Preliminary Guidelines for the Evaluation and Management of Dyslipidemia in Adults Infected with Human Immunodeficiency Virus and Receiving Antiretroviral Therapy: Recommendations of the Adult AIDS Clinical Trial Group Cardiovascular Disease Focus Group

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Dyslipidemia is a prevalent condition that affects patients infected with human immunodeficiency virus (HIV) who are receiving antiretroviral therapy. These preliminary recommendations summarize the current understanding in this area and propose guidelines for management. Existing guidelines for the management of dyslipidemia in the general population formed the general basis for our recommendations. Data on the prevalence and treatment of dyslipidemia of HIV-infected patients, implications of treatment-related dyslipidemia in other chronically ill populations, and pharmacokinetic profiles for the available hypolipidemic agents in non-HIV populations were considered. Although the implications of dyslipidemia in this population are not fully known, the frequency, type, and magnitude of lipid alterations in HIV-infected people are expected to result in increased cardiovascular morbidity. We propose that these patients undergo evaluation and treatment on the basis of existing guidelines for dyslipidemia, with the caveat that avoidance of interactions with antiretroviral agents is paramount.

The Cardiovascular Disease Focus Group, under the auspices of the Complications Research Agenda Committee of the Adult AIDS Clinical Trials Group (AACTG), has recommended that guidelines be developed for use by the AACTG and clinicians to address the approach to lipid abnormalities in the setting of highly active antiretroviral therapy (HAART). We plan to perform regular updates of this work as additional information becomes available from clinical and pharmacokinetic trials. Thus this document should be viewed as a work in progress, similar to the guidelines for the use of antiretroviral (ARV) therapy from the Panel on Clinical Practices for Treatment of HIV Infection. In the absence of definitive data on this important subject, we have drafted these preliminary guidelines to assist clinicians in the evaluation and management of dyslipidemia in adults infected with HIV and receiving ARV therapy.

Background

Abnormalities of lipid metabolism in HIV-infected patients were described well before the advent of HAART [1–6]. Increases in serum triglyceride levels [1] and decreases in cholesterol levels [6] have been associated with disease progression. Patients with AIDS have also had lower levels of high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol, decreased triglyceride clearance, and a greater prevalence of the LDL-B phenotype (predominance of small, dense LDL particles) compared with control patients [2, 4]. Therapy with zidovudine has been associated with a decline, rather than an increase, in serum triglyceride levels [7].
Significant increases in triglyceride and cholesterol concentrations have been associated with all the available protease inhibitors (PIs) [8–22]. Lipid elevations have also been reported in patients receiving nonnucleoside reverse transcriptase inhibitor (NNRTI) therapy [23]. Hypertriglyceridemia associated with PI therapy may be extreme at times [8, 9, 24] with elevations of >1000 mg/dL, particularly with ritonavir. Of particular concern are the increases in LDL cholesterol accompanied by preexisting low levels of HDL [11]. Mulligan and colleagues [11] reported that, compared with a control group receiving lamivudine-based ARV, recipients of PI had a mean cholesterol increase of 32 mg/dL at a mean of 3.4 months of therapy, which included a 27% increase (18 mg/dL) in directly measured LDL cholesterol. Although effective interventions do not yet exist, elevations in lipoprotein(a) could also lead to an increase in CHD risk. These have occurred in both HIV-infected [21] and uninfected [25] subjects receiving PI therapy.

Dyslipidemia appears to be a prevalent condition among patients receiving HAART [13, 20, 26]. Henry et al. [13] have reported that 62 (47%) of 133 PI recipients at one clinic had lipid abnormalities that met the National Cholesterol Education Program (NCEP) guidelines [27] intervention criteria. Behrens et al. [26] have reported that 56 (57%) of 98 PI recipients had hyperlipidemia. Of those, 11% had Fredrickson type IIa hyperlipidemia, 32% type IIb, and 53% type IV or V. Similarly, Keruly et al. [14] have reported that PI recipients were 4.2 times more likely to experience a 50 mg/dL increase of total cholesterol to a level of >200 mg/dL compared with patients not receiving PI (14% vs. 3%). A subset of patients appear to experience extreme elevations of cholesterol to levels of >400 mg/dL (K. Henry, personal communication). A study of ritonavir therapy in HIV-uninfected people who were free of the confounding effects of HIV infection itself, free of other antiviral medications, and free of “HIV-related” immune changes clearly established that this PI can directly cause major increases in lipid levels within 2 weeks of initiation [25]. Total cholesterol increased by 24% and triglycerides increased by 137%. Although a causal relationship between PI therapy and all observed lipid abnormalities has not been definitively established, the high prevalence of dyslipidemia superimposed on a background of disturbed lipid metabolism remains a major concern. Additional unanswered questions include whether non–PI-containing regimens or newer PIs will prove to have different effects on lipid metabolism.

Although anecdotal reports suggest that serious premature vascular events may be related to PI therapy [28–31], it is not yet known whether the lipid perturbations that exist during HAART represent a significant risk factor for development of cardiovascular disease. So far, studies of cardiovascular disease incidence have been limited by brief follow-up periods. Nonetheless, these observations are a reason for heightened concern for the eventual development of increased cardiovascular complications as AIDS-associated mortality decreases because of HAART. It is possible that HIV treatment–related dyslipidemia may have a particularly atherogenic tendency when combined with other HIV-associated and treatment-associated metabolic abnormalities, such as insulin resistance [10, 32, 33], visceral adiposity [34], and chronic infection and immune activation.

On the basis of precedent in other disease states, there is reason to believe that HIV treatment–associated changes in lipid levels are likely to result in some degree of increased cardiovascular risk. For example, subjects with rheumatoid arthritis die predominantly of cardiovascular disease, which accounts for nearly 50% of all deaths [35]. Even though the immune aspects of this disorder may contribute to this outcome, multivariate analyses of the data indicate that corticosteroid use increases mortality, as well as blood pressure and cholesterol levels [36]. Similarly, patients with systemic lupus erythematosus (SLE) have 9-fold the risk of death from coronary artery disease than would be expected on the basis of age and sex [37]. Along with older age and duration of SLE, blood pressure, cholesterol, and duration of prednisone use were relevant to the presence of coronary heart disease (CHD) [38]. It is a considerable problem in that 8% of 225 patients (mean age, 38 years) in this Hopkins Lupus cohort had CHD. After renal transplant, CHD risk is thought to increase 3–5 times, with noted associations with prednisone and cyclosporine use [39]. Heart transplant patients also have similar treatment–related elevations in lipids, and 2 studies have now suggested that lipid-lowering regimens decrease the incidence of vasculopathy [40, 41]. It appears likely that the chronic presence of traditional cardiovascular risk factors increases risk regardless of the etiology, and this same potential certainly exists during the long-term management of HIV-infected subjects.

Drug treatment of HIV-infected patients with dyslipidemia is particularly problematic because of the potential for drug interactions. However, on the basis of the limited available data, tentative guidelines for management are proposed with the understanding that major changes in these guidelines are inevitable as research experience with dyslipidemia in the setting of HIV infection broadens. Furthermore, clinicians must keep in mind that many patients may be at only minimally increased risk due to dyslipidemia. Thus it may be preferable to delay drug therapy in those patients until more is known about the safety and efficacy of drug treatment in this population. As is the case for the general population, the use of nondrug therapies, particularly for those at low risk of cardiovascular complications (i.e., no history of CHD and no significant CHD risk factors) needs to be stressed. Providers caring for HIV-infected patients will need to become adept at evaluating and intervening for modifiable CHD risk factors, which are often associated with greater risk than dyslipidemia alone.

Effects of Switching Antiviral Therapies

Substituting an antiviral agent with a lesser tendency to induce dyslipidemia for an agent with a greater tendency may be
an attractive approach. One published study [42] and 2 abstracts [43, 44] suggest that, in NNRTI-naive patients, substituting nevirapine for PI therapy can improve the patient’s lipid profile. Several studies that have been presented in abstract form [45–50] indicate that the substitution of efavirenz for PI has not consistently had a beneficial effect. Only 1 NNRTI substitution trial has included a control arm that continued PI therapy [43]. Trends for improvement in lipid levels have also been reported with the substitution of abacavir for PI in several abstracts [51–53]. High rates of virologic relapse with substitution of an NNRTI or abacavir for PI have not been reported in these small studies. In practice, however, many patients will have already received NNRTI therapy or are extensively NRTI experienced, and the long-term virologic efficacy of switching is unknown. At present, to our knowledge, there are no studies that compare the effects of treatment switching with those of adding lipid-lowering agents to ongoing successful therapy. Clinicians will need to weigh the risks of new treatment-related toxicities and the possibility of virologic relapse when switching from a PI-based regimen to an NNRTI-based or abacavir-based regimen against the risks of potential drug interactions and new treatment-related toxicities from lipid-lowering agents added to PI-based regimens.

**Evaluation of Patients**

Serum lipids should be evaluated after the patient has fasted for a minimum of 8 h, and preferably for 12 h. Although total cholesterol and HDL cholesterol are not markedly altered when tested in patients who do not fast, measurement of triglycerides and thus the calculation of LDL cholesterol must be performed in a patient who has fasted. In general, the standard screening lipid profile should include measurement of total cholesterol, HDL cholesterol, and triglycerides. LDL and very-low-density lipoprotein cholesterol can then be calculated from standard formulas using these measured values. It is recommended that a fasting lipid profile be obtained before therapy. This should be repeated within 3–6 months after the initiation of HAART. For people with elevated triglycerides levels at baseline, it may be preferable to repeat a lipid profile sooner, within 1–2 months of initiating HAART.

Fasting triglyceride levels will exceed 400 mg/dL in a substantial proportion of PI-treated patients with HIV and will make calculation of LDL cholesterol unreliable. Direct measurements of LDL cholesterol may not be readily available in some clinical laboratories. In patients whose LDL cholesterol cannot be measured because of this, initial intervention decisions can be based on the total cholesterol level, HDL cholesterol level, and triglycerides. The treating clinician must keep in mind that, with high triglyceride levels, total cholesterol levels can be misleading, especially if used as a surrogate for LDL cholesterol treatment.

Patients should be routinely screened for other cardiovascular risk factors such as smoking, hypertension, menopausal status, physical inactivity, obesity, and diabetes. Patients’ family histories should also be assessed for risk factors. In addition, patients with dyslipidemia should be screened for potential exacerbating factors 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 and estrogens on both cholesterol and triglyceride values.

**Who Needs Therapy for Dyslipidemia?**

Hypercholesterolemia. It is reasonable to assume that dyslipidemia in otherwise well-controlled HIV-infected patients will have similar, and perhaps greater, long-term consequences, as does dyslipidemia in the general population. For the purposes of initiating therapy for dyslipidemia, the NCEP guidelines [27] represent a reasonable starting point for HIV-infected patients (table 1).

The primary goals of the NCEP guidelines focus on LDL cholesterol; however, and as stated above, estimation of LDL cholesterol is unreliable in people who are hypertriglyceridemic (serum triglycerides >400 mg/dL). For those patients with serum triglycerides >400 mg/dL, a total cholesterol level of >240 mg/dL or an HDL cholesterol level of <35 mg/dL should prompt initial therapeutic intervention with dietary measures.

Hypertriglyceridemia. Nondrug therapies for elevated triglycerides (e.g., diet and exercise) would be expected to produce little, if any, morbidity and should be initiated in anyone with fasting serum triglyceride levels >200 mg/dL. Elevated triglyceride levels represent an independent risk factor for cardiovascular disease. Historically, this risk was thought to be largely mediated by other risk factors such as low HDL cholesterol [27]. New evidence demonstrates increased CHD risk in people whose triglyceride values are only modestly elevated (200–400 mg/dL). A meta-analysis suggests triglyceride level is an independent risk factor even after adjustment for HDL cholesterol.

**Table 1. National Cholesterol Education Program Treatment decisions made on the basis of low-density lipoprotein cholesterol levels.**

<table>
<thead>
<tr>
<th>Patient statusa</th>
<th>Initiate dietary intervention</th>
<th>Consider drug therapy</th>
<th>LDL-C goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Without CHD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;2 risk factors</td>
<td>&gt;160</td>
<td>&gt;190</td>
<td>&gt;160</td>
</tr>
<tr>
<td>&gt;2 risk factors</td>
<td>&gt;130</td>
<td>&gt;160</td>
<td>&gt;130</td>
</tr>
<tr>
<td>With CHD</td>
<td>&gt;100</td>
<td>&gt;130</td>
<td>&lt;100</td>
</tr>
</tbody>
</table>

**NOTE.** Data are in mg/dL. CHD, coronary heart disease; LDL, low-density lipoprotein. Adapted from National Cholesterol Education Program [27].

a Risk factors include age (men aged >45 years, women aged >55 years or who experienced premature menopause that is not being treated with estrogen replacement therapy), family history of CHD (first-degree male relative with CHD before 55 years of age or first-degree female relative before 65 years of age), current cigarette smoking, hypertension, low HDL cholesterol (<35 mg/dL), diabetes mellitus. In the presence of high HDL cholesterol (>60 mg/dL), subtract 1 risk factor.
terol [54]. A recent study of gemfibrozil therapy for secondary prevention of CHD in men with low HDL cholesterol (<40 mg/dL), but normal values of LDL cholesterol (<140 mg/dL) and a high prevalence of characteristics associated with the metabolic syndrome, showed a 24% reduction in the risk for major cardiovascular events [55]. At 1 year, recipients of gemfibrozil therapy had 31% lower mean triglyceride levels and 6% higher mean HDL cholesterol levels, whereas LDL cholesterol levels did not differ significantly, suggesting that lowering triglyceride levels and raising HDL levels in patients with relatively normal levels of LDL cholesterol can have a major impact on cardiovascular disease.

The absolute value at which drug therapy should be given for isolated hypertriglyceridemia is not defined, but in the absence of CHD risk factors or hypercholesterolemia, elevations beyond 1000 mg/dL (unresponsive to nondrug therapies) carry an increased risk of pancreatitis. Drug therapy should be strongly considered for these people. Patients with histories of pancreatitis may represent a group for whom a lower threshold of triglyceride elevation is appropriate, such as >500 mg/dL.

For patients with extreme elevations (i.e., triglycerides >2000 mg/dL), it is reasonable to initiate nondrug and drug therapies concurrently. For people with isolated hypertriglyceridemia who are at increased risk for CHD or who have established CHD, the threshold level at which drug therapy should be initiated is also not defined. In these patients, drug therapy should be considered when a thorough trial of nondrug therapies fails to result in desirable triglyceride levels. It should be noted that there are significant differences in optimal dietary therapy for patients with severe hypertriglyceridemia and for patients with hypercholesterolemia.

Treatment

Hypercholesterolemia. Nondrug therapies [27] 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 in patients with known established CHD or when there are extreme elevations in cholesterol (>400 mg/dL). Dietary needs are frequently competing in the HIV-infected population, where the need for lipid lowering and weight gain may coexist in patients, who often experience prominent gastrointestinal symptoms. In many patients, it is preferable to address their wasting before their dyslipidemia. Clinicians should consider consultation with a dietitian 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 a recent report of HIV-infected patients [13]. Attention must be given to other correctable risk factors for CHD, such as cigarette smoking, obesity, physical inactivity, diabetes mellitus, and hypertension. Estrogen replacement therapy can be considered where appropriate but may exacerbate hypertriglyceridemia and should be used with caution when baseline triglyceride levels are elevated.

Despite reduction in LDL cholesterol and increased HDL cholesterol, a recent study of estrogen-progestin replacement in secondary CHD prevention showed an early increase in CHD events that offset a later reduction in risk [56], suggesting that this therapy may not be appropriate for the sole purpose of secondary prevention.

Drug therapies for hypercholesterolemia in HIV-infected patients receiving PIs are problematic. The 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, or statins, have been used extensively for first-line therapy for hypercholesterolemia in other settings. Considerable evidence demonstrates their beneficial effects in both reducing the risk of CHD in patients without prior CHD (primary prevention) as well as reducing the progression of coronary artery stenoses and risk of recurrent CHD events (secondary prevention) [57].

The US Food and Drug Administration (FDA) has approved a number of statins for the treatment of hyperlipidemia, including pravastatin, simvastatin, lovastatin, atorvastatin, cerivastatin, and fluvastatin (table 2). Most statin agents can provide similar lowering of LDL cholesterol, even though to a modest extent simvastatin, but particularly atorvastatin, can more substantially influence these cholesterol levels [58]. Simvastatin and lovastatin contain a lactone ring and require metabolism in vivo to release the active component of the drug. Most other metabolites are formed via cytochrome P450 3A4, which are likely to result in interactions between these drugs and CYP3A4 inhibitors such as HIV PIs and the NNRTI delavirdine. Major interactions have been documented for the combination of lovastatin and the potent CYP3A4 inhibitor itraconazole [59] and for the combination of simvastatin and itraconazole [60]. Compared with simvastatin and lovastatin, the disposition of atorvastatin appears to be considerably less affected by inhibitors of CYP3A4. With itraconazole, a 3-fold increase in atorvastatin area under the concentration-time curve and half-life has been demonstrated [61].

<table>
<thead>
<tr>
<th>Agent</th>
<th>Considerations</th>
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<tbody>
<tr>
<td>Lovastatin, simvastatin</td>
<td>Extensively metabolized by CYP3A4; toxicity likely when combined with protease inhibitors.</td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>Metabolized by CYP2C9; interaction with neflina-vir likely.</td>
</tr>
<tr>
<td>Cervitatin</td>
<td>Newest agent; relatively limited published data on drug interactions. May have low likelihood for interactions.</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>Some CYP3A4 metabolism; small amount of anecdotal and research experience in HIV. Modest increases in AUC when coadministered with ritonavir-saquinavir.</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>No significant p430 interactions, primarily renal excretion. Minimally decreased AUC when coadministered with ritonavir-saquinavir.</td>
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</tbody>
</table>

NOTE. AUC, area under the curve.
est statin agent, demonstrates continued biotransformation despite inhibition of CYP3A4, indicating that alternative enzymes also participate in its metabolism. Currently, cerivastatin is found to be processed through both CYP3A4 and 2C8 [62], suggesting its levels may not be significantly altered by PIs, although data are lacking in this regard. Fluvastatin is metabolized by and appears to inhibit CYP2C9 [63]. Pravastatin may be the statin least susceptible to interaction with the CYP3A4 inhibitor itraconazole [60]. It is mainly eliminated unchanged, and it appears that CYP isozymes play only a negligible role in the metabolism of pravastatin [64]. A recent abstract reported that, in HIV-uninfected subjects, the median 24-h concentration area under the curve for pravastatin coadministered with ritonavir-saquinavir decreased a median of 0.5-fold (P < .05), whereas there was a 32-fold increase for simvastatin (P < .001) and a 4.5-fold increase for atorvastatin (P < .001) [65]. Total active atorvastatin levels (which includes atorvastatin plus the 2-hydroxy and 4-hydroxy atorvastatin metabolites) increased by a lesser amount, 74% [66].

Potential problems include significantly increased skeletal muscle toxicity due to increased levels of statins, caused by CYP3A4 inhibition by HIV PIs, and lower levels of PIs (possibly leading to virologic failure), caused by P450 induction by statins. Elevated levels of statins have been associated with the development of rhabdomyolysis, such that the FDA has issued warnings about the use of these medications in patients known to be taking an agent that inhibits metabolism. Similarly, interactions between statin agents and the CYP3A4 inducers nevirapine and efavirenz are possible, and such interactions could result in lower serum concentrations of statins.

None of the statins are known to be strong inhibitors or inducers of CYP3A4, although data are limited in this regard. If this is indeed the case, it is unlikely that the statins would significantly lower or raise levels of PIs. One in vivo study indicates no effect of fluvastatin on cyclosporine trough levels, a drug also metabolized by CYP3A4 [67]. However, in vitro, fluvastatin selectively inhibits CYP2C9 [63]. The active metabolite of nelfinavir is principally formed via the action of CYP isozymes other than CYP3A4, such as CYP2C19 [68]. Because fluvastatin is known to inhibit some of these enzymes, such as CYP2C9, it is possible that a significant drug interaction may result in decreased levels of the active metabolite of nelfinavir.

A small preliminary report of the use of atorvastatin in 29 HIV-infected subjects receiving PIs [13] reported no adverse virologic events during monthly monitoring of plasma HIV RNA levels (K. Henry, personal communication). Pravastatin appeared to have no significant effect on nelfinavir concentrations [66]. However, additional study is needed to define potential statin effects on PI disposition. Given the above potential interactions, it is reasonable to recommend the use of low initial doses of either pravastatin (20 mg daily) or atorvastatin (10 mg daily) in patients with HIV who require drug therapy for hypercholesterolemia and who are taking PIs. Fluvastatin and cerivastatin are acceptable alternative agents, but no data on interaction with PIs have been reported. Lovastatin and simvastatin should be avoided.

Fibrates are viable alternative agents for hypercholesterolemia when it is accompanied by elevated triglycerides. Lipoprotein lipase activity is decreased in hyperlipidemic HIV-infected subjects treated with PIs [69, 70], and there is a shift to the more atherogenic dense LDL [71]. Because fibrates augment LPL activity [72, 73] and also induce a reduction of dense LDL [74], these drugs are reasonable initial choices for treatment of HIV-infected patients with elevations of both cholesterol and triglycerides. Henry et al. [13] have reported a 32% reduction in total cholesterol level in 25 HIV-infected subjects treated with gemfibrozil 600 mg b.i.d. Although fibrates are also metabolized by hepatic p450 enzymes, they appear to primarily affect only CYP4A [75], and clinically significant drug interactions with PIs are unlikely. Although they generally have a greater effect on lowering triglycerides than on LDL cholesterol, many patients will also have hypertriglyceridemia and low HDL cholesterol, which tend to improve with use of fibrates. In the Helsinki Heart Study, the subjects who benefitted most from gemfibrozil therapy were those with high triglycerides and low HDL cholesterol [76], a common profile of the dyslipidemic patient receiving PI therapy. Although fibrates lack the extensive documented benefit on clinical outcomes that the statins possess, their use has been associated with less angiographic progression in certain groups of patients with known CHD [77, 78] as well as reductions in event rates [55, 79]. Concomitant use of fibrates and statin agents may increase the risk of skeletal muscle toxicity, and they should be used together only with caution.

An alternative to gemfibrozil, fenofibrate, recently introduced in the United States after many years of use in Europe, is generally metabolized through a noncytochrome P450 pathway, primarily glucuronide conjugation, with the inactive conjugate mostly excreted in the urine [73]. This fibric acid derivative is therefore unlikely to substantially affect PI levels. Unlike gemfibrozil, data are lacking that demonstrate a reduction in cardiovascular end points with the use of fenofibrate. Although fenofibrate may have potential advantages over gemfibrozil, such as more favorable effects on LDL cholesterol and greater ease of administration, at present there is no compelling reason to prefer fenofibrate to gemfibrozil in HIV-infected patients.

Niacin lowers LDL levels but produces frequent cutaneous flushing and pruritus. Because it causes insulin resistance [80, 81] (even in people without diabetes), niacin should be avoided as first-line therapy in patients receiving HIV PIs. Bile sequestering resins (e.g., cholestyramine and colestipol) are discouraged because their use can be associated with increased triglyceride levels, and their effects on antiviral drug absorption have not been studied.

**Choice of initial drug treatment for hypercholesterolemia (table 3)**. On the basis of statins’ efficacy in other groups of
patients, they represent the reasonable initial choice for the drug treatment of isolated elevation of LDL cholesterol. Until more detailed pharmacokinetic data are available, either pravastatin (20 mg/d initial dose) or atorvastatin (10 mg/d initial dose) is recommended, along with careful monitoring of virologic status and creatine kinase values. Cervinast and fluvastatin are reasonable alternative statin agents. Fibrates, either gemfibrozil (600 mg b.i.d.) or micronized fenofibrate (200 mg once daily), are reasonable alternative agents when statins are not appropriate or when patients fail to respond to adequate doses of statins. Fenofibrate may be preferable because of its greater effects on LDL cholesterol [73]. There exists the possibility of increased risk of myopathy when a fibrate such as gemfibrozil is combined with a statin [27].

Many HIV-infected patients will fall under the classification of combined hyperlipidemia—that is, hypercholesterolemia with hypertriglyceridemia. Either gemfibrozil or fenofibrate or a statin agent represent reasonable initial choices for management.

Hypertriglyceridemia. 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 intervention resulted in a 21% decrease in triglyceride levels in a recent report on HIV-infected patients [13]. Smoking cessation and regular aerobic exercise are general health measures that will reduce triglyceride levels and improve the overall cardiovascular risk profile. Weight reduction should be strongly encouraged if the patient is obese. Fat intake should be decreased, but a concomitant increase in carbohydrate intake may raise triglyceride and lower HDL levels. If this occurs, replacing some of the saturated fat with monounsaturated fat, which will not raise LDL cholesterol, may be valuable. Severe hypertriglyceridemia and hyperchylomicronemia require very-low-fat diets, avoidance of free sugars, and decreased alcohol intake. Fish oils (omega-3 fatty acid supplements) variably decrease triglyceride synthesis and may be tried in patients with severe hypertriglyceridemia (e.g., >1000 mg/dL). At times, omega-3 fatty acid supplement can be associated with further increases in triglyceride levels. Hellerstein et al. [82] demonstrated reduced triglyceride levels with fish oil supplementation in hypertriglyceridemic patients with AIDS wasting, but this approach has not been tested in PI recipients. Although there is some concern about increased insulin resistance in patients with diabetes receiving large doses of omega-3 fatty acids [83, 84], moderate doses (1.7 g/d) do not appear to have this effect [85].

Fibrates represent the cornerstone of drug therapy for hypertriglyceridemia (table 3). Treatment is with gemfibrozil (600 mg b.i.d. 30 min before the morning and evening meals) or micronized fenofibrate (200 mg once daily). Gemfibrozil resulted in a 57% reduction in triglyceride levels and a 32% reduction in cholesterol in HIV-infected patients receiving PIs [13]. Significant drug interactions with common agents used in HIV treatment are unlikely to occur, but these have not yet been studied.

Niacin is effective therapy for hypertriglyceridemia but produces frequent cutaneous flushing and pruritus. Because of its propensity to cause insulin resistance [80, 81] (even in people without diabetes), niacin should be avoided as first-line therapy in patients receiving HIV PIs. Analysis of preliminary data suggests that atorvastatin is safe and effective for lowering triglyceride levels in HIV-infected patients receiving PIs [13]. However, only small numbers of patients were studied; thus further data are needed on pharmacokinetic interactions and virologic outcomes before the use of this agent can be routinely recommended. As a class, HMG-CoA reductase inhibitors are not generally recommended as first-line therapy for isolated hypertriglyceridemia. However, all statins are effective at lowering triglyceride levels when baseline values are elevated [86]. If the use of a fibrate results in inadequate triglyceride lowering, or if LDL levels remain elevated, a cautious trial addition of a statin agent should be considered.

Conclusions

Dyslipidemia is emerging as an important problem in HIV-infected patients on ARV therapy. Although the long-term consequences are unknown, on the basis of experience in other disease states whose therapy is associated with lipid perturbations, it is reasonable to recommend that HIV-infected patients should undergo evaluation and treatment on the basis of the current NCEP guidelines. However, because of the potential for significant drug interactions with commonly used

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**Table 3. Choice of drug therapy for dyslipidemia in people infected with human immunodeficiency virus who are receiving highly active antiretroviral therapy.**

<table>
<thead>
<tr>
<th>Lipid abnormality</th>
<th>First choice</th>
<th>Second choice*</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isolated high low-density lipoprotein cholesterol</td>
<td>Statin</td>
<td>Fibrate</td>
<td>Start with low doses of statins and titrate upward. Patients on protease inhibitors may have increase risk of statin-induced myopathy.</td>
</tr>
<tr>
<td>Combined hyperlipidemia (high cholesterol and high triglycerides)</td>
<td>Fibrate or statin</td>
<td>If starting with fibrate, add statin; if starting with statin, add fibrate Statin</td>
<td>Combining statin and a fibrate may increase risk for myopathy. Combining statin and a fibrate may increase risk for myopathy.</td>
</tr>
<tr>
<td>Isolated hypertriglyceridemia</td>
<td>Fibrate</td>
<td></td>
<td></td>
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* Or if additional treatment is needed.
ARV drugs, the choices of lipid-lowering agents should be limited to those drugs 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 these recommendations represent a useful starting point for the approach to management of dyslipidemia in these people.

Acknowledgments

We wish to thank Dr. John Gerber, for his helpful comments, and Gina-Bob Dubé, for her assistance with the references.

References


