University of KwaZulu-Natal

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An investigation into the effects of concurrent Antiretroviral and African traditional medicines on the CD4 Count and Viral load of HIV infected persons in eThekwini Metropolitan area

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PREFACE AND DECLARATION

PREFACE

This dissertation is ultimately an investigation into the effects of concurrent Antiretroviral and African traditional medicines on the CD4 Count and Viral load of HIV infected persons in eThekwini Metropolitan area. The research was carried out with ethical clearance obtained from University of KwaZulu-Natal Biomedical Research Ethics Committee (BREC REF: BE272/14) and the KwaZulu-Natal Health Research Committee in the provincial Department of Health (REF: HRKM240/14).

DECLARATION

I, Mncengeli Sibanda (Student Number 213570031) declare that the dissertation hereby submitted to the University of KwaZulu-Natal, for the degree of Master of Pharmacy in the Discipline of Pharmaceutical Sciences, is my own work in design and execution (except where duly acknowledged) and has previously not been submitted by me for any degree or examination at this or any other university.

25 July 2016

_____ _____

Surname, Initials (Title) **Date**

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- Special thanks to my parents, Absalom and Ollie Sibanda for their continued love, support and planting the seed of continuous learning and development ever since I was a child.

- Finally, I will like to dedicate this thesis to my wife, Lindiwe and lovely daughters Buhle and Unathi, who have patiently supported me in my studies and ungrudgingly allowed me to pursue my area of interest.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF APPENDICES

ABBREVIATIONS AND ACRONYMS

AIDS	Acquired Immunodeficiency Syndrome
ANC	African National Congress
ART	Antiretroviral Treatment
ARV	Antiretroviral
ATM	Africa Traditional Medicines
–ATM	The cohort of patients who did not take ATM concurrently with ARV
+ATM	The cohort who took ATM concurrently with ARV
CD4	CD4+ Cell or T4 helper lymphocyte
CYP	Cytochrome P450 enzyme system
DDI	Drug-Drug Interaction
DHI	Drug-Herb Interaction
EFV	Efavirenz
HAART	Highly Active Antiretroviral Therapy
HCP	Health Care Professional
HDI	Herb-Drug Interaction
HIV	Human Immunodeficiency Virus
KZN	KwaZulu-Natal
MRSCA	Medicines and Related Substances Control Act 101 of 1965
NDoH	National Department of Health
NDP	National Drug Policy
NVP	Nevirapine
NGO	Non-Governmental Organisation
OMP	Orthodox Medical Practitioners
PDoH	Provincial Department of Health
PK	Pharmacokinetic
PLWA	People living with HIV/AIDS
REC	Research Ethics Committee
SACRA	South Africa Clinical Research Association

SAPC	South African Pharmacy Council
THP	Traditional Health Practitioner
THPA	Traditional Health Practitioners Act (Act 22 of 2007)
TM	Traditional Medicines
USA	United States of America
VL	Viral Load
WHO	World Health Organisation

ABSTRACT

Background – Traditional Medicines (TM) are often used by people living with HIV/AIDS (PLWA) alone or in combination with antiretroviral therapy (ART) to combat illnesses associated with HIV or the side effects of ART. Very few studies on clinical subjects have been carried out to find out the effects of co-administration of TM with ART

Aim

To investigate the effects of concurrent use of prescribed antiretroviral medicines (ARVs) and African Traditional medicines (ATM) on the CD4+ lymphocyte Count and Viral Load (VL) of PLWA in the eThekwini Metropolitan area.

Method:

A descriptive and exploratory study was carried out in two phases at four health facilities offering ART in the eThekwini metro. **Phase 1** was a cross sectional descriptive study aimed at collecting information on patient demographics and ATM use. **Phase 2** of the study was a longitudinal study which involved collection of data from the patient's charts using a case report form. The data was collected retrospectively and prospectively in phase 2.

Results:

281 patients met the inclusion criteria, gave consent to participate in the study and had usable information in their patient files. The majority of the participants were females (194/281, 69.9%) and almost all (272/281, 96.8%) were of African ethnicity and resided in a local township (64.4%). Fourteen out of the 281 (14/281 4.98%) patients reported concurrent use of ATM with ARVs during the study period. The most commonly used ATM was the African potato (9/14, 64.3%) followed by *Sutherlandia* (5/14, 21.4%), Stametta™ and uBhejani. The differences between the two means in the cohort taking ARV alone (–ATM) and the cohort which used ATM and ARVs concurrently (+ATM) at each CD4+ cell count measure were not significant at 5% level for Time 0 (p=0.18), Time 2 (p=0.26) and Time 3 (p=0.09). The differences between the two means in the –ATM and +ATM groups were significant at 5% level for Time 0 (p=0.013), marginally significant at Time 1 (p=0.048), significant at Time 2 (p=0.040) and not significant at Time 3 (p=0.069).

Conclusion:

Concurrent ARV and ATM use is quite low (4.98%) and this may indicate efficient pre-counselling efforts by healthcare professionals before ARV initiation. This study shows that there are no significant differences in CD4+ and inconclusive effects on VL, between patients taking both ARV and ATM concomitantly from those using ARV alone.

CHAPTER 1: INTRODUCTION

1.1 BACKGROUND AND RATIONALE FOR THE STUDY

It is estimated that there are approximately 200,000 African traditional healers in South Africa and that between 70 and 80 per cent of South Africans use the services of Traditional Health Practitioners (THP) [1]. South Africa like many developing countries has a pluralistic healthcare system wherein a modernised first world medical system co-exists with a variety of non-conventional health care systems such as local indigenous systems founded on traditional beliefs and practices [2].

Human immunodeficiency Virus (HIV) and Acquired Immune Deficiency Syndrome (AIDS) has grown to pandemic proportions and has become a major health problem worldwide. South Africa has an estimated 6.8 million people living with HIV and this represents the largest number of people living with HIV (PLWA) in any country [3]. PLWA often use a wide range of traditional medicine (TM) products together with their prescribed antiretroviral medicines (ARVs) in the treatment of HIV/AIDS related illnesses [4].

Although the use of TM is widespread, their use is not well researched, and consequently poorly regulated [5]. Limited clinical trials of efficacy exist, and low-level evidence of harm may indicate the potential for drug interactions with many medicines including the commonly used ARVs [5].

1.2 LITERATURE REVIEW

1.2.1 Epidemiology of TM use

The World Health Organisation (WHO) in its 2014-2023 strategy for Traditional medicines (TM) acknowledges that THP are either the mainstay of primary health care or a significant complement to health care delivery in most developing countries in the world, although their role in the health care system is usually understated [6].

1.2.2 HIV/AIDS and Antiretroviral Therapy (ART)

HIV/AIDS has grown to pandemic proportions and has become a major health problem worldwide. South Africa has an estimated 6.8 million people living with HIV and this represents the largest number of people living with HIV in any country in the world [3].

To date, Antiretroviral therapy (ART) using antiretroviral drugs (ARV) is the only proven management of HIV infection, making their effective distribution and uptake an essential component of any successful HIV management strategy [7]. In 2003, the South African government embarked on a wide-

scale roll-out of the antiretroviral therapy programme [7]. By mid-2011, approximately 1.9 million people were estimated to have been enrolled in this programme [8]. In 2013, the guidelines for ARV treatment in South Africa were revised to recommend the fixed-dose regimen (FDC) which consists of tenofovir (TDF), emtricibatine (FTC) and efavirenz (EFV) as the first line treatment in order to improve adherence and retention [8]. The World Health Organisation (WHO) has also since reviewed its guidelines, and now recommends that ART should be initiated in all adults living with HIV at any CD4+ cell count {9].

1.2.3 Medical Pluralism in the era of HIV/AIDS

Medical pluralism is the co-existence and use of more than one healthcare system for diagnosing and treating diseases [10]. A study in 2008 revealed that 4.1% of 618 PLWA interviewed at three hospitals in KwaZulu Natal (KZN) believed that they could cure HIV through the use of TM only [11]. This same study on treatment naive PLWA also found African Traditional Medicine (ATM) had been used for HIV in the past six months by 51.3% [11].

In Uganda, a 2007 study showed that 63.5 % of PLWA had used ATM after HIV diagnosis and same-day concomitant ATM and ARV use was reported by 32.8% of the patients surveyed [12]. In a tertiary hospital in Kano, Northwest Nigeria, it was found that 4.25% of the 430 patients surveyed used ARV and traditional medicine concomitantly [13]. A study of 67 PLWA done at three ART centres in the Kumasi Metropolis in Ghana found that concomitant ATM and ARV use was reported by 53.2% of the patients [14]. An astounding 98.2% of 388 patients interviewed at the Family Care Centre (FCC) ART clinic in Harare, Zimbabwe, were found to be using at least one ATM concurrently with their ARV medication [15]. A 2012 cross-sectional study which involved 100 participants enrolled at ARV clinics in two South African provinces showed that 79% of PLWA had used ATM prior to a diagnosis of HIV [16]. According to a 2007 study by Malangu, 7.7% of PLWA patients on ART in Pretoria, South Africa, concurrently used traditional health care, based on a self-reported survey on use of TCAM and over-the-counter medicines by HIV patients [17]. Despite the widespread use of TM in HIV/AIDS, a 2009 Cochrane review of Herbal medicines for treating HIV infection and AIDS found insufficient evidence to support the use of herbal medicines in PLWA and that the potential for any benefits needed to be studied further [18].

1.2.4 Antiretroviral Therapy and Drug-Herb Interactions

Typically, drug-drug interactions (DDI) and Herb-Drug interactions (HDI) may occur in at any of the stages of Absorption, Distribution, Metabolism and Excretion (ADME) phases of the pharmaceutical disposition of the drug in the human body affecting the entire pharmacokinetic profile of the drug [19].

Studies have shown that most ARV are metabolised via the cytochrome P450 3A4 enzyme system (CYP3A4) and the P-glycoprotein systems [19]. Herb-induced inhibition or induction of the cytochrome enzymes can alter the metabolism of ARVs, leading to adverse effects or lack of efficacy or drug toxicity [19]. A 2013 study for example, showed that *Sutherlandia* may inhibit clearance of drugs metabolised by the CYP450 pathway and has potential to interact with medicines which are metabolised by the same pathway [20]. *Sutherlandia* has also been shown to have an adverse effect on the absorption and metabolism of Atazanavir in the clinical setting [21].

Mills *et al*. in 2005 showed that extracts of African potato (*Hypoxis hemerocallidea*) had significant effects on cytochrome P450 3A4 in-vitro metabolism and potentially could result in sub-therapeutic plasma concentrations [22].

The above studies on TM and ARV use were affirmed by a 2014 laboratory study of the inhibition of major drug metabolising enzymes by *Hypoxis hemerocallidea (*H. hemerocallidea*), Echinacea purpurea (*E. purpurea*), Moringa oleifera (*M. oleifera*), Taraxacum officinale (*T. officinale*)* and *Lessertia frutescens (*L. frutescens*)* which demonstrated that TM have the potential to interact with ARV [23]. A 2013 study on adult volunteers, by Gwaza *et al.* showed that *hypoxis* when taken concurrently with the ARV drug Lopinavir/Ritonavir (LPV/r) is well-tolerated and is not associated with clinically significant changes in LPV/r pharmacokinetics [24].

1.3 PROBLEM STATEMENT AND CLINICAL SIGNIFICANCE OF THE STUDY

Due to the widespread use of traditional medicines, the high prevalence of HIV/AIDS, and the use of ARVs in HIV infected patients it was pertinent to investigate the effects of concurrent use of ARVs and Traditional medicines on the CD4 count and Viral Load in PLWA. These parameters are good clinical indicators for the patient's health outcomes {9].

This study is significant because it attempts to address some gaps in the current research pertaining to ARV and ATM use in PLWA; Updated data on prevalence of ATM use amongst PLWA is outdated with most available data on trends of ATM use amongst PLWA for the period before the advent of the ARV roll-out programme. In addition, studies concerning concurrent ARV and ATM use and the potential Drug Herb- interactions (DHI), are mostly in-vitro studies [24]. Studies on human subjects are limited and the data is scanty.

Furthermore, covariates and patient characteristics which may influence the treatment outcomes in PLWA who are using ARV and ATM concurrently have not been fully elucidated.

1.4 AIM OF THE STUDY

To investigate the effects of concurrent use of prescribed antiretroviral medicines (ARVs) and African Traditional medicines (ATM) on the CD4+ lymphocyte Count and Viral Load (VL) of PLWA in the eThekwini Metropolitan area of KwaZulu- Natal

1.5 OBJECTIVES OF THE STUDY

The objectives of the study were as follows:

- To determine the prevalence of concurrent African Traditional medicine and ARV use.
- To identify the most commonly used African Traditional medicines in the management of HIV which are used concurrently with ARV in KZN.
- To document the CD4 and VL of patients taking concurrent African Traditional medicine and ARV over a 9-month period.
- To determine the presence of Opportunistic Infections (OI) in patients taking both ARV and African TM if taking ATM results in a negative effect on CD4 and VL.
- To disseminate the findings into the public domain through a recognised and peer reviewed scientific journal.

1.6 METHODOLOGY

1.6.1 Study design

The study was conducted at four public ART clinics in the eThekwini metro in the period October 2014 to November 2015. The clinics were randomly selected from a list supplied by the provincial department of health of facilities that supply ARV treatment in the metro.

1.6.2 Sample size and Selection

Based on the figures outlined in the 2011 operational plan for the comprehensive HIV and AIDS care, management and treatment, a total of 12000 patients was postulated to attend the ART Clinics in the four health facilities in the study period [7]. An alpha error level of 0.1, beta 0.5, was desired for this study and this required a minimum sample size of 265 at ±10% precision level [25]. A sample size of 360 HIV-positive, treatment experienced adults (≥18 years old) was determined to be a suitable number

in order to cater for any 'loss to follow up' patients. Based on the patient responses, the patients were allocated into two groups;

1) The Control group (-ARV) which consisted of patients undergoing ARV treatment but who do not use traditional medicines concurrently.

2) The second group also referred to as the treatment group (+ARV) which consisted of patients who used ARV concurrently with ATM.

Inclusion criteria

The following Inclusion criteria were used for this study;

1) HIV infected patients.
2) Patients must have been stabilised on the same ARV regimen for the past 6 months
3) Patients must be on the same fixed dose ARV regimen.

Exclusion criteria

The following Exclusion criteria will apply;

1) Patients under the age of 18 years.
2) Patient using concomitant chronic western medicine (excluding ARVs).
3) Patients who use other alternative therapies (excluding ATMs)

1.6.3 Data collection technique and instruments

Data was collected by the researcher retrospectively and prospectively over a period of twelve months in two phases;

Phase 1: During phase 1 of the study, data was collected using an anonymous coded questionnaire (Appendix 1) after consent was given by the patients. The code on the questionnaire was written next to the respective spread sheet data. This information was necessary for phase 2 selection of participants.

The structured data extraction form consisting of close-ended questions was used to collect data during interviews with participants. Questionnaires were available in English as well as Zulu and recorded the following criteria;

1. Patient Characteristics (Age, Gender, Ethnicity, Level of Education).
2. Current ARV Regimen.
3. Traditional Medicine Use.

4. Current TM used.

5. Duration of TM Use.

6. Reason for TM Use.

Thereafter exclusion of participants took place based on the exclusion criteria.

Phase 2: Phase two of the study was a longitudinal study (Retrospective, 6 months and prospective 12 months). Patient charts were coded with a unique number to match the questionnaire number. Clinical data obtained from the patient files included;

1. Previous and Current ART Regimen(s).

2. Opportunistic Infections.

3. Patient viral load and CD4+ Lymphocyte Count and weight.

The information obtained was recorded on a Case Report form for each patient (Appendix 2). Prospective data collection was done every 6 months and consisted of serial measurements of the above mentioned clinical variables over a twelve-month period. Prospective data collection was done using patients' medical chart history. No further contact was made with the patient phase 2 of this study and so no information on continued TM use could be ascertained. Information collected consisted only of clinical data recorded in the patient medical chart. This was then recorded on the same Case Report form (Appendix 2).

1.6.4 Pilot Study

A pilot study for Phase 1 of the study was conducted on thirty patients prior to the actual data collection period. This was done in order to review the data collection instruments and assess their suitability for use in the study. This was also done to increase the validity and reliability of the data collection instruments and to ensure content validity for the study. Another aim of the pilot study was to check the feasibility of the study and also amend the questions in the data management tools where necessary. Data from the pilot study was not included in the final analysis.

1.6.5 Ethical considerations

Ethical clearance for the study was obtained from University of KwaZulu-Natal Biomedical Research Ethics Committee (BREC REF: BE272/14), the KwaZulu-Natal health Research Committee (REF:

HRKM240/14) in the provincial Department of Health as well as permission from the Chief Executive Officer's (CEO) of the four health facilities.

Furthermore, written informed consent was obtained from each patient after details of the study, including the aims, risks and benefits of the study, were clearly explained to the patients in a language that the patient was comfortable with. The patient information and consent forms were made available in English, and isiZulu. In addition, the patients were also provided with the telephone number of one of the clinics doctors to answer any questions as well as the UKZN BREC to verify the authenticity of the study. To protect patient confidentiality, especially the patients' HIV status, a unique study number was assigned to each patient and reporting on patient's information was done anonymously. Patients taking part in the study did not receive any direct feedback on their CD4+ levels or any other clinical information unless it was indicative of non-compliance to ARV or treatment failure in which case the responsible clinician was contacted. The study was conducted according to internationally accepted ethical standards and guidelines and all patients were treated according to the regular standard of care without any prejudice or favour.

Participants were informed that they had the right to withdraw from the study at any time if they chose to do so without providing any reason.

1.6.6 Data analysis

Data analysis for this study was both quantitative as well as descriptive. Statistical Package for the Social Sciences Package for Windows® by IBM (IBM SPSS®), Version 21, was utilised for data analysis. All entered data was cross checked/proof read by a second person and corrections were made if necessary.

Results were expressed in terms of frequency, mean values, standard deviations (SD). Frequencies and proportions (%) were calculated to describe categorical variables such as Age, Gender, place of residence, level of education and ATM use. To allow for sorting and counting of responses, categories were developed and responses were sorted and tabulated according to labelled categories.

In the event of the patient charts having missing clinical information (CD4+ and VL measurements), the average CD4+ and/or VL for the available readings was used in the place of the missing data. Average CD4+ and VL for both cohorts at Time 0 (6 months retrospective), Time 1 (Baseline), Time 2 (6 months prospective) and Time 3 (12 months prospective) were determined. The association between the Health outcomes (CD4+ counts and Viral Loads) and use of ATM were examined using a standard t-test for independent means.

1.7 OUTLINE OF THE DISSERTATION

The chapters in this dissertation are presented as follows:

Firstly, in **Chapter 1,** the introduction, background, rationale for the study as well as the literature review for the study are presented. In this chapter, a Socio-epidemiology of TM use in South Africa is given. The phenomenon of medical pluralism is explained as well as the role of the THP in the management of HIV/AIDS as recorded in current literature. Furthermore, the recommended ARV treatment guidelines are outlined and the pharmacokinetics of some ARV drugs as well as commonly used ATM for the management of HIV/AIDS are also reviewed. Literature on in-vitro studies of the pharmacokinetic profiles of some commonly used ATM are cited including Herb-Drug Interactions with antiretroviral medicines. The significance of the study, research questions as well as aims and objectives of the study are also defined. The Chapter concludes by outlining the methodology used in the study including the study design, site, sample selection, data collection instruments and ethical considerations for the two phases of the study.

Chapter 2 is a manuscript derived from this study and reports on the main objective of this study. The manuscript title is, "Effects of concurrent Antiretroviral and African traditional medicines on the CD4 Count and Viral load profiles of People living with HIV/AIDS (PLWA) in the eThekwini Metropolitan area" presented according to South African Medical Journal author guidelines. The manuscript presents the data and results of this study.

Chapter 3 offers the synthesis of the study including a discussion on key findings, conclusions drawn from the research, outlines the limitations of this study and makes recommendations based on the findings of this research.

CHAPTER 2: MANUSCRIPT FOR PUBLICATION

Concurrent use of Antiretroviral and African traditional medicines amongst people living with HIV/AIDS (PLWA) in the eThekwini Metropolitan area of KwaZulu Natal

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Prepared according to the Instructions for Authors of African Health Sciences

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Concurrent use of Antiretroviral and African traditional medicines amongst people living with HIV/AIDS (PLWA) in the eThekwini Metropolitan area of KwaZulu Natal

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Abstract

Background: People living with HIV/AIDS (PLWA) often use African Traditional Medicines (ATM) either alone or in combination with western medicines including Antiretrovirals (ARV).

Objective: To explore the prevalence of concurrent Antiretrovirals (ARV) and African Traditional medicines (ATM) use and determine the effects of any concurrent use on the CD4+ Lymphocyte Count and Viral Load (VL) of PLWA in the eThekwini Metropolitan area.

Methods: A descriptive and exploratory study was carried out on 360 patients. Information was gathered on patient's socio-economic characteristics, ATM usage, outcome measures of HIV disease progression (CD4+ Count, VL). The data was analysed using descriptive statistics, univariate and multivariate analyses.

Results: 4.98% (14/281) of the patients used ATM and ARV concurrently during the study period. Over 65% (185/281) reported ATM use before diagnosis with HIV whilst 77.6% (218/281) reported previous ATM use after their HIV diagnosis but before initiation with ARV. Place of residence ($p=0.004$), age ($p<0.001$) and education level ($P=0.041$) were found to be significantly and positively correlated with ATM use. There were no statistically significant changes in mean plasma CD4+ Count and inconclusive effects on VL during the period of the study in the group taking ARV alone when compared with the group using ARV and ATM concomitantly.

Conclusion: Concurrent ARV and ATM use is quite low (4.98%) when compared to ATM use before HIV diagnosis and after HIV diagnosis but before initiation with ARV. This may point to efficient pre-counselling efforts before ARV initiation by healthcare professionals. This study also demonstrated that there were no significant differences in the CD4+ and inconclusive effects on VL, between patients taking both ARV and ATM concomitantly and those using ARV alone.

Keywords: African traditional medicines; AIDS; ARV; complimentary medicines; Drug-Herb interactions; Herbal medicine; HIV; Indigenous medicine; Medical Pluralism; South Africa

Introduction

Human immunodeficiency Virus and Acquired Immune Deficiency Syndrome (HIV/AIDS) has grown to pandemic proportions and has become a major health problem worldwide. Approximately 36.9 million people worldwide are living with HIV and since 2000 around 25.3 million people have died as a result of AIDS related illnesses [1]. According to the 2014 Joint United Nations Programme on HIV and AIDS (UNAIDS) update, sixty-nine percent of people infected with the HIV live in Sub-Saharan Africa [1]. South Africa has an estimated 6.8 million people living with HIV and this represents the largest number of people living with HIV in any [1]. HIV/AIDS has worsened the demands on the health care system in Africa and has put an already overburdened system under further strain [1]. Antiretroviral therapy (ART) using antiretroviral drugs(ARV) is the only proven management of HIV-infection and have led to reduction in HIV related opportunistic infections and AIDS related deaths, and have thus improved substantially the quality of life in People living with HIV/AIDS (PLWA) [2].

It is estimated that there are approximately 200000 African traditional healers in South Africa and that between 70 and 80 per cent of South Africans use the services of Traditional Health Practitioners (THP) [3]. South Africa like many developing countries has a pluralistic healthcare system wherein a modernised first world medical system co-exists with a variety of non-conventional health care systems such as local indigenous systems founded on traditional beliefs and practices [4].

In South Africa, the use of modern medicines has never fully replaced the indigenous system, and THPs continue to be consulted by the black population including PLWA for a variety of reasons [3]. The commonly treated illnesses including nausea and vomiting, lack of energy, lack of appetite, skin disorders, weight loss and diarrhea. Traditional Medicine (TM) are also used to treat the side effects of ARV drugs as well as fungal infections, dizziness, stomach upsets and pain [5]. Other reasons for TM use in PLWA is to supplement dietary intake, boost energy levels and improve immune response as well as a misguided belief that some TM can cure HIV/AIDS [6]. African traditional medicines (ATM) are regarded as a credible and convenient source of health care and dual treatment regularly takes place as a result [4]. THP thus have a crucial role to play in building the health system of South Africa including the management of PLWA [5].

During the peak of the HIV/AIDS pandemic in the late 1990's before the era of massive ARV roll-out programs, when ARVs were largely unaffordable and inaccessible, ATM were the mainstay of HIV management amongst PLWA in Africa [5]. The advent of ARV rollout programs did not substitute ATM use amongst the population [3] and many studies attest to this. In Uganda for example, a 2007 study showed that 63.5 % of PLWA had used TM after HIV diagnosis and same-day, concomitant ATM and ARV use was reported by 32.8% of the patients surveyed [7]. In a tertiary hospital in Kano, Northwest Nigeria, it was found that 4.25% of the 430 patients surveyed used ARV and traditional medicine concomitantly [8]. A survey of 67 PLWA done at three ART centres in the Kumasi Metropolis in Ghana found that concomitant TM and ARV use was reported by 53.2% of the patients [9]. An astounding 98.2% of 388 patients interviewed at the Family Care Centre (FCC) ART clinic in Harare, Zimbabwe were found to be using at least one ATM concurrently with their ARV medication [10].

A cross-sectional survey done in 2007 among PLWA attending a workplace ART clinic in South Africa found that 23% used ATM concurrently with their ATM [6]. A 2012 cross-sectional study which involved 100 participants enrolled at ARV clinics in two South African provinces showed that less than 20% of participants used TM and ARV simultaneously [11]. However, close to 80% of participants utilised TM before contracting HIV, which is in keeping with approximate estimates by the WHO [12]. According to Malangu, 7.7% PLWA on ART in Pretoria, South Africa, concurrently used traditional health, care and over-the-counter medicines. [13].

Although the use of Traditional Medicines (TM) is widespread, their use is not well researched, and consequently poorly regulated [4]. Limited meta-analyses of safety and efficacy exist and low-level evidence of harm identifies the potential for herb-drug interactions (HDI) with many medicines including the commonly used ARV [14].

The potential HDI may occur in similar fashion to the typical Drug-Drug interactions (DDI) at any of the stages of Absorption, Distribution, Metabolism and Excretion (ADME) phases of the pharmaceutical disposition of the drug in the human body affecting the entire pharmacokinetic profile of the drug [15]. Herb-induced inhibition or induction of the cytochrome enzymes can alter the metabolism of ARVs, leading to adverse effects or lack of efficacy [15]. The concomitant intake of TM in patients using ARVs may result in lowering of plasma drug concentrations resulting in treatment failure, drug resistance and possibly death of the patient [15]. Alternatively, concomitant intake may also result in increased plasma drug concentrations resulting in drug toxicity [15].

Mills *et al*. in 2005 showed that extracts of African potato *(Hypoxis hemerocallidea)* had significant effects on cytochrome P450 3A4 in-vitro metabolism and so potentially could result in sub-therapeutic plasma concentrations [16]. A 2014 laboratory study of the inhibition of major drug metabolising enzymes by *Hypoxis hemerocallidea (*H. hypoxis*), Echinacea purpurea (*E. purpurea*), Moringa oleifera (*M. oleifera*) Taraxacum officinale (*T. officinale*)* and *Lessertia frutescens* (L. frutescens*)* which demonstrated that TM have the potential to interact with ARV [17]. Conversely, a 2013 study on adult volunteers, by Gwaza *et al.* showed that *Hypoxis* when taken concurrently with lopinavir/ritonavir(LPV/r) is well-tolerated and is not associated with clinically significant changes in LPV/r pharmacokinetics [18]. International guidelines for the management of HIV/AIDS recommend the use of plasma viral load (VL) measurements as the key tool in predicting HIV viral suppression and treatment success for patients on ART [19]. In resource limited settings which have inadequate access for VL measurements, treatment outcomes in PLWA on ART are measured using other clinical tools such as CD4+ T-cell (CD4) count, changes in the patient's Body Mass Index (BMI) as well as the presence or absence of opportunistic diseases [20]. Notwithstanding the laboratory studies mentioned above and others, and the known, albeit usually sub-clinical DDI in the components of most ART regimens, there remains no definitive position by most policy makers on the effect of individual ATM on the effects of concurrent use of ART and ATM on VL and CD4+ counts amongst PLWA due to the absence of a large randomised control trials

Aim and Objectives:

The objective of the study was to explore the occurrence of concurrent ART and ATM use amongst PLWA in the eThekwini Metropolitan area with the following aims: to determine the Socio-demographic profiles of the respondents, the types of ATM used and the reasons for their use of ATM with ARV as well as to determine the effects of any concurrent use on the CD4+ Lymphocyte Count and Viral Load (VL) of such patients.

Ethical considerations

Ethical clearance for the study was obtained from University of KwaZulu-Natal Biomedical Research Ethics Committee (BREC REF: BE272/14), the KwaZulu-Natal health Research Committee (REF: HRKM240/14) in the provincial Department of Health as well as permission from the CEO's of the four health institutions before data collection commenced.

Methods

Design, Setting and Study population

The study was conducted in two phases. The first phase was a cross sectional descriptive study aimed at collecting information on patient demographics and ATM use as well as to recruit participants for the second phase of the study. The second phase was a longitudinal study which involved data collection from the patient's charts using a Case Report Form. The study was carried out in the region of the eThekwini metropolitan area. The eThekwini metro is a mostly urban area consisting of approximately 3.5 million people and is located in the east coast of the Republic of South Africa (RSA) [21]. The population is comprised mostly of black African (73.8%), followed by Indian/Asian (16.7%), White (6.6%) and coloureds (2.5%) [21]. The population is serviced with sixteen provincial hospitals and eight community health centres [22]. The study was conducted at four public health facilities that supply ARV treatment in the eThekwini Metropolitan (Metro) area. These facilities were randomly selected from a list supplied by the provincial department of health of facilities that supply ARV treatment in the metro. A minimum sample size of 360 HIV-infected, treatment experienced adults (≥18 years old) was determined to be a suitable number in order to cater for any 'loss to follow up' patients. Every second patient attended to at the health facility was approached with the study information leaflet to participate in the study. After obtaining their consent patients were recruited continuously until the desired sample size of 360 participants who met the inclusion criteria was achieved. Only patients who had been stabilised on the same Fixed Dose first-line ART regimen which consists of tenofovir (TDF), emtricibatine (FTC) and efavirenz (EFV) for the past 6 months were considered for the study. Patients of the FDC were preferred by the researcher as this is the most commonly used first line regimen according to current treatment guidelines [23]. Furthermore, patients on the FDC were deemed to be more likely to be compliant to treatment and so negate non-adherence as a confounder to treatment failure [23].

Instrument, Data Collection, Capture and Analysis

An anonymous coded questionnaire was administered to each of the selected 360 participants The variables gathered included characteristics such as age, gender, ethnicity, level of education and place of residence., Other variables collected were current ARV regimen, previous and current ATM use, names and routes of administration of ATM used, reason for ATM use and awareness of any dangers in concurrent ATM and ARV use. Based on responses from this phase, patients were divided into two cohorts; users of ARV alone (-ATM) or users of both ARV and ATM (+ATM).

Subsequent to the collection of the above mentioned patient data, a second phase of the study was initiated. This was a longitudinal study which involved data collection of patient clinical information from the patient's charts using a Case Report Form (CRF). The data was collected both retrospectively (6 months) and prospectively (over 12 months, in six month intervals). Clinical data collected included CD4+ lymphocyte counts, patient Viral load (VL), treatment failure, presence of Adverse Drug Reactions (ADR) and Opportunistic infections (OI) as well as any documented ATM use if available.

The data was then captured and analysed using Statistical Package for the Social Sciences Package for Windows® by IBM (IBM SPSS®) version 21**.** Results were expressed in terms of frequency, mean values and Standard Deviations (SD). Frequencies and proportions (%) were calculated to describe categorical variables such as Age, Gender, place of residence, level of education and ATM use. Results from open ended questions were captured using IBM SPSS ®. Categories were developed and responses were sorted and tabulated according to labelled categories to allow for sorting and counting of responses.

Average CD4+ and VL for both cohorts at Time 0 (6 months retrospective), Time 1 (Baseline), Time 2 (6 months prospective) and Time 3 (12 months prospective) were determined. In the event of the patient

charts having missing clinical information (one or more missing CD4+ and/or VL measurements), the average of the available readings would be used in the place of the missing data. The association between the Health outcomes (Average CD4+ counts and Viral Loads) and use of ATM were examined using a standard t-test for independent means. A statistician was consulted to verify the statistical analysis.

RESULTS

Excluded Participants.

Out of the subset of 360 patients who met the inclusion criteria and so chosen to participate in this study, 79 patients were excluded due to 'loss to follow-up' either through death (4 patients) or through completely unusable clinical information in the patient charts (absent CD4+ or VL).

Socio-Demographic characteristics

Out of the remaining 281 patients surveyed, 69.9% were females and almost all (96.8%) were of African (black) ethnicity. The mean age of the participants was 39 (with a range from 19 to 69 years). The majority of the participants were relatively under-educated with only 6.7% having obtained a tertiary qualification and most (48.4) only having a primary education. It was also found that the majority of the patients (64.4%) resided in an urban township.

The sample characteristics are depicted in figure 1;

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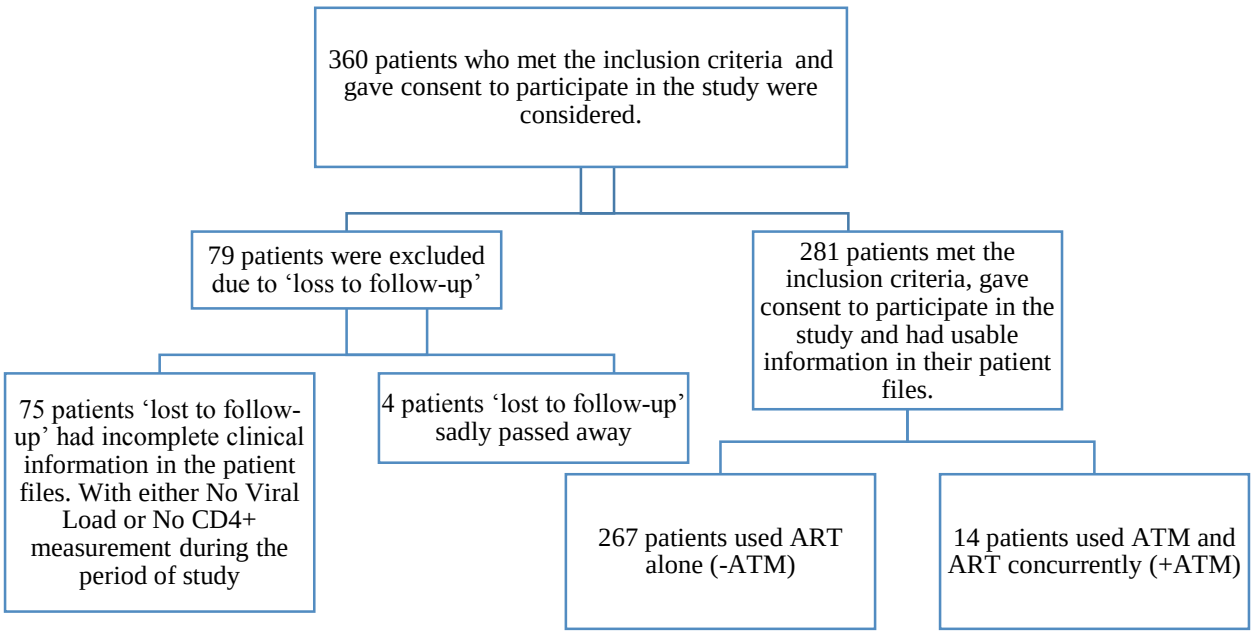

Figure 1: Sample Size Population Characteristics

Demographics and ATM use

The majority (71.4%) of concurrent ATM and ARV (+ATM) users were Africans (black) above the age of 40 and resided in urban townships (57.1%). Most of the patients (85.7%) who took ATM concurrently with ARV had primary education or lower qualification. Sixty-three (22.4%) patients reported to never have used ATM.

Table 1 shows the summary of the demographic characteristics of patients surveyed, stratified by ARV users or ARV and ATM users.

Table 1 : Patient characteristics, October 2014 (n=281)

Patient Characteristic	**ARV users only (%)**	**ARV and ATM users (%)**	**Total [n (%)]**
Age			
18-25	96.3	3.7	27 (9.6)
25-35	97.2	2.8	72 (25.6)
30-35	98.1	1.9	53 (18.9)
40-45	95.3	4.7	43 (15.3)
45-50	92.3	7.7	52 (18.5)
>50	88.2	11.8	34 (12.1)
Gender			
Male	90.8	9.2	87 (30.1)
Female	96.9	3.1	194 (69.9)
Ethnic Group			
Black	94.9	5.1	272 (96.8)
White	0	0	0
Indian	100	0	3 (1.1)
Coloured	100	0	6 (2.1)
Other	0	0	0
Level of Education			
No Education	94.2	5.8	69 (24.6)

Primary Education	94.1	6.9	136 (48.4)
Secondary Education	96.5	3.5	57 (20.3)
Tertiary Education	100	0	19 (6.7)
Place of Residence			
Urban Suburban	98.3	1.7	58 (20.6)
Urban Township	95.6	4.4	181 (64.4)
Peri-Urban	90	10	30 (10.7)
Rural	83.3	16.7	12 (4.3)

14 out of the 281 (4.98%) patients reported concurrent use of ATM with ARV during the study period Of the total patients surveyed. 65.8% reported ATM use before diagnosis with HIV whilst 77.6% reported previous ATM use after their HIV diagnosis (but before initiation with ARV). This is shown in Figure 2 ;

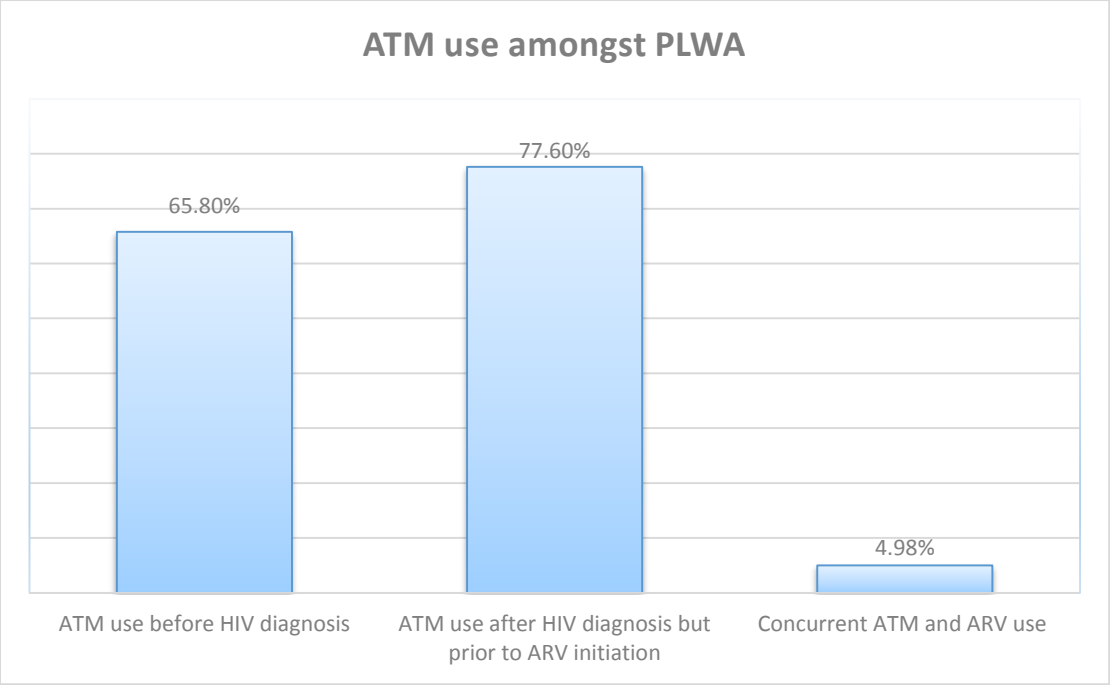

Figure 2: ATM use amongst PLWA

None of the patients in the +ATM cohort had a tertiary qualification and all were of African ethnicity. Univariate analysis for predicting ATM use was significantly as well as positively correlated with

gender (p<0.001), age (p=0.032) education level (p<0.001) as well as place of residence (p=0.032). Multivariate analysis, obtained from combining all independent and controlling factors, for predicting ATM use resulted in education level (p<0.041), place of residence (p=0.004) and age (p<0.001). Further details are elucidated in Table 2.

Table 2 : Statistical association of independent variables to predict ATM use

Patient Characteristic	% Concurrent ARV and ATM use	Univariate p value	multivariate p value
Age			
18-25	7.14	0.032	<0.001
25-35	14.28		
30-35	7.14		
40-45	14.28		
45-50	28.57		
>50	28.57		
Gender			
Male	57.14	<0.001	<0.018
Female	42.86		
Ethnic Group			
Black	100	<0.001	<0.001
Level of Education			
No Education	28.57	<0.001	<0.041
Primary Education	57.14		
Secondary Education	14.29		
Place of Residence			
Urban Suburban	7.14	0.032	0.004
Urban Township	57.14		
Peri-Urban	21.43		
Rural	14.29		

Types of ATM

The most commonly used ATM amongst the +ATM group was the African potato (H. hemerocallidea*;* used in its crude form or commercial preparations such as *Inkomfe* capsules or Moducare®) which was used by 9 patients (64.3%). This was followed by *Sutherlandia* at 21.4%. Two of the +ATM patients routinely used Stametta™ (a commercially prepared mixture of herbs including Aloe, aniseed oil and other nutrients which is sold Over-the-counter in pharmacies and health shops and is purported to 'strengthen the immune system and improve general well-being) and *uBhejani* (a traditional concoction of unknown composition sold in muthi markets in downtown Durban and townships). The average time for utilisation of ATM for the patients who took ARV and ATM concurrently was 4.3 months. In response to whether or not they had informed their medical doctor of their concurrent ATM use, all 14 patients (100%) responded negatively and indicated that their doctors were not aware of their concurrent use of ATM.

Reasons for ATM use

77.5 (218/281) patients claimed to have previously or currently used ATM and cited one or more reasons for using ATM. Reasons for using ATM included to boost immunity (68%), increasing appetite (61%), tonic for fatigue (55%), treating stomach pains/diarrhea (27%), alleviating fever (21%), treating joint pains (13%), treating headaches (11%), treating ARV side effects (7%) and elevating mood (4%). This is depicted in the table below 3;

Table 3 : Utilisation of ATM (n=218)

Indication	Percentage (%) (n=218)
Immune Supplementation	68
Increasing Appetite	61
Tonic	55
Abdominal symptoms (Stomach pain/diarrhea)	23
Fever	21
Joint Pain	13
Headache	11
Treating ARV symptoms	7
Elevating mood	4
No particular reason	2

91% (256/281) of the patients cited knowledge of the potential interactions between ATM and ARV and mentioned that the health care provider had underscored the potential dangers of simultaneous ARV and ATM use to them during pre-counselling before initiation of ART.

Clinical information

Effect on CD4

The majority (72%) indicated living with HIV for at least 3 years. As per the inclusion criteria, all patients surveyed were on the FDC drug, or its singular components (Tenofovir + Emtricibatine/3TC + Efavirenz) for a minimum period of 6 months. Based on the commencement of current ARV regimen, it was found that average period of use of the FDC combination drug at the time of first contact with the patients was 9.3 months. Information on previous ARV regimens was scanty and so was excluded from the study. The mean CD4+ values for the study period are represented in Table 4;

Table 4 : CD4+ Cell counts (n=281)

	-ATM (n=267)		+ATM (n=14)	
	Mean CD4+ (SD)	Change from baseline	Mean CD4+ (SD)	Change from baseline
Time 0, 6 months (Retrospective)	507 (±117.3) cells/mm^3	+1.2%	480 (±66.5) cells/mm^3	-0.6%
Time 1, Baseline	501 (±128.3) cells/mm^3	N/A	483 (±81.5) cells/mm^3	N/A
Time 2, 6 months (Prospective)	519 (±141.0) cells/mm^3	+3.6%	512 (±59.7) cells/mm^3	+6.0%
Time 3, 12 months (Prospective)	552 (±131.5) cells/mm^3	+9.2%	529 (±49.5) cells/mm^3	+9.5%

The mean baseline CD4+ count in the –ATM cohort was 501 cells/$mm^{3.}$ There was a 9.2% increase in CD4+ counts in the –ATM group compared to the base line values after the 12 month prospective measurements subsequent to the 3.6% increase in CD4+ count at the 6-month interval. In comparison, the CD4+ counts in the +ATM cohort responded similarly to the –ATM group with incremental increases in mean CD4+ count of 6.0% and 9.5% at 6-month and 12-month interval respectively. The differences between the two means in the –ATM and +ATM groups at each CD4+ cell count measure were not significant at 5% level for Time 0 (p=0.18), Time 2 (p=0.26) and Time 3 (p=0.09).

Effect on VL

The mean viral loads (VL) for the patients during the study period are recorded in Table 5.

Table 5 : Viral Load (VL) measurements (n=281)

	-ATM (n=267)		+ATM (n=14)	
	Mean Viral Load (SD)	Change from baseline	Mean Viral Load (SD)	Change from baseline
Time 0, 6 months (Retrospective)	21700 (±285.0) copies/mL.	+68.8%	15825 (±34.7) copies/mL.	+35.5%
Time 1, Baseline	12855 (±177.5) copies/mL.	N/A	11677 (±51.3) copies/mL.	N/A
Time 2, 6 months (Prospective)	8824 (±195.8) copies/mL.	-31.35%	9818 (±44.3) copies/mL.	-15.9%
Time 3, 12 months (Prospective)	8355 (±331.5) copies/mL.	-35.00%	9120 (±36.8) copies/mL.	-21.9%

At baseline, the VL in the -ATM group ranged from undetectable to 79120 copies/mL with an average of 12855 copies/mL. The +ATM group had a mean VL of 11677 copies/mL ranging from undetectable to 25435. The VL in the –ATM group reduced by 31.35% and 35% compared to the baseline VL in Time 2 and Time 3 respectively. The differences between the two means in the –ATM and +ATM groups is significant at 5% level for Time 0 (p=0.013), marginally significant at Time 1 (p=0.048), Significant at Time 2 (p=0.040) and not significant at Time 3 (p=0.069).

Discussion

Overall, 65.8% (185/281) of the patients had used ATM before HIV diagnosis and 77.6% (218/281) after diagnosis. This indicated a health seeking approach by the respondents through their ATM practitioners after initial HIV diagnosis. These figures are in line with World Health Organization (WHO) estimates of about 80% worldwide ATM usage and even closer to a South African estimates of around 70% [5, 12].

A majority of the patients surveyed (95.02%) did not use ATM concurrently with ARV. With the paucity of data on the concurrent use of ATM and ARV, and the fact that in-vitro studies indicate possible interactions between commonly used ATM and ARV [15], this finding can be viewed in a positive light. However, 4.98% (14/281) patients did report the concurrent use of ATM with ARV during the study period. The frequency of concurrent ATM use is comparable with similar studies in urban centres in Pretoria, South Africa [13] as well as Kano, Nigeria [8] which had 4.40% and 4.3% prevalence rate of concurrent ATM and ARV use respectively. This study differed vastly with a 2004 Uganda study by Langlois-Klassen *et al* (2007), which reported a rate of 32.8% for concurrent ARV and ATM use [7]. The comparison of the results obtained in the current and other similar studies is compared using Table 6;

Table 8 : Comparison of ATM usage in PLWA

Clinical trial (CT) characteristic	eThekwini Metro, South Africa (n=281)	eThekwini Metro, South Africa (n=222) [5]	Pretoria, South Africa (n=67) [13]	Kano, Northwest Nigeria (n=430) [8]	Kabarole District, Western Uganda (n=137) [7]
Period of study	Current study	2008	2004-2005	2014	2004
Setting	Urban	Urban	Urban	Urban	Rural
Concurrent ATM and ARV use	4.98%	44.4%	4.40%	4.30%	32.80%
ATM use after HIV diagnosis (before initiation of ARV)	77.60%	-	-	20.90%	63.50%
ATM use before HIV diagnosis	65.80%	-	-	27.50%	90.40%

The differences between the current study and the Kabarole could be attributed to different cultural and socio-economic factors. The current study was done in an urban metro in South Africa and the Kabarole study in a rural setting in Western Uganda. The researcher postulates that the lower rate of ATM usage could be due to better access to ART services, as is usually the case in an urban setting, and the fact that the Kabarole study was carried out in 2004 before the extensive ART roll-out programmes initiated by most governments.

It is important to note that a 2008 study by Peltzer and Mnqundaniso in the same setting as the current study (urban eThekwini), found a prevalence rate of 44.4% for simultaneous ARV and ATM use [5]. It could be surmised that even greater access to ARV through universal access programs since 2008 and the reduced costs of these treatments would have resulted in a reduced demand for ATM [6]. Furthermore, there was growing evidence of in-vitro studies which indicated that commonly used South African ATM interacted with ARV [15, 16, 17].

Reduced ATM use in the current study may also be attributed to efforts by health care professionals in communication the potential for Herb-Drug interactions (HDI) to patients during pre-counselling sessions. This study showed that 91% of the patients cited a knowledge of these potential HDI and that the health care provider had underscored the potential dangers of simultaneous ARV and ATM use to them during pre-counselling before initiation of ART. This is further reiterated by the vast differences in ATM use before HIV diagnosis, after HIV diagnosis and after initiation of ARV therapy (65.8%, 77.6% and 4.98% respectively).

The majority of the participants were relatively under-educated with only 6.7% having obtained a tertiary qualification and most (48.4%) only having a primary education. It was also found that the majority of the patients (64.4%) resided in an urban township. This unfortunately mirrors the epidemiology of HIV/AIDS in South Africa which largely affects the uneducated, females and persons of low income [4]. Multivariate analysis, obtained from combining all independent and controlling factors, for predicting ATM use showed that level of education ($p<0.041$), place of residence ($p=0.004$) and age ($p<0.001$) is associated with concomitant ARV and ATM use.

The ATM used were *African Potato*, *Sutherlandia*, *Stametta* and unspecified traditional mixtures (including *uBhejani*). This showed a similar trend to the 2004, Pretoria study by Malangu which highlighted commonly used ATM as African Potato, Coconut as well as unspecified crude herbal mixtures [7].

Concomitant uses of ATM are generally discouraged during ARV treatment and so there is a chance of under reporting of the use of ATM use by the participants. This is expected in subjective measurements due to the perceived possibility of punitive consequences from the health-care-provider by the participant if he/she admits to the use of ATM. This could also explain the finding that in all cases, patients who used ATM concurrently with ARV did not communicate their ATM use to their health care provider. This could also further indicate that patients are aware of the potential risks of concomitant use, but however, continue to do so in their attempt to self-medicate.

Throughout the duration of the study, there was a steady increase in CD4+ counts in the cohort taking ARV alone as well as the cohort that used ATM and ARV concomitantly. Similarly, there was on average, a decline in VL in both cohorts, albeit, at different rates.

The differences between the two VL means in the –ATM and +ATM groups are less than 0.05 and therefore are significant at 5% level for Time 0 (p=0.013), and marginally significant at Time 1 (p=0.048) and significant at Time 2 (p=0.040). However, the differences in the VL means are not significant at Time 3 (p=0.069). As a result of the conflicting p values across the time lines, it can be concluded that the effect of ATM on ARV is inconclusive.

Overall, statistical analysis found that in general, the effect of concomitant ARV and ATM use was not clinically significant. This was in concordance with a 2013 study by Gwaza *et al* on adult volunteers which showed that *hypoxis* is not associated with clinically significant changes in the pharmacokinetics of the ARV agent, LPV/r pharmacokinetics [18].

This study, however, differs from in-vitro studies by Mills *et al*., who in 2005 demonstrated the potential of *hypoxis* to increase metabolism of some drugs including ARV due to its significant effects on cytochrome P450 3A4 in-vitro metabolism [16]. Furthermore, a 2014 laboratory study also showed that H. hemerocallidea, E. purpurea, M. oleifera, T. officinale and L. frutescens inhibited major drug metabolising enzymes and had the potential to interact with ARV [17].

Limitations

The findings of this study may not be generalisable to PLWA in South Africa due to the fact that the study was concentrated in the eThekwini metro area. Several multi-centre studies in various centres (Urban, Per-urban, Rural) could shed more light on the actual prevalence rate of ATM use in PLWA as well as provide more reliable data on the effects of ATM on clinical outcomes of PLWA. Caution is therefore urged in generalising findings to other districts and provinces in the country.

Clinical co-variates such as presence of opportunistic infections, changes in weight (BMI) of the patients and occurrence of Adverse Drug Reactions (ADR) as a result of ATM during the study period could not easily be retrieved from patient charts since the data in the patient charts was often disordered or absent. This information could possibly have added value to the study by demonstrating whether or not concomitant use of ATM and ARV may have resulted in increased occurrence of opportunistic infections, deterioration in weight of the participants or increased the prevalence of Adverse Drug Reactions in the +ATM cohort.

Additionally, there is a need to explore and understand the knowledge, perceptions and attitudes of the health care workers and quantify their possible role, if any, in the continued reduction of prevalence rates of concurrent ATM and ARV use in PLWA.

The limitations of this study could form the basis of future studies on this subject.

Conclusion

This study was able to establish the prevalence of ATM use in PLWA as well as other factors which impact on ATM use. This study was also able to show that there were no significant effects on the CD4+

and inconclusive results on the VL of HIV infected patients in the eThekwini Metropolitan area who use ARV and ATM concurrently. This study was also able to establish the prevalence of ATM use in PLWA as well as other factors which impact on ATM use.

Recommendations

- The use of population pharmacokinetic approach in order to make the results more generalisable and to better establish a link between ARV plasma levels and concurrent ATM use on various patient characteristics.

- The development of a pharmacodynamic model of the data in order to correlate patient characteristics, ARV plasma levels, ATM plasma levels with CD4+ and VL levels.

- Continued vigilance by health care practitioners in counselling patients to not use ATM and ARV concomitantly.
- The full professionalisation of THP and the incorporation of THP in the management of HIV/AIDS.

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Competing Interests

The authors declare that they do not have any commercial interest and did not receive any source of support for the research that may constitute conflict of interest.

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CHAPTER 3: SYNTHESIS

3.1 SYNTHESIS

3.1.1 Phase 1

Overall, 77.6% of the patients in this study had used ATM after HIV diagnosis and 65.8% before diagnosis. These figures are in line with WHO [4] and South African and Worldwide estimates of around 70% and 80% respectively [6]. The majority of the patients surveyed (95.02%) did not use ATM concurrently with ARV. This was a welcome discovery as the effects of concurrent ARV and ATM use in humans are still largely uncertain despite the fact in-vitro studies indicate possible interactions between commonly used ATM and ARV [19].

4.98% patients reported concurrent use of ATM with ARV during the study period. The frequency of concurrent ATM use is comparable with similar studies in urban centres in Pretoria, South Africa [17] as well as Kano, Nigeria [13] which had 4.40% and 4.3% prevalence rate of concurrent ATM and ARV use respectively. This study differed vastly with a 2004 Uganda study by Langlois-Klassen *et al* [12], which reported a rate of 32.8% for concurrent ARV and ATM use. The comparison is shown in Table 1;

Table 3.1: Comparison of ATM usage in PLWA

Clinical trial (CT) characteristic	eThekwini Metro, South Africa (n=281)	eThekwini Metro, South Africa (n=222) [11]	Pretoria, South Africa (n=67) [17]	Kano, Northwest Nigeria (n=430) [13]	Kabarole District, Western Uganda (n=137) [12]
Period of study	Current study	2008	2004-2005	2014	2004
Setting	Urban	Urban	Urban	Urban	Rural
Concurrent ATM and ARV use	4.98%	44.4%	4.40%	4.30%	32.80%
ATM use after HIV diagnosis (before initiation of ARV)	77.60%	-	-	20.90%	63.50%
ATM use before HIV diagnosis	65.80%	-	-	27.50%	90.40%

The vast differences between the current study and the Kabarole study could be attributed to different cultural and socio-economic factors. The current study was done in an urban metro in South Africa and the Kabarole study in a rural setting in Western Uganda. The researcher postulates that the lower rate

of ATM usage in this study could be due to better access to ART services, as is usually the case in an urban setting, and perhaps the better knowledge of potential interactions between ARV and ATM by the patients surveyed. This however needs to be verified by further studies in this field.

It is important to note that a study done in 2008 by Peltzer and Mnqundaniso [11] in the same setting as the current study (urban eThekwini), found a prevalence rate of 44.4% for simultaneous ARV and ATM use. It could be surmised that increased access to ARV through universal access programs and the reduced costs of these treatments could have resulted in a reduced demand for ATM and account for the differences in ATM use between the 2008 and the current study [7]. Furthermore, it could be reasonably assumed that healthcare providers could have increased awareness and counselling to PLWA on the potential of dangers of concomitant ARV and ATM due to the fact that since 2005, there was growing body of evidence which suggested that commonly used South African ATM interacted with ARV in-vitro [22, 23].

This claim was validated by the results of this study which showed that 91% of the patients cited a knowledge of these potential HDI and that the health care provider had underscored the potential dangers of simultaneous ARV and ATM use to them during pre-counselling before initiation of ART. This is further reiterated by the vast differences in ATM before HIV diagnosis, after HIV diagnosis and after initiation of ARV therapy (65.8%, 77.6% and 4.98%, respectively).

There is a chance that the use of ATM use was under reported by the participants, as is expected in subjective measurements. This could be due to the belief of possible punitive consequences if the subject admits to the use of ATM whose concomitant use are largely discouraged in ARV treatment. The results must therefore be viewed with cautious optimism.

The majority of the participants were relatively under-educated with only 6.7% having obtained a tertiary qualification. Most of the participants (48.4%) only had a primary education. It was also found that the majority of the patients (64.4%) resided in an urban township. This unfortunately mirrors the epidemiology of HIV/AIDS in South Africa which largely affects the uneducated, females and persons of low income [4]. Multivariate analysis, obtained from combining all independent and controlling factors, for predicting ATM use showed that level of education level ($p<0.041$), place of residence ($p=0.004$) and age ($p<0.001$) is associated with concomitant ARV and ATM use.

The ATM used where *African Potato*, *Sutherlandia*, Stametta™ and unspecified traditional mixtures (including uBhejani). This showed a similar trend to the 2004, Pretoria study by Malangu [17] which highlighted commonly used ATM as African Potato, Coconut as well as unspecified crude herbal mixtures.

3.1.2 Phase 2

During the study period, there was a steady increase in CD4+ counts in the cohort taking ARV alone (-ATM) as well as the cohort that used ATM and ARV concomitantly (+ATM). Similarly, there was on average, a decline in VL in both cohorts, albeit, at different rates.

During the duration of the study, there was a steady increase in CD4+ counts in the cohort taking ARV alone as well as the cohort that used ATM and ARV concomitantly. Similarly, there was on average, a decline in VL in both cohorts, albeit, at different rates. The differences between the two VL means in the –ATM and +ATM groups are less than 0.05 and therefore not significant at 5% level for Time 0 (p=0.013), and marginally significant at Time 1 (p=0.048) and significant at Time 2 (p=0.040). However, the differences in the VL means are non-significant at Time 3 (p=0.069). As a result of the conflicting p values across the time lines, it can be concluded that the effect of ATM on ARV is inconclusive.

Statistical analysis using a standard t-test for independent means. found that any effect of concomitant ARV and ATM use was not clinically significant. This was in concordance with a 2013 study by Gwaza *et al* study on adult volunteers in Zimbabwe which showed that hypoxis is not associated with clinically significant changes in the pharmacokinetics of the ARV agent, LPV/r pharmacokinetics [24].

A study carried out in 2004 by Mudzviti *et al* [26], found that there was evidence to suggest that some ATM used in Zimbabwe may increase incidence of certain types of adverse events when used in combination with antiretroviral drugs. This study was not able to ascertain such a phenomenon due to various factors including the lack of complete information on patient charts.

3.2 CONCLUSION

This study showed that there was no significant effects of concurrent ATM and ARV use on the clinical outcomes indicative of HIV disease progression (or ARV failure). The prevalence rate of concurrent ARV and ATM use was 4.98%; with the common ATMs used being H. hemerocallidea, *uBhejani* and *Sutherlandia*. The majority of the participants (91%) were aware of the possible interactions between ATM and ARV if taken concurrently.

3.2.1 Limitations of the study

Characteristics such as presence of Opportunistic infections (OI) and serial measurements of patient weight had been included in the initial study protocol. However, the researcher was not able to report on them due to the fact that several of the patient files did not have complete patient information. The

data in the patient charts was often disordered or absent or in some instances did not make sense. For example, a medicine to treat common opportunistic infections (e.g. cotrimoxazole tablets or clotrimazole cream) may have been included in the prescription within the patient charts, but the diagnosis (OI) not specified. Although it may have been reasonable in the above example to conclude the presence of pneumonia and fungal infections respectively, it was not always definitive whether the medicine was for prophylaxis or for treatment. In order to eliminate biases due to the above assumptions and lack of conclusive information, the researcher decided to exclude this information during the data analysis.

Although a patient chart review was a convenient tool for the purposes of this study, several confounders could have been introduced. Possible confounders included the following;

- ATM users did not use the same ATM.
- The researcher was not assured by the participants that ATM use was consistent or intermittent.
- The researcher was not assured of complete adherence to ARV by the participants.

The study findings may not be generalisable to PLWA in the country in general due to the fact that the study was concentrated in four ART centres in the eThekwini metro (urban area). Several multi-centre studies in various centres (Urban, Per-urban, Rural) would result in data which is more generalisable to the South African population. Caution is therefore urged in generalising the findings of this study to other districts and provinces in the country.

The limitations of this study could form the basis of future studies on this subject.

3.3 RECOMMENDATIONS

The following recommendations are made based on the results of the study:

- Continued vigilance by health care practitioners in counselling patients not to use ATM and ARV concomitantly.
- The use of a pharmacometric model on healthy human subjects in order to precisely determine the HDI.
- The use of population pharmacokinetic approach in order to make the results more generalisable and to better establish a link between ARV plasma levels and concurrent ATM use on various patient characteristics.

- The development of a pharmacodynamic model of the data in order to correlate patient characteristics, ARV plasma levels, ATM plasma levels with CD4+ and VL levels.
- Lastly, there is a need to explore and understand the knowledge, perceptions and attitudes of the OMP and quantify the possible role of OMP, if any, in the reduction of prevalence rates of concurrent ATM and ARV use in PLWA.

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APPENDICES

Appendix 1: Phase 1 Data Management Tool

Date	_____	
Questionnaire Number	_____	
Associated Hospital Number	_____	
1. PATIENT CHARACTERISTICS		
Age	18-25	
	25-35	
	30-35	
	40-45	
	45-50	
	>50	
Gender	Male	
	Female	
Ethnic Group	Black	
	White	
	Indian	
	Coloured	
	Other	
Level of Education	No Education	
	Primary Education only	
	Secondary Education Only	
	Tertiary Education	
Place of residence	_____	
2. PHYSICAL EXAMINATION		
Weight	_____	
Height	_____	
ARV Regimen	1._____	
	2._____	
	3._____	
Date of Commencement of Current ARV Regimen	_____	
3. CONCOMITANT TRADITIONAL MEDICINES		
ATM use before HIV diagnos	YES	185
	NO	96
ATM use after HIV diagnosis (but not current)	YES	218
	NO	63
Do you currently take ARV and Tradition Medicines at the same time?	YES	14
	NO	267
How long have you been taking Traditional Medicines Concurrently?		_____
Is your Dr/Health Practitioner aware that you take TM	YES	
	NO	
Reason for Traditional Medicine Use	1._____	
	2._____	

	Name of TM	Route	Dosage	Date of Onset	Ongoing? YES/NO
1					
2					
3					
4					
5					

Are you aware of the potential interactions between TMs and ARV?	YES	
	No	

Appendix 2: Phase 2 Data Management Tool

Data Management Tool/Case Report Form - Phase 2

Date _____

Patient Number _____

Associated Hospital Number _____

HIV DIAGNOSIS

Date of First Diagnosis _____

Date of first ARV _____

HIV Stage (According to WHO Staging) _____

1. ART Regimen

1._____

2._____

3._____

Date of Commencement of Current Regimen _____

2. Previous ART Regimen/s

1._____

2._____

3._____

3. CONCOMITANT DISEASE/Adverse Event (Opportunistic infection)

	Disease	Date of Onset	Ongoing	Hospital Admission (Yes/No)
1				
2				
3				
4				
5				

4. CLINICAL TESTS

	Retrospective Data				Prospective Data					
	3months	2months	1month	**Baseline**	1 Month	2 Months	3 Months	4 Months	5 Months	6 Months
CD4+ Count										
Viral load										
Weight										

Appendix 3a: Study information sheet (English)

Date:

Dear Sir/Madam,

My name is Mncengeli Sibanda, a postgraduate student in the department of Pharmaceutical Sciences, UKZN Westville Campus.

You are being invited to consider participating in a study that involves research *on the effects of concurrent use of ARV and African Traditional medicines on the CD4, VL and weight of HIV infected patients in KZN.*

The aim and purpose of this research is to study the effects of African traditional medicines on Antiretroviral drug efficiency The study is expected to enrol 200 participants in the Ethekwini Metropolitan Area. It will involve me visiting the ARV Clinic looking at your file and prescription chart to determine the effects of traditional medicines on your HIV outcome. If necessary, I will discuss your treatment options with your doctor. The duration of your participation if you choose to enrol and remain in the study is expected to be approximately 6 months.

We hope that the study will create the awareness amongst HIV infected persons on the possible effects of using TMs together with ARV on their overall health.

This study has been ethically reviewed and approved by the UKZN Biomedical research Ethics Committee (BREC REF: BE 727/14).

In the event of any problems or concerns/questions you may contact the researcher at 0725877246 or the UKZN Biomedical Research Ethics Committee, contact details as follows:

BIOMEDICAL RESEARCH ETHICS ADMINISTRATION

Research Office, Westville Campus

Govan Mbeki Building

Private Bag X 54001

Durban 4000

KwaZulu-Natal, SOUTH AFRICA

Tel: 27 31 2604769 - Fax: 27 31 2604609

Email: BREC@ukzn.ac.za

Or contact my Supervisors;

Dr Panjasaram Naidoo (supervisor), Cell: 0839645429; email: naidoopj@ukzn.ac.za Manimbulu Nlooto (Co-supervisor), Cell: 0828450224; email: Nlooto@ukzn.ac.za

Participation in this research is completely voluntary and you may withdraw from participating in the study at any point. In the event of refusal/withdrawal of participation you will not incur penalty or loss of treatment or other benefit to which you are normally entitled.

Confidentiality is paramount in this study and to protect your identity, a unique study number will be assigned to you which will ensure privacy of your information as the results cannot be directly linked to you. Only the study number will be used as a reference in the database to protect your identity. The reporting on patients from this study will be done anonymously. Your name and identity numbers are not included on all questionnaires and data collection forms. All questionnaires and data extraction forms will be coded and no one else except us will have access to your information. Questionnaires and all other instruments used to collect information will be destroyed after five years by shredding after the study is complete. Equally information stored on computers will be protected by a password and will be deleted five years after the study is complete.

Information collected during and after the study will be stored in a locked cupboard for 5 years in the supervisor's office. Thereafter it will be destroyed by shredding.

Patients taking part in the study will not receive direct feedback on their CD4 levels unless it is indicative of non-compliance to ART or treatment failure in which case the responsible clinician will be contacted.

You will not personally incur any costs as a result of participation in the study. Participation is voluntary hence you will not receive any reimbursement for participation. There is no financial remuneration for participation to the study.

Appendix 3b: Study information Leaflet (Zulu)

"Isifundo sokuhlola kokusetshenziswa kwemithi yesintu ndawonye namaphilisi okuthithibalisaisifo se ngculazi (ARV) kubantu abaphetwe yisifosengculazi eKZN"

Mnumzane/Nkosikazi,

Ngingusokhemisi oyenzaizifundoze Masters enyuvesiyase UKZN. Ngiyenza ucwaningo mayelana kokusetshenziswa kwemithi yesintu ndawonye namaphilisi okuthithibalisaisifo se ngculazi.

Ngithanda ukumema ukuthi ubeyinenyeyalo ucwaningo. Ngicela ufunde imininingwanoyalo cwaningo. Uma unemibuzo, ukhululekile ukubuza nomanini, uzothola incazelo ngaphambi kokuthi ukhethe ukubayinxenye yalocwaningo nomaqha.

Locwaningo luzokwenziwa kubobonke abantu abagulayo abaphuza umshanguzowengculazi. Ngizobuka ifayela lakho nemithi obhalelwe yona ngudokotela ukubona ukuthingabe uhlangabeza nanazo izimpawu ezingalindele kanga ezingenziwa ukuphuza umshanguzo. Uma kunesidingo, ngizoxoxisana nodokotela ngemishanguzo yakho.

Imvumo yokwenza locwaningo ngiyithole enyuvesiyase UKZN esikhungwenisase MEDICAL SCH, sekomidi elingu nyazilonke ucwaningo olwenziwa ngabafundi, kanye nemvumo evelakumphathi omkhulu wesibhedlela saseUKZN. Igama lakho alizukubhwalwa ndawonakokonke okuqondenenawe kuzogcinwa kuyimfihlo.

Awuphoqelekile ukubayinxenye yalocwaningo. Uma uvumaukuba yinxenye, uvumelekile ukuyeka ukubayinenye yalocwaningo lungakapheli ngaphandle kokujeziswa. Uma uvuma ukubayinxenye yalocwaningo. Kuzodingeka ukuthi ubhale ephenile sivumelwano salo cwaningo imininingwane yakho enjengegama lakhonesibongo, beseuyasayina.

Ukuba yinxenye kwakho kulolocwaningo kuzoba yintokozo enkulu kithi. Uma ufuna ukucaciseleka nganoma ikuphi okuthinta ucwaningo, sicela ukhululeke ukubuza lowo ozobe exoxisana nawe / ekubuza imibuzo kumbe uthinthe;

BIOMEDICAL RESEARCH ETHICS ADMINISTRATION

Research Office, Westville Campus

Govan Mbeki Building

Private Bag X 54001

Durban

4000

KwaZulu-Natal, SOUTH AFRICA

Tel: 27 31 2604769 - Fax: 27 31 2604609

Email: BREC@ukzn.ac.za

Kumbe uthinte abakhokheli bami;

Dr Panjasaram Naidoo (supervisor), Cell: 0839645429; email: naidoopj@ukzn.ac.za Manimbulu Nlooto (Co-supervisor), Cell: 0828450224; email: Nlooto@ukzn.ac.za

Yimiozithobayo,

M. Sibanda, 0725877246

Appendix 4a: Informed Consent Form (English)

I _____ have been informed about the study entitled "AN INVESTIGATION INTO THE EFFECTS OF CONCURRENT USE OF ARV AND AFRICAN TRADITIONAL MEDICINES ON THE CD4, VL AND WEIGHT OF HIV POSITIVE PATIENTS IN KZN" by Mr. Mncengeli Sibanda.

I understand the purpose and procedures of the study.

I have been given an opportunity to answer questions about the study and have had answers to my satisfaction.

I declare that my participation in this study is entirely voluntary and that I may withdraw at any time without affecting any treatment or care that I would usually be entitled to.

I have been informed about any available compensation or medical treatment if injury occurs to me as a result of study-related procedures.

If I have any further questions/concerns or queries related to the study, I understand that I may contact the researcher on 0725877246.

If I have any questions or concerns about my rights as a study participant, or if I am concerned about an aspect of the study or the researchers then I may contact:

BIOMEDICAL RESEARCH ETHICS ADMINISTRATION

Research Office, Westville Campus

Govan Mbeki Building

Private Bag X 54001

Durban

4000

KwaZulu-Natal, SOUTH AFRICA

Tel: 27 31 2604769 - Fax: 27 31 2604609

Email: BREC@ukzn.ac.za

Or contact my Supervisors;

Dr Panjasaram Naidoo (supervisor), Cell: 0839645429; email: naidoopj@ukzn.ac.za Manimbulu Nlooto (Co-supervisor), Cell: 0828450224; email: Nlooto@ukzn.ac.za

_____ _____

Signature of Participant Date

_____ _____

Signature of Translator Date

Appendix 4b: Informed Consent Form (Zulu)

Isitatimende esimaqondana ngokuhlanganyela ohlolweni lokwelashwa kuPhrojekthi/Yocwaningo

Igamale Phrojekthi/loCwaningo/lohlolo;

"Isifundo sokuhlola kokusetshenziswa kwemithi yesintu ndawonye namaphilisi okuthithibalisa isifo se ngculazi (ARV) kubantu abaphetwe yisifosengculazi eKZN"

Ngilufundile ulwazi/ngizizwile izinhloso nezinjongo zocwaningo oluhlongoziwe futhi nganikezwa nethuba lokubuza imibuzo nganikezwa nesikhathi esanele sokuphinde gicabange.

Ngiyazi ukuthi loluphenyo lungani futhi ngiyavuma ukubawomunye abangenele loluphenyo. Imvume yami incikeko kulandelayo imiphume lange keize imuveze umnikazi. Imiphumela ingasetshenziswa nomaishicile lweukuze abasiza ngokunakekelwa kwabantu abalesifo sengculazi.

Uma ufuna ukucaciseleka nganoma ikuphi okuthinta ucwaningo, sicela ukhululeke ukubuza lowo ozobe exoxisana nawe / ekubuza imibuzo kumbe uthinthe;

BIOMEDICAL RESEARCH ETHICS ADMINISTRATION

Research Office, Westville Campus

Govan Mbeki Building

Private Bag X 54001

Durban

4000

KwaZulu-Natal, SOUTH AFRICA

Tel: 27 31 2604769 - Fax: 27 31 2604609

Email: BREC@ukzn.ac.za

Loba abakhokheli bami;

Dr Panjasaram Naidoo (supervisor), Cell: 0839645429; email: naidoopj@ukzn.ac.za Manimbulu Nlooto (Co-supervisor), Cell: 0828450224; email: Nlooto@ukzn.ac.za

Ngingathokoza kakhulu umaungasayina ifomu lokungivumela ukubangiqhubeke nophenyo. Ngiyabongakakhulu.

_____ _____

Igama (ngamagama amakhulu) Sayina

_____ _____

Indaeo Usuku

Appendix 5: Request for permission from DOH/CEO of Hospital

The Chief Executive Officer,

"X" Hospital

Dear Sir/Madam,

My name is Mncengeli Sibanda; I am an M Pharm student in the Discipline of Pharmaceutical Sciences, College of Health science, University of KwaZulu-Natal, (Westville Campus). I am required to carry out a dissertation in fulfilment of the requirements of my studies. The title of which is *"AN INVESTIGATION INTO THE EFFECTS OF CONCURRENT USE OF ARV AND AFRICAN TRADITIONAL MEDICINES ON THE CD4, VL AND WEIGHT OF HIV POSITIVE PATIENTS IN KZN"*

I kindly request permission to conduct the study at your hospital and request access to Out-patients and their records in the ARV clinic.

Attached, please find a copy of the protocol as well as SREC and MREC approval.

You may also contact my supervisors: Dr Panjasaram Naidoo (supervisor), Cell: 0839645429; email: naidoopj@ukzn.ac.za Manimbulu Nlooto (Co-supervisor), Cell: 0828450224; email: Nlooto@ukzn.ac.za, at UKZN, Discipline of Pharmaceutical Sciences, Westville Campus for more information.

I look forward to your positive response and hearing from you soon.

Yours Sincerely,

_____

Mncengeli Sibanda M. Pharm Student (Cell: 0725877246)

CC: Dr Panjasaram Naidoo, Supervisor (Cell: 0839645429)

Manimbulu Nlooto, Co-Supervisor (Cell: 0828450224)

Appendix 6: BREC approval letter

UNIVERSITY OF KWAZULU-NATAL
INYUVESI YAKWAZULU-NATALI

30 October 2014

Mr Mncengeli Sibanda
16 Cloudsview,
65 Phyllite Avenue,
Zwartkop, Ext 8
Centurion
0157
mncengelis@yahoo.com

PROTOCOL: An Investigation into the effects of concurrent use of ARVs and African traditional medicines on the CD4, Viral Load and weight of HIV positive patients in KwaZulu-Natal: Degree Purposes (Masters). BREC REF: BE272/14.

EXPEDITED APPLICATION

A sub-committee of the Biomedical Research Ethics Committee has considered and noted your application received on 04 June 2014.

The study was provisionally approved pending appropriate responses to queries raised. Your responses received on 23 October 2014 to queries raised on 08 October 2014 have been noted by a sub-committee of the Biomedical Research Ethics Committee. The conditions have now been met and the study is given full ethics approval.

This approval is valid for one year from **30 October 2014.** To ensure uninterrupted approval of this study beyond the approval expiry date, an application for recertification must be submitted to BREC on the appropriate BREC form 2-3 months before the expiry date.

Any amendments to this study, unless urgently required to ensure safety of participants, must be approved by BREC prior to implementation.

Your acceptance of this approval denotes your compliance with South African National Research Ethics Guidelines (2004), South African National Good Clinical Practice Guidelines (2006) (if applicable) and with UKZN BREC ethics requirements as contained in the UKZN BREC Terms of Reference and Standard Operating Procedures, all available at http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx.

BREC is registered with the South African National Health Research Ethics Council (REC-290408-009). BREC has US Office for Human Research Protections (OHRP) Federal-wide Assurance (FWA 678).

The sub-committee's decision will be **RATIFIED** by a full Committee at its meeting taking place on **09 December 2014.**

We wish you well with this study. We would appreciate receiving copies of all publications arising out of this study.

Yours sincerely

Professor D.R Wassenaar
Chair: Biomedical Research Ethics Committee

Appendix 7: Department of Health approval letter

health
Department:
Health
PROVINCE OF KWAZULU-NATAL

Health Research & Knowledge Management sub-component
10 – 103 Natalia Building, 330 Langalibalele Street
Private Bag x9051
Pietermaritzburg
3200
Tel.: 033 – 3953189
Fax.: 033 – 394 3782
Email.: hrkm@kznhealth.gov.za
www.kznhealth.gov.za

Reference : HRKM240/14
Enquiries : Mrs G Khumalo
Telephone : 033 – 395 3189

Dear Mr M Sibanda

Subject: Approval of a Research Proposal

1. The research proposal titled **'AN INVESTIGATION INTO THE EFFECTS OF CONCURRENT USE OF ARV AND AFRICAN TRADITIONAL MEDICINES ON THE CD4, VL AND WEIGHT OF HIV INFECTED PATIENTS IN KZN'** was reviewed by the KwaZulu-Natal Department of Health (KZN-DoH).

The proposal is hereby **approved** for research to be undertaken at Cator Manor clinic, King Edward VIII and RK Khan Hospitals.

2. You are requested to take note of the following:
   a. Make the necessary arrangement with the identified facility before commencing with your research project.
   b. Provide an interim progress report and final report (electronic and hard copies) when your research is complete.

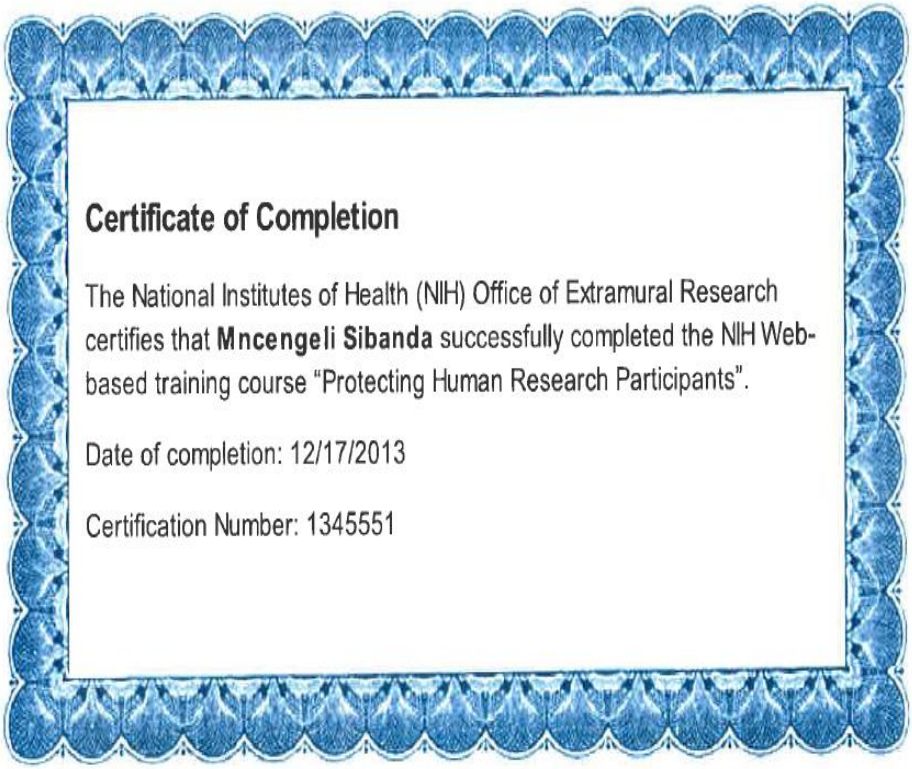
3. Your final report must be posted to **HEALTH RESEARCH AND KNOWLEDGE MANAGEMENT, 10-102, PRIVATE BAG X9051, PIETERMARITZBURG, 3200** and e-mail an electronic copy to hrkm@kznhealth.gov.za

For any additional information please contact Mrs G Khumalo on 033-395 3189.

Yours Sincerely

Dr. E Lutge
Chairperson, KwaZulu-Natal Health Research Committee
Date: 23/10/14

Appendix 8: Certificate in Ethics



Certificate of Completion

The National Institutes of Health (NIH) Office of Extramural Research certifies that **Mncengeli Sibanda** successfully completed the NIH Web-based training course "Protecting Human Research Participants".

Date of completion: 12/17/2013

Certification Number: 1345551

Appendix 9: Certificate in Good Clinical Practices

NIDA Clinical Trials Network

Certificate of Completion

is hereby granted to

Mncengeli Sibanda

to certify that you have successfully completed the six hour, required course on

Good Clinical Practices

Expires: 10 January, 2017

Tracee Williams, Training Coordinator
Clinical Coordinating Center

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