UNIVERSITY OF THE WESTERN CAPE

Faculty of Community and Health Sciences

RESEARCH MINI-THESIS

Prevalence of metabolic risk factors for non-communicable diseases in treatment-naïve HIV patients in inner-city Johannesburg

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

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DECLARATION

I declare that the work titled "*Prevalence of metabolic risk factors for non-communicable diseases in treatment-naïve HIV patients in inner-city Johannesburg*" is my original work and has not been submitted for any degree or assessment in any other university, and that all the sources I have used or cited have been indicated and acknowledged by complete references.

Dr Shilpa Esther Bhaskar

Signed:

Date: 9 August 2023

DEDICATION

I dedicate this mini thesis in memory of my beloved parents who taught me so much during their lifetime's and continue to be my inspiration through the legacy they have left.

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My husband for his constant encouragement and unwavering support without whom I would not have been able to come so far. His support has been my greatest blessing.

Most importantly, I would like to thank God.

ABSTRACT

Background: South Africa faces a quadruple burden of disease with a rising prevalence of both HIV and non-communicable diseases (Cage et al., 2023). Increased life expectancy in people living with HIV (PLWHIV) has contributed to increasing rates of metabolic diseases and co-morbidities. The prevalence of metabolic risk factors among PLWHIV and associated risks need to be addressed to allow strategic integration into healthcare and reduce the rising prevalence of non-communicable diseases. This study aimed to describe the prevalence and patterns of metabolic risk factors in HIV-positive, treatment-naïve participants (those that have not yet initiated treatment) in inner-city Johannesburg.

Methodology: A retrospective, cross-sectional study design was conducted on all patients enrolled in the ADVANCE WRHI060 clinical trial from 2 February 2017 to 8 May 2018 at baseline, before the initiation of ART. Socio-demographic, behavioural and clinical characteristics were extracted from the patient electronic database. For all statistical comparisons, a 5% level of significance was applied; correspondingly 95% confidence intervals were used to describe effect size. Outcome variables were categorised, and the Chi-squared test was used to analyse associations between data. Logistic-regression analysis was used to examine the association between metabolic risk factors and other sociodemographic or behavioural factors.

Ethics clearance was obtained from the Biomedical Research Ethics Committee of the University of Western Cape. Permission to access the ADVANCE WRHI060 patient database was received from Ezintsha Research Clinic. No direct contact with participants was made and patient confidentiality was maintained.

Results: There were 1053 HIV-positive, treatment naïve participants included in this study, with a mean age of 32.5 years and a standard deviation of 7.7. The prevalence of metabolic risk factors was the highest for dyslipidaemia (65.5 %, n=690) followed by hypertension (39.3%, n=414), elevated Body Mass Index (BMI) (36%, n=366), and diabetes (2.6%, n=27). All metabolic risk factors were more prevalent in females than males, except for hypertension. The prevalence of metabolic syndrome (at least three metabolic risk factors) was 14.1%, with a higher prevalence in females compared to males (17.8 % vs. 8.6%; $p<0.001$). Of those aged 50 years and above, almost half had three or more metabolic risk factors (n=14; 9.5%) while those

in younger age groups were progressively less likely to have metabolic syndrome ($p < 0.001$). Just under half of the sample (45.4%, n=489) had at least two metabolic risk factors.

Conclusions: The study highlights a high prevalence of metabolic risk factors among HIV-positive, treatment-naïve participants in inner-city Johannesburg. These findings emphasise the pressing need for integrated healthcare approaches that address both communicable and non-communicable diseases in PLWHIV, particularly in resource-limited settings.

Keywords:

HIV, Non-communicable diseases, Diabetes, Hypertension, Obesity, Dyslipidaemia, AIDS, Metabolic risk factors, Metabolic syndrome

LIST OF ACRONYMS

AIDS	Acquired immunodeficiency syndrome
ART	Antiretroviral therapy
BMI	Body mass index
CVD	Cardiovascular disease
DM	Diabetes Mellitus
eCRF	Electronic Case report forms
HAART	Highly Active Antiretroviral Therapy
HIV	Human immunodeficiency Virus
HDL	High-density lipoprotein
HREC	Human Research Ethics Committee (University of the Witwatersrand)
ICF	Informed Consent Form
IQR	Interquartile range
LMIC	Low- and Middle-Income Country
LDL	Low-density lipoprotein
LGBTQ+	Lesbian, gay, bisexual, and transgender and queer and other identities
NCD	Non-communicable disease
PLWHIV	People Living with HIV
QLFS	Quarterly Labour Force Survey
REDCap	Research Electronic Data Capture
RVD	Retroviral Disease
SANHANES	South African National Health and Nutrition Examination Survey
SEMDSA	Society for Endocrine, Metabolism and Diabetes of South Africa
SOP	Standard Operating Procedure
SSA	Sub-Saharan Africa
UWC	University of the Western Cape
UNAIDS	Joint United Nations Programme on HIV/AIDS
WHO	World Health Organization
WRHI	Wits Reproductive Health and HIV Institute

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CHAPTER 1. INTRODUCTION

1.1 Background

The HIV pandemic remains one of the greatest threats to public health globally (Scheres et al., 2019). South Africa has the largest population of people living with HIV (PLWHIV) in the world, with 7.9 million South Africans diagnosed with HIV in 2022 (UNAIDS, 2022). The aim of the UNAIDS 90-90-90 targets hoped that by 2020, 90% of all PLWHIV should be aware of their HIV status, 90% of those who know their status should be on treatment and 90% of those receiving antiretroviral therapy (ART) should be virally supressed (UNAIDS, 2017). In 2022 reports suggest that for South Africa, successfully 94% of PLWH knew their status, but fell short of last two UNAIDS 90-90 targets at 75% and 69% respectively (UNAIDS, 2022). Although these targets have not been achieved UNAIDS has called for a new 95-95-95 target by 2030. Additionally, the rapid implementation of ART programmes, alongside same-day ART initiation within the public sector in South Africa, has led to an increase in life expectancy and an ageing HIV population (UNAIDS, 2022; SABSSM, 2021).

1.2 Non-Communicable Diseases and HIV in South Africa

This increase in life expectancy has brought about a re-direction in health primacies, where PLWHIV face similar health challenges to those living without HIV infection, and thus are at an increased risk of chronic disease-related comorbidities (Abou et al., 2022). In 2016, mortality from NCDs overtook the death rate due to communicable diseases (Liu et al., 2021). A survey in South Africa showed the prevalence of non-communicable diseases (NCDs) within the general population was as high as 57% in urban areas and accounted for 51% mortality (Liu et al., 2021). These conditions include non-infectious diseases that cannot be passed from person to person (National Department of Health, 2022). In PLWHIV, this may be attributed to various factors including chronic ART exposure, chronic inflammation and lifestyle factors. In addition, NCDs such as diabetes, heart disease, renal failure, non-AIDS-defining malignancies and liver disease have been identified at younger ages in PLWHIV compared to those in un-infected adults (Harris et al., 2018). The rising prevalence of NCDs complicates treatment and care for PLWHIV and increases the burden of disease in low- to middle-income countries like South Africa (van Koeveringe et al., 2023). Treating co-morbidities in PLWHIV especially at younger ages, poses a challenge to both individual healthcare and national

healthcare systems. A multidisciplinary approach is often needed which involves multiple medications, lifestyle changes, increasing costs and social support.

1.3 Metabolic Risk Factors and HIV

The World Health Organization (WHO) and the South African National Department of Health (NDOH) recognise four metabolic risk factors for NCDs that form part of their policy framework for NCD prevention (WHO, 2021; NDOH, 2013). These are overweight/obesity, hypertension/elevated blood pressure, dyslipidaemia and hyperglycaemia/diabetes. The presence of one or more of these metabolic risk factors can increase the chance of developing NCDs (WHO, 2021). HIV infection and ART-induced mechanisms further worsen the onset of these risk factors (Mashinya et al., 2015). It is therefore necessary to study these metabolic imbalances in the context of HIV infection.

1.4 Problem Statement

Success of same-day ART initiation has shifted the disease profile in PLWHIV. Prolonged survival has led to an increasing prevalence of NCDs, thus calling for a holistic approach in the management of PLWHIV. The next step requires inclusion of cardiovascular risk factor assessments to decrease rising conditions like hypertension (HPTN) and diabetes mellitus (DM).

Although high-density healthcare facilities in Johannesburg inner city deliver ART services to patients, there is a lack of comprehensive policies and integrated operational guidelines that emphasise the importance of screening and investigating risk factors that lead to NCDs within HIV populations at a primary healthcare level. This gap in policy and practice hinders the effective management of NCDs among PLWHIV and contributes to the increasing burden of these chronic conditions. In addition, poor surveillance of existing protocols inhibits meeting national targets to reduce NCDs and contributes to the lack of data needed to guide integrated service delivery. The global burden of NCDs is overwhelming, with these chronic conditions accounting for 41 million deaths in 2016, and a disproportionately high burden (78%) in low- and middle-income countries (LMICs) (WHO, 2018). This highlights the importance of accurately estimating NCD risk factors in PLWHIV and implementing targeted interventions to address these risks.

Justification for this study lies in the evolving healthcare landscape for PLWHIV and the growing prevalence of NCDs. Given the global significance especially in LMICs this study seeks to estimate NCD risk factors in PLWHIV in inner city Johannesburg and bring light to target interventions to mitigate these risks. Furthermore, the study hopes to contribute to the understanding of how to enhance the healthcare system's response to the evolving needs of PLWHIV.

1.5 Aims and Objectives

The aim of the study was to describe the prevalence of metabolic risk factors in HIV-positive, treatment-naïve participants at baseline (enrolment) within a clinical trial, ADVANCE WRHI060, at a research clinic in Johannesburg, South Africa.

The objectives of the study were:

- to describe the socio-demographic, behavioural and clinical characteristics of HIV-positive, treatment-naïve patients,
- to determine the presence of one or more metabolic risk factors in HIV-positive, treatment-naïve patients, and
- to determine the factors associated with metabolic risk in HIV-positive, treatment-naïve patients.

1.6 Outline of Mini-Thesis

Chapter 1 provides an introduction and overview of the mini thesis.

Chapter 2 is a literature review which focuses on the impact HIV has had on non-communicable diseases and the prevalence of risk factors with HIV-infected and HIV-non infected individuals.

Chapter 3 outlines the study methodology and setting. This includes a description of the study design, data-collection methods and analysis techniques.

Chapter 4 presents the study results through tables and graphs.

Chapter 5 offers a discussion of the study results correlating to existing literature, including the strengths and limitations of the study.

Chapter 6 draws conclusions and recommendations based on the main research findings.

CHAPTER 2. LITERATURE REVIEW

This following review examines the prevalence and risk factors of NCDs leading to metabolic disease associated with people living with HIV and AIDS (PLWHIV). The differences between treatment-naïve individuals and those on antiretroviral therapy (ART) are reviewed.

2.1 The Impact of HIV on Non-Communicable Diseases

The global prevalence of NCDs has been growing at an alarming rate, leading to increased mortality rates (Schutte, 2019). Even though conventional risk factors such as reduced physical activity and unhealthy diets contribute to chronic NCDs, the natural course of HIV infection and ART therapy influence the danger of developing cardio-metabolic disorders in PLWH (Jericho et al., 2005). Evidence shows that there is an excess risk of cardiovascular disease (CVD) in HIV-positive adults compared to HIV-negative adults (Althoff et al., 2014). It is projected that by the year 2030, NCDs could account for 46% of deaths in Sub-Saharan Africa (SSA), compared to 28% in 2008 (Kavishe et al., 2015).

A 2007 study among HIV-infected veterans, described multimorbidity as a greater risk in HIV-infected veterans, although it occurred at a similar age in matched HIV-uninfected veterans, suggesting that HIV did not accelerate aging (Harris et al., 2018). However, the study showed a higher incidence of end-stage renal disease, myocardial infarction, and non-AIDS-defining cancer in HIV-positive patients compared to HIV-negative veterans (Savvoulidis et al., 2019). Similarly, a recent meta-analysis performed across five continents showed that the prevalence of metabolic syndrome in HIV-infected individuals mirrored that to the general population (Nguyen et al., 2016). Shah et al. (2018) found that the risk of CVD in HIV-positive patients is almost twice as high than HIV- uninfected individuals with a tripling global burden of HIV-associated CVD.

The HIV virus affects inflammation, immune activation and coagulation disorders, playing a role in increasing the risk of coronary artery disease and heart failure (Vachiat et al., 2017). In addition, this is aggravated by harmful side-effects of ART leading to insulin resistance, dyslipidaemia, endothelial dysfunction, and microvascular dysfunction (Vachiat et al., 2017). Moreover, the use of ART, especially older regimens, has been linked to an increased risk of metabolic syndrome and cardiovascular events (Feinstein et al., 2016). For the same reason, Shah et al. (2018) identifies HIV as a risk factor for cardiovascular events in PLWHIV,

explaining that infection with HIV should be viewed as an additional risk, similar to that of traditional risk factors like hypertension, diabetes, dyslipidaemia, and smoking, highlighting the need to recognise this increased risk in HIV-positive patients. (Shah et al., 2018).

There are limited studies on CVD and metabolic risk factors in HIV-infected people in South Africa (Mashinya et al., 2015). A cross-sectional study by Mashinya et al. (2017) on ART patients in rural South Africa, albeit a small sample size, reported that a significant proportion of participants had a moderate to high risk of CVD and emphasised the lack of a good tool to assess CVD risk in African populations. Several studies confirm rising NCD risk with age in rural populations in South Africa (Maimela et al., 2016; Gaziano et al., 2017). Gaziano et al. reported that the rural population assessed had a prevalence of hypertension at 58%, dyslipidaemia over 43% and about two thirds of the cohort had an abnormal BMI. In contrast, when they evaluated risk factors by HIV status, the prevalence of hypertension, diabetes and obesity was much higher in the HIV-uninfected population, with 51% of HIV-negative adults with two or more co-morbidities compared to those HIV-positive at 35% (Gaziano et al., 2017). Comparatively, a study in KwaZulu-Natal, revealed an analogous occurrence of conventional cardiovascular risk factors among individuals with and without HIV (except for body mass), where approximately 80% had at least one of the measured risk factors (Van Heerden et al., 2017).

Zungu et al., also found that HIV-positive educators in public schools in South Africa had several factors that increased their odds of having NCDs and affecting their rates of absenteeism and productivity (Zungu et al., 2019).

2.2 Metabolic Risk Factors for Non-Communicable Diseases

Metabolic risk factors are defined as factors that cause an imbalance in metabolic (chemical) processes within the body that can increase the risk of developing NCDs such as heart disease, diabetes and stroke. The five most common metabolic risk factors, as outlined by the Society for Endocrinology, Metabolism and Diabetes of South Africa (SEMDSA, 2017), are elevated waist circumference, elevated triglycerides, reduced high-density lipoprotein (HDL) cholesterol, elevated blood pressure and elevated fasting glucose. These factors often interact and, when present in combination, may lead to the development of metabolic syndrome, a cluster of conditions that significantly increase the risk of NCDs. In addition, there are several traditional risk factors that can be classified as behavioural or modifiable risk factors that are thought to increase the chance of developing metabolic syndrome such as smoking, lack of

physical activity and eating a high-carbohydrate diet. Non-modifiable risk factors such as a family history of metabolic disease (UpToDate, 2022) age, gender, race and , over the last two decades, the recognition of HIV infection as a risk factor for metabolic diseases has gained prominence (Shah et al., 2018).

2.3 Metabolic Syndrome in HIV Populations

A combination of a minimal rise in blood pressure, plasma lipids and blood glucose can result in a major risk for diabetes, cardiovascular disease, and death (Wilson, 2005). Metabolic syndrome is the term given to individuals who have three or more of these metabolic risk factors. Several definitions have evolved over the years, leading to difficulty in characterising its prevalence and a lack of studies showing patterns or frequency of metabolic syndrome components (Okafor, 2012). According to SEMDSA Guidelines 2017, having at least three of the five risk factors listed above - elevated waist circumference, elevated triglycerides, reduced HDL- cholesterol, elevated blood pressure and elevated fasting glucose - defines the syndrome. A measure is also considered positive if on drug treatment targeting any criteria. Although having a single metabolic risk factor does not warrant a diagnosis of metabolic syndrome, it does signify a much greater risk of serious disease which rises with each additional risk factor (Pruthi et al., 2021). Targeting a single risk factor without consideration of others can lead to selected therapy and possible adverse effects on co-existing risk factors (deNovo Medica, 2018).

A systematic review reported the prevalence of metabolic syndrome in South African women to be as high as 42% and largely associated with obesity (Gradidge et al., 2017). The prevalence of metabolic syndrome in PLWHIV ranges from about 11% to 45% globally (Paula et al., 2013). In comparison, in 2009, the prevalence of metabolic syndrome in a black African population in Cape Town was 31.7%, with higher rates in women (Peer et al., 2015). Another study done in the Eastern Cape, South Africa observed a 27% prevalence of metabolic syndrome in those on ART compared to 15.7% in those not yet on treatment and 21.9% in HIV-negative groups (Awotedu et al., 2010). These studies imply the possible complex interplay between HIV infection, metabolic risk factors and the additional risk of PLWHIV once initiated on ART.

2.3.1 Obesity in HIV-positive patients

Overweight and obesity is defined as a gain in excess body fat, resulting from a surplus in energy intake relative to expendable energy (National Strategy for Prevention and Control of Obesity, 2015). Body Mass Index (BMI) is used to determine health risk according to weight relative to height. A BMI ranging from 25.0 - 29.9 is considered overweight while those ≥ 30 are considered obese. Obesity has been associated with a higher risk of morbidity, disability and death (Zatonska et al., 2021) and is a well-established risk factor for various NCDs, such as CVD, type-2 diabetes, and certain cancers, which can further complicate the health status of PLWHIV (Guaraldi et al., 2011).

Obesity has been rising generally in populations in sub-Saharan Africa, including South Africa (Sartorius et al., 2015). A national survey found that in 2016, 68% of women were obese and 31% of men were overweight or obese (South African Demographic and Health Survey, 2016). Historically, being underweight was stigmatised with having HIV infection, while being overweight was a statement of well-being and affluence (Ndlovu, 1999). With effective HIV treatment, high rates of elevated BMIs and obesity have been found particularly in ageing PLWHIV (Wand & Ramjee, 2013). A French cohort showed nearly half of its patients were overweight or obese at the start of ART initiation (Kuller et al., 2008). Similarly, a recent cross-sectional study at a clinic in the Eastern Cape province showed that more participants were obese before initiating HIV treatment (Nkeh-Chungag et al., 2021).

PLWHIV have higher levels of circulating inflammatory markers which contribute to lipodystrophy causing increased visceral adipose tissue, compared to subcutaneous adipose tissue, of which visceral distribution leads to inflammation, increased insulin resistance, dyslipidaemia and oxidative stress (Parker et al., 2018). Similarly, a recent cross-sectional study at a clinic in Eastern Cape province showed that more participants were obese before initiating HIV treatment (Nkeh-Chungag et al., 2021).

ART-naïve PLWHIV follow similar trends to the general population, although a substantial number of those initiating ART become overweight/obese within one year of treatment, accelerating the risk of multimorbidity (Biggs & Spooner, 2018). The increasing prevalence of obesity among PLWHIV, regardless of treatment status, has significant implications for disease management and overall health outcomes.

2.3.2 *Dyslipidaemia*

Dyslipidaemias are disorders of cholesterol metabolism resulting in abnormal levels of total cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides and high-density lipoprotein (HDL) cholesterol. Several studies have been done to determine the prevalence of dyslipidaemia in PLWHIV (Assefa et al., 2023; Song et al., 2023). HIV-positive patients, both on ART and treatment-naïve, have been reported to exhibit a higher prevalence of dyslipidaemia compared to the general population (Nduka et al., 2013). This trend persists among younger people living with HIV (Seang et al., 2022).

A cross-sectional study among South African adults with comorbidities, such as hypertension and diabetes, irrespective of HIV status, revealed that the total prevalence of dyslipidaemia among the participants was 76.7% with females showing a greater prevalence (75.8%). In addition, a higher prevalence was seen in those with diabetes (77.1%) and hypertension (73.2%) (Masilela et al., 2021) indicating a pattern of multiple risk factors potentiating each other.

Several studies in the African region emphasise the presence of dyslipidaemia. In Johannesburg, Basu (2011) showed 33 to 46% of HIV-positive patients on ART had abnormal lipids. A similar cross-sectional study done in Cameroon, showed the prevalence of total cholesterol and LDL cholesterol in those receiving ART compared to those treatment naïve, to be about five times higher (Nsagha et al., 2015). Similarly, a more recent study in Ethiopia reported a dyslipidaemia prevalence of 55.2% in PLWHIV (Assefa et al., 2023).

Another study of HIV-infected patients who were receiving ART compared to HIV-negative control subjects, showed that dyslipidaemia was significantly higher in those on ART compared to the controls. In addition, the longer the duration of ART, the increased risk of dyslipidaemia (Dave et al., 2016).

Furthermore, decreases in HDL cholesterol naturally progresses in HIV infection, which increases the risk of adverse cardiovascular events despite other risk factors and irrespective of CD4 count (Denue et al., 2013). Nkeh-Chungag et al. (2021) concluded that dyslipidaemia was higher in PLWHIV on treatment who were also hypertensive while endothelial function improved with increasing CD4 count in those on ART (Nkeh-Chungag et al., 2021).

2.3.3 *Elevated Blood Pressure and Hypertension*

Raised blood pressure is the leading global risk factor for CVDs and kidney disease (NCD Risk factor Collaboration, 2017). High blood pressure is closely linked to increased weight and obesity. The Framingham Heart Study indicated that a moderate rise in blood pressure is associated with a two-fold increase in relative risk from CVD compared to those with normal blood pressure (Fedele et al., 2011). In Nigeria, 42% of subjects who underwent screening at a marketplace, were diagnosed with hypertension, of which 70.6% were unaware of their hypertensive condition prior to screening (Ulasi et al., 2011). Similarly, the SEARCH study in Uganda showed an overwhelming 45% of undetected population-based screenings needing referral for blood-pressure control (Kwarisiima et al., 2019).

A study in southern Africa reported the prevalence of hypertension at 33.3%, with the highest prevalence seen in South Africans (ranging from 41.6% to 54.1%) (Gomez-Olive et al., 2017). Similarly, a study by Mashinya et al. (2019) found the prevalence of hypertension among HIV-infected patients in rural South Africa was 32.6%. They concluded that older age, female gender and high BMI were significant risk factors for hypertension in HIV-infected patients in South Africa (Mashinya et al., 2019). A 20% prevalence of hypertension was reported by Brennan et al. (2018) in those initiating ART in HIV clinics within the public sector in South Africa.

Reports of elevated blood pressure at a higher prevalence among treatment-naïve, HIV-infected patients, has been documented, compared to the HIV-negative population (Njelekela et al., 2016). This risk is further increased with longer ART duration (Fahme et al., 2018). A systematic review and meta-analysis of 45 studies conducted in 13 African countries found that the prevalence of hypertension in PLWHIV ranged from 6 to 50% for those on ART, while ART-naive patients had rates between 2 and 41% (Masenga et al., 2019).

Chronic immune activation and inflammation of endothelial cells has been found to contribute to hypertension, but the inflammatory factors that predispose PLWHIV to hypertension are not completely understood (Masenga et al., 2019).

2.3.4 *Elevated glucose and Diabetes (DM)*

A study in USA, showed that there was a 3.8% higher prevalence of diabetes mellitus (DM) in HIV-infected adults in comparison to the general population (Hernandez-Romieu et al., 2017). A systematic review showed that the incidence of prediabetes and diabetes among HIV-

infected adults on ART varied widely across the studies and its prevalence is growing rapidly (Nansseu et al., 2018). One explanation is that HIV-infected persons develop insulin resistance rather than insulin deficiency, making their glucose tolerance lower and increasing the risk of developing type-2 diabetes (Weerakkody et al., 2014). This theory underscores the importance of investigating the mechanisms underlying diabetes in this population of which there is a research gap. With the rise in life expectancy, BMI and the use of ART, diabetic complications will continue to rise (Bailin et al., 2023).

Sub-Saharan Africa (SSA) has been classified an endemic area for diabetes with South Africa having the highest number of adults with diabetes in Africa (IDF Diabetes Atlas, 2021). However, a narrative review conducted in this area on PLWHIV, estimated that the prevalence of dysglycaemia, which includes pre-diabetes and diabetes, ranges from 1 to 47% (Njugana et al., 2018).

The identified common risk factors for dysglycaemia among PLWHIV in Sub-Saharan Africa, such as older age, male gender, and elevated BMI, as reported by Njugana et al. (2018), share similarities with findings in other studies, which have associated diabetes with increased abdominal circumference, older age, and specific ART regimens, as seen in research by Mhlanga and Netangaheni (2023). These consistent risk factors suggest an area of consensus among studies which can further guide future research.

The cost of late detection of NCDs such as diabetes is high. A report published in 2019 estimated that the cost in 2030 for all type-2 diabetes is around R35.1 billion. Where approximately 51% of these estimated costs for 2030 are attributable to management of type-2 diabetes and 49% are attributable to complications" (Erzse et al., 2019). This highlights the financial burden and the need for effective diabetes prevention.

2.3.5 *Smoking and Alcohol Intake*

Traditional risk factors related to behaviour include excessive tobacco and alcohol intake which directly influence metabolic risk factors leading to increasing prevalence of NCDs (WHO, 2022). Increasing urbanisation and associated lifestyle changes in the region, along with improvements in life expectancy, would explain the adoption and increase of smoking and alcohol intake in SSA (Amberir et al., 2019). Despite these two lifestyle factors not being included in the definition of metabolic syndrome, their influence on metabolic disease is well documented. Metabolic changes which are associated with the development of CVDs may

hasten the chronic inflammatory state caused by the presence of HIV coupled with the existence of consumption risk factors, such as smoking and alcohol (Kavishe et al., 2015). Studies have found that both smoking, and alcohol consumption are associated with an increased risk of insulin resistance and type-2 diabetes in HIV-infected individuals (Helleberg et al., 2013) while others reported varied associations attributable to response bias (Tesfaye et al., 2014). Additionally, heavy alcohol intake has been linked to liver disease, dyslipidaemia and accelerated progression of HIV infection (Yan et al., 2021). Freiberg & Kramer (2010) goes on to describe a synergistic effect alcohol has with HIV which increases the risk of myocardial infarctions. Similarly, smoking prevalence in PLWHIV is underreported, excessive and the highest in Africa, and contribute towards infectious and non-infectious diseases (Elf et al., 2018).

2.4 Summary

NCDs coupled with HIV are contributing greatly to morbidity and mortality in SSA, posing a considerable challenge to the healthcare systems in the region. Traditional risk factors and metabolic risk factors lead to changes that increase the risk of developing NCDs in all populations. The initiation of ART has been a crucial component in improving the health outcomes of HIV-infected individuals; however, it may also lead to additional risks for the development of NCDs. It is becoming increasingly important to identify those with metabolic risk factors, in order to mitigate the burden of NCDs in SSA, especially within HIV-infected populations who are already at risk of developing chronic diseases and long-term complications, combined with ART initiation.

CHAPTER 3: METHODOLOGY

3.1 Study Setting

Data were extracted from an existing electronic database which was initially collected from participants visiting research clinics located within the city of Johannesburg district, sponsored by the Wits Reproductive Health and HIV Institute (WRHI), for a clinical trial. The majority of patients were recruited from Region F in Johannesburg district, including Yeoville, Esselen, Hillbrow, Jeppe and Melvern Clinics. In inner-city Johannesburg, high levels of poverty, incoming migrant populations, and marginalised communities such as LGBTQ+, refugees, asylum seekers, and sex workers have contributed to the extreme levels of HIV prevalence. As of 2019, the province reported a HIV-prevalence rate of 13.1% of which 88.9% were diagnosed, 60.9% were on ART and, of those, 87.3% were virally supressed (Spotlight, 2019). Moreover in 2020, the South African health review reported the prevalence of high blood pressure in Gauteng averaged 34.4% with a 47.8% of adults overweight or obese and a 6.6% prevalence of diabetes irrespective of HIV status. These rising rates for those diagnosed with another disease alongside HIV (co-morbidity) continue to increase the burden placed on healthcare facilities in treating and managing co-morbidities.

3.2 Study Design

A retrospective, cross-sectional analytical design was used. The analysis involved a retrospective record review of the data from the ADVANCE WRHI060 randomised clinical trial (Venter et al., 2019). A cross-sectional study uses a group of people who differ in some ways yet share other characteristics that can be identified and studied separately as different cohorts. This method of study assesses a group of people for occurrence of a disease at a point or period and allows for analysis of multiple variables. A similar study conducted in Uganda used a cross-sectional design to identify the prevalence of co-morbidity in PLWHIV on ART (Kansiime et al., 2019). Using this study design was efficient, with no loss to follow up and lower cost. Furthermore, this study design can generate further hypotheses relating to NCDs and HIV that could be studied in the future.

This sub-study reviewed client records from all participants enrolled in ADVANCE who had completed baseline visits between 2 February 2017 and 8 May 2018 before they initiated ART. The study extracted data from client records to describe their sociodemographic, behavioural,

and clinical characteristics. It also looked at the presence of metabolic risk factors or metabolic diseases in treatment-naïve, HIV-positive patients.

3.3 Study Population and Sampling

In the ADVANCE clinical trial, 1053 participants were enrolled into the study and randomised between three ART treatment arms to compare efficacy of treatment with standard of care. They were followed up every six months until the end of the study, where several study procedures and laboratory investigations were carried out primarily to show non-inferiority of Dolutegravir on viral suppression.

All individuals enrolled into the ADVANCE WRHI060 study were selected for data analysis. This included individuals who had tested positive for HIV at the beginning of the ADVANCE WRHI060 study and were recruited randomly from local clinics within Johannesburg from February 2017 to May 2018.

3.3.1 Inclusion Criteria

- Participants who had completed an enrolment visit in the ADVANCE study.
- Age ≥ 18 years and ≥ 40 kg.
- Documented laboratory diagnosis of infection with HIV-1 (positive enzyme-linked immunosorbent assay HIV-1 antibody test) at screening.
- Plasma HIV-1 RNA (VL) ≥ 500 copies/mL.
- Ability to comprehend the full nature and purpose of the study, in the opinion of the investigator, and to comply with the requirements of the entire study.

3.3.2 Exclusion Criteria

- Women who were pregnant at the time of the screening or enrolment visits.
- Active tuberculosis and/or were on antituberculosis therapy at the time of the screening or enrolment visits.
- Any missing laboratory result from the enrolment visit.
- Any critical illness preventing study participation.

All participants who were enrolled into the ADVANCE clinical trial were included in the sub-study involving retrospective secondary data analysis. No variables analysed were found to be missing and, as a result, no further exclusions were made.

3.3.3 Power Calculation

Using an online sample calculator (calculator.net), the sample size must be at least 385 participants, to have a 95% confidence interval, a 5% margin of error and an unlimited population size, or at least 384 698 people on ART in Gauteng province (Human Sciences Research Council, 2019). There were 1053 participants enrolled in the study, and this sub-study used all 1053 participants meeting the inclusion criteria.

3.4 Data Collection

At initiation of ADVANCE WRHI060, the parent study, paper questionnaires were used to capture data manually at the time of enrolment. Patients were assigned a patient ID and interviewed by research staff who filled in the paper questionnaires which were then filed in individual folders assigned to specific patients. Later in the study the data were entered onto an electronic format and follow up of participants was then captured digitally into electronic Case Report Forms (eCRFs). The computerised system conveniently allowed data to be collected retrospectively from the electronic database, REDCap (Research Electronic Data Capture), and exported into Excel spreadsheets.

The following information was exported:

- Sociodemographic characteristics: age, gender, race, marital status, employment status, level of education, country of origin.
- Substance use: use of tobacco, alcohol, and other illicit drugs.
- HIV immunological indices: CD4 count and viral load.
- Laboratory investigations: Lipogram (serum cholesterol serum triglycerides, high-density lipoprotein cholesterol (S-HDL cholesterol)), fasting serum glucose (plasma-fasting glucose).
- Clinical assessments: Blood pressure, BMI.

3.5 Data Analysis

Data were extracted from REDCap into Excel, and then transferred to Stata 15. Participants with missing variables or incomplete forms was excluded from the study. Data were first analysed according to socio-demographic, behavioural and clinical characteristics. Metabolic assessments were then extracted for risk factors quantified using the DAIDS (Division of AIDS, 2017) toxicity criteria as follows:

- Diabetes (pre-existing condition of DM or a fasting serum glucose ≥5.6mmol/L).
- Hypertension (pre-existing condition or systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 85 mmHg).
- Dyslipidaemia (pre-existing condition or abnormal laboratory values: elevated LDL ≥3.37 mmol/L or elevated cholesterol ≥ 5.18mmol/L or decreased HDL -in men <1 mmol/L; in women <1.3 mmol/L; elevated TG≥ 1.7mmol/L).
- Elevated BMI (25.0-29.9= overweight, 30.0-34.9= obese; >35= extremely obese).

Frequencies and percentages were calculated for categorical data and illustrated in tabular form. Outcome variables were categorised, and Chi-square tests were used to test for statistical significance with *p*-value <0.05 as the cut-off. Multivariate logistic-regression analysis was used to check for association between metabolic risk factors and other sociodemographic or behavioural factors.

3.6 Validity and Reliability

Reliability of a study ensures that if a method is repeated in the same manner that its results are reproduceable and consistent within a subject or specimen (Leung, 2013). Repetition of measurements along with follow up of laboratory investigations at all visits, ensured that data collected were reliable and not recorded in error. All abnormal baseline results in ADVANCE were repeated with stricter protocol compared to national guidelines, ensuring safety of patients and precision of data.

Validity within a study ensures that results captured and analysed are “true” (Hufford, 2021). Cause-and-effect constructs were used, as well as internal validity - to assess the degree of causality and external validity - to which the study results can be applied to other populations.

Selection bias was prevented in the main study, ADVANCE WRHI060. Patients who tested positive for HIV were randomly selected from inner-city Johannesburg clinics. They were recruited from clinics where several recruiters went to different clinics simultaneously to find participants for screening. Groups were briefly informed of the study while waiting in queues at clinics and invited to the study site for pre-screening, if they volunteered. Patients were recruited over a year, ensuring that a representative sample of the population was captured. Enrolled participants were randomly assigned to one of the three arms by a digital allocation system on the electronic database. Data were used from all 1053 patients enrolled in the main study.

Measurement bias was reduced by cross-checking of data such as blood pressure and temperature. For example, an elevated blood-pressure reading was always repeated a second time by another staff member to ensure accuracy. All clinical staff recording into the electronic records were trained on capturing data and how to rectify queries in real time. Standard operating procedures (SOPs) were available on all measurements taken, like height and blood pressure, where specific methods were explained to maintain consistency and reduce variation between clinical staff. Dedicated staff members would calibrate measuring instruments regularly to ensure accuracy of results being recorded. Participants called in for baseline visits were told to skip breakfast to record accurate fasting levels of sugar and lipids at baseline. Those who did not fast were rescheduled. Unfortunately, hip and waist circumference were not measured at baseline, and only BMI was used as a measure of adiposity.

The electronic database used, has an audit trail where each participant involved in the study was assigned a unique username and password that allowed for records to be traced. Consequently, any investigative reviews, could ascertain which coordinators, investigators or individuals had modified data by means of the audit trail (ADVANCE protocol, 2016). This ensured that any data recorded incorrectly were attended to before the participant left the site, and information was available on who to direct the query to, in case additional information or procedures were needed. Questionnaires were checked for quality and accuracy in real time after every patient visit.

3.7 Ethics Considerations

An application to the UWC Senate Higher Degrees committee and the UWC Biomedical Research Ethics Committee was obtained. Permission to access participant records was requested from Ezintsha Research Clinic, a sub-division of Wits Health Consortium.

The parent study, ADVANCE WRHI060, received ethics approval from the University of Witwatersrand Human Research Ethics Committee (HREC). In the main study, all participants provided written informed consent prior to study involvement. The process of the informed consent included documenting any queries raised throughout the process. The study staff who conducted the informed consent process also signed the informed consent form (ICF) and adhered to ethical principles approved by University of Witwatersrand HREC. All patients were given a unique participant ID, and any identifiers were hidden within the database to maintain anonymity and protect personal information.

In my retrospective sub-study, there was no interaction between participants and researchers, so no additional ICFs were completed. Analysis of existing electronic data were done, and no additional information was gathered. Regulations stipulated in the Protection of Personal Information Act was adhered to throughout the conduct of this study (POPIA, 2019).

CHAPTER 4: RESULTS

4. 1 Realisation of Sample Size

A total of 1053 adult patients who had a positive rapid antigen test for retroviral disease (RVD) test were enrolled into a clinical trial and included in the final analysis.

4.2 Sociodemographic and Clinical Characteristics of Participants

Table 4.1 presents the demographic and clinical characteristics of the study participants, stratified by gender. The majority of participants enrolled in the study were female (n=623; 59.2%), black (n=1051; 99.8%), and single (n=785; 75.0%). The median age of participants was 32 years with an inter-quartile range (IQR) of 10 years. On average, male participants were slightly older than females (33 vs. 32 years; p= 0.001). Most were South African (62.3%); while 32.3% were from Zimbabwe and 5.4% from other African countries, including Cameroon, Democratic Republic of Congo, Lesotho, Liberia, Malawi, Mozambique, Nigeria, Swaziland and Zambia.

Most participants had completed secondary schooling (84.0%, n=879). There was a statistically significant difference between female and male participants based on education level (p=0.018). More females had secondary education compared to males, 85.3% (n=527) vs. 82.2% (n=352), respectively. Significantly more males were employed or self-employed compared to females (72% vs. 55.4%, p <0.001).

Viral loads were grouped into categories from mild (< 100 000 copies/ml), moderate (100 000-500 000 cp/ml,) and high (>500 000 cp/ml) viral loads. Viral load ranges can be used to assess the stage of infection, monitor the effectiveness of antiretroviral therapy (ART), and predict the risk of disease progression and transmission, with low viral loads suggesting better outcomes. When analysed with CD4 counts, the association seen in the study sample was statistically significant showing that lower CD4 counts were associated with increasing viral loads. Most participants had mildly elevated viral loads below 100 000 cp/ml) (78.3%, n=823). A statistically significant difference was observed in the viral loads between male and female participants (p<0.05). Most of those with mild elevation were females (61.7% vs. 38.3%). A smaller percentage of patients (19.0%) had viral loads between 100 000 and 500 000 copies/ml (moderate viral loads). Again, females were slightly more likely to have viral loads in this range

compared to males (51.5% vs. 48.5%). About 22% of the population had high viral loads exceeding 500 000 copies/ml.

In comparison, 70% of participants had CD4 counts above 200 cells/ul; which indicate adequate immunological function. Females were more likely to have better immunological function compared to males at 73.4% (n=457) vs. 64.4% (n=277) (p=0.002).

Tobacco smokers and those who consumed alcohol were predominantly male with 37.9% and 68.3% of males reported smoking and alcohol use, respectively (p<0.001) (Table 4.1).

Table 4.1: Sociodemographic and clinical characteristics of adult, HIV-positive, treatment-naïve participants (N =1052)

	Total n (%) N=10533	**Female n (%) N=623**	**Male n (%) N=430**	***p*-value**
Age (in years)				
<20	22 (2.1)	12 (1.9)	10 (2.3)	0.001*
20-29	379 (36.0)	257 (41.3)	122 (28.4)	
30-39	462 (43.9)	247 (39.7)	215 (50.0)	
40-49	161 (15.3)	89 (14.3)	72 (16.7)	
50+	29 (2.8)	18 (2.9)	11 (2.6)	
Marital status				
Single	785 (75.0)	488 (78.7)	297 (69.4)	<0.001*
Married/Domestic partner	212 (20.2)	91 (14.7)	121 (28.3)	
Separated/widowed/divorced	41 (7.0)	41 (6.6)	51 (4.87)	
Level of Education				
No schooling	5 (0.5)	1 (0.2)	4 (1.0)	0.018*
Primary	71 (6.8)	32 (5.2)	39 (9.1)	
Secondary	879 (84.0)	527 (85.3)	352 (82.2)	
Tertiary	91 (8.7)	58 (9.4)	33 (7.7)	
Employment status				
Unemployed	389 (37.8)	270 (44.6)	119 (28.0)	<0.001*
Employed/Self-employed	641 (62.2)	335 (55.4)	306 (72.0)	
Country of Origin				<0.001*
South Africa	655 (62.3)	381 (61.4)	274 (63.7)	
Zimbabwe	339 (32.3)	218 (35.1)	121 (28.1)	
Other	57 (5.4)	22 (3.5)	35 (8.1)	
Viral Load (in cp/ml)				0.002*
<100 000	823 (78.3)	508 (81.8)	315 (73.26)	
100 000 - 500 000	200 (19.0)	103 (16.6))	97 (22.6)	
>500 000	28 (2.7)	10 (1.6)	18 (4.2)	
CD4 Cell Count				0.002*
<200	319 (30.29)	166 (26.7)	153 (35.6)	
≥200	734 (69.7)	457 (73.4)	277 (64.4)	

Smoker				
Yes	811 (77.0)	544 (87.3)	267 (62.1)	<0.001*
No	242 (23.0)	79 (12.7)	163 (37.9)	<0.001*
Drinks Alcohol				
Yes	542 (51.5)	249 (40.0)	293 (68.3)	<0.001*
No	510 (48.5)	374 (60.0)	136 (31.7)	
TOTAL	1052 (100)	623 (100)	42 (100)	

* P-value < 0.005

4.2 Prevalence of Metabolic Risk Factors

Table 4.2 below shows the prevalence of metabolic risk factors and metabolic syndrome by gender. Metabolic risk factors analysed in this study sample were diabetes (defined as pre-existing diagnosis or elevated fasting glucose), hypertension (defined as pre-existing diagnosis or elevated diastolic or systolic blood pressures), dyslipidaemia (defined as pre-existing diagnosis or an abnormal lipogram) and elevated BMI (Body Mass Index recorded as either overweight or obese). Of the four risk factors, all but diabetes shows a statistically significant difference between genders. The prevalence of diabetes was 2.6% (n=27) in the sample population, with no significant difference between males and females. Hypertension was present in 39.3% (n=414) of participants, with a significantly higher prevalence in males (43.5%) compared to females (36.4%; p=0.021). Figure 4.1 shows that the nearly all metabolic risk factors were higher in females compared to males, except for hypertension.

Dyslipidaemia was the most prevalent risk factor, present in 65.5% (n=690) of participants. There was a significantly higher prevalence of dyslipidaemia in females compared to males (76.2% vs. 50%; p<0.001).

The distribution of BMI categories among participants showed 64% (n=673) having a normal BMI, 24% (n=252) being overweight, and 12.1% (n=114) being obese. A significantly higher proportion of females were overweight or obese (49.02%) compared to males (15.8%; p<0.001). Overall, over 70% of the participants were either overweight or obese.

Of all the participants, only 16.6% had no metabolic risk factors, 37.9% had one risk factor, 31.4% had two risk factors, 13.6% had three risk factors, and only 0.4% had all four risk factors. Almost half (45.4%) had at least two risk factors at baseline and 148 participants (13.6%) had at least three risk factors, defined as having metabolic syndrome. Of those who had no risk factors, most were males (26.5% vs. 9.8%). In contrast, a higher proportion of females had two

or more risk factors compared to males (55.7% vs. 30.7%). Females were thus more likely to have any one risk factor compared to males (p<0.001).

Of the 148 participants who had defined metabolic syndrome, females (n=111; 17.8%) were more like to have metabolic syndrome compared to males (n=37; 8.6%; p<0.001).

Table 4.2: Prevalence of Cumulative Metabolic Risk Factors amongst treatment-naïve adult HIV patients in inner-city Johannesburg (N=1053)

	Total n (%) N=1053	**Female n (%) N=623**	**Male n (%) n=430**	***p*-value**
Diabetes				
Yes	27 (2.6)	12 (1.9)	15 (3.5)	0.115
No	1026 (97.4)	611 (98.1)	415 (96.5)	
Hypertension				
Yes	414 (39.3)	227 (36.4)	187 (43.5)	0.021*
No	639 (60.7)	396 (63.7)	243 (56.5)	
Dyslipidaemia				
Yes	690 (65.5)	475 (76.2)	215 (50)	<0.001*
No	363 (34.5)	148 (23.7)	215 (50.0)	
BMI				
Normal	673 (64.0)	311 (50.0)	362 (84.2)	<0.001*
Overweight	252 (24.0)	197 (31.7)	55 (12.8)	
Obese	114 (12.1)	127 (18.3)	13 (3.0)	
Metabolic risk factors				<0.001*
0	175 (16.6)	61 (9.8)	114 (26.5)	
1	399 (37.9)	215 (34.5)	184 (42.8)	
2	331 (31.4)	236 (37.9)	95 (22.1)	
3	143 (13.6)	106 (17.0)	37 (8.6)	
4	5 (0.4)	5 (0.8)	0 (0.0)	
Metabolic Syndrome†				
Yes	148 (14.1)	111 (17.8)	37 (8.6)	<0.001*
No	905 (85.9)	512 (82.2)	393 (91.4)	

† The presence of three or more risk factors indicates a diagnosis of metabolic syndrome.

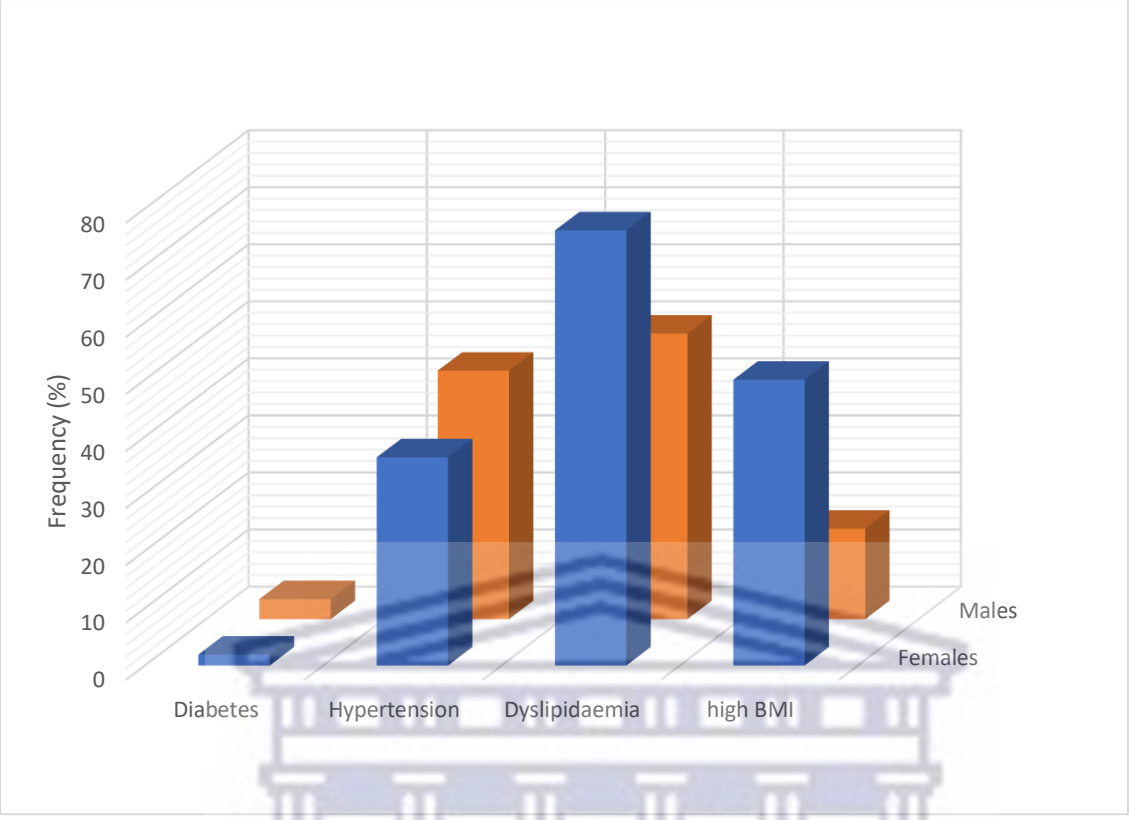


Figure 4.1: Frequency of metabolic risk factors in males and females with HIV

Table 4.3: Prevalence of metabolic syndrome by sociodemographic and clinical characteristics (N = 1052)

		Metabolic syndrome		
	Total n (%) N=1053	**No** n (%) N=905	**Yes** n (%) N=148	***p*-value**
Age (in years)				
<20	22 (2.1)	22 (2.4)	0 (0)	<0.001*
20-29	379 (36.0)	348 (38.5)	31 (21.0)	
30-39	462 (43.9)	398 (44.0)	64 (43.2)	
40-49	161 (15.3)	122 (13.5)	39 (26.4)	
50+	29 (2.6)	15 (1.7)	14 (9.5)	
Marital status				
Single	785 (75.0)	683 (75.9)	102 (68.9)	0.015*
Married/Domestic partner	212 (20.2)	180 (20.0)	32 (21.6)	
Separated/widowed/divorced	51 (4.9)	37 (4.1)	14 (9.5)	
Level of Education				
No schooling	5 (0.5)	4 (0.5)	1 (0.7)	0.716
Primary	71 (6.8)	64 (7.1)	7 (4.7)	
Secondary	879 (84.0)	753 (83.9)	126 (85.9)	
Tertiary	91 (8.7)	77 (8.6)	14 (9.5)	
Employment status				
Unemployed	389 (37.8)	338 (38.3)	51 (34.5)	0.371
Employed/Self-employed	641 (62.2)	544 (61.7)	97 (65.5)	
Viral Load (in cp/ml)				
<100 000	823 (78.3)	712 (78.8)	111 (75.5)	0.655
100 000 - 500 000	200 (19.0)	168 (18.9)	32 (21.8)	
>500 000	28 (2.7)	24 (2.7)	4 (2.7)	
CD4 Cell Count				
<200	319 (30.3)	278 (30.7)	41 (27.7)	0.459
≥200	734 (69.7)	627 (69.3)	107 (72.3)	
Smoker				
Yes	242 (23.0)	220 (24.3)	22 (14.9)	0.011*
No	811 (77.0)	685 (75.7)	126 (85.1)	
Drinks Alcohol				
Yes	542 (51.5)	478 (52.9)	64 (43.2)	0.030*
No	510 (48.5)	426 (47.1)	84 (56.8)	

Table 4.3 shows the characteristics of those with metabolic syndrome compared to those without by different demographic and clinical factors. The older the participants, the more likely they had metabolic syndrome. Of those aged 50 years and above, almost half had three or more metabolic risk factors (n=14; 9.5%) while those in younger age groups were progressively less likely to have metabolic syndrome ($p < 0.001$).

Participants who were separated, widowed or divorced had a significantly higher prevalence of metabolic syndrome (9.5%) followed by participants who were married or in a domestic partnership (21.6 %), and lowest among single participants (68.9%: p=0.015).

There were no statistically significant associations between prevalence of metabolic syndrome with level of education (p=0.716), employment status (p=0.371), CD4 count (p=0.459) and viral load (p=0.655).

Participants who smoked had a significantly lower prevalence of metabolic syndrome compared to non-smokers (n=22; 14.9% vs. n=126; 85.1%; p=0.011). Participants who did not drink alcohol also had a significantly higher prevalence of metabolic syndrome compared to those who did drink alcohol (n=84; 56.8% vs. n=64; 43.2%; p=0.030).

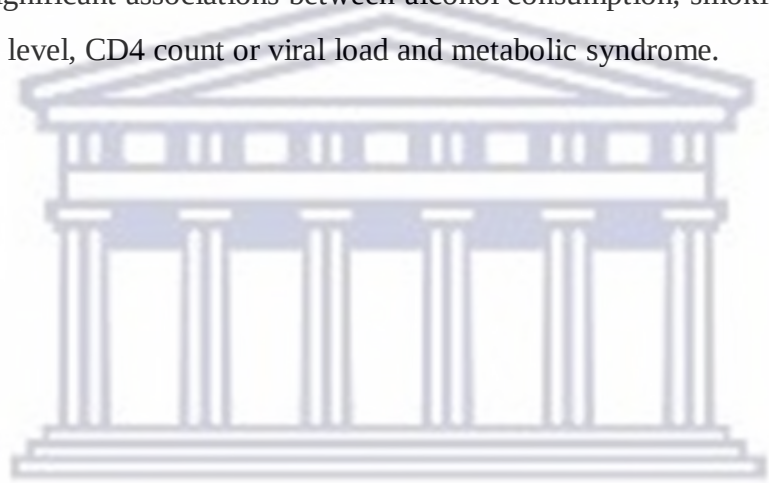
Table 4.4: Determinants of metabolic syndrome amongst treatment-naïve, adult HIV patients in inner-city Johannesburg (N=1052)

	Crude Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)
Age (Reference: <30 years)		
30-39	1.92 (1.22-3.01)	2.14 (1.34-3.42) *
40-49	3.82 (2.28-6.38)	4.02 (2.29-7.06) *
50+	11.14 (4.92-25-18)	12.32 (5.08-29.85) *
Gender (Reference: Females)		
Male	0.43 (0.29-0.64)	0.40 (0.25-0.63) *
Marital Status (Ref: Single)		
Married/ partner	1.19 (0.77-1.83)	1.16 (0.72-1.85)
Separated/ widowed/divorced	2.53 (1.32-4.85)	1.15 (0.57-2.35)
Employed (Ref: Unemployed)		
Self-Employed	1.18 (0.82-1.70)	1.03 (0.69-1.54)
Education (Ref: No schooling)		
Primary	0.44 (0.04-4.48)	0.64 (0.06-7.07)
Secondary	0.67 (0.74-6.04)	1.07 (0.11-10.57)
Tertiary	0.73 (0.76-7.00)	1.06 (0.10-11.21)
Smoking status (Ref: Non-Smoker)		
Current smoker	0.54 (0.34-0.88)	0.69 (0.39-1.20)
Alcohol Use (Ref: No drinking)		
Yes	0.68 (0.48-0.96)	1.06 (0.70-1.60)
CD4 Count (Ref: <200)		
>= 200	1.16 (0.79-1.70)	1.38 (0.89-2.12)
Viral Load (Ref: VL < 100 000 cp/ml)		
100 000 - 500000	1.22 (0.80-1.87)	1.45 (0.90-2.33)
>500 000	1.07 (0.36-3.14)	1.76 (0.55-5.59)

Table 4.4 displays the results of the logistic regression of demographic, behavioural and clinical factors with metabolic syndrome. Having metabolic syndrome was significantly associated with increasing age. Those 30-39 years old had double the odds (OR: 2.1, 95% CI :1.3-3.4) of having metabolic syndrome compared to those under 30 years old. Those 40-49 years old had nearly four times the odds of having metabolic syndrome (OR: 4.0, 95% CI: 2.29-7.06). The odds were further increased to 12 times in those 50 years and older compared to the reference group (OR: 12.3, 95% CI: 5.08-29.85).

Males were 60% less likely to have metabolic syndrome compared to females (OR 0.40, 95% CI :0.3-0.6).

There were no significant associations between alcohol consumption, smoking status, marital status, education level, CD4 count or viral load and metabolic syndrome.



CHAPTER 5: DISCUSSION

5.1 Socio-Demographic Profile of Clinical Trial Participants

Our study sample captured participants visiting clinics in inner-city Johannesburg. They were mostly Black females within the 20–39-year age bracket. This is in keeping with the City of Johannesburg Inner City Plan which indicates that the majority of residents in the inner city are Black African (87.4%) with a median age of 33.9 years old (Statistics South Africa, 2022). Over half of the study population was female compared to males (41%). It is a common finding that females are more commonly recruited in clinical trials as they are generally more willing to participate, more health-conscious and more likely to seek medical care (Shisana et al., 2014). Additionally, women are more likely to be affected by HIV in South Africa, with HIV prevalence rates among women being significantly higher than among men (UNAIDS, 2022).

In this study sample, women were more likely to have completed higher levels of education than male participants who had mostly no schooling or primary schooling. This was consistent with the gender differences seen in the diverse types of qualifications obtained. For example, a higher proportion of men in Johannesburg have completed technical and vocational education and training courses, while women are more likely to have completed university degrees (Statistics South Africa, 2022). There were significant differences in employment status between genders in the study sample. According to data from the Quarterly Labour Force Survey (QLFS) in 2022, men in South Africa are more likely to be employed than women. Specifically, 64.4 % of men are employed, compared to only 53% of women (Statistics South Africa, 2022). This was represented in our sample population where 72% of men were employed or self-employed and only 55.4% of women were employed. This gender gap is likely due to a combination of factors, including discrimination, asylum status, caregiving responsibilities and differences in education levels.

Our study showed that although Zimbabweans made up the second-highest nationality, they were also more likely to be employed compared to the South African group (data not shown). This is in contrast to research that has shown that immigrants in South Africa, particularly those from other African countries, often face significant barriers to employment due to discrimination, lack of access to networks and information, formal employment opportunities and xenophobia (Crush et al, 2015). These barriers to employment can be even worse for women, who may face additional gender-related challenges such as gender-based violence,

limited access to education, finance, assets and property (Department of Women, South Africa.,2015). This was in keeping with our study which showed that within the non-South African nationals, more women were unemployed (38.6%, n=91) compared to men (16.1%, n=24). Similarly, research also highlights that immigrant women in South Africa are more likely to be unemployed than their male counterparts, emphasising the gendered nature of labour market discrimination and exclusion (Chinyakata et al., 2019). In addition, a study of employment and inequality in South Africa, found that while men were more likely to work in skilled and professional occupations, women were more likely to work in low-paying, low-skilled jobs such as domestic work or informal trading (Leibbrandt et al., 2010).

5.2 Clinical profile of HIV-Positive, Treatment-Naïve Participants Enrolled in A Clinical Trial

In this study, females were more likely to have CD4 cell counts greater than 200 cells\ul (73.4%) while males had lower counts (35.6%). Gender differences in CD4 counts among HIV-positive individuals at the time of antiretroviral therapy (ART) initiation have been observed in several studies. One possible explanation is that females tend to seek medical care more frequently than males, leading to earlier diagnosis of HIV infection and earlier initiation of ART (Nakanjako et al., 2011). Another possible explanation is that there may be differences in the way that HIV infection progresses in males and females. For example, some studies have suggested that females may experience slower disease progression than males, which could allow for higher CD4 counts at the time of ART initiation (Auld et al., 2014). The timing of HIV diagnosis could also be the reason behind the differences in viral loads. For instance, females may be more likely to get tested for HIV earlier in the course of their infection, which could result in lower viral loads. This is supported by research showing that women in South Africa are more likely to get tested for HIV and to access HIV-treatment services compared to men (Shisana et al., 2016). This may be attributed to the fact that women receive HIV testing and counselling during antenatal visits and are more likely than men to be seen regularly by healthcare providers.

Viral loads were grouped into categories from mild (<100 000 cp/ml), moderate (<100 000-500 000 cp/ml), and high (>500 000cp/ml) viral loads. Viral-load ranges can be used to assess the stage of infection, monitor the effectiveness of ART, and predict the risk of disease progression and transmission. When analysed with CD4 counts, the association seen in the

study sample was statistically significant showing that lower CD4 counts were associated with increasing viral loads. This is expected in people living with HIV where a higher viral load is associated with a lower CD4 count and typically leads to a faster decline in CD4+ T-cells, which are critical for immune-system function (Claiborne et al., 2015). A lower CD4 count (< 200 cells/µl) is also associated with a higher risk of developing AIDS- and non-AIDS-related complications (Lapadula et al., 2015).

5.3 Prevalence of Metabolic Risk Factors

In our study sample, there was statistically significant differences in the prevalence of metabolic risk factors and thus metabolic syndrome (having three or more risk factors) between males and females in HIV-positive, treatment-naïve participants (17.0% vs. 8.6%). A study conducted by Maimela et al. (2018) reported that the prevalence of metabolic syndrome was higher in HIV-positive patients compared to HIV-negative individuals in South Africa. Their study included a sample of 136 HIV-positive patients, aged 18 years and older, who were treatment-naïve. The prevalence of metabolic syndrome was found to be 29.4% in males and 51.6% in females (Maimela et al., 2018). Additionally, a study conducted by Munyanja et al. (2020) found that HIV-positive patients on ART in Uganda had a high prevalence of metabolic syndrome (51% in males and 62% in females) and other metabolic risk factors.

Although this prevalence was far higher than in our study, it is critical to note that having any two metabolic risk factors has been shown to significantly increase the risk of developing metabolic syndrome. A study by Malik et al. (2018) found that individuals with two metabolic risk factors had a four-fold increased risk of developing metabolic syndrome compared to those with no risk factors. Additionally, a meta-analysis by Mottillo et al. (2010) showed that the presence of two metabolic risk factors increased the risk of metabolic syndrome by 5.5 times. In our analysis, if the prevalence of at least two metabolic risk factors is considered, then the numbers increase by an additional 37.9% in females and 22.1% in males, making the total 55.7% and 30.7% in females and males, respectively – which is similar prevalence to that seen in populations in South Africa.

There is limited research on the risk of developing metabolic syndrome in HIV-positive patients not yet on ART, who have two or more metabolic risk factors. The above studies did not include HIV-positive individuals only, however, several studies found that among treatment-naive HIV-positive patients, the presence of metabolic risk factors was associated

with an increased risk of developing metabolic syndrome after starting ART as well as further going on to develop DM and CVD (Handan et al., 2007; Tesfaye et al., 2014; Munyanja et al., 2016). Furthermore, patients with more metabolic risk factors had a higher incidence of metabolic complications, after starting ART. While these studies focus on the risk of developing metabolic syndrome after starting ART, it suggests that the presence of two or more metabolic risk factors in treatment-naive HIV-positive patients may increase the risk of developing metabolic syndrome.

In our study, dyslipidaemia was found to be the most prevalent metabolic risk factor (65.5%) among the four metabolic risk factors needed to determine the risk of developing NCDs. A 2020 study found that the prevalence of dyslipidaemia among adult patients attending primary healthcare clinics in Johannesburg was much higher than our study population, at 80.3%, while that of obesity was 34.1 % - similar to our sample population (Peer et al., 2012). The overall prevalence for lipid abnormalities and higher BMI was greater in females than men, which is consistent with other global studies that show an association with obesity and dyslipidaemia (Singh et al., 2011). In South Africa, this is also consistent with previous studies that show dyslipidaemia, and a higher BMI is more common in females than in males (Motala et al., 2011). The South African National Health and Nutrition Examination Survey 2012 (SANHANES) reported 30% of men and nearly 70% of women as being overweight or obese. This was similar to our study where half of the females had a high BMI, compared to less than 20% of the males.

This study found that the overall prevalence of diabetes was relatively low at 2.6%, with a slightly higher prevalence in males than in females - but the difference was not statistically significant. This contrasts with the higher prevalence of diabetes reported in the general South African population, where it is estimated that about 9.3% of adults have diabetes (International Diabetes Federation, 2019). This could possibly be due to a lower sample size of males compared to females and the relatively young median age of study participants, although it is still an important risk factor for CVD and a predictor of complications.

The overall prevalence of hypertension in this study was elevated at 39.3%, which was similar to the WHO prevalence rates of 42.0%, based on a survey conducted around the same time (WHO, 2018). There was a significantly higher prevalence in males than in females. This aligns with previous research that has shown that hypertension is more common in males than females in the general South African population. (Peltzer et al., 2013). Lifestyle factors such as smoking

and alcohol consumption may also play a role - these have a higher prevalence in males compared to females and may contribute to the observed gender differences in hypertension, also seen in our study.

5.4 Prevalence of Metabolic Syndrome

A total of 14.1% of our sample population had metabolic syndrome, defined as having at least three risk factors. The prevalence of metabolic syndrome varies globally, but it is estimated to affect approximately 20-25% of the adult population worldwide (Albert et al., 2009). In South Africa, the prevalence of metabolic syndrome is higher than the global average, with estimates ranging from 30% to 50% in different populations (Mayosi et al, 2009). HIV-positive individuals, especially those who are treatment-naive, are also at an increased risk of developing metabolic syndrome, more so after initiating HAART.

A study done in Nigeria (including both ART-experienced patients and ART-naïve patients) found that the prevalence of metabolic syndrome was significantly higher in ART patients compared to ART-naïve patients. Additionally, ART patients had higher rates of obesity, elevated blood pressure, and dyslipidaemia (Ojong et al., 2022). Similarly, a systematic review and meta-analysis of 35 studies published between 2007 and 2019 found that the prevalence of metabolic syndrome in Sub-Saharan Africa was higher in HIV-positive populations compared to HIV-negative populations (21.5% vs. 12.0%) (Todowede et al., 2019). And as our study showed, hypertension was the most common risk factor. Although a smaller proportion of participants had three risk factors, almost half of the cohort had at least two risk factors putting them at risk of developing metabolic syndrome, with even greater chance at the advent of ART initiation and with increasing age.

A study conducted by Kansiime et al. (2019) to determine the prevalence and factors associated with metabolic co-morbidities among people living with HIV on ART in Uganda reported the prevalence of metabolic co-morbidities among HIV-positive individuals on ART was high, with 66.1% having at least one metabolic co-morbidity and 17.2% having three or more. Our study showed half as many had at least one risk factor (37.9%) and 13.6% had three or more. Dyslipidaemia, again, was the most prevalent metabolic co-morbidity, followed by hypertension and diabetes mellitus. The study also identified several risk factors for metabolic co-morbidities, including increasing age, longer duration on ART and higher BMI.

5.5 Factors Associated with Metabolic Risk

In our study, increasing age showed an increase in metabolic risk, where those 50 years and older had over 12 times higher odds of having metabolic syndrome compared to those less than 30 years of age. In our study population, males had 40% lower odds of having metabolic syndrome compared to females. There are several studies globally indicating this relationship as well as several studies in South Africa showing that metabolic prevalence increases with both age and gender, with the highest prevalence in those aged 60 and above (Motala et al., 2011; Peer et al., 2012; Erasmus et al., 2020). The majority of participants were younger in our study population with only one participant over the age of 60 years.

Although of no statistical significance in our study, compared to those with no schooling, individuals with primary, secondary, and tertiary education have odds ratios of 0.64 (95% CI: 0.06-7.07), 1.07 (95% CI: 0.11-10.57), and 1.06 (95% CI: 0.10-11.21), respectively. Indicating a positive correlation with higher education compared to those with primary or no schooling. Statistical significance may have been achieved if the sample size was larger. Similarly, employment status showed no statistical significance between self-employed and employed individuals.

In our study, those who are married or have a partner, are 16% more likely to have metabolic syndrome (95% CI: 0.72-1.85) compared to those who are single (reference group). Similarly, separated, widowed, or divorced individuals have 1.15 times higher odds of having metabolic syndrome (95% CI: 0.57-2.35). However, this was not statistically significant and there is unlikely to be a relationship between marital status and metabolic syndrome. The association between marital status and metabolic syndrome has been investigated in several studies, largely showing a positive relationship, while others find mixed associations. For example, Lazzarino et al (2013) found an association between being married or living with a partner had a reduced risk of mortality from metabolic syndrome. According to Umberson et al (2006), married individuals tend to have better health behaviours, such as regular exercise, healthy diet, and lower rates of smoking and alcohol consumption, which could contribute to a lower risk of metabolic syndrome. Similarly, Jung et al (2017), found that married individuals had a lower prevalence of metabolic syndrome compared to single individuals, this was in contrast to our study, however, this was not statistically significant within our study and confounding factors like age and gender may affect the relationship between metabolic syndrome and marital status.

This study found no statistically significant association between smoking and metabolic syndrome after adjusting for other factors. Other studies predominantly show a higher risk of metabolic risk factors with smoking. For instance, a study among Puerto Rican adults showed that metabolic syndrome was more prevalent in smokers that non-smokers. The study found that heavy smokers were 2.24 times more likely to have metabolic syndrome compared to never smokers (Calo et al, 2014). Similarly, a study in Seoul, South Korea showed that the effect on lipids with smoking (elevated triglyceride and lower HDL levels) correlated with the higher risk of metabolic syndrome in smokers compared to non-smokers (Kim et al, 2021). Gradidge & Crowther also report that smoking increases the risk of metabolic syndrome in South African black women. However, some studies may have confounding factors resulting in mixed conclusions where smoking has been shown to increase metabolic rate and energy expenditure, leading to lower body weight and BMI (Pisinger et al., 2007). Additionally, smoking may decrease appetite and food intake, leading to lower caloric intake and further weight loss (Shuval et al., 2021).

Despite this finding, there is greater evidence reporting that smoking is a risk factor for numerous health problems such as CVD, cancer and respiratory illness, and the benefits of smoking on metabolic syndrome do not outweigh the harms associated with smoking (WHO, 2022). Therefore, smoking cessation should be encouraged for overall health and well-being.

This study found no association between alcohol consumption and the risk of having metabolic syndrome. However, there are other studies that report that alcohol may have a protective effect against metabolic syndrome. Some studies have reported that moderate alcohol consumption can improve insulin sensitivity and reduce the risk of developing metabolic syndrome and type-2 diabetes (Joosten et al., 2008; Koppes et al., 2005). A study examining binge drinking in the United States, showed similar findings which were attributed to the "sick quitter" hypothesis where adults would abstain from alcohol consumption due to potential interactions with medication thus influencing their risk of multimorbidity (Han et al., 2018). Conversely, another study found that heavy alcohol use was associated with insulin resistance, a key factor in the development of metabolic syndrome (Slagter et al.,2018). Nevertheless, several studies conducted describe the negative health outcomes associated with heavy alcohol intake leading to higher levels of triglycerides, LDL levels, total cholesterol and hypertension, all of which are risk factors for metabolic syndrome (Okojie et al., 2020; Capurso & Petrakis., 2016: Rosoff et al., 2019). Ultimately, smoking and excessive alcohol consumption can exacerbate the risk of metabolic syndrome and contribute to the development of NCDs (Steyn et al., 2006).

This study did not find any statistical significance between CD4 of less than 200 and metabolic syndrome. The association between CD4 count, viral load and the odds of having metabolic syndrome could be due to various factors related to the immune system, inflammation and metabolic changes. Those with a higher CD4 count and viral load may have a greater risk for metabolic syndrome due to greater immune activation and inflammation (Appay & Sauce, 2008). A study among HIV-positive adults in the USA showed that an increasing CD4 count was associated with increasing occurrence of metabolic risk factors, however, they attributed a significant portion of this to higher BMI (Mondy et al, 2007). Chronic inflammation is known to contribute to the development of metabolic syndrome, as it can lead to insulin resistance, dyslipidaemia, and other metabolic abnormalities (Hotamisligil, 2006).

Furthermore, a higher viral load reflects more active viral replication, which can have direct effects on lipid and glucose metabolism (Grinspoon & Carr, 2005). The virus may interfere with cellular processes and contribute to the development of metabolic syndrome. The association between CD4 count, viral load, and metabolic syndrome may be influenced by confounding factors such as age, sex, lifestyle factors (smoking, diet, physical activity), and genetic predisposition to metabolic abnormalities. These factors can independently or synergistically contribute to the development of metabolic syndrome (Alberti et al., 2009).

5.6 Limitations of the Study

The larger, parent study had certain inclusion and exclusion criteria for clinical trial eligibility, which resulted in the exclusion of individuals who were critically ill or unable to participate. As a result, the study may have underestimated the prevalence of co-morbid conditions at baseline. This sub-study involved secondary analysis conducted without any external funding or sponsorship.

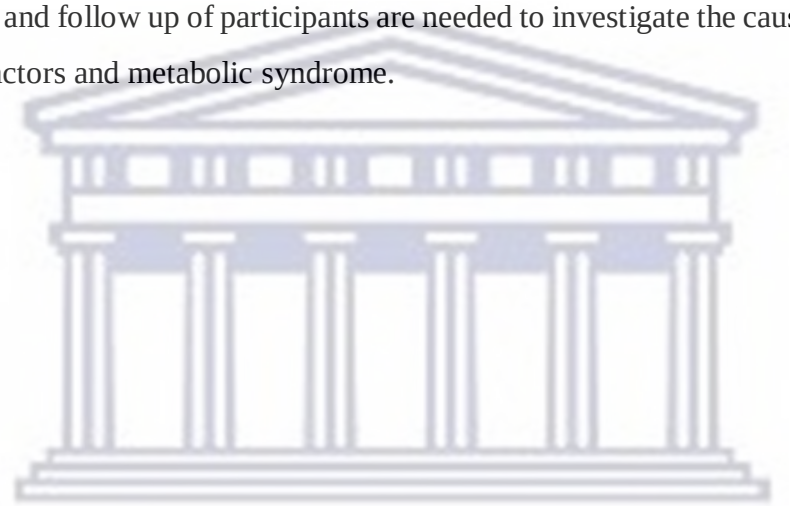
About two thirds of the sample population were female. The over-representation of women in HIV clinical trials can have negative consequences and limit generalisability of the study. For example, it can lead to a lack of understanding about how HIV treatment affects men, who may have different risk profiles compared to women (Wenyen et al., 2019). This can result in a lack of knowledge about how to effectively tailor treatment in HIV-positive men, which can lead to poorer health outcomes for this population.

Unfortunately, other variables such as dietary habits, physical activity levels and psychosocial factors that could impact the prevalence of metabolic risk in the study population, were not

analysed. Furthermore, measures such as HBA1C (glycated haemoglobin to determine average blood sugar levels) and waist-to-hip ratios, which are better indicators for risk for metabolic syndrome, were only added much later in the clinical trial and were not available at screening.

The enrolment of participants at one site might restrict the extent to which our results can be applied to the larger South African population. Despite this, the study does cater to a vast coverage area in Johannesburg for HIV care. The large sample size also increases the statistical power and ability to detect differences between variables.

Of note, this is a cross-sectional study, which means that these findings only provide a snapshot of the association between these factors and metabolic syndrome at a single point in time. Further research and follow up of participants are needed to investigate the causal relationships between these factors and metabolic syndrome.



CHAPTER 6: CONCLUSIONS AND RECOMMENDATIONS

6.1 Conclusion

In conclusion, the prevalence of metabolic risk factors in HIV-positive, treatment-naïve patients is a critical area of investigation. Due to the potential for these factors to contribute to the development of other non-communicable diseases, such as cardiovascular diseases, diabetes and dyslipidaemia, it is crucial for individuals to be aware of these risk factors. Understanding the burden of metabolic risk factors in this population can help inform targeted interventions and management strategies to improve the overall health and well-being of people living with HIV.

Several studies indicate a high prevalence of these risk factors in HIV-positive, treatment naïve individuals (Maimela et al, 2018; Todowede et al., 2019). Baseline screening reveals high levels of risk factors leading towards the development of metabolic syndrome which subsequently pose a significant threat to the emergence of NCDs. Furthermore, the initiation of ART can contribute to or exacerbate these metabolic risk factors, making the need for specific ART regimens and regular monitoring essential. Additionally, the findings suggest that interventions to address these risk factors may need to be tailored to the specific metabolic risk profiles of HIV-positive males and females.

Early identification and intervention can help reduce the risk of CVDs and improve the quality of life for PLWHIV.

6.2 Recommendations

Primary healthcare centres need support to address rising NCDs in HIV-negative and HIV-positive individuals. Clinics testing for HIV and treating PLWHIV need focused interventions to build capacity and train healthcare personnel. In addition to policy frameworks and guidelines, adequate staff training is required to raise awareness of the high levels of NCD and metabolic risk factors as well as on screening methods to identify those at risk and to improve knowledge and skills in managing NCDs among PLWHIV. A multi-disciplinary approach is needed where patients identified can be integrated into the system and receive patient-centred care before development of complicated disease.

The South African National Strategy for the Prevention and Control of Obesity outlines objectives and proposes essential activities for stakeholders, with the primary goal of reducing obesity rates by 10% across all age groups by 2020 (National Strategy for Prevention and Control of Obesity, 2015). Strengthening surveillance and monitoring systems is crucial for tracking the implementation of NCD management protocols, particularly to assess the progress made towards achieving goals like these and to determine the extent of further efforts required. Furthermore, this will empower healthcare providers and policymakers to identify gaps in service delivery and appraise the efficacy of existing interventions.

Further innovative research is needed to inform evidence-based interventions and promote collaboration between researchers, healthcare providers, policymakers and community organisations, both in the public and private sectors, in order to share resources and strategise on best practices.

Lastly, creating an enabling environment for tackling risk factors leading to NCDs is crucial. For example, opportunities for physical activity in safe and clean spaces should be made accessible, along with access to healthy food options.

Investing in prevention of NCDs is of utmost importance as failing to do so could result in significant mortality and increased financial burden.

REFERENCES

Abou Hassan, F.F., Hamdan, M.A.B., El Asmar, K., Mokhbat, J.E. and Melhem, N.M., 2022. Trends & predictors of non-AIDS comorbidities among people living with HIV and receiving antiretroviral therapy in Lebanon. *Medicine*, *101*(13).

Alberti, K.G., Eckel, R.H., Grundy, S.M., Zimmet, P.Z., Cleeman, J.I., Donato, K.A., Fruchart, J.C., James, W.P.T., Loria, C.M. & Smith Jr, S.C. (2009). Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. *Circulation*. 120(16):1640-5. DOI: 10.1161/CIRCULATIONAHA.109.192644

Althoff, K.N., McGinnis, K.A., Wyatt, C.M., Freiberg, M.S., Gilbert, C., Oursler, K.K., Rimland, D., Rodriguez-Barradas, M.C., Dubrow, R., Park, L.S. and Skanderson, M. (2015). Comparison of risk and age at diagnosis of myocardial infarction, end-stage renal disease, and non-AIDS-defining cancer in HIV-infected versus uninfected adults. *Clinical Infectious Diseases*, 60(4): 627-638.

Amberbir, A., Lin, S.H., Berman, J., Muula, A., Jacoby, D., Wroe, E., Maliwichi-Nyirenda, C., Mwapasa, V., Crampin, A., Makwero, M. and Singogo, E. (2019). Systematic review of hypertension and diabetes burden, risk factors, and interventions for prevention and control in malawi: *The NCD BRITE consortium. Global Heart*, 14(2): 109-118.

Amutuhaire, W., Mulindwa, F., Castelnuovo, B., Brusselaers, N., Schwarz, J. M., Edrisa, M., Dujanga, S., Salata, R. A., & Yendewa, G. A. (2018). Prevalence of cardiometabolic disease risk factors in people living with HIV initiating anti-retroviral therapy at a high-volume HIV clinic in Kampala, Uganda. *BMC Public Health,* 18(1): 1-9. DOI: 10.1186/s12889-018-5697-0

Appay, V., & Sauce, D. (2008). Immune activation and inflammation in HIV-1 infection causes and consequences. *The Journal of Pathology*, 214(2): 231-241.

Assefa, A., Abiye, A.A., Tadesse, T.A. and Woldu, M. (2023). Prevalence and Factors Associated with Dyslipidemia Among People Living with HIV/AIDS on Follow-Up Care at a

Tertiary Care Hospital in Ethiopia: A Cross-Sectional Study. *Drug, Healthcare and Patient Safety*, pp.93-102.

Auld, A. F., Mbofana, F., Shiraishi, R. W., Sanchez, M., Alfredo, C., Nelson, L. J., … Ellerbrock, T. V. (2014). Lower CD4 count and higher viral load at antiretroviral treatment initiation among younger versus older HIV-infected adults in Zimbabwe. *AIDS Patient Care and STDs*, 28(6): 282-287. DOI: 10.1089/apc.2013.0345

Awotedu, K., Ekpebegh, C., Longo-Mbenza, B. and Iputo, J. (2010). Prevalence of metabolic syndrome assessed by IDF and NCEP ATP 111 criteria and determinants of insulin resistance among HIV patients in the Eastern Cape Province of South Africa. Diabetes & Metabolic Syndrome: *Clinical Research & Reviews*, 4(4): 210-214.

Bailin, S.S. and Koethe, J.R. (2023). Diabetes in HIV: the Link to Weight Gain. *Current HIV/AIDS Reports*, *20*(1), pp.9-18.

Biggs, C. and Spooner, E. (2018). Obesity and HIV: a compounding problem. *South African Journal of Clinical Nutrition*, 31(4): 6-11.

Brennan AT, Jamieson L, Crowther NJ, et al. (2018). Prevalence, incidence, predictors, treatment, and control of hypertension among HIV-positive adults on antiretroviral treatment in public sector treatment programs in South Africa. *PLOS ONE*, 13(10): e0204020. DOI: 10.1371/journal.pone.0204020

Brennan, A.T., Jamieson, L., Crowther, N.J., Fox, M.P., George, J.A., Berry, K.M., Stokes, A., Maskew, M., Sanne, I., Long, L. and Cassim, N., (2018). Prevalence, incidence, predictors, treatment, and control of hypertension among HIV-positive adults on antiretroviral treatment in public sector treatment programs in South Africa. *PLOS ONE*, *13*(10): e0204020.

Brennan, A.T., Jamieson, L., Crowther, N.J., Fox, M.P., George, J.A., Berry, K.M., Stokes, A., Maskew, M., Sanne, I., Long, L. and Cassim, N. (2018). Prevalence, incidence, predictors, treatment, and control of hypertension among HIV-positive adults on antiretroviral treatment in public sector treatment programs in South Africa. *PLOS ONE*, 13(10): e0204020.

Gage, C.H., Spies, B., Crombie, K., Gwyther, L. and Stassen, W. (2023). The use of emergency medical services for palliative situations in Western Cape Province, South Africa: A retrospective, descriptive analysis of patient records. *SAMJ: South African Medical Journal*, *113*(11), pp.1485-1490.

Calo, W. A., Ortiz, A. P., Suárez, E., Guzmán, M., & Pérez, C. M. (2014). Association of cigarette smoking and metabolic syndrome in a Puerto Rican adult population. *International Journal of Preventive Medicine*, *5*(7): 849–856. (Retraction published *Int J Prev Med*2014 Aug;5(8):1066)

Capurso, N.A. and Petrakis, I. (2016). Dyslipidemia associated with heavy alcohol use. *The American Journal on Addictions*, *25*(3), pp.188-190.

Chinyakata, R., Raselekoane, N.R., Mudau, T.J. and Mapaya, M.G. (2019). Intersectional factors contributing to the vulnerability of young Zimbabwean female immigrants in Johannesburg. *African Renaissance*, *16*(2), pp.143-164.

City of Johannesburg. (2014). Inner City Plan 2014-2018. Available at https://www.joburg.org.za/documents_/Documents/Strategies%20and%20Development%20Plans/Inner%20City%20Plan%202014-2018.pdf

Claiborne, D.T., Prince, J.L., Scully, E., Macharia, G., Micci, L., Lawson, B., Kopycinski, J., Deymier, M.J., Vanderford, T.H., Nganou-Makamdop, K. and Ende, Z. (2015). Replicative fitness of transmitted HIV-1 drives acute immune activation, proviral load in memory CD4+ T cells, and disease progression. *Proceedings of the National Academy of Sciences*, *112*(12): E1480-E1489.

Creswell, J.W., Klassen, A.C., Plano Clark, V.L. and Smith, K.C. (2011). Best practices for mixed methods research in the health sciences. Bethesda (Maryland): *National Institutes of Health*, 2013: 541-545.

Crush, J., Skinner, C., & Chikanda, A. (2015). Growing Informal Cities Project: Informal Migration Entrepreneurship and Inclusive Growth in South Africa, Zimbabwe, and Mozambique. Migration Policy Series No. 68. Series Editor: Prof. Jonathan Crush. Southern African Migration Programme (SAMP), International Migration Research Centre (IMRC)

Dave, J.A., Levitt, N.S., Ross, I.L., Lacerda, M., Maartens, G. and Blom, D. (2016). Anti-retroviral therapy increases the prevalence of dyslipidemia in South African HIV-infected patients. *PLOS ONE*, 11(3): e0151911.

Denue, B.A., Alkali, M.B., Abjah, A.U., Kida, I.M., Ajayi, B. and Fate, B.Z. (2013). Changes in lipid profiles and other biochemical parameters in HIV-1 infected patients newly

commenced on HAART regimen. *Infectious Diseases: Research and Treatment*, 6: IDRT-S10044.

Department of Women, Republic of South Africa (2015). The status of women in the South African economy. [online] Available at: https://www.gov.za/sites/default/files/gcis_document/201508/statusofwomeninsaeconomy.pdf [Accessed 25 May 2023].

Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1, July 2017. Available at: https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf

Elf, J.L., Variava, E., Chon, S., Lebina, L., Motlhaoleng, K., Gupte, N., Niaura, R., Abrams, D., Golub, J.E. and Martinson, N. (2018). Prevalence and correlates of smoking among people living with HIV in South Africa. *Nicotine and Tobacco Research*, 20(9): 1124-1131.

Erasmus, R. T., Soita, D. J., Hassan, M. S., Blanco-Blanco, E., Vergotine, Z., Kengne, A. P., & Matsha, T. E. (2020). High prevalence of metabolic syndrome in a South African mixed ancestry population: a cross-sectional study. *BMC Endocrine Disorders*, 20(1): 1-11.

Erzse, A., Stacey, N., Chola, L., Tugendhaft, A., Freeman, M. and Hofman, K. (2019). The direct medical cost of type 2 diabetes mellitus in South Africa: a cost of illness study. *Global Health Action*, 12(1): 1636611.

Fahme, S. A., Bloomfield, G. S., & Peck, R. (2018b). Hypertension in HIV-related Adults. *Hypertension*, 72(May): 44–55. https://doi.org/10.1161/HYPERTENSIONAHA.118.10893

Fedele, F., Bruno, N. and Mancone, M. (2011). Cardiovascular risk factors and HIV disease. *AIDS Reviews*, 13(2): 119-29.

Feinstein, M.J., Bahiru, E., Achenbach, C., Longenecker, C.T., Hsue, P., So-Armah, K., Freiberg, M.S. and Lloyd-Jones, D.M.(2016). Patterns of cardiovascular mortality for HIV-infected adults in the United States: 1999 to 2013. *The American Journal of Cardiology*, 117(2): 214-220.

Freiberg, M.S. and Kraemer, K.L. (2010). Focus on the heart: alcohol consumption, HIV infection, and cardiovascular disease. *Alcohol Research & Health*, 33(3): 237.

Gaziano, T.A., Abrahams-Gessel, S., Gomez-Olive, F.X., Wade, A., Crowther, N.J., Alam, S., Manne-Goehler, J., Kabudula, C.W., Wagner, R., Rohr, J. and Montana, L. (2017).

Cardiometabolic risk in a population of older adults with multiple co-morbidities in rural South Africa: the HAALSI (Health and Aging in Africa: longitudinal studies of INDEPTH communities) study. *BMC Public Health*, 17(1): 1-10.

Gómez-Olivé, F.X., Ali, S.A., Made, F., Kyobutungi, C., Nonterah, E., Micklesfield, L., Alberts, M., Boua, R., Hazelhurst, S., Debpuur, C. and Mashinya, F. (2017). Regional and sex differences in the prevalence and awareness of hypertension: an H3Africa AWI-Gen study across 6 sites in sub-Saharan Africa. *Global Heart*, 12(2): 81-90.

Gradidge, P. J., & Crowther, N. J. (2017). Review: Metabolic Syndrome in Black South African Women. *Ethnicity & Disease*, 27(2): 189–200. https://doi.org/10.18865/ed.27.2.189

Grinspoon, S., & Carr, A. (2005). Cardiovascular risk and body-fat abnormalities in HIV-infected adults. *New England Journal of Medicine*, 352(1): 48-62.

Guaraldi, G., Orlando, G., Zona, S., Menozzi, M., Carli, F., Garlassi, E., Berti, A., Rossi, E., Roverato, A. and Palella, F. (2011). Premature age-related comorbidities among HIV-infected persons compared with the general population. *Clinical Infectious Diseases*, 53(11): 1120-1126.

Han, B.H., Moore, A.A., Sherman, S.E. and Palamar, J.J., 2018. Prevalence and correlates of binge drinking among older adults with multimorbidity. *Drug and alcohol dependence*, *187*, pp.48-54.

Harris, T.G., Rabkin, M. and El-Sadr, W.M. (2018). Achieving the fourth 90: healthy aging for people living with HIV. *AIDS* , 32(12): 1563.

Helleberg, M., Afzal, S., Kronborg, G., Larsen, C.S., Pedersen, G., Pedersen, C., Gerstoft, J., Nordestgaard, B.G. and Obel, N. (2013). Mortality attributable to smoking among HIV-1–infected individuals: a nationwide, population-based cohort study. *Clinical Infectious Diseases*, 56(5): 727-734.

Hernandez-Romieu, A.C., Garg, S., Rosenberg, E.S., Thompson-Paul, A.M. and Skarbinski, J. (2017). Is diabetes prevalence higher among HIV-infected individuals compared with the general population? Evidence from MMP and NHANES 2009–2010. *BMJ Open Diabetes Research and Care*, *5*(1), p.e000304.

Hotamisligil, G. S. (2006). Inflammation and metabolic disorders. *Nature,* 444(7121): 860-867.

Hsue, P.Y. and Waters, D.D. (2018). Time to recognize HIV infection as a major cardiovascular risk factor. *Circulation*, 138(11): 1113-1115.

Hufford, B (2021). The 4 Types of Validity in Research Design (+3 More to Consider), [Online]. Available at: https://www.activecampaign.com/blog/validity-in-research-design (Accessed: 15 July 2022)

International Diabetes Federation. (2019). IDF Diabetes Atlas, 9th edition. Brussels, Belgium: International Diabetes Federation.

International Diabetes Federation. (2021). IDF Diabetes Atlas, 9th edition. [online] Available at: https://diabetesatlas.org/ [Accessed 17 April 2023].

Joosten MM, Beulens JW, Kersten S, Hendriks HF. (2008). Moderate alcohol consumption increases insulin sensitivity and ADIPOQ expression in postmenopausal women: a randomised, crossover trial. *Diabetologia*. 51(8): 1375-1381.

Jung, Y. A., Kang, L. L., Kim, H. N., Park, H. K., Hwang, H. S., & Park, K. Y. (2018). Relationship between Marital Status and Metabolic Syndrome in Korean Middle-Aged Women: The Sixth Korea National Health and Nutrition Examination Survey (2013-2014). *Korean Journal of Family Medicine*, 39(5): 307–312. https://doi.org/10.4082/kjfm.17.0020

Kansiime, S., Mwesigire, D. and Mugerwa, H. (2019). Prevalence of non-communicable diseases among HIV positive patients on antiretroviral therapy at joint clinical research centre, Lubowa, Uganda. *PLOS ONE*, 14(8): e0221022.

Kavishe, B., Biraro, S., Baisley, K., Vanobberghen, F., Kapiga, S., Munderi, P., Smeeth, L., Peck, R., Mghamba, J., Mutungi, G. and Ikoona, E. (2015). High prevalence of hypertension and of risk factors for non-communicable diseases (NCDs): a population based cross- sectional survey of NCDS and HIV infection in Northwestern Tanzania and Southern Uganda. *BMC Medicine*, 13(1): 1-21.

Kim SW, Kim HJ, Min K, Lee H, Lee SH, et al. (2021) The relationship between smoking cigarettes and metabolic syndrome: A cross-sectional study with non-single residents of Seoul under 40 years old. PLOS ONE 16(8): e0256257. https://doi.org/10.1371/journal.pone.0256257

Koppes LL, Dekker JM, Hendriks HF, Bouter LM, Heine RJ. (2005). Moderate alcohol consumption lowers the risk of type 2 diabetes: a meta-analysis of prospective observational studies. *Diabetes Care*, 28(3): 719-725.

Kuller, L.H., Tracy, R., Belloso, W., Wit, S.D., Drummond, F., Lane, H.C., Ledergerber, B., Lundgren, J., Neuhaus, J., Nixon, D. and Paton, N.I. (2008). Inflammatory and coagulation biomarkers and mortality in patients with HIV infection. *PLoS Medicine*, 5(10): e203.

Kwarisiima, D., Atukunda, M., Owaraganise, A., Chamie, G., Clark, T., Kabami, J., Jain, V., Byonanebye, D., Mwangwa, F., Balzer, L.B. and Charlebois, E. (2019). Hypertension control in integrated HIV and chronic disease clinics in Uganda in the SEARCH study. *BMC Public Health*, 19(1): 1-10.

Lapadula, G., Chatenoud, L., Gori, A., Castelli, F., Di Giambenedetto, S., Fabbiani, M., Maggiolo, F., Focà, E., Ladisa, N., Sighinolfi, L. and Di Pietro, M. (2015) . Risk of severe non-AIDS events is increased among patients unable to increase their CD4+ T-cell counts> 200+/µl despite effective HAART. *PLOS ONE*, 10(5): e0124741.

Lazzarino, A. I., Hamer, M., Stamatakis, E., & Steptoe, A. (2013). The combined association of psychological distress and socioeconomic status with all-cause mortality: a national cohort study. *JAMA Internal Medicine*, 173(1): 22-27.

Leibbrandt, M., Woolard, I., McEwen, H. and Koep, C. (2010). Employment and inequality outcomes in South Africa. *University of Cape Town: Southern Africa Labour and Development Research Unit*, pp.45-6.

Leung, L., 2015. Validity, reliability, and generalizability in qualitative research. *Journal of Family Medicine and Primary Care*. 2015; 4: 324.

Liu, L., Christie, S., Munsamy, M., Roberts, P., Pillay, M., Shenoi, S.V., Desai, M.M. and Linnander, E.L. (2021). Expansion of a national differentiated service delivery model to support people living with HIV and other chronic conditions in South Africa: a descriptive analysis. *BMC Health Services Research*, 21(1): 1-8.

MacDonell, S., & Low, M. (2019, August 5). Graphs that tell the story of HIV in South Africa's provinces. In-Depth, Public Interest Health Journalism. Available at : https://www.spotlightnsp.co.za/2019/08/05/graphs-that-tell-the-story-of-hiv-in-south-africas-provinces [Accessed 04 November 2023].

Maimela, E., Alberts, M., Modjadji, S.E., Choma, S.S., Dikotope, S.A., Ntuli, T.S. and Van Geertruyden, J.P. (2016). The prevalence and determinants of chronic non-communicable disease risk factors amongst adults in the Dikgale health demographic and surveillance system (HDSS) site, Limpopo Province of South Africa. *PLOS ONE*, 11(2): e0147926.

Malik, S., Wong, N. D., Franklin, S. S., Kamath, T. V., L'Italien, G. J., Pio, J. R., … Wong, K. (2018). Impact of the metabolic syndrome on mortality from coronary heart disease, cardiovascular disease, and all causes in United States adults. *Circulation*, 124(4): 415-421. DOI: 10.1161/CIRCULATIONAHA.110.968735

Masenga, S.K., Hamooya, B.M., Nzala, S., Kwenda, G., Heimburger, D.C., Mutale, W., Munsaka, S.M., Koethe, J.R. and Kirabo, A. (2019). Patho-immune mechanisms of hypertension in HIV: a systematic and thematic review. *Current Hypertension Reports*, 21: 1-19.

Mashinya, F., Alberts, M. and Colebunders, R. (2015). Assessment of cardiovascular risk factors in people with HIV infection treated with ART in rural South Africa: a cross sectional study. *AIDS Research and Therapy*, 12(1): 1-10.

Masilela, C., Adeniyi, O.V. and Benjeddou, M. (2022). Prevalence, patterns and determinants of dyslipidaemia among South African adults with comorbidities. *Scientific Reports*, 12(1): 1-11.

Matsha, T. E., Hassan, M. S., Hon, G. M., Soita, D. J., Kengne, A. P., & Erasmus, R. T. (2012). Derivation and validation of a waist circumference optimal cutoff for diagnosing metabolic syndrome in a South African mixed ancestry population. *International Journal of Cardiology*, 158(3): 413-418.

Mayosi BM, Flisher AJ, Lalloo UG, et al. (2009). The burden of non-communicable diseases in South Africa. *Lancet*, 374(9693):934-47. DOI: 10.1016/S0140-6736(09)61087-4

Mhlanga, N.L. and Netangaheni, T.R. (2023). Risks of Type 2 diabetes among older people living with HIV: A scoping review. *South African Family Practice*, *65*(1).

Mondy, K., Overton, E. T., Grubb, J., Tong, S., Seyfried, W., Powderly, W., & Yarasheski, K. (2007). Metabolic syndrome in HIV-infected patients from an urban, midwestern US outpatient population. *Clinical infectious diseases: an official publication of the Infectious Diseases Society of America*, 44(5): 726–734. https://doi.org/10.1086/511679

Motala AA, Esterhuizen T, Pirie FJ, Omar MA. (2011). The prevalence of metabolic syndrome and determination of the optimal waist circumference cutoff points in a rural South African community. *Diabetes Care*, 34(4): 1032-7.

Mottillo, S., Filion, K. B., Genest, J., Joseph, L., Pilote, L., Poirier, P., … Eisenberg, M. J. (2010). The metabolic syndrome and cardiovascular risk: A systematic review and meta-analysis. *Journal of the American College of Cardiology*, 56(14): 1113-1132. DOI: 10.1016/j.jacc.2010.05.034

Muyanja, D., Muzoora, C., Muyingo, A., Muyindike, W., & Siedner, M. J. (2016). High Prevalence of Metabolic Syndrome and Cardiovascular Disease Risk Among People with HIV on Stable ART in Southwestern Uganda. *AIDS Patient Care and STDs*, 30(1): 4-10.

Nakanjako, D., Kiragga, A. N., Ibrahim, F., & Castelnuovo, B. (2011). Gender differences in HIV treatment outcomes following initiation of antiretroviral therapy in Uganda. *Journal of International AIDS Society*, 14(1): 43. DOI: 10.1186/1758-2652-14-43

Nansseu, J.R., Bigna, J.J., Kaze, A.D. and Noubiap, J.J. (2018). Incidence and risk factors for prediabetes and diabetes mellitus among HIV-infected adults on antiretroviral therapy. *Epidemiology*, 29(3): 431-441.

National Department of Health (2015). *Strategy for the Prevention and Control of Obesity in South Africa 2015–2020* [Online]. Available at: https://www.knowledgehub.org.za/elibrary/national-strategy-prevention-and-control-obesity (Accessed :10 July 2022)

National Department of Health. (2013) *Strategic plan for the prevention and control of non-communicable diseases 2013–17* [Online]. Available at: https://extranet.who.int/ncdccs/Data/ZAF_B3_NCDs_STRAT_PLAN_1_29_1_3%5B2%5D.pdf . Accessed: 10 July 2022)

Ndlovo, P.P. (1999). Perceptions of black women of obesity as a health risk. *Curationis*, 22(2): 47-55.

Nduka, C.U., Stranges, S., Kimani, P.K., Sarki, A.M., and Uthman, O.A. (2013). Is there sufficient evidence for a causal association between antiretroviral therapy and diabetes in HIV-infected patients? A meta-analysis. *Diabetes/Metabolism Research and Reviews*, 29(6): 455-469.

Nguyen, K.A., Peer, N., Mills, E.J. and Kengne, A.P. (2016). A meta-analysis of the metabolic syndrome prevalence in the global HIV-infected population. *PLOS ONE*, 11(3): e0150970.

Njelekela, M., Muhihi, A., Aveika, A., Spiegelman, D., Hawkins, C., Armstrong, C., Liu, E., Okuma, J., Chalamila, G., Kaaya, S. and Mugusi, F. (2016). Prevalence of hypertension and its associated risk factors among 34,111 HAART naïve HIV-infected adults in Dar es Salaam, Tanzania. *International Journal of Hypertension*, 2016, 5958382.doi:10.1155/2016/5958382

Njuguna, B., Kiplagat, J., Bloomfield, G.S., Pastakia, S.D., Vedanthan, R. and Koethe, J.R., (2018). Prevalence, risk factors, and pathophysiology of dysglycemia among people living with HIV in Sub-Saharan Africa. *Journal of Diabetes Research*, Volume 2018, 6916497.doi:10.1155/2018/6916497

Nojilana B, Bradshaw D, Pillay-van Wyk V, et al. (2016). Persistent burden from non-communicable diseases in South Africa needs strong action. *South African Medical Journal 2016*. 106: 23–24

Nsagha, D.S., Weledji, E.P., Assob, N.J.C., Njunda, L.A., Tanue, E.A., Ayima, C.W. and Ngowe, M.N. (2015). Highly active antiretroviral therapy and dyslipidemia in people living with HIV/AIDS in Fako Division, Southwest Region of Cameroon. *BMC* Cardiovascular Disorders, 15(1): 1-8.

Oguoma, V. M., Nwose, E. U., Richards, R. S., & Bwititi, P. T. (2017). Cardiovascular disease risk prevention: preliminary survey of baseline knowledge, attitude and practices of a Nigerian rural community. *North American Journal of Medical Sciences*, 9(9): 306-315.

Ojong, E., Iya, B., Djeufouata, J., Ndeh, F., Nsonwu, A., Njongang, V., Etukudo, M., Usoro, C. and Ekpo, J. (2022) . Metabolic syndrome and its components among HIV/AIDS patients on Antiretroviral Therapy and ART-Naïve Patients at the University of Calabar Teaching Hospital, Calabar, Nigeria. *African Health Sciences*,22(1): 410-7.

Okafor, C.I. (2012). The metabolic syndrome in Africa: current trends. *Indian Journal of Endocrinology and Metabolism*, 16(1): 56.

Okojie, O.M., Javed, F., Chiwome, L. and Hamid, P. (2020). Hypertension and alcohol: a mechanistic approach. *Cureus*, *12*(8).

Paula, A.A., Falcão, M.C. and Pacheco, A.G. (2013). Metabolic syndrome in HIV-infected individuals: underlying mechanisms and epidemiological aspects. *AIDS Research and Therapy*, 10(1): 1-8.

Peer N, Lombard C, Steyn K, et al. (2012). Rising diabetes prevalence among urban-dwelling black South Africans. *PLOS One*, 7(9): e43336. DOI:10.1371/journal.pone.0043336

Peer, N., Lombard, C., Steyn, K. and Levitt, N. (2015). High prevalence of metabolic syndrome in the Black population of Cape Town: The Cardiovascular Risk in Black South Africans (CRIBSA) study. *European Journal of Preventive Cardiology*, 22(8): 1036-1042.

Peer, N., Steyn, K., & Levitt, N. (2012). Differential obesity indices identify the metabolic syndrome in Black men and women in Cape Town: the CRIBSA study. *Journal of Human Hypertension*, 26(2): 127-135.

Peltzer K, Phaswana-Mafuya N. (2013). Hypertension and associated factors in older adults in South Africa. *Cardiovascular Journal of Africa*, 24(3): 67-71.

Pisinger, C. and Jorgensen, T. (2007). Waist circumference and weight following smoking cessation in a general population: The Inter99 study. *Preventive Medicine*, 44(4): 290-295.

Pruthi, S. (2021). Metabolic Syndrome, [Online]. Available at: https://www.mayoclinic.org/diseases-conditions/metabolic-syndrome/symptoms-causes/syc-20351916 (Accessed: 20 July 2022)

Puoane, T.R., Tsolekile, L.P., Caldbick, S., Igumbor, E.U., Meghnath, K. and Sanders, D. (2012). Chronic non-communicable diseases in South Africa: Progress and challenges. *South African Health Review*, 2012(1): 115-126.

Rees, H., Delany-Moretlwe, S., Scorgie, F., Luchters, S. and Chersich, M.F. (2017). At the heart of the problem: health in Johannesburg's inner-city. *BMC Public Health*, 17(3): 1-6.

Rosoff, D.B., Charlet, K., Jung, J., Lee, J., Muench, C., Luo, A., Longley, M., Mauro, K.L. and Lohoff, F.W. (2019). Association of high-intensity binge drinking with lipid and liver function enzyme levels. *JAMA network open*, *2*(6), pp.e195844-e195844.

Sartorius, B., Veerman, L.J., Manyema, M., Chola, L. and Hofman, K. (2015). Determinants of obesity and associated population attributability, South Africa: Empirical evidence from a national panel survey, 2008-2012. *PLOS ONE*, 10(6): e0130218.

Savvoulidis, P., Butler, J. and Kalogeropoulos, A. (2019). Cardiomyopathy and heart failure in patients with HIV infection. *Canadian Journal of Cardiology*, 35(3): 299-309.

Schutte, A.E. (2019). Urgency for South Africa to prioritise cardiovascular disease management. *The Lancet Global Health*, 7(2): e177-e178.

Scheres, J. and Kuszewski, K. (2019). The Ten Threats to Global Health in 2018 and 2019. A welcome and informative communication of WHO to everybody. *Public Health Management/Zdrowie Publiczne i Zarzadzanie*, *17*(1).

Seang, K., Javanbakht, M., Lee, S.J., Brookmeyer, R., Pheng, P., Chea, P., Saphonn, V. and Gorbach, P.M. (2022). Differences in prevalence and risk factors of non-communicable diseases between young people living with HIV (YLWH) and young general population in Cambodia. *PloS one*, *17*(6), p.e0269989.

Shah, A.S., Stelzle, D., Lee, K.K., Beck, E.J., Alam, S., Clifford, S., Longenecker, C.T., Strachan, F., Bagchi, S., Whiteley, W. and Rajagopalan, S. (2018). Global burden of atherosclerotic cardiovascular disease in people living with HIV: systematic review and meta-analysis. *Circulation*, 138(11): 1100-1112.

Shisana, O., Rehle, T., Simbayi, L. C., Zuma, K., Jooste, S., Zungu, N., ... & Onoya, D. (2014). South African national HIV prevalence, incidence, behaviour and communication survey 2012. Cape Town: HSRC Press.

Shuval, K., Marroquin, E.M., Li, Q., Knell, G., Gabriel, K.P., Drope, J., Yaroch, A.L., Chartier, K.G., Fennis, B.M. and Qadan, M. (2021). Long-term weight loss success and the health behaviours of adults in the USA: findings from a nationally representative cross-sectional study. *BMJ open*, *11*(7), p.e047743.

Simbayi, L.C.Z.K., Zuma, K., Zungu, N., Moyo, S., Marinda, E., Jooste, S., Mabaso, M., Ramlagan, S., North, A., Van Zyl, J. and Mohlabane, N. (2019). South African national HIV prevalence, incidence, behaviour and communication survey, 2017: towards achieving the UNAIDS 90-90-90 targets, Cape ATown: HSRC Press.

Singh, A.K., Singh, S.K., Singh, N., Agrawal, N. and Gopal, K. (2011). Obesity and dyslipidemia. *Int J Biol Med Res*, *2*(3), pp.824-8.

Slagter, S.N., van Vliet-Ostaptchouk, J.V., Vonk, J.M., Boezen, H.M., Dullaart, R.P., Kobold, A.C.M., Feskens, E.J., van Beek, A.P., van der Klauw, M.M. and Wolffenbuttel, B.H., 2014.

Combined effects of smoking and alcohol on metabolic syndrome: the LifeLines cohort study. *PLOS ONE*, *9*(4): e96406.

Li, X., Song, X., Han, Y., Qiu, Z., Cao, W. and Li, T. (2023). Risk factors and longitudinal changes of dyslipidemia among Chinese people living with HIV receiving antiretroviral therapy. *BMC Infectious Diseases*, *23*(1), p.598.

South African Health Review (2020). Health and related indicators. Available at: https://www.hst.org.za/publications/South%20African%20Health%20Reviews/SAHR_Chapter%2020_17122020_Final.pdf

Statistics South Africa. (2022). Census 2021 statistical release. Available at: https://www.statssa.gov.za/publications/P0302/P03022021.pdf

Steyn, K. and Damasceno, A., (2006). Lifestyle and related risk factors for chronic diseases. *Disease and mortality in sub-Saharan Africa*, *2*, pp.247-65.

Tesfaye, D.Y., Kinde, S., Medhin, G., Megerssa, Y.C., Tadewos, A., Tadesse, E. and Shimelis, T. (2014). Burden of metabolic syndrome among HIV-infected patients in Southern Ethiopia. *Diabetes & Metabolic Syndrome: Clinical Research & Reviews*, *8*(2): 102-107.

Todowede, O.O., Mianda, S.Z. and Sartorius, B. (2019). Prevalence of metabolic syndrome among HIV-positive and HIV-negative populations in sub-Saharan Africa — a systematic review and meta-analysis. *Systematic Reviews*, 8: 1-17.

Ulasi, I.I., Ijoma, C.K., Onwubere, B.J., Arodiwe, E., Onodugo, O. and Okafor, C. (2011). High prevalence and low awareness of hypertension in a market population in Enugu, Nigeria. *International Journal of Hypertension*, Volume 2011(869675).doi: 10.4061/2011/869675

Umberson, D., Williams, K., Powers, D. A., Liu, H., & Needham, B. (2006). You make me sick: Marital quality and health over the life course. *Journal of Health and Social Behavior*, 47(1): 1-16.

UNAIDS Joint United Nations Programme on HIV/AIDS (2014). An ambitious treatment target to help end the AIDS epidemic [Online]. Available at: https://www.unaids.org/sites/default/files/media_asset/90-90-90_en.pdf (Accessed: 15 July 2022)

UNAIDS. (2022). UNAIDS data 2022. Available at: https://www.unaids.org/en/regionscountries/countries/southafrica

Vachiat, A., McCutcheon, K., Tsabedze, N., Zachariah, D. and Manga, P. (2017). HIV and ischemic heart disease. *Journal of the American College of Cardiology*, 69(1): 73-82.

van Heerden, A., Barnabas, R.V., Norris, S.A., Micklesfield, L.K., van Rooyen, H. and Celum, C. (2017). High prevalence of HIV and non-communicable disease (NCD) risk factors in rural KwaZulu-Natal, South Africa. *Journal of the international AIDS Society*, 20(2): e25012.

van Koeveringe, J.M., Liaño Callahan, E., George, M., Russo, T.T., Seifu, B. and Spigt, M., 2023. The challenge of dealing with non-AIDS comorbidities for people living with HIV: Perspectives and experiences of patients and healthcare providers. *Global Public Health*, *18*(1), p.2185798.utt

Venter, W.D., Moorhouse, M., Sokhela, S., Fairlie, L., Mashabane, N., Masenya, M., Serenata, C., Akpomiemie, G., Qavi, A., Chandiwana, N. and Norris, S. (2019). Dolutegravir plus two different prodrugs of tenofovir to treat HIV. *New England Journal of Medicine*, 381(9): 803-815.

Wand, H. and Ramjee, G. (2013). High prevalence of obesity among women who enrolled in HIV prevention trials in KwaZulu-Natal, South Africa: healthy diet and lifestyle messages should be integrated into HIV prevention programs. *BMC Public Health*, 13(1): 1-5.

Wand, H., Calmy, A., Carey, D.L., Samaras, K., Carr, A., Law, M.G., Cooper, D.A. and Emery, S., (2007). INITIO Trial International Coordinating Committee. Metabolic syndrome, cardiovascular disease and type 2 diabetes mellitus after initiation of antiretroviral therapy in HIV infection. *Aids*, *21*(18), pp.2445-2453.

Weerakkody, M.I., Buddhakorala, K. and Somasundaram, N.P. (2014). Diabetes and metabolic complications among patients with HIV and AIDS. *Sri Lanka Journal of Diabetes Endocrinology and Metabolism*, 3(2): 55.

Wilson, P.W., D'Agostino, R.B., Parise, H., Sullivan, L. and Meigs, J.B. (2005). Metabolic syndrome as a precursor of cardiovascular disease and type 2 diabetes mellitus. *Circulation*, 112(20): 3066-3072.

World Health Organization (2017) *Fact sheet; noncommunicable diseases* [Online]. Available at: http://www.who.int/mediacentre/factsheets/fs355/en/(Accessed: 15 July 2022)

World Health Organization (2018). Noncommunicable Diseases Country Profiles 2018. South Africa. Available at : https://www.who.int/nmh/countries/zaf_en.pdf

World Health Organization. Tobacco. https://www.who.int/health-topics/tobacco#tab=tab_1. Accessed March 11, 2023.

Yan, J., Ouyang, J., Isnard, S., Zhou, X., Harypursat, V., Routy, J.P. and Chen, Y. (2021). Alcohol Use and Abuse Conspires With HIV Infection to Aggravate Intestinal Dysbiosis and Increase Microbial Translocation in People Living With HIV: A Review. *Frontiers in Immunology*, 12: 5436.

Zatońska, K., Psikus, P., Basiak-Rasała, A., Stępnicka, Z., Gaweł-Dąbrowska, D., Wołyniec, M., Gibka, J., Szuba, A. and Połtyn-Zaradna, K. (2021). Obesity and chosen non-communicable diseases in pure Poland cohort study. *International Journal of Environmental Research and Public Health*, 18(5): 2701.

Zhou, B., Bentham, J., Di Cesare, M., Bixby, H., Danaei, G., Cowan, M.J., Paciorek, C.J., Singh, G., Hajifathalian, K., Bennett, J.E. and Taddei, C. (2017). Worldwide trends in blood pressure from 1975 to 2015: a pooled analysis of 1479 population-based measurement studies with 19· 1 million participants. *The Lancet*, 389(10064): 37-55.

Zungu, N.P., Mabaso, M.L., Kumalo, F., Sigida, S., Mlangeni, L., Wabiri, N. and Chasela, C. (2019). Prevalence of non-communicable diseases (NCDs) and associated factors among HIV positive educators: findings from the 2015/6 survey of health of educators in public schools in South Africa. *PLOS ONE*, 14(2): e0209756.

APPENDIX 1: Variables extracted from client records (participant files)

DATA EXTRACTION TOOL

PTID	

Demographics:

Age	
Sex	
Race	
Marital Status	
Country of Origin	
Level of Education	
Employment status	

Behavioural:

Smoking	
Alcohol	

Clinical:

CD4	
Viral Load	

Metabolic Risk Factors:

Pre-existing Hypertension or elevated Blood Pressure	
Pre-existing Diabetes or elevated fasting glucose	
Elevated BMI (overweight or obese)	
Dyslipidaemia	

APPENDIX 2: Ezintsha Permission to Conduct Study

APPENDIX 2: *Ezintsha permission to conduct sub-study*

Ezintsha

University of the Western Cape School of Public Health
Robert Sobukwe Rd Bellville
Cape Town, 7535
22 January 2023

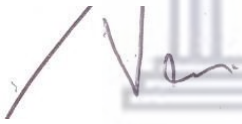
Re: Letter granting permission to use ADVANCE clinical trial data.

Dear Sir/Madam

This letter serves as confirmation that Shilpa Esther Bhaskar Student No 4105255 has been granted permission to use data from the ADVANCE clinical trial Protocol Number: WRHI 060 conducted at Ezintsha, a division of Wits Health Consortium (Pty) Ltd.

The data will be used by the student to conduct a study titled "Prevalence of metabolic risk factors associated with non-communicable diseases in treatment-naïve HIV patients in inner-city Johannesburg", to complete a master's degree in Public Health (MPH). Please note this is not a follow up study and only original data from the participants who initially consented will be used by the student. No additional data will be used beyond what was consented to in the initial trial and no patient interaction is involved in further analysis.

Do not hesitate to contact me should any further information be required. Kind regards,



Prof WD Francois Venter Divisional Head: Ezintsha fventer@ezintsha.org

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

www.ezintsha.org

Ezintsha, a division of Wits Health Consortium at the University of the Witwatersrand
Sunnyside Office Park, 32 Princess of Wales Terrace, Parktown 2193, Johannesburg, South Africa
www.ezintsha.org

INVESTIGATE INNOVATE ADVANCE

APPENDIX 3: Health Research Development Council Ethics Clearance letter

UNIVERSITY of the WESTERN CAPE

25 January 2023

Dr SE Bhaskar
School of Public Health
Faculty of Community and Health Sciences

BMREC Reference Number: BM22/9/12

Project Title: Prevalence of metabolic risk factors for non-communicable diseases in treatment-naïve HIV patients in inner city Johannesburg.

Approval Period: **25 January 2023 – 24 January 2026**

I hereby certify that the Biomedical Science Research Ethics Committee of the University of the Western Cape approved the scientific methodology and ethics of the above-mentioned research project.

Any further amendments, extension or other modifications to the protocol must be submitted to the Ethics Committee for approval.

Please remember to submit a progress report annually by 30 November for theduration of the project.

For permission to conduct research using student and/or staff data or to distribute research surveys/questionnaires please apply via: https://sites.google.com/uwc.ac.za/permissionresearch/home

The permission letter must then be submitted to BMREC for record keeping purposes.

The Committee must be informed of any serious adverse event and/or termination of the study.

Ms Patricia Josias
Research Ethics Committee Officer
University of the Western Cape

NHREC Registration Number: BMREC-130416-050

FROM HOPE TO ACTION THROUGH KNOWLEDGE.

APPENDIX 4: HREC approval for ADVANCE clinical trial (parent study)

University
of the Witwatersrand,
Johannesburg

Human Research Ethics Committee: (Medical)
United States FWA Registered No IRB 00001223
South African National Health Research Ethics Council Registration: REC-250208-004

SECRETARIAT: Suite 189, Private Bag 0600, Houghton 2041, South Africa Tel: +27-11-274 9200 Fax: +27-11-274 9281

02 September 2016 FAXED & COURIERED

Ms N Arulappan
Study Coordinator
Wits Reproductive Health and HA/ institute
Hillbrow Health Precinct
Johannesburg
2038

Fax: 086 600 3495

Dear Ms Arulappan,

PROTOCOL: WRHI 060 - A 96„WEEK RANDOMISED PHASE 3 NON-INFERIORITY STUDY OF DTG + TAF + FTC COMPARED WITH DTG + TDF + FTC AND EFV + TDF+FTC IN PATIENTS INFECTED WITH HIV-i STARTING FIRST-LINE ANTIRETROVIRAL THERAPY

ETHICS REFERENCE NO: 160606B

RE : FINAL ETHICS APPROVAL

This is to certify that the above-mentioned trial has been approved by the University of the Witwatersrand, Human Research Ethics Committee (HREC), and the Protocol/Expert Reviewer. Date of Meeting where trial was reviewed: 24 June 2016.

The University of the Witwatersrand, Human Research Ethics Committee Approval Granted for the above-mentioned study is valid for five years. Where required by Sponsor

to have approval on a more frequent basis it remains the responsibility of the Sponsor and Investigator to apply for continuing review and approval or for the duration of the Trial,

1.It is the responsibility of the Sponsor and Principal Investigator to ensure, where required, that relevant approvals are in place and compliance with the following is adhered to before a trial may begin:

- If trial is being conducted in Provincial Health facilities: Approval from the Hospital CEO / Clinic Manager / District Research Committee (whichever is applicable) be obtained.
- The study is submitted onto The National Health Research Database (NHRD).

The relevant approvals are uploaded onto the NHRD system: Ethics Approval, MCC Approval, Hospital CEO / Clinic Manager / District Research Committee Approval.

* A copy of the MCC Approval and/or MCC Notification letter must be submitted to the Ethics

Secretariat Office for record purposes (IF MCC APPROVAL / NOTIFICATION IS APPLICABLE),

* The study is conducted according to the protocol submitted to the University of the Witwatersrand, Human Research Ethics Committee. Any amendments to the protocol must first be submitted to the Human Research Ethics Committee for approval.

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During the study, the University of the Witwatersrand, Human Research Ethics Committee is informed immediately of:

- Any Unexpected Serious Adverse Events or Unexpected Adverse Drug Reactions, which, in the Investigator and/or the Sponsor's opiniorl are suspected to be related to the study drug. (Refer to POL-IEC-OOI and SOP-EEC-005J Item 3.4).
- Any data received during the trial which, may cast doubt on the validity of the continuation of the study.

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The University of the Witwatersrand, Human Research Ethics C01T)lTlittee is notified of any decision to discontinue the study and the reason stated.

*

The Investigators authorised by this approval participate in this study. Additional Investigators shall be submitted to the University of the Witwatersrand, Human Research Ethics Committee for approval prior to their participation in the study,

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In the event of an authorised Investigator ceasing to participate in the study, the University of the Witwatersrand, Human Research Ethics Committee must be informed and the reason for such cessation

2. PRINCIPLES OF INFORMED CONSENT:

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The University of the Witwatersrand, Human Research Ethics Cotnmittee requires that in all studies, the Principles of InforJ11ed Consent are adhered to. This applies to volunteers as well as patients.

3. PROGRESS REPORTS:

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The University of the Witwatersrand: Human Research Ethics Committee requests that the MCC Progress Reports be submitted twice a year either in March and September or six monthly from start of study to the HREC Secretariat Office - 011 274 9281 and a report of the final results, at the conclusion of the study. (IF APPLICABLE)

4. REIMBURSEMENT TO PATIENTS FOR TRANSPORT:

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The Human Research Ethics Committee: (Medical) is in agreement that reimbursement per visit is according to the Medicines Control Council of SA and that reimbursement should be appropriate according to the situation,

5. TRANSPORT AND STORAGE OF BLOOD AND TISSUE SAMPLES 'N SOUTH AFRICA:

* If blood specimens are to be stored for future analysis and is planned that such analysis wilt be done outside Wits, then the blood 'must be stored at a facility in South Africa agreed with the relevant IRB. with release of sub-samples only once projects have been approved by the local Research Ethics Committee applicable to where the analysis will be done as wet(as by the Wits Human Research Ethics Committee: (Medical).

6. GENETIC TESTING:

* The Human Research Ethics Committee: Medical; will not approve open-ended genetic testing as this does not fit the Human Research Ethics Committee criteria,

7. GOOD CLINICAL PRACTICE:

* The South African Department of Health, Medicines Control Council requires Good Clinical Practice (GCP) Training for ail Investigators in Clinical Trials, and that GCP training be renewed every three (3) years.

As yet, there are no National Guidelines for the content of GCP courses. Until these are available the Wits Human Research Ethics Committee (Medical) will note courses completed by Investigators without approval of the content of the individual courses.

8. THE SUPPORTING APPROVAL DOCUMENTS ARE ATTACHED:

8.1 Ethics Approval Form signed by the Chairperson of the HREC - Kindly return the copy of the Approval Form signed by the Principal Investigator(s) per fax: 01 1 274 9281 for our records (this is applicable with the initial Approval).

8.2 List of members present at the HREC meeting held as per INDEPENDENT ETHICS COMMITTEE APPROVAL FORM

q. WE OAWAIT YOUR RESPONSES AS REQUESTED: Ensure to have these documents forwarded at the earliest for the HREC records.

* MCC Approval letter and/or letter of Notification before the above study may commence / or where an Amendment may be implemented (IF MCC APPROVAL /

NOTIFICAT\ON IS APPLICABLE). It remains the responsibility of the Principal Investigator and/or Sponsor to ensure that the relevant approvals are in place.

* Copy of independent Ethics Declaration Approval Form signed by the Principal Investigator. (this is applicable with the initial Approval),

* Kindly forward the above to the undersigned at fax: 01 1 274 9281 at your earliest convenience.

The above has been noted for the Ethics Committee information and records.

KINDLY FORWARD TO THE RELEVANT INVESTIGATORS / CRA/ SPONSOR / STUDY CO-ORDINA TORS - WHERE APPLICABLE Regards,

PROF PETER CLEATON JONES

For and on behalf of the Human Research Ethics Committee: (Medical)