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Dyslipidemia and lipid management in HIV-infected patients

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Abstract

Purpose of review—Dyslipidemia is highly prevalent among patients living with chronic HIV infection and may confer increased risk of cardiovascular disease in this patient population. This review summarizes recent data investigating lipid abnormalities and its management in HIV-infected patients.

Recent findings—Studies in the last year have evaluated the effects of various lipid-lowering therapies not previously investigated in the HIV patient population. Rosuvastatin is a potent statin that appears to be well tolerated and effective in HIV-infected patients with hypercholesterolemia.

Summary—Dyslipidemia is common in HIV-infected individuals. Medical therapy of lipid disorders needs to take potential drug–drug interactions of lipid-lowering medications and antiretroviral agents into consideration.

Keywords

cardiovascular risk factors; HIV; lipids

Introduction

The scope of this review focuses on the effect of HIV infection and its treatment on lipids as well as the management of lipid disorders in HIV patients. Guidelines for the evaluation and management of dyslipidemia in HIV-infected adults and recommendations from the Infectious Disease Society of American and the Adult AIDS Clinical Trials Group were published in 2003 [1]. Emphasis in this review will be placed on studies published within the last 12–18 months.

Epidemiology

Antiretroviral therapy has greatly improved the survival of HIV-infected patients [2] living today; however, the mortality rates in HIV patients are still higher than in the general population and the proportion of deaths due to non-HIV-related causes including cardiovascular disease are rising [3,4]. Cardiovascular disease is an increasing health problem affecting HIV-infected patients [5,6]. Dyslipidemia is highly prevalent among patients with HIV infection with and without antiretroviral therapy and can contribute to the increased cardiovascular disease risk in this patient population [7,8]. In the Data Collection on Adverse Events of Anti-HIV Drugs (DAD) cohort of 23 468 HIV-infected patients, the investigators found that higher total serum cholesterol, triglycerides and presence of diabetes were associated with an increased incidence of myocardial infarction [9]. Patients with HIV

have increased traditional cardiovascular risk factors including dyslipidemia, smoking, and glucose abnormalities [7,10]. Even in childhood, HIV-infected children receiving antiretroviral therapy were found to have higher total cholesterol and triglycerides, and increased carotid intima-media thickness; thus cardiovascular risk may be heightened among HIV patients even at a young age [11].

Because of the connection of lipid abnormalities to cardiovascular disease, the understanding of the pathophysiology of the disorders in lipid metabolism and the management of lipid disorders in this patient population is important.

Dyslipidemia in HIV patients

HIV infection and its treatment are associated with abnormalities in lipid metabolism. Before the availability of highly active antiretroviral therapy, Grunfeld *et al.* [8] found that patients with AIDS had elevated plasma triglyceride and free fatty acid levels whereas HIV-infected patients without AIDS had decreased total cholesterol and HDL-cholesterol. In the Multicenter AIDS Cohort Study (MACS) cohort, total cholesterol, HDL-cholesterol, and LDL-cholesterol levels declined following HIV seroconversion [12]. In these patients, total cholesterol and LDL-cholesterol levels rose but HDL-cholesterol remained decreased after initiation of highly active antiretroviral therapy. In the Swiss HIV Cohort Study, HIV protease inhibitor use was found to be associated with increases in plasma total cholesterol and triglycerides [13]. Discontinuation of antiretroviral therapy in the SMART study resulted in a decline in total cholesterol and LDL-cholesterol, but HDL-cholesterol declined as well, leading to an unfavorable increase in the total/HDL-cholesterol ratio [14].

Recently, Duprez *et al.* [15] showed that cardiovascular risk in HIV patients was associated with lower levels of small and large HDL-particle concentration independently of other cardiovascular risk factors. Patients with HIV-associated fat redistribution are even more likely to have dyslipidemia, possibly related to excess visceral adipose tissue accumulation [16]. Among patients with HIV-associated lipodystrophy, Hadigan *et al.* [17] found the LDL mean particle size to be less than 20.5 nm and therefore exhibiting a proatherogenic pattern.

Evaluation and treatment of dyslipidemia in HIV patients

Guidelines and recommendations for the evaluation and management of dyslipidemia in HIV-infected adults put forth by the Infectious Disease Society of America (IDSA) and the Adult AIDS Clinical Trials Group (ACTG) in 2003 [1] support the use of the updated recommendations from the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults [Adult Treatment Panel III (ATP III)] [18,19]. Of note, since the IDSA/ACTG Guidelines were written, a more recent update has been published for the NCEP ATP III Guidelines in 2004 [20] that should be taken into consideration when relevant. In addition, several studies relevant to the treatment of dyslipidemia in HIV-infected patients were published since the IDSA/ACTG Guidelines were published in 2003 and will be presented in the current review.

As recommended in the NCEP ATP III and IDSA/ACTG Guidelines, lifestyle counseling on diet and exercise should generally be instituted first. Other modifiable cardiovascular risk factors such as smoking, hypertension and diabetes mellitus should also be addressed. When medications become necessary, then identification of the lipid abnormality needs to be made and the choice of therapy should target the specific abnormality. Silverberg *et al.* [21*] found that lipid-lowering therapies are generally well tolerated in HIV-infected patients but hypertriglyceridemia can be more difficult to treat in HIV-infected patients compared to non-HIV-infected patients.

HMG-CoA reductase inhibitors (statins)

HMG-CoA reductase inhibitors (statins) should be used for elevated LDL-cholesterol or when triglyceride levels are 200–500 mg/dl [1]. Pravastatin and atorvastatin are the statins of choice recommended by the IDSA in HIV patients [1]. Protease inhibitors are inhibitors of cytochrome P450 CYP3A4 and therefore can raise concentrations of many statins, except for pravastatin, fluvastatin and rosuvastatin which are not metabolized by CYP3A4. Simvastatin and lovastatin are contraindicated in patients taking protease inhibitors as they are administered as inactive lactone prodrugs which are metabolized by CYP3A4. Fichtenbaum *et al.* [22] demonstrated 30-fold increase in the median 24-h area under the curve of simvastatin in healthy volunteers treated with ritonavir plus saquinavir. Although pravastatin has generally been thought to be safe in HIV patients, more recently, a drug–drug interaction study demonstrated that concomitant administration of pravastatin with HIV-1 integrase inhibitor raltegravir in healthy volunteers can result in increased concentrations of raltegravir but the investigators thought that this was not likely to be of clinical significance [23]. More recently, an open-label, randomized trial comparing rosuvastatin 10 mg/day to pravastatin 40 mg/day showed that rosuvastatin was more effective in lowering LDL-cholesterol and triglycerides in HIV-infected adults treated with antiretroviral therapy containing ritonavir-boosted protease inhibitors [24*]. As rosuvastatin is the most potent statin currently available and is not metabolized by CYP3A4, it may be a good choice for HIV patients with hypercholesterolemia when they may need a potent statin. Principles for monitoring for statin-related side-effects in the general population should also be followed for HIV patients.

Ezetimibe

When the IDSA/ACTG Guidelines were first published, no data were yet available on the use of ezetimibe, a cholesterol absorption inhibitor, in HIV patients. Since that time, multiple studies have demonstrated that ezetimibe is safe to use in HIV patients and is effective in lowering LDL-cholesterol as monotherapy or in conjunction with statins [25–27].

Fibric acid derivatives and fish oil

Fibric acid derivatives should be considered for patients with triglyceride levels more than 500 mg/dl [1]. If both LDL-cholesterol and triglyceride elevations are present, in an AIDS Clinical Trials Group study (ACTG 5087), Aberg *et al.* [28] found that if triglycerides and LDL-cholesterol were both elevated, then treatment of hypertriglyceridemia first with fenofibrate and then dual therapy with additional pravastatin achieved greater lipid-lowering benefit. In HIV patients on highly active antiretroviral therapy with serum triglyceride concentrations of at least 400 mg/dl and LDL-cholesterol of 160 mg/dl or less participating in another AIDS Clinical Trials Group study (ACTG A5186), fish oil 3 g twice a day decreased triglyceride levels by a median of 283 mg/dl (46%), fenofibrate decreased triglyceride levels by 367 mg/dl (58%), and combination therapy decreased triglyceride levels even further by 65.5% [29]. The combination of fish oil and fenofibrate was well tolerated in the study.

Niacin

For low HDL-cholesterol, niacin can increase HDL-cholesterol but it commonly causes flushing and can cause insulin resistance as well as affect glycemic control in diabetic patients; thus it should be used with caution in HIV patients who may already exhibit insulin resistance or have lipodystrophy. Recently, short-term administration of niacin has been

shown to improve endothelial function in HIV-infected patients with low HDL-cholesterol in a pilot study [30].

Conclusion

Dyslipidemia in HIV patients may contribute to their increased risk of cardiovascular disease. The identification and treatment of lipid abnormalities are important in HIV patients as they are modifiable cardiovascular risk factors. Current guidelines used for the general population including the NCEP ATP III Guidelines as well as the IDSA/ACTG Guidelines for the evaluation and management of lipid disorders in HIV patients can be used to help guide therapy. Lifestyle counseling on diet and exercise should be emphasized in every patient with dyslipidemia. Special consideration to potential drug–drug interactions need to be taken when lipid-lowering therapy is initiated in patients with HIV.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
 - of outstanding interest
- Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 163).
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Key points

- Dyslipidemia is common among HIV-infected patients and can be caused by HIV infection itself or antiretroviral medications.
- Guidelines for the evaluation and treatment of dyslipidemia from the IDSA/ACTG as well as the NCEP ATP III should be considered in each HIV-infected patient with lipid abnormalities to help guide therapy.
- Potential drug–drug interactions between lipid-lowering agents and antiretroviral medications need to be considered when initiating treatment of lipid disorders in the HIV patient population.