Investigating the Impact of a Fixed-Dose Combination Compared to Triple Therapy on Metabolic Syndrome in Patients on Highly Active Antiretroviral Therapy

Aniessa Kazi

209501949

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By

Aniessa Kazi

209501949

Submitted in partial fulfilment of the requirements for the award of the degree of

MASTER OF PHARMACY (PHARMACOLOGY)

Department of Pharmacology, Discipline of Pharmaceutical Sciences, College of Health Sciences, University of KwaZulu Natal, Westville Campus, Durban, South Africa

As the candidate's supervisor, I have approved this dissertation for submission

Signed: Name: Date

PREFACE

The research described in this dissertation was carried out at Addington Hospital, Durban from July 2016 to November 2016.

The study is the original work of the author and has been submitted in fulfilment of the academic requirements for obtaining an M.Pharm Degree in Pharmacology. Information from other sources used in this dissertation has been duly acknowledged in the text and reference section.

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Aniessa Kazi

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Supervisor

DECLARATION

I, **Aniessa Kazi,** declare that

1. The research reported in this thesis, except where otherwise indicated, is my original research.
2. This thesis has not been submitted for any degree or examination at any other university.
3. This thesis does not contain other persons' data, pictures, graphs or other information, unless specifically acknowledged as being sourced from other persons.
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PAPERS

The following papers are in process of submission for publication:

1. Metabolic Syndrome in patients on Highly Active Anti-Retroviral Therapy- A ticking time bomb?
2. A Fixed-Dose Combination of Tenofovir, Efavirenz and Emtricitabine is associated with a reduced incidence of Metabolic Syndrome and Atherogenic Index of Plasma compared to Triple Therapy.

ABSTRACT

Introduction: Southern Africa is home to one of the largest populations with Human Immunodeficiency Virus/ Acquired Immune Deficiency Syndrome (HIV/ AIDS). Although morbidity and mortality rates have reduced with the advent of Highly Active Antiretroviral Therapy (HAART), long-term use may lead to metabolic complications such as insulin resistance, lipodystrophy and dyslipidaemia. These adverse-effects are the components of metabolic syndrome (MetS), associated with an increased risk of cardiovascular disease and type 2 diabetes. Continuous efforts are being made to improve the quality of life of HIV/ AIDS patients whilst controlling the disease state. The introduction of a fixed-dose combination (FDC) pill (EFV/FTC/TDF) as first-line treatment ensures a more favourable side-effect profile, decreased pill burden and improved adherence.

Aims and Objectives: To investigate the incidence and prevalence of metabolic syndrome in HIV patients on HAART triple therapy compared to a fixed-dose combination. To investigate the impact of a single pill compared to triple therapy on the incidence and prevalence of metabolic syndrome in patients on HAART.

Method: Data was collected as a retrospective chart review upon obtaining gatekeeper's permission from Addington Hospital. Questionnaires were used as a collection tool for demographic and anthropometric data in a total of 350 patients. Patients were divided according to HAART regimens, FDC (A) and triple therapy (B). The joint interim statement by the International Diabetes Federation Task Force on Epidemiology and Prevention, National Heart Lung and Blood Institute, American Heart Association, World Health Organisation, International Atherosclerosis Society and International Association for the Study of Obesity was used to define the metabolic syndrome.

Results: Of the patients studied, 62.6% were female and 37.4% male. The overall prevalence of MetS was 16.6%. There was a significant association between HAART regimen and MetS ($p = 0.001$). There was a higher prevalence of MetS among triple therapy patients (23.4%) compared to FDC (9.7%). When adjusted for age, gender, comorbidities and patient markers, the multivariable logistic regression found HAART

regimen, glucose, BMI, and the presence of comorbidities to be significant predictors of MetS.

Conclusion: Patients on triple therapy had 3 times the odds of developing MetS compared to those on FDC. Increased levels of blood glucose, Low-Density Lipoprotein cholesterol (LDL-c), systolic and diastolic blood pressure were significantly positively associated with triple therapy.

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LIST OF ABBREVIATIONS

ABC	Abacavir
AIDS	Acquired Immune Deficiency Syndrome
AIP	Atherogenic Index of Plasma
ATP III	Adult Treatment Panel III
ATV	Atazanavir
BMI	Body Mass Index
BP	Blood Pressure
CI	Confidence Interval
CLAT	Cryptococcal Latex Antigen Test
CrAG	Cryptococcal Antigen
CRABP-1	Cellular Retinoic Acid Binding Protein 1
d4T	Stavudine
DLV	Delavirdine
DM	Diabetes Mellitus
DRV	Darunivir
EFV	Efavirenz
ETR	Etravirine
FDC	Fixed-Dose Combination
FFA	Free Fatty Acids
FTC	Emtricitabine
HAART	Highly Active Antiretroviral Therapy
HALS	HIV Associated Lipodystrophy Syndrome
HDL-C	High-Density Lipoprotein Cholesterol
HIV	Human Immunodeficiency Virus
HPT	Hypertension
IDF	International Diabetes Federation
IDV	Indinavir
IL-6	Interleukin-6
IR	Insulin Resistance
LDL-c	Low-Density Lipoprotein Cholesterol

LPV	Lopinavir
MCP-1	Monocyte Chemoattractant Protein 1
MetS	Metabolic Syndrome
mtDNA	Mitochondrial Deoxyribonucleic Acid
MVC	Maraviroc
NVP	Nevirapine
OR	Odds Ratio
RAL	Raltegravir
RTV	Ritonavir
SD	Standard Deviation
SQV	Saquinavir
3TC	Lamivudine
TB	Tuberculosis
TDF	Tenofovir
TG	Triglyercides
TNF-α	Tumor Necrosis Factor Alpha
TT	Triple Therapy
WHO	World Health Organisation
ZDV	Zidovudine

CHAPTER ONE: INTRODUCTION

1.1 **HIV/ AIDS Epidemiology**

Human immunodeficiency virus/ Acquired Immune Deficiency Syndrome (HIV/ AIDS) immensely contributes to disease burden in South Africa with an estimated total of 7.03 million people and approximately one in five women of reproductive age living with the disease in 2016 [1]. However, the rate of infections in the general population has decreased from 1.27% in 2002 to 1.22% in 2016 [1].

Highly Active Antiretroviral Therapy (HAART), used in the treatment of HIV-1 infections, was initiated in the 1990s. This has aided in slowing down the disease progression from a fatal one to a chronic condition leading to a decrease in morbidity and mortality in these patients [2, 3]. HAART consists of a combination of at least 3 drugs falling in different classes, depending on their mechanism of action [3]. Clinical evidence suggests that there is a reduction in mortality in patients with a CD4 count of < 350 cells/μL who start antiretroviral therapy without delay [4]. The national rollout programme of HAART began in 2005, with at least one service point per district in South Africa. This led to the successful decline in the number of AIDS-related deaths from 325, 241 in 2006 to 150, 759 in 2016 [1].

The goals of HAART are to: improve quality of life, reduce HIV- related morbidity and mortality, provide maximum and durable suppression of viral load and restore or preserve immune function. Antiretroviral agents currently available and approved for use fall into the following classes: [4]

- Nucleoside and Nucleotide Reverse Transcriptase Inhibitors (NRTI)
- Nonnucleoside Reverse Transcriptase Inhibitors (NNRTI)
- Protease Inhibitors (PI)
- Integrase Inhibitors (INSTI)
- Entry Inhibitor: CCR5 Receptor Antagonists (CCR5A), Fusion Inhibitor (FI)

Table 1: Examples of drugs under the different classes of Antiretroviral drugs [4, 5, 7]

NRTI	NNRTI	PI	INSTI	CCR5 RA	FI
Lamivudine (3TC)	Efavirenz (EFV)	Lopinavir (LPV)	Raltegravir (RAL)	Maraviroc (MVC)	Enfuvirtide
Tenofovir (TDF)	Nevirapine (NVP)	Ritonavir (RTV)	Elvitegravir	Vicriviroc	
Zidovudine (ZDV)	Delavirdine (DLV)	Atazanvir (ATV)	Dolutegravir	Aplaviroc	
Stavudine (d4T)	Etravirine (ETR)	Saquinavir (SQV)			
Emtricitabine (FTC)		Indinavir (IDV)			
Abacavir (ABC)		Darunavir (DRV)			

1.2 **HAART Initiation and Regimens**

Previously, HAART initiation required a patient's HIV status to be confirmed and then assessed against the World Health Organisation (WHO) clinical staging. A CD4 count was used to determine eligibility of HAART: initiation (CD4 $\leq$ 500 μl), prioritisation (CD4 $\leq$ 350 μl), fast tracking (CD4 $\leq$ 200 μl) or Cryptococcal Antigen or Cryptococcal Latex Antigen Test (CD4 $\leq$ 100 μl) [8]. If the CD4 count was $\leq$ 500 μl, HAART was initiated regardless of clinical staging, and if HIV was advanced or severe (WHO stage 3 or 4) then HAART is initiated regardless of CD4 counts [8]. However, new WHO guidelines recommend a "treat-all" approach, removing limitations on eligibility. This recommendation dictates that all age groups and populations are eligible for HAART initiation regardless of CD4 count or WHO clinical staging [6].

As per the 2016 WHO consolidated guidelines on HAART use, the first-line treatment for adults should include 2 NRTIs plus a NNRTI or INSTI [6]. The preferred first-line drugs for HAART initiation are TDF + 3TC or FTC + EFV as a combination (based on body weight and if there are no contraindications). By the end of 2014, almost 70% of the global population were on this first-line regimen and only 60% were taking it as a fixed-dose combination (FDC). This specific regimen was chosen, with moderate quality evidence suggesting that it is less frequently associated with severe adverse events and has better virological suppression and treatment response as compared to NNRTI (once or twice daily dosing) or PI-based regimens [6]. South African HAART regimen guidelines are adapted from international guidelines and appear below (refer to table 2 and 3).

Table 2: South African Guidelines for HAART Regimens [8] - First-line Regimen

New initiation for: adolescents > 15 years weighing > 40 kg, adults, all HIV/TB co-infection, all HBV co-infection	TDF + 3TC (or FTC) + EFV as a fixed-dose combination
EFV Contraindication*	TDF + 3TC (or FTC) + NVP or LPV/r
TDF Contraindication**	ABC + 3TC + EFV or NVP

* EFV contraindication may manifest as: intolerance to EFV, significant psychiatric comorbidity and interference with daily function.

** There is a TDF contraindication if there is a creatinine clearance of < 50mL/min.

No patients should be on d4T, pre-existing patients to be changed to TDF.

A patient is considered for a second-line regimen if there is virological failure (viral load > 1000 copies/mL) on at least two occasions, occurring for two months regardless of patient adherence.

Table 3: South African Guidelines for HAART Regimens [8] - Second-line Regimen

Failure on a TDF- based regimen	AZT + 3TC + *LPV/r AZT + TDF + 3TC + LPV/r (if HBV co-infected)
Failure on d4T or AZT based regimen	TDF + 3TC (or FTC) + LPV/r
Dyslipidaemia (total cholesterol > 6mmol/L)	Change LPV/r to ATV/r

or diarrhoea associated with LPV/r	
Anaemia or renal failure	Change to ABC

*LPV/r: Combination of lopinavir with ritonavir. Extensive toxicity and a high pill burden have discouraged the use of ritonavir on its own in a PI-based regimen. Ritonavir had been used as a boosting agent after it was found to change the pharmacokinetic parameters of the PI to which it is added. These parameters include: area under the curve, maximum concentration, minimum concentration and half-life. Boosted ritonavir leads to inhibition of hepatic and intestinal cytochrome P450 3A, resulting in a significant improvement in the bioavailability and half-life of PIs [9]. Low-dose ritonavir is used and enhances exposure to the concomitant PI without markedly adding to the side-effect profile of the regimen. Boosted therapy has been successful in maintaining high levels of viral suppression in both HAART- naïve and those failing on other HAART regimens [9, 10].

A third-line ad-hoc committee of experts is required to review patients failing on second-line regimens. Patients on PIs for at least a year with inadequate virological suppression are eligible for genotype resistance testing. Third-line regimens comprise of: Raltegravir, Darunavir/Retravirine, specifically tailored as per patient history and genotype interpretation [8].

1.3 **Fixed-Dose Combination (FDC) Antiretroviral Therapy**

A fixed-dose combination is a combination of two or more active pharmaceutical ingredients in a single pill [11]. The first-line FDC antiretroviral drug rolled out in South Africa contains: efavirenz (EFV), emtricitabine (FTC) and tenofovir (TDF) [12]. In 2013, new ART guidelines required that all newly initiated patients, as well as pregnant patients regardless of CD4 count and provided they are tolerant, should be started on the EFV/FTC/TDF fixed-dose combination [13]. However, patients who fail on first-line regimen and those weighing < 40 kg are to be excluded. Patients weighing < 40kg require a lower doses of EFV (400 mg) as opposed to the 600 mg formulated in the FDC. Lower dose EFV is required as clearance is affected by body weight. A higher body weight is associated with a decrease in EFV plasma concentration [14]. The dosage may be changed to the EFV/FTC/TDF FDC combination once patients regain the weight [13].

HAART regimens are generally complex with a high pill burden, frequent dosing, drug-drug interactions and various food requirements. Adverse events are common with HAART and may lead to discontinuation in early phases of therapy, dose interruptions, and significant reductions in the quality of life [15, 16, 21]. Discontinuation and

noncompliance have serious consequences as they may lead to the emergence of resistance [17]. Efforts are continuously being made to simplify regimens and ensure that undesirable adverse-effects are kept to a minimum [18].

The fixed-dose combination of EFV/FTC/TDF is bioequivalent to the administration of its individual components [19]. The side-effect profile for the EFV/FTC/TDF combination is similar to that of its individual components [13]. A study done by Pozniak et al. showed that the fixed-dose combination of EFV/FTC/TDF was superior in achieving and maintaining an HIV RNA level < 400 copies/ml and an increase in CD4 cells when compared to a fixed-dose zidovudine/lamivudine and efavirenz over a 96-week period [20].

EFV/FTC/TDF is suggested to be advantageous as it reduces the pill burden thereby improving adherence. It is comparatively cost effective when compared to the triple drug regimen [13]. Reports on patients receiving the EFV/FTC/TDF fixed-dose combination showed that 64% of patients thought the new regimen was "much better" than their previous regimen by week 4, and by week 48 this number increased to 85% [21].

Patients have shown significantly higher adherence (> 95%) with a once daily tablet regimen than multiple tablet regimens. This, in turn, is associated with a lower risk of hospitalization and reduction of inpatient costs [22].

1.4 **Adverse- effects of HAART**

Long-term exposure to HAART is associated with toxicities that are making it increasingly difficult to successfully manage HIV-infected patients [23]. Deleterious adverse-effects may be experienced by up to 50% of patients with the most common being: rash, hypersensitivity reaction, anaemia, gastrointestinal (GI) discomfort, jaundice, and undesirable effects on the central nervous system (CNS). Gastrointestinal side-effects include diarrhoea, nausea, and vomiting [5, 15, 24].

1.4.1 **Nonnucleoside reverse transcriptase inhibitors (NNRTI)**

NNRTIs (EFV, NVP, ETR) inhibit the activity of reverse transcriptase directly and suppress HIV replication. All drugs in this class are associated with: rash (including Steven Johnson Syndrome), hepatotoxicity and drug-drug interactions [5]. Nevirapine (NVP) use is most commonly associated with the development of a rash, which may be

life threatening, requiring discontinuation in approximately 5% of patients. The rash may be life-threatening if accompanied by fever and systemic hypersensitivity, especially hepatitis [5]. NNRTIs significantly increase plasma High-Density Lipoprotein cholesterol (HDL-c) levels. NVP containing antiretroviral regimens are associated with better lipid profiles due to the fact that they cause increased plasma concentrations of HDL-c [25].

EFV is commonly associated with adverse-effects affecting the central nervous system. These effects occur most commonly within 2-6 weeks of therapy. Central nervous disturbances may manifest as: abnormal/ vivid dreams, dizziness, headache, insomnia, somnolence, impaired concentration, and mania. These reactions may occur in as many as 40% of patients [5, 26].

ETR is associated with the development of a rash and hepatotoxicity [29]. NNRTIs are not generally associated with GI toxicity [29].

1.4.2 **Nucleoside and nucleotide reverse transcriptase inhibitors (NRTI)**

The drugs in this class are nucleoside or nucleotide (TDF) analogues that act as false substrates for reverse transcriptase and terminate the viral DNA chain elongation [5]. Major toxicities of NRTI therapy are thought to be secondary to inhibition of mitochondrial DNA polymerase [26, 27]. Long-term use can result in lactic acidosis or symptomatic hyperlactataemia, as a result of mitochondrial toxicity [5]. Mechanisms of NRTI-induced mitochondrial toxicity include competitive inhibition, incorporation into mtDNA causing premature chain termination (i.e. mtDNA deletions), impairment of mitochondrial enzymes (i.e. deficiency in electron transport chain subunits encoded by mtDNA, or a direct effect of NRTIs on adenylate kinase and ADP/ATP translocase), uncoupling of oxidative phosphorylation and triggering of mitochondria-induced apoptosis [28]. Didanosine and stavudine are most likely to cause hyperlactataemia and its combination should be avoided, whilst those on abacavir, lamivudine and emtricitabine are least likely to do so [5].

Impaired synthesis of mitochondrial enzymes, that generate ATP by oxidative phosphorylation, may cause neuropathy associated with stavudine, didanosine, zalcitabine and myopathy associated with stavudine [26, 27]. Concurrent use of zidovudine and stavudine is best avoided as intracellular activation of stavudine is inhibited [5].

Stavudine exhibits preferential inhibition of viral reverse transcriptase with relatively low inhibition of host cell DNA polymerase. Initial clinical studies showed significant antiviral effects displayed by stavudine with acceptable safety [30]. However, its use is now discouraged due to long-term toxicity such as lipoatrophy (of face and limbs), hypertriglyceridaemia and neuropathy [4]. Fat redistribution with stavudine use may present itself as loss of subcutaneous fat, facial wasting, truncal adiposity, enlarged breast and buffalo hump [8]. There have been reported cases of increased morphological changes when used in combination with lamivudine [31]. Clinical and metabolic abnormalities associated with stavudine use are partially reversible upon drug withdrawal or substitution [32]. Saint-Marc et al. analysed the levels of plasma triglycerides and pyruvate when stavudine was either substituted with zidovudine (ZDV) and lamivudine (3TC) (NRTI group) or ZDV/ ABC (PI group). After 6 months of discontinuation, plasma triglycerides dropped by 46% and 36% in the two groups respectively, and pyruvate levels dropped by 37.5% and 20.8% respectively [32].

There are serious dose-limiting adverse-effects associated with didanosine, which include peripheral neuropathy and pancreatitis. They occur more often in patients with higher doses, renal failure and advanced HIV infection. Frequent GI discomfort with didanosine use should be treated with caution, as it may be a sign of evolving pancreatitis [5, 29].

Lamivudine is generally well tolerated with relatively fewer adverse-effects. The most common experienced are diarrhoea, malaise, fatigue, headache and sleep disturbances. This drug is primarily excreted via the kidneys therefore doses must be adjusted accordingly in patients with renal dysfunction [33].

Drug hypersensitivity reactions, commonly experienced in HAART patients, are associated with all NNRTIs, abacavir and amprenavir. The rash usually begins one to three weeks after initiation and manifests as an erythematous, maculopapular, pruritic rash with or without fever [26]. An estimated 5% of patients initiated on abacavir experience hypersensitivity reactions within the first 6 weeks of treatment necessitating discontinuation if experienced [34, 35].

Tenofovir is known to be nephrotoxic and should be used with caution in patients with renal dysfunction as it may cause renal impairment, proteinuria and Fanconi Syndrome [5]. Gallant et al. [36] showed a small but statistically significant change in creatinine clearance

with tenofovir use. These changes may not be clinically significant in patients with normal renal function at baseline, however they may become significant if renal impairment is present [36, 37]. Tenofovir is also associated with osteopaenia (more so than stavudine) and mild to moderate GI effects [5, 38].

Approximately 5-10% of HAART patients experience anaemia or granulocytopaenia due to bone marrow suppression caused by zidovudine. Other adverse-effects may include, nausea, anorexia, headache, and fatigue. A decrease in the recommended dose of zidovudine has shown improved tolerability [26, 34, 39].

1.4.3 **Protease inhibitors (PI)**

PIs inhibit the protease enzyme, thereby preventing the cleavage of viral proteins and resulting in immature, non-infectious HIV viral particles [5]. PIs may cause metabolic abnormalities, such as hypercholesterolaemia, hypertriglyceridaemia, and insulin resistance. The lopinavir/ ritonavir combination is most commonly associated with diarrhoea, lipodystrophy and metabolic disorders [5].

Regimens that included indinavir were discontinued due to renal colic, a common side-effect of the drug. This is due to indinavir being poorly water-soluble resulting in its crystallisation in urine and causing an obstruction between the renal tubules and urethra. *In vitro* studies have shown that indinavir can inhibit lipogenesis and this may occur via altered retinoid acid signaling [26, 40].
Atazanavir and indanivir inhibit the uridine diphosphate glucoronyl transferase (UGT) 1A1 enzyme, which causes interference with the metabolism of bilirubin and may lead to jaundice or scleral icterus. In a study by Molina et al. of atazanavir/ritonavir versus lopinavir/ritonavir, 4% of the atazanavir arm had grade 2-4-jaundice and/ or icterus [29, 41].

1.4.4 **Integrase inhibitor (INSTI)**

Integrase is an enzyme essential for viral replication and catalyzes two reactions that mediate the insertion of reverse-transcribed viral genome into the host DNA. Therefore INSTIs inhibit integration and viral replication in cells [33]. Common adverse-effects of INSTI (RAL) include, headache, insomnia, dizziness and fatigue [29].

1.4.5 **CCR5 antagonists**

CCR5, a chemokine, acts as a major co receptor for HIV-1 entry in the cell. CCR5 antagonist therefore blocks HIV-1 entry and infection of cells [34]. At clinical doses of maraviroc, vicriviroc and aplaviroc, common adverse-effects include: headache, nausea, cramps, flatulence and diarrhoea. *In vitro* studies demonstrate good tolerability of these drugs [7].

1.4.6 **Fusion inhibitor**

The known drug in this class enfuvirtide (T-20) targets a step in viral entry. It inhibits conformational change in HIV-1 transmembrane glycoprotein (gp41) that is necessary for the fusion of HIV-1 and target cell membranes [37]. Known adverse-effects of enfuvirtide are injection site reactions, hypersensitivity reactions and pneumonia [29].

Since integrase inhibitors, CCR5 antagonists and fusion inhbitors are relatively new, not much is known about the long-term adverse-effects of these drugs.

1.5 **Metabolic Syndrome (MetS)**

Metabolic syndrome is defined as a group of risk factors used to identify an individual's susceptibility in developing cardiovascular disease or type 2 diabetes [42]. In 1988 "Syndrome X" was proposed by G.M. Reaven [43] and was later known as insulin resistance syndrome. He noted patients with a cluster of abnormalities who were at higher risk for cardiovascular disease. The term "metabolic syndrome" originated when WHO and the Adult Treatment Panel III of the National Cholesterol Education Program (ATP III/NCEP) proposed criteria, which enabled the identification of patients with an increased risk of cardiovascular disease [43]. The cluster of components of metabolic syndrome confers a risk beyond that of the sum of individual components [43]. Metabolic syndrome has varying criteria selected by different bodies such as the WHO, ATP III and International Diabetes Federation (IDF), all of which allude to the same cardiovascular risk [41]. Various clinical definitions led to confusion amongst clinicians when it came to identifying patients with metabolic syndrome. The IDF and American Heart Association/ National Heart, Lung, and Blood Institute (AHA/NHLBI) representatives therefore met in

an attempt to reconcile the different definitions and released the interim joint statement including various bodies harmonizing the definition of metabolic syndrome [44].

The components of metabolic syndrome include (Table 4): central obesity, raised fasting glucose, raised blood pressure, dyslipidaemia i.e. raised triglycerides (TG) and lowered HDL-c [44].

1.6 **Clinical Criteria for Diagnosing Metabolic Syndrome**

Table 4: Clinical markers used to diagnose metabolic syndrome by different bodies [44-46]

Risk Factor	ATP III	IDF	WHO	Harmonised
Abdominal Circumference/ Body Mass Index (BMI) (kg/m^2)	Men: > 102 cm Women: > 88 cm	> 30 kg/m^2	> 30 kg/m^2	Population- and country-specific definitions- sub Saharan Africa Men: ≥ 94 cm Women: ≥ 80 cm
Triglycerides	≥ 1.70 mmol/L	> 1.70 mmol/L	≥ 1.70 mmol/L	≥ 1.70 mmol/L OR drug treatment for elevated triglycerides
HDL-Cholesterol	Men: < 1.00 mmol/L Women: < 1.30 mmol/L	Men: < 1.00 mmol/L Women: < 1.30 mmol/L	Men: < 0.90 mmol/l Women: < 1.00 mmol/L	Men: < 1.00 mmol/L Women: < 1.30 mmol/L
Blood Pressure	≥ 130/≥ 85 mmHg	> 130/85 mmHg	≥ 140/ ≥90 mmHg	≥ 130/≥ 85 mmHg OR drug treatment in a patient with a history of hypertension
Fasting Glucose	≥ 6.1 mmol/L	> 5.6 mmol/L	Insulin resistance defined by: -Type 2 diabetes- Impaired fasting glucose	≥ 5.55 mmol/L OR drug treatment of elevated glucose

			-Those with normal glucose levels (<6.1 mmol/L) glucose uptake below lowest quartile for background population under investigation under hyperinsulinaemic, euglycaemic conditions	
Urinary albumin excretion rate			≥ 20 micrograms/min	

Between 20-25% of the global adult population is estimated to have MetS and are twice as likely to die from, and three times more likely to suffer from heart attack or stroke in comparison with people without MetS [45, 47].

Side-effect profiles of certain antiretroviral agents match the markers of MetS and have thus been implicated in its pathogenesis. Prevalence of metabolic syndrome among HIV-infected patients globally ranges from 17.0% to 45.4% and 10% to 21% in Sub Saharan Africa (Table 5) [48-52].

1.7 **Global Prevalence of MetS**

Table 5: Prevalence of metabolic syndrome in HAART patients by studies conducted in different countries [23, 48, 42- 60]

Area	Prevalence	Year	Reference
Barcelona	17%	2005	53
Italy	20.8%	2007	54
New South Wales, Australia	ATP: 7.8% IDF: 8.5%	2007	55
Taiwan	26.2%	2011	52
Colorado	20%	2012	56
Brazil	30%	2013	57
Cameroon	NCEP: 30.7% IDF: 32.8%	2013	58
Southern Ethiopia	ATP: 18.1% IDF: 25%	2014	23
Miami	30%	2015	59
Burkina Faso	18%	2015	48
South West Uganda	Male: 58% Female: 62%	2016	60

The risk of metabolic syndrome increases with age and varies between ethnicities [56]. Prevalence of metabolic syndrome may also be dependent on sex, the population surveyed, genetic predisposition and lifestyle (e.g. diet and level of physical activity) [61]. Persons with metabolic syndrome are not only susceptible to cardiovascular disease and diabetes, but are also predisposed to conditions such as cholesterol gallstones, fatty liver, polycystic ovary syndrome and some forms of cancer [46].

PIs are strongly associated with metabolic syndrome, however recent studies show that all classes of HAART are associated with the syndrome to varying degrees [52]. It has been shown that the prevalence of metabolic syndrome increases with duration of exposure to HAART [52]. Stavudine has the highest association with metabolic syndrome and HIV-related fat accumulation [50, 51].

1.8 Components of MetS in HIV Patients on HAART

1.8.1 Abnormal fat distribution

Lipodystrophy is a broad term used to describe metabolic disturbances characterised by various manifestations of fat redistribution that may occur as complete or partial loss of adipose tissue of the extremities (lipoatrophy) and/or central adipose tissue accumulation (lipohypertrophy) [42, 73]. After the introduction of HAART, there were reports of changes in body fat accumulation, particularly central fat accumulation (abdominal obesity) and lipoatrophy of the arms, legs and face [62]. It was then classified into a syndrome of peripheral lipoatrophy with central hypertrophy, particularly associated with PI use [43]. Lipoatrophy in HIV-infected patients is characterized by loss of subcutaneous fat in the face, buttocks and extremities. This results in the appearance of sunken cheeks, exaggerated musculature, bones, arteries and veins. Lipohypertrophy is characterised by truncal obesity, dorsocervical fat accumulation and breast enlargement [63, 64].

Common metabolic abnormalities found in HAART-associated lipodystrophy patients are: hyperglycaemia, hyperinsulinaemia, hypercholesterolaemia, and hypertriglyceridaemia [65]. Exposure to PIs, duration of NRTI/ PI use, increase in age, gender, duration and severity of HIV-disease, viral load and extreme changes in BMI have been recognised as potential risk factors [65].

Various pathways have been postulated in the pathophysiology and etiology of HIV-associated lipodystrophy. Occurrence of HIV-Associated Lipodystrophy Syndrome (HALS) is a result of complex interactions of viral factors and antiretroviral agents [65]. The effects of HAART on adipose tissue could be associated with a local inflammatory state via the increased production of pro-inflammatory cytokines (tumor necrosis factor alpha (TNF-α), interleukin-6 (IL-6), monocyte chemoattractant protein-1 (MCP-1)) and the decreased level of adiponectin. Adipocyte metabolism is controlled by these pro-inflammatory cytokines, which decrease adiponectin production and induce insulin resistance, leading to increased lipolysis. The broken down free fatty acids are poorly metabolised by other tissues and result in lipotoxicity, i.e. triglyceride depots with liver steatosis, Very Low-Density Lipoprotein cholesterol (VLDL-c) overproduction, muscle intramyocellular fat depots and the onset of insulin resistance. The progressive accumulation of TNF-α may play a role in metabolic changes as it inhibits the uptake of

free fatty acids by adipocytes via the suppression of lipoprotein lipase activity leading to fat wasting (TNF-α and other pro-inflammatory cytokines impair PPARγ expression and promote adipocyte lipolysis) [42, 65].

Previously, HIV-infected patients experienced a wasting syndrome, however central weight gain and peripheral fat loss with HAART use is becoming more prevalent. The peripheral fat loss/ wasting should be distinguished from other wasting conditions associated with HIV e.g. AIDS wasting syndrome, cachexia, malnutrition, adrenal insufficiency and severe chronic infections [65]. A study done at the University of Alabama by Tate et al. [66] noted that after a 6-month period, patients who were prescribed a PI exhibited a significant increase in BMI. There was an increase in overweight patients from 24% to 31% over a 24-month period. Within the same period the prevalence of obesity increased from 20% to 25% [66]. A study done by Krishnan et al. highlighted the significant role of body mass index on metabolic syndrome after antiretroviral initiation. Patients with a high BMI at antiretroviral initiation were less likely to improve their metabolic syndrome status and could be at heightened risk for the onset of cardiovascular disease [56].

Central obesity is a key factor to meet the IDF definition of the metabolic syndrome [63, 64]. However, the occurrence of central obesity is controversial as certain data collected on patients with peripheral lipoatrophy supports the concept that during fat loss, visceral fat is relatively spared, giving the impression of increased abdominal girth, hence pseudotruncal obesity [63]. Hyperlipidaemia together with central obesity have been associated with a higher incidence of arteriosclerosis [67].

The development of fat wasting is enhanced when PIs and NRTIs are used together. This overlapping toxicity may be due to mitochondrial dysfunction as PI-associated insulin resistance and increased fatty acid flux may affect mitochondrial function. Mitochondrial toxicity is prominently associated with NRTI use and thus may have a synergistic effect when used together [68]. Abdominal subcutaneous lipoatrophy is a possible reason for certain HIV-infected patients not being diagnosed with metabolic syndrome, as they do not meet the waist circumference criterion. Lipoatrophy results in a lower body mass index and cannot be a reliable substitute for waist circumference and has led to discussion toward a possible recalibration of these parameters for HIV-infected persons [43].

J Miller et al. [69] observed that patients taking only NRTIs had different symptoms of lipodystrophy as opposed to patients taking both NRTIs and PIs. Patients on NRTIs and PIs had presented with symptoms of peripheral fat loss and abdominal distension. The NRTI group was associated solely with lipoatrophy of which these patients had additional symptoms of higher lactate and alanine aminotransferase, lower albumin, cholesterol, triglyceride and insulin levels [64, 69]. It is known that metabolic and body-fat abnormalities are common among HIV-infected adults receiving nucleoside-analogue and PI therapy. There is preliminary evidence that suggests that these patients have an increased risk of cardiovascular disease [70].

NRTIs have been associated with alterations in body fat deposition and metabolic alterations, particularly changes in serum triglyceride concentrations. These alterations are less evident in patients using tenofovir + lamivudine as opposed to those using zidovudine/ didanosine/ stavudine + lamivudine [25, 71]. The NRTI most strongly associated with lipoatrophy is stavudine with a 30% incidence of over a 2-year period, particularly when used together with didanosine [14, 70].

The aetiology of lipodystrophy includes the alteration of mitochondrial function, specifically with NRTI use [72]. Mitochondrial toxicity is associated with prolonged use of NRTIs leading to lactic acidosis [5]. The mechanisms involved in mitochondrial toxicity include: competitive inhibition, incorporation into mitcochondrial DNA (mtDNA) leading to premature chain termination, impairment of mitochondrial enzymes, uncoupling of oxidative phosphorylation and triggering of mitochondrial-induced apoptosis [28].

Mitochondrial DNA polymerase, essential for mtDNA replication, is acutely sensitive to NRTIs. mtDNA encodes genes for vital enzymes of the respiratory oxidative phosphorylation electron transport chain [65]. Inhibition of mtDNA polymerase leads to mtDNA depletion, respiratory chain dysfunction with subsequent toxicity and reduced energy production [27, 73]. mtDNA is crippled by NRTI use, which leads to lactate accumulation and subsequent development of lactic acidosis. This is a potent trigger of adipocyte death and leads to lipodystrophic changes [65, 73, 74]. Mitochondrial toxicity is responsible for pathological changes and irreversible damage to intracellular metabolism [75]. Patients with HIV-associated lipoatrophy were found to have a decrease in mtDNA levels by a mean of 44% [73]. Factors contributing to mitochondrial toxicity may be:

underlying organ dysfunction, concomitant HIV-1 opportunistic diseases and administration of drugs with similar toxicity profiles [26].

A retrospective study by Aldeen et al. [76] found that 16% of patients on nevirapine and two NRTIs developed lipodystrophy. All these cases were associated with an undetectable HIV-1 RNA levels. Self-reports by patients revealed symptoms of peripheral fat loss and central obesity [76]. Recent data shows powerful anti-adipogenic effect of EFV in cultured adipose cells, suggesting its ability to cause fat wasting [77].

PIs were thought to be the reason behind early clinical cases of lipodystrophy [42, 78]. Carr et al. found that after two years of potent PI containing therapy, lipodystrophy was very common and was rated severe by 11% of patients. Lipodystrophy was progressive in most cases and did not resolve spontaneously [79].

PIs bind to the catalytic region of HIV-1 aspartyl protease with approximately 60% homology with the sequence of the lipid binding domain of the Low-Density Lipoprotein Receptor (LDL-R) such as, Low-Density Lipoprotein Receptor-related Protein (LRP) and C-terminal region of Cellular Retinoic-Acid Binding Protein type 1 (CRABP-1)[78, 80]. LRP binds to LPL and hydrolyses free fatty acids, promoting accumulation in adipocytes. Remnants of triglyceride-rich proteins are removed from circulation by the LDL receptor [42]. PIs bind to LRP on the capillary endothelium and interfere with the LRP-LPL complex [42]. This leads to a reduced cleavage of fatty acids from circulating triglycerides by the LRP-lipoprotein lipase complex and reduced hepatic uptake of chylomicrons [67]. This results in hyperlipidaemia leading to fat redistribution to the abdomen, insulin resistance and type 2 diabetes (in patients who are susceptible) [67].

Lipodystrophy associated with PI use is induced by impairing the conversion of retinoic acid to cis-9-retinoic acid by: 1) Binding to CRABP-1. This protein facilitates the binding of retinoic acid (RA) to nuclear retinoic acid receptors. RA that is bound to CRABP-1 is a better substrate for metabolic enzymes than free RA. CRABP-1 binds to intracellular RA and facilitates the conversion to cis-9-RA, which is a major ligand for retinoic X receptor (RXR). Heterodimerisation of RXRα-PPARγ enhances binding activity of cis-9-RA to RXR [65, 67, 73, 78]. PIs inhibit SREBP-1 activation of this heterodimer. Cell culture studies and animal studies show PI administration results in an increase in *de novo* lipogenesis and cholesterol synthesis through suppression of SREBP-1 [70, 78]. The cis-9-RA-RXR-

PPARγ molecular complex rescues adipocytes from apoptosis and increased adipocyte differentiation. Inhibition of CRABP-1 results in apoptosis and impaired differentiation of peripheral adipocytes. There is relative sparing of intraabdominal and visceral adipocytes thereby contributing to the development of changes in fat distribution [65]. 2) Inhibiting cytochrome P450-3A isoforms. Inhibition of these isoforms that metabolise RA leads to a reduction of RXR stimulation and impaired differentiation of peripheral adipocytes resulting in lipid release of decreased lipid storage [67].

PIs may induce lipoatrophy by inhibiting sterol regulatory enhancer–binding protein 1 (SREBP1)–mediated activation of the heterodimer consisting of adipocyte retinoid X receptor and peroxisome proliferator–activated receptor γ (PPARγ) or related transcription factors such as PPARγ coactivator 1. *In vitro* studies have shown that PIs can inhibit lipogenesis and adipocyte differentiation, stimulate lipolysis, and impair SREBP1 nuclear localization [70].

1.8.2 **Dyslipidaemia**

Patients infected with HIV may present with an elevation in total cholesterol, Low-Density Lipoprotein cholesterol (LDL-c), Triglycerides (TG) and decreased HDL-c levels [42]. Abnormal lipid levels are associated with the infection and worsen after the initiation of therapy. Viraemia- associated dyslipidaemia includes decreased plasma concentrations of total cholesterol, HDL-c and LDL-c and a subsequent increase in plasma triglycerides (as a result of impaired clearance of TG-rich proteins) [24]. The presence of abnormal lipid levels has been associated with metabolic syndrome resulting from visceral fat accumulation with insulin resistance [5, 42].

During early stages of HIV infection there is a decrease in HDL-c levels and as the disease progresses LDL-c levels decrease modestly. With the progression to advanced disease, VLDL-c increases. There exists a negative link between HIV RNA and HDL-c levels with very high HIV RNA levels being associated with increased triglycerides and VLDL-c. Treatment with HAART causes a dissociation of HDL-c and triglycerides. PIs were previously associated with comparatively lower HDL-c levels, however newer trials showed no change in HDL-c levels in patients treated with ritonavir, lopinavir/ritonavir, indinavir, and atazanavir. NNRTIs (nevirapine and efavirenz), on the other hand, increase HDL-c levels [43, 81]. Neither of these NNRTIs restores HDL-c to normal levels in patients

who begin therapy with HDL-c levels around 25 mg/dL (0.65mmol/L) [43].

Ombeni et al. observed an increase in the prevalence of dyslipidaemia in HAART patients as CD4 counts began to rise and the viral load was suppressed. They concluded that the immune recovery in patients led to an elevation in lipid levels, augmenting the elevation caused by HAART [82]. The prevalence of dyslipidaemia in all HAART patients ranges from 20-28% depending on the criteria and population investigated. A cross sectional DAD study showed the prevalence of hypercholesterolaemia, hypertriglyceridaemia and low HDL-cholestrol to be 10-27%, 23-40% and 19-27% respectively, depending on the antiretroviral regimen used [72].

PIs are strongly associated with alterations in lipid metabolism and may cause fasting hypertriglyceridaemia and elevated LDL-c. Up to 70% of patients receiving PI therapy develop dyslipidaemia and require lipid-lowering therapy such as statins [84]. The pathways by which PI-induced dyslipidaemia occurs are not fully understood but suppression of nuclear SREBP-1 in the liver has been suggested [72]. Carr et al. [85] hypothesized that PI therapy may cause unspecified reactions with proteins that regulate lipid metabolism viz. cytoplasmic-acid binding protein type 1 and LRP. The subsequent inhibition may be the cause of hyperlipidaemia and contribute to central fat deposition and insulin resistance [85]. A study conducted by Calza et al. found that 60% of patients who were on a PI-based regimen for 12 months exhibited hypertriglyceridaemia, and hypercholesterolaemia was detected in 42.4% [83].

Regimens containing potent PIs such as indinavir, ritonavir and nelfinavir cause serum lipid alterations in up to 50-70% of patients. Hypertriglyceridaemia occurs in 60-100% of these patients, while hypercholesterolemia occurs in 10-70% of patients [86]. Lopinavir was also linked to hypercholesterolaemia and hypertriglyceridaemia [87].

Tenofovir (NRTI) appears to reduce the levels of non-HDL-cholesterol, LDL-cholesterol and total cholesterol [88]. NRTIs including zidovudine, stavudine and lamivudine have also become associated with the occurrence of dyslipidaemia via mitochondrial toxicity [80].

1.8.3 **Insulin resistance and glucose intolerance**

Insulin resistance (IR) occurs over time when adipose tissue and skeletal muscle cells become less sensitive to insulin. Glucose can no longer be absorbed and remains in the

blood triggering the production of more insulin. The demand for increased insulin production leads to exhaustion of pancreatic β-cells until the pancreas is unable to produce sufficient insulin leading to hyperglycaemia and type 2 diabetes [45]. Non-HIV causes of insulin resistance may include; obesity (especially visceral), physical inactivity, the use of certain drugs and acute bacterial infection [89].

The majority of overweight or obese patients display signs of Insulin Resistance (IR) but not all have metabolic disturbances. Central obesity is a key factor in the diagnosis of IR. Visceral adipose tissues secrete adipocytokines such as, leptin, resistin, TNF-α and IL-6, which induce insulin resistance together with plasminogen activator inhibitor-1. Adiponectin is an important adipocytokine responsible for protection against the development of type 2 diabetes mellitus, hypertension, inflammation and atherosclerotic vascular disease [90]. TNF-α and IL-6 are elevated in HIV infection and influence normal suppression of hepatic glucose production and insulin-stimulated glucose uptake. Peripheral insulin sensitivity can be indirectly influenced by TNF-α by the stimulation of TG and free fatty acid (FFA) production in the liver [91].

Intramuscular accumulation of lipids, as a result of lipodystrophy, is associated with impaired insulin actions in the skeletal muscle cells. Abnormalities in fat distribution and lower extremity lipoatrophy lead to impaired glucose homeostasis. In HIV-infected patients the mechanisms of glycaemic dysregulation and associated defects in lipid metabolism and secretion are (in part) due to defects in lipid metabolism and inflammation, leading to insulin resistance and impaired glucose tolerance / fasting glucose [92].

The risk of IR in HIV-infected patients may be due to the pro-inflammatory effects of HIV and the direct or indirect (e.g. changes in body fat distribution) consequences of HAART [93]. HAART impairs glucose tolerance by: 1) the induction of peripheral IR in skeletal muscles and adipose tissues, 2) compensatory impairment of pancreatic β-cells [93]. Factors contributing to insulin resistance may be PI use, restoration to health, fat and aging [89]. There is up to 60% prevalence of IR in HAART patients, depending on the criteria and techniques used for diagnosis [72]. Altered pancreatic β-cell function has been noted in HIV-1 patients on HAART when compared to controls. This occurred mainly with PI exposure, leading to an impairment of glucose sensing with inhibition of insulin release [77].

Prior to the introduction of PIs, HIV-infected patients generally had normal or decreased glucose levels, without the presence of insulin resistance [63]. Since the late 1990s many patients on PI-containing HAART regimens developed non-insulin dependent diabetes mellitus. This is associated with impaired glucose tolerance, insulin resistance, high fasting plasma insulin and C-peptide levels; as well as elevated proinsulin and insulin [42, 64]. The high prevalence of hyperlipidaemia and insulin resistance associated with PI use leads to an increased risk of cardiovascular diseases and diabetes [94]. *In vitro* research shows that PIs can directly impair insulin signalling in insulin-responsive tissues at therapeutic doses. However, further investigations are required to elucidate the underlying mechanisms in an *in vivo* context [68].

PIs may affect insulin sensitivity by various mechanisms such as insulin receptor substrate-1 (IRS-1) phosphorylation and subsequent glucose uptake from adipocytes. Lipodystrophy may also result in β-cell dysfunction and is associated with impaired feedback of insulin on β-cells [98]. PIs induce IR by reducing insulin-mediated glucose uptake by GLUT4, identified as a direct target of PIs. The direct effect on GLUT4 was supported by demonstrating blockage of glucose transport in non-insulin sensitive calls transfected with GLUT4 [89]. Initial observations of GLUT4 targeting were noted with indinavir use which inhibited insulin-stimulated glucose uptake in 3T3-L1 adipocytes but did not affect early insulin signalling events or the translocation of intracellular GLUT1 or GLUT4 transporter to the cell surface [91]. Indinavir showed a 45% intrinsic inhibition of GLUT4 transport activity in a dose-dependent manner. Similar effects on glucose transport were demonstrated by other PIs and may be responsible for iatrogenic complications seen in these patients [94]. GLUT4 intrinsic transport activity is potently decreased by PIs, without substantially affecting early insulin signalling or GLUT4 translocation [94].

Behrens et al. confirmed in their study that there is a complex alteration in glucose and insulin metabolism in patients on HAART [85]. It was shown that patients on PIs were associated with a higher rate of diabetes mellitus, impaired glucose tolerance and early secretion of pro insulin. There were significantly higher rates of disproportional secretion of pro insulin and delayed insulin secretion in hyperlipidaemic patients on PIs compared to normolipidaemic patients on PIs [85].

NRTIs have also been linked to alterations in glucose tolerance mediated by

mitochondrial toxicity [95, 92]. Munshi et al. assessed the contribution of didanosine to the development of diabetes and hyperosmolar nonketotic diabetic syndrome [95]. Hyperglycaemia was reported in 82 patients and it was concluded that didanosine potentially causes diabetes and hyperosmolar nonketotic diabetic syndrome [95].

K Samaras et al. [30] evaluated the incidence and prevalence of metabolic syndrome and subsequent diagnosis of cardiovascular disease and type 2 diabetes in HIV-infected adults over a 3-year period. During this period there was a 5% incidence of type 2 diabetes and those who met the criteria for metabolic syndrome at baseline showed an increase risk of developing Type 2 Diabetes Mellitus (T2DM). There was also an increased risk of T2DM in patients who progressed to metabolic syndrome during their follow-up [30].

1.8.4 **Elevated blood pressure**

Atherogenic effects of certain antiretroviral drugs result in the thickening of the arterial wall thus causing hypertension and cardiovascular disease in these patients [96]. PI's may promote the formation of atherosclerotic lesions by increasing CD36-dependent cholesterol ester accumulation in macrophages, a scavenger-receptor pathway that is thought to mediate the formation of atherosclerotic lesions [70]. Prospective studies of hypertension in patients on PIs and NRTIs show no significant increases in blood pressure [43]. However, upon examination of individual medication, lopinavir/ritonavir was significantly associated with systolic elevation in blood pressure. Systolic hypertension is an important predictor of cardiovascular disease and raises concern in patients on a lopinavir/ritonavir-containing regimen [97].
In Malaysia, a cross sectional study showed no significant link between HAART and hypertension [96]. Regimens including zidovudine, stavudine and PIs had no statistical significance of hypertension. Patients exhibiting a hypertensive state were more likely as a result of lifestyle, age and higher BMI/ waist circumference [96].

Reports suggest that HAART is associated with an increase in both peripheral and coronary arterial diseases [27]. The presence of hypertension is stronger in patients on PIs or NNRTIs than those who are treatment naïve [70]. At this stage, NRTIs and PIs cannot be linked to hypertension [97].

It is hoped that these metabolic abnormalities that lead to the metabolic syndrome will be minimal with FDC use. The study sets out to ascertain whether it is a more favourable long-term treatment option. It is hypothesised that FDC use will have a decreased prevalence of metabolic syndrome and patients will exhibit more favourable clinical markers.

1.9 **Aim**

To investigate the incidence and prevalence of metabolic syndrome in HIV patients on HAART triple therapy compared to fixed-dose combination.

1.10 **Objectives**

1. To determine the incidence and prevalence of metabolic syndrome in patients on HAART
2. To investigate the impact of a single pill compared to triple therapy on the incidence and prevalence of metabolic syndrome in patients on HAART.

CHAPTER TWO: MATERIALS AND METHODS

2.1 **Ethical Approval**

Application for ethical approval was made to the Biomedical Research and Ethics Committee of the University of KwaZulu Natal on 31 March 2016. Provisional ethical approval was granted on 08 June 2016 with minor queries. Once all queries were addressed, full ethical approval was granted on 11 July 2016. The BREC reference number assigned to the aforementioned application is BE227/16.

2.2 **Study**

The study was undertaken as a retrospective chart review, with patients that fulfil the criteria being randomly selected. Selected patients were all pre-existing HAART patients on treatment for the duration of a minimum of 3 years. Relevant data was extracted from patient files and collected in the form of a questionnaire. The researcher filled out the questionnaires without patient interaction as access was only made to the patient files due to the study design. Data collection went as far as back as 3 years starting from 2013 (the roll-out of the FDC programme). Clinical data was collected over 3 years with one value being recorded per year, as patients have 6-monthly clinic visits.

2.3 **Location**

The study was conducted at Addington Hospital, a National Department of Health facility in the central Durban area. A gatekeeper letter was sent to the CEO, Dr. M Ndlangisa, and permission was granted on 9 May 2016. Further permission was requested and granted from Dr. J Bayat to use the Ikusasa ARV Clinic.

2.4 **Sample Size**

Assuming that the prevalence of metabolic syndrome in patients on ARV is 10% and using a power of 80% and a confidence level of 95%, a sample size of 196 per group, was calculated to detect a difference prevalence of 10% between patients on a fixed-dose combination and a triple therapy regimen. The sample size calculation formula used was

$$n = \frac{(z_{\alpha/2} + z_{\beta})^2 (p_1(1-p_1) + p_2(1-p_2))}{(p_1 - p_2)^2}$$

2.5 **Inclusion Criteria**

- Adult patients (patients above the age of 18 years),
- HIV infected patients who were on HAART for at least 3 years.
- Males and females
- All races were included
- HAART regimens included variations of triple therapy regimens that include NRTIs, NNRTIs, PIs (depending on patient specific factors and tolerability)
- A single pill, which contains efavirenz/tenofovir/emtricitabine.

2.6 **Exclusion Criteria**

- Patients under the age of 18 years
- Pregnancy

2.7 **Criteria for MetS**

The criteria for metabolic syndrome will be in accordance with that of the Joint Interim Statement: Any 3 of the following:
Waist circumference: Men- 94 cm Women 80 cm OR Body mass index ≥ 30.00 kg/m^2
Raised triglycerides ≥ 1.70 mmol/L OR drug treatment for elevated triglycerides
Reduced HDL-c < 1.0mmol/L in males and < 1.30 mmol/L in females
Elevated blood pressure ≥ 130/85 mmHg OR antihypertensive drug treatment in a patient with a history of hypertension
Raised fasting plasma glucose ≥ 5.55 mmol/L OR random glucose ≥ 7.80 mmol/L OR drug treatment of elevated glucose.

2.8 **Data Capture**

Data was captured using Microsoft Excel for Mac version 14.2.0 and sent to the statistician, Ms. Y Balakrishna (Medical Research Council) to be analysed.

2.9 **Analysis**

Analysis was done using STATA version 14 (StataCorp., College Station, TX, USA). Data was described using means (standard deviation) and frequencies and percentages. Associations between categorical variables were tested using either Pearson's chi square test or Fisher's exact test, where applicable. Differences in continuous variables between groups were tested using oneway ANOVA. Univariable and multivariable logistic regression was carried out to determine significant predictors of metabolic syndrome in patients. Results were significant for $p < 0.05$. Atherogenic Index of Plasma was calculated using the following formula: AIP= $\log_{10}$ (TG/HDL-c) [111]. AIP 1, 2 and 3 were calculated from plasma lipid determinations done at 12 months intervals for all patients with the necessary available information.

CHAPTER THREE: RESULTS

Of the 350 (n) patients surveyed, all met the inclusion criteria. The majority were female-62.6% and 37.4% males, with a collective overall mean age of 41.4 years. Group A comprised of the FDC regimen and group B the triple therapy (TT) regimen. From the information available there were no pregnant women or family history of chronic conditions. There was insufficient evidence as to whether patients were smokers or not and therefore this factor could not be included. A total of 53.3% were employed.

3.1 **Age**

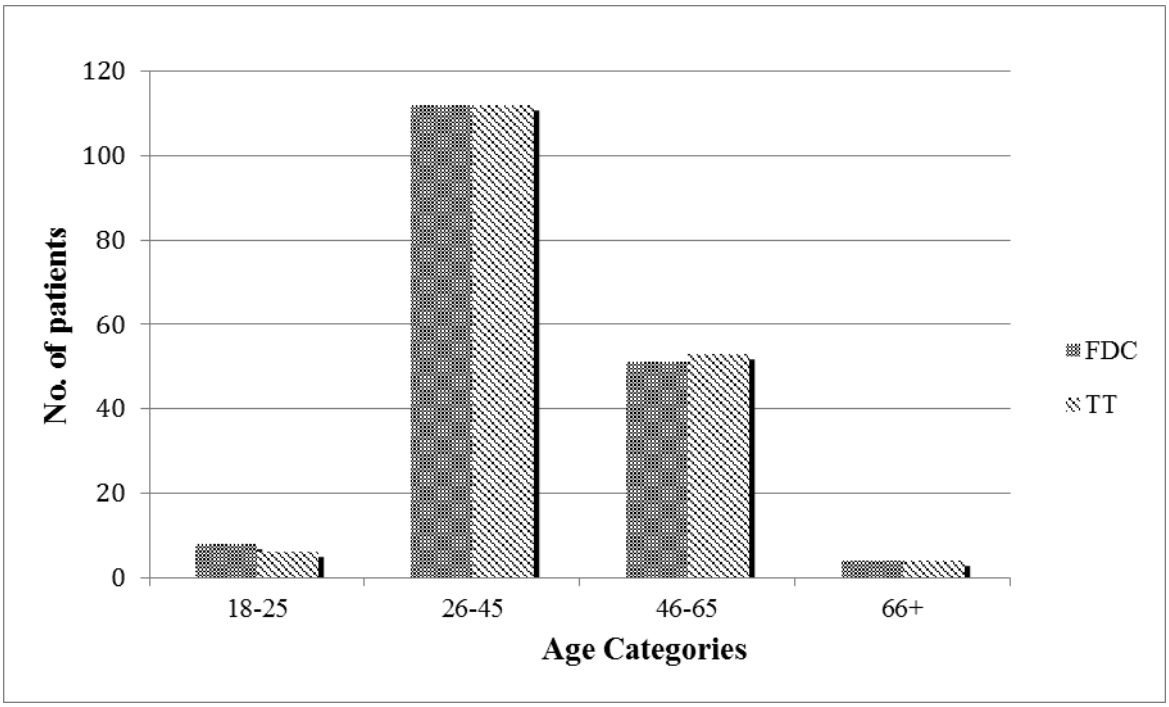

Figure 1: Age distribution among patients on FDC and TT.

The highest patient group was within the age range of 26-45 years (64%) and the lowest above 66 years of age (2.3%). The mean age was calculated to be 41.4 ± 10.92 years. The mean age calculated in both A and B was 40.51 ± 11.11 and 42.33 ± 10.67, respectively. There was no association between HAART regimen and age category ($p = 0.955$) and no significant difference between the mean ages ($p = 0.119$).

3.2 **Gender**

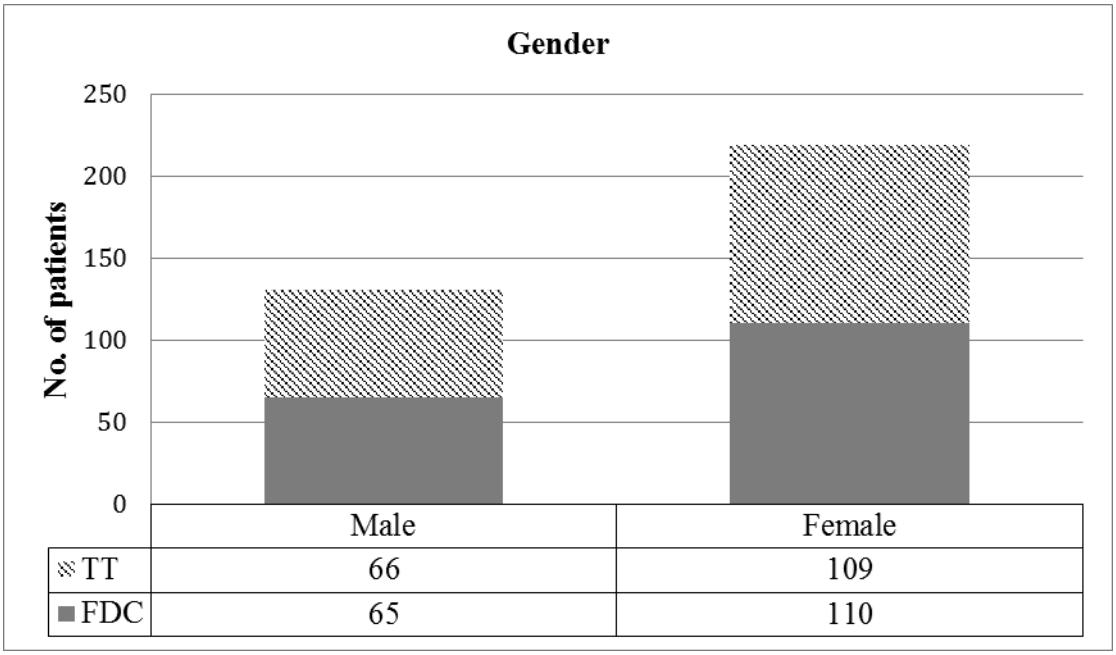

Figure 2: Gender distribution among patients on FDC and TT.

Figure 2 shows the numbers of males and females per group. There was no significant association found between the gender of the patient and the HAART regimen ($p = 0.912$).

3.3 **Ethnicity**

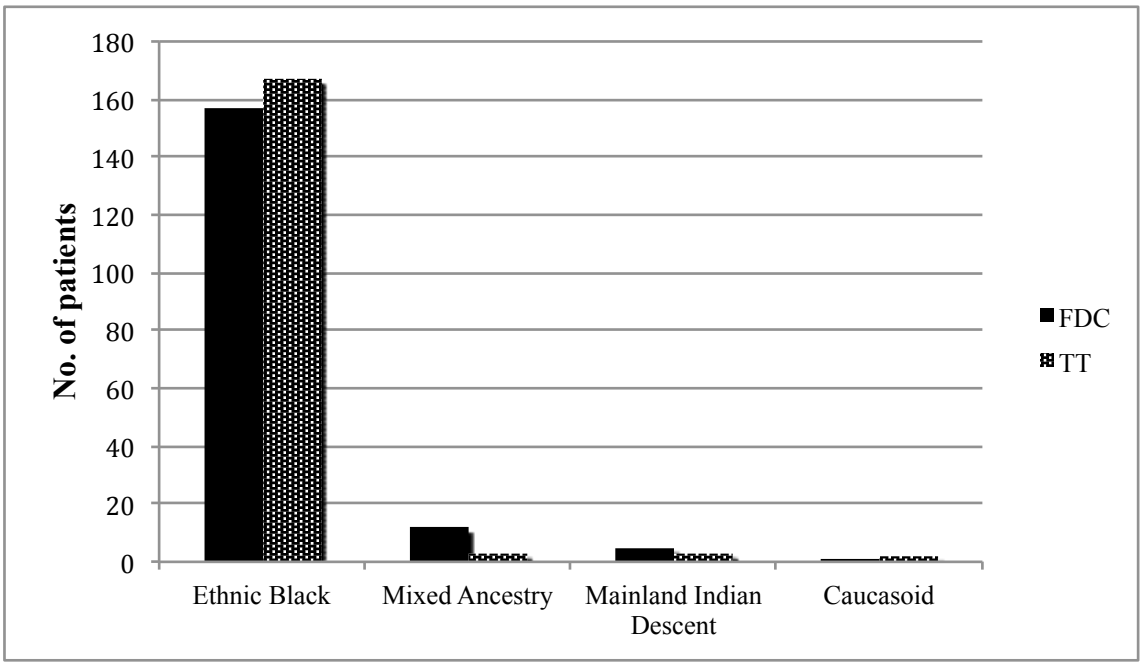

Figure 3: Ethnic profiling of patients on FDC and TT.

The vast majority of patients were Ethnic Black (92.6%), followed by Mixed Ancestry (4.3%), Mainland Indian Descent (MID) (2.3%) and Caucasoid (0.9%). There was no significant association between HAART regimen and ethnicity ($p = 0.088$).

3.4 **Regimen**

An equal number of patients were in both group A and B (n=175). All patients within group A were on the EFV/FTC/TDF fixed-dose combination. Group B comprised of various triple therapy regimens, shown in Figure 4.

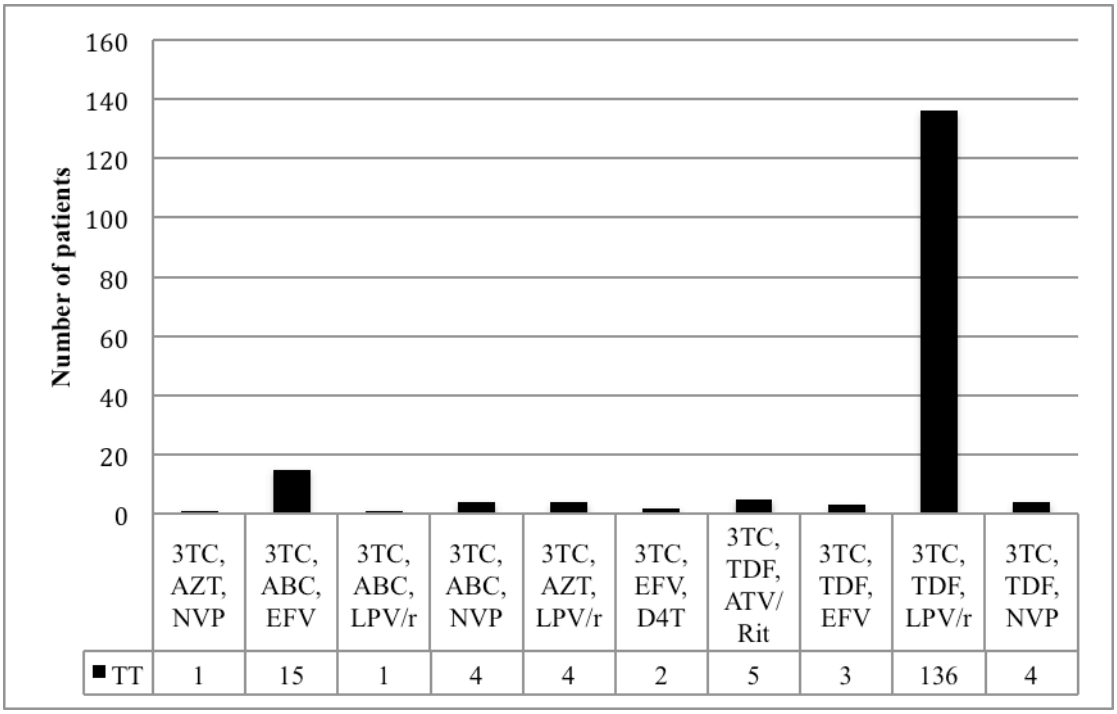

Figure 4: Number of patients on variations of triple therapy regimens.

A total of 146 patients were on a PI-based regimen. The remainder (n = 29) were on a regimen consisting of 2 NRTIs + 1 NNRTI. The most common PI-based regimen included LPV/r: 77.7% in combination with 3TC and TDF. The variations in regimens included:

Lamivudine (3TC), Zidovudine (AZT), Nevirapine (NVP)

Lamivudine, Abacavir (ABC), Efavirenz (EFV)

Lamivudine, Abacavir, Lopinavir/ Ritonavir (LPV/r)

Lamivudine, Abacavir, Nevirapine

Lamivudine, Zidovudine, Lopinavir/ Ritonavir

Lamivudine, Efavirenz, Stavudine (d4T)

Lamivudine, Tenofovir (TDF), Atazanavir/ Ritonavir (ATV/r)

Lamivudine, Tenofovir Efavirenz

Lamivudine, Tenofovir, Lopinavir/ Ritonavir

Lamivudine, Tenofovir, Nevirapine

3.5 **Comorbidities**

A total of 82 patients had comorbidities, 36 of which were in the FDC group and 46 in TT group. There was no significant association found between HAART regimen and the generalised presence of comorbidities (p = 0.207).

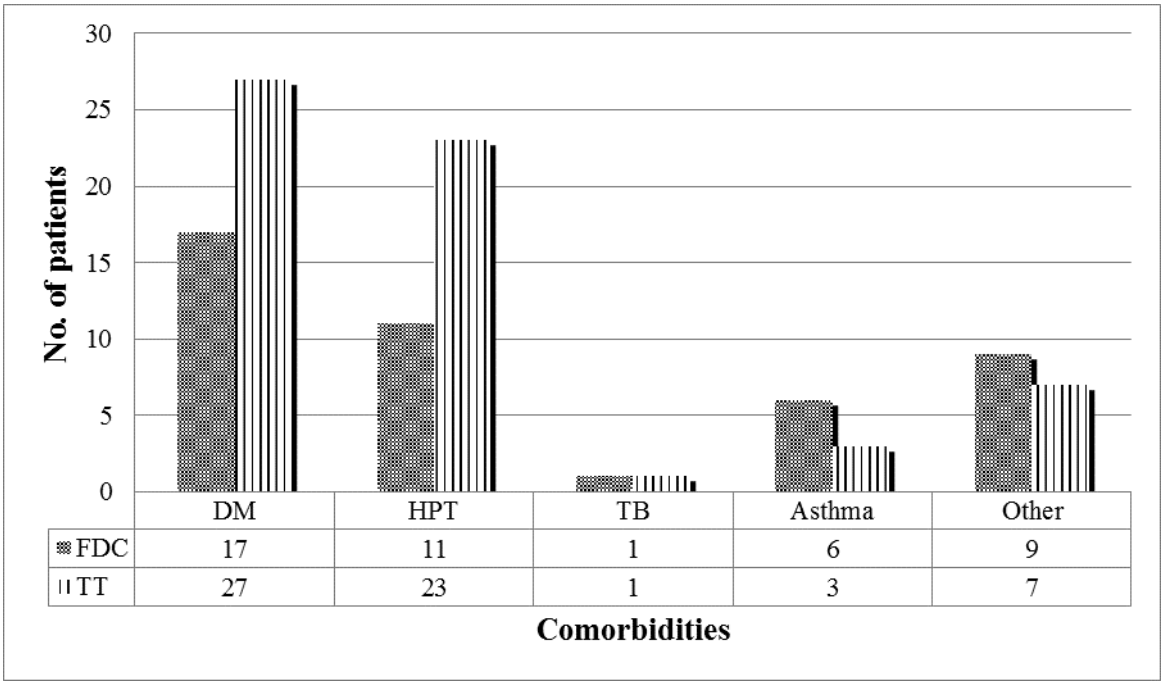

Figure 5: Distribution of patients with comorbidities.

(DM = Diabetes Mellitus, HPT = Hypertension, TB = Tuberculosis)

However, upon examining individual comorbidities, hypertension was found to be significantly associated with HAART regimen (p = 0.033). Group B had a total of 13.1% hypertensive patients and 6.3% in group A. Of those in group B with comorbidities, 17 of 46 patients had diabetes alone, 12 patients had hypertension alone and those that had a combination of diabetes and hypertension made up 15.6% of the total group with comorbidities.

The “other” category comprised of: epilepsy, psychosis, hyperthyroidism, acute renal failure, breast cancer, bipolar disorder, peripheral neuropathy and arthritis.

3.6 **Current medication**

A total of 86 patients were on additional medication, most of whom were on antihyperglycaemic agents (12.3%) and antihypertensive agents (9.7%). Patients on lipid-lowering therapy (statins) made up 4.6% of the study population and were not significantly associated with HAART regimen (p = 0.306). Patients on "other" medication consisted of: beta-agonist inhalers for the treatment of asthma, antiepileptic agents, antipsychotic agents, thyroxine, anti-inflammatories and chemotherapeutic agents.

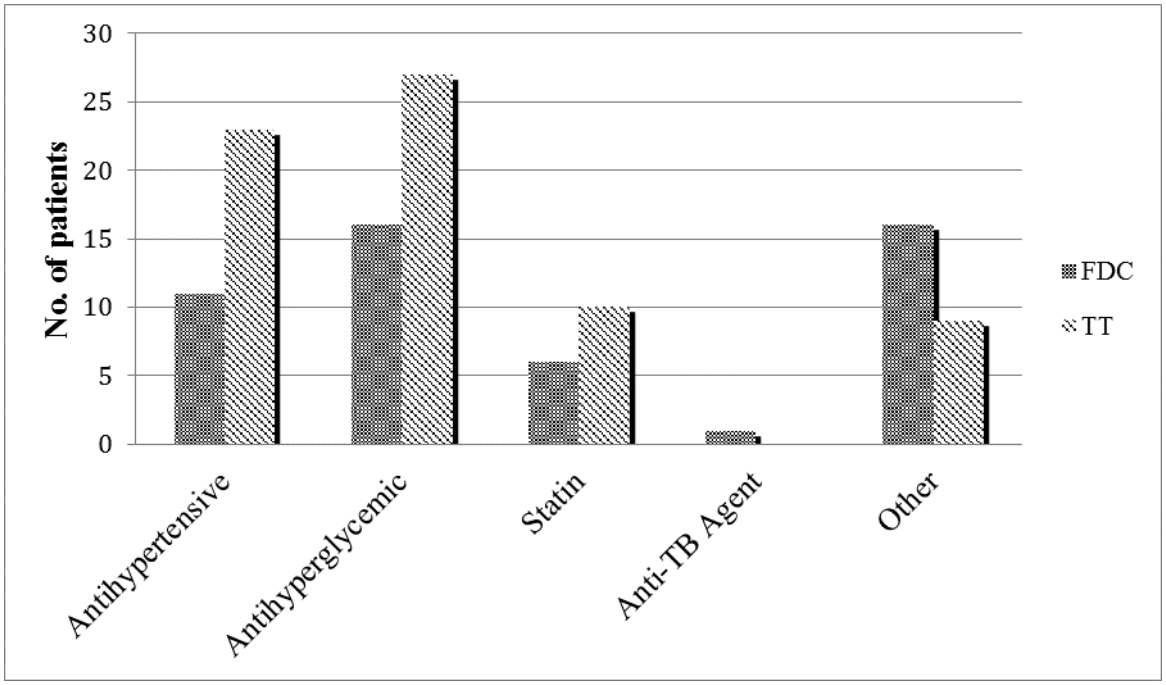

Figure 6: Number of patients on additional medication.

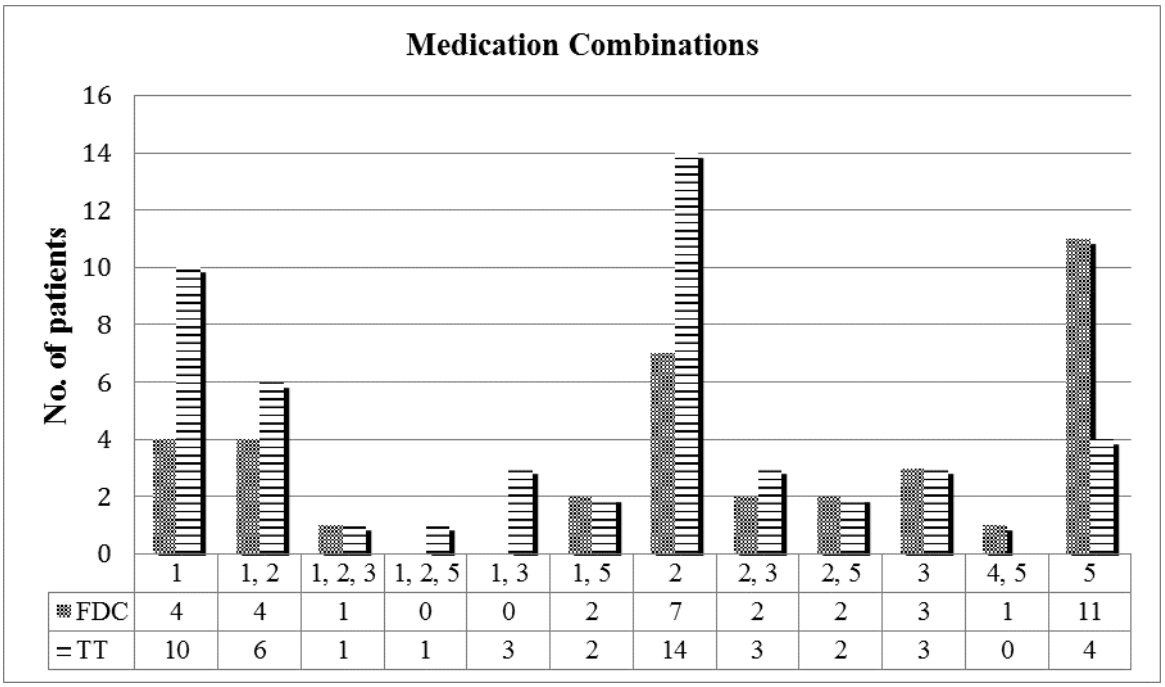

Figure 7: Current medication combinations

1. Antihypertensive agent
2. Antihyperglycaemic agent
3. Statin
4. Anti-tuberculosis agent and
5. Other

A higher number of patients were found to be on a combination of medication in group B. The most common medication included antihypertensive agents and antihyperglycaemic agents.

3.7 Mean Values of Clinical Markers

Table 6: Mean values of clinical markers with standard deviation

	FDC	N	TT	N
Random blood glucose (mmol/L)	5.45 ± 1.99	175	6.06 ± 2.13	175
Total fasting cholesterol (mmol/L)	4.34 ± 0.95	17	4.81 ± 1.40	152
HDL- cholesterol (mmol/L)	1.31 ± 0.51	17	1.25 ± 0.37	152
LDL- cholesterol (mmol/L)	2.23 ± 0.78	17	2.76 ± 1.03	148
Triglycerides (mmol/L)	1.52 ± 0.79	17	1.75 ± 1.29	151
BMI (kg/m^2)	27.04 ± 5.74	174	27.33 ± 4.82	168
Systolic Blood pressure (mmHg)	118.27 ± 10.39	175	123.39 ± 10.95	173
Diastolic Blood pressure (mmHg)	75.07 ± 7.56	175	78.93 ± 6.87	173

N= number of patients

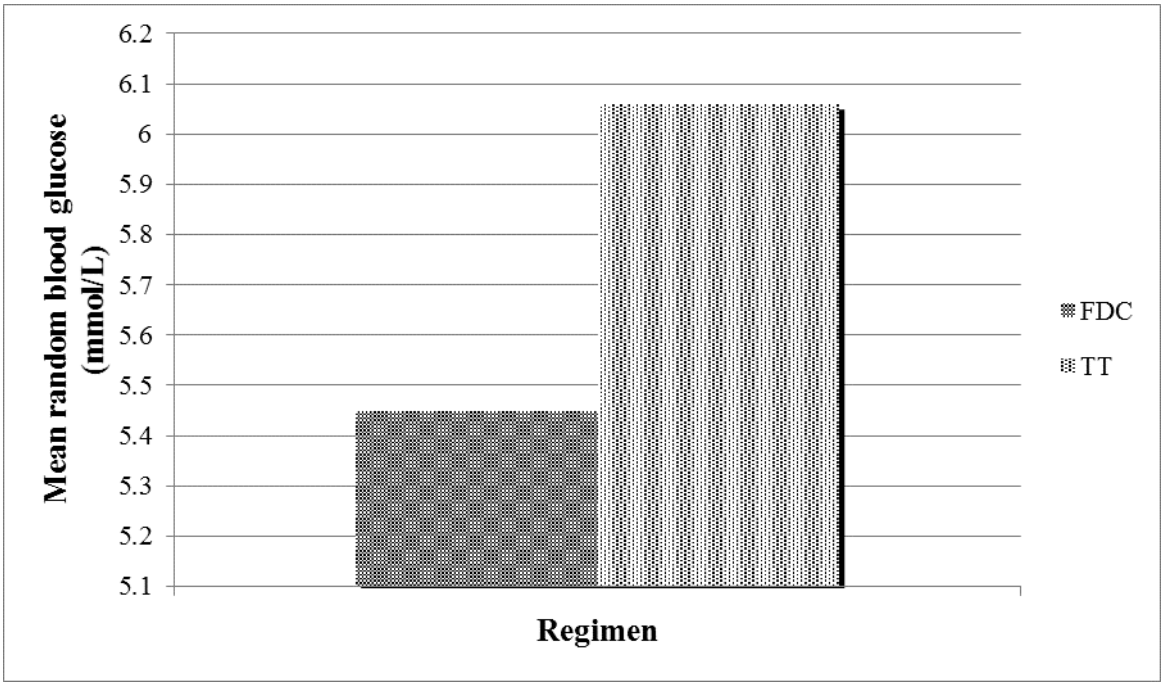

Figure 8: Mean random blood glucose readings among FDC and TT groups.

Both groups had glucose readings for all patients (n =175 per group). The mean glucose in group A was 5.45 mmol/L ± 1.99 and 6.06 mmol/L ± 2.13 in group B.

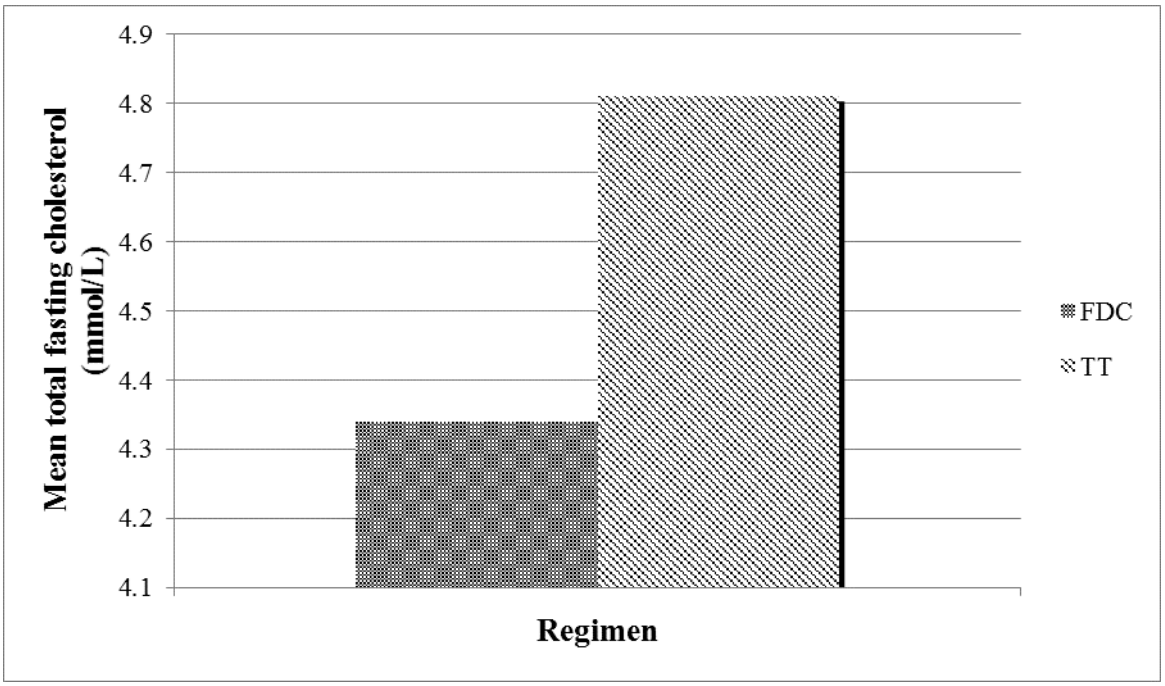

Figure 9: Mean total fasting cholesterol readings among FDC and TT groups.

Group A had a mean cholesterol value of 4.34 mmol/L ± 0.95 among 17 patients. Group B had a mean cholesterol value of 4.81 mmol/L ± 1.40 among 152 patients. Differences in mean total fasting cholesterol levels between group A and B were not statistically significant ($p = 0.18$).

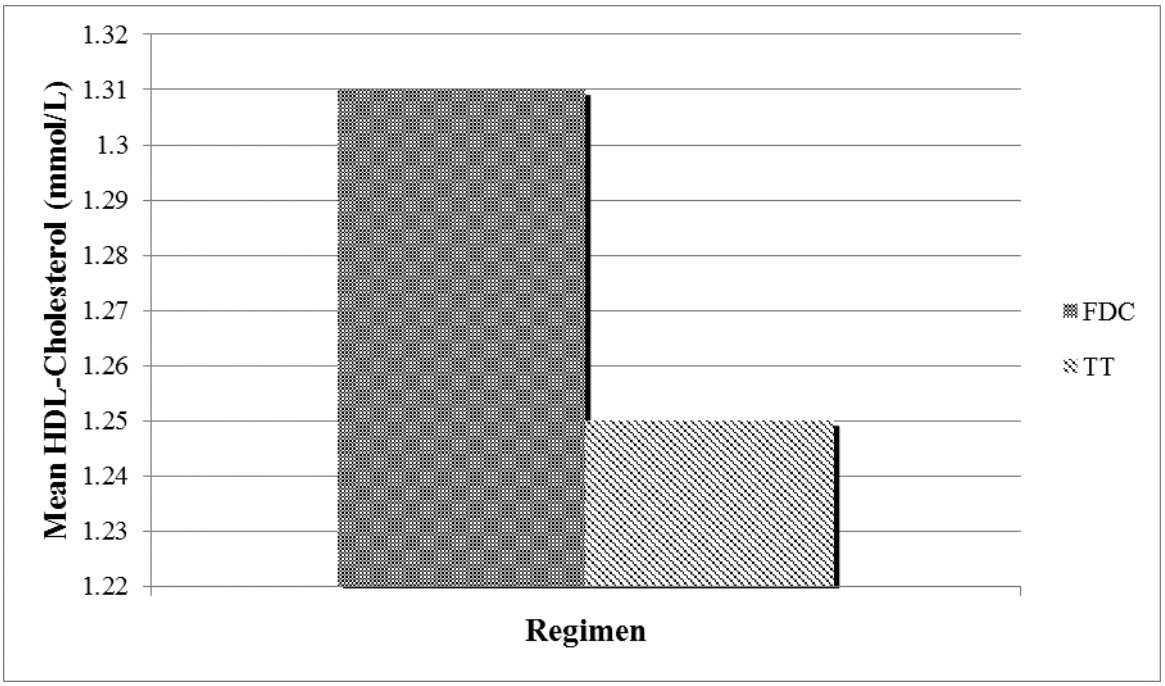

Figure 10: Mean High-Density Lipoprotein cholesterol (HDL-c) among FDC and TT groups.

The mean HDL-cholesterol was higher in group A, 1.31 mmol/L ± 0.51 among 17 patients, compared to group B, 1.25 mmol/L ± 0.37 among 152 patients. Differences in mean HDL-c levels between group A and B were not statistically significant ($p = 0.55$).

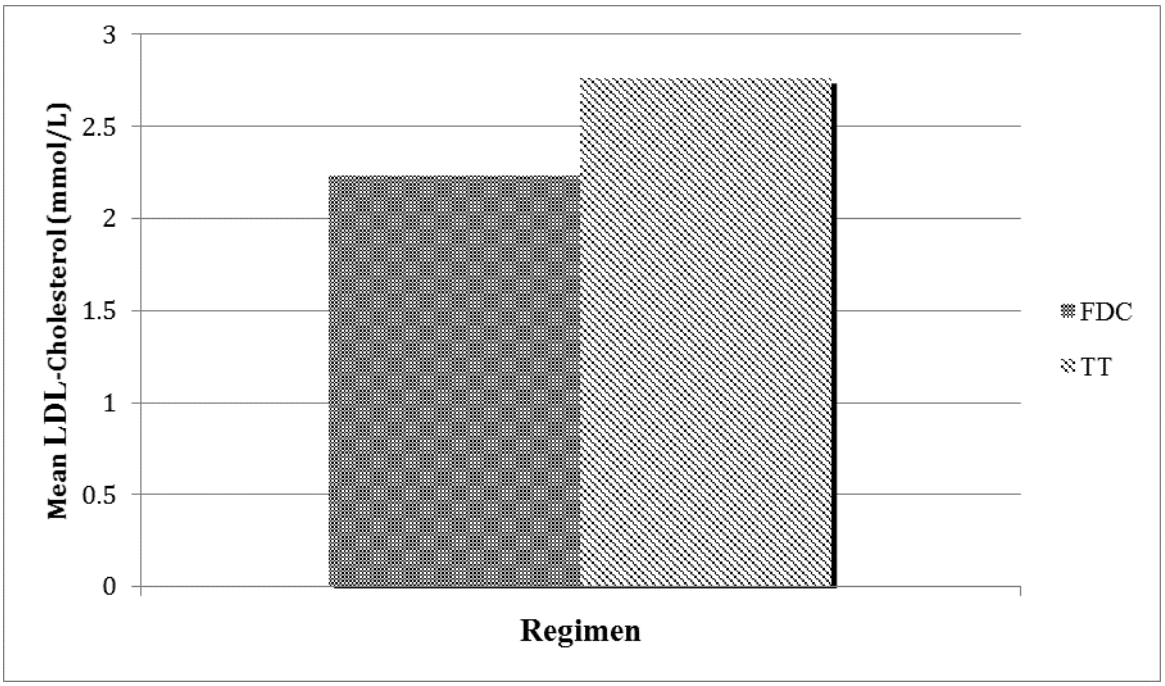

Figure 11: Mean Low-Density Lipoprotein cholesterol (LDL-c) among FDC and TT groups.

The mean LDL-c was higher in group B, 2.76 mmol/L ± 1.03 among 148 patients. Mean LDL-c was 2.23 mmol/L ± 0.78, among 17 patients in group A. 4 of the 152 patients with lipid profiles had LDL-c levels that were too high to calculate.

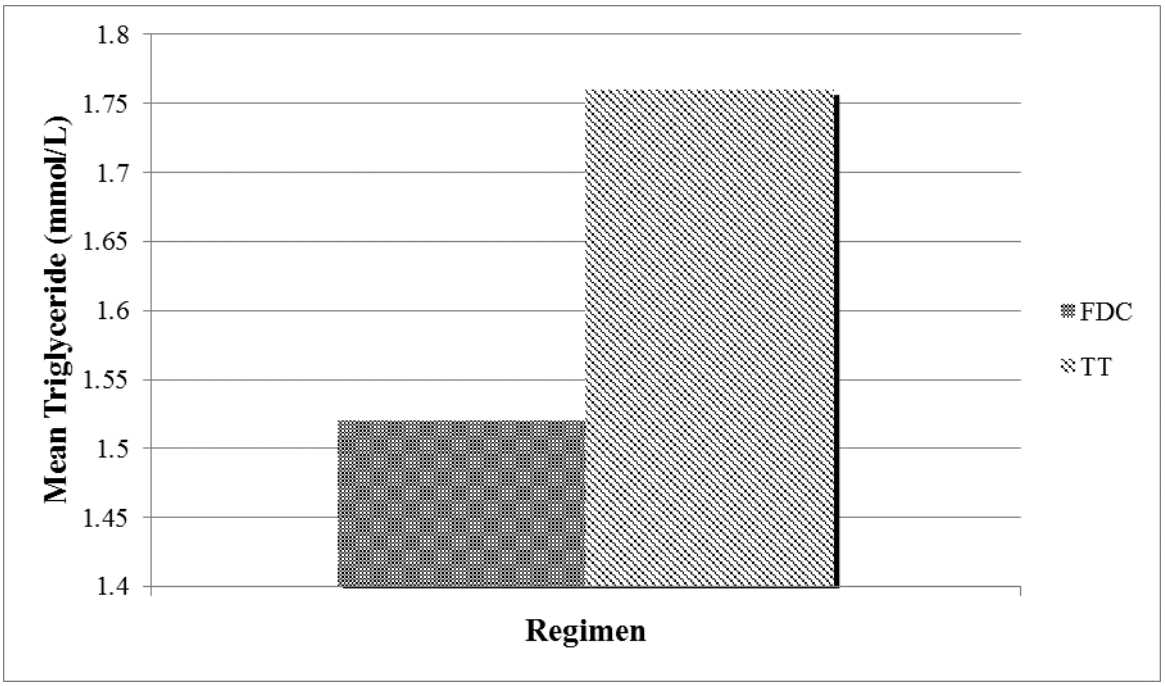

Figure 12: Mean triglyceride readings among FDC and TT groups.

The mean triglyceride readings were 1.52 mmol/L ± 0.79 in group A among 17 patients and 1.75 mmol/L ± 1.29 in group B among 151 patients. Differences in mean triglyceride levels between group A and B were not statistically significant ($p = 0.47$).

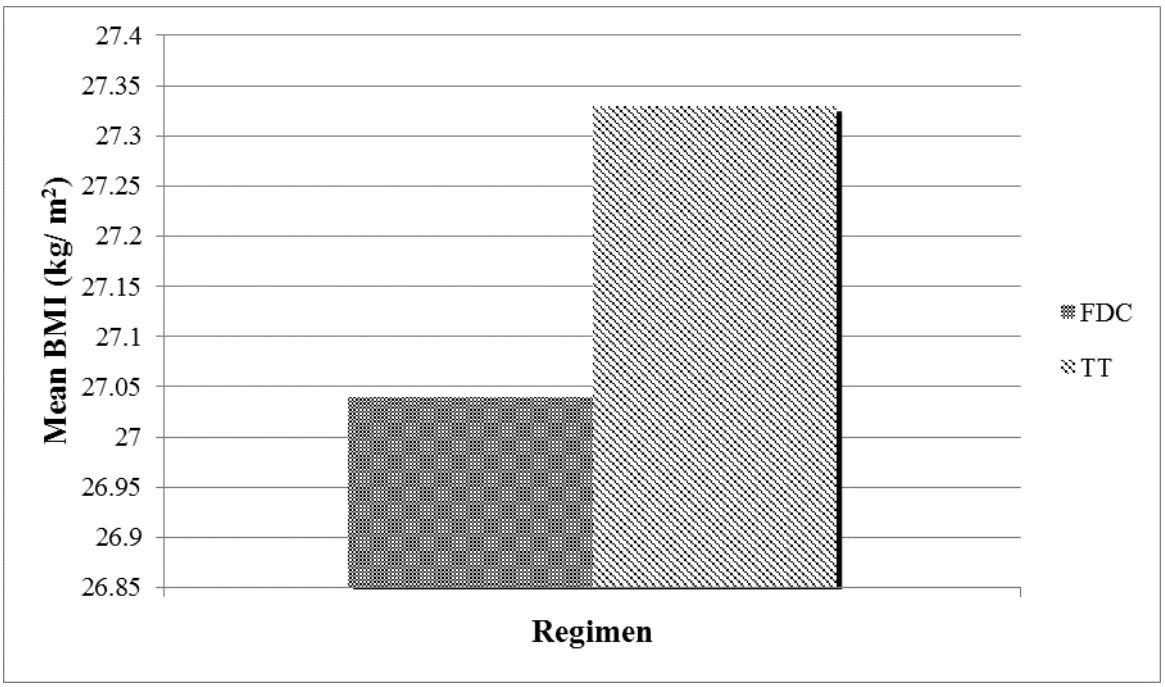

Figure 13: Mean Body Mass Index (BMI) among FDC and TT groups.

BMI was defined using the WHO criteria, where patients are classified as underweight (< 18.50 kg/m^2), normal (18.5-24.99 kg/m^2) overweight (≥ 25.00 kg/m^2) and obese (≥ 30.00 kg/m^2). [49]

The mean body mass index (BMI) in group A was 27.04 kg/m^2 ± 5.74 and 27.33 kg/m^2 ± 4.82 in group B. Mean values of BMI between group A and B were not statistically different or significant ($p = 0.61$).

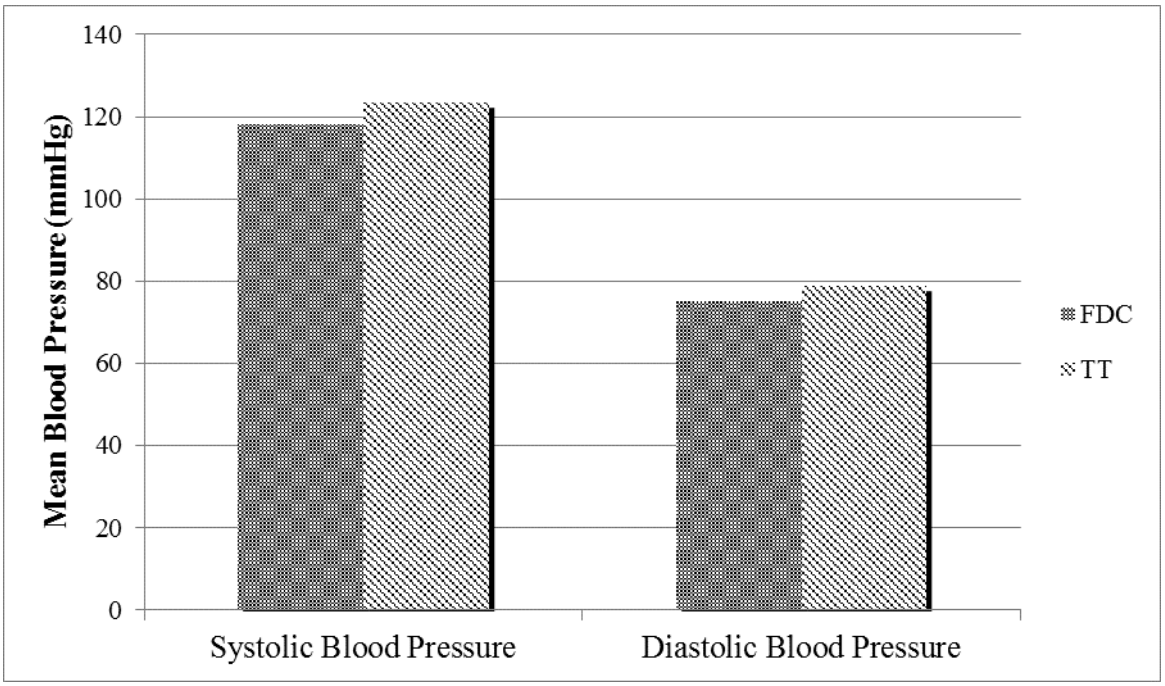

Figure 14: Mean systolic and diastolic blood pressure among FDC and TT groups.

Mean blood pressure readings were taken from 175 patients in both groups. The mean systolic and diastolic blood pressure (BP) readings were both higher in the TT group. Group A had a mean systolic BP of 118.27 mmHg ± 10.39 and diastolic BP of 75.07 mmHg ± 7.56. Mean systolic and diastolic BP in group B were 123.39 mmHg ± 10.95 and 78.93 mmHg ± 6.87, respectively. Mean systolic and mean diastolic blood pressures were positively significantly associated with HAART regimen ($p < 0.001$).

3.8 Prevalence of Metabolic Syndrome (MetS)

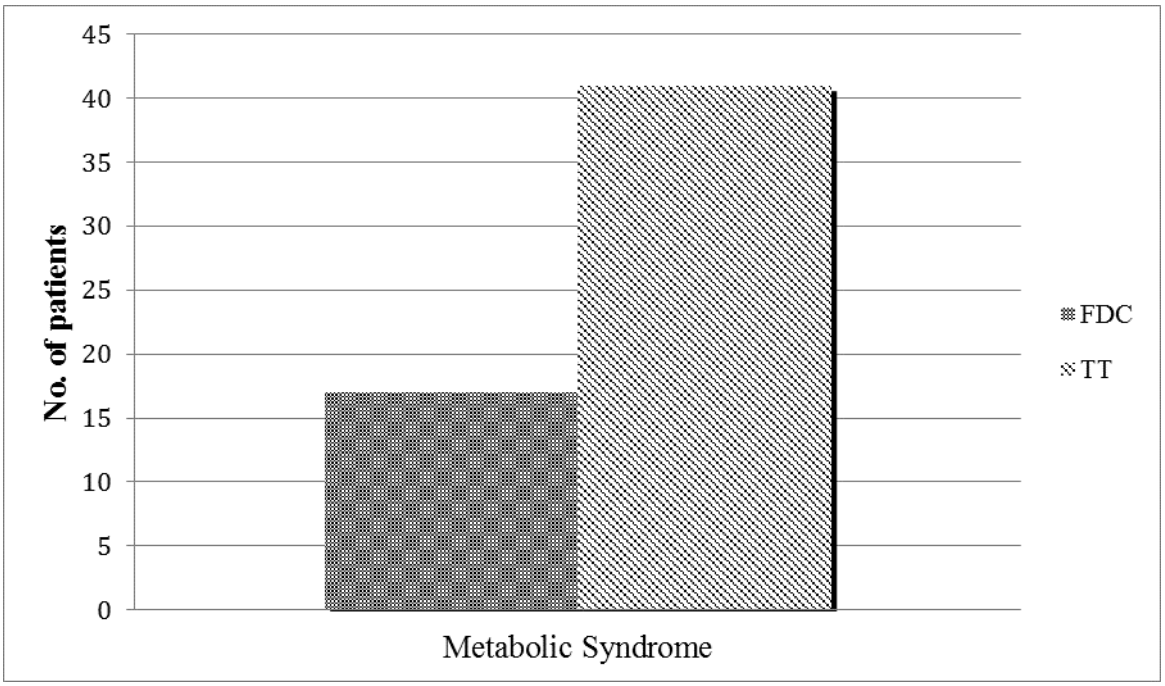

Figure 15: Prevalence of metabolic syndrome (MetS).

There was a 16.6% overall prevalence of metabolic syndrome. The prevalence was found to be higher with the triple therapy regimen (11.7%) compared to the FDC regimen (4.9%). Odds ratio: 2.84 (confidence interval 1.54-5.24).

3.9 Individual Factors compared to MetS

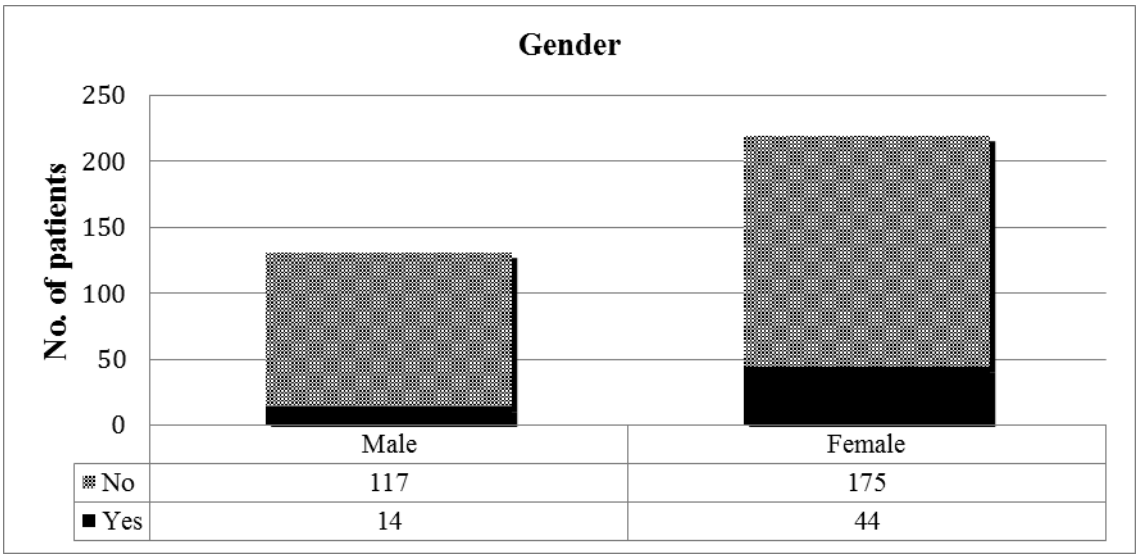

Figure 16: Prevalence of MetS in males and females.

From the results obtained, there was a higher prevalence of MetS in females compared to males. There is a 1.26 times increased likelihood of MetS occurring in a female (p = 0.022).

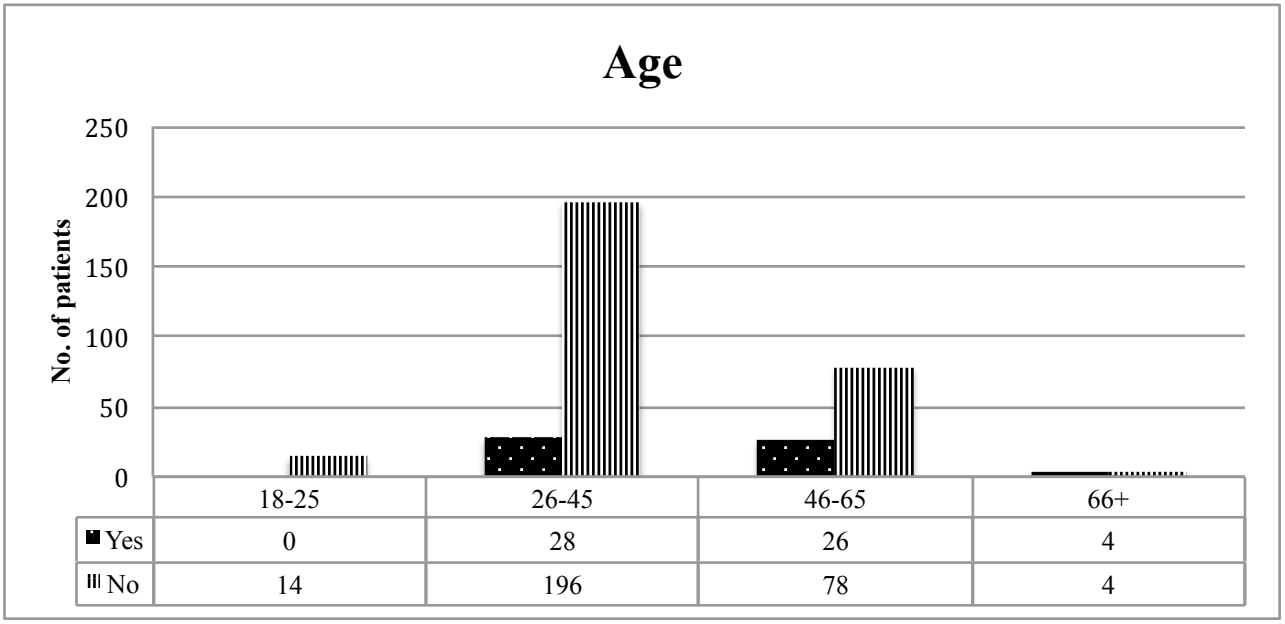

Figure 17: Prevalence of MetS among different age groups.

Metabolic syndrome most commonly occurred in patients in age groups 26-45 (48.3%) and 46-65 (44.8%). Age was significantly associated with MetS (p = 0.001).

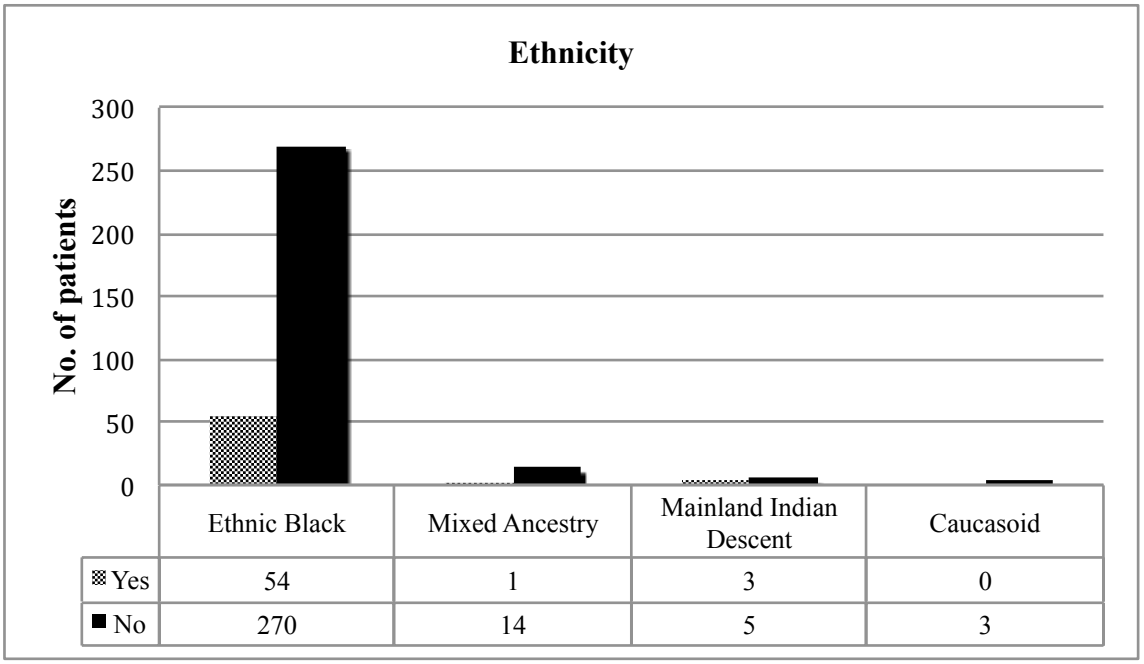

Figure 18: Prevalence of MetS among different ethnicities.

Although the patient number for the MID group was low, 3 out of the 8 patients were at risk for MetS, the highest prevalence per ethnicity group. It is to be noted that of the 8 MID patients, 5 had comorbidities. Of the total of 15.4% had MetS in the Ethnic Black group.

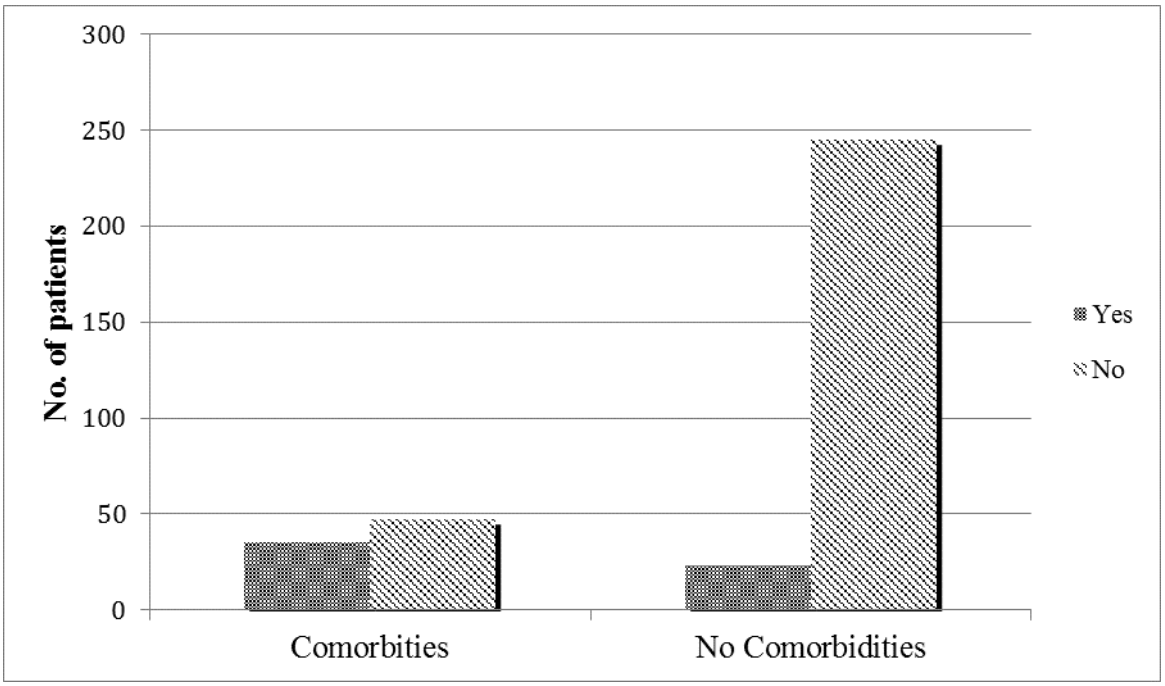

Figure 19: Prevalence of MetS in the presence of comorbidities.

A significant percentage of patients (60.3%) with comorbidities had metabolic syndrome. Of the group with no known comorbidities, 8.6% had MetS. Presence of diabetes alone had the highest prevalence (44.1%), whilst the combined presence of diabetes and hypertension had a prevalence of 29.4%. However, more patients were at risk for MetS within the group of patients with hypertension and diabetes (83.3%) as opposed to diabetes alone (53.6%).

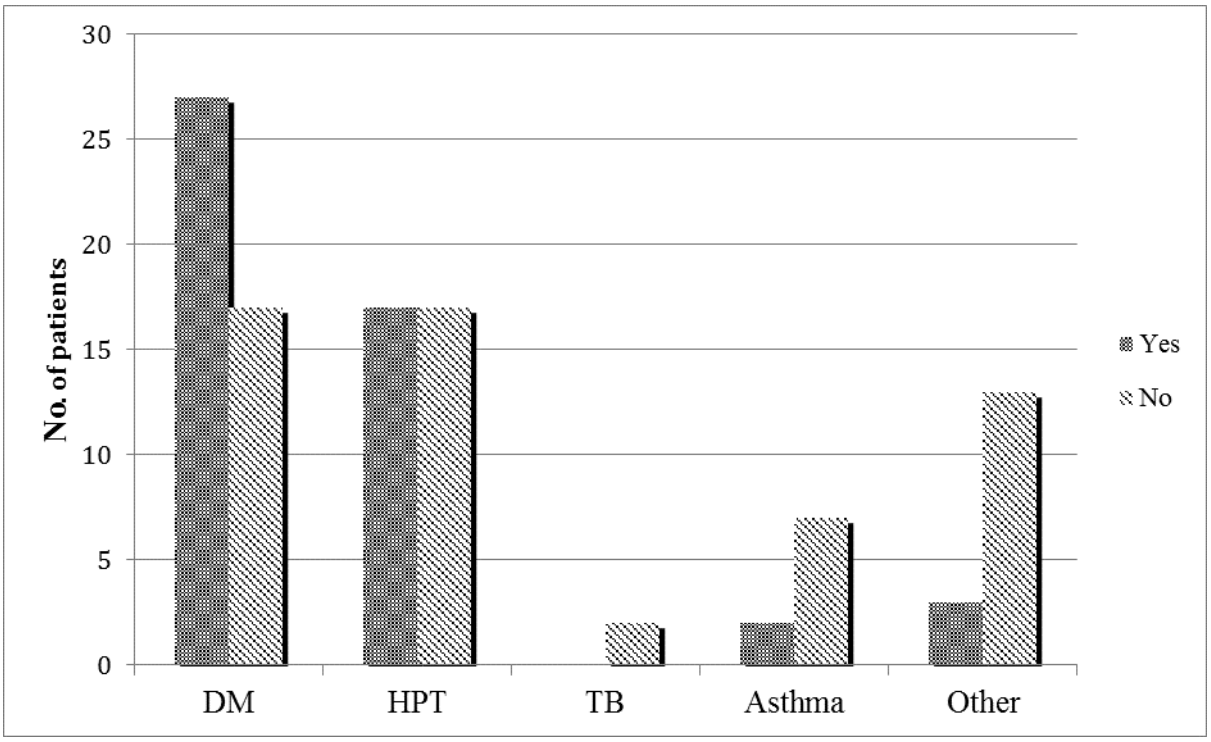

Figure 20: Prevalence of MetS among individual comorbidities.

The presence of MetS is almost 1.5 times more in diabetic patients than those without. There is an equal distribution of prevalence in patients with and without hypertension.

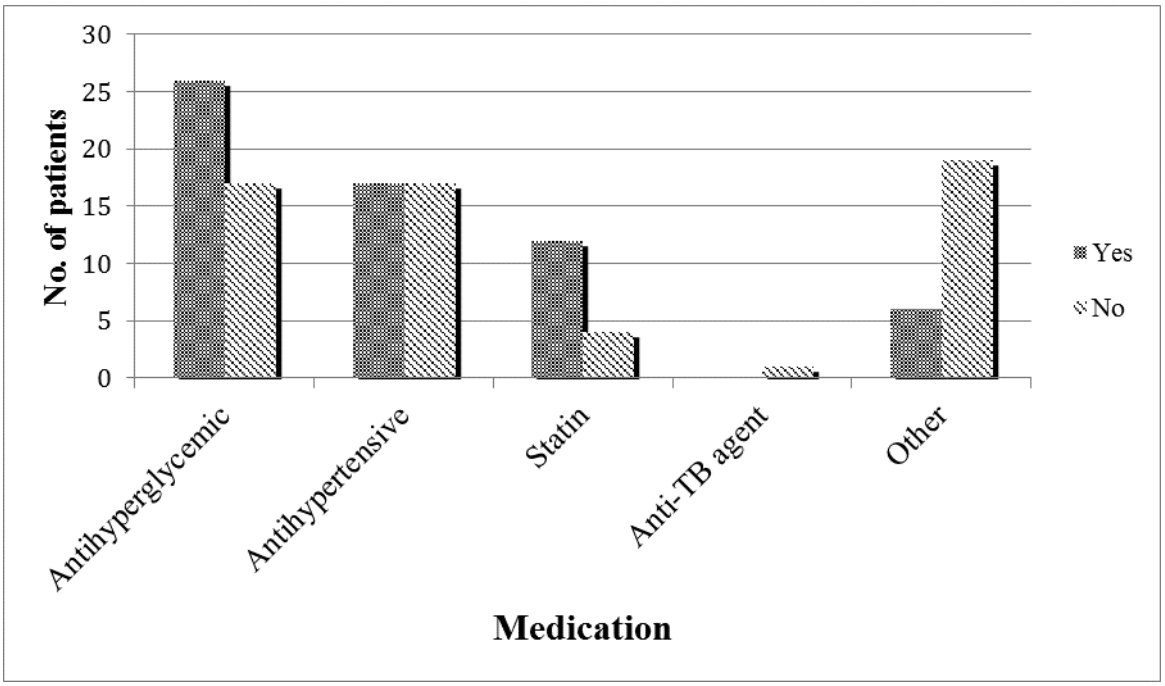

Figure 21: Prevalence of MetS with concomitant medication.

The highest prevalence of MetS is in the group on antihyperglycaemic agents (60.5%) and constitutes as 44.8% of the total number of patients with MetS. There is a 50% split in the number of patients on antihypertensive agents with MetS. Patients on antihypertensive agents constitute 16.6% of all patients with MetS.

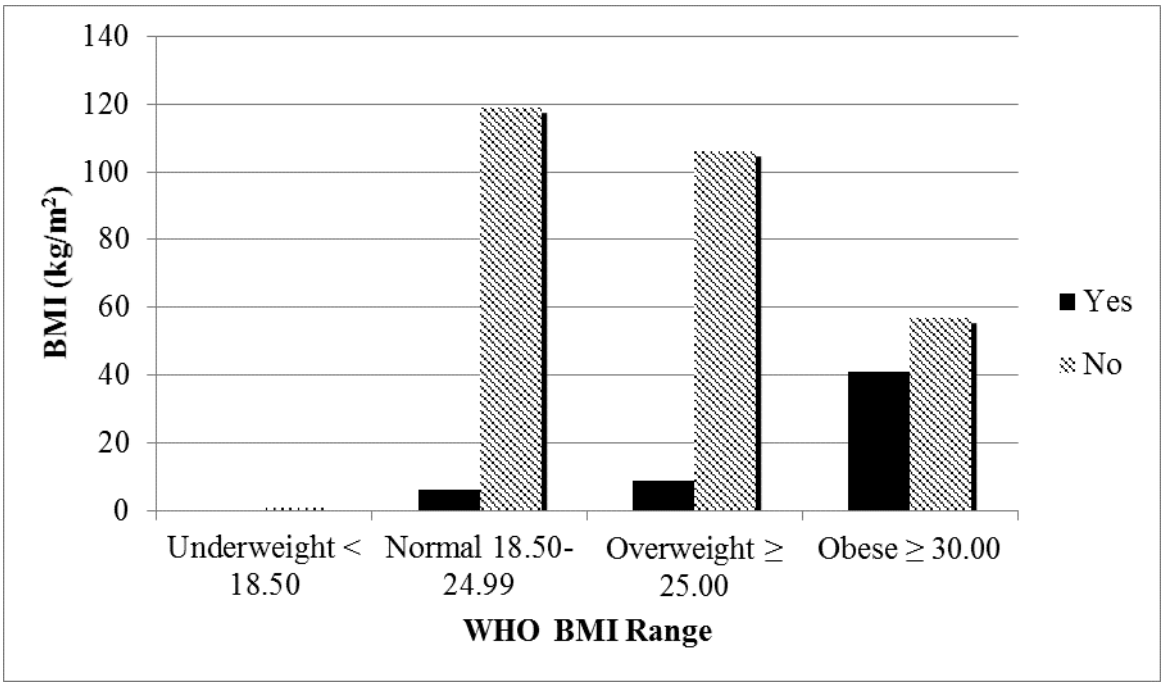

Figure 22: Prevalence of MetS in WHO categories [49] of BMI.

Prevalence of MetS gradually increases as BMI increases. The highest incidence of MetS was in patients with a BMI ≥ 30.00 kg/m^2 (73.2%). There is a significant relationship between BMI and the incidence of MetS ($p < 0.001$). The odds ratio (OR) for every BMI value increase from the mean is 1.28 (Confidence Interval: 1.54-5.24).

3.10 **Atherogenic Index of Plasma**

Atherogenic Index of Plasma (AIP) is a calculation of the logarithmic ratio of HDL-c to TG, as a predictor of cardiovascular disease [109].

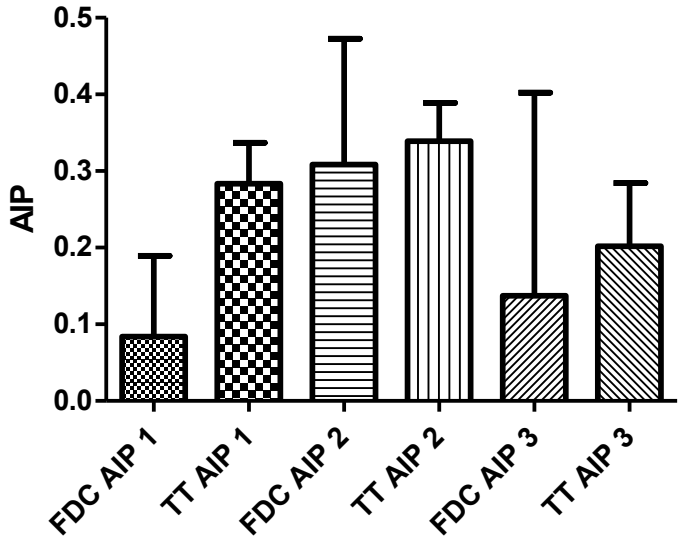

Figure 23: Mean calculated AIP values in the FDC and TT groups over a 3-year period.

AIP was calculated for HDL-c and TG readings taken at yearly intervals for 3 consecutive years (AIP 1, 2 and 3).

The differences between the two treatment groups were not statistically significant. The mean AIP values for the TT group were higher than those of the FDC group. Values were lower at baseline, increased in the second reading, and returned to near baseline values, creating a trend for both groups. (The first reading taken was used as the baseline value).

CHAPTER FOUR: DISCUSSION AND CONCLUSION

The aim of this study was to investigate the incidence and prevalence of metabolic syndrome in HIV patients on HAART triple therapy compared to a fixed-dose combination of EFV/FTC/TDF. It was hypothesized that patients on triple therapy would have a higher association with metabolic syndrome. The results obtained confirmed this statement, with the univariable logistic regression showing almost 3 times the odds of developing MetS with triple therapy compared to the FDC. The overall prevalence of MetS was 16.6%, consistent with prevalence in sub Saharan African countries [45-49]. The findings indicate that significant predictors of MetS were HAART regimen (TT), blood glucose, BMI and the presence of comorbidities. There was a marked difference between the two groups with respect to: glucose ($p = 0.006$), LDL-c ($p = 0.04$), systolic BP ($p < 0.001$) and diastolic BP ($p < 0.001$). All these factors were higher in patients on a triple therapy regimen.

4.1 Demographics

There were 219 females studied compared to 131 males (Figure 1). The incidence of MetS (Figure 16) in the total study population was higher in females (12.5%) compared to males (4%). Of the 58 patients that were at risk for MetS, 75.6% were female. The likelihood of MetS occurring in females is 1.3 times greater than in males. Gender was significantly associated with the incidence of MetS ($p = 0.022$). The greater prevalence of MetS in females than males (regardless of criteria used) was in line with previous studies done [56-57, 99, 100, 106]. These studies concurred that being female was significantly associated with the development of MetS. Leal et al. found a higher prevalence of MetS in females with odds ratios of 2.36:1 using NCEP/ATPII criteria and 2.75:1 using IDF/ AHA/ NHLBI criteria [102]. Aside from race and ethnicity, the increased susceptibility of developing MetS in females may be due to biological (e.g. hormonal regulation of body weight and adiposity), psychological and environmental factors [58, 61].

The study population was predominantly middle-aged, with the overall mean age being 41.4 years of age. There was no significant difference between the mean ages ($p = 0.119$) in both HAART regimen groups. No significant association was found between HAART regimen and age category ($p = 0.955$), however presence of MetS was significantly

associated with age (p = 0.001). The prevalence of MetS was highest among patients in age groups 26-45 years (48.3%) and 46-65 years (44.8%), consistent with data suggesting that risk of MetS increases with age (Figure 17). Patient numbers were, however, highest within these age categories, and upon further analysis per category, patients who were 66+ years of age had a 50% incidence of MetS. Previous studies conducted found significant associations between patients ≥ 40 years of age and the presence of MetS [59-60, 99, 100]. A study by Jerico et al. suggested a significant association between age groups, the incidence of MetS was 5.1% in patients < 30 years and 27% in patients between 50-59 years of age [53]. A directly proportionate relationship between age and risk of MetS has been well established.

Most patients were Ethnic Black (92.6%) and the remainder (7.4%) accounted as Mixed Ancestry, Mainland Indian Descent (MID) or Caucasoid origin (Figure 3). Due to a large disparity in patient numbers, no conclusion could be made regarding the relationship between ethnicity and MetS. There was no association found between the choice of regimen and ethnicity (p = 0.088). A pattern of higher patient numbers on FDC in the non-ethnic black groups was noticed. The Ethnic Black group was the only group to have more patients on TT than FDC. This could possibly be due to new initiations on HAART treatment, as FDC was only phased in during 2013. Higher numbers of patients in this group on TT could have been preexisting patients prior to 2013. Even though there was significantly more Ethnic Black than MID patients, the prevalence of MetS within the MID group was 37.5%. The overall distribution of MetS among ethnicities was 93.1% of Ethnic Black patients, 1.72% Mixed Ancestry patients and 5.17% Indian patients (Figure 18). There was no incidence of MetS amongst Caucasoid patients.

4.2 **Patient Groups (FDC and TT)**

A heterogeneous mix of patients on triple therapy was chosen, with regimens being tailored to the individual. The objective of the study was to ascertain the difference in the incidence and prevalence of MetS in both groups as a whole, and not just one specific triple therapy regimen. This was done to demonstrate whether and FDC of EFV/FTC/TDF was more favourable with respect to metabolic complications, reaffirming the move toward this combination as first-line treatment. Significant differences were found between the FDC and TT group. Aside from the higher prevalence of MetS in group B,

random blood glucose, LDL-c, triglyceride and blood pressure readings were higher in this group. There was an equal distribution (n =175) of patients between the both groups. All five clinical markers were not always available for each patient, however a minimum of three was always available. Amongst group B, the highest number of patients was on a PI-based regimen (n = 146), indicating that the majority of patients on triple therapy were on second-line treatment. Although there has been a recall on the usage of stavudine, two patients were on a stavudine-based regimen. These patients were older and could have been stable on this regimen, hence the continuation. Both patients on the stavudine-based regimen had comorbidities including, hypertension and diabetes, and their HDL-c and TG levels were within an acceptable range.

4.3 **Metabolic Syndrome**

MetS was defined using the joint interim statement, which is more inclusive as it accounts for gender differences, preexisting conditions, and concurrent medication e.g. statins, antihyperglycaemic agents and antihypertensive agents [44]. Overlooking preexisting conditions and/ or current medication may be misleading, as clinical markers may be controlled and within an acceptable range. This may produce a false impression that these markers will not confer a risk. The overall prevalence of MetS was 16.6%, in line with sub Saharan Africa (10-21%) statistics [48-52]. Of this percentage, a higher prevalence was found group B, 11.7% compared to 4.9% from group A (Figure 15). Among the 58 patients with MetS, 41 were on TT and 17 on the FDC, confirming the hypothesis. The results indicate that the odds of developing MetS are 2.84 times more likely on triple therapy compared to the fixed-dose combination. Upon further examination of group B, the incidence of MetS was highest among patients on an LPV/r containing regimen (87.8%) and constituted 62.1% of all patients with MetS. The use of LPV/r is known to have a high association with the incidence of MetS [101]. PIs were initially thought to be the only class linked to MetS, and its high association with MetS is demonstrated by the results obtained [52]. This reinforces the information on the metabolic adverse-effect profiles of different HAART drugs. PIs are known to lead to peripheral lipodystrophy, central weight accumulation, hyperlipidaemia, and insulin resistance (some of which were noticed within the results) [59]. The use of PIs in group B was a significant contributor to abnormal glucose, LDL-c and TG levels. Elevated blood pressure, both systolic and diastolic, was significantly noted in the TT group. Of the patients with LDL-c levels

available, 4 patients had levels that were too high to calculate. All of them were on a PI-based regimen, more specifically including LPV/r. The FDC combination of EFV/FTC/TDF had better clinical outcomes when compared to TT.

4.4 Comorbidities and Current Medication

The incidence of comorbidities was comparatively higher amongst those in group B (56.1%), with the highest incidence occurring in PI-based regimens, and 43.9% within group A (Figure 5). This could be as a direct result of treatment, progression of disease or underlying factors. There was no significant association found between the incidence of comorbidities and HAART regimens ($p = 0.207$). Of all the patients in the study, the most frequently occurring comorbidities were diabetes and hypertension, or a combination of both. A total of 81.3% of patients with comorbidities had diabetes, hypertension or both. Overall, the presence of multiple comorbidities had no significant relationship with HAART regimen ($p = 0.278$). When comparing between the two groups, the presence of diabetes and hypertension was higher among patients in group B (61.4% and 67.7% respectively). The incidence of tuberculosis, asthma and diseases classified as other were independent of HAART regimen.

The presence of comorbidities had a significant relationship with the risk of MetS ($p < 0.001$). 60.3% patients with comorbidities had MetS and 39.7% had no incidence of MetS (Figure 19). From the results obtained, the presence of comorbidities is found to be a significant contributor to MetS. There was a 29.4% incidence of MetS among patients with diabetes and hypertension. With diabetes or hypertension occurring as the only comorbidity, the incidence of MetS was 44.1% and 11.8%, respectively. Among all diabetic patients, there was a 61.4% incidence of MetS ($p < 0.001$). The high number of diabetic patients with MetS is expected, as diabetes is one of the end points of MetS [42]. It is probable that these patients would have exhibited components MetS prior to being diagnosed as diabetic, however this cannot be confirmed from the available data. It is important to note that not all individuals with MetS will develop diabetes as some may only develop cardiovascular disease. Among patients with hypertension, 50% had MetS ($p < 0.001$). TB, asthma and conditions classified as other, had no association with the incidence of MetS.

Patients on concurrent medication made up 24.6% of the total study sample (Figure 6). All patients who were diagnosed as diabetic or hypertensive were on appropriate treatment for these conditions. There were 16 patients on lipid lowering therapy, all of which were on a statin. Of these 16 patients, 50% of them were on a PI-based regimen including LPV/r. Statins are used primarily to reduce LDL-c levels, although their effects are beyond lipid-lowering as they also aid in the prevention of cardiovascular disease [24]. This is particularly useful in patients with MetS, however statins should be taken cautiously in patients on PIs and NRTIs as they are metabolised by the same pathway (CYP 3A4) and may affect bioavailability [24].

Although there were two patients recorded with TB, only one of the patients was recorded under anti-TB therapy. From the information at hand, the appropriate treatment was not found in the patients file, however this does not necessarily mean that the patient was not treated for this indication. Taking the setting into account, it is not uncommon for a patient to have multiple files, depending on the clinic they are visiting and thus may have been recorded elsewhere.

The presence of concurrent medication had a significant association with the incidence of MetS ($p = 0.005$). When each category was looked at individually, patients on antihyperglycaemic agents, antihypertensive agents and statins had a significant association with the incidence of MetS (Figure 21).

There was a 50% split between patients on antihypertensive agents and those who were not with respect to the incidence of MetS ($p < 0.001$). Patients on antihyperglycaemic agents had a 60.5% incidence of MetS ($p < 0.001$). Patients on statin therapy had the highest incidence of MetS (75%) among them ($p < 0.001$). There was no significant association between patients on other current medication and the incidence of MetS ($p = 0.300$).

4.5 **Clinical Markers**

The clinical markers studied in these patients were random blood glucose, cholesterol, HDL-c, LDL-c, TG, systolic BP, diastolic BP and BMI. The mean value for each marker was calculated from the number of patients with available clinical readings (Table 6). The mean values for all the aforementioned markers were higher in group B, with the exception of HDL-c, which was higher in group A. Significant differences were found

when comparing the two groups, with respect to, glucose ($p = 0.006$), LDL-c ($p = 0.04$), systolic BP ($p < 0.001$) and diastolic BP ($p < 0.001$). These clinical markers were classified as risk factors if: random glucose ≥ 7.8 mmol/L, blood pressure ≥ 130/85 mmHg, HDL-c < 1.00 mmol/L in males and < 1.30 mmol/L in females, triglycerides ≥1.70mmol/L and BMI ≥ 30.00 kg/m^2. The overall mean TG value (1.72 mmol/L) and LDL-c level (2.71 mmol/L) were the only mean value above the acceptable range.

4.5.1 **Glucose**

Statistical analysis showed a significant relationship with blood glucose levels and HAART regimens (Figure 8). In the clinic setting, fasting blood glucose was not frequently tested due to impracticality; therefore random blood glucose was instead tested. Mean random blood glucose values were higher in group B (6.06 mmol/L) than group A (5.45 mmol/L). The results indicate that there is just over a 2 fold increased odds of MetS with every unit increase from the mean glucose. There was a significant relationship found between elevated blood glucose values and MetS ($p < 0.001$). Hyperglycaemia is a marker for insulin resistance and in the presence of glucose tolerance, leads to elevated blood glucose and development of diabetes mellitus [105]. Majority of patients on PI-based regimens with MetS were either diabetic or had elevated blood glucose levels. PIs are known to play a role in the development of insulin resistance, via the reduction in glucose uptake by GLUT4 [89]. Previous studies have shown that PIs, IDV and LPV/r, can cause insulin resistance and may be reversible upon discontinuation [101]. Clinically, these results are confounded by the fact that the blood glucose is a random measurement, and reflects postprandial blood glucose.

4.5.2 **HDL- Cholesterol and Triglycerides**

The information available for cholesterol was limited as not all patients had their lipid profiles done routinely. Jacobson et al. found that low HDL-c and high TG levels were the most common criteria used to diagnose MetS [104]. From the information available, mean HDL-c levels were 1.31 mmol/L and 1.25 mmol/L in group A and B, respectively (Figure 10). There was no significant relationship found between HDL-c levels and HAART regimen ($p = 0.061$) and could possibly be due to gaps in information.

The mean triglyceride levels were significantly positively associated with HAART regimen ($p = 0.023$) (Figure 12). Group B had a mean TG level of 1.75 mmol/L, which was higher than the acceptable range (values ≥1.70 mmol/L were considered a risk for MetS). Between group A, the mean TG level was lower than group B, 1.52 mmol/L. A study by Riddler et al. found untreated HIV-infected patients had lower HDL-c and LDL-c levels compared to controls and after HAART initiation the changes in levels were not significant. However, triglyceride levels were elevated in the presence of untreated HIV-infected patients and were significantly increased after HAART initiation, suggestive of a direct result of treatment [107]. Factors that may also lead to the elevation in TG levels include: current or history of severe immune depression, time since HIV diagnosis and presence of opportunistic infections [31]. Dyslipidaemia is characterised by elevated TG, LDL-c, total cholesterol and decreased HDL-c levels and is associated with HAART treatment [24, 42, 57]. Between the patients who were at risk for MetS, 69% had a total cholesterol ≥ 4.50 mmol/L and 70.7% had LDL-c levels ≥ 2.59 mmol/L. Patients in group B on a PI-based regimen had a higher prevalence of elevated total cholesterol, TG, LDL-c and decreased HDL-c, putting them at risk of dyslipidaemia. Lipid abnormalities commonly occur within the first 12 months of HAART treatment and progressively worsen over time. Ritonavir is known to have a significant effect on total cholesterol and TG levels, leading to hyperlipidaemia [31].

The atherogenic index of plasma (AIP) is used by clinicians to calculate the risk of cardiovascular disease and may be used as a predictor of atherosclerosis. The high predictive value of AIP may be owing to its strong correlation with lipoprotein particle size. The ratio of HDL-c to triglycerides has been shown to be a strong predictor of myocardial infarction [109, 110]. AIP is defined as the base 10 logarithm of the ratio of TG to HDL-c (mmol/ L). The suggested risk categories for AIP are, low < 0.11, intermediate: 0.11-0.21, high > 0.21.

Using the mean TG and HDL-c levels in group A and B, the AIP calculated was 0.06 (low) and 0.15 (intermediate), respectively. Of the patients who were considered at risk (AIP > 0.21), 74.5% had MetS, suggesting an increased risk of developing of cardiovascular disease. Of the patients in group B that presented with features of MetS calculated AIP, suggested that 14.6% were at low risk, 9.8% were at an intermediate risk and 75.6% were at high risk of developing cardiovascular diseases. On the other hand, patients in group A that presented with features of MetS, 20% were at low risk, 10% at

intermediate risk and 70% were at high risk of developing cardiovascular diseases. Even though there were no statistically significant differences between FDC and TT patients, these results suggested that patients treated with the EFV/FTC/TDF FDC had a lower risk of cardiovascular events (Figure 23).

A general trend was observed in both groups, with AIP values starting low, increasing over time and eventually decreasing closer to the baseline values (initial reading taken) (Figure 23). Higher risk values in group B compared to group A may be due to the FDC slowing down the progression to MetS.

It is evident from the AIP calculations that HAART use and MetS contribute to the increased likelihood of adverse cardiovascular events.

4.5.3 **Body Mass Index**

Body mass index is used to categorise patients as underweight, normal, overweight or obese, using weight and height. Body mass index is calculated as an individuals weight (kg) divided by their height squared (m^2). According to WHO guidelines, an individual is classified as overweight if BMI $\geq$ 25.00 kg/m^2 and $\geq$ 30.00 kg/m^2 as obese [49]. Waist circumference was not routinely done on patients and therefore could not be used as a marker. The mean BMI calculated varied between the two groups, being higher in group B. Mean BMI in group A was 27.04 kg/m^2 and 27.33 kg/m^2 in group B. The incidence of MetS was significantly associated with BMI readings ($p < 0.001$). Patients who had a BMI of $\geq$ 30.00 kg/m^2 had a 73.2% incidence of MetS (Figure 22). The mean BMI amongst these patients was 32.54 kg/m^2. From the results it can be concluded that there 1.29 increased likelihood of MetS with every unit increase in BMI. Studies have shown a high association between BMI and MetS [53, 102]. Fat gain may be due to restoration of health after HAART initiation, however these effects occur initially, followed by possible peripheral fat wasting (notably with thymidine analogues) [101]. The use of BMI as a risk factor has limitations such as, being unable to distinguish between fat and lean mass and not taking into account distribution of body fat [103]. In addition, a person may be within the acceptable BMI range but still have metabolic alterations; alternatively a person with a BMI $\geq$ 30.00 kg/m^2 may have no metabolic alterations [49]. To ensure accuracy of risk factors, a Body Adiposity Index (BAI) has been proposed, however its effectiveness in identifying MetS is yet to be ascertained [103].

4.5.4 **Blood Pressure**

Both mean systolic ($p = 0.071$) and mean diastolic ($p = 0.168$) blood pressures had no significant association with MetS. They were, however, significantly associated with HAART regimen ($p < 0.001$). The overall mean of systolic and diastolic blood pressure was 120.82 mmHg and 76.99 mmHg respectively (Figure 14). Mean blood pressure values were higher in group B than group A. As blood pressure readings increase by a factor, there is an increased likelihood of MetS by 14.3% with systolic BP and 21.6% with diastolic BP. Elevations in both systolic and diastolic BP were noticed among Cameroonian patients and had a significant relationship with MetS ($p < 0.0001$) [58]. Previous studies suggest that a higher BMI could serve as an explanation for elevated BP [59]. Blood pressure elevation due to HAART has been observed by some studies, however many others did not confirm a correlation between the two [108]. Prospective studies have noted an increase in blood pressure readings, particularly with LPV/r, whereas those on ATV, EFV, IDV or Nelfinavir were less likely to experience an increase in blood pressure [97].

4.6 **Management**

Increased periods of exposure to HAART may lead to cardiovascular diseases therefore patients should be screened for fasting blood glucose and lipid profiles prior to initiation of therapy. Regular follow-ups should be encouraged and adhered to in order to monitor clinical markers [100]. Non-pharmacological intervention may be implemented, e.g. proper diet and exercise, to help decrease the chances of developing MetS. A proper diet, to ensure reduction in body mass, should include adjusted caloric intake, diversification of meals, reduced intake of simple sugars and animal fat and increased intake of vegetables, fruit, fish and fibre-rich products [75].

Patients with deranged lipid profiles may be treated with lipid lowering agents. HAART-associated dyslipidaemia is difficult to manage due to potential interactions between drugs, intolerance and low patient adherence. There are several alternatives in the treatment of HAART-associated dyslipidaemia e.g. inhibitors of intestinal cholesterol absorption, statins, fibrates, fish oil and niacin [80].

Current practices in the treatment of MetS in patients on HAART include the option of switching antiretroviral agents. Switching from PIs to NNRTI's or NRTI's may partly

reverse metabolic changes and does not affect antiviral efficacy in virally supressed patients [72].

4.7 **Conclusion**

The purpose of the study was to investigate the incidence and prevalence of MetS in HIV patients on HAART triple therapy compared to a fixed-dose combination. The results obtained indicate a significantly higher incidence and prevalence of MetS among patients on a triple therapy regimen compared to a fixed-dose combination of EFV/FTC/TDF. Significant differences in patients' clinical markers (higher in those a triple therapy regimen) were noted. Blood glucose, LDL-c and blood pressure readings were markedly elevated in patients on triple therapy. When adjusted for age, gender, comorbidities and clinical markers, multivariable logistic regression found the significant predictors of MetS to be: HAART regimen, glucose, BMI and the presence of comorbidities. It can be concluded that the risk of MetS is not solely dependent on HAART regimens, but rather based on a combination of individual (genetic and lifestyle) factors, the progression and impact of the HIV disease and HAART. The results may also serve as evidence so as to augment the move toward using the EFV/FTC/TDF fixed-dose combination as first-line treatment due to its lower prevalence of MetS. Aside from the advantages of decreased pill burden and cost, the scientific evidence suggests that long-term use of the EFV/FTC/TDF fixed-dose combination is more favourable with respect to metabolic complications.

4.8 Study Limitations and Recommendations

The shortcomings encountered included lack of information available on patients. There were insufficient fasting blood glucose results available and random glucose had to be used. Waist circumferences were not routinely done in HIV patients, however BMI was frequently recorded and thus used. I would recommend that a similar study be done prospectively, to ensure more stringent adherence to the definition of MetS. A prospective study will allow follow up and better availability of information. Lipid profiles were not available for all the patients in both treatment groups as this test is reserved for patients who require lipid monitoring (due to disease states or risk factors) and patients on PIs. In order for more accurate conclusions to be made, it is recommended that all patients have lipid profiles ordered for them when studied prospectively. Since the risk factors are multifactorial, patient factors that can be controlled, e.g. initiation date of HAART, should be kept constant.

REFERENCES

1. Mid-year population estimates. (2016). *Statistics South Africa*. 1-20
2. Crum E, Nancy F, Riffenburgh MPH, Robert H, Wegner S, Agan B, et al. Feb (2006). Comparisons of Causes of Death and Mortality Rates Among HIV-Infected Persons: Analysis of the Pre-, Early, and Late HAART (Highly Active Antiretroviral Therapy). *J Acquir Immune Defic Syndr,* 1, 41(2), pp. 194-200.
3. Kent A, Sepkowitz M. (2001). AIDS- The First 20 Years. *The New England Journal of Medicine*, 344(23), pp. 1764-1772.
4. Meintjes G, Black J, Conradie F, Cox V, Dlamini S, Fabian J, Maartens G, Manzini T, Mathe M, Menezes C, Moorhouse M, Moosa Y, Nash J, Orrell C, Pakade Y, Venter F, Wilson D. (2014). Adult antiretroviral therapy guidelines 2014 By the Southern African HIV Clinicians Society. *SAJHIVMED,* 15(4), pp. 121-143.
5. Division of Clinical Pharmacology, Faculty of Health Sciences, University of Cape Town. (2010). *South African Medicines Formulary*. Ninth Edition. Cape Town: Health and Medical Publishing Group of the South African Medical Association.
6. World Health Organisation. (2016) Consolidated Guidelines on the use of antiretroviral drugs for treating and preventing HIV infection, Recommendations for public health approach, Second Edition, pp. 1-180.
7. Wetsby M, van der Ryst E. (2005). CCR5 antagonists: host-targeted antivirals for the treatment of HIV infection. *Antiviral Chemistry & Chemotherapy*, 6, pp. 339–354.
8. National Department of Health South Africa. (2015). National Consolidated Guidelines for the Prevention of Mother-to-Child Transmission of HIV (PMTCT) and the Management of HIV in Children, Adolescents and Adults. pp. 1-119.
9. Wensing A, van Maarseveen N, Nijhuis M. (2010). Fifteen years of HIV Protease Inhibitors: raising the barrier to resistance. *Antiviral Research,* 85(1), pp. 59–74.
10. Zeldin RK, Petruscke RA. (2004). Pharmacological and therapeutic properties of ritonavir-boosted protease inhibitor therapy in HIV-infected patients. *Journal of Antimicrobial Therapy*, 53, pp. 4-9.
11. Gautam CS, Saha L. (2008). Fixed dose drug combinations (FDCs): rational or

irrational: a viewpoint. *British Journal of Clinical Pharmacology*, 65(5), pp. 795-796.

12. Department of Health, Republic of South Africa. (2013) Revised Anti-Retroviral Treatment Guideline Update For Frontline Clinical Health Professionals. pp. 1-42.
13. Davies N. (2013). South African Clinician Society, Fixed-dose combination for adults accessing antiretroviral therapy. *SAJHIVMED*, 14(1), pp. 41-43.
14. Stohr W, Back D, Dunn D, Sabin C, WinstonA, Gilson R, Pillay D, Hill T, Ainsworth J, Pozniak A, Leen C, Bansi L, Fisher M, Orkin C, Anderson J, Johnson M, Easterbrook P, Gibbons S, Khoo S. (2008). Factors influencing efavirenz and nevirapine plasma concentration: effect of ethnicity, weight and co-medication. *Antiviral Therapy*, 13, pp. 675–685.
15. Kim M.J, Kim S, Chang H, Kim Y, Jin S, Jung H, Park J.H, Kim S, Lee J.M. (2015). Comparison of Antiretroviral Regimens: Adverse Effects and Tolerability Failure that Cause Regimen Switching. *Infect Chemother*, 47(4), pp. 231-238.
16. Max B, Sherer R. (2000). Management of the Adverse Effects of Antiretroviral Therapy and Medication Adherence. *Clinical Infectious Diseases*, 30(2), pp. S96–116.
17. Bangsberg D, Acosta P, Gupta R, Guzman D, Riley E, Harrigan R, Parkin N, Deeks S. (2006). Adherence–resistance relationships for protease and non-nucleoside reverse transcriptase inhibitors explained by virological fitness. *Official Journal of the International AIDS Society*, 20(2), pp. 223-231.
18. Airoldi M, Zaccarelli M, Bisi L, Bini T, Antinori A, Mussini C, Bai F, Orofino G, Sighinolf L, Gori A, Suter F, Maggiolo F. (2013). One-pill once-a-day HAART: a simplification strategy that improves adherence and quality of life of HIV-infected subjects. *Patient Preference and Adherence*, 4, pp. 115-125.
19. Mathias A.A, Hinkle J, Menning M, Hui J, Kaul S, Kearney BP. (2007). Bioequivalence of Efavirenz/Emtricitabine/Tenofovir Disoproxil Fumarate Single-Tablet Regimen, *J Acquir Immune Defic Syndr*, 46(2), pp. 167-73.
20. Pozniak A, Gallant J.E, DeJesus, E; Arribas, J.R, Gazzard B, Campo R.E, Chen S, McColl D, Enejosa J, Toole J.J, Cheng, A.K, for the Study 934 Group. (2006). Tenofovir Disoproxil Fumarate, Emtricitabine, and Efavirenz Versus Fixed-Dose Zidovudine/Lamivudine and Efavirenz in Antiretroviral-Naive Patients: Virologic, Immunologic, and Morphologic Changes-A 96-Week Analysis, *J Acquir Immune Defic Syndr,* 43(5), pp. 535-40.

21. DeJesus E, Young B, Morales-Ramirez J, Sloan, Ward D, Flaherty J, Ebrahimi R, Maa J, Reilly K, Ecker J, McColl D, Seekins D, Farajallah A. (2009). Simplification of Antiretroviral Therapy to a Single-Tablet Regimen Consisting of Efavirenz, Emtricitabine, and Tenofovir Disoproxil Fumarate Versus Unmodified Antiretroviral Therapy in Virologically Suppressed HIV-1-Infected Patients. *J Acquir Immune Defic Syndr 1*, 51(2), pp. 163-74.
22. Sweet D, Altice F, Cohen C, Vandewalle B. (2016). Cost-Effectiveness of Single- Versus Generic Multiple-Tablet Regimens for Treatment of HIV-1 Infection in the United States. *PLoS ONE.* 11(1): e0147821.
23. Tesfaye DY, Kinde S, Medhin G, Megerrsa YC, Tadewos A, Tadesse E, Shimelis T. (2014). Burden of metabolic syndrome among HIV-infected patients in Southern Ethiopia. *Diabetes Metab Syndr,* 8(2), pp. 102-107.
24. Oh J, Hegele R. (2007). HIV-associated Dyslipidaemia: Pathogenesis and Treatment, *Lancet Infect Dis*, 7(12), pp. 787-796.
25. Souza SJ, Luzia LA, Santos SS, Helen P, Rondó C. (2013). Lipid profile of HIV-infected patients in relation to antiretroviral therapy: a review. *Rev Assoc Med Bras*, 59(2), pp. 186-98.
26. Carr A, Cooper D. (2000). Adverse effects of antiretroviral therapy. *The Lancet*, 356, pp. 1423-1430.
27. Dalakas MC, Monzon ME, Bernardini I, Gahl WA, Jay CA. (1994). Zidovudine-induced mitochondrial myopathy is associated with muscle carnitine deficiency and lipid storage. *Ann Neurol*, 35(4), pp. 482-487.
28. Kakuda T. (2000). Pharmacology of Nucleoside and Nucleotide Reverse Transcriptase Inhibitor-Induced Mitochondrial Toxicity. *Clinical Therapeutics*, 22(6), pp. 685-708.
29. Hawkins T. (2010). Understanding and managing the adverse effects of antiretroviral therapy. *Antiviral Research*, 85, pp. 201–209.
30. Schaad H, Petty B, Grasela D, Christofalo B, Raymond R, Stewart M. (1997). Pharmacokinetics and Safety of a Single Dose of Stavudine (d4T) in Patients with Severe Hepatic Impairment. *Antimicrobial Agents And Chemotherapy*, 41(2), pp. 2793–2796.
31. Norris A, Dreher M. (2004). Lipodystrophy Syndrome: The Morphologic and Metabolic Effects of Antiretroviral Therapy in HIV Infection. *Journal Of The Association of Nurses In Aids Care*, 15(6), pp. 46-64.

32. Saint-Marc T, Jean-Loius T. (1999). The effects of discontinuing stavudine therapy on clinical and metabolic abnormalities in patients suffering from lipodystrophy. *AIDS*, 13(15), pp. 2188-9.
33. Espeseth A, Felock P, Wolfe A, Witmer M, Grobler J, Anthony N, Egbertson M, Melamed J, Young S, Hamill T, Cole J, Hazuda D. (2000). HIV-1 integrase inhibitors that compete with the target DNA substrate define a unique strand transfer conformation for integrase. *Proc Natl Acad Sci*, 92(21), pp. 11244-11249.
34. Fätkenheuer G, Pozniak A, Johnson M, Plettenberg A, Staszewski S, Hoepelman IM, Saag M, Goebel F, Rockstroh J, Dezube B, Jenkins T, Medhurst C, Sullivan J, Ridgway C, Abel S, James I, Youle M, Van der Ryst E. (2004). Evaluation of dosing frequency and food effect on viral load reduction during short-term monotherapy with UK-427,857 a novel CCR5 antagonist. *Medscape General Medicine*, 6, pp. 11–16.
35. Walensky RP, Goldberg JH, Daily JP. (1999). Anaphylaxis after re-challenge with abacavir. *AIDS*, 13(8), pp. 999–1000
36. Gallant JE, Parish MA, Keruly JC, Moore RD. (2005). Changes in renal function associated with tenofovir disoproxil fumarate treatment, compared with nucleoside reverse-transcriptase inhibitor treatment. *Clin Infect Dis*, 40, pp. 1194–98.
37. Wei X, Decker J, Liu H, Zhang Z, Arani R, Kilby J, Saag M, Wu X, Shaw G, Kappes J. (2002). Emergence of Resistant Human Immunodeficiency Virus Type 1 in Patients Receiving Fusion Inhibitor (T-20) Monotherapy. *Antimicrobial Agents And Chemotherapy*, pp. 1896–1905.
38. Calmy A, Hirschel B, Cooper A, Carr A. (2007). Clinical update: adverse effects of antiretroviral therapy. *Lancet*, 370, pp. 12-14.
39. Rochster H, Dieterich D, Bozzette S, et al. (1990). Toxicity of combined ganciclovir and zidovudine for cytomegalovirus disease associated with AIDS: an AIDS Clinical Trials Group study. *Ann Intern Med*, 113, pp. 111–17.
40. Roca B, Gomez C, Arnedo A. (1999). Stavudine, Lamivudine and lndinavir in Drug Abusing and Non-drug Abusing HIV-infected Patients: Adherence, Side Effects and Efficacy. *Journal of Infection*, 39, pp. 141-145.
41. Molina JM, Andrade-Villanueva J, Echevarria, J, Chetchotisakd P, Corral J, David N, Moyle G, Mancini M, Percival L, Yang R, Thiry A, McGrath, D. (2008). Once-daily atazanavir/ritonavir versus twice-daily lopinavir/ritonavir, each in combination with tenofovir and emtricitabine, for management of antiretroviral-

naive HIV-1-infected patients: 48 week efficacy and safety results of the CASTLE study. *Lancet,* 372, pp. 646–655.

42. Capeau J. (2007). From lipodystrophy and insulin resistance to metabolic syndrome: HIV infection, treatment and aging, *Curr Opin HIV AIDS,* 2:247-252.
43. Pao V, Lee GA, Grunfeld C. (2008). HIV Therapy, Metabolic Syndrome, and Cardiovascular Risk. *Current Medicine Group,* 10, pp. 61–70.
44. Alberti K.G.M.M, Eckel R.H, Grundy S.M, Zimmet P.Z, Cleeman J.I, Donato K.A., et al. (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, pp. 1640-1645.
45. Albert G, Zimmet P, Shaw J, Grundy SM. (2006). The IDF consensus worldwide definition of the metabolic syndrome. *International Diabetes Federation*, pp. 1-16
46. Grundy S, Brewer HB, Cleeman J, Smith S, Lenfant C. (2004). Definition of Metabolic Syndrome: Report of the National Heart, Lung, and Blood Institute/American Heart Association Conference on Scientific Issues Related to Definition. *Circulation*, 109, pp. 433-438.
47. Stern M, Williams K, Gonzalez-Villalpando C, et al. (2004). Does the metabolic syndrome improve identification of individuals at risk of type 2 diabetes and/or cardiovascular disease? *Diabetes Care*, 27(11), pp. 2676-2681.
48. Guira O, Tie'no H, Diende're' AE, Sagna Y, Diallo I, Yame'ogo B, Zoungrana L, Yame'ogo TM, Bognounou R, Drabo JY. (2015). Features of Metabolic Syndrome and Its Associated Factors during Highly Active Antiretroviral Therapy in Ouagadougou, Burkina Faso. *Journal of the International Association of Providers of AIDS Care,* 15(2), pp. 159-163.
49. Murguia-Romero M, Jimenez-Flores R, Villalobos-Molina R, Mendoza-Ramos MI, Reyes-Reali J, Sigrist-Flores SC, Méndez-Cruz AR. (2012). The body mass index (BMI) as a public health tool to predict metabolic syndrome. *Open Journal of Preventative Medicine,* 2(1), pp. 59-66.
50. Martinez E, Domingo P, Galindo MJ, Milinkovic A, Arroyo J. (2004). Risk of metabolic abnormalities in patients infected with HIV receiving antiretroviral therapy that contains lopinavir–ritonavir. *Clin Infect Dis*, 38, pp. 1017–23.

51. Jemsek JG, Arathoon E, Arlotti M, Perez C, Sosa N, Pokrovskiy V, et al. (2006). Body fat and other metabolic effects of atazanavir and efavirenz, each administered in combination with zidovudine plus lamivudine, in antiretroviral-naive HIV- infected patients. *Clin Infect Dis*, 42, pp. 273–80.

52. Wu P, Hung C, Liu W, Hsieh C, Sun H, Lu C, Wu H, Chien K. (2012). Metabolic syndrome among HIV-infected Taiwanese patients in the era of highly active antiretroviral therapy: prevalence and associated factors. *J Antimicrob Chemother*, 67, pp. 1001–1009.

53. Jerico' C, Knobel H, Montero M, Ordon˜Ez-llanos J, Guelar A, et al. (2005). Metabolic Syndrome Among HIV-Infected Patients. *Diabetes Care*, 28(1), pp. 132-137.

54. Bonfanti P, Giannattasio C, Ricci E, Facchetti R, Rosella E, Marzia Franzetti MD. (2007). HIV and Metabolic Syndrome, A Comparison With the General Population. J *Acquir Immune Defic Syndr*, 45(4), pp. 426-431.

55. Wand H, Calmy A, Carey DL, Samaras K, Carr A, Law MG, Cooper DA, Emery S. (2007). Metabolic syndrome, cardiovascular disease and type 2 diabetes mellitus after initiation of antiretroviral therapy in HIV infection. *AIDS*, 21, pp. 2445–2453.

56. Krishnan S, Schouten JT, Atkinson B, Brown T, Wohl T, McComsey TA, Glesby MJ, Shikuma C, Haubrich R, Tebas P, Campbell TB, Jacobson DL. (2012). Metabolic syndrome before and after initiation of antiretroviral therapy in treatment-naïve HIV-infected individuals. *J Acquir Immune Defic Syndr*, 61(3), pp. 381-389.

57. Werberich A, Ceren J, Romancini J, Gomes de Assis Pimentel G, Junior M, Pupulin A. (2013). Metabolic Syndrome in People with HIV/AIDS. *World Journal of AIDS*, 3, pp. 293-297.

58. Dimodi H, Etame L, Nguimkeng B, Mbappe F, Ndoe N, Tchinda J. (2014) Prevalence of Metabolic Syndrome in HIV-Infected Cameroonian Patients. *World Journal of AIDS*, 4, pp. 85-92.

59. Tiozzo E, Konefal J, Adwan S, Martinez LA, Villabona J, Lopez J, et al. (2015). A cross-sectional assessment of metabolic syndrome in HIV-infected people of low socio- economic status receiving antiretroviral therapy. *Diabetology & Metabolic Syndrome*, 7(15), pp. 1-23.

60. Muyanja D, Muzoora C, Muyingo A, Muyindike W, Siedner MJ. (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), pp. 4-10.

61. Pradhan A. (2014). Sex Differences in the Metabolic Syndrome: Implications for Cardiovascular Health in Women. *Clinical Chemistry,* 60(1), pp. 44-52.
62. Samaras K, Wand H, Law M, Emery S, Cooper D, Carr A. (2007). Prevalence of Metabolic Syndrome in HIV- Infected Patients Receiving Highly Active Antiretroviral Therapy Using International Diabetes Foundation and Adult Treatment Panel III Criteria. *Diabetes Care*, 30(1), pp. 113-119.
63. Safrin S, Grunfeld C. (1999). Fat distribution and metabolic changes in patients with HIV infection. *AIDS*, 13, pp. 2493–2505.
64. Jain R, Furfine E, Pedneault L, White A, Lenhard J. (2001). Metabolic complications associated with antiretroviral therapy. *Antiviral Research,* 51(3), pp. 151–177.
65. Leow M, Addy C, Mantzoros C. (2003). Human Immunodeficiency Virus/Highly Active Antiretroviral Therapy-Associated Metabolic Syndrome: Clinical Presentation, Pathophysiology, and Therapeutic Strategies. *Journal of Clinical Endocrinology & Metabolism*, 88(5), pp. 1961-1976.
66. Tate T, Willig AL, Willig JH, Raper JL, Moneyham L, Kempf M, Saag MF, Mugavero MJ. (2012). HIV infection and obesity: Where did all the wasting go? *Antivir Ther*, 17(7), pp. 1281-1289.
67. Graham NM. (2000). Metabolic Disorders Among HIV-infected Patients Treated with Protease Inhibitors: A Review. *J Acquir Immune Defic Syndr*, 25(1), pp. S4-11.
68. Nolan D, Mallal S. (2001). Getting to the HAART of insulin resistance. *AIDS*, 15, pp. 2037-2041.
69. Miller J, Carr A, Law M, Cooper D. (2000). A syndrome of lipoatrophy, lactic acidaemia and liver dysfunction associated with HIV nucleoside analogue therapy: contribution to protease inhibitor-related lipodystrophy syndrome. *AIDS*, 14(3), pp. F25–F32.
70. Grinspoon S, Carr A. (2005). Cardiovascular Risk and Body-Fat Abnormalities in HIV-Infected Adults. *N Engl J Med,* 352, pp. 48-62.
71. Randell PA, Jackson AG, Boffito M, Back DJ, Tjia JF, Taylor J, et al. (2010). Effect of boosted fosamprenavir or lopinavir-based combinations on whole-body

insulin sensitivity and lipids in treatment-naive HIV-type-1-positive men. *Antivir Ther*, 15, pp. 1125-1132.

72. Jeroen P. H. van Wijk and Manuel Castro Cabezas. (2011). "Hypertriglyceridemia, Metabolic Syndrome, and Cardiovascular Disease in HIV-Infected Patients: Effects of Antiretroviral Therapy and Adipose Tissue Distribution," *International Journal of Vascular Medicine*, 2012: 201027, doi:10.1155/2012/201027.
73. Tershakovec A, Frank I, Rader D. (2004). HIV-related lipodystrophy and related factors. *Atherosclerosis*, 174(1), pp. 1-10.
74. Villaroya F, Domingo P, Giralt M. (2005). Lipodystrophy associated with highly active anti-retroviral therapy for HIV infection: the adipocyte as a target of anti-retroviral-induced mitochondrial toxicity. *TRENDS in Pharmacological Sciences*, 26(2), pp. 88-93.
75. Drelichowska J, Kwiatowska W, Knysz B, Witkiewicz W. (2015). Metabolic Syndrome in HIV- positive Patients. *HIV & AIDS Review*, 14(2), pp. 35-41.
76. Aldeen T, Wells C, Hay P, Davidson F, Lau R. (1999). Lipodystrophy associated with nevirapine-containing antiretroviral therapies. *AIDS*, 3, pp. 865–867.
77. Villaroya F, Domingo P, Giralt M. (2010). Drug-induced lipotoxicity: Lipodystrophy associated with HIV-1 infection and antiretroviral treatment. *Biochimica et Biophsyica Acta*, 1801(3), pp. 392-399.
78. Anuurad E, Semrad A, Berglund L. (2009). Human Immunodeficiency Virus and Highly Active Antiretroviral Therapy–Associated Metabolic Disorders and Risk Factors for Cardiovascular Disease. *Metabolic Syndrome and Related Disorders*, 7(5), pp. 401-410.
79. Carr A, Samaras K, Thorisdottir A, et al. (1999). Diagnosis, prediction, and natural course of HIV-1 protease-inhibitor-associated lipodystrophy, hyperlipidaemia, and diabetes mellitus: a cohort study. *Lancet*, 353, pp. 2093–2099.
80. Cunha J, Morganti L, Maselli F, Stern ACB, Spada C, Bydlowski SP. (2015). Impact of antiretroviral therapy on lipid metabolism of human immunodeficiency virus-infected patients: Old and new drugs. *World J Virol*, 4(2), pp. 56-77.
81. El-Sadr WM, Mullin CM, Carr A, et al. (2005). Effects of HIV disease on lipid, glucose and insulin levels: results from a large antiretroviral-naive cohort. *HIV*

Med, 6, pp. 114–121.

82. Ombeni W, Kamuhabwa AR. (2015). Lipid Profile in HIV-Infected Patients Using First-Line Antiretroviral Drugs, *Journal of the International Association of Providers of AIDS Care,* 15(2), pp. 164-171.
83. Calza L, Manfredi R, Colangeli V, Tampellini L, Sebastiani T, Pocaterra D, Chiodo F. (2005). Substitution of nevirapine or efavirenz for protease inhibitor versus lipid-lowering therapy for the management of dyslipidaemia. *AIDS*, 19, pp. 1051-1058.
84. Busari OA, Busari OE. (2013). Cardiac Diseases and Metabolic Syndrome in HIV Infection. *Archives Medical Review Journal*, 22(3), pp. 377-392.
85. Behrens G, Dejam A, Schmidt H, Balks H, Brabant G, Körner T, Stoll M, Schmidt R. (1999). Impaired glucose tolerance, beta cell function and lipid metabolism in HIV patients under treatment with protease inhibitors. *AIDS*, 13(10), pp. 9.
86. Manfredi R. (2000). Management of dyslipidemia in patients with HIV disease. *Clin Microbiol Infect*, 6, pp. 579-584.
87. Freitas P, Carvalho D, Souto S, et al. (2011). Impact of Lipodystrophy on the prevalence and components of metabolic syndrome in HIV- infected patients. *BMC Infect Dis*, 11, pp. 246.
88. Brown T, Glesby M. (2011). Management of the metabolic effects of HIV and HIV drugs. *Nat Rev Endocrinol*, 8(1), pp. 11–21.
89. Grunfeld C. (2008). Insulin Resistance in HIV infection: drugs, host responses, or restoration to health? *Topics in HIV Medicine*, 16(2), pp. 89-93.
90. Kassi E, Pervanidou P, Kaltsas G, Chrousos G. (2011). Metabolic syndrome: definitions and controversies. *BMC Medicine*, 9, pp. 48.
91. Hruz P. (2006). Molecular mechanisms for altered glucose homeostasis in HIV infection. *Am J Infect Dis*, 2, pp. 187–192.
92. Galescu O, Bhangoo A, Ten S. (2013). Insulin resistance, lipodystrophy and cardiometabolic syndrome in HIV/AIDS. *Rev Endocr Metab Disord*, 14, pp. 133–140.
93. Young F, Critchley J, Johnstone L, Unwin N. (2009). A review of co-morbidity between infectious and chronic disease in Sub Saharan Africa: TB and Diabetes Mellitus, HIV and Metabolic Syndrome, and the impact of globalization.

Globalization and Health, 5, pp. 9.

94. Murata H, Hruz PW, Mueckler M. (2000). The Mechanism of Insulin Resistance Caused by HIV Protease Inhibitor Therapy. *The Journal of Biological Chemistry,* 275(27), pp. 20251–20254.
95. Munshi M, Martin R, Fonseca V. (1994). Hyperosmolar Nonketotic Diabetic Syndrome Following Treatment of Human Immunodeficiency Virus Infection With Didanosine. *Diabetes Care*, 17(4), pp. 316-317.
96. Hejazi N, Huang MSL, Lin K, Choong L. (2014). Hypertension among HIV-Infected Adults Receiving Highly Active Antiretroviral Therapy (HAART) in Malaysia. *Global Journal of Health Science*, 6(2), pp. 58-71.
97. Crane H, van Rompaey S, Kitahata M. (2006). Antiretroviral Medications Associated With Elevated Blood Pressure Among Patients Receiving Highly Active Antiretroviral Therapy. *AIDS*, 20(7), pp. 1019-1026.
98. Palios J, Kadoglou N, Lampropoulos S. (2012). The Pathophysiology of HIV-/HAART-Related Metabolic Syndrome Leading to Cardiovascular Disorders: The Emerging Role of Adipokines. *Experimental Diabetes Research,* 2012, pp. 1-7.
99. Leal J, Fausto M, Carneiro M. (2016). Anthropometric Risk Factors for Metabolic Syndrome in HIV patients. *Medical Express*, 3(4)M160405, pp. 1-8.
100. Hirigo A, Tesfaye D. (2016). Influences of gender in metabolic syndrome and its components among people living with HIV virus using antiretroviral treatment in Hawassa, southern Ethiopia. *BMC Research Notes,* 9, pp. 145.
101. Nix L, Tien P. (2014). Metabolic Syndrome, Diabetes and Cardiovascular Risk in HIV. *Curr HIV/AIDS Rep*, 11(3), pp. 271–278.
102. Ervin R. (2009). Prevalence of Metabolic Syndrome Among Adults 20 Years of Age and Over, by Sex, Age, Race and Ethnicity, and Body Mass Index: United States, 2003–2006. *National Health Statistics Reports*, 13, pp. 1-5.
103. Beraldo R, Meliscki G, Silva B, Navarro A, Bollela V, Schmidt A, Foss-Freitas M. (2016). Comparing the Ability of Anthropometric Indicators in Identifying Metabolic Syndrome in HIV Patients. *PLOS ONE*, 11(2): e0149905.
104. Jacobson DL, Tang AM, Spiegelman D, et al. (2006). Incidence of metabolic syndrome in a cohort of HIV-infected adults and prevalence relative to the US population (National Health and Nutrition Examination Survey). *J Acquir Immune Defic Syndr*, 43(4), pp. 458–466.
105. Schneider C. (2014). Metabolic syndrome and diabetes. *DiabetesCare,* 11(3), pp.

271.

106. Alvarez C, Salazar R, Galindez J, Rangel F, Castaneda M, Lopardo G, Cunha C, Roldan Y, Sussman O, Gutierrez G, Cure-Bolt N, Seas C, Carcamo C, Castrillo M. (2010). Metabolic syndrome in HIV-infected patients receiving antiretroviral therapy in Latin America. *Braz J Infect Dis,* 14(3), pp. 256-263.

107. Riddler SA, Smit E, Cole SR, Li S, Chmiel JS, Dobs A, Palella F, Visscher B, Evans R, Kingsley LA. (2011). Impact of HIV infection and HAART on serum lipids in men. *JAMA*, 289(22), pp. 2978–2982.

108. Costa LA, Almeida AG. (2015). Cardiovascular disease associated with human immunodeficiency virus: A review. *Rev Port Cardiol*, 34(7-8), pp. 479-491.

109. Dobiasova M. (2006). AIP--atherogenic index of plasma as a significant predictor of cardiovascular risk: from research to practice. *Vnitr Lek*, 52(1), pp. 64-71.

110. Nwagha UI, Ikekpeazu EJ, Ejezie FE, Neboh EE, Maduka IC. (2010). Atherogenic index of plasma as useful predictor of cardiovascular risk among postmenopausal women in Enugu, Nigeria. *African Health Sciences*, 10(3), pp. 248-252.

111. Holmes DT, Frohlich J, Buhr KA. (2008). The concept of precision extended to the atherogenic index of plasma. *Clinical Biochemistry*, 41(7-8), pp. 631-635.

APPENDICES

Appendix 1: Ethics approval

UNIVERSITY OF KWAZULU-NATAL
INYUVESI YAKWAZULU-NATALI

11 July 2016

Ms A Kazi (209501949)
Discipline of Pharmacology
School of Health Sciences
aniessa.5@gmail.com

Protocol: The comparison of the incidence and prevalence of metabolic syndrome in HIV/AIDS patients on a single pill fixed dose combination and triple therapy.
Degree: MPharm
***BREC reference* number:** BE227/16

EXPEDITED APPLICATION

The Biomedical Research Ethics Committee has considered and noted your application received on 31 March 2016.

The study was provisionally approved pending appropriate responses to queries raised. Your response received on 07 July 2016 to queries raised on 28 June 2016 have been noted and approved by a sub-committee of the Biomedical Research Ethics Committee. The conditions have now been met and the study is given **full ethics approval.**

This approval is valid for one year from **11 July 2016.** To ensure uninterrupted approval of this study beyond the approval expiry date, an application for recertification must be submitted to BREC on the appropriate BREC form 2-3 months before the expiry date.

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

Your acceptance of this approval denotes your compliance with South African National Research Ethics Guidelines (2015), South African National Good Clinical Practice Guidelines (2006) (if applicable) and with UKZN BREC ethics requirements as contained in the UKZN BREC Terms of Reference and Standard Operating Procedures, all available at http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx.

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

The sub-committee**'s** decision will be **RATIFIED** by a full Committee at its meeting taking place on **16 August 2016.**

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

Yours sincerely

Professor J Tsoka-Gwegweni
Chair: Biomedical Research Ethics Committee

cc supervisor: owirap@ukzn.ac.za
Postgraduate Office: nenep1@ukzn.ac.za

Biomedical Research Ethics Committee
Professor J Tsoka-Gwegweni (Chair)
Westville Campus, Govan Mbeki Building
Postal Address: Private Bag X54001, Durban 4000
Telephone: +27 (0) 31 260 2486 **Facsimile:** +27 (0) 31 260 4609 **Email:** brec@ukzn.ac.za
Website: http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx

1910 - 2010
100 YEARS OF ACADEMIC EXCELLENCE

Founding Campuses: Edgewood Howard College Medical School Pietermaritzburg Westville

Appendix 2: Data collection tool

DATA COLLECTION TOOL

PATIENT PARTICULARS

CODE: _____

AGE	1. 18-25	3. 45-65	DATE OF BIRTH			
	2. 25-45	4. 65 +				
GENDER			1. Male		2. Female	
ETHNICITY	1. Ethnic Black		2. Mixed Ancestry		3. Mainland Indian Descent	
	4. Caucasoid		5. Other			
SMOKER			1. Yes		2. No	
IF YES, AMOUNT SMOKED PER DAY	1. 1-5		2. 5-10		3. > 10	
PREGNANT			1. Yes		2. No	
CURRENTLY EMPLOYED			1. Yes		2. No	
COMORBIDITIES			1. Yes		2. No	
IF YES, SPECIFY	1. Diabetes		2. Hypertension		3. TB	
			4. Asthma		5. Other	
CURRENT MEDICATION	1. Anti-hypertensive		2. Antihyper-glycaemic		3. Statin	
			4. Anti-tuberculosis agent		5. Other	
ANTIRETROVIRAL REGIMEN			1. FDC		2. Triple therapy	
IF TRIPLE THERAPY, SPECIFY REGIMEN:						

DOES THE PATIENT CONSUME ALCOHOL	1. Yes		2. No	
IS THERE A FAMILY HISTORY OF CHRONIC ILLNESS?	1. Yes		2. No	

Patient Markers:	**Date:**				
Random Glucose ≥ 7.80 mmol/L					
Blood Pressure ≥ 130/85 mmHg					
High-density Lipoproteins M: <1.00mmol/L W: <1.30mmol/L					
Low-density Lipoproteins Cholesterol					
Total Triglycerides ≥1.70mmol/L					
BMI ≥ 30 kg/m^2					

DOES THE PATIENT MEET THE CRITERIA FOR METABOLIC SYNDROME	1. Yes		2. No	

Appendix 3: Gatekeeper letter

health
Department:
Health
PROVINCE OF KWAZULU-NATAL

ADDINGTON HOSPITAL
OFFICE OF THE CHIEF EXECUTIVE OFFICER

P.O. BOX 977
DURBAN
4000
Tel: 031-327-2970 Email: reshma.boodhai@kznhealth.gov.za
www.kznhealth.gov.za

Reference: *9/2/3/R*

Date: 9th May 2016

Principal Investigator:
- **Ms A Kazi**

PERMISSION TO CONDUCT RESEARCH AT ADDINGTON HOSPITAL: "THE COMPARISON OF THE INCIDENCE AND PREVALENCE OF METABOLIC SYNDROME IN HIV/AIDS PATIENTS ON A SINGLE PILL FIXED DOSE COMBINATION AND TRIPLE THERAPY"

I have pleasure in informing you that permission has been granted to you by Addington Hospital Management to conduct the above research.

Please note the following:

1. Please ensure that you adhere to all the policies, procedures, protocols and guidelines of the Department of Health with regards to this research.
2. This research will only commence once this office has received confirmation from the Provincial Health Research Committee in the KZN Department of Health.
3. Please ensure this office is informed before you commence your research.
4. Addington Hospital will not provide any resources for this research.
5. You will be expected to provide feedback on your findings to Addington Hospital.

DR M NDLANGISA
HOSPITAL MANAGER
ADDINGTON HOSPITAL

Appendix 4: Department of Health approval

health
Department:
Health
PROVINCE OF KWAZULU-NATAL

Physical Address: 330 Langalibalele Street, Pietermaritburg
Postal Address: Private Bag X9051
Tel: 033 395 2805/ 3189/ 3123 Fax: 033 394 3782
Email: hrkm@kznhealth.gov.za
www.kznhealth.gov.za

DIRECTORATE:
Health Research & Knowledge Management

HRKM Ref: 200/16
NHRD Ref: KZ_2016RP33_135

Date: 6 July 2016

Dear Ms A. Kazi
UKZN

Approval of research

1. The research proposal titled **'Investigating the impact of a Fixed Dose Combination compared to Triple Therapy on metabolic syndrome in patients on HAART'** was reviewed by the KwaZulu-Natal Department of Health.

   The proposal is hereby **approved** for research to be undertaken at Addington Hospital.

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

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

For any additional information please contact Mr X. Xaba on 033-395 2805.

Yours Sincerely

Dr E Lutge
Chairperson, Health Research Committee
Date: 07/07/16

Appendix 5: Results

```
. do "C:\Users\YBALAK~1\AppData\Local\Temp\STD0i000000.tmp"

. tab age arvregimen, chi row col
```

Key
frequency *row percentage* *column percentage*

age	arvregimen 1	2	Total
1	8	6	14
	57.14	42.86	100.00
	4.57	3.43	4.00
2	112	112	224
	50.00	50.00	100.00
	64.00	64.00	64.00
3	51	53	104
	49.04	50.96	100.00
	29.14	30.29	29.71
4	4	4	8
	50.00	50.00	100.00
	2.29	2.29	2.29
Total	175	175	350
	50.00	50.00	100.00
	100.00	100.00	100.00

Pearson chi2(3) = 0.3242 Pr = 0.955

```
. sum age_cont, detail
```

age_cont

Percentiles		Smallest		
1%	21	20		
5%	25	20		
10%	27	20	Obs	350
25%	34	21	Sum of Wgt.	350
50%	41		Mean	41.42571
		Largest	Std. Dev.	10.91929
75%	48	70		
90%	55	70	Variance	119.2309
95%	62	76	Skewness	.5590993
99%	70	87	Kurtosis	3.533755

```
. bysort arvregimen: sum age_cont, detail

-> arvregimen = 1
```

age_cont

Percentiles		Smallest		
1%	20	20		
5%	25	20		
10%	26	21	Obs	175
25%	32	22	Sum of Wgt.	175

50%	40		Mean	40.51429
		Largest	Std. Dev.	11.11789
75%	47	67		
90%	54	68	Variance	123.6076
95%	63	70	Skewness	.4925461
99%	70	76	Kurtosis	3.024034

-> arvregimen = 2

age_cont

	Percentiles	Smallest		
1%	21	20		
5%	25	21		
10%	30	22	Obs	175
25%	35	22	Sum of Wgt.	175
50%	41		Mean	42.33714
		Largest	Std. Dev.	10.67092
75%	48	66		
90%	55	66	Variance	113.8684
95%	62	70	Skewness	.6681879
99%	70	87	Kurtosis	4.100008

```
. oneway age_cont arvregimen, means standard obs
```

arvregimen	Summary of age_cont Mean	Std. Dev.	Obs.
1	40.514286	11.117893	175
2	42.337143	10.670916	175
Total	41.425714	10.919288	350

Analysis of Variance

Source	SS	df	MS	F	Prob > F
Between groups	290.745714	1	290.745714	2.45	0.1185
Within groups	41320.8229	348	118.737997		
Total	41611.5686	349	119.230856		

Bartlett's test for equal variances: chi2(1) = 0.2921 Prob>chi2 = 0.589

```
. tab gender arvregimen, chi row col
```

Key
frequency *row percentage* *column percentage*

gender	arvregimen 1	2	Total
0	110 50.23 62.86	109 49.77 62.29	219 100.00 62.57
1	65 49.62 37.14	66 50.38 37.71	131 100.00 37.43
Total	175 50.00 100.00	175 50.00 100.00	350 100.00 100.00

Pearson chi2(1) = 0.0122 Pr = 0.912

```
. tab ethnicity arvregimen, chi row col
```

Key
frequency *row percentage* *column percentage*

ethnicity	arvregimen 1	2	Total
1	157 48.46 89.71	167 51.54 95.43	324 100.00 92.57
2	12 80.00 6.86	3 20.00 1.71	15 100.00 4.29
3	5 62.50 2.86	3 37.50 1.71	8 100.00 2.29
4	1 33.33 0.57	2 66.67 1.14	3 100.00 0.86
Total	175 50.00 100.00	175 50.00 100.00	350 100.00 100.00

Pearson chi2(3) = 6.5420 Pr = 0.088

```
. tab smoker
```

smoker	Freq.	Percent	Cum.
0	350	100.00	100.00
Total	350	100.00	

```
. tab pregnant
```

pregnant	Freq.	Percent	Cum.
0	350	100.00	100.00
Total	350	100.00	

```
. tab employed arvregimen, chi row col
```

Key
frequency *row percentage* *column percentage*

employed	arvregimen 1	2	Total
0	76	87	163
	46.63	53.37	100.00
	43.68	49.71	46.70
1	98	88	186
	52.69	47.31	100.00
	56.32	50.29	53.30
Total	174	175	349
	49.86	50.14	100.00
	100.00	100.00	100.00

Pearson chi2(1) = 1.2771 Pr = 0.258

. tab comorbidities arvregimen, chi row col

Key
frequency *row percentage* *column percentage*

comorbidities	arvregimen 1	2	Total
0	139	129	268
	51.87	48.13	100.00
	79.43	73.71	76.57
1	36	46	82
	43.90	56.10	100.00
	20.57	26.29	23.43
Total	175	175	350
	50.00	50.00	100.00
	100.00	100.00	100.00

Pearson chi2(1) = 1.5926 Pr = 0.207

. tab comorbidities_specify arvregimen, exact row col

Key
frequency *row percentage* *column percentage*

Enumerating sample-space combinations:
stage 14: enumerations = 1
stage 13: enumerations = 2
stage 12: enumerations = 3
stage 11: enumerations = 4
stage 10: enumerations = 5
stage 9: enumerations = 6
stage 8: enumerations = 7
stage 7: enumerations = 8
stage 6: enumerations = 9
stage 5: enumerations = 19
stage 4: enumerations = 50
stage 3: enumerations = 114
stage 2: enumerations = 281
stage 1: enumerations = 0

comorbidities_specify	arvregimen 1	2	Total
1	11 39.29 32.35	17 60.71 36.96	28 100.00 35.00
1, 2	5 41.67 14.71	7 58.33 15.22	12 100.00 15.00
1, 2, 4	0 0.00 0.00	1 100.00 2.17	1 100.00 1.25
1, 4	1 100.00 2.94	0 0.00 0.00	1 100.00 1.25
1, 4, 5	0 0.00 0.00	1 100.00 2.17	1 100.00 1.25
1, 5	0 0.00 0.00	1 100.00 2.17	1 100.00 1.25
2	4 25.00 11.76	12 75.00 26.09	16 100.00 20.00
2, 3	0 0.00 0.00	1 100.00 2.17	1 100.00 1.25
2, 4	1 100.00 2.94	0 0.00 0.00	1 100.00 1.25
2, 5	1 33.33 2.94	2 66.67 4.35	3 100.00 3.75
3, 5	1 100.00 2.94	0 0.00 0.00	1 100.00 1.25
4	3 75.00 8.82	1 25.00 2.17	4 100.00 5.00
4, 5	1 100.00 2.94	0 0.00 0.00	1 100.00 1.25
5	6 66.67 17.65	3 33.33 6.52	9 100.00 11.25
Total	34 42.50 100.00	46 57.50 100.00	80 100.00 100.00

Fisher's exact = 0.278

```
. tab diabetes arvregimen, chi row col
```

Key
frequency *row percentage* *column percentage*

diabetes	arvregimen 1	2	Total
0	156 51.32 90.17	148 48.68 84.57	304 100.00 87.36
1	17 38.64 9.83	27 61.36 15.43	44 100.00 12.64
Total	173 49.71 100.00	175 50.29 100.00	348 100.00 100.00

Pearson chi2(1) = **2.4718** Pr = **0.116**

```
. tab hpt arvregimen, chi row col
```

Key
frequency *row percentage* *column percentage*

hpt	arvregimen 1	2	Total
0	162 51.59 93.64	152 48.41 86.86	314 100.00 90.23
1	11 32.35 6.36	23 67.65 13.14	34 100.00 9.77
Total	173 49.71 100.00	175 50.29 100.00	348 100.00 100.00

Pearson chi2(1) = **4.5424** Pr = **0.033**

```
. tab tb arvregimen, chi row col
```

Key
frequency *row percentage* *column percentage*

tb	arvregimen 1	2	Total
0	172 49.71 99.42	174 50.29 99.43	346 100.00 99.43
1	1 50.00 0.58	1 50.00 0.57	2 100.00 0.57
Total	173 49.71 100.00	175 50.29 100.00	348 100.00 100.00

Pearson chi2(1) = 0.0001 Pr = 0.993

```
. tab asthma arvregimen, chi row col
```

Key
frequency *row percentage* *column percentage*

asthma	arvregimen 1	2	Total
0	167 49.26 96.53	172 50.74 98.29	339 100.00 97.41
1	6 66.67 3.47	3 33.33 1.71	9 100.00 2.59
Total	173 49.71 100.00	175 50.29 100.00	348 100.00 100.00

Pearson chi2(1) = 1.0623 Pr = 0.303

```
. tab other_comorb arvregimen, chi row col
```

Key
frequency *row percentage* *column percentage*

other_comorb	arvregimen 1	2	Total
0	164 49.40 94.80	168 50.60 96.00	332 100.00 95.40
1	9 56.25 5.20	7 43.75 4.00	16 100.00 4.60
Total	173 49.71 100.00	175 50.29 100.00	348 100.00 100.00

Pearson chi2(1) = 0.2867 Pr = 0.592

```
. tab currentmedication arvregimen, exact row col
```

Key
frequency *row percentage* *column percentage*

```
Enumerating sample-space combinations:
stage 13: enumerations = 1
stage 12: enumerations = 2
stage 11: enumerations = 3
stage 10: enumerations = 4
stage 9:  enumerations = 10
stage 8:  enumerations = 28
stage 7:  enumerations = 85
stage 6:  enumerations = 142
stage 5:  enumerations = 249
stage 4:  enumerations = 426
stage 3:  enumerations = 1023
stage 2:  enumerations = 1898
stage 1:  enumerations = 0
```

currentmedication	arvregimen 1	2	Total
0	1 100.00 2.63	0 0.00 0.00	1 100.00 1.15
1	4 28.57 10.53	10 71.43 20.41	14 100.00 16.09
1, 2	4 40.00 10.53	6 60.00 12.24	10 100.00 11.49
1, 2, 3	1 50.00 2.63	1 50.00 2.04	2 100.00 2.30
1, 2, 5	0 0.00 0.00	1 100.00 2.04	1 100.00 1.15
1, 3	0 0.00 0.00	3 100.00 6.12	3 100.00 3.45
1, 5	2 50.00 5.26	2 50.00 4.08	4 100.00 4.60
2	7 33.33 18.42	14 66.67 28.57	21 100.00 24.14
2, 3	2 40.00 5.26	3 60.00 6.12	5 100.00 5.75
2, 5	2 50.00 5.26	2 50.00 4.08	4 100.00 4.60
3	3 50.00 7.89	3 50.00 6.12	6 100.00 6.90

4, 5	1	0	1
	100.00	0.00	100.00
	2.63	0.00	1.15
5	11	4	15
	73.33	26.67	100.00
	28.95	8.16	17.24
Total	38	49	87
	43.68	56.32	100.00
	100.00	100.00	100.00

Fisher's exact = 0.281

. tab antihpt arvregimen, chi row col

Key
frequency *row percentage* *column percentage*

antihpt	arvregimen 1	2	Total
0	164	152	316
	51.90	48.10	100.00
	93.71	86.86	90.29
1	11	23	34
	32.35	67.65	100.00
	6.29	13.14	9.71
Total	175	175	350
	50.00	50.00	100.00
	100.00	100.00	100.00

Pearson chi2(1) = 4.6910 Pr = 0.030

. tab antihyperglycaemic arvregimen, chi row col

Key
frequency *row percentage* *column percentage*

antihyperglycaemic	arvregimen 1	2	Total
0	159	148	307
	51.79	48.21	100.00
	90.86	84.57	87.71
1	16	27	43
	37.21	62.79	100.00
	9.14	15.43	12.29
Total	175	175	350
	50.00	50.00	100.00
	100.00	100.00	100.00

Pearson chi2(1) = 3.2081 Pr = 0.073

```
. tab statin arvregimen, chi row col
```

Key
frequency *row percentage* *column percentage*

statin	arvregimen 1	2	Total
0	169	165	334
	50.60	49.40	100.00
	96.57	94.29	95.43
1	6	10	16
	37.50	62.50	100.00
	3.43	5.71	4.57
Total	175	175	350
	50.00	50.00	100.00
	100.00	100.00	100.00

```
          Pearson chi2(1) =   1.0479   Pr = 0.306
```

```
. tab antitb arvregimen, exact row col
```

Key
frequency *row percentage* *column percentage*

antitb	arvregimen 1	2	Total
0	174	175	349
	49.86	50.14	100.00
	99.43	100.00	99.71
1	1	0	1
	100.00	0.00	100.00
	0.57	0.00	0.29
Total	175	175	350
	50.00	50.00	100.00
	100.00	100.00	100.00

```
          Fisher's exact =                 1.000
  1-sided Fisher's exact =                 0.500
```

```
. tab other_med arvregimen, chi row col
```

Key
frequency *row percentage* *column percentage*

other_med	arvregimen 1	2	Total
0	159 48.92 90.86	166 51.08 94.86	325 100.00 92.86
1	16 64.00 9.14	9 36.00 5.14	25 100.00 7.14
Total	175 50.00 100.00	175 50.00 100.00	350 100.00 100.00

Pearson chi2(1) = 2.1108 Pr = 0.146

. tab tripletherapy_specify

tripletherapy_specify	Freq.	Percent	Cum.
3TC, AZT, NVP	1	0.57	0.57
ABC, 3TC, EFV	15	8.57	9.14
ABC, 3TC, LPV\r	1	0.57	9.71
ABC, 3TC, NVP	4	2.29	12.00
AZT, 3TC, LPV\r	4	2.29	14.29
EFV, D4T, 3TC	2	1.14	15.43
TDF, 3TC, ATZ\RIT	5	2.86	18.29
TDF, 3TC, EFV	3	1.71	20.00
TDF, 3TC, LPV\r	136	77.71	97.71
TDF, 3TC, NVP	4	2.29	100.00
Total	175	100.00	

. tab alcohol

alcohol	Freq.	Percent	Cum.
0	350	100.00	100.00
Total	350	100.00	

. tab familyhistory

familyhistory	Freq.	Percent	Cum.
0	350	100.00	100.00
Total	350	100.00	

. tab1 diabetes hpt tb asthma other_comorb, miss

-> tabulation of diabetes

diabetes	Freq.	Percent	Cum.
0	304	86.86	86.86
1	44	12.57	99.43
.	2	0.57	100.00
Total	350	100.00	

-> tabulation of hpt

hpt	Freq.	Percent	Cum.
0	314	89.71	89.71
1	34	9.71	99.43
.	2	0.57	100.00
Total	350	100.00	

-> tabulation of tb

tb	Freq.	Percent	Cum.
0	346	98.86	98.86
1	2	0.57	99.43
.	2	0.57	100.00
Total	350	100.00	

-> tabulation of asthma

asthma	Freq.	Percent	Cum.
0	339	96.86	96.86
1	9	2.57	99.43
.	2	0.57	100.00
Total	350	100.00	

-> tabulation of other_comorb

other_comorb	Freq.	Percent	Cum.
0	332	94.86	94.86
1	16	4.57	99.43
.	2	0.57	100.00
Total	350	100.00	

```
. tab1 antihpt antihyperglycaemic statin antitb other_med, miss
```

-> tabulation of antihpt

antihpt	Freq.	Percent	Cum.
0	316	90.29	90.29
1	34	9.71	100.00
Total	350	100.00	

-> tabulation of antihyperglycaemic

antihyperglycaemic	Freq.	Percent	Cum.
0	307	87.71	87.71
1	43	12.29	100.00
Total	350	100.00	

-> tabulation of statin

statin	Freq.	Percent	Cum.
0	334	95.43	95.43
1	16	4.57	100.00
Total	350	100.00	

-> tabulation of antitb

antitb	Freq.	Percent	Cum.
0	349	99.71	99.71
1	1	0.29	100.00
Total	350	100.00	

-> tabulation of other_med

other_med	Freq.	Percent	Cum.
0	325	92.86	92.86
1	25	7.14	100.00
Total	350	100.00	

```
. bysort arvregimen: tabstat glucose_mean cholesterol_mean hdl_mean ldl_mean triglycerides_mean
> n systolic_mean diastolic_mean , stat(n mean sd p50 p25 p75 min max)
```

-> arvregimen = 1

stats	glucos~n	choles~n	hdl_mean	ldl_mean	trigly~n	bmi_mean	systol~n	diasto~n
N	175	17	17	17	17	174	175	175
mean	5.446667	4.341569	1.305882	2.228137	1.515	27.04023	118.2743	75.07238
sd	1.995736	.9536373	.5117173	.7770995	.7980064	5.746098	10.3953	7.566806
p50	5	4.413333	1.16	2.306667	1.38	26.83333	117	74.66666
p25	4.5	3.56	1.02	1.825	.9933333	22	112	70.33334
p75	5.666667	5.096667	1.476667	2.62	1.806667	31.33333	122.3333	78.66666
min	3.466667	2.8	.48	.44	.5566667	17.66667	93	57.33333
max	22.2	5.783333	2.52	3.85	3.785	45	162	104.6667

-> arvregimen = 2

stats	glucos~n	choles~n	hdl_mean	ldl_mean	trigly~n	bmi_mean	systol~n	diasto~n
N	175	152	152	148	151	168	173	173
mean	6.059619	4.810055	1.247467	2.761667	1.745806	27.33333	123.3892	78.92871
sd	2.134176	1.402655	.3705413	1.029489	1.295744	4.82205	10.95316	6.879433
p50	5.366667	4.6	1.175	2.655	1.456667	26.33333	121.3333	79
p25	4.8	3.855	1.018334	2.053333	.96	23.66667	116	74.33334
p75	6.4	5.448333	1.41	3.29	2.015	30.5	129.3333	83.33334
min	3.9	2.13	.3966667	.96	.31	18.33333	100.3333	61.33333
max	17.73333	10.125	2.74	7.016667	10.165	40.33333	170.6667	103.3333

```
. tab arvregimen metabolicsyndrome, chi row col
```

Key
frequency *row percentage* *column percentage*

arvregimen	metabolicsyndrome 0	1	Total
1	158	17	175
	90.29	9.71	100.00
	54.11	29.31	50.00
2	134	41	175
	76.57	23.43	100.00
	45.89	70.69	50.00
Total	292	58	350
	83.43	16.57	100.00

```
           |     100.00      100.00 |     100.00

         Pearson chi2(1) =  11.9036   Pr = 0.001
```

```
. oneway glucose_mean arvregimen, means standard obs
```

arvregimen	Summary of glucose_mean Mean	Std. Dev.	Obs.
1	5.4466668	1.9957365	175
2	6.0596191	2.1341759	175
Total	5.7531429	2.0858573	350

Source	Analysis of Variance SS	df	MS	F	Prob > F
Between groups	32.8746722	1	32.8746722	7.70	0.0058
Within groups	1485.55473	348	4.26883543		
Total	1518.4294	349	4.35080058		

```
Bartlett's test for equal variances:  chi2(1) =   0.7798  Prob>chi2 = 0.377
```

```
. oneway cholesterol_mean arvregimen, means standard obs
```

arvregimen	Summary of cholesterol_mean Mean	Std. Dev.	Obs.
1	4.3415686	.95363729	17
2	4.8100548	1.4026554	152
Total	4.762929	1.3692855	169

Source	Analysis of Variance SS	df	MS	F	Prob > F
Between groups	3.35582649	1	3.35582649	1.80	0.1817
Within groups	311.634559	167	1.8660752		
Total	314.990385	168	1.87494277		

```
Bartlett's test for equal variances:  chi2(1) =   3.4407  Prob>chi2 = 0.064
```

```
. oneway hdl_mean arvregimen, means standard obs
```

arvregimen	Summary of hdl_mean Mean	Std. Dev.	Obs.
1	1.3058824	.51171727	17
2	1.2474671	.37054126	152
Total	1.2533432	.38555983	169

Source	Analysis of Variance SS	df	MS	F	Prob > F
Between groups	.052174494	1	.052174494	0.35	0.5551
Within groups	24.9220972	167	.149234115		
Total	24.9742717	168	.148656379		

```
Bartlett's test for equal variances:  chi2(1) =   3.5143  Prob>chi2 = 0.061
```

```
. oneway ldl_mean arvregimen, means standard obs
```

arvregimen	Summary of ldl_mean Mean	Std. Dev.	Obs.
1	2.2281373	.7770995	17
2	2.7616667	1.0294888	148
Total	2.706697	1.0175299	165

Source	Analysis of Variance SS	df	MS	F	Prob > F
Between groups	4.34053634	1	4.34053634	4.28	0.0402
Within groups	165.45966	163	1.01508994		
Total	169.800196	164	1.03536705		

Bartlett's test for equal variances: chi2(1) = 1.9264 Prob>chi2 = 0.165

```
. oneway triglycerides_mean arvregimen, means standard obs
```

arvregimen	Summary of triglycerides_mean Mean	Std. Dev.	Obs.
1	1.515	.7980064	17
2	1.7458057	1.2957442	151
Total	1.7224504	1.2545628	168

Source	Analysis of Variance SS	df	MS	F	Prob > F
Between groups	.813972573	1	.813972573	0.52	0.4737
Within groups	262.031974	166	1.57850587		
Total	262.845947	167	1.57392782		

Bartlett's test for equal variances: chi2(1) = 5.1617 Prob>chi2 = 0.023

```
. oneway systolic_mean arvregimen, means standard obs
```

arvregimen	Summary of systolic_mean Mean	Std. Dev.	Obs.
1	118.27429	10.3953	175
2	123.38921	10.953158	173
Total	120.81705	10.964183	348

Source	Analysis of Variance SS	df	MS	F	Prob > F
Between groups	2276.05867	1	2276.05867	19.97	0.0000
Within groups	39437.9632	346	113.982553		
Total	41714.0219	347	120.21332		

Bartlett's test for equal variances: chi2(1) = 0.4712 Prob>chi2 = 0.492

```
. oneway diastolic_mean arvregimen, means standard obs
```

arvregimen	Summary of diastolic_mean Mean	Std. Dev.	Obs.
1	75.07238	7.5668056	175
2	78.928709	6.8794329	173
Total	76.989463	7.4764899	348

Analysis of Variance

Source	SS	df	MS	F	Prob > F
Between groups	1293.75779	1	1293.75779	24.73	0.0000
Within groups	18102.8139	346	52.3202713		
Total	19396.5717	347	55.8979011		

Bartlett's test for equal variances: chi2(1) = 1.5615 Prob>chi2 = 0.211

```
. oneway bmi_mean arvregimen, means standard obs
```

arvregimen	Summary of bmi_mean Mean	Std. Dev.	Obs.
1	27.04023	5.7460978	174
2	27.333333	4.8220497	168
Total	27.184211	5.3065848	342

Analysis of Variance

Source	SS	df	MS	F	Prob > F
Between groups	7.34300108	1	7.34300108	0.26	0.6103
Within groups	9595.16309	340	28.2210679		
Total	9602.50609	341	28.1598419		

Bartlett's test for equal variances: chi2(1) = 5.1714 Prob>chi2 = 0.023

```
.
. logistic metabolicsyndrome i.arvregimen
```

Logistic regression — Number of obs = 350; LR chi2(1) = 12.21; Prob > chi2 = 0.0005; Log likelihood = -151.05346; Pseudo R2 = 0.0388

metabolicsyndrome	Odds Ratio	Std. Err.	z	P>|z|	[95% Conf.	Interval]
2.arvregimen	2.843723	.8856978	3.36	0.001	1.544452	5.236005
_cons	.1075949	.0274636	-8.73	0.000	.0652413	.1774439

```
. logistic metabolicsyndrome bmi_mean
```

Logistic regression — Number of obs = 342; LR chi2(1) = 69.09; Prob > chi2 = 0.0000; Log likelihood = -117.9286; Pseudo R2 = 0.2266

metabolicsyndrome	Odds Ratio	Std. Err.	z	P>|z|	[95% Conf.	Interval]
bmi_mean	1.286055	.0458315	7.06	0.000	1.199292	1.379094
_cons	.0001249	.0001385	-8.11	0.000	.0000142	.0010977

```
. logistic metabolicsyndrome glucose_mean

Logistic regression                             Number of obs     =        350
                                                LR chi2(1)        =      81.13
                                                Prob > chi2       =     0.0000
Log likelihood = -116.59415                     Pseudo R2         =     0.2581

------------------------------------------------------------------------------
metabolicsyndrome | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
------------------+-----------------------------------------------------------
     glucose_mean |   2.115346   .2365498     6.70   0.000     1.699008    2.633708
            _cons |   .0020266   .0014449    -8.70   0.000      .000501     .008197
------------------------------------------------------------------------------

. logistic metabolicsyndrome cholesterol_mean

Logistic regression                             Number of obs     =        169
                                                LR chi2(1)        =       9.15
                                                Prob > chi2       =     0.0025
Log likelihood = -98.914175                     Pseudo R2         =     0.0442

------------------------------------------------------------------------------
metabolicsyndrome | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
------------------+-----------------------------------------------------------
 cholesterol_mean |   1.447054   .1841263     2.90   0.004     1.127654    1.856921
            _cons |   .0716056   .0465567    -4.06   0.000     .0200221    .2560842
------------------------------------------------------------------------------

. logistic metabolicsyndrome systolic_mean

Logistic regression                             Number of obs     =        348
                                                LR chi2(1)        =      86.03
                                                Prob > chi2       =     0.0000
Log likelihood = -113.77948                     Pseudo R2         =     0.2743

------------------------------------------------------------------------------
metabolicsyndrome | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
------------------+-----------------------------------------------------------
    systolic_mean |   1.143055   .0205483     7.44   0.000     1.103482    1.184047
            _cons |   1.17e-08   2.66e-08    -8.01   0.000     1.33e-10    1.02e-06
------------------------------------------------------------------------------

. logistic metabolicsyndrome diastolic_mean

Logistic regression                             Number of obs     =        348
                                                LR chi2(1)        =      76.36
                                                Prob > chi2       =     0.0000
Log likelihood =  -118.6128                     Pseudo R2         =     0.2435

------------------------------------------------------------------------------
metabolicsyndrome | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
------------------+-----------------------------------------------------------
   diastolic_mean |   1.216042     .03434     6.93   0.000     1.150565    1.285244
            _cons |   3.41e-08   7.84e-08    -7.48   0.000     3.76e-10    3.09e-06
------------------------------------------------------------------------------

. logistic metabolicsyndrome age_cont

Logistic regression                             Number of obs     =        350
                                                LR chi2(1)        =      25.51
                                                Prob > chi2       =     0.0000
Log likelihood = -144.40152                     Pseudo R2         =     0.0812

------------------------------------------------------------------------------
metabolicsyndrome | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
------------------+-----------------------------------------------------------
         age_cont |   1.068434   .0146386     4.83   0.000     1.040125    1.097514
            _cons |   .0108681   .0070423    -6.98   0.000      .003052    .0387004
------------------------------------------------------------------------------
```

```
. logistic metabolicsyndrome i.gender

Logistic regression                               Number of obs     =        350
                                                  LR chi2(1)        =       5.53
                                                  Prob > chi2       =     0.0187
Log likelihood = -154.39452                       Pseudo R2         =     0.0176

------------------------------------------------------------------------------
metabolicsyndrome | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
------------------+-----------------------------------------------------------
         1.gender |    .475913   .1567027    -2.26   0.024     .2496057    .9074038
            _cons |    .2514286  .0424025    -8.19   0.000     .1806603    .3499182
------------------------------------------------------------------------------

. logistic metabolicsyndrome i.comorbidities

Logistic regression                               Number of obs     =        350
                                                  LR chi2(1)        =      45.48
                                                  Prob > chi2       =     0.0000
Log likelihood = -134.41674                       Pseudo R2         =     0.1447

------------------------------------------------------------------------------
metabolicsyndrome | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
------------------+-----------------------------------------------------------
  1.comorbidities |    7.93247   2.475743     6.64   0.000     4.302753    14.62415
            _cons |    .0938776  .020473    -10.85   0.000     .0612251    .1439441
------------------------------------------------------------------------------

. logistic metabolicsyndrome age_cont i.gender i.arvregimen glucose_mean bmi_mean systolic_mear
> ic_mean i.comorbidities

Logistic regression                               Number of obs     =        340
                                                  LR chi2(8)        =     198.49
                                                  Prob > chi2       =     0.0000
Log likelihood = -52.865798                       Pseudo R2         =     0.6525

------------------------------------------------------------------------------
metabolicsyndrome | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
------------------+-----------------------------------------------------------
         age_cont |   1.002781   .0275318     0.10   0.919     .9502454    1.05822
         1.gender |   1.266197   .7716414     0.39   0.699        .3835    4.18059
     2.arvregimen |   9.377876   6.504999     3.23   0.001     2.408049    36.52108
     glucose_mean |   2.435583     .48495     4.47   0.000     1.648617    3.598206
        bmi_mean |   1.494764   .1112254     5.40   0.000     1.291917     1.72946
    systolic_mean |   1.076005   .0436547     1.81   0.071     .9937567    1.165061
   diastolic_mean |   1.099381   .0755478     1.38   0.168     .9608489    1.257887
  1.comorbidities |   6.082045   3.935522     2.79   0.005     1.711042    21.61914
            _cons |   2.36e-17   1.39e-16    -6.51   0.000     2.32e-22    2.39e-12
------------------------------------------------------------------------------

.
. tab gender metabolicsyndrome, chi row col

+----------------+
| Key            |
|----------------|
|     frequency  |
| row percentage |
| column percentage |
+----------------+
```

gender	metabolicsyndrome 0	1	Total
0	175	44	219
	79.91	20.09	100.00
	59.93	75.86	62.57
1	117	14	131
	89.31	10.69	100.00
	40.07	24.14	37.43
Total	292	58	350
	83.43	16.57	100.00
	100.00	100.00	100.00

Pearson chi2(1) = 5.2436 Pr = 0.022

```
. tab age metabolicsyndrome, chi row col
```

Key
frequency *row percentage* *column percentage*

age	metabolicsyndrome 0	1	Total
1	14	0	14
	100.00	0.00	100.00
	4.79	0.00	4.00
2	196	28	224
	87.50	12.50	100.00
	67.12	48.28	64.00
3	78	26	104
	75.00	25.00	100.00
	26.71	44.83	29.71
4	4	4	8
	50.00	50.00	100.00
	1.37	6.90	2.29
Total	292	58	350
	83.43	16.57	100.00
	100.00	100.00	100.00

Pearson chi2(3) = 17.2768 Pr = 0.001

```
. tab ethnicity metabolicsyndrome, exact row col
```

Key
frequency *row percentage* *column percentage*

```
Enumerating sample-space combinations:
stage 4:  enumerations = 1
stage 3:  enumerations = 2
stage 2:  enumerations = 7
stage 1:  enumerations = 0
```

ethnicity	metabolicsyndrome 0	1	Total
1	270	54	324
	83.33	16.67	100.00
	92.47	93.10	92.57
2	14	1	15
	93.33	6.67	100.00
	4.79	1.72	4.29
3	5	3	8
	62.50	37.50	100.00
	1.71	5.17	2.29
4	3	0	3
	100.00	0.00	100.00
	1.03	0.00	0.86
Total	292	58	350
	83.43	16.57	100.00
	100.00	100.00	100.00

Fisher's exact = 0.266

```
. tab comorbidities metabolicsyndrome, chi row col
```

Key
frequency *row percentage* *column percentage*

comorbidities	metabolicsyndrome 0	1	Total
0	245	23	268
	91.42	8.58	100.00
	83.90	39.66	76.57
1	47	35	82
	57.32	42.68	100.00
	16.10	60.34	23.43
Total	292	58	350
	83.43	16.57	100.00
	100.00	100.00	100.00

Pearson chi2(1) = 52.8124 Pr = 0.000

```
. tab comorbidities_specify metabolicsyndrome, exact row col
```

Key
frequency *row percentage* *column percentage*

```
Enumerating sample-space combinations:
stage 14: enumerations = 1
stage 13: enumerations = 2
stage 12: enumerations = 3
stage 11: enumerations = 4
stage 10: enumerations = 5
stage 9:  enumerations = 6
stage 8:  enumerations = 7
stage 7:  enumerations = 8
stage 6:  enumerations = 9
stage 5:  enumerations = 22
stage 4:  enumerations = 74
stage 3:  enumerations = 325
stage 2:  enumerations = 1269
stage 1:  enumerations = 0
```

comorbidities_specify	metabolicsyndrome 0	1	Total
1	13 46.43 28.26	15 53.57 44.12	28 100.00 35.00
1, 2	2 16.67 4.35	10 83.33 29.41	12 100.00 15.00
1, 2, 4	0 0.00 0.00	1 100.00 2.94	1 100.00 1.25
1, 4	0 0.00 0.00	1 100.00 2.94	1 100.00 1.25
1, 4, 5	1 100.00 2.17	0 0.00 0.00	1 100.00 1.25
1, 5	1 100.00 2.17	0 0.00 0.00	1 100.00 1.25
2	12 75.00 26.09	4 25.00 11.76	16 100.00 20.00
2, 3	1 100.00 2.17	0 0.00 0.00	1 100.00 1.25
2, 4	1 100.00 2.17	0 0.00 0.00	1 100.00 1.25
2, 5	1 33.33 2.17	2 66.67 5.88	3 100.00 3.75
3, 5	1 100.00 2.17	0 0.00 0.00	1 100.00 1.25
4	4 100.00 8.70	0 0.00 0.00	4 100.00 5.00
4, 5	1 100.00 2.17	0 0.00 0.00	1 100.00 1.25

5	8	1	9
	88.89	11.11	100.00
	17.39	2.94	11.25
Total	46	34	80
	57.50	42.50	100.00
	100.00	100.00	100.00

Fisher's exact = 0.002

```
. tab diabetes metabolicsyndrome, chi row col
```

Key
frequency *row percentage* *column percentage*

diabetes	metabolicsyndrome 0	1	Total
0	274	30	304
	90.13	9.87	100.00
	94.16	52.63	87.36
1	17	27	44
	38.64	61.36	100.00
	5.84	47.37	12.64
Total	291	57	348
	83.62	16.38	100.00
	100.00	100.00	100.00

Pearson chi2(1) = 74.4169 Pr = 0.000

```
. tab hpt metabolicsyndrome, chi row col
```

Key
frequency *row percentage* *column percentage*

hpt	metabolicsyndrome 0	1	Total
0	274	40	314
	87.26	12.74	100.00
	94.16	70.18	90.23
1	17	17	34
	50.00	50.00	100.00
	5.84	29.82	9.77
Total	291	57	348
	83.62	16.38	100.00
	100.00	100.00	100.00

Pearson chi2(1) = 31.0980 Pr = 0.000

```
. tab tb metabolicsyndrome, exact row col
```

Key
frequency *row percentage* *column percentage*

tb	metabolicsyndrome 0	1	Total
0	**289** **83.53** **99.31**	**57** **16.47** **100.00**	**346** **100.00** **99.43**
1	**2** **100.00** **0.69**	**0** **0.00** **0.00**	**2** **100.00** **0.57**
Total	**291** **83.62** **100.00**	**57** **16.38** **100.00**	**348** **100.00** **100.00**

```
          Fisher's exact =                 1.000
  1-sided Fisher's exact =                 0.699
```

```
. tab asthma metabolicsyndrome, chi row col
```

Key
frequency *row percentage* *column percentage*

asthma	metabolicsyndrome 0	1	Total
0	**284** **83.78** **97.59**	**55** **16.22** **96.49**	**339** **100.00** **97.41**
1	**7** **77.78** **2.41**	**2** **22.22** **3.51**	**9** **100.00** **2.59**
Total	**291** **83.62** **100.00**	**57** **16.38** **100.00**	**348** **100.00** **100.00**

```
          Pearson chi2(1) =   0.2303   Pr = 0.631
```

```
. tab other_comorb metabolicsyndrome, chi row col
```

Key
frequency *row percentage* *column percentage*

other_como rb	metabolicsyndrome 0	1	Total
0	278 83.73 95.53	54 16.27 94.74	332 100.00 95.40
1	13 81.25 4.47	3 18.75 5.26	16 100.00 4.60
Total	291 83.62 100.00	57 16.38 100.00	348 100.00 100.00

Pearson chi2(1) = 0.0688 Pr = 0.793

```
. tab currentmedication metabolicsyndrome, exact row col
```

Key
frequency *row percentage* *column percentage*

```
Enumerating sample-space combinations:
stage 13: enumerations = 1
stage 12: enumerations = 2
stage 11: enumerations = 3
stage 10: enumerations = 4
stage 9:  enumerations = 10
stage 8:  enumerations = 28
stage 7:  enumerations = 91
stage 6:  enumerations = 191
stage 5:  enumerations = 491
stage 4:  enumerations = 1087
stage 3:  enumerations = 3208
stage 2:  enumerations = 8373
stage 1:  enumerations = 0
```

currentmed ication	metabolicsyndrome 0	1	Total
0	1 100.00 2.04	0 0.00 0.00	1 100.00 1.15
1	11 78.57 22.45	3 21.43 7.89	14 100.00 16.09
1, 2	2 20.00 4.08	8 80.00 21.05	10 100.00 11.49
1, 2, 3	0 0.00 0.00	2 100.00 5.26	2 100.00 2.30
1, 2, 5	0 0.00 0.00	1 100.00 2.63	1 100.00 1.15
1, 3	1 33.33 2.04	2 66.67 5.26	3 100.00 3.45
1, 5	3 75.00 6.12	1 25.00 2.63	4 100.00 4.60

2	12	9	21
	57.14	42.86	100.00
	24.49	23.68	24.14
2, 3	1	4	5
	20.00	80.00	100.00
	2.04	10.53	5.75
2, 5	2	2	4
	50.00	50.00	100.00
	4.08	5.26	4.60
3	2	4	6
	33.33	66.67	100.00
	4.08	10.53	6.90
4, 5	1	0	1
	100.00	0.00	100.00
	2.04	0.00	1.15
5	13	2	15
	86.67	13.33	100.00
	26.53	5.26	17.24
Total	49	38	87
	56.32	43.68	100.00
	100.00	100.00	100.00

Fisher's exact = 0.005

```
. tab antihpt metabolicsyndrome, chi row col
```

Key
frequency *row percentage* *column percentage*

	metabolicsyndrome		
antihpt	0	1	Total
0	275	41	316
	87.03	12.97	100.00
	94.18	70.69	90.29
1	17	17	34
	50.00	50.00	100.00
	5.82	29.31	9.71
Total	292	58	350
	83.43	16.57	100.00
	100.00	100.00	100.00

Pearson chi2(1) = 30.4383 Pr = 0.000

```
. tab antihyperglycaemic metabolicsyndrome, chi row col
```

Key
frequency *row percentage* *column percentage*

antihyperglycaemic	metabolicsyndrome 0	1	Total
0	275 89.58 94.18	32 10.42 55.17	307 100.00 87.71
1	17 39.53 5.82	26 60.47 44.83	43 100.00 12.29
Total	292 83.43 100.00	58 16.57 100.00	350 100.00 100.00

Pearson chi2(1) = 68.3168 Pr = 0.000

```
. tab statin metabolicsyndrome, chi row col
```

Key
frequency *row percentage* *column percentage*

statin	metabolicsyndrome 0	1	Total
0	288 86.23 98.63	46 13.77 79.31	334 100.00 95.43
1	4 25.00 1.37	12 75.00 20.69	16 100.00 4.57
Total	292 83.43 100.00	58 16.57 100.00	350 100.00 100.00

Pearson chi2(1) = 41.4016 Pr = 0.000

```
. tab antitb metabolicsyndrome, exact row col
```

Key
frequency *row percentage* *column percentage*

antitb	metabolicsyndrome 0	1	Total
0	291 83.38 99.66	58 16.62 100.00	349 100.00 99.71
1	1 100.00 0.34	0 0.00 0.00	1 100.00 0.29
Total	292 83.43 100.00	58 16.57 100.00	350 100.00 100.00

Fisher's exact = 1.000
1-sided Fisher's exact = 0.834

```
. tab other_med metabolicsyndrome, chi row col
```

Key
frequency *row percentage* *column percentage*

other_med	metabolicsyndrome 0	1	Total
0	273 84.00 93.49	52 16.00 89.66	325 100.00 92.86
1	19 76.00 6.51	6 24.00 10.34	25 100.00 7.14
Total	292 83.43 100.00	58 16.57 100.00	350 100.00 100.00

Pearson chi2(1) = 1.0746 Pr = 0.300

```
. tab bmi_cat metabolicsyndrome, exact row col
```

Key
frequency *row percentage* *column percentage*

```
Enumerating sample-space combinations:
stage 4:  enumerations = 1
stage 3:  enumerations = 2
stage 2:  enumerations = 62
stage 1:  enumerations = 0
```

bmi_cat	metabolicsyndrome 0	1	Total
1	1 100.00 0.35	0 0.00 0.00	1 100.00 0.29
2	119 95.20 42.05	6 4.80 10.71	125 100.00 36.87
3	106 92.17 37.46	9 7.83 16.07	115 100.00 33.92
4	57 58.16 20.14	41 41.84 73.21	98 100.00 28.91
Total	283 83.48 100.00	56 16.52 100.00	339 100.00 100.00

Fisher's exact = 0.000

```
. oneway age_cont metabolicsyndrome, means standard obs
```

metabolicsyndrome	Summary of age_cont Mean	Std. Dev.	Obs.
0	40.089041	10.219193	292
1	48.155172	11.901351	58
Total	41.425714	10.919288	350

Analysis of Variance

Source	SS	df	MS	F	Prob > F
Between groups	3148.28019	1	3148.28019	28.48	0.0000
Within groups	38463.2884	348	110.526691		
Total	41611.5686	349	119.230856		

Bartlett's test for equal variances: chi2(1) = 2.3532 Prob>chi2 = 0.125

```
. oneway bmi_mean metabolicsyndrome, means standard obs
```

metabolicsyndrome	Summary of bmi_mean Mean	Std. Dev.	Obs.
0	26.134033	4.724073	286
1	32.547619	4.8913154	56
Total	27.184211	5.3065848	342

Analysis of Variance

Source	SS	df	MS	F	Prob > F
Between groups	1926.32618	1	1926.32618	85.32	0.0000
Within groups	7676.17991	340	22.5769997		
Total	9602.50609	341	28.1598419		

Bartlett's test for equal variances: chi2(1) = 0.1127 Prob>chi2 = 0.737

```
.
end of do-file

.
```

	FDC AIP 1	TT AIP 1	FDC AIP 2	TT AIP 2	FDC AIP 3	TT AIP 3
Number of values	10	41	6	39	4	24
Minimum	-0.3800	-0.6100	-0.4200	-0.2400	-0.5700	-0.3200
25% Percentile	-0.2025	0.0400	0.0525	0.0800	-0.3875	-0.1450
Median	0.0750	0.3000	0.4050	0.3900	0.2050	0.1250
75% Percentile	0.3300	0.5050	0.5925	0.5300	0.5950	0.4950
Maximum	0.6100	1.270	0.6900	1.190	0.7100	1.180
Mean	0.0840	0.2834	0.3083	0.3391	0.1375	0.2018
Std. Deviation	0.3335	0.3434	0.4025	0.3103	0.5296	0.4052
Std. Error	0.1055	0.05364	0.1643	0.04969	0.2648	0.08272
Lower 95% CI of mean	-0.1546	0.1750	-0.1140	0.2385	-0.7052	0.03073
Upper 95% CI of mean	0.3226	0.3918	0.7307	0.4397	0.9802	0.3729
Sum	0.8400	11.62	1.850	13.23	0.5500	4.844