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Original Article

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The Effect of First- and Second-Line Antiretroviral Therapies on Lipid Profile of HIV/AIDS Patients

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Abstract

Background: There has been a significant decrease in HIV-related mortality following the introduction of antiretroviral therapies. This increase in life expectancy has caused an increased risk of cardiovascular and metabolic diseases. Lipid metabolism could be affected by the virus itself or antiretroviral medications. In this study, an attempt was made to investigate the effect of first- and second-line HIV medications on lipid profile in HIV/AIDS patients.

Methods: The present study is a retrospective cohort study. The medical records of 66 AIDS patients older than 18 years, who referred to the Behavioral Counseling Center of Imam Khomeini Hospital during the years 2009 to 2014, were retrieved. The patients were assigned into two groups including first- (36 patients) and second-line (30 patients) treatment groups. To ensure that the patients' baseline information was matched, demographic information and baseline lipid profile were compared between two groups and no significant difference was found between them. To examine and compare the effect of HIV medications on lipid metabolism, patients' lipid profile at the baseline and 6 months after treatment was compared.

Results: The results showed that only triglyceride level was significantly affected by the type of HIV medication regimen ($p<0.05$). It was significantly higher in second-line medication group**.** Although the lipid profile (Cholesterol, HDL, and LDL levels) showed an overall increase over the course of treatment in both groups, it was not statistically significant.

Conclusion: In both groups, following antiretroviral medications (the first-and second-line), lipid profiles increased. Moreover, the triglyceride level was higher in second-line medications. Therefore, early screening and lipid lowering agents should be considered in HIV/AIDS patients receiving the retroviral medications in long term to prevent further cardiovascular complications.

Keywords: Acquired immunodeficiency syndrome, Anti-retroviral agents, Cholesterol, HDL, HIV infections, Triglycerides

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Introduction

AIDS is the disease of chronic HIV infection and causes impaired cellular and humoral immune functions. The disease was first diagnosed in homosexual men in 1981. Ever since, more than 70 million people worldwide have been infected. Approximately 90% of infected people are living in developing countries and around 80% of them are infected through sex (1). In 2018, the Center for Disease Control of Iran reported a total number of 60000 people infected with HIV, of whom 15000 (25%) were female and 46000 (75%) were male (2). Most HIV infections (about 62%) occurred among injecting drug users (3).

There has been a significant decrease in HIV-related mortality following introduction of ARTs. There are currently five classes of ARTs used to treat HIV; the first group are nucleoside- and Nucleotide-analogue Reverse Transcriptase Inhibitors (NRTIs), the second group are Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs), the third group are Protease Inhibitors (PIs), the fourth group are Fusion Inhibitors (FIs), and the last group are Integrase Strand Transfer Inhibitors (INSTIs) (4). The oal of ARTs is to reduce the virus replication and thus improve the immune activity in order to delay the HIV progression. Highly Active Antiretroviral Therapy (HAART) is an HIV treatment regimen defined as the combination of three or more antiretroviral drugs. The main purpose of HAART is the co-administration of different types of antiretroviral drugs to inhibit the viral replication through several mechanisms so that propagation of a virus with resistance to a single agent becomes inhibited by the action of the other two agents (5-7). There are currently more than 30 different HAART regimens that are commonly used to control HIV, in dual or triple therapy (8). Introducing HAART in 1995 has significantly increased the life expectancy in HIV patients. This increase in life expectancy has caused an increased risk of cardiovascular and metabolic diseases (9).

HIV/AIDS-associated changes in lipid metabolism have been investigated in numerous studies. It has been shown that the lipid metabolism could alter due to infection with the immunodeficiency virus itself or following the Antiretroviral Therapies (ARTs) (10). Fat-burning diets and exercise can help improve lipid abnormalities in AIDS patients; however, the lipid lowering medications would be only necessary in severe cases of hyperlipidemia. The use of Protease Inhibitor drugs (PIs) in such patients is difficult due to the drug interaction, toxicity, and resistance (11). Due to the importance of hyperlipidemia and long term cardiovascular complications of ARTs in AIDS patients, and given the fact that these complications could be prevented by early diagnosis and prevention with lipid lowering agents (11,12), in the present study, an attempt was made to investigate the effect of first- and second-line HIV medications on lipid profile among AIDS patients.

Materials and Methods

The present study is a retrospective cohort study. The medical records of 88 patients older than 18 years referred to the Behavioral Counseling Center of Imam Khomeini Hospital between 2009 to 2014 were retrieved and reviewed. The patients were assigned into two groups including first- and second-line treatment groups (13) (Table1). Only the patients who received the ART medication for at least 6 months (66 patients) were included. The patients who had stopped taking Kaletra (Lopinavir/Ritonavir) or were diagnosed with hepatitis B or C (22 patients) were excluded. To ensure that the patients in two groups were matched before treatment, the demographic information and lipid profiles in both groups were compared at the baseline to confirm there was no significant difference between two groups. To evaluate the effect of ART on lipid profiles, patients' lipid profile before and after the treatment was compared. The SPSS® version 22 (IBM North America, New York, NY, USA) was used to analyze the data. The descriptive statistics were employed to report the mean, standard deviation, maximum, and minimum for patients' characteristics and lipid profile. Mann-Whitney U and Chi-squared tests were used to compare the lipid profiles between two groups. The significance level was set at 0.05.

Table 1. First- and second-line treatment (WHO recommendation for first- and second-line ART)

First-line treatment	Second line-treatment
Zidovudine	Lopinavir/Ritonavir
Lamivudine	Atazanavir/Ritonavir
Efavirenz	Tenofovir/Emtricitabine
Nevirapine	
Tenofovir	
Stavudine	

Results

A total of 66 patients with HIV/AIDS were studied. Of these, 36 received the first-line treatment and 30 received the second-line treatment. There was no significant difference in demographic characteristics and lipid profile between two groups at baseline (Table 2).

The patients' lipid profile at the baseline and six months after treatment initiation was compared to determine the effect of treatment on lipid metabolism. The lipid profile (Triglyceride, cholesterol, HDL, and LDL levels) apparently increased in both groups following 6months of treatment. The triglyceride level was significantly higher in patients undergoing second-line

Table 2. Demographic and baseline information of the patients

Variable	Minimum	Maximum	Mean	Standard deviation	p-value*
Age (year)					
First-line treatment	28	63	39.8	1.3	0.985
Second-line treatment	30	68	40.9	1.9	
Length of time with HIV					
First-line treatment	5	9	6.8	1.5	>0.999
Second-line treatment	4	10	6.3	1.9	
BMI					
First-line treatment	19.8	42.7	25.7	1.5	0.999
Second-line treatment	18.5	37.1	24.7	1.1	
CD4 count					
First-line treatment	117	922	403.2	35.3	0.281
Second-line treatment	24	1944	439.6	64.9	
Viral load					
First-line treatment	47	900	267.8	72.3	0.943
Second-line treatment	47	590	251.2	50.3	
Triglyceride					
First-line treatment	54	330	126.2	9.7	0.186
Second-line treatment	73	1247	206.93	42.2	
Cholesterol					
First-line treatment	82	265	159.7	6.8	0.338
Second- line treatment	109	308	172.6	8.7	
HDL					
First- line treatment	10	110	37.2	3.2	0.064
Second- line treatment	24	70	40.9	1.9	
LDL					
First- line treatment	43	218	92.1	6.4	0.469
Second- line treatment	17	148	92.2	5.9	

*Mann-Whitney U test

Table 2. (continued). Frequency of gender

Gender	First- line treatment	Second- line treatment	p-value*
Female	15	10	0.612
Male	21	20	

*Chi-squared test

treatment (Mean=285.1 SD=61.9) compared to first-line patients (Mean=149.2, SD=14.8); however, the cholesterol, HDL, and LDL levels did not show any significant differences between two groups after 6 months of treatment (Table 3).

Discussion

In this study, lipid levels (Triglyceride, cholesterol, HDL, and LDL) increased in both groups receiving antiretroviral therapy (both first- and second-line regimens) after 6 months of treatment initiation. Furthermore, the results indicated significant increase in triglyceride level in second-line group compared to first-line group over the course of treatment. The increase in triglyceride and cholesterol levels has been shown to be associated with an increase in cardiovascular events in HIV/AIDS patients, suggesting the need for early diagnosis and treatment with lipid lowering drugs to prevent such complications over the course of antiretroviral therapy. Therefore, the routine lipid check-up is recommended for HIV patients receiving antiretroviral therapy. In a similar study in Nigeria, the changes in serum lipid profile were reported among HIV-positive individuals receiving HAART. Although there were some improvements in lipid profile following ART, the overall trend showed abnormal values for lipid elements such as LDL and cholesterol after treatment (14). Similarly in our study, LDL level was significantly increased in HIV patients receiving ART. Another study in which the lipid levels of 50 HIV patients were assessed over the course of HIV infection, the results showed a significant decrease in mean serum cholesterol, even at the early stages of the disease, which is inconsistent with our study. Moreover, in CD4 >500, the HDL level decreased as the CD4 count dropped over the course of disease (15). In a study in Cameroon, the lipid profiles in HIV-positive individuals treated with antiretroviral drugs were assessed. Although the total cholesterol was lower in HIV patients receiving ART, it was not significant. This study found that HIV infection could cause a gradual increase in triglyceride and a progressive decrease in cholesterol, HDL, and LDL levels (16).

Changes observed in cholesterol metabolism in HIV patients may be explained by lipid peroxidation (17). These changes may have major impacts on immune system. Malnutrition can also produce fat-induced abnormalities associated with an increase in some cytokines. In addition, an increase in triglyceride appears to be associated with a decrease in the activity of hepatic lipase and lipoprotein lipase and studies have shown that the half-life of triglyceride-rich particles in AIDS patients is three times higher than in HIV patients. These disorders of triglyceride metabolism could explain the findings of our study. However, in some studies, the cholesterol level has

Table 3. Lipid profiles of patients 6 months after treatment

Variable	Minimum	Maximum	Mean	Standard deviation	p-value*
Triglyceride					
First- line treatment	57	393	149.2	14.8	0.019
Second- line treatment	60	1444	285.1	61.9	
Cholesterol					
First- line treatment	95	412	197.4	8.8	0.439
Second- line treatment	118	292	205.1	9.4	
HDL					
First- line treatment	18	90	49.4	2.4	0.282
Second- line treatment	26	87	52.0	2.8	
LDL					
First- line treatment	55	171	112.6	4.9	0.318
Second- line treatment	21	171	103.9	7.1	

*Mann-Whitney U test

been shown to decrease during viral infections (15,16). The mechanisms responsible for these changes have not been clearly understood. One suggested theory is that the large amounts of small LDL proteins activate macrophage deposition receptors that increase triglyceride synthesis and decrease triglyceride catabolism (decrease triglyceride degradation). Triglyceride level could elevate in HIV patients at the early stage of the disease. Previous studies have found that triglyceride level in patients with CD4<350 is significantly higher (18). The increase in serum triglyceride could also be due to the increase in low-density lipoprotein (VLDL) from the natural compound, which could be associated with an increase in hepatic fatty acids synthesis. A decrease in total cholesterol and HDL seems to occur before the triglyceride rise in the blood (16,19). Level of ApoA1, which is the main component of HDL and apoprotein B and a major LDL apoprotein, is low in HIV infection. It has also been shown that the decrease in cholesterol level, especially HDL, could occur long before elevation of triglycerides in HIV patients (16).

Parasitic, viral, and bacterial infections could disrupt the lipid metabolism by increasing triglyceride levels, especially during the acute phase of disease. In vitro studies have shown that a decrease in LDL and HDL levels could occur in the acute phase of viral diseases, even before triglyceride rise (16). Another study in which the researchers compared the lipid profiles of HIV/AIDS patients in different antiretroviral medication groups showed that the patients with HIV/AIDS who did not receive ART had higher level of triglyceride and lower level of total cholesterol and lipoprotein concentrations. Similar to our study, the researchers found that protease inhibitors, especially Indinavir and Lopinavir, are commonly associated with increased level of cholesterol, LDL, and triglycerides. On contrary, Atazanavir appeared to have more positive effects on lipid profile. Therefore, it seems that the HIV infection itself and the type of drug can exert distinct changes in lipid metabolism (20,21). Likewise in another study, one month regimen of Lopinavir/Ritonavir showed a significant decrease in LDL size (24.81 *vs*. 25.16 *nm*, p<0.05) and a significant increase in the level of cholesterol (5.53 *vs*. 4.49 *mmol/l*, p<0.001), and TG (4.20 *vs*. 2.01 *mmol/l*, p<0.001) (22). Another study suggested an increase in HDL cholesterol level and a decrease in triglyceride level with more exposure to NNRTI-based therapy, whereas triglyceride level could increase with more exposure to the PI-based therapy (23). These changes have been suggested to be due to some interactions between antiretroviral drugs (especially PIs) and lipid metabolism. The lipoprotein lipase and hepatic lipase are the two enzymes involved in lipoprotein–triglyceride removal and their levels could decrease in patients receiving PIs (24,25).

In another study, the effects of second- line HIV treatment such as Abacavir on lipid profile of 104 AIDS patients receiving HAART were assessed; after 28 weeks of treatment with Abacavir, there was a significant decrease in total cholesterol, LDL and triglyceride but there was no significant change in HDL (26) which contradicted our result. In another study, the lipid profile and liver enzymes of HIV infection and AIDS patients were evaluated to determine the relationship between changes in fat and liver proteins. Contrary to our findings, this study showed that the serum cholesterol and HDL levels could significantly be lower in HIV/AIDS patients compared to controls. On the other hand, triglyceride and Very Low Density Lipoprotein Cholesterol (VLDL-C) levels were significantly higher in HIV/AIDS patients compared to healthy controls (18). This study suggested the measurement of lipid profile and liver enzymes as a good indicator for disease progression in HIV infection. Considering the increased cholesterol level after initiation of ART treatment, assessment of lipid levels before and at least 6 months after initiation of treatment may be an effective measure in preventing hyperlipidemia and its complications among HIV/AIDS patients (18).

Conclusion

In this study, lipid profile (Triglyceride, cholesterol, HDL, and LDL levels) increased in both treatment groups following 6 months of ART medication. Furthermore, the triglyceride level was significantly higher in second-line group compared to the first-line group. This change in lipid profiles could address similar findings in HIV/AIDS patients receiving such treatment regimens. Furthermore, early screening and treatment for such lipid disorders are

strongly recommended in order to prevent premature cardiovascular diseases in HIV/AIDS patients.

Limitation

There were some shortcomings in the present study; the small number of HIV/AIDS patients in the present study could reduce generalizability of the results to other HIV infected population; however, our study suggested the similar changes in lipid profile for HIV/AIDs patients receiving ART medication. Furthermore, the potential effect of first- and second-line HIV medication was reported on lipid profile following 6 months of treatment which could address such changes over the course of different HIV treatment. Another limitation of the study was controlling the influencing factors on lipid profile, most importantly the diet and underlying diseases. Therefore, more rigorous prospective epidemiological studies, controlling all the confounding factors, should be conducted to evaluate the effect of different ART medications on lipid profiles in HIV/AIDS patients.

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Conflict of Interest

The authors declared no conflict of interests.

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