DYSLIPIDEMIA IS A MAJOR SIDE EFFECT OF LONG-TERM ANTIRETROVIRAL THERAPY

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ABSTRACT

The aim of this study was to investigate the impact of different antiretroviral therapy on the lipid status of HIV patients with emphasis on modern-generation drugs. A cross-sectional study was conducted at Clinic for Infectious Diseases at the University Clinical Center Kragujevac and included forty-six patients with HIV infection on antiretroviral therapy for a minimum of twelve months. Lipid status parameters were analyzed in relation to the length of administration and the type of antiretroviral therapy used (integrase inhibitors or other antiretroviral therapy groups). The average duration of antiretroviral therapy intake ± standard deviation was 5.59 ± 3.649. Statistically significant higher values of low-density lipoprotein cholesterol were recorded after six years of antiretroviral therapy that does not belong to the group of integrase inhibitors compared to a period of less than three years ($p<0.05$). After six years of the administration of all groups of antiretroviral therapy, low-density lipoprotein cholesterol and total cholesterol values increase significantly compared to all other groups ($p<0,01$ and $p<0,05$, respectively). Patients on integrase inhibitors therapy compared to other antiretroviral therapy groups, show statistically significant higher total cholesterol values ($p<0,05$). Although low-density lipoprotein cholesterol values show a tendency to increase over time in both (integrase inhibitors and other antiretroviral therapy) groups, they do not differ, which means that integrase inhibitors do not have a greater impact on low-density lipoprotein cholesterol growth. Despite the use of modern-generation antiretroviral therapy, dyslipidemia is present in a significant percentage of HIV patients.

Keywords: *Dyslipidemia, HIV, antiretroviral therapy, INSTI.*

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INTRODUCTION

HIV continues to be a major global public health issue. In 2021, 650 000 people died from HIV-related causes and 1.5 million people acquired HIV. There were an estimated 38.4 million people living with HIV at the end of 2021 (1). Antiretroviral therapy (ART) is able to control HIV in most patients but not to cure the disease. Therefore, HIV remains in the reservoirs with potentially harmful effects and ART needs to be continuously given. Modern ART has significantly extended the life expectancy of those suffering from HIV infection and improved the quality of life. However, it has been observed that HIV-infected patients suffer from comorbidities such as cardiovascular disease, kidney disease, diabetes, and liver metabolic diseases at a much earlier age than the general population with possible deleterious consequences such as neurocognitive decline, frailty and multimorbidity.

First, a number of conditions, such as personal factors, family origin, age, and gender affect the level of lipid parameters. Studies have shown that HIV infection itself increases the risk of metabolic disorders independently of ART. Abnormal lipid levels have been reported early in ART-naive persons living with HIV (PLHIV) and are associated with the presence of acute infection. In contrast, other studies have shown that HIV infection and ART are equally represented in the development of metabolic disorders, which contributes to the development of non-AIDS comorbidities (2, 3). ART can induce raised levels of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and triglycerides (TG), as well as variable effects on high-density lipoprotein cholesterol (HDL-C) levels (4, 5, 6).

The first generation of ART, such as nucleoside analog reverse transcriptase inhibitors (NRTIs) and protease inhibitors (PIs) often caused dyslipidemia with metabolic consequences. The replacement of these molecules by newer ones, allowed to minimize the metabolic adverse effects of ART. But, contemporary ART as integrase inhibitors (INSTI) was recently also associated with weight and fat gain and possibly impaired glucose metabolism (7).

The mechanisms involved in causing metabolic disorders are poorly understood. Besides ART usage, HIV is still present in tissue reservoirs and has metabolic implications. Also, PLHIV receive several ART at a given time and have been often long-term exposure to a number of first-generation ART, with possible residual effects. ART adverse effects differ according to the class but also to the individual drug.

In addition, INSTI is at present the most used ART class, recommended in ART-naïve and ART-experienced PLHIV so the main goal is to understand the mechanisms involved in the INSTI effects on lipid profile.

MATERIALS AND METHODS

Our study was conducted in the Clinic for Infectious Diseases at the University Clinical Center Kragujevac. The study was approved by the Institutional Ethical Committee and it was in compliance with Helsinki Declaration.

The study was designed as cross-sectional and it included forty-six patients with proven HIV infection on ART for a minimum of twelve months who were treated at the Clinic for Infectious Diseases. Study data were collected from the outpatient clinic histories. The following variables were examined: age, gender, number of CD4 cells at the time of disease detection, viral load, type of ART, and length of ART usage. Laboratory values were obtained during routine outpatient examinations, from the blood sample, by standard laboratory tests. Biochemical parameters of lipid status - TC, TG, LDL-C and HDL-C were measured and presented in mmol per liter. Furthermore, the patients were divided into three groups in relation to the length of ART administration. The first group consisted of patients who used ART for less than three years, the second group of patients who took ART between three and six years, and the third group of patients who used ART for more than 6 years. Lipid status parameters were compared between these three groups of patients regardless of the type of ART therapy applied. After that, all the patients were divided into two groups depending on the type of ART therapy used and lipid status parameters were compared between groups. The first group included patients who used some of the drugs from the INSTI group. The second group included patients who used drugs from the other ART groups. Separately, the same comparison of lipid status parameters according to the length of ART use was conducted in patients who used only drugs from non-INSTI groups.

The software used for the analyses was SPSS version 26 (SPSS Inc, Chicago, IL). The study data were tested by descriptive statistics. Parameters of lipid status were presented by mean ± standard error. The other continuous variables were presented by mean ± standard deviation. Also, categorical variables were depicted with percentages.

The continuous variables were compared using the Independent samples t-test, One-way ANOVA or Mann-Whitney U test, and Wilcoxon's rank sum depending on the normality of distribution. P value was significant if less than 0.05.

RESULTS

Our study included forty-six PLHIV on ART. Out of them, 80.4% were men and 19.6% were women, while the mean age ± standard deviation was 41.85 ± 10.172. In relation to the initial CD lymphocyte count, the criteria for AIDS (CD4 lymphocyte count less than 200/mm^3) was fulfilled by 30.4% of patients, while the criteria for late presenters (CD4 lymphocyte count less than 350/mm3) were fulfilled by 54.3%. Viral load was determined in relation to the number of HIV copies detected with polymerase chain reaction

(PCR) in serum. Negative PCR was detected in 89.1% of patients, 40-100 copies per mm^3 of blood were detected in 6.5% and 400-500 copies were detected in 4.3%.

The average duration of ART intake ± standard deviation was 5.59 ± 3.649. There were 35.6% of patients who used ART for less than three years, 26.7% between three and six years, and 37.8% for more than 6 years. According to the type of applied ART, drugs from the INSTI group were used by 58.7% of patients (raltegravir frequency was 19.6% and lamivudine/abacavir/dolutegravir was 39.1%), and drugs from other ART groups were used by 41.3% of patients. Within the non-INSTI group, the frequency of tenofovir/emtricitabine was 26.1%, emtricatibine/tenofovir/rilpivirine was 30.4%, lamivudine-abacavir was 4.3%, darunavir/cobicistat was 8.7% and efavirenz was 2.2%.

In the group of patients who used only drugs from the non-INSTI group, statistically significant higher LDL-C values were observed after six years of drugs use compared to a period of fewer than three years (*Figure 1*). When we look at the lipogram parameters after six years of the administration of all groups of ART (INSTI and non-INSTI), LDL-C and TC values increase significantly compared to all other groups (*Figure 2*). Group of patients on INSTI therapy compared to other ART groups (non-INSTI), show statistically significant higher TC values in the INSTI group. Although LDL-C values show a tendency to increase over time in both groups, they do not differ, which means that INSTI does not have a greater impact on LDL-C growth compared to other ART therapy (*Figure 3*).

Other parameters of lipid status do not show significant differences during the years of follow-up.

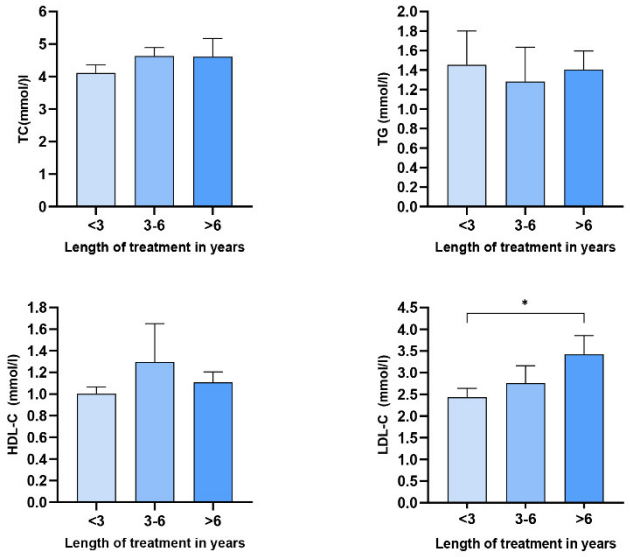

Figure 1. Values of lipid status parameters in three groups of patients according to the length of treatment with other (non-INSTI) ART. The values are presented as mean ± standard error of the mean (SEM), *denotes a significant difference p<0.05.

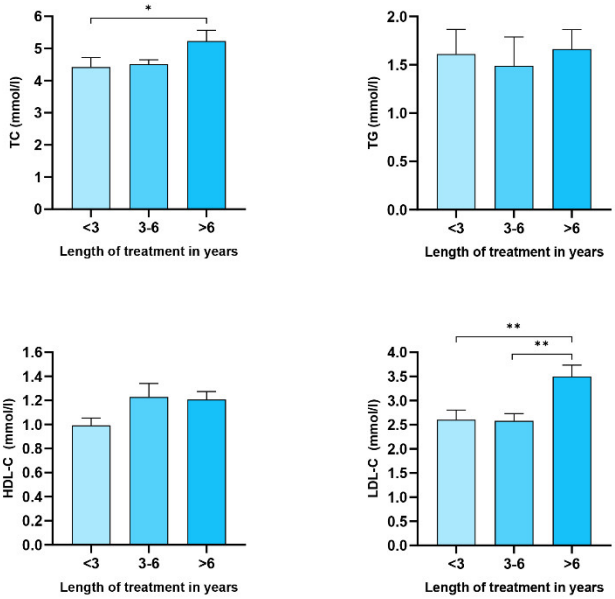

Figure 2. Values of lipid status parameters in three groups of patients according to the length of all ART administration (INSTI and non-INSTI group). The values are presented as mean ± standard error of the mean (SEM), *denotes a significant difference p<0.05, **denotes a significant difference p<0.01.

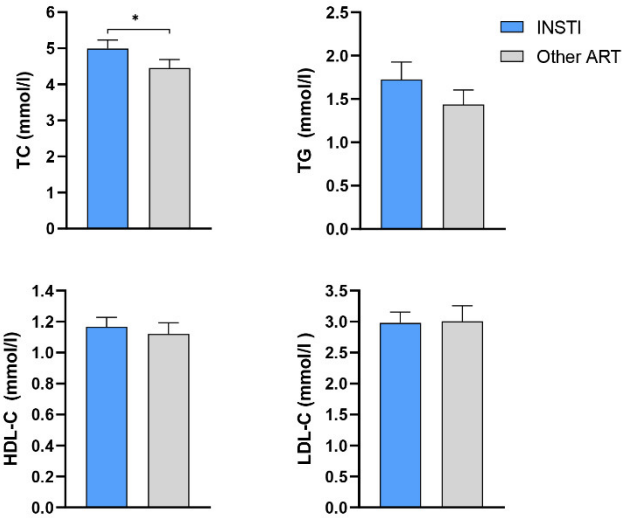

Figure 3. Values of lipid status parameters in relation to the type of ART applied. The values are presented as mean ± standard error of the mean (SEM), *denotes a significant difference p<0.05.

DISCUSSION

The occurrence of lipid disorders in people living with HIV is multifactorial. Previously, when ART was not available as it is today, various disorders of lipid metabolism were recorded in untreated patients (8).

It is considered that high viremia and low CD4 T lymphocytes have a significant influence on the occurrence of dyslipidemia in untreated persons with HIV (9). HIV interferes with the role of gut-associated lymphoid tissue, GALT because it depletes the residual Th 17 lymphocytes that are involved in the homeostasis of the intestinal epithelium. Therefore, microbial translocation is thought to be the main mechanism for immune activation and chronic inflammation (10). As a consequence of the direct effect of the virus, endothelial dysfunction occurs, which is characterized by a decrease in the anti-inflammatory and antithrombotic properties of the endothelium, an increase in the permeability of the endothelium, proinflammatory cytokines, and the expression of adhesion molecules. Due to the increased permeability of the endothelium and the transmigration of leukocytes, infiltrations rich in LDL-C occur, which represent the initial changes in arteriosclerosis, a process that is responsible for the development of cardiovascular comorbidities (3, 11).

Today, in the era of modern ART, the initiation of therapy occurs at the time of diagnosis, so lipid profile data in untreated patients are more difficult to obtain today. Determining the effect of a specific ART on the lipid profile is difficult because the therapy includes several drugs, and different classes of ART and different drugs within the class have a different effects on the lipid profile. In general, hyperlipidemia ranges from 28% to 80% according to different studies, which is consistent with the data in our research (12).

Initiation of ART treatment results in long-term viral suppression, reduction of inflammation, and immune reconstitution. However, it was found that the levels of cytokines in PLHIV on ART are similar to those of healthy controls, but who is older between 4 and 12 years, which indicates premature aging and the development of comorbidities (13).

The results of our research showed that the values of LDL-C and TC increase depending on the length of ART administration, which indicates its cumulative effect and the impact of ART on the occurrence of comorbidities. Traditionally, dyslipidemia was previously mostly associated with older drugs from the group of protease inhibitors, which were not included in our research, while only Darunavir was represented in 8.7% of respondents. Also, from the NNRTI group, only one patient recorded the presence of Efavirenz, while from this group, Rilpivirine was the most common. When we analyzed lipid profile values in the group of patients who did not have integrase inhibitors, the results showed that LDL-C values increased during the follow-up period. On the other hand, TC stood out in the INSTI group, as a parameter whose values increased over time, while INSTI did not show a negative impact on other lipid parameters. However, we cannot exclude an effect of previous therapies which may influence our results.

Examination of dyslipidemia in different classes of ART was a specifical subject of the RESPOND study on 4577 patients. Their results showed that dyslipidemia was less common with INSTI than with protease inhibitor. Compared with dolutegravir, dyslipidemia was more common with elvitegravir/cobicistat and raltegravir, but less common with rilpivirine (14).

It has already been described the association of INSTI, but also tenofovir-alafenamide (TAF), with weight gain, being higher compared to older groups of drugs (about 1 kg more in the first year) (15). Also, recent research has shown an increase in the risk of progression of steatosis in INSTI and TAF (16).

It is known that modern ART is much more potent than older groups of drugs and that it strongly suppresses viremia. Despite this, however, low levels of inflammation occur, affecting cholesterol transport and inducing pro-inflammatory changes in lipids, which lead to the development of arteriosclerosis and the occurrence of cardiovascular comorbidities, as well as increased mortality (12, 17).

CONCLUSIONS

Our results show that despite the use of modern-generation ART, dyslipidemia is present in a significant percentage of our patients. Dyslipidemia is involved in the development of the metabolic syndrome and represents a risk for the development of cardiovascular comorbidities, which today represent the most important cause of death in the group of non-AIDS diseases.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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