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Serum Lipid Profiles, Blood Glucose, and High-Sensitivity C-Reactive Protein Levels Among People Living with HIV Taking Dolutegravir and Ritonavir-Boosted Atazanavir-Based Antiretroviral Therapy at Jimma University Medical Center, Southwest Ethiopia, 2021

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Background: Long-term use of antiretroviral therapy, especially dolutegravir and boosted-atazanavir, raises concerns about cardio-vascular disease. Thus, this study aimed to assess lipid profiles, blood glucose, and high-sensitivity C-reactive protein levels among people living with HIV on dolutegravir and ritonavir-boosted atazanavir-based therapy.

Methods: An institutional-based comparative cross-sectional study was conducted from November 4, 2021, to January 4, 2022. An equal number of dolutegravir- and ritonavir-boosted atazanavir-treated patients (n = 64 each) was enrolled. A consecutive sampling was used to select participants. The Chi-square, Student's *t*-test, Mann–Whitney *U*-test, and logistic regression were used as appropriate statistical tests using SPSS Version 25.0. Statistical significance was set at p < 0.05.

Results: Dyslipidemia was found in 67.2% (43/64) of ritonavir-boosted atazanavir group and 48.4% (31/64) of dolutegravir group. The dolutegravir group had significantly higher mean and median values of high-density lipoprotein and random blood sugar, respectively, as well as lower median triglyceride and high-sensitivity C-reactive protein levels than the ritonavir-boosted atazanavir group. Ritonavir-boosted atazanavir-based regimens (AOR=3.4, 95% CI: 1.5, 8) and age >40 years were predictors of dyslipidemia, while BMI ≥25 kg/m^2 (AOR=3.7, 95% CI: 1.3, 10.8) and dolutegravir-based regimens (AOR=4.6, 95% CI: 1.5, 14) were predictors of hyperglycemia. Ritonavir-boosted atazanavir-based regimens (ARR=3, 95% CI: 1.3, 8) and BMI ≥25 kg/m^2 (ARR=2.5, 95% CI: 1.1, 6) were associated with increased high-sensitivity C-reactive protein by 1–3 mg/L. The risk of increased high-sensitivity C-reactive protein by >3 mg/L was greater in those patients with a CD4 cell count of <500 cells/mm^3 (ARR=5, 95% CI: 1.1, 24).

Conclusion: When compared to ritonavir-boosted atazanavir-based regimens, dolutegravir had favorable lipid profiles and high-sensitivity C-reactive protein but unfavorable blood glucose levels. Therefore, baseline blood glucose, lipid profiles, and high-sensitivity C-reactive protein levels should be routinely measured in patients on these regimens.

Keywords: high-sensitivity C-reactive protein, dolutegravir, dyslipidemia, hyperglycemia, antiretroviral therapy

Introduction

Since the introduction of antiretroviral therapy (ART), the mortality and morbidity of people living with HIV have been reduced.[1] Even if ART improves and prolongs life, it presents additional burden for people living with HIV from which

atherosclerotic cardiovascular disease (ASCVD) accounts for 46% of all fatalities.[2] The prevalence of cardiovascular disease (CVD) has increased over the past 20 years, with sub-Saharan Africa presenting the greatest effects.[3] An elevated risk of ASCVD was observed in 71.1% of people living with HIV in Ethiopia taking highly active antiretroviral therapy (HAART).[4]

People living with HIV present with higher levels of dyslipidemia and hyperglycemia and increased high-sensitivity C-reactive protein (hsCRP) levels compared with general populations, which make them a group at higher risk of developing ASCVD.[5–10]

According to studies, using dolutegravir (DTG) and ritonavir-boosted atazanavir (ATV/r) for HIV treatment has been linked with abnormal lipid profile levels.[11,12] Basically, patients who were switched to DTG-based therapy observed with significant decrease in total cholesterol (TC), triglyceride (TG), and TC/HDL-C ratio (total cholesterol/high density lipoprotein-cholesterol) than protease inhibitors (PI), which makes it the best drug in reducing the risk of having CVD.[13,14] However, study from Zambia showed a higher prevalence of low HDL-C was found in patient treated by DTG (59%) than ATV/r (44%) containing ART regimens, which is the likely contributing factor for CVD.[15] From study in Ethiopia, higher median values of TG and lower mean values of HDL-C were found among patients treated with ATV/r compared with the efavirenz (EFV)-based regimen of ART.[12]

Protease and integrase inhibitors induce insulin resistance, resulting in hyperglycemia through inhibition of glucose transporter 4 (GLUT4) and chelation of magnesium ions, respectively.[16–23] Case presentations support these concepts by explaining that patients who shift from EFV to DTG-based ART develop abnormal laboratory findings suggestive of diabetes mellitus and higher mean levels of blood glucose, respectively.[24,25] Based on reports from studies, an increase in blood glucose level was seen in patients with DTG-containing therapy.[26–28] Conversely, another study showed higher mean levels of blood glucose were found among patients treated with ART containing protease inhibitors, and significant improvement was seen after switching from boosted-protease inhibitors (PI/r) to ART containing DTG.[29,30]

Moreover, HIV- and ART-induced inflammation and persistent immune activation with pro-inflammatory molecules persistently increase serum hsCRP levels in people living with HIV.[31,32] It has been shown that increased serum hsCRP levels were independently associated with non-AIDS comorbidities like ASCVD.[33] One study from Ethiopia indicated a higher level of hsCRP in ART-experienced people than ART-naïve people living with HIV.[34] The use of DTG and ATV/r is associated with raised serum hsCRP levels.[30] However, multiple studies have shown a favourable decrease in the mean hsCRP level in patients received DTG than boosted-protease inhibitors.[35–38] Several studies have found that a low CD4 cell count, duration of HIV and HAART, higher body mass index (BMI), older age, and deranged anthropometric parameters all contribute to metabolic abnormalities, inflammation, and an increased risk of CVD.[39–43]

As a result of improved coverage of free ART services, thousands of people living with HIV receive ART, with an overall-free ART coverage of 97.1%.[44] Dolutegravir is a relatively new integrase inhibitor recommended by the World Health Organization (WHO) as well as by the national guidelines of Ethiopia as the preferred first-line regimen that is effective, has a high antiviral potency, and can be used without pharmacological enhancements for people living with HIV.[45–48] Even though ATV/r in combination with 3TC (lamivudine) plus TDF (tenofovir) can be used as first-line therapy for patients not eligible for DTG and EFV, it is widely used as second-line therapy in Ethiopia.[45] Most of the patients were exposed to these regimens of ART.

Routine care currently provided to people living with HIV on DTG and ATV/r-based ART does not include measuring baseline levels of lipid profile, blood glucose, and hsCRP, which are important parameters for improving treatment outcomes and for the early detection and prevention of CVD. To the best of our knowledge, there is no well-documented evidence supporting dyslipidemia, hyperglycemia, and elevated hsCRP levels in relation to DTG and ATV/r-based ART in sub-Saharan African countries, including Ethiopia. Therefore, the present study was designed to assess lipid profiles, blood glucose levels, hsCRP levels, and their associated factors among adult HIV patients receiving DTG and ATV/r-based antiretroviral therapy at Jimma University Medical Center, Southwest Ethiopia.

Methods and Materials
Study Area and Setting
The study was conducted at the ART clinic of the Jimma University Medical Center (JUMC). Jimma Town is located 360 km south-west of Addis Ababa, Ethiopia's capital city. JUMC has a separate ART clinic that provides services for people living

with HIV/AIDS. The total number of adult patients who received ART was 3079 (until October 1, 2021). Of these, 1500 were on first-line ART containing TDF+3TC+DTG, and 167 were on second-line ART containing ATV/r+3TC+TDF. Currently, the JUMC ART clinic provides comprehensive health services in the following areas: voluntary counselling and testing (VCT), prevention of mother-to-child transmission of HIV, follow-up services for HIV-infected patients on ART therapy, and treatment of opportunistic infections. The clinic also provides services to patients from surrounding villages and nearby towns.

Study Design and Period
An institutional-based comparative cross-sectional study was conducted from November 4, 2021, to January 4, 2022.

Study Populations
All adults living with HIV receiving DTG and ATV/r-based ART at the ART clinic of JUMC were the source population. All selected adults living with HIV who received DTG and ATV/r-based ART at the JUMC ART clinic during the study period were included in the study population.

Eligibility Criteria
Patients aged ≥18 years who had received DTG-based and ATV/r-based regimens for at least 6 months (because serum lipid profiles were more likely affected after 6 months of taking ART[49]) and who volunteered to participate in the study were included. Patients taking DTG-based and ATV/r-based ART regimens for less than 6 months, patients with known diabetes mellitus and pregnancy due to metabolic changes such as dyslipidemia and hyperglycemia,[50,51] pre-existing liver and renal problems, active cancer, and patients on anti-tuberculosis drugs due to the presence of changes in serum levels of hsCRP,[52–55] patients taking lipid-lowering drugs, and those who did not volunteer to participate in the study were excluded.

Sample Size Determinations and Sampling procedure
The number of participants included in the study was calculated using the G* power statistical power analysis version 3.1 software. The sample size was calculated by considering $\alpha = 0.05$, power $(1–\beta) = 80\%$, with a DTG to ATV/r ratio of 1:1, two independent groups mean t-test, and an effect size = 0.5. The computed sample size was 128. Of these, 64 were in the DTG-based group and 64 were in the ATV/r-based group. A consecutive sampling technique was applied. All participants who fulfilled the inclusion criteria and were ready to participate were included in the study until the required sample size of 128 was achieved.

Data Collection Procedures
Before data collection, training was provided to the data collectors for 1 day by the principal investigator. Data collectors introduced themselves to make connections with patients. Training was provided to two nurses regarding the objective, methodology, and ethical issues of the study, as well as on interview approach and how to measure anthropometric parameters. Trained nurses collected sociodemographic and related clinical data using a checklist prepared in English and then translated into Afan Oromo and Amharic languages. The questionnaire was back-translated into English to check for consistency. The time of initiation of HAART, medical history, WHO clinical stage, and viral load values were recorded using a structured questionnaire from the medical record card. A 5 mL sample of venous blood was collected from each study participant for laboratory testing by laboratory technologists.

Anthropometric Measurements
Anthropometric measurements such as height, weight, waist circumference, and hip circumference were collected by ART-trained nurses using a standard balance and an SECA meter. After the weight and height were measured, the BMI was calculated by dividing the individual's weight in kilograms by the square of their height in meters (kg/m^2). BMI was categorized as obese if BMI ≥25 kg/m^2 and normal if BMI <25 kg/m^2. The range of abnormal waist circumference for males and females was >102 cm and >88 cm, respectively. The cut-off for the waist–hip ratio was ≥0.9 for males and ≥0.85 for females, according to the criteria of the WHO guidelines.[56,57]

Blood Sample Collection

To determine the serum lipid profiles, hsCRP, random blood sugar (RBS), and CD4 cell count, 5 mL of blood was collected from study participants using plain yellow-topped tubes by qualified professionals under aseptic conditions. Before centrifugation, whole blood was applied to the test strip and pipetted for the RBS and CD4 cell count measurements, respectively. The remaining blood was centrifuged at 3000 rpm for 5 min. The serum obtained was stored at 4 °C until the analysis of lipid profiles and hsCRP levels.[58] Lipid profiles and hsCRP levels were determined using a Roche Cobas 6000 analyzer. Blood glucose was determined using a glucometer, and the CD4 cell count was determined using a BD FACSPresto™ near the patient CD4 count system, which consisted of a FACSPresto counter machine and a BD FACSPresto ™ Cartridge kit.

Operational and Standard Definitions

Dyslipidemia: abnormally elevated levels of any type of lipoprotein in the blood of an individual. TC, LDL-C, TG, and HDL-C levels ≥200 mg/dL, ≥130 mg/dL and ≥150 mg/dL, and <40 mg/dL, respectively, were considered abnormal.[59]
Hyperglycemia: Elevated random blood glucose levels of ≥200 mg/dl according to the American Diabetes Association (ADA) criteria.[60]
hsCRP levels: hsCRP protein classified based on the risk of CVD, <1 mg/L being low risk, 1–3 mg/L being moderate risk, and >3 mg/L being high risk, based on the American Heart Association (AHA) and Centers for Disease Control and Prevention (CDC).[61]
CD4 cell count ≥500 cells/mm^3: level indicating normal range and a competent immune system.[62]
CD4 cell count <500 cells/mm^3: level indicating a compromised immune system.[62]
Viral loads above 1000 copies/mL: level indicating virological failure and high viral loads in the blood.[63]
Viral loads below 1000 copies/mL: level indicating suppressed viral loads.[63]

Data Analysis Procedures

The data were checked, cleaned, entered into Epi-data software version 3.1, and exported to SPSS version 25.0. Simple descriptive statistics were used to present the participants' sociodemographic characteristics. Categorical variables were presented as numbers and percentages, computed using the chi-square test to detect differences between the groups, while continuous variables were presented as mean ± standard deviation and median (IQR); the Student's *t*-test for variables showing normality and the Mann–Whitney *U*-test for variables that did not show normality were then used to detect differences between the groups. Binary and multivariable logistic regression analyses were performed to identify the factors associated with dyslipidemia and hyperglycemia. Variables with p-values <0.25 in bivariable logistic regression were fitted into the multivariable logistic regression model for the final analysis. Multinomial logistic regression was performed to detect the predictor variables with increased hsCRP levels. Statistical significance was set at p<0.05 for all analyses of variables. Hosmer Lemeshow and Pseudo R square tests were checked, and problems were not found. Finally, the data were presented in the form of text, tables, and figures.

Data Quality Management

Data collection was controlled by the principal investigator, and the collected data were checked for completeness, consistency, and clarity. Blood samples for biochemical assays were collected with adherence to the standard operating procedure (SOP). Following quality control measures that meet established acceptance criteria, the patient's sample was run by the laboratory machine.

Ethical Consideration

Before data collection, ethical clearance was obtained from the Institutional Review Board of Jimma University (ref. No.: IHRPG1/5/2021). After it was given to JUMC and a permission letter had been obtained from the hospital, data collection had started. Written informed consent was obtained from all patients before the interviews after providing information about the purpose and method of the study. Participants were coded to ensure confidentiality, and their information was kept confidential during data analysis. COVID-19 infection prevention measures recommended by the

WHO were strictly followed during data collection to reduce the risk of infection transmission. This study was conducted in accordance with Declaration of Helsinki.

Results
Sociodemographic Characteristics of the Study Participants
Of the total 128 participants, 64 were DTG-treated, and 64 were ATV/r-treated. Among patients on DTG-based and ATV/r-based regimens, 48.4% (31/64) and 37.5% (24/64), respectively, were older than age 40 years, with an insignificant difference between them. Among our study groups, an insignificant difference was detected for most of the participants' sociodemographic characteristics (see Table 1).

Clinical and Anthropometric Characteristics of the Study Participants
This study revealed that 35.9% (23/64) and 57.8% (37/64) of patients treated with DTG-based and ATV/r-based ART (p-value=0.013), respectively, were taking HAART for >24 months. In addition, approximately 54.7% (35/64) of DTG-treated and 53.1% (34/64) of ATV/r-treated patients had a BMI ≥ 25 kg/m^2 (p=0.9) (Table 2).

Table 1 Sociodemographic Characteristics of People Living with HIV Taking DTG-Based and ATV/r-Based ART at JUMC, Southwest Ethiopia from November 4, 2021, to January 4, 2022 (n=128)

Variables	Category	Exposure Category		p-value [c]
		DTG n (%)	ATV/r n (%)	
Age	18–40	33 (51.6)	40 (62.5)	0.21
	>40	31 (48.4)	24 (37.5)	
Gender	Male	25 (39.1)	22 (34.4)	0.58
	Female	39 (60.9)	42 (65.6)	
Religion	Muslim	18 (28.1)	23 (35.9)	0.23
	Orthodox	21 (32.8)	18 (28.1)	
	Others	25 (39.1)	23 (35.9)	
Ethnicity	Oromo	28 (43.8)	36 (56.3)	0.49
	Amhara	16 (25)	13 (20.3)	
	Others	20 (31.3)	15 (23.4)	
Marital status	Married	46 (71.9)	53 (82.8)	0.34
	Unmarried	18 (28.1)	11 (17.2)	
Educational status	Cannot read and write	5 (7.8)	5 (7.8)	0.77
	Primary	18 (28.2)	17 (26.6)	
	Secondary and above	41 (64.1)	42 (65.6)	
Occupational status	Employed	15 (23.4)	20 (31.3)	0.90
	Unemployed	49 (76.6)	44 (66.7)	
Income	<5000	34 (53.1)	33 (46.9)	0.86
	≥5000	30 (46.8)	31 (53.2)	
Residence	Urban	56 (87.5)	42 (65.6)	0.40
	Rural	8 (12.5)	22 (34.4)	
Smoking status	Yes	0 (0)	1 (1.6)	0.32
	No	64 (100)	63 (98.4)	
Alcohol use	Yes	5 (92.2)	7 (10.9)	0.55
	No	59 (7.8)	57 (89.1)	
Physical activity	Yes	24 (37.5)	15 (23.4)	0.80
	No	40 (62.5)	49 (76.6)	
Type of oil used for cooking	Liquid	40 (62.5)	34 (53.1)	0.28
	Solid	24 (37.5)	30 (46.9	

Note: c: chi-square statistical test.
Abbreviations: DTG, dolutegravir; ATV/r, ritonavir-boosted atazanavir; n, number.

Table 2 Clinical and Anthropometric Characteristics of People Living with HIV Taking DTG and ATV/r-Based ART at JUMC, Southwest Ethiopia from November 4, 2021, to January 4, 2022 (n=128)

Variables	Category	Exposure Category		p-value
		DTG-Based ART n (%)	ATV/r-Based ART n (%)	
CD4 cell count (cells/mm^3)	≥ 500	30 (46.9)	26 (40.6)	0.47
	< 500	34 (53.1)	38 (59.4)	
Viral load (copies/mL)	≤ 1000	61 (95.3)	58 (90.6)	0.3
	> 1000	3 (4.7)	6 (9.4)	
Duration of HIV (years)	≤ 5	34 (53.1)	38 (59.9)	0.053
	>5	30 (46.9)	26 (40.6)	
Duration of HAART (months)	≤ 24	41 (64.1)	27 (42.2)	0.013
	> 24	23 (35.9)	37 (57.8)	
WHO clinical staging	I	15 (23.4)	15 (23.4)	0.079
	II	34 (53.1)	23 (35.6)	
	III	15 (23.4)	26 (40.6)	
	IV	0	0	
BMI (kg/m^2)	< 25	29 (45.3)	30 (46.9)	0.9
	≥ 25	35 (54.7)	34 (53.1)	
Waist circumference (cm)	< cut-of	38 (59.4)	34 (53.1)	0.48
	≥ cut-of	26 (40.6)	30 (46.9)	
Waist–hip ratio	< cut-of	46 (71.9)	30 (65.6)	0.5
	≥ cut-of	18 (28.1)	22 (34.4)	

Note: c: Chi square test.
Abbreviations: DTG, dolutegravir; ATV/r, ritonavir-boosted atazanavir; n, number; HIV, human immunodeficiency virus; HAART, highly active antiretroviral therapy; BMI, body mass index; WHO, World Health Organization.

Prevalence of Serum Lipid Profiles Among Study Participants

Among all persons involved in the study, 48.4% (31/64) of the DTG-treated patients and 67.2% (43/64) of the ATV/r-treated patients had at least one lipid abnormality (p = 0.03). The results of the current study also showed that the proportion of TG ≥ 150 mg/dl was 40.6% (26/64) among patients on DTG-based ART and 62.5% (40/64) among patients on ATV/r-based ART (p = 0.01) (Table 3).

Prevalence of Serum Blood Sugar Among Study Participants

Regarding the RBS level, a higher proportion of hyperglycemia was found in patients treated with DTG-based ART (35.9%, 23/64) than in those treated with ATV/r-based ART (10.9%, 7/64) (p = 0.001) (Figure 1).

Prevalence of Serum hsCRP Levels Among Study Participants

Concerning the prevalence of hsCRP (Figure 2), the present study showed that the prevalence of hsCRP > 3 mg/L and hsCRP of 1–3 mg/L was lower in patients treated with DTG-based ART (12.5%, 8/64, and 37.5%, 24/64), respectively, than in those treated with ATV/r-based ART (17.2%, 11/64, and 51.6%, 33/64), respectively. However, the prevalence of hsCRP levels <1 mg/L was higher among patients treated with DTG (50%, 32/64) than among those treated with ATV/r (31.3%, 20/64) (p = 0.013).

Mean and Median Values of Serum Lipid Profiles, RBS, and hsCRP Levels Among Study Participants

A higher mean HDL-C level (41.3±10.3 vs 32.7±11.3 mg/dl) was observed among patients taking DTG-based ART than among those receiving ATV/r-based ART (p = 0.01). A lower median level of TG was observed among patients on DTG-based regimens, 131.8 mg/dl, IQR (102–202), than those on ATV/r-based regimens of ART, 165.35 mg/dl, IQR (132–238)

Table 3 Prevalence of Lipid Profiles Among People Living with HIV Taking DTG-Based and ATV/r-Based ART at JUMC, Southwest Ethiopia from November 4, 2021, to January 4, 2022 (n=128)

| Variables	Category	Exposure Category		p-value
		ATV/r-Based ART n (%)	DTG-Based ART n (%)	
Dyslipidemia	Yes	43 (67.2)	31 (48.4)	0.03
	No	21 (32.8)	33 (51.6)	
TC (mg/dl)	< 200	49 (76.6)	48 (75)	0.84
	≥ 200	15 (23.4)	16 (25)	
LDL-C (mg/dl)	< 130	41 (64.1)	43 (67.2)	0.71
	≥ 130	23 (35.9)	21 (32.8)	
HDL-C (mg/dl)	≥ 40	37 (57.8)	27 (42.2)	0.07
	< 40	27 (42.2)	37 (57.8)	
TG (mg/dl)	< 150	24 (37.5)	38 (59.4)	0.01
	≥ 150	40 (62.5)	26 (40.6)	
TC/HDL ratio	< 5	28 (43.7)	31 (48.4)	0.38
	≥ 5	36 (56.3)	33 (51.6)	

Note: c; implies chi-square statistical test.
Abbreviations: ART, antiretroviral therapy; ATV/r, ritonavir-boosted atazanavir, n, number; DTG, dolute-gravir; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, trigly-ceride; TC/HDL, total cholesterol to high-density lipoprotein ratio.

(p-value = 0.01). The results of the present study also revealed that the median level of RBS detected for DTG was 156 mg/dl, IQR (123–217), and for ATV/r was 138 mg/dl, IQR (123–156) (p = 0.04). The median level of hsCRP for DTG-based ART was 0.85 mg/L, IQR (0.5–1.5), and for ATV/r-based ART was 1.8 mg/L, IQR (0.9–3.6) (p-value = 0.01) (Table 4).

Factors Associated with Dyslipidemia in PLWH on DTG and ATV/r-Based ART

Binary and multiple logistic regression analyses of the factors associated with dyslipidemia are presented in Table 5. All variables with p < 0.25 (age, gender, type of oil, regimen type, CD4 cell count, BMI, WC, WHR, and duration of taking
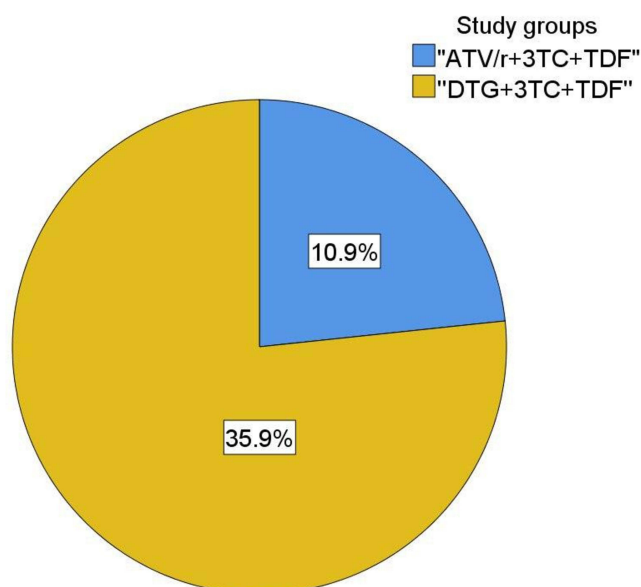
Figure 1 Prevalence of RBS among people living with HIV taking DTG and ATV/r based ART at JUMC, Southwest Ethiopia, 2021.
Abbreviations: NB: c, implies chi-square statistical test; RBS, random blood sugar; ATV/r, ritonavir-boosted atazanavir; 3TC, lamivudine; TDF, tenofovir; DTG, dolutegravir.
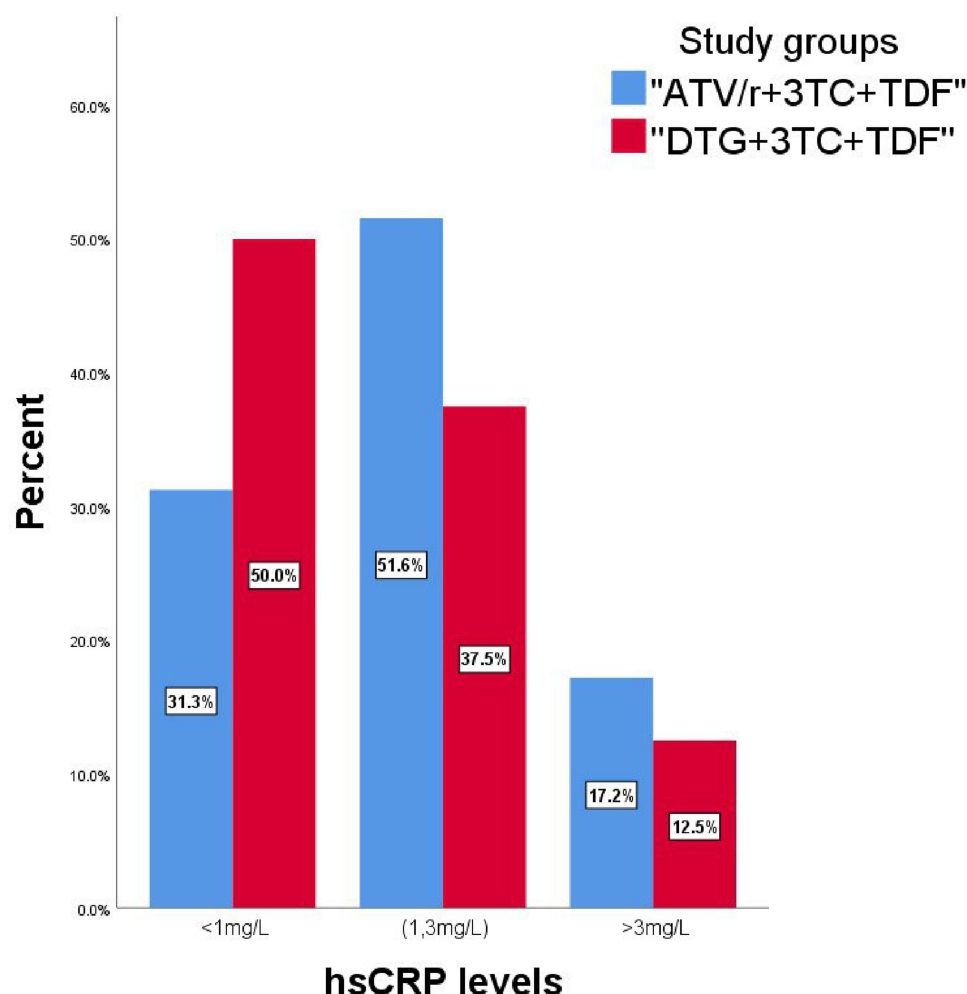
Figure 2 Prevalence of hsCRP among people living with HIV taking DTG and ATV/r-based ART at JUMC, Southwest Ethiopia, 2021.
Abbreviations: NB: c, implies chi-square statistical test; hsCRP, highly sensitive c-reactive protein; ATV/r, ritonavir-boosted atazanavir; 3TC, lamivudine; TDF, tenofovir; DTG, dolutegravir.

HAART) were included in the multivariate analysis. After adjusting for all these variables in multiple logistic regressions, ATV/r-based ART (AOR = 3.4; 95% CI: 1.5, 7.8; p = 0.04) and age >40 years (AOR = 2.85; 95% CI: 1.3, 6.3; p = 0.03) were identified as significant predictors of dyslipidemia.

Table 4 Comparison of Lipid Profiles, RBS, and hsCRP Levels Among People Living with HIV Taking DTG and ATV/r-Based ART at JUMC, Southwest Ethiopia from November 4, 2021, to January 4, 2022 (n=128)

Variables	DTG-Based ART	ATV/r-Based ART	P-value
TC (mg/dl) [Mean ± SD][a]	175.6±38.7	169.7± 42	0.40
LDL-c (mg/dl) [Mean± SD][a]	86.369 ±25.94	90.54 ±25.319	0.36
HDL-c (mg/dl) [Mean± SD][a]	41.3± 10.3	32.7 ±11.3	0.01
TC/HDL-c ratio [Mean± SD][a]	4.47 ±1.53	5.02±1.84	0.07
TG (mg/dl) [Median (IQR)][b]	132 (102–202)	165.35 (132–238)	0.01
RBS (mg/dl) [Median (IQR)][b]	156 (123–217)	138 (123–156)	0.04
hsCRP (mg/L) [Median (IQR)][b]	0.85 (0.5–1.5)	1.8 (0.9–3.57)	0.01

Note: [a]Independent sample *t*-test, [b]Mann Whitney *U*-test.
Abbreviations: IQR, interquartile range; SD, standard deviation; DTG; Dolutegravir, ATV/r, ritonavir-boosted atazanavir; ART, antiretroviral therapy; TC, total cholesterol; LDL-C, low-density lipoprotein; HDL, high-density lipoprotein; TG, triglyceride; RBS, random blood sugar; hsCRP, high-sensitivity C-reactive protein.

Table 5 Factors Associated with Dyslipidemia Among People Living with HIV Taking DTG-Based and ATV/r-Based ART at JUMC, Southwest Ethiopia from November 4, 2021, to January 4, 2022 (n=128)

Variables		Dyslipidemia		Binary Analysis		Multivariable Analysis	
		Yes	No	COR (95% CI)	P-value	AOR (95% CI)	P-value
Age (years)	18–40	36	37	1			
	>40	38	17	2.29 (1.1, 4.78)	0.03	2.85 (1.3, 6.3)	0.03
Gender	Female	50	31				
	Male	24	23	0.5 (0.21, 1.1)	0.10	0.65 (0.3, 1.34)	0.24
Type of oil used for cooking	Liquid	39	35	1			
	Solid	35	19	1.66 (0.8–3.4)	0.17	1.3 (0.55, 2.85)	0.57
Regimen type	DTG	31	33	1			
	ATV/r	43	21	2.18 (1.06, 4.5)	0.03	3.4 (1.5, 7.8)	0.04
CD4 cell count (cells/mm^3)	≥ 500	28	28	1			
	< 500	46	26	1.8 (0.9, 3.6)	0.12	1.75 (0.8, 3.8)	0.15
BMI (kg/m2)	< 25	30	29	1			
	≥ 25	44	25	1.7 (0.8, 3.5)	0.14	1.9 (0.9, 4.2)	0.13
WC	Normal	37	35	1			
	Abnormal	37	19	1.8 (0.9, 3.8)	0.09	2 (0.94, 4.4)	0.07
Duration of HAART (months)	≤ 24	33	35	1			
	>24	41	19	2.28 (1.1, 4.7)	0.03	1.5 (0.6, 3.3)	0.37
WHR	≤Cut-of	46	42	1			
	>Cut-of	28	12	2.13 (0.96, 4.7)	0.06	1.4 (0.5, 3.8)	0.5

Note: 1; reference category.
Abbreviations: CI, confidence interval; COR, crude odds ratio; AOR, adjusted odds ratio; ATV/r, ritonavir-boosted atazanavir; DTG, dolutegravir; BMI, body mass index; WC, waist circumference; HAART, highly active antiretroviral therapy; WHR, waist-hip ratio.

Factors Associated with Hyperglycemia in PLWH on DTG-Based and ATV/r-Based ART

Multivariable logistic regression was performed for all explanatory variables (age, gender, CD4 cell count, BMI, physical activity, type of regimen, and duration of HIV infection since the first diagnosis) with $p < 0.25$ in the binary logistic regression (Table 6). In multiple logistic regression analyses, BMI and DTG-based ART were identified as the determinants of

Table 6 Factors Associated with Hyperglycemia Among People Living with HIV Taking DTG and ATV/r-Based ART at JUMC, Jimma, Southwest Ethiopia from November 4, 2021, to January 4, 2022 (n=128)

Variables		Hyperglycemia		Binary Analysis		Multivariable Analysis	
		Yes	No	COR (95% CI)	p-value	AOR (95% CI)	p-value
Age (years)	18–40	9	64	1			
	>40	21	34	4.39 (1.8, 10.6)	0.001	2.67 (0.97, 7.37)	0.06
Gender	Female	23	58	1			
	Male	7	40	0.4 (0.17, 1.1)	0.087	0.7 (0.223, 2.2)	0.54
CD4 cell count (cells/mm3)	≥500	9	47	1			
	<500	21	51	2.15 (0.9, 5.2)	0.087	1.47 (0.51, 4.2)	0.46
BMI (kg/m2)	<25	9	50	1			
	≥25	21	48	2.43 (1.01, 5.8)	0.047	3.70 (1.27, 10.8)	0.02
Regimen type	ATV/r	7	57	1			
	DTG	23	41	4.56 (1.8, 11.7)	0.001	4.61 (1.47, 14.4)	0.01
Duration of HIV (years)	≤5	12	60	1			
	>5	18	38	2.4 (1.03, 5.5)	0.043	1.7 (0.62, 4.8)	0.30
Physical activity status	No	17	72	1			
	Yes	13	26	2.11 (6.9, 4.95)	0.084	2.73 (0.98, 7.6)	0.05

Note: 1; reference category.
Abbreviations: CI, confidence interval; COR, crude odds ratio; AOR: Adjusted odds ratio; BMI, body mass index; ATV/r, ritonavir-boosted atazanavir; DTG, dolutegravir; HIV, human immunodeficiency virus.

Table 7 Factors Associated with the Levels of hsCRP Among People Living with HIV Taking DTG-Based and ATV/r-Based ART at JUMC, Southwest Ethiopia from November 4, 2021, to January 4, 2022 (n=128)

Variables		Categories	Binary Analysis		Multivariable Analysis	
			CRR (95% CI)	p-value	ARR (95% CI)	p-value
1–3 mg/L	Age (years)	18–40	1			
		>40	1.9 (0.9, 4)	0.09	2.26 (0.97, 5.3)	0.06
	Gender	Female	1			
		Male	1.7 (0.8, 3.6)	0.16	2.25 (0.9, 5.4)	0.07
	BMI (kg/m2)	<25	1			
		≥25	2.3 (1.1, 4.9)	0.03	2.5 (1.1, 5.8)	0.03
	Duration of HAART (months)	≤24	1			
		>24	2 (1, 4.6)	0.05	1.06 (0.4, 2.8)	0.89
	DTG +3TC+TDF	N/A	1			
	ATV/r+3TC+TDF	N/A	2.6 (1.2, 5.5)	0.01	3.3 (1.3, 8.4)	0.01
>3 mg/L	Gender	Female				
		Male	3.2 (0.8, 13)	0.10	2.5 (0.5, 12.1)	0.26
	WC (cm)	Normal				
		Abnormal	0.43 (0.12, 1.6)	0.20	0.25 (0.05, 1.15)	0.07
	CD4 cell count (cells/mm3)	≥500	1			
		<500	4.4 (1.1, 17.9)	0.04	5.1 (1.1, 23.9)	0.04

Note: 1: Reference category of predictors; reference category: <1 mg/L.
Abbreviations: CRR, crude relative risk; ARR; Adjusted relative risk; CI, confidence interval; BMI, body mass index; HAART, highly active antiretroviral therapy; ATV/r, ritonavir-boosted atazanavir; DTG, dolutegravir; 3TC, lamivudine; TDF, tenofovir; WC, waist circumference, N/A, not applicable.

hyperglycemia. It was observed that the odds of developing hyperglycemia was four times (AOR = 3.7; 95% CI: 1.27, 10.8; p-values = 0.02) greater in patients with a BMI ≥ 25 kg/m^2 than in patients with BMI <25 kg/m^2. Our study also indicated that patients receiving DTG-based ART were five times (AOR=4.61; 95% CI: 1.47, 14.4; p-value=0.01) more likely to have hyperglycemia than those receiving ATV/r-based ART.

Factors Associated with Raise hsCRP Level in PLWH on DTG-Based and ATV/r-Based ART

Table 7 presents the factors associated with hsCRP levels compared to the reference category of <1 mg/L. Variables with p < 0.25 in the bivariate analysis were included in the multinomial logistic regression. In the adjusted analysis, the risk of patients with BMI ≥ 25 kg/m^2 developing hsCRP levels of 1–3 mg/L rather than <1 mg/L was two times (ARR = 2.5; 95% CI: 1.1, 5.8; p-value = 0.03) higher than those with BMI < 25 kg/m^2. The risk of patients on ATV/r-based ART having an hsCRP level of 1–3 mg/L rather than <1 mg/L was three times higher (ARR = 3.3; 95% CI: 1.3, 8.4; p = 0.013) than those on DTG-based ART. In patients with CD4 cell counts < 500 cells/mm^3, the risk of a having hsCRP level >3 mg/L rather than <1 mg/L was five times more likely than for patients with CD4 cell counts ≥500 cells/mm^3.

Discussion

This study was designed to assess serum lipid profiles, blood glucose, and hsCRP levels and their associated factors among people living with HIV receiving DTG-based ART and ATV/r-based ART. The result of this study showed that higher median values of TG were found among ATV/r- than DTG-treated patients, which was in line with an observational cohort study conducted in Italy,[64] a trial study from six European[65] countries, a cohort study from Taiwan,[13] and a study from Ethiopia.[66] Similarly, a study conducted in Italy[11] and a cross-sectional study in Ethiopia[12] also strengthened our findings. However, our result was in conflict with a study from Germany. A possible reason for this conflict of results might be differences in taking boosted atazanavir (in the German study, atazanavir was unboosted, whereas it was ritonavir-boosted in the current study) and duration of ART (most of them take for 6 months and for more than 24 months in Germany and the present study, respectively), in addition to study design and sociodemographic differences.[67]

In the present study, the higher proportion of TG ≥150 mg/dl found among ATV/r- (62.5%) than DTG-treated patients (40.5%) was comparable with the cross-sectional study conducted in Addis Ababa, Ethiopia.[12] However, our finding was lower than that of a randomized study conducted in Spain[68] that showed a higher prevalence of TG ≥150 mg/dl in patients treated with ATV/r-based ART (37.82%). Differences in state of taking sample (fasting in Spain versus random in our study), ART exposure of the participants (ART-naïve for Spain versus ART experienced in our study), sample size (large and small sample size in Spain and current study, respectively), study design, and sociodemographic characteristics of the participants might be contributing to these incomparable findings.

The current study also found a statistically significantly higher mean level of HDL-C in DTG compared to ATV-r treated patients, which was in agreement with studies carried out in Italy.[69,70] Similarly, our study was supported by a trial conducted in Italy[11] and a cross-sectional study from Ethiopia,[12] which claimed that there was a significantly lower mean value of HDL-C in patients treated with the ATV/r-based ART regimen. On the contrary, our study result was in disagreement with the study result from Spain.[14] Duration of ART (all of them were less than 6 months and 35.9% of them were taking DTG for greater than 6 months in Spain and our study, respectively), sample size (33 versus 128 in Spain and current study, respectively), along with lifestyle and study design variability, might be playing a role in this disagreement of findings.

Regarding blood glucose levels, a significantly higher median value of RBS was detected in DTG (156 mg/dl) than in ATV/r-treated patients (138 mg/dl). In the current study, a higher prevalence of RBS was also observed in patients treated with DTG (35.9%) than in those treated with ATV/r-based regimen (10.9%). These findings were in line with studies conducted in Uganda,[24] Saudi Arabia,[28] and USA,[27] but not in line with study from Italy.[30] This conflicting result might be more likely due to the difference in duration of ART and the proportion of male participants (85.6% in Italy versus 36.7% in our study). Furthermore, the current study was designed to assess the serum hsCRP levels in patients taking DTG-based and ATV/r-based antiretroviral therapy. We found a significant difference and a lower median hsCRP level among DTG patients as compared to patients treated with ATV/r-based ART. The proportion of patients with hsCRP levels >3 mg/L and 1–3 mg/L, respectively, were 12.5% and 37.5% for DTG- and 17.5% and 51.6% for ATV/r-based regimens. Studies carried out in France,[36,71] Spain,[14] and Italy[30] all strengthen our findings by showing a significant decrease from the baseline mean of hsCRP level in HIV patients who switched from ATV/r-based to DTG-based regimens of ART. In contrast, our finding was incomparable to a study done in USA.[72] This inconsistency might be because of differences in ART exposure of the participants involved (ART-naïve in their study, while ART experienced in our study), proportion of male participants (90% in USA study versus 34.4% in our study), duration of ART (2 years versus 57.8% of them had above 2 years), in addition to study design and genetic variations.

In the present study, patients with a BMI ≥25 kg/m^2 were more likely to have hyperglycemia than patients with a BMI <25 kg/m^2. This is consistent with a study from Kampala, Uganda[73] and USA,[74] and Ethiopia.[75,76] Hyperglycemia in obese patients is due to increased release of free fatty acids to activate protein kinases and pro-inflammatory cytokines like interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) released from adipose tissue impair insulin signalling and causes insulin resistance.[77,78] In addition, our study demonstrated that patients on the DTG-based ART regimen were 4.6 times more likely to have hyperglycemia than patients on the ATV/r-based ART regimen. Studies done in India[26] and Brazil[79] reported results that are in line with our study findings. DTG-induced hyperglycemia is hypothesized to be due to the induction of low levels of intracellular Mg^{2+} by chelation. Mg^{2+} is important for insulin signalling and its chelation thus affects insulin signalling that end with insulin resistance.[23]

Likewise, the current study found that age >40 years was significantly associated with dyslipidemia. This is consistent with studies done in Tanzania[29] and Ethiopia.[78,79] A change in the hepatic sinusoidal endothelium with reduced endocytosis of lipoproteins and delayed clearance of chylomicrons as a result of decreased activity of the lipoprotein lipase enzyme might explain older age-induced dyslipidemia.[80,81] According to our study, a significant association was also found between ATV/r-based regimens and dyslipidemia, which is in agreement with a study carried out in Tanzania[29] and Brazil.[5] A possible mechanism for ATV/r-induced dyslipidemia was through binding with and inhibition of cytoplasmic retinoic acid-binding protein-1 (CRABP-1) and sterol regulatory element-binding protein (SREBP).[7,82] SREBP-1 and CRABP-1 are regulatory proteins involved in the stimulation of adipocyte differentiation, thus their

inhibition leads to decreased triacylglycerol storage, increased free fatty acid release, and ended up with an increase in dyslipidemia.[83]

Moreover, this study attempted to identify the factors associated with increased hsCRP levels. Accordingly, there is 2.5 times more risk of having an increased hsCRP level by 1–3mg/L rather than <1 mg/L for patients with a BMI ≥25 kg/m². This is in line with.[84,85] In addition, ATV/r-based regimens were significant predictors of elevated hsCRP by 1–3 mg/L rather than hsCRP <1 mg/L, which is in line with.[86] Furthermore, a CD4 cell count of <500 cells/mm³ was identified as a predictor of increased hsCRP levels by >3 mg/L rather than <1 mg/L. This finding is in agreement with a study conducted in India.[87] The observed association of obesity with increased hsCRP was described partly by obesity-induced hyperplasia and hypertrophy of adipocytes with increased secretion of pro-inflammatory cytokines especially IL-6, which intern results in secretion of CRP by the liver.[88] ATV/r inhibits USP18 (Ubiquitin-specific peptidase 18), which is the repressor of interferons involved in the activation of nuclear factor kappa B (NF-kB) (the main driver of IL-6 and other cytokine production flowed by raised level of CRP).[36]

Strength and Limitation of the Study

As a strength, to the best of our knowledge, this was the first study in Ethiopia that attempted to assess the effects of DTG and ATV/r-based regimen on serum lipid profiles, blood glucose, and high-sensitivity C-reactive protein levels among people living with HIV, hence ultimately adding to the limited data. Despite the aforementioned strength, this study has several weaknesses. This is a comparative cross-sectional study; thus, we cannot associate causal relationships between the factors and outcomes under study. In addition, the study sample size was small; thus, it is difficult to generalize the findings to larger populations. The laboratory determination of lipid profiles and blood glucose was done at random, which may affect our study result. Moreover, there was a baseline difference in HAART duration between the two groups, which may have affected the outcome variables. Moreover, HIV-positive ART-naïve controls were not included, which may remove the effect of ART taken before starting DTG and ATV/r-based regimens.

Conclusion and Recommendation

In general, our findings indicated that patients treated with ATV/r had atherogenic lipid profiles and higher hsCRP levels than those treated with DTG. However, hyperglycemia was observed in patients treated with DTG-based regimens. This study also demonstrated that dyslipidemia was predicted by older age and ATV/r-containing regimens, hyperglycemia was predicted by BMI ≥25 kg/m2 and DTG-containing regimens, and the risk of increased hsCRP levels of 1–3 mg/L was significantly predicted by ATV/r-based regimens and BMI ≥25 kg/m2, while increased hsCRP levels >3 mg/L were predicted by a CD4 cell count <500 cells/mm3. Therefore, measuring baseline lipid profiles and hsCRP levels for HIV patients on ATV/r-based regimens, particularly those with a higher BMI, older age, and lower CD4 cell count, should be part of routine care. In addition, routine monitoring of blood glucose in HIV patients on DTG-based regimens and those with a higher BMI should be an important element of care to prevent and predict the early risk of CVD. To achieve this, policymakers should take these factors into account when developing public health initiatives on ART side effects management and when strengthening ongoing non-communicable disease reduction programs. Awareness should also be created for patients at every visit to the ART clinic by health-care providers regarding the possible side effects of ART. We propose that researchers conduct a prospective cohort study with a larger sample size to draw an exact conclusion regarding the effects of DTG and ATV/r on serum lipid profiles, blood glucose, and hsCRP levels. Finally, we suggest performing a comparative analysis of DTG-containing and ATV/r-containing ART in ART-naïve, HIV-positive patients.

Abbreviations

ART, antiretroviral therapy; ASCVD, atherosclerotic cardiovascular disease; ATV/r, ritonavir-boosted atazanavir; AZT; Zidovudine, BMI, body mass index; CD4, cluster of differentiation 4; CVD, cardiovascular disease; DTG, dolutegravir; EFV, efavirenz; HDL-C, high-density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein; IL-6, interleukin-6; JUMC, Jimma University Medical Centre; LDL-C, low-density lipoprotein cholesterol; NF-kB; nuclear factor kappa B; RBS, random blood sugar; SPSS, statistical package for social sciences; TDF, tenofovir; TC, total cholesterol.

Data Sharing Statement

All the necessary materials can be found in the text. Due to the privacy policy, confidential data materials could be obtained from the corresponding author upon request.

Acknowledgments

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors declare that they have no competing interests in this work.

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