Original Research Article

Lipid Abnormalities among Libyan HIV-Infected Patients Receiving Antiretroviral (ARV) Drugs and ARV Naïve Patients

Abstract

Introduction: Majority of untreated or Anti-Retroviral (ARV) treated HIV subjects may experience a lot of metabolic alterations including dyslipidemia, lipodystrophy and insulin resistance.

Aim: Due to the shortage of research data related to HIV infection. We conducted this study to assess the lipid profile in HIV infected subjects and to find a correlation between liver function enzymes and other biomarkers and serum lipid alterations among Libyan HIV subjects.

Materials and Methods: Case control study included 121 Libyan HIV-1 positive subjects (101 subjects were on First-line ARV treatment regimens and 21 untreated "Naïve") from Benghazi Medical Center (BMC) and Benghazi center for infectious diseases and immunology (BCIDI) during 2018-2019 to evaluate lipid profile and other biochemical parameters. Control group included 70 age-matched HIV negative individuals. The age range of the study participants was 20-45years.

Results: The means of CD4 count in the ARV treated HIV subjects were significantly ($P < 0.014$) lower compared CD4 count of untreated HIV group. The mean total cholesterol (TC) level of ARV treated HIV subjects (174 ± 42 mg/dl) was significantly ($P<0.012$) increased compared to untreated HIV subjects (149 ± 31mg/dl). In accordance, LDL-C levels showed a significant ($P < 0.014$) increase in the ARV treated HIV subjects compared to the untreated HIV subjects. On the other hand, mean HDL-C showed no significant alteration in the ARV treated HIV subjects compared to untreated HIV subjects.

Conclusion: In ARV-treated HIV patients showed higher TC and LDL-C suggesting a role of these drugs upon lipid metabolism.

The mechanism by which HIV drugs affect lipid profile need to be fully understood

by further research.

Unaltered HDL-C and LDL/HDL atherogenic risk ratio indicate reduced risk for developing cardiovascular disease among HIV subjects.

Keywords:, HIV/AIDS, Antiretroviral drugs, Infectious Disease, Libyan HIV patients, Dyslipidemia.

Introduction

HIV is one of the main public health issues and it is one of the 10 leading causes of death worldwide. HIV represents a huge burden on the Human immunodeficiency virus (HIV) is classified as a member Retroviruses class and sub family Lentiviridae. The HIV causes a life-threatening condition known acquired immunodeficiency syndrome (AIDS) which is characterized by a marked disruption of immune system. One of the most remarkable manifestations is the progressive infection of CD4+ cells leading to immunosuppression that finally resulted in AIDS [1].

HIV was discovered during the beginning of 1980's, and since then its incidence started to increase worldwide to reach millions of infected individuals. Since the beginning of the pandemic; 79.3 million individuals were infected with HIV and total death numbers are about 36.3 million people. According to WHO, in 2021, 38.4 million individuals were living with HIV (Global HIV & AIDS statistics — Fact sheet, 2021).

In a recent work, Daw et al., 2019, reported that from 1993 to 2017 the total number of people registered and living with HIV (PLHIV) in Libya was 8486 which represents a low prevalence rate [3]. Bannazadeh and Soroush 2019, suggested that the decreased prevalence rates of HIV are due to that the MENA countries (including Libya) are religiously and culturally conservative [4]. These facts were confirmed by previous work between 1986 to 1987, which found no positive HIV cases among 2064 Libyans form both genders screened for HIV Giasuddin et al., 1988 [5]. Furthermore, in 1991, the same group of scientists completed the screening by testing 10 thousand samples and again they found no HIV infections. Giasuddin et al., 1991 [6].

In the early nineties (1990), the introduction of highly active antiretroviral therapy (HAART) resulted in a marked reduction in morbidity and mortality from HIV

infection [7, 8]. The WHO antiretroviral guidelines preferred the first-line regimen of using two nucleotide/nucleoside reverse transcriptase inhibitors (NRTIs), such as, tenofovir (TDF) and lamivudine (3TC) together with non-nucleotide/nucleoside reverse transcriptase inhibitor (NNRTI), for instance, efavirenz (EFV) and nevirapine (NVP) and a second-line ARV regimen of boosted protease inhibitor (PI) supported by NRTIs (WHO, ARVs Guidelines, 2013) which caused a delay in the progression of the disease, an increase in life expectancy and made an improve in the quality of life of HIV infected subjects [9,10]. Using ART were accompanied by metabolic changes and appearance of side effects including dyslipidemia and insulin resistance [11,12]. Dyslipidemia appeared during the first three months of using ART were characterized by an increase in total cholesterol, triglycerides, low density lipoprotein (LDL-c), very low-density lipoprotein (VLDL), and low levels of high-density lipoprotein (HDL-c) [13,14].

Recent evidences showed up to 80% increase in the prevalence of marked lipid alterations which is considered as a risk factor for cardiovascular disease (CVD) in HIV and AIDS cases receiving ARVs and percentage of the prevalence of dyslipidemia depends on the investigated population and the design of the study [15,16]. Recent evidences reported that using PIs for a long duration, exert atherogenic effects including hypertriglyceridemia, increased levels of LDL, and decreased HDL concentrations [17-19]. Furthermore; the changes on lipid metabolism were also confirmed by the work of Galli et al., (2002) who reported alterations lipid metabolism in healthy adult after using ARVs including NRTIs, NNRTIs, and PIs [20].

The exact cause of metabolic disturbances related to ARVs are not fully understood, during the last decade, Cotter et al. (2011) suggested that HIV infection impairs the reverse cholesterol transport (RCT) in both macrophages and monocytes; which finally leads to dyslipidemia which is a major cardiovascular risk factor [21].

$CD4^+$ and $CD8^+$ are two types of white blood cells in your blood. CD4 cells are also called T-helper cells, T-suppressor cells, and cytotoxic T-cells. They help the body fight infections. $CD8^+$ cells are also called cytotoxic T-lymphocytes. The use of HAART for HIV-infected patients, represented a new perspective on life for HIV patients [22]. The use of HAART was shown to effectively suppress the replication of

HIV-1 indicated by reduction in HIV load followed by an increase in $CD4^+$ cell count which is a sign of recovery of the immune system. The overall effect of ARV drugs was expressed by the marked reduction in mortality and morbidity, which has led to a longer and better quality of life for HIV-1patients [23, 24]. Due scarcity of HIV research work in Libya, this research aimed to investigate the effect of ARV drugs on lipid profile, liver function enzymes and other biochemical parameters among Libyan HIV patients in the Libyan eastern area and Benghazi city.

Materials And Methods

Study design: This case control study was conducted in the laboratory of Benghazi center for infectious diseases and immunology (BCIDI) and Benghazi Medical center (BMC) during the period of 2018-2019 to evaluate Lipid profile and liver enzymes in HIV cases under antiretroviral drugs and HIV cases who were not on ARV drugs (Naive). Control group included age-matched HIV negative individuals.

Sample collection: Blood samples were collected from the study participants into vacuum test tubes (plain, ethylene diaminetetra acetic acid "EDTA"). The blood collected in plain tubes were centrifuged and transferred into secondary tubes in clinical chemistry analyzer Cobas Integra 400 plus for estimation of lipid profile, glucose and liver function enzymes. HIV viral load was performed by real time PCR from Abbott. CD4 counts were assayed using whole blood samples (drawn in EDTA-containing tubes). CD4 counts were assayed by flow cytometry using Facs calibuer.

Study population:101 cases on different ARV drug regimens and 21 cases not on ARV drugs (Naive) were included in the study. Generally, the age of the study ranged from 20 to 45 years old. The selected HIV positive cases were single genotype and were on ARV triple combination and the cases were without previous hepatitis C "HCV" or hepatitis B "HBV" infections. HIV patients from different genotypes, or using old ARV drug lines, or on statins were excluded from the study. 70 HIV-negative age matched subjects were considered as control group (**table 1**).

Table 1: Study population

Status	Study population
HIV- positive cases on ARVs	101
HIV- positive cases not on ARVs	21
HIV- negative (control)	70
Total	192

The 101 HIV positive selected cases were stratified into four groups according to the treatment regimens (table 2), These HIV-infected patients who were using ARV drugs triple combination therapy for more than 24 weeks.

Table 2: HIV positive cases on treatment regimens.

S. No.	ART classes	Group	No.
1	**2NRTIs + NNRTI**	FTC + TDF + EFV	36
2	**2NRTIs + PI**	FTC+ TDF + LPV/r	25
3	**2NRTIs + INSTI**	FTC+ TAF + EVG/c or RAL	40

Where; NRTIs include: Emtricitabine (FTC) and Tenofovir (TDF); NNRTI is Efavirenz (EFV); PI is Lopinavir (LPV); INSTI (Integrase Strand Transfer Inhibitor) include Elvitegravir (EVG) and Raltegravir (RAL) which are Integrase inhibitors. Fasting blood glucose was estimated by the enzymatic-colorimetric reference method with hexokinase. Lipid profile including; total cholesterol (TC), HDL cholesterol, LDL cholesterol and triglycerides (TAG) were investigated by CHOD/PAP, PEG-precipitation, homogeneous enzymatic colorimetric assay and GPO/PAP methods respectively. Liver function enzymes alanine transaminase (ALT) and aspartate transaminase (AST) were checked by standardized method described by IFCC.

Lymphocytes counts (CD4 and CD8) were estimated by the fully automated BD FACS Calibur depends on single platform technology which designed to enable determination of both absolute and percentage of lymphocytes. Sample preparation and procedure were performed according to manufacturer instruction. HIV viral load

was performed by real time PCR (Abbott) fully automated device. It is estimated by Abbott Real Time HIV-1 (m2000sp) assay uses RT-PCR to generate amplified product from the RNA genome of HIV-1 in clinical specimens.

3.6. **Statistical analysis:**

The data collected in data sheet were recorded in Microsoft Excel then imported in (Statistical Package for Social Sciences) SPSS version 26 and the statistical analysis was chosen according to Kolmogorov-Smirnov method and values were considered significant at $p<0.05$ at confidence interval 95%. Statistical work was done as follows: The independent t-test is used to test the difference between the two groups (patients on ARV drugs and not on ARV drugs), in the variables; CD4, CD4%, CD8, CD8%. while Mann-Whitney was used to test the difference between the two groups in HIV viral load. One-way analysis of variance (ANOVA) was used to test the difference between the variables (Blood Glucose, Cholesterol, LDL, HDL and LDL/HDL) of the three groups (patients on ART, not on ART and control), while Kruskal-Wallis test was used to test the different between the three groups in the variables; ALT, AST and TG.

Results

This work consisted, 101 ARV treated HIV individuals, 21 untreated HIV individuals and of 70 HIV negative age and sex matched individuals used as controls (**Figure 1**).

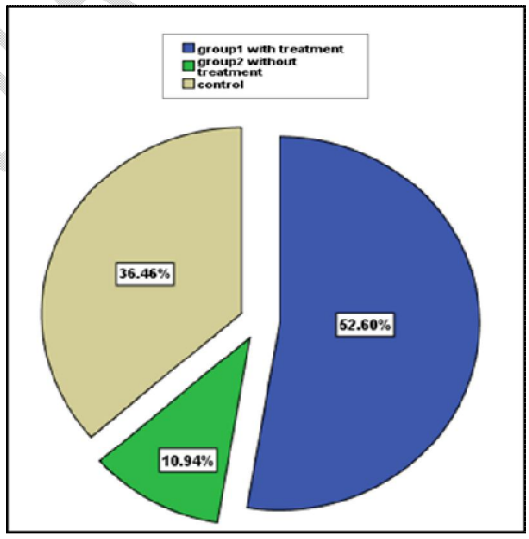

Figure 1: The percentages of HIV cases and control included in the study

In regard to gender, the study population includes 112 females (58.9%) and 80 males (41.1%) (**Figure 2**).

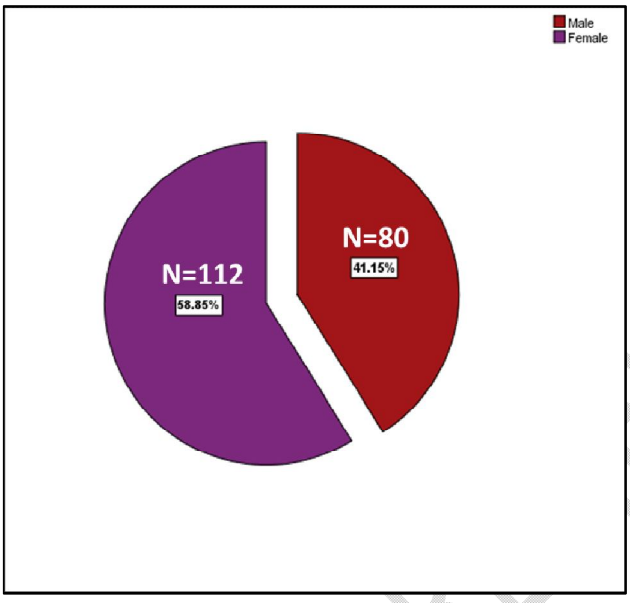

Figure 2: Percentages of male and female within study subjects.

Age: The ages of the participants were grouped into 5 age groups generally the ages of the study ranged from 20 to 45 years old **(Figure 3)**. The vast majority of the cases were within the age category ≥ 25.

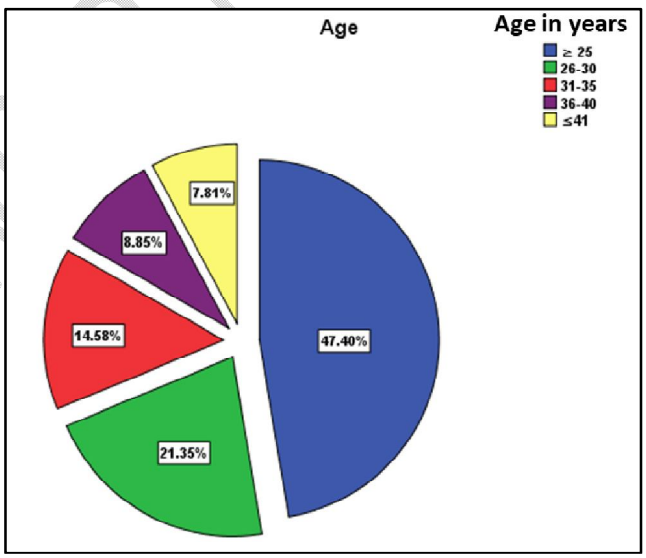

Figure 3: The distribution of age groups within study subjects

Viral Load: The viral load of the ARV treated HIV group was 40311.9 copies/ml which was increased compared to 5172.7 copies/ml of HIV untreated group (**Figure 4**).

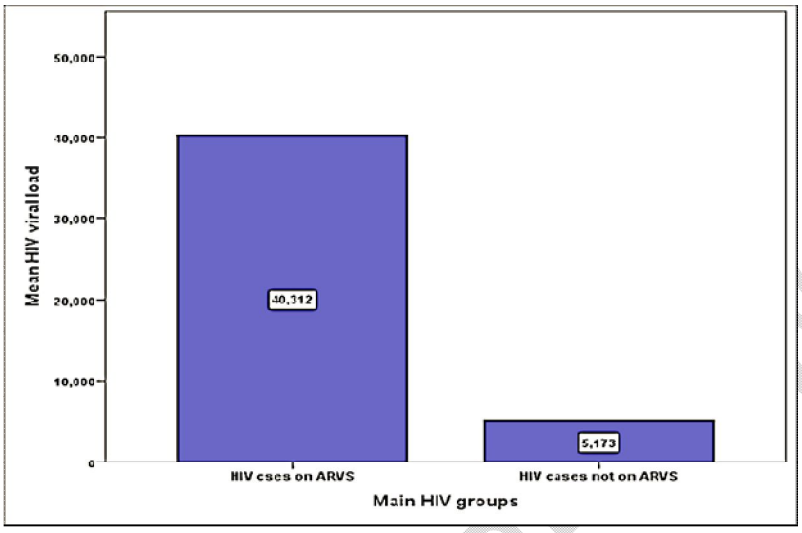

Figure 4: Viral load of treated HIV cases was increased compared to untreated HIV.

Classification of HIV positive cases according to their CD4

All HIV positive subjects were stratified according to WHO classification of CD4 counts. The results showed that the majority of the HIV positive cases: 81 subjects (66.39%) had the highest CD4 count more than 500 cell/ mm^3 (clinical stage 1), whereas the lowest CD4 count;16 cases (6.56%) had CD4 counts between 394-200 cells/mm^3 (clinical stage 3) **(table 3**).

Table 3: Classification of HIV positive cases according to their CD4

Clinical stages	CD count cell/ mm^3	HIV-associated immunodeficiency	No. of HIV +ve cases	% of HIV +ve cases
1	**≥ 500**	None significant	81	66.39
2	**499-350**	Mild	16	13.11
3	**394-200**	Advanced	8	6.56
4	**< 200**	Severe	17	13.93

Comparing CD4 and CD8 within the study groups: The means of CD4 count and CD4% in the ART treated HIV subjects were 648.3 ± 400.5 and 24.6 ± 11.1 which were significantly (P <0.014 and P <0.039, respectively) lower compared CD4 count and CD4% of untreated HIV group (884.5 ± 369.8 and 29.90 ± 8.6, respectively). On

the contrary, the mean of CD8 count was higher (1322.77 ± 667.080) in ARV treated HIV group compared to HIV group not on ARV (1239.6 ± 538.8). CD8% was significantly (P <0.025) increased in ARV treated HIV group compared to CD8% of untreated HIV group.

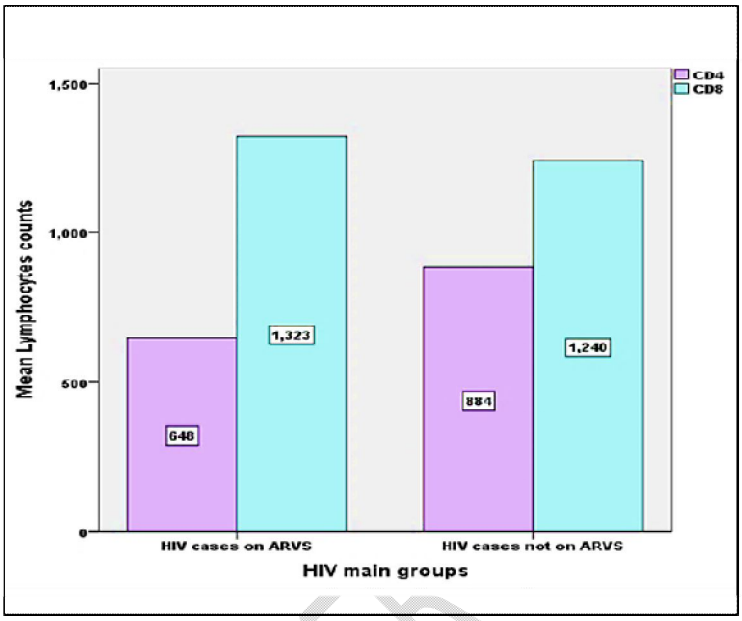

Figure 5: Comparing CD4 and CD8 between the study groups: CD4 increased in untreated group (Naïve) compared to ARV treated HIV group, but no significant change in CD8% between both of the groups.

Lipid profile and other parameters in ARV-treated HIV and untreated HIV and healthy control subjects:

The serum total cholesterol (TC) levels were stratified according to normal range based on NCEP guidelines (http://www.nhlbi.nih.gov/guidelines/cholesterol/atglance) as shown in the **table** 5.

Table 4: cholesterol status among the study subjects according to its levels.

Status	N.	Percentage
Normal	169	88.0%
Borderline high	12	6.3%
High	9	4.7%

The mean total cholesterol (TC) level of ARV treated HIV subjects (174 ± 42 mg/dl) was significantly (P<0.012) increased compared to untreated HIV subjects (149 ± 31mg/dl) (**Figure 4**). Meanwhile, TC levels of ARV treated HIV subjects were highly

significant (P<0.000) increased compared to healthy control TC levels (151 ± 27mg/dl) (**Figure 6**).

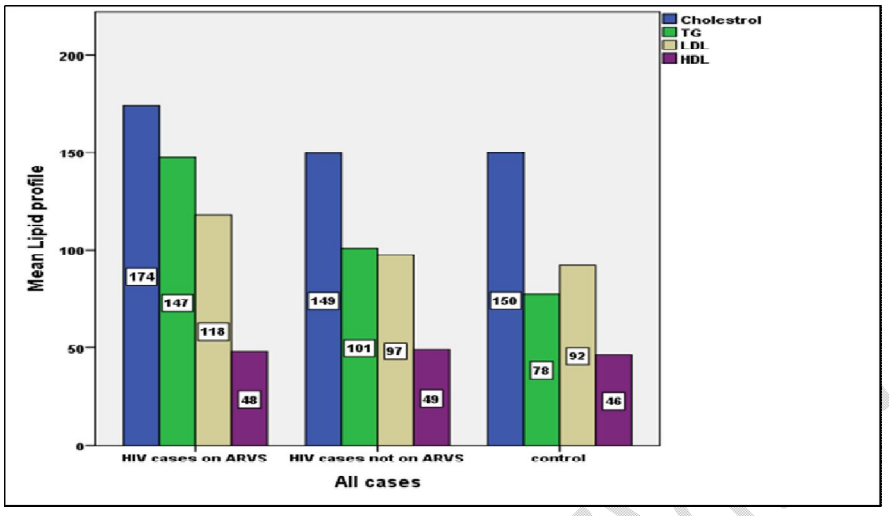

Figure 6: Mean levels of lipid profile (TC, LDL-C, HDL-C and TG) of ART treated and untreated HIV groups and healthy control group.

In accordance, LDL cholesterol levels (118 ± 34mg/dl) showed a significant (P <0.014) increase in the ARV treated HIV subjects compared to LDL-C of the untreated HIV subjects (97 ± 31mg/dl). In the same manner, the mean LDL-C level of the ARV treated HIV subjects was highly significant (P <0.000) increased compared to the mean of LDL-C of the healthy controls (93 ± 26mg/dl) (**Table 5**).

Table 5: comparison between the mean levels of TC, LDL-C and TG between ARV treated, untreated HIV and healthy control groups.

Dependent Variable	Groups		P-value
	I	J	
Cholesterol	HIV cases on ARVs	HIV not on ARVs	0.005*
		Control	0.000*
	HIV not on ARVs	Control	0.851
LDL-C	HIV cases on ARVs	HIV not on ARVs	0.007*
		Control	0.000*
	HIV not on ARVs	Control	0.573
TG	HIV cases on ARVs	HIV not on ARVs	0.019*
		Control	0.000*
	HIV not on ARVs	Control	0.090

* Means that the test is significant at 5%

As clear from **figure 6** the mean serum level of triglycerides (147 ± 112 mg/dl) of ARV treated HIV subjects showed a high significant (P<0.019 and P<0.000 respectively, **table 5**) increase compared to mean TG levels (101 ± 62mg/dl) of untreated HIV subjects and mean TG of the healthy control (79 ± 36mg/dl). On the other hand, mean serum levels of HDL cholesterol (48 ± 17mg/dl) showed no significant alteration in the ARV treated HIV subjects compared to untreated HIV subjects and healthy control (49 ± 24 mg/dl and (50 ± 16 mg/dl). In a similar way, no significant change found in LDL/HDL ratio (2.8 ± 1.3) of the ARV treated HIV subjects compared to LDL/HDL ratio of untreated HIV subjects and healthy control (2.3 ± 1.16 and 2.3 ± 1.5).

Blood glucose: A significant (P<0.004) increase (Table5) seen in the mean blood glucose concentration (105 ± 30) of the ARV treated HIV subjects compared to healthy control group (95 ± 13), but the change was not significant in the mean level of Blood glucose in ARV treated HIV subjects compared to glucose level (104 ± 16) of untreated HIV subjects (**Figure 7**).

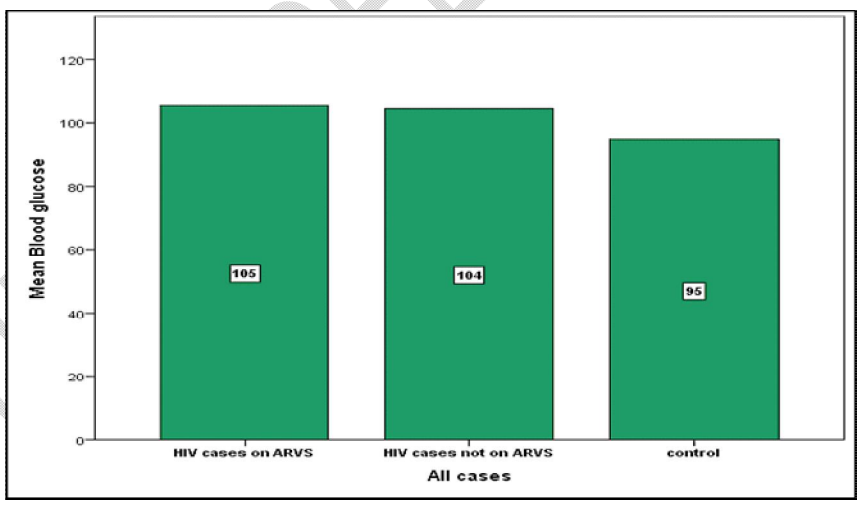

Figure 7: Mean levels of b. glucose of ARV treated, untreated HIV and control groups.

Liver function enzymes:

The mean ALT levels for both ARV treated and untreated HIV groups (22 ± 16 u/l and 23±12 u/l respectively), showed a highly significant (P<0.000 and P<0.001 respectively) increase compared to the mean ALT activity of the healthy control (17 ±

15 u/l). In the same manner, the mean AST values for both ARV-treated and untreated HIV groups (23 ± 14u/l and 26 ± 15 u/l respectively) were significantly (P<0.001 and P<0.006 respectively) increased compared to the mean AST level of the control (19 ± 6 u/l) (**Figure 8**).

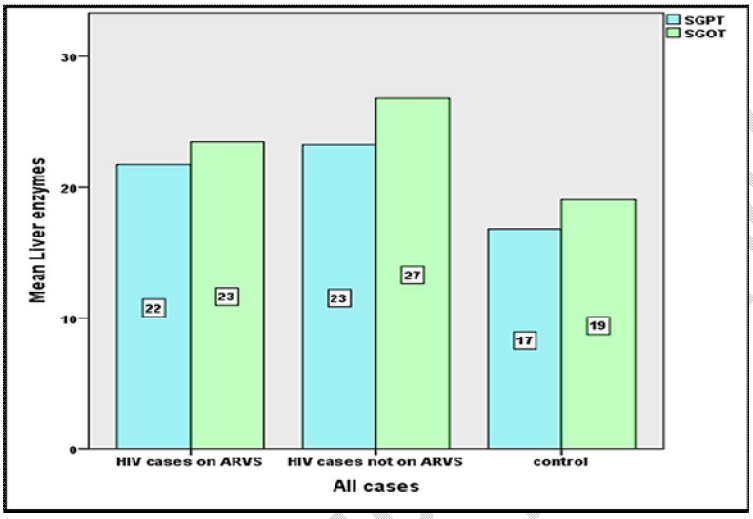

Figure 8: Mean activity of ALT and AST of ART treated, untreated HIV and control groups.

Discussion

In 1988, the wide spread of HIV in Libya made it a national problem [25]. Recently the prevalence in Libya increased from 0.13% in 2004 to 0.2% in 2019. This is very low compared to the African country in Zimbabwe where HIV prevalence is 14.4% as mentioned in National AIDS Council Preliminary Report, 2015 [26]. In the current study, the mean levels of ALT and AST for both ARV-treated and untreated HIV were highly significant increased compared to the mean ALT and AST activity of the healthy control but not significant changed when compared with that of the untreated HIV group. This finding was in contrast with the study of Shiferaw et al., (2016) who found had higher mean ALT of ARV-treated HIV-1 individuals (P value: 0.002). Furthermore, the previous evidence showed that prevalence of abnormally elevated liver enzyme was 20% in ARV-treated and 22.0% in untreated HIV patients which was higher compared to our findings [27]. In the same line, Owiredu et al. (2011), found an increased ALT activity of the ARV- treated HIV subjects [28]. The high

levels of liver enzymes in the current research were very low compared to the work of Gil et al., 2007, who showed prevalence of 22.6% among HIV patients in Cameroon [29]. Murphy et al., 2007 suggested that the specific class of ARV drugs caused the mitochondrial toxicity of the liver cells and possibly other organs that may cause failure of liver [30]. In the same line, a previous work of our research group led by Menesi et al., 2017, showed significant increases in the liver enzyme activities (ALT, AST and ALP) in patients suffering pulmonary tuberculosis with HIV co-infection, which indicate hepatic toxicity [31].

To our knowledge, this is the first study which investigated lipid abnormalities among Libyan HIV subjects. The current work showed significantly higher levels of serum total cholesterol (TC), LDL-C and triglycerides (TG) of the ARV-treated HIV subjects compared to those of the untreated HIV (ARV-Naïve). However, no significant change existed by comparing HDL-C concentrations among the study groups. These findings were in agreement with Low et al., (2019) who found similar results of the lipid profile by comparing HIV subjects treated with ARVs for more than one year and ARV-Naïve [32]. In accordance, Palios et al., (2010) found an increase in TC levels of ARV-treated and untreated HIV subjects [33]. These findings were in the same line with the work of Haubrich et al., in 2009, who found metabolic changes on lipid metabolism after treatment of HIV-negative volunteers with ARVs including; NRTIs, NNRTIs, and PIs [34]. These findings are in support of the changes on lipid profile in the ARV-treated HIV subjects in the current work. The alterations of lipid profile in our study and the previous evidences indicated an atherogenic effects ARV drug Protease inhibitors (PIs) were used by our study patients, are believed to inhibit lipid biosynthesis and promote lipolysis of subcutaneous fat. Accordingly, NRTIs, decrease the rate of lipogenesis and also implicated in mitochondrial toxicity and reduced mitochondrial DNA by inhibiting DNA polymerase γ. PIs are also implicated in reducing the uptake of remnant chylomicrons and VLDL [35]. Moreover, PIs promote TG production in the liver via up-regulating the rate limiting enzymes participated in TG synthesis leading to accumulation of TG-rich lipoproteins in the liver [36]

The data of present research found no significant change in lipid profile of ARV-Naïve group compared to HIV negative controls. These results were disagreement with the study of Fourie et al., 2010 who found changes in lipid parameters in HIV-1

and AIDS caused by the effect of infection and before the ARV treatment had been established. Lipid alterations included hypertriglyceridemia but the TC, LDL-c and HDL-c levels were reduced in untreated HIV subjects compared to HIV-negative subjects [37]. In the same line with the work of Zephy et al., 2015, reported a reduced cholesterol, HDL-C, LDL-C levels and an increase in TG among ARV-untreated HIV patients when compared to healthy subjects which contradicted the present study [38]. In contrast with the present work, the study of Nayyar (2019) also found a decreased levels of TC and LDL-C in the HIV and AIDS subjects. However, TG levels were increased which is in accordance with the finding of our study [39].

Dyslipidemia in ARV-treated HIV patients may occur due to various factors including increased serum levels of inflammatory cytokines (tumor necrosis factor alpha (TNF-α and interleukin-6), reduced lipid clearance, and elevated rate of VLDL production by the liver. In 2000, Ducobu and Payen suggested that increased levels of TNF- α and IL-6 resulted in lipid peroxidation, platelet activation and release of reactive oxygen species [40]. It is worth mentioning that the mechanisms behind changes in lipid parameters in HIV subjects are still not completely understood, but evidence suggested may be supported by other factors including genetic and environmental factors, as well as by drugs [41].

Normal HDL levels in the present study may reflect a positive prognosis status of the HIV patients. This conclusion was in accordance with Llibre et al., 2006 and Bernal et al. (2008) who suggested that the low HDL levels before and at early stage of ARV implementation may indicate the incomplete control of the process of inflammation [42-43]. In this respect, reduced HDL levels may be utilized as biomarker to reflect the degree of chronic inflammation. In the same line with this conclusion, HDL levels in ARV-treated HIV subjects in the current work, showed a significant positive correlation with the levels of CD4 ($P<0.017$), which means that HDL values get increased as the CD4 counts elevated. In addition, LDL/HDL ratio, which reflects the degree of the risk of atherogenesis, showed no significant change in the ARV-treated HIV group compared to ARV-Naïve subjects in the current study. This finding is in agreement with recent studies, which showed similar data and partly consistent with the MACS study which suggested that the high TC/HDL ratio and other lipid parameters occurred during the early stages of establishing ARV treatment [44, 45]. However, the current study is in contrast with the work of Nguemaïm et al. (2010),

who reported high atherogenic risk ratio (TC/HDL) in ARV-treated HIV compared to ARV-Naïve HIV subjects in Cameroon [46].

The current study showed an in increase in cholesterol, LDL and TG among untreated-HIV subjects the levels of these lipids were more elevated in ARV-treated HIV group, the mechanism that causes the elevation in these lipid parameters requires excessive research work to fully understand this mechanism. However, normal HDL and LDL/HDL risk ratio indicate a good prognosis of the patients in the present work. The present work is case control study. The present work does not investigate the serum levels of the subject before establishing ARV treatment and does not monitor the changes on lipid profile over different duration periods. Future work is needed to assess the effects of every treatment regimen upon lipid profile as well as assessing serum levels of TNF- α and IL-6 and measures of lipid peroxidation and antioxidant profile Although the current work has showed a link between HIV (ARV-treated and untreated) and lipid alterations but its nature as an observational study, it cannot confirm a causal relationship between the HIV infection, ARV-drugs induced dyslipidemia.

Conclusions

The levels of TC and LDL-C were higher in HIV positive subjects under ARVs regimens than the untreated HIV patients indicated a clear effect of ARV drugs upon lipid metabolism. The mechanism of the effects of ARV drugs upon lipid profile is not fully illustrated and require further investigation at the molecular levels. The current results showed non-significant alteration in the HDL-C and LDL/HDL risk ratio suggested a decreased risk for developing cardiovascular abnormalties among HIV subjects. The present study suggests that a routine checkup of the lipid profile should be established for monitoring the cardiovascular risk especially for patients who are on ARVs treatment.

Ethical Approval:

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

Consent

As per international standard or university standard, patient(s) written consent has been collected and preserved by the author(s).

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