

Dyslipidemia in HIV-infected individuals

ABSTRACT

Metabolic complications continue to play a major role in the management of HIV infection. Dyslipidemia associated with HIV infection and with the use of combined antiretroviral therapy includes elevations in triglycerides, reduced high-density cholesterol, and variable increases in low-density and total cholesterol. The association between dyslipidemia and specific antiretroviral agents has been underscored. Multiple pathogenic mechanisms by which HIV and antiretroviral agents lead to dyslipidemia have been hypothesized, but they are still controversial. The potential clinical and pathological consequences of HIV-associated hyperlipidemia are not completely known, but several studies reported an increased risk of coronary artery disease in HIV-positive individuals receiving combined antiretroviral therapy. HIV-infected persons who have hyperlipidemia should be managed similarly to those without HIV infection in accordance with the National Cholesterol Education Program. Life style changes are the primary target. Statins and fibrates and/or modification in antiretroviral therapy are possible approaches to this problem.

Keywords: HIV/AIDS; dyslipidemia; combined antiretroviral therapy; nutrition, Public Health.

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INTRODUCTION

Combined antiretroviral therapy (cART) significantly modified the prognosis of individuals infected by the Human Immunodeficiency Virus-1 (HIV), with marked improvement in morbidity and mortality rates worldwide.¹⁻⁴ Nevertheless, several clinical aspects have been developed along with the longer longevity of HIV individuals, most of them related to other chronic conditions or to the antiretroviral treatment (ART).^{5,6} Metabolic abnormalities such as insulin resistance and disturbances in glucose homeostasis, modified adiposity physiology with lipids alterations might result in clinical complications including glucose intolerance or diabetes mellitus; altered body fat distribution, with lipoatrophy (loss of subcutaneous fat mostly in the face and periphery) or and lipohypertrophy (localized fat gain most often central and visceral adiposity).^{7,8}

Some of these perturbations can be associated with ART. Protease inhibitors (PI) show direct effect on human adipose and

specific effects on insulin resistance which may contribute to the overall adipose imbalance and development of lipodystrophy, and metabolic syndrome in HIV-positive individuals.⁷⁻⁹ In addition, nucleoside reverse transcriptase inhibitors (NRTIs) may induce mitochondrial dysfunction, which could result in effects on adipose tissue, lactic acidosis, myopathy, peripheral neuropathy, hepatic steatosis and pancreatitis as well.^{8,10,11} Although less involved, non-nucleoside reverse transcriptase inhibitors (NNRTIs), mainly efavirenz, might be associated with metabolic disorders, including dyslipidemia.^{7,12}

Those changes in metabolism and mitochondrial toxicity could eventually be associated with a greater chance of cardiovascular events and death.¹³⁻¹⁵ Although some association has already been elucidated, the relationship between antiretroviral drugs, metabolic syndrome, dyslipidemia, and cardiovascular events is still far from being fully clarified. The purpose of this review is

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to discuss the development of dyslipidemia and lipodystrophy, its relation to cardiovascular events, and its best management in individuals with HIV infection.

Overall body changes & lipodystrophy syndrome in HIV infection

These alterations taken together, named “lipodystrophy syndrome associated with HIV”, were first described in 1998 and included dyslipidemia, lipoatrophy, accumulation of centripetal intra-abdominal fat, and metabolic syndrome.⁷ The prevalence of the syndrome varies from 11% to 83% in the different studies already conducted.^{16,17}

Body changes are associated both with accumulation (lipohypertrophy) and/or with loss (lipoatrophy) in body fat. In the case of lipohypertrophy, it is possible to find increased abdominal circumference (omental, retroperitoneal, and mesenteric), increased breast size, and accumulation of fat in dorsocervical region (buffalo hump).^{7,15}

On the other hand, lipoatrophy, which is more related to nucleoside reverse transcriptase inhibitors (mainly thymidinic analogues, zidovudine - ZDV and stavudine - d4T), includes loss of subcutaneous fat in the gluteal region, arms and legs, along with vascular prominence in upper and lower limbs, decreased temporal and periorbital fat pad, and the appearance of nasolabial double fold.^{18,19}

These body habitus modifications are usually associated with alterations in plasma lipids and presence of metabolic syndrome. There may be an increase in total cholesterol and low-density lipoprotein (LDL-c) fraction, and triglycerides, which are clearly associated with pro-atherogenic profile.^{20,21}

Pathophysiology of dyslipidemia with and without cART

Lipids alterations, with increased triglycerides, due in part to decreased clearance of very low-density lipoprotein (VLDL-c) and the reduction of high-density lipoprotein (HDL-c) in circulation, were reported even before the use of antiretroviral drugs.²² Direct lipid changes related to HIV disease and/or inflammatory factors could partially explain these alterations, which could be exemplified by the fact that low CD4+ T-cell count might be considered a major atherosclerosis risk factor in HIV-infected individuals.^{22,23}

Generally speaking, PIs are associated with dyslipidemia, which is highest with ritonavir and boosted PIs.^{9,14,24} Several theories have been proposed to explain the contribution of PIs in dyslipidemia, although none of them explains all aspects. Carr *et al.*⁷ proposed a theory based on the finding of molecular structural

homology between the catalytic site of HIV protease and two human proteins involved in lipid metabolism, the protein binding of retinoic acid cytoplasmic type I (CRABP-1 - Cellular Retinoic Acid Binding Protein 1) and protein related to the receptor for low-density lipoprotein (LDL-R). Therefore, most PIs would inhibit steps of lipid metabolism, probably depending on the gene expression of the involved receptor. PI connected to CRABP-1 would decrease the activation of the receptor of 9-cis retinoic acid and dimerization with the receptor activated by the peroxisome proliferator γ (PPAR γ - Peroxisome Proliferator Activated Receptor-gamma), which has a key role in the differentiation of adipocytes and apoptosis of these cells, and further improves the peripheral sensitivity to insulin. Such changes would lead to the release of lipids into the circulation and hyperlipidemia.

Another proposed mechanism is the inhibition of the activity of the plasmatic lipoproteic lipase by PI, which binds to the LDL-R. The difficulty in capturing the chylomicron and the hepatic clearance of triglycerides by complex endothelial lipoprotein lipase-LRP, in turn, would mean a lower uptake by the liver and triglycerides by cleavage of the fatty acids in glycerol. However, this hypothesis has yet to be confirmed.²⁵

In the same way factors that could increase the activity of the protein link to the sterol regulatory element 1 (SREBP-1 - Sterol Regulatory Element Binding Protein 1) might lead to increased lipogenesis and increased production of VLDL-c. Experiments done in animals with ritonavir showed marked increase of VLDL-c in the presence of a diet rich in fat, and a significant increase in the levels of liver apolipoprotein B (Apo B).²⁶ Therefore, the increase in triglycerides caused by ritonavir could be related to the enhancement in the production of hepatic lipoprotein, by inhibiting the proteasome-mediated degradation of Apo B and SREBP-1 in the liver.²⁷

Similarly, genetic predisposition may explain, in part, the variability between patients in relation to the effects of PIs on the metabolism of lipids. Most individuals when exposed to ritonavir may have significant increases in plasma levels of triglycerides, while in others this elevation does not occur.^{28,29} However, the genes involved in these phenomena are not yet known.

Generally, PIs (except atazanavir) seem to inhibit the function of GLUT-4 in the transport of glucose, which reduces the uptake of glucose mediated by insulin in skeletal muscles and in adipocytes, which can lead to changes in lipid metabolism.^{9,30,31}

PI can also induce insulin resistance by the inhibition of translocation of SREBP-1c, directly or indirectly via PPAR γ receiver.³² SREBP-1 regulates the growth and synthesis of glucose, differentiation and maturation of adi-

pocytes and increased glucose through the adipocytes. The process of adipocyte differentiation may increase the synthesis and secretion of adiponectin, a cytokine that sensitizes insulin action.³³ Since PPAR γ is preferentially expressed in peripheral adipocytes, it is expected that the inhibition of protein carrier of retinoic acid by the PIs could result in apoptosis and damaged differentiation of adipocytes contributing to the development of changes in the fat distribution and insulin resistance.³⁴

Furthermore, the class of NRTIs can also be associated with the development of dyslipidemia and insulin resistance and their consequences, as already explained. The NRTIs (mainly the thymidine analogues, d4T and ZDV) reduce the synthesis of mitochondrial DNA by inhibiting DNA polymerase gamma.³⁵ As a result there is a depletion of mitochondrial DNA, enzyme deficiency, oxidative phosphorylation and induction of subcutaneous adipocytes apoptosis.^{10,11,36}

Atherosclerotic disease in HIV infection and AIDS

Many studies have demonstrated an association between cART and increased risk in coronary events when compared to the general population, which may be related to dyslipidemia and to the duration of cART exposure.^{13,14,37,38} The largest study of cardiovascular epidemiology in HIV-infected individuals on cART is the Data Collection on Adverse Effects of Anti-Retroviral Drugs (D:A:D), a multicohort study. D:A:D has shown an increased relative risk of acute myocardial infarction of 1.26 (26% more) per year of exposure to cART in the first four to six years, and the recent use (up to 6 months) of abacavir, didanosine, lopinavir or indinavir were independently associated with increased risk.^{13,14,38} It is important to consider that traditional risks, such as tobacco smoking, dyslipidemia, diabetes and hypertension, were also increased in these studies. In order to estimate the 10-year cardiovascular risk in relation to the time of cART exposure, the Framingham score was evaluated in D:A:D participants.⁴⁰ With the caveat that Framingham scores could under evaluate the coronary risk in HIV-infected individuals, this study showed that the chance for first cardiovascular event increased with time of exposure to ART (relative risk per year of exposure: 1.26, 95%, CI: 1.15 to 1.38).

There is only one major study that found no difference in cardiovascular disease in HIV-infected individuals on cART.³⁹ Although controversial, this was a retrospective analysis of 36,766 HIV-infected individuals on cART, between 1993 and 2001, with respect to overall mortality, mortality for specific cardiovascular and cerebrovascular events, and rates of hospitalization. Hospital admissions for cardiovascular and brain diseases and

the fatality rate decreased (1.7% to 0.9%, 21.3% to 5.0% from 1995 to 2001, respectively). However, the study sites were known to not offer good cardiovascular care, which could lead to a selection bias in the study. Also, it has been noticed that the prescription of lipid reducing agents gradually increased over the time.

In the Study of Strategies for Addressing the Anti-Retroviral Therapy (SMART), individuals were randomized to continue cART or to temporarily interrupt their treatment when the CD4 cell count was higher than 350 cells/mm³ and for restarting when it had fallen to less than 250 cells/mm³.⁴¹ This study was stopped prematurely by the high incidence of adverse outcomes including fatal and non-fatal cardiovascular events in the group with cART interruption. Given the general impression that cART is associated with increased risk of cardiovascular disease, it would be expected to see a reduction of these events. However, the relative risk of these complications was 1.5 times greater in the group of patients discontinuing cART compared to the group that remained on therapy. This reinforces the hypothesis in which HIV itself is considered an independent risk factor for cardiovascular disease.

Incidence of dyslipidemia in HIV infection and AIDS

Before cART, the main metabolic alteration was related to wasting, with protein-energy malnutrition, characterized by depletion of lean mass and fat. Unfavorable changes in lipid profile, with reduction in the levels of HDL-c and mild elevation in the levels of triglycerides, also occurred in advanced disease because of changes in inflammatory cytokines, phenomenon also found in other chronic inflammatory disorders not caused by HIV.²²

Unfortunately, as already mentioned, cART can be associated with the development of dyslipidemia. The abnormalities in lipid profile generally occur after the beginning of ART, frequently between the third and sixth month, but its emergence may be early in regimens containing PIs.^{9,42,43} The prevalence of dyslipidemia in HIV-infected individuals on cART varies from 30% to 80% depending on drug combination and diagnostic definition criteria, and the most common include hypertriglyceridemia (40% to 80%), and hypercholesterolemia (10% to 50%).^{16,24,44}

Changes in lifestyle and dyslipidemia in HIV infection and AIDS

Scientific evidence about the effectiveness of diet indicates that a limited energy intake from simple sugars and fats, the replacement of saturated fat and trans unsaturated fat by the increased consumption of fruits, vegeta-

bles, whole cereals, and nuts confer significant benefits for the health of general population. Epidemiological surveys have shown the synergistic effect of changes in lifestyle, such as “healthy” diet that provide a “shield” against the development of several non-transmissible chronic diseases, including cardiovascular disease, hypertension, diabetes mellitus, obesity and dyslipidemia in the non-HIV population.^{46,47} Although epidemiological surveys have not yet been conducted among HIV-infected individuals, most studies support changes in lifestyle as a major goal to be addressed.⁴⁸⁻⁵⁵ Also, as expected, better results were achieved in individuals with adherence to diet modifications.

Our group assessed the impact of physical conditioning and diet on low levels of lipids in HIV-infected individuals with dyslipidemia and lipodystrophy. Although of short duration and dealing primarily with aerobic exercise and therapeutic intervention, there was no consistent changes in plasma lipids.⁴⁹ Fitch *et al.*, evaluated whether changes in lifestyle could have beneficial effect on cardiovascular risk factors in patients on HAART and manifestations of the metabolic syndrome. After six months, despite improvement in the physical condition, diet habit and abdominal circumference in the group that changed the way of life, there was no significant improvement in plasma lipids compared to the control group.⁵⁰

The amount of fiber, alcohol and fat in diet may play an important role in dyslipidemia associated with HIV.⁵⁰⁻⁵⁵ Some components of diet, such as saturated, monounsaturated and polyunsaturated fat, fiber and alcohol, were directly linked to insulin resistance and hypercholesterolemia, whereas diet rich in fiber was inversely associated.^{51,52} Also, high amounts of alcohol were linked to high levels of LDL. These associations were independent of age, sex, distribution of body fat and time of exposure to PIs.

Barrios *et al.* prospectively evaluated the effectiveness of a low-fat diet in the reduction of cholesterol and triglycerides in 230 HIV-infected individuals. Those with good adherence to diet had a reduction of 11% and 10% in the levels of cholesterol and in 12% and 23% in the levels of triglycerides after 3 and 6 months, respectively. Adherence to diet was also associated with significant weight loss. The impact on the abovementioned metabolic parameters was more noticeable among individuals on PIs and after 6 months (cholesterol decreased 13% and 22% and triglycerides 15% and 49% at 6 and 6 months, respectively).⁵⁴

The management of HIV-infected individuals with dyslipidemia needs to be validated, specified and individualized. Currently, the recommendations of the Adult AIDS Clinical Trials Group (ACTG), based on the NCEP,

must be followed for the prevention and management of dyslipidemia associated with cART. These guidelines are primarily directed towards a healthy way of life, with physical activity and a balanced diet,²⁴ but this approach is empiric as there is no sufficient clinical evidence to support it.

Omega 3 and dyslipidemia in the acquired immunodeficiency syndrome

It is known that omega 3 (fish oil) is associated with a reduction in cardiovascular events in general population.⁵⁶ Diet supplementation with omega 3 and exercise were compared in HIV-infected patients who had triglyceride levels greater than 200 mg/dL. After 16 weeks of follow-up, there was no significant difference in the levels of triglycerides between groups. However, LDL-c levels did significantly increase in the fish oil arm, but not in the diet and exercise arm (22% versus 18%, respectively).⁵⁷

Gerber *et al.* randomized 100 patients with hypertriglyceridemia on cART to receive fenofibrate or fish oil for eight weeks. Of 47 subjects on fish oil, 4 (8.5%) and of 48 on fenofibrate, 8 (16.7%) achieved TG < 200 mg/dL.⁵⁹ When both interventions were offered to individuals who have not responded, 22% more reached target levels of triglycerides. As observed in the other study, there was an increment of LDL-c.^{57,58}

Another study also demonstrated the benefits of polyunsaturated fatty acids omega 3 (PUFA) in HIV-infected individuals with triglyceride levels above 300 mg/dL. In the eighth week, patients who received PUFA showed an average reduction of 25% in the levels of triglycerides compared to a 1% increase in those who received the paraffin oil ($p = 0.0033$). In this study, nutritional guidance was also significantly important to reduce triglycerides.⁵⁹

Hypolipemiant drugs in HIV infection and AIDS

Drug therapy becomes necessary when changes in lifestyle are not effective in reducing lipid level.²⁴ Statins are the agents of choice (to reduce total cholesterol and LDL-c) and fibrates (to reduce triglycerides levels), especially gemfibrozil, fenofibrate and bezafibrate.^{24,60-74} In extreme condition, the association of both classes could be tried. However, these should be avoided as they could be associated with adverse effects, potential drug interactions, adherence problems and increased treatment costs.

There are few data from clinical trials with the use of statins in HIV-infected individuals. Most statins are metabolized by the cytochrome P450, isoenzyme 3A4 (CYP3A4), which is inhibited by most PIs. This could lead to an increase in serum levels of the statin and

higher chance to adverse effects. Some statins are not recommended and others are considered safe to use along with cART.^{24,60} Simvastatin and lovastatin, which are highly metabolized by CYP3A4, are contraindicated; atorvastatin and rosuvastatin can be used with caution; and although with the lowest potency, pravastatin and fluvastatin could be more safely used, as they are mostly not metabolized by CYP3A4 isoenzyme.^{24,61}

Henry *et al.* investigated the effect of atorvastatin and gemfibrozil compared to diet and exercise in HIV-positive individuals with hypertriglyceridemia. Diet and exercise decreased the levels of total cholesterol and triglycerides in 11% and 21% respectively, while gemfibrozil in combination with atorvastatin reduced the levels of total cholesterol and triglycerides by 30% and 60% respectively.⁴⁷ Similarly, Miller *et al.* showed that gemfibrozil and diet (low saturated fat) decreased serum levels of triglycerides in 120 mg/dL, when compared to diet ($p = 0.08$).⁶³

To evaluate the effectiveness of fibrates (bezafibrate, gemfibrozil and fenofibrate) and statins (pravastatin and fluvastatin) in the management of hyperlipidemia associated with the administration of PI-based cART, Calza *et al.* followed 288 dislipidemic individuals submitted to diet and physical activity. At the end of at least three months, 61% of the subjects responded to diet, and 106 (39%) in whom lipid levels did not decrease, were randomized to either one hypolipemiant drug. Individuals treated with fibrates had a reduction of 41% and 23%, in the levels of triglycerides and total cholesterol, respectively, after six months of treatment, and 41% and 22% in one year (LDL-c decreased by 23% and HDL-c increased by 20%). In the statin group there was a 36% and 27% reduction of triglycerides and total cholesterol after 6 months, and 34% and 25% after one year (LDL-c reduced by 26% and HDL-c increased by 24%).⁶⁰

Recently the effectiveness of switching PIs for NNRTI (nevirapine or efavirenz) or hypolipemiant (statin and fibrate) was evaluated in 138 patients during 12 months.⁶⁴ At the end of follow-up, there was a reduction in the levels of triglycerides by 25% in the group with nevirapine, 9% in the group with efavirenz, 41% with pravastatin and 47% with bezafibrate, which favoured hypolipemiant. Similar results were found with respect of total cholesterol and LDL-c. This study showed that in mixed hyperlipidemia associated with cART and non-responsive to changes in lifestyle, treatment with a statin or a fibrate was more effective than switching PIs for NNRTIs.

A Brazilian study assessed the behavior of lipid profile before and after treatment with bezafibrate in 84 subjects with persistent hypertriglyceridemia that was not controlled with diet only. There was a significant

reduction in levels of triglycerides (from 640 mg/dL to 372 mg/dL, $p < 0.0001$) and total cholesterol (from 253 mg/dL to 228 mg/dL, $p < 0.01$).⁶⁵

In order to evaluate the effect of new drugs for lowering lipids not entirely metabolized by CYP3A4 in HIV-positive population, Calza *et al.* administered 10 mg/day of rosuvastatin in 16 patients with hypertriglyceridemia that were taking lopinavir/ritonavir. After 24 weeks there was an average reduction in the levels of total cholesterol and triglycerides of 21.7% and 30.1% respectively.⁶⁴ Similarly, Van der Lee *et al.* found a reduction in the levels of total cholesterol and LDL-C, 27.6% and 31.8%, respectively (the levels of rosuvastatin were 1.6 times higher when compared with healthy volunteers).⁶⁶ In both studies the drug was considered relatively safe.

Palacios *et al.* evaluated the efficacy and safety of atorvastatin 10 mg for the treatment of hypercholesterolemia in 20 patients using antiretroviral therapy for at least 12 months. Atorvastatin was safe and effective with a significant reduction in the levels of total cholesterol and LDL-c after 24 weeks of follow-up.⁶⁷

Ezetimibe can be as effective as fluvastatin to reduce LDL-c⁶⁹ and can have additive effect on lipids when administered along with other hypolipemiant drug.^{69,70,75}

On the basis of all relevant published data, we have prepared a concise, evidence-based update of the current understanding of the clinical presentation. Tables 1 and 2 summarize results of trials conducted to treat dyslipidemia. Although less effective than hypolipemiant agents, sometimes could be easier to change ART due to problems with adherence, risk of interactions and/or increasing toxicity.⁷⁶⁻⁸⁰

Management of dyslipidemia in HIV-positive individuals

In summary, treatment guidelines for the management of dyslipidemia in these patients are the same as those recommended for the general population.²⁴ Life style modification is the primary and first target of treatment. Drug treatment for dyslipidemia in HIV-infected persons on cART can be complex, given the possible drug interactions, toxicity, intolerance, and even impair adherence. There is strong enough evidence to support the use of fibrates to treat hypertriglyceridemia. They are relatively safe and not associated with major side effects. They also can decrease to some extent cholesterol level as well. On the other hand, hypercholesterolemia drug management is not so simple. Statins, the preferred drug class to decrease cholesterol, might be associated with side effects and drug interaction which could interfere to cART treatment. While fluvastatin and pravastatin are safe, although not very effective, simvastatin and lovastatin are contraindicated in individuals on

Table 1. Summary of trials that evaluated hypolipidemic therapy in individuals with dyslipidemia on cART

Study	Type of intervention	Design (total n)	Length of trial	Interventions (n) and comparisons (n)	Dyslipidemia	Statistically significant results showing change(s) in lipid parameter(s)	Type of analysis
Calza 2002 ⁷¹	Hypolipidemic therapy PI-based antiretroviral therapy	Randomized, prospective study (69 patients)	12 months	Bezafibrate 400mg (25) vs Gemfibrozil 600mg (22) vs Fenofibrate 200mg (22)	TG > 300 mg/dL TC > 250 mg/dL	All patients ↓ TG 41 % ↓ TC 22 % ↓ LDL-C 22.5 % ↑ HDL-C 20 %	On-treatment
Miller 2002 ⁷²	Diet and hypolipidaemic therapy PI	Randomized Double-blind	16 weeks*	Gemfibrozil 600 mg (17) vs placebo (20)	TG ≥ 265.8 mg/dL	→ Gemfibrozil ↓ TG 19% ↓ TC 3% ↑ HDL-C 11% Placebo → ↑ TG 7% ↓ TC 3% ↑ HDL-C 8%	Intention to treat
Palacios 2002 ⁶⁷	Hypolipidaemic therapy cART	No randomized	24 weeks	Atorvastatin 10 mg (20)	TC > 240 mg/dL, with or without high triglycerides	Atorvastatina → ↓ TG 41 % ↓ TC 27 % ↓ LDL-C 37 % ↑ HDL-C 4 %	No serious adverse side effects
Calza 2003 ⁶⁰	Hypolipidaemic therapy PI-based antiretroviral therapy	Open-label, randomized, prospective study (106 patients)	12 months	Bezafibrate 400mg (25) vs Gemfibrozil 600mg (22) vs Fenofibrate 200mg (22) vs Pravastatin 20 mg (19) vs Fluvastatin 20 mg (18)	TG > 300 mg/dL TC > 290 mg/dL	Fibrato → ↓ TG 41 % ↓ TC 22 % ↓ LDL-C 22.5 % ↑ HDL-C 20 % Statins → ↓ TG 35 % ↓ TC 25 % ↓ LDL-C 26 % ↑ HDL-C 24 %	On-treatment Statins and fibrates revealed a similar, significant efficacy in the treatment of diet-resistant hyperlipidaemia

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Badiou 2004 ^{##73}	Hypolipidemic therapy NRTI NNRTI PI	Randomized	3 months*	Fenofibrate 200 mg (18) vs Vitamin E 500 mg (18)	TG ≥ 180 mg/dL	Fenofibrate ↓ TG 40% ↓ TC 14% ↑ HDL-C 15% ↓ LDL-C 14% Vitamin E: no significant changes	Fenofibrate increases LDL size and enhances LDL resistance to oxidation. Vitamin E supplementation only improves LDL resistance to oxidation.
Mallon 2006 ⁷⁴	Hypolipidemic therapy PI-containing therapy	Randomized placebo-controlled (33 patients)	16 weeks	Pravastatin 40 mg (16) vs placebo (17)	TC > 250 mg/dL	Pravastatin ↑ TG 4 % ↓ TC 8 % ↑ HDL-C 2 % Placebo ↑ TG 5 % ↓ TC 5 % ↑ HDL-C 0 %	Intention to treat No significant between-group difference
Negredo 2006 ⁷⁵	Hypolipiaemic therapy PI → 62.5% NNRTI → 60%	Prospective Open-label One-arm (19 patients)	24 weeks	Ezetimibe 10 mg added to pravastatin 20 mg	LDL-C ≥ 130 mg/dL use of pravastatin 20 mg	Ezetimibe ↓ LDL-C 61.5%	61.5% of patients achieved the endpoint of the study (LDL-C < 130 mg/dL)

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Coll 2006 ⁶⁸	Hypolipidemic therapy NNRTI or PI	Randomized (20 patients)	6 weeks	Ezetimibe 10 mg (10) vs Fluvastatin 80 mg (10)	LDL-C \geq 130 mg/dL	Ezetimibe ↓ TC 10% ↓ LDL-C 20% Fluvastatin ↓ TC 17% ↓ LDL-C 24%	Ezetimibe monotherapy effectively decreases LDL-cholesterol in HIV-infected patients
Bennett 2007 ⁷⁰	Hypolipidemic therapy PI → 24 NNRTIs → 25 NRTIs → 29 TZD → 1 No ART → 1	Retrospective	More than 4 weeks	Standard lipid lowering therapy added to Ezetimibe 10 mg (33) Pravastatin → 2 Rosuvastatin → 15 Atorvastatin → 7 Fenofibrate → 17 Niacin → 2 Salmon oil → 4	TC > 200 mg/dL LDL-C > 135 mg/dL	Ezetimibe ↓ TG 34 % ↓ TC 21 % ↓ LDL-C 35 % ↑ HDL-C 8 %	Univariate analysis was used to compare the differences between the and post treatment using the Wilcoxon rank sum test for paired non-parametric samples. No adverse events.

Legend: * Calza 2002: bezafibrate (400 mg qd of its long-acting formulation), gemfibrozil (600 mg bid) or fenofibrate (200 mg qd). ** Miller 2002: Including 4 weeks of pre-treatment diet. # Calza 2003: bezafibrate (400 mg qd of its long-acting formulation), gemfibrozil (600 mg twice a day), fenofibrate (200 mg qd), pravastatin (20 mg qd), or fluvastatin (20 mg qd). ## Badiou 2004: Fenofibrate (200 mg/day)¹⁸ and/or Vitamin E (500 mg/day)¹⁸ for a first period of 3 months and the association of both for an additional 3-month period.

Table 2. Summary of trials that analyzed antiretroviral switch to treat dyslipidemia

Study	Type of intervention	Design (total n)	Duration of trial	Interventions (persons) and comparisons (persons)	Dyslipidemia	Statistically significant results showing change(s) in lipid parameter(s)	Type of analysis
Negredo 2002 ⁶⁹	Antiretroviral substitution	Randomized trial	24 weeks	NVP (16) vs PI-continuation (18)	TC ≥ 200 mg/dL LDL-C ≥ 130 mg/dL TG ≥ 200 mg/dL HDL-C ≤ 35 mg/dL	NVP → ↓ TC 8.3% ↓ LDL 14% ↑ HDL 20% PI-continuation → no significant changes	Presumed intention to treat (as no dropouts)
	PI → NVP						
	PI → PI-continuation						
Martinez 2003 ⁴² NEFA Study	Antiretroviral substitution	Randomized	12 months	Abacavir (149) vs Efavirenz (156) vs Nevirapine (155)		TG → not significantly different TG < 400 mg/dL ABC → 4% NVP → 12% EFV → 13% TC and TC < 240 mg → significantly lower in the ABC group	Intention to treat
	PI → ABC						
	PI → EFV						
Fisac 2005 ^{**76} Substudy (LipNEFA)	Antiretroviral substitution	Randomized	24 months	Abacavir (29) vs Efavirenz (32) vs Nevirapine (29)		ABC → ↓ TC 14% ↓ Non-HDL-C 10% EFV → ↑ HDL-C 115% ↓ TC/HDL-C 14% ↓ Non-HDL-C 11% NVP → ↑ HDL-C 21% ↓ TC:HDL ratio 19%	Intention to treat
	PI → ABC						
	PI → EFV						
	PI → NVP						

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Keiser 2005 ⁷⁷	Antiretroviral substitution PI → ABC PI → PI-continuation	Pilot study Randomized Open-label (104 patients)	28 weeks	Abacavir (52) vs PI-continuation (52)	TC > 200 mg/dL	ABC → ↓ TC 42 mg/dL ↓ LDL-C 14 mg/dL ↓ TG 134 mg/dL ↑ HDL-C 0,2 mg/dL PI-continuation → significantly with proportion of patients maintaining HIV-1 RNA <400 or <50 copies/mL	Intention to treat Abacavir switch and PI-continuation arms did not differ
Calza 2005 ⁶³	Antiretroviral Substitution PI → NVP PI → EFV PI + pravastatin PI + bezafibrate	Randomized Open-label	12 months	NVP (29) vs EFV (34) vs Pravastatin 20 mg (36) Bezafibrate 400 mg (31)	Mixed hyperlipidaemia	NVP → ↓ TG 25.2% ↓ TC 27.1% ↓ LDL-C 25.2% ↑ HDL-C 3.1% EFV → ↓ TG 9.4% ↓ TC 10.2% ↓ LDL-C 8.7% ↑ HDL-C 1.9% Pravastatin → ↓ TG 41.2% ↓ TC 45.8% ↓ LDL-C 39.6% ↑ HDL-C 10.2% Bezafibrate → ↓ TG 46.6% ↓ TC 37.6% ↓ LDL-C 35.1% ↑ HDL-C 7.7%	Intention to treat Hypolipidemic therapy proved significantly more effective in the management of cART-related hyperlipidaemia than the switching therapy from PI to nevirapine or efavirenz.

Table 2. Summary of trials that analyzed antiretroviral switch to treat dyslipidemia

Study	Type of intervention	Design (total n)	Duration of trial	Interventions (persons) and comparisons (persons)	Dyslipidemia	Statistically significant results showing change(s) in lipid parameter(s)	Type of analysis
Moyle 2006 ⁷⁸	Antiretroviral Substitution AZT or d4T → TDF AZT or d4T → ABC	Randomized Open-label (105 patients)	48 weeks	TDF (52) vs ABC (53)	Evident moderate to severe lipoatrophy	TDF → ↓ TG 16.5% ↓ TC 8% ↓ LDL-C 8% ↓ HDL-C 8.5% ABC → ↑ TG 4% ↑ TC 4% ↑ LDL-C 3% ↑ HDL-C 0.8%	Intention to treat TDF may have modest advantages over abacavir for changes in lipids
Libre 2006 ⁷⁹	Antiretroviral Substitution d4T → TDF	Prospective Open-label (352 patients)	48 weeks	TDF (352)	TC > 220 mg/dL TG > 200 mg/dL	TDF → ↓ TC 8.5% ↓ LDL-C 6% ↓ TG 18% ↓ HDL-C 2%	The substitution of tenofovir for stavudine causes a sustained improvement of dyslipidaemia.
Milinkovic 2007 ⁸⁰	Antiretroviral Substitution d4T 40 mg → d4T 40 mg d4T 40 mg → d4T 30 mg d4T 40 mg → TF	Randomized (58 patients)	24 weeks	d4T 40 (22) vs d4T 30 (19) vs TDF (17)	d4T 40 → ↑ TG 19 mg/dL ↑ TC 22 mg/dL d4T 30 → ↓ TG 23 mg/dL ↓ TC 4 mg/dL TDF → ↓ TG 79 mg/dL ↓ TC 28 mg/dL	Both strategies were associated with a trend toward a decrease in plasma lipids, the only significant changes were observed among those who switched to tenofovir	

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cART which includes PI and/or ritonavir (risk of severe adverse event). The statin plasma levels are highly increased when used along with these agents. The other statins atorvastatin and rosuvastatin have better therapeutic index; they are more efficacious and could be more safely used. Conversely, the non-nucleosides efavirenz, and nevirapine can induce CYP3A4, which would decrease the statin levels. Therefore, the statin dose should be titrated in order to achieve the desirable target. Therefore, we still need to develop more friendly and safe antiretroviral drugs while a cure is not yet found to HIV infection.

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