

Dyslipidaemia Associated with the Highly Active Antiretroviral Therapy in AIDS Patient: Reversion After Switching (Stavudine to Tenofovir and Lopinavir/Ritonavir to Atazanavir/Ritonavir)

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Antiretroviral therapy has been associated with hyperlipidemia in AIDS patients. This case illustrates the classic metabolic effects associated to the HAART including protease inhibitors and/or stavudine. It was showed that the management of the HAART-associated dyslipidaemia with conventional antihyperlipidemic therapy may fail, being the switching strategy the best option.

Key Words: AIDS, dyslipidaemia, switching strategy.

Highly active antiretroviral therapy (HAART), in combinations including protease inhibitors (PIs), has achieved sustained suppression of HIV replication and reduced morbidity and mortality rates in patients with advanced HIV infection [1].

Dyslipidaemia, which includes hypercholesterolemia, hypertriglyceridemia and mixed lipid disorders, is a disturbance frequently observed in persons with HIV infection. Many antiretroviral drugs induce changes in lipid profiles. Protease inhibitors (PIs) seem most consistently to affect lipid levels compared with other antiretroviral classes. However, elevation of cholesterol has been observed with the use of efavirenz and nucleoside reverse transcriptase inhibitors (NRTIs), such as stavudine [2].

Typically, the lipid profile of patients infected with HIV, who were receiving protease inhibitors, is characterized by the combined effects of the patient's underlying disease (HIV) and antiretroviral pharmacotherapy (protease inhibitors). Serum levels of total cholesterol, triglycerides and LDL-cholesterol are usually elevated, while HDL-cholesterol levels are often reduced [3,4].

Fat redistribution or lipodystrophy, hypertriglyceridemia, hypercholesterolemia, insulin resistance and diabetes mellitus have been extensively reported in subjects treated with protease inhibitor-based antiretroviral regimens. In particular, dyslipidaemia occurs in up to 70-80% of HIV-infected individuals receiving HAART and can be associated with all the available PIs, although hypertriglyceridemia seems to be more frequent in patients treated with ritonavir, ritonavir/saquinavir, or ritonavir/lopinavir. The potential long term consequences of HAART-associated hyperlipidemia are not completely understood, but an increased risk of premature coronary artery disease has been reported in young HIV-positive persons receiving PIs [5].

With regard to newer PIs, the real incidence of metabolic abnormalities has not been defined yet for amprenavir, whereas the occurrence of hyperlipidemia seems more frequent in subjects receiving a lopinavir/ritonavir-based treatment [6-8]. On the other hand, preliminary studies have shown that atazanavir, a novel azapeptide PI, is not associated with increase in total cholesterol, LDL cholesterol, or triglyceride serum levels [9].

Case Report

A 34 year-old man, diagnosed with AIDS on 25/08/1997. The HAART was initiated including zidovudine, lamivudine and didanosine, being maintained in normal limits the metabolic parameters: total cholesterol=130.0 mg/dL, HDL-cholesterol=40.8 mg/dL, LDL-cholesterol=65.4 mg/dL, triglycerides=119.0 mg/dL and glucose=93 mg/dL and the patient had CD₄ lymphocytes=103 cells/mm³ and viral load=400 copies/mm³.

The HAART was modified to stavudine, lamivudine and efavirenz on 31/08/2000, due to therapeutic failure, expressed by CD₄ lymphocytes=109 cells/mm³ and viral load=7,300 copies/mm³. There was increase of the total cholesterol=209.0 mg/dL, of the LDL-cholesterol=115.0 mg/dL, of the triglycerides=274.0 mg/dL, and of glucose=100 mg/dL.

On 16/07/2002, with CD₄ lymphocytes=64 cells/mm³ and viral load=68,000 copies/mm³, there was new modification in HAART, being switched efavirenz to lopinavir/ritonavir. The patient evolved with immunologic and virologic improvement (CD₄ lymphocytes=193 cell/mm³ and viral load=80 copies/mm³), however, there was significant worsening of metabolic parameters: total cholesterol=346.0 mg/dL, HDL-cholesterol=26.0 mg/dL, triglycerides=2,462.0 mg/dL and glucose=124 mg/dL.

It was prescribed antihyperlipidemic therapy (bezafibrate 400 mg/day) being observed the following results: total cholesterol=263.0 mg/dL, HDL-cholesterol=22.0 mg/dL, triglycerides=1,314.0 mg/dL and glucose=99 mg/dL.

Subsequent laboratory investigations, without bezafibrate, showed triglycerides and cholesterol levels of 4,152.0 mg/dL and 418.0 mg/dL, respectively. The abdominal ultrasonography showed hepatic steatosis.

Antihyperlipidemic therapy was initiated again, but with another fibrate, ciprofibrate 200 mg/day associated with

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Table 1. Metabolic and immunological parameters with different HAART regimens and different therapeutics approaches

HAART/Parameters	1 a.	2 a.	3 a.	4 a.	5 a.	6 a.	7 a.	8 a.
Total chol. (mg/dL)	130	209	346	263	418	270	126	193
HDL- chol. (mg/dL)	41	39	26	22	—	—	34	49
LDL- chol. (mg/dL)	65	115	—	—	—	—	79	96
Triglyc. (mg/dL)	119	274	2462	1314	4152	478	68	242
Glucose (mg/dL)	93	100	124	99	118	101	102	125
CD4 Lymph.(cell/mm ³)	103	109	193	—	268	—	213	—
Viral Load (copies/mm ³)	400	7300	80	—	750	—	290	—

HAART regimens and different phases of treatment:

1 a. phase: Zidovudine, lamivudine and didanosine. 2 a. phase: Stavudine, lamivudine and efavirenz. 3 a. phase: Stavudine, lamivudine and lopinavir/ritonavir. 4 a. phase: Stavudine, lamivudine, lopinavir/ritonavir and bezafibrate. 5 a. phase: Stavudine, lamivudine and lopinavir/ritonavir. 6 a. phase: Stavudine, lamivudine, lopinavir/ritonavir, ciprofibrate and nicotinic acid. 7 a. phase: Tenofovir, lamivudine, atazanavir/ritonavir and ciprofibrate. 8 a. phase: Tenofovir, lamivudine, atazanavir/ritonavir.

nicotinic acid 1,000 mg/day. The patient was followed for 3 months, however, the improvement of the metabolic abnormalities was partial: total cholesterol=270.0 mg/dL, triglycerides=478.0 mg/dL and glucose=101 mg/dL. In this phase of the HAART, CD₄ lymphocytes were 268 cells/mm³ and viral load was 750 copies/mm³.

Due to the difficulty to control the lipid levels, the HAART was modified again, switching from stavudine to tenofovir and lopinavir/ritonavir to atazanavir/ritonavir, on September 13, 2005. After 6 months, still using ciprofibrate 100 mg/day, the metabolic parameters evolved with significant improvement, being observed total cholesterol=126.0 mg/dL, HDL-cholesterol=34.0 mg/dL, LDL-cholesterol=79.0 mg/dL, triglycerides=68.0 mg/dL and glucose=102.0 mg/dL.

After 2 months, the patient was evaluated without ciprofibrate, and the metabolic parameters observed were: total cholesterol=193.0 mg/dL, HDL-cholesterol=49.0 mg/dL, LDL-cholesterol=95.6 mg/dL, triglycerides=242.0 mg/dL and glucose=125 mg/dL.

Discussion

The use of protease inhibitors (PIs) has been associated with hyperlipidemia, which is more common and more severe than the observed before the advent of the HAART [10].

More recently, higher triglycerides levels were reported in subjects taking stavudine, compared with tenofovir-based regimen. The evaluation and management of dyslipidaemia is based on the future risk of developing symptomatic coronary artery disease [2].

This case illustrates the classic metabolic effects associated to the HAART, including protease inhibitors and/or stavudine.

After lifestyle modifications and antihyperlipidemic therapy, no satisfactory results were obtained, without reaching total control of dyslipidaemia.

Antihyperlipidemic therapy frequently fails to return serum levels of total cholesterol and triglycerides to the normal limits. As such, coronary risks are likely to persist in a number of individuals with protease inhibitors-associated hyperlipidemia. Therefore, discontinuing

protease inhibitor therapy and replacing the offending agent with another less lipogenic medication may be beneficial in a number of patients [11].

It was demonstrated that the management of the dyslipidaemia associated to the HAART with conventional antihyperlipidemic therapy, pharmacologic and non pharmacologic, may fail, being the switching strategy the best option to these cases. It has the potential advantage of avoiding pharmacologic intervention for elevations in lipid levels [12].

Calza et al. found that the pharmacological treatment of the dyslipidaemia with pravastatin or bezafibrate associated to the permanence of the HAART had an antihyperlipidemic efficacy greater than the switching from the PI to nevirapina or efavirenz [13].

Switching from a PI to nevirapina or abacavir has generally resulted in an improvement in total cholesterol and triglycerides levels, whereas switching to efavirenz has produced less consistent results [14]. Studies of switches from stavudine to abacavir have yielded inconclusive results. These trials have generally demonstrated persistent viral suppression for 6-12 months after switching regimens [15-17].

Studies comparing the effects of treatment switching and the effects of adding lipid-lowering agents to ongoing successful therapy have not been reported. Clinicians will need to weigh the risks of new treatment-related toxicities and the possibility of virologic relapse when switching antiretroviral drugs. The risks of potential drug interactions and new treatment-related toxicities from lipid-lowering agents that are added to existing regimens must be evaluated too [10].

This case also demonstrates that many trials are necessary to show the best way to approach the patients with AIDS receiving HAART and presenting dyslipidaemia.

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