REVIEW

Evaluation and Management of Dyslipidemia in Patients with HIV Infection

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OBJECTIVE: **Persons with HIV infection develop metabolic abnormalities related to their antiretroviral therapy and HIV infection itself. The objective of this study was to summarize the emerging evidence for the incidence, etiology, health risks, and treatment of dyslipidemias in HIV disease.**

DESIGN: **Systematic review of original research with quantitative synthesis.**

MAIN RESULTS: **Dyslipidemia is common in persons with HIV infection on highly active antiretroviral therapy (HAART), but methodologic differences between studies preclude precise estimates of prevalence and incidence. The typical pattern includes elevated total cholesterol, low-density lipoprotein cholesterol, and triglycerides, which may be markedly elevated. The dyslipidemia may be associated with lipodys-trophy, insulin resistance, and, rarely, frank diabetes mellitus. Exposure to protease inhibitors (PIs) is associated with this entire range of metabolic abnormalities. PI-naïve patients on nucleoside reverse transcriptase inhibitors (NRTIs) may develop lipodystrophy, insulin resistance, hypercholesterolemia, and possibly modest elevations in triglycerides but not severe hypertriglyceridemia, which appears to be linked to PIs alone. Most studies have not found an association between CD4 lymphocyte count or HIV viral load and lipid abnormalities. The pathogenesis is incompletely understood and appears to be multifactorial. There are insufficient data to definitively support an increased coronary heart disease risk in patients with HIV-related dyslipidemia. However, some of the same metabolic abnormalities remain firmly established risk factors in other populations. Patients on HAART with severe hypertriglyceridemia may develop pancreatitis or other manifestations of the chylomicronemia syndrome. Some of the metabolic derangements (particularly hypertriglyceridemia) may improve upon replacing a PI with a nonnucleoside reverse transcriptase inhibitor. The limited experience suggests that fibrates, pravastatin, and atorvastatin can safely treat lipid abnormalities in HIV-infected patients.**

CONCLUSIONS: **Patients with HIV infection on HAART should be screened for lipid disorders, given their incidence, potential for morbidity, and possible long-term cardiovascular risk. Treatment decisions are complex and must include assessments of cardiac risk, HIV infection status, reversibility of the dyslipidemia, and the effectiveness and toxicities of lipid-lowering medications. The multiple potential drug interactions with antiretroviral or other HIV-related medications should be considered in lipid-lowering drug selection and monitoring.**

KEY WORDS: **hyperlipidemia; triglycerides; HIV; lipodystrophy; protease inhibitors; HAART.**
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Highly active antiretroviral therapy (HAART), in combinations including protease inhibitors (PIs), has achieved sustained suppression of HIV replication and reduced morbidity and mortality rates in patients with advanced HIV infection.[1–3] For many patients, HIV infection has become a chronic disease, requiring long-term management strategies and greater attention to disease prevention issues. In terms of coronary heart disease (CHD) risk, many of these patients develop dyslipidemia, which may be associated with insulin resistance, glucose intolerance, and fat redistribution.[4,5] This constellation of metabolic abnormalities has been termed the HIV-related lipodystrophy syndrome. The pathogenesis is unknown but appears to be multifactorial, involving interactions between host genetic factors, HIV infection, and antiretroviral drugs. While estimates of prevalence vary widely, up to 50% of patients with HIV infection develop 1 or more features of the syndrome,[4,6] putting them at risk for complications of severe hypertriglyceridemia, psychological morbidity, and possibly accelerated atherosclerosis and CHD. In managing these metabolic disturbances, physicians face the difficult decision to alter antiretroviral therapy, often despite sustained HIV viral suppression, or to initiate pharmacologic treatment.

In this article, I review the emerging evidence for the characteristics, incidence, etiology, CHD risks, noncardiac complications, and treatment of dyslipidemias in HIV disease and offer an approach to evaluation and management.

METHODS

Review Process

I searched the MEDLINE database from 1985 to April 2002 and the AIDSLINE database from 1985 to December 2000, combining the MeSH heading "HIV" with the headings "hyperlipidemia, cholesterol, triglycerides, lipodystrophy, diabetes mellitus, insulin resistance, glucose intolerance, *or* coronary disease." I also reviewed the reference lists of the retrieved articles. I included any article that reported primary data on lipid abnormalities in patients with HIV infection. Because this is a rapidly evolving field and, for many clinical questions, the evidence is limited to case series or small observational studies, I chose not to exclude any articles on methodologic grounds. Rather, I noted methodologic limitations in the text and tempered my inferences and recommendations accordingly. I excluded newsletter articles and abstracts of conference proceedings because of the lack of peer review and access to detailed reports of the studies. My synthesis was strictly qualitative, since the individual studies were too clinically heterogeneous and methodologically variable to justify a quantitative summary of the data.

RESULTS

My review included 93 published articles, including 17 case reports or case series, 14 cross-sectional studies, 26 cohort studies, 13 trials, and 10 biochemical or physiologic studies.

Characteristics, Predictors, and Prevalence of Dyslipidemia in Patients with HIV Infection

In the pre-HAART era, the few studies examining lipid levels in patients with HIV disease focused on lipid levels as markers of chronic inflammation. Investigators documented depressed total cholesterol and low-density lipoprotein (LDL) levels in patients with early disease and predominantly modestly elevated triglycerides in patients with advanced HIV infection.[7,8] High-density lipoprotein (HDL) cholesterol was lower in patients with lower CD4 lymphocytes and more immune activation.[9]

In recent years, clinicians observed elevated cholesterol and often markedly elevated triglyceride levels in HIV patients maintained on HAART. The dyslipidemia was often associated with other metabolic abnormalities, including insulin resistance and lipodystrophy, characterized by accumulation of visceral fat, an enlarged dorsocervical fat pad, and atrophy of subcutaneous fat in the face, buttocks, and extremities. This constellation of findings has been termed the HIV-related lipodystrophy syndrome. In many ways, it resembles the rare congenital and autoimmune disease-related lipodystrophy syndromes.[10]

Association with HAART, Including PIs. Several case reports[11–14] and cross-sectional studies[15–19] found an association between PI exposure and hypercholesterolemia and hypertriglyceridemia. In one of these studies, the same differences persisted after following the patients for 2 years.[4] In addition, many pre–post longitudinal studies found higher cholesterol and triglyceride levels in patients after they started taking PIs (Table 1). Many of these reports included PI-exposed patients with severe hypertriglyceridemia (>1,000 mg/dL). Compared to other PIs, ritonavir was associated with a higher rate of hypertriglyceridemia.[5,19–21]

All of the studies that examined cholesterol fractions found significantly higher LDL levels in patients exposed to PIs.[4,15,20,22,23] Three of the 4 studies that documented HDL cholesterol showed lower HDL cholesterol values in PI-exposed patients, but none of the differences achieved statistical significance.[15–17,20] Hypoalphalipoproteinemia would be expected, since it is associated with hypertriglyceridemia.

In addition, several investigators determined predictors of dyslipidemia in multivariate analyses of longitudinal data. In a 5-year retrospective cohort study, PI use (incidence rate ratio [IRR] = 6.1), baseline triglycerides (IRR = 2.9), and baseline hyperglycemia (IRR = 3.4) were independently associated with hypertriglyceridemia.[5] Hypercholesterolemia was associated with PI use (IRR = 2.8) and also with nucleoside reverse transcriptase inhibitor (NRTI) regimens not including PIs (IRR = 2.5). Notably, HIV RNA levels, CD4 cell count, and weight change were neither predictors of hyperlipidemia nor confounders of the relationship with PIs. In another longitudinal study, which examined time-dependent factors in a multivariate analysis, the initiation of PIs was a strong independent predictor of hypertriglyceridemia.[24] And finally, Vergis et al. demonstrated that adherence to a PI-containing HAART regimen was associated with a greater likelihood of developing elevated LDL cholesterol and severe (>800 mg/dL) hypertriglyceridemia.[23]

Association with NRTIs in PI-naïve Patients. Although the above studies clearly suggest a role of protease inhibitors in the etiology of the HIV-related lipodystrophy syndrome, the fat redistribution has been observed in PI-naïve patients taking various combinations of NRTIs.[25–31] And in a randomized trial, there was a higher incidence of lipodystrophy in patients receiving ritonavir, saquinavir, and stavudine than in patients taking the 2 PIs alone.[32] In 2 multivariable analyses of cross-sectional and longitudinal data,[6,33] the use of several NRTIs persisted as an independent risk factor for lipodystrophy, but did not in a third.[5] Among the NRTIs, stavudine had the strongest and most consistent association with fat redistribution in many of these studies.

The association between NRTIs and dyslipidemia is less clear. A small cross-sectional study found higher triglyceride levels in patients taking stavudine.[26] In a prospective but uncontrolled study, Galli et al. followed 335 PI-naïve patients taking 2 NRTIs for a median exposure

of 748 days. Ten percent of patients developed total cholesterol levels >250 mg/dL, and 23% developed triglyceride levels >200 mg/dL.[30] Exposure to stavudine in this cohort was associated with an increased risk of developing hypertriglyceridemia. However, 3 longitudinal controlled studies did not find association between NRTIs and hypertriglyceridemia.[5,24,29] In one of these cohort studies, patients had an increased risk of lipodystrophy upon the initiation of any HAART regimen, but developed hypertriglyceridemia only after exposure to PIs.[29] In another, NRTI exposure *was* associated with the development of hypercholesterolemia but not hypertriglyceridemia.[5]

Association with Non-nucleoside Reverse Transcriptase Inhibitors in PI-naïve Patients. None of the non-nucleoside teverse transcriptase inhibitors (NNRTIs) have been definitely implicated in the development of dyslipidemia or any component of the HIV-related lipodystrophy syndrome. Most of data on NNRTIs comes from "switching studies" (see reversibility section below), in which NNRTIs were substituted for PIs in patients with dyslipidemia. In a cross-sectional study of 351 patients referred for dyslipidemia, total cholesterol was higher in patients on 1 NRTI, 1 NNRTI and a PI than in patients on 2 NRTIs and a PI.[18] There was no difference in triglyceride levels.

Additional Associations with Dyslipidemia. In terms of additional predictors (beyond HAART regimens) of dyslipidemia, studies consistently identify nutritional factors but vary in finding associations with HIV status factors. Nonetheless, a few well-conducted analyses did not find associations with indicators of HIV infection status, such as CD4 lymphocyte count or HIV viral load.[5,24,30] In addition, several studies found a correlation between fat redistribution and lipid disorders[16,34,35] while others found no difference in lipid metabolism in patients with or without lipodystrophy.[36,37]

Prevalence and Incidence of Lipid Disorders. It is not possible to derive a precise incidence of dyslipidemias from these studies, since they used different observation periods, cut-off values for "hyperlipidemia," and definitions of "lipodystrophy," and included patients with lipid disorders at baseline. Using 200 to 240 mg/dL as a threshold for "hypercholesterolemia," prevalence rates range from 33% to 82% in patients on PIs.[15,16,20,38] The prevalence range for triglycerides >200 to 250 mg/dL was 43% to 66%.[15,16,23,38]

Only 2 studies collected incidence data. Tsiodras et al. determined a 24% 5-year cumulative incidence rate of hypercholesterolemia (>240 mg/dL) and a 19% incidence of hypertriglyceridemia (>500 mg/dL) in patients on HAART, with most of these events occurring after the initiation of PI therapy.[5] And in a 2-year longitudinal study, Galli et al. found a 10% incidence of hypercholesterolemia (>250 mg/dL) and a 23% incidence of hypertriglyceridemia (>200 mg/dL) in PI-naïve patients taking 2 NRTIs.[30]

Similarly, estimates of the incidence of fat redistribution vary widely, depending on study methodology. Two studies found a greater risk of developing fat redistribution in women.[30,39] While one can demonstrate insulin resistance and impaired glucose tolerance (by glucose tolerance tests) in many of these patients, the prevalence of frank diabetes mellitus is low.[4,16,40]

In summary, while many of these studies suffer from the limitations of retrospective record review or confounding differences between study groups, several themes emerge. Dyslipidemia is quite common in HIV-infected patients taking HAART. The characteristic pattern is elevated total cholesterol, elevated LDL cholesterol, and elevated triglycerides, including severe hypertriglyceridemia in some patients. In the longitudinal studies, the lipid changes occurred within 3 months (and often sooner) of initiating antiretroviral medications and pre-dated the onset of fat redistribution. The evidence clearly supports an association between PI exposure and dyslipidemia. NRTIs may be associated with hypercholesterolemia and possibly milder hypertriglyceridemia, but studies report conflicting data. While some studies find an interrelationship between lipodystrophy and lipid abnormalities, others find an independent association between PIs, in particular, and hypertriglyceridemia.

Pathogenesis of Dyslipidemia in Patients with HIV Infection

Several pathophysiologic models have been proposed to explain the development of dyslipidemia in HIV-infected patients, involving several proposed interactions between the virus, antiretroviral therapies, and host factors.[41–48] In one model, PIs, through various proposed actions, cause increased activity of sterol regulatory element–binding protein (SREBP), which alters adipocyte differentiation (contributing to lipodystrophy) and reduces leptin levels.[48] In hepatocytes, SREBP induces lipogenic genes, which leads to increased hepatic very-low-density lipoprotein production. The increased lipid levels and reduced leptin levels, in turn, cause insulin resistance, which further activates SREBP, thus perpetuating the cycle.

PIs may inhibit several proteins involved in lipid metabolism and adipocyte regulation, including LDL receptor–related protein and cytoplasmic retinoic acid–binding protein-1, which share a high degree of homology with PIs' catalytic site.[41] However, emerging in vitro data suggest a more complicated mechanism, since different PIs have differential effects on these systems.[46,49] Additionally, PIs inhibit pre-secretory proteasomal degradation of nascent apolipoprotein B, the principal protein component of triglyceride and cholesterol-rich lipoproteins.[50] Interestingly, PI-induced dyslipidemia is not unique to HIV-infected patients, since transient lipid abnormalities have been reported in HIV-negative persons taking HAART (including PIs) for post-exposure prophylaxis.[51]

The role of NRTIs in the HIV-related lipodystrophy syndrome has been attributed to mitochondrial toxicity[52] but this hypothesis has been challenged.[53] Regarding the effects of HIV infection itself, cytokine activation appears to influence lipid metabolism. The decrease in cholesterol in early infection, in one study, was not related to cytokine levels, but the later development of hypertriglyceridemia was correlated with interferon α levels.[8] Host genetic factors also play a role, as shown by differences observed among patients with different apolipoprotein E[44,46] and apolipoprotein C-III polymorphisms.[54] And finally, while the HIV-related lipodystrophy syndrome shares some clinical features with Cushing's syndrome, it cannot be explained by abnormalities in the hypothalamic/pituitary/adrenal metabolic axis.[28,55]

Coronary Heart Disease Risk in Patients with HIV Infection and Dyslipidemia

Several cases of "premature CHD" have been reported in HIV patients with dyslipidemias associated with HAART.[56–61] However, most of these patients had 1 or more other established CHD risk factors, including smoking, diabetes mellitus, hypertension, cocaine use, or male gender and age greater than 45 years. In a cross-sectional study, HIV-infected individuals had more femoral or carotid artery atherogenic plaques than controls. Again, however, the cases had a higher proportion of traditional cardiovascular risk factors.[62] One study documenting endothelial dysfunction in HIV patients taking PIs provides indirect pathophysiologic evidence of an increased risk of CHD.[63] In non–HIV-infected patients, endothelial dysfunction is a marker for CHD,[64] predicts future CHD events,[65] and responds to lipid-lowering therapy.[66]

In the only published epidemiologic study, investigators retrospectively analyzed a cohort of 4,993 HIV-infected patients treated at one hospital from 1983 to 1998.[67] They found a higher incidence of myocardial infarction between 1995 and 1998, which corresponds to the introduction of HAART. The association with HAART persisted in a multivariable analysis, but, with the exception of age, traditional CHD risk factors were not included in the model.

Given the paucity of data, we must extrapolate from studies in the general population. Elevated LDL cholesterol, decreased HDL cholesterol, and a high cholesterol:HDL ratio are clearly associated with an increased risk of CHD. However, hypertriglyceridemia, the most prominent feature of dyslipidemia in HIV-infected patients, has not been conclusively established as an independent risk factor for CHD. Even the 2 most recent analyses found conflicting results. One study found a relative risk of 1.1 for men and 1.4 for women,[68] while another found no independent association.[69]

Considering the entire combination of metabolic disturbances, the HIV-related lipodystrophy syndrome shares many features with the more common "metabolic syndrome," which includes hypertension, abdominal obesity, insulin resistance, and "atherogenic dyslipidemia." Atherogenic dyslipidemia refers to the triad of high triglycerides, low HDL cholesterol, and small, dense LDL particles. HIV-infected patients with fat distribution, in one study, were more likely than matched controls to exhibit features of the metabolic syndrome.[35] And in a small metabolic study, 5 HIV-infected patients on HAART had a reduced ratio of large to small LDL particles compared to 6 healthy controls.[70] Several studies have shown an increased incidence of CHD events in non–HIV-infected populations with the metabolic syndrome.[71,72]

Complications of Hypertriglyceridemia in Patients with HIV Infection

Extremely high triglyceride levels (>1,000 mg/dL) are usually associated with fasting chylomicronemia and can cause the "chylomicronemia syndrome," which includes acute pancreatitis, abdominal pain with normal pancreatic enzymes, dyspnea, memory loss, lipemia retinalis, and eruptive xanthomata.[73] In addition, non-alcoholic steatohepatitis is associated with hypertriglyceridemia but can also been seen in patients with normal lipids. In HIV patients on protease inhibitors with extremely high triglycerides, clinicians reported cases of pancreatitis[74] and lipemia retinalis,[75] both of which resolved with discontinuing the PI and initiating lipid-lowering therapy.

Clinicians attributed respiratory failure in 1 patient with obstructive lung disease to the central adiposity of the HIV-related lipodystrophy syndrome.[76] Finally, some patients suffer significant psychological morbidity related to their body habitus changes.

Reversibility of Lipid Abnormalities after Switching Antiretroviral Medications

Studies of the reversibility of lipid abnormalities, including trials and observational studies, are listed in Table 2. In addition, 2 case reports described the lipid changes after PIs were discontinued because of complications of hypertriglyceridemia. In a man with pancreatitis, triglycerides decreased from 5,957 mg/dL to 2,234 mg/dL 2 weeks after discontinuing all antiretroviral agents, including ritonavir.[74] Triglycerides decreased from 4,684 mg/dL to 2,414 mg/dL in another man with pancreatitis and lipemia retinalis after discontinuing ritonavir and saquinavir.[75]

The inconsistency of these studies precludes definite conclusions about the reversibility of features of the HIV-related lipodystrophy syndrome. Nonetheless, the majority of studies showed a decrease in triglycerides upon replacing a PI with a NNRTI (nevirapine or efavirenz), a NRTI (abacavir), or another PI (nelfinavir). Hypercholesterolemia and fat redistribution, in contrast, tended to persist despite discontinuation of PIs. Discontinuing stavudine, the most consistently implicated NRTI, decreased triglycerides but not cholesterol in one observational study.[77] Of note, 1 reviewer cites 3 research abstracts (unpublished to date)

that showed no change or an increase in triglycerides upon replacing a PI with efavirenz.[78]

Effectiveness of Pharmacologic and Nonpharmacologic Treatment

While low-saturated-fat diets and weight loss (if obese) are recommended for most patients with hypertriglyceridemia, little is known about the effect of these interventions in HIV patients. Furthermore, many of these patients have already lost weight from the lipoatrophy associated with this syndrome. In 1 series of 20 HIV patients on protease inhibitors, the mean triglyceride level decreased by 21% (337 to 266 mg/dL) after an unspecified diet and exercise program.[79] Diet had little effect on lipids in another small study.[80]

The few studies of pharmacologic treatment of dyslipidemias in HIV patients on protease inhibitors are summarized in Table 3. There were no cases of myositis or rhabdomyolysis reported in these studies. In addition, 1 group reported 77% and 84% reductions in triglycerides in 2 patients treated with fenofibrate.[81] From this quite limited experience, it appears that fibrates safely effect large reductions in triglycerides in patients with HIV (50% or more in patients with severe hypertriglyceridemia). Atorvastatin and pravastatin affect more modest reductions in triglycerides and lowered cholesterol by 16% to 25%.

Treatment of Fat Redistribution in Patients with HIV-related Lipodystrophy

In preliminary studies, patients on metformin[82] and recombinant human growth hormone[83] gained weight and lost some visceral abdominal fat. In a group of non–HIV-infected patients with lipodystrophy syndromes, treatment with troglitazone resulted in an increased proportion of body fat without an increase in visceral fat.[84] Overall, these are early small studies showing modest benefits of uncertain clinical significance, and we must await larger trials. At this point, however, it seems to make sense to use metformin or a thiazolidinedione for the small proportion of patients with HIV-related lipodystrophy who require pharmacologic treatment of lipodystrophic diabetes. Finally, there is a single report of successful liposuction of a dorsocervical fat pad in a man who developed lipodystrophy on HAART.[85]

Approach to Patients with HIV-related Dyslipidemia

Evaluation. The prevalence of lipid disorders in patients on HAART is high enough to justify screening. The Adult AIDS Clinical Trial Group Cardiovascular Disease Focus Group (AACTG) recommends obtaining a fasting lipid profile before initiating antiretroviral therapy and repeating it within 3 to 6 months.[86] Once discovered, the evaluation of dyslipidemia, as in any patient, should include a consideration of the etiology of the lipid disorder and an assessment of overall cardiac risk. Most patients will have etiologies in addition to HIV-related lipodystrophy syndrome, including other secondary causes (diseases and drugs), inherited metabolic disorders, and lifestyle factors. Secondary causes should be treated or eliminated if possible. Improving glucose control in patients with diabetes, in particular, can affect dramatic reductions in triglycerides[87] in non–HIV-infected individuals. Among the inherited syndromes, only the lipoprotein lipase disorders and familial dysbetalipoproteinemia can result in the severe (>1,000 mg/dL) hypertriglyceridemia seen in many HIV-infected patients. Persons with the other genetic disorders develop moderate hypertriglyceridemia (200 to 500 mg/dL), unless they also acquire a secondary disease or drug exposure.[73]

Extrapolating from the general population, cardiac risk can be estimated by the Framingham Heart Study formula.[88] The level of CHD risk should guide the intensity of therapy. This is especially important in primary prevention, which involves interventions in disease-free individuals.

Specific lipid goals for patients with HIV infection have not been established. The AACTG suggests applying the National Cholesterol Education Program (NCEP)[89] guidelines, which recommend setting LDL targets on the basis of cardiac risk. In their third report, the NCEP identified the metabolic syndrome, triglycerides (accounted in "non-HDL cholesterol"), and HDL cholesterol as secondary targets, reflecting accumulating evidence of their contribution to CHD risk. For patients with "very high triglycerides (greater than 500 mg/dL)," the NCEP recommends initially targeting therapy to lower triglycerides before turning to LDL to further assess CHD risk. In this case, the CHD risk-based targets for "non-HDL cholesterol" are set 30 mg/dL higher than the LDL targets.

Therapeutic Decision Making. Patients with severe hypertriglyceridemia (>1,000 mg/dL) are at risk for pancreatitis and other complications and require triglyceride-lowering treatment. Lipid-lowering therapy in other patients should be directed toward cardiovascular risk reduction. Since this benefit may accrue only in the long term, clinicians should reserve this intervention for patients with high CHD risk and a favorable HIV-related prognosis, which can be predicted from CD4 cell count and HIV viral load based on a population-based analysis of mortality rates among therapy-naïve patients starting HAART.[90]

Once the decision to treat is made, clinicians face the difficult choice of either altering the HAART regimen, hoping to reverse the lipid disorder, or initiating pharmacologic therapy. Close communication and consultation with an HIV specialist is critical in the decision-making process. In the previous sections, I have reviewed the evidence base for the considerations involved in this complex decision (Table 4). There is no right answer to

this question, given the limited data at present. In many cases, the goal of continued HIV virus suppression will drive the decision making. Thus, in a patient with an undetectable viral load who has failed several antiretroviral medications and is otherwise tolerating her HAART, clinicians will be reluctant to alter the antiretroviral regimen, despite its possible metabolic complications. In this circumstance, early initiation of pharmacologic lipid-lowering therapy makes sense. In contrast, the development of dyslipidemia in a patient experiencing additional adverse effects of his first HAART regimen may tip the scales toward switching antiretroviral medications as the first step. In this case, substituting a NNRTI for a PI may lower serum triglycerides. Of course, HIV viral rebound will occasion a change in a patient's HAART regimen. In this case, this risk of metabolic consequences should weigh in the selection of new antiretroviral medications. Finally, patients' preferences remain especially important in this decision, given the level of uncertainty.

Lipid-lowering Therapy. As summarized above, there are very little data on dietary interventions in HIV-infected persons. Nonetheless the NCEP "therapeutic lifestyle diet"[89] represents a reasonable recommendation in that it poses little risk and can achieve modest reductions in lipids in other populations. Calorie restriction, however, should be recommended with caution in patients already losing weighed from severe lipoatrophy. The limited published experience in HIV-infected patients shows the effectiveness and safety of fibrates and 2 HMG Co-A reductase inhibitors or "statins" (atorvastatin and pravastatin). For more information on lipid-lowering efficacy, CHD risk reduction, adverse reactions, and drug interactions, we must extrapolate from clinical studies in non–HIV-infected patients and pharmacokinetic studies of antiretroviral and lipid-lowering drugs.

Fibric acid derivatives (fibrates) effect large reductions in triglycerides and raise HDL cholesterol in patients with severe hypertriglyceridemia.[91–93] In this setting, LDL cholesterol may remain unchanged or even rise with fibrates. However, this may be balanced by a shift toward larger LDL particles, which may be less atherogenic.[94,95] Niacin also substantially lowers triglycerides, raises HDL, and lowers LDL cholesterol. In a recent trial comparing the 2 drugs in patients with HDL <40 mg/dL and triglycerides <400 mg/dL, niacin (2,000 mg/day) provided a greater increase in HDL (26% vs 13%), while gemfibrozil effected greater reduction in triglycerides (40% vs 29%).[96] Niacin has more adverse effects, including hepatitis (more likely with some sustained-release forms)[97,98] and insulin resistance,[99] which is an issue in patients with lipodystrophic diabetes. Finally, fish oil can reduce triglycerides, but its use is limited by an unpleasant aftertaste, eructation, weight gain, and possible LDL cholesterol elevations.

For HIV-infected patients without severe hypertriglyceridemia, CHD risk reduction is the goal of lipid-lowering therapy. Extrapolating the general population, several trials have shown a reduction in CHD events over a fairly wide spectrum of patients treated with statins.[100] Statins remain the most effective drugs for LDL cholesterol lowering. While less potent than fibrates or niacin, they do lower triglycerides in a dose-dependent fashion that follows their potency for LDL lowering.[101] Among the statins, pravastatin and atorvastatin are the most likely to avoid dangerous drug interactions with PIs, as described below.

In addition to effectiveness, one must consider important toxicities and interactions between lipid-lowering and HIV-related medications in these patients. The risk of clinically significant myopathy (creatine kinase elevated >10 times normal with symptoms) in patients treated with statins as monotherapy is low (<0.5%).[102] The risk increases if a statin is combined with a fibrate. Early studies of the combination of lovastatin and gemfibrozil found a risk of 5%.[103] In more recent studies using lower doses and different statins, investigators found a lower risk, suggesting that statins and fibrates can be safely combined, if necessary, in patients with normal renal, hepatic, and thyroid function.[104–107] Cerivastatin was recently withdrawn from the market as a result of several cases of rhabdomyolysis, renal failure, and fatality, occurring mostly in patients who were also taking a fibrate or who were predisposed to myopathy from other medical conditions. Nonetheless, this remains a relatively rare event.[108]

Drug interactions that raise statin levels are of particular concern in patients with HIV infection. Most statins, with the exception of pravastatin, which undergoes sulfation, are metabolized by the 3A4 isoform of the cytochrome P-450 system (CYP-3A4).[109] (Fluvastatin appears to be metabolized by CYP-2C9 in addition to CYP-3A4.) Drugs that inhibit this enzyme, listed in Table 5, may result in increased statin levels, leading to myopathy and, rarely, rhabdomyolysis.[110] All of the protease inhibitors inhibit CYP-3A4, with ritonavir representing the most potent inhibitor.[111,112] In a pharmacokinetic study that combined several statins with ritonavir, simvastatin levels were increased by a factor of 32, atorvastatin levels were increased by a factor of 4.5, and pravastatin levels were decreased by a factor of 0.5.[111] Clinicians recently reported a case of rhabdomyolysis in a patient taking cerivastatin in combination with gemfibrozil and indinavir.[113] In the limited published experience in HIV patients, there were no cases of myopathy in a total of 49 patients taking a protease inhibitor and either pravastatin or atorvastatin and 19 patients taking a protease inhibitor, atorvastatin, and gemfibrozil.[79,80,114,115]

Regarding other antiretroviral drugs, nevirapine induces CYP-3A4, and efavirenz may inhibit or induce this enzyme, depending on co-administered drugs. The NRTIs are eliminated by the kidneys and thus do not interact with other drugs through the cytochrome P-450 system.

Finally, bile acid-binding resins, in general, should be avoided in patients with HIV-related dyslipidemia because they elevate triglyceride levels and interfere with the absorption of other medications.[116]

Table 1. Longitudinal Studies of PI Exposure and Dyslipidemia

Author and Year	Study Design	*n*	Study Period	Patients	Antiretroviral Medication	Total cholesterol* Percent Change	Total cholesterol* Proportion Over Cutpoint	Triglycerides* Percent Change	Triglycerides* Proportion Over Cutpoint
Periard 1999[20]	Pre–post retrospective controlled cohort	121	Variable	93 Cases had more-advanced HIV disease, fewer HIV-RNA copies, higher triglycerides, and lower HDL cholesterol	Indinavir added to NRTIs	+16%†	12%→35% (>240 mg/dL)	−6%	
					Nelfinavir/saquinavir added to NRTIs	+28%†	5%→33% (>240 mg/dL)	+6%	
					Ritonavir/saquinavir added to NRTIs	+44%†	7%→44% (>240 mg/dL)	+100%†	
				28 Controls	Remained on NRTIs alone	+2%	11%→14% (>240 mg/dL)	−6%	
Segerer 1999[38]	Pre–post retrospective controlled cohort	239	12 Mo	148 Cases (CD4 lymphocytes 194) PI-naïve at baseline	PI added to 2 NRTIs	+13%†	50% (>200 mg/dL)	+25%†	39%→43% (>200 mg/dL)
				91 Controls (CD4 lymphocytes 233)	Remained on 2 NRTIs alone	No change		No change	No change
Roberts 1999[22]	Pre–post uncontrolled cohort	17	48 Wk	Antiretroviral-naïve patients referred to clinical trials unit	Treatment started with indinavir in combination with 2 NRTIs	+23%†		+43%†	
Churchill 1998[117]	Uncontrolled trial	25	48 Wk	13 Antiretroviral-naïve and 12 saquinavir experienced	Treatment started with ritonavir and saquinavir	"Significant increase"		+160%†	36% (>440 mg/dL)
Danner 1995[118]	Phase 2 activity and safety RCT	84	4-Wk trial then 32-wk maintenance	PI-naïve patients with CD4 lymphocytes ≥50	Cases given ritonavir Controls given placebo	+30% to 40%† No change		+200% to 300%† No change	
Roge 2001[21]	Randomized trial	111	36 Wk	Subgroup of patients from one center of a multicenter virologic efficacy study. All were either already on or started on 2 NRTIs	Indinavir Ritonavir Ritonavir/saquinavir			+11% +25% +43%†,‡	

* *Blank boxes, data not reported.*

† $P < .05$ *for pre versus post comparison.*

‡ $P < .01$ *versus indinavir group.*

No change, investigators reported "no change" but did not report numerical effect size or P *value; NRTIs, nucleoside reverse transcriptase inhibitors.*

Table 2. Antiretroviral Medication-Switching Studies

Author and Year	Study Design	*n*	Patients	Medication Change	Total Cholesterol	Triglycerides	Reversal of Lipodystrophy	Viral Load Rebound
Barreiro 2000[119]	RCT	138	PI-containing regimen; viral load <50 copies/mL HIV-RNA	Cases: nevirapine for PI	−7%	−9%	50% Patients had "partial reversal"	11%*
				Controls: remained on PI	−12%	−12%	No change	29%
Carr 2001[120]	RCT	81	Lipodystrophy on PI-containing regimen; viral load <50 copies/mL HIV-RNA	Cases: abacavir, nevirapine, adefovir, and hydroxyurea for PI	−25%*	−35%*,†	Cases had a greater decline in visceral *and* subcutaneous fat by DEXA	2%
				Controls: remained on PI	−10%	−6%		17%
Ruiz 2001[121]	Open-label RCT	106	PI-containing regimen; lipodystrophy and sustained HIV-RNA suppression	Cases: nevirapine for PI	−9%†	−20%†	No change in several measures	21%
				Controls: remained on PI	No change	No change	No change in several measures	23%
Wensing 2001[122]	Controlled trial	26	Ritonavir-containing regimen; capsules became temporarily unavailable; HIV-RNA <400 copies	Cases: nelfinavir ± saquinavir for ritonavir	−7%†	−35%†		None
				Controls: remained on ritonavir (liquid)	No change	No change		None
Walli 2001[123]	Controlled trial	31	Sustained virologic control on first PI-containing HAART regimen; 19 patients randomized to groups; 11 distributed "by patient request"	Cases: abacavir for PI	−41 mg/dL† (median change)	−46 mg/dL† (median change)		19%
				Controls: remained on PI	+4 mg/dL (median change)	+12 mg/dL (median change)		18%
Martinez 1999[124]	Uncontrolled cohort	23	PI-containing regimen; patient requested change because of BHC despite HIV virologic suppression	Nevirapine for PI	−22%†	−57%†	Waist: hip ratio decreased from 0.91 to 0.85*	5% (1 patient)
Martinez 2000[125]	Uncontrolled cohort	20	PI-containing regimen; patient requested change because of BHC despite HIV virologic suppression	Efavirenz for PI	No change	−31%†	Waist: hip ratio decreased from 0.92 to 0.87*	5% (1 patient)
Duncombe 2000[126]	Uncontrolled cohort	21	PI-containing regimen; patient requested change because of BHC despite HIV virologic suppression	Nelfinavir for either indinavir or ritonavir plus saquinavir	No change	−38%†	Partial reversal in 52% of patients by physical appearance	
Saint-Marc 1999[77]	Uncontrolled cohort	29	On HAART (14 on NRTIs alone; 15 on PI-containing regimen)	Stavudine discontinued	No change	−46%† (NRTI) −36%† (NRTI and PI)	Increase in subcutaneous fat by CT scan	
Doser 2001[127]	Retrospective uncontrolled cohort	47	PI-containing regimen changed due to incomplete response (6), side effects (9), or other reason (22)	Efavirenz for ritonavir	−5%	−33%*,†		NA
				Efavirenz for non-ritonavir PI	−2%	−9%		NA

* $P < .05$ *for case versus control comparison.*

† $P < .05$ *for post versus pre comparison.*

Blank box = data not reported; NA, not applicable; RCT, randomized controlled trial; No change = investigators reported "no change" but did not report numerical effect size or P *value; BHC, body habitus change; HAART, highly active antiretroviral therapy; NRTIs, nucleoside reverse transcriptase inhibitors; DEXA, dual energy x-ray absorptiometry; CT, computed tomography.*

Table 3. Studies of Pharmacologic Treatment of Dyslipidemias in HIV Patients

	Study Design	*n*	Patients	Medication	Cholesterol (mg/dL)				Triglycerides (mg/dL)			
					Pre	Post	Change	*P* Value	Pre	Post	Change	*P* Value
Hewitt 1999[128]	Retrospective case series at HIV clinic	9	HIV patients on HAART including PIs; CD4 152, viral load 13,200	Gemfibrozil (600 mg BID)					1,803	417	−77%	Not reported
Murillas 1999[114]	Retrospective case series at 1 center	15	HIV patients on HAART, including PIs	Atorvastatin (10 – 20 mg QD)	363	273	−25%		1,000	650	−35%	Not reported
Henry 1998[79]	Prospective uncontrolled trial	35	HIV patients on HAART, including PIs	Gemfibrozil (*n* = 25) (600 mg BID)	317	216	−32%	.002	1,373	576	−57%	.01
				Atorvastatin (*n* = 10) (at least 10 mg QD)	270	220	−19%	.004	274	213	−21%	.12
				Combination (*n* = 19)*	312	220	−30%	.004	1,355	540	−60%	.01
de Luis 2001[129]	Prospective uncontrolled trial	9	HIV patients on HAART, including PIs; all had triglycerides >500	Fenofibrate (201 mg QD)	250	227	−9%	>.05	989	263	−73%	<.05
Manfredi 2001[19]	Prospective uncontrolled trial	49	HIV patients on HAART, including PIs; triglycerides >300 in spite of diet	Benzfibrate (400 mg QD)			−25%	<.001			−35%	<.001
Baldini 2000[115]	Prospective open-label uncontrolled trial	19	HIV patients on HAART, including PIs; CD4 334	Pravastatin (20 mg QD)	313	254	−19%	<.01	813	512	−37%	<.01
Moyle 2001[80]	Prospective open-label randomized trial	31	HIV patients on HAART including PIs; all had cholesterol >250	Diet + Pravastatin (40 mg QD)	289	243†	−16%	<.05	350	323	−8%	NS
				Diet alone	285	274	−4%	NS	359	316	−12%	NS

* *The "combination" group represents 19 of the gemfibrozil patients who were subsequently also given atorvastatin.*

† P = *.051 compared to diet alone.*

NS, non-significant; blank box, data not reported; HAART, highly active antiretroviral therapy.

Table 4. Decision-making Considerations in Patients with HIV-related Dyslipidemias

Considerations
Health risks (cardiac and non-cardiac) associated with the patient's dyslipidemia and other metabolic derangements
Status of the patient's HIV infection
Reversibility of the metabolic derangements with discontinuing of offending antiretroviral medications
Effectiveness, other adverse effects, and tolerability of the current antiretroviral regimen
Availability, potential effectiveness, and potential adverse effects of alternative antiretroviral medications
Safety, efficacy, and cardiac risk reduction with nonpharmacologic and pharmacologic lipid-lowering treatments
Patient preferences

Conclusion

Dyslipidemia is common in persons with HIV infection. The typical pattern in patients on HAART includes elevated total cholesterol, elevated LDL cholesterol, and elevated triglycerides, including severe hypertriglyceridemia in some patients. The lipid abnormalities may be associated with insulin resistance, glucose intolerance, and lipodystrophy, characterized by truncal obesity, enlarged dorsocervical fat pad, and lipoatrophy of the face, buttock, and extremities. Exposure to PIs is clearly associated with this entire range of metabolic abnormalities. PI-naïve patients on NRTIs may develop lipodystrophy, insulin resistance, hypercholesterolemia, and possibly modest elevations in triglycerides, but not severe hypertriglyceridemia, which appears to be linked to PIs alone. NNRTIs have not been implicated in these metabolic derangements. Fat redistribution and dyslipidemia are correlated in patients on HAART, but PIs, in particular, may also cause hypertriglyceridemia directly in patients without lipodystrophy. Most studies have not found an association between CD4 lymphocyte count or HIV viral load and lipid abnormalities. The pathogenesis is incompletely understood and appears to be multifactorial.

Table 5. Drugs that Affect the CYP3A4 Enzyme[109–111]

CYP3A4 Inhibitors	CYP3A4 Inducers
Protease inhibitors	Efavirenz
Efavirenz	Nevirapine
Delavirdine	Barbiturates
Erythromycin	Carbamazepine
Clarythromycin	Phenytoin
Cyclosporine	Rifabutin
Itraconazole	Rifampin
Fluconazole	Troglitazone
Ketoconazole	
Fluoxetine	
Fluvoxamine	
Paroxetine	
Nefazodone	
Sertraline	
Verapamil	
Diltiazem	
Zafirlukast	
Grapefruit juice*	

* *Inhibits CYP3A4 in the gut but not in the liver.*

There are insufficient data to definitively support an increased CHD risk in patients with HIV-related dyslipidemia. However, some of the same metabolic abnormalities remain firmly established risk factors in other populations. Patients on HAART with severe hypertriglyceridemia may develop pancreatitis or other manifestations of the chylomicronemia syndrome. Finally some patients with severe lipodystrophy suffer psychological morbidity from the body habitus changes. Some of the metabolic derangements (particularly hypertriglyceridemia) may improve upon replacing a PI with an NNRTI, such as nevirapine or efavirenz. However, this cannot be anticipated with certainty. The limited experience suggests that fibrates, pravastatin, and atorvastatin can safely treat lipid abnormalities in HIV-infected patients.

Patients with HIV infection on HAART should be screened for lipid disorders, given their incidence, potential for morbidity, and possible long-term cardiovascular risk. Treatment decisions are complex and must include assessments of cardiac risk, HIV infection status, reversibility of the dyslipidemia, and the effectiveness and toxicities of lipid-lowering medications. The multiple potential drug interactions with antiretroviral or other HIV-related medications should be considered in lipid-lowering drug selection and monitoring.

Many persons with HIV infection (and their physicians) are turning their attention to emerging chronic disease and prevention issues as they live longer and suffer less morbidity. While the complexity of antiretroviral therapy increasingly requires involvement by HIV specialists, the evaluation and management of their lipid disorders may justify an increased role for the general internist in their care.

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