Annual costs incurred on managing adverse drug reactions attributable to fixed-dose combination Highly Active Anti-Retroviral Therapy (HAART) in an outpatient ARV clinic in Gauteng.

BY

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

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PREFACE

This dissertation is presented in manuscript format. The findings of the study are presented in chapter 3, as a manuscript as required by the regulations of the University of KwaZulu-Natal. This manuscript was submitted for publication in the *Value in Health: Regional Issues.* The reference list is cited according to the instructions for authors as required by the *Value in Health: Regional Issues.* A complete reference list is included at the end of every chapter and according to the reference style of the University of KwaZulu-Natal.

The dissertation consists of four chapters as follows:

- Chapter 1: provides an introduction to the study as well as the aims, objectives and a brief overview of the methodology.
- Chapter 2: provides the literature background to the study.
- Chapter 3: consists of the results, discussion and conclusion written in a manuscript format.
- Chapter 4: provides the general conclusions, recommendations, limitations and strengths of the study.

ABSTRACT

Objective

The aim of the study is to identify adverse drug reactions attributable to tenofovir- and zidovudine-based fixed-dose combinations of highly active anti-retroviral therapy and, subsequently, to determine the annual costs incurred managing these adverse drug reactions and the budget implications of these costs at an outpatient anti-retroviral clinic in Mamelodi, Pretoria.

Methods

This retrospective cohort study reviewed de-identified clinical data for adverse drug reactions. The study was carried out at Stanza Bopape ARV Clinic in Mamelodi, Pretoria. De-identified medical charts of HIV-positive patients were analysed for clinical information and laboratory data of adult patients who started on HAART between July 2017 and June 2018. Data collection commenced in October 2018.

Based on the costs and the incidence rates of adverse drug reactions observed in the analysis, a decision tree model was established to estimate the cost impact of adverse drug reaction management on the clinic's budget.

Results

A total of 469 patient files were analysed (62% female vs 38% male). The mean age at the start of anti-retroviral therapy for the cohort was 36.6yrs (95% CI 35.74-37.45) and the mean baseline CD4 count was 380 (95% CI 343-418). Incidence of adverse drug reactions to tenofovir- or zidovudine-based fixed-dose combinations of anti-retroviral therapy was found to be 24.95%. The ADRs reported with the use of TDF and AZT based HAART regimens were rash (n=45, 27%), decreased glomerular filtration rate (n=34,

21%), trouble sleeping (n=39, 21%), severe diarrhoea (n=19, 12%), nausea and vomitting (n=18, 11%), decreased heamoglobin or anaemia (n=4, 2%), headaches (n=4, 2%), dizziness (n=2, 5.3%).

The study revealed that ZAR427.30 was the cost attributed to adverse drug reactions due to tenofovir-based regimens whilst ZAR467.94 was the cost attributed to adverse drug reactions due to zidovudine-based regimens, per patient, annually. Costs attributed to gastro-intestinal related adverse drug reactions were the highest in comparison to other adverse drug reactions. Estimated total cost of adverse drug reactions attributed to zidovudine-based therapy was ZAR8003.98 (US$556.40) and estimated total cost of adverse drug reactions attributed to tenofovir-based anti-retroviral therapy per annum was ZAR33 788, 23 (US$2348.80) for 1221patients initiated on antiretroviral therapy between July 2017 and June 2018.

Conclusion

Despite our estimated costs to the clinic, due to adverse drug reactions, being lower than similar studies, there remains a notable budget impact on a resource-limited setting. These estimates will allow for cost due to adverse drug reactions caused by tenofovir- and zidovudine-based anti-retroviral therapy to be accounted for in budgets at the anti-retroviral clinic.

Keywords: Adverse drug reactions, cost analysis, highly active anti-retroviral therapy, tenofovir, zidovudine.

DECLARATION 1 - PLAGIARISM

I, Grace Chikeya, declare that:

1. The research reported in this thesis, except where otherwise indicated, is my original work.
2. The work described in this thesis has not previously been submitted to UKZN or other tertiary institutions for purposes of obtaining an academic qualification, whether by myself or any other party.
3. This thesis does not contain other persons' writing, unless specifically acknowledged as being sourced from other researchers. Where other written resources have been quoted, then:
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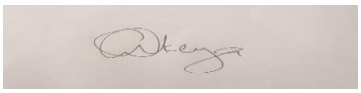
Signed  Date: 08/09/2020

This is to certify that the contents of this thesis are the original work of Ms Grace Chikeya and as the candidate's supervisors, we have approved this thesis for submission.

Supervisor: Dr. Varsha Bangalee

Signed: _____ Date: 8/12/2020

Co-Supervisor: Prof. Frasia Oosthuizen

Signed: _____ Date: 9/12/2020

DECLARATION 2 – ETHICS APPROVAL

Ethical approval for the study was obtained from the Biomedical Research Ethics Review Committee of the University of KwaZulu-Natal (BE404/17) – (Annexure 1), as well as the gatekeeper approval from the Gauteng Department of Health, Tshwane Research Committee (PROJECT # 61/2018, NHRD REF GP_201805_034) – (Annexure 2).

DECLARATION 3 – MANUSCRIPT PUBLICATION

1. My contribution to the project was as follows:
Grace Chikeya: Author – contributed to the project by performing all literature reviews, data and statistical analyses, interpretation of the results as well as manuscript preparation and writing of dissertation.

2. The contributions of others to the project were as follows:
Dr Varsha Bangalee*:* Supervisor – supervision of the concept of the study and writing of the dissertation and manuscript.
2. The contributions of others to the project were as follows:
Prof Frasia Oosthuizen*:* Co-supervisor – supervision of writing of the dissertation and manuscript.

DEDICATION

Nothing is impossible with you Lord; this journey has been a true testimony of this. I thank You. I dedicate this thesis to my awesome family for their relentless support in all of my academic endeavours. A special mention to my mother, Pamela Fostina, my rock in all times. All your teachings and guidance will forever be with me. Dear mama, you are appreciated.

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To my husband Itayi Chikowore, I appreciate your advice and guidance from day one, proof-reading all my work, you are amazing. My beloved son Anashe, all of this is for you. I appreciate the support and sacrifices that are too many to mention, that both you guys made. Without you guys, this would not have been possible. I will always appreciate all of it.

LIST OF ACRONYMS AND ABREVIATIONS

AIDS	Acquired Immunodeficiency Syndrome
ADR	Adverse Drug Reaction
ART	Antiretroviral Therapy
AZT	Zidovudine
CD4	Cluster of differentiation 4
d4T	Stavudine
EFV	Efavirenz
HAART	Highly Active Antiretroviral Treatment
HIV	Human Immunodeficiency Virus
NDoH	National Department of Health (South Africa)
NHLS	National Health Laboratory Services
NRTIs	Nucleoside Reverse Transcriptase Inhibitors
NNRTIs	Non-Nucleoside Reverse Transcriptase Inhibitors
PV	Pharmacovigilance
TB	Tuberculosis
TDF	Tenofovir
UNAIDs	Joint United Nations Programme on HIV/AIDs
WHO	World Health Organisation
UKZN	University of KwaZulu-Natal

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CHAPTER ONE

INTRODUCTION

Pharmaceuticals have the innate risk of causing harm (adverse drug reactions) as well as doing good (efficacy).[1] At every phase of drug development, until it's end use, the concept of benefit outweighing risk is used to assess whether the pharmaceutical will be prescribed or not. Benefit-risk assessment is not limited to the pharmaceuticals' efficacy but also cost implications.[1] Costs associated with the risk of causing harm (adverse drug reactions) should be included in financial benefit-risk assessment**.**

1.1 **Background and Rationale for this Study**

The costs of pharmaceuticals have been on the rise in the last couple of decades, much to the disgruntlement of payers such as governments, as well as advocacy groups who speak on behalf of the general population.[2] Over the years, there have been calls for transparency in the pricing of pharmaceuticals. This has led to organisations and nations setting up regulatory bodies to control and set up standards for the pricing of pharmaceuticals. As a result, more research has been carried out and published on the costs of pharmaceuticals.[2]

Albeit, the increased research on costs of pharmaceuticals, there is still a research gap on the impact of adverse drug reactions on these costs. Adverse drug reactions (ADRs) lead to increased healthcare costs. Analysis of the costs of pharmaceuticals would be insufficient if the costs of adverse drug reactions associated with them are not factored as well.[3] Studies on the costs attributable to ADRs and the budget impact of these costs are limited especially in South Africa.

HIV/AIDS has a great level of disease burden on South Africa. According to the UNAIDS data, in 2018, South Africa had the largest anti-retroviral therapy programme in the world with just over 4.8million people on treatment then.[4] It is therefore in the interest of the payers that cost of Highly Active Anti-Retroviral Therapy (HAART) as well as those of ADRs associated with them are known. This is beneficial for budgeting purposes. In order to analyse the budget impact, incidence of the ADRs need to be considered. Based on reviewed studies carried out in developing countries the incidence of adverse drug reactions to Highly Active Anti-Retroviral Therapy (HAART) ranges from 4.6% to 89.8%.[4-19] A South African study reported an incidence of adverse drug

reactions (ADRs) to HAART as 37%.[19] This is a fairly high figure and demonstrates the need to analyse the cost involved in medically managing these adverse drug reactions.

1.2 Research Questions

This study focused on the following research questions:

1.2.1 What are the adverse drug reactions (ADRs) attributable to tenofovir- and zidovudine-based fixed-dose combinations of Highly Active Anti-Retroviral Therapy (HAART) and their incidence?

1.2.2 What are the direct costs of preventing and managing adverse drug reactions for tenofovir- and zidovudine-based HAART regimens?

1.2.3 Impact on ARV clinic budgets in Gauteng. What is the contribution of HAART ADRs on the clinic's budget?

1.3 Aims and Objectives of the Study

The aim of the study is to identify adverse drug reactions attributable to tenofovir and zidovudine-based fixed-dose combinations of highly active anti-retroviral therapy and subsequently, determine the annual costs incurred managing these adverse drug reactions and the budget impact of these costs at an outpatient anti-retroviral clinic.

1.4 Significance of the Study

This study gives an indication of the direct costs incurred in managing adverse drug reactions attributable to fixed-dose combination HAART in an outpatient facility. The National Department of Health (NDoH) embarked on a programme to ensure that all HIV positive patients are identified through testing as well as initiated on ARVs. ARV clinics were set up mostly as outpatient facilities within easy access to communities. One of the results of this rollout is that an unprecedented number of patients where initiated on HAART and the number is still rising. HAART increases the life expectancy of HIV positive patients which also means increased duration on treatment as well as increased risk of ADRs. This scenario advocates for increasing knowledge of the cost implications of ADRs to HAART.

Adverse drug reactions are a major cause of patient-related morbidity and mortality as well as increased healthcare costs and knowledge of such costs will play a huge role in effective budgeting in ARV clinics or facilities.

1.5 Research Methodology

1.5.1 Study Design and Setting.

A retrospective cohort study was carried out. Stanza Bopape ARV Clinic capture's all medical data from the patients' files onto a computer system, i.e. the Tier System. Previously captured medical records of enrolled de-identified patients were analysed. Costs incurred (laboratory charges and pharmaceutical charges) were extracted from Stanza Bopape Primary Health Clinic's accounting system as well as its suppliers such as National Health Laboratory Services (NHLS) billing system.

1.5.2 Data Analysis

Patients were separated into 2 groups i.e. case and control. Case groups were those patients that recorded an ADR, while the controls were those that did not. They were compared for age at HAART initiation, baseline CD4, total HAART costs, total laboratory costs and total direct costs using the independent sample t-test.

To estimate the impact of costs attributable to ADRs, a Decision Tree Model was established. Based on the results collected, from the above analysis, a novel budget impact model was built in Microsoft® Excel®.

1.5.3 Ethical Approval

Full ethical approval was obtained from the University of Kwazulu-Natal's Biomedical Research Ethics Review Committee (BREC) - reference number BE404/17 **(**Annexure 1)

1.5.4 Gate-keeper Approval from Gauteng Department of Health, Tshwane Research Committee.

This study's gatekeeper approval was obtained from the Gauteng Department of Health, Tshwane Research Committe (PROJECT # 61/2018, NHRD REF GP_201805_034). **(**Annexure 2)

Chapter 1 Summary

This chapter summarizes the study's rationale and significance, research questions, aims, objectives and a brief outline of the research methodology.

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CHAPTER TWO

LITERATURE REVIEW

2.1 Introduction

Pharmaceuticals are at the centre of ensuring the welfare of patients. They curtail the distress and costs that come along with the disease. Their rational use ensures that society can prevent and control various diseases.[1] Antiretroviral drugs are no exception to this phenomenon. Highly Active Anti-Retroviral Therapy (HAART) has significantly improved the health and socioeconomic outcomes of the infected population, making HIV a manageable disease. It has reduced morbidity and mortality in HIV positive patients significantly. Without therapy, probably more than 90% of all HIV+ patients die from AIDS.[2]

As well as being an integral part of health care, pharmaceuticals are both a product and an asset for trading. They come at a cost for the payer and society as a whole.[3] Global healthcare costs have been reported to be rising at an alarming rate with costs of pharmaceuticals being at the driving centre of the exponential increase.[4] This has prompted the need for more data on costs associated with pharmaceuticals.

Costs associated with pharmaceuticals are not the only detrimental factor; pharmaceuticals often come with adverse reactions. According to the World Health Organization (WHO), an adverse drug reaction (ADR) is defined as "a response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or the modifications of physiological function."[5] All medicines carry the risk of causing ADRs. ADRs are one of the key causes of morbidity and mortality in healthcare.[6] The effects of ADRs and their management is costly owing to the increased incidence of healthcare utilisation they bring. ADRs may also trigger prescription cascades or even hospitalisation. Often unrecognized ADRs require the prescription of new medications.[7] ADRs are associated with two main inversely correlated costs, i.e. the cost of treating diseases due to ADRs and the cost of evading them. When one arm increases, the other automatically decreases. The impact and the management of ADRs, in the USA, has been reported to cost up to 30.1 billion dollars annually. [8] All these costs need to be incorporated when carrying out a pharmacoeconomic evaluation on a pharmaceutical.

Different anti-retroviral therapy (ARV) drug classes have different side effects that include lactic acidosis, neuropsychiatric symptoms, rash, liver toxicity, and lipid abnormalities, gastrointestinal intolerance, glucose abnormalities amongst others. They are at times associated with serious side effects, such as osteonecrosis, renal failure, Stevens-Johnson syndrome (SJS) and bone demineralization.[8-11] The reported economic burden of these ADRs is significant. In the United States, the direct cost incurred in treating ADRs to HAART per episode can escalate up to several thousand dollars.[12-14] In comparison, these costs might be lower in South Africa and other developing countries. However, when compared the per capita spending on health, these cost associated with ADRs is significantly high.[15]

In an effort to increase knowledge on the economic burden of these ADRs, locally, more studies with need to be commissioned.

2.2 Pharmacovigilance

2.2.1 History of Pharmacovigilance

History informs us that, many congenitally deformed babies were born to mothers who had used thalidomide during pregnancy. Thalidomide had been marketed for the treatment of nausea during pregnancy in the 1950s and 1960s.[5] These births led to coming together of the international community, through the World Health Organisation, in an effort to deal with drug safety. International Drug Monitoring commenced in 1968. The project was set up to ensure the timeous reporting of ADRs as well as efficiently alert individual countries to the patterns of ADRs that were emerging across the world. These patterns might not be evident from their local data alone.[5]

Pharmacovigilance systems were developed in most developed countries following the thalidomide catastrophe.[5] These systems use spontaneous reporting amongst other methods to collect data on ADRs. They analyse, assimilate the available data, and submit it to the WHO Collaborating Centre for International Drug Monitoring, known as the Uppsala Monitoring Centre.[16]

2.2.2 Global Pharmacovigilance

Pharmacovigilance starts long before a product is introduced onto the market and continues for as long as the product remains available in the market. It involves two main phases. These are the

pre-marketing/trial phase and post-marketing/approved drug phase.[17] The pre-marketing/trial phase involves serious adverse events analysis reports during Phase I-III of the drug development cycle whilst the post-marketing/approved drug phase involves passive and active surveillance during Phase IV of the drug development cycle.[17]

The primary focus of pharmacovigilance, in the beginning, was regulatory. This included detecting (diagnosing, reporting) ADRs of registered drugs.[17] It was set to detect ADRs not observed during the pre-marketing studies (Phase I-III). Clinical trials have limitations when it comes to discovering and assessing ADRs. These limitations include selection bias, sample size, and limited follow-up duration. [17] Due to these limitations, data on ADRs from clinical trials may not necessarily reflect the real incidences and variety of ADRs due to the pharmaceutical in question. Thus, real data on the safety of the pharmaceuticals may only be deduced when it is used by millions of patients in clinical practice.[7]

In a real-world setting, after a drug is marketed, case reports and epidemiological studies are used to obtain data on ADRs. These have a better chance at unveiling scarce ADRs as well as revealing the real incidence rate of common, predicted ADRs. However, these studies have fewer controls, in comparison to the clinical trials, resulting in increased difficulty to ascertain the causal relationship between the pharmaceutical and the adverse drug reaction.[7] Despite these challenges, in the post-approval scenario, product safety data must be collected, organized, analysed and reported properly. There is value in quantifying incident levels and frequency for identified ADRs as this can vary from its pre-marketing occurrence, as alluded to earlier. [18] In addition, there is also an emphasis on broadening pharmacovigilance activities to include poor efficacy, prescribing errors, incorrect usage, manufacturing or stability standards not met.[19]

These above-mentioned activities are major components of post-marketing research or surveillance. Post-marketing drug surveillance (PMS) refers to the " monitoring of drugs once they reach the market after clinical trials". [18] These studies collect and analyse ADRs observed from a real-world setting.[20] They are of great value in ensuring that relevant and good quality data is collected on predicted and unpredicted ADRs, allowing for additional classification of the ADRs. This is possible as more information on the ADR is gathered from case to case in a clinical setting.[21]

As the biological sciences progressed, in the pre- phases of drug production, pharmacovigilance gradually moved towards earlier, cautious consideration of the dangers and possible benefits of drugs.[21] Technological advancements observed in recent years have allowed for research and development of complex medicines. Complex medicines are more accessible to patients than they were in previous decades. [21] Being fairly new on the market, there is limited data on the ADRs of these complex medicines. At the present stage, pre-marketing research data is mostly used to the obtain data on their respective ADRs. Risk evaluation of these complex medicines is warranted. [21] With complex medicines, pharmacovigilance focus shifts to the pre-marketing stages. These have also allowed for more comprehensive risk evaluation and possible benefits in the manufacturing phase much earlier. Growing consumer concern for the safety of more advanced medications, coupled with emerging research, has led pharmaceutical innovators, regulators, and healthcare practitioners to cooperate on the creation of recommendations for improved pharmacovigilance and earlier medication risk management.[21]

2.2.3 Status of Pharmacovigilance Activities in South Africa

Developing countries only started developing national pharmacovigilance systems decades later, after their developed-world counterparts. South Africa has progressed since becoming a member of the International Drug Monitoring Network of the World Health Organization (WHO) in 1992. [17] Locally, prior to becoming a member of the International Drug Monitoring Network, the foundations for the development of a national pharmacovigilance system had been laid in South Africa. These included the declaration on the Medicines and Related Substances Control Act 101 of 1965 and the formation of various committees such as the National Adverse Drug Event Monitoring Centre (NADEMC) and a Pharmacovigilance (PV) expert committee, which laid the framework and guidelines for passive surveillance of ADRs.[17]

HIV/AIDS and TB epidemics catapulted pharmacovigilance activities in South Africa. There was a need for knowledge of the risks associated with pharmaceuticals utilised in the implemented national programmes, which responded to these epidemics.[17] Both the TB epidemic and the HIV crisis have acted as primary factors of service delivery innovation, control, and assessment. [22] Throughout South Africa, these successful monitoring programs were primarily limited to studying the effects of HIV and TB drugs. As they progress, they have developed into positive pharmacovigilance interventions throughout public health.[22] The pharmacovigilance activities

involved formation of national registers for collection of clinical data including adverse drug reaction observed.[22]

Globally there is a transition from solely relying on passive/spontaneous reporting in pharmacovigilance to active surveillance. Active surveillance involves patient registries, cohort studies amongst other activities. South Africa has also started to introduce patient registries and record-linkages in its pharmacovigilance system. [21]

Mehta *et al.* (2017) highlighted the value of a strong national pharmacovigilance program in response to the rising pressures of drug-induced disease. It helps to educate real-world evidence-based care programs, to enhance the outcomes of chronic diseases such as HIV, Tuberculosis, hypertension and diabetes through effective clinical intervention, and to ensure the safety of large-scale pharmacotherapy such as vaccines.[16]

Despite all the years of experience mentioned above, South Africa's pharmacovigilance systems need to be improved and streamlined. Pharmaceutical manufacturers, the South African Health Products Regulatory Authority (SAHPRA), public healthcare programs as well as healthcare professionals carry out pharmacovigilance activities in South Africa.[23] Despite having a common goal, which is collection and analysis of data on ADRs, these groups have varied objectives. Pharmaceutical manufacturers and South African Health Products Regulatory Authority (SAHPRA), public healthcare programs, healthcare professionals focus on the pharmaceuticals, systems, and patients respectively.[23] There is a need for these stakeholders to liaise, pool resources and complement each other to improve South Africa's pharmacovigilance status.

2.2.4 Risk Factors for Adverse Drug Reactions

ADRs, in general, are classified into two basic types. Type A (on-target) reactions are "predictable from the known pharmacology of the drug and show a clear dose-response relationship".[24] Type B (off-target) reactions are "those that are difficult to predict from the known pharmacology of the drug".[24] Type B ADRs are usually detected after the drug is marketed and show no clear dose-response relationship. Their etymology is usually more complex than the Type A ADRs.[24] ADRs, in general, have a complex etymology. Various factors, which could be genomic or metabolic in nature, influence their etymology. Adverse drug reactions can also be classified as dose/drug-induced reactions, allergic reactions, or idiosyncratic reactions.[25-27] The existence of other diseases

and genetic factors are also risk factors modulating the occurrence of ADRs. The existence of other diseases or co-morbidities can result in an alteration of a particular pharmaceutical's pharmacokinetics.[26] ADRs occur at a different rate depending on the concentration of various drug metabolites in circulation. In some instances, the drug metabolites are responsible for the ADRs observed.[27] Pharmacokinetic properties of the pharmaceutical, its dosage, number of times it is administered, route of administration are also risk factors that modulate ADR occurrence.[25,26] In addition, particular populations such as kidney or liver failure patients and geriatrics may have a propensity for increased ADR occurrence due to altered drug metabolism.[25, 26]

It is almost axiomatic that all drugs, in addition to the desired ones, have the potential to produce undesirable effects.[22] Pharmaceutical care warrants a good understanding of the risk factors and a tailored healthcare approach to meet the patient's needs.

2.2.5 Challenges of Pharmacovigilance - Underreporting

Pharmacovigilance in practice experiences various challenges, which include, underreporting of ADRs. This is a common and overwhelming problem.[28-30]

A systematic review of 37 studies by Hazell and Shakir found a median under-reporting rate of 94%.[29] There are many factors, which contribute to the phenomenon of under-reporting of ADRs. Most nations, including South Africa, are primarily adopting the spontaneous or voluntary ADR reporting system. This system, although more affordable, presents various challenges. The issues include whether reporting practice is instilled in health care practitioners, the accuracy of reports, confusion as to whether a product has triggered a reaction or it is a different health condition presenting itself, time constraints hampering reporting, reporting liability problems, publication of reporting expectations and patient participation in reporting.[31]

In addition, Terblanche et al. (2017), carried out a study in a South African public health hospital which reported that 53.8% of the healthcare professionals who participated gave not "knowing how to report" ADRs as the reason for not reporting.[32] Ironically, this study has shown that some factors reported causing low ADR reporting rates and poor-quality reporting such as bad attitude and insufficient knowledge could be addressed.[32] There are also patient-related reasons for underreporting like failure to recognize ADR or inability to link the ADR with a drug.[30]

An essential factor for drug safety is timely reporting of ADRs to drug regulatory bodies but under-reporting is a major challenge. This is a universal concept affecting both developed and developing countries. This is despite developing countries having human and material resources to tackle the issue.[31]

2.3 Pharmacoeconomics

There is a growing realisation in the global community that resources are limited, and this concept applies to healthcare too. Various factors come into play in terms of healthcare financing. These include increasing rates of inflation and limited budgets. Due to this realisation, health care policymakers, over the last three decades, have had to appraise healthcare initiatives in terms of the benefits and costs. In order to be added onto various payers' formularies, new healthcare initiatives not only have to go through an economic evaluation but also have to be found economically beneficial.[33] This phenomenon led to the birth of health economics and its sub-branch, pharmacoeconomics.

Pharmacoeconomics is defined as "the description and analysis of the costs and consequences of pharmaceutical products and services and their impact on individuals, health care systems and society."[19] It is a field of economics that compares the costs and outcomes of various pharmaceutical products and treatment strategies.[19] Therefore, pharmacoeconomic analyses are used to evaluate drugs for formulary status.

Pharmacoeconomic concepts and methods have been in use since the early seventies.[34] The trend in the use of pharmacoeconomics in formulary decision making, disease management programs as well as determining the cost-effectiveness of healthcare interventions is on the increase.

2.3.1 Pharmacoeconomic Evaluations

Economic evaluations allow for comparison between the costs and the benefits associated with a pharmaceutical.[34] They take into consideration both costs and consequences to differentiate therapies.[34, 35]

Costs are not limited to the price of a pharmaceutical but also societal effects such as loss of income, stress and time used to acquire medical help.[36] The different types of healthcare costs

analysed include direct (medical and non-medical costs), indirect and intangible costs. [36] Benefits also vary from cure, quality-adjusted life-year (QALY) gained or income gained when healthy or well. [36]

Costs and benefits vary depending on the perspective of the analysis. The perspective of an economic evaluation is a statement of the point(s) of view from which the analysis is conducted. The analysis can have more than one perspective.[37] Perspectives can be that of a payer, health care sector or societal.[37]

2.3.2 Healthcare Costs and Financing

According to a WHO report on global public health spending, in 2016, the world spent $7·5 trillion on health. There is an enormous disparity in per capita spending on health between developed and developing countries. Per capita spending on health in developed countries has been reported to be as high as $2000, versus only $100 to $400 developing coutries.[38] In the absence of sustainable new health investment initiatives, rising health spending efficiency remains the backbone to achieving global health goals.

Numerous reports detail the world's healthcare outlays.[39-41] In 2018, the World Health Organization updated its global health outlays, up to 2016.[39] The Organisation for Economic Cooperation and Development (OECD) has also released new data on official donor assistance for health in developing countries.[40] Policy Cures Research released its latest g-finder survey in January 2019, monitoring global drug development expenses for neglected diseases up to 2017.[41] Schäferhoff et al. (2019*)* analysed these three data sources to establish patterns of healthcare funding. They also evaluated if the world is well on its way to mobilizing the funds required to achieve health objectives set out in the third sustainable development goal (SDG 3).[39- 42] The analysis showed that healthcare outlays are rising. However, they remain inadequate for most governments of developing countries to finance universal health coverage, especially without donor funding.[42]

In South Africa, the healthcare system is divided into two parallel systems, public and private sectors depending on the source of funding. The government, together with donors, is responsible for funding the public sector whilst profit and non –profit companies fund the private sector.[43] These tiers operate separately with little mixing. Previous papers have reported that the public

sector accounts for only 20% of healthcare spending in South Africa yet it is responsible for the health of 80% of the population. On the other hand, these reports note that the private sector accounts for 80% of healthcare spending on only 20% of the population.[43] This gives a picture of how unequal access to health services in South Africa is. In order to address this inequity and also comply with the developmental goals of universal health coverage, South Africa has developed a framework for a National Healthcare Insurance. This is currently being piloted in 10 districts within the country.[43]

2.3.2 Pharmacoeconomics in South Africa

Implementation of pharmacoeconomics in South Africa has not been without its own challenges. Although the definition was adopted in 1996 in the National Drug Policy (NDP), the regulations allowing for the setting up of a pricing committee and the resulting Transparent Pricing System Regulations were only concluded and adopted in 2003 and 2004 respectively.[34] The Pharmacoeconomic Guidelines were only developed almost a decade later in 2013.[34] The aim of these was to provide guidance on conducting and submitting a pharmacoeconomic analysis. At present, pharmacoeconomic submission are voluntary with the plans of making them mandatory in future.

2.4 Pharmacoeconomics of Adverse Drug Reactions

Pharmacoeconomics applied to pharmacovigilance activities is an important aspect that helps to improve the rational use of medicinal products. ADRs increase patient morbidity and mortality and raise the overall cost of health.[8] Through recording identified or suspected ADRs, health care providers and patients may assist in detecting patterns and trends. This is necessary for the regulatory oversight or removal from the market of products that may not have a favourable risk-benefit ratio. [8]

Economic analyses supported data sources have shown that the entire cost of drug therapies is often much above the monetary price paid.[42] When analysing the financial burden of pharmaceuticals, all costs and benefits must be taken into account. The benefits of a drug are expressed as the therapeutic effects shown in clinical trials. The risks include that they may cause adverse events, among other health implications.[3]

Various studies show that the costs of drug-related adverse events are significant.[38-49] Depending on the perspective, the costs may vary substantially, according to the studies. Methodological differences such as the data sources for ADR, costs identification and methods of cost measurement result in varied costs reported.[8] However, all these studies confirm that the costs of ADRs influence the outcome of a health economic analysis or pharmacoeconomic studies. Incremental cost estimates per ADR episode occurring in the hospitalized patients can range from $US1049.69 to $US5972.74.[40-42] In non-hospitalized patients, the incremental cost estimate per ADR episode which results in hospitalization can range from $2427.45 to $5187.50.[43-55]There are limited studies on the cost of ADRs carried out in Africa. This could be due to limited resources, such as infrastructural, financial and skilled human resources.[7] The studies carried out reported significantly lower costs compared to those reported on studies carried out in developed countries. This phenomenon can also be attributed to the limited resources, previously mentioned.[56-58]

Akhideno et al. (2018) carried out a study on the economic burden, impact, and consequence of adverse drug reactions among medical inpatients in Nigeria. They found that the average cost of medications for treating ADRs among inpatients was $US24.38 per ADR episode. Throughout this research, it was confirmed that the central nervous system and the gastrointestinal system corresponding to the antidiabetic medication – insulin use causing neuroglycopenic symptoms and use of non-steroidal anti-inflammatory drugs (NSAIDs) causing NSAID-induced gastroenteritis / GIT bleeding, respectively – were the most frequently affected body systems by ADRs.[57]

Schnippel et al. (2018) carried out a study on the direct costs of managing adverse drug reactions during rifampicin-resistant tuberculosis treatment in South Africa. They estimated that the incremental costs of ADR management were US$380.17 annually per patient initiating on multi-drug-resistant tuberculosis or rifampicin-resistant tuberculosis (MDR/RR-TB) treatment. The incremental costs of ADR management for the public health sector in South Africa were US$4.76 million, 8.3% of the estimated cohort costs of MDR/RR-TB treatment ($57.55 million) for the 2015 cohort of 12 527 patients.[58] The link between pharmacoeconomics and pharmacovigilance allows future and current ADRs to be monetized and budgeted for. This will also allow for better planning and cost savings for the institutions or patients involved.

2.5 Mini Scoping Review on Incidence and Types of ADRs to HAART

In an effort to review available information on incidence and types of ADR to HAART, a mini-scoping review was conducted. Specific review techniques and methodology as outlined by Levac et al. (2010) were applied.[59] This guided the development of a search strategy and criteria to identify and appraise articles that focused on economic evaluations as well as incidence reports on adverse drug reactions attributable to Highly Active Anti-Retroviral Therapy. All studies identified were used the analysis. The data from studies included in the scoping review were extracted and summarised in Table 1. The data extracted included general information about the article (source, author and year of publication of each article), as well as information on the study design and study outcome measures.

Many studies have been carried out on the incidence and risk factors of HAART induced ADRs.[60-69] These studies have shown that ADRs to HAART are common causes of morbidity, change in treatment and even mortality. ADRs to HAART vary in severity and duration. The main events associated with the use of antiretroviral medicinal products include altered psychosis, body fat distribution (lipodystrophy), altered sleep patterns, anaemia and neutropenia, hypersensitivity reactions, hepatic disorders, altered bone structure (osteopenia and osteoporosis), muscle damage (myopathy), acute pancreatitis, nausea, diarrhoea and lactic acidosis.[70-79]

Author Country, Year Data Source	**Study Design**	**ADRs Identified**	**Drug Related to ADR**	**Number of Cases**	**Incidence**
Chowta et al. India, 2018 Google Scholar	Prospective observational	Haemoglobin or absolute anaemia	zidovudine	26	15,2%
		Nonspecific feeling of being unwell	tenofovir	1	0,6%
		Lactic acidosis	stavudine	3	1,8%
		Peripheral neuropathy	stavudine	2	1,2%
		Pancreatitis	stavudine	1	0,6%
		Dyslipidaemia	stavudine	2	1,2%
		Lipoatrophy		1	0,6%
		Nausea		28	16,4%
		GI Intolerance		17	9,9%
		Hepatoxicity		14	8,2%
		Rash and Itching	nevirapine	26	15,2%
		Neutropenia		9	5,3%
		Thrombocytopenia		8	4,7%
		Headache and Insomnia		2	1,2%

Table 2.1: Studies on the Incidence of ADRs to HAART

Author Country, Year Data Source	Study Design	ADRs Identified	Drug Related to ADR	Number of Cases	Incidence
Yang et al. International Journal of Infectious Diseases China, 2019	Retrospective observational	Decrease in GFR rate	Tenofovir		
			TDF regimens showed a better plasma lipid profile but mild renal dysfunction as compared to non-TDF based regimens. Patients with high BMI, high baseline TG, high baseline TCH and low baseline eGFR should be closely monitored when using TDF-based ART.		
Luma et al. Cameroon, 2012 Pubmed	Cross sectional clinical chart review	Peripheral neuropathy		15	4%
		CNS ADRs		12	4%
		GIT ADRs		12	4%
		Skin reactions		7	2%
		Lipid system reactions		6	2%
		Haemoglobin or absolute anaemia		7	2%
		Nonspecific feeling of being unwell		4	1%
		Lactic acidosis		3	1%

Table 2.1: Studies on the Incidence of ADRs to HAART cont.

Author Country, Year Data Source	Study Design	ADRs Identified	Drug Related to ADR	Number of Cases	Incidence
Lorio et al. Nicaragua,2014 Google Scholar	Retrospective, observational	CNS related		20	2,9%
		GI related		12	1,7%
		Dermatologic		8	1,2%
		Heamatologic		3	0,4%
		Renal		1	0,1%
		Endocrine		1	0,1%
Agada et al. Nigeria, 2016 Google Scholar	Cross-sectional retrospective	CNS related		42	36,2%
		GI related		48	41,4%
		Dermatologic		4	3,4%
		Heamatologic		13	11,2%
		Renal		4	3,4%
		Endocrine		3	2,6%
		Cardiovascular		15	12,9%
		Musculoskeletal system		39	33,6%

Table 2.1: Studies on the Incidence of ADRs to HAART cont.

Author Country, Year Data Source	STUDY DESIGN	ADRs identified	Drug Related to ADR	Number of cases	Incidence
Eluwa et al. Nigeria,2012 Google Scholar		Central and Peripheral NS related		37	1,4%
		GI related		9	0,3%
		Dermatologic		26	1,0%
		Cardiovascular		2	0,1%
		Systemic Symptoms		3	0,1%
		Musculoskeletal		1	0,0%
Mudzviti et al. Zimbabwe, 2015 Pubmed	Retrospective patient medical records review	Generalised skin rash		13	5,9%
		Papular rash		6	2,7%
		Erythematous rash		3	1,4%
		Stevens- Johnson syndrome		2	0,9%
		urticarial reaction		1	0,5%
Raikar et al. India, 2018 Google Scholar	Retrospective	Gastrointestinal system		36	12%
		Dermatology		33	11%
		Central nervous system		19	7%
		Musculoskeletal system		10	3%
		Others		15	5%

Table 2.1: Studies on the Incidence of ADRs to HAART cont.

Author Country, Year Data Source	Study Design	ADRs Identified	Drug Related to ADR	Number of Cases	Incidence
Ndangije et al. Uganda,2015 Reference list	Prospective cohort study	Increased creatinine ([1.2 g/dL)	tenofovir	43	0,42%
		Creatinine clearance[90 mL/min		43	0,42%
		Creatinine levels not provided		10	0,10%
		Proteinuria		25	0,24%
		Glycosuria and proteinuria		11	0,11%
		Bone demineralization		5	0,05%
		Bilateral pitting pedal oedema		6	0,06%
		Facial puffiness		4	0,04%
		Renal Toxicity		53	0,52%
Singh et al India, 2016 Google Scholar	Prospective cross sectional observational study	Hematological		50	8,4%
		Gastrointestinal		39	6,6%
		Cutaneous		35	5,9%
		Neurological		16	2,7%
		Musculoskeletal		15	2,5%
		Metabolic		8	1,3%
		Cardiovascular		6	1,0%
		Hepatic toxicity		4	0,7%
		Psychiatric disorders		3	0,5%
		IRIS		2	0,3%
		Others		10	1,7%

Table 2.1: Studies on the Incidence of ADRs to HAART cont.

Author Country, Year Data Source	Study Design	ADRs Identified	Drug Related to ADR	Number of Cases	Incidence
Sadiq et al. India, 2016 Google Scholar	Prospective observational study	Anemia		14	16%
		Gastritis		14	16%
		Vomiting		13	14%
		Rashes		12	13%
		Loss of appetite		10	11%
		Sedation		9	10%
		Lipodystrophy		9	10%
		Oesophageal candidiasis		7	8%
		Diarrhoea		6	7%
		Giddiness		5	6%
		Hepatic dysfunction		6	7%
		Peripheral neuropathy		3	3%
		Fever		1	1%

Table 2.1: Studies on the Incidence of ADRs to HAART cont.

Author Country, Year Data Source	Study Design	ADRs Identified	Drug Related to ADR	Number of Cases	Incidence
Kumar et al. India, 2017 Pubmed	Retrospective	Red blood cell disorder		326	29,10%
		Metabolic and nutritional		83	7,41%
		Central and peripheral nervous		119	10,62%
		Gastrointestinal system		221	19,73%
		Liver and biliary system		57	5,08%
		Psychiatric Disorders		24	2,14%
		Skin and appendages disorders		119	10,62%
		Urinary system disorders		24	2,14%
		White cell and RES disorders		13	1,21%
		Body pain whole		8	0,71%
		Resistance Mechanism disorder		104	9,28%
		Musculo-Skeletal disorder		22	1,96%

Table 2.1: Studies on the Incidence of ADRs to HAART cont.

Author Country, Year Data Source	Study Design	ADRs Identified	Drug Related to ADR	Number of Cases	Incidence
Divaka et al. India,2012 Google Scholar	Prospective cohort study	Aneamia		26	6,50%
		Nausea		12	3,00%
		Gastritis		5	1,25%
		Rash		25	6,25%
		Vomiting		9	2,25%
		Itching		9	2,25%
		Headache		2	0,50%
		Peripheral Neuropathy		4	1,00%
		S.J.S		4	1,00%
		Anorexia		5	1,25%
		Insomnia		1	0,25%
		Stomatitis		1	0,25%
		Body ache		4	1,00%

Table 2.1: Studies on the Incidence of ADRs to HAART cont.

Incidence data from the studies in Table 1 was extracted on to Microsoft Excel and analysed. (Table 2.2). Data on 4404 patients was extracted from the studies included in the literature review analysis. 34% of the patients in the analysis experienced at least one ADR to HAART.

	Total Participants	CNS related	GI related	Dermatologic	Haematological	Renal	Endocrine	Cardiovascular	Musculoskeletal system	Systemic	Hepatic
Chowta et al.	171	4	45	26	43	0	4	0	1	3	0
Radhakrishnan et al.	110	8	11	5	17	2	4	0	0	2	7
Luma et al.	339	27	12	7	7	0	9	0	0	4	0
Lorio et al.	692	20	12	8	3	1	1	0	0	0	0
Eluwa et al.	265	37	9	26	3	0	0	2	1	0	0
Sadiq et al.	90	9	40	9	10	0	5	0	3	0	4
Raikar et al.	289	19	36	33	15	0	0	0	10	0	0
Mudzviti et al.	221	0	0	25	0	0	0	0	0	0	0
Singh et al.	595	19	39	12	50	0	8	6	0	0	4
Kumar et al.	1400	69	107	57	220	12	40	0	11	54	27
Adaga et al.	232	42	48	4	13	4	3	15	39	0	0
Total number of	**4404**	**254**	**358**	**212**	**381**	**19**	**74**	**23**	**64**	**63**	**43**

Table 2.2: ADR occurrence frequency analysed

The reported ADRs associated with the use of ARVs were Haematological (n=381,8.65%),GI related (n=358, 8.13%), CNS related (n=254, 5.77%), Dermatologic (n=212, 4.81%), Renal (n=19, 0.42%), Endocrine related (n=74, 1.68%), Musculoskeletal related (n=64, 1.46%), Systemic (n=63, 1.43%), Hepatic (n=43, 0.97%) and Cardiovascular (n=43, 0.52%). (Fig 1)

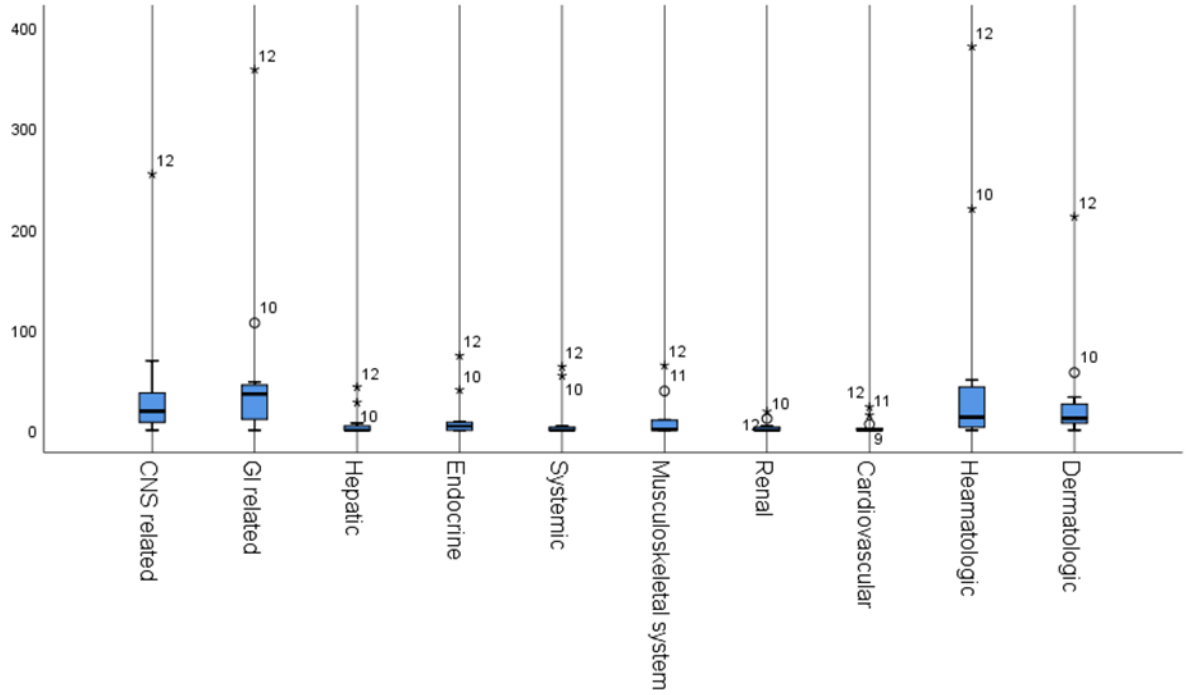

FIG 2.1: Boxplot showing the measure of spread of the various ADRs

This literature review aimed to analyse the data available on ADRs to HAART in terms of incidence of ADRs. Studies from developing countries were collated and analysis on ADR incidence was carried out. The incidence of ADRs to HAART reported in the collated analysis was 34%. This lies within the range seen in the literature reviewed.

The studies reviewed on incidence were carried out in developing countries mostly. This was important, as there tend to be significant differences in the psychological and socioeconomic support of HIV positive patients in comparison to developed countries. Public health sectors of developing countries experience challenges such as co-morbidities and malnutrition that confound the incidence of ADRs.[63] In addition, constraint resources result in limited laboratory testing which inhibits prompt and accurate diagnosis of toxicities. Use of herbal medicines as well as the high prevalence of opportunistic infections are also factors that allude to increased incidence of some of the ADRs due to drug-interactions. [71] Host biology or genetics are associated with differences in the pharmacokinetics and metabolism of the pharmaceutical. This alters the body's response leading to varied observed drug toxicity.[71]

2.6 Costs of HAART in South Africa

In South Africa, the national government funds the bulk of the national HIV program. According to the 2019 budget, this program receives a significant portion of the total grant allocation. This is in a bid to continue the implementation of the universal test-and-treat policy for antiretroviral treatment and to provide services intended to prevent the spread of HIV. It received in excess of R25billion per annum.[80] HAART is the major cost contributor to implementing HIV programs. It contributes between 56% and 77% of the total costs of HIV programs in South Africa.[81]

South Africa National Treatment guidelines adopt and are in line with the WHO's treatment guidelines. The various HAART regimens differ in costs as well as effectiveness.

Bendavid et al. (2011) adopted a mathematical simulation model of the progression of HIV/AIDS to determine the cost-effectiveness of various antiretroviral regimens that constitute the World Health Organization's Treatment Guidelines. In this study, they analysed 5 treatment regiments namely:

1. Tenofovir + lamivudine + efavirenz (TDF/3TC/EFV);

2. Tenofovir + lamivudine + nevirapine (TDF/3TC/NVP);

3. Stavudine + lamivudine + nevirapine (d4T/3TC/NVP;

4. Zidovudine + lamivudine + efavirenz (AZT/3TC/EFV); and

5. Zidovudine + lamivudine + nevirapine (AZT/3TC/NVP).[77]

They used the model to determine the annual direct cost incurred in patients that remained in care. The following assumptions were adopted for modelling, amongst others:

1. The patients presented when already ill and treatment was initiated immediately (during this era, patients had to wait until CD4 count dropped to 350 or below before HAART was initiated).

2. Co-morbidities, its toxicities and the incidence rates of these two affect the effectiveness of HAART.

3. All patients have access to CD4 monitoring at treatment initiation as well as during treatment.

Cost-effectiveness was determined as the ability of the regimen to decrease the viral load and therefore decrease mortality. They found that annual costs for patients on HAART and remaining in care ranged between US$810 and US$1713. Three HAART treatment regiments, namely, TDF/3TC/EFV; TDF/3TC/NVP and AZT/3TC/EFV, were found to be cost-effective. D4T/3TC/NVP was found to be the most expensive whilst AZT/3TC/NVP was the least effective. These findings were in line with current WHO HAART guidelines[82]

2.6 Costs of ADRS associated with HAART

There are limited studies on the costs of ADRs associated with HAART compared to those of the incidence of the ADRs. Despite this, the studies analysed all show that costs associated with ADR are significant. Table 2.3 summarises the studies carries out on the costs associated with HAART adverse drug reactions.

Homar et al. (2012) carried out a study comparing healthcare costs for patients on fixed-dose combinations (FDCs) of antiretroviral agents compared to separate individual antiretroviral agents. The study was carried out in the Belearic Islands, Spain using a hospital inpatients database. The costs analysed were consultations with health professionals, admission/ward costs, procedures (e.g. liver biopsy, colonoscopy, ultrasounds) and laboratory studies (e.g. urinalysis, viral load, lymphocyte subpopulation studies, liver profile, coagulation profile). They found that patients on separated individual antiretroviral agents had higher healthcare costs compared to fixed-dose combination antiretroviral.[83]

Author Country, Year Data Source	Study Design	ADRs Identified	Drug Related to ADR as Observed	Number of Cases	Incidence	Perspective	Cost (US$)	Cost Description	Conclusion
Radhakrishnan et al India, 2017 Google Scholar	Retrospective, observational	Aneamia	Zidovudine	15	13,6%	Payer	15,5	Laboratory costs, treatment costs, hospital stay costs	Overall direct costs associated with treating ADRs to HAART was found to be high, thus increasing the overall cost of HIV therapy
		Nausea & vomiting	Zidovudine	7	6,4%		18		
		Hepatoxicity	Nevirapine	7	6,4%		17,45		
		Peripheral neuropathy	Stavudine	6	5,5%		14,7		
		Pancreatitis	Stavudine	4	3,6%		141,9		
		Rash	Efavirenz	3	2,7%		45,8		
		Stevens–Johnson	Nevirapine	2	1,8%		208,5		
		Renal failure	Tenofovir	2	1,8%		120,8		
		Depression	Efavirenz	2	1,8%		215,3		
		Pancytopenia	Zidovudine	2	1,8%		108,3		
		Diarrhea	Ritonavir	2	1,8%		83,1		
		Gastritis	Efavirenz	2	1,8%		59,3		
		Fever	Zidovudine	2	1,8%		36,6		

Table 2.3: Economic Evaluations on the management of ADRs to HAART

Author Country, Year Data Source	Study Design	ADRs identified	Number of cases	Perspective	Cost (US$)	Cost Description	Conclusion
Simpson et al	Cross-sectional	CNS related	427	Payer	Of the 2548 NNRTI-treated patients, 29.3% experienced AEs. During the 12 months following NNRTI initiation, the mean annual total health care cost was $27 299 (efavirenz: $26 185; other NNRTIs: $34 993) and AE-associate costs were $608 (efavirenz: $554; other NNRTIs: $979) among all NNRTI users.		
USA, 2014		GI related	146				
		Dermatologic	93				
		Lipid Disorders	312				
Pubmed		Hepatoxicity	55				
Dekoven et al	retrospective case–control database study	Depression	173	Payer	Differences in median total all-cause health care costs observed for diabetes/insulin resistance management (US$14 547 median all-cause health care costs during time periods identified as diabetes/insulin resistance medical events versus US$11 237 without diabetes/insulin resistance events; P <0.05 .0021), lipid disorders (US$12 825 versus US$10 033; P<0.05 .0004), and renal disorders (US$1389 versus US$0; P < .0001. This study concluded that health care costs of ART AEs should be key consideration for payers/providers in HIV management.		
USA,2015		Diabetes/Insulin	115				
		Diarrhea	181				
		Dizziness	69				
Google		Hepatic disorders	38				
		Lipid disorders	497				
		Nausea/vomiting	132				
		Rash	228				
		Renal disorders	93				
		Somnolence/sleep	317				

Table 2.3: Economic Evaluations on the management of ADRs to HAART cont.

Radhakrishnan et al. (2012) carried out a study in a tertiary care teaching hospital in Southern India. The study aimed to analyse the direct costs of ADRs to HAART in HIV/AIDS patients. Costs analysed included hospital stay costs, pharmacy (drugs) cost and laboratory investigations costs. In their study incidence of ADRs due to HAART was 50.9%, the majority of ADRs to HAART, causality assessment was 'probable', and 'possible' by WHO probability scale. Based on the modified Hart wig and Siegel scale, of the 56 observed ADRs, 6 were mild (10.7%), 42 were moderate (75%) and 8 were severe (14.3%). The direct cost incurred in managing ADRs to HAART reported was INR 72428(US$ 1574.51). They reported increased costs associated with ADRs as severity increased. The total mean direct cost seems less in a developing country like India, compared to developed countries like the United States where the direct cost incurred in treating ADRs to HAART ranges to several thousand dollars. However, when compared the per capita spending on health in India, this cost associated with ADRs is significantly high.[15]

Dekoven et al. (2016) carried out a study to estimate health care costs associated with medical events identified as HAART-attributable ADRs. The study was carried out in the United States of America (USA) using a pharmaceutical claims database. The ADRs analysed in this study were depression, dizziness, diarrhoea, hepatic disorders, nausea/vomiting, rash, renal disorders, and somnolence/sleep effects, diabetes/insulin resistance and lipid disorders. Pharmacy costs analysed included costs of ART as well as costs of medications associated with the treatment of the ADRs. Their analysis showed that pharmacy costs had the highest attributable costs. They observed that costs attributable to ADRs analysed were in excess of US$23434 for the study. This confirms that costs associated with treatment or prevention of HAART ADRs are a primary factor to be considered in HIV control for the payers/providers.[12]

Johnston et al. (2013) carried out a retrospective study to compare the incidence and healthcare costs of medically attended adverse effects in atazanavir-and darunavir-based antiretroviral therapy among U.S. Medicaid patients receiving routine HIV care. This study analysed in-patient, outpatient and pharmacy costs. They found that the total healthcare costs attributable to ADRs were $8127 for the duration of the study. This amount is significant and should be considered when analysing the cost of HAART.[13]

Simpson et al. (2014) carried out a study to assess the incidence and costs of ADRs among patients with HIV infection treated with nonnucleoside reverse transcriptase inhibitors (NNRTIs) from the health care system perspective. They enrolled 2548 NNRTI-treated patients

over a period of 5 years. ADRs observed were rash, nausea or vomiting, diarrhoea, dizziness, headache, sleep-related symptoms, hepatotoxicity, lipid disorder, depression, anxiety, and suicide or self-injury. A total of 29.3% of the study participants experienced ADRs. The mean incremental costs per episode from US$1580 to US$12 833.[14]

Irrespective of the different settings in which the above studies were conducted, they all agree that the cost of managing ADRs attributed to HAART is significantly high. Most of the studies reviewed were carried out in high-income settings. In resource-limited settings, the cost of managing these ADRs is relatively unknown and hence not factored into budget estimations. This warrants the need to analyse these costs at a local level.

2.7 Chapter Summary

This chapter summarizes the literature review on the pharmacovigilance of HAART as well as the costs associated adverse drug reactions of HAART.

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CHAPTER 3

MANUSCRIPT FOR SUBMISSION AND PUBLICATION

3.1 Introduction

This chapter describes the general findings and discussion of the results of the study and is presented in the form of a manuscript entitled "Annual costs incurred on managing adverse drug reactions attributable to fixed-dose combination Highly Active Anti-Retroviral Therapy (HAART) in outpatient ARV clinics in Gauteng- a study in Stanza Bopape ARV Clinic, Mamelodi East, Pretoria".

3.2 Manuscript

Annual costs incurred on managing adverse drug reactions attributable to fixed-dose combination Highly Active Anti-Retroviral Therapy (HAART) in outpatient ARV clinics in Gauteng.

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ABSTRACT

Objective

The aim of the study is to identify adverse drug reactions attributable to tenofovir- and zidovudine-based fixed-dose combinations of highly active anti-retroviral therapy and, subsequently, to determine the annual costs incurred managing these adverse drug reactions and the budget implications of this at an outpatient anti-retroviral clinic in Mamelodi, Pretoria.

Methods

This retrospective cohort study reviewed de-identified clinical data for adverse drug reactions. Medical charts of HIV-positive patients, who were on either tenofovir- or zidovudine-based fixed-dose combinations of anti-retroviral therapy, were analysed. Based on the costs and the incidence rates of adverse drug reactions observed in the analysis, a decision tree model was established to estimate the cost impact of adverse drug reaction management on the clinic's budget.

Results

A total of 469 patient files were analysed (62% female vs 38% male). The mean age at the start of anti-retroviral therapy for the cohort was 36.6yrs (95% CI 35.74-37.45) and the mean baseline CD4 count was 380 (95% CI 343-418). Incidence of adverse drug reactions to tenofovir- or zidovudine-based fixed-dose combinations of anti-retroviral therapy was found to be 24.95%. The ADRs reported with the use of TDF and AZT based HAART regimens were rash (n=45, 27%), decreased glomerular filtration rate (n=34, 21%), trouble sleeping (n=39, 21%), severe diarrhoea (n=19, 12%), nausea and vomitting (n=18, 11%), decreased heamoglobin or anaemia (n=4, 2%), headaches (n=4, 2%), dizziness (n=2, 5.3%).

The study revealed that ZAR427.30 was the cost attributed to adverse drug reactions due to tenofovir-based regimens whilst ZAR467.94 was the cost attributed to adverse drug reactions due to zidovudine-based regimens, per patient, during the first year of treatment. Costs attributed to gastro-intestinal related adverse drug reactions were the highest in comparison to other adverse drug reactions. Estimated total cost of adverse drug reactions attributed to zidovudine-based therapy was ZAR8003.98 (US$556.40) and estimated total cost of adverse drug reactions attributed to tenofovir-based anti-retroviral therapy per annum was ZAR33 788, 23 (US$2348.80) for 1221patients initiated on antiretroviral therapy between July 2017 and June 2018 at the clinic.

Conclusion

Despite our estimated costs to the clinic, due to adverse drug reactions, being lower than similar studies, there remains a notable budget impact on a resource-limited setting. These estimates will allow for cost due to adverse drug reactions caused by tenofovir- and zidovudine-based anti-retroviral therapy to be accounted for in budgets at the Anti-Retroviral clinic.

Keywords: Adverse drug reactions, cost analysis, highly active anti-retroviral therapy, tenofovir, zidovudine.

Introduction

Human Immunodeficiency Virus (HIV) and Acquired Immunodeficiency Syndrome (AIDS) remain the greatest public health crisis in the world today and is the fourth leading cause of mortality in the world.[1] The concern is not only a major public health issue, but also a socio-economic and developmental crisis that affects all sectors of the population.[2]

According to the UNAIDS statistics, in 2018 7.7 million people in South Africa were HIV-positive.[1] This makes South Africa home to the largest number of HIV positive people worldwide. In addition, South Africa has the largest Antiretroviral Therapy (ART) program in the world. In 2018, more than 4.5 million people were receiving ART, which equates to 62% of people living with HIV in the country.[1] These statistics show that there are still several interventions required to minimise the effects of HIV/AIDS.

Highly Active Anti-Retroviral Therapy (HAART), a combination therapy of three or more anti-retroviral drugs, has significantly improved the health outcomes of the infected population, making HIV a manageable disease. It has reduced morbidity and mortality in HIV-positive patients significantly. Without therapy, probably more than 90% of all HIV-positive patients will die from AIDS.[3] The increase in life expectancy of HIV-positive patients on HAART also means increased duration on treatment as well as increased incidence of common, as well as rare adverse drug reactions (ADRs). Cost of managing and treating the ADRs become significant as nations try to meet the 90-90-90 target set by UNAIDS. This target aims that by 2020, 90% of all HIV-infected individuals be diagnosed, 90% of patients with a diagnosis to have initiated treatment and 90% of those who have initiated treatment to be virally suppressed.[1]

Zidovudine (AZT) and tenofovir (TDF) (non-nucleoside reverse transcriptase inhibitors (NNRTI)) form the backbone of first-line antiretroviral therapy as per the World Health Organization's guidelines.[4] Studies have been carried out to compare the TDF and AZT regimens for efficacy and cost-effectiveness.[5,6,7,8,9] One such prospective study, conducted in South Africa, compared the efficacy of TDF-based HAART vs AZT-based HAART regimens.[5] This was done by comparing the ability of the HAART regimens to reduce viral loads to undetectable levels as well as comparing the rate of need for drug substitutions. The results indicated that fixed-dose TDF-based HAART had superior efficacy in terms of decreasing viral load to undetectable levels compared to fixed-dose AZT-based HAART. It

also had the least regimen substitutions recorded.[5] Likewise, other studies have also shown that TDF-based HAART was superior to AZT-based HAART in achieving an undetectable viral load and increasing CD4 levels.[6, 7, 8] In contrast, large randomized clinical trials carried out in different countries found no significant difference in virological suppression between TDF and AZT treatment groups.[9] Other studies in South Africa and Indonesia also found no significant differences in terms of regimen switches and virological suppression between patients on TDF-based HAART vs AZT-based HAART.[10,11] Studies comparing cost effectiveness of TDF- and AZT-based HAART have generally found TDF-based HAART regimens more cost effective than AZT-based regimens.[12,13]

Many studies have been carried out on the incidence and risk factors of HAART induced ADRs.[14-20] There are however, limited studies looking into the costs associated with the management of the ADRs. In resource-limited settings, the cost of managing these ADRs is relatively unknown and hence not factored into budget estimations.

An adverse drug reaction is defined as 'a response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modifications of physiological function.'[3] ADRs are common causes of morbidity and mortality as well as a significant contributor to increased healthcare costs. In order to understand the impact of ADRs on healthcare costs, all costs and benefits have to be taken into account. ADRs are associated with two main inversely correlated costs, i.e. the cost of treating diseases due to ADRs and the cost of evading them. When one arm increases, the other decreases.[14]

Based on the review and literature search, it was found that there were limited studies analysing the cost of management and prevention of ADRs attributed to HAART in South Africa. The consideration of the healthcare costs of ADRs is paramount in understanding the total impact on the cost of managing HIV as well as the value of HAART. The aim of the study is to identify adverse drug reactions attributable to tenofovir- and zidovudine-based fixed-dose combinations of highly active anti-retroviral therapy and, subsequently, to determine the annual costs incurred managing these adverse drug reactions and the budget implications of this in an outpatient anti-retroviral clinic in Gauteng.

Methods

Study Setting and Population

Study was carried out at a Community Health Center, in Mamelodi, Pretoria. The Community Health Center caters for all types of primary healthcare services, including an ARV clinic.

Ethical approval

Permission to conduct the study was obtained from the Biomedical Research Ethics Review Committee of the University of KwaZulu-Natal (BE404/17) and gatekeeper approval was obtained from the Gauteng Department of Health, Tshwane Research Committe (PROJECT # 61/2018, NHRD REF GP_201805_034). Confidentiality was duly maintained, and basic prnciples of research ethics were adhered to.

Sampling and data collection

The study was a retrospective cohort study. De-identified clinical information and laboratory data of adult patients who started on HAART between July 2017 and June 2018 was analysed. The clinic utilises an electronic system called the Tier System to capture and store patients' medical information. Medical history previously captured on the Tier System was retrieved to fulfil the aims of the study.

Inclusion/Exclusion criteria

The following inclusion/exclusion criteria was used to enrol patients into the study. Patients were included if they were at least 18 years old, HIV- positive and on HAART. Patients were required to be on either a tenofovir- or zidovudine-based fixed-dose combination HAART for at least 12 months continuously at the time of enrolment. They needed to have been initiated on either a tenofovir- or zidovudine-based fixed-dose combination HAART between June 2017 and June 2018. Exclusion criteria encompassed having co-morbidities such as hepatitis, tuberculosis (TB), diabetes or cardiovascular diseases. Patients were also excluded if there was incomplete data recorded on their medical charts.

Causality and Severity

At the Clinic, ADRs are documented as part of the observation and treatment plan. There is no causality confirmed on the medical charts or on the Tier system. Events of interest for this study included documented ADRs. The WHO Causality Assessment Tool was used to ascertain

causality and severity of the ADRs. [21] This tool details criteria used to evaluate the causal association between ADRs and the pharmaceuticals in question. The categories used are unassessable/unclassifiable, conditional/unclassified, unlikely, possible, probable/likely and certain in order of certainty.[21]

Severity of adverse reactions was assessed using the Hartwig scale and classified as mild, moderate and severe.[22] According to the Hartwig scale, 'ADRs are considered severe if patient outcomes fall in category permanent harm, lead to death and required any intensive medical care admission due to an ADR. ADRs are considered moderate if withdrawal of suspected drug therapy is required, needing antidote, and lead to increase in the hospital stay or reason for admission. Finally, ADRs are classified as mild if it does not require any change in the treatment or not requiring an antidote.'[22]

Statistical Analysis

The data, obtained from electronic patient medical records, was transcribed onto Microsoft Office Excel® spreadsheets. Data obtained included patient's date of birth, gender, HIV diagnosis date, date of HAART start, stage at ART start, baseline viral load count, last viral load result and date, baseline creatinine level, creatinine level, baseline CD4, latest CD4 count, full blood count dates, last HAART visit dates, pregnancy status on ART start, treatment notes, ADR reported and the HAART regimen that was involved. Patients were separated into 2 groups i.e case and control. Case groups were those patients that recorded an ADR, while the control group included patients not experiencing any ADR. The 2 groups were compared for age at HAART initiation, baseline CD4, total HAART costs, total laboratory costs and total direct costs using the independent sample t-test.

Cost Analysis

Direct cost associated with TDF- and AZT-based HAART were analysed. Direct medical costs are those costs incurred for medical products and services used to prevent, detect, and/or treat a disease. Costs incurred (laboratory charges and pharmaceutical charges) were extracted from the Clinic's accounting system as well as its suppliers such as National Health Laboratory Services billing system (Table 1).

Input Parameters	
Input	**Unit costs of resources used (South African Rand-ZAR)**
Laboratory Tests	
HIV Viral Load	R1200.90
CD4 count	R300.50
Creatinine Level Test	R51.70
Full Blood Count (FBC)	R50.06
Pharmaceuticals Dispensed	
Tenofovir/Lamivudine/Efavirenz (TDF/3TC/EFV) 28s	R105.08
Tenofovir/Emtricitabine/Efavirenz (TDF/FTC/EFV) 28s	R125.21
Zidovudine/Lamivudine 28s	R56.00
Nevirapine tablets	R39.00
Efavirenz 28s	R42.00
Loperamide tablets	R1.80
Ferrous Sulphate tablets 28s	R4.68
Trepiline 25mg tablets 28s	R3.10
Allergex 4mg tablets	R1.14
Allercet 10mg tablets	R2.72
Biocort Cream	R6.80

Table 3.1: Input Parameters

Perspective

The payer's perspective was used for this analysis. The study was carried out at a provincial clinic therefore the Gauteng Health Department is the payer in this analysis.

Budget Impact Analysis

A decision tree model was established to estimate the impact of costs of ADR management on the clinic's budget. This estimate was for the number of patients initiated on TDF and AZT based HAART during the year of analysis, which was 1221 patients. Based on the data collected, and the results from the above analysis, a novel budget impact model was built in Microsoft® Excel®. The model simulated the natural occurrence and progression of observed ADRs to TDF- and AZT-based HAART. It starts at initiation of TDF- or AZT-based HAART where patients in a state of absence of ADRs. From being in a state of absence of ADRs, patients can progress to the development of an ADR state or stay in a state absence of ADRs. In the event that patients develop an ADR, they are treated, which leads to either cure or non-cure (ADR not resolved). When cured, the patient returns to a state of absence of ADRs.

Studies have shown that most ADRs caused by HAART occur within the first year of treatment.[23,24] Therefore, the consequences and associated healthcare expenditure are assessable in a short-term period. The time horizon was set to one year, in line with the data collected and analysed.

Sensitivity Analysis

In order to address the uncertainty, a two-way sensitivity analysis was carried out. Mean costs attributable to ADRs as well as ADR incidence were the variables. The lower and upper bound for the 95% confidence interval for the mean cost attributable to ADRs was utilised to observe how the model outputs change as the inputs are changed. TDF-based HAART and AZT-based HAART ADR incidences were derived from literature and utilised in the two-way sensitivity analysis. AZT-based HAART ADR incidences utilised were 0.052 [17], 0.084 [25] and 0.244 [19]. TDF-based HAART ADR incidences utilised were 0.0196 [26] 0.084 [25] and 0.39 [27].

Results

Sampling and Overview of participant demographics

Figure 1 below details how the inclusion-exclusion criteria was utilised and how the study sample was derived.

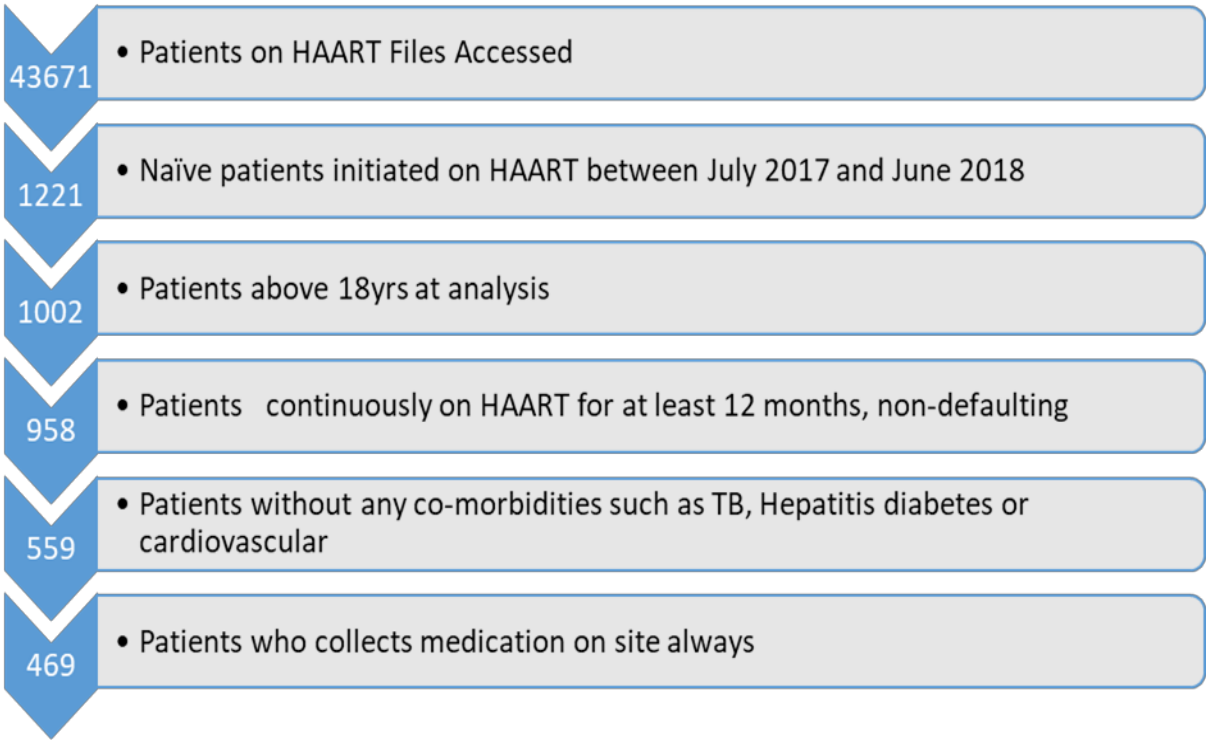

Fig 3.1: Sampling Flow Chart

In this study, 469 patients charts were eligible for analysis. In this study, 469 patient-charts were eligible for analysis. The mean age at the start of HAART for the cohort was 36.6yrs (95% CI 35.74-37.45); the mean baseline CD4 count was 380 (95% CI 343-418). 62% of the patients analysed were female. 454 patients (96,8%) on TDF based HAART, whilst only 15 patients (3.2%) were on AZT based HAART. The patients breakdown according to regimens:

1. Tenofovir + emtricitabine + efavirenz (n=448);
2. Tenofovir + lamivudine + efavirenz (n=6);
3. Zidovudine + lamivudine + efavirenz(n=12); and
4. Zidovudine + lamivudine + nevirapine(n=3).

These patients were grouped according to ADR status (present or absent). Patients who presented with ADRs to TDF or AZT based HAART and those who had not experienced an

ADR with TDF or AZT based HAART were compared with independent t-test for gender, age, and CD4 count at HAART initiation.

	ADR Present		ADR Absent	
	TDF Based Regimen	**AZT Based Regimen**	**TDF Based Regimen**	**AZT Based Regimen**
Gender				
Female	65	8	215	3
Male	42	2	132	2
Age				
18-30	37	4	82	2
31-40	40	6	149	3
41-50	28		87	
51-60	2	0	21	0
>60	0	0	8	0
CD4				
<350	60	7	115	4
≥350	47	3	232	1

Table 3.2: Patient Demographics

Analysis of ADRs associated with HAART

On analysis, 117 patients of the cohort experienced at least one ADR in the first year of treatment. All observed ADRs occurred within the first 6 months of initiation of HAART with the exception of renal ADRs. Renal ADRs were only observed at least 8 months after HAART initiation.The overall incidence of ADRs to HAART was found to be 24.95%. Eleven patients experienced two ADRs. The majority of ADRs reported were experienced by female patients (n=68, 58.1%) as opposed to male patients (n=49, 41.9%).

This study found AZT-based HAART regimens had a higher ADR incidence (n=10, 66.67%), compared to TDF-based HAART regimens (n=107, 23.57%). The ADRs were observed with the following regimens tenofovir + emtricitabine + efavirenz (88,0%); tenofovir + lamivudine + efavirenz (3.4%); zidovudine + lamivudine + efavirenz(6.1%) and zidovudine + lamivudine + nevirapine(2.5%).

Causality for ADRs observed was classified as "possible", as per the WHO Causality Assessment Tool. ADRs met the following criteria to be classified as "possible":

- The event is a specific clinical or laboratory phenomenon linked to HAART. The time elapsed between the administration of the drug and the occurrence of the event is plausible.
- The dates of drug administration and date of onset of the event was documented. Patients received the anti-retroviral medicines prior to the first mention of the event of interest
- The outcome of withdrawal of the suspected medicine was not known and the medicine was not withdrawn

All observed and documented ADRs did not warrant a change in treatment and neither did they require an antidote. As a result, they were classified as mild according to the Hartwig Scale.

The ADRs reported with the use of TDF and AZT based HAART regimens were rash (n=45, 27%), decreased glomerular filtration rate (n=34, 21%), trouble sleeping (n=39, 21%), severe diarrhoea (n=19, 12%), nausea and vomitting (n=18, 11%), decreased heamoglobin or anaemia (n=4, 2%), headaches (n=4, 2%), dizziness (n=2, 5.3%).

Factors Influencing ADR occurance

The ADRs observed were analysed for factors influencing their incidence. The factors analysed were age at initiation of HAART, CD4 count at HAART initiation and adherence. viral load

Proportion of patients with undetectable Viral Load at HAART start (*P*=.341) and adherence (*P*=.229) were found not to be statistically significantly different between the patients who experienced ADRs (present) and those who did not (absent). Age at HAART initiation (*P*=.020) and CD4 count at initiation of HAART (*P*=0.002) were the only factors found to have a statistically significant outcome as patients that experienced ADRs reported a lower CD4 count and a lower average age at HAART initiation as presented in Table 3.3.

	TDF based			AZT based			Total ADR Present vs ADR Absent	TDF based VS AZT based
	ADR Present	ADR Absent	p-value	ADR Present	ADR Absent	p-value	p-value	p-value
Age at HAART initiation	35,19	37,22	0,053	31,60	33,00	0,756	0,024	0,060
CD4 Count at HAART Initiation (Cells/µl)	338,77	417,08	0,000	277,90	500,80	0,097	0,002	0,001
Adherence	94,20%	93,30%	0,176	91,18%	93,55%	0,230	0,229	0,644
Proportion of patients with undetectable Viral Load at HAART start	69%	59%	0,251	38%	21%	0,091	0,341	0,294
Number of days on HAART	412	415	0,351	400	401	0,966	0,232	0,08
Creatinine Clearance at HAART Initiation (Cells/µl)	86,87	84,18	0,084					

Table 3.3: Factors influencing the incidence of ADRs

Cost Analysis

Table 3.4 summarises HAART costs, laboratory costs and total costs obtained on analysis. HAART costs within regimens were not significantly different between the patients who experienced ADRs compared to the patients who did not (*P*=.10). On the contrary, laboratory

(*P*=.003) and total direct costs (*P*<.001) where significantly higher in patients with ADRs for both regimens

	TDF based			AZT based		
	ADR Present	ADR Absent	p-value	ADR Present	ADR Absent	p-value
Total HAART Costs	R1 733,81	R1 733,13	0,986	R1 312,50	R1 281,00	0,629
Total Laboratory Costs	R1 687,24	R1 630,76	0,003	R2 227,12	R1 917,29	0,003
ADR Meds Cost	R10,01	R0.00	0,001	R26.55	R0.00	0,001
Total Costs	R3 795,79	R3 368,49	0,000	R3 666,17	R3 198,23	0,004

Table 3.4:Components of charges Analysed

The above ADRs were further grouped according to the body system the drug(s) affected as presented in Table 3.5. Analysis of the ADRs was then carried out as per body system. Costs attributed to GI related ADRs were highest in comparison with other ADRs for both HAART regimens.

Regimen	**ADRs**	**No of ADRs**	**Incidence**	**Total mean direct cost**	**Mean direct cost per ADR per annum**	**p-value**
AZT based	GI Related	6	40,00%	R 3 637,30	R439,07	0,004
	CNS Related	1	6,00%	R 3 639,97	R441,74	0,017
	Dermatologic	4	26,67%	R 3 327,18	R128,95	0,035
	Haematological	4	26,67%	R 3 458,14	R259,91	0,043
TDF based	GI Related	31	6,83%	R 3 458,59	R90,10	0,009
	CNS Related	40	8,81%	R 3 432,71	R64,22	0,032
	Dermatologic	43	9,47%	R 3 504,31	R135,82	0,000
	Renal	34	7,49%	R 3 566,25	R197,76	0,000

Table 3.5: Incidence and Mean Direct Cost per ADR per annum

The study found that ZAR427.30 attributed to ADRs due to TDF-based regimens compared to ZAR467.94 attributed to ADRs due to AZT-based regimens per patient during the first year of treatment.

Budget Impact Analysis

A decision tree model was developed to estimate annual cost associated with ADRs at a clinic. The incidences rates of ADRs observed in above analysis were utilised as probabilities of occurrence of the ADRs as presented in Figure 3.2. Cost per ADR used in the model were derived from the retrospective chart review carried out. Conditional probabilities were derived from the decision tree analysis.

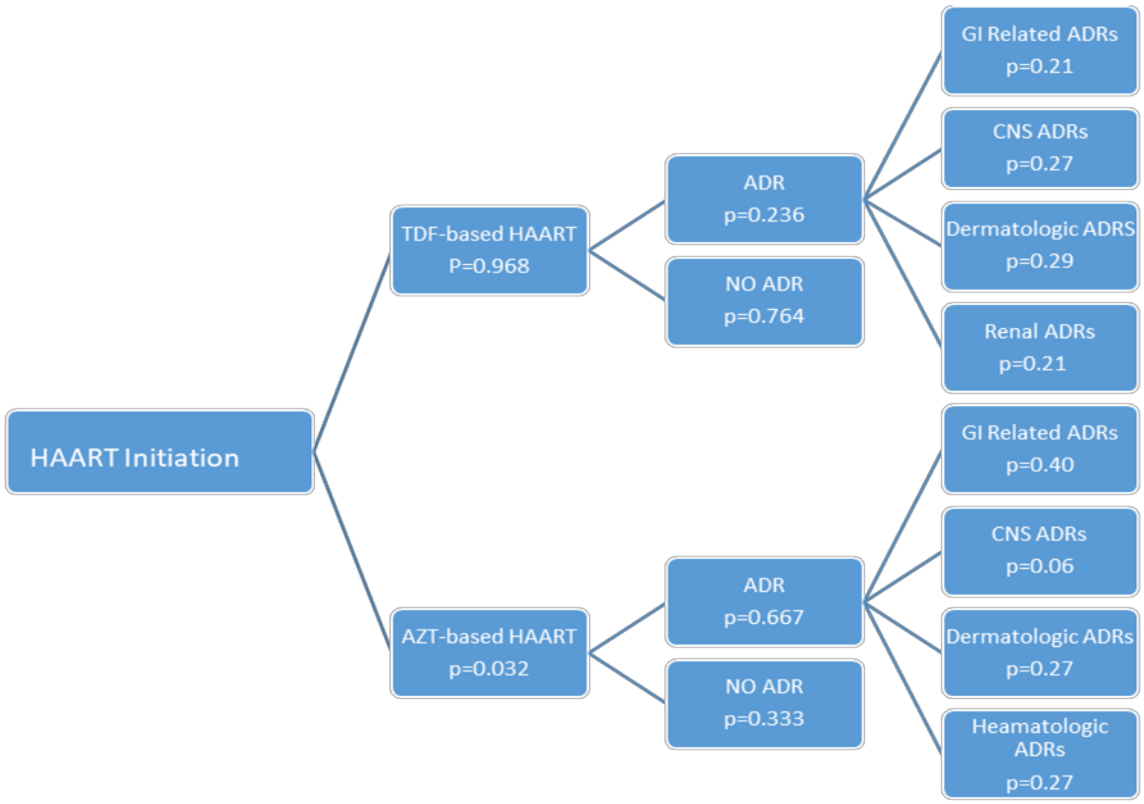

Fig 3.2: A decision-tree model used in the budget impact analysis

For AZT-based regimens, the following conditional probabilities were derived; gastro-intestinal related (p=0,0085), central nervous system-related (p=0,00128), haematological (p=0,00576) and dermatologic (p=0,00576). For TDF-based regimen, the following conditional probabilities were derived; gastro-intestinal-related (p=0,04797), central nervous system related(p=0,06168), dermatologic (p=0,06625), and renal (p=0,05254).This analysis

was based on the number of patients initiated on TDF- or AZT-based HAART during the year analysed, which is 1221 patients (Fig 1: Sampling Flow Chart).

The model estimated costs attributable to ADRs associated with TDF-based HAART as follows; gastro-intestinal related ADRs (ZAR5 277,73), central nervous system related ADRs (ZAR4 836,57), dermatologic ADRs (ZAR10 986,64) and renal ADRs (RZA12 687,30). With AZT-based HAART, the model estimated costs attributable to ADRs as follows: GI-related ADRs (ZAR4 577,05), CNS related ADRs (ZAR690,73), dermatologic ADRs (ZAR907,35) and heamatologic ADRs (ZAR1828,85). Fig 3 details the predicted costs per annum of ADRS in South African Rands.

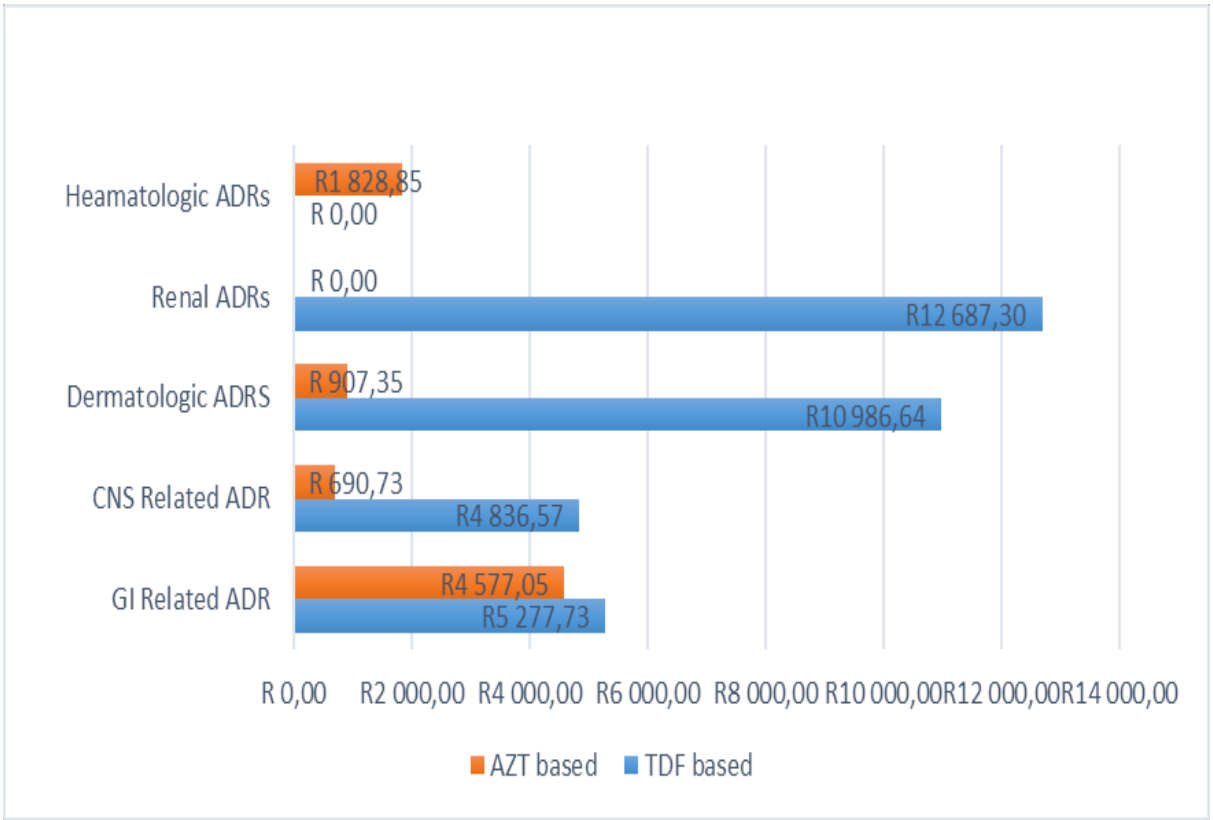

Fig 3.3: Predicted Costs of ADRs per Annum

In order to simplify comparison with results of previous studies, final costs were converted to US dollars using the rate of US$1 equivalent to ZAR14.3853.[28] Estimated total cost of ADRs attributed to AZT based HAART is ZAR8003.98 (US$556.40) and estimated total cost of ADRs attributed to TDF based HAART per annum is ZAR33 788.23 (US$2 348.80).

Sensitivity Analysis

Fig 4 presents side-by-side two-way sensitivity analysis of costs attributable to ADRs of TDF-based and AZT-based HAART. Mean costs attributable to ADRs as well as ADR incidence were the variables. Costs attributable to ADRs for TDF-based HAART rose as high as ZAR83 948.06 (US$5 835.68) whilst costs attributable to ADRs for AZT-based HAART rose as high as ZAR13 150.81(US$914.18).

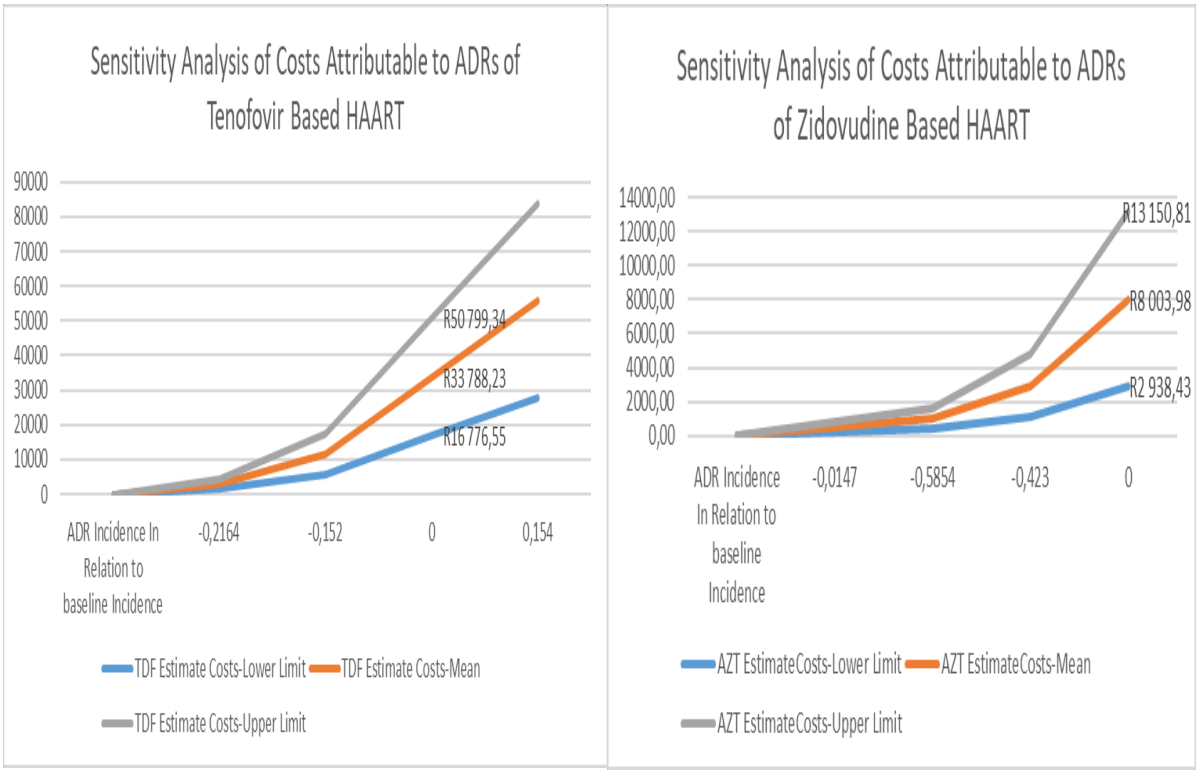

Fig 3.4: Sensitivity Analysis of Costs Attributable to ADRs of Tenofovir Based and Zidovudine Based HAART Side by Side

Discussion

The aim of the study was to identify adverse drug reactions attributable to TDF- and AZT-based fixed-dose combinations of HAART, and subsequently, determine the annual costs incurred managing these adverse drug reactions and the budget impact of these costs in an outpatient anti-retroviral clinic. Baseline characteristics were not significantly different between the cases and controls except for baseline CD4 count and age at HAART initiation. This is in line with previous studies that have shown that lower CD4 counts had a propensity for increased risk of ADR occurrence.[29]All ADRs observed were classified as mild in terms of severity. This was expected, as moderate and severe ADRs would likely require a change in treatment or hospitalisation that would have resulted in exclusion from the analysis.

The overall incidence of ADRs to HAART was found to be 24.95%. This is comparable, though lower, to another study carried out in South Africa that reported an incidence of 37%.[30] The incidence was however notably lower in comparison to other studies which recorded incidences as high as 89%.[16, 17, 18, 19] The relatively lower incidence could have been due to the fact that patients with co-morbidities were excluded in the analysis. It has been previously reported that patients with comorbidities are three times more likely to experience an ADR than those with no comorbidities.[31]

Prior studies on costs attributable to ADRs of HAART are limited, especially in developing countries. This study found that per patient costs attributed to ADRs due to TDF-based regimens and AZT-based regimens during the first year of treatment where ZAR427.30 (US$29.70) and ZAR467.94 (US$32.53) respectively. Costs attributable to ADRs observed in this study were notably lower than those observed in studies carried out in the USA. [32-34] Although costs attributable to ADRs of HAART are lower in developing counties, when national per capita spending on health is factored as well budget impact, the costs remain significant.

Johnston *et al.*(2013) reported the costs attributable to ADRs ranging from US$ 3 to US$ 43 per ADR per month.[32] Therefore their per annum figures would be approximately 12 times more compared to those observed in our study. Similarly, Simpson *et al.* (2014) reported mean costs associated with managing an AE-associated costs as $608.[33] In a study carried out in India, Radhakrishnan *et al.* (2012) reported mean direct cost incurred in treating per ADR in hospitalized patients with HAART as ranging from INR 524.4 (US$ 11.4) to INR 17521.4

(US$ 380.9).[35] This study was carried out in a hospital setting, therefore due to hospitalization, the costs attributable to ADRs would be higher than our observed costs. Despite being slightly higher than the costs we observed, their costs were also very low compared to those reported in studies from developed countries.[32-34]

Estimated total cost of ADRs attributed to AZT-based HAART is R8003.98 (US$556.40) and estimated total cost of ADRs attributed to TDF-based HAART per annum is R33 788.23 (US$2348.80). As expected, the estimate is even lower compared to costs observed in studies carried out in developed countries. Johnston *et al.* (2013) found that total healthcare costs attributable to ADRs were $13 000 over 12 months.[32] When other factors are taken into consideration, this value might be an underestimate. Radhakrishnan *et al.* (2012) found that as severity of ADRs increased, costs associated with ADRs also markedly increased. [35] Co-morbidities and polypharmacy have also been found as a risk factor for increased incidence and severity of ADRs to HAART.[32] Our study excluded patients with co-morbidities; therefore, the value estimated could also be underestimated.

Conclusion

Adverse drug reactions impact on adherence to HAART. Prevention and management of ADRs and costs thereof are tantamount to the success of HAART. Despite our estimated costs being lower that other studies, they can be significant in a resource limited setting. Any funds allocated to management of ADRs are funds directly taken away from other healthcare functions such as treatment or staffing, in such a setting. These estimates will allow for cost implications of ADRs to TDF and AZT-based HAART to be accounted for in budgets at the ARV clinic.

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CHAPTER 4
CONCLUSIONS

4.1 Introduction

This study was carried out to identify adverse drug reactions attributable to tenofovir- and zidovudine-based fixed-dose combinations of highly active anti-retroviral therapy and, subsequently, to determine the annual costs incurred managing these adverse drug reactions and the budget implications of this in an outpatient anti-retroviral clinic. The rationale of this study was based on previous research conducted in other countries, which showed significantly high costs of managing, and preventing ADRs associated with HAART.[1-5] There were no studies in South Africa analyzing costs attributable to ADRs. This gap identified led to this study being carried out.

4.1.1 Strengths of the study methodology and design

The study was a retrospective chart analysis; therefore, minimal costs were involved with data collection.

4.1.2 Limitations of the study

- Data was collected from routine medical charts not intended for research purposes and therefore prone to reporting bias, which results in underreporting.
- Severity of ADRs was not reported in the medical charts. The investigator deduced it with no second opinion.
- Indirect cost such as disability, work productivity losses related to absenteeism and other financial cost was also associated in the management of HIV/AIDS. These costs however were not analysed due to the limited scope of the study.

4.2 Conclusions drawn from the study findings

4.2.1 Analysis of ADRs associated with HAART

Baseline characteristics were not significantly different between the participants with ADRs and those without except for baseline CD4 count. This congruent with a previous study which have shown that lower CD4 counts had a propensity for increased risk of ADR occurrence.[6]

All ADRs observed were classified as mild in terms of severity. This was expected as moderate and severe ADRs would likely require a change in treatment or hospitalisation, which would have resulted in exclusion from the analysis. The observed ADRs mostly occurred within the first 6 months after treatment initiation except for the renal ADRs, which were mostly noted after 6months on treatment. Studies have shown that most ADRs to HAART occur within the first year of treatment.[7, 8]

The overall incidence of ADRs to HAART was found to be 24.95%. This is comparable, though lower, to another study also carried out in South Africa, which reported an incidence of adverse drug reactions (ADRs) to HAART as 37%. [9] The incidence in our study was however significantly lower in comparison other studies which recorded incidences as high as 89%.[10, 11, 12, 13] The relatively lower incidence could have been because patients with co-morbidities were excluded in analysis. Patients with comorbidities are three times more likely to experience an adverse drug reaction than those with no comorbidities.[14]

4.2.2 Cost Analysis

Prior studies on costs attributable to ADRs of HAART are limited, especially in developing countries. This study found that costs attributed to ADRs due to TDF based regimens and AZT based regimens during the first year of treatment were R427.30 (US$29.70) and R467.94 (US$32.53) respectively. Costs attributable to ADRs observed in this study were significantly lower than the costs observed in studies carried out in the USA. [3-5] Although costs attributable to ADRs of HAART are lower in developing counties, when national per capita spending on health is factored as well budget impact, the costs are significant.

Johnston *et al.* (2013) reported the costs attributable to ADRs ranging from US$ 3 to US$ 43 per ADR per month.[3] Therefore their per annum figures would be approximately 12 times more compared to those observed in our study. Similarly, Simpson *et al.* (2014) reported mean costs

associated with managing an AE-associated costs as $608.[4] In a study carried out in India, Radhakrishnan *et al.* (2012) reported mean direct cost incurred in treating per ADR in hospitalized patients with HAART as ranging from INR 524.4 (US$ 11.4) to INR 17521.4 (US$ 380.9). [2] This study was carried out in a hospital setting, therefore due to hospitalization; the costs attributable to ADRs would be higher than our observed costs. Despite the costs in this study being higher than the costs we observed, their reported costs were also very low compared to those reported in studies from developed countries. [3-5]

Severe adverse drug reactions are generally not treated in an outpatient setting as hospitalization would be required. Therefore, costs observed in this study do not reflect those attributed by more severe reactions associated with HAART such as Stevens–Johnson syndrome (SJS), renal failure or bone demineralization observed in other studies. Severity of ADRs has a directly proportionate impact on healthcare costs, i.e. severe ADRs are associated with higher costs compared to moderate as well as mild ADRs.[2-15]

4.2.3 Budget Impact Analysis

Estimated total cost of ADRs attributed to AZT based HAART is R8003.98 (US$556.40) and estimated total cost of ADRs attributed to TDF based HAART per annum is R33 788, 23 (US$2348.80). Although modest, these figures influence the ARV clinic's pharmaceutical budget.

When other factors are taken into consideration, this value might be an underestimate. Radhakrishnan *et al.* (2012) found that as severity of ADRs increased, costs associated with ADRs also markedly increased.[2] Our study, excluded patients with co-morbidities therefore the value estimated could also be underestimated as it has been reported that co-morbidities and polypharmacy are risk factors for increased ADR incidence rates.[14] Sensitivity analysis carried out reveals that increasing incidence of ADRs markedly increased the estimate costs attributable to ADRs.

4.3 **Significance of the study**

Adverse drug reactions influence adherence to HAART. Prevention and management of ADRs and costs thereof are tantamount to the success of HAART. Analysis of the costs of HAART would be insufficient if the costs of adverse drug reactions associated with them are not

factored as well.[16] This scenario advocates for more knowledge of the cost implications of ADRs to HAART. Studies on the costs attributable to ADRs and the budget impact of these costs are limited especially in South Africa.

One of the results of the NDoH ARV rollout programmes is that an unprecedented number of patients are initiated on HAART. The consideration of the health care costs of ADRs is paramount in understanding the total impact on the costs of managing HIV. This study contributes to the knowledge of the economic burden of ADRs to HAART.

4.4 **Recommendations**

Research on the cost of ADRs relies on good pharmacovigilance systems as well as record keeping systems. South African pharmacovigilance systems are currently being improved or initiated in many government institutions. As these systems improve, it is of great importance to look into larger research studies, which utilise economic modelling systems to ascertain the cost of HAART ADRs.

Despite our estimated costs being lower than those of other studies, they are significant in a resource-limited setting. In a resource-limited setting, any funds allocated to management of ADRs are funds directly taken away from other functions such as additional patients on HAART or additional staff members. These estimates will allow for cost implications of ADRs to TDF and AZT-based HAART to be accounted for in budgets at the ARV clinic. More CHCs will have to be surveyed to enable proper and more diverse recommendations on the costs attributable to HAART

4.5 **Chapter summary**

This final chapter highlighted the conclusions drawn from the findings of the study, described the significance, strengths and limitations of the study, as well as provided recommendations for pharmacoeconomic analysis of adverse drug reactions of HAART.

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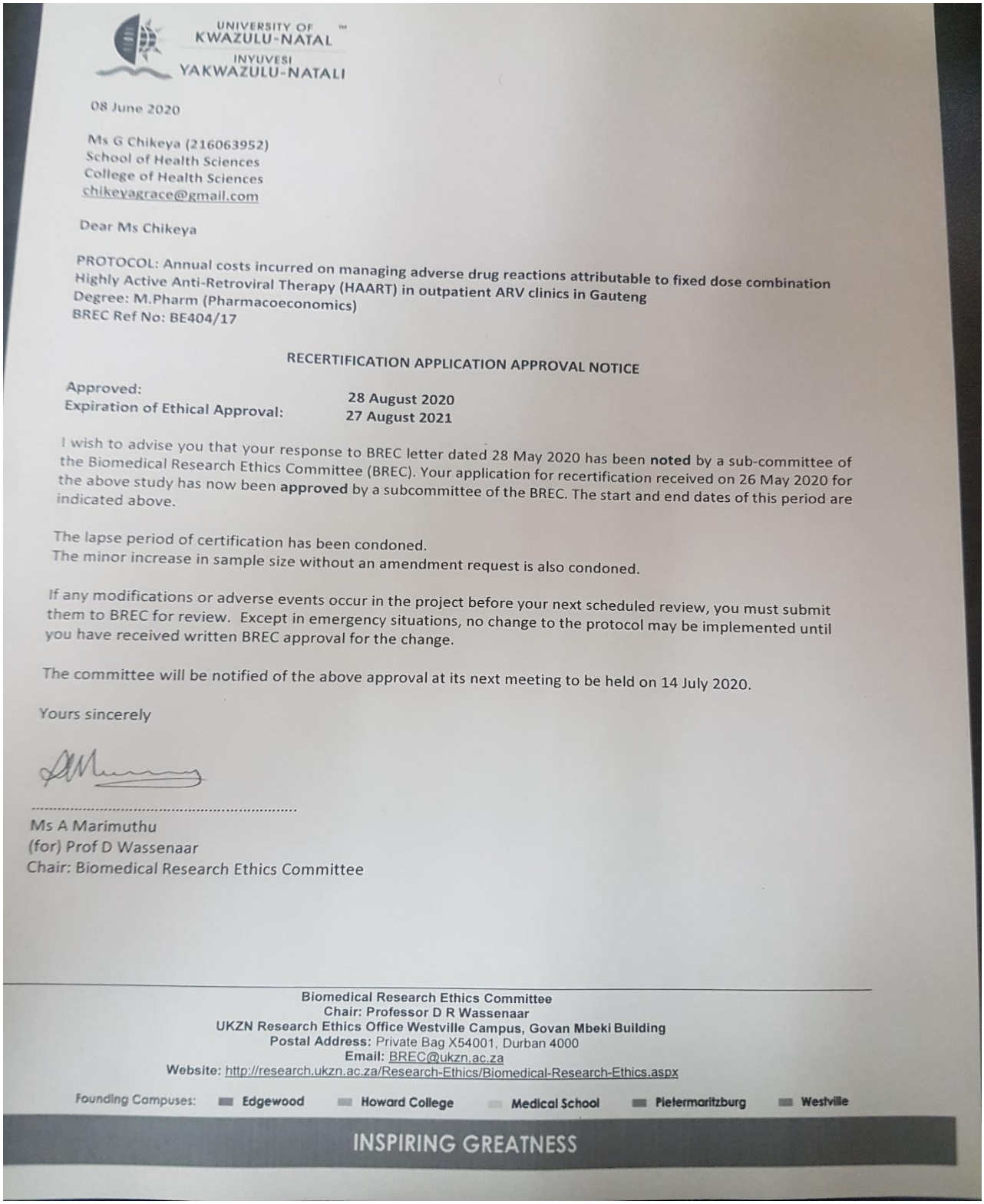
ANNEXURE 1

Ethical approval obtained from the University of KwaZulu-Natal



UNIVERSITY OF KWAZULU-NATAL
INYUVESI YAKWAZULU-NATALI

08 June 2020

Ms G Chikeya (216063952)
School of Health Sciences
College of Health Sciences
chikeyagrace@gmail.com

Dear Ms Chikeya

PROTOCOL: Annual costs incurred on managing adverse drug reactions attributable to fixed dose combination Highly Active Anti-Retroviral Therapy (HAART) in outpatient ARV clinics in Gauteng
Degree: M.Pharm (Pharmacoeconomics)
BREC Ref No: BE404/17

RECERTIFICATION APPLICATION APPROVAL NOTICE

Approved: 28 August 2020
Expiration of Ethical Approval: 27 August 2021

I wish to advise you that your response to BREC letter dated 28 May 2020 has been **noted** by a sub-committee of the Biomedical Research Ethics Committee (BREC). Your application for recertification received on 26 May 2020 for the above study has now been **approved** by a subcommittee of the BREC. The start and end dates of this period are indicated above.

The lapse period of certification has been condoned.
The minor increase in sample size without an amendment request is also condoned.

If any modifications or adverse events occur in the project before your next scheduled review, you must submit them to BREC for review. Except in emergency situations, no change to the protocol may be implemented until you have received written BREC approval for the change.

The committee will be notified of the above approval at its next meeting to be held on 14 July 2020.

Yours sincerely

.....
Ms A Marimuthu
(for) Prof D Wassenaar
Chair: Biomedical Research Ethics Committee

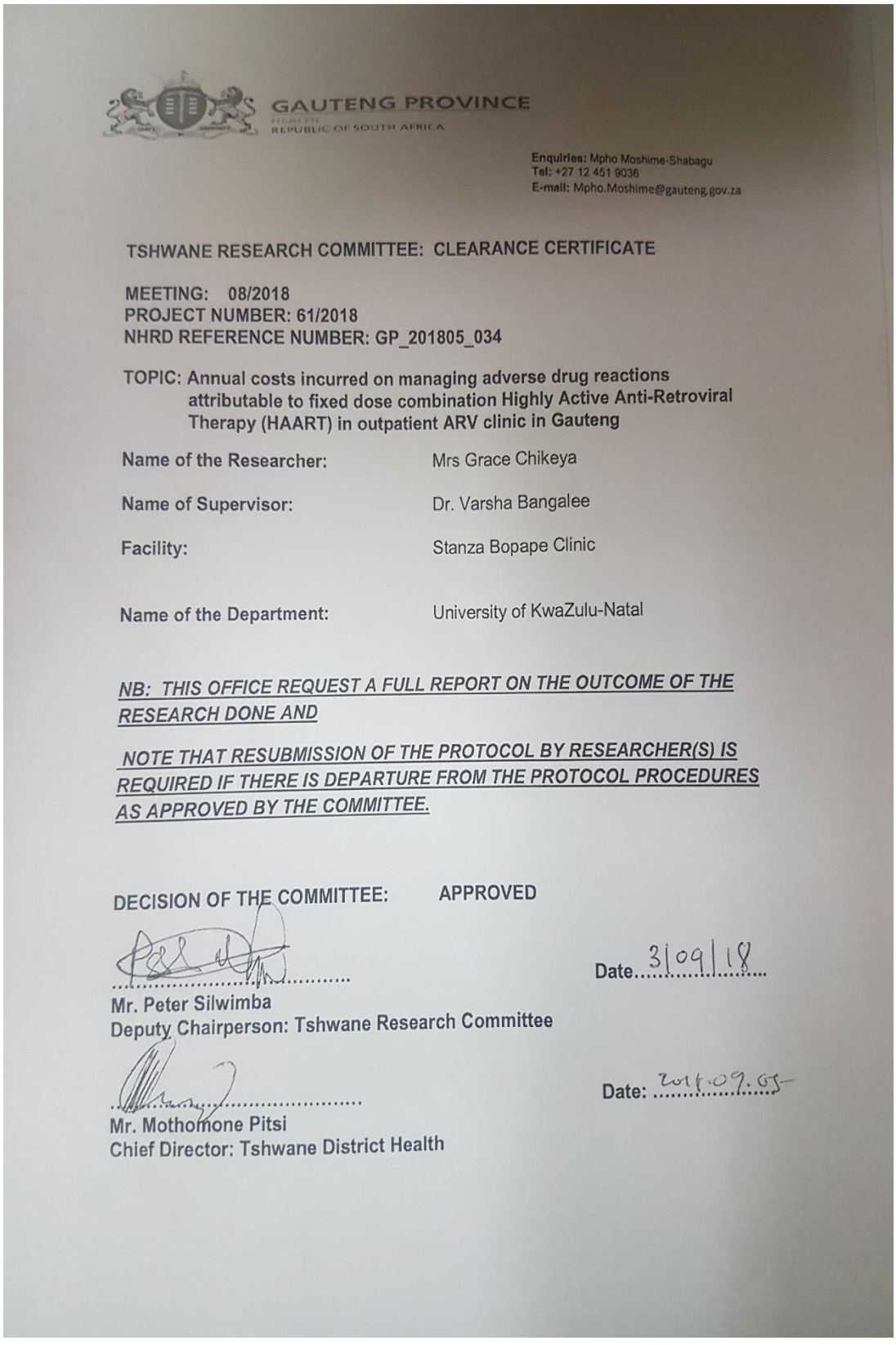
Biomedical Research Ethics Committee
Chair: Professor D R Wassenaar
UKZN Research Ethics Office Westville Campus, Govan Mbeki Building
Postal Address: Private Bag X54001, Durban 4000
Email: BREC@ukzn.ac.za
Website: http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx

Founding Campuses: Edgewood Howard College Medical School Pietermaritzburg Westville

INSPIRING GREATNESS

ANNEXURE 2

Ethical approval letter obtained from the Tshwane Research Committee



GAUTENG PROVINCE
REPUBLIC OF SOUTH AFRICA

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TSHWANE RESEARCH COMMITTEE: CLEARANCE CERTIFICATE

MEETING: 08/2018
PROJECT NUMBER: 61/2018
NHRD REFERENCE NUMBER: GP_201805_034

TOPIC: Annual costs incurred on managing adverse drug reactions attributable to fixed dose combination Highly Active Anti-Retroviral Therapy (HAART) in outpatient ARV clinic in Gauteng

Name of the Researcher:	Mrs Grace Chikeya
Name of Supervisor:	Dr. Varsha Bangalee
Facility:	Stanza Bopape Clinic
Name of the Department:	University of KwaZulu-Natal

NB: THIS OFFICE REQUEST A FULL REPORT ON THE OUTCOME OF THE RESEARCH DONE AND

NOTE THAT RESUBMISSION OF THE PROTOCOL BY RESEARCHER(S) IS REQUIRED IF THERE IS DEPARTURE FROM THE PROTOCOL PROCEDURES AS APPROVED BY THE COMMITTEE.

DECISION OF THE COMMITTEE: APPROVED

Date 3/09/18

Mr. Peter Silwimba
Deputy Chairperson: Tshwane Research Committee

Date: 2018.09.05

Mr. Mothomone Pitsi
Chief Director: Tshwane District Health

ANNEXURE 3

Author guidelines for manuscript publication: Value in Health Regional Issues

Value in Health
REGIONAL ISSUES

Submission Checklist

Authors
- ☐ Limit number of authors to 10
- ☐ Ensure that all authors meet the criteria for authorship (see ICMJE guidelines)

Highlights
- ☐ Include "Highlights" section as part of manuscript file

Abstract
- ☐ Include structured abstract (ie, Objectives, Methods, Results, Conclusions) as part of manuscript file and as part of the free-form field in the submission process
- ☐ Limit abstract to 250 words

Title
- ☐ Include a **blinded title page** (with no identifying author, funding, or acknowledgement information for peer review)
- ☐ Include an **unblinded title page** (with all author information for publication)

Manuscript Files
- ☐ Maintain blinding throughout the manuscript (ie, no identifying information on the blinded title page, acknowledgements, funding statement, manuscript file names, author responses to reviewers' comments, etc)
- ☐ Delete old versions of uploaded files (eg, manuscript, tables, figures, etc) that have been revised. Only keep files that have not changed in the revised paper.
- ☐ Adhere to word limit for specific article types (see Instructions for Authors)
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- ☐ Turn off line numbering—the system automatically includes line numbers in the final PDF

References
- ☐ Provide complete list of references (formatted in AMA style) at the end of the manuscript

Graphic Elements
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- ☐ Adhere to limit for specific manuscript types (see Instructions for Authors)

Revised Manuscripts
- ☐ Provide a detailed (blinded) set of responses to the reviewers'/editors' comments
- ☐ Upload both a clean and a tracked changes version of your revised manuscript
- ☐ Provide publication quality figures (300 dpi at a size of 3" x 5") in the following file types: JPG, PNG, GIF, TIF, EPS, etc
- ☐ Return completed authorship forms and conflict of interest forms signed by each author

ANNEXURE 4

Journal submission Response

Submission Confirmation

Thank you for your submission

Submitted to
Value in Health Regional Issues
Manuscript ID
VIHRI-CEEWAA-2020-0167
Title
Annual costs incurred on managing adverse drug reactions attributable to fixed-dose combination Highly Active Anti-
Retroviral Therapy (HAART) in an outpatient ARV clinic in Gauteng.
Authors
Chikeya, Grace
Bangalee, Varsha
Oosthuizen, Frasia
Date Submitted
11-Aug-2020
Author Dashboard

- **Home**
- **Author**
- **Review**