ADDIS ABABA UNIVERSITY

COLLEGE OF HEALTH SCIENCES

DEPARTMENT OF BIOCHEMISTRY

SERUM LIPID PROFILES OF PATIENTS TAKING EFAVIRENZ BASED ANTIRETROVIRAL REGIMEN COMPARED TO RITONAVIR BOOSTED ATAZANAVIR WITH AN OPTIMIZED BACK GROUND AT ZEWDITU MEMORIAL HOSPITAL, ADDIS ABABA, ETHIOPIA: COMPARATIVE CROSS-SECTIONAL STUDY

ABEBE MUCHE (BSc)

A thesis submitted to the School of Graduate Studies of Addis Ababa University, Department of Biochemistry in partial fulfillment of the requirements for the Degree of Master of Science in Medical Biochemistry.

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Advisor: Daniel Seifu (PhD)

Co-advisors: 1. Menakath Menon (PhD)

2. Wondwossen Amogne (MD, PhD)

3. Aster Shoa Amare (MD)

ADDIS ABABA UNIVERSITY

SCHOOL OF GRADUATE STUDIES

This is to certify that the dissertation prepared by Abebe Muche, entitled, " **Serum lipid profiles of patients taking efavirenz based antiretroviral regimen compared to ritonavir-boosted atazanavir with an optimized back ground at Zewditu Memorial Hospital, Addis Ababa, Ethiopia: comparative cross sectional study**," and submitted in partial fulfillment of the requirements for the degree "Master of Science in Medical Biochemistry" in the department of Biochemistry complies with regulations of the university and meets the accepted standards with respect to originality and quality.

Signed by the Examining Committee:

Examiner: Dr. Solomon Mequanint…..…….. Signature…… Date……..…

Advisor:

Dr. Daniel Seifu ……Signature……..... Date……

Co-advisors:

Dr. Menakath Menon. ……. Signature……..... Date……

Dr. Wondwossen Amogne..... Signature……..Date…….

Dr. Aster Shoa Amare..... Signature .....Date.....

_____

Chair of Department or Graduate Program Coordinator

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ACRONYMS AND ABBREVIATION

3TC	Lamivudine
AIDS	Acquired Immune Deficiency Syndrome
ART	Anti Retroviral Therapy
ATV	Atazanavir
ATV/r	Ritonavir-boosted atazanavir
AZT	Zidovudine
BMI	Body Mass Index
CD4	Cluster of Differentiation four
CVD	Cardio Vascular Disease
EFV	Efavirenz
HAART	Highly Active Anti Retroviral Therapy
HDL-C	High Density Lipoprotein- Cholesterol
HIV	Human Immune Deficiency Virus
LDL-C	Low Density Lipoprotein-Cholesterol
LPV/r	Ritonavir-boosted lopinavir
NNRTI	Non Nucleoside Reverse Transcriptase Inhibitor
NRTI	Nucleoside Reverse Transcriptase Inhibitor
NtRTI	Nucleotide Reverse Transcriptase Inhibitor
NVP	Nevirapine
RTV	Ritonavir
SPSS	Statistical Package for Social Sciences
TDF	Tenofovir Disoproxil Fumarate
TG	Triglyceride
TC	Total Cholesterol
TC/HDL-C	Total Cholesterol/High Density Lipoprotein-Cholesterol
TG/HDL-C	Triglyceride/High Density Lipoprotein-Cholesterol
WHO	World Health Organization
ZMH	Zewditu Memorial Hospital

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ABSTRACT

Background: Dyslipidemia represent significant health care concerns in Human immune deficiency virus (HIV) infected patients taking highly active antiretroviral therapy due to their association with cardiovascular disease risk. There is limited data regarding the effects of boosted atazanavir (ATV/r) treatment in the lipid profiles of Ethiopian HIV patients. Thus, this study compares the lipid profile changes of HIV patients on ATV/r-based regimen compared to efavirenz (EFV)-based regimen, while the background nucleos/tide backbone is optimized.

Objective: To compare serum lipid profiles of EFV with ATV/r-based regimens with optimized nucleos/tide background in Ethiopian adult HIV-1 infected patients and assess associated factors of serum lipid profiles at antiretroviral therapy Clinic of Zewditu Memorial Hospital, Addis Ababa, Ethiopia.

Materials and methods: A comparative Hospital based cross-sectional study was conducted among adult HIV-infected patients at Zewditu Memorial Hospital, Addis Ababa, Ethiopia, from July-September 2017. Equal number of EFV and ATV/r-treated patients (n = 90 each) taking for one year and above were included in the study. Serum lipid parameters (triglyceride (TG), total cholesterol (TC), high density lipoprotein cholesterol (HDL-C), and low density lipoprotein cholesterol (LDL-C)) were measured using fully automated mind ray, Chemistry analyzer. Data comparison used chi-square test, Student t-test and Mann-Whitney U test. Multivariate regression analysis and p-value<0.05 was used to identify associated factors of serum lipid profiles.

Results: In the present study ATV/r-treated group resulted significantly higher in the median values of TG [207 (56-1094) vs. 145(42-768) mg/dL; p=0.001] and the mean value of TG/HDL-C ratio (6.6 vs. 4.4; p=0.001) as compared to EFV-treated group. EFV-treated group showed significantly higher in the mean value of HDL-C (44.7 vs. 38.7mg/dL; p= 0.001) as compared to ATV/r-treated group. No significant difference was found in TC (p=0.5), LDL-C (p=0.6), TC/HDL-C (p=0.5) and LDL-C/HDL-C (p=0.1) between EFV and ATV/r-treated patients. In ATV/r-treated patients, CD4 count and body mass index (BMI) was significantly associated with TC. In EFV-treated patients, BMI was significantly associated with increased serum LDL-C and TC in female participants.

Conclusion: In conclusion, ATV/r raises TG and TG/HDL-C while, HDL-C was higher in EFV than ATV/r-treated group. Both groups have less atherogenic lipid profiles in terms of TC/HDL-C and LDL/HDL-C.

Keywords: Dyslipidemia, Antiretroviraltherapy, Cardiovascular disease, Efavirenz, Ritonavir-boosted atazanavir.

1. INTRODUCTION

1.1. Background

1.1.1. Overview of HIV/AIDS

Human immune deficiency virus (HIV) is a lentivirus (literally meaning “slow virus”; a member of the retrovirus family) that slowly attacks and destroys the immune system, the body’s defense against infection, leaving an individual vulnerable to a variety of other infections and certain malignancies that eventually cause death. There are two main types of HIV i.e. HIV type 1(HIV-1) and HIV type 2 (HIV-2). HIV-1 is the most prevalent throughout the world whereas HIV-2 is prevalent in West Africa (Luckheeram *et al.*, 2011).

The acquired immune deficiency syndrome (AIDS) epidemic is one of the most destructive epidemics in the history of humankind, since the beginning of the epidemic, more than 70 million people have been infected with the HIV virus and about 35 million people have died of HIV (end 2015). In 2015 alone, 1.1 million people died of AIDS-related illness. An estimated of 36.7 million people were living with HIV by the end of 2015, including 2.1 million people were newly infected in the same year. Access to antiretroviral treatment for AIDS remains limited in some areas of the world, although more people are receiving treatment today than in the past. As of June 2016, 18.2 million people living with HIV were accessing antiretroviral therapy(ART) as compared to 7.5million in 2010(WHO, 2015).

Sub-Saharan Africa is the most affected region, 25.7million people living with HIV, accounting for two thirds of the global figure. An estimated 812,000 people died of AIDS-related illness in 2015, and a further 1.3 million became infected with HIV in the same year(UNAIDS, 2016).

According to WHO, about 1.14% of the population of Ethiopia, live with HIV by the end of 2015 (WHO, 2015). This number will be increased in the next subsequent year, according to Ethiopian public health institute (EPHI) HIV related estimates and projections report, about 718, 500 people would be living with HIV by the end of 2017, including 27,288 people newly infected by the same year. The national HIV prevalence is 1.16% for 2017. An annual AIDS death during the same period was 3,173 this number will be decreased to 599 by the end of 2021(EPHI, 2017).

Antiretroviral programs in Ethiopia have made a tremendous impact in reducing HIV-related deaths and have been available in Ethiopia since 2003. The scale up of free ART services has been one of the greatest achievements of the HIV program response over the last decade. According to the Federal HIV/AIDS prevention and control office (FHAPCO), ART program services have expanded on a large scale and have substantially decreased AIDS deaths and possibly contributed to the decline in HIV incidence since 2005(FHAPCO, 2014). According to ministry of health (MOH) of Ethiopia, in 2016 around 398,277 adults and 21,686 children under the age of 15 are taking ARV. Based on the spectrum estimate the 2017 ART need is 665,116 for adults and 57,132 for children under 15 years of age (MOH, 2017).

1.1.2. HIV treatment

A decade ago, having AIDS was almost equivalent to a death sentence. Since 1996, with the introduction of combined antiretroviral treatment, AIDS has become chronic, manageable disease. Advances in highly active antiretroviral therapy (HAART) have enabled the suppression of viral replication (Porcoa *et al.*, 2004), revealing lower morbidity and mortality rates associated with the infection. Thus, it improves quality of life and longevity of individuals living with HIV/AIDS(Althoff *et al.*, 2016)

HIV infection is treated with three classes of antiretroviral medications. ART is the use of HIV medicines to treat HIV infection. People on ART take a combination of HIV medicines from at least two different HIV drug classes every day. Because each class of drugs is designed to target a specific step in the HIV life cycle, ART is very effective at preventing HIV from multiplying thus less HIV in the body protects the immune system and prevents HIV infection from advancing to AIDS. It also reduces the risk of HIV drug resistance. ART can't cure HIV, but HIV medicines help people with HIV live longer, healthier lives(WHO, 2016).

Up-to-date, there are about twenty-five Food and Drug Administration approved antiretroviral drugs in the world, which have been now divided into six classes of therapeutic mechanisms and categories (Da-Yong *et al.*, 2017). Five classes of antiretroviral drugs are now available: Nucleoside reverse transcriptase inhibitors (NRTIs), Non-nucleoside reverse transcriptase inhibitors (NNRTIs), Protease inhibitors, Entry inhibitors and Fusion Inhibitors(WHO, 2016).

1.1.3. Drug regimens

Currently, WHO recommend that ART should be initiated in all adults living with HIV, regardless of WHO clinical stage and at any CD4 cell count(WHO, 2016). The WHO encourages a public health approach to ease the scale-up of antiretroviral use in resource limited settings. This approach advises that antiretroviral treatment programmes be standardized to reach as many patients as possible. Therefore, countries select their own first line regimens and a limited number of second-line regimens. Selection of the regimens depends on several reasons: potency, side effects, laboratory monitoring requirements, potential for maintenance of future treatment choices, expected patient adherence, coexisting conditions, pregnancy or the risk of it, availability and cost(WHO, 2004).

Ministry of health (MOH) in Ethiopia recommends that using simplified, less toxic and more convenient regimens as fixed-dose combinations for first-line regimens. Once daily regimen comprise of NRTI backbone (tenofovir (TDF)+Lamivudine (3TC)) and one NNRTI (EFV) are maintained as the preferred choices in adults, adolescents and children older than ten years (Table 1)(MOH, 2014).

Table 1: Summary of First-line ART regimens for adults, adolescents, pregnant women and children.

Population	Preferred 1st line regimens	Alternative 1st line regimens
Adult including pregnant and breast feeding women	TDF+3TC+EFV	AZT+3TC+NVP/EFV TDF+3TC+NVP
Adolescents (10-19) years ≥35kg	TDF+3TC+EFV	AZT+3TC+NVP/EFV TDF+3TC+NVP ABC+3TC+EFV
Children 3 years to 10 years	ABC+3TC+EFV AZT+3TC+EFV	ABC+3TC+NVP AZT+3TC+NVP TDF+3TC+EFV/NVP
Children < 3years	ABC+3TC+LPV/r AZT+3TC+LPV/r	ABC+3TC+NVP AZT+3TC+NVP

Key: AZT = Zidovudine, TDF = Tenofovir Disoproxil Fumarate, ART= Antiretroviral Therapy, 3TC = Lamivudine, LPV/r = Ritonavir-boosted lopinavirr, ATV/r = Ritonavir-boosted atazanavir, NVP = Nevirapine, EFV = Efavirenz, ABC = Abacavir

Monitoring individuals receiving ART is important to ensure the success of treatment, to identify adherence problems and determine whether and which ART regimens should be switched in case of treatment failure. The value of viral load testing as a more sensitive and early indicator of treatment failure is increasingly recognized. Viral load testing should be done after initiation of ART at 6 months, 12 months and every 12 months then after in order to detect treatment failure proactively. If treatment failure is diagnosed, the entire first-line drug should be changed to second-line regimen. The second-line drugs should include at least two new drugs, one or more of them from a new class. This increases the likelihood of treatment success and minimizes the chance of cross-resistance (MOH, 2014).

Using a boosted protease inhibitor + two NRTI backbone as a fixed-dose combination is recommended as the preferred strategy for second-line ART for adults, adolescents and also for children when NNRTI containing regimens were used in first-line ART. The following sequence of second-line NRTI options is recommended: After failure on a TDF + 3TC-based first-line regimen, use Zidovudin (AZT) +3TC + ritonavir-boosted Lopinavir (LPV/r) or ritonavir-boosted atazanavir (ATV/r) in the second-line regimens (Table 2)(MOH, 2014).

Table 2: Summary of sequencing options for preferred first- and second- line ART regimens in adults, adolescents, pregnant women and children.

Population	(1st line regimen used) previous exposure	2nd line regimens
Adult , adolescents, pregnant women and breast feeding women	AZT+3TC+EFV/NVP	TDF+3TC+ATV/r or LPV/r
	TDF+3TC+EFV/NVP	AZT+3TC+ATV/r or LPV/r
	ABC+3TC+EFV/NVP	AZT+3TC+ATV/r or LPV/r
Children younger than 3 years	ABC+3TC+LPV/r	No change from 1st line
	AZT+3TC+LPV/r	ABC/AZT+3TC+NVP
Children older than 3 years	AZT+3TC+EFV	ABC+3TC+LPV/r
	ABC orTDF+3TC+EFV	AZT+3TC+LPV/r

Key: AZT= Zidovudine, TDF= Tenofovir Disoproxil Fumarate, ART= Antiretroviral Therapy, 3TC= Lamivudine, LPV/r= Ritonavir-boosted lopinavir, ATV/r= Ritonavir-boosted atazanavir, NVP= Nevirapine, EFV= Efavirenz, ABC= Abacavir

1.1.4. Atazanavir and efavirenz-based regimens

Atazanavir (ATV) is a protease inhibitor used as part of combination therapy in the treatment of HIV-1 infection, which selectively inhibits the virus-specific processing of viral gag and gag–pol polyproteins, thereby preventing the formation of mature virions. It is metabolized by CYP3A4/3A5 and is an inhibitor of CYP3A4, P-glycoprotein, uridine diphosphate-glucuronosyl transferease 1A1 (UGT1A1)(Dickinson *et al.*, 2009).

ATV, administered at a dosage of 400 mg per day, showed efficacy similar to that of efavirenz and nelfinavir in treatment-naive patients (Wood, 2008). It was also effective in treatment experienced HIV patients, and preliminary data in antiretroviral treatment-experienced patients suggested that ATV 300 mg dosed in combination with ritonavir (RTV) 100mg appears as efficacious as lopinavir/ritonavir (LPV/RTV)(Giuntini *et al.*, 2010).

Atazanavir, which is typically administered with low-dose RTV, has been an important innovation in the treatment of adult HIV infection owing to its ease of dosing, virologic potency, minimal toxicity, lower effect on lipid and glucose metabolism, high genetic barrier to resistance and favorable resistance profile. Its distinct resistance profile is characterized by a signature substitution of isoleucine for leucine at codon 50 (I50L) in the protease inhibitor gene. This signature mutation strengthens its uniqueness and its potential benefit for treatment-naive and treatment experienced patients(Goldsmith and Perry, 2003).

Atazanavir has been shown to possess a unique benefit/risk profile that addresses the hyperlipidemia currently emerging in the HIV-infected patients population chronically treated with HAART regimens. Compared to other protease inhibitors, ATV has no adverse impact on cholesterol, triglyceride, and other metabolic parameters, including insulin and glucose(Gatell *et al.*, 2007).In addition, in patients who developed hyperlipidemia due to prior HAART regimens, ATV has been shown to decrease lipid concentrations to near normal levels(Havlir and O'Marro, 2004; Achenbach *et al.*, 2011).

Efavirenz (EFV) is a first generation NNRTI of HIV-1 and is one of the preferred components of the first-line treatment regimen of HIV infection worldwide. EFV is amongst the molecule that target HIV-1 reverse transcriptase, preventing the formation of viral double-stranded DNA from the single-stranded viral RNA genome(MOH, 2014).

From adherence perspective, NNRTI-based regimens are among the simplest to take, particularly with the co-formulated tablet of TDF, 3TC, and EFV, which allows for once-daily dosing with a single tablet(MOH, 2014).

EFV is principally metabolized by the cytochrome P450 system to hydroxylated metabolities with subsequent glucuronidation of these hydroxylated metabolites. These metabolites are essentially inactive against HIV-1. The most important adverse effects of efavirenz involve the CNS. Up to 53% of patients report some CNS or psychiatric side effects, but <5% discontinue the drug for this reason. CNS symptoms may occur with the first dose and last for hours; more severe symptoms may require weeks to resolve. Patients commonly report dizziness, impaired concentration, dysphoria, vivid or disturbing dreams, and insomnia(Flexner, 2011).

1.1.5. Toxicities of HAART

Almost all antiretroviral drugs have some adverse effects. These toxicities could be specific to a single drug, shared by a class of drugs, or could be shared by all antiretroviral drugs. Also, some of the drugs have toxicities shared by other drugs commonly used in HIV infected patients. A variety of metabolic abnormalities has been associated with HAART, such as lipodystrophy, insulin resistance and dyslipidemia. Some of these changes are related to a higher risk of cardiovascular disease (CVD)(Altizani *et al.*, 2016). CVD is an increasing health problem affecting HIV-infected patients.

Dyslipidemia can affect any lipid parameter, including low density lipoprotein cholesterol(LDL-C) level, total cholesterol (TC),High density lipoprotein cholesterol (HDL-C) levels, triglyceride (TG) or a combination of these lipids (Bhagavan, 2002). Dyslipidemia consisting of hypertriglyceridemia together with depressed concentrations of HDL-C and elevated LDL-C, is being observed with increasing frequency among HIV patients and HIV pateints on ART(Armstrong *et al.*, 2011; Chastain *et al.*, 2015) and can contribute to the increased CVD risk in this patient population. The cause of the increased CVD risk in HIV-infected patients is multi-factorial, involving traditional CVD risk factors, HIV infection-associated risk factors, and ART associated risk factors(Chow *et al.*, 2016).

The treatment options available for the management of dyslipidemia in HIV infection are similar to those in the general population. Treatment strategies include non-pharmacological approaches such as changes to diet and life style, a cholesterol-lowering diet and lifestyle modifications are often recommended, and include smoking cessation, increasing exercise and addressing any medical conditions(Janet, 2011)as well as switching to a less metabolically active antiretroviral regimen without compromising antiretroviral efficacy. Pharmacological treatment may include statin drugs, fibrates, niacin, or cholesterol absorption inhibitors, in addition to management of co-morbidities such as increased global cardio-metabolic risk and insulin resistance(Husain and Ahmed, 2015).

1.2. Literature review

1.2.1. Serum lipid profiles

The plasma lipoproteins are spherical complexes of lipids and specific proteins (apolipoproteins or apoproteins).The lipoprotein particles include chylomicrons, very low density lipoprotein (VLDL), low density lipoprotein, and high density lipoprotein. They differ in lipid and protein composition, size, and density. Lipoproteins function both to keep their component lipids soluble as they transport them in the plasma, and also to provide an efficient mechanism for transporting their lipid contents to (and from) the tissues(Rodwell *et al.*, 2009).

In humans, the transport system is less perfect than in other animals and, as a result, humans experience a gradual deposition of lipids especially cholesterol in tissues. This is a potentially life-threatening occurrence when the lipid deposition contributes to plaque formation, causing the narrowing of blood vessels (atherosclerosis**)(**Harvey and Ferrier, 2011**).**

Low density lipoprotein particles, associated with the Apo lipoprotein molecule Apo lipoprotein B, contain much less triacylglycerol than their VLDL predecessors, and have a high concentration of cholesterol and cholesteryl esters. The primary function of low density lipoprotein particles is to provide cholesterol to the peripheral tissues where they are internalized through the low density lipoprotein receptor by receptor-mediated endocytosis. Genetic defects that result in loss of function of low density lipoprotein receptor cause inherited hyperlipidemia**(**Harvey and Ferrier, 2011)**.**IncreasedconcentrationsofserumLDL-Careassociatedwithanincreased risk of myocardial infarction and stroke, and reaction of LDL-C with reactive oxygen species is an early step in atherosclerotic plaque formation(Ference *et al.*, 2017).

HDL-C contains Apo lipoprotein A-1. Formation of HDL-C occurs in the liver and intestine, which both synthesize and secrete ApoA-I. Shortly after secretion as a lipid poor protein, ApoA-I interacts with the cholesterol–phospholipid transporter ATP Binding Cassette A1 expressed by hepatocytes and enterocytes to acquire lipids, thereby generating nascent high density lipo proteinparticle(Rader, 2006).

Plasma lipid profiles are measured for cardiovascular risk prediction and have now become almost a routine test. The test includes four basic parameters: TC, TG, HDL-C and LDL-C. Worldwide, there is broad variation in serum lipid profile patterns among different population groups. Increased serum

levels of TC, TG, LDL-C, and decreased serum HDL-C level are known to be associated with major risk factors for CVD (Choudhury *et al.*, 2014). Dyslipidemia, comprising of altered lipid panels was common in HIV patients as well as patients on ART.

LDL-C concentration has been the prime index of CVD risk and the main target for therapy. However, several lipoprotein ratios or "atherogenic indices" have been defined in an attempt to optimize the predictive capacity of the lipid profile. Total/HDL-cholesterol (TC/HDL-C) and LDL/HDL cholesterol (LDL/HDL-C) ratios are risk indicators with greater predictive value than isolated parameters used independently, particularly low density lipoprotein(Millán *et al.*, 2009).

In addition to the individual serum lipid parameters various studies showed that lipid ratios are better health risk predictor. They are an important assessment tool for cardiovascular and other health risks. Most used lipid ratios are TC/HDL, LDL/HDL-C and triglyceride/high density lipoprotein-cholesterol (TG/HDL-C).TC/HDL-C and LDL-C/HDL-C ratios are useful for the assessment of heart disease risk. The Framingham Heart study confirms these two ratios help assess heart-disease risk(Li *et al.*, 2015).

The LDL/HDL-C ratio appears to be as useful as the TC/HDL-C ratio. The LDL/HDL-C ratio had a slightly higher predictive power for coronary heart disease (CHD) as compared with the TC/HDL-C ratio. It may have more predictive power for CHD if hypertriglyceridaemia is taken into account(Pereira, 2012). The subjects with combined high levels of LDL/HDL-C and TG had nearly four-times higher CHD risk compared with those without(Li *et al.*, 2015).

The ratio of TG to HDL-C was found to be a powerful independent indicator of extensive coronary disease and insulin resistance. It is initially an atherogenic index that has proven to be a highly significant independent predictor of myocardial infarction, even stronger than TC/HDL-C and LDL/HDL-C(Ranjit *et al.*, 2015). Thus, high TG to low HDL-C abnormality has been considering risk assessment and drug therapy for CHD (Kumar and Anand, 2009). With this ratio it is possible to approximately determine the presence and extent of coronary artery disease by non-invasive methods(Ranjit *et al.*, 2015).

The atherogenic link between high TG and HDL-C is due to the higher plasma concentration of TG, VLDL that generates small dense LDL-C during lipid exchange and lipolysis. These LDL-C particles accumulate in the circulation and form small, dense LDL-C particles, which undergo accelerated catabolism, thus closing the atherogenic circle(Ranjit *et al.*, 2015).

The ratio of TG/HDL-C was reported to be inversely correlated with the plasma level of small, dense LDL particles (sdLDL). As one component of atherogenic dyslipidaemia, sdLDL was found to be associated with an increased risk for CHD. But the determination of plasma sdLDL levels was not widely used in clinical practice due to the disadvantages of being labour intensive, technically demanding, expensive, and slow to produce results. Thus, TG/HDL-C might be a surrogate marker for sdLDL with better clinical and economic significance(Li *et al.*, 2015).

1.2.2. Dyslipidemia in HIV infected patients

The pattern of HIV-associated dyslipidemia does not mirror that seen in the general population, and within HIV it differs between those who are on ART and those who are not. HIV infection by itself, or in combination with genetic and/or environmental factors, may cause metabolic abnormalities as a manifestation of a dynamic relationship between the HIV virus and the host.HIV is a chronic disease associated with dyslipidemia and insulin resistance(Kramer *et al.*, 2009). HIV infection causes lipid alteration with decreases early in the infection in TC, LDL-C and HDL-C and increases later in TG levels(Souza *et al.*, 2013).

The possible mechanisms for HIV-induced dyslipidemia are increased cytokine levels, decreased lipid clearance, and increased hepatic synthesis of VLDL. Cytokines such as tumor necrosis factor alpha (TNF-α) and interleukin-6 (IL-6) appear to promote lipid peroxidation, besides endothelial and platelet activation, and the production of reactive oxygen species(Husain and Ahmed, 2015). .

HIV infection also triggers inflammatory reactions of the immune system and enhances β-adrenergic stimulation of adipose tissue and thus advance adipose tissue lipolysis. An increased adipose tissue lipolysis in turn results in an increased potential for secondary elevation in hepatic fatty acid levels, providing a stimulus for TG synthesis and secretion as VLDL particles(Anuurad *et al.*, 2009). A level of HDL-C also decreases as a result of immune activation as early in HIV infection by impairing ATP-binding cassette transporter A1-dependent cholesterol efflux from macrophages may contribute to increased risk of atherosclerosis in HIV-infected patients(Mujawar *et al.*, 2006).

1.2.3. Dyslipidemia in HIV infected patients on ART

As mentioned earlier, the innovation of HAART, a combination of potent antiretroviral agents, including Protease inhibitors, NRTIs, and NNRTIs, has substantially decreased mortality among HIV-positive patients (Althoff *et al.*, 2016). However, over time HAART has been associated with a number of metabolic and anthropometric abnormalities, including dyslipidemia and insulin resistance as well as subcutaneous fat loss (lipoatrophy) and abdominal obesity (lipomegaly) (Demo *et al.*, 2014), all of which potentially may contribute to an increased risk of CVD (Altizani *et al.*, 2016).

An abnormal lipid levels often occurs in HIV-infected patients who receive ART. The blood lipid profiles of such patients change within three months after receiving ART, and reach a plateau after six to nine months. ART hyperlipidemia includes high TC, high TG, increased LDL-C, increased VLDL, increased levels of apolipoprotein (apoB), and variable levels of plasma HDL-C(Chastain *et al.*, 2015). It has been associated with an increased risk for CVD among these patients(Tsai *et al.*, 2017).The degree of dyslipidemia associated with ART varies greatly, both between and within drug classes (Fontas *et al.*, 2004)and depending on the co-existence of other metabolic abnormalities such as HIV-associated lipodystrophy(Rao *et al.*, 2006).

The effects of NRTIs on lipids are generally mild and there is a high degree of heterogeneity regarding the lipid response. Individuals who started their first antiretroviral regimen, TDF with emtricitabine (FTC) or 3TC was associated with lower levels for TC, LDL-C, TG, and HDL-C, compared with other NRTI(Crane *et al.*, 2011).

NNRTIs will increase serum HDL-C and decrease the ratio of TC/HDL-C. From NNRTIs, use of nevirapine (NVP) is associated with better lipid profile as compared to EFV. It increases the level of HDL-C by producing more apo lipoprotein A1. A prospective study showed that HDL-C was significantly larger for patients receiving NVP (42.5%) than for patients receiving EFV (33.7%; $p = 0.036$), while the increase in TC was lower (26.9% and 31.1%, respectively; $p = 0.073$), resulting in a decrease of the TC: HDL-C ratio for patients receiving NVP (4.1%) and an increase for patients receiving EFV ($p= 0.001$)(Van Leth *et al.*, 2004).

In ongoing prospective analysis of NVP and ATV/r in lipid profiles, NVP showed a potentially less atherogenic lipid profiles than ATZ/r. The use of ATZ/r was associated with higher mean TG levels.

However, the mean TC/HDL-C level in both groups was similarly declines after 48 weeks. The proportion of study participants on NVP group having TC>200mg/dL, TG>150mg/dL, HDL-C>40mg/dL, and LDL-C>130mg/dL were 84(22.34%), 64 (17.02%), 204 (54.26%), 60 (15.96%) respectively. For ATV/r-treated participants having TC≥200mg/dL, TG≥150mg/dL, HDL-C≥40mg/dL, and LDL-C ≥130mg/dL were36 (18.65%), 73 (37.82%), 94 (48.70%), 15 (7.98%) and 24 (12.44%) respectively(Podzamczer *et al.*, 2011).

Integrase Inhibitors have so far not have been shown to induce any consistent lipid abnormalities when used in antiretroviral-naive patients. Neither raltegravir nor elvitegravir, when compared with EFV, demonstrate increases in TC or LDL-C to the same extent as those seen with EFV (Powderly, 2010).

Protease inhibitors are more associated with dyslipidemia. For example, indinavir and ritonavir, is associated with dyslipidemia characterized by elevations in TC and LDL-C, and TG (Danner *et al.*, 1995). Importantly, these early studies did not differentiate between different types of protease inhibitors. In contrast, the protease inhibitor ATV is associated with improved lipid profiles in patients with HIV(Carey *et al.*, 2010). Some studies suggested that an association between protease inhibitors as a drug class and increased dyslipidemia events among HIV-infected patients(Bhowmik *et al.*, 2016).

A prospective cohort study conducted in Canada showed that changes in lipid profile following initiation of a protease inhibitor regimen over 12 months. The results were 20% increase in the levels of TC, HDL-C and LDL-C and TG after twelve months treatment initiation. Protease inhibitors available during in that follow-up includes indinavir, nelfinavir, saquinavir, and ritonavir(Levy *et al.*, 2005).

Ritonavir containing protease inhibitor regimen is associated with hypertriglyceridemia. a prospective study conducted in India indicated that patient's switching to ritonavir-boosted protease inhibitor resulted in hypertriglyiceridemia and hypercholesterolemia. The trend of dyslipidemia increased from 6 months to1year but the HDL-C improved from 6 months to one year, this change improved the TC to HDL ratio. After one year of treatment the range of TG was 110 to 386mg/dL and that of TC was 214 to 465 mg/dl respectively (Bhowmik *et al.*, 2016).

An observational prospective study done in Zimbabwean patients showed that after ≥48 weeks of second-line ART predominantly consisting of a combination of ritonavir-boosted protease inhibitor

and NNRTI with or without NRTIs there was a marked increase in lipid levels; relative increases of TC (59%), LDL-C (61%), HDL-C (71%) and TG (29%). The ratio of TC/HDL-C remained unchanged (Gomo *et al.*, 2014).

1.2.4. Possible mechanism of ART on lipid alteration

The pathogenesis of lipid abnormalities associated with HAART is complex and not fully understood. It may involve genetic predisposition (Tarr *et al.*, 2005). The possible mechanism involved in ART related dyslipidemia may be reduction in the catabolism of VLDL, increased production of VLDL, impaired catabolism of free fatty acid, increased liver TG synthesis, increased secretion of apolipoproteins B containing lipoproteins and reduced expression of low density lipoprotein receptors, and reduction in farnesoid X receptors activity (Estrada and Portilla, 2011).

The possible mechanism of protease inhibitors to alter serum lipid profiles is by binding to low density lipoprotein receptor-related protein (LRP), reducing the cleavage of fatty acids from circulating TGs by the LRP-lipoprotein lipase complex on vascular endothelium, and impairing the uptake of remnant hepatic chylomicron and VLDL. It may directly stimulate hepatic TG synthesis through up-regulation of mRNA production in hepatic cells for key enzymes involved in the TG biosynthetic pathway, leading to the hepatic accumulation of TG-rich lipoparticles(Green, 2002). In addition, protease inhibitors modulate the expression of genes in adipocyte and hepatocyte through sterol regulatory element-binding proteins, cytoplasmic retinoic-acid binding protein type 1, peroxisome proliferators activated receptors, and apo CIII, events that contribute to the development of atherogenic dyslipidemia(Green, 2002).

1.2.5. Efavirenz and ritonavir boosted atazanavir on lipid profiles

Switching to ATV results in a significant improvement in HIV therapy induced hyperlipidemia and a valuable option to improve atherogenic lipid profiles while maintaining virologic control(Ulrike *et al.*, 2005). Patients receiving un-boosted ATV seemed to have a better lipid profile than those on boosted atazanavir (167 and 188 mg/dL for TC and 164 and 202 mg/dL for TGs, respectively) (Giuntini *et al.*, 2010).

Efavirenz is a beneficial effect in the protective HDL-C and related to EFV plasma concentrations. It was associated with an improvement in the atherogenic index of LDL-C/HDL-C or TC/HDL-C ratios.

A prospective study showed that after 36 months of follow up period mean levels of HDL was 44mg/dL. This EFV concentration-dependent change in lipid profile may suggest an EFV-specific beneficial effect and explains the association between HDL-C increase and adequate suppression of HIV-1 infection(Pereira *et al.*, 2006).

HIV-1 infected patients who received EFV compared with ATV/r both in combination with abacavir (ABC)+3TC or TDF+ emitrctabin had significantly greater increased in all cholesterol levels but not in TC/HDL-C ratios(Daar *et al.*, 2011). Additionally, ATV was associated with less mean values of lipid profiles as compared to EFV. Their lipid profiles as follows: the mean levels of TC, TG, LDL-C, HDL-C and TC/HDL-C was 161mg/dL,136 mg/dL, 91mg/dL, 43mg/dL, and 4.0 respectively among ATV users. The mean levels of TC, TG, LDL-C, HDL-C and TC/HDL-C on EFV users was 185mg/dL, 149mg/dL,106mg/dL, 45mg/dL and 4.3, respectively(Jemsek *et al.*, 2006).

From Los Angeles, USA a randomized, 2-arm study comparing the antiviral efficacy and safety between ATV and EFV both in combination with open-label fixed-dose AZT + 3TC, showed that ATV-treated patients relative to EFV-treated patients did not demonstrate significant increases in TC, LDL-C, or TG over 48 weeks of therapy. The mean values of TC, LDL-C, HDL-C and TG on the ATV/r group was178mg/dL, 100mg/dL, 41 mg/dL, and 120mg/dL respectively. On EFV group 186mg/dL,120mg/dL, 50mg/dL and 175mg/dL for mean values of TC, LDL-C, HDL-C and TG, respectively(Squires *et al.*, 2004).

In another a prospective cohort study done in USA, showed that both EFV and ATV/r are similar beneficial declines in the TC/HDL-C ratio. Both ATV/r and EFV users had increased in serum HDL-C and decreased in TC/HDL-C ratio. In comparison to individuals initiating EFV, ATV/r users on average had lower HDL-C and non-HDL-C, but similar declines in TC/HDL-C ratio. In addition, the average levels of TC was almost similar in both groups(Ganesan *et al.*, 2009).

In a randomized trial of antiretroviral-naïve patients initiated to ATV/r and EFV both in combination with TDF + emtrictabine over 48 weeks showed that EFV users had greater increased in mean differences in TC, LDL-C and HDL-C as compared to ATV/r users. No significant differences was found in mean ratios of TC/HDL-C between the two groups(Gotti *et al.*, 2012).

Comparative trials between EFV, LPV/r and ATV/r indicated that the risk for hypertriglyceridemia is lower with EFV than with the use of LPV/r, but there is a greater likelihood of hypercholesterolemia compared to ATV/r. However, in most cases, no change in the TC/HDL-C ratio was seen between the EFV and ATV/r groups(Michael and Heneri, 2015).

A cross sectional study done at Addis Ababa, Ethiopia, showed that EFV users was a trained of lipid profile derangement as compared to treatment naïve HIV patients in terms of TC, HDL-C, LDL-C, TG and TC/HDL-C. The abnormal percentage of lipid profiles was 43.9%, 24.4%, 39%, 36.6% and 29.3%, respectively(Belay *et al.*, 2014).

1.2.6. Associated factors of lipid profile in HIV-1 infected patients

As reported by several epidemiological studies from different populations there is a significant association between different anthropometric indicators and dyslipidemia. Some anthropometric indexes or measures, like body mass index (BMI), and other measures of body fat distribution have been utilized in most of the studies to analyze the relation between cardiovascular risk factors and adiposity(Beraldo *et al.*, 2016; Ghorbanian, 2012; Zhang *et al.*, 2018; Kestila *et al.*, 2012; Pelegrini *et al.*, 2012).Waist circumference has been the best anthropometric indicators, with excellent correlation to abdominal imaging and high association with cardiovascular risk factors. It evaluates the fat deposition in the abdominal region (Beraldo *et al.*, 2016).

Demographic and HIV disease characteristics influence lipid, glucose and insulin parameters in antiretroviral naive patients. In patients with established HIV infection, deleterious lipid profiles were noted before HIV therapy was initiated. Patients with characteristics associated with more advanced HIV disease have unfavorable lipid profiles and evidence of insulin resistance(El-Sadr *et al.*, 2005).A case control study done in China showed that, the TC, HDL-C and LDL-C levels were decreased in the acute HIV infection and chronic HIV infection groups as compared to the HIV negative controls(Wang *et al.*, 2016a).

Some studies showed that there was a significant association between different antiretroviral drug regimens and abnormal lipid profiles. For example, patients receiving a NRTI/ NNRTI + protease inhibitor regimen had the highest hyperlipidemia risk(Tsai *et al.*, 2017).In another study, protease use and duration of HIV was not correlated with dyslipidemia (Nery *et al.*, 2011).

The association of clinical features and demographic factor to serum lipid levels was controversial. For example, a prospective cohort study conducted in London among EFV users indicated that, there was no association between demographic, clinical and anthropometric indicators with HDL-C level (Mahungu *et al.*, 2009).

However, a cross sectional study done in Cameroon showed that, gender, age, BMI, duration with HIV and HAART initiation, receiving HAART was significantly and positively associated with raised TC and LDL-C. The adjusted odds ratio (95 % CI) of HAART treated versus HAART-naïve was 6.24 (2.33–17.45) for TC ≥200 mg/dL and 5.28 (1.17–16.32) for LDL-c 130 mg/dL. Use of ART was not positively associated with decreased HDL-C, increased TG and raised TC/HDL-C ratio(Nsagha *et al.*, 2015).

Similarly, a cross sectional study conducted in Addis Ababa, Ethiopia, at a defense Hospital, showed that there was a significant association between serum TG levels and age >40 as well as BMI>25(p= 0.037, 95%CI 2.44(1.06-5.64) and p=<0.001, 95%CI10.83(1.38-84.37)) respectively. It also found that there was a significant association of serum levels of TC, LDL-C with BMI (p=0.025,95%CI2.31(1.04-7.66), p=<0.001, 95%CI 3.20(1.71-7.55)) respectively(Habtamu *et al.*, 2014).

There is a correlation between CD4+ count and lipid profile. When the level of CD4+ became low then the concentrations of TG are high and lower concentration of TC and LDL-C. In contrast, low concentrations of HDL-C are found in HIV-infected patients, regardless of the $CD4^+$ count(Lichtenstein *et al.*, 2010).In another cross-sectional study, CD4+ cell count was positively correlated with TC, HDL-C, and LDL-C as well as ratios of TC/HDL-C and LDL-C/HDL-C(Kamoru *et al.*, 2017). In addition, a study conducted in Addis Ababa, Ethiopia also found a positive association of CD4 count and TC levels among HAART HIV patients (Belay *et al.*, 2014).

In summary, HIV patients receiving EFV and ATV/r containing ART were similarity and differences in the mean values of lipid parameters. The mean values of TC/HDL-C and LDL-C/HDL-C were similar or no differences in both groups. TC, LDL-C and HDL-C increased in the EFV-treated group as compared to ATV/r-treated group. Whereas serum mean value of TG was higher in patients receiving ATV/r than EFV-treated patients. Clinical and anthropometric indicators are those factors associated with dyslipidemia but their association is still controversial may be present or absent depending on the study area and methods.

1.3. Statement of problem

Hypertriglyceridemia and elevated total and LDL-C levels, together with low HDL-C, are known to increase cardiovascular risk in the general population and may similarly predispose HIV-infected subjects to accelerated coronary illness (Chastain *et al.*, 2015). Dyslipidemia are estimated to be frequent events in patients using HAART and mostly occurred in patients with the use of protease inhibitors(Bhowmik *et al.*, 2016). The data collection on adverse events of anti-HIV drugs study reported a 26% increase in the estimated risk of myocardial infarction per year of exposure to protease inhibitor containing combination ART (Ulrike *et al.*, 2005).

Among different class of antiretroviral drugs, protease inhibitor use was associated with dyslipidemia and morphological signs of CVD, such as increased carotid intima thickness or atherosclerotic lesions (Rhew *et al.*, 2003). However, TDF with EFV or ATV was associated with the most favorable lipid profiles, while the protease inhibitor regimens without TDF and ATV were associated with least favorable lipid profiles(Achhra *et al.*, 2012). Currently, WHO recommends the use of ritonavir-boosted atazanavir, this boosting of ATV with ritonavir significantly increases plasma triglyceride levels(Ulrike *et al.*, 2005). Increments of triglycerides are an independent risk factor to CVD in addition to low levels of HDL-C and highly correlated with pancreatitis(Wang *et al.*, 2016b).

Worldwide, there is a broad variation in serum lipid profile patterns among different population groups(Foulkes *et al.*, 2006). Therefore, evaluation and monitoring of modifiable risk factors can be beneficial to reduce CVD morbidity and mortality of the Ethiopian patients. The present study will compare serum lipid profiles between EFV and ATV/r-treated adult HIV patients and assess associated factors of serum lipid profiles in the study area and give recommendations so as to minimize CVD morbidities and mortalities.

1.4. Justification of the study

There is a scarcity of literature documenting lipid changes on second-line ART in sub Saharan Africa. There is thus an urgent need for more studies that assess lipid changes during the use of various combinations of antiretroviral drugs in Sub-Saharan African patients taking second-line regimens. We compared the lipid profiles of HIV-1 patients receiving the WHO recommended first-line therapy with that of patients on second-line therapy subsequent to first line treatment failure.

As mentioned earlier WHO recommends that EFV as part of first-line therapy and ATV/r as part of second-line therapy. In resource-limited settings, EFV and ATV/r remain cornerstones of ART. The comparative safety of regimens based on ATV/r and EFV are, however, incomplete. Most studies come from the developed world.

The current study was conducted in a setting where virtually all treated adult HIV-1 patients are almost always started on an NNRTI-based regimen as a first-line therapy, and shifted to protease inhibitors-based regimens only after failure of the first-line therapy. The NNRTI efavirenz is a widely used first agent in triple combination therapy for the treatment of HIV-1 infection. ATV/r is a ritonavir-boosted protease inhibitors widely used as a component of second-line therapy. Unlike other protease inhibitors, atazanavir has demonstrated little dyslipidemic impact in ARV-naïve and treatment experienced patients(Havlir and O'Marro, 2004), and its use may limit the need for lipid-lowering drugs to reduce the risk of CVD(Wood, 2008). However, evidences in the support of the characterization of lipid profiles regarding ATV/r in sub-Saharan countries including Ethiopia are scarce. Very limited comparative data exist for ATV/r and EFV, both used in combination with TDF and 3TC.

1.5. Significance of study

This study is planned to compare serum lipid profiles of patients taking EFV and ATV/r based ART as well as to examine the associated factors for serum lipid profiles. Since there is no adequate published work on this aspect on Ethiopian population, it will be the base line for future research. It is also important for the physician or health personnel who take care of the HIV patients to identify which regimen is more associated with dyslipidemia. It helps policy makers to give much attention to serum lipid profiles of HIV-1 infected patients in order to control dyslipidemia; therefore, cardiovascular risk factor in these patients can be predicted at an early stage.

1.6. Hypothesis

Null Hypothesis- There is no difference in mean values of serum lipid profiles of adult HIV-1 infected patients taking between EFV and ATV/r-based regimen.

Alternate Hypothesis- There is difference in mean values of serum lipid profiles of adult HIV-1 infected patients taking between EFV and ATV/r-based regimens.

2. OBJECTIVES

2.1. General Objective

To compare serum lipid profiles of EFV with ATV/r-based regimens with optimized nucleos/tide background in Ethiopian adult HIV-1 infected patients and assess associated factors of serum lipid profiles at ART Clinic of Zewditu Memorial Hospital, Addis Ababa, Ethiopia.

2.2. Specific objective

- To compare serum lipid profiles among adult HIV-1 infected patients taking EFV and ATV/r-based regimens.
- To examine the associations of demographic, clinical features and anthropometric parameters with serum lipid profiles in adult HIV-1infected patients receiving EFV and ATV/r-based regimens.

3. MATERIALS AND METHODS

3.1. Study period and area

The study was conducted at ART Clinic of Zewditu Memorial Hospital (ZMH)from July 1–September 30/2017.ZMH was established in 1925 at the current site of Finfine Restaurant Hall in Addis Ababa as maternity and child health service delivery facility. ZMH is under Addis Ababa City Administration Health Bureau. It is the first ART services delivery site (since July 2003) and has grown to become the largest HIV care and treatment site in the country. ZMH is a 250-bed general hospital providing outpatient and inpatient services like internal medicine, Gyn-OBS, Surgery etc. It is also used as a clinical attachment site for postgraduate students from Addis Ababa University.

ART clinic currently delivers comprehensive HIV/AIDS services in the following areas: HIV counseling and testing, provider initiative and counseling test, prevention of mother to child, ART (adult and pediatric), palliative care TB/HIV, post-exposure prophylaxis, pre cervical cancer evaluation and treatment, nutrition assessment and supplementation treatment, youth psychosocial support services, pharmacy, monitoring and evaluation, and data management and quality assurance.

As of August 2017, number of adults and children who are on ART were 6818. From this 6666 were adults greater than or equal to 15 years, of which 6132 were on first-line ART and the rest 534 were on second-line ART. From the first-line, 3111 patients were on TDF+3TC+EFV-based regimen and from the second-line, 144 patients were on TDF+3TC+ATV/r-based regimen.

3.2. Study design

Hospital based cross-sectional study design of comparative nature was conducted.

3.3. Source population

All adult HIV-1 infected people receiving HAART at ART Clinic of ZMH.

3.4. Study population

All adult HIV-1 infected people who were on follow up for at least 1 year on TDF/3TC/EFV and TDF/3TC/ATV/r-based regimens at ART Clinic of ZMH.

3.5. Eligibility criteria

3.5.1. Inclusion criteria

Study participants were included in the study

- If he or she is 18 years and above.
- If he or she had follow up for 1 year and above without interruption in both groups.(record review)
- If he or she was voluntary to participate in this study.

3.5.2. Exclusion criteria

- ✓ Study participants with mental health problems, hearing impairments or any other serious health problems and those patients who would not able to provide the appropriate information were excluded.
- ✓ Known diabetes mellitus, known renal problem, thyroid problem, pregnancy and on anti tuberculosis drugs were excluded.(record review)
- ✓ Use of lipid-lowering agent.

3.6. Sample size determination

The size of study participants that were recruited into the research was calculated using the G* power version 3.1 software by selecting t-test of means. Sample size was calculated by considering alpha=0.05, power (1-Beta) =0.9 (90%) with EFV- to ATV-based regimens ratio of 1:1and effect size (d) =0.5. The total sample became 172. The number of participants enrolled into the study was 180 (90 for EFV-based group, and 90 for ATV/r-based group).

3.7. Sampling procedure and techniques

Convenience sampling method was applied; all consecutive EFV and ATV/r-treated individuals fulfilling the inclusion criteria and attending ZMH ART clinic during the study period were included until the required sample size was achieved.

3.8. Study variables

3.8.1. Independent variables

- ❖ Socio-demographic characteristics,
  - Age and sex
- ❖ Smoking status,
- ❖ Alcohol use,
- ❖ Physical exercise
- ❖ CD4 count,
- ❖ Duration of treatment,
- ❖ Duration of HIV-infection since first diagnosis,
- ❖ Anthropometric indicators.

3.8.2. Dependent variable

- ❖ Serum TC level
- ❖ Serum TG level
- ❖ Serum LDL-C level
- ❖ Serum HDL-C level

3.9. Operational and standard definitions

- Dyslipidemia: synonymous with hyperlipidemia or lipid abnormalities are abnormally elevated levels of any lipoproteins in the blood. We classified lipid abnormalities according to the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP-III) guidelines. We considered TC, LDL-C and TG of >200mg/dL, >130mg/dL and >200mg/dL, respectively as elevated and HDL-C of <40mg/dL as low, irrespective of gender. Participants who had at least one abnormal lipid parameter were classified as dyslipidemic.
- Anthropometric indicators: Parameters for the measurement of the human body and its individual parts thereby yielding a quantitative index of their variability. They include age, height, weight, body mass index, waist circumference, waist to hip ratio etc.
- Alcoholic beverage drinkers: Individuals were classified as follows: those drinking on average one or more drink(s) daily; those drinking 4 to 6 drinks weekly; those drinking 1to 3 drinks weekly; and those drinking less than one drink weekly. (One drink is defined as one bottle of beer, one glass of wine or one shot of liquor).

- Never drinkers: Individuals who are not drinking currently, and have never drank alcoholic beverages at all.
- Good drug adherence (Adherence rate ≥95%): Is defined by missing < 2 dose of 30 doses or <3 doses of 60 doses; and it was adopted from Ethiopian Federal Ministry of Health, HIV care/ART follow up form.

3.10. Data collection and procedure

Two trained Nurses working at ART Clinic of ZMH collected the data within three-month period. One supervisor nurse controlled the data collection procedure. One day training was given to both data collectors and supervisor. The data collectors introduce them to make rapport with patients. Interviewer administered structured questionnaire data collection tool was used. The data collection was mainly focused on the objective of the study. All necessary information was collected from patients using clinical data and patients' medical records (charts) using structured formats (see Annex) consisting of collection of data on socio-demographic characteristics, medical history, including duration of treatment, current medication, and laboratory investigations and recorded using data abstraction format (see Annex 5). All the data collection formats were filled in the ART Clinic of ZMH.

3.11. Anthropometric measurements

The weight of the study participants was measured using a standard balance, and the height was measured by using a height-measuring device attached to the balance. BMI was calculated by dividing weight (kg) by height (m^2). BMI (kg/m^2) is recognized as the measure of overall obesity(Tambe *et al.*, 2010).Using the WHO classification, four categories of BMI can be identified as follows: underweight, <18.5 kg/m^2;normal, >18.5–24.9 kg/m^2; overweight, >25.0–29.9 kg/m^2; and obesity, >30 kg/m^2(WHO, 2000). The participants' ages were also recorded.

Waist and hip circumference of the patients were also measured. Waist circumference was measured over light clothing at the level halfway between the iliac crest and the costal margin in the mid-axillary line after exhaling, when the lungs were at their functional residual capacity, with the subject in standing position with the body weight evenly distributed across the feet. Hip circumference was measured over light clothing at the level of greater trochanters with the subject in standing position and both feet together.

While the cut-off point considered for waist circumference (WC) was >80cm for females and >90cm for males to define overweight, the cut-off taken for waist to hip ratio was >0.8 for females and >0.9 for males as per the criterion of the WHO(WHO, 2011).

3.12. Blood sample collection

For determination of serum lipid profiles such as TC, TG, HDL-C and LDL-C, after overnight fasting, 5 ml venous blood sample was collected from both groups by phlebotomy laboratory technician under aseptic conditions; skin over the vein was cleaned by 70% alcohol then specimens was transferred to serum separator container and centrifuged at 3000 rpm for 10 minutes. Serum was separated into a clean and sterile container and stored at –80°C.

3.13. Serum lipid profile determination

Measurement of serum samples such as serum TC, TG, LDL-C and HDL-C were assessed using calibrated fully automated Mind ray BS-200E, clinical chemistry analyzer (China) according to the reagent manufacturer's instruction in central laboratory of ZMH.

3.13.1. Serum total cholesterol determination

Cholesterol was measured enzymatically in serum in a series of coupled reactions. Cholesterol esters are converted to cholesterol and fatty acids by an enzyme cholesterol esterase. Then cholesterol is oxidized with oxygen by cholesterol oxidase in to cholest-4-en-3-one and hydrogen peroxide (H_2O_2). The H_2O_2then reacts with 4-Amminoantipyrine (4-AAP) by peroxidase enzyme to yield a red colored quinoneimine dye. The reaction sequence is as follows:

$$\text{Cholesterol ester} + H_2O \xrightarrow{\text{Cholesterol Esterase}} \text{Cholesterol} + \text{Fatty acid}$$

$$\text{Cholesterol} + O_2 \xrightarrow{\text{Cholesterol Oxidase}} \text{Cholest-4-en-3-one} + H_2O_2$$

$$2H_2O_2 + \text{4-AAP} \xrightarrow{\text{Peroxidase}} \text{Quinoneimine} + 4\,H_2O$$

The intensity of the red color produced is directly proportional to the total cholesterol in the sample when read at 500 nm(Hopkins, 2004).

3.13.2. Serum triglyceride determination

Triglycerides in the samples are hydrolyzed by lipase to glycerol and fatty acids. The glycerol is then phosphorylated by ATP to glycerol-3-phosphate and ADP in a reaction catalyzed by glycerol kinase.

Glycerol-3-phosphate is then converted to dihydroxyacetone phosphate (DAP) and hydrogen peroxide (H_2O_2) by glycerophosphate oxidase (GPO). The H_2O_2 then reacts with 4-aminoantipyrine (4-AAP) in a reaction catalyzed by peroxidase to yield a red colored quinoneimine dye.

The intensity of the color produced is directly proportional to the concentration of triglycerides in the sample when read at 500nm(Hopkins, 2004).

Triglycerides + $3H_2O$ $\xrightarrow{\text{lipase}}$ Glycerol + fatty acids

Glycerol + ATP $\xrightarrow{\text{glycerol kinase}}$ Glycerol -3-P + ADP

Glycerol -3-P + O_2 $\xrightarrow{\text{GPO}}$ DHAP + H_2O_2

H_2O_2 +4-AAP $\xrightarrow{\text{peroxidase}}$ Quinoneimine + H_2O

3.13.3. HDL-cholesterol determination

The HDL-C liquicolor test is a direct homogeneous enzymatic assay for the quantitative determination of HDL-C. The test combines two steps, the first step eliminating chylomicrons, VLDL and LDL by specific enzymatic degradation. The next step determines the remaining HDL by the well-known enzymatic reaction cascade cholesterol esterase (CE), cholesterol oxidase (CHO) and peroxidase. In the final reaction hydrogen peroxideoxidises a chromogen (N-(2-hydroxy-3-sulfopropyl)-3, 5-dimethoxyaniline) under the catalytic action of peroxidase. The resulting color change is monitored spectrophotometrically at 593 nm and directly proportional to the HDL concentration in the sample.

Reaction principles are as follows:

1st step: LDL, VLDL and chylomicrons $\xrightarrow{\text{CHE +CHO}}$ cholestenone + H_2O_2

$2H_2O$ $\xrightarrow{\text{Catalase}}$ $2H_2O + O_2$

2nd step: HDL $\xrightarrow{\text{CHE + CHO}}$ cholestenone + H_2O_2

H_2O_2 + chromogen $\xrightarrow{\text{peroxidase}}$ quinine pigment

3.13.4. LDL-cholesterol determination

A direct homogeneous enzymatic assay for the quantitative determination of LDL-C was used in a two reagent formats. The first reagent contains Good's buffer [pH 6.8; *N*-(2-hydroxy-3-sulfopropyl)-3, 5-dimethoxyaniline, sodium salt], cholesterol esterase (CE), cholesterol oxidase (CO), catalase, polyanions, and amphoteric surfactants, which selectively protect LDL from enzyme reaction.

The non-LDL-C reacts with cholesterol esterase (CE) and cholesterol oxidase (CO), producing hydrogen peroxide (H_2O_2), which is consumed by catalase. The second reagent contains Good's buffer (pH 7.0), 4-aminoantipyrene, peroxidase, sodium azide, and deprotecting reagent.

The nonionic surfactants remove the protecting agent from LDL, enabling the specific reaction of CE and CO with LDL-C. The resulting hydrogen peroxide yields color with Trinder's reagent and 4-aminoantipyrene in the presence of peroxidase. The blue color complex produced has an absorbance of 555nm which is proportional to the concentration of LDL-C in the sample(Nauck *et al.*, 2002).

Reaction principles

1st step: HDL, VLDL, and chylomicrons $\xrightarrow{CE + CO}$ cholestenone + H_2O_2

$2H_2O_2 \xrightarrow{Catalase} 2H_2O_2 + O_2$

2nd step: LDL $\xrightarrow{CE+ CO}$ cholestenone + H_2O_2

H_2O_2 + chromogen $\xrightarrow{Peroxidase}$ quinine dye

3.14. Data quality Assurance and management

Both the data collectors and supervisors were trained for half day on the objective and methodology of the research, data collection approach. The questionnaire was translated to Amharic language and back translated into English by another person to check for consistency. The data collection questionnaire was well prepared and all variables were filled on the data extraction format daily. The blood samples for biochemical assay was collected by adherence with standard operation procedures (SOP) and measurement of analyses were carried out after running quality control samples. All the laboratory procedures were handled by professional laboratory technologists. All the tests were standardized and automated.

3.15. Data processing and analysis

Data was checked, cleaned and entered in to Epi-data software version 3.1, and then it was exported to SPSS version 22.0 software for analysis. The results of the descriptive statistics were expressed as frequency and percentage. Chi-square ($\chi 2$) test was used to compare categorical variables. Continuous variables were presented as mean ± standard deviation and median (Inter quartile range). Student t-test was performed to detect differences between groups on continuous variables that did show normality. While Mann-Whitney U test was performed on continuous variables that did not show normality.

Correlation analysis was performed and multivariable linear regression models were constructed to examine the association of independent variables with TC, LDL-C and HDL-C for all study participants. Relevant independent variables were selected for the inclusion of the initial models and the stepwise fit multivariable regression, which eliminates (or adds) covariates in a stepwise fashion, was used with the criteria $p<0.05$ for removal from (or inclusion in) the final model.

3.16. Ethical consideration

Before starting data collection and preliminary study, ethical clearance letter with protocol number M.Sc.1/17 was obtained from the Departmental Research and Ethics Review Committee, Department of Biochemistry, College of Health Sciences, Addis Ababa University. Collaboration letter for data collection was also obtained from ZMH. The objective of the study was briefly clarified and explained for each participant, before enrolling any of the eligible study participants. Samples and data were collected after informed consent had been obtained from the study participants. Confidentiality, anonymity, neutrality, accountability and academic honesty was maintained throughout the study, for example, by using codes. They were informed that there is no any incentive or harm for their participation in this study. The findings of the study will be disseminated for health care professionals and other concerned bodies for better care of the HIV patients than ever.

4. RESULTS

4.1. General characteristics of study participants

One hundred eighty (90 EFV and90 ATV/r) treated adult HIV-1 infected patients participated in this study. The mean age for EFV and ATV/r treated patients was 41.2 ± 8.8and 42.2± 8.8 years old respectively. Therefore, EFV and ATV/r treated adult HIV-1 infected patients were age-matched (Independent Samples T-test, % CI = 95, p-value = 0.4). The number of females were 55/90 (61.1%) in the EFV-treated group and 52/90 (57.8%) in the ATV/r-treated group. So, the sex of EFV-treated patients was well matched with the ATV/r-treated patients (chi-square test, % CI=95, p-value = 0.7) (Table 3).

The clinical features obtained from patients' medical records showed that, the median last CD4+ cell count was lower in ATV/r-treated as compared to EFV-treated group. Months since first HIV positive diagnosis were higher in ATV/r-treated group as compared to EFV-treated group. ATV/r-treated group was on HAART longer than EFV-treated group. Patients in EFV-treated group have been on their current regimen longer than ATV/r-treated group (Table 3). Considering history of hypertension and family history of lipid disorder, all of the study participants responded 'no'. Considering smoking status, all of 180 participants responded 'no' for current smoking status. Self-reported treatment or drug adherence rate showed that ≥ 95% or good drug adherence in both groups. In the present study, no differences were observed in the average BMI of the two groups.

Table 3: Baseline characteristics of study participants at ART Clinic of ZMH, Addis Ababa, Ethiopia, 2018

Variables	EFV-treated n=90	ATV/r-treated n=90	p-value
Age, [mean (SD)]	41.2±8.8	42.2±8.8	0.4
Sex, Female [n (%)]	55 (61.1%)	52 (57.8%)	0.7
CD4+ count at enrolment(cell/ml) [median (IQR)]	454 (103-1655)	355 (40-1041)	**0.002***
Viral load determined last 6 months [n (%)]	39 (43.3%)	40 (44.4%)	0.7
Undetectable viral load (<50copies/cell) [n (%)]	35 (89.7%)	30 (75%)	0.2
Months since first HIV diagnosis [median (IQR)]	108 (16-164)	138 (35-240)	**<0.001***
Months on HAART [median (IQR)]	89 (15-163)	133 (34-174)	**<0.001***
Months on current regimen [median (IQR)]	48 (15-156)	25 (13-44)	**<0.001***
Prophylaxis drugs for OIs [n (%)]	12 (13.3)	12 (13.3)	1.0
Body mass index [mean SD]	25.0±4.2	24.3±4.4	0.2
<18 [n (%)]	4 (4.4%)	5 (5.6%)	0.6
18-24 [n (%)]	41 (45.6%)	48 (53.3%)	
25-30 [n (%)]	35 (38.9%)	30 (33.3%)	
>30 [n (%)]	10 (11.1%)	7 (7.8%)	
Waist circumference			
Male >cut off value [n (%)]	14 (40%)	15 (30.6%)	0.5
Female >cut off value [n (%)]	34 (61.8%)	24 (58.5%)	0.9
Waist to hip ratio			
Male >cut off value [n (%)]	10 (28.6%)	5 (10.2%)	0.06
Female >cut off value [n (%)]	17 (30.9%)	8 (19.5%)	0.06
Physical exercise [n (%)]	54 (60%)	50 (55.6%)	0.7
Alcohol drinking habit [n (%)]	10 (11.1%)	4 (4.4%)	0.6

Key: Continuous variables are reported as mean (SD) and median (IQR), categorical variables are reported as number and percentage, SD= Standard Deviation, IQR= Inter Quartile Range,*= statistically significant by using chi-square tests (categorical) or Mann Whitney U test and Independent t-test (continuous), EFV= Efavirenz, ATV/r=Ritonavir-boosted atazanavir. OIs= Opportunistic Infections, n= number, %= percentage

4.2. Serum lipid levels of study participants

Lipid profile tests (TC, TG, HDL-C and LDL-C) were performed for 180 (90 EFV& 90 ATV/r)-treated participants. According to the results, TG ≥200mg/dL was detected in 24/90 (26.7%) of EFV-treated group and 47/90 (52.2%) of ATV/r-treated group. HDL-C<40mg/dL was detected in 35/90 (38.9%) of EFV-treated group and 47/90(52.2%) of ATV/r-treated group. The ratio of TC/HDL-C ≥5 was detected in 24/90 (26.7%) of EFV-treated group and 29/90 (32.2%) of ATV/r-treated group (Table 4).

Table 4: ***Percentages of EFV and ATV/r treated HIV patients having abnormal levels of lipid profiles at ART Clinic of ZMH, Addis Ababa, Ethiopia, 2018***

Variables	Categories	EFV-treated (n=90, %)	ATV/r-treated (n =90, %)	p-value
Total dyslipidemia	Present n (%)	73 (81.1)	77 (85.6)	0.5
TC	≥200 mg/dL	25 (27.8)	26 (28.9)	0.9
TG	≥200 mg/dL	24 (26.7)	47 (52.2)	**0.01***
LDL-C	≥129 mg/dL	49 (54.4)	41 (45.6)	0.3
HDL-C	<40 mg/dL	35 (38.9)	47 (52.2)	0.1
TC/HDL-C ratio	≥5	24 (26.7)	29 (32.2)	0.5

Key: n= number, %=percentage TC = Total Cholesterol, HDL-C = High-Density Lipoprotein-Cholesterol, LDL-C = Low Density Lipoprotein-Cholesterol, TG = triglyceride, TC/HDL-C ratio = Total cholesterol/High-Density Lipoprotein-Cholesterol ratio, EFV= Efavirenz, ATV/r= Ritonavir-boosted atazanavir, *= statistically significant.

The results of this study also showed that the median serum TG level of EFV and ATV/r-treated based participants was145 (42- 768) mg/dL and 207 (56-1094) mg/dL. The average level of serum HDL-C was found to be 44.7 ±12.4mg/dL and 38.7±9mg/dL in EFV and ATV/r-treated groups respectively (figure 1).

Independent sample t-test was performed to see if there was statistical significant difference in the mean values of serum TC, LDL-C and HDL-C between EFV and ATV/r-treated adult HIV-infected patients. It was found that the mean level of serum HDL-C was significantly lower in the ATV/r-treated group than EFV-treated group (p=0.001)(Fig. 1).

Mann-Whitney U test was performed to see if there was statistical significant difference in the median serum TG value. It was found that the median value of serum TG was significantly higher in the ATV/r-treated group than EFV-treated group (p=0.001).

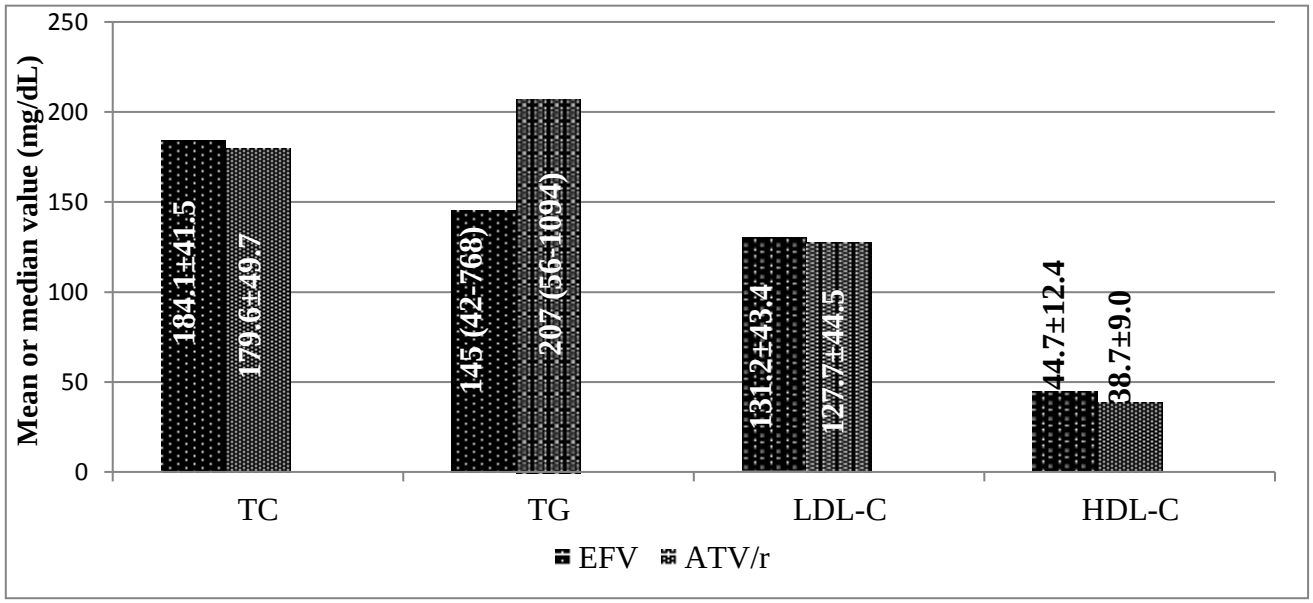


Figure 1: Comparisons of mean of lipid parameters between EFV and ATV/r-treated patients at ART Clinic of ZMH, Addis Ababa, Ethiopia, 2018.

Key: TC= Total Cholesterol, TG=Triglyceride, LDL-C= Low Density Lipoprotein-Cholesterol, HDL-C =High Density Lipoprotein-Cholesterol, *= statistical significance, continuous variables are presented as mean±SD for TC, LDL-C and HDL-C and median (IQR) for TG. IQR=Inter Quartile Range, SD= Standard Deviation

The average TG/HDL-C ratio was 4.4±3.6 in EFV-treated group and 6.6± 5.5 in ATV/r-treated group. The mean LDL-C/HDL-C ratio was 3.1±1.2 in EFV-treated group and 3.4±1.2 in ATV/r-treated group (Fig.2). Independent sample t-test was done to see if statistical significant difference in the mean ratios of TC/HDL-C, TG/HDL-C and LDL-C/HDL-C. It was found that mean TG/HDL-C ratio was significantly higher in ATV/r-treated group than EFV-treated group (p=0.001).

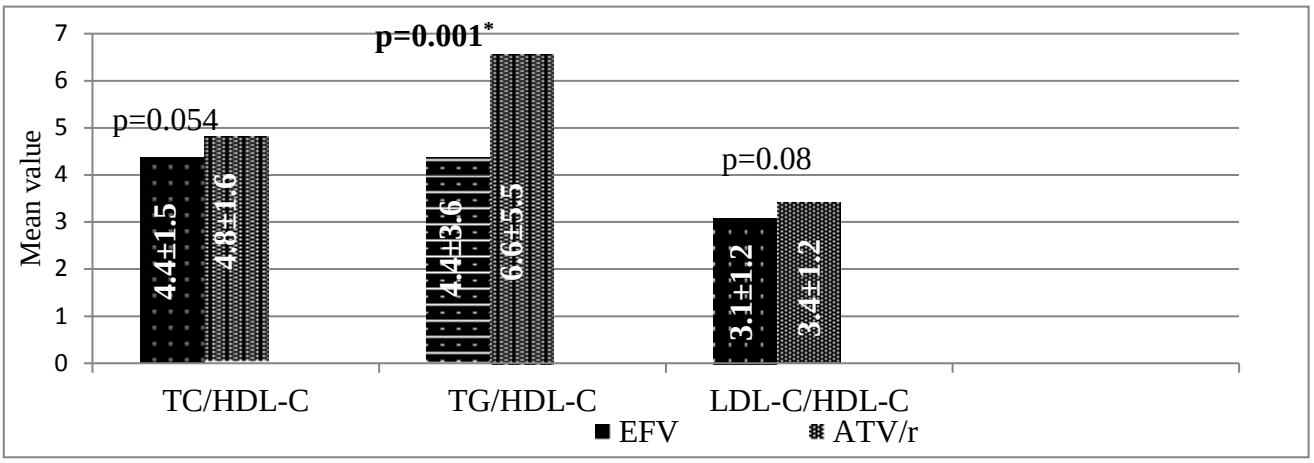


Figure 2: Comparisons of mean values of lipid ratios between EFV- and ATV/- treated patients at ART Clinic of ZMH, Addis Ababa, Ethiopia, 2018

Key: TC/HDL-C= Total Cholesterol/High Density Lipoprotein-Cholesterol, TG/HDL-C= Triglyceride/ High Density Lipoprotein-Cholesterol, LDL-C/HDL-C= Low Density Lipoprotein-Cholesterol/ High Density Lipoprotein-Cholesterol, EFV Efavirenz, ATV/r= Ritonavir-boosted atazanavir

Considering sex, in female EFV- and ATV/r-treated adult HIV-1 infected patients, the median values of TG were 123(42-768)mg/dL and 184(71-481)mg/dL; the average values of HDL-C were found to be(46.3±13.3 and 39.8 ±8.7 mg/dL) respectively. In addition, the results of the present study showed that in the serum of male EFV and ATV/r-treated HIV-1 infected patients, the mean values of LDL-C were 140.4±48.9mg/dLand118.9±40.8 mg/dL(Table 5).

Table5*: *Lipid levels of study participants of EFV and ATV/r-treated male and female adult HIV patients at ART Clinic of ZMH, Addis Ababa, Ethiopia, 2018.

Lipid panels in (mg/dL)	Female			Male		
	EFV	ATV/r	p-value	EFV	ATV/r	p-value
TC(mean, SD)	176.4±32.8	189.7±54.5	0.1	196.1±50.4	171.1±44.1	**0.02***
TG(median(IQR))	123(42-768)	184(71-481)	**0.001***	210(71-768)	219(56-1094)	0.9
LDL(mean, SD)	125.4±38.8	138.1±46.8	0.1	140.4±48.9	118.9±40.9	**0.03***
HDL(mean, SD)	46.3±13.3	39.8±8.7	**0.01***	42.4±10.6	37.8±9.3	**0.04***

Key: EFV=Efavirenz, AVR/r= Ritonavir boosted atazanavir, SD= Standard deviation, *statistically significant difference, TC= Total Cholesterol, TG= Triglyceride, LDL-C= Low Density Lipoprotein- Cholesterol, HDL-C= High Density Lipoprotein Cholesterol.

4.3. Correlation and regression analysis of lipid profiles with predictors in ATV/r-treated group

Bivariate, Pearson correlation test was carried out to determine any association (relationship) between serum levels of lipid profiles and clinical characteristics. Last CD4 count was positively correlated and significant with TC (r=0.286, p=0.02) and HDL-C (r=0.206, p=0.02). Serum LDL-C level was significantly associated with sex (p=0.02). Waist circumference and waist-hip ratio was correlated with TC among female participants (p=0.008 and p=0.04) respectively (Table 6). Multivariate regression analysis was done for predictors to the dependant variables and found TC level was associated with CD4 count (adjusted R^2 =0.082, β-coefficient=0.06, p=0.006). Again TC level was associated with waist circumference among female participants (adjusted R^2= 0.146, β-coefficient=0.409, p=0.008).

Table 6: Correlation analysis of lipid profiles with predictor variables in ATV/r-treated group (N=90)

Predictors	TC		LDL-C		HDL-C		TG	
	r	p	r	p	r	p	ρ	*p*
Age	-0.036	0.8	-0.046	0.9	-0.060	0.8	0.044	0.7
Sex	-0.187	0.06	-0.215	0.02	-0.110	0.2	0.180	0.08
Physical exercise	-0.023	0.5	-0.058	0.8	0.087	0.3	-0.085	0.4
Cd4 count	0.286	**0.02**	0.196	0.3	0.206	0.02	0.042	0.7
HIV + since 1st diagnosis	0.091	0.7	0.176	0.9	-0.069	0.7	0.133	0.2
Duration on HAART	0.104	0.6	0.166	0.6	-0.080	0.6	0.135	0.2
Duration on ATV/r	0.080	0.4	0.171	0.09	0.123	0.2	0.058	0.6
Female anthropometric indicators								
Waist circumference	0.409	**0.008**	0.275	0.08	0.205	0.2	-0.133	0.5
Waist to hip ratio	0.318	**0.04**	0.121	0.4	0.134	0.4	-0.088	0.6
Body mass index	0.264	0.1	0.137	0.4	0.162	0.3	0.160	0.3
Male anthropometric indicators								
Waist circumference	0.237	0.1	0.264	0.06	0.196	0.2	0.151	0.6
Waist to hip ratio	0.211	0.1	0.259	0.07	0.098	0.5	0.112	0.7
Body mass index	0.238	0.1	0.234	0.1	-0.160	0.3	0.00 2	0.5

Key: r= Pearson correlation coefficient, p= p value for Pearson correlation, ρ = Spearman Rank Correlation Coefficient, *P* = p-value for Spearman correlation, TC =Total Cholesterol, TG= Triglyceride, LDL-C= Low Density Lipoprotein-Cholesterol, HDL-C= High Density Lipoprotein-Cholesterol, HIV= Human Immune Deficiency Syndrome Virus, HAART= Highly Active Anti Retroviral Therapy, CD4= Cluster of Differentiation, ATV/r= Ritonavir-boosted atazanavir.

4.4. Correlation and regression analysis of lipid levels with predictors in EFV-treated group

The analyses showed that serum LDL-C level was significantly correlated with duration of HIV positive since first diagnosis (p=0.04). It also correlated with waist hip ratio (p=0.02) and BMI (p=0.001) among female participants. Serum TC levels was significantly correlated with waist circumference (p=0.02) and BMI (p=0.001) among female participants (Table 7). Multivariate regression analysis was done for all predictors to the dependent variables and found that BMI was associated with LDL-C levels (Adjusted R^2 =0.170, β-coefficient=0.430, p=0.01) and TC levels (adjusted R^2=0.209, β coefficient= 0.473, p=0.001) in female participants.

Table 7: Correlation analysis of lipid profiles with predictor variables in EFV-treated group (N=90)

Predictors	TC		LDL-C		HDL-C		TG	
	r	p	r	p	r	p	ρ	*p*
Age	0.181	0.2	0.147	0.4	0.152	0.06	0.046	0.7
Sex	0.233	0.1	0.169	0.2	-0.154	0.2	0.121	0.2
Physical exercise	0.109	0.3	-0.046	0.6	-0.168	0.2	0.203	0.6
HIV + since 1st diagnosis	0.090	0.4	0.108	0.04	-0.075	0.9	0.150	0.1
HAART	0.055	0.3	0.015	0.06	-0.087	0.7	0.202	0.06
Duration on EFV	0.146	0.2	0.038	0.9	0.002	0.6	0.022	0.8
CD4 count	0.082	0.5	0.004	0.8	0.130	0.06	0.004	0.8
Female anthropometric indicators								
Waist circumference	0.315	0.02	0.249	0.06	-0.020	0.8	0.248	0.07
Waist-hip ratio	0.201	0.1	0.313	0.02	0.114	0.4	0.244	0.07
Body mass index	0.473	0.001	0.430	0.001	-0.011	0.9	0.250	0.06
Male anthropometric indicators								
Waist circumference	0.030	0.9	0.026	0.8	-0.271	0.1	-0.145	0.4
Waist-hip ratio	0.211	0.2	0.170	0.3	0.097	0.6	0.086	0.6
Body mass index	-0.003	0.9	-0.096	0.6	-0.309	0.07	-0.002	0.9

Key: r= Pearson correlation coefficient, p= p value for Pearson correlation, ρ = Spearman Rank Correlation Coefficient, *P* = p-value for Spearman correlation, TC =Total Cholesterol, TG= Triglyceride, LDL-C= Low Density Lipoprotein-Cholesterol, HDL-C= High Density Lipoprotein-Cholesterol, HIV= Human Immune Deficiency Syndrome Virus, HAART= Highly Active Anti Retroviral Therapy, CD4= Cluster of Differentiation, EFV= Efavirenz

5. DISCUSSION

With rapid scale up of ART and the increasing usage of antiretroviral drugs to prevent HIV, the need to monitor side effects of these drugs has increased substantially. HIV-infected patients are known to have an increased risk of CVD compared with the general population, with a significantly elevated mortality rate from cardiovascular events(Chow *et al.*, 2016). Dyslipidemia represents significant health care concerns in HIV infected patients due to its direct association with increased CVD risk (Husain and Ahmed, 2015).So that assessing of serum lipid profiles in HIV patients on ART help in early prediction of CVD.

The present study compared serum lipid profiles as well as lipid ratios between ninety EFV- and ninety ATV/r- treated adult HIV-1 infected patients and assessed associated factors of dyslipidemia. Data coming from this study ascertained that 61.1% of the study participants were females in EFV-treated group and 57.8% in ATV/r-treated group. The mean age for EFV and ATV/r treated patients was 41.2 ± 8.8 and 42.2 ± 8.8 years old respectively. The lipid parameters measured in both groups were TC, TG, LDL-C, and HDL-C. The values of serum lipid profiles in the study participants on ATV/r-treated group were 179.6±49.7 for TC, 207 (56-1094) for TG, 127.7±44.5 for LDL-C and 38.7±9.0 for HDL-C, whereas in the EFV-treated group the values were 184.1±41.5 for TC, 145(42-768) for TG, 131.2±43.4 for LDL-C and 44.8±12.4for HDL-C.

The results of the current study revealed that there was a statistically significant difference between ATV/r- and EFV-treated groups in median TG values (p=0.011) (Figure 1). The likely explanation of elevated levels of TG on the ATZ/r-treated group might be due to the addition of low dose ritonavir which increases significantly serum or plasma TG levels (Danner *et al.*, 1995; Ulrike *et al.*, 2005). In line with the results of this study, a study done in Florida-USA by Michael and Heneri (2015) reported that the ATV/r- and EFV-treated study participants were statistically different in the values of serum TG.

The study participants having TG ≥200mg/dL were higher in ATV/r-treated group (52.2%) as compared to EFV-treated group (26.7%). For ATV/r-treated group, it was higher than the prevalence reported from the study conducted in Barcelona-Spain by Podzamczer et al. (2011) that compared ATV/r to nevirapine and found that 37.8%abnormal TG levels. This variation might be due to difference in the socio-economic status of study participants and duration of exposure to the

treatment. The other possible explanation might be that some of the study participants in Podzamczer et al.'s (2011) study were on lipid lowering drugs.

For EFV-treated group, it was lower than the prevalence reported from the study conducted in Addis Ababa-Ethiopia by Belay et al. (2014) which was 36.6%.This variation might be due to difference in the cut-off value used and sample size. In Belay et al. (2014), the cut of value was TG ≥ 150 mg/dL, which is lower than that used in our study (TG≥200mg/dL). Another possible explanation might be treatment duration that may contribute to the difference.

Although there has been some controversy regarding the role of TG in cardiovascular risk, the adult treatment panel III classification of the national cholesterol education program guidelines clearly state that elevated serum TG levels are associated with increased risk of coronary heart disease and are commonly associated with other lipid and non lipid risk factors. In addition, some species of TG-rich lipoproteins, notably cholesterol-enriched remnant lipoproteins, promote atherosclerosis and predispose patients to coronary heart disease. Furthermore, they recommend that, in persons with high serum TG, in addition to the lowering of LDL-C, a reduction in remnant lipoproteins is also advisable(Grundy *et al.*, 2004). However, the relationship between very high TG levels and an increased risk of clinical pancreatitis is well known(Wang *et al.*, 2016b).

The average value of HDL-C was significantly lower (p=0.001)in the ATV/r-treated group as compared to EFV-treated group (Figure 1).This result is in agreement with a study conducted in USA by Squires et al.'s (2004) and Ganesan et al.'s (2009) results that reported lower HDL-C in ATV/r-treated group than in EFV-treated group. Several confounding factors contribute to our observation. First, duration of current treatment with EFV-treated group is nearly double that of the ATV/r-treated group. Second, CD4 count was higher in the EFV-treated group as compared to ATV/r-treated group.

Available data also suggested that a long term therapy with EFV and its concentration is directly proportional to HDL-C levels(Pereira *et al.*, 2006). In addition, genetic variation may also be attributed to the changes in HDL-C levels(Tarr *et al.*, 2005).Interestingly, it has been shown that efavirenz-induced increase in HDL-C is influenced by the gene multi drug reasistance-1(MDR-1)polymorphism that codes for the drug transporter P-glycoprotein. Differences in the *MDR-1* gene polymorphism have been related to the EFV concentration in plasma and to the immune recovery of CD4 lymphocyte cell counts(Hadri *et al.*, 2004).

The proposed molecular mechanism by which EFV increase the HDL-C levels were through down regulation of the activity of the plasma cholesterol transfer protein (CETP) expression through antagonism of the lipid transcription factor, LXR. CETP, which is known to regulate human lipoprotein cholesterol ester to TG exchange and affect HDL-C levels, suggests a potential molecular mechanism for the influence of EFV on human lipid profiles(Flint *et al.*, 2007).

In the same pattern, the average ratio of TG/HDL-C was significantly higher (p=0.001) in the ATV/r- treated group as compared to EFV-treated group of the present study (Figure 2). This is due to high levels of TG and low levels of HDL-C on the ATV/r-treated group as a result their ratio became high. Even if there is no similar study regarding the TG/HDL-C ratio, it has greater predictive power than each of the single standard lipid parameters and superior to the other ratios in order to predict insulin resistance(Du *et al.*, 2014). Furthermore, a TG/HDL-C ratio of ≥3 has been shown to be closely correlated to insulin resistance(Zati *et al.*, 2017).

However, the capacity of TG/HDL-C to predict insulin resistance may vary by race. For example, a study done in South Africa among overweight women that includes West Africa, Black South Africans and African Americans showed that the TG/HDL-C ratio was not predict insulin resistance(Knight *et al.*, 2011). On the other hand, studies in overweight women of Whites suggest that the TG/HDL-C ratio effectively identifies insulin resistance. Yet, the pattern of the dyslipidemia of insulin resistance differs in African Americans and Whites, and therefore the ability of the TG/HDL-C to predict insulin resistance may vary by race. In Whites, the dyslipidemia of insulin resistance follows the classic pattern of elevated TG and low HDL-C. However, in African Americans, West Africans and Black South Africans, normal TG with low HDL-C is the characteristic lipid profile of insulin resistance(Sumner *et al.*, 2010).

The mean values of TC and LDL-C were not show statistically significant differences between EFV and ATV/r-treated groups. However, the mean values of TC and LDL-C were slightly higher in EFV-treated group as compared to ATV/r-treated group. This is corroborated by the results of Ganesan et al. (2009) and Squires et al. (2004).The higher TC in EFV-treated participants is likely due to both higher HDL-C and LDL-C values.

Similarly, it was found that both groups were not significantly different in the mean ratios of TC/HDL-C and LDL-C/HDL-C. In comparison to EFV, ATV/r-treated group was slightly higher in mean values of TC/HDL-C and LDL-C/HDL-C. Michael and Heneri (2015) and Gotti et

al.(2012)also reported that both EFV and ATV/r-treated adult HIV patients were similar in mean ratios of TC/HDL-C. TC/HDL-C and LDL-C/HDL-C ratios are indicator of CVD risk with greater predictive value than isolated parameters used independently(Zhu *et al.*, 2015). The predictive capacities of these ratios are supported by data suggesting that an increase in HDL-C is more prevalently associated with plaque regression. This may be particularly interesting in patients with features of the metabolic syndrome(Millán *et al.*, 2009).

The current study had investigated the associations of some demographic, clinical features and anthropometric indices (BMI, WC, and waist-to-hip ratio) and lipid abnormalities in EFV- and ATV/r-treated group. Accordingly, CD4 count showed significantly positive association with serum TC levels among study participants on ATV/r-treated group. In agreement with the results of this study, Belay et al. (2014) and Kamoru et al. (2017) reported significantly positive correlation with CD4 among HAART patients. Waist circumference also significantly associated with TC among female participants in ATV/r-treated group. In agreement with these results, a study done by Beraldo et al. (2016) reported significant association between waist circumference and TC levels.

An increased waist circumference is most likely associated with elevated risk factors of CVD because of its relation with visceral fat accumulation, and the mechanism may involve excess exposure of the liver to fatty acids and release of detrimental adipocytokines and lower levels of beneficial adipocytokines and these have multiple detrimental effects, including proinflammatory damage, altered signaling pathways and reactive oxygen species production, on beta cells and other tissues resulting in disease states like hypertension and diabetes (Dalton *et al.*, 2003).

Increased BMI showed significantly positive association with serum TC and LDL-C among female participants in the EFV-treated group. Importantly, anthropometric indicators in male participants were not significant determinants of any lipid variables in both groups. The reason behind this was unclear.

There was no statistically significant association observed between HDL-C and TG levels with predictor variables. Similar finding had been reported in studies conducted in London by Mahungu et al.(2009). There was no association between duration of HIV positive since first diagnosis and duration on HAART and serum lipid parameters in both groups. These results agree with the study results of Nery et al. (2011). The observed difference between EFV and ATV/r-treated groups on associated factors of serum lipid levels was unknown.

6. CONCLUSION

The results of the present study evaluated serum lipid profiles of ATV/r compared with EFV-treated groups, when combined with TDF/3TC.Our research found that ATV/r raises TG and TG/HDL-C while, HDL-C was higher in EFV than ATV/r-treated participants. Even though there were no statistically significant differences, the mean values of TC and LDL-C were slightly higher in EFV- than in ATV/r-treated group. The ratio of TC/HDL-C and LDL-C/HDL-C was higher in ATV/r- than EFV-treated group. Therefore, we accept the alternative hypothesis stating that there is a difference in lipid profiles between EFV and ATV/r-treated groups. Assigning conventional risk increments to lipoprotein fraction changes, EFV-treated patients would on balance likely have lower cardiovascular risk due to their substantially increased HDL-C in the face of a modest increase in TC resulting in a lower TC: HDL-C ratio.

This study also showed that CD4 count showed statistically significant association with TC levels among ATV/r-treated group. Waist circumference also associated with TC in female participants of ATV/r-treated group.TC and LDL-C were associated with BMI among female participants in EFV-treated group.

7. STRENGTH AND LIMITATION

7.1. Strength of the study

To the best of our knowledge, this is one of the first studies on the metabolic effects of ATV/r-based regimen from the Ethiopian HIV-infected patients. In addition, all lipid ratios which were not done by previous studies were included and the associations between anthropometric indicators and lipid profiles were assessed.

7.2. Limitation of the study

Despite the aforementioned strengths, this study has several weaknesses.

- ✓ Because the study was conducted in only one General Hospital, it may be difficult to represent the whole HIV-1 infected patients on EFV and ATV/r-based regimen in the population.
- ✓ Nutritional factors and dietary habits were not taken into consideration in this study.
- ✓ Limitation of related literatures to compare and discuss some of the findings.
- ✓ There were baseline differences of the two groups on CD4 count, duration with HIV, duration on HAART and duration on current treatment so it may be affect the outcome variables.
- ✓ Being a cross-sectional study by design it cannot observe prospectively and thus cannot associate causal relationships between the factors under study.

8. RECOMMENDATION

The following recommendations are suggested to further investigate and evaluate lipid profiles in HIV patients taking EFV and ATV/r:

- Nutritional factors and dietary habits should be assessed in further studies.
- There should be timely evaluation of lipoprotein subclass of the HIV patients on ART (EFV and ATV/r) to prevent cardio vascular disease complications that develop as a result of dyslipidemia.
- Monitoring and evaluation of TG and HDL-C in HIV patients taking ATV/r based regimen is important.
- Clinicians treating HIV-infected patients should reassure that the use of both ATV/r and EFV-based regimens results in a favorable lipid profile, in terms of TC and TC/HDL-C.
- Further studies should be conducted with larger sample size using prospective study design to investigate the effect of EFV and ATV/r on serum lipid profiles.

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APPENDIX

Annex 1. Information sheet for participants (English version)

Principal Investigator: **Abebe Muche**
Addis Ababa University College of
health sciences Department of
Medical Biochemistry

Dear participant! Here, I the undersigned, at Addis Ababa University College of Health Sciences, Department of Biochemistry Graduate Study Program, currently I will be undertaking research on a topic entitled as "Serum lipid profiles of patients taking efavirenz based antiretroviral regimen compared to ritonavir-boosted atazanavir with an optimized background at Zewditu Memorial Hospital". For this study, you will be selected as a participant and before getting your consent, you need to know all necessary information related to the study which will be detailed as follows.

Introduction: Privacy is the state of being free from intrusion, and in the context of health care it concerns the responsibility of a care provider to protect a clients from any disclosure, even unintentional, of personal health data, by providing security to the patient and the patient's records. Confidentiality, in contrast, is the limiting of information to only those for whom it is appropriate. Therefore this information sheet briefly provides the necessary guide to be considered during the study.

Objective of this study is to compare serum lipid profiles of patients taking efavirenz based antiretroviral regimen and ritonavir-boosted atazanavir and to examine associated factors with serum lipid profiles at Zewditu Memorial Hospital.

Participants to be included: All HIV positive patients who receive HAART and meet the inclusion criteria will be included in the study.

Risks and discomfort: There is no risk in participating in this study. You will be asked to give one or two small blood samples, taken from your arm by the routine safe method for drawing blood by a health care professional. Risks from this are minimal. There could be minor pain and change in color of your skin following the blood drawing and which would disappear in short

duration. The amount of blood taken from each volunteer throughout the study period is 5 ml, which will not affect your health.

Benefits and incentives: The result of the finding may, if it is helpful, be communicated to your physician for use in the management of the disease. You will have the chance to know your test result. You will not be provided with any direct incentives for your participation in the research.

Confidentiality: All information about the participants will be kept confidential. Logbooks used in the laboratory will have no names but codes. The information sheet that links the coded number to patient name will be locked inside a box and it will not be revealed to anyone except your physician and the principal investigators.

Participant Rights: Your participation is entirely voluntary and up to you to decide. There is no penalty if you do not agree to participate. Also you have the right not to answer any questions you do not want to. You have full right to withdraw from participating in this study at any time before and after consent without explaining the reason. Your decision will not affect your right to get health service that you are otherwise entitled to.

Persons to contact: If you have any question, you can ask at any time. If you have additional questions about the study, you can contact the:

Principal investigator: Abebe Muche, cell phone-0938373278, E-mail abebemuche3@gmail.com

Thank you for your cooperation.

If you are voluntary to participate in the study, we kindly request you to provide your response for the questionnaire in the next page.

Instruction: A. the questionnaire contains closed ended questions so circle the letter of your choice (you can answer more than one choice).

Annex 2. Information sheet participants (Amharic Version)

የመረጃና የስምምነት ቅፅ

ለጥናቱ ተሳታፊዎች በሙሉ፤ እኔ አበበ ሙጨ በአዲስ አበባ ዩኒቨርሲቲ ጤና ሳይንስ ኮላጅ የሜዲካል ባዮኬሚስትሪይ ትምህርት ክፍል የድህረ ምረቃ ተማሪ ስሆን የመመረቂያ ፅሁፌን በዘውዲቱ መታሰቢያ ሆስፒታል የአዋቂዎች ተመላላሽ የኤች አይ ቪ ኤድሥ ህሙማን ታካሚዎች በደማቸው ውስጥ ያለውን የቅባት መጠንና እንዲሁም ሌሎች ከኤች አይ ቪ ኤድስ ጋር ግንኙነት ያላቸውን ነገሮች መጠንና ሁኔታ መለካት ነው:: ለዚህ ጥናት ደግሞ እርስዎ የተመረጡ ስለሆነ አስፈሊጊውን መረጃ እንዲሰጡን በትህትና እንጠይቃለን፡፡

የመረጃ ሰብሳቢውስም_____የአባት ስም_____የተጠያቂው መለያ ቁጥር_____

መግቢያ፤ የጥናቱ ሚሰጥራዊነት ሙለ ለሙሉ የተጠበቀ ነው፡፡ እንዲሁም ጥናቱ በሙሉ ፈቃደኝነት የሚሰራ መሆኑ፣ በፈለጉት ሰአት ጥናቱን የማቋረጥ ወይም ያለመሳተፍ መብትዎ የተጠበቀ ነው፡፡

የጥናቱ አላማ፤ የኤች አይ ቪ ኤድሥ ህሙማንን በደማቸው ውስጥ ያለውን የቅባት መጠንና እንዲሁም ሌሎች ከኤች አይ ቪ ኤድስ ጋር ግንኙነት ያላቸውን ነገሮች መጠንና ሁኔታ መለካት ነው::

ጥናቱ የሚያካትታቸው ተሳታፊዎች፤ መረጃ በሚሰበሰብበት ወቅት ለህክምና የሚመጡ ህሙማን ይካተታሉ፡፡

ሀ. የጥናቱ መረጃ፡- ጤና ይስጥልኝ፤ እንደምን አደሩ፣ እንደምን ዋሉ፣እንደምን አመሹ [እንደአስፈላጊነቱ በመረጃ ሰብሳቢው]፡፡ ስሜ----------ይባላል፡፡ የመጣሁት በአዲስ አበባ ዩኒቨርሲቲ ህክምናና ጤና ሳይንስ ኮላጅ የሁለተኛ ዲግሪ ተማሪ በሆነው በተማሪ አበበ ሙጨ እየተሰራ ባለዉ ጥናታዊ ፅሁፍ ዙሪያ በመረጃ ሰብሳቢነት ሲሆን በዛሬው ዕለት እዚህ የተገኘሁት ከኤች አይ ቪ ኤድሥ ህመም ጋር ተያይዞ በደማቸው ውስጥ ያለውን የቅባት መጠንና እና ተያያዥነት ያላቸውን ምክንያቶች በሚመለከት በሚደረገው ጥናት ዙሪያ መረጃ ለመሰብሰብ ነዉ፡፡ ይህ ጥያቄ የተዘጋጀው ለምርምር ስራ ሲሆን በአዲስ አበባ ዩኒቨርስቲ በጥናትና ምርምር ኮሚቴ ተገምግሞ እንደ አስፈላጊነቱ ግድፈት ካለበት እርማት ይደረግበታል፡፡

በዚህ ጥናት በመሳተፍዎ የሚያገኙት ቀጥተኛ የሆነ ጥቅም የለም ቢሆንም ከዚህ ጥናት የሚገኘው ውጤት በቀጥታ ማህበረሰቡን የሚጠቅም ሲሆን ለእርስዎ ደግሞ እርካታን እንደሚሰጥዎት ተስፋ አደርጋለሁ፡፡ ከጥናቱ የሚገኘው መረጃ ከላይ ከተጠቀሰው አላማ ውጭ ለሌላ ተግባር የማይውል ሲሆን መረጃ በሙሉ በሚስጥር የሚጠበቅ መሆኑን ቃል እየገባሁ ለወድፊቱም ለሚፍለጉት የጤና አገልገሎት በእርስዎም ሆነ በቤተሰብዎ ላይ ምንም አይነት ተፅእኖ እንደሌለው ልንገልፅልዎት እንወዳለን፡፡

በማንኛውም ጉዳይ መረጃ ማግኘት ከፈለጉ ወይም ጥያቄ መጠየቅ ከፈልጉ ዋናውን የጥናቱ ባለቤትን አቶ አበበ ሙጨ በሚከተሉት አድራሻዎች ማግኘት ይችላሉ፡፡

ስልክ ቁጥር፡0938373278 ፣ኢሜል አድራሻ፡abebemuche3@gmail.com

Annex 3. Informed consent form (English Version)

In undersigning this document, I am giving my consent to participate in the study entitled as assessment of serum lipid profile of patients taking efavirenz and ritonavir boosted atazanavir ART at Zewditu Memorial Hospital, Addis Ababa, Ethiopia. I have been informed that the purpose of this study is to assess serum lipid profiles and associated factors at Zewditu Memorial Hospital, Addis Ababa, Ethiopia; I have understood that participation in this study is entirely voluntarily. I have been told that my answers to the questions will not be given to anyone else and no reports of this study ever identify me in any way. I have also been informed that my participation or non-participation or my refusal to answer questions will have no effect on me. I understood that participation in this study does not involve risks. I understood that Abebe Muche is the contact person if I have questions about the study or about my rights as a study participant.

Respondent‘s signature_____

Interviewer Name _____ Signature _____Date_____

Annex 4. Informed consent form (Amharic Version)

የፈቃደኝነት ማረጋገጫ ቅፅ

የምርምር ጥናቱ ክፍል የሆኑ መረጃዎችና ሂደቶች ከተብራሩልኝበኃላ ለተመላላሽ የኤች አይ ቪ ኤድሥ ህሙማን ታካሚዎች በደማቸው ውስጥ ያለውን የቅባት መጠንና እንዲሁም ተዛማጅነት ያላቸውን ጉዳዮች ለማጥናት በተዘጋጀው ጥናታዊ ፅሁፍ ለመሳተፍ ሙሉ ፈቃደኝነቴን አሳይቻለሁ::እኔም በተብራራልኝ መንገድ ተረድቻለሁ:: ምርምሩ ምንም የተለየ የጎንዘብ ጥቅማ ጥቅም የሌለው፣አደጋ የማያስከትል መሆኑን እንዲሁም የሚደረገው ተሳትፎ እና መረጃ በሚሰጥር የሚያዝና ለማንም ተላልፎ የማይሰጥ መሆኑን ተረድቻለሁ:: ስለዚህ በዚህ የምርምር ጥናት ላይ ለመሳተፍ ፈቃደኛ መሁኔን በፊርማየ አረጋግጣለሁ::

የመረጃ ሰብሳቢው ስም----------

የተሳታፊው ስም----------

ፊርማ ----------

ቀን ----------

Annex 5. Questionnaire (English Version)

Part 1- Socio-Demographic, anthropometric and clinical information

Patient initials:_____

Cod No._____

Unique ART No. _____

1. Age-------- years (as given), Date of birth _____

2. Sex A. Male B. Female

3. What is your ethnicity? A. Amhara B. Oromo C. Tigre D. SNNPR E. others-------

4. What is your marital status? A. Single B. Married C. Divorced D. Widowed/er

5. Address: city_____ Woreda_____Kebele____

6. What is your religion? A. Orthodox Christian B. Muslim C. Protestant D. Other

7. What is your educational status? A. Illiterate B. Reading and writing only

C. Primary school D. Secondary school E. College/university completed

8. Occupation A. Civil servant B. Private Business C. Pensioner D. Student E. Other (specify)_____

9. Do you perform physical exercise? A. Yes B. No

10. Alcohol consumption: A. Yes B. No

If yes then

Types of alcohol	Quantity		
	Daily	Weekly	Monthly
Bottles of beer			
Glasses of wine			
Pints of hard liquor			

11. Smoking history

A. Currently a smoker, specific pack/year ----------

B. Quitted smoking, last smoked number of pack per year smoked before quitting_____

C. Never smoked

D. Missing information

12. Duration of time with the disease (HIV/AIDS) since diagnosis in months----------

13. Duration of taking HAART in months----------

14. Duration of taking the current treatment----------

15. During the past 30 days, on how many days have you missed taking all your doses?

A. None B. One day C. Two day D. Three days D. Four days

16. During the past 60 days, on how many days have you missed taking all your doses?

A. none B. one day C. Two day D. Three days E. Four days

17. Other medication_____

18. WHO stage

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

19. Last CD4 count level---------- date

20. Viral load values----------Date----------

Annex 6. Questionnaire (Amharic Version)

ክፍል አንድ፡ ማህበራዊና ስነ-ህዝባዊ መረጃዎችን በተመለከተ የተዘጋጀ ቃለ መጠይቅ

ስም----------

ካርድ ቁጥር----------

ልዩ የART ቁጥር----------

1. እድሜዎት ስንት ነው? _____ዓመት፣ የተወለዱበት ቀን----------

2. ፆታ? ሀ. ወንድ ለ. ሴት

3. ብሔርዎ ምንድን ነው? ሀ.አማራ ለ.ትግሬ ሐ.ኦሮሞ መ. ሌላ ይግለጹ

4.የጋብቻ ሁኔታዎስ? ሀ. ያላገባ/ች ለ.ያገባ/ች ሐ. የፈታ/ች መ. የሞተበት/ባት ሰ. ተለያተው የሚኖሩ

5. አድራሻ፡ ከተማ ---------- ወረዳ -------- ቀበሌ---------

6. መደበኛ የትምህርት ደረጃዎ ስንት ነው? ሀ. ማንበብም ሆነ መፃፍ አልችልም ለ. ማንበብና መፃፍ እችላለሁ

ሐ አንደኛ ደረጃ ያጠናቀቅሁ (1-8) መ. ሁለተኛ ደረጃ የጠናቀቅሁ (9-12) ሰ. ኮሌጅ/ዩኒቨረሰቲ ያጠንቀቅሁ

7.ስራ ሀ. የመንግስት ሰራተኛ ለ. የግል ሰራተኛ ሐ. ጥሮተኛ መ. ተማሪ ሰ. ሌላ----------

8. የአካል ብቃት እንቅስቃሴ ያደርጋሉ? ሀ. አዎ ለ. አላደርግም

9.አልኮል ይጠጣሉ? ሀ.አዎ ለ. አልጠጣም

አዎ ካሉ

የአልኮሉአይነት	የሚጠጡት የአልኮል ብዛት መጠን		
	በቀን	በሳምንት	በወር
ቢራ በጠርሙስ			
ወይን በብርጭቆ			
አስካሪ መጠጥበመለኪያ			

11.ሲጋራን ማጨስን በተመለከተ

ሀ. አሁን የጨሳሉ ካጨሱ በአመት ምን ያህል ፓኬት ያጨሳሉ?----------

ለ. ማጨስ ከማቆምዎ በፊት ምን ያህል ፓኬት በአመት ያጨሱ ነበር?----------

ሐ. አጭሽ አላውቅም

12. ኤች አይ ቪ ተመርምረው በደምዎ ወስጥ መኖሩን ካወቁ ምን ያህል ጊዜ ሆነዎት (በወር)? ----------

13. የኤች አይ ቪ ኤድስ መድሀኒትን መውሰድ ከጀመሩ ስንት ጊዜ ሆነዎታል (በወር)?----------

14. አሁን እየወሰዱት ያለውን መድሀኒት ምን ያህል ጊዜ ሆነዎታል (በወር)?----------

15. በባለፈው አንድ ወር ውስጥ መድሀኒቱን ያልተወሰደበት ቀን ብዛት

ሀ. ምንም ቀን የለም ለ. አንድ ቀን ሐ. ሁለት ቀን መ. ሶስት ቀን ሠ. አራት ቀን

16. በባለፈው ሁለት ወር ውስጥ መድሀኒቱን ያልተወሰደበት ቀን ብዛት

ሀ. ምንም ቀን የለም ለ. አንድ ቀን ሐ. ሁለት ቀን መ. ሶስት ቀን ሠ. አራት ቀን

17. ሌላ የሚወስዱት መድሀኒት ካለ----------

18. የ ኤች አይ ቪ/ኤድስ በሽታ ደረጃ በአለም ጤና ድርጅት መሰረት

ሀ. መጀመሪያ ደረጃ ለ. ሁለተኛ ደረጃ ሐ. ሦስተኛ ደረጃ መ.አራተኛ ደረጃ

19. የ CD4 መጠን---------- ቀን----------

20. የ ቫይረስ መጠን ቀን---------- መጠን----------

Declaration

I declare that this research paper entitled: **Serum lipid profiles of patients taking efavirenz based antiretroviral regimen compared to ritonavir-boosted atazanavir with an optimized back ground at Zewditu Memorial Hospital, Addis Ababa, Ethiopia: Comparative cross-sectional study** is my original work and has not been presented for any degree in any other university, and that all sources of materials used for the research have duly been acknowledged.

Abebe Muche

Signature_____

Date_____