Comparative Assessment of the Magnitude of Hyperlipidemia in HIV-Infected Patients Receiving Lopinavir/r- and Atazanavir/r-Based Antiretroviral Drugs

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Abstract

Objective: To assess prevalence of hyperlipidemia in patients receiving lopinavir boosted with ritonavir (LPV/r) and atazanavir boosted with ritonavir (ATV/r) antiretroviral drugs. **Methods:** HIV-infected patients (300) were recruited in the study between December 2015 and April 2016. Lipid profile including triglycerides (TG), high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol (LDL-C) were assessed. **Results:** Prevalence of derangement in TG was 71.0% in patients using LPV/r compared to 44% in those using ATV/r ($P = .01$). Use of LPV/r was independently associated with increased total cholesterol (TC; $P = .001$) and TG ($P = .0003$). Females had raised levels of TC compared to males ($P = .00008$). Body mass index of ≥ 25 kg/m^2 was also associated with raised TC ($P = .002$) and LDL-C ($P = .006$). **Conclusion:** LPV/r was significantly associated with lipid derangements, indicating the need to regularly monitor lipid profile in patients using LPV/r.

Keywords

ARVs, hyperlipidemia, HIV, LPV/r, ATV/r

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What Do We Already Know About This Topic?

The use of antiretroviral drugs, especially protease inhibitors in HIV-infected patients, is associated with various metabolic abnormalities including hyperlipidemia

How Does Your Research Contribute to the Field?

The findings of this study indicate that lopinavir boosted with ritonavir (LPV/r) is significantly associated with lipid derangements, and therefore, patients using this drug should be closely monitored for hyperlipidemia

What Are Your Research's Implications toward Theory, Practice, or Policy?

This study recommends routine monitoring of lipid profile and other cardiovascular risk factors as part of care and treatment in HIV-infected patients receiving LPV/r

Introduction

The use of highly active antiretroviral therapy (HAART) has significantly reduced morbidity and mortality in people living with HIV (PLWHIV). The overall prevalence of HIV infection has decline from 7% in 2003 to 5.1% in 2011 across the regions in Tanzania.[1] However, the use of antiretroviral (ARV) drugs in HIV-infected patients has been associated with various metabolic abnormalities including hyperlipidemia.[2] Several studies have reported increased risk of noncommunicable diseases such as cardiovascular disease (CVDs) among PLWHIV using ARV drugs.[3-6]

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The use of ARV drugs, especially protease inhibitors (PIs), has been associated with abnormalities in glucose metabolism, lipid derangement, and changes in body fat deposition.[2] Risks that are attributed by alterations in lipid levels and abnormal glucose metabolism may promote atherosclerosis and formation of high-risk plaque, thus increasing the risk of CVDs and diabetes mellitus.[1]

All of the PIs with exception of atazanavir (ATV) have been reported to cause elevation of low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), and triglycerides (TGs).[7] Lipid alterations may be the result of a reduction in the catabolism of very low-density lipoprotein (VLDL) and increased VLDL production induced by PIs. Other mechanisms potentially responsible for dyslipidemia are the reduction in the hydrolysis of TG-rich lipoprotein, impaired catabolism of free fat acid (FFA), and a reduction in FFA trapping. Protease inhibitors may also increase hepatic TG synthesis through expression of key enzymes in the biosynthesis of TG. Lipoprotein lipase hydrolyzes FFA from TG and promotes its accumulation in adipocytes. The PI-induced and subsequent activation of unfolded protein response may present the mechanism of dyslipidemia caused by PIs.[7]

Lopinavir boosted with ritonavir (LPV/r) and ATV boosted with ritonavir (ATV/r) have been shown to increase insulin resistance and reduce insulin secretion by interfering with GLUT-4-mediated glucose transport. Risk factors for development of diabetes with PIs (LPV/r and ATV/r) therapy include positive family history of diabetes, weight gain, lipodystrophy, old age, and hepatitis C infection. LPV/r and ATV/r interfere with cellular retinoic acid–binding protein type 1 that interacts with peroxisomal proliferator–activated receptor (PPAR) γ. Inhibition of PPAR-γ promotes adipocyte inflammation, release of free fatty acids, and insulin resistance.[8] Hyperglycemia resolves in almost all patients when PIs are discontinued.[9,10]

Control measures to reduce increased metabolic abnormalities and their associated complications are necessary in order to reduce morbidity and mortality in PLWHIV. Due to limited financial resources, there are no many alternative ARV drugs for PLWHIV in developing countries. In Tanzania, there are no adequate data on the magnitude of lipid derangement in patients who are using PIs in the Care and Treatment Center Clinics (CTCs). Therefore, in this study, we assessed the magnitude of hyperlipidemia in HIV-infected patients receiving LPV/r- and ATV/r-based ARV drugs. Patient characteristics such as age, sex, alcohol use, smoking, and body mass index (BMI) were assessed as risk factors for metabolic abnormalities and subsequent development of CVDs in PLWHIV.[1,11]

Methodology

Study Design and Setting

This was a hospital-based, cross-sectional study. Participants were recruited between December 2015 and April 2016 at the CTC of the Mnazi Mmoja Hospital, in Dar es Salaam, Tanzania. Mnazi Mmoja Hospital, located in Ilala municipality in Dar es Salaam, provides care and treatment to PLWHIV through its CTC by using second-line ARV drugs. At the time of the study, the hospital was providing care to 2160 PLWHIV using second-line ARV drugs. The second-line ARV drugs that are used at the CTC include PIs (LPV/r and ATV/r) and nonnucleoside reverse transcriptase inhibitors (NNRTI; saquinavir [SQV] and efavirenz [EFV]).

Study Population

The study population for this study was PLWHIV aged ≥18 years and were using second-line ARV drugs, specifically LPV/r and ATV/r. A total of 300 HIV-infected patients who had been using LPV/r and ATV/r for ≥24 weeks were recruited into the study. The reason for selecting the duration of ≥24 weeks for ARV drug use is based on the fact that by this time the effect of ARV drugs on serum lipid profile is established.[12]

Data Collection

Data collected included sociodemographic characteristics such as age, sex, marital status, smoking, education, occupation, exercise, alcohol use, and duration on first-line antiretroviral therapy (ART). Clinical data that were collected included waist circumference, blood pressure, concomitant illnesses and medications, and lipid profile markers (LDL-C, high-density lipoprotein cholesterol [HDL-C], TC, and TG levels). Patient's CTC card 1 (CTC_1) and CTC card 2 (CTC_2) were used to obtain the history of HIV infection and ARV drug use among the study participants. The CTC_1 contains information that identifies HIV-infected patients to their respective care and treatments clinics, while CTC_2 is used to collect detailed information such as type of ARV drugs used, investigations carried out, and data on viral load tests of the patient.

Determination of Lipid Profile

Blood was taken for measurements of HDL-C, LDL-C, TC, and TG cholesterol (TG-C). Blood sample of 4 mL for assessment of lipid profile was taken from a brachial vein and placed in a plain vacutainer. Blood samples were kept at room temperature and analyzed on the same day, within hours of sample collection. Samples were analyzed using automated Metrolab 2300 Plus of model 10012816 manufactured by UV-VIS METROLAB S.A in South Korea.

Demographic Information

Sociodemographic data included age, sex, height, weight, and BMI of patients. Weight was measured by using seca scale, with the patients on bare feet. Height was measured by using a standard height board with participants on bare feet. The BMI was calculated as weight in kilograms divided by height in meter square (kg/m^2).

Operational Definitions

Concentrations of serum lipids were graded according to the criteria established by American Association of Clinical Endocrinologists.[13] In this study, hypercholesterolemia was defined as total serum cholesterol of $\geq$200mg/dL. Hypertriglyceridemia was defined as serum TG of $\geq$150 mg/dL, decreased HDL-C was defined as serum HDL-C levels of <40 mg/dL, and increased LDL-C was considered at a level of $\geq$130 mg/dL. Patients' BMI were categorized as underweight (< 18.5 kg/m^2), normal (18.5-25 kg/m^2), overweight (25-29 kg/m^2), and obese ($\geq$30 kg/m^2).

Statistical Analysis

Blood samples for laboratory analysis were analyzed immediately after withdrawn from patients. Data entry and management were performed using Microsoft Excel 2010 (Microsoft Corporation Inc, Redmond, Washington). Statistical analysis was done using Statistical Package for Social Sciences (SPSS) software (version 16.0). Student t test and analysis of variance (ANOVA) were used to assess differences between-group means. A single model logistic regression was computed to determine the association of independent factors such as smoking, alcohol consumption, obesity, age, and ARV drug use with abnormal level of each lipid profile. P value of less than .05 was considered statistically significant at 95% confidence level.

Multivariate analysis was performed to examine the effect of independent variables on the values of dependent variables. Multiple ANOVA (MANOVA) was used to conduct multivariate analysis involving 2 or more related dependent variables while controlling for the correlations among them. For MANOVA, P value of less than .01 was considered as statistically significant at 99% confidence level. Thus, the effect of ART, smoking, alcohol consumption, obesity, and age (independent variables or predictor variables) on blood pressure, weight, and waist circumference were determined. Levels of TG-C, HDL-C, LDL-C, and VLDL-C were also assessed.

Ethical Approval and Informed Consent

Ethical clearance was sought from the ethical review board of Muhimbili University of Health and Allied Sciences (Ref. No. MU/PGS/SAEC/Vol.XVI/38). Permission to undertake the study was granted by Ilala Municipal Medical Officer. The purpose of the study and the role of the participants were well explained in the consent form, and participation took place after participants had read and voluntarily signed the informed consent form. All questions and queries were consistently answered and clarified before consenting through signing a written informed consent form. Confidentiality was maintained throughout the study period. Apart from the research team that mainly consisted of medical personnel and the CTC staff, data were not accessed by any other person.

Each study participant was informed of his or her physical assessment and blood test results and given appropriate health education. Additionally, every participant was given a hard copy of the feedback form for both physical measurements and blood tests performed. If the study participant was found to have either metabolic abnormalities or risk factor, the information was communicated to the in-charge of CTC for further assessment and management according to the National Guidelines.[14,15]

Results

Patients Characteristics

Demographic characteristics of the study participants are shown in Table 1. A total of 300 PLWHIV were enrolled in the study, comprising of 82 (27.3%) males and 218 (72.7%) females. Two groups of patients were investigated: the first group of 150 HIV-infected patients (110 females and 40 males) were using LPV/r; the second group of 150 HIV-infected patients (108 females and 42 males) were receiving ATV/r. The overall mean age of the participants was 46 $\pm$ 9 years, with age-groups of 41 to 50 (38.7%) and >50 (32.7%) years constituting majority of the study participants. About three-quarters (70.7%) of the participants had attained primary level of education, and more than half (55.3%) were married. Fifty-six (18.7%) patients reported drinking alcohol, while 8 (2.7%) patients admitted to be current cigarette smokers.

Majority (70.7%) of the participants were self-employed, and 76.7% were doing moderate physical exercises on regular basis. Only 4.3% of patients were diagnosed with concomitant diseases including tuberculosis (TB) and asthma and were using medications for these conditions. Among 300 study participants, 2 (1.32%) and 60 (20%) were found to be hypertensive and obese, respectively. The mean duration for first-line ARV drug use among the participants was 121 $\pm$ 50 months, while the mean duration for the use of PIs was 33 (21) months.

The mean weight of the study participants was 65.6 (15.6) kg, while the mean weights of the patients receiving LPV/r and ATV/r were 62.8 (11.6) kg and 68.6 (18.3) kg, respectively. The mean waist circumference for the study participants was 99.2 (83.7) cm. Patients receiving ATV/r and LPV/r had mean waist circumference of 107.6 (117.0) cm and 90.8 (14.7) cm, respectively. Mean BMI was 25.3 (6.2) kg/m^2, while mean BMI for patients receiving LPV/r and ATV/r was 24.42 (4.4) kg/m^2 and 26.25 (7.4) kg/m^2, respectively.

Hyperlipidemia and Characteristics of Lipid Profiles

The prevalence of lipid derangement among HIV-infected patients who were using PIs in this study was very high (92.7%). The TC-HDL-C ratio for patients receiving LPV/r and ATV/r was 8.0 (7.2) mg/dL and 7.4 (4.9) mg/dL,

Table 1. Demographic Characteristics of the Study Participants.[a]

Variables	n (%)	Patients on LPV/r, n (%)	Patients on ATV/r, n (%)
Age-group, years			
21-30	13 (4.3)	7 (4.7)	6 (4.0)
31-40	73 (24.3)	37 (24.7)	36 (24.0)
41-50	116 (38.7)	62 (41.3)	54 (36.0)
50 +	98 (32.7)	44 (29.3)	54 (36.0)
Sex			
Male	82 (27.3)	40 (26.7)	42 (28.0)
Female	218 (72.7)	110 (73.3)	108 (72)
Education level			
No formal education	10 (3.3)	0 (0)	10 (6.7)
Primary education	212 (70.7)	118 (78.7)	94 (62.7)
Secondary education	64 (21.3)	28 (18.7)	36 (24.0)
College/university	14 (4.7)	4 (2.7)	10 (6.7)
Marital status			
Single	44 (14.7)	22 (14.7)	22 (14.7)
Married	166 (55.3)	89 (59.3)	77 (51.3)
Separated	6 (2.0)	4 (2.7)	2 (1.3)
Divorced	22 (7.3)	8 (5.3)	14 (9.3)
Widow/widower	62 (20.7)	27 (18.0)	35 (23.3)
Occupation			
Peasant	7 (2.3)	1 (0.7)	6 (4.0)
Unemployed	13 (4.3)	5 (3.3)	8 (5.3)
Self-employed	212 (70.7)	102 (68.0)	110 (73.3)
Employed	50 (16.7)	32 (21.3)	18 (12.0)
Others	18 (6.0)	10 (6.7)	8 (5.3)
Alcohol drinkers	56 (18.7)	19 (12.7)	37 (24.7)
Cigarette smokers	8 (2.7)	2 (1.3)	6 (4.0)
Diabetes mellitus	8 (2.7)	2 (1.3)	6 (4.0)
Hypertension	2 (0.7)	2 (1.3)	0
BMI, kg/m^2			
<18.50	30 (10.0)	13 (8.7)	17 (11.3)
18.50-24.99	30 (10.0)	81 (54.0)	60 (40.0)
25.00-29.99	69 (23.0)	36 (24.0)	33 (22.0)
≥30	60 (20.0)	20 (13.3)	40 (26.7)
Waist circumference	221 (73.7)	114 (76.0)	107 (71.3)
Male ≥ 94 cm	32 (10.0)	18 (12.0)	14 (9.3)
Female ≥ 81 cm	189 (63.00)	96 (64.0)	93 (62.0)

Abbreviations: ATV/r, atazanavir boosted with ritonavir; BMI, body mass index; LPV/r, lopinavir boosted with ritonavir.
[a]n = 300.

Table 2. Lipid Profile with Respect to Individual Protease Inhibitors Used by Patient.

Type of Lipid	Mean (Standard Deviation), mg/dL			P Value
	All Patients, n = 300	Patients Using LPV/r, n = 150	Patients Using ATV/r, n = 150	
Total cholesterol, (mg/dL)	212.75 (58.12)	228.63 (62.24)	196.87 (48.93)	<.00001
HDL-C, (mg/dL)	39.79 (26.04)	42.43 (28.54)	37.14 (23.06)	.08
LDL-C, (mg/dL)	86.69 (30.89)	92.20 (36.29)	81.18 (23.13)	.002
Triglycerides, (mg/dL)	144.06 (77.93)	161.68 (89.69)	126.43 (59.32)	.00008
TC-HDL-C ratio	7.72 (6.17)	8.02 (7.22)	7.42 (4.90)	.41

Abbreviations: ATV/r, atazanavir boosted with ritonavir; BMI, body mass index; HDL-C, High-density lipoprotein cholesterol; LDL-C, Low-density lipoprotein cholesterol; LPV/r, lopinavir boosted with ritonavir; SD, standard deviation; TC, total cholesterol.

respectively, as shown in Table 2. The overall mean for TC and HDL-C of the participants were 212.75 (58.11) mg/dL and 39.79 (26.08) mg/dL, respectively. These mean values are abnormal in comparison to the normal range of TC (< 200 mg/dL) and HDL-C (≥ 40 mg/dL).[14] The mean LDL-C, 86.69 (30.88) mg/dL, and TG, 144.06 (77.93) mg/dL, were found to be within normal range as shown in Table 2.

Table 3. Lipid Profile with Respect to Sex of Patients.[a]

Type of Lipid	Sex	Mean (SD)	P Value
Total cholesterol, mg/dL	Female	220.78 (55.683)	.00008
	Male	191.4 (59.348)	
High-density lipoprotein, mg/dL	Female	41.11 (25.643)	.15
	Male	36.28 (26.904)	
Low-density lipoprotein, mg/dL	Female	90.7 (31.485)	.0002
	Male	76.02 (26.561)	
Triglycerides, mg/dL	Female	138.24 (69.879)	.07
	Male	159.52 (94.889)	
TC-HDL-C ratio	Female	7.768 (6.6397)	.83
	Male	7.591 (4.7267)	

Abbreviations: HDL-C, high-density lipoprotein cholesterol; standard deviation; TC, total cholesterol.
[a]n = 300.

Table 4. Lipid Profile with Respect to Body Mass Index of Patients.[a]

Type of Lipid	BMI, kg/m²	Mean (SD)	P Value
Total cholesterol, mg/dL	≥ 30	228.47 (44.662)	.008
	18.50-24.99	207.92 (59.697)	
High-density lipoprotein, mg/dL	≥ 30	45.83 (26.72)	.04
	18.50-24.99	37.42 (26.165)	
Low-density lipoprotein, mg/dL	≥ 30	93.97 (18.645)	.05
	18.50-24.99	86.4 (35.806)	
Triglycerides, mg/dL	≥ 30	135.43 (66.768)	.07
	18.50-24.99	156.81 $\pm$ 96.277	

Abbreviations: BMI, body mass index; SD, standard deviation.
[a]n = 300.

Levels of TC, LDL, HDL, and TG among Patients using LPV/r and ATV/r

The mean TC, 228.63 (62.24) mg/dL, and LDL-C, 92.20 (36.29) mg/dL, were significantly higher in patients using LPV/r than those using ATV/r ($P < .05$). Also, the mean TG was significantly higher in patients using LPV/r than those using ATV/r ($P < .005$). However, there was no statistically significant difference between the group means for HDL-C and TC–HDL-C ($P > .05$; Table 2).

Hyperlipidemia with Respect to Age, Sex, BMI, Waist Circumference, Co Medication, and Duration of HIV Infection in Patients

A significant difference in mean values of lipid profile was observed between patients with age of ≥40 years and <40 years. Patients with age of ≥40 years had higher mean values of TC, 216.95 (57.24) mg/dL; LDL-C, 89.48 (32.09) mg/dL; and TG, 151.39 (83.92) mg/dL, compared to TC, 198.43 (59.20) mg/dL; LDL-C, 77.16 (24.21) mg/dL; and TG, 119.04 (44.76) mg/dL, in patients with age of <40 years. With exception of LDL-C and TC-HDL-C ratios, there were statistical significance differences ($P \leq .05$) in other lipid parameters between the 2 age groups.

Significant difference was also observed in lipid profile mean values between females and males. Females had elevated mean values of TC, 220.78 (55.68) mg/dL, and LDL-C, 90.70 (31.48) mg/dL, in comparison to TC, 191.40 (59.35) mg/dL, and LDL-C, 76.02 (26.56) mg/dL, of males (Table 3).

Obese (BMI ≥ 30 kg/m²) patients had raised levels of mean TC, 228.47 (44.66) mg/dL, and LDL-C, 93.97 (18.65) mg/dL, in comparison to nonobese patients who had relatively lower TC, 207.92 (59.70) mg/dL, and LDL-C ($P = .05$). However, nonobese patients had low HDL-C mean value, 37.42 (26.17) mg/dL, compared to obese patients, 45.83 (26.72) mg/dL, $P = .04$, as shown in Table 4. Patients with concomitant administration of other drugs (apart from ARV drugs) such as hypertensive drugs, oral contraceptives, and anti-TB drugs had higher mean value of TG, 181.00 (56.25) mg/dL, compared to TG, 141.70 (78.60) mg/dL, $P = .04$, of patients with no concomitant administration of other drugs.

There were also significant differences in mean values of TC, LDL-C, and TG between patients with abnormal and normal waist circumference. Males with waist circumference of ≥94 cm and females with >80 cm had higher mean values of TC, 220.65 (56.21) mg/dL; LDL-C, 90.52 (30.20) mg/dL; and TG, 151.72 (74.40) mg/dL, compared to TC, 190.65 (57.97) mg/dL; LDL-C, 75.96 (30.41) mg/dL; and TG, 122.61 (83.87) mg/dL, in patients with smaller waist circumference.

Association of BMI, Sex, Obesity, Alcohol, Smoking, Comorbidities, Waist Circumference, and Co Medication with Abnormal Lipid Profile

The BMI of ≥25kg/m² was significantly and positively associated with raised levels of TC ($P = .002$) and LDL-C ($P = .006$). Female sex was strongly associated with elevated levels of TC ($P = .0004$), LDL-C ($P = .02$), and TG ($P = .005$). Obese patients were significantly associated with raised levels of TC ($P = .008$) and FBG ($P = .03$). Alcohol consumption and smoking were significantly associated with decreased levels of HDL-C ($P = .04$) and elevated FBG ($P = .003$). There was also significant association between co-infection with TB with raised levels of LDL-C ($P = .001$) and decreased levels of HDL-C ($P = .01$). Waist circumferences of ≥ 94 cm for males and >80 cm for females were significantly associated with raised levels of TC ($P = .0003$) and TG ($P = .006$) and low levels of HDL-C ($P = .03$). Moreover, there was a significant association between concomitant use of ARV drugs and anti-TB drugs among patients with elevated levels of TC ($P = .02$) and TG ($P = .02$). Table 5 shows the prevalence of lipid derangements with respect to the use of LPV/r and ATV/r in HIV-infected patients.

Association of the Use of LPV/r and ATV/r with Other Variables Regarding Lipid Derangement in HIV-Infected Patients

Multivariate logistic regression analysis on the risk factors was performed to adjust for the potential confounding factors. In

Table 5. Prevalence of Lipid Derangements with Respect to the Use of LPV/r and ATV/r in HIV-Infected Patients.[a]

Type of Lipid	Prevalence (%)		
	LPV/r	ATV/r	P Value
Total cholesterol ≥ 200 mg/dL	65.30	50.70	.095
HDL-C <40 mg/dL	53.30	65.30	.177
LDL-C ≥130 mg/dL	10.70	0.00	NA
Triglycerides ≥150 mg/dL	47.30	29.30	.012
TC-HDL-C ratio ≥5.0	69.30	68.00	.889

Abbreviations: ATV/r, atazanavir boosted with ritonavir; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LPV/r, lopinavir boosted with ritonavir; NA, not available; TC, total cholesterol.
[a]n = 300.

multivariate analysis, the use of LPV/r was significantly and positively associated with raised TC ($P = .001$) and TG ($P = .0003$). Patients who were using LPV/r were 2.5 times more likely to have high TC compared to those who were using ATV/r (odds ratio [OR] = 2.5, 95% confidence interval [CI]: 1.26-5.10). In addition, patients who were using LPV/r were also 2.7 times more likely to have high TC compared to those who were using ATV/r (OR = 2.7, 95% CI: 1.34-5.53). Age of ≥ 40 years significantly and positively predicted raised levels of TC ($P = .0002$). Age of ≥ 40 years had also marginal significance on increased levels of TG ($P = .01$).

The study also found an association between female sex and abnormal lipid profile parameters. Female sex significantly and positively predicted raised levels of TC ($P = .002$). Females were more likely to have raised LDL-C compared to male counterparts (OR = 5.0, 95% CI: 0.48-52.03). However, a significant and inverse association was found between female sex and abnormal levels of TG (OR = 0.4, 95% CI: 0.19-0.85). Patients with ≥ 25 BMI had statistically significant increased levels of TC ($P = .001$) and LDL-C ($P = .004$). There were no significant differences in the levels of TC, HDL-C, and TG among patients who had been using PIs for ≥ 55 months when compared to those who used the same drugs for <55 months (Table 6).

On the other hand, patients who had HIV infection for ≥ 42 months were about 7 times more likely to have raised levels of TG compared to those who had the infection for <42 months (OR = 7.7, 95% CI: 0.93-64.17). Concomitant use of ARV drugs with other drugs was also significantly and positively associated with abnormal higher levels of TG ($P = .001$). Table 6 shows association of the use of LPV/r and ATV/r with other variables regarding lipid derangement in HIV-infected patients as assessed using multivariate logistic regression analysis.

Discussion

The results of this study indicate that majority of HIV-infected patients who were using second-line ARV drugs had blood lipid derangements. The use of LPV/r was significantly associated with lipid derangements compared to patients using

ATV/r. The prevalence of lipid derangement in this study is higher than 18% which was reported by Samaras et al.[16] In the latter study, the researchers investigated patients who were using HAART therapy including PIs with or without ritonavir, NNRTIs, and nucleoside reverse transcriptase inhibitors (NRTIs).[16] The prevalence of lipid derangement in the current study is also higher than 77.5% which was reported in our recent study in HIV-infected patients who were using first-line ARV drugs at Muhimbili National Hospital in Dar es Salaam.[17] In the latter study, patients were using triple therapy combinations of ARV drugs including zidovudine, lamivudine, EFV, nevirapine, and tenofovir.

Studies have shown that individual PIs have different effects on lipid metabolism.[18] Both NNRTIs and NRTIs have low prevalence on inducing metabolic abnormalities compared to PIs.[17] Therefore, the difference in prevalence of metabolic abnormalities in different studies could be due to the number and type of ARV drugs used in HIV-infected patients. PIs induce a subsequent activation of unfolded protein response resulting in dyslipidemia.[7] The current study has reported 58% prevalence of hypercholesterolemia (TC ≥ 200 mg/dL) with an incident rate ratio of 1:3. The prevalence of hypercholesterolemia in this study is comparable to 60% reported from a Swiss cohort study.[19] Although our study was cross sectional in which patients were not followed up, the Swiss cohort study followed up patients for consecutive 6 years. This indicates persistent hypercholesterolemia in HIV-infected patients using PIs.

Prevalence of increased TG (≥ 150 mg/dL) in this study was 42%, with incident rate ratio of 1:6. Prevalence of increased TG in the current study is relatively higher than 35.7% reported in a Swiss cohort study.[19] In the latter study, several types of PIs including SQV, nelfinavir, LPV/r, and ATV/r were investigated. Therefore, the effect of individual ARV drugs on lipid derangement could not be determined. In the present study, half of the participants were using LPV/r, which has been widely associated with increased TG.[20]

The 49.3% prevalence of hyperlipidemia in the current study is slightly higher in patients receiving LPV/r than in those using ATV/r (43.3%). LPV/r is associated with hyperlipidemia, which causes elevation in LDL-C, TC, and TGs.[7] ATV/r induces hyperlipidemia by reducing hydrolysis of TG lipoprotein, impaired catabolism of FFA, and a reduction in FFA trapping.[7] Several comparative studies have suggested that ATV may not disrupt lipids to the same extent as other PIs. In a study comparing the effects of ATV/r and LPV/r on lipid profiles in HIV-infected patients, ATV/r (7%) was associated with low prevalence of hyperlipidemia compared to LPV/r (18%).[8] High prevalence of hypercholesterolemia, LDL-C, and TG was also observed to be most prevalent in patients receiving LPV/r compared to those receiving ATV/r. These findings are similar to those reported by other researchers, suggesting that LPV/r has a profound effect on lipid metabolism compared to ATV/r.[7,21,22]

In this study, 73.7% of patients had abnormal waist circumference. The current study also reported high levels of TGs among patients with abnormal waist circumference. It is postulated that high levels of TGs cause fat gains in the trunk and upper back,

Table 6. Association of Study Variables with Lipid Derangements in Patients.

Explanatory Variables	TC ≥ 200 mg/dL AOR (99% CI)	HDL-C < 40 mg/dL AOR (99% CI)	LDL-C ≥130 mg/dL AOR (99% CI)	TG ≥ 150 mg/dL AOR (99% CI)
Use of PIs				
ATV/r	1.00	1.00	1.00	1.00
LPV/r	2.5 (1.26-5.10)	0.6 (0.30-1.12)	NA	2.7 (1.34-5.53)
P value	.001	.03	NA	.0003
Age-group, years				
Age < 40	1.00	1.00	1.00	1.00
Age ≥ 40	3.3 (1.43-7.44)	0.6 (0.28-1.42)	NA	2.5 (1.0-6.4)
P value	.0002	.15	NA	.01
Sex				
Male	1.00	1.00	1.00	1.00
Female	2.5 (1.15-5.28)	0.5 (0.25-1.16)	5.0 (0.48-52.03)	0.4 (0.19-0.85)
P value	.002	.04	.08	.002
Alcohol intake				
Nondrinker	1.00	1.00	1.00	1.00
Drinker	1.1 (0.46-2.70)	1.7 (0.68-4.24)	1.1 (0.02-50.23)	0.6 (0.23-1.59)
P value	.76	.14	.97	.18
Smoking				
Nonsmoker	1.00	1.00	1.00	1.00
Smoker	0.8 (0.07-8.09)	0.9 (0.09-10.07)	NA	1.4 (0.16-11.98)
P value	.77	.94	NA	.7
BMI, kg/m^2				
BMI < 25	1.00	1.00	1.00	1.00
BMI ≥ 25	2.5 (1.21-5.00)	0.5 (0.28-1.06)	8.1 (1.25-52.53)	0.75 (0.37-1.55)
P value	.001	.02	.004	.31
Duration of PI use				
<55 months of use	1.00	1.00	1.00	1.00
≥ 55 months of use	0.8 (0.31-2.19)	1.5 (0.58-4.02)	NA	0.36 (0.12-1.08)
P value	.610	.26	NA	.02
Duration of HIV				
<42 months	1.00	1.00	1.00	1.00
≥ 42 months	1.2 (0.19-7.09)	1.1 (0.22-5.80)	0.4 (0.02-7.45)	7.7 (0.93-64.17)
P value	.830	.85	.42	.01
Comorbidities				
Without diseases	1.00	1.00	1.00	1.00
With diseases	0.4 (0.07-2.14)	0.2 (0.03-1.40)	51.4 (0.95-2780.17)	1.0 (0.17-4.71)
P value	.150	.03	.01	.86
Co Medication				
Not on medication	1.00	1.00	1.00	1.00
On medication	6.6 (0.82-53.64)	2.4 (0.50-11.32)	NA	7.2 (1.47-35.68)
P value	.02	.16	NA	.001
Exercise				
No regular exercises	1.00	1.00	1.00	1.00
Performing regular exercises	1.0 (0.43-2.28)	0.9 (0.38-1.93)	1.2 (0.09-17.62)	1.6 (0.70-3.80)
P value	.98	.63	.84	.14

Abbreviations: AOR, Adjusted Odds Ratio; ATV/r, atazanavir boosted with ritonavir; BMI, body mass index; CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; LDL-C, Low-density lipoprotein cholesterol; LPV/r, lopinavir boosted with ritonavir; NA, not available; PI, protease inhibitor; TC, total cholesterol; TG, triglyceride.

known as visceral adipose tissue (VAT) gains.[23] The VAT is due to ectopic intracellular lipid deposition in the skeletal muscle. The expansion of VAT that occurs during HIV/HAART therapy is associated with macrophage infiltration, decreased adiponectin secretion, and the release of inflammatory factors.[23]

The current study reported a high prevalence (46.7%) of increased TC (≥ 200 mg/dL) in females than in males (11.3%). Lipid profile changes are more pronounced in women than in men due to complex hormonal modifications in females. Estrogen may also directly influence lipid metabolism through the suppression of gene expression and activity of lipoprotein lipase.[24] Moreover, hormonal changes in menopause plays an important role in derangement of serum lipid levels and increase the risk of CVDs. Lipid levels in postmenopausal women have increased TC, and these changes persist even after adjustment for age.[24]

High prevalence of increased TC observed in females correlates with those reported in similar studies conducted in Iran and Cameroon.[25,26] In the current study, association of increased TC with female sex was still profound even after adjustment for other factors. Similar to the findings of the Cameroonian study,[26] females in our study had 2.4 times more raised TC than males. In this study, higher levels (≥ 150 mg/dL) of TG was significantly higher in males than females. High levels of TG in HIV-infected patients is suggested to be due to inflammation with subsequent cytokine release and decreased hepatic clearance related to a role of apolipoprotein E.[27]

The rate of release of FFA from adipose tissue into the circulation increases with age. Increased levels of FFA leads to an increase in synthesis of LDL-C, hence increasing the risk of CVDs.[28] In the current study, prevalence of TC derangement among patients with age of ≥ 40 years was 62.9% compared to 42.5% in younger patients. Other studies have also confirmed increased TC among older HIV-infected patients using PIs.[26,29]

BMI of ≥ 25 is associated with increased TG and FFA, decreased HDL-C, HDL dysfunction, and normal or slightly increased LDL-C with increased small dense LDL-C. In this study, higher levels of TC (≥ 200 mg/dL) was 2.3 times more in patients with BMI of ≥ 25 kg/m^2 compared to patients with BMI of <25 kg/m^2. A study conducted in Southern Ethiopia also reported a profound association between TC, LDL-C, and TG with BMI of ≥ 25 kg/m^2.[11] The BMI of ≥ 25 kg/m^2 increases cardiovascular risk through risk factors such as increased fasting plasma TG, TC, high LDL-C, low HDL-C, elevated blood glucose and insulin levels, and high blood pressure.[30] The development of small dense LDL-C in obesity is mainly due to increased TG concentrations, and small dense LDL-C are relatively slowly metabolized for more than 110 hours, which enhances its atherogenicity.[31]

Prevalence of cigarette smoking and alcohol intake in this study was 2.7% and 18.7%, respectively. The prevalence of alcohol intake in this study was lower than 52.0% that was reported in a similar study conducted in Dar es Salaam and Mbeya regions in Tanzania.[1] A study conducted in Nigeria reported 22% prevalence of cigarette smoking in HIV-infected patients.[32] The observed differences in the prevalence of cigarette smoking and alcohol intake among HIV-infected patients in these studies could be due to the lifestyle of a particular population, availability and use of counseling programs in the CTCs, and methodological approach used to assess cigarette smoking and alcohol intake.

Elevated TG levels are common in HIV-infected persons for several reasons among them being physiological distress that results from HIV infection itself.[27,33] HIV infection itself causes dysregulation of cytokines that affect both lipid and glucose metabolism. In this study, most patients (95.3%) had HIV infection for ≥ 42 months. The current study reported a positive association between duration of HIV infection and abnormal levels of TGs. Contrary to these findings, the study conducted in Cameroon reported association between the duration (≥ 42 months) of HIV infection with abnormal levels of

TC.[26] The difference observed could be due to longer duration of HIV infection and exposure to ARV drugs. In early stage of HIV infection, there are no remarkable changes in TC and LDL-C seen except an increase in TG and decrease in HDL-C, but TC and LDL-C are all increased when patients start using PIs.[27]

Proportion of patients who were concomitantly using ARV drugs with other drugs was 6%. Out of these, 0.7% were using hypertensive drugs, 2% were using oral contraceptives, and 3% were using anti-TB drugs. Using multivariate analysis, the current study established an association between the use of anti-TB drugs and increased levels of TC and TG. Rifampicin, which is one of the components of anti-TB drug combination inhibits CYPA71, a rate-limiting enzyme in the conversion of cholesterol to bile acids. Inhibition of this enzyme may cause increased levels of cholesterol when the latter is not converted to bile acids.[34] Since lipid metabolism occurs in the liver, the alteration in the plasma lipid levels may be related to the fact that hepatotoxicity is a major side effect of rifampicin and that rifampicin is an effective liver enzyme inducer. These results suggested that increased concentration of circulating TG in the blood may be an early and reliable indicator of hepatotoxicity.[35,36]

Conclusion

This study revealed that the prevalence of lipid derangement was high (92.7%) among PLWHIV receiving PIs. The prevalence of lipid abnormalities was higher in patients receiving LPV/r than ATV/r. With or without an account of confounders, the use of LPV/r was significantly associated with increase of atherogenic lipid profile.

The study has also established an independent association between risk factors, such as age (≥ 40 years), female sex, BMI (≥ 25 kg/m^2), and coadministration of anti-TB drugs with lipid derangement among HIV-infected patients using PIs. Based on these findings, it is recommended that routine monitoring of lipid profile and other cardiovascular risk factors in patients receiving PIs at the CTCs is necessary. It is also recommended to strengthen interventional programs on health education at every CTC in order to create awareness on metabolic abnormalities caused by ARV drugs and related risk factors.

Limitations

This study was cross-sectional, and since no baseline lipid measurements were collected before initiation of PIs, the results found here do not exclude patients who already had existing lipidemias. Therefore, lipid derangements in patients found in this study cannot be solely attributed to the use of PIs. Despite this shortcoming, other studies have confirmed that these drugs substantially cause lipid derangement, and therefore, baseline lipid measurements and routine monitoring are recommended in individuals starting PIs including LPV/r.[37]

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