Addis Ababa University

College of Health Sciences

School of Pharmacy

Department of Pharmacology and Clinical Pharmacy

Cardiometabolic syndrome among HIV patients on protease inhibitors based anti-retroviral treatment at Zewuditu Memorial Hospital (ZMH).

By: Yitayal Ababu

A Thesis Submitted to the Department of Pharmacology and Clinical Pharmacy, School of Pharmacy, College of Health Sciences, Addis Ababa University in partial fulfillment of the requirements for the Master of Science degree in pharmacology (clinical).

Oct, 2019 Addis Ababa, Ethiopia

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This is to certify that the thesis prepared by Yitayal Ababu, entitled: Cardiometabolic syndrome among HIV patients on protease inhibitors based anti-retroviral treatment at Zewuditu Memorial Hospital and submitted in partial fulfillment of the requirements for the Master of Science degree in pharmacology (clinical) complies with the regulations of the University and meets the accepted standards with respect to originality and quality.

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Abstract

Cardiometabolic syndrome among HIV patients on protease inhibitors based anti-retroviral treatment at Zewuditu Memorial Hospital

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September, 2019 Addis Ababa University

The human immunodeficiency virus is a human T-cell lymphotropic retrovirus of the lentivirus subgroup that induces immune-suppression and causes the acquired immunodeficiency syndrome (AIDS). Anti-retroviral therapy (ART) has definitely decreased mortality and increased the quality of life of affected individuals but using highly active anti-retroviral therapy (HAART) containing especially protease inhibitors (PIs) in HIV infection management has led to increased prevalence of cardiometabolic syndrome (CMS). Although several studies on CMS in HIV-positive patients on HAART, and the risk of cardiovascular disease (CVD) has been conducted in many countries, there are few researches especially on PIs conducted in Ethiopia. Therefore, the aim of this study was to narrow this gap and determine the magnitude of CMS components including hypertension, dyslipidemia and diabetes to identify the risk of CVD among HIV-positive patients on HAART. Hospital based prospective cohort study was conducted at Zewditu Memorial Hospital between March 2018 to December 2018**.** The source population included all HIV patients who were on chronic HAART follow up. All HIV patients that met the inclusion criteria were recruited over a four-month period. Socio-demographic, medical history, behavioral and dietary exposures were obtained from patient self-report data using a structured questionnaire. The data were entered and processed using SPSS version 23 statistical software. Ethical clearance was obtained from Institutional Review Board of the College of Health Sciences, Addis Ababa University and Addis Ababa Health Bureau. One hundred forty patients, 52 males (37.1%) and 88 females (62.9%) were included in the study. Using Adult Treatment Pannel III criteria 59 patients (42.1%) were diagnosed for the presence of CMS. The prevalence of hypertension, hypertriglyceridemia, impaired fasting glucose (IFG) and abnormal waist circumference were 50.0%, 65.7%, 67.1% and 47.1%, respectively. In multivariate analysis, having abnormal BMI, i.e., over weight (AOR: 4.87, CI: 1.49-15.69) and total cholesterol ≥ 200 mg/dl (AOR: 3.67, CI: 1.17-11.49) were independently associated with CMS. High prevalence of CMS (42.1%) among HIV infected patients receiving PIs was observed. Prevalence in CMS components was also higher, IFG being the most prevalent one.

Keywords: Dyslipidemia; Impaired Fasting Glucose; Hypertension; Obesity; Protease Inhibitors based Anti-retroviral Therapy

Acknowledgement

I would like to express my deepest gratitude to the department of pharmacology and clinical pharmacy for giving me an ample time and facilitating anything with regard to conducting this research. In addition to this, I am also very grateful to my advisors, Dr.Solomon Mequanente, Prof. Eyasu Makonnen and Dr. Aster Shawamare for their constructive comments and suggestions in conducting this research and writing the thesis. Our gratitude also goes to Ato Abebe Teshome and Sr.Tizita W/Yes for helping us in collecting data and facilitating anything we wanted with regard to our research and the laboratory staff for their great help at Zewditu Memorial Hospital.

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List of Abbreviations/Acronyms

ABC	Abacavir
Apo B	Apolipoprotein B
ART	Antiretroviral therapy
ARV	Antiretroviral
ATV/r	Atazanavir/ritonavir
BMI	Body mass index
CVD	Cardiovascular diseases
CMS	Cardiometabolic syndrome
CRABP1	Cytoplasmic retinoic acid-binding protein type 1
DM	Diabetes mellitus
EFV	Efavirenz
FPG	Fasting plasma glucose
GLUT-4	Glucose transporter type 4
HAART	Highly active antiretroviral therapy
HDL	High density lipoprotein
HTN	Hypertension
IFG	Impaired fasting glucose
IDF	International diabetes federation
3TC	Lamivudine
LRP1	LDL receptor related protein type 1
LDL	Low density lipoprotein
LPV/r	Lopinavir/ritonavir

MS	Metabolic syndrome
NCEP	National cholesterol education program
NVP	Nevirapine
NRTIs	Nucleoside reverse transcriptase inhibitors
NNRTIs	Non-nucleoside reverse transcriptase inhibitors
OR	Odds ratio
PPARγ	Perixisome proliferator activated receptor γ
PI	Protease inhibitor
RXR	Retinoid X receptor
SPSS	Statistical package for the social sciences
SREP-1	Sterol regulatory element protein-1
TC	Total cholesterol
TDF	Tenofovir desoproxil fumarate
TG	Triglyceride
VLDL	Very low density lipoprotein
WHO	World Health Organization
AZT	Zidovudine

1. Introduction

1.1. Background

The human immunodeficiency virus (HIV) is a human T-cell lymphotropic retrovirus of the lentivirus subgroup that induces immunosuppression and causes the acquired immunodeficiency syndrome (AIDS). The lentivirus subgroup causes “slow” infections, meaning there is a latent clinical phase between infection and outbreak of disease. There is currently no cure for HIV – it is a life-long and chronic infection. There are two types of human immunodeficiency viruses – HIV-1 and HIV-2 – that can both cause AIDS. While HIV-1 is found worldwide, the less severe and virulent HIV-2 is mainly prevalent in West Africa (Mellin, 2015).

Since the recognized beginning of the epidemic in the 1980s, almost 78 million people have been infected with HIV and 35 million have died from the consequences. In 2013, there were 35 million people infected with HIV worldwide, with an incidence (rate of annual new infections) of 2.1 million and a mortality rate of 1.5 million per year. 71% of all people living with HIV/AIDS live in sub-Saharan Africa (Mellin, 2015).The HIV epidemic in Ethiopia is heterogeneous by sex, geographic areas and population groups. It is highest in Gambella (4.8 %), followed by Addis Ababa (3.4%).In 2017, there were an estimated 613,000 people living with HIV, of whom 62 percent females (Federal HIV/AIDS Prevention and Control Office, 2018). According to HIV Related Estimates and Projections for Ethiopia–2017, 131,280 people were estimated to be living with HIV in Addis Ababa in 2019, of whom 60.36 percent being females (The Ethiopian Public Health Institute, 2017).

The introduction of highly active anti-retroviral therapy (HAART) over the last few decades has significantly modified the devastating effects of HIV by prolonging survival and improving patients’ quality of life. In parallel, increasing cardio-metabolic complications have been documented since the introduction of HAART. Early data established that HAART regimens (especially protease inhibitors (PIs)) are associated with increased metabolic changes that are usually associated with a higher risk for cardiovascular diseases (CVD) (typically coronary and peripheral artery disease, strokes) (Abaid, 2016).

The government of Ethiopia took several steps in preventing further disease spread, and in increasing accessibility to HIV care, treatment and support for persons living with HIV. Free anti-retroviral (ARV) service was launched in January 2005 and public hospitals start providing free ARVs in March 2005. Currently ART service is available in 913 Health facilities of which 765 are Health centers. On the basis of the 2010-2014 strategic plan ART coverage for adults (age 15+) has reached 76% but the coverage remains low (23.5%) for children (age <15) living with HIV. All HIV positives are eligible for ART. The ideal time for ART initiation depends on the clinical condition and readiness of the client. For HIV positive clients who understand and accept the importance of early initiation, ART is initiated as early as possible. Using simplified, less toxic and more convenient regimens as fixed-dose combinations is recommended for first-line ART. Once-daily regimens comprising NRTI backbone (TDF + 3TC) and one NNRTI (EFV) are maintained as the preferred choices in adults, adolescents and children older than ten years. Using a boosted PI + two NRTI combinations (determined by the drug used in first-line therapy) is recommended as the preferred strategy for second-line ART for adults, adolescents (Table 1). Once patients are switched to second line regimen, strong adherence support should be continued and viral load monitoring should be started after six months of second line treatment and then every 12 months (Federal Ministry of Health, 2017).

The long-term use of HAART is strongly associated with disruption of the carbohydrate and lipid metabolism, subsequently resulting in the development of metabolic diseases, such as type 2 diabetes mellitus (DM2) and dyslipidaemia (Mashao, 2016). PIs have been particularly associated with several adverse effects, including GI symptoms (such as diarrhoea, nausea and vomiting), dyslipidaemia, insulin resistance and fat redistribution (lipohypertrophy), some of which are well recognized risk factors for cardiovascular disease (Naggie & Hicks, 2010).

Table 1: Summary of 1st and 2nd-line ART regimens

Population	Preferred 1st line regimens	Alternatives 1st line regimens	Preferred 2nd line regimens	
Adults	TDF + 3TC +EVF (FDC)	AZT +3TC + EVF AZT +3TC + NVP TDF + 3TC + NVP	If AZT was used in 1st line ART	TDF +3TC +LPV/r or ATV/r
			If TDF was used in 1st-line ART	AZT + 3TC +LPV/r or ATV/r
Adolescents(10 to 19 years) ≥35kg		AZT +3TC + EFV AZT +3TC + NVP TDF + 3TC + NVP ABC + 3TC + EFV		

Source: Adopted from(Federal Ministry of Health, 2017)

Presence of Metabolic syndrome increases the risk of developing DM2 and CVD. For these reasons, the metabolic syndrome has more recently been referred to as cardiometabolic syndrome (CMS)(Rice *et al*., 2011).The presence of CMS is defined using the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III)(NCEP-ATP III, 2006) and the International Diabetes Federation (IDF) (Alberti *et al*., 2006), which are both the most widely used definitions. According to NCEP-ATP III, the presence of any 3 of the following clinical abnormalities would meet the criteria for the definition: waist circumference ≥88 cm in women and ≥102 cm in men, triglycerides ≥150 mg/dL, HDL < 50 mg/dL in women or <40 mg/dL in men, fasting plasma glucose ≥ 100 mg/dl, or blood pressure ≥130/≥85 mmHg(NCEP-ATP III, 2006). IDF defines this syndrome as the presence of at least three of the following five components: waist circumference (adjusted for Africans) ≥80 cm in women and ≥94 cm in men plus two of the following: triglycerides ≥l50 mg/dL or specific treatment for this lipid abnormality, HDL <40 mg/dl in males and <50 mg/dl in females, fasting plasma glucose ≥ 100 mg/dL or previously diagnosed DM2, systolic blood pressure ≥ 130 mmHg, or diastolic blood pressure ≥ 85 mmHg (Alberti *et al*., 2006).

Prevalence of CMS among HIV-infected patients globally ranges from 17.0% to 45.4% (Martínez *et al*., 2004) and in Africa; it ranges from 13% to 58% for CMS, 2.1% to 26.5% for diabetes, 20.2% to 43.5% for pre-diabetes and 13% to 70% for dyslipidemia (Husain *et al*., 2017). Berhane *et al*., 2012 reported that CMS was detected in 21.1% of patients on HAART in Jimma, Ethiopia after 12 months of ART (Berhane *et al*., 2012). The study in Australia also showed that CMS was more common in those patients receiving protease inhibitors (Samaras *et al*., 2007).

1.2. Statement of Problem

The introduction of HAART in the management of HIV infection has significantly reduced morbidity and mortality rates in HIV-positive patients. However, HAART especially PIs have created a new burden of metabolic disorders that are risk factors for CVD (Kiage *et al*., 2013).

The epidemic proportion of CMS in the world today and its subsequent downstream impact on cardiovascular system herald a catastrophic impact on the world population with anticipated tens of millions of avoidable deaths. Considering the health and economic factors projected to occur due to the effects of this syndrome, the forecast is dismal and bodes poor for individual nations and for humanity as a whole. Unless concerted efforts with clear and concentrated action plans are carried out by the world community to address this silent and little noted epidemic, the cost in lives lost may be in excess of those caused by natural disasters, man-made disasters, accidental deaths and even major conflicts and wars (Kelli *et al*., 2015).

In sub-Saharan Africa, an interesting association between HIV infection and its treatment with two classes of ART; Nucleoside Reverse Transcriptase Inhibitors (NRTIs) and PIs, have been made with increased prevalence of CMS, diabetes and cardiovascular disease (Young *et al*., 2009).

CMS is a major public-health and medical challenge that is on the increase globally (Alberti *et al*., 2006). In Africa, diabetes as component of CMS affects more than 14 million people, and it is expected that by 2030, 28 million individuals will be affected (Whiting *et al*, 2011). According to Alberti *et al*., CMS patients have increased risk of myocardial infarction up to 3- to 4-fold, of

stroke up to 2- to 4-fold, and a 2-fold risk of dying from these CMS components (Alberti *et al*., 2006).

Although several studies on CMS in HIV-positive patients on HAART, and the risk of CVD have been conducted in many countries, there are few researches, especially on PIs, conducted in Ethiopia. The other thing, the prevalence of HIV patients in sub-Saharan Africa as mentioned earlier accounts for 71% of HIV population in the world. Ethiopia is one of the high HIV prevalence countries in Africa *i.e*., this high prevalence will in turn causes the occurrence of new diabetic cases on account of adverse effects attributed to the use of HAART especially PIs. In addition to this, the case of DM is increasing alarmingly. This further increases the prevalence of DM and other components of CMS, thereby presenting challenges in the treatment process, and also creates a burden on the finances of these individuals.

There is a controversy on the burden of CMS on account of PIs in comparison with other HAART regimen. Jacobson *et al*., 2006 reported that PI drugs have been associated with more severe dyslipidaemia compared to NNRTI, which is a feature of CMS. This would explain at least in part the high prevalence of CMS in patients on PI (Jacobson *et al*., 2006). On the contrary Mbunkah *et al*., 2014 reported that the patients on first-line drugs demonstrated the highest CMS prevalence (15/62; 24.2%) followed by the ART-naïve group of patients (7/61; 11.5%) and the lowest prevalence was among patients on PIs (5/50; 10%) (Mbunkah *et al*., 2014).These reports support the need of further research to clearly describe the relationship between PIs and cardio-metabolic components.

1.3. Significance of the study

Different studies showed that HAART especially PIs cause CMS but there were no research on PIs but HAART in general in the Ethiopian context and hence this study's findings will help identify cardio metabolic risk factors attributed to the side effects of PI based antiretroviral therapy and the other associated risk factors.

The burden would be enormous if HIV-infected individuals come down with other chronic diseases such as hypertension, diabetes or hyperlipidemia that are characteristics of CMS, and risk factors for CVD. Thus, the results obtained in this study could provide insights into the factors that contribute to developing CMS in HIV-infected individuals, with a view of developing intervention programs on lifestyle changes (diet and exercise) to prevent CMS while on antiretroviral drugs especially on PIs containing HAART regimen. These intervention programs could minimize the risk for cardiovascular disease, reduce patients' medical expenditures, and cost of health care generally, thereby promoting positive social change by improving the quality of life of these groups of individuals.

The controversial issues on the magnitude of PIs on the prevalence of CMS compared to other HAART regimen may be solved. The findings of the study will also be used as reference for those who will be seeking information on this.

As stated above there has been a research gap on CMS and its components on account of PIs based ART and hence, this study will narrow this gap and determine the relationship between PI based ART regimen and CMS components including hypertension, dyslipedemia, diabetes and obesity to identify the risk of CVD among HIV-positive patients receiving PIs based regimens at Zewditu Memorial Hospital.

2. Literature Review

2.1. Prevalence of cardiometabolic syndrome and its Components in PIs based ART Regimens

A study conducted in Boston reported that the cumulative incidence of new-onset hyperglycemia, hypercholesterolemia, hypertriglyceridemia, and lipodystrophy after initiation of PIs based ART was 5%, 24%, 19%, and 13%, respectively (Tsiodras *et al*., 2000). PIs were independently associated with hyperglycemia, hypercholesterolemia, hypertriglyceridemia and lipodystrophy. The association between hypertriglyceridemia and ritonavir was stronger than for other PIs. In contrast, the incidence of hyperglycemia, hypercholesterolemia, and lipodystrophy did not vary significantly across different PIs (Tsiodras *et al*., 2000).

A research in New Jersey showed that seven (6%) of one hundred seventeen patients not previously known to be diabetic but received PIs developed symptomatic DM. According to this study, eight other patients had one or more serum glucose values >150 mg/dL and the mean random glucose values for patients who did not develop diabetes were higher during therapy than prior to initiation of PIs (Dever *et al*., 2000).

Another research conducted in Boston revealed that the prevalence of CMS was greater in PI treated than non-PI-treated HIV-infected patients (45 vs. 19%, P= 0.001) and also showed that PI-treated patients demonstrated significantly increased triglycerides compared with non-PI-treated patients (63 vs. 38%, P= 0.02), and a significantly higher proportion of PI-treated patients demonstrated elevated blood pressure (30 **vs.** 8%, P= 0.004**)** (Johnsen *et al*., 2006).

According to the study done in Thailand, the proportion of dyslipidemia, hypertriglyceridemia, low HDL-cholesterol and CMS in HIV patients receiving PIs based HAART regimen were 70%,43.8% , 38.8% and 10% respectively (Santiprabhob *et al*., 2017).The research in Cameroon also showed that the prevalence of CMS among the patients on PIs was 10% (5/50) (Mbunkah *et al*., 2014).

A study conducted in Taiwan university hospital reported that use of PIs was significantly associated with the presence of metabolic syndrome (OR 1.63; 95% CI 1.10–2.43). One hundred

and fifty patients (32.23%) were diagnosed for the presence of CMS out of 464 patients who were on PIs based ART **(**Wu *et al*., 2012**).**

2.2. Mechanism of cardiometabolic syndrome

HIV protease is responsible for a critical step during the HIV life cycle, i.e. the proteolytic cleavage of polypeptide precursors into mature enzymes and structural proteins. PIs are peptide-like chemicals that competitively inhibit the action of HIV protease. Such drugs inhibit proteolytic cleavage of HIV Gag and poly proteins which are important structural and enzymatic components of the new virus and thus prevents conversion of HIV particles into the mature virus (Fig.1) (Imamichi, 2005).

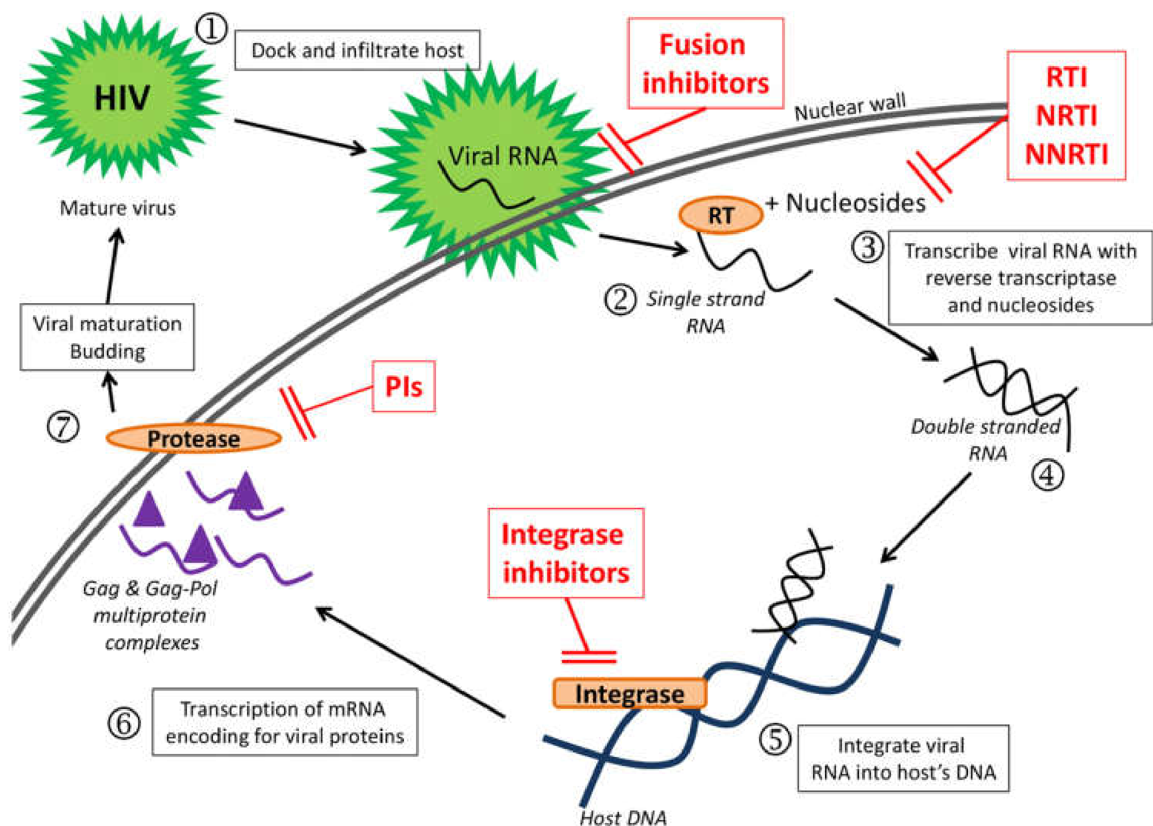

Figure 1: HIV lifecycle and anti-retroviral drug targets

Source: adapted from (Reyskens & Essop, 2014)

HIV PIs are implicated in the development of cardiovascular complications with greater risk for acute myocardial infarction (AMI) and coronary syndromes. PIs can trigger metabolic side-effects that resemble the CMS, a combination of risk factors that predispose patients to future onset of type 2 diabetes mellitus and CVD (Grundy *et al*., 2004). Increased TG and low-density lipoprotein (LDL) cholesterol levels together with decreased HDL cholesterol levels are the most common lipid changes associated with HIV/HAART (Mercié *et al*., 2000). In support, PIs lead to significant hypertriglyceridemia and low HDL-C, a strongly athrogenic pattern. This is associated with increased risk for myocardial infarction (MI) in HIV-infected patients. HDL can inhibit the expression of E-selectin or other adhesion molecules by vascular endothelial cells exposed to cytokines and this results in decreased binding of inflammatory cells, which is consistent with functional inhibition of atherosclerosis. Furthermore, supportive evidence for such HDL-mediated anti-atherogenic mechanisms is available from clinical studies where increased levels of adhesion molecules correlated with low HDL-cholesterol levels (Hernández *et al*., 2003).

The pathogenesis of dyslipidemia in this instance is complicated and includes several factors such as the effects of different drug classes, HIV itself, genetic predisposition, immunological and hormonal influences. In addition, traditional risk factors (e.g. male sex, age, increased BMI, family history of CVD and sedentary lifestyle) also affect pathogenic mechanisms that can contribute to HAART-induced dyslipidemia (Calza *et al*., 2008).

In-vivo lipoprotein turnover studies have shown that increased plasma triglyceride-rich very low density lipoprotein (VLDL) levels result from either decreased catabolism of these particles because of HIV infection itself, HAART-related increased production of VLDL, (Carpentier *et al*., 2005) or protease inhibitor-mediated impaired catabolism of VLDL (Shahmanesh *et al*., 2005). HAART treatment impairs hydrolysis of triglyceride-rich lipoproteins by plasma and tissue lipases (Reeds *et al*., 2006) and disrupts normal post-prandial free fatty acid and

In cultured hepatocytes, protease inhibitor treatment protects apolipoprotein B from degradation by intracellular proteasomes, thus increasing secretion of apolipoprotein B-containing lipoproteins (Liang *et al*., 2001). Furthermore, protease inhibitor-induced lipodystrophy in HIV

is associated with decreased expression of the LDL receptor and related receptors, which increases plasma LDL concentration (Petit *et al*., 2002).

Altered intracellular lipid metabolism has been attributed to the structural homology (approximately 60% at the aminoacid level) between the catalytic region of HIV protease and both cytoplasmic retinoic acid-binding protein type 1 (CRABP1) and LDL-receptor-related protein type 1 (LRP1). CRABP1 is involved in the conversion of retinoic acid to cis-9-retinoic acid, which binds the retinoid X receptor-peroxisome proliferator-activated receptor γ (RXR-PPARγ) heterodimer, stimulating adipocyte differentiation and inhibiting apoptosis.Protease inhibitors might bind to CRABP1, thus inhibiting the formation of cis-9-retinoic acid, leading to reduced RXR-PPARγ activity and peripheral lipoatrophy, mainly on limbs and the gluteal region. Hyperlipidaemia results from impaired storage capacity and increased flux of circulating lipids. The decrease in RXR-PPARγ activity results in apoptosis of peripheral adipose stores, decreased adiponectin, and insulin resistance. Central and visceral adipose stores are spared, however, and expand with weight gain, contributing to insulin resistance. Protease inhibitors, particularly ritonavir, inhibit cytochrome P450 3A4 (CYP3A4), which would reduce the formation of cis-9-retinoic acid, decrease the activity of RXR-PPARγ targets, leading to lipoatrophy and worsened dyslipidaemia (Carr *et al*., 1998).

LRP1 normally binds to lipoprotein lipase on capillary endothelium, which hydrolyses free fatty acids (FFAs) from triglyceride, promoting their accumulation in adipocytes (Hu *et al*., 2017). Protease inhibitor binding to LRP1 would interfere with LRP1-lipoprotein lipase complex formation, reducing adipose storage capacity and increasing plasma triglyceride-rich lipoproteins. FFAs that failed to enter adipocytes would remain in the plasma, to be taken up into the liver, increasing hepatic synthesis of triglyceriderich lipoproteins. Protease inhibitors might also directly stimulate hepatic triglyceride synthesis, possibly by upregulating expression of key triglyceride biosynthetic enzymes (Zimmermann *et al*., 2001).

HAART-related dyslipidaemia may involve genetic predisposition, since not all patients taking HAART have comparable metabolic disturbances. For instance, promoter polymorphisms—namely –482C>T and –455T>C—in the *APOC3* gene were associated with increased plasma concentrations of triglyceride and depressed HDL in HIV patients (Tarr *et al*., 2005). Also, the –

1131T>C promoter polymorphism in the *APOA5* gene was associated with hypertriglyceridaemia in protease inhibitor-treated patients. Variable responses to protease inhibitors have also been associated with other DNA polymorphisms (Guardiola *et al*., 2006).

The impact of PIs on glucose metabolism ranges from impaired glucose tolerance to DM (Tanwani & Mokshagundam, 2003). Protease inhibitors have been found to increase insulin resistance (IR) and reduce insulin secretion by inhibiting GLUT-4 mediated glucose transport The GLUT-4 transporter, mainly expressed in tissues such as skeletal muscle, cardiac muscle and fat, is responsible for most of the body's glucose disposal (Kalra *et al*., 2011).

In patients with CMS, insulin resistance and chronic elevation of FFAs can contribute to increased blood pressure. Vascular resistance results in part from a loss of vasodilation and an increase in vasoconstriction. The vasodilatory effects of insulin are diminished in the context of insulin resistance (Eckel *et al*., 2005). In contrast, FFA can act as a vasoconstrictor, whereas elevated interleukin 6 (IL-6) and other adipocytokines may further contribute to vascular resistance and hypertension. Atherogenic dyslipidemia also contributes to vascular dysfunction. The presence of chronically elevated circulating FFAs can lead to vascular inflammation and damage (Caglayan *et al*., 2005). Hypertriglyceridemia and low HDL-C level are causes of endothelial dysfunction and are independently associated with fatal and nonfatal CVD (Lind, 2002).

3. Objectives

General Objective

To determine cardiometabolic syndrome and its components associated with the use of PI based ART

Specific objectives are:

1. To determine the effects of short-term PIs based antiretroviral exposure on blood pressure, glycaemic level, triglyceride level and waist circumference over a follow-up period of six-months
2. To assess time dependent cardiometabolic components with the use of PIs based ART
3. To investigate factors associated with changes in CMS and CMS components including abnormal waist circumference, impaired fasting glucose , hypertension, hypertriglyceridemia

4. Methodology

4.1. Study area and study period

The study was conducted at Zewiditu Memorial Hospital (ZMH) where numbers of HIV patients on PIs based ART were believed to be relatively larger. The study was conducted between March to December 2018.

Addis Ababa is the capital city of Ethiopia. The population of Addis Ababa was estimated to be 7.8236 Million in the year 2019 (https://population-of-addis-ababa-2019.html).It is located in the heart of the country surrounded by Oromia region and covers about 540 Km2 of which 18.2 Km2 are rural.

Zewditu Memorial Hospital located in centre of Addis Ababa, Ethiopia. It is a teaching and general referral hospital affiliated with Addis Ababa University and under the administration of Addis Ababa health bureau (Yazie *et al*., 2018). Zewditu became the largest HIV clinic in Ethiopia, with 18,000 patients in its care and 6,500 of these were adults put on ART (Asemahagn *et al*, 2018).

4.2. Study design

Hospital based prospective cohort study was conducted at the above mentioned heath facility between March to December 2018.

4.3. Source and study population

The source population included all HIV patients, who were on chronic HAART follow up. The study participants were HIV patients that met the inclusion criteria.

4.4. Inclusion criteria

All adult HIV/AIDS patients of either sex aged 18 years and above who were on PIs based ART for less than or equal to three years and those who would be candidates for PIs based ART and had no abnormal blood glucose, elevated blood pressure and dyslipidemia at baseline were included in the study.

4.5. Exclusion criteria

Patients with known neuropsychiatric disorders, liver failure and renal failure; those who are pregnant and breast-feeding mothers were excluded from the study.

4.6. Sample size determination

The sample size required to determine cardiometabolic complications associated with the use of PI based ART was computed using single population proportion formula (Fosgate, 2009). In calculating the sample size, the proportion of CMS of HIV patients on PIs was considered to be 10% based on the studies done on PIs (Mbunkah *et al*., 2014; Santiprabhob *et al*., 2017)**.**Then considering a 5% margin of error (d2) and critical value at 95% CI ($Z\alpha/2=1.96$), the required sample has been calculated to be 139.

$$n = \frac{(Z\alpha/2)^2 P (1-P)}{d^2}$$

$$n = \frac{(1.96)^2 \; 0.1(1-0.1)}{(0.05)^2} = 139$$

Where, n is the sample size, *z* is the selected critical value of desired confidence level, p is the estimated proportion and d is the desired level of precision

Based on the sample size required Zewditu Memorial Hospitals was selected taking in to account the current population size on PIs i.e., 446 HIV population were on PIs and average of 15 patients were shifted to the 2nd line ART regimen monthly in the hospital mentioned above and hence over a 4-month period, consecutive HIV patients presenting for scheduled follow up clinic visits were recruited. Those who consent for the study and met the inclusion criteria were enrolled following informed consent. Enrollment was continuous till sample size was met.

4.7. Method of data collection and procedures

Socio-demographic, medical history, behavioral and dietary exposures were obtained from patient self-report using a structured questionnaire or reading the questionnaire to those who were illiterate. A modified WHO stepwise approach was used to develop surveillance questionnaire to collect cardiometabolic risk data and serum samples were analyzed for fasting glucose level and lipid profile (total cholesterol (TC) and TGs). Physical/anthropometric examinations were recorded by trained ART nurses. Three blood pressure (BP) measurements were taken three minutes apart, while the average value of the 2nd and 3rd measurements was used as BP level in the analysis. Height and weight were measured with participants wearing light clothing and barefooted. Waist circumference was taken at the midpoint between the lower margin of the last palpable rib and the top of the iliac crest (hip bone), with the patient wearing light clothing. Body mass index (BMI) was calculated by dividing weight in kilogram (kg) to height in meter squared (m2) (Abaid, 2016).

4.8. Study variables

4.8.1. Dependent variables

- Presence or absence of dyslipidemia (Serum TG and TC)
- Fasting blood glucose level
- Blood pressure
- Abdominal obesity(Waist circumference)
- CMS

4.8.2. Independent variables

•Socio-demographic data (age, gender, marital status, educational status, employment status, smoking status)

• Height, weight, WHO stage of HIV/AIDS

•PI containing HAART regime

●Duration of ART regimen

●Physical activity

●Alcohol consumption

●Family history

●Co-trimoxazole prophylaxis therapy

4.9. Operational definitions

Highly active antiretroviral therapy (HAART): A cocktail of a minimum of three classes of antiretroviral drugs.

Cardiometabolic syndrome (CMS): CMS is a combination of any three of the five CMS components (hyperglycemia, hypertension, hypertriglyceridemia, low HDL cholesterol, and central obesity).

Hyperglycemia: Hyperglycemia is defined as elevated blood glucose level ≥ 100 mg/dL

Impaired fasting glucose: defined as fasting blood glucose level between 100mg/dl to 125 mg/dl

Hypertension: Hypertension is defined as elevated blood pressure greater or equal to 130/85

Hypertriglyceridemia: defined as TG level ≥ 150mg/dl

Dyslipidemia is defined as HDL<50mg/dl in women or <40mg/dl in men, LDL>130mg/dl, Tc ≥200mg/dl, TG ≥ 150mg/dl or being on lipid lowering medicine

Abnormal waist circumference: measurement of waist circumference ≥ 102cm for men and ≥ 88cm for women

Obesity: Obesity is defined as BMI ≥ 30 kg/m^2.

According to national institute on alcohol abuse and alcoholism (NIAAA) on alcohol intake:-

No alcohol intake: For those patients who never had a habit of drinking alcohol

Moderate alcohol intake: Drinking as up to 4 alcoholic drinks for men and 3 for women in a single day and a maximum of 14 drinks for men and 7 drinks for women per week.

Heavy alcohol intake: drinking 5 or more alcoholic drinks for males or 4 or more for females at the same time or within couple of hours on 5 or more days in the past month.

Sedentary life style: life style involving little or no physical activity

Low physical activity: activity less than 150 minutes per week

Moderate physical activity: activity between 150 minutes to 300minutes per week

High physical activity: activity more than 300minutes per week

4.10. Data quality assurance

The following measures were undertaken to assure quality of data: The assigned nurses were trained on the aim of the study, how to recruit participants, collect data and manage anything related to the study. Properly designed structured questionnaire was used and translated to local languages and back translated by different individuals. The collected data were reviewed every day and checked for completeness and consistency of response by the principal investigator.

4.11. Data processing and analysis

The data were entered and processed using SPSS version 23 statistical software. Descriptive statistics using frequency distribution was performed for socio-demographic, epidemiological, clinical, and laboratory values. The prevalence of CMS was determined based on the operational definition used in the study. The association between categorical independent and dependent variables were assessed using chi-square test and those significant variables in chi-square test were entered in binary logistic regression model to determine the strength of their association. In multivariate logistic regression all significant variables with p value less than 0.25 were entered to adjust the impact of confounders. Mean of dependent continuous variables at different time was compared using repeated measure of ANOVA and categorical variables were compared with McNemar test at different time. Student's t test was performed to compare mean of continuous variable and P-value of less than 0.05 was considered to be statistically significant.

4.12. Ethical considerations

Ethical clearance was obtained from Institutional Review Board of the College of Health Sciences, Addis Ababa University and Addis Ababa Health Bureau (AAHB). The study was conducted in

selected health facility after getting permission from the hospital. Participation was entirely voluntary, and written informed consent was obtained from the study participants.

Any information obtained during the study was kept confidential. No person or group of people outside the research team had access to their information. Any information that could potentially expose recognition of a particular study participant like patient name, medical record number was excluded from the data collection tools.

Samples collected were used only for this research not for other. The collected samples were analyzed at the facility where participants were attending their health care services.

5. Results

5.1. Socio-demographic characteristics of the study participants

A total of 152 HIV patients on PI based ART were recruited, of these, 10 patients were lost to follow-up, while two patients died during the study period. Only 140 patients, 52 males (37.1%) and 88 females (62.9%) completed the study and data from these participants were included for the analysis. Thirty- two patients were PI naïve and the rest were PI experienced patients. Participants took PI based ART for a mean duration of 22.01 months ranged from 6 to 42 months until their last follow-up period. Thirty-nine participants (27.9%) were on TDF/3TC/ATV/r, one (0.7%) on TDF/3TC/LPV/r, 77 (55%) on ABC/3TC/ATV/r, 8 (5.7%) on ABC/3TC/LPV/r, 14 (10%) on AZT/3TC/ATV/r and one (0.7%) were on AZT/3TC/LPV/r. The mean age of participants was 41.77±10.19 years ranged from 20 to 67 years; the majorities were in the age group of 36-45 (45.7%) and followed by the age group 26-35 (23.6%). The majorities of study participants were non-smokers with moderate physical exercise habit and never drank alcohol (Table 2).

Table 2:Socio-demographic characteristics of HIV-patients on PI based ART at Zewuditu Memorial Hospital, Addis Ababa, Ethiopia, March to December 2018 (N=140)

Variables		**Number (%)**
Sex	Male	52(37.1)
	Female	88(62.9)
Age	18-25	3(2.1)
	26-35	33(23.6)
	36-45	64(45.7)
	46-55	23(16.4)
	56-65	13(9.3)
	>65	4(2.9)
Education	No formal schooling	24(17.1)
	Primary school completed	49(35.0)
	Secondary school completed	43(30.7)
	College/University completed	24(17.1)
Smoking status	Never smoke	139(99.3)
	Smoking	1(0.7)
Alcohol intake	Never drink	124(88.6)
	Light drinking	12(8.6)
	Moderate drinking	3(2.1)
	Heavy drinking	1(0.7)
Physical exercise	Sedentary	26(18.6)
	Low	27(19.3)
	Moderate	63(45.0)
	High	24(17.1)

5.2. Baseline clinical characteristics of the patients

Nobody developed CMS or its components at baseline. Forty patients (28.57%) had a family history of cardiovascular diseases and more than half of patients had normal weight (52.9%) and their mean BMI was 23.43 $\pm$ 4.53 (13.89-37.73). The majority or 132 (94.3%) were WHO stage one patients. Table 3 shows baseline clinical characteristics of participants.

Table 3:Baseline clinical characteristics of HIV-patients on PI based ART at Zewuditu Memorial Hospital, Addis Ababa, Ethiopia, March to December 2018 (N=140)

Variables	**All patients, N=140**
Family history, n (%)	
Diabetes	9(6.4)
Hypertension	16(11.4)
DM &hypertension	8(5.7)
DM, hypertension & heart disease	3(2.1)
DM, hypertension &dyslipidemia	2(1.4)
Hypertension & dyslipidemia	2(1.4)
BMI (kg/m^2), n (%)	
Under weight (<18.5)	19(13.6)
Normal (18.5-24.9)	74(52.9)
Over weight (25-29.9)	37(26.4)
Obese (>30)	10(7.1)
WHO staging, n (%)	
Stage one	132(94.3)
Stage two	2(1.4)
Stage three	5(3.6)
Stage four	1(0.7)
Waist circumference (cm), mean(SD)	83.39(5.29)
Systolic blood pressure (mmHg), mean(SD)	113.04(14.67)
Diastolic blood pressure (mmHg), mean(SD)	75.66(8.65)
Total cholesterol (mg/dl), mean(SD)	173.63(28.91)
Triglyceride (mg/dl), mean(SD)	128.08(27.14)
Fasting blood glucose (mg/dl), mean(SD)	92.21(8.39)

BMI, body mass index; DM, diabetes mellitus; SD, standard deviation

5.3 Prevalence of cardiometabolic syndrome and its components

According to ATP criteria the overall prevalence of CMS was 42.1% of which 46.3% (50) of experienced patients and 28.1% (9) of PI naïve patients developed CMS during the study period. The prevalence of hypertension, hypertriglyceridemia, impaired fasting glucose and abnormal waist circumference were 50.0%, 65.7%, 67.1% and 47.1%, respectively, and 17 patients

(12.1%) which include, 14(12.96%) PI experienced and 3(9.38%) PI naïve developed DM. The proportion of hypertriglyceridemia and impaired fasting glucose was somewhat higher in males than female *i.e.*, 69.2% and 75.0% of males versus 63.6% and 62.5% of females developed these components respectively but the opposite was true in case of abnormal waist circumference, 65.9% of females and 15.38% of males were diagnosed for abnormal waist circumference. Forty females (45.5%) and 19 males (36.5%) developed CMS (Table 4).

Table 4:Prevalence of cardiometabolic syndrome and its components in HIV-patients on PI based ART at Zewuditu Memorial Hospital, Addis Ababa, Ethiopia, March to December 2018 (N=140)

Variables	**All patients N=140 Number (%)**	**PI naïve patients N=32 Number (%)**	**PI-experienced patients N=108 Number (%)**
Systolic BP ≥ 130 mmHg	51(36.43)	5(15.63)	46(42.59)
Diastolic BP ≥ 85 mmHg	59(42.14)	9(28.13)	50(46.3)
WC (ATP criteria) ≥ 88cm in females and ≥ 102cm in males	66(47.1)	12(37.5)	54(50.0)
Triglyceride ≥ 150 mg/dl	92(65.7)	22(68.8)	70(64.81)
FBS ≥ 100 mg/dl	94(67.1)	22(68.88)	72(66.7)
CMS ≥ 3 ATP criteria	59(42.1)	9(28.1)	50(46.3)

ART, antiretroviral treatment; PI, protease inhibitor; BP, blood pressure; WC, waist circumference; FBS, fasting blood sugar; CMS, cardiometabolic syndrome; ATP, adult treatment panel; ZMH, Zewditu memorial hospital.

5.3.1. Prevalence of cardiometabolic syndrome and its components at different visiting time

In general the prevalence of CMS and its components declined from second(two-months) to third visit (six-months) except fasting blood sugar level, which increased from 53.6% (75) to 56.4% (79)(Fig. 2).

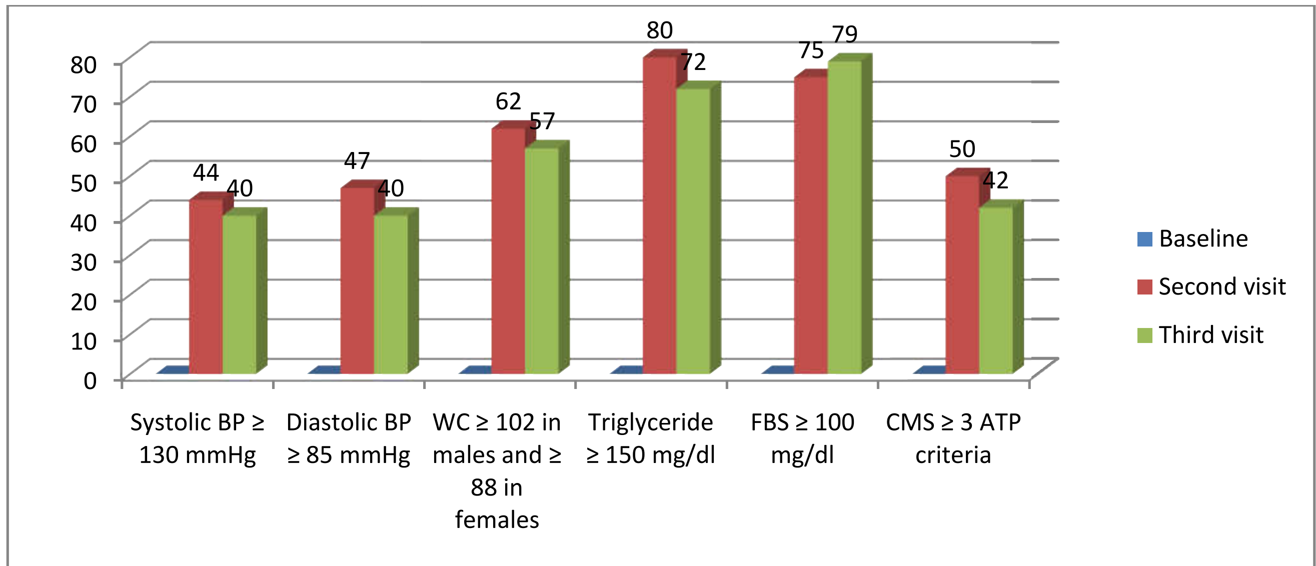

Figure 2: Prevalence of cardiometabolic syndrome and its components at different visiting time

In repeated measure of ANOVA, the mean of each continuous variables measured at three different time was compared with one another. Mean of systolic blood pressure, triglyceride, impaired fasting glucose and waist circumference between time one (baseline) and time two (2nd visit) and time one and time three (3rd visit) was significantly different but there was no significant difference between time two (2nd visit) and time three (3rd visit). In diastolic pressure a significant mean difference was observed between time one and two, and between time two and three (Table 5).

Table 5: Pair wise comparisons of mean of cardiometabolic syndrome components at three different times

Variables	Mean			Pair wise comparisons of time	p value
	T1	T2	T3		
Systolic BP, mmHg	113.04	119.89	119.45	T1 & T2	<0.001
				T1 & T3	<0.001
				T2 & T3	1.000
Diastolic BP, mmHg	75.66	79.83	76.74	T1 & T2	<0.001
				T1 & T3	1.000
				T2 & T3	0.006
WC, cm	83.39	89.66	89.70	T1 & T2	<0.001
				T1 & T3	<0.001
				T2 & T3	1.000
Triglyceride, mg/dl	128.08	170.96	177.56	T1 & T2	<0.001
				T1 & T3	<0.001
				T2 & T3	1.000
FBS, mg/dl	92.21	103.80	105.77	T1 & T2	<0.001
				T1 & T3	<0.001
				T2 & T3	0.164

CMS, cardiometabolic syndrome; BP, blood pressure; WC, waist circumference; FBS, fasting blood sugar; T1, time 1; T2, time 2; T3, time 3.

In non-parametric (McNemar) test, in all CMS and its components, there was a significant difference of case diagnosed between baseline (T1) and 2nd visit (T2) and between baseline and 3rd visit (T3) ($p<0.001$) but not between 2nd visit and 3rd visit (Table 6).

Table 6:Non-parametric test of cardiometabolic syndrome and its components at three different times

Variables	Frequency T1	T2	T3	Pair wise comparisons	p value
High BP	0	60	51	T1 & T2	<0.001
				T1 & T3	<0.001
				T2 & T3	0.137
High WC	0	62	57	T1 & T2	<0.001
				T1 & T3	<0.001
				T2 & T3	0.267
High TG	0	80	72	T1 & T2	<0.001
				T1 & T3	<0.001
				T2 & T3	0.216
IFG	0	75	79	T1 & T2	<0.001
				T1 & T3	<0.001
				T2 & T3	0.607
CMS	0	50	42	T1 & T2	<0.001
				T1 & T3	<0.001
				T2 & T3	0.170

CMS, cardiometaboic syndrome; BP, blood pressure; WC, waist circumference; TG, triglyceride; IFG, impaired fasting glucose; T1, baseline; T2, 2nd visit; T3, 3rd visit.

5.4. Facors associated with Prevalence of cardiometabolic syndrome and its components

In chi-square test categorical variables were compared with each other based on their effect on dependent variables and CMS components were also compared with respect to CMS. Among independet variables, BMI was associated with CMS (P< 0.001) and all CMS components were significantly associted with CMS (p< 0.001). Sex with abnormal waist circumference (P<0.001), age with hypertension (P=0.018) and hypertriglyceridemia (P=0.037) were significantly associated. The high proportion of patients who developed hypertension (73.91%) and hypertriglyceridemia (78.26%) fell in the age group between 46 and 55 but age didn't have an impact on other parameters like CMS, fasting blood glucose and waist circumference.

PI history whether it is PI naïve or experienced, was significantly associated with hypertension (P=0.005) but not with CMS (P=0.067), abnormal waist circumference (P=0.213), hypertriglyceridemia (P=0.68), impaired fasting glucose (P=0.826).Fifty six percent (61/108) of PI experienced patients developed hypertension but only 28.13% (9/32) in case of PI naïve patients.Current ART regimen and its duration and type of PIs (ATV/r or LPV/r based ART) were not associated with the development of both CMS and its components (Table 7).

BMI had a significant impact on occurrence of CMS (P<0.001), abnormal waist circumference (P<0.001) and hypertension (P=0.001) but not on hypertriglyceridemia (P=0,075) and impaired fasting glucose (P=0,562).

Alcohol consumption, co-trimoxazole prophylaxis therapy (P=0.517), and family history of diabetes, hypertension, cardiac disease and dyslipidemia (P=0.12) didn't have relation with CMS but physical activity had a significant effect on CMS (P=0.001), those having sedentary life style had high risk of CMS compared to others (73.1%).

Those variables which were significant in chi-square test were included in logistic regression to determine their odds ratio. In this univariate analysis, those having abnormal BMI *i.e.,* over weight (25-29.9) and obese (>30), sedentary life style, low physical activity and total cholesterol ≥ 200 mg/dl had a significant relationship with CMS and all the CMS components, hypertension (OR:33.26, 95% CI:12.24-90.34, P<0.001), hypertriglyceridemia (OR:9.51, 95% CI:3.68-24.60, P<0.001),impaired fasting glucose (OR:11.07, 95% CI:4.01-30.53, P<0.001) and abnormal waist circumference (OR:6.78, 95% CI:3.20-14.35, P<0.001) were significantly associated with CMS. The overall p value and odds ratio are presented in Table 7 and association of factors and CMS components with CMS and without CMS at the 2nd and 3rd visits are also presented in Table 8.

Table 7: Summary of chi-square test (X2) and logistic regression for CMS

Variables	CMS N (%)	X^2 / LR	p value	Logistic regression	
				COR	AOR
Sex		1.066	0.302		
Male	19(36.54)				
Female	40(45.45)				
Age		9.103	0.162		
18-25	0(0)				
26-35	9(27.27)				0.035(0.01-0.96)
36-45	30(46.88)				0.19(0.009-3.989)
46-55	13(56.52)				0.047(0.002-1.204)
56-65	5(38.46)				0.124(0.005-3.386)
>65	2(50.0)				
Alcohol intake		2.513	0.473		
Never drink	51(41.13)				
Light drinking	5(41.67)				
Moderate drinking	2(66.67)				
Heavy drinking	1(100)				
Physical exercise		16.771	0.001		
Sedentary	19(73.08)			6.37(2.39-16.98)	12.98(1.93-87.43)
Low	14(51.85)			2.53(1.04-6.11)	12.21(1.61-92.71)
Moderate	18(28.57)				
High	8(33.33)				
BMI (kg/m^2)		22.725	<0.001		
Under weight	0(0)				
Normal	22(30.14)				
Overweight	20(55.56)			6.82(2.88-16.14)	4.87(1.49-15.96)
Obese	8(66.67)			11.69(3.07-44.50)	12.22(2.06-72.53)
PI history		3.343	0.067		
Naïve	9(28.13)				0.22(0.03-1.4)
Experienced	50(46.3)				4.66(0.72-30.3)

Table 7. Continued

Variables	**CMS N (%)**	**X^2 / LR**	**p value**	**Logistic regression**	
				COR	**AOR**
ART regimen		9.011	0.109		
TDF/3TC/ATV/r	17(43.59)				
TDF/3TC/LPV/r	1(100)				0.84(0.24-2.92)
ABC/3TC/ATV/r	35(45.45)				0.82(.06-11.25)
ABC/3TC/LPV/r	3(37.5)				0.64(0.06-6.97)
AZT/3TC/ATV/r	2(14.29)				
AZT/3TC/LPV/r	1(100)				
ART duration		5.481	0.241		
0-6 months	9(28.13)				1.04(0.08-14.13)
7-12 months	2(25.0)				0.74(0.16-3.30)
13-24 months	18(45.0)				1.58(0.314-7.96)
25-36 months	17(47.22)				
37-42 months	13(54.17)				
Total cholesterol		6.876	0.009		
<200 mg/dl	21(30.88)			0.30(0.14-0.63)	0.27(.09-0.85)
≥ 200 mg/dl	38(52.78)			3.35(1.58-7.11)	3.67(1.17-11.49)

CMS, cardiometabolic syndrome; LR, Likelihood Ratio; COR, crude odds ratio; AOR, adjusted odds ratio; ART, antiretroviral treatment

Table 8: Factors associated with cardiometabolic syndrome

Variables	2nd visit			3rd visit		
	CMS (n=50)	Non-CMS (n=90)	p-value	CMS (n=42)	Non-CMS (n=98)	p-value
Age in years	44.52 ±9.17	40.24 ±10.45	0.017	44.45 ± 9.06	40.62 ± 10.47	0.041
Sex, n (%)			0.835			0.321
Males	18(34.6)	34(65.4)		13(25.0)	39(75.0)	
Females	32(36.4)	56(63.6)		29(33.0)	59(67.0)	
Alcohol intake (%)			0.437			0.468
Never drink	45(36.3)	79(63.7)		36(29.0)	88(71.0)	
Light drinking	3(25.0)	9(75.0)		4(33.3)	8(66.7)	
Moderate drinking	1(33.3)	2(66.7)		2(66.7)	1(33.3)	
Heavy drinking	1(100.0)	0(0.0)		0(0.0)	1(100.0)	
Physical exercise, n (%)			<0.001			0.001
Sedentary	19(73.1)	7(26.9)		15(57.7)	11(42.3)	
Low	10(37.0)	17(63.0)		10(37.0)	17(63.0)	
Moderate	14(22.2)	49(77.8)		14(22.2)	49(77.8)	
High	7(29.2)	17(70.8)		3(12.5)	21(87.5)	
BMI (kg/m^2)	25.99 ±3.83	22.11± 4.23	<0.001	26.67 ± 3.53	22.29 ± 4.3	<0.001
Type of PIs, n (%)			0.337			1.000
ATV/r based	45(34.6)	85(65.4)		39(30.0)	91(70.0)	
LPV/r based	5(50.0)	5(50.0)		3(30.0)	7(70.0)	
PI history, n (%)			0.063			0.043
Naïve	7(21.9)	25(78.1)		5(15.6)	27(84.4)	
Experienced	43(39.8)	65(60.2)		37(34.3)	71(65.7)	
ART regimen, n (%)			0.052			0.338
TDF/3TC/ATV/r	16(41.0)	23(59.0)		11(28.2)	28(71.8)	
TDF/3TC/LPV/r	1(100.0)	0(0.0)		1(100.0)	0(0.0)	
ABC/3TC/ATV/r	28(36.4)	49(63.6)		26(33.8)	51(66.2)	
ABC/3TC/LPV/r	3(37.5)	5(62.5)		2(25.0)	6(75.0)	
AZT/3TC/ATV/r	1(7.1)	13(92.9)		2(14.3)	12(85.7)	
AZT/3TC/LPV/r	1(100.0)	0(0.0)		0(0.0)	1(100.0)	
ART duration in months	21.34 ±12.22	16.3 ±12.20	0.021	25.33 ± 11.55	20.61 ± 12.58	0.039

Table 8. Continued

Variables	**2nd visit**			**3rd visit**		
	CMS (n=50)	Non-CMS (n=90)	p-value	CMS (n=42)	Non-CMS (n=98)	p-value
Family history, n (%)			0.092			0.694
DM	3(33.3)	6(66.7)		2(22.2)	7(77.8)	
HTN	7(43.8)	9(56.2)		5(31.3)	11(68.7)	
DM & HTN	5(62.5)	3(37.5)		2(25.0)	6(75.0)	
DM, HTN &cardiac	2(66.7)	1(33.3)		2(66.7)	1(33.3)	
DM, HTN &DLA	0(0.0)	2(100.0)		0(0.0)	2(100.0)	
HTN & DLA	2(100.0)	0(0.0)		1(50.0)	1(50.0)	
None	31(31.0)	69(69.0)		30(30.00	70(70.0)	
CPT, n (%)			0.361			0.491
Yes	33(33.3)	66(66.7)		28(28.3)	71(71.7)	
N0	17(41.5)	24(58.5)		14(34.1)	27(65.9)	
TC, mg/dl	194.5 ±38.7	176.8 ±38.9	0.011	215.33 ± 48.05	180.2 ± 43.83	<0.001
Systolic BP, mmHg	134.26 ±17.93	111.91 ± 19.6	<0.001	134.05 ± 17.8	113.19 ± 20.99	<0.001
Diastolic BP, mmHg	88.68 ± 9.96	74.91 ± 11.28	<0.001	86.55 ± 11.59	72.53 ± 14.77	<0.001
WC, cm	96.93 ± 7.47	85.62 ± 10.19	<0.001	98.93 ± 7.61	85.74 ± 10.61	<0.001
TG, mg/dl	208.18 ±80.07	143.61 ± 64.98	<0.001	225.4 ± 102.69	147.73 ± 71.11	<0.001
FBS, mg/dl	110.48 ± 23.05	100.09 ± 20.51	0.007	117.76 ± 25.07	100.63 ± 17.04	<0.001

CMS, cardiometabolic syndrome; Non-CMS, without cardiometabolic syndrome; DM, diabetes mellitus; HTN, hypertension; DLA, dyslipidemia; CPT, co-trimoxazole prophylaxis therapy; BP, blood pressure; TG, triglyceride; TC, total cholesterol; WC, waist circumference; FBS, fasting blood sugar. All data are expressed as mean ± SD/ number (%).

6. Discussion

Use of HAART has resulted in a dramatic decrease in morbidity and mortality of HIV infected patients, but HAART especially PIs based was increasingly associated with the emergence of cardiometabolic events.CMS following the administration of PIs based ART was observed in our study population.

In the present study, we found that 59 patients (42.1%) had a complete picture of CMS. This was comparable with the study done in Boston that reported 45.0% of PIs treated HIV patients who were diagnosed with CMS (Johnsen *et al.*, 2006). Study in Ecuador revealed that 36.67% of PI treated patients developed CMS (Villamar *et al.*, 2011). Another study also reported that 150 patients (32.23%) were diagnosed for the presence of CMS out of 464 patients who were on PIs based ART (Wu *et al*., 2012).In the contrary study conducted in Cameroon and Thailand showed that the prevalence of CMS among the patients on PIs based therapy was only 10% **(**Mbunkah *et al*., 2014**;** Santiprabhob *et al*., 2017).This was even lower than CMS study done in Southern Ethiopia, Hawasa and South West Ethiopia, Jimma in HAART treated patients in general. According to Tesfaye *et al* and Berhane *et al*., the prevalence of CMS associated with the use of HAART in general using ATP criteria was 16.8% (Tesfaye *et al*., 2014) and 21.1% (Berhane *et al*., 2012), respectively. This implies that even though this was so in majority of researches, CMS prevalence in PIs treated patients was higher than among those treated by HAART in general. Several other studies reported the prevalence rates of CMS that varied from 10-72.6% (Samaras *et al*., 2007; Mbunkah *et al*., 2014; Santiprabhob *et al.*, 2017). Differences in study populations, host genetic factors, ethnicities, ART classes/types of PIs and variability in diagnostic criteria may all contribute to variation in prevalence.

We also found impaired fasting glucose to be the most prevalent CMS component (67.1%) followed by hypertriglyceridemia (65.7%), hypertension (50.0%) and abnormal waist circumference (47.1%). Prevalence of two components of CMS, hypertriglyceridemia and hypertension were somewhat comparable to the study done in Boston. As to this report the prevalence of hypertriglyceridemia and hypertension were 63% and 30%, respectively (Johnsen *et al*., 2006). In Nigerian study, 79% of patients receiving PIs based ART developed hypertriglyceridemia (Salami *et al*., 2009). In impaired fasting glucose, the result was

inconsistent with findings by Toritorios *et al* that reported 5% of HIV patients on HAART developed hyperglycemia after the initiation of PI based therapy (Tsiodras *et al*., 2000), similarly another study from South Africa presented 24% of patients receiving LPV/r based ART were diagnosed with hyperglycemia (Abaid, 2016).

A number of researches reported that hypertriglyceridemia was the most prevalent component of CMS on account of PIs based ART (Johnsen *et al*., 2006; Santiprabhob *et al.*, 2017**;** Pao *et al*., 2008), but in our study impaired fasting glucose was the most prevalent component, this implies that diabetic case is increasing from time to time, this may be owing to factors associated with the life style of our community in addition to PI based HAART regimen. The difference may also be associated with differences in study populations, host genetic factors, ethnicities, duration of PIs and other factors as described above for reasons in CMS prevalence differences.

In both repeated measure of ANOVA to compare mean of continuous variable and non-parametric **(**McNemar**)** test to compare categorical variables, we could see a significant change in CMS components between baseline and 2nd visit and baseline and 3rd visit but not between 2nd and 3rd visit. From this we can understand that 6 months follow up period was not enough to observe a significant change between visits, therefore, longer period is required to clearly observe time effect of PIs.

In student's t test we tried to compare mean of continuous variables of CMS components with those developed CMS and not developed CMS, thereby we could find that there were a significant change in the level of systolic blood pressure (134.05 ± 17.8 Vs 113.19 ± 20.99), diastolic blood pressure (86.55 ± 11.59 Vs 72.53 ± 14.77), waist circumference (98.93 ± 7.61 Vs 85.74 ± 10.61), triglyceride (225.4 ± 102.69 Vs 147.73 ± 71.11) and fasting blood glucose (117.76 ± 25.07 Vs 100.63 ± 17.04) with p value <0.001 for all at the end of six months follow-up period with duration of PIs ranged from 6-42 months. This finding was comparable with the previous study on prevalence of CMS in HIV infected patients receiving HAART in general by Samaras *et al* that presented mean of systolic blood pressure (134 ± 16 Vs 121 ± 14, p<0.0001), diastolic blood pressure (81 ± 10 Vs 75 ± 10, p<0.0001), waist circumference (93 ± 12 Vs 85 ± 10, p<0.0001), triglyceride (380.85 ± 265.71 Vs 212.57 ± 265.71, p<0.0001) and FBS (109.8 ± 36 Vs 88.2 ± 14.4, p<0.0001) were significantly different among patients diagnosed with CMS

and non-CMS (Samaras *et al*., 2007). Study on PIs that compare mean of CMS components with CMS and non-CMS are not available that is why we used studies on HAART regimen in general for comparison. Even though this is so, the means were somewhat higher on PIs based regimen compared to HAART in general except level of triglyceride when compared with Samaras *et al* result. Another study on HAART in general by Mbunkah *et al* showed that mean of triglyceride was 125.5 ± 73 Vs 83.7 ± 40.4, p=0.014 (Mbunkah *et al*., 2014), among patients developed metabolic syndrome and not developed CMS and hence the result on level of triglyceride was inconsistent, this might be on account of the proportion of PIs on HAART regimen might be different, duration of HAART exposure and the like. Therefore, another research on PIs with longer duration of follow-up is required to clearly demonstrate means of CMS components as a result of PIs exposure.

In univariate analysis, BMI, physical activity and total cholesterol were highly associated with the development of CMS. BMI and total cholesterol were higher among patients diagnosed with CMS than patients with non-CMS. The mean of age, ART duration both at 2nd and 3rd visit, PIs history (PI naïve or experienced) at the 3rd visit were also associated with CMS ($p<0.05$). Self reported smoking habit, alcohol consumption, family history, co-trimoxazole prophylaxis therapy (CPT), medication history other than ART drugs, sex and ART regimens were not related with the presence of CMS ($p>0.05$).

In multivariate analysis, those variables with p value less than 0.25 were entered in to logistic regression to adjust the impact of confounders and hence BMI ≥ 25-29.9 kg/m2 or those HIV patients who were overweight and total cholesterol ≥ 200mg/dl were independently associated with the development of CMS, therefore having high cholesterol and being overweight might predispose an individual to develop CMS and in turn cause for the occurrence of T2DM and cardiovascular disease.

Many studies demonstrated that women were higher in number with the presence of CMS than men (Mbunkah *et al*., 2014; Villamar *et al.*, 2011; Guiaro et al., 2017), but in our study they didn't differ that much in prevalence. This might be assumed that 50% of women who participated in this study were small business owner, daily laborer, cleaner and the like and

hence their energy requirement is assumed to be almost equivalent to men's as they had high level of activity.

About 99% of patients recruited in this study were non-smokers. Therefore, it is difficult to make analysis whether smoking did have an impact or not. The effect of alcohol consumption on CMS reports from different researches are inconsistent for example, the study in Australia showed a significant association between alcohol consumption and CMS (p=0.007) (Samaras *et al*., 2007) but no association was observed in study done in Southern Ethiopia, Hawassa (Tesfaye *et al*., 2014). The same is true for family history, similar finding was shown that family history of diabetes (p=0.205), and hypertension and heart disease (p=0.396) were not related with the development of CMS (Santiprabhob *et al*., 2017), however, association was there from a report by Wu *et al*., 2012 (Wu *et al*., 2012).

In the present study, no difference on risk of CMS was observed on patients who were on different ART regimen/type of PIs. On the basis of type of PIs we were not able to assess the association between LPV/r and ATV/r based ART with CMS because the number of patients on LPV/r based were very much less as compared to ATV/r based ART and both regimens were ritonavir boosted PIs. As to Temple *et al* ritonavir is a prototype of PI, and causes the most severe metabolic abnormalities in humans and animal models (Temple *et al.*, 2003). In animal experimental studies, use of ritonavir for two weeks also caused elevation of plasma triglycerides and alterations on glycemic levels (Lenhard *et al*., 2000; Xu *et al*., 2004). This implies that the effect might be due to presence of ritonavir. In this study, there was no a significant difference between two PIs classes, if there was a significant difference, it might be believed that the effect was on account of ATV/LPV because ritonavir was there in both ATV and LPV and hence it is difficult to compare the effect of one drug over the other. However, one of the previous studies showed that exposure to LPV/r for 36-71 months has been associated with prevalence of CMS in comparison with other PIs (OR: 1.78; CI: 1.03-3.07; p=0.02) (Wu *et al*., 2012). Jeric *et al*. also reported that Lopinavir/ritonavir was associated with CMS more than other PIs (OR: 2.46; CI: 1.28-4.71; p=0.007) (Jeric *et al*., 2005).

In the present study, duration of PIs showed no association between CMS and categorical duration of PIs but mean duration of 21.34 $\pm$ 12.22 at the 2nd visit (p=0.021) and 25.33 $\pm$ 11.55

months at the 3rd visit (p=0.039) were significantly associated with the occurrence of CMS. From this we can understand that the small categorical duration masked not to see time effect of PIs.

PI history, being PI naïve or PI experienced patients had a significant association with CMS at the 3rd visit (p=0.043).Five PI naïve patients (15.6%) and 37 PI experience patients (34.3%) developed CMS at 3rd visit but at the 2nd visit no association was there between PI naïve or experienced patients with CMS (p=0.063). Therefore, further investigation may be required at larger sample size to generate concrete evidence.

Mean of BMI at the 2nd and 3rd visit among patients with CMS was 25.99 $\pm$ 3.83 and 26.67 $\pm$ 3.53, respectively. BMI $\geq$ 25kg/m^2 (overweight and obese) were significantly associated with the development of CMS. This result was similar with the study done in Ecuador (Villamar *et al*., 2011) and Southern Ethiopia (Tesfaye *et al*., 2014).

It has long been established that physical activity and exercise are associated with better overall health, well-being and reduced body fat. In a study on Leisure Time Sedentary Behavior (LTSB), the odds ratio for having CMS was 1.94 in men with 4 hr/day of LTSB compared to those with one hour/day of LTSB. Four hours of LTSB was associated with 1.88 OR of increased waist dimension, 1.84 OR of reduced HDL and 1.55 OR for systemic arterial hypertension. In women greater than four hours of LTSB was associated with an OR of 1.54 for CMS (Kelli *et al*., 2015). Similarly, our finding showed those individuals having sedentary lifestyle and low physical activity were significantly associated with CMS (p<0.001) but studies in Australia and Southern Ethiopia didn't show an association between physical activity and development of CMS (Samaras *et al*., 2007; Tesfaye *et al*., 2014**)**. This might be due to the fact that data on physical activity were collected self reportedly, there for there might be subjective bias that resulted in misleading the researcher to wrong conclusion.

Age of patients in the majority of previous reports had an impact on the occurrence of CMS **(**Villamar *et al.*, 2011**;** Wu *et al*., 2012; Tesfaye *et al*., 2014; Guiaro *et al*., 2017)**,** but in our case, in small scale category, age didn't have a significant association with CMS. However, in large scale *i.e*., age > 40 was significantly associated with CMS (p=0.044). Patients who were

>40 years (44.1%) were diagnosed with CMS more than those patients who were ≤ 40 years (27.8%) this implies that small scale categories of age might mask the effect not to be observed .

As stated above total cholesterol was higher among patients diagnosed with CMS than non-CMS. Total cholesterol mean at the 2nd and 3rd visit were 194.5 ± 38.7 and 215.33 ± 48.05 respectively. Total cholesterol ≥ 200mg/dl had a significant effect on the presence of CMS (OR: 3.35, 95% CI: 1.58-7.11, p=0.002). Similarly, report by Tesfaye *et al*., 2014 also showed that total cholesterol ≥ 200mg/dl was significantly associated with the development of CMS (OR: 2.5, 95% CI: 1.4-4.5, p<0.001) (Tesfaye *et al*., 2014).

7. Limitations

Among laboratory parameters which were to be analyzed, HDL, the most important CMS component, couldn't be analyzed. Had it been done the result might have been different, and impact of lipid profiles could have better been assessed. Our follow-up period was too short (6 months) to clearly observe changes. Therefore, a longer period with enough budgets is required to run the research smoothly and to come up with good and reliable findings. The sample size was also small and hence it is difficult to generalize the result for the entire population of HIV infected adults receiving PIs based ART with this sample size. We didn't have a control to know effect of HIV by itself in the absence of HAART.

8. Conclusion

Our study demonstrates high prevalence of CMS (42.1%) among HIV infected patients receiving PIs based ART in comparison with CMS as a result of HAART in general or 1st line drugs (2NRTIs + 1NNRTI). BMI and total cholesterol were independently associated with the presence of CMS and hence not only ART but also other factors play a role in prevalence. Our finding also shows prevalence of CMS components were high in PIs based therapy. Impaired fasting glucose was the most prevalent CMS component as opposed to many other studies on PIs.

9. Recommendations

As CMS has been found to be a risk factor for CVD, screening and preventive procedures should be implemented in routine care of patients receiving PIs based ART. Our report including from other scholars confirmed that PIs are the leading cause for metabolic alterations; therefore, future studies should focus on selecting PI class which might have better metabolic effect. Even though PIs undesirable effect is known, researches on CMS on account of PIs use are very limited so large scale researches should be conducted to understand the magnitude of CMS and associated factors in big HIV population treated with PIs and to design CMS associated CVD controlling strategies.

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Appendices

Annex I: Participant Information Sheet and Informed Consent

PART I: PARTICIPANT INFORMATION SHEET

Title of the project**:** Cardiometabolic syndrome among HIV patients on protease inhibitors based anti-retroviral treatment at Zewuditu Memorial Hospital

Name of principal investigator: _______________________________________

Address:____

I am here to conduct a research entitled as above. I am inviting you to take part in this clinical study. I will give you all the required information on the study. Along the course of giving you the information, if there are any words, concepts, information or clarification that you do not understand or you require, please do not hesitate to stop me and ask and I will be more than happy to answer. You are not required to decide now or today whether to take part in the study or not. However, I am encouraging you to freely talk to anyone that you feel comfortable with about taking part in the study or not.

Human Immunodeficiency Virus (HIV) infection is now a common medical condition which` requires treatment with at least three combinations of drugs called HAART. Even if anti-retroviral therapy (ART) has definitely decreased mortality and increased the quality of life of affected individuals using HAART especially protease inhibitors in HIV infection management has led to increased prevalence of diabetes mellitus, insulin resistance, lipoatropy, fat redistribution, dyslipidemia and hypertension. it is not known whether the PIs based HAART regimen has the same or different side effects as the 1st line HAART as to the Ethiopian context (especially relating to those that can cause raised cholesterol in blood, diabetes mellitus and high blood pressure)- all of which are known to lead to heart problems and stroke. Therefore, the purpose of this study is to determine the cardiometabolic abnormalities associated with the use 2nd line, protease inhibitor (PI) based ART.

Please note that participation in this study is entirely voluntary. You have the right to and you are free to decide to participate or not. In case you initial decide to participate and later

change your mind, you have the right to and you are free to stop participating. Irrespective of whether you decide to participate in the study, the standard and quality of care and services that will be offered to you will be the same. If you choose not participate in this study, you will be offered the treatment and care that is currently routinely offered to HIV infected individuals in this health facility. Your choice and rights will be respected at all times.

If you agree to take part and you are found to be fit to take part in the study, the entire duration that you will be required to take part in the study will be 6 months. You will be required to come at the start, after 4 weeks from start, then after 8, 12 and 24weeks. However, there might be situations where the researcher may feel that you have to come for additional visits due to special reasons.

There are no immediate personal benefits for you due to your participation in this study. However, after the study is completed, it is expected that it will be known whether the level of side (unwanted) effects relating to factors that cause high blood cholesterol, diabetes mellitus and high blood pressure (which are known to lead to heart problems and stroke) of PI based ART. This will help you in knowing preventive measures a head of time as other associated risk factors are there, that exacerbate the situation together with the drug. And certainly there are future community and societal benefits as a result of your participation in this study.

The confidentiality of your identity will not be compromised as a result of your participation in this study. Your identity will not be shared to other study participants. Any information that will be collected relating to you will be kept absolutely confidential and secured.No person or group of people outside the research team will have access to your information. For the purpose of this study, you will be identified only with a number and your name or address will not appear.

PART II: CERTIFICATE OF CONSENT

Study identification number _ _ _ _ _ _

I have read the Participants' Information Sheet, or it has been read to me. I have had an opportunity to ask questions about the study and all questions that I have asked have been answered to my satisfaction. I agree to participate in the study. By giving consent, I understand that I voluntarily agreed to participate in the study. And that I am free to withdraw from the study at any time, for which I do not have to give any reason and this will not affect the quality of care that will be offered to me.

Name of participant__________________________

Signature of participant_______________________

Date-------/---------/------------

I attest to the fact that I witness that (s)he had opportunity to ask questions, and all his/her questions were answered. I consent that the potential participant gave consent freely.

Name of witness _____________________
Signature of witness __________________
Date _ _/ _ _/ _ _ _ _

I confirm that I have accurately read the participants information sheet to the potential participant and ensured that she/he understood the content. I confirm that the potential participant was given ample opportunity to ask questions and I have answered all his/her questions to the best of my knowledge. I can also confirm that the potential participant was not coerced in to giving consent and that she/he did that voluntarily and freely.

Name of person taking consent__________________________

Signature of person taking consent_______________________

Date---------/-------/----------

Annex II: Questionnaire

Addis Ababa University

College of Health Sciences

School of Pharmacy

Department of Pharmacology and Clinical Pharmacy

Cardiometabolic syndrome among HIV patients on protease inhibitors based anti-retroviral treatment at Zewuditu Memorial Hospital

This questionnaire is prepared in order to assess cardiometabolic risk factors among RVI patients on PI based regimens. Your participation here is very indispensible for the study and you will also benefit from the results to be obtained. Therefore, you are kindly requested to respond for the following questions. Choosing more than one is possible for a single question.

For closed ended questions, encircle on the letter.

For open ended questions, write your response in the space provided

Health Facility:________________________

Participant Identification Number:___________________

Date of enrollment______________________

Date of PIs based started__________________

Demographic Data

1. Sex: A. Male B. Female

2. If female, pregnant status: A. pregnant B. non-pregnant

3. Age (yrs):_______

4. What is the highest level of education you have completed?

A. No formal schooling B. Primary school C. Secondary School

D. College/University completed E. Post graduate degree

5. Which of the following best describes your main employment status?

A. Government/non-government employee B. Self employed C. Unemployed

D. Student E. Home maker

6. If you are worker, what is your occupation?---

Behavioral and Dietary Data

7. Do you currently smoke any tobacco products, such as cigarettes, cigars or pipes?

A. Yes B. No

8. If yes, on average, how many units of cigarettes do you smoke each day?__________

9. Have you ever consumed an alcoholic drink?

A. Yes B. No

10. If yes, how frequently have you consumed an alcoholic drink?

A. Daily B. 5-6 days per week C. 1-4 days per month D. Less than once a month

11. How many units of alcohol do you drink per day/week/month?______________

12. What type of oil or fat is most often used for meal preparation in your house hold?

A. Vegetable oil B. Sunflower oil C. Palm oil D. Niger oil E. Olive oil F. Soya bean oil
G. If others, specify:__________________

13. On average, how frequently do you eat protein diet?

A. Daily B. 5-6 days per week C. 1-4 days per month D. Less than once a month

14. If daily, how many servings of protein diet do you eat on one day?

A. One B. Two C. Three D. Four

Physical activity

15. Does your work involve vigorous-intensity activity that causes large increases in breathing or heart rate? A. Yes B. No

16. If yes, in a typical week, how many days do you do vigorous-intensity activities as part of your work?-----------------------------

17. How much time do you spend doing vigorous-intensity activities at work on a typical day?-----------------------------

18. How many days per week and how much time per day do you spend doing vigorous-intensity sports, fitness or recreational activities?---

19. How much time do you usually spend sitting or reclining on a typical day?-------------------

Past and Current Medical History

20. Have you ever been told that you have raised blood pressure or hypertension?

A. Yes B. No

21. Have you ever been told that you have raised blood sugars or diabetes?

A. Yes B. No

22. Do you have a family history of hypertension, diabetes or CVD?

A. Yes B. NO

23. If yes, what was the case?

A. Hypertension B. Diabetes C. CVD D. All

24. Have you ever been told that you have raised serum cholesterol?

A. Yes B. No

25. Have you ever taken medications other than ARV drugs?

A. Yes B. No

26. If yes, would you tell us the drugs with suggestive time i.e their staring time, duration, Strength and the like?

____

____

27. If any other co-infection, please write them:_______________________________________

Initial and Current ART Regimens

28. Initial ART regimen and its duration:____________________________________

29. Current ART regimen and its duration:___________________________________

Current Status of the Disease

30. CD4 count (cells/mm3):__________

31. HIV viral load (copies/ml):_________

32. WHO Stage:

A. Stage 1 B. Stage 2 C. Stage 3 D. Stage 4

Physical Examination

33. Weight_______(kg) Height________(m) BMI__________(kg/m^2)

34. Waist circumference (cm)____________

35. Blood pressure: Systolic___________(mmHg) Diastolic__________(mmHg)

Laboratory

36. Lipid profile: Total Cholestrol_________(mg/dl) Triglycerides_________(mg/dl)

LDL___________(mg/dl) HDL_____________(mg/dl)

37. Fasting Blood Sugar__________(mg/dl)

Annex III: Amharic version of Participant Information Sheet and Informed Consent

የስምምነት ሰነድ

ክፍል 1. ስለጥናቱ ተሳታፊ የሚገልጽ ገጽ

የጥናቱ ርዕስ፡ **ፕሮቴዝ ኢንሂቢተርን መሠረት ያደረገ ፀረ ኤች አይ ቪ መድሃኒት ጋር ተያይዞ የሚመጣ ካርድዮሜታቦሊክ ስይንድሮም**

የዋናውተመራማሪ ስም---

አድራሻ ---

ከላይ በተገለፀው ረዕስ ጥናት ለማድረግ እዚህ እገኛለሁ እናም እርስዎ የጥናቱ ተሳታፊ እንዲሆኑ እጋብዝወታለሁ፡፡ ስለጥናቱ አስፈላጊ መረጃዎችን ሁሉ እሰጥወታለሁ፡፡ ስለጥናቱ ስገልፅልዎት ምናልባት ያልገባዎት ነገር ካለ እኔን ለመጠየቅ ሆነ ለጥያቄዎት መልስ ስሰጥ በደስታ መሆኑን አይጠራጠሩ፡፡ ጥናቱ ላይ ለመሳተፍ ዛሬውኑ እንዲወስኑ አይገደዱም ምናልባትምነፃ ሆነውአስበውበት ከሚፈልጉት ሠውጋርምመክረውበት መወሠን ይችላሉ፡፡

ኤች አይ ቪ በአሁኑ ጊዜ ሁሉምሠውየሚያውቀውና ህክምናውምቢያንስ ሶስት ዓይነት ፀረ ኤች አይ ቪ መድሃኒት የያዘ ነው፡ ይህ ፀረ ኤች አይ ቪ መድሃኒት በበሽታውምክንያት የሚሞቱትን በከፍተኛ መጠን እየቀነሰ እና ሕይወታቸውን እያሻሻለውቢመጣም መድሃኒቱን መጠቀምበተለይ ፕሮቴዝ ኢንሂቢተርን መሠረት ያደረገ ፀረ ኤች አይ ቪ መድሃኒት እንደ የጐንዮሽ ውጤት የሚከተሉትን ችግሮች ሊያመጣ ይችላልማለትምየደምግፊት‹፣ የስኳር በሽታ ፣ የኮልስትሮል መጠን ከፍ ማለት፣ ቦርጭ፣ የኢንሱሊን ሆርሞን ያለመስራት ችግር ፣ የልብበሽታእንዲሁም ስትሮክ ሊከሰት ይችላል፡፡

ጥናቱ ላይ ለመሳተፍ ምንም ዓይነት አስገዳጅ ነገር የለም ሙሉ በሙሉ በፈቃደኝነት ላይ የተመሠረተ ነው፡ ጥናቱ ላይ መሳተፍ ወይም ያለመሳተፍ እንዲሁም ጥናቱ ላይ መሳተፍ ከጀመሩምበኋላ ቢሆን በማንኛውምሰዓት ያለመሳተፍ ሙብትዎ የተጠበቀ ነው፡ ሌላውጥናቱ ላይ ተሳተፉም አልተሳተፉም ያገኙት የነበረው የህክምና አገልግሎት ሁሌ አንድ ዓይነት ነው፡ ምናልባት ጥናቱ ላይ ለመሳተፍ ከወሰኑ ጥናቱ ሊወስድ የሚችለውጊዜ ስድስት ወር ነው፡ ጥናቱ መድሃኒቱን መውሰድ ሲጀምሩ፣ 4ኛ ሳምንት፣ 8ኛ ሳምንት፣ 12ኛ ሳምንት እና 24ኛው ሳምንት ላይ በጤና ተቋሙ እንዲገኙ/እንዲመጡ ይጠይቃል ሆኖም በተለየ ምክንያት

ለተጨማሪ ጊዜ ተመራማሪው እንደአስፈላጊነቱ ሊጠራዎት ወይም እንዲገኙ ሊጠይቅዎት ይችላል፡፡

ጥናቱ ላይ በመሳተፍዎ ወዲያውኑ ከጥናቱ የሚገኘውን ጥቅም ላያገኙ ይችላሉ ይሁንና ጥናቱ ከተጠናቀቀ በኋላ ከላይ የተዘረዘሩትን አላስፈላጊ የጐንዮሽ ውጤቶች ደረጃቸውእንዲታወቅ ይደረጋል ይህም እርስዎን አስቀድመው ችግሮቹ ከመከሰታቸው በፊት የመከላል እርምጃ እንዲወስዱ ያግዝዎታል ምክንያቱም ከመድሃኒቱ በተጨማሪ ሌሎች ተጓዳኝ የሆኑ ነገሮችም ችግሩን የበለጠ ሊያባብሱ ይችላሉ ስለዚህ በዚህም ላይ ተጨማሪ ግንዛቤ ይኖርዎታል አስፈላጊውንም እርምጃ እንዲወስዱ አቅም ይሰጥዎታል ከዚህም በተጨማሪ እርስዎ በመሳተፍዎ ለማሕበረሰቡ ወደፊት ከፍተኛ ጥቅምይኖረዋል፡፡

ጥናቱ ላይ በመሳተፍዎ የእረስዎን ማንነት ሊገልፁ የሚችሉ ነገሮች ሁሉ በሚስጢር የተጠበቁ ናቸው፡፡ ከጥናቱ የሚገኝ ማንኛውም ግኝት በተለይ እርስዎን የሚመለከት ጉዳይ ከጥናቱ ተመራማሪዎች በስተቀር በምንም ዓይነት ሁኔታ ለሌላ የጥናቱ ተሳታፊም ይሁን 2ኛ፣ 3ኛ ወገን አይገለጽም ምስጢር ሆኖ እንደተጠበቀ ይኖራል ለዚህም ሲባል ማንነትዎን የሚገልጽ ስም፣ ካርድ ቁጥር እና የመሳሰሉት አይኖሩም እርስዎ ጥናቱ ላይ የሚወከሉት በተለየ ኮድ/ቁጥር ነው፡፡

ክፍል 2. የስምምነት ምስክር ወረቀት

የጥናቱ መለያ ቁጥር ---------------------------------

ስለጥናቱ ተሳታፊ የሚገልፀውን ሀተታ አንብቤዋለሁ ወይም ተነቦልኛል ስለጥናቱም የመጠየቅ ዕድል ነበረኝ ለጠየኳቸው ጥያቄዎች ሁሉ መልስ አግኝቻለሁ በጥናቱም ለመሳተፍ ተስማምቻለሁ፡፡ ይህን ስምምነት ሳደርግ በጥናቱ ላይ ለመሳተፍ ምንም አይነት አስገዳጅ ነገር ያለመኖሩ እና ሙሉ በሙሉ በፈቃደኝነት ላይ የተመሠረተ መሆኑን ተረድቻለሁ እንዲሁም ከጥናቱ በማንኛውም ሰዓት ካለምንም ምክንያት ያለመሳተፍ ወይም የማቋረጥ መብቴ የተጠበቀ ነው ይህንን ስል ለእኔ በሚደረገው የህክምና አገልግሎት ላይ ምንም ዓይነት ተፅዕኖ አይኖረውም፡፡

የተሳታፊውስም--

የተሳታፊውፊርማ---------------------------------------

ቀን ---------/----------/-----------------

ተሳታፊው የመጠየቅ እድል እንደነበራቸው እና ለጥያቄዎቻቸው ምላሽ እንዳገኙ በእውነት ያለሀሰት እመሰክራለሁ እንዲሁም ተሳታፊው ፍቃዳቸውን የሠጡት በነፃነት መሆኑን እስማማለሁ፡፡

የመስካሪውስም---

የመስካሪውፊርማ---

ቀን ------------/-------------/---------------

ስለታሳታፊው የሚገልፀውን ሃተታ ለጥናቱ ተሳታፊ በትክክል ማንበቤን እና የጥናቱን ይዘት እንደተረዱት አረጋግጣለሁ፡፡ የጥናቱ ተሳታፊ ጥያቄ ለመጠየቅ ሰፊ ዕድል እንደነበራቸው እና በአለኝ አቅም ሁሉ ለሁሉም ጥያቄዎቻቸው መልስ መስጠቴን እነዲሁም ተሳታፊው ፍቃዳቸውን እንዲሠጡ ከተፅዕኖ ነፃ እንደነበሩ እና ፍቃዳቸውንም ሲሰጡ በፈቃደኝነት እና በነፃነት መሆኑን አረጋግጣለሁ፡፡

የቃል ተቀባይ(ተመራማሪው) ስም--

የቃል ተቀባይ(ተመራማሪው) ፊርማ---

ቀን --------------/--------------/--------------

Annex-IV: Amharic version of questionnaire

መጠይቅ

አዲስ አበባ ዩኒቨርስቲ

ጤና ሳይንስ ኮሌጅ

ፋርማሲ ት/ቤት

ፋርማኮሎጂ እና ክሊኒካል ፋርማሲ ት/ክፍል

ፕሮቴዝ ኢንሂቢተርን መሰረት ያደረገ ፀረ ኤች አይ ቪ መድሃኒት ጋር ተያይዞ የሚመጣ ካርድዮሜታቦሊክ ስይንድሮም በዘውዲቱ ሆስፒታል

ይህ መጠይቅ የተዘጋጀው ፕሮቴዝ ኢንሂቢተርን መሰረት ያደረገ ፀረ ኤች አይ ቪ የሚወስዱ ህሙማን ላይ ከመድሃኒቱ በተጨማሪ ለካርድዮሜታቦሊክ ስይንድሮም የሚያጋልጡ ነገሮች ላይ መረጃ ለመሰብሰብ ነው

የእርስዎ በጥናቱ ላይ መሳተፍ በጣምጠቃሚነውከጥናቱ ከሚገኘውውጤትምተጠቃሚይሆናሉ ስለዚህ ለሚከተሉት ጥያቄዎች መልስ እንዲሠጡን በትህና እጠይቃለሁ

የምርጫጥያቄዎችን ማክበብ ይችላሉ ነገር ግን ለደረቅ ጥያቄዎቹ ባሉት ክፍት ቦታዎች ላይ በመጻፍ መመለስ ይችላሉ

የጥናቱ ቦታ---

የጥናቱ ተሳታፊ መለያ ቁጥር --------------------------

ጥናቱ ውስጥ የገቡበት ቀን ---------------------------

ወደ ሁለተኛ አማራጭፀረ-ኤች አይ ቪ መድሃኒት የገቡበት ቀን --------------------------------

ዲሞግራፊ መረጃ

1. ጾታ   ሀ.ወንድ   ለ.ሴት

2.ሴት ከሆኑ የእርግዝና ሁኔታ

ሀ.ነፍሰ ጡር   ለ.እርግዝና የለም

3. እድሜ(በአመት)-----------

4. ያለዎት የትምህርት ደረጃ

ሀ.ኢመደበኛ ትምህርት   ለ.1ኛ ደረጃ ያጠናቀቀ   ሐ.2ኛ ደረጃ ትምህርት ያጠናቀቀ   መ. ኮሌጅ/ዩኒቨርስቲ ያጠናቀቀ   ሠ.ድህረ ምረቃ ዲግሪ

5. ከሚከተሉት የስራ ዓይነት ውስጥ የትኛው እርስዎን በደንብ ይገልፀዎታል

ሀ.የመንግስት/የመንግስት ያልሆነ ተቀጣሪ   ለ.የግል ስራ   ሐ.ስራ አጥ   መ.ተማሪ   ሠ. የቤት እመቤት

6. ሠራተኛ ከሆኑ ስራዎት ምንድን ነው?-------------------------------

የባህሪ እና የአመጋገብ መረጃ

7. በአሁኑ ጊዜ ጥምባሆ እና የጥምባሆ ውጤቶችን ያጨሳሉ?

ሀ.አዎ   ለ.አላጨስም

8. መልስዎ አዎ ከሆነ በቀን ውስጥ ምን ያክል ሲጋራ/ጥምባሆ ያጨሳሉ?--------------------------------

9. የአልኮል መጠጥ ይጠቀማሉ?

ሀ.አዎ   ለ.አልጠጣም

10. መልስዎት አዎ ከሆነ ምን ያክል ጊዜ ይጠቀማሉ?

ሀ.በየቀኑ   ለ.በሳምንት ከ5-6 ቀን   ሐ.በወር 1-4 ቀን   መ.በወር ከ 1ጊዜ በታች

11. ምን ያክል የአልኮል መጠጥ ይጠጣሉ(በቀን/በሳምንት/በወር)?---

12. ለቤት ውስጥ ምግብ ማብሰያ በአብዛኛውን ጊዜ የሚጠቀሙበት የምግብ ዘይት ምንድን ነው?

ሀ. የአትክልት ዘይት ለ. የሱፍ ዘይት ሐ. የዘንባባ (ፓልም) ዘይት መ. የኑግ ዘይት ሠ. የወይራ ዘይት

ረ. የአኩሪ አተር ዘይት ሸ. ሌላ ከሆነ --------------------------

13. በአማካይ ፕሮቲንነት ያላቸውን ምግቦች ምን ያክል ጊዜ ይጠቀማሉ?

ሀ. በየቀኑ ለ. ከ 5-6 ቀን በሳምንት ሐ. በወር 1-4 ቀን መ. በወር ከ 1 ጊዜ በታች

14. በየቀኑ የሚመገቡ ከሆነ በቀን ውስጥ ምን ያክል ጊዜ ፕሮቲንነት ያላቸውን ምግቦች ይመገባሉ?

ሀ. አንድ ጊዜ ለ. ሁለት ጊዜ ሐ. ሶስት ጊዜ መ. አራት ጊዜ

አካላዊ እንቅስቃሴ

15. ስራዎት ጠንከር ያለ የአካል እንቅስቃሴ የሚጠይቅና አተነፋፈስዎትን ወይም የልብ ምትዎትን የሚጨምር ዓይነት ነው?

ሀ. አዎ ለ. አይደለም

16. መልስዎት አዎ ከሆነ በሳምንት ውስጥ ምን ያክል ቀናት ጠንከር ያለ አካላዊ እንቅስቃሴ እንደ አንድ የስራዎ ክፍል ያደርጋሉ?---

17. በቀን ውስጥስ ምን ያክል ሰዐት ለዚህ ጠንከር ላለ የአካል እንቅስቃሴ ያጠፋሉ?---

18. በሳምንት ስንት ቀን እንዲሁም በቀን ምን ያክል ሰዓት ጠንከር ላለ ስፖርት፣ ለአካል ብቃት ማጎልመሻ ወይም እንደመዝናኛ ላሉ የእንስቃሴ ዓይነት ያጠፋሉ?--

19. በቀን ውስጥ ምን ያክል ሰዓት በአብዛኛው ጊዜ ተቀምጠው ወይም ጋደም ብለው ያሳልፋሉ?-----------------------------

ያለፈ ወይም የአሁን ጊዜ የህክምና የጤና መረጃ

20. ከፍ ያለ የደም ግፊት ወይም የደም ግፊት በሽታ እንዳለብዎት ተነግርዎት ያውቃል?

ሀ. አዎ ለ. አያውቅም

21. ከፍ ያለ የስኳር መጠን የስኳር በሽታ እንዳለብዎ ተነግርዎታል?

ሀ. አዎ ለ. አልተነገረኝም

22. ከቤተሰብዎ የደምግፊት ፣ የስኳር ወይምከልብ ጋር የተያያዘ በሽታ የነበረበት ነበር?

ሀ. አዎ ለ. የለም

23. መልስዎት አዎ ከሆነ ምን ነበር በሽታው?--------------------------------

24. ከፍ ያለ የኮሌስትሮል መጠን እንዳለብዎ ተነግሮዎት ያውቃል?

ሀ. አዎ ለ. አያውቅም

25. ከፀረ ኤች አይ ቪ መድሃኒት ውጪሌላ መድሃኒት ወስደው ያውቃሉ?

ሀ. አዎ ለ. አላውቅም

26. መልስዎት አዎ ከሆነ የሚወስዱት/የወሰዱት መድሃኒት ዓይነት፣ መቼ እንደተጀመረ፣ ለምን ያክል ጊዜ፣ መጠኑን ቢገልፁልኝ?--

27. ከኤች አይ ቪ ቫይረስ ኢንፌክሽን ውጭሌላ ኢንፌክሽን ካለብዎ ቢገልጹልኝ?--

ሲጀምሩ እና አሁን እየወሰዱ ስላሉት ፀረ ኤች አይ ቪ መድሃኒት

28. ሲጀምሩ የወሰዱት ፀረ ኤች አይ ቪ መድሃኒት እና ለምን ያህል ጊዜ እንደወሰዱ---

29. አሁን እየወሰዱት ያሉት ፀረ እች አይ ቪ መድሃኒት እና ለምን ያህል ጊዜ እንደወሰዱ ---------------------------------------

አሁን ስላለውየበሽታውሁኔታ

30. የሲዲ-4 ህዋስ ቁጥር (ህዋሳት/ሚሜ^3)------------------------------------

31. የኤች ኤይ ቪ ቫይረስ መጠን (ኮፒ/ሚሜ^3)--------------------------------

32. የ አ ለ ም ጤና ድ ር ጅ ት የ በ ሽ ታ ው ደ ረ ጃ

ሀ . ደ ረ ጃ -1 ለ . ደ ረ ጃ -2 ሐ . ደ ረ ጃ -3 መ. ደ ረ ጃ -4

አ ካ ላ ዊ ምር መራ

33. ክ ብደ ት ----------------(ኪ.ግ) ቁ መት ----------------(ሜ) ቢ ኤ ምአ ይ --------------------(ኪ.ግ /ሜ^2)

34. የ ወገ ብ ል ክ ---------------(ሴ.ሜ)

35. የ ደ ም ግ ፊ ት ፡ ሲ ስ ቶ ሊ ክ ------------------(ሚሜሜ) ዲ ያ ስ ቶ ሊ ክ -------------------(ሚሜሜ)

ላ ቦ ራ ቶ ሪ

36. የ ቅ ባ ት መጠን ፡ ጠቅ ላ ላ የ ኮ ሌ ስ ትሮል መጠን ---------------(ሚግ /ዴ.ሊ) ት ራ ይ ግ ላ ይ ሰ ራ ይ ድ -------------(ሚግ /ዴ.ሊ) ኤ ል ዲ ኤ ል ------------------(ሚግ /ዴ.ሊ) ኤ ች ዲ ኤ ል -------------------(ሚግ /ዴ.ሊ)

37. የ ስ ኳ ር መጠን (የ ፆ ም)----------------------(ሚግ /ዴ.ሊ)