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High-Risk Dysmetabolism Disorders Associated with HAART-Treated HIV Disease, and Reimbursement of Lipid-Lowering Drugs, in a Clinical and a Socio-Economic Perspective

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Abstract

The significant advances achieved in the management of HIV disease, thanks to highly active antiretroviral therapy, are at risk of being frustrated by the recent changes in the cost reimbursement rules for all lipid-lowering drugs available in Italy. Unfortunately, the remarkably increased life expectancy achieved since mid-1996 by HIV-infected persons after the introduction of protease inhibitors and combined anti-HIV treatment, is accompanied by significant risks of developing diet-uncontrolled hypercholesterolemia and/or hypertriglyceridemia, often concurrent with insulin resistance, visceral adiposity, and hypertension, all known factors which can strongly predispose to severe cardiovascular events. International and national health care system recommendations regarding the reimbursability of lipid-lowering drugs have to take into careful consideration of this "special" category of patients (HIV-infected ones). These patients are exposed to a very frequent and severe, drug-induced dyslipidemia, and a subsequently elevated and progressively increasing cardiovascular risk, despite their proportionally lower mean age compared with that of the general at-risk population, and the lack of many concurrent risk factors which are employed to calculate the strict need for a lipid-lowering therapy, and its consequent cost reimbursement by the different health care systems. **(AIDS Reviews 2005;7:155-60)**

Key words

Antiretroviral therapy. HIV-associated dyslipidemia. Risk of cardiovascular events. Lipid-lowering drugs. Prescription. Reimbursement. Health care systems.

The background: HIV infection, antiretroviral therapy, metabolic alterations, dyslipidemia and related risks, and efficacy of lipid-lowering therapy in this setting

The introduction of highly active antiretroviral therapy (HAART) has remarkably changed the natural history of human HIV infection, leading to a dramatic improvement in the survival of HIV-infected patients. However, a broad range of clinical and laboratory disturbances of lipid and glucose metabolism have been increasingly recognized after the introduction of potent antiretroviral combinations[1-7]. Dyslipidemia may involve up to 70-80% of HIV-infected patients treated with protease inhibitor-based antiretroviral therapy, and includes hypertriglyceridemia in the majority of cases (60-100% of treated patients), followed by hypercholesterolemia (10-50% of subjects undergoing HAART), while hyperinsulinemia and hyperglycemia are less frequently reported (5-20% of cases)[8-12]. Even though elevated plasma lipid levels have been associated with all the available protease inhibitors, hypertriglyceridemia seems more frequent in patients treated with ritonavir and lopinavir/ritonavir combination regimens, and may sometimes be severe, reaching very elevated levels

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(over 1000 mg/dl). Hypercholesterolemia has also been observed in subjects treated with all the available protease inhibitors. As a whole, hyperlipidemia tends to be most severe with ritonavir and lopinavir/ritonavir; amprenavir and nelfinavir tend to have intermediate effects, whereas indinavir and saquinavir tend to show less evident effects. On the other hand, the recently approved protease inhibitor atazanavir seems to have the most favorable impact on lipid metabolism[11-16]. Furthermore, some antiretroviral compounds belonging to a different class (i.e. efavirenz, among the non-nucleoside reverse transcriptase inhibitors), also seem to be responsible for a persisting or even worsening serum lipid profile, either in patients who were pretreated by protease inhibitors, or even in antiretroviral-naive subjects[17,18].

Since the HAART availability has led to a notable extension of life expectancy in HIV-positive patients, possibly until an advanced age[19,20], prolonged and uncontrolled hyperlipidemia could significantly impact on the long-term prognosis and outcome of these persons, so that a serious concern is mounting about the increased risk of cardiovascular and other hyperlipidemia-related complications. Literature evidence clearly shows that increased plasma lipid levels are associated with higher low-density lipoprotein (LDL) cholesterol concentrations and atherogenic tendency, and the clinical consequences are unfortunately demonstrated by the increased risk of myocardial infarction and cerebrovascular events in HAART-treated patients in comparison with the general population[16,21-24], and this phenomenon is expected to rise, paralleling the increase of patients' lifespan[19,20].

The potential clinicopathologic consequences of HIV-associated dyslipidemia are not completely known, but several anecdotal observations and some case series report an increased risk of premature coronary artery disease and myocardial infarction in young HIV-infected individuals treated with HAART, as well as peripheral atherosclerosis, pancreatic enzyme abnormalities and acute pancreatitis, and cutaneous xanthomas[25-33]. Most protease inhibitors are associated with rapid, marked, and sustained increases in serum lipid levels that are consistent with a significantly increased 10-year risk for coronary disease, as determined in the Framingham Heart Study[16,24]. Insulin resistance syndrome, hypercholesterolemia, hypertriglyceridemia, low levels of HDL cholesterol, and truncal (visceral) adiposity are known to significantly increase the cardiovascular risk in HIV-negative populations, and may similarly predispose HIV-infected subjects to accelerated cardiovascular events[24,29-35]. The concerns about the long-term risk of coronary artery disease from these lipid metabolism disorders have been recently confirmed by the "DAD" study[22]. In this prospective, observational trial involving 23,468 HIV-positive patients from 11 different cohorts, Friis-Möller, et al. showed that HAART administration was associated with a 26% relative increase in the rate of myocardial infarction per year of exposure during the first 4-6 years of treatment, although the absolute event rate was proportionally low (as described by an incidence of 3.5 events per 1000 person-years), and must be balanced against the expected HAART benefits[22].

Although hypolipidemic diet and physical exercise may partially act against dyslipidemia, modification of HAART regimens (excluding the protease inhibitors), or the administration of lipid-lowering drugs (such as statins, and/or fibrates, and/or omega-3 fatty acids), must be considered when plasma lipid levels remain significantly increased, or dyslipidemia persists for three months or more. A simplification of the HAART regimen in patients with stable immunologic/virologic condition by switching from protease inhibitors to other drug classes usually leads to a significant decrease in plasma lipid levels, but the risk of anti-HIV treatment failure is higher when patients had previously received suboptimal anti-HIV therapies, or were not completely virologically suppressed[36,37]. On the other hand, a lipid-lowering pharmacologic treatment is advisable when a simplified anti-HIV therapy is not applicable or fails, and when serum lipid concentrations are excessively increased, or dyslipidemia tends to persist for many consecutive months. Our recent data of a randomized trial clearly show that hypolipidemic drugs (either statins or fibrates) act significantly better on serum lipid profiles compared with simplified therapy (towards efavirenz or nevirapine), in patients who abandon a protease inhibitor-based HAART (Calza L, Manfredi R, et al., unpublished observation). Unfortunately, the choice of hypolipidemic drugs is often influenced by adjunctive problems due to the expected drug-drug interactions with antiretroviral compounds and other eventual underlying pharmacologic treatments, increased toxicity, and decreased patient adherence caused by the need to administer multiple concomitant pharmacologic regimens[4,6,7,12,16,38]. Consequently, it is reasonable to recommend the use of statins as first-line treatment of hypercholesterolemia: in particular, pravastatin or low-dosage atorvastatin are suggested, while the use of fluvastatin (characterized by a slightly lower efficacy) may be considered as a

second-line regimen. On the contrary, simvastatin and lovastatin should be avoided because of their increased risk of pharmacologic interactions with protease inhibitors[12,39-44]. On the other hand, fibrates represent the cornerstone of drug therapy for hypertriglyceridemia and mixed hyperlipidemia. Treatment with gemfibrozil, bezafibrate or fenofibrate generally results in a significant reduction in triglyceride and also cholesterol levels in HIV-infected patients who receive a protease inhibitor-containing HAART, with a more evident improvement of hypertriglyceridemia[7,40,42]. Recent data demonstrate an additive effect for the statin/fibrate combination therapy: however, this association should only be used with great caution and very careful monitoring because of the known increased risk of skeletal muscle toxicity[12,16,25-27,41,45], which can be concurrently prompted by HIV itself and underlying diseases and treatments[45]. A recent pilot study of ours demonstrated the activity of omega-3 polyunsaturated fatty acids on HAART-associated moderate hypertriglyceridemia[47]. These compounds, although being less effective than fibrates, act significantly better than an isolated dietary-exercise program, are completely safe, do not have any kind of drug-drug interactions in the field of HIV infection, and may be very useful in treating the most frequent mixed dyslipidemia with predominant hypertriglyceridemia, by a safe association of a statin and omega-3 polyunsaturated fatty acids[47].

Dyslipidemia, cardiovascular risk prevention, and lipid-lowering drugs: an international scenario

Recent, authoritative commentaries underlined the major risk of cardiovascular events in HIV-infected patients with a severely and long-term altered serum lipid profile[16,24].

When considering the general population, the dyslipidemia-related rise of cardiovascular risk is well acknowledged, and a number of recommendations and guidelines have been proposed on national or international grounds (i.e. NCEP ATP III for the USA, those of the European Joint Task Force, the Helsinki Heart Study, the Scandinavian ASCOT and 4S studies for Europe, and many others), to identify patients at risk of primary or relapsing cardiovascular events, to establish prescription rules, and to make a rational use of lipid-lowering drugs. These recommendations have been drawn from extensive population studies aimed at identifying the broad spectrum of risk factors, and multiple, extensive, randomized, clinical trials involving pharmacologic and non-pharmacologic strategies to correct or contain dyslipidemia as a major risk factor of atherogenesis[45,48-54]. Further investigations underlined the positive impact of pharmacologic recommendations in different clinical settings (i.e. ATP-III, EURO-ASPIRE II, L-TAP, and many others), and also omega-3 fatty acids have been shown to play a significant role in the prophylaxis of cardiovascular disorders, although protection seems greater for patients who had already suffered a cardiovascular event[51].

However, management practices and attitudes may have very different geographic patterns, as demonstrated by a survey which compared two very different European regions (Sicily, Italy and Stockholm, Sweden), and detected an unexpectedly different predisposition to testing lipids and prescribing lipid-lowering drugs, which proved to be earlier in Italy compared to Sweden[55]. Different strategies and interpretations may also occur among physicians in the same country, thus creating both physicians' and patients' uncertainty about these therapeutic recommendations and their practical application[48,52,56].

However, drug-related costs are perceived as a factor limiting prescriptions, drug acceptance and compliance by patients in multiple surveys[48,52,57], in Italy too[49], especially when patients have no rights to rely on for a reimbursement of the cost of these lipid lowering drugs.

Prescription policies of lipid-lowering drugs, and their potentially severe implications in the management of HIV disease treated with combination antiretrovirals

While from a strictly pharmacoeconomic point of view it could be advisable to limit the free prescription of lipid-lowering agents only to ascertained high-risk subjects[58], this sudden restriction of the free availability of these drugs will force the majority of treated, HIV-infected patients to limit or interrupt their treatment, due to increased expenditures and the frequently limited income of patients living with HIV[59]; most of them are unemployed drug addicts or former drug addicts, homeless, and immigrants, who usually lack money for their daily life[8]. Furthermore, when considering the very elevated costs of antiretroviral drugs and the entire management of HIV infection[59], the adjunctive expenses for an eventual lipid-lowering therapy are much more contained. At our hospital, the cheapest HAART combination is lamivudine-stavudine-indinavir

Table 1. Recommendations for selecting lipid-lowering therapy in HIV-infected patients undergoing HAART. Strength of recommendation and quality of clinical evidence are indicated in parentheses (adapted from Dubé, et al.)[12]. As mentioned above, unfortunately the majority of treated patients suffer from a mixed hyperlipidemia, which often should deserve dual therapy. Moreover, niacin is not available in Italy

Dyslipidemia	First-choice therapy	Alternative therapy	Drugs and dosages
Elevated LDL-cholesterol (or non-HDL cholesterol), with triglycerides < 500 mg/dl	Statin (B-I)	Fibrate (C-I), or niacin (C-III)	– Pravastatin (20-40 mg/day) (A-I) – Atorvastatin (10 mg/day) (B-II) – Fluvastatin (20-40 mg/day) B-II)
Elevated triglycerides (> 500 mg/dl)	Fibrate (B-I)	Niacin (C-III), or fish oil (C-III)	– Gemfibrozil (600 mg bid) – Fenofibrate (200 mg/day) – Bezafibrate (400 mg/day)

(15.7 Euros/day in 2004), while the most costly regimen is zidovudine-lamivudine-lopinavir/ritonavir (25.8 Euros/day, in the same time period) (R. Manfredi, S. Sabbatani, unpublished data, 2005). In comparison, the most used statin (pravastatin 20 mg/day) is expected to cost around 1.33 Euros/day, while the most prescribed fibrate (bezafibrate 400 mg/day) has a very low cost, of about 0.31 Euros/day, compared with omega-3 fatty acids (administered at 1 g twice daily), which cost 2.19 Euros/day. As a matter of fact, the majority of regulations regarding the prescription of lipid-lowering drugs to the general population appear very restrictive in the setting of HIV disease, especially when delicate and life-threatening conditions like cardiovascular diseases are of concern, and life-long treatments to be fully paid by the large majority of patients living with HIV are expected. The formulation of these novel guidelines took into account only studies enforced by very hard end-points, such as the development of a major vascular accident and/or related death, and not only favorable laboratory end-points (such as the lipid lowering effect), so that primary prevention of cardiovascular events is now limited to very high-risk patients, in favor of secondary prophylaxis.

Furthermore, when taking into account a larger series of variables, including the completely altered prognosis of HIV disease (from a life-threatening disease borne by prolonged hospitalization and extremely elevated morbidity and mortality), the "socially and economically accepted" cost of HAART and laboratory monitoring of HIV disease (including periodic check of T-cell subsets, HIV viral load, HIV resistance testing, and in the future, also therapeutic drug monitoring)[8,59], and when considering the well-known medical and socio-economic costs of cardiovascular accidents[48-50], there is no doubt that some intervention to make lipid-lowering drugs easily accessible to HIV-infected patients with elevated, HAART-induced dyslipidemia who do not match the most strict guidelines, such as the recent and deeply discussed Italian update carried out in November 2004[61,62], should be done as soon as possible. Finally, the only updated recommendations for HIV-associated dyslipidemia formulated by Dubé, et al.[12], and summarized in table 1, cannot be fulfilled in the majority of Italian patients (who are forced to give up payment prescriptions), with all the expected consequences on mid- and long-term cardiovascular health. The novel Italian prescription guidelines for lipid-lowering agents[61,62] actually exclude the great majority of our patients from free availability, since their proportionally low mean age and the frequent absence of diabetes mellitus, systolic hypertension, and antihypertensive drug use (compared with the general population with hyperlipidemia), give an estimated risk of a major cardiovascular event < 20% at 10 years. Moreover, the great majority of subjects on HAART need a primary prevention, since the secondary one considers less than 1% of followed patients in our experience[4,40,42,60]. As a matter of fact, until November 2004 both fibrates and statins were prescribed for free to patients with familial dyslipidemia, and hyperlipidemia not responsive to dietary suggestions, and with a high risk of a first or a repeated major cardiovascular event (as established by specialist reference centers). Moreover, omega-3 fatty acids were completely reimbursed to all patients with hypertriglyceridemia not responsive to diet and exercise, as a means of primary and secondary prophylaxis of cardiovascular events. Starting from end-November, 2004, the prescription rules for all available lipid-lowering compounds significantly changed[60,61]. From a practical point of view, all lipid-lowering drugs are now completely reimbursed only to patients with genetically ascertained familiar hyperlipidemia (which represents a very rare event), while diet-

resistant hypercholesterolemia gives the right to a free prescription of statins only when a documented coronary disease, diabetes mellitus, or a previous cardiovascular event occurred, or on the grounds of a very elevated (≥ 20%) risk of a major cardiovascular event within 10 years is foreseen, based on a calculation including patient's gender, age, cigarette smoking, systolic blood pressure, total and HDL serum cholesterol levels, confirmed diabetes mellitus, and ongoing antihypertensive therapy[60,61]. When considering diet-resistant hypertriglyceridemia, only an ascertained familial background or a prior cardiovascular event make prescriptions of fibrates and omega-3 fatty acids reimbursable for the general population, without any exception for special patient groups[60,61]. Unfortunately, the Italian Committee did not take into account the emerging problem of HIV-infected patients, whose HAART-related increased life expectancy becomes seriously threatened by persistent, high-level dyslipidemia and dysmetabolism[1-7], with the unavoidable, connected cardiovascular events and other complications such as pancreatitis[16,21-24,33].

In conclusion, the prescription rules of lipid-lowering agents urgently needs a rapid, uniformly agreed, and effective reevaluation by competent organisms, which have to take into careful account the special, risky situation of patients living with HIV, who have disease progression blocked by a cost-effective HAART, but are at a very increased risk of seeing their life expectancy seriously limited by major cardiovascular events and other disorders prompted by persistently elevated serum lipid levels, in the absence of primary pharmacologic prevention with active drugs.

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