Metabolic syndrome among people with Human Immunodeficiency Virus on Anti-retroviral Therapy at Princess Marina Hospital in Gaborone-Botswana

By

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DECLARATION

I, **Mr. Desire Bekithemba Mhlabi**, hereby declare that the work on which this dissertation is based, is original (except where acknowledgement indicate otherwise) and that neither the whole work nor any part of it has been , is being, or shall be submitted for another degree at this or any other university.

…… ……

Signature Date

DEDICATION

To my late mother, Perpetua and baby love Desiree

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ACRONYMS AND ABBREVIATIONS

3TC	Lamivudine
AIDS	Acquired Immunodeficiency Syndrome
ALT	Alanine Aminotransferase
AMI	Acute Myocardial Infarction
ART	Antiretroviral Treatment
ARV	Antiretroviral
AST	Aspartate Aminotransferase
ATPIII	Adult treatment panel 3
AZT	Zidovudine
BMI	Body Mass Index
CD4	Cluster of Differentiation 4
CVD	Cardiovascular Disease
DBP	Diastolic Blood pressure
EFV	Efivarenz
FTC	Emtricitabine
GDP	Gross Domestic Product
HAART	Highly Active Antiretroviral Therapy
HCT	HIV Counseling and Testing
HDL-C	High Density Lipid Cholesterol
PI	Protease Inhibitor
PMH	Princess Marina Hospital
IDCC	Infectious Disease Centre Clinic

IDF	International Diabetes Federation
LDL-C	Low Density Lipid Cholesterol
LPV/r	Lopinavir
MASA	Setswana word meaning "*New Dawn*"
MI	Myocardial Infarction
MOH	Ministry of Health
MREC	Medunsa Campus Research Ethics Committee
MS	Metabolic Syndrome
NACA	National Aids Coordinating Agency
NCTP	National Cholesterol Treatment Program
NNRTIs	Non-Nucleoside Reverse-Transcriptase Inhibitors
NRTIs	Nucleoside Reverse-Transcriptase Inhibitors
NVP	Nevarapine
RTV	Rotonavir
SBP	Systolic Blood Pressure
SD	Standard Deviation
TDF	Tenofovir
UN	United Nations
UNAIDS	United Nations AIDS Agency
UNICEF	United Nations Children's Fund
US	United States of America
WHO	World Health organization

SUMMARY

Background and Purpose of the study

Botswana was the first country in Africa to aim to give antiretroviral treatment to all its HIV positive deserving citizens in 2001. This brought about a significant improvement in survival and quality of life of HIV infected patients as well as a dramatic decrease in the incidence of opportunistic infections. However, although many reports about metabolic abnormalities and abnormal body fat distribution among people on ART have been published elsewhere, little is known about this in Botswana. The purpose of this study was to investigate the prevalence and factors associated with development of metabolic syndrome among people with HIV on ART at the IDCC Clinic at Princess Marina Hospital, Gaborone, Botswana.

Methods

This was a cross-sectional study based on patient interviews and review of records. A structured questionnaire and a data collection form were used to collect data on demographic, socioeconomic, lifestyle, clinical and laboratory data. Metabolic Syndrome was defined using the International Diabetes Federation (IDF) criteria. Patients who consented to participate were interviewed and their records were reviewed to collate data. Only patients that had been on treatment from January to December 2010 were included.

Results

A total of 190 subjects participated in the study, 141 (74.2%) females and 49 (25.8%) males. The age of the participants ranged from 24 to 71 with a median age of 40.5 years (IQR: 35 – 49). The overall prevalence of metabolic syndrome in this study was 11%. Metabolic syndrome was associated with traditional risk factors such as hypertension and high triglycerides; but with some unique features such as age, current employment and current NRTI use were also identified. In the bivariate analysis to identify the determinants of metabolic syndrome, the odds for developing MS were higher among participants who were married, employed, on a salary and used ART regimens containing NRTIs. High cholesterol, fasting blood glucose and triglycerides were also associated with the development of metabolic syndrome. There was a significant association with age as people over 45 years were significantly shown to have metabolic syndrome than the younger ones. The median age of participants who had metabolic syndrome was higher at 45 years (IQR: 39 – 53 years) that those without metabolic syndrome at 40 years (IQR: 34 – 48). Married participants were 13 times more likely to develop MS than their unmarried counterparts [OR (95%CI)]: 13 (1.91 - 88.35), p=0.009]. Participants who were employed and had a salary as their source of income were 27.54 times more likely to develop MS although the difference was not statistically significant. The type of regimen affected the prevalence of metabolic syndrome; in fact Up to 17 of the 21 participants with metabolic syndrome used a combination of drugs with NRTIs and NNRTIs as well as PI in 8 cases. So the use of a protease inhibitor based ART regimen increased the odds of developing MS by 51.57 times [OR (95%CI)]: 51.57 (1.55 – 1709.64), p=0.027]; while in case of NRTIs the odds were 78.53 times more for the likelihood to develop MS [OR (95%CI)]: 78.53 (1.10 – 5565.50), p=0.044].

Although there was no significant association between the duration of ART and the development of metabolic syndrome; the median duration of ART among participants with metabolic syndrome was higher at 68 months (IQR: 51 – 80) compared to those without metabolic syndrome at 56 months (IQR: 40 – 68). With regard to sex, 16.3% of the male participants had metabolic syndrome compared to 9.2% among the females; but the difference was not statistically significant.

Conclusion

In conclusion, the prevalence of metabolic syndrome was low, affecting only 11% of the study participants. The factors associated with the occurrence of the syndrome were the male sex, the long duration on treatment, being married, employed, and over 45 years old. The most significant factors were being on NRTIs and PIs containing regimens. These findings suggest that patients on antiretroviral treatment with the above characteristics should be monitored regularly for metabolic syndrome.

CHAPTER 1: INTRODUCTION

1.0 Background

Metabolic syndrome was first described in 1998 by Reaven as "Syndrome X," although it was previously alluded to as multi-metabolic syndrome or insulin resistance syndrome. Metabolic syndrome is an aggregation of central obesity and metabolic abnormalities that confer and increased risk of cardiovascular disease and type 2 diabetes mellitus. It is thus said to consist of a cluster of metabolic risk factors including dyslipidemias, impaired carbohydrate metabolism, obesity and high blood pressure. Several definitions have been suggested for the metabolic syndrome including the US National Cholesterol Treatment Program – Adult treatment panel III criteria, the International Diabetes Federation definition and the WHO definition.

According to Alberti & Zimmet (1998) the WHO definition of metabolic syndrome which was later adopted in 1999 is impaired glucose tolerance, impaired fasting glycemia, diabetes plus two or more of the following:

- Waist-Hip Ratio > 0.85 (women) 0.90 (man) and/or BMI > 30kg/m^2
- Fasting triglycerides ≥ 1.70 mmol/L
- SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg
- Fasting Cholesterol ≥ 5.2 mmol/L

The US National Cholesterol Education Program-Adult Treatment Panel 3 (NCEP-ATP III) defined metabolic syndrome as any three or more of the following:

- Waist circumference > 88 cm (woman), > 102 (man)
- Fasting triglycerides ≥ 1.70 mmol/L
- SBP ≥ 130 mmHg and/or DBP ≥ 85 mmHg
- Fasting Cholesterol ≥ 5.2 mmol/L
- Fasting Glucose ≥ 6.1mmol/L

The International Diabetes Federation (IDF) definition of metabolic syndrome by Alberti et al., (2005), includes a waist circumference > 80 cm (woman), > 94 (man) plus two of the following:

- Fasting triglycerides > 1.70 mmol/L or use of triglycerides lowering drugs
- SBP ≥ 130 mmHg and/or DBP ≥ 85 mmHg, or blood pressure lowering treatment
- Fasting plasma glucose ≥ 5.6 mmol/L, or anti-diabetic treatment
- Fasting Cholesterol ≥ 5.2 mmol/L

This IDF definition of metabolic syndrome therefore dictates that central obesity plays a central role and hence mandatory in the criteria.

This chapter introduces the dynamics associated with the development of metabolic syndrome among people with HIV using antiretroviral therapy. ART has positively modified the natural history of HIV infection, leading to a significant reduction in morbidity and mortality. However, long-term toxicity of the drugs is being recognized, and a variety of other abnormalities including dyslipidemias, fat redistribution, hypertension and insulin resistance. There is a concern that people on ART in the long term may be at increased risk for cardiovascular disease.

1.1 HIV in Africa

Sub-Saharan Africa is more heavily affected by HIV and AIDS than any other region in the world. The 2009 UNAIDS report on the global AIDS epidemic estimates that 22.4 million people are living HIV in the region which is around two-thirds of the total worldwide. The report further states that in 2008 alone around 1.4 million people died from AIDS in the sub region while 1.9 million new HIV infections were recorded. The social and economic consequences of the AIDS epidemic are widely felt as it continue to devastate communities and families, rolling back decades of development progress.

Prevalence rates of HIV in Africa differs by region and country with countries like Somalia and Senegal reporting under 1% while Namibia, South Africa, Zambia and Zimbabwe report prevalence rates of between 15 – 20%. The highest prevalence rates of between 23 – 27% are reported in Botswana, Lesotho and Swaziland.

The sub-Saharan Africa region therefore faces challenges related to

- Reducing new HIV infections by educating and empowering people to protect themselves and others.
- Coping with the impact of deaths as a result of AIDS, ever increasing number of orphans.
- Providing healthcare, anti-retroviral treatment, and support for people living with HIV related illnesses

Antiretroviral drugs (ARVs) which significantly delay the progression of HIV to AIDS allowing people with HIV to live relatively normal, healthy lives have been difficult to come by for many in need Africans with WHO, UNAIDS and UNICEF reporting in 2010 that less than 4 in 10 of those in need of treatment are actually receiving it. Botswana pioneered the provision of ARVs in Africa by starting a national treatment program in 2002.

1.2 Overview of Botswana's healthcare system and HIV

Botswana is a landlocked country in the Southern African region bordered by South Africa, Zimbabwe, Zambia and Namibia (UN, 2007) and has an estimated population of 1.84 Million people sparsely distributed over a semi-arid land of about 582,000 square kilometers. Botswana is regarded as a middle income country, with a per capita GDP of US$ 6, 200 as at 2009. The official language in Botswana is English but ethnically Botswana is almost homogenous with 79% of the population speaking Setswana, 11% Kalanga, 3% SeKgalagadi, 2% Sembukushu, 2% Sesarwa with the remaining 3% speaking a range of other languages.

The healthcare system in Botswana is based on the Primary Healthcare Model with emphasis on access to basic health services. Healthcare provision has been a joint responsibility of the Ministries of Health and that of Local Government although the Ministry of Health has now been tasked with taking overall responsibility. The public health system comprises 2 referral hospitals, 6 district hospitals, 17 primary hospitals, 1 mental hospital, 257 clinics, 336 health posts and 761 mobile units. Just like the rest of the sub region, human resources for health are scarce in Botswana with a reported 40 physicians and 265 nurses per 100, 000 people in 2004.

1.2.1 HIV in Botswana

Botswana is one of the countries hardest hit by HIV with an estimated 300,000 adults or one quarter of the population aged 15 and over living with HIV (UNAIDS 2010). UNAIDS (2010) also reports an HIV prevalence of 24.8 % among 15 – 49 year olds, the second highest in the world after Swaziland. According to the United Nations (2004) life expectancy in Botswana fell from 65 years in 1990 – 1995 to less than 40 years in 2000 – 2005, a figure about 28 years lower than it would have been without HIV/AIDS. An estimated 93,000 children have one or both parents to the AIDS epidemic with the economic output of Botswana being reduced by the loss of skilled manpower particularly in the mining and agriculture sectors.

In 1999, the National AIDS Coordinating Agency (NACA) was formed and given the responsibility to mobilize and coordinate a multi-sectoral national response to HIV and AIDS. The First National Strategic framework (2003 – 2009) spearheaded the multi-sectoral national response leading to developments like introduction of routine HIV testing, increased VCT centers and the provision of ARV through the public sector.

1.2.2 HIV and AIDS treatment in Botswana

In response to the emergency posed by the AIDS epidemic, Botswana became the first African Country to aim to provide antiretroviral drugs to all its needy citizens. The expected benefits of the program were

- to enable people with HIV to live longer, healthier lives
- to offer incentive for HIV testing and to lower the rate of transmission
- to decrease the number of children orphaned each year by AIDS
- to maintain skills in the workforce necessary for economic development

In 2002 the national antiretroviral program was given the name MASA, a Setswana word for "New Dawn". By May 2004, more than 24,000 people had been enrolled by MASA program reaching up to 36,000 by end of year, 43,000 by June 2005 and 54,378 by September and according to WHO (2006), 85% of people in need of drugs were receiving them by end of 2005. NACA reported in April 2010 that by the end of 2009 coverage had reached 89.8 % when around 145,000 people were receiving treatment with estimated increases of up to 170,000 in 2010. However the latest WHO guidelines (implemented in 2010) recommend starting treatment earlier meaning that coverage in Botswana is at about 83% in 2010. Mass treatment at such a magnitude has not come without challenges among them adverse events of drugs among people using them.

Before the commencement of antiretroviral treatment, baseline laboratory investigations recommended include full blood count, full chemistry including AST/ ALT, glucose, urea, creatinine, total cholesterol, triglycerides and RPR. Current recommendations are that glucose, total cholesterol and triglycerides are monitored only annually among patients on PI-based HAART. CD4 and HIV viral load monitored at 3 and 6 months post HAART initiation and if it has reached the target CD4 of > 400 cells/μL and VL < 400 copies/ mL then monitoring is done every 6 months for adults and remains every 3

months for patients under 20 years old due to high failure rates among pediatric and adolescent patients.

1.3 Background of ART

Antiretroviral drugs are divided into five drug classes:

- Protéase Inhibitors (PIs) – Indinavir, Atazanavir, Tipranavir, Darunavir, Nelfinavir, Fosamprenavir and Saquinavir
- Nucleoside Reverse Transcriptase Inhibitor (NRTIs) – Abacavir, Tenofovir, Stavudine, Lamivudine, Didanosine, Emtricitabine and Zidovudine
- Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTIs) – Efivarenz, Nevarapine
- Entry Inhibitors - Fusion Inhibitor (Enfuvirtide) and CCR5 Inhibitor (Maraviroc)
- Integrase Inhibitors - Raltegravir

The 2008 Botswana guidelines for HAART states that, the first-line regimen is made of 2 NRTIs and EFV or NVP; while the second-line regimen consists of 2 NRTIs and LPV/r.

1.3.1 Standard regimen for first-line therapy

TDF 300mg OD, 3TC 150mg BD or 300mg OD, EFV 200mg capsules or 600mg tablets. Co-formulated regimens include TDF/FTC ("Truvada"): 300mgTDF + 200mgFTC or a combination of TDF/FTC/EFV ("Atripla"): 300mgTDF + 200mg FTC + 600mg EFV. Other dosages include NVP 200mg BD

1.3.2 Standard regimen for second-line therapy

AZT 300mg BD, 3TC 150mg BD or 300mg OD, LPV/r 400mg/ RTV 100mg BD. Kaletra (LPV/r 133mg/ RTV 33mg): 3 capsules BD while Aluvia (LPV/r 200md/RTV 50mg): 2 tablets BD.

1.4 Metabolic Syndrome among HIV Positive people on HAART

The introduction of highly active antiretroviral therapy (HAART) significantly improved the clinical outcome of HIV disease, with increased survival rates but is also associated adverse events such as lactic acidosis, renal complications, liver complications, lipodystrophy and metabolic syndrome among others.

Barbaro et al (2009) suggested that HAART regimens, especially those including protease inhibitors (PI) have shown to cause in a high proportion of people lipodystrophy/ lipoatrophy and metabolic disorders (dyslipidemia, insulin resistance) changes than in the general population. Samaras (2007) reported that HAART confers immunological and survival advantages albeit at the cost of induction of significant metabolic disturbances like insulin resistance, dyslipidemia, diabetes mellitus, adipocyte physiology disturbances and lipodystrophy. These complications have become apparent with increasingly widespread and longer term use of HAART.

1.4.1 Metabolic Complications

The occurrence of a metabolic syndrome can be associated with some complications such as:

- **Insulin Resistance** – this is reduced action of circulating insulin to induce uptake of glucose into cells. This is a core feature in type 2 diabetes mellitus patients. Reaven (1988) described insulin resistance as "common soil" from which all metabolic diseases develop. Insulin resistance is therefore considered as the link for abdominal obesity, diabetes mellitus, coronary heart disease, hypertension and dyslipidemia.
- **Dyslipidemia** – characterized by abnormal total cholesterol, HDL cholesterol, LDL cholesterol and triglycerides.

- **Lipodystrophy** – characterized by changes in body fat partitioning while Lipoatrophy refers to the diminution of fat tissue in the subcutaneous tissues of the limbs. Guaraldi et al (2008) suggested from clinical experience that lipodystrophy has a profound impact on quality of life with body image changes that may stigmatize patients, eroding self-esteem, decreasing socialization including sexual relations leading to anxiety and depression. They went on the explain that lipodystrophy may result in involuntary disclosure of HIV status and may be correlated to suboptimal adherence to therapy
- **Hypertension** – Persistent high blood pressure
- **Diabetes Mellitus** – Development of type 2 or late onset diabetes mellitus usually associated with obesity.

1.5 Problem statement

According to WHO 2010 guidelines, 83% of people needing ART in Botswana are receiving medication. Highly Activated Antiretroviral Therapy (HAART) has dramatically changed the prognosis of AIDS, but in some cases may lead to long-term toxicities of antiretroviral drugs. Since the introduction of ART, there has been a significant improvement in survival of patients infected with HIV together with a dramatic decrease in the incidence of many opportunistic infections. Metabolic abnormalities and abnormal fat distribution have however been observed and follow a similar pattern to that described for metabolic syndrome. Literature has also shown that there is accumulating evidence of association between HAART and development of chronic heart disease. A major chronic complication is the metabolic syndrome, including hyperlipidemia, lipodystrophy (LD), and impaired glucose metabolism. The Botswana 2008 guidelines for laboratory investigations for HIV positive people on HAART includes CD4, HIV Viral load, Full blood count, liver function tests, kidney function tests every 3 months and annually tests are recommended for glucose, total cholesterol, HDL and LDL cholesterol, and triglycerides at the discretion of the attending clinician or if a patient is on PI based HAART. These guidelines are based on the Kitso training manual, (2008) produced by

the Botswana-Havard Partnership for HIV Research. This manual is used to train health workers advances in HIV management.

The net effect of ART in Botswana may be survival and improved quality of life for people living with HIV, it is expected that complications of ART including metabolic abnormalities will be observed and the magnitude of the problems has not yet been explored. With over 145,000 people on HAART in Botswana ,the extent to which the metabolic syndrome or its components is associated with this widespread use of HAART by HIV positive people in Botswana is unknown hence this was investigated at a local hospital level to answer the questions below.

1.5.1 Research Questions

- What is the prevalence of metabolic syndrome in a sample of HIV positive people on ART at the IDCC Clinic in Gaborone, Botswana?
- What is the distribution of the metabolic syndrome among these patients with regard to socio-demographic and clinical factors?
- What factors are associated with the presence of metabolic syndrome in these patients?

1.5.2 Purpose of the study

To investigate the prevalence and clinical factors associated with development of metabolic syndrome among people with HIV on ART at the IDCC Clinic at Princess Marina Hospital, Gaborone, Botswana.

1.5.3 Objectives of the study

i) To determine the prevalence of metabolic syndrome in HIV positive people on antiretroviral therapy at the IDCC Clinic at Princess Marina Hospital, Gaborone-Botswana.

ii) To determine the distribution of metabolic syndrome among HIV positive people on ART with regard to socio-demographic factors (age, and gender) of the patients at the IDCC Clinic at Princess Marina Hospital, Gaborone-Botswana.

iii) To determine the clinical factors (body mass index, comorbidities, drug regimen, smoking status, alcohol drinking status, and duration of treatment) associated with the presence of metabolic syndrome in these patients

1.5.4 Operating Definition

Metabolic Syndrome – for purposes of this study has been defined using the IDF 2005 definition as follows, waist circumference > 80 cm (woman), > 94 (man) plus two of the following

- Fasting triglycerides > 1.70 mmol/L or use of triglycerides lowering drugs
- SBP ≥ 130 mmHg and/or DBP ≥ 85 mmHg, or blood pressure lowering treatment
- Fasting plasma glucose ≥ 5.6 mmol/L, or anti-diabetic treatment
- Fasting Cholesterol ≥ 5.2 mmol/L

1.6 Justification and rationale for the study

Studies have shown that although HAART has had considerable success in improving the mortality and morbidity outcomes of people infected with HIV, long-term treatment can result in the appearance of several secondary effects among them HAART treatment associated lipodystrophy syndrome (HALS) (Lukman et al, 2007). The author further stated that HALS is usually associated with peripheral fat wasting, central adiposity, in some cases lipomatosis, as well as systemic insulin resistance and hyperlipidemia (components of metabolic syndrome). The current Botswana guidelines for laboratory investigations for people on HAART do not include metabolic

syndrome components like obesity and also the guidelines recommend testing of lipids and glucose only annually; but for other biochemical markers like liver function tests and kidney function tests they are investigated quarterly. Since, HAART is a lifetime commitment, metabolic syndrome components tend to develop slowly over time. It is envisaged that the findings of this study may point out the need for a policy shift with regard to the testing for metabolic syndrome components. Moreover, knowing the extent of the problem will assist clinicians in taking the necessary precautionary measures in the management of HIV positive people on ART to reduce the risk of developing metabolic syndrome.

CHAPTER 2: LITERATURE REVIEW

2.0 Introduction

This section summarizes the literature with a focus on the work that has been done previously regarding the metabolic syndrome. There is a brief focus on prevalence rates of metabolic syndrome in various population groups and regions of the world. The review also elaborates on the demographic factors and clinical characteristics and their association with development of metabolic syndrome.

2.1 Prevalence of Metabolic Syndrome among patients on HAART

Several studies have been carried out on the subjects of metabolic syndrome, HIV/ AIDS, ART and Metabolic Syndrome among HIV positive on ART. Studies across regions have studied prevalence rates of metabolic syndrome, risk factors associated with metabolic syndrome, prevalence rates of HIV, HIV treatment programs, and adverse events of HIV treatment including metabolic syndrome. Not a lot of studies have been carried out in Botswana on metabolic syndrome but a few notables include a study by Sales *et al., (2009)* in a cohort of asymptomatic and antiretroviral treatment-naïve HIV positive adults while another by Garrido *et al., (2009)* focused on metabolic syndrome among health workers at a Seventh-day Adventist run hospital.

The prevalence of metabolic syndrome varies significantly between countries and ethnic groups with Europeans and white Americans having rates between 20 and 30% (Park *et al* 2003). Sidorenkov *et al (2010)* concluded that the prevalence of metabolic syndrome is associated with lifestyle, demographic, socio-economic, and genetic factors. Sales conducted a study in Botswana whose objective was to determine the prevalence of metabolic syndrome in a cohort of asymptomatic and antiretroviral treatment- naïve HIV + adults and reported a prevalence of 7.7% with high percentages of obesity (11.6%) and hypertension (31.9%).

Numerous studies carried out outside Africa estimated the prevalence of metabolic syndrome in HIV-positive HAART recipients and in a study among a large international cohort, Samaras et al (2007) reported that the prevalence of metabolic syndrome among people using HAART was between 14% (IDF definition) and 18% (ATP III definition) and that metabolic syndrome was more common among participants using PIs. Samaras also observed that MS was associated with greater insulin resistance, lipid disturbances, higher BMI, and use of Lopinavir-Ritonavir boosted and Didanosine. Palacios et al (2007) concluded that the prevalence of metabolic syndrome in a cohort of HIV-infected HAART recipients increased from 16% to 25% over a 48 week follow-up with an incidence rate of 14/100 patient years. Wand et al (2007) did a 3 year study following HAART initiation in HIV treatment-naïve patients and reported a baseline prevalence of 9% with an incidence of 12/100 per years. Wand H et al further reported that the risk of diabetes was increased 4 to 5 fold and cardiovascular disease 3 fold among patients developing metabolic syndrome. Another study reported that the prevalence of metabolic syndrome in HIV infected individuals varied from 15% to 25.5% considering the difference in ethnicity and habits of populations (Squillace et al., 2008).

Brown et al (2005) reported that 10% of HIV patients treated with HAART developed diabetes during 4 years of follow-up, compared with 3% in HIV – sero-negative men. After adjusting for age and BMI, this difference represented a 4-fold increase in relative risk of developing diabetes. In a study in Brazil, Da Silva et al (2008) reported no significant difference in the prevalence of MS among HIV positive people and HIV negative people at 13% and 12% respectively using the ATP III definition. This was in contrast to what Alvarez et al (2010) reported in a study focusing on metabolic syndrome in HIV –infected patients receiving ART in Latin America who reported a prevalence rate of 20.2%.

2.2 Metabolic Syndrome and Age

Age, body mass index, postmenopausal status, diet rich in saturated fats, carbohydrates and smoking have been positively associated with metabolic syndrome (Sidorenkov et al, 2010). In a study in Nigeria, Ogbera (2010) explained that the role of age as a risk factor for metabolic syndrome could not be over-emphasized. He noted an increase in the prevalence of metabolic syndrome from 11% (20 – 29 year age group) to 89% among participants in the older (70 – 79 year age group). In Botswana, Sales et al (2009) reported age as a significant risk factor for metabolic syndrome among asymptomatic and antiretroviral treatment-naïve adults with an odds ratio of 1.10 (95% CI 1.04, 1.16, $p< 0.01$).

Age may also be a risk factor associated with HAART induced metabolic syndrome as reported by Grabar et al. (2006) that the elderly have a slower immunologic response to ART and an increased risk of developing cardiovascular disease by the association of aging, HIV infection and ART.
Using simple binary logistic regression analysis for potential associated factors for metabolic syndrome, Termizy and Mafauzy (2009) reported age as risk factor and they went on to demonstrate that age was the only independent variable that was statistically significant in the multivariate analysis using multiple binary logistic regression.

2.2.1 Metabolic Syndrome and Gender

In a study in Nigeria, Ogbera (2010) reported that the frequency of occurrence of metabolic syndrome was similar between male (83%) and female (86%) participants with type 2 Diabetes mellitus.

2.3 Obesity and Metabolic Syndrome

The International Diabetes Federation (IDF) suggests that central obesity is a pre-requisite in the definition of metabolic syndrome. Following this statement, Termizy and Mafauzy (2009) suggested that since central obesity is a feature of metabolic syndrome then the high prevalence of metabolic syndrome at a study in Malaysia was linked to the obesity epidemic. This study however found no association between metabolic syndrome and severity of obesity and therefore postulated that since the severity of obesity does not influence the risk of having metabolic syndrome, then once obesity sets in, the probability of having metabolic syndrome may be higher than for non-obese people. Sales et al (2009) reported BMI as a significant risk factor for metabolic syndrome with odds ratio of 1.26 (95% CI: 1.16, 1.36, $p< 0.01$)

2.3.1 Comorbidities and Metabolic Syndrome

Termizy & Mafauzy, (2009) reported that the lowest comorbidities to metabolic syndrome was raised fasting glucose at 17%, then high triglycerides at 36%, followed by reduced HDL Cholesterol at 40% and raised blood pressure at 42%. ART can have a wide range of adverse events such as gastrointestinal effects, fatigue and nausea. Headache and nausea are associated with AZT while nightmares are linked with use of EFV. Other adverse events include anemia, peripheral neuropathy and hypersensitivity reactions.

Lipodystrophy is characterized by loss of fat in the face and limbs and may be accompanied by accumulation of fat on the trunk and back of the neck. The alterations may stigmatize some patients as they look like AIDS patients thereby compromising their adherence potentially leading to treatment failure. Together with other metabolic disorders such as dyslipidemia and insulin resistance lipodystrophy can increase the risk of cardiovascular disease

in the long term. Milinkovic & Martinez, (2005) suggested that lipodystrophy among HIV infected patients should be considered as an adverse event of antiretroviral therapy

2.3.2 Metabolic Syndrome and ART drug regimens

Shlay (2007) reported that PI-based ART increases total and HDL – Cholesterol as well as triglycerides and these lipid effects were demonstrated to occur early. NRTIs and NNRTIs are less connected to dyslipidemias unless in combination as Shlay (2007) mentioned that combined therapy induces more severe lipid disturbances than single therapy with those whose triglycerides are high at HAART initiation showing greater deterioration in LDL-cholesterol and triglycerides. In the DAD study, Friis-Moleer et al., (2007) concluded that the incidence of acute myocardial infarction was 1.53/1000 person years in those who were not exposed to PIs and 6.01/1000 person-years among those who were exposed to PIs while Mary-Krause et al. (2003) investigated the impact of PIs on risk of myocardial infarction among HIV positive males and found that it was diagnosed in 60 men among 88,029 person years and 49 of the men were receiving PIs demonstrating a relationship between PI use and myocardial infarction, with a high incidence among men exposed to PIs for more than 18 months. Although, it has been reported that the use of NNRTIs may also be associated with lipid elevations among HIV-infected people although the significance is yet to be verified; there are few clinical data to support increased cardiovascular risk with the use of NRTIs (Kontorinis and Dieterich, 2003; Maggiolo, 2009).

2.3.3 Smoking, Alcohol Consumption and Metabolic Syndrome

Myong et al. (2009) did a study whose objective was to determine the relationship between lifestyle implementation and metabolic syndrome. The prevalence of metabolic syndrome was 13.3% but the odds ratios for metabolic syndrome increased in proportion to the number of bad habits

and the concluded that poor lifestyle like smoking, poor diet, lack of exercise and unhealthy alcohol consumption was associated with an increased likelihood for metabolic syndrome. While of the opinion that smoking is positively associated with metabolic syndrome, Sidorenkov et al. (2010) suggested inverse associations for physical activity, education, income, and alcohol intake.

2.3.4 ART Duration and Metabolic Syndrome

Jose A Perez-Molina et al (2008) suggested that HAART plays a central role in the development of lipodystrophy and associated metabolic alterations although adipose tissue disorders are already present in naïve HIV-1 infected patients. They state that although PIs were the first drugs to be associated with lipodystrophy, duration of therapy with some nucleoside reverse transcriptase inhibitors (NRTIs) was also subsequently observed to be associated with the onset of lipoatrophy.

Mulligan K et al (2001) (25) mentioned HAART duration and CD4 count at HAART initiation as factors associated with lipoatrophy with other studies establishing NRTI (particularly Stavudine) as a major contributor to peripheral lipoatrophy. The DAD study (Data collection on adverse events of anti-HIV drugs study) was conducted among a multinational cohort in 20 countries across Europe, USA and Australia by Friis-Moleer et al (2003). This study investigated the incidence of cardiovascular disease in patients with HIV and the association of risk factors for CVD and ART, and confirmed the existence of an association between duration of ART and increased risk of acute myocardial infarction.

2.4 Conclusion

From the literature, the prevalence rates for metabolic syndrome ranges from 7.7% among ART naïve HIV positive people, through 10% among people on treatment and up to 25% in some sections of the world particularly the developed world. Most of the studies suggested age as a significant risk factor with increase in age increasing the likelihood of MS. Use of PI based ART regimen has also been suggested as being strongly associated with the development of MS. Studies reviewed did not demonstrate gender as an independent risk factor while some studies linked obesity and hypertension to development of MS.

CHAPTER 3: METHODS

3.0 Introduction

This chapter introduces the methods used to obtain process and analyze information. Details of study setting, population, sampling as well as criteria for participation in the study are also discussed. Ethical considerations and approvals for carrying out the study are also explained.

3.1 Study design

This was a cross-sectional study based on administering a questionnaire to participants and reviewing their medical/clinical records. Waist circumference measurements were collected from the participants and recorded, and blood samples were collected and sent to the laboratory for biochemical markers. Blood pressure measurements were taken in triplicate and an average reading recorded. This design was chosen because it was affordable and could be done within the limited time and resources available.

3.2 Study Setting, Population and sampling

The study was conducted at the Infectious Disease Centre Clinic (IDCC) located within the Princess Marina Hospital (PMH). PMH is the biggest public tertiary referral hospital in Botswana with a 500 bed capacity and is located in the capital city (Gaborone). The population of Gaborone in 2010 was estimated at almost 250 000 people although a full census is pending in 2011. The study population comprised of all HIV positive people on antiretroviral treatment at Princess Marina Hospital from January to December 2010. The IDCC clinic only caters for the management of HIV positive people on ART hence convenience sampling was used since all the attendants to the clinic met the basic criteria of being HIV positive and being on ART. Participants still had to meet the eligibility criteria listed described below.

3.2.1 Eligibility Criteria

Informed consent was obtained for all participants. The research tool was approved by the Botswana Ministry of Health, Health Research Unit.

Inclusion criteria

- Patients living with HIV and receiving ART for at least 6 months
- Patients whose ART was started from the hospital and were over 18 years of age

Exclusion criteria

- Patients who suffered from diabetes, hypertension, and obesity before the start of ART
- Patients receiving HAART for other viral infections like Hepatitis B
- Very Sick patients

3.3 Data collection procedures

Questionnaires were administered by the Researcher and two trained research assistants, who were qualified nurses during August 2010. The interviews were conducted during three weeks. These assistants and the investigator collated data also from patients' files. Participant's waist circumferences were measured using a standard tape measure and recorded. Blood pressure was measured using a standardized digital blood pressure measuring machine in triplicate and an average recorded. Blood samples were collected by qualified phlebotomists and transported immediately to the Botswana-Havard Partnership HIV Research Laboratory (BHP) for analysis. Tests done on the equipment at the BHP laboratory are calibrated as regularly as required by methods and are also subjected to daily internal quality control monitoring. The laboratory participates in the International Thistle EQA program for external proficiency in the general chemistry category and is also ISO 17025 accredited by the South Africa National Accreditation System (SANAS).

Blood glucose, total cholesterol, HDL cholesterol and triglycerides levels were measured using the Roche Cobas 400 Plus analyzer. High Cholesterol was defined as > 5.2 mmol/L, High Triglycerides were defined as > 1.7 mmol/L while low HDL was defined as < 1.04 mmol/L. Participants were defined as having diabetes mellitus if their Fasting glucose was > 7.0 mmol/L, reported a history of diabetes, or were currently receiving treatment for diabetes (insulin or oral hypoglycemic agents).

Data on the participant's socioeconomic status was obtained from responses elicited from using a structured questionnaire. Levels of education were defined as Primary > 7 years, Secondary 8 – 12 Years, Tertiary including vocational training, college or University education, and other (which included none). Alcohol intake, tobacco use and use of recreational drugs was evaluated and classified as current use and non-current use.

3.3.1 Pre-testing

The data collection tool was pretested at the Gaborone Extension 2 ARV Clinic on 10 participants. Based on the experience from the pretesting, the data collection tool was then adjusted on sections for lifestyle and commencement of ART.

3.3.2 Conduct of interviews

Interviews were conducted by the researcher on personal medical history focusing on obesity, diabetes and hypertension prior to the use of ART. An interviewer administered questionnaire was used to collect all the relevant information. Three consecutive blood pressure measurements were recorded using a digital sphygmomanometer with appropriate cuff sizes and an average of the three was used in the present analysis. Participants' weight was done and recorded as part of their normal triage process.

Blood samples were drawn for the determination of glucose, total cholesterol, triglycerides and HDL cholesterol. Blood glucose was determined by the glucose-oxidase method using a Roche Cobas 400 plus analyzer. Total cholesterol, triglycerides and HDL Cholesterol were measured by enzymatic colorimetric methods determined using the Cobas Integra 400 Plus at the Botswana-Havard Partnership HIV Research Laboratory.

3.4 Data Analysis

Data collected was captured into Microsoft Excel (Microsoft Corp) and then exported to STATA v.11 (STATA Corp., College Station, TX) for analysis. Baseline characteristics were summarized using medians and inter-quartile range (IQR) for continuous variables. Bivariate Logistic regression was used to evaluate characteristics associated with the presence of metabolic syndrome. The following characteristics were considered for inclusion in the models; age, gender, body mass index, blood pressure, smoking status, alcohol consumption status, use of recreational drugs, ART regimen and duration of ART. Stepwise backward elimination technique was used to arrive at the final model. In this technique, analysis started with a "full model" containing all potential predictor variables collected during the study and these were then eliminated in a stepwise fashion using a significance level of 5% ($p<0.05$). All variables significant at the 20% level ($p<=0.20$) in the univariate analysis were considered for inclusion in the initial "full model". The models were tested for goodness of fit using the Hosmer-Lemeshow goodness of fit test. Interaction between all the significant variables in the model was also investigated.

3.5 ETHICAL CONSIDERATIONS

Every effort was made to ensure that procedures in conducting the study were in compliance with the ethical standards of the Helsinki Declaration as outlined below:

- Ethical approval for the research was sought from the Medunsa Campus Research Ethics Committee (MCREC) at the University of Limpopo. Further ethical approval was granted by the Botswana Ministry of Health Research Unit. To conduct research at the Princess Marina Hospital, approval was sought and granted by the PMH Institutional Research Committee as well as the IDCC Clinic Site Manager
- The privacy and dignity of the participants was preserved.
- The study and procedures were fully explained to the participants and they were also informed that their participation was voluntary.
- Prospective participants were informed of their right not to take part in the study as well as their right to withdraw at any stage in the study.
- Prospective participants were also informed that the study will involve an invasive phlebotomy procedure for collection of a blood sample and that the procedure may cause some pain or discomfort. It was also further explained that blood was going to be drawn by a qualified and experienced phlebotomist and that the samples will be used for study purposes only.
- Prospective participants who understood and volunteered to take part in the study were given a consent form to read, understand and sign if they agreed with the information about the study.
- No personal identifiers (names or addresses) of patients were collated, only their national identity number, date of birth and gender were recorded and subsequently used to assist track the results in the electronic medical records.
- Patient's records were given back to the participants for filing purposes.

CHAPTER 4: RESULTS

4.0 Introduction

This chapter presents the findings of the study. It starts with a description of the sample and ends with the presentation of the results of the bivariate analysis.

4.1 Socio-demographic characteristics of participants

A total of 204 questionnaires were completed but 14 were ruled out for analysis due to missing or incomplete laboratory biochemistry results. Therefore 190 (93%) of the participants were included in the final analysis because they had complete data.

Of the 190 participants, 49 (25.8%) were males and 141 (74.2%) were females. The ages of the participants ranged from 24 years to 71 years with mean age (SD) of 41.9 (9.0) years. Most of the participants, 80 (42.1%) were in the 31 – 40 year age group with a modal age of 34 years. The median age of the participants was 40.5 years. The prevalence of metabolic syndrome was 11% (21/190), with 13 (61.9%) females and 8 (38.1%) males. The age range of participants who had metabolic syndrome was 36 years – 71 years with a mean age of 48.1 years. The average duration of ART treatment since enrolment for the participants was 54.8 months with a median of 56 months. Table 4.1 below summarizes the socio-demographic characteristics of the respondents.

Table 4. 1: Socio-demographic characteristics of respondents (n=190)

VARIABLE	*GROUP*	*FREQUENCY*	*PERCENTAGE*
AGE	21 – 30	15	7.9
	31 – 40	80	42.1
	41 – 50	57	30.1
	51 – 60	34	17.9
	> 60	4	2.0
	TOTAL	**190**	**100**
GENDER	Male	49	25.8
	Female	141	74.2
	TOTAL	**190**	**100**
MARITAL STATUS	Not Married	156	82.1
	Married	34	17.9
	TOTAL	**190**	**100**
LEVEL OF EDUCATION	Primary	86	45.3
	Secondary	86	45.3
	Tertiary	18	9.4
	TOTAL	**190**	**100**
EMPLOYMENT STATUS	Unemployed	76	40.0
	Employed	114	60.0
	TOTAL	**190**	**100**
INCOME SOURCES	Employment	114	60.0
	Family	76	40.0
	TOTAL	**190**	**100**
LIFESTYLE	Smoker	107	56.3
	Non-smoker	83	43.7
	TOTAL	**190**	**100**
	Alcohol Use	83	43.7
	Non-Alcohol Use	107	56.3
	TOTAL	**190**	**100**
	Recreational drugs Use	0	0
	No Recreational Drugs	190	100
	TOTAL	**190**	**100**

As illustrated in table 4.1, a majority of the participants 156 (82.1%) were not married (single, cohabiting, divorced or widowed while only 34 (17.9%) reported being currently married. With regards to level of education, 86 (45.3%) of the participants finished at primary level while another, 86 (45.3%) went up to secondary, while only 18 (9.4%) had tertiary education qualifications. A majority of the participants 114(60 %) were employed and reported employment as their source of income while 76 (40 %) mentioned that they were unemployed and had family as their source of income.

In terms of lifestyle variables, 107 (56.3%) of the participants reported current smoking or tobacco use, while 83 (43.7%) reported alcohol use. None of the participants reported using recreational drugs.

4.2 Clinical and Biochemical Results

4.2.1 Clinical and biochemical data of the sample

Table 4. 2: Clinical and biochemical characteristics of respondents (n=190)

Variable	Frequency	Percentage
Now hypertensive	37	19.5
Now obese	19	10.0
Fasting Blood Glucose		
Low	1	0.5
Normal	171	90.0
High	18	9.5
TOTAL	**190**	**100**
Triglycerides		
Low	1	0.5
Normal	156	82.1
High	33	17.4
TOTAL	**190**	**100**
HDL-Cholesterol		
Low	4	2.1
Normal	174	91.6
High	12	6.3
TOTAL	**190**	**100**
Total Cholesterol		
Normal	146	76.8
High	44	23.2
TOTAL	**190**	**100**
METABOLIC SYNDROME	**21**	**11.1**

With regards to the metabolic syndrome components and biochemical tests, 37 (19.5%) of all the participants now had hypertension while 19 (10%) were obese. High fasting blood glucose was recorded in 18 (9.5%) with 33 (17.4%) having high triglycerides levels, 44 (23.2%) reporting high total cholesterol and

only 4 (2.1%) had low HDL-Cholesterol. Metabolic syndrome was therefore among 21 of the 190 participants representing a prevalence rate of 11.1%

4.2.2 ART Duration

Development of MS based on ART duration

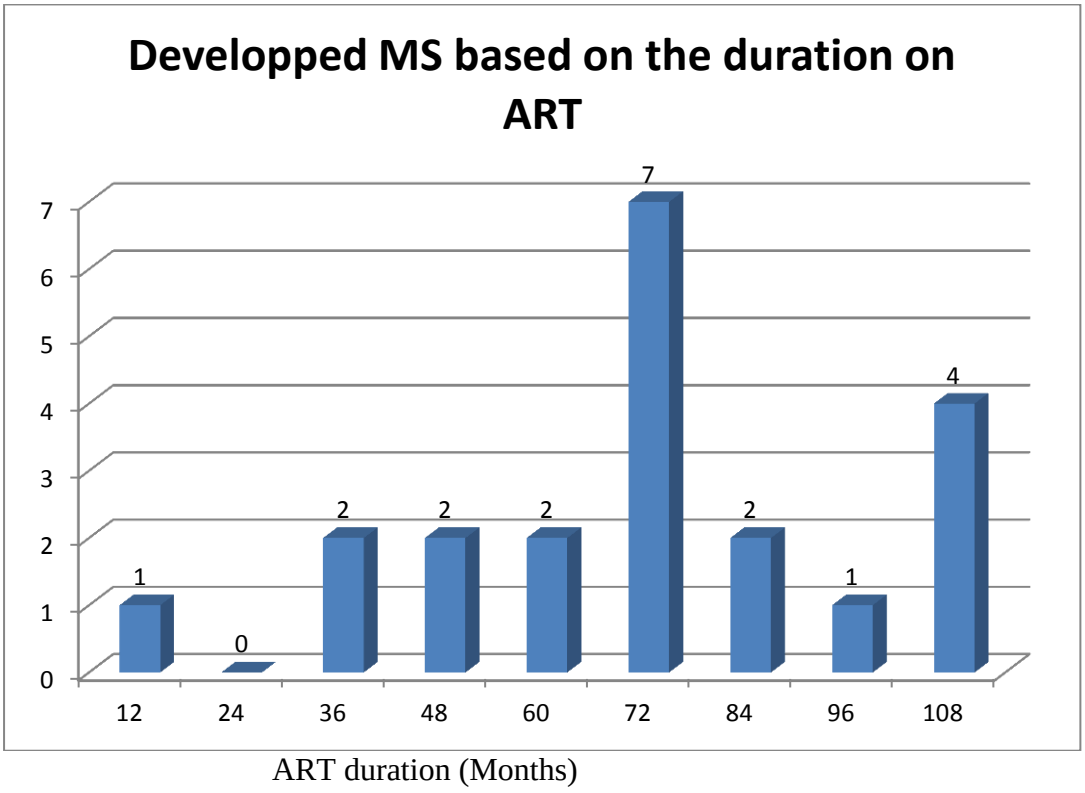

Figure 4. 1: Metabolic syndrome and duration of ART

Figure 4.2 shows the duration of treatment for participants who developed MS. The median duration of ART was 56 months (almost 5 years). Most of the participants who developed metabolic syndrome had been on ART for an extended period of time as represented by 7 (33.3%) who had been on treatment for 72 months and 4 (19.0%) who had been on treatment for 108 months. Fewer, 1 (4.8%) developed metabolic syndrome within the first 24 months of ART.

4.3 Prevalence of Metabolic Syndrome

4.3.1. Overall prevalence of metabolic syndrome

The prevalence of metabolic syndrome was 11% as represented by 21 of the 190 respondents. A majority 13 (61.9) of the participants who had metabolic syndrome were females while 8 (38.1%) were males. Most of the participants with MS were in the 41 – 50 year age group as represented by 33.3%.

Table 4. 3: *Characteristics of participants by metabolic syndrome status*

- ***n (Total)=190)***
- ***n (No MS) = 169***
- ***n (MS) = 21***

Variable	*Total*	*No MS*	*MS*	*p-value*
AGE , median (IQR)	40.5 (35-49)	40 (34-48)	45 (39-53)	**0.003**
GENDER, n (%)				
Female	141 (74.2%)	128 (75.7%)	13 (61.9%)	0.17
Male	49 (25.8%)	41 (24.3%)	8 (38.1%)	
Marital Status , n (%)				
Not Married	156 (82.1%)	146 (86.4%)	10 (47.6%)	**0.001**
Married	34 (17.9%)	23 (13.6%)	11 (52.4%)	
Education Level , n (%)				
Primary	86 (45.3%)	73 (43.2%)	13 (61.9%)	0.33
Secondary	86 (45.3%)	79 (46.8%)	7 (33.3%)	
Tertiary	18 (9.5%)	17 (10.1%)	1 (4.8%)	
Income Sources , n (%)				
Salary	114 (60%)	101 (60%)	13 (61.9%)	0.77
Family and friends	76 (40%)	68 (40%)	8(38.1%)	
Smoking status , n (%)				
Yes	107 (56.3%)	95 (56.2%)	12 (57.1%)	0.94
No	83 (43.7%)	97 (43.8%)	9 (42.9%)	
Employment status , n (%)				
Unemployed	71 (40%)	65 (40%)	11 (52.4%)	0.36
Employed	114 (60%)	104 (60%)	10 (47.6%)	
Alcohol Use , n (%)				
Yes	83 (43.7%)	72 (42.6%)	11 (52.4%)	0.4
No	107 (56.3%)	97 (57.4%)	10 (47.6%)	
ART duration , median (IQR)	56 (40-68)	56 (40-68)	68 (51-80)	
ART Regimen-containing				
PI No	155 (82%)	142 (84.5%)	13 (61.9%)	**0.01**
PI Yes	34 (18%)	26 (15.5%)	8 (38.1%)	
NNRTI No	2 (1.1%)	0	2 (9.5%)	**<0.001**
NNRTI Yes	187 (98.9%)	168 (100%)	19 (90.5%	
NRTI No	27 (14.2%)	23 (13.6%)	4 (19.1%)	0.5
NRTI Yes	163 (85.8%)	146 (86.4%)	17 (81%)	

Table 4.3 above summarizes the baseline characteristics of all the participants as well as giving a comparison of participants with and those without MS. The median age of participants who had metabolic syndrome was higher at 45 years (IQR: 39 – 53 years) that those without metabolic syndrome at 40 years (IQR: 34 – 48). With regards to gender and metabolic syndrome, 16.3% of the male participants had metabolic syndrome compared to 9.2% among the females. Most (11 = 52.4%) of the participants who had metabolic syndrome were married and a similar percentage had up to primary level of education as well as being unemployed. A majority of the participants with metabolic syndrome (57.1%) reported tobacco use. The median duration of ART among participants with metabolic syndrome was higher at 68 months (IQR: 51 – 80) compared to those without metabolic syndrome at 56 months (IQR: 40 – 68). Up to 17 of the 21 participants with metabolic syndrome used a combination of drugs with NRTIs and NNRTIs with only 8 reporting PI use.

4.3.2 Characteristics of participants with Metabolic Syndrome

Table 4. 4: Demographic characteristics of respondents with MS (n= 21)

VARIABLE	*GROUP*	*FREQUENCY*	*PERCENTAGE*
AGE	21 - 30	0	0.0
	31 - 40	6	28.6
	41 - 50	7	33.3
	51 - 60	5	23.8
	> 60	3	14.3
	TOTAL	**21**	**100**
GENDER	Male	8	38.1
	Female	13	61.9
	TOTAL	**21**	**100**
MARITAL STATUS	Not Married	10	47.6
	Married	11	52.4
	TOTAL	**21**	**100**
LEVEL OF EDUCATION	Primary	13	61.9
	Secondary	7	33.3
	Tertiary	1	4.8
	TOTAL	**21**	**100**
EMPLOYMENT STATUS	Unemployed	11	52.4
	Employed	10	47.6
	TOTAL	**21**	**100**
INCOME SOURCES	Employment	9	42.9
	Family	12	57.1
	TOTAL	**21**	**100**
LIFESTYLE	Smoker	12	57.1
	Non-smoker	9	42.9
	TOTAL	**21**	**100**
	Alcohol Use	11	52.4
	Non-Alcohol Use	10	47.6
	TOTAL	**21**	**100**

Table 4.4 illustrates the demographic characteristics of the respondents who had metabolic syndrome. Most of the respondents with metabolic syndrome were in the 41 – 50 years age group represented by 7 (33%). They were 13 (61.9%) females and 8 (38.1%) males while 11 (52.4%) of the respondents were married. A similar percentage (52.4%) of the respondents had up to primary education level, been unemployed and used alcohol. A majority (12 or 57.1%) reported smoking cigarettes.

4.3.3 Distribution of Metabolic Syndrome based on clinical parameters

Table 4. 5: Clinical and biochemical parameters of participants with MS (n=21)

VARIABLE	*OUTCOME*	*FREQUENCY*	*PERCENTAGE*
HYPERTENSION	Yes	16	76.2
	No	5	23.8
	TOTAL	**21**	**100**
OBESITY	Yes	10	47.6
	No	11	52.4
	TOTAL	**21**	**100**
Fasting Blood Glucose	Normal	10	47.6
	High	11	52.4
	TOTAL	**21**	**100**
Triglycerides	Normal	7	33.3
	High	14	66.7
	TOTAL	**21**	**100**
HDL Cholesterol	Low	1	4.8
	Normal	19	90.4
	High	1	4.8
	TOTAL	**21**	**100**

Table 4.5 summarizes the clinical and biochemical parameters of the participants who had metabolic syndrome. A majority of these participants were on PIs 13 (61.9%) and 16 (76.2%) were hypertensive as well as high triglyceride levels (14 or 66.7%).

4.3.4 ART Regimen Use among people with Metabolic Syndrome

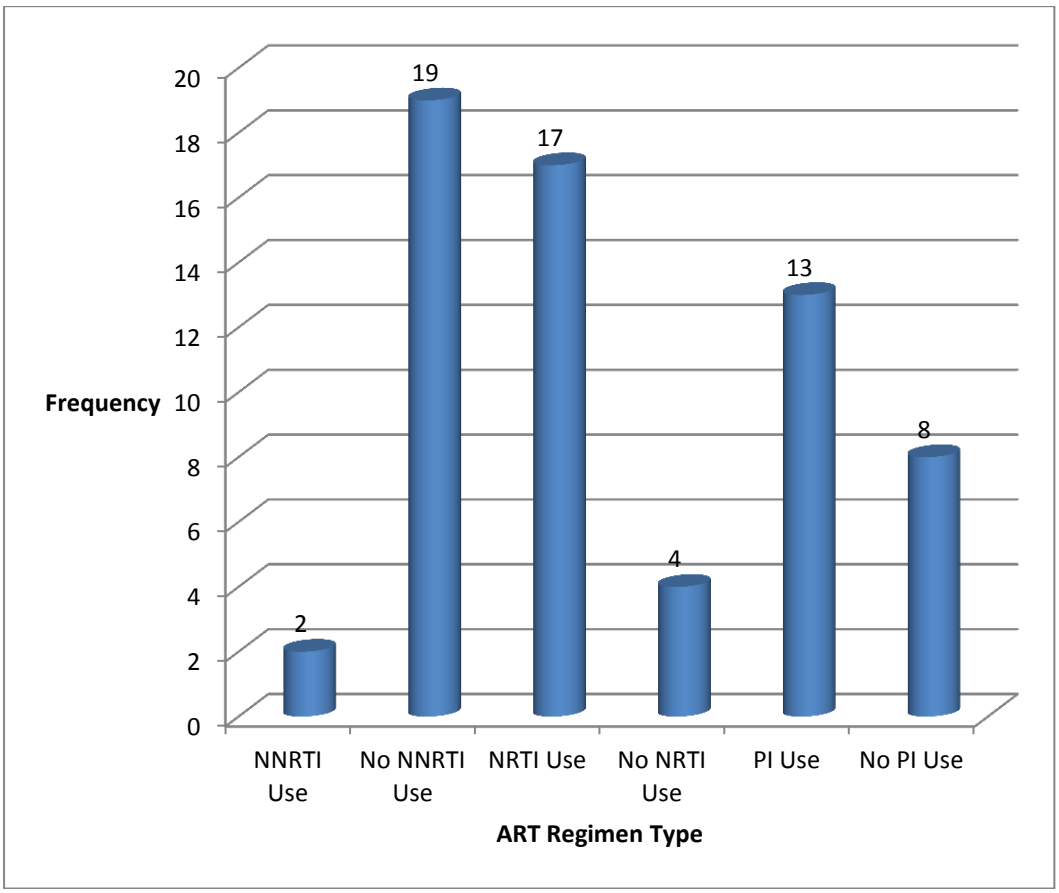

Figure 4. 2: Frequencies of ART drug regimens and metabolic syndrome

Figure 4.6 above illustrates the use of ART drug regimens among participants with metabolic syndrome. Most, 17 (81%) of the participants with metabolic syndrome used ART drug combination with NRTIs while 13 (61.9%) used PI based regimens. Only 2 (9.5%) of the participants with MS used NNRTI based regimens.

4.3.5 Bivariate Analysis

The results of the bivariate analysis are shown in table 4.6 below.

Table 4. 6: Bivariate analysis of the variables with MS

VARIABLE	Crude OR	95%CI	p-value
Age (< 41 years vs. 41 and above)	1.85	0.28 - 12 10	0.523
Gender (Male vs. Female)	0.41	0.05 - 2.91	0.373
Marital status (Married vs. not Married)	**13**	**1.91 - 88.35**	**0.009**
Education (up to Primary vs. Secondary and over)	0.79	0.13 - 4.90	0.809
Employment (Employed vs. Not Employed)	**0.01**	**0.00 - 0.62**	**0.026**
Income (Salary vs. Family Sources)	**27.54**	**0.82 - 916.73**	**0.063**
Smoking Status (Yes vs. No)	0.56	0.04 - 7.97	0.676
Alcohol Use (Yes vs. No)	3.06	0.16 - 57.03	0.451
ART Duration (< 60 months vs. 60 months and over)	2.15	0.40 - 11.50	0.368
ART Regimen (PI Use vs. No PI Use)	**51.57**	**1.55 - 1709.64**	**0.027**
ART Regimen (NRTI Use vs. No NRTI Use)	**78.53**	**1.10 - 5565.50**	**0.044**
Cholesterol (High vs. Normal)	**54.72**	**11.99 - 249.60**	**< 0.001**
Fasting Blood Glucose (High vs. Normal)	**25.3**	**8.06 - 79.32**	**< 0.001**
Triglycerides (High vs. Normal)	**15.68**	**5.62 - 43.72**	**< 0.001**
HDL Cholesterol (Low vs. Normal)	2.71	0.26 - 27.46	0.396

The bivariate analysis to identify the determinants of metabolic syndrome is presented in table 4.6 above. Among the variables studied, the odds for developing MS were significantly higher among participants who were married, employed, on a salary and used ART regimens with PIs and NRTIs combinations. High cholesterol, fasting blood glucose and triglycerides were also associated with the development of metabolic syndrome. No association was found for age, gender, education level, current smoking, current alcohol use, ART duration and low HDL cholesterol levels.

Married participants were 13 times more likely to develop MS than their unmarried counterparts [OR (95%CI)]: 13 (1.91 - 88.35), p=0.009. Participants who were employed and had a salary as their source of income were 27.54 times more likely to develop MS although the difference was not statistically [OR (95%CI)]: 27.54 (0.82 – 916.73), p=0.063. Use of a protease inhibitor based ART regimen increased the odds of developing MS by 51.57 times [OR (95%CI)]: 51.57 (1.55 – 1709.64), p=0.027]; while those on NRTI were 78.53 times more likely to develop MS [OR (95%CI)]: 78.53 (1.10 – 5565.50), p=0.044]. But, there was no significant association between the duration of ART and the development of metabolic syndrome [OR (95%CI)]: 2.15 (0.40 – 11.50), p= 0.368.

Conclusion

The prevalence of metabolic syndrome was 11%. Factors associated with the development of MS were male sex, long duration of treatment, being married, employed and over 45 years of age. The most significant factors were being on NRTIs and PI based ART regimens.

CHAPTER 5: DISCUSSION, CONCLUSION AND RECOMMENDATIONS

5.0 Introduction

This chapter discusses the findings of the study, presents the conclusions and recommendations made based on the findings. It also highlights the limitations of this study.

5.1 Socio-demographic characteristics of the respondents

Most of the participants in the study were women; they made 74.2% of the total. This finding reflects the epidemic as women constitute the majority of those who are infected with HIV and on antiretroviral treatment. Similarly, the majority of participants were not married (55.3%). This is in line with the general population in Botswana where, many people are not married. It was however encouraging to note that 45.3% of the participants had up to secondary level of education while 57.4% reported being employed which improves sources of income and betters the quality of life. Our findings on the socio-demographic variables are similar to what has been reported by Bussmann et al. (2008). In their study, they reported that, based on 633 patients, the median age was 34.8 years, while 60% them were women. In this study, the median age was 40.5 years.

A significant number of the participants reported smoking and alcohol use and these are lifestyle factors that increase chances of developing MS and also negatively affect ART effectiveness (drug-alcohol interactions) and adherence to treatment. Alcohol use may alter judgment, resulting in people forgetting to take medications as prescribed. However, this study shows that alcohol drinking status and smoking status did not influence significantly the prevalence of MS. This finding is in contrast with previous reports by Freiberg and colleagues (2004) who reported that alcohol consumption was

significantly and inversely associated with the prevalence of the following three components of the metabolic syndrome: low serum HDL cholesterol, elevated serum triglycerides, high waist circumference, as well as hyperinsulinemia. Similarly, Myong et al. (2009) conducted a study whose objective was to determine the relationship between lifestyle implementation and metabolic syndrome. Their findings were a prevalence rate of 13.3% which is almost similar to this study but the odds ratios for metabolic syndrome increased in proportion to the number of bad habits. They then concluded that poor lifestyle like smoking, poor diet, lack of exercise and unhealthy alcohol consumption was associated with an increased likelihood for metabolic syndrome.

5.2 Prevalence of Metabolic Syndrome

Literature suggests prevalence of metabolic syndrome between 15 and 25% particularly in the western world as reported by among others Alvarez et al., (2010) and Jerico *et al*., (2004). The prevalence of metabolic syndrome in this study is was 11% compared to 7.7% among ART naïve HIV positive people in the same population group (Sales *et al., 2009)*. This demonstrates a slight increase in prevalence rates and can be attributed to the use of ART as participants in this study were reported not to have had MS before initiation of ART.

The prevalence rate of MS in this study is comparable with studies done by Da Silva *et al*., (2008) in Brazil who reported a prevalence rate of 13% while Brown *et al*., (2005) concluded a prevalence rate of 10%. These were however in contrast with the conclusion of Alvarez et al., (2010) who reported a higher rate of 20.2% in Latin America, a rate consistent with those of the developed world (16 – 25%). Meanwhile in another study conducted in Spain, Jerico *et al*., (2004), reported a prevalence of MS to be 17% increasing with age from 5.1% among the under 30 year olds to 27% for those on the 50 – 59

year age group. The difference in prevalence rates from this study and others done particularly in the developed world may be attributed to overall lifestyle differences and a generally higher burden of obesity in the developed world.

Most prevalent components for MS in this study were hypertension, high triglycerides and high fasting blood glucose. Comparing participants with MS and total participants, high triglycerides were in 66.7% of the respondents with MS compared with 17.4% in the entire group, hypertension 76.2% compared to 19.5% while fasting blood glucose was 52.4% in the group with MS and 9.5% in the whole group. The pattern of raised MS components is consistent with that concluded by Alvarez et al., (2010) who reported high triglycerides, low HDL and high blood pressure as the most prevalent components.

Some other studies have compared the prevalence of MS between HIV-infected and non-HIV infected people and found similar of higher prevalence rates among the HIV infected group with Bonfanti et al., (2007) reporting a prevalence rate of 20.8% among HIV positive participants higher than 15.8% in the HIV negative control group. There was no HIV negative control group in this study hence the difficulty of determining if the prevalence rate found in this study will differ with the general population.

5.3 Metabolic syndrome, gender and age

Although the frequencies of MS represented a higher percentage of males with MS (16.9%) as compared to woman (9.2%), results from the bivariate analysis suggested no significant difference in odds for developing MS between male and female participant. Although participants over 40 years were 1.85 times more likely to develop MS than those less than 40, the difference was not significant. This is different from the findings of Alvarez et al., (2010) in Latin America who reported that females had a higher prevalence of MS than males and there concluded gender as a risk factor

associated with development of MS. The findings of this study are also inconsistent with a study by Njelekela et al., among adults in an East African setting which noted gender disparities in cardiovascular disease risk factors with high levels of obesity, abdominal obesity, and metabolic syndrome among women.

5.4 Other factors associated with metabolic syndrome

This study identified several independent risk factors for metabolic syndrome through bivariate analysis. Among them was marital status, use of PI based ART regimen and use of NRTI based ART regimen. Use of PI based regimens increased the chances of developing MS by over 50%. This association is supported by literature particularly the use of Lopinavir/r boosted by Rotonavir and Didanosine has been found to be independently associated with MS in a multivariate analysis by Alvarez *et al*., (2010) in Latin America.

In another study, Mondy et al. (2007) found that current use of ART was not different among participants with and without MS, but that the use of PI based regimens was associated with higher triglyceride levels. Another study in Spain by Jerico et al. (2005) reported that past and current use of Stavudine correlated with metabolic syndrome. The conflict in findings may be explained by difference in the pattern of lipid derangements associated with specific components of ART, including thymidine analogues and PIs, in particular Rotonavir-boosted PI regimens, but may also be associated with differences in population groups investigated and probably gender, lifestyle and race differences that have not been explored adequately. This study also revealed an association between use of NRTI-based ART regimen and the development of MS. Note R et al., (2003) reported that although NRTIs can modify fat metabolism and fat distribution, the mechanism of these

modifications and the roles of NRTIs are unknown. There was no association between MS and use of NNRTI based regimens.

This study also found an association between development of MS and raised MS components like glucose, cholesterol and triglycerides. These findings echo those of Bonfanti et al., (2007) in a study in Italy who also reported a greater prevalence of lipid and glucose abnormalities among people with HIV. They were some inconsistencies on the HDL Cholesterol findings with the results from Termizy & Mafauzy, (2009) who reported that the lowest co-morbidity to metabolic syndrome was raised fasting glucose at 17%, then high triglycerides at 36%, followed by reduced HDL Cholesterol at 40% and raised blood pressure at 42%.

There was a significant likelihood for metabolic syndrome among the married, employed and participants whose source of income was salary. This can be explained by general affordability of highly refined foodstuffs afforded by those on salary as well as possible lack of exercise by married people who also have family responsibilities over and above their usual work schedule.

There was no association between age and development of MS as opposed to findings by Graber et al., (2006) who reported that age may also be a risk factor associated with HAART induced metabolic syndrome and also that the elderly have a slower immunologic response to ART and an increased risk of developing cardiovascular disease by the association of aging, HIV infection and ART. The findings of this study with regards to age were also in contrast with those done in Nigeria by Ogbera (2010) who explained that the role of age as a risk factor for metabolic syndrome could not be over-emphasized. He noted an increase in the prevalence of metabolic syndrome from 11% (20 – 29 year age group) to 89% among participants in the older (70 – 79 year age group). In Botswana, Sales et al (2009) reported age as a significant risk

factor for metabolic syndrome among asymptomatic and antiretroviral treatment-naïve adults with an odds ratio of 1.10 (95% CI 1.04, 1.16, p< 0.01)

The difference in MS outcome based on gender was not significant and this was consistent with the conclusion of Ogbera (2010) who that the frequency of occurrence of metabolic syndrome was similar between male (83%) and female (86%) participants among people with type 2 Diabetes mellitus.

5.5 Limitations of the study

The main limitation for this study was the non-random selection of study participants that may affect the representativeness of the sample. Absence of controls from the general population also makes it difficult to draw conclusions regarding significance of the data. The study was confined to Gaborone hence generalization of its findings to the Botswana population may not be accurate. Other limitations include the fact this was a cross-sectional study, so causal relationships could not be established due to lack of temporality.

5.6 Conclusions

The purpose of this study was to investigate the prevalence and factors associated with development of metabolic syndrome among people with HIV on ART at the IDCC Clinic at Princess Marina Hospital, Gaborone, Botswana. The overall prevalence of metabolic syndrome in this study was 11%. Metabolic syndrome was associated with traditional risk factors such as hypertension and high triglycerides; but with some unique features such as age, current employment and current NRTI use were also identified. In the bivariate analysis to identify the determinants of metabolic syndrome, the odds for developing MS were higher among participants who were married, employed, on a salary and used ART regimens containing NRTIs. High

cholesterol, fasting blood glucose and triglycerides were also associated with the development of metabolic syndrome. There was a significant association with age as people over 45 years were significantly shown to have metabolic syndrome than the younger ones. The median age of participants who had metabolic syndrome was higher at 45 years (IQR: 39 – 53 years) that those without metabolic syndrome at 40 years (IQR: 34 – 48). Married participants were 13 times more likely to develop MS than their unmarried counterparts [OR (95%CI)]: 13 (1.91 - 88.35), p=0.009]. Participants who were employed and had a salary as their source of income were 27.54 times more likely to develop MS although the difference was not statistically significant. The type of regimen affected the prevalence of metabolic syndrome; in fact Up to 17 of the 21 participants with metabolic syndrome used a combination of drugs with NRTIs and NNRTIs as well as PI in 8 cases. So the use of a protease inhibitor based ART regimen increased the odds of developing MS by 51.57 times [OR (95%CI)]: 51.57 (1.55 – 1709.64), p=0.027]; while in case of NRTIs the odds were 78.53 times more for the likelihood to develop MS [OR (95%CI)]: 78.53 (1.10 – 5565.50), p=0.044]. Although, there was no significant association between the duration of ART and the development of metabolic syndrome; the median duration of ART among participants with metabolic syndrome was higher at 68 months (IQR: 51 – 80) compared to those without metabolic syndrome at 56 months (IQR: 40 – 68). With regard to sex, 16.3% of the male participants had metabolic syndrome compared to 9.2% among the females; but the difference was not statistically significant.

In conclusion, the prevalence of metabolic syndrome was low, affecting only 11% of the study participants. The factors associated with the occurrence of the syndrome were the male sex, the long duration on treatment, being married, employed, and over 45 years old. The most significant factors were being on NRTIs and PIs containing regimens. These findings suggest that patients on antiretroviral treatment with the above characteristics should be monitored regularly for metabolic syndrome.

5.7 Recommendations

1. Because alcohol use is reported to be associated with metabolic syndrome, patients should be advised to stop drinking alcohol
2. Since regimens containing NRTIs, NNRTIs and PIs seem to increase the risk of metabolic syndrome, patients on regimens containing these drugs should be monitored regularly
3. Lifestyle modifications including regular exercise schedule should be advised in patients over 45 years old since there is increased risk of metabolic syndrome even in the absence of HIV
4. Further prospective studies are needed in order to determine exactly when the metabolic syndrome starts.

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APPENDICES

APPENDIX 1: Medunsa Research and Ethics Committee Clearance Certificate

UNIVERSITY OF LIMPOPO
Medunsa Campus

MEDUNSA RESEARCH & ETHICS COMMITTEE

CLEARANCE CERTIFICATE

P O Medunsa
Medunsa
0204
SOUTH AFRICA

Tel: (012) 521 4000
Fax: (012) 560 0066

MEETING: 02/2010

PROJECT NUMBER: MREC/H/18/2010: PG

PROJECT :

Title: Metabolic syndrome among people with human immunodeficiency virus on anti-retroviral therapy at Princess Marina Hospital in Gaborone-Botswana

Researcher: Mr D Mhlanga
Supervisor: Dr N Malanga
Department: Public Health - Epidemiology
School: Health Care Sciences
Degree MPH

DECISION OF THE COMMITTEE:

MREC approved the project

DATE: 03 March 2010

PROF N EBRAHIM
DEPUTY CHAIRPERSON MREC

Note:
i) Should any departure be contemplated from the research procedure as approved, the researcher(s) must re-submit the protocol to the committee.
ii) The budget for the research will be considered separately from the protocol.
PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

APPENDIX 2: Botswana MOH, Health Research and Development Division Approval

Telephone: (267) 363200
FAX (267) 353100
TELEGRAMS: RABONGAKA
TELEX: 2818 CARE BD

MINISTRY OF HEALTH
PRIVATE BAG 0038
GABORONE

REPUBLIC OF BOTSWANA

REFERENCE NO: PPME 13/18/1 PS V (105) 26 May 2010

Health Research and Development Division

Notification of IRB Review: New application

Desire Bekithemba Mhlabi
C/O Bokamoso Private Bag 00205
Gaborone

Protocol Title:	**METABOLIC SYNDROME AMONG PEOPLE WITH HUMAN IMMUNODEFIFIENCY VIRUS ON ANTI-RETROVIRAL THERAPY AT PRINCESS MARINA HOSPITAL IN GABORONE**
HRU Protocol Number:	HRU 00624
Sponsor:	N/A
HRU Review Date:	25 May 2010
HRU Expiration Date:	24 May 2011
HRU Review Type:	HRU reviewed
HRU Review Determination:	Approved
Risk Determination:	Minimal risk

Dear Mr Mlhabi

Thank you for submitting a new Application for the above referenced Protocol.
This approval includes the following:

1. Application form
2. Proposal
3. Consent Form

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.

1

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.

If you have any questions please do not hesitate to contact Mr. P. Khulumani at pkhulumani@gov.bw, Tel +267-3914467 or Mary Kasule at mkasule@gov.bw or marykasule@gmail.com Tel: +267-3632466

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. 9A 11 or Ministry of Health website: www.moh.gov.bw or can be requested via e-mail from Mr. Kgomotso Motlhanka, e-mail address: 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. 9A 11 or Ministry of Health website: www.moh.gov.bw or can be requested via e- mail from Mr. Kgomotso Motlhanka, e-mail address: kmotlhanka@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.

Do not hesitate to contact us if you have any questions. Thank you for your cooperation and your commitment to the protection of human subjects in research.

Yours sincerely

P. Khulumani
For Permanent Secretary

PERMANENT SECRETARY
MINISTRY OF HEALTH
RESEARCH UNIT
26 MAY 2010
P/BAG 0038
GABORONE
REPUBLIC OF BOTSWANA

2

APPENDIX 3: Princess Marina Hospital; Institutional Research and Ethics Committee Approval

Princess Marina Hospital
P.O. Box 258
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REPUBLIC OF BOTSWANA

Tel: 3621400
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INSTITUTIONAL RESEARCH AND ETHICS COMMITTEE

Date: 5th July 2010

Our Ref: PMH2//10-048

Desire B Mhalabi
Department of Epidemiology
National school of Public Health
University of Limpopo
Medunsa Campus
South Africa

Dear Desire

Re: PMH048: Metabolic Syndrome among people with HIV on ART AT PMH in Gaborone –Botswana

Reference is made to above titled study submitted to Research and Ethics Committee of Princess Marina Hospital. Following a review, the study has been approved on the condition that the researcher;

- Seeks permission from the head of the department in which study will be conducted.
- Resubmit for approval should any change be made to the protocol.
- Provide both a hard and an electronic copy of the report when the study is finished

This study permit is valid for a period of one year, from the date of this letter.

The Committee would like to communicate its support in this very important endeavour. Your continued communication and update is greatly appreciated.

Yours truly

(Y.P. GUREJA)

Y.P. Gureja
Chairperson

APPENDIX 4: IDCC Clinic; Institutional Head of Department Approval

TELEPHONE: 3621400
FAX: 3973776
PLOT NO. 1836
HOSPITAL WAY

REPUBLIC OF BOTSWANA

PRINCESS MARINA HOSPITAL
P. O. BOX 258
GABORONE
BOTSWANA

August 09, 2010

Desire B Mhlabi
Department of Epidemiology
National school of Public Health
University of Limpopo
Medunsa Campus
South Africa

Dear Mhlabi

Re: PMH048: Metabolic Syndrome among people with HIV on HAART at PMH in Gaborone- Botswana

Reference is made to the above titled study as submitted to the Research and Ethics Committee of Princess Marina Hospital. The study was approved by the institution pending permission from the Head of the department in which the study is to be carried out. Permission is thus granted as of today for the study to be carried out at the IDCC clinic.

For any enquiries please contact me at (+267) 362 1613/1621.

Thank you.

Yours faithfully

Dr U Maposa
Medical Officer
IDCC Site Manager
Princess Marina Hospital