

Guidelines for the Evaluation and Management of Dyslipidemia in Human Immunodeficiency Virus (HIV)–Infected Adults Receiving Antiretroviral Therapy: Recommendations of the HIV Medicine Association of the Infectious Disease Society of America and the Adult AIDS Clinical Trials Group

Michael P. Dubé,¹ James H. Stein,² Judith A. Aberg,³ Carl J. Fichtenbaum,⁴ John G. Gerber,⁶ Karen T. Tashima,⁷ W. Keith Henry,⁸ Judith S. Currier,⁹ Dennis Sprecher,⁵ and Marshall J. Glesby,¹⁰ for the Adult AIDS Clinical Trials Group Cardiovascular Subcommittee

¹Indiana University, Indianapolis; ²University of Wisconsin, Madison; ³Washington University, St. Louis, Missouri; ⁴University of Cincinnati and ⁵Cleveland Clinic, Ohio; ⁶University of Colorado, Denver; ⁷Brown University, Providence, Rhode Island; ⁸University of Minnesota, St. Paul; ⁹University of California at Los Angeles; and ¹⁰Cornell University, New York, New York

EXECUTIVE SUMMARY

Dyslipidemia is a common problem affecting HIV-infected patients receiving antiretroviral therapy. Since publication of preliminary guidelines in 2000 [1], numerous studies have addressed the risk of cardiovascular disease, the mechanisms of dyslipidemia, drug interactions, and the treatment of lipid disorders in HIV-infected patients. In addition, 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]) have been published [2] that materially affect the clinical approach to lipid disorders in the general population.

A working group of clinical scientists, consisting of members of the Cardiovascular Subcommittee of the

AIDS Clinical Trials Group, updated the preliminary recommendations to assist clinicians in the evaluation and treatment of lipid disorders among HIV-infected adults. Data regarding the prevalence and incidence of dyslipidemia and cardiovascular disease in HIV-infected patients, pharmacokinetic profiles for hypolipidemic agents, and treatment trials of dyslipidemia in HIV-infected patients were considered. Although the implications of dyslipidemia in this population are not fully known, preliminary data indicate increased cardiovascular morbidity among HIV-infected individuals, suggesting that measures to reduce cardiovascular risk should be provided.

We recommend that HIV-infected adults undergo evaluation and treatment on the basis of NCEP ATP III guidelines for dyslipidemia, with particular attention to potential drug interactions with antiretroviral agents and maintenance of virologic control of HIV infection. When drugs become necessary, we recommend as initial therapy pravastatin or atorvastatin for elevated low-density lipoprotein cholesterol levels and gemfibrozil or fenofibrate when triglyceride concentrations exceed 500 mg/dL.

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Reprints or correspondence: Dr. Michael P. Dubé, Wishard Hospital, 1001 W. 10th St., OPW-430, Indianapolis, IN 46202 (mpdube@iupui.edu).

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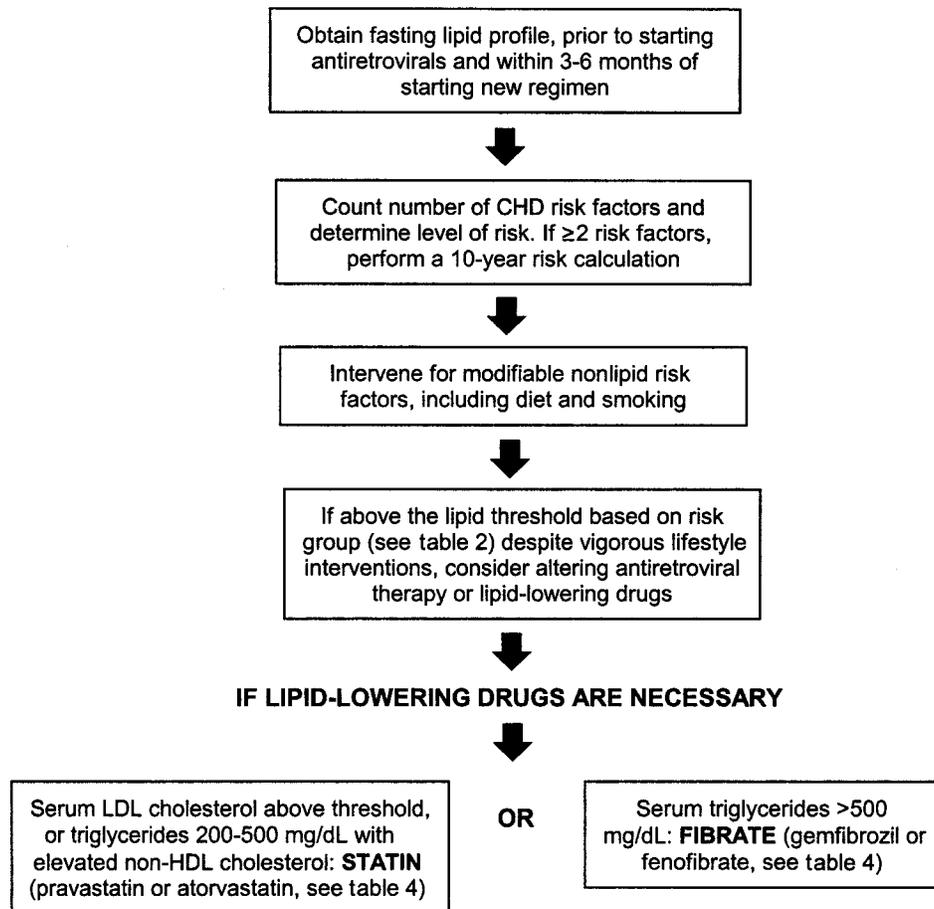


Figure 1. General approach to lipid disorders and cardiovascular risk in HIV-infected patients receiving HAART. See text for additional explanation. CHD, coronary heart disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

INTRODUCTION

Cardiovascular disease and stroke are by far the leading causes of death and morbidity in the United States [3]. As the prognosis for HIV-infected persons steadily improves, these individuals will incur an increased risk for other major causes of morbidity and mortality, independent of any specific HIV- or treatment-related issue. Cardiovascular disease occurs earlier and at a higher rate in certain populations, such as black persons, that increasingly overlap with the epidemiology of HIV infection. It is reasonable to anticipate that this problem will worsen in the midst of the epidemic of obesity and diabetes in the United States [4] and elsewhere [5], an epidemic that disproportionately affects Hispanic and non-Hispanic black persons [6]. The close relationship between HIV care providers and their patients affords a major opportunity for primary and secondary prevention of non-HIV-related conditions, such as cardiovascular disease. These recommendations will assist the HIV clinician's efforts to broaden the health benefits associated with ongoing clinical care for adults in the HIV clinic. A comprehensive approach for evaluation and treatment of dyslipi-

demia in HIV-infected adults receiving antiretroviral therapy is outlined in figure 1. For particular recommendations and statements, the strength of the supporting evidence and quality of the data are rated by use of an Infectious Diseases Society of America–United States Public Health Service grading system [7] (table 1). A rating of A–E indicates the strength of a recommendation, and the Roman numerals I–III indicate the quality of the supporting evidence. These ratings are presented in parentheses after specific recommendations.

LIPID DISORDERS DUE TO HIV INFECTION

Abnormalities of lipid metabolism in HIV-infected patients were described before the advent of HAART [8–13]. Increased serum triglyceride [8] and reduced total cholesterol [13] concentrations were associated with advanced HIV disease. Patients with AIDS have also had lower levels of high-density lipoprotein (HDL) cholesterol (HDL-C) and low-density lipoprotein (LDL) cholesterol (LDL-C), decreased triglyceride clearance, and a

Table 1. Infectious Diseases Society of America–United States Public Health Service grading system for rating recommendations in clinical guidelines.

Category, grade	Definition
Strength of recommendation	
A	Good evidence to support a recommendation for use
B	Moderate evidence to support a recommendation for use
C	Poor evidence to support a recommendation
D	Moderate evidence to support a recommendation against use
E	Good evidence to support a recommendation against use
Quality of evidence	
I	Evidence from ≥ 1 properly randomized, controlled trial
II	Evidence from ≥ 1 well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies (preferably from >1 center); from multiple time-series; or from dramatic results of uncontrolled experiments
III	Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees

predominance of small, dense LDL particles, compared with controls [9, 11]. Therapy with zidovudine alone was associated with reduced cytokine activation and a decrease in serum triglyceride levels [14].

TREATMENT-ASSOCIATED LIPID DISORDERS

Protease inhibitors (PIs). Use of HIV PIs has been associated with hyperlipidemia that is more common and more severe than what was observed before the advent of HAART [1, 15–22]. Sixty-two (47%) of 133 PI recipients at one clinic [20] had lipid abnormalities that met the 1994 NCEP intervention criteria [23]. In the Swiss HIV Cohort, hypercholesterolemia and hypertriglyceridemia were 1.7–2.3 times more common among individuals receiving HAART that contained a PI [24]. Hypercholesterolemia (cholesterol level, >240 mg/dL) and severe hypertriglyceridemia (triglyceride level, >500 mg/dL) occurred in 60% and 75% of subjects, respectively, receiving HIV PIs at one center, with respective incident dyslipidemia rate ratios of 2.8 and 6.1 attributable to use of these medications [25].

The dyslipidemia associated with use of HIV PIs often includes hypercholesterolemia. Much of the increase is in the level of very-low density lipoproteins (VLDLs) and, to a lesser extent, intermediate-density lipoproteins (IDLs) [16, 19, 26, 27]. HDL-C levels tend not to change [16, 19, 21, 26, 27] or to increase [28–30]. Inconsistent changes in small and large HDL particles have been described [26–28]. Increased LDL-C levels have been reported in some studies [16, 19, 21, 28–30] but not others [26, 27]. Compared with patients receiving lamivudine-based antiretroviral therapy, PI recipients had a mean increase in the total cholesterol level of 32 mg/dL at a mean

of 3.4 months of therapy, which included a 27% increase (18 mg/dL) in the directly measured LDL-C level [19].

Hypertriglyceridemia is also common and appears to be especially severe in patients taking ritonavir [16–18, 26]. Increased triglyceride concentrations have been found in all lipoprotein fractions and are accompanied by hyperapobeta-lipoproteinemia, which is associated with an increased risk of vascular events [16, 19, 21, 26, 27, 31]. Lipoprotein(a) excess has been described inconsistently, but it may be exacerbated in individuals with this disorder before HAART initiation [16, 21, 26].

There are few systematic comparisons of the lipid effects of different PIs. In a randomized trial, total cholesterol increases were comparable between the fixed-dose combination of lopinavir-ritonavir and nelfinavir (mean increases of 53 and 48 mg/dL, respectively), but increases in the triglyceride level were significantly greater with lopinavir-ritonavir than with nelfinavir (125 and 47 mg/dL, respectively) [32]. Lipid abnormalities tend to be most marked with ritonavir [16] and lopinavir-ritonavir [33, 34]. Amprenavir [29] and nelfinavir [16, 34] tend to have intermediate effects, whereas indinavir [16, 28, 35] and saquinavir [36, 37] tend to have the fewest effects. The recently approved PI atazanavir appears to have little, if any, effect on lipid concentrations, as determined on the basis of preliminary reports [38].

Nucleoside reverse-transcriptase inhibitors (NRTIs). Subjects in clinical care have failed to show differences in nonfasting cholesterol and triglyceride levels associated with receipt of stavudine- compared with zidovudine-containing regimens [39]. However, in a prospective, randomized study reported in abstract form, antiretroviral-naïve subjects who initiated therapy with stavudine-lamivudine-nelfinavir had significant increases in total cholesterol, LDL-C, and triglyceride levels, compared

with subjects receiving zidovudine-lamivudine-nelfinavir [40]. Elevations in nonfasting triglyceride levels were more common in association with stavudine-didanosine-indinavir than with zidovudine-lamivudine-indinavir in a published randomized study [41]. The NRTI tenofovir was associated with lesser increases in cholesterol and triglyceride levels than was stavudine, as published in a recent abstract [42]. Additional data are needed before any firm conclusions can be drawn regarding the relative tendencies of individual nucleoside analogues to alter lipid profiles.

Nonnucleoside reverse-transcriptase inhibitors (NNRTIs).

The NNRTIs cause alterations in the lipid profiles, although generally to a lesser degree than has been observed with PIs. NNRTI use is associated with substantial increases in HDL-C levels to a degree not generally seen with PIs. Efavirenz or indinavir given with NRTIs raised total cholesterol levels within 4–8 weeks of therapy, but subjects who received both efavirenz plus indinavir experienced the greatest increases in the total cholesterol level [43]. HDL-C levels also increased significantly among subjects receiving the efavirenz-containing regimens, accounting for 25% of the increase in total cholesterol. The ratio of total cholesterol to HDL-C did not increase among the subjects receiving efavirenz plus NRTIs, but it did when indinavir was coadministered [44]. In a randomized trial, both the LDL-C level and the HDL-C level increased among subjects receiving nevirapine or indinavir in combination with NRTIs [28]. However, HDL-C levels increased more with nevirapine than with indinavir, resulting in a favorable decrease in the ratio of total cholesterol to HDL-C with nevirapine. In a direct comparison reported in abstract form, nevirapine recipients had smaller increases in triglyceride levels, greater increases in HDL-C levels, and larger decreases in the ratio of total cholesterol to HDL-C than did efavirenz recipients, although the differences were relatively small in magnitude [45].

EFFECTS OF SWITCHING ANTIVIRAL THERAPIES

The association of increased serum lipid levels with certain antiretroviral therapies has led to exchanging the potentially offending component for another drug. This switching strategy has the potential advantage of avoiding pharmacologic intervention for elevations in lipid levels. However, because of the multifactorial nature of dyslipidemia in HIV infection, abnormalities may not resolve simply by switching drugs. A summary of the effects on lipids of switch studies, many of which have been presented in abstract form only, was recently published [46]. Switching from a PI to nevirapine or abacavir has generally resulted in an improvement in total cholesterol and triglyceride levels [47–55], whereas switching to efavirenz has produced less consistent results [56]. Studies of switches from stavudine to

abacavir [57–59] have yielded inconclusive results. These trials have generally demonstrated persistent viral suppression for 6–12 months after switching regimens.

In patients with a favorable treatment history (i.e., no previous receipt of an NRTI-based regimen that was less than fully suppressive and no history of virologic rebound occurring while receiving treatment), switching from a potentially lipid level-increasing PI to nevirapine or abacavir may be preferable to a pharmacologic intervention with a lipid-lowering drug (C-III). In practice, however, many patients will have already received NNRTI therapy or are extensively NRTI experienced. Studies comparing the effects of treatment switching to those 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 to the risks of potential drug interactions and new treatment-related toxicities from lipid-lowering agents that are added to existing regimens.

MECHANISMS OF PI-RELATED LIPID DISORDERS

The mechanisms by which PIs lead to dyslipidemia have not been definitively characterized. PI-associated dyslipidemia is complex, multifactorial, and associated with multiple hepatocyte, adipocyte, and endothelial enzyme abnormalities.

PI-associated insulin resistance and altered expression of the apolipoprotein C-III gene may mediate PI-associated dyslipidemia [60]. In healthy individuals, PIs do not appear to affect the activity of lipoprotein lipase, although reductions in the hepatic lipase activity have been observed [26]. Several PIs have increased triglyceride synthesis and ritonavir increased cholesterol synthesis in cultured hepatocytes [61]. In mice, administration of ritonavir activates genes under the control of sterol-regulatory element-binding protein (SREBP)-1c [62]. Inhibition of proteasome activity may lead to increased levels of SREBP-1c and apolipoprotein B-100 in hepatocytes [63, 64]. Other mechanisms that may increase hepatic SREBP-1c levels in patients receiving HIV PIs include improved nutritional status, hyperinsulinemia, hypoleptinemia, and impaired function of cytoplasmic retinolic acid-binding protein-1 (CRABP-1) [65].

RISK OF CARDIOVASCULAR DISEASE

To date, few epidemiologic studies have been able to directly assess potential associations between dyslipidemia and the incidence of coronary heart disease (CHD) in HIV-infected patients. A prospective, observational study involving 23,490 patients and 36,479 person-years of follow-up has reported a modest relative increase in the risk of myocardial infarction of

27% per year with use of regimens including NRTIs plus either a PI or an NNRTI [66]. Increased serum cholesterol levels were also associated with increased risk, but this preliminary report did not assess PI use separately in its analysis. Other investigators have retrospectively analyzed cohorts for temporal trends in the incidence of myocardial infarction or CHD-associated mortality in relation to the general availability of PI therapy or, more specifically, use of PIs by individuals. In the Frankfurt HIV Cohort, the rate of myocardial infarction increased in the era of PI therapy, and receipt of a PI-based regimen remained associated with myocardial infarction after adjustment for age [67]. PI use has been associated with myocardial infarction after adjustment for nonlipid cardiac risk factors [68], and an abstract about a retrospective study reported an association between myocardial infarction and duration of PI use [69]. In contrast, a large retrospective study from the Veterans Administration Hospitals in the United States indicated that the incidence of hospitalization or death due to cardiovascular or cerebrovascular events remained stable while PI use increased [70]. Others have reported that HIV seropositivity [71, 72] or traditional cardiac risk factors plus nadir CD4 cell count and duration of NRTI use [73] were associated with CHD events, rather than use of PIs per se.

Interpretation of these conflicting results is limited by the retrospective nature of the studies, the short durations of follow-up relative to the natural history of atherosclerosis, small numbers of cardiac events, the potential for biased ascertainment of cases, and inconsistent adjustment for confounding factors. Nonetheless, although the specific contributions of dyslipidemia and PI use to risk remain uncertain, many of these preliminary findings suggest that the risk of coronary events is increased in HIV-infected patients. These findings provide a strong rationale for initiating conventional risk-reducing interventions in patients who have the potential for long-term survival while using HAART, regardless of whether PIs are a component of the antiretroviral regimen.

Surrogate end-point data, such as data on carotid atherosclerosis and endothelial dysfunction, which are known to predict future adverse cardiovascular events, also suggest that the metabolic changes in patients taking PIs are atherogenic. In a cross-sectional study, use of PIs was associated with an increased incidence of carotid atherosclerotic plaque, compared with HIV-infected individuals not taking PIs and HIV-negative control subjects [74]. However, one study did not find this association [75]. Coronary artery calcification (noted by CT) was increased in a study of black PI recipients, compared with control subjects [76]. In a cross-sectional study, subjects receiving PIs had impaired vascular endothelial function, the strongest predictor of which was the use of a PI [27]. In subjects receiving PIs, triglyceride-rich lipoproteins and cholesterol-rich remnants predicted endothelial dysfunction, suggesting that the

metabolic changes associated with PIs, such as dyslipidemia, might mediate increased cardiovascular risk. An abstract reported endothelial dysfunction after administering indinavir for 4 weeks to healthy, HIV-uninfected subjects [77], supporting a potential direct drug effect of PIs on the endothelium or a secondary effect of insulin resistance due to PIs [35, 78].

EVALUATION OF PATIENTS

Risk stratification. The NCEP ATP III guidelines, which adjust the intensity of risk reduction therapy to the patient's risk of having an adverse coronary event, provide a starting point for the evaluation of HIV-infected patients [2]. First, the number of risk factors for CHD that modify LDL-C goals (table 2) are counted. For patients who have ≥ 2 risk factors for CHD, a risk assessment tool (available in [2] and at <http://hin.nhlbi.nih.gov/atpIII/calculator.asp>) based on the Framingham Heart Study is then used to estimate 10-year risk of myocardial infarction or cardiac death.

After determining the appropriate risk category, LDL-C goals are identified next (table 3) [2]. The highest-risk patients—those with established coronary artery disease—are treated most aggressively, with a target LDL-C level of <100 mg/dL. In addition, patients without established CHD but with a similar 10-year risk estimate ($>20\%$) are considered to have a “CHD risk equivalent” and are treated equally aggressively. Patients with CHD risk equivalents include those with type 2 diabetes mellitus, other forms of atherosclerotic disease, or a calculated 10-year CHD risk estimate of $>20\%$.

Severe hypertriglyceridemia (triglyceride level, >500 mg/dL) will be present in a considerable proportion of HIV-infected patients. Reduction of the triglyceride level becomes a primary

Table 2. Categorical coronary heart disease risk factors that modify low-density lipoprotein (LDL) cholesterol goals.

Risk factor	Definition
Cigarette smoking	...
Hypertension	Blood pressure of ≥ 140 mm Hg or receipt of antihypertensive medication
Low high-density lipoprotein cholesterol level ^a	Level, <40 mg/dL
Family history of premature CHD	Male first-degree relative <55 years old or female first-degree relative <65 years old
Age	>45 years for men and >55 years for women

NOTE. Note that a diagnosis of diabetes mellitus is now considered an equivalent to a known diagnosis of coronary heart disease (CHD; see text for additional explanation). Adapted from [2].

^a An elevated high-density lipoprotein cholesterol level (≥ 60 mg/dL) is considered a “negative” risk factor. If this is present, subtract 1 factor from the above risk factor total.

Table 3. National Cholesterol Education Program treatment decisions based on low-density lipoprotein (LDL) cholesterol level.

Risk category	LDL cholesterol level, mg/dL		
	Goal	Initiate therapeutic lifestyle change	Consider drug therapy
CHD or risk equivalent	<100	≥100	≥130 ^a
>2 risk factors and 10-year risk of ≤20%			
10-year risk of 10%–20%	<130	≥130	≥130
10-year risk of <10%	<130	≥130	≥160
0–1 risk factors	<160	≥160	≥190 ^b

NOTE. Therapeutic lifestyle changes include dietary and exercise intervention (see the section on nondrug therapies in Hypercholesterolemia). Reduction of the LDL cholesterol level is a primary goal of therapy. Reduction in the non-high-density lipoprotein (HDL) cholesterol level is a secondary goal of therapy when the triglyceride level is >200 mg/dL. Non-HDL cholesterol goals (see text) are 30 mg/dL higher than LDL cholesterol goals. Adapted from [2]. CHD, coronary heart disease.

^a For an LDL cholesterol level of 100–129 mg/dL, drug therapy is optional; consider treating HDL cholesterol and triglyceride disorders.

^b For an LDL cholesterol level of 160–189 mg/dL, drug therapy is optional.

target for these individuals. If moderate elevations are present (200–500 mg/dL), then non-HDL cholesterol (total cholesterol level minus HDL-C level) becomes a secondary target for therapy if LDL-C goals have been achieved [2]. Non-HDL-C represents all cholesterol carried by lipoproteins currently considered to be atherogenic, which includes LDL, VLDL, IDL, and lipoprotein(a) [2, 79]. Measurement of non-HDL-C is particularly useful in individuals with high triglyceride levels and makes treatment of triglyceride disorders less confusing. Non-HDL-C is an independent predictor of cardiovascular events [80, 81]. The target non-HDL-C level for each risk category is 30 mg/dL higher than the corresponding LDL-C target, representing the normal contribution of VLDL-C to the non-HDL-C concentration.

Metabolic syndrome. The NCEP ATP III identified the metabolic syndrome as a secondary target for intervention. Several features of the metabolic syndrome overlap with common features of HIV treatment-associated lipodystrophy, such as hyperinsulinemia, glucose intolerance, an atherogenic lipoprotein phenotype, a prothrombotic state [82], and central obesity. Patients with the metabolic syndrome are encouraged to lose weight, using dietary modification and increased physical activity. Patients who also have moderate to severe lipodystrophy should be encouraged to increase physical activity, but excessive weight loss has the potential to exacerbate lipodystrophy.

Measurement of lipid values. Evaluation of serum lipid levels should be performed after fasting for a minimum of 8 h, and preferably for 12 h, and the levels should be determined before initiation of antiretroviral therapy (B-III). The standard screening lipid profile should include measurement of total cholesterol, HDL-C, and triglyceride levels [2]. Using these measured values, LDL-C and non-HDL-C levels are calculated. This should be repeated within 3–6 months after the initiation

of HAART, then yearly, unless abnormalities are detected or therapeutic interventions are initiated (B-III). For individuals with an elevated triglyceride level (>200 mg/dL) at baseline, it may be preferable to repeat a lipid profile sooner (e.g., within 1–2 months after initiating HAART).

Nonlipid risk factors. Interventions should be routinely offered for other modifiable cardiovascular risk factors, such as smoking, hypertension, physical inactivity, obesity, and diabetes mellitus. For smokers, smoking cessation, for example, is a far more powerful means of reducing risk for cardiovascular conditions than is use of lipid-lowering drugs. In addition, the clinician should be alert for potential exacerbating conditions, such as excessive alcohol use, hypothyroidism, renal disease, liver disease, and hypogonadism. The clinician should also consider the effects of glucocorticoids, β -blockers, thiazide diuretics, thyroid preparations, and hormonal agents (such as androgens, progestins, and estrogens) on both cholesterol and triglyceride values.

WHICH HIV-INFECTED PATIENTS NEED THERAPY FOR DYSLIPIDEMIA?

It is reasonable to assume that dyslipidemia in HIV-infected patients with otherwise virologically well-controlled infection will have similar—and perhaps greater—long-term consequences than will dyslipidemia in the general population. Although unproven, it is also reasonable to assume that the benefits of lipid-lowering interventions will also extend to HIV-infected persons. Enthusiasm for drug therapy for dyslipidemia should be tempered with the understanding that interventions for advanced immunosuppression, opportunistic infections, malignancies, and HIV-associated wasting should take precedence during the initial stages of treatment. There is currently no evidence that HIV-

infected patients should be offered interventions for lipid abnormalities that are more aggressive than those used for the general population. Target values for LDL-C and non-HDL-C levels can be found in table 3.

TREATMENT

Hypercholesterolemia

Nondrug therapies. Nondrug therapies [2] should generally be instituted first and given a thorough trial before instituting drug therapies, except when there is an urgent need to intervene, such as for individuals with CHD (or a CHD risk equivalent) or when there are extreme elevations in the LDL cholesterol level (>220 mg/dL). Competing dietary needs are frequently identified for patients with HIV infection, for whom the need for decreasing the lipid level and weight gain (e.g., lean muscle mass) may coexist. Patients with advanced HIV disease and wasting often experience prominent gastrointestinal symptoms, limiting dietary options. In many patients, it will be preferable to address their wasting before their dyslipidemia.

Clinicians should consider consultation with a dietician as a first step or when initial attempts at dietary intervention fail to have the desired effect. Dietary and exercise intervention resulted in a significant 11% decrease in cholesterol levels in HIV-infected patients [20]. Diet plus supervised cycling and resistance training thrice weekly reduced the total cholesterol level by 18% and the triglyceride level by 25% in subjects with fat wasting [83]. Attention must be given to other modifiable risk factors for CHD, such as cigarette smoking, diabetes mellitus, and hypertension. Hormone replacement with estrogen/progestin is no longer recommended for primary [84] or secondary [85] CHD prevention (A-I).

Drug therapies for HIV-infected individuals. The findings of prospective studies involving lipid-lowering drugs in HIV-infected subjects are shown in table 4.

HMG-CoA reductase inhibitors. The HMG-CoA reductase inhibitors, or statins, have been used extensively as first-line therapy for hypercholesterolemia in the general population. Considerable evidence demonstrates their benefits in both reducing the risk of CHD in patients without prior CHD (primary prevention) and reducing the progression of coronary artery stenoses and risk of recurrent CHD events (secondary prevention) [86]. A statin is a recommended first choice for elevated LDL-C levels or for elevated non-HDL-C levels when triglyceride levels are 200–500 mg/dL (B-I).

The statins pravastatin [88, 91], atorvastatin [20], and fluvastatin [89] have been studied in small numbers of PI-treated, HIV-infected subjects. Significant toxicities have not been reported in these studies. In many of these studies, LDL-C data were not reported or were available for only a subset of subjects. Overall, the cholesterol-lowering effects of statins in subjects

receiving PIs have been modest, and many subjects have not reached cholesterol goals with a statin alone [20, 88–89]. The efficacy of statins in subjects not receiving PIs has not been reported.

Fibric acid derivatives. Fibrates are less optimal alternative agents for hypercholesterolemia (C-I). When triglyceride levels are normal, modest LDL-C reduction (5%–20%) can be achieved with fibrates. When triglyceride levels are elevated, fibrates generally lead to slight increases in LDL-C levels. Fenofibrate (200 mg q.d.) resulted in a median increase in the LDL-C level of 11 mg/dL among 88 HIV-infected subjects with elevated levels of both LDL-C and triglycerides [91]. The median reduction in non-HDL-C level associated with fenofibrate was 18 mg/dL; this was due to a preferential effect on triglyceride-rich lipoproteins. Generally, fibrates should be reserved for treatment of triglyceride levels of >500 mg/dL. Unlike with gemfibrozil [94, 95], data are lacking that demonstrate a reduction in cardiovascular end points with the use of fenofibrate. At the present time, there is no compelling reason to prefer fenofibrate to gemfibrozil in HIV-infected patients.

Other agents. Niacin decreases LDL-C and non-HDL-C levels while increasing the HDL-C level, but it produces frequent cutaneous flushing. Although uncommon, hepatotoxicity can be severe [96, 97]. Because niacin causes insulin resistance [98, 99] (even in nondiabetic individuals), it has been suggested that niacin should generally be avoided as first-line therapy for patients receiving PIs or who have lipodystrophy until additional safety data are available (C-III). Recent studies, however, suggest that niacin has only mild or transient effects on control of glycemia in diabetic subjects [100–102]. Niacin was generally well-tolerated in a report of HIV-infected subjects with low HDL-C levels [103]. Use of bile-sequestering resins (cholestyramine, colestipol, and colesevalam) is not recommended (C-III). Use of these resins can be associated with increased triglyceride levels, and their effects on the absorption of antiviral drugs have not been studied. Ezetimibe, a new cholesterol absorption inhibitor that lowers LDL-C levels by 17%–21% [104, 105], has not been tested in an HIV-infected population. Its lack of side effects and P450 interactions [106] makes this a potentially promising agent for use in patients with HIV infection and elevated LDL-C levels.

Hypertriglyceridemia

Nondrug therapies. Nondrug therapies should be instituted first and given a thorough therapeutic trial. Clinicians should consider consultation with a dietician as a first step or when initial attempts at dietary intervention fail to have the desired effect. Dietary and exercise advice resulted in a 21% decrease [20] and a formal resistance-training program resulted in a 27% decrease [107] in triglyceride levels among HIV-infected patients. In another study, only those subjects who reported

Table 4. Findings of selected prospective studies of lipid-lowering drugs in HIV-infected subjects.

Author (year), reference	Study design	Intervention (no. of subjects)	Lipid criteria for entry	Baseline lipid values, mg/dL ^a	Main results ^a
Baldini (2000) [87]	Open, single-arm	Pravastatin, 20 mg q.d. (19)	"Abnormal" TC or TG	Median TC, 313; median TG, 813	Median TC, ↓19%; median TG, ↓37%
Moyle (2001) [88]	Placebo-controlled, randomized	Dietary advice plus pravastatin, 40 mg q.d. (15), vs. placebo (16)	TC, >240 mg/dL	Mean TC, 290; mean TG, 351; mean LDL-C (<i>n</i> = 11), 180	Mean TC, ↓17%; mean LDL-C, ↓19% (<i>n</i> = 11); no significant change in TG; 4 (27%) of 16 subjects receiving pravastatin reached TC of <212 mg/dL
Doser (2002) [89]	Placebo-controlled, cross-over	Fluvastatin, 40 mg q.d. (16)	Hyperlipidemia	Mean TC, 310; mean TG, 400	Mean TC, ↓17%; no significant change in TG; 8 (50%) of 16 subjects had both TC of <270 mg/dL and TG of <266 mg/dL
Palacios (2002) [90]	Open-label, single-arm	Atorvastatin, 10 mg q.d. (20)	TC, >240 mg/dL	Mean TC, 299; mean TG, 319; mean LDL-C (direct), 204	Mean TC, ↓27%; TG, ↓41%; LDL-C, ↓37%; more than half of subjects attained TC of <240 mg/dL and LDL-C of <130 mg/dL
Aberg (2002) [91]	Randomized, open-label	Fenofibrate, 200 mg q.d. (88), pravastatin, 40 mg q.d. (86), or both (136) if failed to reach lipid goal values	LDL-C (direct), >130 mg/dL; TG, >200 mg/dL	Median TC, 270; median TG, 326; median LDL-C (direct), 155	Fenofibrate: median LDL-C, ↑8%; TG, ↓35%; and HDL-C, ↑12%; pravastatin: median LDL-C, ↓19%; TG, ↓9%; and no change in HDL-C; both: median LDL-C, ↓9%–12%; TG, ↓24%–48%; 5%–16% of subjects reached a combined lipid goal based on LDL-C, HDL-C, and TG
Palacios (2002) [92]	Open-label, single-arm	Fenofibrate, 200 mg q.d. (20)	TG, >400 mg/dL	Mean TC, 256; mean TG, 812	Mean TC, ↓14%; TG, ↓54%; LDL-C, not reported; 70% of subjects attained TG of <400 mg/dL
Miller (2002) [93]	Placebo-controlled, randomized	Dietary advice plus gemfibrozil, 600 mg b.i.d. (17), vs. placebo (20)	TG, >266 mg/dL	Mean TC, 278; mean TG, 577	Mean TG, ↓18%; no change in TC or HDL-C; 1 of 17 subjects receiving gemfibrozil reached a TG of <177 mg/dL

NOTE. HDL-C, high-density lipoprotein cholesterol level; LDL-C, low-density lipoprotein cholesterol level; TC, total cholesterol level; TG, triglyceride level.

^a Among treated subjects.

Table 5. Recommendations for choice of initial drug therapy for dyslipidemia in HIV-infected individuals receiving antiretroviral therapy.

Lipid abnormality	Therapy		Comments (rating)
	First choice (rating)	Alternative(s) (rating)	
Elevated LDL-C level or elevated non-HDL-C level with triglyceride level of 200–500 mg/dL	Statin (B-I)	Fibrate (C-I) or niacin (C-III)	Start with low doses of statins and titrate upward; with CYP3A4 inhibitors (PIs or delavirdine), pravastatin, 20–40 mg q.d. (A-I), or atorvastatin, 10 mg q.d. (B-II), initial dose is recommended; fluvastatin, 20–40 mg q.d., is an alternative (B-II); fibrate may elevate the LDL-C level when the triglyceride level is elevated; niacin may worsen insulin resistance; combining fibrate and statin increases the risk of rhabdomyolysis (use with caution and monitor for clinical evidence of myopathy)
Triglyceride level, >500 mg/dL	Fibrate (B-I)	Niacin (C-III) or fish oils (C-III)	Reduction of triglyceride level becomes a primary target in these individuals; drug interactions with fibrates are unlikely; Gemfibrozil dosage is 600 mg b.i.d., and fenofibrate dosage is 54–160 mg q.d.; niacin may worsen insulin resistance

NOTE. HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; PI, protease inhibitor. Ratings are defined in table 1.

good dietary compliance appeared to benefit, with a mean reduction in the triglyceride level of 23% at 6 months [108]. Smoking cessation and regular aerobic exercise are general health measures that will reduce the triglyceride level and improve the overall cardiovascular risk profile. Weight reduction should be strongly encouraged if obesity is present. Hyperglycemia due to diabetes mellitus must be managed aggressively [109], with consideration of treatment with insulin sensitizers, such as metformin and thiazolidenediones [110], when appropriate. Fat intake should be decreased, but a concomitant increase in carbohydrate intake may increase triglyceride and lower HDL-C levels. If this occurs, replacing some of the saturated fat with monounsaturated fat or omega-3 polyunsaturated fats may be valuable. Severe hypertriglyceridemia and hyperchylomicronemia require very low-fat diets, avoidance of simple sugars, and decreased or elimination of alcohol intake. Fish oils (omega-3 fatty acid supplements) variably decrease triglyceride synthesis and may be tried (C-III). Triglyceride levels decreased in conjunction with fish oil supplementation in hypertriglyceridemic patients with AIDS wasting [111], but this approach has not been tested in PI recipients. When extreme elevations are present (>2000 mg/dL, or >1000 mg/dL in persons with a history of pancreatitis), it is reasonable to institute both drug and nondrug therapies simultaneously.

Drug therapies. Data on drug therapies are shown in table 4. Among 17 PI-treated male subjects who had a median baseline triglyceride concentration of 498 mg/dL, a mean triglyceride decrease of 109 mg/dL occurred in conjunction with receipt of gemfibrozil (600 mg b.i.d.), although only 1 subject achieved normal levels [93]. Fenofibrate use resulted in a median decrease of 118 mg/dL reported in an abstract [91].

Niacin is effective therapy for hypertriglyceridemia but

should be avoided as first-line therapy in patients receiving HIV PIs or who have lipoatrophy (C-III) (see above). L-carnitine given orally at a dosage of 3 g per day resulted in a 141 mg/dL (28%) decrease in mean triglyceride levels in an open, single-arm study [112]. Statins are not generally recommended as first-line therapy for isolated hypertriglyceridemia, particularly when triglyceride levels are >500 mg/dL (C-III). However, all statins are effective at decreasing triglyceride levels when baseline values are elevated [113] and thus are useful in combined disorders.

Choice of Initial Drug Treatment for Hyperlipidemia

Recommendations for choice of initial drug therapy for dyslipidemia in HIV-infected individuals receiving antiretroviral therapy are shown in table 5.

Elevated LDL-C level, or elevated non-HDL-C level in patients with a triglyceride level of 200–500 mg/dL. Either pravastatin, (20–40 mg q.d. starting dose) (A-I), or atorvastatin (10 mg q.d. starting dose) (B-II) is recommended (see the section Drug-Drug Interaction Considerations, below), along with careful monitoring of virologic status and for hepatic and skeletal muscle toxicity. Fluvastatin (20–40 mg q.d. starting dose) is a reasonable alternative (B-II). A fibrate, either gemfibrozil (600 mg b.i.d.) (B-I) or micronized fenofibrate (54–160 mg q.d.) (B-I), are reasonable alternative agents only when statins are not appropriate.

Triglyceride level of >500 mg/dL. First-line treatment is gemfibrozil (600 mg b.i.d.) given 30 min before morning and evening meals (B-I) or micronized fenofibrate (54–160 mg q.d.) (B-I). Fish oils and niacin are alternative agents (C-III).

Table 6. Considerations for antiretroviral drug effects on the metabolism of lipid-lowering drugs.

Lipid-lowering drug class, drug	Effect(s) of drug combination					
	Ritonavir	Nelfinavir	Other PIs	Nevirapine	Efavirenz	Delavirdine
Statins						
Simvastatin	Inhibition ↑↑ AUC (contraindicated)	Inhibition ↑↑ AUC (contraindicated)	Inhibition ↑↑ AUC (contraindicated)	Probably none	Unknown	Inhibition ↑↑ AUC (contraindicated)
Lovastatin	Inhibition ↑↑ AUC (contraindicated)	Inhibition ↑↑ AUC (contraindicated)	Inhibition ↑↑ AUC (contraindicated)	Probably none	Unknown	Inhibition ↑↑ AUC (contraindicated)
Atorvastatin	Inhibition ↑ AUC (use with caution)	Inhibition ↑ AUC (use with caution)	Inhibition ↑ AUC (use with caution)	Probably none	Probably none	Inhibition ↑ AUC (use with caution)
Fluvastatin	Possible induction	Possible induction	Probably none	Probably none	Probably none	Inhibition ↑ AUC
Pravastatin	Induction of metabolism, possible reduced effect	Unknown (possible induction)	Probably none	Probably none	Probably none	Probably none
Fibrates						
Gemfibrozil	Possible induction, possible reduced effect	Possible induction	Probably none	Probably none	Probably none	Probably none
Fenofibrate	Possible induction, possible reduced effect	Possible induction	Probably none	Probably none	Probably none	Probably none

NOTE. Adapted from [133]; used with permission. AUC, area under the curve; PI, protease inhibitor.

APPROACH TO REFRACTORY DISORDERS

Few data are available to guide the use of combination lipid-lowering drugs in HIV-infected patients. It is clear, however, that first-line therapies often fail to meet target lipid goals [20, 88–89, 93]. On the basis of studies involving HIV-uninfected subjects, the addition of a fibrate [114–118] or niacin [102, 117, 119–122] to the treatment regimen can be considered for those with elevated LDL-C or non-HDL-C levels that fail to respond adequately to full doses of a statin. Combination fibrate-statin therapy should only be used with great caution because of the risk of myopathy [123]. The combination of atorvastatin and gemfibrozil was safe in a small study of HIV-infected subjects [20], as was the combination of pravastatin and fenofibrate in a preliminary report [91]. The risk of myopathy may be increased in patients with HIV infection because of the use of other potentially myotoxic drugs, such as zidovudine [124]; because of agents that can inhibit the metabolism of statins, such as PIs and itraconazole (see the section Drug-Drug Interaction Considerations, below); or because of HIV itself [125]. When used in combination with fibrates, pravastatin (B-I) and fluvastatin (C-III) may be the preferred statins.

The addition of niacin to statin therapy may be safer than use of a statin-fibrate combination, but it has not been studied in HIV-infected subjects. Patients treated with niacin should have regular evaluation of fasting glucose levels, and a standard 75-g, 2-h oral glucose-tolerance test should be considered, particularly when lipodystrophy or traditional risk factors for type 2 diabetes mellitus are present [110, 126]. For elevated triglyceride levels that are inadequately responsive to fibrate therapy and maximal lifestyle changes, the addition of a fish oil supplement or niacin [127] can be considered (C-III). Addition of a statin to a fibrate regimen when elevated triglyceride level

is the predominant abnormality (e.g., when triglyceride levels are >500 mg/dL and LDL-C or non-HDL-C levels are at or near goal levels) is not generally recommended. Referral to an expert in treating dyslipidemia in patients with HIV infection should be considered for refractory disorders.

DRUG-DRUG INTERACTION CONSIDERATIONS

PIs and NNRTIs are metabolized by or affect the function of various cytochrome P450 (CYP) isoforms [128–130]. All the PIs used clinically variably inhibit CYP3A4. Ritonavir is by far the most potent inhibitor of this CYP isoform, with indinavir, nelfinavir, amprenavir, and saquinavir being sequentially less potent inhibitors [131]. The NNRTI delavirdine is both a substrate and inhibitor of CYP3A4, whereas nevirapine is a substrate and inducer of CYP3A4. Efavirenz may have some inhibitory activity on CYP3A4, but its predominant effect is potent induction [129, 132]. Considerations for drug-drug interactions are listed in table 6.

The primary route of metabolism for most statins is via oxidation using CYP3A4. Lovastatin and simvastatin are administered as inactive lactone prodrugs that are avidly metabolized by intestinal and liver CYP3A4. When CYP3A4 is inhibited, more of the lactone prodrug is available for hydrolysis to the active form [134]. Pravastatin, atorvastatin, and fluvastatin are administered directly as the active hydroxy-acid [135]. Pravastatin is eliminated by multiple metabolic pathways, particularly glucuronidation [136], but CYP3A4 has no role in the metabolism of pravastatin [137]. Fluvastatin uses CYP2C9 for metabolism and also appears to inhibit this isoform [138].

Inhibitors of CYP3A4 increase the concentration of certain statins [139, 140]. Indeed, rhabdomyolysis has been reported

in patients taking simvastatin and PIs [141, 142]. Fichtenbaum et al. [143] reported that, in healthy volunteers treated with ritonavir (400 mg) plus saquinavir (400 mg) twice daily, the median 24-h area-under-the-curve (AUC_{0-24}) for simvastatin acid increased 30-fold. Ritonavir-saquinavir increased atorvastatin exposure by 3.4-fold, but the total active atorvastatin activity (atorvastatin plus its active metabolites) increased only by 79%. In contrast, the median AUC_{0-24} for pravastatin decreased by 50% in presence of ritonavir-saquinavir. Consistent with the lack of in vitro effect of statins on CYP3A4 activity, pravastatin did not affect the pharmacokinetics of nelfinavir and its active metabolite, nor did any of the 3 statins affect the pharmacokinetics of ritonavir or saquinavir [143]. Similarly, nelfinavir increased the AUC_{0-24} of total simvastatin activity 5-fold and that of total atorvastatin activity by 74% [144]. Lopinavir-ritonavir resulted in a 5-fold increase in atorvastatin exposure and a large decrease in the formation of the active metabolites [145]. However, pravastatin exposure did not change with the addition of lopinavir-ritonavir, perhaps because a lower dose of ritonavir (100 mg twice daily) was used than that used by Fichtenbaum et al. [143] (400 mg twice daily).

It is possible that drug-drug interactions occur with NNRTIs and statins, but data are not available. Nevirapine is a selective inducer of CYP3A4, whereas efavirenz is a mixed inducer and inhibitor of CYP3A4. There is a possibility that these drugs will induce the metabolism of statins, but induction might also result in the increased generation of active metabolites. Delavirdine, a potent inhibitor of CYP3A4, would be expected to have similar but lesser interactions than ritonavir with concomitant use of simvastatin, lovastatin, or atorvastatin.

On the basis of these data, simvastatin and lovastatin should not be used in patients taking PIs or delavirdine (E-III) (table 6). Atorvastatin can probably be used with caution, at low initial doses, in patients taking PIs (B-I), although extensive safety data are lacking. Pravastatin appears to be safe for use with PIs (A-I). It is not known whether the efficacy of pravastatin will be diminished when used concomitantly with ritonavir, but higher doses of pravastatin may be necessary in the presence of ritonavir or other agents that induce enzymes responsible for the metabolism of pravastatin. Fluvastatin may also be a safe alternative for use with PIs (B-II) [89] on the basis of its known metabolism and the relative lack of significant interaction with other CYP3A4 and CYP2C9 inhibitors [146]. Any of the statins can probably be used safely in persons taking efavirenz or nevirapine (C-III), although more data are needed.

Drug-drug interactions are unlikely with other classes of antiretrovirals and lipid-lowering agents. Fibrates are conjugated by glucuronidation with renal elimination [147]. Because ritonavir and nelfinavir are known inducers of glucuronidation, induction of fibric acid metabolism might occur, with potential diminished efficacy of these drugs.

CONCLUSIONS

Dyslipidemia has emerged as an important problem in HIV-infected individuals receiving antiretroviral therapy. Although the long-term consequences are unknown, it is reasonable to recommend that HIV-infected adults undergo evaluation and treatment based on the NCEP ATP III guidelines [2]. In most instances, nonpharmacologic interventions are given a thorough trial before consideration of drug therapy. Because of the potential for significant drug interactions with commonly used antiretroviral drugs, the choices of lipid-lowering agents should be limited to those agents with a low likelihood of interactions. Until more is known about the safety, efficacy, and drug interactions of lipid-lowering drugs in HIV-infected patients, we believe that these recommendations represent a useful starting point for the management of dyslipidemia in these individuals.

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