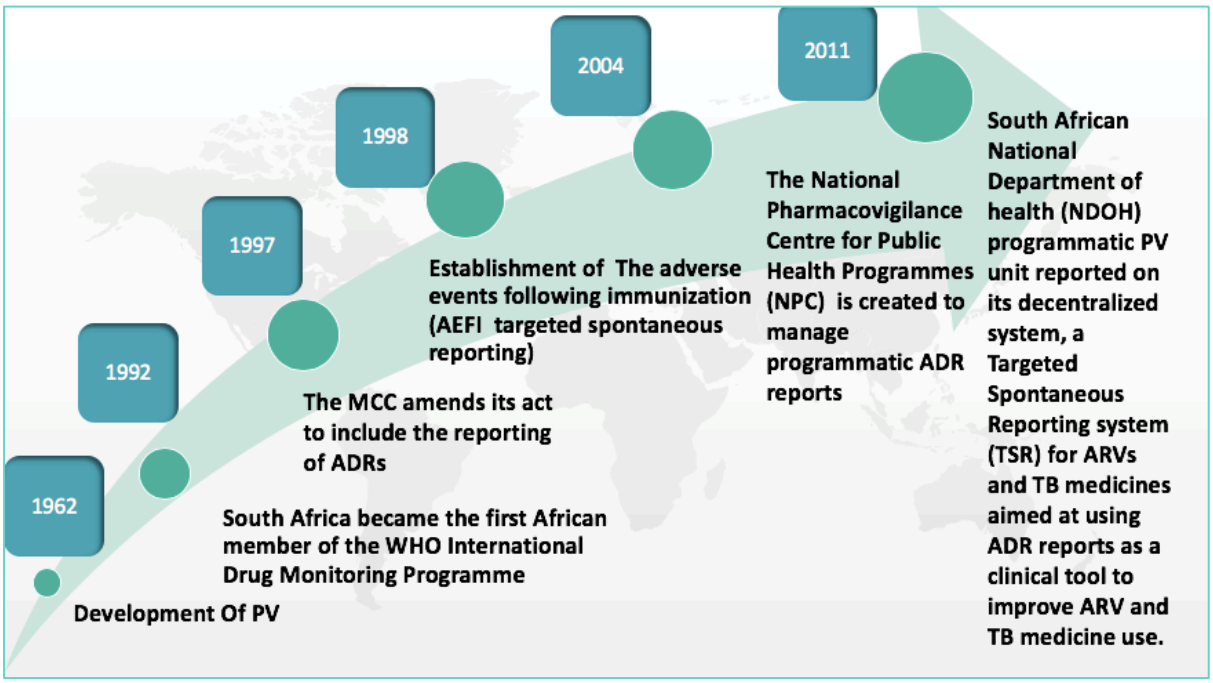


Figure 2.3: Basic Pharmacovigilance activities in South Africa

2.2.2 Pharmacovigilance and HIV

South Africa has one of the highest prevalence of HIV infected people globally and currently has the world's largest ART programme. This epidemic contributes towards the leading causes of morbidity and mortality in the country. Although ARV therapy improves the quality of life both physically and emotionally for patients, the risk of ADRs are enhanced in these patients due to the effect of the disease as well as the complex drug regimens that they are administered.[21] Consequently, the improved treatment outcomes and quality of life may be nullified by ADRs specifically at the beginning of treatment. Due to toxicity concerns reported, patients are reluctant to start or adhere to ART. These ADRs threaten the public's confidence in the safety of ART thereby leading to non-adherence, reduction in treatment efficacy and an increase in secondary drug resistance. They are a major public health issue and result in financial and economic burden on health systems.[29]

ART aims to repair the body's immune system, supress the viral load, reduce opportunistic infections and most importantly improve patient quality of life. Thus, treatment involves intensive quality assurance to achieve optimum patient outcomes and the prevention and management of side effects, this is done through PV.[29] Since the rollout of ARVs in government in 2003; the development of the PV programme in South Africa has been poor. This could be as a result of scarcity of resources, infrastructure and expertise. Systematic reporting in all provinces is uncommon and ADRs are intermittently identified. The detection, intervention and effective case management of ADRs primarily at treatment level has become a preference in South Africa due to the impact it has on the management, care and support of HIV patients. PV needs to be better integrated into clinical practice to optimise patient therapy. Essentially, the quality of a PV system should be measured by the degree to which it improves patient care and informs policy.[21]

2.3 The NCD epidemic

The incidence of NCDs continues to rise globally.[30] NCDs are a predominant cause of mortality worldwide and in South Africa. Together with HIV and TB, injuries and trauma, maternal and child mortality, NCDs form the 'quadruple burden of diseases', a term used to describe the health challenges South Africa faces. The comorbidity of NCDs is increasingly common among HIV infected patients.[31]

HIV and NCDs are syndemic and affiliated with an increase in NCDs among HIV-positive patients. Studies investigating comorbid NCDs among adults living with HIV have shown there to be frequent cases of patients diagnosed with HTN, type 2 diabetes mellitus, cancer, asthma and congestive cardiac failure.[4,31,32,33] Hypercholesterolemia was also identified to be considerably high among HIV patients.[33] In 2012, a study conducted by Negin J et al.[35] investigating the prevalence of HIV and chronic comorbidities among older adults revealed that chronic diseases were more common among all older adults in comparison with those aged 18–49. It was also reported that the overall health of older patients with HIV is weak and these patients require more attention due to poverty, nutrition and access to disability and health services. The determinants of NCDs among HIV patients deviate based on the specific NCD considered. Customarily, increased age and immune suppression, obesity, social deprivation and prolonged exposure to ART are among the common NCD risk factors found amid the HIV population.[4] The growing morbidity and mortality rates of NCDs among patients on ARVs serves as a threat to the substantial health gains obtained within the past decade in the HIV-infected community.[36] Comorbidities increase the complexity of patient management, often leading to poor health outcomes and increased costs for both patient and healthcare systems.[31,33] The costs of comorbidities to economies, individuals, societies and healthcare system are substantial, especially in South Africa where poverty levels are high with rising costs for healthcare utilization.[31] Action against the soaring NCD burden affecting HIV patients is imperative, these NCDs are adding great pressure to the current challenges in the fight against HIV.[4]

In view of the escalating universal NCD pandemic, a greater understanding of the interactions between long-term HIV, HIV treatment and NCD comorbidities will enable the maintenance of gains in HIV-infected populations while improving NCD control and

treatment. Designing and conducting studies on NCDs among patients on ARVs will assist in the establishment of both profitable interventions and improvements within the current HIV and healthcare systems in LMICs. This will result in the incorporation of both HIV and NCD diagnosis and treatment.[36]

2.4 Drug-Drug Interactions among HIV patients

Due to the wide range of ARV drugs dependent on the cytochrome P450 (CYP450) system and/or various transporters and the need to treat the increasing number of comorbid conditions, DDIs are of great concern among HIV-infected patients.[37,38] Many of these medications affect the activity of the CYP450 isoenzymes (responsible for the metabolism of frequently prescribed drugs) resulting in the inhibition of the activity of some isoforms while inducing the activity of others. The impact of the ARV agents on CYP450 isoenzymes can lead to a number of clinically significant DDIs.[37]

Dos Santos et al.[38] conducted a study in Brazil investigating pDDIs in patients that were given ART. It was found that the prevalence (52.2%) of pDDIs in patients given ART was higher in comparison to other research. It was also interesting to note that 32.5% of the ART prescribers lacked any sort of specialization, this may have impacted the occurrence of DDIs. The study also noted that moderate and higher severity pDDIs does not only lead to therapeutic toxicity but can also be obstructive in tests used for detection of HIV resistance to ARV drugs. This highlights the importance of detecting pDDIs and the possible adverse outcomes that occur without a coherent PV system.

Approximately 5% of drug use-related side effects in primary care may be brought on by DDIs. Studies have indicated there to be an association between increased age and increased risk for DDIs among HIV patients.[39] Despite all patients on ART being at risk for pDDIs, the risk is heightened in certain patient groups and clinical scenarios:

- *New HIV Drugs*

  The evaluation for potential for DDIs that occurs within the clinical phase of drug development is at most insufficient. Drugs within a particular class cannot be presumed to have roughly similar potential for interaction. The emergence of

unexpected DDIs after licensing may result in a decrease in therapeutic effect of ARVs. This accentuates the necessity for standard protocols for interaction screening of new drugs and clinical vigilance as experience in their use develops.[40,41]

- *Decentralized care*

  Over the next few years, HIV treatments run the risk of progressively decentralizing to primary or secondary care settings. Prescribers with a lesser degree of expertise in ARVs may be less likely to detect DDIs or recognise the impact of their adverse effects.[41]

- *Lack of monitoring in resource-poor settings*

  The absence of PV facilities and laboratory monitoring linked with the high background of illness in developing countries like South Africa may mask clinically significant DDIs. Moreover the symptomatic treatment of illness and widespread use of traditional and herbal medicines make it difficult to compile a complete list of patient medications.[41]

- *Comorbidities and polypharmacy in an aging population*

  The triumph of the ART programme in South Africa was apparent in the increases in national life expectancy, rising from 61.2 years in 2010 to 67.7 years in 2015.[42] This has led to a significant increase in the percentage of older HIV individuals.[43] The risk of DDIs may be primarily enhanced among the aging HIV population as a result of the simultaneous treatments for multiple comorbidities and ART.[43] Polypharmacy, defined as “the concomitant use of multiple medications (five or more medications)”, is inevitable for patients on ART in both developed and developing settings.[40,43] Polypharmacy has been associated with increasing age and with an increased risk of ADRs, increased hospitalizations, poor adherence and DDIs.[40] A cross-sectional analysis among HIV patients in the USA aimed to determine the degree of polypharmacy and the risk of ARV DDIs among different patient groups. The study showed that a higher degree of ARV/non-ARV combinations were prescribed to older patients. These combinations were contraindicated or had potential for a clinically

significant interaction. It was deduced that as HIV-infected patients age and experience multiple comorbidities, systematic reviews of current medications by providers may reduce risk of such exposures.[43]

DDIs are one of the main subsets of medication errors in developed countries, and ARVs are among the most therapeutically risky drugs for clinically significant DDIs. Data collection in developing countries are scarce, though it is likely that clinically significant DDIs are prevalent among HIV patients with comorbid illnesses. The risk for such DDIs are arguably higher due to limited laboratory monitoring, elevated levels of background illness (which may result in adverse effects being overlooked), lack of affordable alternative treatments, use of fixed dose combinations (which offers less flexibility for DDI management) and lack of PV data. Additionally, there is a higher cost of treatment failure in these settings, since options are limited compared with developed countries.[41] In order to establish the best pharmaceutical care for HIV patients that have comorbid chronic illnesses, emphasis has been placed on the recognition and management of DDIs.[44,45] Table 2.2 below displays the most common DDIs that occur between ARVs and co-medicated agents used for common chronic illnesses.

Table 2.2: Common DDIs between ARVs and agents used for chronic illnesses.[37]

DDIS among ARVs	Concomitant use of ARVs agents from the same class is generally avoided. Non-nucleoside reverse transcriptase inhibitors (NNRTIs), Protease Inhibitors (PIs), and maraviroc (a CCR5 antagonist), are metabolized by the CYP450 system making them highly susceptible to DDIs.[46]
Antihypertensive Drugs	The frequency of HTN among HIV-infected patients has increased from 5.9% to 36.5%. Amidst the class of the antihypertensive agents, calcium channel blockers (CCB) seem to have the greatest potential to interact with ARVs. Both classes of drugs are metabolized by the isoenzyme, CYP3A4. Other antihypertensive agents that interact with ARVs include several of the β-blockers: Propranolol, Carvedilol, metoprolol, pindolol, and timolol. Interactions may occur between these drugs and CYP2D6 inhibitors, such as Efavirenz or Ritonavir.[37]
HMG-CoA Reductase Inhibitors (Statins)	Dyslipidaemia frequently occurs among HIV patients due to the HIV-related effects and ARV medications, it also contributes to the increased cardiovascular risk among HIV-infected patients. From the statins, Simvastatin, Lovastatin, and Atorvastatin are considerably metabolized by CYP3A4 and most likely to interact with PIs.[37]
Oral hypoglycaemic agents	Diabetes mellitus is progressively found in an aging HIV population. Some ARV agents may impair glucose tolerance or even lead to hyperglycaemia. Sulfonylureas are CYP2C9 substrates and their concentrations may be affected by the NNRTIs, Etravirine and Efavirenz, the PI, Ritonavir and the integrase inhibitor, Elvitegravir. Repaglinide and Nateglinide are substrates of CYP3A4, CYP2C8 and CYP2C9, and co-administration of PIs and NNRTIs may increase or decrease exposure to these agents.[37]

Table 2.2 highlights the common DDIs found among ART patients on treatment for comorbid illnesses. Dismissal of the potential for DDIs could lead to unsuccessful pharmacological action of the drug(s) dispensed as well as the occurrence of adverse effects. These adverse effects can result in non-adherence to prescribed regimens, leading to poor clinical outcomes for the illnesses the medications were meant to treat.[47]

2.5 Management of drug-drug interactions

Although DDIs among ARVs are often inevitable, the management of these interactions can be improved. Low awareness and identification of clinically significant DDIs are a major barrier to safe ARV prescribing, additional attention should be given to drug-related adverse effects and drug efficacy.[39,41] HCPs should make use of available online resources to routinely screen for important DDIs before initiating new medications. To achieve better therapeutic outcomes and conserve patients in care, a variety of strategies can be adopted by HCPs to successfully address the multitude of challenges facing HIV patients. Executive measures that can be initiated to minimize the risk of adverse outcomes from clinically significant DDIs involve the integration of national treatment programmes for HIV and other diseases (with protocols that reduce DDIs), development of a wide area of networks for PV and improvement in the quality of prescribing through training and education of HCPs. Increased knowledge of conventional interactions involving ARVs on a country-specific basis will allow for targeted training, monitoring and protocol development.[41]

2.5.1 Multidisciplinary care

Many HIV affected patients may not reach optimum care as they are faced with certain constraints, namely; logistical barriers (means of transportation and elderly and/ or child care), coordination barriers (locating an HCP and navigating the healthcare system), individual barriers (drug-dependence, mental illnesses, HIV-related aging, and the occurrence of comorbidities) and systemic barriers (poverty, stigmatization and access to suitable housing).[48] The use of a Multidisciplinary care team may reduce these barriers for patients. Depending on the overall health of the patient, specific HCPs are required. The different types of professionals are found in Table 2.3 below:

Table 2.3: Professionals constituting a multidisciplinary team.[49]

Primary HIV Care Provider	The primary provider could be a medical doctor, a physician assistant or a nurse practitioner who is tasked with planning the patients treatment regimen, prescribing ARV medication and observing their progress.
Infectious Disease Specialist	The infectious specialist in the case of an HIV patient will diagnose and manage infections that are common among HIV patients, infections such as Hepatitis C, TB and certain types of pneumonia.
Nurses and Medical Assistants	These HCPs provide care and assistance during visits to the Doctor; blood tests and other laboratory samples are taken by them.
Mental Health Provider	6 out of 10 HIV patients are affected with depression. The HIV care team should include a psychologist, counsellor, or psychiatrist who is able to treat any mental health disorders and to offer emotional support.
Nutritionist/Dietitian	HIV patients require a diet that can help boost their immune system, this can be provided by a nutritionist or dietician.
Social Worker	Help patients navigate their daily challenges.
Other Team Members may include members who provide: • Spiritual care • Substance use/abuse counselling • Transportation assistance	

Based on published literature, 55% of patients in multidisciplinary care continue with medical care for at least a year in comparison to only 43% of patients in standard care. Research also reveals that patients in various models of multidisciplinary care were 3.3% to 8.1% more adherent to medication than those in standard care and the insertion of pharmacist support in the care team substantially improves adherence and better therapeutic outcomes.[48] By working together and communicating efficiently, a multidisciplinary approach has a better advantage of identifying pDDIs and managing them so as to provide the patient with an improved quality of life.

2.5.2 Patient-Professional relationship

A positive trusting relationship with successful communication between patients and HCPs improves the effectiveness of care utilization and health outcomes.[50] Studies have reported that trust between patients and their HCP is the foundation for effective treatments and fundamental for patient-centred care.[51,52] A study conducted by Chou Ying-Chi[53] in 2019 investigating the influence of risk of DDIs and time availability on patient trust, satisfaction and co-operation with clinical pharmacists has indicated that patient trust is positively influenced by the risk of DDIs and time availability, this in turn has a positive effect on patient satisfaction and co-operation between patients and clinical pharmacists. If HCPs communicate effectively with patients, patients will be more at ease with the clarified information and receive better service. Consequently, patients who receive better care have more trust in the healthcare system and have better therapeutic outcomes.

2.5.3 Integration of care

There is a need for the integration of care for patients on ARVs with NCDs. An integrated service wherein health care personnel provide services to both groups of patients within the same establishment as well as provide adherence support for both NCDs and ARVs. Studies from 2 Cambodian provincial hospitals wherein the induction of chronic disease clinics for the combined care of HIV/AIDS, Diabetes, and HTN has shown retention rates in patients with Diabetes and HTN. The outcome of patients on ARVs had improved with CD4 levels increasing.[54] Extending such facilities to the primary care level would promote patient access as well as provide a more comprehensive service by allowing patients with comorbidities to have their NCD and ARV treatment care reviewed in one visit. This will also aid in decreasing the amount of DDIs between ARVs and NCDs as medication given from one facility has a smaller chance of interactions compared to medications received from multiple physicians and pharmacies.[33]

2.5.4 The role of a pharmacist

In the past, a pharmacist was tasked with the production and dispensing of a limited number of drugs. With the growing number of accessible drugs and the increasing complexity of drug therapy, such as the treatment of HIV-related diseases, the role of a pharmacist is now more patient-centred rather than product-centred.[55] Pharmacists are identified as established and integral members of HIV health care teams. Their involvement in the care of HIV infected patients has been associated with improved patient outcomes, including enhanced adherence, reduced pill burden and dosing frequency, greater increases in CD4 cell counts, higher rates of viral suppression and decreases in medication errors.[56] In most cases, pharmacists are the patients last contact with the health care system before therapy is initiated thus placing pharmacists in a position to effectively monitor drug regimens. With their intricate knowledge of medicine, they are able to relate unanticipated symptoms encountered by patients to potential adverse effects of their drug therapy.[55] They have the opportunity as well as the training, to detect the occurrence of polypharmacy and possible DDIs and ADRs. Pharmacists can also counsel patients on the many questions regarding drug safety and side effects, they can discuss the possibility of adverse effects of medications in a balanced manner, with emphasis on the benefits of therapy and presentation of strategies for managing these effects.[55,56] Pharmacists are able to serve as an intermediary for the patient and prescriber by discussing any concerns the patient may have with their prescriber and assisting in finding strategies to improve adherence especially among HIV patients, pharmacists can also help patients manage ARV side effects by making certain recommendations.[57] One of the duties of a pharmacist is to prevent the use of unsafe drug regimens and to prevent the dispensing of interacting drugs. Pharmacists are required to use a medical screening programme for this challenge.[58]

A recent study at St Luke's/Roosevelt (SLR) Hospital Centre (New York, NY) reported that the knowledge and experience of a clinical pharmacist can often help distinguish between significantly important and unimportant DDIs and can assist in a doctor's decision-making regarding drug therapy. The involvement of pharmacists in this study led to a statistically significant decrease in number of interactions, DDI rates decreased by 65%. The daily evaluation of patients' files as well as the pharmacist's involvement showed an improvement in the identification of DDIs. The study

recommends that pharmacists should be included in therapeutic decisions as this assists in the management of DDIs.[59] The intervention of clinical pharmacists used when solving or preventing drug-related problems are largely approved and adopted by prescribers. An acceptance rate of 41–96% has been reported.[60] Randomized controlled studies show that interventions made by clinical pharmacists following consultations with physicians cause a decrease in the occurrence of inappropriate prescribing as well as fewer ADRs.[60,61]

Pharmacists play vital roles in optimizing HIV treatment outcomes in multiple ways and in all medical settings. These include; ensuring patients are taking a complete and appropriate regimen, recommending alternative therapy, dose or formulation adjustments and mitigating DDIs. In an effort to improve the quality of care in HIV-infected patients, more institutions are partaking in several forms of ART stewardship, often composed of a team led by pharmacists specialized in infectious diseases and/or HIV.[62] From the studies mentioned above, it may be deducted that the majority of interventions made by a pharmacist are of high clinical significance for the patient. Thus, pharmacists have a key role to play in the prevention, identification and reporting of DDIs.

2.6 Conclusion

From the data reviewed, it was found that there is a scarce amount of evidence-based data on HIV and NCD drug interactions. Thus, a robust method to determine the prevalence of pDDIs among medications is required. Such a study has the potential to increase the knowledge of the pharmacokinetics and pharmacodynamic interactions among HIV medications (in South Africa). The study can also be used as a guide in ARV therapy programmes. In doing so, South African PV systems can be strengthened. It was also found that a pharmacists' role has become essential in the management of chronic diseases in patient-centred medical facilities. Furthermore, the use of electronic information systems has been a milestone in identifying and intervening drug related problems such as DDIs. These systems provide a valuable source for cost-effectiveness/ outcome analysis. It can be noted that the presence of pharmacists on ward rounds, better communication between prescribers and pharmacists as well as the use of a multidisciplinary approach leads to a decrease in

DDIs and better clinical outcome for patients. Based on the literature reviewed, pharmacists should be used more effectively in the healthcare system to help reduce drug related problems and improve the outcome of pharmacotherapy.

CHAPTER 3

METHODOLOGY

A mixed methods research design was employed to achieve the objectives of this study. Creswell[63] defined mixed methods research as “a procedure for collecting, analysing, and ‘mixing’ of both quantitative and qualitative research and methods in a single study to understand a research problem.” Mixed method research enhances the integrity of findings, allows for more divergent results and minimizes unimethod bias.[64,65]

In this study, Creswell and Plano's convergent parallel design was employed. This method is also known as the “triangulation” design and is used to incorporate complementary quantitative and qualitative results to establish a greater understanding of the research topic.[66] The outline of the convergent design used is depicted in Figure 3.1 below. Phase 1 included a quantitative cross-sectional retrospective analysis of patient files to determine the prevalence and management of pDDIs and phase 2 employed a qualitative approach wherein pharmacists’ perceptions on DDI management strategies were determined. Within the convergent design, the parallel-database variant was adopted. This allowed for the two sets of data to be collected and analysed independently and then synthesized during the discussion.

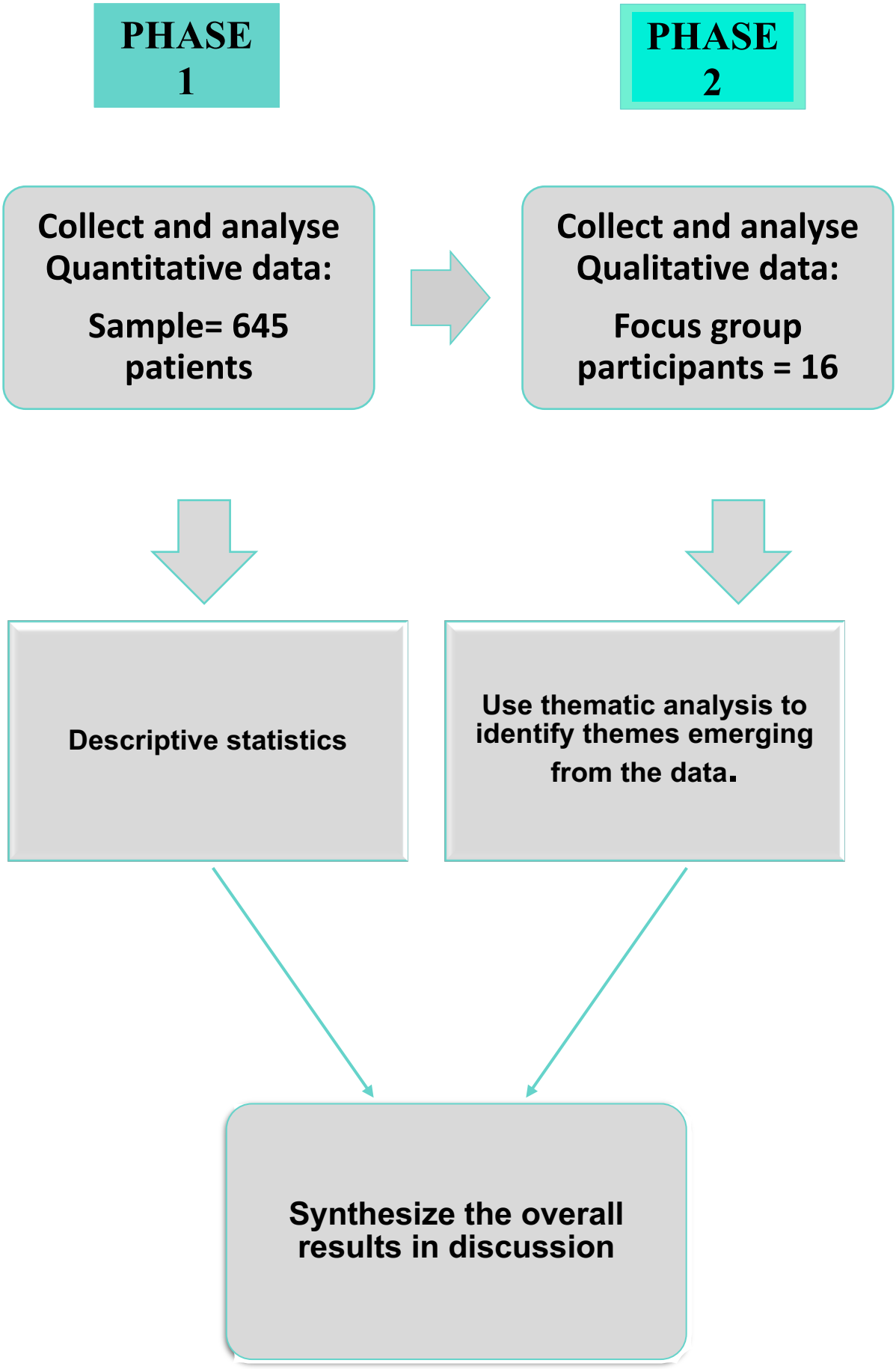


Figure 3.1: An overview of the study design[66]

3.1 Phase 1

3.1.1 Study site

The quantitative retrospective analysis of patient records was conducted at the Themba Lethu HIV Clinic (TLC) in Gauteng. The clinic is a large public-sector, outpatient, accredited ARV treatment initiation and on-going treatment site located within a tertiary teaching hospital. This specific site was chosen as all prescriptions dispensed at the clinic capture patient and prescription data on an electronic capturing system simplifying the data extraction process. The data was obtained through Right To Care (RTC), a non-government organization, involved in the capturing of patient data and prescriptions at the clinic. TLC is a government/public organisation that works in partnership with RTC. Permission to access patient files had been obtained from the tertiary hospital CEO offices and TLC (Appendix B1).

3.1.2 Participants

TLC uses TherapyEdge-HIV™ as the patient management system and Trimed® as the dispensing system. Patient information is captured into an electronic medical record at the time of the patient encounter. Data of patients who visited the clinic from the year 2015 to 2017 and were prescribed ARVs and agents used to treat cardiovascular, respiratory, epileptic, endocrine or psychotic conditions were filtered out of the patient database. These patients were included in the study based on the criteria depicted in Table 3.1.

Table 3.1: Inclusion and Exclusion Criteria for the study sample.

Inclusion Criteria	Exclusion Criteria
1. HIV positive patients on ART.	1.Patients < 18 years of age
2. HIV patients on treatment for an NCD (including epilepsy, psychosis, endocrine, cardiovascular or respiratory conditions).	2. Patients not attending the clinic for the full 3-year-period.
3. All prescriptions consisting of two or more drugs were analysed.	3. Pregnant patients

3.1.3 Sample size

Sample size was determined using a statistical analysis equation shown in Equation 3.1 below:

$$N = \frac{z^2pq}{e^2}$$

N= Sample size
z= 1.96 for a 95% confidence interval
p= Expected prevalence
30% prevalence =0.3[67]
e= Level of precision= (0.05)

Equation 3.1: Sample size calculation used to determine sample population of the study.[68]

Using a confidence interval of 1.96 and a 95% confidence level, the appropriate sample size for this study was 322.69 patients. This was then doubled to produce more accurate results. A sample size of 645 was used.

3.1.4 Data collection

The patient files extracted from the TherapyEdge-HIV™ patient database contained symptom history, lab results, doctor's notes, prescriptions and a therapy evaluation system that detects DDIs, provides information of each drug as well as possible side effects. Patient files from January 2015 to December 2017 were analysed for pDDIs. These files were encoded and stored on a password protected device to maintain confidentiality. All the information accessed by the researcher remained anonymous as no patient names were recorded, only demographic, drug and clinical information was captured as per data collection sheet attached in Appendix B2.

3.1.5 Data collection tools

3.1.5.1 Screening of prescriptions for pDDIs

Once the patient data forms were captured, the information was transcribed on a Microsoft Excel™ sheet. pDDIs were identified using Lexicomp®, a computerized drug and clinical information programme.[69] Lexicomp® was accessed through UpToDate® via the university's access. Lexicomp® software is able to provide a risk rating category with each pDDI and recommends the necessary actions required to respond to the interaction. The risk rating categories are found in Table 2 attached in Appendix B3. Drugs listed on each prescription were entered into the Lexicomp® programme, the

software then identified and categorized all pDDIs as per Table 3 attached in Appendix B4. From the prescriptions, each drug was analysed for any potential interaction with the other drugs.

3.1.5.2 Determining the prevalence of DDIs

Prescriptions between January 2015 and December 2017 was analysed for the prevalence of pDDIs. The prevalence of pDDIs was determined according to Equation 3.2 below:

$$\% \text{ Prev.} = \frac{Np}{Nt} \times 100$$

Where: % Prev. = Prevalence proportion
Np = Number of pDDIs that occurred
Nt = Total number of pDDIs

Equation 3.2: Prevalence calculation used to determine the prevalence of pDDIs.[70]

pDDIs were also assessed according to the different patient groups that fell within the study populations to determine which patients are at greater risk for DDIs. These include: demographic characteristics (advancing age (18-28, 29-39,40-50, 51-60, >60) and gender) .

3.1.6 Data analysis

Data was categorically captured on Microsoft Excel™. Statistical analysis was then used to explore the overall prevalence of pDDIs as well as the prevalence of pDDIs and their risk ratings. The statistical analysis was descriptive in nature. Categorical variables, including gender, age, comorbidities, number of pDDIs and severity of pDDIs are presented in the form of frequencies and percentages. Analysis was conducted to determine associations between age, gender, number of comorbidities and pDDIs using chi-square tests for categorical variables and Wilcoxon and Kruskal-Wallis tests for continuous variables. Logistic regression analysis was used to determine the associations between number of comorbidities and pDDIs. The results are shown as odds ratios with 95% confidence intervals (CI). A p value< 0.05 was considered statistically significant. Furthermore, the list of most frequent pDDIs

alongside their risk ratings and potential adverse outcome were reported. All statistical procedures were performed using STATA Version 15.

3.2 Phase 2

The qualitative component of the study consisted of three focus groups wherein pharmacists and pharmacy personnel from both the clinic and tertiary hospital participated.

3.2.1 Study site

The focus group sessions were conducted at the RTC meeting room above the clinic. The venue was in close proximity to both the clinic and hospital and accommodated all participants comfortably.

3.2.2 Sample and sample size

The non-probability purposive sampling method was applied to select participants that share pharmaceutical knowledge. This method was chosen as the research question being addressed is specific to the characteristics of the particular group.[71] A total of 16 participants participated in the focus groups. The group members comprised of 9 pharmacists; 1 pharmacy intern; 3 post basic pharmacist assistants; 2 basic pharmacist assistants and 1 learner basic pharmacist assistant. Females constituted of 68.75% of the sample. 50% of the participants had between 5-10 and >10 years of work experience. 56.25% of the participants encountered DDIs once a week and over 81.25% mentioned that they have not been trained in the management of DDIs.

3.2.3 Data collection

On approval of ethics, emails were sent out to personnel at TLC and the hospital pharmacy. The emails invited pharmacy personnel to the focus groups and provided a brief description of the study. Logistical details and administrative tasks (dates, office/venue bookings) were confirmed. On entering the venue, participants were provided with participant information forms which provided the participant with detailed information relating to the study. Thereafter, participants were required to complete informed consent forms and informed audio recording forms (Appendix B5).

Participants were provided with a numerical label as a means of identification. Two recording devices were used to record the focus group discussions and the researcher had an assistant as the acting scribe. Qualitative data was transcribed verbatim. Transcribed copies of data were stored on a password protected device, only accessible to the researcher and supervisors. The average duration for the focus groups was 60 minutes/ 1 hour.

3.2.4 Data collection tools

Demographic questionnaires were provided to the participants, these were completed prior to the focus group discussions (Appendix B6). The material used during the focus group addressed DDIs and its management. The focus groups were based on a broad set of questions adapted from a study by Anthierens[72] et al. (Appendix B7). However, questions deviated depending on responses from participants.

3.2.5 Data analysis

Braun and Clarke's[73] principles of thematic analysis were applied to the qualitative data from the focus groups. The focus group recordings were subjected to an inductive and essentialist thematic analysis wherein the identification, analysis and reporting of themes or patterns occurred. Braun & Clarke's 6-step framework plan was implemented as follows:

3.2.5.1 Familiarization with the data

The researcher transcribed the data from the focus groups and proofread the transcripts with assistance from the audio tapes. This allowed the researcher to have a better grasp of the participants' views.

3.2.5.2 Generating initial codes

Once the transcripts were confirmed for accuracy, coding was done for the identification of patterns and key words. A code book was then developed from which themes and sub-themes emerged.

3.2.5.3/ 3.2.5.4 Search for/ Review themes

The researcher combined and discarded initial themes that were deemed unnecessary. These were then compared against the combined abstracts of data to explore whether the theme worked in relation to the data.

3.2.5.5 Defining and naming themes

The researcher defined the themes and potential subthemes within the data to ensure the themes connect logically and meaningfully and are able to tell a coherent story.

3.2.5.6 Producing the report

A report was then produced explaining how the findings in the study meet the required objectives.

3.2.6 Self-reflexivity

Self-reflexivity relates to the practice of self-critique through which the researcher considers how her own experiences might or might not have impacted the research process.[74,75] As part of the study, the researcher was engaged in face-to-face contact with study participants. The researcher's professional background and experiences as a qualified pharmacist may have influenced her interactions with participants during the focus groups.

In an attempt to maintain research focus by grouping biases and attitudes of the researcher so that her influence on the research process would be minimized, the researcher maintained a reflective journal. After every focus group, the researcher noted down her immediate thoughts and interpretations before analysing the data. This allowed the researcher to capture in its raw state her own attitudes and responses without it being transferred to the data. Bias was also minimized by employing peer examination, whereby the research was discussed with colleagues and supervisors who were impartial to the study.

3.2.7 Ethics

For the quantitative phase, permission to access patient files had been obtained from the tertiary hospital CEO offices and TLC. This is a retrospective analysis of patient data, thus informed patient consent for the viewing of patient data was not necessary.

In the second phase of the study, the qualitative research, all patient data forms and questionnaires remained anonymous and confidential throughout, with the forms only being accessible by the researcher. The focus groups were recorded, and participants were required to sign informed consent forms and informed audio recording forms. Only the researcher, supervisors and ethics committee, if required, may listen to the recordings, which will be destroyed after the appropriate time. Although no personal or identifying information was associated with the recording or transcripts, the focus groups were not completely confidential as participants were exposed to each other and there was a risk of personal or confidential information being shared among the group members. The participants were asked to keep what was said in the group confidential, however, this was beyond the researcher's control.

Ethics approval was granted by the University of the Witwatersrand Human Research Ethics Committee (HREC) (No. **M180660**) (See Appendix B8).

CHAPTER 4

RESULTS

As described in Chapter 3, this study employed a convergent parallel mixed-methods design. The parallel-database variant was used. This allowed for the quantitative and qualitative data to be analysed independently and only brought together during interpretation.[63]

Results are presented in two sections. In the first section, Quantitative procedures for a convergent design are followed, the data was collected and analysed. In the second section, Qualitative findings and major themes from the focus groups are addressed; specific quotes were included as examples of responses. In chapter 5, the results of each phase will be discussed and then synthesized.

4.1: Phase 1- Determining the prevalence of pDDIs between ARVs and agents used to treat cardiovascular, respiratory, epileptic, endocrine and psychotic conditions.

4.1.1 General characteristics of study participants

Of the 645 patients analysed, females represented 62.79% of the sample population. Majority of the patients were between the ages of 40-50 and 51-60 respectively (43.88%, 31.63%). The average number of pDDIs per patient was 2.41 (± 2.41). A total of 195 comorbid diagnoses were made. Of the files analysed, there was no recording of a comorbid condition in 70% of the patient files. The most frequent conditions recorded was TB in 116 patients (60%) and HTN in 50 patients (25.64%). Additional comorbid conditions captured are represented in Table 4.1.1 below. The average number of comorbidities per patient found was 1.37 (± 0.58).

Table 4.1.1: Demographic variables and nature of pDDIs

Variables	n	%
Male	240	37.21
Female	405	62.79
Age mean (±SD)	50.7 (± 9.36)	
18-28	6	0.93
29-39	56	8.68
40-50	283	43.88
51-60	204	31.63
>60	96	14.88
Comorbid conditions diagnosed, mean (±SD)	1.37 (± 0.58)	
TB	116	60
HTN	50	25.64
Hypercholesterolemia	11	5.64
Dyslipidaemia	9	4.62
Diabetes	9	4.62
Peripheral Neuropathy	7	4
Epilepsy	3	1.54
Respiratory	2	1.03
Hepatitis B	1	0.51
Total number of DDIs	5,584	16
Risk ratings of pDDIs		
Minor interactions (Category B)	202	3.37
Moderate interactions (Category C)	3,834	63.94
Major interactions (Category D)	1,534	25.58
Contraindicated interactions (Category X)	14	0.23
Number of pDDIs per patient, mean (±SD)	2.41 (± 2.41)	

4.1.2 Comorbidities

Comorbidities were present throughout the different age groups. Results indicated that the highest number of comorbidities recorded was 4. A logistic regression test determined that patients older than 50 years of age were four times more likely to have 3-4 comorbidities (odds ratio 4.1 with a 95% CI of [1.5, 11.2]) compared to patients below the age of 50. Figure 4.1.1 depicts the number of comorbidities found in each age group.

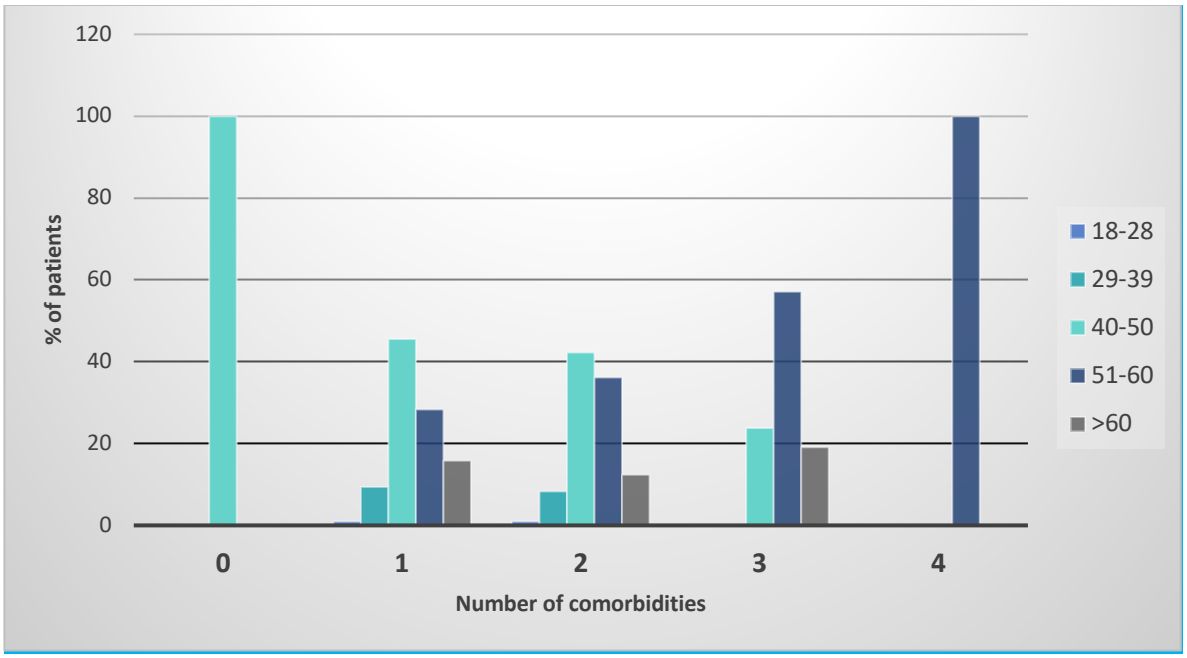


Figure 4.1.1: Patients presenting with comorbidities within each age group

Cases wherein patients were diagnosed with multi-morbidities were also identified. Such cases comprised of TB and HTN (3.08%), hypercholesterolemia, HTN and TB (0.51%) as well as cases wherein patients had both diabetes and HTN (1.03%). These results are further represented in Figure 4.1.1 below.

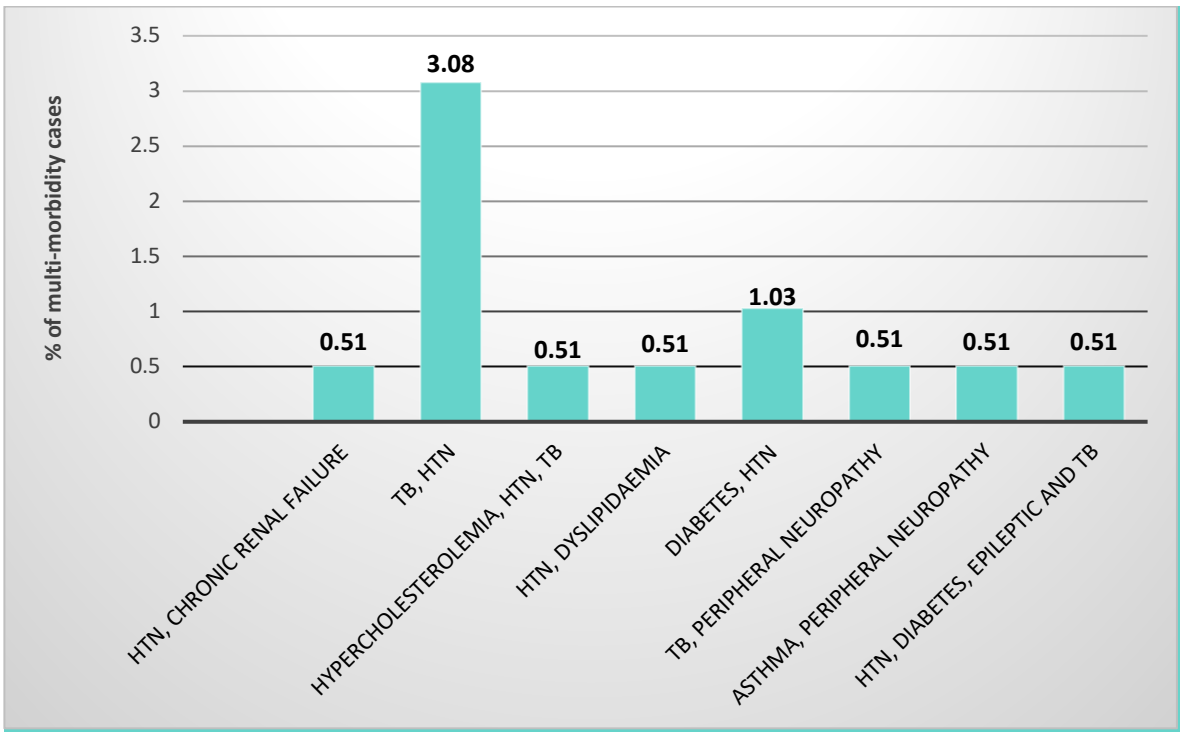


Figure 4.1.2: % of patients presenting with different multi-morbidity cohorts.

4.1.3 Drug-Drug Interactions

During the course of the 3 years, a total prevalence of 16% was determined. A total of 5,584 potential interactions were identified with an average of 2.41(± 2.41) interactions per patient. Figure 4.1.3 demonstrates the different type of risk ratings of pDDIs that occurred among patients in each year. The identification of pDDIs throughout the years (2015-2017) shows a p-value= 0.000, this indicates that there was a statistical significance among the pDDIs over the years.

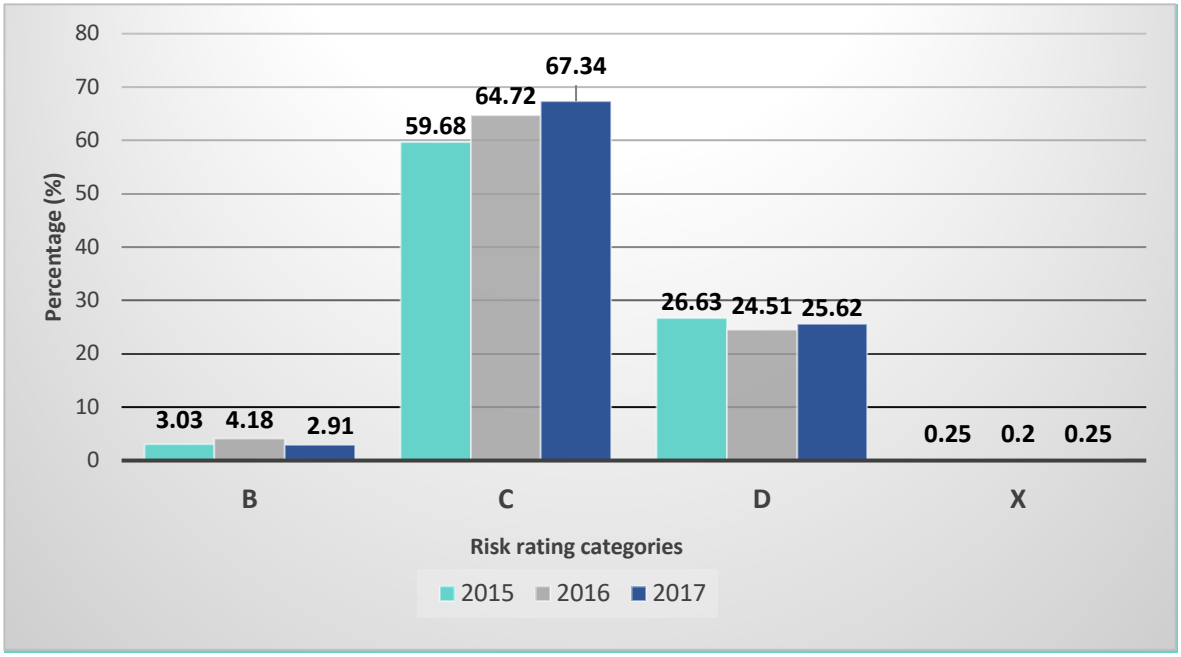


Figure 4.1.3: Risk rating categories of potential drug-drug interactions over the years 2015-2017

Among the 645 patients, only 6.87% of the population presented with no pDDIs. The most common pDDI rating found between ARVs and NCDs was Category C, moderate interactions (63.94%) followed by Category D, major interactions (25.58%). Figure 4.1.4 illustrates the prevalence and risk ratings of the pDDIs identified throughout the 3-year period.

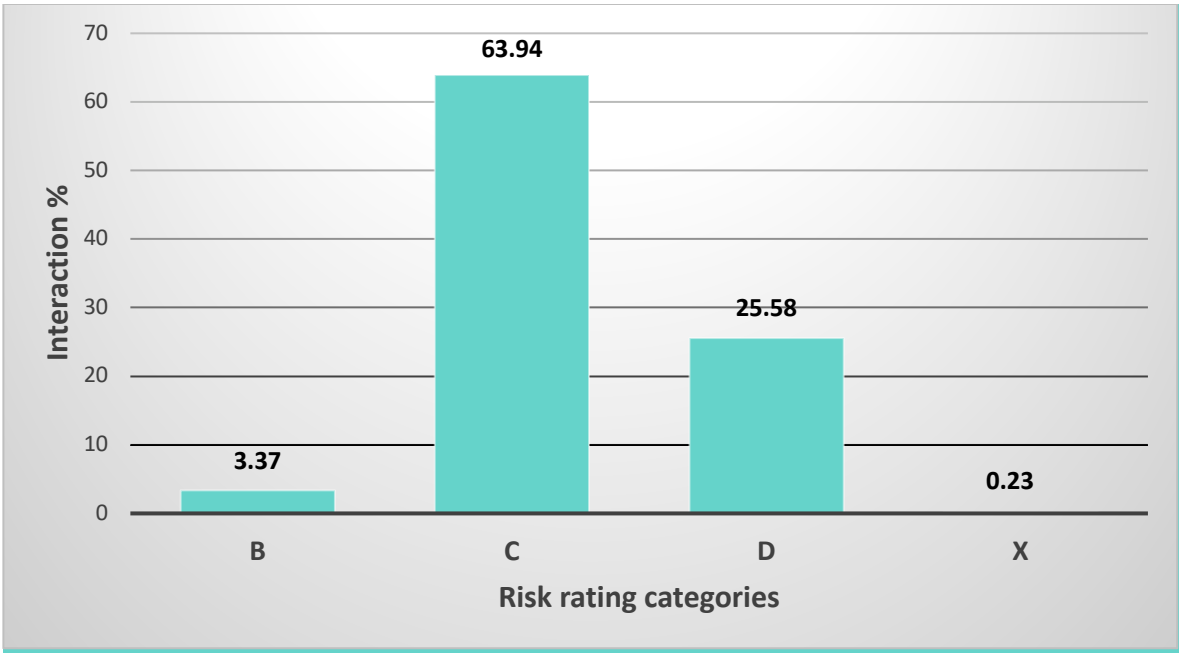


Figure 4.1.4: Risk ratings of the identified potential drug-drug Interactions between ARVs and NCDs

Table 4.1.2 enlists the most frequent interactions, their pDDI categories and potential adverse outcomes. Potential adverse outcomes of widespread interactions included bleeding, QT-interval prolongation, arrhythmias, gastrointestinal haemorrhage, additive hypotensive effects, increased risks of myopathy, drug toxicity and reduction in therapeutic effectiveness.

Table 4.1.2: Most prevalent identified pDDIs, their risk ratings and potential adverse outcomes

Type of drug-drug interactions	Risk rating	Number of interactions (n=5,584)	Potential adverse outcomes
Loperamide and Ritonavir	B	62	Increased blood levels of Loperamide.[76]
Salbutamol and Budesonide	B	8	Increased risk of hypokalemia.[77]
Diflucan and Efavirenz	B	5	Increased risk of an irregular heart rhythm.[78]
Norvasc and Feldene	B	4	Increased blood pressure.[79]
Amitriptyline and Efavirenz	C	408	Increase risk of an irregular heart rhythm(Arrhythmia).[80]
Atorvastatin and Efavirenz	C	436	Decreased effects of atorvastatin.[80]
Zidovudine and Ritonavir	C	339	Decreased plasma concentrations of Zidovudine.[81]
Tenofovir Disoproxil Fumarate (TDF) and Lopinavir	C	226	TDF serum levels increased.[82]
Pravastatin and Efavirenz	C	137	Decreased effects of Pravastatin.[83]
Enalapril and Hydrochlorothiazide	C	107	Additive hypotensive effects.[84]
Lopinavir and Ritonavir	D	544	Increased plasma levels of Lopinavir. Metabolic disorders including hyperglycaemia.[82]
Atorvastatin and Ritonavir	D	211	Increased risk of myopathy.[82]
Atazanavir and Ritonavir	D	119	Increases blood plasma concentrations of Atazanavir.[85]
Emtricitabine and Lamivudine	X	3	Headaches, diarrhoea, nausea, and rash.[86]
Simvastatin and Lopinavir	X	1	Increased risk of myopathy.[87]
Bactrim and Flagyl	X	1	QT prolongation and ventricular arrhythmias.[88]
Carbamazepine and Efavirenz	X	2	Reduced plasma concentration and effects of both medication.[89,90]

4.1.4 pDDI-associated risk factors investigated

4.1.4.1 Diseases affiliated with pDDIs

The top five diagnoses recorded in the files were TB, HTN, Hypercholesterolemia, Dyslipidemia and Diabetes. These were analyzed to determine the number of scripts containing a category C and D pDDI (Table 4.1.3).

Table 4.1.3: Chronic diseases and pDDIs (total number of scripts n = 5938)

Disease	Patients (n=645)	Prescriptions containing a category C interaction	Prescriptions containing a Category D interaction
TB	116 (60%)	106	27
HTN	50 (25.64%)	45	19
Hypercholesterolemia	11 (5.64%)	11	1
Dyslipidemia	9 (4.62%)	10	1
Diabetes	9 (4.62%)	9	3

4.1.4.2 Number of comorbidities associated with pDDIs

The risk of patients having more than one pDDI increased among patients diagnosed with 3-4 comorbidities (p= 0.0042) compared to patients diagnosed with 1 or 2 comorbid conditions.

4.1.4.3 The impact of gender

Although 62.79% of the patients in the sample were female, gender was not associated with an increased risk of pDDIs (p= 0.41). There were no statistical association between gender and pDDIs. The variables were independent of each other.

4.1.4.4 The impact of age

From the data analysed, category C and D (moderate and major interactions) were predominantly found among patients between 40-50 years of age. Potentially contraindicated interactions, category X, was for the most part identified among older patients over the age of 50. This is depicted in Table 4.1.4 below.

Table 4.1.4: Exposure to pDDIs stratified with respect to patients' age groups

	Risk rating (%)			
Age groups (years)	**B**	**C**	**D**	**X**
18-28	0.99	0.57	0.59	0.00
29-39	12.87	12.58	14.07	7.14
40-50	48.02 *	40.97 *	50.03 *	21.43
51-60	22.77	32.93	25.87	35.71 *
>60	15.35	12.95	9.45	35.71 *

*= age bands wherein risk ratings were the highest

The association between pDDIs and age was found to be statistically significant (p= 0.007). The risk of pDDIs increased significantly among patients over the age of 50. This can be seen in Figure 4.1.5 below.

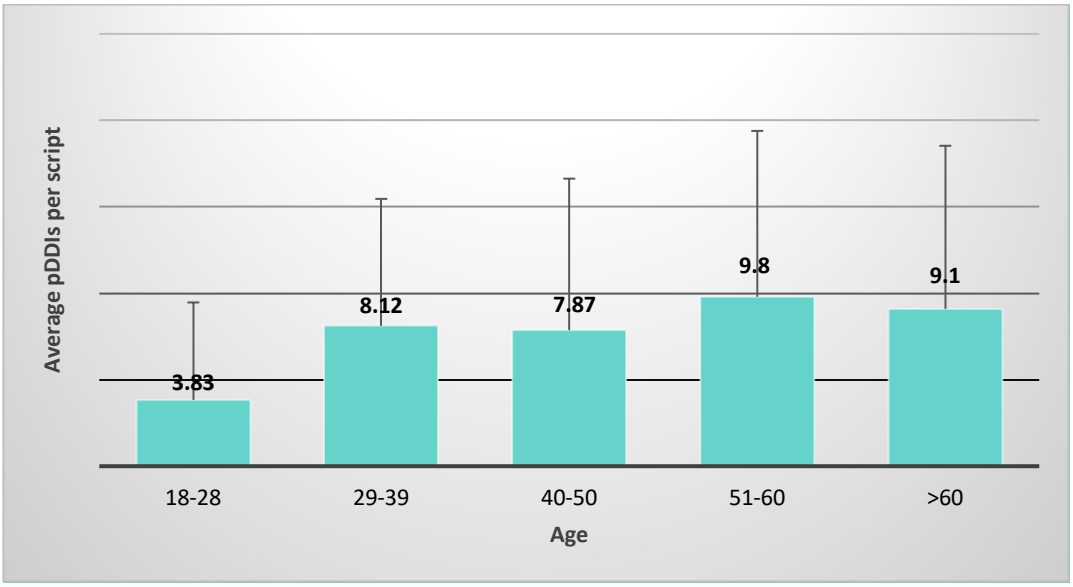


Figure 4.1.5: Distribution of potential drug-drug interactions among the different age bands.

4.2: Phase 2- Exploring the perceptions of pharmacists and pharmacy personnel on DDI management strategies.

Thematic analysis was used to analyse data from the focus groups. The identified themes and subthemes are presented in Table 4.2.1. Participants from the different focus groups are represented as P1, F1 (Participant 1, Focus group 1).

Table 4.2.1: Identified themes and subthemes emerging from focus groups

Themes	Subthemes
4.2.1: Potential risk factors that contribute towards DDIs	4.2.1.1: Patient ratios 4.2.1.2: Prescribing errors 4.2.1.3: Polypharmacy 4.2.1.4: Poor communication with patients 4.2.1.5: Clinic hopping
4.2.2: Perceived barriers in the detection and management of DDIs	4.2.2.1: Insufficient knowledge 4.2.2.2: Attitude of pharmacy personnel 4.2.2.3: Pharmacist- Prescriber relationship
4.2.3: Recommendations/ Strategies to manage DDIs	4.2.3.1: Patient education 4.2.3.2: Training of pharmacy personnel 4.2.3.3: Electronic systems 4.2.3.4: Multidisciplinary teams for HIV patients

4.2.1 Potential risk factors that contribute towards DDIs

Feedback from the focus groups indicated there to be a number of contributing factors that were perceived by pharmacy personnel within the institution that contributes towards pDDIs. These include patient ratios, prescribing errors, polypharmacy, poor patient communication and clinic hopping.

4.2.1.1 Patient ratios

Both pharmacies (clinic and hospital) experience large patient volumes daily. Among the three focus groups, all of the participants mentioned that pressure due to large patient volumes in relation to pharmacy staff limits their time with patients and thus leads to pDDIs being overlooked. This was illustrated by P2, F3:

"But I think we miss 99.99% of them [pDDIs] because of the pressure that's on us, we just there to push the numbers especially on overwhelming days."

To further support this statement, P1, F2 mentioned:

“Firstly, we are pressed for time because we need to basically work as fast as possible to get rid of that 800 people that are sitting in front of your face and also there’s no time, there’s really no time…”

Healthcare services includes an overall assessment of the patients therapeutic regimen as well as counselling of the patient.[91] In cases where patient numbers are high, staff at the pharmacy have limited time to spend with each patient. This was demonstrated by P2,F3:

“We don’t have time to analyse the script because we just pushing the numbers. And no time for the patient too, we don’t even counsel our patients, so to speak.”

The high patient volume affects the rates of frequent patient counselling provision and review of prescriptions which could potentially lead to the prevalence of pDDIs.

4.2.1.2 Prescribing errors

When questioned about the change in prescribing practices over time, several participants explained that the patient-prescriber ratio is much higher now compared to the past. Prescribers have to limit their time with patients which ultimately affects the quality of care each patient is given. Nine of the participants perceived that a patient's medical history is often overlooked by prescribers. This then presumably leads to pDDIs as illustrated by P2, F2:

"But if a doctor doesn't even have that chance [to ask about patient history] because they just trying to push the queue, obviously prescribing errors are on an increase purely because they're in a rush. Sometimes the doctor doesn't even remember the patient, which makes sense because if you've seen 100 patients in a short space of time, you wouldn't remember all 100 of them. So meaning in that 100 you probably would have made certain errors, prescribing errors, even in the scripts themselves, they forget to write sometimes the patient names, the date of birth, like simple stuff on the prescription wouldn't even be there so I don't know if that's to blame the fact that they don't have enough time with each patient which obviously compromises the quality of that counselling period which will obviously affect how they prescribe. So it just cascades kind of thing. So I think what changes is that they are more people sick now than before."

Data from the focus group discussions indicated that high patient numbers are one of the main causes of prescribing errors that lead to pDDIs being prevalent. Oversight in patient history and counselling of patients also contribute to pDDIs being undetected as described in the abovementioned quote.

Four of the participants stated that prescribing errors were the primary source of pDDIs. This was demonstrated by P2, F3:

"To manage the DDIs… I think mostly with the doctors, the prescribing needs to be controlled because that's where it starts."

The assumption was made that pDDIs can be controlled if prescribing errors are decreased.

4.2.1.3 Polypharmacy

Due to large patient volumes and limited time, there is an apparent oversight in patient history by prescribers, participants among each focus group mentioned that patients are being treated symptomatically. This results in a higher number of medications being administered to patients. The greater the number of medications a patient is on, the higher the chances that patient will be exposed to pDDIs. This was illustrated by P2,F1:

"So that's why I said, its uhh symptomatic treatment. This one doesn't work, put the other one… If that doesn't work …Then they are taking a whole lot. See for example, in the case of hypertension, the protocol says start with Ridaq 12.5mg then increase to 25mg, now this isn't working, put them on Perindopril, now continue Perindopril parallel down the line maybe after 6 months it's still not working, add another drug, maybe Amlodipine so now it is carrying on. If Ridaq isn't working why do you carry that one, take it out…. Those are the things that really causes interactions- without taking the history and symptomatic treatment."

When asked what contributes towards pDDIs. P2,F3's response was:

"Polypharmacy sometimes, the Drs are just ..sometimes I think they just prescribing."

Majority of the participants mentioned that incomplete patient history often leads to patients being treated symptomatically, prescribers are adding onto drug regimens rather than eliminating and trying different drugs, this then results in polypharmacy, a common risk factor of DDIs.[91]

4.2.1.4 Poor communication with patients

Participants acknowledged that lack of communication between HCPs and patients contributed towards the prevalence of pDDIs. Many of the participants mentioned the breakdown in communication with patients are as a result of the pharmacy set up and patient's reluctance to divulge information regarding their medication and health. Participants explained that the pharmacy set up does not allow for much privacy. This discourages patients from being more open with their HCPs as illustrated by P1,F2:

"At main pharmacy its very hectic and there's a lot of times when you do need that privacy but there's another patient standing in that patients personal space and even if you tell them to sit down, they don't listen to you. So there's certain things that obviously some people will be very uncomfortable disclosing, even if they have to talk to the doctor, sometimes they don't say certain things even cultural things, like maybe they won't want to say this is something that's bugging me."

Patients do not communicate with HCPs regarding other medication that they are taking (traditional or herbal), they do not mention certain things that might be bothering them (side effects they experience). The lack of information from patients presumably contributes to the prevalence of pDDIs. This was demonstrated by P1, F1:

"Sometimes they go the doctor and tell the doctor and when they come to us, we ask them if they experience some of the side effects and then when they become open with us, we are able to advise the patients, but it becomes difficult if they don't open up to us."

The breakdown in communication among the members of the healthcare system leads to important information being overlooked. This was exclaimed by P2, F3:

"There's absolutely no communication and there's a lot of information I think that we miss, the patients miss, the Drs miss, you know, everybody…"

4.2.1.5 Clinic Hopping

Five of the participants felt that one of the main contributors to pDDIs is clinic hopping. Patients visit multiple clinics, resulting in the administration or prescribing of multiple medications. Pharmacy personnel perceived that patients do not necessarily disclose this information to the pharmacy staff. This was discussed by P2,F3:

“And another thing, our patients also go to different hospitals and clinics, so they go to Johannesburg Gen and they get Amtas there, then they come to us and they get something that will react with Amtas, but they don’t tell us, we can’t pick it up. They go to Bara, get different medication from there and they take as they please.”

This was further demonstrated by P4, F1:

"I think another thing to add to that [factors that cause DDIs] is when a patient will take meds and go to different clinics. What would make it worse is if they take it incorrectly and not report it immediately when they see the symptoms. Continuing to take the medication incorrectly results in worse side effects.”

The data suggests that patients do not immediately disclose the additional medications that they are dispensed at different clinics. This statement further suggests that the co-administration of multiple medicines from different clinics result in worsening of side effects hinting at possible DDIs.

4.2.2 Perceived barriers in the detection and management of DDIs

Among the focus groups carried out, participants disclosed several factors that impede the detection and management of pDDIs. As such, three subthemes emerged. These include insufficient knowledge, attitude of pharmacy personnel and the pharmacist-prescriber relationship.

4.2.2.1 Insufficient knowledge

Among all three focus group discussions, participants indicated that they lacked sufficient knowledge on the identification and management of DDIs. The importance of this education was echoed when 81.25% of the participants in the focus groups mentioned they had not been trained in the management of DDIs.

When probed about possible reasons as to why pDDIs were not identified by pharmacy personnel, P2, F1 answered:

"I think as an HCP, lack of knowledge that's one thing, and ignorance."

This was the primary view among the focus group discussions. Participants revealed that they did not have the appropriate knowledge to deal with the vast amount of pDDIs. This was demonstrated by P2, F3:

"*Yes, we're lacking the knowledge as well. I did my pharmacy 20 years ago, you find that you've forgotten and its overwhelming as well, there's a lot of drugs, there's a lot to remember."*

Participants mentioned that they would be more likely to detect and manage pDDIs by *"Updating the knowledge".* (P1, F3)

This was further demonstrated by P2, F3:

"If we keep up with the knowledge we would be able to pick up certain interactions…"

4.2.2.2 Attitude of pharmacy personnel

Among the focus groups conducted, it could be noted that even though participants were aware of the factors that led to pDDIs, the majority of them expressed that the environment in which they worked would not allow for possible improvement in their interactions with patients. This was illustrated by P2, F1:

"But the only thing is you are seeing a lot of patients. For example, the main pharmacy now, there's about 200 patients waiting and there's no place to sit, patients are standing. How efficiently can we interact with each and every patient, you know. It's a practical possibility that you just want to push them out."

Participants coherently admitted to not analysing scripts for pDDIs, but rather *"just go according to the prescriber."* (P3, F2). When questioned about the dispensing system used by the hospital pharmacy, the lack of interest in patient history was highlighted by P1, F3:

"It's just a dispensing system. The patient will come with their script, you'll get their unique number from inside the file, you'll process the script as per and then a lot of the time, I don't know if my colleagues do it, we don't even bother to look at what they were taking before verse what they taking now (laughing), we just go with it."

The apparent disregard for patient history indicates how pDDIs might go by undetected.

Most of the participants were also not inclined to the idea of increasing time for patient counselling so as to better therapeutic outcomes. The participants exclaimed that adding a few extra minutes to counsel patients in the hope of decreasing medical issues *"is just not practical."* (P2, F3)

This was further demonstrated by P1, F3:

"Take 100 patients , 1 minute per patient , 100 minutes and you take 600 patients , 600 minutes, so… It can be doable [proper counselling] but it's just not practical, it's

just crazy. And also, the pressure that the patients put on us also, because pharmacy is the last stop, they just want to be out of there."

4.2.2.3 Pharmacist- Prescriber relationship

A common thread through the various narratives of participants was the complex relationship pharmacy personnel shared with prescribers. Across the focus groups, a difference in opinion was noted when participants were asked about their relationship with prescribers. Pharmacy personnel at the clinic commented that the prescribers work and communicate well with them, "They're always helpful." (P7, F2).

P4, F2 further demonstrated:
"I think the communication between us and the prescribers is not that bad because if there's something that I'm not sure of ill go to the prescriber and they'll clear it up for me."

However, pharmacy personnel from the hospital mentioned that their relationship with prescribers was *"Not good, to be honest".* (P2,F2)

Participants explained that when they are faced with problematic scripts such as pDDIs and duplications, pharmacy personnel have to work together with prescribers to help manage these interactions. In most cases the prescribers work together with the staff to fix the issue, however there are cases where prescribers are difficult to work with as stated by P1,F2:

"A lot of the time like P2 said, they're [prescribers] not very forthcoming, they don't want to believe that they do wrong and they don't want to like sort of understand that they have missed something, I mean we all human we do make mistakes…"

The participants pointed out that prescribers did not interact with them on a professional level and had a tendency of undermining the staff's pharmaceutical knowledge. Discussing this, P2, F2 noted:

"I think it's that superiority complex I think, I think it's the unwillingness to learn from each other and to actually appreciate the fact that you are an expert in this area and you are an expert in that area and actually trusting that okay you going to do your part and I can do my part and if there's a part of mine that I see you overstepping, to be able to let you know in a good way and for us to be able to interact in a professional way because sometimes I don't think its professional at all because when you call them, like she was saying you call them about Warfarin, they don't interact on a professional level with you, you know what I mean. We end up talking about who knows better, who has the ability to … It's more of an ego battle, if I can put it that way."

The tension with prescribers leads to poor management of pDDIs within the pharmacy.

4.2.3 Recommendations/ Strategies to manage DDIs

Overall, participants offered a range of recommendations to help identify and manage pDDIs. These include patient education, availability of DDI screening systems, training of pharmacy personnel and the use of multidisciplinary teams.

4.2.3.1 Patient education/ counselling

The importance of educating patients on their medication was agreed upon by all participants. Education in the form of posters, leaflets and oral presentations were some of the suggestions made by participants. Majority of the participants mentioned the use of *"Leaflets in the waiting room that they can read while waiting." (P1,F1)*

Five of the participants suggested oral presentations to help inform patients about the dangers of DDIs. This was demonstrated by P2,F1:

"Maybe while they are waiting it's better to communicate, talk to them. Some patients can read but some, they can't. I think oral presentations might help. At least maybe 50% can reach them, other 50% are not interested, its fine they can read."

Participants among all focus groups also mentioned the importance of continuous counselling, instead of warning the patient against something once off, HCPs should continuously remind them, this was illustrated by P4, F2:

"So maybe u should just keep telling them, not at the end of the day."

Participants noted the importance of empowering patients as this would enable them to be more alert while on their medication and more communicative with the pharmacist about potential problems.

4.2.3.2 Electronic systems

Participants explained that TLC uses TherapyEdge-HIV™ as the patient management system. This system alerts prescribers to possible DDIs, however, pharmacy personnel do not have access to these alerts. The hospital pharmacy does not have a patient management system, only a dispensing system that does not alert them to any pDDIs. With this in mind, participants unanimously felt that electronic patient management systems used to capture patient information and identify pDDIs would be better "*safety wise*" (P2, F1) and would also help fill the missing information gap that contributes towards pDDIs. P1,F2 explained:

"I do understand that TLC is gone paperless but a lot of the times there's no file so there's no history for the other doctors from the other clinics to now see what is going on, like what the patient is already on, whether it's working for them or not. So maybe if there was sort of a more comprehensive history taking [like TLCs electronic system] then it would help."

Participants also mentioned that having a DDI system would be preferable as opposed to basing DDIs on their own knowledge and research as this has not helped in the past. This was illustrated by P2, F1:

"I think from my point of view, the electronic system might help, you know, it's not possible to remember everything or at a business site it's not possible to refer each and every drug or something for an interaction."

The use of an electronic patient database minimizes issues such as patient history being overlooked, missing patient information and prescribing errors all of which lead to the presence of pDDIs.

4.2.3.3 Training of pharmacy personnel

All of the participants expressed interest in participating in training programmes which they felt would give them a better chance of detecting and managing DDIs. This was demonstrated by P4, F1:

"We need more training on the drugs so that when we see a script with interactions, we'll know this, and this don't go together."

With more training, staff would be better equipped to detect and manage pDDIs. The participants mentioned that training would help them familiarise themselves with common DDIs, this would be especially helpful on days when staff are strained for time due to large patient numbers. This was illustrated by P2, F2:

"If we get more training to be familiar with looking and actually immediately picking them [DDIs] up I think it will be easier. Because even on a busy day, if your eyes are trained to quickly pick up these interactions, I think it will be easier to identify and like, so you can isolate that case. So even if you seeing 800 patients, it doesn't mean it's going to be 800 different cases of interactions, even if it's just 10 at least if you can pinpoint those 10 and isolate it so you can spend just that little more time with it to try and make things better, I think that will be the best."

4.2.3.4 Multidisciplinary teams for HIV patients

A participant suggested the allocation of a set of specific doctors used to treat HIV patients and their comorbidities, to which a unified agreement was then made. P2, F2 illustrated:

"I'm thinking what if they are specific doctors that are allocated to deal with just this [HIV and comorbidities]…. instead of making it all the doctors, because the interns that come and go, the speed dials that don't work, there's all sorts of problems when it comes to communicating with doctors, so I would say, why don't they allocate doctors that specifically deal with this and are on the lookout for interactions between the ARVs and NCDs."

Among the focus groups, all of the participants mentioned that the administration of such a team would create better patient-prescriber relationships and help overcome some of the major factors that contributes towards pDDIs. If patients are seen by familiar faces on an ongoing basis, they are more likely to get comfortable and open up to these HCPs. This was demonstrated by P1, F2:

"It would mean that that patient would be seeing that doctor on a continuous basis, so that doctor already knows what's happening, can adjust [medications] if there's a need, can advise accordingly as to what the patient needs to do and also build that relationship with that patient, and maybe they won't be so like reluctant then, because now they see the same person for a couple of months and they get comfortable."

The use of a multidisciplinary team will help patients familiarise themselves with a set of doctors, patients will now be more at ease to speak to their doctors about any medical related issues they might be experiencing, and doctors would also be able to counsel the patients better.

Enabling such a unit would also improve the relationship between pharmacy personnel and prescribers. The pharmacy staff could acquaint themselves with the doctors within the team and if there are any script issues they would know who to contact. This was illustrated by P2,F2:

"It's just a matter of allocation as opposed to, would you say you need to employ more doctors. If u seeing 100 patients, but 100 different patients as opposed to seeing patients but 100 similar patients, I don't know if you get what I mean. So making it more of a focussed attention for them. So even if it's like 10 doctors that are appointed for ARVs only then at least I know that even if you on leave or whatever I know that Dr A,B and C are usually the ARV doctors, so even if A isn't here, B is here, and I'm sort of comfortable with B or C because I know these are doctors , it's not like interns coming in and out or new Drs coming in and out."

CHAPTER 5
DISCUSSION

This chapter is divided into three sections. Section A highlights the purpose of the research. Section B discusses the findings of the quantitative component of the study followed by the findings of the qualitative phase. Thereafter, in Section C an integrated discussion of the data emanating from the quantitative and qualitative methods follows. The reason for employing this technique is to present a cohesive discussion. The simultaneous discussion of the two data sets will allow for the exploration of the depth and breadth of emerging data.

5.1 Section A

Purpose of the research

This study aimed to investigate the prevalence and management of pDDIs among ARVs and medication used to treat NCDs. Three study objectives were identified: 1) Determining the prevalence of pDDIs between ARVs and agents used to treat cardiovascular, respiratory, epileptic, endocrine and psychotic conditions, 2) Classifying the severity of such pDDIs and 3) Qualitative exploration of pharmacists and pharmacy personnel's perceptions on DDI management strategies.

According to Creswell[92], mixed methods are utilized to "confirm quantitative measures with qualitative experiences." These methods provide strengths that counteract the weakness of both quantitative and qualitative research and also enhances research studies.[63,92] The quantitative methods provided data for the detection of pDDIs. Frequently diagnosed NCDs were also recorded as well as possible factors that led to pDDIs. pDDIs were identified using Lexicomp®. Results from the quantitative data analysis showed that pDDIs were prevalent among prescriptions and no recordings of pDDI management was noted. Analysis and interpretation of the focus group data led to information concerning the attitude of pharmacy personnel towards potential interactions.

5.2 Section B

5.2.1 Quantitative data

From the results procured, it was noted that the majority of patients were female (62.79%) and between the ages of 40-50 and 51-60 respectively (43.88%, 31.63%). This correlates with studies indicating the increasing tendency in HIV prevalence among people aged 50 years and older.[35,93] Over the years, mortality rates of women aged 15-54 years have increased rapidly with more than 50% of these deaths caused by HIV, 16% to infections and maternal causes and most of the remainder (24%) caused by the growing incidence of NCDs. Globally and in South Africa, the majority of aging patients seeking healthcare are women.[94]

HIV patients are at a higher risk of NCDs as certain ARV medications heightens the risk of heart disease and diabetes, while HIV itself increases the risk of certain cancers.[95] The amount of reports on cardiac events (acute myocardial infarction (MI), heart attacks) among HIV infected patients has drastically increased. Studies have reported there to be a decrease in HIV-related deaths and an increase in non-HIV–related deaths mainly due to cardiovascular diseases (CVDs), substance abuse and non-AIDS–defining cancers.[93,95] In Kenya, screening of almost 5800 patients found higher rates of CVD risk factors, specifically HTN in HIV infected patients than the general population. There were also indications that higher blood glucose levels are associated with second-line ARV therapy.[95] Many of these NCDs increase in frequency as people age as seen in the current study. Within the study conducted, all of the patients were concomitantly treated for HIV as well as NCDs. The average number of comorbidities per patient found was 1.37 (± 0.58) and patients with a higher number of comorbidities were ≥ 50 years of age. The most common comorbid conditions diagnosed were TB (60%), HTN (25.64%), hypercholesterolemia (5.64%), dyslipidaemia (4.62%), diabetes (4.62%), asthma (1.03%), peripheral neuropathy (4%) and epilepsy (1.54%). These diseases are among the most prevailing conditions in South Africa and fall within the country's quadruple burden of diseases.[35] From the study conducted, it was noted that the most diagnosed NCD was HTN, this aligns with other studies reporting the high prevalence of HTN among HIV infected patients.[96,97,98] Research has suggested that HTN is prevalent between 13-49% of HIV infected patients.[68]

The results from this study indicated that there was a statistically significant increase among the the pDDIs identified throughout the 3-year period (p-value=0.000). The odds for pDDI exposure were associated with a higher number of comorbidities (p= 0.0042) and the prevalence of pDDIs increased significantly among patients over the age of 50 (p= 0.007). This is conducive with a study conducted by Neto et al.[99] showing a higher relative risk of pDDIs in older patients with a diagnosis of 3 or more diseases. In the current study, only 6.87% of the prescriptions had no pDDIs. The majority of interactions were category C (moderate interactions) with 63.94%. Most of these interactions occurred between ARVs (Zidovudine and Lopinavir, TDF and Lopinavir) and ARVs and antihypertensives (Atorvastatin and Efavirenz, Pravastatin and Efavirenz). Category C interactions were consistent among all age groups although patients between the ages of 40-50 held the highest amount of category C interactions (40.97%), followed by patients between the ages of 51-60 (32.93%). Category C interactions are classified as clinically significant. However, the benefits of these two medications simultaneously administered outweigh the risks. HCPs are advised to implement an appropriate monitoring plan for possible negative effects.[100]

Category D interactions (major severity) was identified as the second highest pDDI with 25.58%. The most frequent interactions of category D occurred between Atazanavir and Ritonavir, Atorvastatin and Lopinavir and Atorvastatin and Bezafibrate. 50.03% of category D, major interactions, were present among patients between 40-50 years of age and 25.87% in patients between the ages of 51-60. In such cases, therapy modification should be considered and specific actions should be taken to reduce the toxicity following the co-administration such agents.[100] Among the most frequent comorbidities diagnosed, the scripts from files in which TB and HTN were diagnosed recorded the highest prevalence of major interactions (category D). The risk is augmented by altered pharmacokinetics as a result of disease factors such as impaired renal and hepatic function. Thus, pDDIs are more likely to manifest as clinical effects in these patients.

The lowest category of pDDIs recorded was Category X (contraindicated) with 0.23%. Examples include potential interactions between Slow K and Amitriptyline, and Carbamazepine and Efavirenz. 35.71% of these pDDIs were identified in patients over

the age of 50. Although these patients were exposed to such contraindicated pDDIs, their scripts showed no signs of changes to drug regimens. The use of such agents is generally avoided as the risks outweigh the benefits.[100] These findings align with other studies reported.[42,101,102] Potential adverse outcomes of the pDDIs identified include cardiac arrest, cases of hypoglycaemia and increased risk of myopathy. The pDDIs also affect drug concentration levels which negatively influences therapy outcomes. These adverse outcomes highlight the importance of careful identification and monitoring of pDDIs so as to improve the quality of the prescription process and the safety of drug therapy. Such duties fall within the scope of practice of a pharmacist.

5.2.2 Qualitative findings

The members of the focus groups consisted of different pharmacy personnel; pharmacists, pharmacist assistants, pharmacy interns and post basic assistants. The hierarchy of positions might have been a factor that lead to the pharmacists and participants with dominant personalities taking charge of the conversation. It could be noted that there were cases where the quieter participants might have spoken more if given the opportunity.

Three overarching themes were derived from the qualitative data collection phase, these themes expand into sub-themes. Each theme and its encompassing categories were formulated based on the commonalities associated across the quotes and ideas conveyed by the participants.

5.2.2.1: Theme 1- Potential risk factors that contribute towards DDIs

All participants felt it was the setting in which they worked in that contributed to the prevalence of pDDIs. They indicated that one of the main contributors towards pDDIs was the high patient ratios, "*the pharmacy sees an average of 800 patients a day*." As a result of the high patient numbers, both pharmacy personnel and prescribers may be required to process prescriptions at higher rates, thus reducing their ability to adequately evaluate prescriptions and counsel patients effectively. This then contributes to medical errors like pDDIs. This finding is consistent with other reports concerning workload and medication errors such as pDDIs.[103]

Factors such as clinic hopping, polypharmacy and poor communication were also seen as significant risk factors of pDDIs. Clinic hopping occurs when patients visit different clinics without necessarily informing their HCPs about the other medications they are on. This results in patients administering multiple medications simultaneously all of which have potential for DDIs. Another contributing risk factor of pDDIs mentioned, was polypharmacy. Participants indicated that in most cases where patient history is omitted, patients are treated symptomatically, prescribers are adding onto drug regimens rather than eliminating and trying different drugs, all of which results in polypharmacy, *"…the Drs are just.. sometimes I think they're just prescribing."* Polypharmacy has been affiliated with increasing age and with an increased risk of ADRs, poor adherence, hospitalizations and DDIs.[98]

Lastly, the breakdown in communication between patients and pharmacy personnel was identified as a contributing factor towards pDDIs. Participants stated the lack of appropriate private counselling areas has resulted in patients being hesitant to disclose certain information regarding their health and medications, *"There's absolutely no communication and there's a lot of information I think that we miss, the patients miss, the Drs miss, you know, everybody…"* Failure to communicate in healthcare can result in non-adherence, patient dissatisfaction and an increase in preventable adverse effects. Research has indicated that 27% of medical malpractice is caused by communication failures. Effective communication in healthcare is crucial as it leads to positive health outcomes and a reduction in medical errors and patient injury.[104]

5.2.2.2: Theme 2- Perceived barriers in the detection and management of DDIs

Pharmaceutical care requires pharmacists to work together with the patient and other HCPs to "promote health, prevent disease, assess, monitor, initiate, and modify medication use to assure the safety and effectiveness of drug therapy regimens."[105] This includes detecting potential interactions among medications that may cause the patient harm. Participants from the study reported barriers that prevent them from identifying and managing pDDIs, these include; educational barriers, the attitude of pharmacy personnel and pharmacist-prescriber relationships. The findings of the study carried out indicated that although 56.25% of the participants encountered DDIs once a week, their knowledge on DDIs is inadequate. Participants revealed that they're "*lacking the knowledge"* to detect pDDIs and 81.25% of them mentioned they have not been trained in the management of DDIs.

Participants attitude towards improving patient outcomes by enhancing pharmaceutical care was predominantly negative. They pointed out that attempting to change their current situation was futile. They believed that implementing pharmaceutical services such as proper counselling and identification of pDDIs is "*just not practical"* due to the high patient numbers. Another hindrance towards the detection and management of pDDIs was the pharmacist-prescriber relationship. Pharmacists at the hospital mentioned their complex relationship with prescribers as a possible barrier towards identifying and managing pDDIs. The pharmacists mentioned that the prescribers have a "superiority complex" and do not interact with them in a professional manner. The participants explained this behaviour often made it difficult to work with prescribers when dealing with problematic scripts. TLC personnel commented that they have a better relationship with prescribers which leads to less prescribing errors occurring in TLC compared to the hospital pharmacy. The barriers mentioned in the study are conducive with other studies that showed lack of training, lack of acceptability by physicians, pharmacists' lack of therapeutic knowledge and clinical problem-solving skills as some of the main challenges that hindered the application of pharmaceutical care.[106, 107]

5.2.2.3: Theme 3- Recommendations/ Strategies to manage DDIs

Throughout the focus group discussions, participants suggested various ways to help identify and manage pDDIs, these include; patient education, training of pharmacy personnel, availability of electronic systems and multidisciplinary care for HIV patients. Patient education is significant in reducing the risk of certain DDIs and increasing adherence.[103] Participants mentioned the importance of empowering patients with regards to their medication. They suggested the use of leaflets, oral presentations, verbal instructions from the HCP and patient instruction leaflets given with the prescription to help educate patients so that they would be more alert while on their medication.

Another suggestion made for the management of pDDIs was the need for training. Participants strongly expressed their interest in training programmes to help identify and manage pDDIs, *"We need more training on the drugs so that when we see a script with interactions, we'll know this, and this don't go together."* They also mentioned that although a patient management system exists in the clinic, pharmacy personnel have no access to the pDDI alert system. All pharmacy personnel felt that they should have access to an electronic patient database that alerts pDDIs as it will to a large extent reduce possible medical complications and consequences, "*I think from my point of view, the electronic system might help, you know, it's not possible to remember everything or at a business site it's not possible to refer each and every drug or something for an interaction."*

Lastly, the use of multidisciplinary teams for HIV patients was recommended. Participants felt that using such a team would improve patient-prescriber relationships and help overcome some of the major factors that contributes towards pDDIs. HIV patients are constantly at risk for other opportunistic diseases. The rise of NCDs among these patients has now left them seeing multiple physicians. This leads to symptomatic treatment, polypharmacy and eventually potential for DDIs, all of which affect patient adherence. By using a multidisciplinary care team that works together and communicates efficiently, pDDIs will be identified and managed better which results in patients living a life of improved quality.[108]

5.3 Section C: Integration of quantitative and qualitative results

Studies have indicated that an estimated 23–41% of DDIs occur in HIV.[7] This could be due to the cocktail of drugs used to treat comorbidities, alongside ARVs, consequently, the potential for DDIs arises. According to published literature, 18-30% of all hospitalized patients encounter a DDI, DDIs are responsible for 3-5% of all hospital admissions and 30% of these patients have a second drug reaction during their hospital stay.[8] In this study, the prevalence of pDDIs in patients treated for HIV and other comorbidities was 16% with a statistical significance identified throughout the 3-year period (p-value=0.000). This may be attributed to factors such as increased age, polypharmacy, the presence of comorbidities and the involvement of multiple physicians, all of which are common among HIV patients.[109] No statistically association were found between gender and pDDIs, which is consistent with findings described in previous studies.[9,39,110] Among the pDDIs identified, moderate pDDIs were mostly observed, however, major pDDIs were also observed in a substantial number among older patients. These DDIs lead to many adverse drug effects (ADEs), decreasing patient quality of life and adding onto the rising costs associated for both the patient and healthcare system.[111] Therefore, the identification and appropriate management of these pDDIs is essential to help lessen the burden on South Africa's overstretched health system.

Pharmaceutical care warrants that pharmacists not only dispense medications, but also take on the responsibility of improving the quality of patient therapeutic outcomes.[112] This includes detecting any drug related problems such as pDDIs. Pharmaceutical care is a practitioner driven service that depicts the barriers observed by pharmacist's are of great significance in the application of the service.[113] The study conducted revealed that pharmacy personnel would like to provide pharmaceutical care but have difficulty finding time for it. This mirrors the findings of a review conducted by Foppe Van Mil.[112] In his review he mentions assessing the behaviour of pharmacists with regard to pharmaceutical care. The review concluded that pharmacists are prepared to provide care and recognize its necessity, but they are still faced with many barriers in practice.[112] This is conducive with the finding of the study carried out.

Pharmacy personnel have accepted that the detection and management of pDDIs falls within the scope of pharmaceutical care, however they have reported that high patient numbers heighten the risk of dispensing a pDDI. This was seen within the study where only 6.87% of the prescriptions analysed had no pDDIs. Participants also felt that prescription errors contributed towards pDDIs. Prescription volumes in pharmacy settings have risen at phenomenal rates since the mid-1990s. The increase in the number of prescriptions is guided by a variety of factors, involving availability of a larger amount of medications, an increase in the overall population and an increase in the number of elderly patients who take more medications.[112] All of these factors are common among HIV patients with comorbid illnesses.

Participants from the study mentioned the widespread use of medicines, particularly in older patients, prescribed by different physicians, often unaware of other prescriptions or self-prescriptions by the patient, can significantly increase the risks of polypharmacy and hence pDDIs. This was conducive with the findings of the study where the high prevalence of pDDIs was associated to age and an increased number of comorbidities. The risk of pDDIs is likely to rise in an aging HIV population due to polypharmacy for the treatment of multiple comorbidities as well as the simultaneous use of ART.[110,114] Holtzman C et al.[43] conducted a study on the extent of polypharmacy and the risk of DDIs among HIV patients of different age groups. The results indicated that a wider range of non-HIV drugs increases the risk of clinically significant interactions for older patients, notably those over the age of 50. These results can be attributed to the complex drug therapy regimens these patients are prescribed which may have a negative effect on the pharmacokinetics and pharmacodynamics of the drugs involved through induced changes in drug metabolism and excretion as well as the body's response to drugs.[99,115] Such predictors should be considered in clinical practice to prevent negative clinical consequences of DDIs. The occurrence of these pDDIs may result in decreased therapeutic benefit, adverse effects, or patient harm.

Closer attention needs to be paid to pDDIs, specifically cardiovascular, antihypertensive, antiarrhythmic, digitalis, CNS drugs and diuretics, particularly in terms of side effects and the resultant economic burden that they may produce.[105] All of the abovementioned drug classes are frequently used in treatment for HIV patients

with comorbid illnesses. From the study conducted, it was found that the top five diagnoses found in HIV patients were TB, HTN, hypercholesterolemia, dyslipidemia and diabetes. Patients on medication for these diseases were found to have both moderate and major pDDIs. This emphasizes the importance of correct policies of writing prescriptions and being up-to-date on drug information for both prescribers and pharmacists as it may significantly increase the chances of the appropriate drugs being selected for treatment and hence quicker patient recovery.[105]

The importance of a well-structured educational/training program was highlighted in both the quantitative and qualitative phases of the study. Pharmacy personnel should be able to understand the mechanisms by which drugs interact with each other in order to be able to identify and manage possible interactions. The mechanism of an interaction can be critical in predicting the time course of an interaction, it may also provide information on how to minimize the risk of adverse outcomes. For the purpose of identifying pDDIs, the HCP must have both a general knowledge about DDIs and a patient's complete detailed medication list. Continuous training will enable HCPs to predict how drugs are likely to interact with other medications the patient is on.[116] The training should prioritize the importance of patient data collection (patient medical and personal history including prescription and OTC medications). Furthermore, the importance of allocating time to address patients' medications and treatment plans should be emphasized, all of which will help reduce medical errors and promote therapeutic outcomes.[106]

Studies assessing patients' knowledge, needs and opinions about medicines and their attitudes towards pharmacists have reported on the confined knowledge of patients and their need for information and understanding.[58,117] Within the study conducted, lack of communication with patients was seen as a contributing factor towards pDDIs and the importance of providing patients with information about their medication and possible risk factors to pDDIs and adverse outcomes was highlighted.[55] Research has demonstrated that cases wherein patients are not provided the opportunity or do not feel comfortable enough to tell their story/history, often lead to incomplete data upon which clinical decisions are made. This gives rise to medicine related issues that ultimately results in patient's non-adherence to therapy.[118] Extensive research has shown that no matter how knowledgeable a healthcare practitioner is, if they are not

able to communicate well with patients, they may be of no help. A healthcare practitioner's communication skills establish strong positive relationships with the patient's capacity to follow through with medical recommendations, coexist with their chronic medical condition and adopt preventive health behaviour. [117,118]

Healthcare practitioners need to be aware of the measures that should be taken to reduce the likelihood of an adverse outcome. The majority of pDDIs do not result in clinical manifestations if they are managed adequately, e.g. by avoiding the combination entirely, dosage adjustments of the object drug, spacing dosing times to avoid the interaction or monitoring for early detection.[58,117] However, given the frequency of combination treatment, even a low penetrance of complications caused by DDIs will to a considerable degree impact drug safety.[119] Potential for DDIs should be considered at every step of the drug-delivery process (prescribing, dispensing and administration of a medicine). The risk of interactions may also be heightened due to the restrictions of pharmacy's accessibility to online DDI alert systems and the deficiencies that these systems might have. Research has indicated that although the presence of an electronic patient database helps diminish challenges faced by HCPs, screening systems for pDDIs have not been as successful as anticipated.[33,120] There is insufficient information on whether computerized DDI screening is actually beneficial in reducing interaction morbidity and mortality in pharmacy settings. These systems have certain deficiencies and limitations such as excessive number of drug interactions on the systems, pharmacists find that the drug interaction screening systems detect a large number of DDIs of questionable clinical significance. Another challenge with the system is the different drug classes not handled correctly. Findings from certain studies indicate that many pharmacy computer systems may be operating at low levels of sensitivity and specificity when screening for DDIs.[120] This aligns with the study conducted as TLC does have a screening system in place that detects drug interactions, however, based on the interactions identified, one can comment that the system is either not being used correctly or does not seem to be working. Therefore, strategies for the monitoring of potentially clinically significant interactions are required.

Pharmacists are specially trained to recognize medication-related problems, they play an integral role in protecting the public from the dangers presented by pDDIs, which have been identified as an important subset of medication errors. There have been multiple studies that highlighted the importance of a pharmacist in the reduction of DDIs and other medicine-related issues.[59,117,121] Nevertheless, there will always be challenges that HCPs are confronted with. In the study conducted, the computerised DDI screening systems available to prescribers at TLC was not sufficient enough to diminish the incidence of pDDIs. Other barriers that impede pharmaceutical care were also identified by pharmacy personnel. Emphasis was placed on additional identification and management strategies required to help reduce the occurrences of pDDIs. This included better communication between HCPs and patients; pharmacists need to establish a communicative pathway with patients in order to ascertain a list of all the current medication used (OTC, herbal etc). Agents that have a potential for DDIs, drugs with a narrow therapeutic index, should also be identified and given special attention. Updated software used to screen DDIs should be used rigorously by prescribers and pharmacists, thus, assisting in the identification and management of DDIs. The knowledge of trained pharmacists on DDIs can decrease the likelihood of affiliated adverse outcomes, provide better patient-quality care, adjust therapeutic regimens, and avoid associated medical-legal issues. Hence, guidelines concerning the widespread of pDDIs along with their potential adverse outcome and management strategies should be developed.

CHAPTER 6

STRENGTHS AND LIMITATIONS

6.1 Strengths

Peer examination was ensured as the study was subject to scrutiny by an expert in the field of qualitative research. A well-documented audit trail of materials and processes was also utilized to provide a clear and accurate picture of the methods used in this study. All research processes were clearly explained throughout the study (from sample size description, data collection, context of the study to production of the final report), this helped establish trustworthiness of the study.[122] In phase 1 of the study, the files of patients attending the HIV clinic were analysed, in phase 2, the sample for the study were pharmacy personnel working in a clinical environment, representing the overall population of healthcare workers at a tertiary public hospital i.e. the study site. Conclusions drawn in this study are specific to the hospital and clinic site, thereby deductions made will pertain to the study population. The study could be easily replicated within a different study population in order to assess the prevalence of DDIs and the its management in other settings. Although similarities may be present, based on the literature review of similar studies and their results, it is not necessarily expected that the results will be consistent in another setting.

6.2 Limitations

In phase 1 of the study, patient files were evaluated retrospectively, potential interactions from over-the-counter drugs and herbal medications that were not recorded may have been overlooked. It is recommended that a further study is conducted assessing interactions that include these medicines. Additionally, the DDI software used did not include dosages and there is a possibility that certain interactions are dependent on drug dosage. There were also further limitations to the study with regards to the use of the online patient database. The following factors contributed to limitations associated with the database used:

- Poorly recorded information (missing diagnoses and reasons for stopping certain medications)
- Therapy evaluation forms were not provided for every patient

The missing information may result in misclassification. The study was conducted at TLC but phase 2 of the study (focus groups) consisted of pharmacy personnel from both TLC and the main hospital. This led to difference of opinions among the members. It is recommended that a similar study be performed at the hospital pharmacy in order to get a comprehensive view of the prevalence of DDIs and management strategies in the main hospital pharmacy.

CHAPTER 7

FUTURE RECOMMENDATIONS

Based on the study conducted, the following recommendations can be made:

- Inclusion of pharmacists in the drug therapy management processes will help produce improved patient outcomes. Therefore, effective pharmacist-prescriber collaborative working relationships need to be implemented to enhance pharmaceutical care.
- Training of HCPs in the identification and management of DDIs from the basic assistants level all the way to pharmacists. Continuous training will help HCPs become familiar with DDIs and enhance the provision of pharmaceutical care.
- Allowing pharmacists and pharmacy personnel access to the electronic patient database that alerts prescribers for pDDIs. In instances where prescribers might have missed pDDIs, staff at the pharmacy now have a chance to identify them.
- DDI informative guidelines: Placement of a chart that includes the most common DDIs as well as the management strategies for these interactions at each dispensing station for the pharmacist.
- Educational programmes on communication to help pharmacy personnel interact effectively with other health care providers and patients.
- Visuals aid such as leaflets and posters put up in the waiting rooms could help educate patients on the possible DDIs they may encounter and what procedures need to be followed. The leaflets should be in different languages, so patients can read them while waiting in line.
- Oral presentations performed in waiting rooms can promote education. Pharmacy personnel can engage with patients in their home language, it can be an interactive way of getting patients to ask questions and learn about their medication.
- Multidisciplinary teams for HIV patients: The use of a Multidisciplinary care team may reduce pDDIs among HIV patients, improves patient's quality of life and also make it easier for patients to navigate the healthcare system.

Similar studies which identify the potential for DDIs at other institutions could be performed in order to properly assess the prevalence of DDIs and its management strategies used by HCPs in other environments. From this, further recommendations could be made.

CHAPTER 8

CONCLUSION

This study aimed to determine the prevalence and management of DDIs between ARVs and chronic medication among HIV infected patients. Results indicated that older patients with a higher number of comorbidities are at a higher risk of potential DDIs. Common diseases such as tuberculosis, hypertension, dyslipidaemia and diabetes are the diagnoses that are most likely associated with potential DDIs. Risk factors for DDIs include advanced age, comorbidities, polypharmacy, multiple physicians which often leads to prescribing errors, all of these factors are commonly found among HIV patients.

Within the study, moderate DDIs featured the highest (63.94%) which suggests that the DDIs were not severe, however, being able to identify these is critical for patient care as it leads to reduced costs for both the patient and healthcare system and results in improved clinical outcomes. The risk factors identified in this study may help in the design of interventions that reduce the risk. The participants of the focus group expressed that although they have a basic understanding of DDIs and its effects, lack of training and practice as well as resource-restraints has left them incapable of identifying and managing these interactions. Continuous training of HCPs is thus the best option to manage DDIs. Other management options include software-based screening of DDIs, these systems need to be made accessible and used correctly by pharmacy personnel to help identify and manage potential interactions. Pharmacy personnel should not decide based entirely on the DDI alert but should consider the patient's full drug profile. They should make use of published data and apply the information so that the risk of DDIs and ADRs can be minimized. The pharmacy personnel should also be made aware of the importance of pharmaceutical care and the vital role that they play in drug therapy management. The knowledge and experience of a pharmacist can often help distinguish between clinically important and unimportant DDIs thus, improving patient safety.

REFERENCES

1] Avert [Internet]. HIV and AIDS in South Africa. [update 2019 Jan 18; cited 2019 May 19]. Available from: https://www.avert.org/professionals/hiv-around-world/sub-saharan-africa/south-africa

2] Nojilana B, Bradshaw D, Pillay-van Wyk V, Msemburi W, Somdyala N, Joubert JD, Groenewald P, Laubscher R, Dorrington RE. Persistent burden from non-communicable diseases in South Africa needs strong action. S Afr Med J. 2016 Apr 1;106(5):23-4.

3] Patel P, Rose CE, Collins PY, Nuche-Berenguer B, Sahasrabuddhe VV, Peprah E, et al. Noncommunicable diseases among HIV-infected persons in low-income and middle-income countries: a systematic review and meta-analysis. AIDS. 2018 Jul 1; 32(Suppl 1): S5–S20.

4] Zungu NP, Mabaso ML, Kumalo F, Sigida S, Mlangeni L, Wabiri N,et al. Prevalence of non-communicable diseases (NCDs) and associated factors among HIV positive educators: Findings from the 2015/6 survey of Health of Educators in Public Schools in South Africa. PLoS One. 2019 Feb 8;14(2):e0209756.

5] Sogarwal R, Mehra S. Approaches to Address NCD among PLHIV in Low and Middle Income Countries. J AIDS Clin Res. 2015 Jun 15; 6:472

6] Aids Info [Internet]. HIV/AIDS glossary.[cited 2019 May 19]. Available from: https://aidsinfo.nih.gov/understanding-hiv-aids/glossary/213/drug-drug-interaction

7] Marzolini C, Elzi L, Gibbons S, Weber R, Fux C, Furrer H, et al, Prevalence of comedications and effect of potential drug-drug interactions in the Swiss HIV Cohort Study. Antivir Ther. 2010;15(3):413-23.

8] Hussar DA. Drug Interactions, Clinical Toxicology. J Clin Toxicol.1976; 9(1):107-118.

9] Kapp P, Klop A, Jenkins L. Drug interactions in primary health care in the George subdistrict, South Africa.SAFPJ. 2013;55(1):78-84.

10] Mousavi S, Ghanbari G. Potential drug-drug interactions among hospitalized patients in a developing country. Caspian J Intern Med. 2017 Autumn; 8(4): 282–288.

11] Snyder BD, Polasek TM, Doogue MP. Drug interactions: principles and practice. Aust Prescr .2012 Jun 1;35(3)85-8

12] Vilar S, Lorberbaum T, Hripcsak G, Tatonetti NP. Improving Detection of Arrhythmia Drug-Drug Interactions in Pharmacovigilance Data through the Implementation of Similarity-Based Modeling. PLoS One. 2015 Jun 12;10(6):e0129974

13] Aljadani R, Aseeri M. Prevalence of drug–drug interactions in geriatric patients at an ambulatory care pharmacy in a tertiary care teaching hospital. BMC Res Notes. 2018; 11: 234.

14] Andersson ML, Böttiger Y, Kockum H, Eiermann B. High Prevalence of Drug-Drug Interactions in Primary Health Care is Caused by Prescriptions from other Healthcare Units. Basic Clin Pharmacol Toxicol. 2018 May;122(5):512-516.

15] Yesufl TA, Belayl AZ, Sisay EA, Gebreamlak ZB. Prevalence and Clinical Significance of Potential Drug-Drug Interactions at Ayder Referral Hospital, Northern Ethiopia. J Dev Drugs. 2017 Oct 3;6(3).

16] Toklu HZ, Mensah E. Why do we need pharmacists in pharmacovigilance systems? Online J Public Health Inform. 2016; 8(2): e193.

17] Peterson M, Yiannoutsos CT, Justice A, Egger M. Observational Research on NCDs in HIV-Positive Populations: Conceptual and Methodological Considerations. J Acquir Immune Defic Syndr. 2014 Sep 1; 67(0 1): S8–16.

18] World Health Organization.[Internet].Essential medicines and health products.[updated 2018;cited 2018 February 12].Available from: http://www.who.int/healthsystems/topics/medicines/en/

19] Graan RV, Viljoen M, Rheederes M, Motara F. Retrospective clinical analysis of adverse drug reactions associated with antiretroviral therapy in Tlokwe district, South Africa. S Afr Fam Pract.2017 Sep 27; 60(1):31-36.

20] Mehta U. Pharmacovigilance: The devastating consequences of not thinking about adverse drug reactions. CME. 2011;29(6):247-251.

21]Mehta U, Kalk E, Boulle A, Nkambule P, Gouws J, Rees H, et al. Pharmacovigilance: A public health priority for South Africa. S Afr Health Rev. 2017;2017:125-133. Epub 2017 Aug 23.

22] Cullinan K.[Internet]. Collision of HIV and NCDs.[updated 2017 Dec 1;cited 2018 July 14].Available from https://www.health-e.org.za/2017/12/01/collision-hiv-ncds/

23] World Health Organization.The safety of medicines in public health programmes: Pharmacovigilance an essential tool.Switzerland:World Health Organization; 2006.

24] Uppsala Monitoring Centre.[Internet]. A long-term commitment to patient safety.[updated 2018;cited 2018 Feb 12].Available from: https://www.who-umc.org/about-us/our-story/

25] Terblanche A. Pharmacovigilance and the reporting of adverse drug reactions. S Afr Pharm J. 2018;85 (6):65-68

26] Dheda M [Internet].Perspectives on the Emergence of Pharmacovigilance in Public Health Programmes in South Africa.[updated 2016 june;cited 2018 july 14].Available from:https://www.researchgate.net/publication/303914546_Perspectives_on_the_Emergence_of_Pharmacovigilance_in_Public_Health_Programmes_in_South_Africa

27] Maigetter K, Pollock AM, Kadam A, Ward K, Weiss MG.Pharmacovigilance in India, Uganda and South Africa with reference to WHO's minimum requirements.Int J Health Policy Manag. 2015 Mar 9;4(5):295-305.

28] World Health Organization [Internet]. Essential Drugs Monitor No. 032: Drug And Therapeutics Committees: Vehicles For Improving Rational Drug Use; [updated 2016 Jan 28; cited 2018 July 19]. Available from: http://apps.who.int/medicinedocs/en/d/Js4940e/6.html

29] Dheda M. Decentralized HIV/AIDS pharmacovigilance in South Africa: Mpumalanga as pilot province for national roll- out. J AIDS HIV Res.2013 Sep; 5 (9), pp. 357-365.

30] Hunter DJ, Reddy KS. Noncommunicable diseases. N Engl J Med. 2013; 369:1336–1343.

31] Kengne PA, Sayed B [Internet]. Non-communicable diseases.[cited 2019 Jun 19]. Available from:https://www.hst.org.za/publications/District%20Health%20Barometers/12%20(Section%20A)%20Non-communicable%20diseases.pdf

32] Magodoro IM, Esterhuizen TM, Chivese T. A cross-sectional, facility-based study of comorbid non-communicable diseases among adults living with HIV infection in Zimbabwe. BMC Res Notes. 2016 Aug 2;9:379

33] Chhoun P, Tuot S, D.Harries A, Kyaw NTT, Pal K, Mun P, et al. High prevalence of non-communicable diseases and associated risk factors amongst adults living with HIV in Cambodia. PLoS One. 2017 Nov 9;12(11):e018759

34] Van Heerden A, Barnabas RV, Norris SA, Micklesfield LK, van Rooyen H, Celum C.High prevalence of HIV and non-communicable disease (NCD) risk factors in rural KwaZulu-Natal, South Africa. J Int AIDS Soc. 2017 Oct;20(2).

35] Negin J, Matiniuk A, Cumming RG, Naidoo N, Phaswana-Mafuva , Madurai L, et al. Prevalence of HIV and chronic comorbidities among older adults. AIDS. 2012 Jul 31;26 Suppl 1:S55-63.

36] Narayan V,Miotti PG,Anand NP,Kline LM,Harmston C,Gulakowski R, Vermund SH. HIV and Noncommunicable Disease Comorbidities in the Era of Antiretroviral Therapy: A Vital Agenda for Research in Low- and Middle-Income Country Settings.J Acquir Immune Defic Syndr.2014 Sep

37] Hughes CA, Tseng A, Cooper R. Managing drug interactions in HIV-infected adults with comorbid illness.CMAJ. 2015 Jan 6; 187(1): 36–43.

38] Dos Santos WM, Secoli SR, Padoin SMM.[Internet]. Potential drug interactions in patients given antiretroviral therapy.[updated 2016;cited 2018 Oct 27].Available from: http://www.scielo.br/pdf/rlae/v24/0104-1169-rlae-24-02832.pdf

39]Foy M, Sperati CJ, Lucas GM, Estrella MM. Drug Interactions and Antiretroviral Drug Monitoring.Curr HIV/AIDS Rep. 2014 Sep; 11(3): 212–222.

40] Seden K, Back D, Khoo S. Antiretroviral drug interactions: often unrecognized, frequently unavoidable, sometimes unmanageable. J Antimicrob Chemother. 2009 Jul;64(1):5-8

41] Khoo SH, Gibbons S, Seden K, Back DJ.Systematic Review: Drug-drug Interactions between Antiretrovirals and medications used to treat TB, Malaria, Hepatitis B&C and opioid dependence.[dissertation]. Liverpool: University of Liverpool; 2009.

42] Avert [Internet]. Global information and education on HIV and AIDS. [updated 2018 October 16;cited 2018 Oct 17].Available from: https://www.avert.org/professionals/hiv-around-world/sub-saharan-africa/south-africa

43] Holtzman C, Armon C, Tedaldi E, Chmiel JS, Buchacz K, Wood K, et al,. Polypharmacy and risk of antiretroviral drug interactions among the aging HIV-infected population. J Gen Intern Med. 2013 Oct;28(10):1302-10.

44] Ruzicka DJ, Imai K, Takahashi K, Naito T. Comorbidities and the use of comedications in people living with HIV on antiretroviral therapy in Japan: a cross-sectional study using a hospital claims database. BMJ Evid Based Med.2018; 8(6).

45] Funke B, Esser, Stellbrink H-J, Spinner C.D, Wursthorn K, Witte V.[Internet].High prevalence of comorbidities and concomitant medication in HIV-infected patients in Germany carries a high potential for drug-drug interactions with antiretroviral therapy. [updated 2017 October 27; cited 2018 Oct 17].Available from: http://www.natap.org/2017/EACS/EACS_92.htm

46] U.S. Pharmacist [Internet]. Drug–Drug Interactions with HIV Antiretroviral Therapy. [Updated 2008 Apr 18; cited 2019 Jun 19]. Available from: https://www.uspharmacist.com/article/drugdrug-interactions-with-hiv-antiretroviral-therapy

47] Khalsa JH, Elkashef A. Drug Interactions between Antiretroviral Medications and Medications Used in the Treatment of Drug Addiction: Research Needs. Am J Addict. 2010 Jan 1; 19(1): 96.

48] Broeckaert L, Challacomvve L. Does multidisciplinary care improve health outcomes among people living with HIV and/or HCV? A review of the evidence.[updated 2015; cited 2019 Jun 11]. Available from: https://www.catie.ca/en/pif/fall-2015/does-multidisciplinary-care-improve-health-outcomes-among-people-living-hiv-andor-hcv-

49] Web MD [Internet]. HIV treatment plan.[Updated 2018 Aug 14; cited 2019 Jun 11].Available from: https://www.webmd.com/hiv-aids/hiv-treatment-team#2

50] Nijhawan A, Kim S, Rich JD. Management of HIV Infection in Patients With Substance Use Problems. Curr Infect Dis Rep. 2008 Sep; 10(5): 432–438.

51] Calnan M, Rowe R. Researching trust relations in health care: conceptual and methodological challenges—introduction. Journal of health organization and management. 2006;20(5):349–58.

52] Croker JE, Swancutt DR, Roberts MJ, Abel GA, Roland M, Campbell JL. Factors affecting patients' trust and confidence in GPs: evidence from the English national GP patient survey. BMJ open. 2013;3(5).

53] Chou YC, Dhang VC, Yen HY, Lai KM. Influence of Risk of Drug–Drug Interactions and Time Availability on Patient Trust, Satisfaction, and Co-operation with Clinical Pharmacists. Int J Environ Res Public Health. 2019 May; 16(9): 1566.

54] World Health Organization [Internet]. Offering integrated care for HIV/AIDS, diabetes and hypertension within chronic disease clinics in Cambodia.[updated 2007 Nov; cited 2019 Jun 19]. Available from: https://www.who.int/bulletin/volumes/85/11/06-036574/en/

55] Ansari JA. Drug Interaction and Pharmacist. J Young Pharm. 2010 Jul-Sep; 2(3): 326–331.

56] Tseng A, Foisy M, Hughes CA, Kelly D, Chan S, Dayneka N, et al,. Role of the Pharmacist in Caring for Patients with HIV/AIDS: Clinical Practice Guidelines. Can J Hosp Pharm. 2012 Mar-Apr; 65(2): 125–145.

57] Healio Infectious Disease News [Internet]. Pharmacists play crucial role in HIV care continuum.[updated 2015 April; cited 2019 Jun 19]. Available from: https://www.healio.com/infectious-disease/hiv-aids/news/print/infectious-disease-

news/%7B293233a7-086b-475b-b4a6-042987fdcc92%7D/pharmacists-play-crucial-role-in-hiv-care-continuum

58] Becker ML, Kallewaard M, Caspers PW,Schalekamp T,Stricker BH. Potential determinants of drug-drug interaction associated dispensing in community pharmacies.Drug Saf. 2005;28(5):371-8.

59] Rivkin A, Yin H. Evaluation of the role of the critical care pharmacist in identifying and avoiding or minimizing significant drug-drug interactions in medical intensive care patients. J Crit Care Med.2011 Feb;26(1): 104.e1-104.e6

60] Viktil KK, Bilx HS. The impact of clinical pharmacists on drug-related problems and clinical outcomes.Basic Clin Pharmacol Toxicol. 2008 Mar;102(3):275-80.

61] Hanlon JT, Lindblad CI, Gray SL. Can clinical pharmacy services have a positive impact on drug-related problems and health outcomes in community-based older adults? Am J Geriatr Pharmacother 2004;2:3–13.

62] Contagion Live [Internet]. A Pharmacist's Role in HIV Antiretroviral Stewardship in the Hospital. [updated 2017 Mar 7; cited 2019 Jun 19]. Available from: https://www.contagionlive.com/publications/contagion/2017/february2017/a-pharmacists-role-in-hiv-antiretroviral-stewardship-in-the-hospital

63] Creswell, JW, Clark VLP. Designing and conducting mixed methods research.2nd ed. Thousand Oaks, Calif: SAGE Publications.

64] Subedi D. Explanatory Sequential Mixed Method Design as the Third Research Community of Knowledge Claim. Am J Educ Res. 2016; 4(7): 570-577.

65] Mixed Methods Approach in Research: Using an Example Focused on Gender and Race[Internet]. Massachusetts Institute for college and career readiness.[cited 2019 July 8].Available from:http://sites.bu.edu/miccr/files/2017/03/02.10.2017-SRF-Forum-Mixed-Method-Slides.pdf

66] Creswell, JW, Clark VLP. Designing and conducting mixed methods research.2nd ed. Thousand Oaks, Calif: SAGE Publications: Figure 3.3, Flowchart of the basic procedure in implementing a convergent design; p.79.

67] Navalón CI,Miguel JJF, Cánovas JJG, Redondo LR. Identification of potential clinically significant drug interactions in HIV-infected patients: a comprehensive therapeutic approach. HIV Med. 2014 Dec 18 ;16(5):273-279.

68] Statistics How to [Internet]. Sample Size in Statistics (How to Find it): Excel, Cochran's Formula, General Tips.[updated 2018; cited 2018 May 18]. Available from: https://www.statisticshowto.datasciencecentral.com/probability-and-statistics/find-sample-size/

69] Lexi-Comp® [Internet]. Lexi-Interact data fields.[updated 2019; cited 2019 May 20]. Available from: http://webstore.lexi.com

70] European Patients' academy [Internet]. Epidemiologic concepts: incidence and prevalence. [updated 2016 Jun 17; cited 2019 Sep 6]. Available from: https://www.eupati.eu/pharmacoepidemiology/epidemiologic-concepts-incidence-and-prevalence/

71] Laerd Dissertation.[Internet].Purposive Sampling.[updated 2012;cited 2018 May 20]. Available from http://dissertation.laerd.com/purposive-sampling.php

72] Anthierens S, Tansens A, Petrovic M, Christiaens T. Qualitative insights into general practitioners views on polypharmacy. BMC Fam Pract. 2010 Sep 15;11:65.

73] Maguire M, Delahunt B. Doing a Thematic Analysis: A Practical, Step-by-Step Guide for Learning and Teaching Scholars. AIChE J. 2017;3:3352-3354.

74] Esha P. Reflexivity: Situating the researcher in qualitative research. Soc Sci Med. 2013;2:98-106.

75] Birks Y, Harrison R, Bosanquet K, et al. An exploration of the implementation of open disclosure of adverse events in the UK: a scoping review and qualitative exploration. Southampton (UK): NIHR Journals Library; 2014 Jul. (Health Services and Delivery Research, No. 2.20.) Appendix 8, Detailed statement for reflexivity. Available from: https://www.ncbi.nlm.nih.gov/books/NBK259820/

76] Drugs.com [Internet]. Drug Interactions between Loperamide and Lopinavir/Ritonavir.[updated 2019 Aug 1;cited 2019 Sep 6] Available from: https://www.drugs.com/drug-interactions/loperamide-with-lopinavir-ritonavir-1482-0-1484-0.html

77] Drugs.com[Internet]. Drug Interactions between Salbutamol and Budesonide.]updated 2019 Aug 1; cited 2019 Sep 6]. Available from: https://www.drugs.com/interactionscheck.php?drug_list=4310,1090&types%5B%5D=major&types%5B%5D=minor&types%5B%5D=moderate&types%5B%5D=food&types%5B%5D=therapeutic_duplication&professional=1

78] Drugs.com[Internet]. Drug Interactions between Diflucan and Efavirenz. [updated 2019 Aug 1;cuted Sep 6]. Available from: https://www.drugs.com/interactions-check.php?drug_list=1096-630,963-0

79] Drugs.com [Internet]. Drug Interactions between Norvasc and Piroxicam.[updated 2019 Aug 1; cited 2019 Sep 6]. Available from: https://www.drugs.com/drug-interactions/norvasc-with-piroxicam-172-78-1881-0.html

80] Drugs.com [Internet]. Drug Interactions between Atorvastatin and Efavirenz.[updated 2019 Aug 1; cited 2019 Sep 6]. Available from: https://www.drugs.com/interactions-check.php?drug_list=963-0,276-0

81] Drugs.com [Internet]. Drug Interactions between Ritonavir and Zidovudine. [updated 2019 Aug 1; cited 2019 Sep 6]. Available from: https://www.drugs.com/drug-interactions/ritonavir-with-zidovudine-2021-0-2322-0.html?professional=1

82] Division of Clinical Pharmacology, Faculty of Health Science; University of Cape Town. South African Medical Formulary.11th ed, Health and Medical Pub. Group of the South African Medical Association,. Rondebosch, South Africa; 2014.

83] Drugs.com [Internet]. Drug Interactions between Efavirenz and Pravastatin. [updated 2019 Aug 1; cited 2019 Sep 6]. Available from: https://www.drugs.com/drug-interactions/efavirenz-with-pravastatin-963-0-1929-0.html

84] Drugs.com [Internet]. Drug Interactions between Enalapril and Hydrochlorothiazide. [updated 2019 Aug 1; cited 2019 Sep 6]. Available from: https://www.drugs.com/interactions-check.php?drug_list=972-0,1257-0

85] Drugs.com [Internet]. Drug Interactions between Atazanavir and Ritonavir. [updated 2019 Aug 1; cited 2019 Sep 6]. Available from: https://www.drugs.com/drug-interactions/atazanavir-with-ritonavir-272-0-2021-0.html

86] RxList[Internet]. Emtriva.[updated 2019; cited 2019 Sep 6]. Available from: https://www.rxlist.com/emtriva-drug.htm#side_effects

87] RxList[Internet]. Simvastatin.[updated 2019; cited 2019 Sep 6]. Available from: https://www.rxlist.com/simvastatin-drug.htm#interactions

88] Drugs.com [Internet]. Drug Interactions between Bactrim and Flagyl. [updated 2019 Aug 1; cited 2019 Sep 6]. Available from: https://www.drugs.com/drug-interactions/bactrim-with-flagyl-2128-1386-1617-988.html?professional=1

89] Drugs.com [Internet]. Drug Interactions between Carbamazepine and Efavirenz. [updated 2019 Aug 1; cited 2019 Sep 6]. Available from: https://www.drugs.com/drug-interactions/carbamazepine-with-efavirenz-497-0-963-0.html

90] RxList [Internet]. Drug Interactions between Carbamazepine and Efavirenz oral. [updated 2019; cited 2019 Sep 6]. Available from:https://www.rxlist.com/drug-interactions/carbamazepine-oral-and-efavirenz-oral-interaction.htm

91] Bjerrum L, Gonzalez Lopez- Valcarcel B, Petersen G. Risk factors for potential drug interactions in general practice. Eur J Gen Pract. 2008;14(1):23-9.

92] Creswell JW. Research design: qualitative, quantitative, and mixed methods approaches. 4th ed. Thousand Oaks, California: SAGE Publications; 2014

93] Mahy M, Autenrieth CS, Stanecki K, Wynd S. Increasing trends in HIV prevalence among people aged 50 years and older: evidence from estimates and survey data. AIDS. 2014 Nov;28 Suppl 4:S453-9

94] Doyal L, Hoffman M. The growing burden of chronic diseases among South African women. Can Med Educ J. 2009 Oct; 279(10).

95] Smart T. [Internet]. HIV and non-communicable diseases (NCDs). Nam AIDSmap; [updated 2011 Oct 6; cited 2019 Aug 6]. Available from: http://www.aidsmap.com/news/oct-2011/hiv-and-non-communicable-diseases-ncds

96] Xu Y, Chen X, Wang K. Global prevalence of hypertension among people living with HIV: a systematic review and meta-analysis. J Am Soc Hypertens. 2017 Aug;11(8):530-540.

97] Carter M. [Internet]. Hypertension in patients with HIV associated with obesity, fat loss and previous treatment with stavudine. Nam AIDSmap; [updated 2016 May 13; cited 2019 Aug 6]. Available from: http://www.aidsmap.com/news/may-2016/hypertension-patients-hiv-associated-obesity-fat-loss-and-previous-treatment

98] Santos WM, Secoil SR, Padoin SM. Potential drug interactions in patients given antiretroviral therapy. Rev Lat Am Enfermagem. 2016 Nov 21;24:e2832.

99] Obreli Neto PR, Nobili A, Marusic S, Pilger D, Guidoni CM, Baldoni Ade O et al. Prevalence and predictors of potential drug-drug interactions in the elderly: a cross-sectional study in the brazilian primary public health system. J Pharm Pharm Sci. 2012;15(2):344-54.

100] Lexi-Comp® [Internet]. Lexi-Interact data fields.[updated 2019; cited 2019 Aug 6]. Available from: http://webstore.lexi.com.

101] UNAIDS.[Internet]. People aged 50 years and older. The Gap report. 2014.[updated 2014 Sep; cited 2019 Aug 6]. Available from: https://www.unaids.org/sites/default/files/media_asset/12_Peopleaged50yearsandolder.pdf

102] Cooney D, Pascuzzi K. Polypharmacy in the elderly: focus on drug interactions and adherence in hypertension. Clin Geriatr Med. 2009 May;25(2):221-33.

103] Malone DC, Abarca J, Skrepnek GH, Murphy JE, Armstrong EP, Grizzle AJ, Rehfeld RA, Woosley RL. Pharmacist Workload and Pharmacy Characteristics Associated With the Dispensing of Potentially Clinically Important Drug-Drug Interactions. Med Care. 2007 May;45(5):456-62.

104] Tiwary A, Rimal A, Paudyal B, Sigdel KR, Basnayat B. Poor communication by health care professionals may lead to life-threatening complications: examples from two case reports. Wellcome Open Res. 2019; 4: 7.

105] Okonta JM, Okonta EO, Ofoegbu TC. Barriers to Implementation of Pharmaceutical Care by Pharmacists in Nsukka and Enugu Metropolis of Enugu State. J Basic Clin Pharm. 2012 Mar;3(2):295-8.

106] Ahmadizar F, Soleymani F, Abdollahi M. Study of Drug-Drug Interactions in Prescriptions of General Practitioners and Specialists in Iran 2007-2009. Iran J Pharm Res. 2011 Fall;10(4):921-31.

107] Elayeh E, Akour A, Almadaeen S, AlQhewii T, Basheti IA. Practice of pharmaceutical care in community pharmacies in Jordan. Trop J Pharm Res. 2017 Feb; 16(2): 463

108] Saberi P, Dong BJ, Johnson MO, Greenblatt RM, Cocohoba JM. The impact of HIV clinical pharmacists on HIV treatment outcomes: a systematic review. Patient Prefer Adherence. 2012; 6: 297–322.

109] Ismail M, Iqbal Z, Khattak MB, Javaid A, Khan TM. Prevalence, type and predictors of potential drug-drug interactions in pulmonary ward of a tertiary care hospital. Afr J Pharm Pharmacol. 2011;5(10):1303–1309

110] Weingart SN, Toth M, Sands DZ, Aronson MD, Davis RB, et al. (2003) Physicians' decisions to override computerized drug alerts in primary care. Arch Intern Med 163: 2625–2631.

111] Hansten PD. Drug interaction management. Pharm World Sci. 2003 Jun;25(3):94-7

112] Foppe Van Mil JW, Schulz M. A Review of Pharmaceutical Care in Community Pharmacy in Europe. Harvard Health Policy Rev. 2006; 7(1):155-168.

113] Farris KB, Schopfl ocher DP. Between Intention and behaviour: an application of community pharmacists' assessment of pharmaceutical care. Soc.Sci. Med 1999; 49: 55-66.

114] Gazzaruso C, Bruno R, Garzaniti A, Giordanetti S, Fratino P, Sacchi P, et al. Hypertension among HIV patients: prevalence and relationships to insulin resistance and metabolic syndrome. J Hypertens. 2003 Jul;21(7):1377-82.

115] Nobili A, Pasina L, Tettamanti M, Lucca U, Riva E, Marzona I et al. Potentially severe drug interactions in elderly outpatients: results of an observational study of an administrative prescription database. J Clin Pharm Ther. 2009 Aug;34(4):377-86.

116] Bell HM, McElnay JC, Hughes CM. Societal Perspectives on the Role of the Community Pharmacist and Community based Pharmacy Services. J Soc Adm Pharm 2000;17(2):119- 128.

117] Abarca J, Colon LR, Wang VS, Malone DC, Murphy JE, Armstrong EP. Evaluation of the performance of drug-drug interaction screening software in community and hospital pharmacies. J Manag Care Pharm. 2006 Jun;12(5):383-9.

118] Dr Anwar S. Impact and importance of effective communication in healthcare delivery. The Daily Star. 2017 Jul 16

119] Indermitte J, Erba L, Beutler M, Bruppacher R, Haefeli WE, Hersberger KE. Management of potential drug interactions in community pharmacies: a questionnaire-based survey in Switzerland. Eur J Clin Pharmacol. 2007 Mar;63(3):297-305.

120] Saverno KR, Hines LE, Warholak TL, Grizzle AJ, Babits L, Clark C, et al. Ability of pharmacy clinical decision-support software to alert users about clinically important drug–drug interactions. J Manag Care Pharm. 2006 Jun;12(5):383-9.

121] Shafiekhani M, Moosavi N, Firouzabadi D, Namazi S. Impact of Clinical Pharmacist's Interventions on Potential Drug-Drug Interactions in the Cardiac Care Units of Two University Hospitals in Shiraz, South of Iran. J Res Pharm Pract. 2019 Oct 16;8(3):143-148.

122] Qualitative research guideline project [Internet]. Lincoln and Guba's Evaluative Criteria. [updated 2008; cited 2019 Jun 19]. Available from: http://www.qualres.org/HomeLinc-3684.html

APPENDICES

Abstract of podium presentation:

Appendix A1

DRUG-DRUG INTERACTIONS AMONG HIV PATIENTS WITH COMORBID ILLNESSES

A retrospective study conducted in a tertiary hospital in Gauteng

Aaminah Munshi; Rubina P Shaikh; Neelaveni Padayachee; Belinda Strydom

Department of Pharmacy and Pharmacology, Faculty of Health Sciences, University of the Witwatersrand, 7 York Road. Parktown, 2193, Johannesburg, South Africa

*Correspondence:Rubina.Shaikh@wits.ac.za

Introduction: The advent of antiretroviral therapy (ART) has led to an increase in the lifespan of HIV patients who are now faced with new challenges such as the onset of non-communicable diseases (NCDs). These NCDs fall within South Africa's quadruple burden of diseases. As a result, the cocktail of treatments provided has led to the potential for drug-drug interactions (DDIs) which heightens the risk of patients facing drug-related adverse events. The study aimed to investigate the prevalence of DDIs between ARTs and other medication used to treat concomitant diseases.

Methods: A retrospective study was conducted at a tertiary institute in Gauteng. 645 electronic patient files were analysed over a 3-year period. Potential DDIs were identified and categorised through Lexicomp®.

Results: A total of 5,584 pDDIs were found. The most common pDDI rating found was Category C (63.94%). Most of these interactions occurred between ARVs (Zidovudine and Ritonavir, Tenofovir Disoproxil Fumarate (TDF) and Lopinavir) and ARVs and NCDs (Atorvastatin and Efavirenz, Pravastatin and Efavirenz). The second highest pDDI category identified was Category D (25.58%). Examples included Atazanavir and Ritonavir, Atorvastatin and Lopinavir and Atorvastatin and Bezafibrate. The lowest prevalence of pDDIs was recorded for category X, contraindicated (0.23%). The most common type of category X interaction occurred between NCDs, Slow K and Amitriptyline. It was found that the highest number of pDDIs detected was among older patients between the ages of 51-60 years. The most frequent comorbid diagnoses made were Tuberculosis (TB) (60%) and Hypertension (HT) (25.64%).

Discussion: Although moderate DDIs featured the highest which suggests that the drug interactions were not severe, being able to identify these is critical for patient care. Updated software to screen DDIs should be used rigorously by prescribers and pharmacists. Older patients are at a higher risk of potential DDIs, this could be due to their age-related diseases and poly pharmacy.

Abstracts of Papers Submitted:

Appendix A2

THE ROLE OF PHARMACISTS IN THE MANAGEMENT OF DRUG-DRUG INTERACTIONS: A FOCUS ON HIV AND COMORBIDITIES

Aaminah Munshi; Rubina P Shaikh[1]; Neelaveni Padayachee[1]; Belinda Strydom[2]

Department of Pharmacy and Pharmacology, Faculty of Health Sciences, University of the Witwatersrand, 7 York Road. Parktown, 2193, Johannesburg, South Africa

Dr B Strydom

Right to Care, Right e-Pharmacy Department, Pharmacy Program Manager

Email: Rubina.Shaikh@wits.ac.za

Abstract

Pharmacovigilance targets the safe and effective use of medicine. This is crucial in the increase in non-communicable diseases (NCDs) the HIV population is currently facing. These patients are concomitantly treated for both HIV and NCDs. The increase in medications has given rise to medical errors such as drug-drug interactions (DDIs) which heightens the risk of patients facing drug-related adverse events. Pharmacists are drug experts who play a crucial role in healthcare systems to maintain the rational and safe use of medicines. This review aimed to explore the role of PV in developing countries, specifically with regards to the HIV/AIDS epidemic and the comorbidities patients face. Secondly the link between ARV treatment and other comorbidities was covered and lastly, the occurrence of DDIs, its management and the role of a pharmacist in such cases was investigated. From the data reviewed, it was found that there is a scarce amount of evidence-based data on HIV and NCD drug interactions. Thus, a robust method to determine the prevalence of potential DDIs among medications is required. Such a study has the potential to increase the knowledge of the pharmacokinetics and pharmacodynamic interactions among HIV medications. The study can also be used as a guide in ARV therapy programmes. In doing so, PV systems can be strengthened. It was also found that a pharmacists' role has become essential in the management of chronic diseases in patient-centred medical facilities. Given their advanced training, pharmacists are able to monitor the performance of drugs and identify potential DDIs and adverse drug reactions earlier thereby reducing high healthcare costs. Furthermore, the use of electronic information systems has been a milestone in identifying and intervening drug related problems such as DDIs. It can be noted that the presence of pharmacists on ward rounds, better communication between prescribers and pharmacists as well as the use of a multidisciplinary approach leads to a decrease in DDIs and better clinical outcome for patients. Based on the literature reviewed, pharmacists should be used more effectively in the healthcare system to help reduce drug related problems and improve the outcome of pharmacotherapy.

Appendix A3

POTENTIAL DRUG-DRUG INTERACTIONS AMONG HIV PATIENTS WITH COMORBID ILLNESSES

A retrospective study conducted at an HIV Clinic in Gauteng, South Africa

Aaminah Munshi; Rubina P Shaikh[1]; Neelaveni Padayachee[1]; Belinda Strydom[2]

Department of Pharmacy and Pharmacology, Faculty of Health Sciences, University of the Witwatersrand, 7 York Road. Parktown, 2193, Johannesburg, South Africa

Dr B Strydom

Right to Care, Right e-Pharmacy Department, Pharmacy Program Manager

Email: Rubina.Shaikh@wits.ac.za

Abstract

Background: The advent of antiretroviral therapy (ART) has led to an increase in the lifespan of HIV patients who are now faced with new challenges such as the onset of non-communicable diseases (NCDs). These NCDs fall within South Africa's quadruple burden of diseases. The cocktails of treatment used in these cases have led to the potential for drug-drug interactions (DDIs).

Aim: To investigate the prevalence of pDDIs between ARTs and other medication used to treat comorbidities.

Setting: The study was conducted at an HIV Clinic (TLC) in Gauteng.

Methods: 645 electronic patient files were analysed over a 3-year period. Potential DDIs were identified and categorised through Lexicomp®.

Results: A total of 5,584 potential DDIs (pDDIs) were found. The most common pDDI rating found was Category C, 63.94%. The second highest pDDI category identified was Category D, 25.58%. The lowest prevalence of pDDIs was recorded for category X, 0.23%. Advancing age and a higher number of comorbidities were associated with an increased risk of pDDIs.

Conclusion: These findings fortify the need to monitor patient therapy through proper follow up for any adverse events due to simultaneous administration of multiple drugs. Updated software to screen pDDIs should be used rigorously by prescribers and pharmacists for the identification and management of pDDIs. Prescribers should communicate with pharmacists regarding a patient's drug therapy as the knowledge and experience of a pharmacist can often help distinguish between clinically important and unimportant DDIs.

Appendix A4

QUALITATIVE EXPLORATION OF DRUG-DRUG INTERACTIONS AND ITS MANAGEMENT AMONG PHARMACISTS AND PHARMACY PERSONNEL

Aaminah Munshi; Nabeelah Bemath[1]; Rubina P Shaikh[1]; Neelaveni Padayachee[1]; Belinda Strydom[2]
Department of Pharmacy and Pharmacology, Faculty of Health Sciences, University of the Witwatersrand, 7 York Road. Parktown, 2193, Johannesburg, South Africa

Ms Nabeelah Bemath
Bachelor of Health Sciences Academic Coordinator, Medical School, Faculty of Health Sciences, 7 York Road. Parktown, 2193, Johannesburg, South Africa

Dr B Strydom
Right to Care, Right e-Pharmacy Department, Pharmacy Program Manager

Email: Rubina.Shaikh@wits.ac.za

Abstract

Background: Pharmacists play an important role in protecting the public from the dangers posed by medical errors such as potential drug-drug interactions (pDDIs). The presence of DDIs increase the toxicity of prescribed medications and causes therapeutic failure. DDIs contribute towards hospital admissions and adds on to the higher costs associated for both the patient and healthcare system. The potential clinical consequences of such interactions are foreseeable; therefore they are considered preventable medication-related problems.

Objectives: To determine DDI management strategies employed by pharmacists and to explore their perceptions on such strategies using focus groups.

Methods: Pharmacy personnel from a tertiary institute and HIV clinic were invited to partake in focus groups for the study. A total of 3 focus groups took place. The material used during the focus group addressed DDIs and its management. The audiotaped sessions were transcribed verbatim and analysed using thematic content analysis.

Results: The focus groups consisted of 16 participants. Females represented more than 68% of the sample. Three themes emerged from the analysis; Potential risk factors that contribute towards DDIs, Perceived barriers in the detection and management of DDIs and Recommendations to manage DDIs. All HCP participants were aware of the prevalence of DDIs among prescriptions, 56.25% mentioned they encounter DDIs at least once a week and 81.25% had no training in the management of DDIs. Factors such as high patient ratios, prescribing errors, polypharmacy, poor communication with patients and clinic hopping were perceived as contributing factors to DDIs. Barriers that impede the identification and management of pDDIs were found to include attitude of pharmacy personnel, pharmacist-prescriber relationships, resource-related constraints and lack of knowledge. Participants recommended appropriate training to help identify and manage DDIs. Improving patient education was also highlighted as a significant factor in reducing the risk of certain DDIs and increasing patient adherence. In addition, participants expressed that the use of an electronic patient database that alerts pDDIs will to a large extent reduce possible medical complications and consequences. Lastly, the use of multidisciplinary teams for HIV patients was recommended.

Conclusion: Improvement in drug safety is essential in terms of patient morbidity/mortality and in economic terms. Pharmacists are specially trained to recognize medication-related problems, they play an integral role in protecting the public from the dangers presented by pDDIs, which have been identified as an important subset of medication errors. These findings fortify the need for increased vigilance of drug therapy by pharmacists in the prevention of drug related problems.

Appendix B1

Permission letters from the hospital and clinic

Right to care
Treating Health Seriously

1st October 2018

TO WHOM IT MAY CONCERN:

PROTOCOL PERMISSION LETTER FROM THERAPY EDGE DATABASE GATEKEEPER

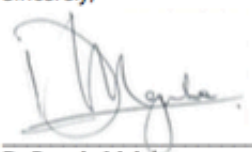
This letter confirms that **Aaminah Munshi** and her team will have access to the requested variables (**patient files that include prescriptions (antiretroviral regimen and drugs used for other co-morbidities,lab reports and doctor's notes**) from the Therapy Edge electronic medial record (EMR) in use in Right to Care's HIV treatment program.

The data will be used as part of the analysis proposed by **Aaminah** in the protocol, "**Determining the incidence,prevalence and management of drug-drug interactions in HIV patients with co-morbid illness**".

The Therapy Edge EMR is stored on an encrypted server and access is password-protected, with access restricted to clinical and programmatic staff.

If there are any further questions or concerns, please do not hesitate to contact me at pappie.majuba@righttocare.org.

Sincerely,



Dr Pappie Majuba
Managing Director; RTC NPC (SA)

Themba Lethu Wing, Helen Joseph Hospital, Perth Road, Westdene, 2092
Tel: 011 276 8850 • Direct: 011 276 8830 • Mobile: 082 600 5303
www.righttocare.org | www.facebook.com/rtcsa Email: pappie.majuba@righttocare.org

Helen Joseph Hospital, Themba Lethu Wing, Perth Road, Westdene, 2092
Company Secretary: Mr Heinrich Stevens.

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

Gauteng Department of Health
Helen Joseph Hospital
Enquiries: Dr. M. Mukansi
Research Committee: Chairperson
Tel :(011) 489-0306/1087
Fax :(011) 489 1038
E mail:Murimisi.mukansi@wits.ac.za

08 June 2018

To whom it may concern

Subject: HELEN JOSEPH HOSPITAL RESEARCH COMMITTEE APPLICATION

PROTOCOL TITLE: Investigating potential drug-drug interactions between Antiretroviral and Antipsychotics.
Protocol Ref No: Aaminah Munshi

Ethic Clearance: Pending
Principal investigator: Aaminah Munshi

Department: Pharmacy Department

Committee Recommendations
The Committee is giving you Conditional access that while awaiting the final ethical clearance certificate from the university of Witwatersrand HREC.
It is the duty of the researcher to collect the data to the relevant department after the Research Committee approved the study.

Dr. M. Mukansi
Chairperson of HJH Ethic and Research Committee

Appendix B2

Patient Data Collection Sheet

DATA COLLECTION SHEET					
Prescription Number :		**Gender:**	**Age:**	**Race:**	
Prescription contents i.e. drugs					
ARVs	**Antipsychotics**	**Antiepileptics**	**Cardiovascular**	**Respiratory**	**Other drugs**
Lab Report					
Doctor's Notes					

Appendix B3

Risk Rating Categories as Presented by Lexicomp for Each Drug-Drug Interaction adapted from Dirin et al.

Table2: Risk Rating Categories as Presented by Lexicomp for Each Drug-Drug Interaction adapted from Dirin et al.

Risk rating	Action	Description
A	No known Interaction	No pharmacodynamic or pharmacokinetic interactions between the specified agents were demonstrated.
B	No action Needed	Interactions may occur between the specified agents, however, there is little evidence of clinical concern resulting from their concomitant use.
C	Monitor therapy	The specified agents may interact with each other in a clinically significant manner. The benefits of concomitant use of these two medications usually outweigh the risks. A suitable monitoring plan should be implemented to identify potential negative effects. Dosage adjustments of one or both agents may be needed in a minority of patients.
D	Consider therapy modification	The two medications may interact with each other in a clinically significant manner. A patient-specific assessment must be carried out to determine whether the benefits of concomitant therapy out weight the risks. Specific actions must be taken in order to realize the benefits and/or minimize the toxicity resulting from the concomitant use of the agents. These actions may include aggressive monitoring empiric dosage changes or choosing alternative agents.
X	Avoid Combination	The specified agents may interact with each other in a clinically significant matter. The risks associated with concomitant use of these agents usually outweigh the benefits. These agents are generally considered contraindicated.

Appendix B4

Prescription data: Drugs, NCDs, DDIs (Identification and classification of potential DDIs using Lexicomp software).

Table 3: Prescription data: Drugs, NCDs, DDIs (Identification and classification of potential DDIs using Lexicomp software).

Prescription No.	DDIs	Age	Race	Gender	No. of comorbidities	Type of comorbidities	Drug 1	Drug 2	Drug 3	Interaction	Risk Rating
#	Yes	18-28			2	2	Drug L	Drug M	Drug N	L and N	Category B
		29-39	✓							M and N	Category X
		40-50									
		51-60									
		>60									

Appendix B5

Participant Information Sheet

Department of Pharmacy and Pharmacology
School of Therapeutic Sciences, Faculty of Health Sciences
7 York Road, Parktown, 2193, South Africa ● Tel: +27 11 717 2552 ● Fax: +27 11 642 4355

Study title:

Name of Principle Investigator: Aaminah Munshi

Name of Organization: Witwatersrand University

Part I: Information Sheet

Introduction
I am Aaminah Munshi, a master's student at Wits University. My research study aims to determine the incidence, prevalence and management of drug-drug interactions (DDIs) among HIV infected patients on treatment for Non-communicable diseases (NCDs) within public sector institutes in Gauteng.
You do not have to decide today whether or not you will participate in the research. Before making such a decision, you can talk to anyone you feel comfortable with about the research. If you have questions later, you can ask them of me or of another researcher.

Purpose of the research
DDIs can result in the worsening of symptoms, hospital admissions as well as increased rates of deaths. I would like to find ways in which such incidents can be minimized. I believe that you can help me by providing your knowledge of DDIs and its management. I would like to learn about your personal experiences with DDIs primarily between antiretrovirals(ARVs) and treatment for NCDs and how such interactions can be managed. I want to learn about the different ways in which pharmacists deal with DDIs and what their views are on it.

Type of Research Intervention
This research will involve your participation in a group discussion that will take about one hour. Questions will be asked to help guide the conversation.

Participant Selection
You are being invited to take part in this research because I feel that your experience as a pharmacist can contribute much to our understanding and knowledge of local health practices.

Voluntary Participation
Your participation in this research is entirely voluntary. It is your choice whether to participate or not. The choice that you make will have no bearing on your job or on any work-related evaluations or reports. You may change your mind later and stop participating even if you agreed earlier.

Procedures
I am asking you to help me learn more about DDIs and its management. I am inviting you to take part

in this research project. If you accept, you will be asked about your views on DDIs among HIV patients, the role of a pharmacist in relation to DDIs and its management thereof and your opinions on elements that could reduce DDIs.

You are invited to take part in a discussion with 7-8 other pharmacist. This discussion will be guided by me, the primary researcher. The group discussion will start with me making sure that you are comfortable. Any questions that you might have about the research will be answered.
Questions will be asked, and I will give you time to share your knowledge. The questions will be about DDIs, is management, the role of a pharmacist regarding DDIs and elements that can be used to reduce such DDIs.
No personal practices or stories will be asked, and you do not have to share any knowledge that you are not comfortable sharing.
The discussion will take place at the specific hospitals (Helen Joseph main and Themba Lethu Clinic (TLC)) and no one else but the people who take part in the discussion and the research team which include my supervisors and myself will be present during this discussion. Two recording devices will be used to record the entire session. The entire discussion will be recorded, but no-one will be identified by name on record. The recordings will be kept in a secure space in which only the research team will have access to it. The information recorded is confidential, and no one else except my supervisors (Rubina Shaikh, Neelaveni Padayachee) and I will have access to the tapes.

Duration
The research takes place over a period of 2 months. During that time, the group discussion will be held and will take about one hour. A total of 2 focus group discussions will take place each time with a different group of participants.

Risks
There is a risk that you may share some personal or confidential information by chance, or that you may feel uncomfortable talking about some of the topics. However, we do not wish for this to happen. You do not have to answer any question or take part in the discussion if you feel the questions are too personal or if talking about them makes you uncomfortable.

Benefits
There will be no direct benefit to you. However, by gaining insight of pharmacists opinions regarding healthcare problems ,these issues can be addressed by a robust pharmacovigilance (PV) system and a comprehensive, safe, and effective health care system can be achieved which will benefit both the patient and healthcare professional.

Reimbursements
You will not be provided any incentive to take part in the research.

Confidentiality
The research being done in the hospital may draw attention and if you participate you may be asked questions by other people in the hospital. We will not be sharing information about you to anyone outside of the research team. The information that will be collected from this research project will be kept private. Any information about you will have a number on it instead of your name. Only the researcher will know what your number is, and that information will not be shared with or given to anyone except the research team.

We will ask you and others in the group not to talk to people outside the group about what was said in the group. We will, in other words, ask each of you to keep what was said in the group confidential. You should know, however, that we cannot stop or prevent participants who were in the group from sharing things that should be confidential.

Sharing the Results
Nothing that you tell us today will be shared with anybody outside the research team, and nothing will be attributed to you by name. The knowledge that we get from this research will be used in the study and published so that others may be made aware of the findings.

Right to Refuse or Withdraw
You do not have to take part in this research if you do not wish to do so and choosing to participate will

not affect your job or job-related evaluations in any way. You may stop participating in the discussion at any time that you wish without your job being affected.

Who to Contact

If you have any questions, you can ask them now or later. If you wish to ask questions later, you may contact any of the following:

Aaminah Munshi
076 785 5686
aaminah005@gmail.com

Rubina Shaikh
0117172369
Rubina.Shaikh@wits.ac.za

Certificate of Consent for the study titled, "Determining the incidence, prevalence and management of Drug-Drug Interactions between Antiretrovirals and concomitant drugs used in the treatment of Non-communicable diseases."



Department of Pharmacy and Pharmacology
School of Therapeutic Sciences, Faculty of Health Sciences
7 York Road, Parktown, 2193, South Africa ● Tel: +27 11 717 2552 ● Fax: +27 11 642 4355

Informed Consent Form for Qualitative interview-based study

This informed consent form is for pharmacists within tertiary hospitals who are invited to participate in research, titled "Determining the incidence ,prevalence and management of Drug-Drug Interactions between Antiretrovirals and concomitant drugs used in the treatment of Non-communicable diseases."

Part II: Certificate of consent

I have read the participant information leaflet. I have had the opportunity to ask questions about it and any questions I have, have been answered to my satisfaction. I consent voluntarily to be a participant in this study.

Print Name of Participant_____

Signature of Participant _____

Date _____
Day/month/year

Consent to audio recording the discussions within the focus group

Department of Pharmacy and Pharmacology
School of Therapeutic Sciences, Faculty of Health Sciences
7 York Road, Parktown, 2193, South Africa ● Tel: +27 11 717 2552 ● Fax: +27 11 642 4355

Part III : Consent to audio recording the discussions within the focus group.

STUDY NAME: Determining the incidence, prevalence and management of drug-drug interactions between antiretrovirals and concomitant drugs used in the treatment of Non-communicable diseases.

RESEARCHER'S NAME & AFFILIATION: Aaminah Munshi (Primary Investigator)

- This study involves the audio recording of your discussion within the focus study.
- Neither your name nor any other identifying information will be associated with the audio or audio
- recording or the transcript.
- Only the research team will be able to listen to the recordings.
- The tapes will be transcribed by the researcher and erased once the transcriptions are checked for
- accuracy. Transcripts of your interview may be reproduced in whole or in part for use in presentations or written products that result from this study.
- Neither your name nor any other identifying information (such as your voice or picture) will be used in presentations or in written products resulting from the study.

By signing this form, I am allowing the researcher to audio tape me as part of this research.

Participant's Signature: _____Date:_____

Appendix B6

Focus group demographic details questionnaire

Please answer the following questions in the spaces provided, circle or tick the most appropriate options.

1. Age:……

2. Are you: (please tick as necessary) □ Male □ Female □ Rather not say

3. Please indicate your race:

□Asian □Black □Coloured

□Indian □White □Rather not say

4.What is your current professional status?

□ Pharmacist
□ Pharmacist intern
□ Other: (please describe) _____

5.How many years of experience have you had in this current job?

□ <1 Year □ 1-2 Years
□ 2-5 Years □ 5-10 Years
□ >10 Years

6.How often have you encountered drug-drug interactions in patient prescriptions ?

□ At least once a day
□ Once a week
□ Multiple times a week

7. Have you had any training in the management of drug-drug interactions?

□Yes □No

Please elaborate: _____

_____

Thank you for taking the time to complete this questionnaire

Appendix B7

Questions adapted from Anthierens et al.

Broad Questions

What are your views on DDIs among HIV patients on ARVs?

In your opinion, can something be done in order to reduce DDIs?

What could be a specific role for a pharmacist in relation to DDIs and its management thereof?

Specific Questions and Prompts

What are important factors contributing to DDIs?

Do you think prescribing practices have changed over time?

Are there specific elements that could help reduce DDIs? (types of interventions, education, …)

Appendix B8

Ethics clearance

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG

R14/49 Ms A Munshi

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M180660

NAME: (Principal Investigator)	Ms A Munshi
DEPARTMENT:	School of Therapeutic Sciences Department of Pharmacy and Pharmacology Medical School University
PROJECT TITLE:	Determining the incidence, prevalence and management of drug-drug interactions between antiretrovirals and concomitant drugs used in the treatment of non-communicable diseases
DATE CONSIDERED:	29/06/2018
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Ms R Shaikh
APPROVED BY:	Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	26/09/2018

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary on 3rd floor, Phillip V Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.
I/We fully understand the conditions under which I am/we are authorised to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated from the research protocol as approved, I/we undertake to resubmit to the Committee. I agree to submit a yearly progress report. When a funder requires annual re-certification, the application date will be one year after the date of the meeting when the study was initially reviewed. In this case, the study was initially reviewed in June and will therefore reports and re-certification will be due early in the month of June each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature

Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix B9

Plagiarism report

841221:1]Investigating_the_prevalence_and_management_of_p.

ORIGINALITY REPORT

11%	7%	7%	5%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	www.who.int Internet Source	1%
2	link.springer.com Internet Source	1%
3	Kapp, PA, AC Klop, and LS Jenkins. "Drug interactions in primary health care in the George subdistrict, South Africa: a cross-sectional study", South African Family Practice, 2013. Publication	<1%
4	Mohammad Ismail, Sidra Noor, Umme Harram, Inamul Haq et al. "Potential drug-drug interactions in outpatient department of a tertiary care hospital in Pakistan: a cross-sectional study", BMC Health Services Research, 2018 Publication	<1%
5	www.sapj.co.za Internet Source	<1%