

**UNIVERSITY OF THE WESTERN CAPE**  
**Faculty of Community and Health Sciences**  
**RESEARCH MINI THESIS**

**PREVALENCE OF NON-AIDS DEFINING CONDITIONS AND THEIR  
ASSOCIATIONS WITH VIROLOGIC TREATMENT FAILURE AMONG ADULT  
PATIENTS ON ANTI-RETROVIRAL TREATMENT IN BOTSWANA**

A mini thesis written in partial fulfilment of the qualification of Master in Public Health in the School of Public Health of the University of the Western Cape.



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## **Declaration**

I declare that “PREVALENCE OF NON-AIDS DEFINING CONDITIONS AND THEIR ASSOCIATIONS WITH VIROLOGIC TREATMENT FAILURE AMONG ADULT PATIENTS ON ANTI-RETROVIRAL TREATMENT IN BOTSWANA” is my own work and that it has not been submitted for any degree or examination in any other university and that all the sources I have used or quoted have been indicated and acknowledged by complete references.

Dr. Patrick Maburu Dintle Masokwane

Signed



Date: 4 July 2016



## **Dedication**

This thesis is written in memory of two women who played a key role in my life, firstly my biological mother Mrs Annette Mosadidi Masokwane, and my mother-in-law, Ms Agnes Mmangaka Talane. The latter's passing on during my data collection period, gave me greatest impetus to always go on, no matter what the challenges are, something that the former always inscribed in me.



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To my wife, Mrs Neo Masokwane and my sons Ditso and Balogun, I would like to say that you really showed me what loving and caring is. You were the strongest link for me in my studies.

## List of abbreviations

3TC	Lamivudine
ALLU	Alluvia (Lopinavir/ Ritonavir)
ARV	Antiretroviral
CBV	Combivir
d4T	Stavudine
DALY	Disability Adjusted Life Year
FTC	Emtricitabine
HAART	Highly Active Anti-retroviral Therapy
HTN	Hypertension
IDCC	Infectious Diseases Care Clinic
NACA	National AIDS Coordinating Agency
NADC	Non-AIDS Defining Conditions
NCD	Non-Communicable Disease
NVP	Nevirapine
RAL	Raltegravir
RTV	Ritonavir
STEPS	WSTEPwise approach to Surveillance
TRU	Truvuda (Emtricitabine/Tenofovir)
UNAIDS	United Nations AIDS Programme
WHO	World Health Organisation

## ABSTRACT

**Background:** The recognition of HIV/AIDS as a chronic life-long condition globally in recent years has demanded a different perception and an alignment to its association with other chronic diseases. Both HIV and other chronic non-communicable diseases are significant causes of morbidity and mortality. Their combined DALY contributions for Botswana would be significant if research and strategies in controlling these conditions are not put in place. Natural aging and specific HIV-related accelerated aging of patients who are on antiretroviral treatment means that age-related diseases will adversely affect this population.

Princess Marina Hospital Infectious Diseases Care Clinic has been in operation since 2002. The clinic has initiated over 16 000 patients on anti-retroviral treatment (ART) since 2002. The current study estimated the prevalence of non-AIDS defining conditions (NADCs) in the attendees of the clinic in 2013. The majority of patients that attended the clinic had been on treatment for over three years with some patients more than ten years. These ART experienced patients were more likely to be susceptible to chronic non-communicable diseases, including non-AIDS defining conditions. The nomenclature used in classification of NADCs in the current study was appropriate for resource-limited settings; because the study setting offered HIV treatment under resources constraints.

**Aim:** The current study characterised non-AIDS defining conditions, and determined their associations with virologic treatment failure in a cohort of patients that were enrolled at Princess Marina Hospital antiretroviral clinic in Gaborone, Botswana.

**Methods:** A retrospective cross sectional study of records of patients who attended the Princess Marina Infectious Diseases Care Clinic in 2013. Stratified random sampling of a total of 228 patients' records was achieved from a total population of 5,781 records. Data was transcribed into a Microsoft Excel Spreadsheet and then exported to Epi-Info statistical software for analysis.

**Results:** Eighty (35%) cases of NADCs were reported/diagnosed in the study sample; with 27% (n=62) of the patients having at least one condition, 6.7% (n=17) two conditions, and 0.4% (n=1) three conditions. The top prevalent conditions were hypertension (n= 40), hyperlipidaemia (n=7)

and lipodystrophy (n=7). The prevalence of NADCs on the various categories of patients compared with the total sample population was as follows: active patients (prevalence ratio=0.70), transferred out patients (prevalence ratio = 1.24), patients who died (prevalence ratio=2.04) and patients who were lost to follow-up (prevalence ratio =2.86). The prevalence of NADCs was significantly associated with increasing age ( $p<0.001$ ); having social problems ( $p=0.028$ ); having been on treatment for over three years ( $p=0.007$ ); an outcome of death ( $p = 0.03$ ) and being lost to follow-up ( $p=0.007$ ). The study showed that being controlled on second line or salvage regimen ( $p=0.014$ ) and the presence of adherence problems in the past was associated with virologic failure ( $p=0.008$ ). There was no association of presence of NADCs to virologic failure.

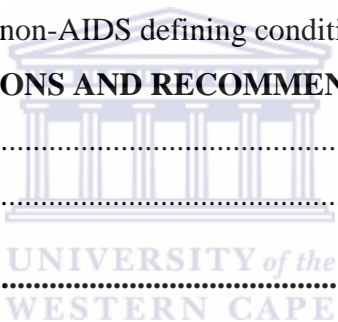
**Conclusions:** There was significant morbidity of non-AIDS defining conditions in the Princess Marina Infectious Diseases Care Clinic shown by a prevalence of NADCs in the clinic of 35% in 2013. The significant associations of the presence of NADCs and virologic failure with outcomes of death and loss to follow-up illustrate the adverse effects that NADCs are having, and calls for strategies to address multi-morbidities in HIV patients on antiretroviral treatment.

## TABLE OF CONTENTS

<b>Title page</b> .....	<b>i</b>
<b>Declaration</b> .....	<b>ii</b>
<b>Dedication</b> .....	<b>iii</b>
<b>Acknowledgements</b> .....	<b>iv</b>
<b>List of abbreviations</b> .....	<b>v</b>
<b>ABSTRACT</b> .....	<b>vi</b>
<b>1. CHAPTER 1 INTRODUCTION</b> .....	<b>1</b>
1.1 Background.....	1
1.2 HIV and non-communicable diseases.....	3
1.3 HIV virologic treatment failure.....	4
1.4 Treatment of HIV/AIDS in Botswana.....	5
1.5 Description of study setting.....	5
1.6 Problem statement.....	7
1.7 Outline of thesis.....	8
<b>2. CHAPTER 2 LITERATURE REVIEW</b> .....	<b>9</b>
2.1 Outline of Literature review.....	9
2.2 Definition of Non-AIDS defining conditions.....	9
2.3 Non-AIDS Defining Conditions s associated with HIV.....	10
2.4 Virologic treatment failure among HIV patients.....	13
2.5 Non-AIDS defining conditions and anti-retroviral treatment failure.....	15
2.6 Summary of literature review.....	16
<b>3. CHAPTER 3 METHODOLOGY</b> .....	<b>18</b>
3.1 Aims and objectives.....	18
3.2 Study design.....	18
3.3 Study population and sampling.....	18
3.4 Data collection.....	22
3.5 Data analysis.....	22
3.6 Pilot study.....	23
3.7 Validity and reliability.....	23



3.8	Generisability.....	24
3.9	Ethics considerations.....	24
<b>4.</b>	<b>CHAPTER 4 RESULTS.....</b>	<b>26</b>
4.1	Socio-demographic characteristics of respondents.....	26
4.2	Prevalence of non-AIDS defining conditions.....	32
4.3	Treatment of non-AIDS defining conditions.....	34
4.4	Associations of non-AIDS defining conditions.....	36
<b>5.</b>	<b>CHAPTER 5 DISCUSSION OF RESULTS.....</b>	<b>42</b>
5.1	Study design, limitations and impact on results.....	42
5.2	Characteristics of respondents.....	44
5.3	The prevalence of non-AIDS defining conditions.....	46
5.4	Associations of non-AIDS defining conditions.....	49
5.5	Treatment of HIV and non-AIDS defining conditions.....	50
<b>6.</b>	<b>CHAPTER 6 CONCLUSIONS AND RECOMMENDATIONS.....</b>	<b>52</b>
6.1	Conclusions.....	52
6.2	Recommendations.....	52
	<b>REFERENCES.....</b>	<b>54</b>



**LIST OF TABLES**

Table 4.1	Socio-demographic and clinical characteristics of respondents.....	29
Table 4.2	Frequencies of all the non-AIDS defining conditions.....	33
Table 4.3	Control of the prevalent non-AIDS defining conditions.....	35
Table 4.4	NADCs prevalence by socio-demographic and clinical characteristics....	38
Table 4.5	Virologic status by socio-demographic and clinical characteristics.....	41

**LIST OF FIGURES**

Figure 4.1	Sampling flow diagram.....	26
Figure 4.2	Age distribution of respondents.....	31

**APPENDICES**

APPENDIX 1 Data capture tool .....68  
APPENDIX 2 Princess Marina Hospital Ethics Clearance letter.....72  
APPENDIX 3 Health Research Development Council Ethics Clearance letter.....73  
APPENDIX 4 Sample Confidentiality pledge.....75



## CHAPTER 1. INTRODUCTION

### 1.1 Background

According to the World Health Organisation (WHO) (2013), there were 35 million people globally living with HIV in 2013. Sub-Saharan Africa bears the brunt of the pandemic with 70% of the global disease. The Botswana AIDS Impact Survey 2013 found the national HIV prevalence in the population aged 18 months to 64 years as 19% (Botswana Central Statistics Office, 2013). The peak prevalence was in the age group 35 to 39 years with 43.7%.

The Millennium Development Goals (MDGs) are a set of goals that were set by United Nations in September 2000 at the world summit of the United Nations (United Nations, 2000). There were eight (8) such goals in total - all targeted for the year 2015. These goals were packaged in a document adopted by the 149 member states that attended the United Nations General assembly in September 2000 called the “Millennium Declaration”. The document contained a statement of values, principles and objectives of the international agenda for the twenty-first century. MDG 6 goal primarily addressed a group of diseases that included HIV, TB and Malaria and mandated countries to combat malaria, HIV/AIDS and other infectious diseases. These goals were reviewed periodically by countries and regions to identify bottlenecks in their implementation. In MDG 6 the United Nations General Assembly pledged to combat HIV/AIDS, malaria, tuberculosis and other infectious diseases. Many countries used MDG 6 as a yardstick to evaluate how they were performing in relation to combating HIV/AIDS, malaria, tuberculosis and other infectious diseases.

The 2014 evaluation of the MDGs by UNAIDS have documented varying achievements in the different MDG goals in the world (United Nations, 2014). Southern Africa has seen some equivocal results with respect to MDG 6. Most of these results were negative. Gains made from running successful antiretroviral treatment (ART) programmes for HIV patients in countries such as Zimbabwe, Botswana and South Africa, have been met with losses in other areas. These losses included persisting new HIV infections especially in females of ages 15 to 24years (UNAIDS, 2014). Exacerbations of new infections are mainly due to failures of behavioural change initiatives with regard to reducing alcohol use and unsafe sexual practices such as unprotected

sexual contact, multiple and concurrent sexual relationships and intergenerational sexual relationships (Delva and Abdool Karim, 2014; Harrison *et al.*, 2015; United Nations, 2014). A high prevalence of HIV also leads to a large proportion of the general population with the chronic HIV disease and therefore carrier status of the infection. The high prevalence results in increased potential to spread the infection to the population that is not infected.

With the target period of the MDGs drawing to an end, a world agenda on HIV/AIDS has been set by UNAIDS called 'Agenda 2030 and post MDG' (UNAIDS, 2014). This agenda focus is on elimination of the disease by 2030. Whilst the failures of MDG6 particularly in the cluster of HIV/AIDS are evident, a more proactive scaled up approach to HIV/AIDS care has been designed in Agenda 2030. One of the programme goals is the 90-90-90 initiative where a commitment is made that by 2020: more than 90% of the HIV-infected population should know their HIV status, more than 90% of those eligible for treatment should be on regular treatment and that 90% of those on treatment should have virologic suppression. This commitment by UNAIDS and governments will need involvement of all stakeholders.

For a successful Agenda 2030, UNAIDS calls for governments and civil societies of all countries, to identify implementable solutions to eliminate HIV/AIDS by 2030. These should include policy, financing and dealing with issues such as stigma, discrimination, and making the most of civil society engagements (UNAIDS, 2015). Engagements would include making deliberate efforts to finance HIV treatment with antiretroviral drugs and implementing robust prevention strategies for all facets of society.

In light of the above, recognition is made that in 2013 the World Health Assembly (WHA) made a commitment to lobby for a concerted effort to control non-communicable diseases (NCDs) (WHO, 2013). Section 27 of the pact calls for Ministries of Health from the member countries to: "Note with concern the possible linkages between non-communicable diseases and some communicable diseases, such as HIV/AIDS" (WHO, 2013, p. 14). The plight of NCDs and the recognition of HIV/AIDS as a communicable disease with a chronic status, enhance the need to make connections in relation to services for these diseases (Mahungu Rodger & Johnson, 2009). The current study recognises HIV/AIDS as an important condition that the world has to combat.

The study also recognises NCDs as important causes of morbidity that must be addressed. Hence, an appreciation of the prevalence of non-AIDS defining conditions (NADCs) in the urban antiretroviral clinic, in Botswana is a good starting point for the country and a yardstick for the future.

The prevalence of NADCs in this centre presents an opportunity to find out the magnitude of these NCDs. The study achieved such baseline statistic, in which these NCDs are documented in a centre that was the first to commence antiretroviral treatment (ART) in the country. It was also vital to determine the relationships, commonalities and treatment problems associated with NADCs and HIV/AIDS. Reconciling these relationships and problems is an attempt at realising the recommendation of the WHA of 2013, of appreciating linkages between HIV and NCDs. This is important for management of both the NCDs and HIV/AIDS.

The main objectives of the study were; to determine the prevalence of NADCs in 2013 in Princess Marina IDCC, to describe clinical and socio-demographic characteristics of the cohort and describe problems of NADCs. In addition a secondary objective was to determine if there was any association of presence of NADCs and HIV virologic treatment failure. The study documentation of the NADCs presents a starting point as the country make strategies to combat NCDs in HIV infected patients.

## **1.2 HIV/AIDS and non-communicable diseases**

The plight of non-communicable diseases (NCDs) in HIV, including their prevalence, diagnosis and management, has been an area that has received a lot of attention in the literature. However, few studies were conducted in resource-poor settings (Hirschhorn *et al.*, 2012). NCDs increase in prevalence with advancing age. With control of HIV/AIDS by antiretroviral medicines, most HIV patients are aging and tend to succumb easily to non-communicable diseases. By and large most NCDs are not related to immune-suppression by HIV/AIDS. Some NCDs commonly occur in immune-competent HIV-infected patients and are referred to as non-AIDS defining conditions (NADCs) or non-AIDS defining events (NAEs). Classification of NADCs is not standard, and there are differing classifications for developed and developing countries, such as Botswana, which often provide ARV treatment under resource-poor settings. Hirschhorn *et al.* (2012) note

that in the studies in the developed countries classification tends to concentrate on cardiac, renal, hepatic and metabolic conditions, whilst studies from resource poor countries report psychological, malignancies and non-AIDS-related respiratory conditions as additional examples of NADCs. The current study utilises Hirschhorn *et al.* (2012)'s classification in recognition of Botswana as a provider of ARV treatment under resource-limited setting.

Wester *et al.* (2011) and Hirschhorn *et al.* (2012) noted that there are variations in nomenclature of non-AIDS defining conditions. NADCs refer to conditions that are associated with HIV, but are non-AIDS-related. AIDS-related diseases are associated and emanate from immune-suppression caused by AIDS. In this regard a cardiac condition like dilated cardiomyopathy, can occur in the classification scheme of AIDS in the context of very low CD4 count, indicating severe disease and advanced disease by WHO classification (Botswana Ministry of Health, 2012; WHO, 2013). Such a condition is AIDS-related. When the condition occurs in the context of an immune competent HIV-infected patient, it is clearly not related to AIDS. This distinction is important because most of NADCs and NCDs have existed before HIV was discovered. In the context of another aetiology of chronic diseases, notably cancer, it is clear that cervical cancer, non Hodgkin Lymphoma and Kaposi sarcoma are agreeably AIDS-related; and therefore not NADCs (Ruiz *et al.*, 2009). An important distinction is to highlight that NADCs have varying associations with HIV, as Ruiz *et al.* (2009) noted with some types of cancers. The authors observed varying degrees of associations of the different types of cancers and HIV infection. The current study described the prevalence of the NADCs with no emphasis on the degree of association to HIV infection.

### **1.3 HIV Virologic treatment failure**

High virologic failure among patients on HIV treatment can be an indicator of poor performance of an ART programme (WHO, 2013). It must be mentioned that as a lone indicator it can be a subjective measure and may be applied assuming that all other indices such compliance and socio-economic status, that may have bearing on performance of an ART service, are equal. In addition, recent evidence in relation to virologic treatment failure suggests that in resources where viral load is done as part of an HIV treatment programme, other subjective measures such as immunological (for example, CD4 count evaluations ) or clinical assessments may not add

value (Ford *et al.*, 2013). The authors note that when virologic measurements are in place they give better evaluation of how the clientele are doing relative to their care. Virologic status is a much more robust measure of failure or control of the patient. They argue that whilst CD4 count measurements by percentage may indicate good or poor immunologic status, the measure does not accurately indicate HIV treatment failure of the patient. Immunologic status may not reflect the failure or control status of patients because measurements such as CD4 counts have variations even amongst immune-competent patients (Williams *et al.*, 2006).

#### **1.4 Treatment of HIV/AIDS in Botswana**

Botswana commenced treatment of eligible HIV patients with antiretroviral medicines in 2002 (Farahani *et al.*, 2014). By November 2012 more than 200 000 patients had been enrolled in various facilities spanning the country. These treatments have been made available by government at no cost to the patient. In addition, Farahani *et al.* (2014) observed that the HIV treatment programmes realized good outcomes in reducing mortality and morbidity associated with HIV. They measured mortality rate drops from 12.6, 1.16 and 0.15 per 100 person years, at three months, at 2 years and during the latter seven years of the review, respectively. It can be concluded that a sizeable proportion of patients under treatment live normal and productive lives, and that not many people are dying from the condition as was the case before commencement of antiretroviral treatment (ART).

#### **1.5 Description of the Study Setting**

The Princess Marina Hospital Infectious Disease Care Clinic, which started operation in 2002, was the first public outpatient clinic to provide antiretroviral treatment in Botswana. The Infectious Diseases Care Clinics (IDCCs) as these ART clinics are commonly known in Botswana, were started as a government initiative to directly treat infectious diseases mainly HIV and tuberculosis. The clinic in Princess Marina was the first clinic in the government programme for treatment for HIV infection with anti-retroviral drugs. Hence it has the oldest HIV patient cohort. It also serves as the main referral centre for HIV patients whose treatment is complicated by many factors, such as co-morbidities and HIV viral resistance. The clinic has initiated more than 16 000 patients on ART since its inception.

In Princess Marina Hospital, HIV/AIDS care is provided in one outpatient site, the IDCC, with other outpatients' clinics, such as the diabetic clinic in the same hospital but at other sites. The ART clinics also provide some limited care to patients with non-communicable diseases. Majority of these patients rely on other outpatients' clinics such as diabetic and medical outpatients' clinics for care of NCDs. The facility is staffed by medical officers, nurses and HIV specialists including visiting specialists. There were eight (8) nurses, three (3) medical officers and five (5) HIV specialists that manned the facility at the time of the study. Most of the patients had been transferred out to other ART clinics in relevant localities and by end of December 2013, 5,758 patients were followed up at the clinic. These cohorts were patients with treatment problems or who were domiciled within the catchment area of the clinic. This translated to between 100 and 120 patients per day being followed up as outpatients. The Princess Marina Hospital IDCC also had a dedicated outpatient service for patients who had HIV treatment problems such as virologic failure, known as the HIV Failure Clinic. This service was run concurrently within the site to cater for patients with HIV treatment failure and had access to HIV specialists on regular basis.

With a limited capacity both from human and material resources, the IDCC's HIV Failure Clinic was managed by HIV specialists and medical officers in the absence of specialists. It is noteworthy that as this service is in what is a tertiary hospital in Botswana setting, the medical officers had access to telephonic consultations with the specialists. In addition there were Dermatology and Social Work clinics that consulted both ART and other patients.

Since its inception, the Princess Marina Hospital IDCC has fared relatively well in the management of HIV. The successes of the clinic include: having managed to transfer out patients to other IDCCs that the centre also inducted in management of HIV (this includes other public sector and private sector clinics) and, maintaining a resource base for HIV care in the country whilst still fulfilling primary care IDCC function. However, some challenges remain. A high staff turnover, limitations in terms of material resources and HIV treatment-related issues are among the challenges in the centre. The other challenges include: constraints of follow-up of defaulters and a reduction in staff especially HIV specialists. These problems are partially associated with the receding of donor funding that has led to the HIV treatment program being almost entirely government-funded.



## 1.6 Problem Statement

Non-AIDS defining conditions such as non-communicable diseases like diabetes and hypertension, and cancers are concerns that often have to be addressed in HIV treatment. The main reasons why these diseases increase in prevalence in the HIV-infected population is that patients on HIV treatment age and are susceptible to age related diseases such as NADCs. In addition this population is prone to other NCD-related risk factors such as smoking, alcohol use and obesity to name just a few. As the HIV pandemic matures there is need to identify and deal with more than one chronic disease, with the added burden of HIV or NCDs. Inevitably treating conditions that need, more often than not, life-long treatment is important. Their prevalence has not been documented sufficiently in Botswana both in the general population and in HIV-infected people. Whilst operational problems are appreciated, some clinical and epidemiological studies about conditions in the patients have not been routinely documented. Co-morbid conditions have not been defined well in HIV patients in the IDCC. This is despite being high on the Botswana Ministry of Health Research Agenda (Botswana Ministry of Health, 2010; Botswana National AIDS Coordinating Agency, 2013). Furthermore, their association to virologic treatment failure amongst HIV patients has not been investigated in Princess Marina Hospital adult ARV clinic. Chronic diseases like diabetes, hypertension and cancer need to be treated by several drugs that may affect the efficacy of HIV drugs through interactions. In addition, poly-pharmacy problems, and the possibility of toxicity may be increased contributing to adverse drug reactions (ADRs), which may in the end have a bearing on HIV virologic treatment failure. The first line treatment failure rate in Princess Marina Infectious Diseases Care Clinic for 2013 was 3% and the second line HIV virologic treatment failure rate was 6% for the same year (IDCC, 2013). It is very important to keep this statistic as low as possible. Therefore, any factors that may alter this rate should be investigated and appropriate measures taken to address it. Any correlations that can be established with the NADCs will be important in the IDCC tackling of HIV treatment failure.

Botswana ARV clinics, including the current site in Gaborone, have for over five (5) years been providing routine virologic load testing. It therefore became an added benefit to assess any association of NADCs prevalence with virologic treatment failure. It must be mentioned that definitive virologic treatment failure to an HIV clinician is an emergency which must be

contained and whose rate must be kept low in a programme. It was also a secondary objective that was important to assess in the context of the Botswana HIV treatment programme as it offers virologic level testing. The presence of this test in the Botswana HIV programme is vital. Rutherford *et al* (2014) asserts that virologic treatment failure is more accurately confirmed by viral load testing compared to other assessments such as clinical or immunological assessments. Viral load testing as a confirmation of antiretroviral treatment failure has been utilised in PMH IDCC. It is likely that the patients that were documented as having been in failure were indeed in failure as far as Rutherford *et al* (2014) perspective holds. Association of virologic antiretroviral with NADCs or the lack thereof would inform the management of NADCs in patients who are failing HIV treatment.

### **1.7 Outline of thesis**

In Chapter 2 the literature on non-AIDS defining conditions is visited with emphasis on studies done in sub-Saharan Africa. The review primarily focuses on HIV/AIDS, non-AIDS defining conditions and antiretroviral failure.

Chapter 3 lays the methodology of the study. The thesis portrays a clear aim to determine prevalence of NADCs in the Princess Marina Hospital adult anti-retroviral clinic. The design, data collection and analysis methods are presented for the study. This details a cross-sectional analytic study of patients' clinical outpatient records utilising a structured data capture tool.

In Chapter 4 the study results are presented. An analysis of the results is made to present them with statistical parameters to allow interpretations, inferences and conclusions about them.

Chapter 5 presents a brief discussion of the results making relevance to pertinent studies in the same topic.

In Chapter 6, the conclusion and the study recommendations are drawn from the research findings.

## CHAPTER 2. LITERATURE REVIEW

### 2.1 Outline of literature review

The literature was searched from the perspective of these two categories, HIV virologic treatment failure and non-AIDS defining conditions, as the main topics of interest. This was done by searching for literature on using “co morbidities in HIV”, “HIV virologic treatment failure”, “non-AIDS defining conditions” and “HIV associated non-AIDS” in the University of Western Cape databases, notably EBSCOhost Web, Springerlink, Sage and Scopus. Other databases including online free access such as Google scholar were also accessed. The studies were chosen based on relevance to the present study. Combinations of the search terms were used to further sieve the literature, initially identifying studies whose designs were similar to this study, to assist in how best it could be carried out. Secondly an attempt to find high level evidence studies such as systematic reviews, meta-analyses or randomised controlled trials in this field was used to identify studies that have been elaborate and comprehensive in non-AIDS defining conditions or non-communicable diseases in HIV.

The literature was also selected with a view to obtaining literature relevant to sub Saharan Africa of which Botswana is part. In addition, selective searches for HIV/ AIDS journals were also made to further redirect and adapt pertinent studies. There were no language restrictions in the search. Nevertheless studies that did not have an English translation version could not be used mainly due to a time constraint. In the review, grey literature was not used in this study.

### 2.2 Definition of Non-AIDS Defining Conditions

Non-AIDS defining conditions (NADCs) are conditions that occur in HIV-infected patients that are not related to the immune suppression caused by HIV. These typically include cardiovascular, renal, hepatic-related conditions and non-AIDS-related cancers (Wester *et al.*, 2011). Although, HIV/AIDS is an infectious disease it has recently been recognised as a chronic disease (Mahungu *et al.*, 2009; Deeks Lewin and Havlir, 2013; Hayward, 2014). Furthermore, since HIV treatment prolongs the lives of HIV-infected patients, and prevalence of most

conditions like hypertension, type 2 diabetes increases with age; prevalence of these NADCs conditions will more likely increase with time amongst the HIV-infected who are on treatment and living long.

Hirshhorn *et al.* (2012) classified NADCs into: non-AIDS defining malignancies, renal, cardiovascular, mental health and neuro-cognitive, osteoporosis and osteopenia and chronic respiratory disorders. It is vital to note that AIDS defining conditions are associated with low immunological and clinical status and were easily distinguishable as they occurred earlier on in the patient's treatment. This is important for AIDS-related HIV-induced nephropathy, cardiomyopathies such as dilated cardiomyopathies that often occur at the lowest range of CD4 count. Nevertheless pulmonary hypertension, essential hypertension and chronic renal failure that occur in the confines of an immune-competent patient are clearly NADCs (Barbaro, 2002; Cho and Kopp, 2004). As Hirshhorn *et al.* (2012) and Lambert *et al.* (2015) observed, acute exacerbations of chronic obstructive pulmonary disease have an association with HIV infection. It is important to observe that some of the AIDS defining conditions may prevail even after immune-competence, meaning that they should not be captured as NADC. It must however be highlighted that in the study the patients selection i.e. a group of patients on HIV treatment for some time, were more likely to be affected by NADC as opposed to AIDS-related diseases. This was because majority of patients were immune-competent and virologically suppressed on treatment.

### **2.3 Non-AIDS Defining conditions associated with HIV**

The suggested associations of NADCs and HIV-infected status are multi-factorial and include lifestyle factors, immune response due to continued replication of the virus, and antiretroviral therapy. Demographics also have been suggested to play a role, with the aging population of patients on HAART and the increase of NCDs with increasing age (Wester *et al.*, 2012). In addition, the inflammatory response posed by HIV-infected individuals has been suggested as the mechanism that gives a high risk of metabolic and vascular conditions (Hirshhorn *et al.*, 2012). Several studies have documented an increased prevalence of diabetes in patients on HIV treatment (Galli *et al.*, 2012; Gapaeu *et al.*, 2012). Hypertension and diabetes can occur as part of a syndrome called metabolic syndrome. This is a group of conditions which includes

hypertension, abnormal fat distribution around the waist and hip, abnormal lipid profile and abnormal sugar metabolism. Different organisations have definitive but related criteria. This abnormal fat distribution around the body is called lipodystrophy. It can imply either increased fat in some areas or reduced fat in other areas in the body or both (Briggs and Drabek, 2001; Mutimura *et al.*, 2007; Vol Blanco *et al.*, 2010).

Some cardiovascular disease has been shown to be significantly higher in HIV-infected patients. In addition they call for a more vigilant approach to HIV treatment and caution with medications (Rolls *et al.*, 2014). Myocardial infarction was observed to be increased in patients on HAART by the Data Collection on Adverse events of Anti-HIV Drugs (DAD) study (Justice *et al.*, 2008; Worm *et al.*, 2009). Hypertension has not been associated with a higher prevalence in HIV, with most population studies showing prevalence similar to the general population (Factor *et al.*, 2013; Munroe *et al.*, 2012; Arruda Júnior *et al.*, 2010).

Wester *et al.* (2012) documented NADCs in a study utilizing a clinical trial in Botswana and compared the NADCs in the cohort with those observed in Nashville, Tennessee in the United States of America. Do *et al.* (2010) also documented some psychosocial co-morbidity, such as depression, alcohol abuse and social problems that were associated with poor adherence and treatment failure.

Monroe *et al.* (2011) reported that most HIV clinicians are not comfortable treating medical conditions such as cardiovascular conditions but prefer to refer them to physicians. The study also revealed a correlation between poor diabetic control and hypertension to virologic treatment failure. This correlation may mean that on the converse, optimising diabetes and hypertension care may also improve HIV treatment. This study also identified a need to intensify adherence interventions to optimise care of co-morbidities. According to Viktil *et al.* (2007), poly-pharmacy has been defined as the “concurrent use of multiple drugs” (p.187). Furthermore some researchers have discriminated between minor (two drugs) and major (more than four drugs) poly-pharmacy. Its problems have been associated with the effect of taking multiple medications/treatments. This often refers to the treatments cumulative effect on each other and on the conditions for which they are being taken (McCleod and Makay, 2008). Therefore the

medications have to be prescribed taking consideration of the others that are taken for the other diseases. Taking note of all these factors, an integrated model for the coordination of care of these patients with multiple morbidities may be warranted. Janssens *et al.* (2007) recommend one such a model of integrated clinics in Thailand, and detail its benefits which include convenience and cost benefits. Such benefits were also observed by Rolls *et al.* (2014) in London where the benefits of an HIV co-morbidity clinic were assessed.

From having to manage more than one lifelong disease that needs several treatment modalities, it remains clear that, management of co-morbid NCDs such as hypertension and diabetes with HIV is a challenge that will need to be faced both from a clinical and policy perspective. Gineau and Hallen (2012) advocated for increased research into the association of NCDs with HIV infection. The authors also highlight how lessons learnt in HIV management may be of vital importance in NCD management. Management of HIV medicines compliance which is often done by pill counting of the actual tablets that the patient has remaining, may be one of the borrowed principles that can be used to check compliance to hypertension medicines for example. In addition if compliance to diabetes, hypertension or any other condition medication can be stressed like compliance to anti-retroviral treatment, these conditions may benefit from such emphasis. This would be important since non-compliance to such medication can lead to equally dangerous results such as stroke or myocardial infarction. Other areas such as healthy diet, avoidance of alcohol and tobacco use and the importance of exercise can be important benefits that are cross cutting and can benefit the HIV/ AIDS and the other conditions. Such integrated clinics could yield good results in areas of commonalities.

Most of the literature on non-AIDS defining conditions is in resource rich settings and a majority of these studies have predominantly been on cardiovascular conditions (Blanco *et al.*, 2010; Glenby, 2005). Some prevalence studies have been done on specific conditions such as hypertension and diabetes in HIV positive patients (Dusara *et al.*, 2009; Hatsu *et al.*, 2009). In Botswana a study by Wester *et al.* (2012) compared the incidence of NADCs in a Gaborone setting to an urban setting in Nashville Tennessee in America. The most common conditions were cardiovascular conditions. In addition the researchers found a comparatively similar incidence of NAEs in the two settings, but Botswana rates were higher on standardising for

population differences. That study acknowledged the problem of NADCs and recommended planning, monitoring, diagnosis and treatment of NADCs. In the review the literature relating to Botswana was limited in these conditions. Save the study by Wester *et al.* (2012), two other studies involved estimation of prevalence of hypertension and diabetes respectively in cohorts that were going to be initiated on HAART (Dusara *et al.*, 2009; Hatsu *et al.*, 2009). These studies were conducted as part of a clinical trial establishing the safety and efficacy of antiretroviral treatments in Botswana. Hypertension was estimated at 18.5% by Dusara *et al.* (2009) in an HIV positive cohort in Botswana. Diabetes mellitus was estimated at 4.6% in an HIV-infected cohort, compared to 7.2% in the general population by Hatsu *et al.* (2009).

The Veterans Aging Cohort Study (VACS) and the DAD studies were the largest prospective multicentre studies that reported important associations of HIV including on prevalence of NADCs (Justice *et al.*, 2008; Baker *et al.*, 2009; Worm *et al.*, 2009; Nurutdinova, 2012; Petoumenos *et al.*, 2012). Such prospective studies meant that the patients were followed up in time and the conditions occurrences were observed and documented. In most of the studies the results showed significant prevalence of NCDs in patients who were on HIV treatment. Whilst the notion of NADCs or non-AIDS defining event (NADE) was evident in the literature, standardization of terminology has not been achieved. For example, the two main documents in the current review notably Wester *et al.* (2011) and Hirshhorn *et al.* (2012) classify them differently. Some of the literature was on mortalities associated with NADCs. It must be pointed out that mortality of non-AIDS defining conditions may surpass that of AIDS-related conditions as was shown in one prospective cohort study (Masia *et al.*, 2013). The study also showed that HAART was protective against some NAEs notably psychiatric and renal diseases. Therefore NADCs are important to document and find any correlations or associations relative to HIV/AIDS.

#### **2.4 Virologic Treatment Failure among HIV patients**

According to WHO Guidelines on HIV treatment (2013), HIV virologic failure is defined as “plasma viral load above 1000 copies/ml based on two consecutive viral load measurements after three months, with adherence support”. This means that virologic failure is arrived at when two readings of viral load are persistently higher than 1000 copies per millilitre despite confirmed

adherence to medication. The definition of virologic failure as opposed to immunological or clinical failure needs reference viral load measures. This is opposed to CD4 count or clinical progression of HIV disease respectively in immunological and clinical failure. These are evidenced by symptomatic progression of the disease or by a deterioration of immunologic measures such as CD4 count. Virologic failure means that the HIV viral infection is not suppressed by treatment as it ought and often means the disease may progress. Rutherford *et al.* (2014) rationalise, after a systematic review of performance of WHO 2010 guidelines of immunologic and clinical guidelines that virologic measurements through viral load testing is a more reliable indicator of treatment failure. They concluded that virologic failure is best predicted by viral load testing as other modalities (such as immunologic assessments) do not predict it sufficiently.

Some of associations of HIV treatment failure have been documented clearly in several studies; with majority of the studies being case control type studies (Datay *et al.*, 2010; Merlin *et al.*, 2010; Sarmiento-Castro, 2011; Krantz *et al.*, 2011). Some prospective studies such as one by Montfort *et al.* (1998) all consistently pointed to adherence to antiretroviral treatment as the main determinant of HIV treatment failure. In addition the study reported that some specific HIV treatment regimen were more associated with failure. It is worth noting that some NADCs are associated with HIV treatment failure as detailed by Merlin *et al.* (2013), where depression and other mood disorders, were shown to be associated with HIV treatment failure

Studies that are of the same design as the current study include Sato and Okinawa (2013) who showed poly-pharmacy as a major deterrent of compliance. One qualitative study reiterated that multiple morbidity in HIV cause distress and may sometimes cause problems of adherence (Monroe *et al.*, 2014). In one study Krantz *et al.* (2011) showed the presence of nevirapine in the initial regimen, treatment interruptions and low CD4 count at baseline as factors associated with virologic treatment failure in a case control study. Race and the presence of depressive symptoms were documented factors associated with failure by McFall *et al.* (2013).



As a collective for virologic treatment failure, Sarmiento-Castro *et al.* (2011), summarise the factors associated with HIV virologic treatment failure and classify the factors as those relating to: the patient, the virus, and the treatment. Patient-related risk factors include sex, baseline CD4 count, HIV staging at initiation whilst virus associated risk factors include resistant mutations. Treatment factors include efficacious medications, dosing, adverse drug reactions, and time to drug switch.

It was reported, in most of the reviewed studies that different factors relating to failure had been observed. However, one consistently significant factor is non-adherence to medications (Sarmiento-Castro *et al.*, 2011; Merlin *et al.*, 2012). Pain, mood disorder and substance abuse were related with poor adherence in a study done by Merlin *et al.* (2012). Such psychological factors were observed by Do *et al.* (2010) in a study in Botswana. Therefore non-adherence seems to be the single most important factor that leads to virologic failure. This was evidenced by Ehlers and Tshisuyi (2015) in a recent cross sectional study in rural Botswana.

## **2.5 Non-AIDS Defining Conditions and Anti-Retroviral Treatment Failure**

Co-morbidities have been established as a major reason necessitating drug switch. In a cross sectional study, performed in Tanzania Jima *et al.* (2007) documented that about 25% of drug switches that are being made are due to co-morbidities. Antiretroviral drugs have toxicities that can exacerbate chronic conditions.

The systemic review of Hirschhorn *et al.* (2012) identifies some NCDs that have implications on anti-retroviral treatment. The authors note the tenfold risk of osteoporosis in HIV positive patients compared to age matched controls. Tenofovir is also associated with such osteopenia and osteoporosis. It is also worth noting that the systematic review document has revealed a slightly high prevalence rate of COPD in some studies. The association of mental illness, notably depression with adherence and anti-retroviral failure is corroborated by Hirshhorn *et al.* (2012) in agreement with studies elsewhere (Do *et al.*, 2010).

Non-AIDS defining cardiovascular conditions such as myocardial infarction have been associated with an atherogenic blood profile due to HIV infection (Ibouko Idoku and Ani, 2013).

The DAD study showed a significantly higher incidence of myocardial infarction in HIV patients compared to the general population (Worm *et al.*, 2009). Some anti-retroviral treatments are contraindicated in dysrhythmias so it is very important when treating these patients. HIV associated nephropathy is a common glomerulonephritis-type kidney disease that is often seen in HIV patients (Kagee, 2010). In addition some medications are nephrotoxic such as tenofovir. Hepatitis is often seen in the background of Hepatitis C or B infections as co-morbidities or can be seen on the background of treatment toxicity. Some non-AIDS malignancies such as Hodgkin disease and anal cancer have also been documented in HIV patients (Hirshhorn *et al.*, 2012; Ruiz, 2009).

Taking NADCs, HIV/AIDS and antiretroviral failure in context of the literature that was accessed, the following are worth noting. NADCs have been documented in several studies internationally and in Botswana. Their classification has not been standardised. In addition some NADCs such as cardiovascular conditions have been studied extensively in some countries, especially developed countries, whilst limited research has been done in resources limited settings. Treatment of NADCs is an important consideration in the management of HIV and vice versa. This was shown in the literature in form of: documented warrant of HIV treatment regimen change due to NADC, treatment toxicities exacerbating NADCs and drug-drug interactions. HIV treatment failure was shown to be mainly multi-factorial, with adherence to HIV treatment as the main problem across most of the studies. Some NADCs were shown to be associated more with antiretroviral failure.

## **2.6 Summary of literature review**

As a broad agenda is set internationally for recognition of HIV/AIDS as a chronic disease, it became clear in this review that there is extensive literature on HIV and non-communicable diseases. Firstly, in Botswana prevalence studies have been on diseases such as diabetes and hypertension, each individually studied. Some studies were on HIV patients and others on the general population. Extensive international studies such as DAD study and VACS had given a redirection in the need for policy change. The studies have given impetus to World Health Organisation to recommend changes in guidelines of HIV treatment. In view to low income and

middle income countries settings, the literature showed several higher level evidence studies, including a systematic review and prospective cohort studies with various outcomes. There is a general observation in the studies that NCDs are a problem that must be addressed in the HIV-infected population.



## CHAPTER 3. METHODOLOGY

### 3.1 Aims and Objectives

The aims of this study were to determine the prevalence of non-AIDS defining conditions and their associations with virologic treatment failure in a cohort of HIV patients that were enrolled at the Princess Marina Infectious Diseases Care Clinic in 2013.

The objectives of the study were to:

1. determine the prevalence of NADCs;
2. describe clinical and socio-demographic characteristics associated with the NADCs;
3. describe treatment problems including drug interactions, adverse drug reactions and any other problem such as drug alterations due to NADCs treatment; and
4. determine associations between prevalence of NADCs and virologic treatment failure.

### 3.2 Study Design

The study design was a retrospective, analytical cross-sectional design. This design was chosen because the aim of the study was to provide a baseline statistic. In addition the records were available in the clinic and could be easily accessed. Therefore there was a source of data that could be accessed easily. Other designs such as prospective studies would take a much longer time frame and require more resources. These were not feasible as this study had a time constraint. The study involved accessing a sample of records of patients who had been seen in Princess Marina Hospital (Gaborone) in the year 2013 and establish a period prevalence of NADCs.

### 3.3 Study Population and Sampling

The arrangement of the filing of the Princess Marina Infectious Diseases Care Clinic was seen and it became clear that there is an organised filing system utilizing three personalised identifiers. However, it became clear that the electronic files and the actual personal files needed reconciliation. There was evidence that quality initiatives on the filing were being taken on an ongoing basis. A records file audit that reconciled all files had been carried out in December 2014. This audit had reconciled both the electronic and the manual files. According to the audit

that was carried in 2014, there were 5,578 patients who were regularly followed up in the clinic at the end of December 2013. This was included 1,956 males and 3,922 females. In addition the site produced reports and maintained regular registers including those of all transfer outs, transfer-ins, deaths, lost to follow ups and active patients. There were 31 deaths, 129 transfers to other clinics and 43 patients declared lost to follow-up from the group that attended the IDCC in 2013. Therefore the total population under study was 5,781 patients. During the pilot the data assistants were introduced to the facility staff. The clinic was toured and all areas that kept files were accessed. The study team was familiarized with the storage and retrieval of files from their locations. These included observations and practical retrieval of files from their locations. All registers and statistics were made available to the team.

### **3.3.1 Case Definition**

For this study, non-AIDS defining conditions (NADCs) are defined as conditions that occur in HIV-infected patients that are not related to the immune suppression caused by HIV. Therefore all non-communicable diseases were eligible except if they are documented as AIDS defining.

The following classification was used, which was based on the study by Hirschhorn *et al.* (2012):

#### **1. Non-AIDS-related Malignancies:**

All malignancies were recorded as cases except HIV/ AIDS associated below

#### **2. Cardiovascular diseases**

All chronic cardiovascular conditions that are not AIDS associated were regarded as cases,

#### **3. Chronic kidney diseases**

All chronic kidney diseases that occurred in the confines of immune-competence were recorded

4. Hepatic conditions were all recorded except conditions of an infective nature such as hepatitis related to viral hepatitis.

#### **5. Mental health and neuro-cognitive disorder**

All psychological and mental health conditions

#### **6. Non communicable chronic respiratory diseases**

All chronic non communicable respiratory conditions were recorded

7. Osteoporosis, osteoarthritis and osteopenia
8. Other chronic diseases- This case definition allowed for any chronic condition that had not been known to be associated with HIV, to be recorded. This was done such that cases that are clearly not-AIDS (immune suppression) associated conditions could be recorded. This was done knowing the current weakness of classifications. In the end it allowed an inclusion of cases that are definitely not AIDS-related but would not be exclusive to Hirschhorn *et al.* (2012) classification and thus enabled recording of such cases.

### **Case Exclusions Criteria**

The following exclusions in the cases were made:

1. Non Hodgkin lymphoma, cervical cancer and Kaposi sarcoma were excluded and treated as AIDS-related
2. AIDS-related heart diseases such as stage 3 and 4 conditions e.g. dilated cardiomyopathy were excluded
3. AIDS-related neuro-cognitive impairment such as known stage 3 and 4 conditions formerly known as ADC (Aids dementia complex) were excluded
4. Chronic Infectious diseases such as viral hepatitis were excluded

It is reiterated that infectious diseases were not included in this study as; that is, those that are related to HIV immune-suppression. Therefore, hepatitis due to infective causes was not included in this study. As stated earlier, hepatitis or herpetic conditions, to name a few, can and may be defined as chronic diseases. Hepatitis B related disease can be diagnosed in childhood or adulthood and maintain a chronic phase that is a diseased state without any sequelae, hence a chronic disease. These were excluded for the study because they are infectious diseases.

### **3.3.2 Eligible study population**

The population under study was patients shown in medical records, who had attended Princess Marina Infectious Diseases Care Clinic in 2013 beginning on 01 January to 31 December 2013. Another inclusion criteria is that the patients whose records were included should have been aged

18 years and above in 2013. In the event that the record had not been in the age bracket of 18 and above, this record was excluded. Records of both male and females were included.

### ***Exclusion criteria***

The following exclusion criteria were applied on records: Data collected was going to be transcribed, so any record that showed destruction by wear and tear was judged ineligible, therefore excluded.

### **3.3.3 Sampling**

The total study population of 5,781 was divided into four strata of 5,578 active patients, 129 patients transferred out in 2013, 31 patients who had died in 2013 and 43 patients lost to follow-up. To maintain a power of 80% and 95% confidence intervals, the sample size required was calculated as 218 using Epi Info. This utilised a prevalence of NCDs of the general population by DALY of 18% (WHO, 2010). This was used because the prevalence of NADCs was not known in the population of interest it was decided that oversampling of the whole population should be done to take a population size of 300. This would compensate for an unknown prevalence and anticipated non-response. It came out clearly that the deaths, transfer outs and the lost to follow-ups were a small proportion of the total population. It was then resolved that non-proportionate sampling should be employed in the smaller strata. This would give a more reliable representation of the outcome (Bruce, Pope and Stanistreet, 2008; Rothman and Greenland, 1998), notably NADCs. At the end it was 15 files from the deaths, the lost to follow-up group each, and 60 files from the transferred group that were sampled, using a table of random numbers, generated against the non-name record identifiers.

The 210 records in the active files were sampled using systematic random sampling through the patient's attendance registers that are completed by doctors on daily basis. There were 678 such pages varying from 6 to 40 attendances. Using random numbers 678 numbers pages were sampled and three nth attendees were selected leading to 5<sup>th</sup>, 9<sup>th</sup> and the 31<sup>st</sup> attendees being randomly selected. This sampling methodology was the only feasible one, since there was no uniform sampling frame. All the active patients' files were kept with the more those 16000 files of patients that were ever started on treatment in the facility.

### 3.4 Data Collection

The study used the annexed data collection tool. The annexed tool (Appendix 1) was the third and final version that was utilized after the pilot period. The files that were sampled were isolated and data extracted in a more presentable way. The data were expressed in the form of a spreadsheet using Microsoft excel, and were then cleaned using Microsoft Excel for typographical, duplicates and any ambiguous entries.

The variables that were transcribed were divided four-fold: i) demographics including, location of living, gender, psychosocial issues and year of commencement of treatment ii) NADCs presence and treatment of NADCs iii) HIV treatment including treatment regimen, previous treatment switches and iv) virologic and immunological status including virologic control and CD4 count.

### 3.5 Data Analysis

Microsoft Excel was used to depict descriptive statistics, including frequencies and graphs. The main conditions which were measured were NADCs as detailed in the case definition. Virologic treatment failure was assessed as an *a priori* association along with other clinical and socio demographics. Furthermore, the data were imported into an Epi Info (Version 7.1.4.0) project file for analysing further associations including relationships between age and NADC presence. Chi-square tests were used to compare categorical variables. The significance level chosen was 95% confidence level. This was because the same significance level was used in the sample selection.

For multivariate analysis, logistic regression was used to determine the independent socio-demographic and clinical characteristics for the prevalence of virologic treatment failure using parameters that had a p-value of  $<0.25$  on univariate analysis. Only presence of NADC was brought into the multivariate model with a p-value greater than 0.25 with the value of 0.26. The main rationale was that it was the main exposure of interest with relation to the study objective and the p-value was not far above cut off value.



### **3.6 Pilot Study**

The study was piloted at the site from 16 February 2015 to 18 February 2015. The data capture tool was piloted by having two doctors who were attending doctors at the clinic complete it based on patient records. The tool was used for the records of patients who attended for the days of 16<sup>th</sup> to 18<sup>th</sup> February 2014. The following factors came out as potential measurement errors. Demographics such as date of commencement of treatment, in particular the months were not consistent. It was decided that the year of commencement which became uniform should be used. Other variables notably employment status, alcohol use and smoking history were consistently not available and were taken off the tool. There was a need to group the social problems together and have them as categories.

On putting the question prompts to clarify the required variable the inter-user reliability scored at an average of 96% of all the variables scored. The intra-user consistency of the tool stood at 100% for ten files used by two doctors. In total there were three versions of the tool that led to the final tool as seen in Appendix 1.

The pilot period allowed the data assistants access to the records room and also to plan for how the records would be used and filed to allow continuity of care. The study rooms, liaison nurse for the study and other logistics for the study were all arranged during the pilot period.

### **3.7 Validity and Reliability**

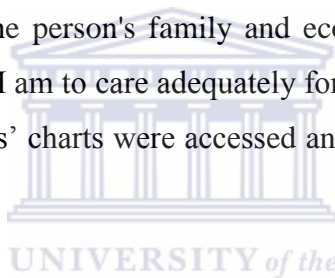
Validity is a measure of the accuracy of a test or instrument (Bruce, Pope and Stanistreet, 2009). Therefore the data capture tool ability to produce accurate results as detected from the records was important. This was fulfilled by piloting of the instrument and was achieved with an inter user agreement of 96%, i.e. taking cognizance of the variables that were scored by three groups of doctors. The kappa value for all the variables that were captured on the final version of the tool was 0.95, indicating a relatively robust tool. Reliability was assured by repeating transcription by the same doctors several hours after they had completed the questionnaires.

### **3.8 Generalisability**

The findings in this study were extrapolated to the Princess Marina Infectious Diseases Care Clinic for 2013 and not any other population. Whilst stratified random sampling was used using different sampling frame and oversampling, an argument is made that the population was a homogenous grouping with one common denominator of attendance of the IDCC in 2013. Nevertheless strata specific prevalence and analysis were done that were generalisable to the strata.

### **3.9 Ethics Considerations**

The Hippocratic Oath that medical doctors subscribe to, mentions several tenets one of which states, “I will remember that I do not treat a fever chart, a cancerous growth, but a sick human being, whose illness may affect the person's family and economic stability. My responsibility includes these related problems, if I am to care adequately for the sick” (Tyson, 2014). Therefore it was important that as the patients’ charts were accessed and means established not to interfere with their clinical care.

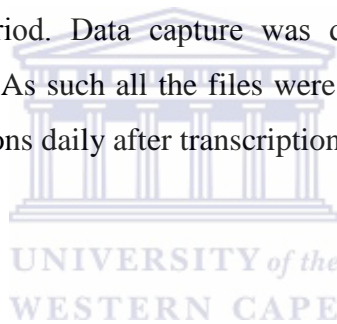


In agreement with above, Helsinki declaration of the World Medical Assembly articulates why the health, well-being and rights of patients, who are involved in medical research, must be protected. The physician's knowledge and research must also take account of these rights. The study was firstly granted approval by the University of the Western Cape Senate Research Committee. Thence it was granted permission by the Princess Marina Hospital Ethics Committee and the Health Research and Development Council (HRDC) in the Ministry of Health of Botswana. The HRDC advised that due to the time constraints, and as a study for academic reasons only, which does not undergo more rigorous ethical requirements, the application should enclose a request of waive of consent from patients whose files were sampled.

The ethical clearance by the Princess Marina Hospital Ethics Committee was given on 4<sup>th</sup> February 2015. This was followed by the Ministry of Health of Botswana HRDC on 16<sup>th</sup> February 2015. As the national requirement all human health research a pilot could be carried

only when these two documents were available, therefore necessitating a shorter time period for pilot.

It is recognised that this study did not involve human subjects directly although it involved human subjects' data. The health research assistants were knowledgeable in issues of confidentiality as they were employed in a similar clinic elsewhere. They were sworn to confidentiality and a sample of the confidentiality pledge is attached in Appendix 4. Not anywhere were the names, confidential information used in accordance with the principles of respect, confidentiality and non-maleficence. Only one non-name system identifier was used so that there could be a way to track a record in the case of clarifications in the file when requested. As a study that aims to inform the health system, it clearly has beneficence to the use of this hospital archive, to use to inform policy and practise. In the sampled files, three of the files had to be seen during the study period. Data capture was done a day prior to the patients' consultation and the file returned. As such all the files were accessible when requested. All the files were filed back to their positions daily after transcription.



## CHAPTER 4. RESULTS

### 4.1 Socio demographic and clinical characteristics of respondents

There was a total eligible population of 5781 patients that attended the clinic in 2013, as shown in the sampling flow diagram in Figure 4.1. The categories of patients were: 5,578 patients who were active on site, 129 who were transferred out during the year, 31 patients who died and 43 patients who were lost to follow-up. With an intended oversampling of 300, a total of 228 records of those sampled were accessed with 150 from active patients, 14 from patients who had died 8 from patients who were lost to follow-up and 55 from patients who were transferred to other ARV sites in 2013. There was a total “non-response” of 24% overall which was seen as a result of unavailability of the records at their location. Only one record showed ineligibility as the reason for exclusion.

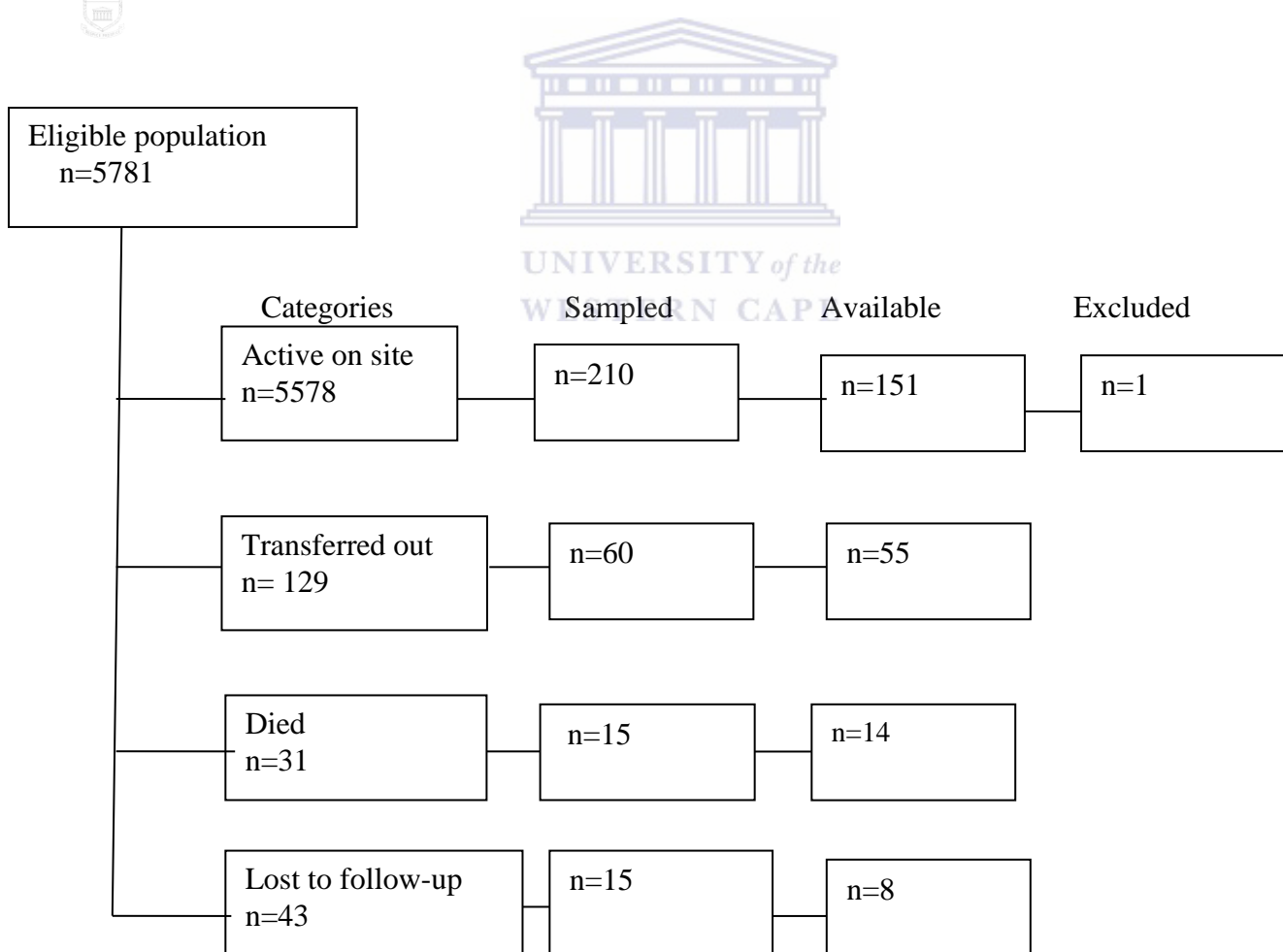


Figure 4.1 Sampling flow diagram

The socio-demographic and clinical characteristics of the respondents are shown in Table 4.1 below. The mean age and standard deviation of the patients were  $45.3 \pm 19.5$  years. A scatter plot of the distribution of ages is shown in Figure 4.2. It showed a relatively normal distribution of age as evidenced by the best line of fit plot. The age range was from 22 to 81 years and IQR was 14 years. The male to female ratio was 1:1.52. The location of living was documented in 204 of the 228 patients. As can be seen of those whose location of living was known, about 64% of the population lived within 20km of Gaborone which was a classification given to those who lived in the city and villages around the city. The patients were commenced on treatment from 2001 to 2013. The majority of patients had taken treatment for 5 to 10 years (56.3%).

Pertaining to adherence and psychosocial factors, 29.4% of records showed evidence of the patient having had adherence problems in the past. These were in the forms of habitual defaulting, infrequent missing of doses and non-adherence related to social problems. As shown in Table 4.1, 22 of the records (9.5%) documented various social problems. Of these 22 patients different categories of problems were documented including transport (7), family problems (5), personal problems (11) and other social problems (6). Nine (9) records documented more than two categories of these problems.

As seen in Table 4.1, the pre-treatment (baseline) CD4 count and the last CD4 count in the patients charts in 2013 were recorded. The baseline CD4 count ranged from 0 to 768 cells per cubic millilitre, with a median of 133 cells per cubic millilitre. The last CD4 count recorded in 2013 ranged from 11 to 2006 cells per cubic millilitre and a median of 505 cells per cubic millilitre. This is CD4 count that was recorded after the patients had been on treatment for a while. The CD4 counts categories are classified according to WHO immunological staging classification. It can be seen that the majority of CD4 counts in the baseline count were in the category of below 200 cells per cubic millilitre (79.7%). In contrast 52.5% (118) of the final CD4 counts recorded in 2013 were in the category of above 500 cells per cubic millilitre. The two groups of CD4 count were not normally distributed and the variances of the two counts were different. This was confirmed by an F test of variances ( $p < 0.001$ ). As a result the two medians could not be statistically analysed for differences of the two groups. It is however noted that the

CD4 count in 2013 was greater than the baseline in more than 98% of respondents and it can be assumed that ART resulted in an increase in CD4 count.

The treatment of the respondents with antiretroviral drugs was documented. As shown in table 4.1 a majority of cases were treated on first line of treatment (85.5%) and on one of the following combinations: combivir/nevirapine (21.9%), combivir/evafirenz (25.9%), atripla (23.2%) and truvada/nevirapine (10.5%). The distribution of the regimen is shown in the table and as seen the most frequent combinations were combivir/evafirenz (25.9%) combivir/ nevirapine (23.2%), and atripla (21.9%). A total of 31 cases (13.6%) were on second line HIV treatment and only two patients (0.88%) were maintained on salvage regimen using four drugs. It is also noted that 125 cases (54.8%) had never changed regimen in comparison with 103 (45.2%) who had treatment changes in the past.

In all patients whose virologic status was known, 207 (90.8%) patients had their virologic status as controlled and 16 (7.0%) were classified as patients in virologic failure. One (1) patient had a viral blip. This is a case in which the viral load is elevated above 50 copies per millilitre on one occasion and then reverts to undetectable levels in subsequent tests. Four (4) patients had unrecorded virologic status because of an unrecorded viral load in scheduled visits in 2013. The HIV viral load blip and the cases with unrecorded virologic status were excluded in analysis involving virologic status.

Table 4.1 Socio-demographic and clinical characteristics of respondents

	Frequency (n)	Percentage (%)
<b>Gender</b>		
Male	90	39.7
Female	137	60.3
<b>Age (years)</b>		
≤ 30	7	3.1
31 ≤ 40	70	30.7
41 ≤ 50	83	36.4
51 ≤ 60	55	24.1
61 ≤ 70	10	4.4
≥ 71	3	1.3
<b>Duration of treatment</b>		
Less than five years	48	21.2
Five to ten years	128	56.3
Over ten years	51	22.5
<b>Initial CD4 count (cells/mm<sup>3</sup>)</b>		
0-199	173	79.7
200-349	31	14.3
350-499	10	4.6
>500	3	1.4
<b>Final CD4 count (cells/mm<sup>3</sup>)</b>		
0-199	18	8.0
200-349	43	19.1
350-499	46	24.4
>500	118	52.5
<b>Adherence problems</b>		
Yes	67	29.4
No	161	70.6
<b>Social problems categories</b>		
None	204	89.5
Personal	11	4.8
Family	5	2.1
Transport	7	3.1
Other	6	2.6
Multiple categories	9	3.9

**Distance from home**

Within 20km	130	63.7
Between 20 and 40km	47	23.0
Between 40 and 100km	8	3.9
Within 500km	16	7.8
Over 500km	3	1.5

**HIV Treatment categories**

First line	195	85.5
Second line	31	13.6
Salvage treatment	2	0.88

**Treatment combinations**

Combivir/efavirenz	59	25.9
Atripla	53	23.2
Combivir/ Nevirapine	50	21.9
Truvada/ Nevirapine	24	10.5
Truvada/ ALLU	22	9.6
Combivir/ ALLU	5	2.2
Abacavir/3TC/ALLU	4	1.8
Abacavir/3TC/NVP	2	0.9
Abacavir/3TC/EFV	2	0.9
Atripla/ Abacavir	2	0.9
ABC/TEN/ ALLU	2	0.9
D4T/ATV/VitriVir/3TC	1	0.4
RAL/FTC/RTV/DRV	1	0.4
Tenofovir/3TC/Abacavir	1	0.4

**HIV treatment switches**

No switches	125	54.8
Some switches	103	45.2

**Virologic status**

Controlled	207	92.8
Failure	16	7.2

**Patient outcome**

Active patients	150	65.8
Transferred out	56	24.6
Died	14	6.1
Lost to follow-up	8	3.5



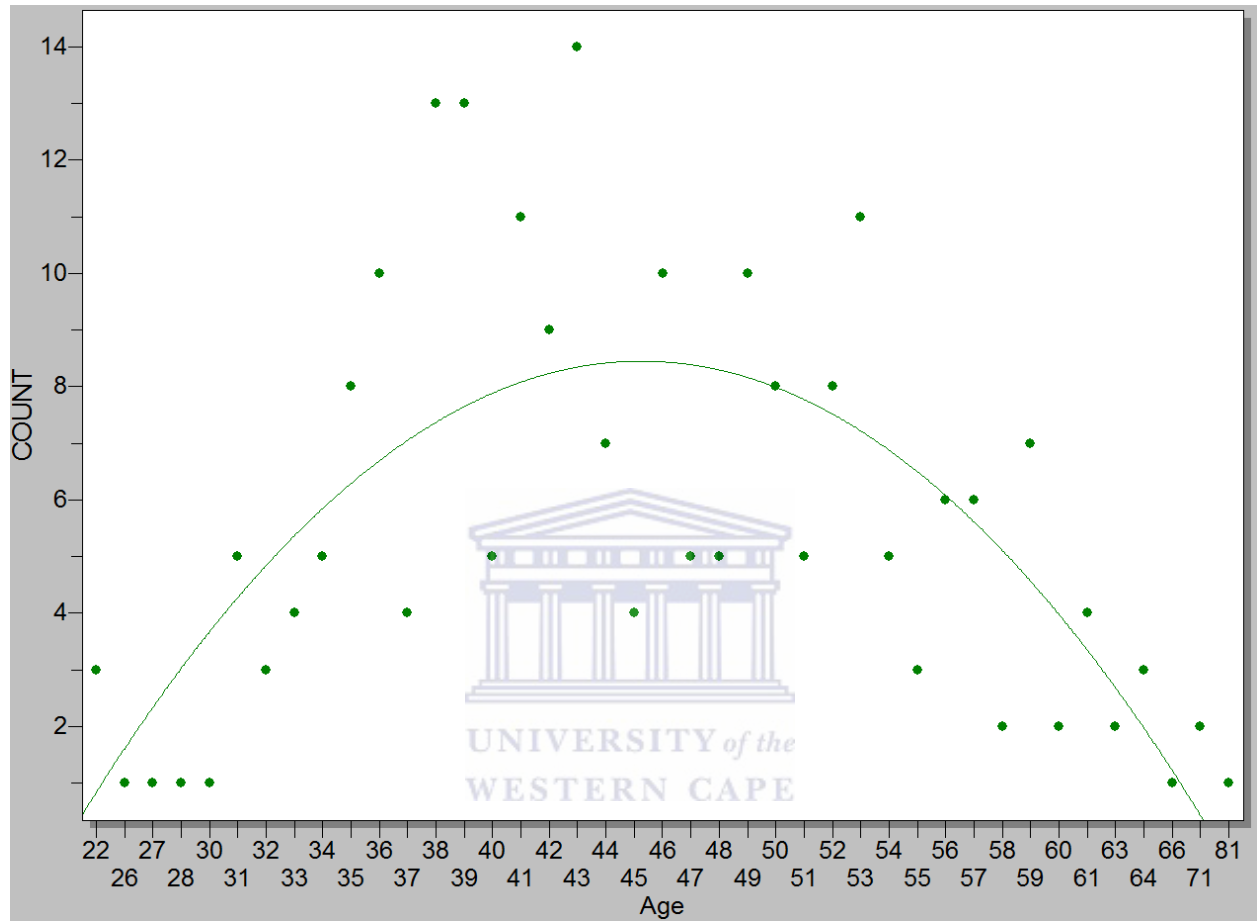


Figure 4.2: Age distribution of the respondents

## 4.2 Prevalence of Non-AIDS Defining Conditions

There were 80 recorded cases of NADCs. All the cases are documented in Table 4.2. In total 62 patients had evidence of one NADC, 16 patients had a second NADC and one patient had a third NADC. The prevalence of NADCs in the whole sample (of 228) calculates as 350 per 1000 population.

For active patients, thirty-eight (38) conditions were detected in 150 patients. Thirty (30) patients had one NADC only; seven (7) of them had a second NADC; and one (1) patient had a third NADC. The prevalence of NADCs in the active patients calculates as 254 per 1000, which translates to a prevalence ratio of 0.70. For respondents who died, ten (10) NADCs were detected. Seven (7) of these respondents had one NADC and three (3) respondents had a second NADC. This category consisted of fourteen (14) patients. The prevalence of NADCs in the respondents who died calculates as 714 per 1000 population which translates to a prevalence ratio of 2.04. In patients who were transferred to other ARV sites, 21 patients had one NADC; with 3 of those (21) having a second NADC. The total number of respondents who were transferred to other sites was fifty-five (55). The prevalence of NADC was calculated as 436 per 1000 population, which is equivalent to a prevalence ratio of 1.24. In patients who were lost to follow-up, 6 patients had one NADC with 2 having second NADC. The number of respondents who were lost to follow-up was eight (8). The prevalence of NADCs translated to 1000 cases per 1000 population and a resultant prevalence ratio of 2.86.

Hypertension was the most frequent NADCs with 40 cases reported. Using Hirshhorn *et al.*'s (2012) classification it is noted that the conditions can be divided into the following: Non-HIV-related cancers (3), Cardiovascular diseases (48), and Psychological/Mental problems (3), Metabolic (17), Chronic Kidney Disease (2) and lastly Other Conditions (7).

Table 4.2: Prevalence of the Non-AIDS defining conditions

<b>Category of disease</b>		<b>Frequency</b>
<b>Cardiovascular</b>	Hypertension	40
	Erectile Dysfunction	3
	Cerebro-vascular Accident	2
	Congestive Cardiac Failure	1
	Left Ventricular Hypertrophy	1
	Varicose Veins/ venous Ulcers	1
<b>Metabolic</b>	Hyperlipidaemia	7
	Lipodystrophy	7
	Diabetes Mellitus Type II	3
	Gynaecomastia	1
<b>Psychological/mental health</b>	Alcohol Abuse	2
	Schizophrenia	1
<b>Chronic kidney disease</b>	Chronic Renal Failure	2
<b>Non-HIV-related malignancy</b>	Advanced colon cancer	1
	Advanced Cancer Of The Bladder	1
	Advanced Breast Cancer	1
<b>Other</b>	Chronic Allergic Rhinitis	1
	Benign Prostatic Hyperplasia	1
	Menorrhagia	1
	Osteoarthritis	1
	Hypothyroidism	1
	Coagulopathy	1
<b>Total number of NADCS</b>		<b>80</b>

### 4.3 Treatment of Non-AIDS Defining Conditions

Treatment of the NADCs was documented in the records. Table 4.3 shows the level of control of the prevalent conditions. The control of the condition was captured based on the written documentation of control in the chart or evidence of clinical indicators such as blood pressure or other profile that are documented consistently within normal values. For all the conditions, the level of control of all the NADCs was as follows: 60% (48) of conditions were controlled, 21.2% (17) were uncontrolled, 7.5% (6) were progressive and for 11.3% (9), the control was unknown.

The level of control of the three most common conditions hypertension, lipodystrophy and hyperlipidaemia is also shown. Thirty (30) of the cases of hypertension (75%) were controlled, compared to 8(20%) which were uncontrolled and 2 (5%) whose control was not known. The cases of hypertension were managed on lifestyle modification such as diet, exercise and alcohol avoidance and on antihypertensive medications. The combinations of these antihypertensive drugs included single drug therapies and multiple drug treatments. All treatment of lipodystrophy involved switching of the anti-retroviral drugs usually involving removal of stavudine or zidovudine, which are the drugs that are mainly associated with lipodystrophy. Two (2) cases of lipodystrophy were uncontrolled compared with five (5) cases that were controlled. Hyperlipidaemia was treated using lifestyle modifications mainly entailing diet and exercise and only 2 cases were treated with atorvastatin, a lipid lowering drug. All the cases of hyperlipidaemia were controlled on treatment.

Treatment of other conditions such as malignancies, diabetes and some cases of hypertension were managed at other outpatient settings, and had no management documented in the charts. These contributed to the proportion whose control could not be determined from the records. It is observed that some of the NADCs were progressive, in particular the malignancies. In total 12 cases (15%) were referred for management at other outpatients departments namely Urology (2), Oncology (3), Social Work (3), Ear Nose and Throat (1), Dermatology (1) Gynaecology (1) and Cardiology (1).

Table 4.3 Control of the prevalent non-AIDS defining conditions

<b>Condition (frequency)</b>	<b>Percentage of condition controlled (%)</b>
Hypertension (40)	75
Erectile Dysfunction (3)	33
Cerebro-vascular Accident (2)	0
Congestive Cardiac Failure(1)	100
Left Ventricular Hypertrophy (1)	0
Varicose Veins/ venous Ulcers (1)	0
Hyperlipidaemia (7)	100
Lipodystrophy (7)	71
Diabetes Mellitus Type II (3)	0
Gynaecomastia (1)	100
Alcohol Abuse (2)	0
Schizophrenia (1)	100
Chronic Renal Failure (2)	0
Advanced Colon Cancer (1)	0
Advanced Bladder Cancer (1)	0
Advanced Breast Cancer (1)	0
Chronic Allergic Rhinitis (1)	0
Benign Prostatic Hyperplasia (1)	0
Menorrhagia (1)	0
Osteoarthritis (1)	100
Hypothyroidism (1)	100
Coagulopathy (1)	100

#### 4.4 Associations of Non-AIDS Defining Conditions

Table 4.4 is a summary of associations that were tested against the prevalence of NADCs. Age was assessed by dividing age into two categories, below 50 years and 50 years and above. This was done because NCDs prevalence increases with age. Fifty was chosen as a cut point on considering that most NCDs start increasing progressively above 50 years of age. The study also took cognisance of the range of ages that were observed in the study of 22-81 years.

There were statistically significant associations between age and the presence of one NADC ( $p < 0.001$ ) and two NADCs ( $p = 0.03$ ). Those respondents who were 50 years and older had three times the odds of having at least one NADC compared to those younger than 50 years ( $OR = 2.96 [1.61-5.42]$ ). Presence of social problems was also significantly associated with presence of NADCs ( $p = 0.028$ ). All the social problems categories were grouped together into presence or absence of social problems, without analysing separate ones individually. This was mainly due to the small numbers involved with individual social problems. Those respondents who had social problems had almost two and a half times the odds of having at least one NADC compared to those with no social problem ( $OR = 2.47 [1.01-6.04]$ ). Length on treatment was divided into two categories, below three years and above three years. Those respondents who had been on treatment for three years or above had almost six times the odds of having at least one NADC compared to those who had taken treatment for less than three years ( $OR = 5.87 [1.36-25.4]$ ).

The respondents categories notably being actively followed up at the clinic ( $p < 0.01$ ), being lost to follow-up ( $p < 0.01$ ) and death ( $p = 0.033$ ) were associated with the presence of NADCs. Respondents who were actively followed at the clinic at the time were 40% less likely to have NADC compared to those who were not ( $OR = 0.39 [0.22-0.72]$ ). Outcome of death and being lost to follow up was associated with higher odds of having a NADC. Respondents who died had three times the odds of having had an NADC compared to those who were alive ( $OR = 2.90 [0.97-8.61]$ ). In comparison respondents who were lost to follow-up had nearly nine times the odds of having an NADC compared to those who were not lost to follow-up ( $OR = 8.78 [1.72-44.8]$ ).

The following variables were not significantly associated with presence of NADCs: gender, non-adherence to medications, and outcome of transfer to other facilities and second line or salvage regimen of HIV treatment. There was no differences in the prevalence of NADCs between males and females ( $p= 0.4$ ). Adherence to medications did not show any association with presence of NADC ( $p=0.39$ ). Respondents who were controlled on first line treatment showed no statistically significant difference in prevalence of one NADC when compared with those on second line or salvage treatment ( $p=0.7$ ). Similarly respondents who had treatment switches did not show any statistically significant difference in prevalence of NADCs compared to those who were controlled on one treatment ( $p=0.23$ ). Respondents who were transferred out to other facilities did not show any statistically significant differences in the prevalence of NADCs compared to respondents who had not been transferred to other facilities ( $p=0.3$ ).

The variables that showed associations with presence of NADCs namely: age, length of treatment, history of social problems and outcomes of death, loss to follow-up and being active on site, could not be fitted in a logistic regression model due to low numbers. These variables were analysed for potential associations with each other, to find out if they could be potential confounders. The age category of 50 years and above was associated with higher outcome of death ( $p=0.01$ ), when compared to the age of below 50 years. Respondents who were aged 50 years and above had four times the odds of death ( $OR=3.95 [1.27-12.23]$ ) compared to respondents who were aged less than 50 years. Potentially age could have confounded the relationship between presence of NADC and death. Respondents who had social problems in the past were statistically more likely to be lost to follow-up ( $p=0.007$ ), compared to those who had no social problems. This meant that respondents who had social problems had six times the odds of being lost to follow-up ( $OR= 6.34 [1.41-28.6]$ ) compared to those with no history of social problems.

Table 4.4 Prevalence of NADCs by socio-demographic and clinical variables

Characteristic	Presence of NADC (%)	Absence of NADC (%)	Crude Odds ratio (95% CI)	p value
<b>Gender</b>				
Male	25 (41.0)	65 (39.2)	1.08 (0.59-1.96)	0.4
Female	36 (59.0)	101 (60.8)	1	
<b>Age (in years)</b>				
≥50	30(48.4)	44(26.5)	2.96 (1.61-5.42)	<0.001
< 50	32 (51.6)	122 (73.5)	1	
<b>Presence of social problems</b>				
Yes	10 (16.1)	12 (7.2)	2.47 (1.01-6.04)	0.028
No	52 (83.9)	154 (92.8)	1	
<b>Length of treatment (years)</b>				
≤3	2 (3.2)	27 (16.4)	5.87 (1.36-25.4)	0.007
>3	60 (96.8)	138 (83.6)	1	
<b>History of non-adherence</b>				
Yes	21 (33.8)	46 (27.7)	0.76(0.41-1.42)	0.39
No	41 (66.2)	118 (71.3)	1	
<b>Treatment line</b>				
Second/salvage	10 (16.2)	23 (13.9)	1.20 (0.53-2.68)	0.7
First line	52 (83.8)	143 (86.1)	1	
<b>Treatment switches</b>				
Yes	32 (51.6)	71 (42.8)	1.42 (0.79-2.56)	0.23
No	30 (48.4)	95 (57.2)	1	
<b>Active at site</b>				
Yes	31 (50)	119 (71.7)	0.40 (0.22-0.72)	0.002
No	31(50)	47(28.3)	1	
<b>Death</b>				
Died	7 (11.2)	7 (4.22)	2.90 (0.97-8.61)	0.033
Alive	55 (88.70)	159(95.7)	1.	
<b>Transferred out</b>				
Yes	18 (29.0)	38 (22.9)	1.38(0.71-2.66)	0.3
No	44(71.0)	128 (77.1)	1	
<b>Lost to follow-up</b>				
Yes	6 (9.7)	2 (1.2)	8.78(1.72-44.8)	0.006
No	56(90.3)	164 (98.8)	1	



As a primary outcome of interest virologic failure was assessed against exposure of the presence of NADC and it was not associated with the presence of NADC ( $p=0.3$ ). In addition virologic status was assessed against several clinical and socio-demographic characteristics. There was a statistically significant association between non-adherence to medications and virologic treatment failure ( $p < 0.001$ ). Respondents who were not adherent to their HIV treatment had nearly thirteen times the odds of having virologic failure compared to those who were adherent (OR= 13.1[3.58-47.8]). Similarly respondents who were on second line or salvage HIV treatment were more likely to be in virologic treatment failure than those who were on first line HIV treatment ( $p < 0.001$ ). They had thirteen times the odds of having virologic treatment failure (OR= 13.3[4.43-40.1]) compared to those on first line HIV treatment. Respondents who had switched treatment in the past, were more likely to have virologic treatment failure than those who had never switched treatment ( $p=0.02$ ). Those respondents who switched treatment in the past had four times the odds of having HIV virologic failure (OR = 4.14 [1.29-13.26]). It was also observed on analysis that respondents who had social problems in the past were more likely to have virologic treatment failure ( $p=0.001$ ). The respondents who had social problems in the past had six times the odds of having virologic treatment failure (OR = 6.26 [1.91-20.6]).

Further statistically significant associations were revealed. Outcome of death was associated with virologic treatment failure ( $p=0.003$ ). Respondents who died had five times the odds of having virologic treatment failure (OR= 5.08 [1.22-21.0]) compared to those who had not died. In converse it was observed patients who were followed up at the clinic site were 20% less likely to have virologic treatment failure than those who were not actively followed at site by end of 2013 (OR = 0.2 [0.06-0.61],  $p=0.003$ )

The statistically significant associations of virologic treatment failure namely: treatment line, history of non-adherence, history of treatment switches, history of social problems, being active on treatment at site and death were subjected to logistic regression analysis, with the variable of presence of NADC added *a priori* as the main exposure of interest in the study objective. Table 4.5 shows the adjusted odds ratios. Finally the independent associations of virologic treatment failure were: being on second line or salvage treatment (Adjusted Odds Ratio (AOR) =

6.38[1.45-26.10],  $p = 0.014$ ) and history of non-adherence to medications (AOR = 6.51 [1.62-26.10],  $p = 0.008$ ).

The following associations were not significantly associated with virologic treatment failure: gender, age, presence of one NADC, presence of two NADCs, length of HIV treatment, being transferred to other clinics and being lost to follow-up. There was no differences in the prevalence virologic treatment failure for both males and females ( $p = 0.5$ ). Similarly respondents who were aged 50 years and above did not show any statistically significant differences in prevalence of virologic failure compared those who were aged less than 50 years ( $p = 0.6$ ). In the same token respondents who had been on treatment for over three years had no statistically different prevalence of virologic treatment failure compared to those who were treated for three years or less. There was no statistically significant differences in prevalence of virologic treatment failure for respondents who had at least one NADC compared to those with no NADCs ( $p = 0.26$ ). Similarly respondents with two NADCs did not show any differences in prevalence of virologic treatment failure when compared with those who did not have two NADCs ( $p = 0.8$ ). When compared with those on who were not transferred to other clinics, respondents who were transferred to other ARV clinics did not show any statistically significant difference in the prevalence of virologic treatment failure ( $p = 0.07$ ). Likewise respondents who were lost to follow-up showed no statistically significant differences in their prevalence of virologic treatment failure compared to those who were not lost to follow-up ( $p = 0.4$ )

Table 4.5 Virologic status by socio-demographic and clinical variables

Characteristic	Virologic Failure	Virologic Control	Crude Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)
<b>Gender</b>				
Male	6 (37.2)	82 (39.1)	0.91 (0.32-2.59)	
Female	10 (62.5)	124 (60.9)	1	
<b>Age category</b>				
< 50	12 (75.0)	71 (34.3)	0.63 (0.19-2.05)	
≥50	4 (25.0)	136 (65.7)	1	
<b>Treatment line</b>				
Second/salvage	10 (62.5)	23 (11.1)	13.3 (4.43-40.1)	6.38 (1.45-28.1)
First line	6 (37.5)	184 (88.9)	1	
<b>Presence of one NADC</b>				
Yes	6 (37.2)	56 (27.1)	1.62 (0.56-4.66)	1.19 (0.33-4.30)
No	10 (62.5)	151 (72.9)	1	
<b>Presence of two NADC</b>				
Yes	1 (6.25)	15 (7.2)	0.85 (0.11-6.91)	
No	15 (97.3)	192 (92.8)	1	
<b>History of social problems</b>				
Yes	5 (31.2)	14 (6.7)	6.26 (1.91-20.6)	2.69 (0.70-10.28)
No	11 (68.8)	193 (93.3)	1	
<b>Length of treatment</b>				
≤ 3	2 (12.5)	26 (12.6)	1.01 (0.22-4.70)	
>3	14 (87.5)	180 (87.4)	1	
<b>Treatment switches</b>				
Yes	4 (25.0)	87 (42.0)	4.14 (1.29-13.26)	0.96 (0.19-4.68)
No	12 (75.0)	95 (58.0)	1	
<b>History of non-adherence</b>				
Yes	3 (18.7)	51 (24.6)	13.1 (3.58-47.8)	6.51(1.62-26.10)
No	13 (81.3)	156 (75.4)	1	
<b>Active at site</b>				
Yes	5 (31.2)	143 (69.1)	0.2 (0.06-0.61)	3.37 (0.59-19.40)
No	11 (68.8)	64 (30.9)	1	
<b>Death</b>				
Died	3 (18.7)	9 (4.4)	5.08 (1.22-21.0)	2.71 (0.78-9.42)
Alive	13 (81.3)	198 (95.6)	1	
<b>Transferred from site</b>				
Transferred	7 (43.7)	48 (23.2)	2.58 (0.91-7.2)	
Not transferred	9 (56.3)	159 (76.8)	1	
<b>Lost to follow-up</b>				
Yes	1 (6.2)	7 (3.4)	1.9 (0.22-16.5)	
No	15 (93.8)	200 (96.6)	1	

## CHAPTER 5. DISCUSSION OF RESULTS

### 5.1 Study design, limitations and impact on results

The study limitations are that this study had financial and time constraints. There was limited sponsorship for material resources and data clerks for only two weeks. As a result the study could not be done for a longer time period, in which all sampled files could be traced. Therefore there could be some misclassification bias, with the non-responders. If there was no time constraint, the sampled files could have been obtained making sure that the level of bias was reduced. It is always common that files that were not available at their position were associated with some problems such as relating to treatment, or would have necessitated discussions with other doctors. So there is a possibility that such non response cases could have contributed significantly to the outcomes. It then remained that for the rest of the study the principal investigator was also involved with the records including ensuring that they were all filed appropriately. Nevertheless there were no major patient outcomes relating to filing of the records as there was reliable assistant from the clinic staff. To cater for measurement bias, associated with this positivist study, at the last two days of transcription, a medical doctor who did not take part in the pilot, assisted in the transcription of the records. This intervention was made to ensure that the researcher expectations of outcome were not predominantly skewing data. A more appropriate solution would have been to use independent data capturers who were conversant with the study to capture the data, without using the investigator. This option was not available due to funding constraint.

Whilst this cross sectional study showed there is a problem of NADCs, the magnitude of the problem might be more or less pronounced. To begin with the sample size calculation used a general population statistic of 2010 as an estimate of prevalence. There is a possibility that the sample size may have been inadequate. Utilising the study result prevalence, the desirable sample size is slightly more (330). There are some pertinent findings that were observed with regard to the operations of the clinic. It was worrying that documentation of some key socio-economic data such as marital status, smoking status, alcohol use and employment status were not routinely captured. These may not have been found important for an outpatient clinic, however it may arguably be emphasized that such details are also important in clinical decisions.

It was explained that such data were captured as a once off record but it was observed that the information was not seen in all the files. The absence of these important socio-demographic details meant that they could not be assessed in the analysis. It is of concern as some of these factors such as smoking and alcohol use are involved in the aetiology of NCDs. They could have acted as confounders that could have been analysed, had they been available.

It was also clear that the computer based in patient management system is used mainly for booking patients and for ordering investigations. However, by and large a standardized form of keeping the OPD notes was in use and it was adequately completed. This was evidenced by having only one record excluded based on legibility. There was a concern that there were some missing data that should have been kept such as viral load, and location of living in the OPD notes. Nevertheless, as a source record, the OPD records were able to provide required information.


There was however one observation made relative to documentation. It appeared that problems of the NADCs and HIV were not routinely documented. From all the 80 cases with non-AIDS defining problems, there was scanty documentation of problems caused by NADCs relative to HIV treatment. Furthermore, there was an observation that reasons of switches were also not readily documented.

In using the multiple logistic regression analysis, the assessment was also limited to few potential confounders notably age, NADC presence social problems, non-adherence to medications and an outcome. This was because the sample size was not large enough to include more potential confounders in the test. Stratified analysis was also not possible for some of the associations with NADCs due to the small numbers.

The study design and lack of a uniform sampling frame had an influence and possibly bias on the study. Selection bias was noted in having a total non-response rate of 24%. This was 26% in the active patients, 6.6% in dead patients records, 8.3% in the transferred out patients records and 46 percent in lost to follow up group. As had been noted the prevalence in all these groups is different. Had more of the active files been available, the possibility is that the outcome could

have been different. Nevertheless, it was decided that these files would not be actively searched for as it had been learnt that some files are almost always lagging behind in filing. Such files are kept at various staff offices and searching for them would have been a laborious exercise.

The study was limited to outpatient's hard copies and electronic records were used to only corroborate the non-naming file identifier. This was essentially due to time constraints. It also became apparent that the electronic records had not been actively updated consistently for the last two years due to shortage of staff. They could have been used to document blood investigations and results, however according to Ministry of Health policy; data collected over 6months or more is archived and protected. Access to these would have required clearances, a task, which was not feasible at that point in time.

 As commonly expected in a cross sectional study, the associations that were confirmed, and their lack thereof, have less bearing on causality because of the nature of evidence related to this type of study. Therefore, the relationship between age and NADCs, outcome of death and loss to follow-up to presence of NADC would bear more weight if it were a different study design such as prospective case cohort.

  
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## **5.2 Characteristics of respondents**

The age range and the sex ratio are concomitant with an adult ARV treatment site, with the clustering of patients at the age category of 31-60 years being reported in some sites in Botswana in the past (Bene and Darkoh, 2014). A more recent cross sectional study revealed age distribution that has the same pattern as the one observed in the current study (Ehlers and Tshisuyi, 2015). Most of these studies show predominant attendance of clinics by females, an observation that was observed in the current study. The other end of the age bracket indicates that a geriatric population needs to be catered for in HIV care. Indeed there were 4 patients aged over 65 years and over 34 who were aged 55 years and above. These age categories were also represented by Bene and Darkoh (2014) and similarly Ehlers and Tshisuyi (2015). This study age and gender demographics was therefore consistent with other similar studies in an HIV-infected population, on ART in Botswana.

The distribution of patient location in those who showed a record of location is also in agreement with the IDCC criteria. It is observed that over 64% were patients within the clinic's catchment area. However it is noted that some were from locations, which were over 500km away from the clinic. This is understandably a group for whom care has to be optimized, following their referral, either due to treatment problems, co-morbidities or any complications that needed specialist care. An analysis of the categories of location of living against prevalence of NADC or virologic status was not considered owing to the 24 returned missing entries for location of living. Therefore whilst the analysis showed no statistically significant association with the two attributes, that may not have been the case if the 24 missing entries were recorded.

Previous problems of compliance were documented in the form of documented reported missed doses, defaulting of treatment including recurrent defaults. This included mild forms where few doses were missed, deliberate missing of several doses and stopping of treatment. Observation of compliance problems in 29.4% of this cohort is an outcome worth noting. Weiser *et al.* (2013) studied compliance problems, in three clinics in Botswana and reported compliance rate of 56% by health worker assessment in the cohort. This meant lack of compliance of 44%. They also observed an agreement between health provider and patient reported compliance of 68%. The current study statistic, although is better than Weiser *et al.* (2013), still raises concern. The two studies are similar in that they are both cross sectional studies, however they differ in that in the medical records both health provider and patient reported compliance were at interplay, as was with this study.

The former study used patient interviews. It is also worth noting that Weiser *et al.* (2003) and this study definitely do not compare like with like as their definitions of compliance by the former study were more thorough than in this study. A blunt comparison of both studies however is that the reported health worker assessment of compliance, showed improvement comparing the situation in 2000, as investigated by Weiser *et al.* (2003), and findings of the present study for 2013.

The adherence rate observed in the current study of 70.1% can be compared to Kgatlwane *et al.* (2006) at 77% and Weiser *et al.* (2003) of 54%. These cannot be arguably assumed to show an improvement in adherence over the years from 2003. The difference in study measurement methods is appreciated. Kgatlwane *et al.* (2006) used three measures that were averaged: pill count, two day adherence recall and user reported adherence. The authors averaged the three types of adherence statistics to arrive at the statistic of 77%. The current study utilized health care provider reported adherence from the chart. Garber *et al.* (2004) reviewed the literature on concordance of self reported adherence and other measures and found varying concordance of the various measures.

It may therefore not be justified to compare the three studies above. It is noted that the study designs for the three studies are different and, therefore, not completely comparable. However, a period prevalence of non-adherence of 29.4% in this cohort shows that adherence to HIV medication was still a problem that should be addressed in this setting. Moreover, some of the cases were defaulters who had been reinitiated on treatment more than twice in their care. This area of HIV care is certainly an area of much needed research and policy intervention, as it has tremendous morbidity and cost implications.

### **5.3 The prevalence of non-AIDS defining conditions**

The prevalence of these conditions of 350 patients per 1000 in 2013 is significant and is a yardstick for which future reference could be measured. The prevalence of hypertension in this group was 17.5%. In addition, hypertension with either hyperlipidaemia and diabetes or lipodystrophy showed a prevalence of 2.6%, and that being 15% of all hypertensive patients. Other than the fourth criteria of insulin resistance (Sekhar *et al.*, 2004), which was not routinely investigated, this group of patients had at least two or three conditions that commonly defined the metabolic syndrome by most criteria.

Various studies have shown equivocal findings of the prevalence of hypertension on HIV positive patients compared to HIV negative controls. Whilst Bergersen *et al.* (2003) and Jerico *et al.* (2005) showed a similar prevalence of hypertension on the HIV positive patients and controls, Gazzaruso *et al.* (2003) have shown significant differences. The prevalence of hypertension in



Botswana in general population was estimated at 33.1% in 2007 according to the STEPS survey and a further study on its prevalence was done in 2014 (African Union, 2013). This study will go a long way in demonstrating the comparability of these rates when the 2014 STEPS results are out. It may not be advisable to be quick to point out the results of this NADC study as an indication of a lower hypertension prevalence compared to the general population since STEPS statistic was for 2007. This clearly calls for further studies with more resources to elucidate the magnitude of the problem.

Dusara *et al.* (2009) documented a prevalence of hypertension of 18.5% on an HIV positive cohort in Botswana in 2009. The prevalence in the current study is comparable to Dusara *et al.* (2009). It must however be noted that that cohort was a HAART naive group as compared to this study where all patients had been on treatment. This was an important finding since Dusara *et al.* (2009) study was from the TSHEPO study which was one the first randomised trials that established safety of antiretroviral treatment in Botswana. The fact that this study corresponds to a higher level study in the form of a clinical trial is an important finding. Furthermore, the cohort of Dusara *et al.* (2009) was later transferred to the current study site. The prevalence of hypertension compares to 26.2% reported by Kagaruki *et al.* (2014) observed in a cross sectional study in an urban setting in Tanzania.

It is noted that the three (3) cases of cancer were registered all at an advanced stage. It has been shown that a significant proportion of non-AIDS associated cancers seem to be more prevalent in HIV positive cases (Ruiz, 2009). It had further been suggested that cancers in HIV-infected patients tend to be more aggressive than in the non HIV-infected (Silverberg and Abrams, 2007; Patel *et al.*, 2008). This may account for why all the cancers noted in this cohort were at an advanced stage. Pertaining to prevalence of cancer in the cohort, there were no available data to compare prevalence statistics for cancer in Botswana.

It is important to note that this group of patients is expected to have a high hypertension and indeed non-AIDS defining conditions. As detailed before, the criteria for admission into Princess Marina Infectious Diseases Care Clinic, is that the patients should have problems with their treatment, have co-morbidities or be resident in the clinic catchment area. Therefore a high

prevalence rate of chronic diseases and hypertension is expected. It is assumed that such a situation would not have to be the case in all other clinics. This was also corroborated by the lower prevalence in the transferred out patients than in the active patients. Transferred out patients form part of the peripheral clinics clientele and such patients HIV treatment would have been stabilised. It would therefore be expected that those with co-morbidities would stay with Princess Marina Infectious Diseases Care Clinic.

Bergersen *et al.* (2003) and Baekken *et al.* (2008) noticed an equal prevalence of hypertension in the group with HIV and general population and those who are HAART naive. However Baekken *et al.* (2008) reported significant proportion of hypertension in patients who had treatment of HAART for over 5 years. In this particular study the length of treatment on HAART was not associated with hypertension. Such a difference in Baekken *et al.* (2008) compared to the current study could be affected by study design as the former used a case control study as opposed to a cross sectional archive study. It would perhaps be better left for further research. Several authors have argued that the hypertension is often increased in HAART patients by a metabolic syndrome that is more associated with HAART (Blanco *et al.*, 2010; Jerico *et al.*, 2002). There is also another version that attributes this to the length of period of a chronic HIV infection affecting cytokine cascades.

It is noted that osteoporosis and osteopenia was not noticed anywhere in the records. This was contrary to Hirschhorn *et al.* (2012) estimate that these two conditions have ten-fold prevalence in HIV patients on HAART. A possibility could be that the condition was not investigated or suspected. A criterion for confirmation of osteoporosis and osteopenia requires bone density scans and other blood investigations such as calcium and hormonal profile may be needed (Kanis, 2015). There was an observation that bone density scans were not routinely taken in this setting. There is a significant observation that some patients were taking medication that can potentially cause osteopenia. It is noted that tenofovir has been significantly associated with osteopenia and osteoporosis (Hirschhorn *et al.*, 2012; Knobel *et al.*, 2001). It is suspected that these conditions are less reported. In addition in the column of data capture remarks, more than 5 patients had indicated that they experienced chronic pain of some sort. Two cases of osteoarthritis were recorded.

Alcohol abuse occurred as the main psychiatric/psychological disorder that occurred in this setting alongside a case of schizophrenia. Perhaps unexpectedly mood disorders were not observed in this cohort. It must however be noted that several records showed concerns of psychological stress issues and were referred to social work department. Such could have appeared as mood disorders in definitive diagnoses in the other outpatient departments.

#### **5.4 Associations of non-AIDS defining conditions**

The association of age with presence of NADC is expected, because it is a known fact that chronic disease prevalence increases with age. In addition some studies have shown correlations of multi morbidity with age; even in the HIV population (Rodriguez-Penney *et al.*, 2013). There was no association of presence of NADCs with gender. Some studies have shown certain conditions prevalence predisposition to male e.g. hypertension as was seen in some studies on HIV positive patients (Baekkam *et al.*, 2003). This was not seen in this particular cohort.

Prevalence of NADCs was higher in patients who had been on ART longer than three years in comparison with those who had been on treatment for less than three years. This is to be expected since treatment of HIV is associated with conditions such as lipodystrophy that arise as a result of the side effects of medications.

In the cohort for the present study, clinic outcomes of death and loss to follow up were associated with the presence of NADCs. This is an observation worth visiting. It suffices to say the presence of a diseased state is perhaps always associated with higher possibility of death than none diseased state. Said in another way, it can be held that NADCs significantly caused death in this cohort. In this study design it is always an inherent weakness of causality in any association that is observed. Another study type e.g. case control type assessing a group of mortalities of NADCs on HAART compared to NADCs without HAART would probably have more strength in causality. Such mortality studies have shown significant contribution of NADCs to HIV-infected population (Hooshyar *et al.*, 2007).

Brinkhof Pujades-Rodriguez and Egger (2009) summarized studies on patient who were lost to follow-up, whilst on ART programmes in resources limited settings in a meta-analysis. The

review showed that in the studies 20 to 60% of patients who were lost to follow-up died. In addition 34% of the patients who were traced and found to have died had the cause of death as non-AIDS defining illnesses. Therefore the current study corroborates with Brinkhof *et al.* (2009) in the contribution of NADCs in patients who were lost to follow-up. The common reasons for not returning to the clinic in Brinkhof *et al.* (2009) review were transfer to another programme, financial problems and improving or deteriorating health. These reasons might have been at play in the current study and it is important to notice that loss of follow-up due to improving or deterioration might reflect a lack of understanding or the need for life-time treatment regardless of state of health,

The physical burden of multi-morbidity has been associated with psychosocial distress and psychological illness (Mendenhall *et al.*, 2012). Their study showed that having these conditions was a burden on the patients and that caused them distress. It could be that such factors contributed to losses to follow-up where in the clientele multi-morbidity caused the patients to default follow-up. This remains an area for research, and may give insight into the problem of multi-morbidity. Indeed it has been shown in a systematic analysis that caring for co-morbidities demands targeted interventions for the population, especially risk factors and functional disabilities (Smith *et al.*, 2012).

In this cohort the first line failure rate was 3.16%. It was observed that 30.10% of those in second line or salvage were in failure. As a result there was an association of being in failure related to second line or third line. These results have to be looked at in the context of the study site. As a snap shot 30.10% of those on second line or salvage were failing. However the Princess Marina ART clinic follows up stable patients routinely, twice a year, and failing patients more frequently. It may mean that in the subsequent visits that were not recorded in the year such second line patients would not be failing. This could explain the high second line failure rate.

### **5.5 Treatment of HIV and Non-AIDS Defining Conditions**

In this study, in relation to treatment of NADCs it was observed that 21.2% of the conditions control was not documented either due to the fact that the treatment was given in another clinic or that documentation was not indicated.

This study could not adequately assess the treatment or compliance to the Botswana HIV Treatment Guidelines, however, on a general observation; the treatment was in accordance with the guidelines. Almost all recommended regimen were as stipulated. However a stepwise interrogation of the changes could not be assessed and was beyond the document scope.

It is noted that the first line failure rate was 3.16% closely linked to the reported statistic of 3% given by Princess Marina Infectious Diseases Care Clinic annual statistics, 2013. Overall 7.2% were in virologic failure. It is also observed that 30.10% of those in second line or salvage were in failure. This is important and must be interpreted appropriately. Of relevance is that such patients are seen several times and may have at certain times in the same year converted back to virologically controlled status. Such is the inherent weakness of a cross sectional study on an outcome that can revert to normal. As a prevalence statistic 30.10% of those in second line or salvage therapy, were in virologic failure.

The treatment of the two common conditions hypertension and hyperlipidaemia were looked at and in particular the control of the conditions was assessed. An observation that was common to all the NADCs is that a significant proportion of hypertension and hyperlipidaemia were uncontrolled. Nevertheless the treatment categories observed are suggestive of adherence to the Botswana National Treatment Guidelines, 2007 with lifestyle modifications and single drug diuretic and calcium channel blocker being the majority. As with HIV treatment a stepwise interrogation could not be done.

## CHAPTER 6. CONCLUSIONS AND RECOMMENDATIONS

### 6.1 Conclusions

A prevalence of a group of non-AIDS defining illnesses and conditions was determined at 35% translating to 350 per 1000 of population of attendees of the Princess Marina Hospital adult antiretroviral clinic for the year 2013. This prevalence varied along represented outcome groups of the cohort at the end of 2013. For patients who remained active at the site in December 2014, the prevalence ratio comparing those who were active at the clinic to the whole group was 0.70. For those who were transferred out the prevalence ratio was 1.24. These were in comparison with prevalence ratios of NADCs of 2.04 and 2.86 for those who died and those who were lost to follow-up respectively, still using the whole sample population as reference. There were associations of having NADCs to age, outcome of death and lost to follow-up and having social problems. There was no association of NADCs to virologic treatment failure. This study confirms significant morbidity related to non-communicable diseases in HIV population on treatment. As a one-time traverse of the problem, this study alone cannot, and is not expected to instruct policy change. However, it calls for further research on possible policy changes. An integrated management of chronic diseases may be advocated for. This is in relation to the large proportion of patients who had their other conditions managed elsewhere.

The study, like many other studies previously, shows non-adherence to HIV treatment as one of the major determinants of virologic failure.

### 6.2 Recommendations

The prevalence of these chronic diseases and the associations elicited call for further research into these conditions. It also appeals for strategies to manage these conditions alongside HIV as a concerted effort and not fragmented. Perhaps what has been emulated for TB and HIV may be warranted in NADCs management. For example, managing cardiovascular diseases in a combined Cardiovascular and HIV clinic may help address the combined morbidities. Such policy decisions may not come without further research. The magnitude of this problem may not have been represented accurately due to the study limitations and may call for more studies in relation to these conditions.

The following recommendations are made:

- Documentation at the ARV clinics should include social determinants such as marital status, smoking and alcohol use.
- More studies should be done for other ARV clinics to appreciate this problem. It is advocated that one or more studies with more weight such as prospective cohort be done to elucidate the problem of chronic non communicable diseases in HIV.
- Other type of studies such as case control study may be necessary to find out causality particularly in relation to outcomes such as death and loss to follow-up. It is felt that other conditions may have been recorded elsewhere in the year 2015 e.g. Emergency Room and Vascular clinic.
- There is a need to explore using integrated clinics for patients with both NCDs and HIV to find if there might be a benefit for these patients with multi-morbidity.



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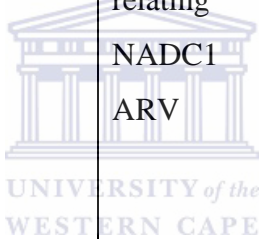
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APPENDIX 1 Data capture tool


Research number (research identifier)	Age	Gender(M=male F=female)	Location of living in KM 1=within 20km, 2= within 40Km, 3=within 100km, 4=within 500km 5= over 500km	Has there ever been a compliance/adherence problem in the past? (YES/NO)	Were there any of the following social issues (specify relevant): 1.Transport problems 2.Family problems 3. Personal problems 4.Other social problems	HIV treatment line (specify)	Treatment line 1= first line 2 =second line 3= 3rd line salvage	(non name identifier)
	Year of first treatment	Previous treatment switches (YES/NO)	SWITCHES	Initial CD4 count (cells/mm3)	Last CD4 count in 2013 (cells/mm3)	Last virological level in 2013	Outcome of patient (1=Active 2= Transferred out 3=Loss)	Virologic status (1=Controlled 2=Failure)

								to follow-up 4. Died)	
Is there a non-AIDS defining condition shown in the record? -NADC1 (YES/NO)	Specify NADC 1	Specify-List the treatment of NADC1	List the problems relating to NADC1 and ARV	Were there any problems warranting change of treatment of HAART or NADC relating to either HAART or NADC treatment?					What is the level of control of the NADC ?(controlled, uncontrolled, progressive, unknown)



<p>Is there a non-AIDS defining condition shown in the record NADC2? (YES/NO)</p>	<p>Specify NADC2</p> 	<p>Specify-List the treatment of NADC 2</p>	<p>List the problems relating to NADC2 and ARV</p>	<p>Were there any problems warranting change of treatment of HAART or NADC2 relating to either HAART or NADC treatment?</p>	<p>What is the level of control of the NADC? (controlled, uncontrolled, progressive, unknown)</p>
<p>Is there a third non-AIDS defining condition shown in the record NADC3 (YES/NO)</p>	<p>Specify NADC 3</p>	<p>Specify-List the treatment of NADC3</p>	<p>List the problems relating to NADC1 and ARV.</p>	<p>Were there any problems warranting change of treatment of HAART or NADC relating to either HAART or NADC treatment?</p>	<p>What is the level of control of the NADC? (controlled, uncontrolled, progressive, unknown)</p>



Is there evidence of more than three NADCs	Specify List the NADCs	Specify list treatment of the NADCs Treatment	Specify-list problems of NADC and ARV	Was there any problems warranting change of treatment of HAART or NADC	What is the level of control of the NADCS ?(controlled, uncontrolled, progressive, unknown)
<p>Data capturer's remarks</p> <div data-bbox="919 654 1178 899" style="text-align: center;">  <p>UNIVERSITY of the WESTERN CAPE</p> </div>					

APPENDIX 2

PLOT 1836 HOSPITAL WAY  
TELEPHONE: 3621400  
FAX: 3973776



RE PUBLIC OF BOTSWANA

PRINCESS MARINA HOSPITAL  
P. O. BOX 258  
GABORONE  
BOTSWANA

REF: PMH 5/79(138)  
Dr Patrick Masokwane  
Ministry of Health  
Gaborone

4<sup>th</sup> February 2015

Dear Dr Masokwane

**RE: Prevalence of non-AIDS defining conditions in adult patients on antiretroviral treatment and their association with HIV virologic treatment failure in Botswana**

The Research and Ethics Committee (REC) of Princess Marina Hospital reviewed your request to conduct the study with the aforementioned title on January 29, 2015 and **full approval** is given.

You are requested to observe the following:

1. You must get approval from head of department in the unit that you intend to do your research
2. You will not change any aspect of your research without permission from the REC
3. You need to report any unforeseen circumstances including the termination of the study to the REC
4. You should allow the REC access to the study at anytime for purposes of auditing
5. This permission is valid for a duration of 1 year 30<sup>th</sup> January 2015 to 29<sup>th</sup> January 2016
6. At the end of the study, you are asked to give the research and ethics committee a hard copy and soft copy of your report

Thanking You

Sincerely,

A handwritten signature in black ink, appearing to read 'Gladness O. Thomelang'.

Gladness O. Thomelang  
Secretary Research and Ethics Committee

APPENDIX 3

TELEPHONE: 363 2766  
FAX: 391 0647  
TELEGRAMS: RABONGAKA  
TELEX: 2818 CARE BD



Republic of Botswana

MINISTRY OF HEALTH  
PRIVATE BAG 0038  
GABORONE

REFERENCE NO: PPME 13/18/1 IX (208)

16 February 2015

Health Research and Development Division

Notification of IRB Review: New application

Dr Patrick Masokwane  
P.O. Box 32  
Gaborone

Protocol Title:



**THE PREVALENCE OF NON-AIDS  
DEFINING CONDITIONS IN ADULT  
PATIENTS ON ANTIRETROVIRAL  
TREATMENT AND THEIR ASSOCIATION  
WITH HIV VIROLOGIC TREATMENT  
FAILURE IN BOTSWANA**

HRU Approval Date:	16 February 2015
HRU Expiration Date:	16 February 2016
HRU Review Type:	HRU reviewed
HRU Review Determination:	Approved
Risk Determination:	Minimal risk

Dear Dr Masokwane

Thank you for submitting new application for the above referenced protocol. The permission is granted to conduct the study.

This permit does not however give you authority to collect data from the selected site without prior approval from the management. Consent from the identified individuals should be obtained at all times.

The research should be conducted as outlined in the approved proposal. Any changes to the approved proposal must be submitted to the Health Research and Development Division in the Ministry of Health for consideration and approval.

Furthermore, you are requested to submit at least one hardcopy and an electronic copy of the report to the Health Research, Ministry of Health within 3 months of completion of the study.

Approval is for academic fulfillment only. Copies should also be submitted to all other relevant authorities.

#### **Continuing Review**

In order to continue work on this study (including data analysis) beyond the expiry date, submit a Continuing Review Form for Approval at least three (3) months prior to the protocol's expiration date. The Continuing Review Form can be obtained from the Health Research Division Office (HRDD), Office No. 7A.7 or Ministry of Health website: [www.moh.gov.bw](http://www.moh.gov.bw) or can be requested via e-mail from Mr. Kgomotso Motlhanka, e-mail address: [kgmmotlhanka@gov.bw](mailto:kgmmotlhanka@gov.bw). As a courtesy, the HRDD will send you a reminder email about eight (8) weeks before the lapse date, but failure to receive it does not affect your responsibility to submit a timely Continuing Report form.

#### **Amendments**

During the approval period, if you propose any change to the protocol such as its funding source, recruiting materials, or consent documents, you must seek HRDC approval before implementing it. Please summarize the proposed change and the rationale for it in the amendment form available from the Health Research Division Office (HRDD), Office No. 7A.7 or Ministry of Health website: [www.moh.gov.bw](http://www.moh.gov.bw) or can be requested via e-mail from Mr. Kgomotso Motlhanka, e-mail address: [kgmotlhanka@gov.bw](mailto:kgmotlhanka@gov.bw). In addition, submit three copies of an updated version of your original protocol application showing all proposed changes in bold or "track changes".

#### **Reporting**

Other events which must be reported promptly in writing to the HRDC include:

- Suspension or termination of the protocol by you or the grantor
- Unexpected problems involving risk to subjects or others
- Adverse events, including unanticipated or anticipated but severe physical harm to subjects.

If you have any questions, please do not hesitate to contact Mr. P. Khulumani at [pkhulumani@gov.bw](mailto:pkhulumani@gov.bw), Tel: +267-3914467 or Lemphi Moremi at [lamoremi@gov.bw](mailto:lamoremi@gov.bw) or Tel: +267-3632754. Thank you for your cooperation and your commitment to the protection of human subjects in research.

Yours sincerely



P. Khulumani  
**For Permanent Secretary**



MINISTRY OF HEALTH

**Vision:** Model of Excellence in Quality Health Services

**Values:** *Botho, Equity, Timeliness, Customer Focus, Teamwork, Accountability*



APPENDIX 4



**UNIVERSITY of the WESTERN CAPE  
DEPARTMENT OF RESEARCH DEVELOPMENT**

**UNIVERSITY OF THE WESTERN CAPE**

**Faculty of Community and Health Sciences**

**School of Public Health**



**CONFIDENTIALITY PLEDGE OF RESEARCH ASSISTANT**

**STUDY TITLE:**

**THE PREVALENCE OF NON-AIDS DEFINING CONDITIONS IN ADULT PATIENTS ON ANTI-RETROVIRAL TREATMENT AND THEIR ASSOCIATION WITH HIV VIROLOGIC TREATMENT FAILURE IN BOTSWANA**

**Principal Investigator: Dr P. Masokwane (MPH Student University of Western Cape/Principal Medical Officer-Ministry of Health Botswana.)**

I \_\_\_\_\_ of Omang/Passport number \_\_\_\_\_ as a research assistant to the above mentioned study do make a confidentiality pledge for this study.

I pledge that I will not divulge the names or any identifying details in the records that I may see under this study to anybody or any third party.

I am aware that these records carrying confidential information of patients are under custody of Princess Marina Hospital.

I am aware that any breach of confidentiality on my side will not be liability of the Principal Researcher, the Ministry of Health or University of the Western Cape. I am aware that such breach may lead to ethical or legal ramifications that I may be answerable to.

Signed: \_\_\_\_\_

Witness: \_\_\_\_\_