

HIV-associated dyslipidaemia: pathogenesis and treatment

Jisun Oh, Robert A Hegele

Dyslipidaemia, consisting of hypertriglyceridaemia together with depressed concentrations of high-density lipoprotein cholesterol and elevated low-density lipoprotein cholesterol, is being observed with increasing frequency among HIV patients. Pathogenic mechanisms include effects of the virus itself, effects of the antiretroviral drugs on key metabolic pathways, and drug-associated adipose repartitioning with subsequent development of insulin resistance and associated metabolic derangements. Diagnostic methods include a fasting lipoprotein profile and assessment of secondary factors. Treatment strategies include non-pharmacological approaches such as changes to diet and lifestyle, as well as switching to a less metabolically active antiretroviral regimen without compromising antiretroviral efficacy. Pharmacological treatment may include statin drugs, fibrates, niacin, or cholesterol absorption inhibitors, in addition to management of comorbidities such as increased global cardiometabolic risk and insulin resistance.

Introduction

Highly active antiretroviral therapy (HAART) has transformed HIV infection from an acute illness to a manageable chronic condition. However, the remarkable decreases in morbidity and mortality and increase in life expectancy caused by HAART have been accompanied by an increase in several clinical and metabolic complications. The metabolic disturbances, seen in about half of HAART-treated patients, include dyslipidaemia, hyperinsulinaemia, and adipose tissue redistribution.^{1,2} HAART-associated dyslipidaemia is characterised by hypertriglyceridaemia with depressed plasma concentrations of high-density lipoprotein (HDL) cholesterol and increased total cholesterol, with or without increased low-density lipoprotein (LDL) cholesterol.³ This profile is also mechanistically linked with the insulin resistance and fat redistribution syndromes that complicate HAART therapy. However, dyslipidaemia can occur without obvious lipoatrophy and insulin resistance, suggesting either that these are mechanistically independent or perhaps that dyslipidaemia is a sensitive early marker of disease, related to earlier diagnosis and more careful clinical assessment of HIV patients.

Persistent dyslipidaemia in HIV patients appears to be associated with increased cardiovascular risk,^{4,5} with a relative rate of myocardial infarction of 1.2 per year of protease inhibitor exposure.⁵ Clinical trial evidence from the non-HIV population supports the benefits of correcting dyslipidaemia in high-risk individuals. Increasing recognition of HIV-associated dyslipidaemia has been paralleled by studies of various lipid-lowering treatments. This Review will focus on diagnosis and treatment of HIV-associated dyslipidaemia, while recognising the importance of insulin resistance and lipodystrophy (see panel 1) as mechanistically related comorbidities.

Pathogenesis of HIV-associated dyslipidaemia HIV viraemia

HIV-associated dyslipidaemia was recognised for years before the widespread use of protease inhibitor-based HAART.^{6,7} Viraemia-associated dyslipidaemia is characterised mainly by decreased plasma concentrations of total, LDL, and HDL cholesterol,^{3,6,8,9} and later elevated

plasma triglyceride.³ Low HDL cholesterol has been correlated with immune activation early in the course of HIV infection,¹⁰ the repercussions of which may extend beyond atherosclerosis because of HDL's numerous functions, including antioxidant and anti-inflammatory activities.¹¹⁻¹⁴

Triglyceride-rich lipoproteins and HDL cholesterol are synthesised and secreted into the plasma from the liver and intestine. HIV-1 contributes to low plasma HDL cholesterol by impairing ATP-binding cassette transporter A1-dependent cholesterol efflux from macrophages.¹⁵ Furthermore, inflammation in general stimulates endothelial lipase and phospholipase A2, which can reduce plasma HDL.¹⁴ Additionally, HDL is triglyceride-enriched in hypertriglyceridaemia, becoming a more avid substrate for hepatic lipase-mediated clearance.¹⁴

HIV-associated dyslipidaemia is very similar to that observed in other chronic infections. Elevated interferon α in advanced HIV disease is correlated with elevated

Lancet Infect Dis 2007; 7: 787-96

Schulich School of Medicine and Dentistry, University of Western Ontario London, ON, Canada (J Oh MD, Prof R A Hegele MD)

Correspondence to: Prof Robert A Hegele, Blackburn Cardiovascular Genetics Laboratory, Roberts Research Institute, 406-100 Perth Drive, London, ON, N6A 5K8 Canada. Tel +1 519 663 3461; fax +1 519 663 3037; hegele@roberts.ca

Panel 1: Clinical features associated with HIV lipodystrophy syndrome

Fat atrophy (lipoatrophy)

- Face: sunken cheeks, hollow temples, sunken eyes, prominent zygomatic arch
- Extremities: prominent veins, skinny or muscular appearance
- Buttocks: loss of contour, loose skin folds

Fat accumulation (lipohypertrophy)

- Abdomen: increased abdominal girth with visceral fat accumulation
- Dorsocervical or supraclavicular fat pad

Related findings

- Hypertriglyceridaemia, usually with depressed high-density lipoprotein cholesterol
- Hypercholesterolaemia
- Insulin resistance, dysglycaemia progressing to glucose intolerance
- Gynaecomastia (breast enlargement)

plasma triglyceride,¹⁶ resulting from impaired clearance of triglyceride-rich lipoproteins.^{17,18} Similarly, tumour necrosis factor (TNF) α is elevated in drug-naive HIV patients¹⁹ and increases further during opportunistic infections. TNF α interferes with free fatty acid metabolism and lipid oxidation, and attenuates insulin-mediated suppression of lipolysis.¹⁹ Finally, the nutritional state of HIV patients, including weight loss and protein depletion,^{3,20,21} might contribute to reduced plasma total, HDL, and LDL cholesterol. Some of these pathways are shown in the figure.

Antiretroviral-induced dyslipidaemia

The pathogenesis of HAART-related dyslipidaemia is complex and involves various drug-induced effects, in association with hormonal and immunological influences superimposed upon genetic predisposition.^{22,23} Compared with healthy controls, HIV patients already have abnormal lipoprotein concentrations before initiation of HAART, which worsen after initiation of therapy. The lipoprotein profile associated with HAART features increased plasma triglyceride, increased total and LDL cholesterol, and decreased HDL cholesterol.^{24–28} These fundamental proatherogenic changes can be further accompanied by increases in small dense LDL particles,²⁹ lipoprotein (a),^{26,30,31} and apolipoproteins B,^{32,33} C-III,^{33,34} E,³⁵ and H.³⁶

In-vivo lipoprotein turnover studies have shown that increased plasma triglyceride-rich very low density lipoprotein (VLDL) levels result from either decreased catabolism of these particles because of HIV infection itself,¹⁷ HAART-related increased production of VLDL,¹⁷ or protease inhibitor-mediated impaired catabolism of VLDL.³⁷ Also, HAART treatment impairs hydrolysis of triglyceride-rich lipoproteins by plasma and tissue lipases,^{38–40} disrupts normal post-prandial free fatty acid and lipoprotein catabolism,^{40,41} and interferes with peripheral fatty acid trapping,⁴¹ all perhaps because of the interaction of these fatty acids with the master transcriptional regulator sterol regulatory element binding protein 1 (SREBP1).⁴² Protease inhibitor treatment is also associated with abnormal accumulation of intramyocellular fat,⁴³ leading to insulin resistance, which further increases plasma apolipoprotein B-containing and triglyceride-rich lipoproteins.⁴⁴ Some of these pathways are shown in the figure.

In cultured hepatocytes, protease inhibitor treatment protects apolipoprotein B from degradation by intracellular proteasomes, thus increasing secretion of apolipoprotein B-containing lipoproteins.⁴⁵ Furthermore, protease inhibitor-induced lipodystrophy in HIV is associated with decreased expression of the LDL receptor⁴⁶ and related receptors,⁴⁷ which increases plasma LDL concentration.

Another proposed mechanism underlying the dyslipidaemia is HAART-induced mitochondrial alterations.⁴⁸ HAART, especially with protease inhibitors

in conjunction with nucleoside reverse transcriptase inhibitors (NRTIs), inhibits mitochondrial DNA polymerase γ , leading to mitochondrial DNA depletion, respiratory chain dysfunction, and reduced energy production.⁴⁸ Mitochondrial respiratory chain inhibition may be responsible for abnormalities in several cell types, including adipocytes, leading to lipoatrophy.⁴⁸ Mitochondrial dysfunction in skeletal muscle may lead to insulin resistance, with secondary dyslipidaemia.⁴⁹ Interactions between protease inhibitors and cellular proteases acting in mitochondrial biogenesis could also underlie metabolic alterations.⁵⁰

Altered intracellular lipid metabolism has been attributed to the structural homology (approximately 60% at the amino acid level) between the catalytic region of HIV protease and both cytoplasmic retinoic acid-binding protein type 1 (CRABP1) and LDL-receptor-related protein type 1 (LRP1).⁵¹ CRABP1 is involved in the conversion of retinoic acid to cis-9-retinoic acid, which binds the retinoid X receptor-peroxisome proliferator-activated receptor γ (RXR-PPAR γ) heterodimer, stimulating adipocyte differentiation and inhibiting apoptosis.⁵¹ Protease inhibitors might bind to CRABP1, thus inhibiting the formation of cis-9-retinoic acid, leading to reduced RXR-PPAR γ activity and peripheral lipoatrophy, mainly on limbs and the gluteal region.⁵¹ Hyperlipidaemia results from impaired storage capacity and increased flux of circulating lipids. The decrease in RXR-PPAR γ activity results in apoptosis of peripheral adipose stores, decreased adiponectin, and insulin resistance. Central and visceral adipose stores are spared, however, and expand with weight gain, contributing to insulin resistance. Protease inhibitors, particularly ritonavir, inhibit cytochrome P450 3A4 (CYP3A4), which would reduce the formation of cis-9-retinoic acid, decrease the activity of RXR-PPAR γ targets, leading to lipoatrophy and worsened dyslipidaemia.^{3,51}

LRP1 normally binds to lipoprotein lipase on capillary endothelium, which hydrolyses free fatty acids (FFAs) from triglyceride, promoting their accumulation in adipocytes.⁵² Protease inhibitor binding to LRP1 would interfere with LRP1-lipoprotein lipase complex formation, reducing adipose storage capacity and increasing plasma triglyceride-rich lipoproteins.⁵³ FFAs that failed to enter adipocytes would remain in the plasma, to be taken up into the liver, increasing hepatic synthesis of triglyceride-rich lipoproteins. Protease inhibitors might also directly stimulate hepatic triglyceride synthesis, possibly by upregulating expression of key triglyceride biosynthetic enzymes.⁵⁴

HAART-related dyslipidaemia may involve genetic predisposition, since not all patients taking HAART have comparable metabolic disturbances. For instance, promoter polymorphisms—namely $-482C>T$ and $-455T>C$ —in the *APOC3* gene were associated with increased plasma concentrations of triglyceride and depressed HDL in HIV patients.^{33,55} Also, the $-1131T>C$ promoter polymorphism

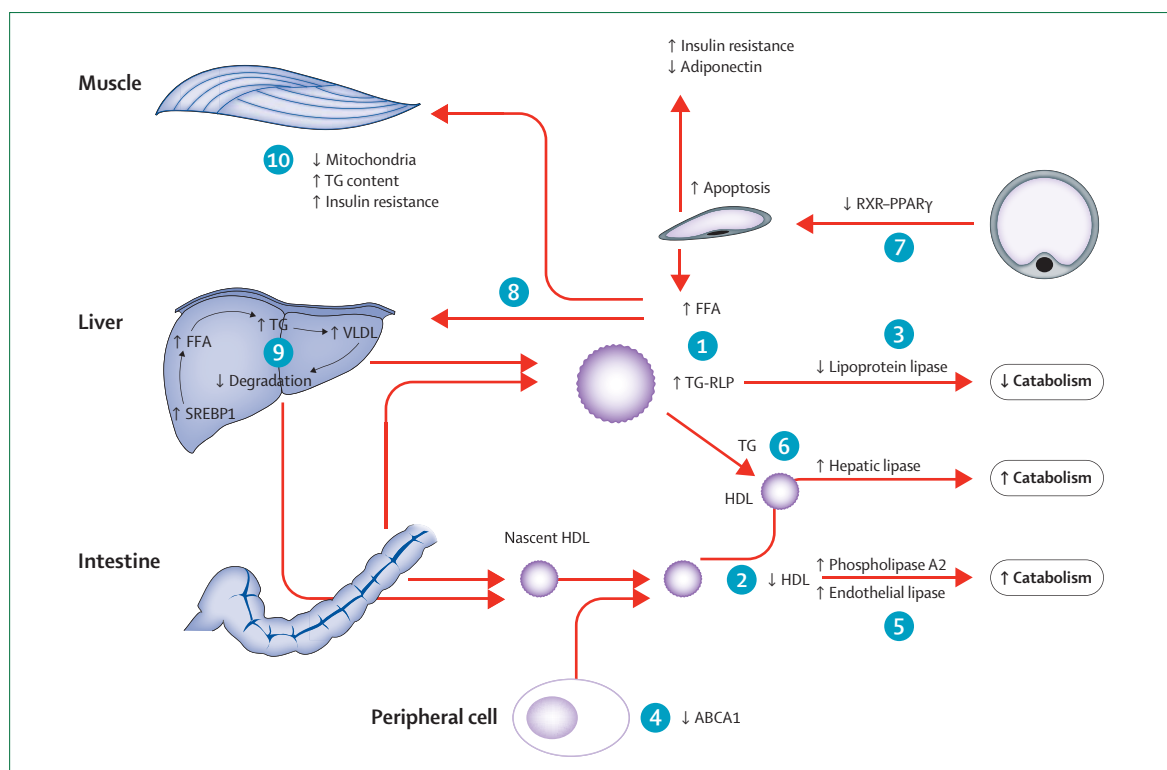


Figure: Schematic representation of selected mechanisms underlying HIV-associated dyslipidaemia

Mechanisms are caused by effects of the virus itself and effects of highly active antiretroviral treatment (HAART). The two fundamental biochemical disturbances are: (1) increased triglyceride (TG)-rich lipoproteins (RLPs), particularly very-low-density lipoprotein (VLDL); and (2) decreased high-density lipoprotein (HDL). The inflammatory cytokine response to HIV infection: (3) decreases lipoprotein lipase activity, which results in accumulation of TG-RLP; (4) decreases cholesterol efflux from peripheral cells via the ATP-binding cassette protein A1 (ABCA1), which results in decreased formation of HDL; and (5) increases activity of phospholipase A2 and endothelial lipase, which results in increased catabolism of HDL. Increased plasma TG results in (6) abnormal TG-enrichment of HDL, which increases catabolism via hepatic lipase. HAART causes redistribution of adipose tissue as a result of (7) decreased retinoid X receptor- γ (RXR-PPAR γ) activity. (8) Free fatty acid (FFA) spillovers from apoptotic peripheral adipocytes increase FFA flux to the liver and skeletal muscle. In the liver (9), increased FFA supply and upregulation of the TG synthetic pathway, through the sterol regulatory element binding protein-1 (SREBP1) and downstream targets, increase hepatic TGs and ultimately secretion of TG-rich VLDL, while protease inhibitors interfere with intracellular degradation of VLDL and related particles. In the muscle (10), HAART is associated with mitochondrial depletion, which in turn compromises FFA oxidation; as a result, intramyocellular and intermyocellular TG content increases. Insulin resistance in liver and skeletal muscle compounds the metabolic disturbances, including dyslipidaemia.

in the *APOA5* gene was associated with hypertriglyceridaemia in protease inhibitor-treated patients.²³ Variable responses to protease inhibitors have also been associated with other DNA polymorphisms.⁵⁵⁻⁵⁷

Finally, return to health with therapy might lead to increases in LDL and triglyceride. However, many HIV patients continue to consume a poor quality atherogenic diet, which might affect plasma lipoproteins. Furthermore, although the molecular mechanisms are unclear, NRTIs and non-NRTIs (NNRTIs) may also have a harmful effect on plasma lipoproteins.

Diagnosis of HIV-associated dyslipidaemia

The predominant HIV-associated lipid profile is mixed or combined hyperlipidaemia, with elevation in total cholesterol and triglyceride together with depressed HDL cholesterol. Isolated hypertriglyceridaemia with low HDL cholesterol and isolated hypercholesterolaemia caused by high LDL cholesterol are seen less commonly. Diagnosis of HIV-associated dyslipidaemia involves a

determination of plasma triglyceride and total, LDL, and HDL-cholesterol after 12 h of fasting.

Identification and treatment of secondary causes of dyslipidaemia

Rare familial hyperlipidaemias should be ruled out by careful evaluation of family history and by examination for corneal arcus, xanthelasmata, and xanthomata.⁵⁸ Clinical and biochemical evidence should be sought to rule out secondary causes of hyperlipidaemia, such as diabetes (fasting glucose and glycated haemoglobin), obesity, hypothyroidism (thyrotropin), nephrotic syndrome (screening for proteinuria), other renal disease (serum creatinine), or hepatic or biliary disease (serum transaminases, alkaline phosphatase, and bilirubin), and alcohol abuse should be identified and appropriately managed. Additionally, a medication review may identify agents that worsen dyslipidaemia including steroid derivatives and oral contraceptives. Among diabetic HIV patients, improved insulin sensitivity either through

lifestyle change or judicious use of biguanides or thiazolidinediones, and improved glycaemic control with sulfonylureas, alpha-glucosidase inhibitors, incretin-

enhancing strategies, or insulin itself, contribute to an improved lipid profile.

Treatment of HIV-associated dyslipidaemia

Cardiovascular risk reduction

Strategies to treat HIV-associated dyslipidaemia include diet and exercise, switching to a non-protease inhibitor-based regimen, conventional pharmacological options, including statins, fibrates, niacin, and some unconventional options. An overall approach is outlined in panel 2.

In the HIV-negative population, hypertriglyceridaemia, depressed plasma HDL cholesterol, insulin resistance, diabetes mellitus, and truncal adiposity each increase cardiovascular disease risk. HAART-treated individuals also appear to have increased vascular disease risk.^{4,5,59,60} Elevated plasma triglyceride in this group has also been associated with acute pancreatitis⁶¹ and eruptive cutaneous xanthomas that are characteristic of severe hypertriglyceridaemia.

There are no prospective, double-blind, randomised trials that prove the cardiovascular benefit of aggressive lipid-lowering in HIV patients. Nevertheless, even without such evidence, it is reasonable to assume that the benefits of lipid-lowering that have been observed in HIV-uninfected patients with high cardiovascular risk, such as those with multiple risk factors, metabolic syndrome, insulin resistance, diabetes, dyslipidaemia and pre-existing cardiovascular disease, will also be observed in HIV patients.⁶⁰ Current recommendations for evaluation and treatment of dyslipidaemia in HIV-infected adults include those from the National Cholesterol Education Program Adult Treatment Panel III guidelines⁶⁰ and suggest target levels similar to those recommended for HIV-uninfected patients who are at high risk of cardiovascular disease.

Diet and lifestyle

Managing HIV-associated dyslipidaemia must wherever possible include non-drug interventions. Management of any dyslipidaemic patient should include prudent diet,^{62,63} reduced total caloric intake, attaining ideal bodyweight, and increased physical activity. These first steps may yield additional health benefits in HIV-associated dyslipidaemia. However, such measures are often inadequate to correct the metabolic disturbances.^{3,60}

Consultation with a dietician may be required, since patients with advanced HIV disease can have marked gastrointestinal symptoms. Also, dietary recommendations to increase muscle mass might conflict with recommendations to improve dyslipidaemia.⁶⁰ A recent randomised study showed that dietary intervention in drug-naive HIV patients prevented development of dyslipidaemia after 6 and 12 months.⁶⁴ Exercise can also help—for example, structured exercise plus diet decreased total cholesterol and triglyceride by 11% and 21%, respectively, in HIV-infected patients.² Also,

Panel 2: Approach to management of HIV-associated dyslipidaemia

Diet and lifestyle

- Trial of non-drug therapies, although efficacy may be limited
- Increased exercise; resistance training
- Prudent diet, reduced total calories, reduced calories from fat, reduced saturated and trans fats, low glycaemic index foods
- Competing dietary needs may warrant dietician consultation

Switching antiviral agents

- Protease inhibitor class associated with more severe dyslipidaemia, especially hypertriglyceridaemia
- Descending rank order of hyperlipidaemia induction: ritonavir>amprenavir/nelfinavir>indinavir/saquinavir/lopanavir>atazanavir
- NNRTI or NRTI classes induce dyslipidaemia to a lesser degree than protease inhibitors
- Differences in dyslipidaemia associated with NNRTIs—eg, less dyslipidaemia with tenofovir compared with stavudine
- Cautions with switching: compromise of virological efficacy, inconsistent metabolic response, and drug interactions

Treatment of insulin resistance

- Insulin sensitivity in HIV improved with metformin, thiazolidinediones, or leptin, with uncertain long-term benefit

Dyslipidaemia treatment

- Statins directed to elevated total and LDL cholesterol and baseline triglycerides less than 5 mmol/L
 - Depending on dose and agent, LDL cholesterol reduction up to 50% and triglyceride reduction up to 25%
 - Generally well tolerated with modest to good efficacy
 - Unlikely to achieve target lipid levels as monotherapy
 - Potential for significant drug interactions since statins and HAART drugs are both metabolised by CYP3A4
 - Fluvastatin, rosuvastatin, and pravastatin appear less CYP3A4-dependent, so these may be preferable, especially when the patient is exposed to more intensive doses and greater numbers of other agents
- Fibrates are well tolerated with modest efficacy; appropriate to consider when baseline triglyceride more than 5 mmol/L
 - Triglyceride reduction up to 50% and LDL cholesterol reduction up to 25%
 - Unlikely to achieve target lipid levels
 - Fibrate-statin combination requires periodic monitoring of creatine kinase and liver transaminases
- Ezetimibe appears to be well tolerated and can be used as monotherapy in statin intolerance or mild dyslipidaemia, or in combination with other agents for more severe dyslipidaemia
 - LDL cholesterol reduction up to 25%
- Niacin to be used cautiously in protease inhibitor-related dyslipidaemia, side-effects include flushing, skin rash, and pruritis; consider longer acting forms—eg, extended release niacin
- Omega-3 fatty acids (fish oils)—eicosapentaenoic acid and docosahexaenoic acid—lower plasma triglyceride by up to 50% and raise HDL by up to 20% in small studies; more research is required

CYP3A4=cytochrome P450 3A4. HAART=highly active antiretroviral therapy. HDL=high-density lipoprotein. LDL=low-density lipoprotein. NNRTI=non-nucleoside reverse transcriptase inhibitor. NRTI=nucleoside reverse transcriptase inhibitor.

16 weeks of resistance training was associated with improved fasting triglyceride, decreased adipose tissue mass and increased muscle mass in HIV-infected men with hypertriglyceridaemia.⁶⁵

Switching antiviral agents

Another strategy to improve HAART-associated dyslipidaemia is to carefully consider switching the antiviral agent to a less metabolically active family member, without compromising antiviral efficacy. Among protease inhibitors, dyslipidaemia appeared to be greatest with ritonavir (particularly with shorter-term, intensive booster doses).³ Amprenavir and nelfinavir have intermediate effects on plasma lipids,⁶¹ indinavir and saquinavir have even fewer, and lopinavir has the most favourable lipid profile.⁶⁶ Atazanavir has negligible effects on serum lipids.⁶⁷ Total and LDL cholesterol concentrations increased significantly more in patients on nelfinavir (increases of 24% and 28%, respectively) than on atazanavir (increases of 4% and 1%, respectively; $p < 0.01$).⁶⁸ Switching from nelfinavir to atazanavir reduced total cholesterol and triglyceride with no apparent antiviral compromise.⁶⁹ Tipranavir, a non-peptidic protease inhibitor, is a newer option in patients with multidrug resistance, but elevates total cholesterol and triglyceride more than older protease inhibitors.^{67,70} Head-to-head data for protease inhibitors are not available for cardiovascular endpoints.

Another strategy to control dyslipidaemia has been discontinuation of the protease inhibitor within HAART regimens and switching to an NRTI or NNRTI. For antiretroviral-naïve patients, HAART regimens including at least one NNRTI, or abacavir and two NRTIs, might be as efficacious as protease inhibitor-based regimens,^{61,71,72} although they are not the standard of care. Other studies have shown that switching a protease inhibitor for either an NNRTI or NRTI, such as nevirapine, efavirenz, or abacavir, in patients with long-lasting viral suppression has antiviral efficacy similar to earlier protease inhibitor-based combinations.⁷³⁻⁸² However, there is some risk of development of drug-resistant virus variants, particularly with NNRTIs.⁶⁰ Additionally, both NNRTIs and NRTIs are not completely free of harmful metabolic effects.

Switching protease inhibitors for NRTIs appears to improve the lipid profile. For example, switching to abacavir from dyslipidaemia-associated protease inhibitors improved fasting lipids, maintained virological suppression, and simplified treatment in a study of 301 HIV-infected adults.⁸³ Differences between individual NRTIs with respect to effects on the lipid profile have also been reported. For example, when 352 HIV-infected adults were switched from stavudine to tenofovir, there was no loss of drug efficacy and a modest and sustained improvement of dyslipidaemia, particularly elevated plasma triglyceride.⁸⁴ NNRTIs have also been associated with altered lipid profiles, although the disturbances

appear less severe than with protease inhibitors. Additionally, NNRTIs were associated with increased HDL cholesterol⁶⁰ and a more favourable lipid profile than protease inhibitors.⁶⁶

When comparing NNRTIs, plasma triglyceride tended to increase less with nevirapine than with efavirenz.⁶⁶ Although effects of individual NRTIs remain incompletely defined, stavudine was associated with greater cholesterol and triglyceride elevations than zidovudine and tenofovir.⁶⁰ The addition of fusion inhibitors, such as enfuvirtide, to existing therapies had little effect on plasma lipids.⁸⁵

Statins

3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, or statins, are used extensively in the general population to reduce LDL cholesterol, and have shown considerable benefit in both primary and secondary prevention of vascular disease.⁸⁶ Pravastatin,⁸⁷⁻⁹¹ simvastatin,⁹²⁻⁹⁴ rosuvastatin,^{95,96} and fluvastatin⁹¹ were evaluated in small studies of patients with HIV-associated dyslipidaemia; each drug showed modest improvement of dyslipidaemia, with most patients not reaching targets.⁶⁰ Although statins might have effects beyond lipid-lowering,^{97,98} their main cardiovascular benefit results from reducing plasma LDL cholesterol.

Statins and components of HAART therapy share processing pathways. For example, most statins are metabolised by hepatic CYP3A4, perhaps interacting with agents that are similarly metabolised,⁹⁹ including protease inhibitors and NNRTIs, but also cyclosporin, erythromycin, itraconazole, and oral anticoagulants. Statins are also substrates for P-glycoprotein, a drug transporter present within the small intestine, which might influence drug bioavailability.¹⁰⁰

Coadministration of ritonavir plus saquinavir to HIV-negative volunteers increased tissue exposure to simvastatin by more than 30-fold and to atorvastatin by more than three-fold.¹⁰¹ Elevated plasma statin levels possibly increase risk of liver toxicity (ranging from serum transaminase elevations to very rare acute hepatitis) and skeletal muscle toxicity (such as myalgias, serum creatine kinase elevations, and even rare rhabdomyolysis), especially for simvastatin¹⁰¹⁻¹⁰⁷ and atorvastatin.^{108,109} Fluvastatin is metabolised by cytochrome P450 2C9 (CYP2C9), whereas pravastatin and rosuvastatin undergo little metabolism through the cytochrome P450 enzyme system. Rosuvastatin reduced total cholesterol and triglyceride in 16 patients by 22% and 30%, respectively, with favourable tolerability in protease inhibitor-associated dyslipidaemia.⁹⁵ Efavirenz, a mixed inducer-inhibitor of CYP3A4, induced statin metabolism with median decreases of 58%, 34%, and 40% of plasma levels of simvastatin, atorvastatin, and pravastatin, respectively, in a study of 52 HIV-negative patients.¹¹⁰ HIV patients taking indinavir and treated with fluvastatin or pravastatin had significantly

reduced plasma total and LDL cholesterol ($p < 0.05$).⁹¹ Treatment with pravastatin 40 mg daily for 12 weeks was also associated with increased subcutaneous fat in 33 HIV-infected men.¹¹¹ Thus, for HIV-associated increased LDL cholesterol, it seems reasonable to consider treatment with pravastatin, fluvastatin, or rosuvastatin, with periodic monitoring of serum transaminases (aspartate transaminase and alanine transaminase) and creatine kinase. However, without definitive endpoint studies, the particular statin selected is often determined by personal experience.

Fibrates

Fibrates, which are agonists of PPAR α , have a well-established tolerability and efficacy profile for patients with hypertriglyceridaemia and mixed hyperlipidaemia. In HIV-uninfected patients, fibrates appear less effective than statins in preventing cardiovascular events.¹¹² In general, both fibrates and statins as monotherapy have moderate effects on plasma lipids, with good tolerability.^{113–116} Several fibrates, including gemfibrozil,^{115,117–119} fenofibrate,^{120–127} and bezafibrate^{89,128} have been evaluated in small studies of patients with HIV-associated dyslipidaemia. For example, a 16-week randomised, double-blind study showed that gemfibrozil reduced plasma triglyceride by 25% but did not affect CD4 count, HIV RNA load, or protease inhibitor toxicity in HIV-infected patients with hypertriglyceridaemia.¹¹⁵ A 3-month randomised, open-label prospective study of 36 HIV-positive adults showed that fenofibrate was associated with 40%, 14%, and 17% decreases in plasma triglyceride, total cholesterol, and apolipoprotein B, respectively, and with 15% and 11% increases in HDL cholesterol and apolipoprotein A1, respectively.¹²⁰ In this study, both statins and fibrates had similar efficacy and tolerability.¹²⁰ After 1 year, fibrate monotherapy was associated with reduced triglyceride and total cholesterol by 41% and 22%, respectively, whereas statin monotherapy was associated with reduced triglyceride and total cholesterol by 35% and 25%, respectively.¹²⁰ Thus, fibrates would seem to be the preferred treatment for patients with HIV-associated dyslipidaemia characterised mainly by hypertriglyceridaemia (triglyceride > 5 mmol/L). Periodic monitoring of serum creatinine, creatine kinase, and transaminases should be undertaken with such treatment.

Combination of statins and fibrates

Combining statins with fibrates has been cautioned because of the potential risk of skeletal muscle toxicity. However, recent studies with large numbers of non-HIV patients have reduced this concern,¹¹² with the exception of contraindication for the statin-gemfibrozil combination. A retrospective study of fibrates, statins, or both in combination, found superior lipid lowering in patients with HIV-associated dyslipidaemia who received the statin-fibrate combination than in those receiving either

class individually.¹¹⁶ A randomised, open-label 48-week trial of patients with HIV-associated dyslipidaemia showed that the pravastatin-fenofibrate combination was safe and markedly improved all lipid variables.¹¹³ However, careful monitoring of clinical symptoms, such as myalgias, and biochemical variables, such as serum transaminases, creatine kinase, and creatinine, is prudent until more extensive efficacy and tolerability data for the statin-fibrate combination in HIV-associated dyslipidaemia are available. Sub-maximal statin doses should be used and the combination is best avoided in patients with marked renal impairment.

Ezetimibe

Ezetimibe inhibits intestinal cholesterol absorption,¹²⁹ without metabolism through the CYP3A4 pathway. As monotherapy, ezetimibe can reduce LDL cholesterol by 20% or more;^{130,131} preliminary data from five patients treated for 12 weeks with ezetimibe 10 mg showed reductions of total and LDL cholesterol and triglyceride of 14%, 17%, and 26%, respectively, with a 9% increase in HDL cholesterol (Hegele RA, unpublished data). Ezetimibe might be useful in the treatment of statin-intolerant or severely dyslipidaemic HIV patients who are not at target lipid levels.

Niacin (nicotinic acid)

Niacin, whose molecular mechanism of action is incompletely characterised, can be effective for hypertriglyceridaemia. The use of fast-acting crystalline niacin has been cautioned in dyslipidaemic HIV patients, because of frequent adverse effects including flushing, cutaneous rash pruritus, and exacerbation of insulin resistance and hyperuricaemia.¹³² However, a recent 14-week study of extended release-niacin (Niaspan) in HAART-treated HIV patients showed significant 14%, 34%, and 19% decreases in total cholesterol, triglyceride, and non-HDL cholesterol, respectively.¹³³ Notably, three of 11 patients developed new onset glucose intolerance. Extended release-niacin use was generally well tolerated and associated with a good safety profile. Side-effects, such as flushing, itching, and headaches, were initially reported in about 50% of patients, but such symptoms improved after 14 weeks of treatment. Most adverse effects were controlled with 325 mg aspirin daily.¹³³

Other agents

Acipimox, a long-acting niacin analogue, was associated with improved insulin sensitivity and a modest but significant reduction in triglyceride in 23 HIV-infected adults ($p < 0.01$).¹³⁴ Recombinant methionyl human leptin was associated with improved insulin sensitivity, fasting plasma insulin, HDL cholesterol, and truncal fat mass¹³⁵ in seven patients. Omega-3 fatty acids—namely eicosapentaenoic acid and docosahexaenoic acid—lower plasma triglyceride in HIV-associated dyslipidaemia.¹³⁶ A 16-week randomised study in patients with

HAART-associated hypertriglyceridaemia showed that fish oil supplementation reduced plasma triglyceride by 20%. A treatment strategy of improved diet and exercise alone reduced plasma triglyceride by only 6%; however, this strategy was associated with a 22% increase in plasma LDL cholesterol.¹³⁷ Other studies have similarly shown benefits of omega-3 fatty acids.^{138,139} Polyunsaturated ethyl esters of omega-3 fatty acids plus fibrates in HAART-treated HIV patients reduced plasma triglyceride more than diet and exercise alone.¹⁴⁰

Additionally, tetradecylthioacetic acid (an agent with an uncharacterised mechanism of action) in combination with diet showed improved plasma lipoprotein levels in a study of ten dyslipidaemic HIV patients.¹⁴¹ Plasma levels of TNF α were decreased during the tetradecylthioacetic acid phase of the study.¹⁴¹ A randomised, double-blind, placebo-controlled pilot study in 14 dyslipidaemic HIV patients over 8 weeks showed that cholestin, through an unknown mechanism, lowered total and LDL cholesterol by 31% and 32%, respectively, compared with 8% and 26% with placebo, with no changes in HDL or triglyceride and no adverse effects.¹⁴² L-carnitine at 3 g daily, through an unknown mechanism, appeared to lower serum triglyceride in 16 dyslipidaemic HIV patients.¹⁴³

Conclusion

Dyslipidaemia among HIV patients, particularly those receiving antiretroviral therapy, is increasingly encountered in the clinic. HIV infection and the use of antiretroviral therapy are associated with increased cardiovascular disease risk. Dyslipidaemia, although multifactorial, has been associated with HIV infection itself, as well as the use of antiretroviral agents. Treatment options include diet and exercise, control of secondary factors contributing to dyslipidaemia, switching among antiretroviral treatments, and strategic use of a variety of pharmaceutical agents. Future studies should be aimed at evaluating and clarifying the role of various agents in treating HIV-associated dyslipidaemia and at further elucidating mechanisms and optimum treatments for this important complication of HIV treatment.

Search strategy and selection criteria

Data for this Review were identified by searches of Medline, Current Contents, and references from relevant articles for the period January, 1990, to May, 2007. Search terms were "HIV" AND "dyslipidemia", "cholesterol", "triglyceride", "lipoprotein", "apolipoprotein", "hyperlipidemia", "antiretroviral", "protease inhibitor", "nucleoside reverse transcriptase inhibitor", "NRTI", "non-nucleoside reverse transcriptase inhibitor", and "NNRTI", OR "statin", "3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor", "fibrate", or "fibric acid derivative", and "cholesterol absorption inhibitor". All relevant identified articles were English-language papers.

Conflicts of interest

We declare that we have no conflicts of interest.

Acknowledgments

RAH is supported by the Jacob J Wolfe Distinguished Medical Research Chair, the Edith Schulich Vinet Canada Research Chair (Tier I) in Human Genetics, a Career Investigator award from the Heart and Stroke Foundation of Ontario, and operating grants from the Canadian Institutes for Health Research, the Heart and Stroke Foundation of Ontario, the Ontario Research Fund, and Genome Canada through the Ontario Genomics Institute.

References

- Carr A, Samaras K, Burton S, et al. A syndrome of peripheral lipodystrophy, hyperlipidaemia and insulin resistance in patients receiving HIV protease inhibitors. *AIDS* 1998; **12**: F51–58.
- Henry K, Melroe H, Huebesch J, Hermundson J, Simpson J. Atorvastatin and gemfibrozil for protease-inhibitor-related lipid abnormalities. *Lancet* 1998; **352**: 1031–32.
- Penzak SR, Chuck SK. Hyperlipidemia associated with HIV protease inhibitor use: pathophysiology, prevalence, risk factors and treatment. *Scand J Infect Dis* 2000; **32**: 111–23.
- Friis-Moller N, Sabin CA, Weber R, et al. Combination antiretroviral therapy and the risk of myocardial infarction. *N Engl J Med* 2003; **349**: 1993–2003.
- Friis-Moller N, Reiss P, Sabin CA, et al, for the DAD Study Group. Class of antiretroviral drugs and the risk of myocardial infarction. *N Engl J Med* 2007; **356**: 1723–35.
- Constans J, Pellegrin JL, Peuchant E, et al. Plasma lipids in HIV-infected patients: a prospective study in 95 patients. *Eur J Clin Invest* 1994; **24**: 416–20.
- Hellerstein MK, Grunfeld C, Wu K, et al. Increased de novo hepatic lipogenesis in human immunodeficiency virus infection. *J Clin Endocrinol Metab* 1993; **76**: 559–65.
- Asztalos BF, Schaefer EJ, Horvath KV, et al. Protease inhibitor-based HAART, HDL, and CHD-risk in HIV-infected patients. *Atherosclerosis* 2006; **184**: 72–77.
- Rose H, Woolley I, Hoy J, et al. HIV infection and high-density lipoprotein: the effect of the disease vs the effect of treatment. *Metabolism* 2006; **55**: 90–95.
- Zangerle R, Sarcletti M, Gallati H, Reibnegger G, Wachter H, Fuchs D. Decreased plasma concentrations of HDL cholesterol in HIV-infected individuals are associated with immune activation. *J Acquir Immune Defic Syndr* 1994; **7**: 1149–56.
- Coll B, van Wijk JP, Parra S, et al. Effects of rosiglitazone and metformin on postprandial paraoxonase-1 and monocyte chemoattractant protein-1 in human immunodeficiency virus-infected patients with lipodystrophy. *Eur J Pharmacol* 2006; **544**: 104–10.
- Khovidhunkit W, Memon RA, Shigenaga JK, et al. Plasma platelet-activating factor acetylhydrolase activity in human immunodeficiency virus infection and the acquired immunodeficiency syndrome. *Metabolism* 1999; **48**: 1524–31.
- Pirich C, Efthimiou Y, O'Grady J, Zielinski C, Sinzinger H. Apolipoprotein A and biological half-life of prostaglandin I₂ in HIV-1 infection. *Thromb Res* 1996; **81**: 213–18.
- Rader DJ. Molecular regulation of HDL metabolism and function: implications for novel therapies. *J Clin Invest* 2006; **116**: 3090–100.
- Mujawar Z, Rose H, Morrow MP, et al. Human immunodeficiency virus impairs reverse cholesterol transport from macrophages. *PLoS Biol* 2006; **4**: e365.
- Shinohara E, Yamashita S, Kihara S, et al. Interferon alpha induces disorder of lipid metabolism by lowering postheparin lipases and cholesteryl ester transfer protein activities in patients with chronic hepatitis C. *Hepatology* 1997; **25**: 1502–06.
- Carpentier A, Patterson BW, Uffelman KD, Salit I, Lewis GF. Mechanism of highly active anti-retroviral therapy-induced hyperlipidemia in HIV-infected individuals. *Atherosclerosis* 2005; **178**: 165–72.
- Das S, Shahmanesh M, Stolinski M, et al. In treatment-naive and antiretroviral-treated subjects with HIV, reduced plasma adiponectin is associated with a reduced fractional clearance rate of VLDL, IDL and LDL apolipoprotein B-100. *Diabetologia* 2006; **49**: 538–42.

- 19 Haugaard SB, Andersen O, Pedersen SB, et al. Tumor necrosis factor alpha is associated with insulin-mediated suppression of free fatty acids and net lipid oxidation in HIV-infected patients with lipodystrophy. *Metabolism* 2006; **55**: 175–82.
- 20 Grunfeld C, Kotler DP, Hamadeh R, Tierney A, Wang J, Pierson RN. Hypertriglyceridemia in the acquired immunodeficiency syndrome. *Am J Med* 1989; **86**: 27–31.
- 21 Grunfeld C, Kotler DP, Shigenaga JK, et al. Circulating interferon-alpha levels and hypertriglyceridemia in the acquired immunodeficiency syndrome. *Am J Med* 1991; **90**: 154–62.
- 22 Fisher SD, Miller TL, Lipshultz SE. Impact of HIV and highly active antiretroviral therapy on leukocyte adhesion molecules, arterial inflammation, dyslipidemia, and atherosclerosis. *Atherosclerosis* 2006; **185**: 1–11.
- 23 Guardiola M, Ferre R, Salazar J, et al. Protease inhibitor-associated dyslipidemia in HIV-infected patients is strongly influenced by the APOA5-1131T>C gene variation. *Clin Chem* 2006; **52**: 1914–19.
- 24 Berthold HK, Parhofer KG, Ritter MM, et al. Influence of protease inhibitor therapy on lipoprotein metabolism. *J Intern Med* 1999; **246**: 567–75.
- 25 Fessel WJ, Follansbee SE, Rego J. High-density lipoprotein cholesterol is low in HIV-infected patients with lipodystrophic fat expansions: implications for pathogenesis of fat redistribution. *AIDS* 2002; **16**: 1785–89.
- 26 Periard D, Telenti A, Sudre P, et al. Atherogenic dyslipidemia in HIV-infected individuals treated with protease inhibitors. The Swiss HIV Cohort Study. *Circulation* 1999; **100**: 700–05.
- 27 Pernerstorfer-Schoen H, Jilma B, Perschler A, et al. Sex differences in HAART-associated dyslipidaemia. *AIDS* 2001; **15**: 725–34.
- 28 Riddler SA, Smit E, Cole SR, et al. Impact of HIV infection and HAART on serum lipids in men. *JAMA* 2003; **289**: 2978–82.
- 29 Feingold KR, Krauss RM, Pang M, Doerrler W, Jensen P, Grunfeld C. The hypertriglyceridemia of acquired immunodeficiency syndrome is associated with an increased prevalence of low density lipoprotein subclass pattern B. *J Clin Endocrinol Metab* 1993; **76**: 1423–27.
- 30 Constans J, Pellegrin JL, Peuchant E, et al. High plasma lipoprotein (a) in HIV-positive patients. *Lancet* 1993; **341**: 1099–100.
- 31 Kritz H, Efthimiou Y, Stamatopoulos J, Najemnik C, Sinzinger H. Association of lipoprotein(a), prostaglandin I(2)-synthesis stimulating plasma factor, biological half-life of prostaglandin I(2) and high-density lipoproteins in HIV-1 infection of different stages. *Prostaglandins Leukot Essent Fatty Acids* 2000; **63**: 309–14.
- 32 Rimland D, Guest JL, Hernandez-Ramos I, Del Rio C, Le NA, Brown WV. Antiretroviral therapy in HIV-positive women is associated with increased apolipoproteins and total cholesterol. *J Acquir Immune Defic Syndr* 2006; **42**: 307–13.
- 33 Bard JM, Lassalle R, Capeau J, et al. Association of apolipoproteins C3 and E with metabolic changes in HIV-infected adults treated with a protease-inhibitor-containing antiretroviral therapy. *Antivir Ther* 2006; **11**: 361–70.
- 34 Bonnet F, Balestre E, Thiebaut R, et al. Fibrates or statins and lipid plasma levels in 245 patients treated with highly active antiretroviral therapy. Aquitaine Cohort, France, 1999–2001. *HIV Med* 2004; **5**: 133–39.
- 35 Grunfeld C, Doerrler W, Pang M, Jensen P, Weisgraber KH, Feingold KR. Abnormalities of apolipoprotein E in the acquired immunodeficiency syndrome. *J Clin Endocrinol Metab* 1997; **82**: 3734–40.
- 36 Stefas E, Rucheton M, Graafland H, et al. Human plasmatic apolipoprotein H binds human immunodeficiency virus type 1 and type 2 proteins. *AIDS Res Hum Retroviruses* 1997; **13**: 97–104.
- 37 Shahmanesh M, Das S, Stolinski M, et al. Antiretroviral treatment reduces very-low-density lipoprotein and intermediate-density lipoprotein apolipoprotein B fractional catabolic rate in human immunodeficiency virus-infected patients with mild dyslipidemia. *J Clin Endocrinol Metab* 2005; **90**: 755–60.
- 38 Purnell JQ, Zambon A, Knopp RH, et al. Effect of ritonavir on lipids and post-heparin lipase activities in normal subjects. *AIDS* 2000; **14**: 51–57.
- 39 Sekhar RV, Jahoor F, Pownall HJ, et al. Severely dysregulated disposal of postprandial triacylglycerols exacerbates hypertriglycerolemia in HIV lipodystrophy syndrome. *Am J Clin Nutr* 2005; **81**: 1405–10.
- 40 Reeds DN, Yarasheski KE, Fontana L, et al. Alterations in liver, muscle, and adipose tissue insulin sensitivity in men with HIV infection and dyslipidemia. *Am J Physiol Endocrinol Metab* 2006; **290**: E47–53.
- 41 van Wijk JP, Cabezas MC, de Koning EJ, Rabelink TJ, van der Geest R, Hoepelman IM. In vivo evidence of impaired peripheral fatty acid trapping in patients with human immunodeficiency virus-associated lipodystrophy. *J Clin Endocrinol Metab* 2005; **90**: 3575–82.
- 42 Miserez AR, Muller PY, Spaniol V. Indinavir inhibits sterol-regulatory element-binding protein-1c-dependent lipoprotein lipase and fatty acid synthase gene activations. *AIDS* 2002; **16**: 1587–94.
- 43 Torriani M, Thomas BJ, Barlow RB, Librizzi J, Dolan S, Grinspoon S. Increased intramyocellular lipid accumulation in HIV-infected women with fat redistribution. *J Appl Physiol* 2006; **100**: 609–14.
- 44 Beatty G, Chu J, Kulkarni K, et al. Relative effects of insulin resistance and protease inhibitor treatment on lipid and lipoprotein metabolism in HIV-infected patients. *HIV Clin Trials* 2004; **5**: 383–91.
- 45 Liang JS, Distler O, Cooper DA, et al. HIV protease inhibitors protect apolipoprotein B from degradation by the proteasome: a potential mechanism for protease inhibitor-induced hyperlipidemia. *Nat Med* 2001; **7**: 1327–31.
- 46 Petit JM, Duong M, Duvillard L, et al. LDL-receptors expression in HIV-infected patients: relations to antiretroviral therapy, hormonal status, and presence of lipodystrophy. *Eur J Clin Invest* 2002; **32**: 354–59.
- 47 Reeds DN, Mittendorfer B, Patterson BW, Powderly WG, Yarasheski KE, Klein S. Alterations in lipid kinetics in men with HIV-dyslipidemia. *Am J Physiol Endocrinol Metab* 2003; **285**: E490–97.
- 48 Cossarizza A, Riva A, Pinti M, et al. Increased mitochondrial DNA content in peripheral blood lymphocytes from HIV-infected patients with lipodystrophy. *Antivir Ther* 2003; **8**: 315–21.
- 49 Pinti M, Salomoni P, Cossarizza A. Anti-HIV drugs and the mitochondria. *Biochim Biophys Acta* 2006; **1757**: 700–07.
- 50 Zaera MG, Miro O, Pedrol E, et al. Mitochondrial involvement in antiretroviral therapy-related lipodystrophy. *AIDS* 2001; **15**: 1643–51.
- 51 Carr A, Samaras K, Chisholm DJ, Cooper DA. Pathogenesis of HIV-1-protease inhibitor-associated peripheral lipodystrophy, hyperlipidaemia, and insulin resistance. *Lancet* 1998; **351**: 1881–83.
- 52 Hu C, Oliver JA, Goldberg MR, Al-Awqati Q. LRP: a new adhesion molecule for endothelial and smooth muscle cells. *Am J Physiol Renal Physiol* 2001; **281**: F739–50.
- 53 Zimmermann R, Panzenbock U, Wintersperger A, et al. Lipoprotein lipase mediates the uptake of glycated LDL in fibroblasts, endothelial cells, and macrophages. *Diabetes* 2001; **50**: 1643–53.
- 54 Carr A, Samaras K, Thorisdottir A, Kaufmann GR, Chisholm DJ, Cooper DA. Diagnosis, prediction, and natural course of HIV-1 protease-inhibitor-associated lipodystrophy, hyperlipidaemia, and diabetes mellitus: a cohort study. *Lancet* 1999; **353**: 2093–99.
- 55 Tarr PE, Taffe P, Bleiber G, et al. Modeling the influence of APOC3, APOE, and TNF polymorphisms on the risk of antiretroviral therapy-associated lipid disorders. *J Infect Dis* 2005; **191**: 1419–26.
- 56 Favuel J. An interaction between apo C-III variants and protease inhibitors contributes to high triglyceride/low HDL levels in treated HIV patients. *AIDS* 2001; **15**: 1297–406.
- 57 Foulkes AS, Wohl DA, Frank I, et al. Associations among race/ethnicity, ApoC-III genotypes, and lipids in HIV-1-infected individuals on antiretroviral therapy. *PLoS Med* 2006; **3**: e52.
- 58 Hegele RA. Monogenic dyslipidemias: window on determinants of plasma lipoprotein metabolism. *Am J Hum Genet* 2001; **69**: 1161–77.
- 59 Calza L, Manfredi R, Chiodo F. Hyperlipidaemia in patients with HIV-1 infection receiving highly active antiretroviral therapy: epidemiology, pathogenesis, clinical course and management. *Int J Antimicrob Agents* 2003; **22**: 89–99.
- 60 Dube MP, Stein JH, Aberg JA, et al. Guidelines for the evaluation and management of dyslipidemia in human immunodeficiency virus (HIV)-infected adults receiving antiretroviral therapy: recommendations of the HIV Medical Association of the Infectious Disease Society of America and the Adult AIDS Clinical Trials Group. *Clin Infect Dis* 2003; **37**: 613–27.

- 61 Guo JJ, Jang R, Louder A, Cluxton RJ. Acute pancreatitis associated with different combination therapies in patients infected with human immunodeficiency virus. *Pharmacotherapy* 2005; **25**: 1044–54.
- 62 Ruotolo G, Howard BV. Dyslipidemia of the metabolic syndrome. *Curr Cardiol Rep* 2002; **4**: 494–500.
- 63 Volek JS, Feinman RD. Carbohydrate restriction improves the features of metabolic syndrome. Metabolic syndrome may be defined by the response to carbohydrate restriction. *Nutr Metab (Lond)* 2005; **2**: 31.
- 64 Lazzaretti R. Nutritional intervention protects against the development of dyslipidemia in patients who start HAART: a randomized trial. XIV International AIDS Conference; Toronto, Canada; Aug 13–18, 2006. Abstract 2192713.
- 65 Yarasheski KE, Tebas P, Stanerson B, et al. Resistance exercise training reduces hypertriglyceridemia in HIV-infected men treated with antiviral therapy. *J Appl Physiol* 2001; **90**: 133–38.
- 66 Young J, Weber R, Rickenbach M, et al. Lipid profiles for antiretroviral-naïve patients starting PI- and NNRTI-based therapy in the Swiss HIV cohort study. *Antivir Ther* 2005; **10**: 585–91.
- 67 Cahn PE, Gatell JM, Squires K, et al. Atazanavir—a once-daily HIV protease inhibitor that does not cause dyslipidemia in newly treated patients: results from two randomized clinical trials. *J Int Assoc Physicians AIDS Care (Chic Ill)* 2004; **3**: 92–98.
- 68 Grover SA, Coupal L, Gilmore N, Mukherjee J. Impact of dyslipidemia associated with highly active antiretroviral therapy (HAART) on cardiovascular risk and life expectancy. *Am J Cardiol* 2005; **95**: 586–91.
- 69 Calaz L. Substitution of nevirapine or efavirenz for protease inhibitor versus lipid-lowering therapy for the management of dyslipidemia. *AIDS* 2005; **19**: 1051–58.
- 70 Hicks CB, Cahn P, Cooper DA, et al. Durable efficacy of tipranavir-ritonavir in combination with an optimised background regimen of antiretroviral drugs for treatment-experienced HIV-1-infected patients at 48 weeks in the Randomized Evaluation of Strategic Intervention in multi-drug resistant patients with Tipranavir (RESIST) studies: an analysis of combined data from two randomised open-label trials. *Lancet* 2006; **368**: 466–75.
- 71 Calza L, Manfredi R, Colangeli V, et al. Substitution of nevirapine or efavirenz for protease inhibitor versus lipid-lowering therapy for the management of dyslipidaemia. *AIDS* 2005; **19**: 1051–58.
- 72 Carr A, Hudson J, Chuah J, et al. HIV protease inhibitor substitution in patients with lipodystrophy: a randomized, controlled, open-label, multicentre study. *AIDS* 2001; **15**: 1811–22.
- 73 Clotet B, van der Valk M, Negredo E, Reiss P. Impact of nevirapine on lipid metabolism. *J Acquir Immune Defic Syndr* 2003; **34** (suppl 1): S79–84.
- 74 Justesen US, Hansen IM, Andersen AB, et al. The long-term pharmacokinetics and safety of adding low-dose ritonavir to a nelfinavir 1250 mg twice-daily regimen in HIV-infected patients. *HIV Med* 2005; **6**: 334–40.
- 75 McComsey G, Bhumbra N, Ma JF, Rathore M, Alvarez A. Impact of protease inhibitor substitution with efavirenz in HIV-infected children: results of the First Pediatric Switch Study. *Pediatrics* 2003; **111**: e275–81.
- 76 Negredo E, Ribalta J, Paredes R, et al. Reversal of atherogenic lipoprotein profile in HIV-1 infected patients with lipodystrophy after replacing protease inhibitors by nevirapine. *AIDS* 2002; **16**: 1383–89.
- 77 Pereira SA, Branco T, Corte-Real RM, et al. Long-term and concentration-dependent beneficial effect of efavirenz on HDL-cholesterol in HIV-infected patients. *Br J Clin Pharmacol* 2006; **61**: 601–04.
- 78 Ribera E, Rodriguez-Pardo D, Rubio M, et al. Efficacy and safety of once-daily combination therapy with didanosine, lamivudine and nevirapine in antiretroviral-naïve HIV-infected patients. *Antivir Ther* 2005; **10**: 605–14.
- 79 Roberts AD, Liappis AP, Chinn C, et al. Effect of delavirdine on plasma lipids and lipoproteins in patients receiving antiretroviral therapy. *AIDS* 2002; **16**: 1829–30.
- 80 van der Valk M, Kastelein JJ, Murphy RL, et al. Nevirapine-containing antiretroviral therapy in HIV-1 infected patients results in an anti-atherogenic lipid profile. *AIDS* 2001; **15**: 2407–14.
- 81 van Leth F, Hall DB, Lange JM, Reiss P. Plasma lipid concentrations after 1–5 years of exposure to nevirapine or efavirenz together with stavudine and lamivudine. *HIV Med* 2006; **7**: 347–50.
- 82 Wood R, Phanuphak P, Cahn P, et al. Long-term efficacy and safety of atazanavir with stavudine and lamivudine in patients previously treated with nelfinavir or atazanavir. *J Acquir Immune Defic Syndr* 2004; **36**: 684–92.
- 83 Keiser PH, Sension MG, DeJesus E, et al. Substituting abacavir for hyperlipidemia-associated protease inhibitors in HAART regimens improves fasting lipid profiles, maintains virologic suppression, and simplifies treatment. *BMC Infect Dis* 2005; **5**: 2.
- 84 Llibre JM, Domingo P, Palacios R, et al. Sustained improvement of dyslipidaemia in HAART-treated patients replacing stavudine with tenofovir. *AIDS* 2006; **20**: 1407–14.
- 85 Miro O, Garrabou G, Lopez S, et al. Metabolic and mitochondrial effects of switching antiretroviral-experienced patients to enfuvirtide, tenofovir and saquinavir/ritonavir. *Antivir Ther* 2006; **11**: 625–30.
- 86 Baigent C, Keech A, Kearney PM, et al. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90 056 participants in 14 randomised trials of statins. *Lancet* 2005; **366**: 1267–78.
- 87 Boccarda F, Simon T, Lacombe K, et al. Influence of pravastatin on carotid artery structure and function in dyslipidemic HIV-infected patients receiving antiretroviral therapy. *AIDS* 2006; **20**: 2395–98.
- 88 Bonnet F, Aurillac-Lavignolle V, Breilh D, et al. Pravastatin in HIV-infected patients treated with protease inhibitors: a placebo-controlled randomized study. *HIV Clin Trials* 2007; **8**: 53–60.
- 89 Manfredi R, Chiodo F. Disorders of lipid metabolism in patients with HIV disease treated with antiretroviral agents: frequency, relationship with administered drugs, and role of hypolipidaemic therapy with bezafibrate. *J Infect* 2001; **42**: 181–88.
- 90 Moyle GJ, Buss NE, Gazzard BG. Pravastatin does not alter protease inhibitor exposure or virologic efficacy during a 24-week period of therapy. *J Acquir Immune Defic Syndr* 2002; **30**: 460–62.
- 91 Benesic A, Zilly M, Kluge F, et al. Lipid lowering therapy with fluvastatin and pravastatin in patients with HIV infection and antiretroviral therapy: comparison of efficacy and interaction with indinavir. *Infection* 2004; **32**: 229–33.
- 92 Giguere JF, Tremblay MJ. Statin compounds reduce human immunodeficiency virus type 1 replication by preventing the interaction between virion-associated host intercellular adhesion molecule 1 and its natural cell surface ligand LFA-1. *J Virol* 2004; **78**: 12062–65.
- 93 Issat T, Nowis D, Jakobisiak M, Golab J. Lovastatin potentiates antitumor effects of saquinavir against human lymphoma cells. *Oncol Rep* 2004; **12**: 1371–75.
- 94 Moncunill G, Negredo E, Bosch L, et al. Evaluation of the anti-HIV activity of statins. *AIDS* 2005; **19**: 1697–700.
- 95 Calza L. Rosuvastatin for the treatment of hyperlipidemia in HIV-infected patients receiving protease inhibitors: a pilot study. *AIDS* 2005; **19**: 1103–05.
- 96 Kapur NK. Rosuvastatin: a highly potent statin for the prevention and management of coronary artery disease. *Expert Rev Cardiovasc Ther* 2007; **5**: 161–75.
- 97 Hurlimann D, Chenevard R, Ruschitzka F, et al. Effects of statins on endothelial function and lipid profile in HIV infected persons receiving protease inhibitor-containing anti-retroviral combination therapy: a randomised double blind crossover trial. *Heart* 2006; **92**: 110–12.
- 98 Stein JH, Merwood MA, Bellehumeur JL, et al. Effects of pravastatin on lipoproteins and endothelial function in patients receiving human immunodeficiency virus protease inhibitors. *Am Heart J* 2004; **147**: E18.
- 99 Neuvonen PJ, Niemi M, Backman JT. Drug interactions with lipid-lowering drugs: mechanisms and clinical relevance. *Clin Pharmacol Ther* 2006; **80**: 565–81.
- 100 Estrada V, De Villar NG, Larrad MT, Lopez AG, Fernandez C, Serrano-Rios M. Long-term metabolic consequences of switching from protease inhibitors to efavirenz in therapy for human immunodeficiency virus-infected patients with lipodystrophy. *Clin Infect Dis* 2002; **35**: 69–76.
- 101 Fichtenbaum CJ, Gerber JG, Rosenkranz SL, et al. Pharmacokinetic interactions between protease inhibitors and statins in HIV seronegative volunteers: ACTG Study A5047. *AIDS* 2002; **16**: 569–77.
- 102 Aboulafia DM, Johnston R. Simvastatin-induced rhabdomyolysis in an HIV-infected patient with coronary artery disease. *AIDS Patient Care STDS* 2000; **14**: 13–18.

- 103 Cheng CH, Miller C, Lowe C, Pearson VE. Rhabdomyolysis due to probable interaction between simvastatin and ritonavir. *Am J Health Syst Pharm* 2002; **59**: 728–30.
- 104 Fichtenbaum CJ, Gerber JG. Interactions between antiretroviral drugs and drugs used for the therapy of the metabolic complications encountered during HIV infection. *Clin Pharmacokinet* 2002; **41**: 1195–211.
- 105 Hare CB, Vu MP, Grunfeld C, Lampiris HW. Simvastatin-nelfinavir interaction implicated in rhabdomyolysis and death. *Clin Infect Dis* 2002; **35**: e111–12.
- 106 Hellinger FJ, Encinosa WE. Inappropriate drug combinations among privately insured patients with HIV disease. *Med Care* 2005; **43** (suppl 9): I1153–62.
- 107 Moro H, Tsukada H, Tanuma A, et al. Rhabdomyolysis after simvastatin therapy in an HIV-infected patient with chronic renal failure. *AIDS Patient Care STDS* 2004; **18**: 687–90.
- 108 Castro JG, Gutierrez L. Rhabdomyolysis with acute renal failure probably related to the interaction of atorvastatin and delavirdine. *Am J Med* 2002; **112**: 505.
- 109 Mah Ming JB, Gill MJ. Drug-induced rhabdomyolysis after concomitant use of clarithromycin, atorvastatin, and lopinavir/ritonavir in a patient with HIV. *AIDS Patient Care STDS* 2003; **17**: 207–10.
- 110 Gerber JG, Rosenkranz SL, Fichtenbaum CJ, et al. Effect of efavirenz on the pharmacokinetics of simvastatin, atorvastatin, and pravastatin: results of AIDS Clinical Trials Group 5108 Study. *J Acquir Immune Defic Syndr* 2005; **39**: 307–12.
- 111 Mallon PW, Miller J, Kovacic JC, et al. Effect of pravastatin on body composition and markers of cardiovascular disease in HIV-infected men—a randomized, placebo-controlled study. *AIDS* 2006; **20**: 1003–10.
- 112 Keech A, Simes RJ, Barter P, et al. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. *Lancet* 2005; **366**: 1849–61.
- 113 Aberg JA, Zackin RA, Brobst SW, et al. A randomized trial of the efficacy and safety of fenofibrate versus pravastatin in HIV-infected subjects with lipid abnormalities: AIDS Clinical Trials Group Study 5087. *AIDS Res Hum Retroviruses* 2005; **21**: 757–67.
- 114 Calza L, Manfredi R, Chiodo F. Statins and fibrates for the treatment of hyperlipidaemia in HIV-infected patients receiving HAART. *AIDS* 2003; **17**: 851–59.
- 115 Miller J, Brown D, Amin J, et al. A randomized, double-blind study of gemfibrozil for the treatment of protease inhibitor-associated hypertriglyceridaemia. *AIDS* 2002; **16**: 2195–200.
- 116 Visnegarwala F, Maldonado M, Sajja P, et al. Lipid lowering effects of statins and fibrates in the management of HIV dyslipidemias associated with antiretroviral therapy in HIV clinical practice. *J Infect* 2004; **49**: 283–90.
- 117 Calza L, Manfredi R, Chiodo F. Use of fibrates in the management of hyperlipidemia in HIV-infected patients receiving HAART. *Infection* 2002; **30**: 26–31.
- 118 Hewitt RG, Shelton MJ, Esch LD. Gemfibrozil effectively lowers protease inhibitor-associated hypertriglyceridemia in HIV-1-positive patients. *AIDS* 1999; **13**: 868–69.
- 119 Martinez E, Domingo P, Ribera E, et al. Effects of metformin or gemfibrozil on the lipodystrophy of HIV-infected patients receiving protease inhibitors. *Antivir Ther* 2003; **8**: 403–10.
- 120 Badiou S, Merle De Boever C, Dupuy AM, Baillat V, Cristol JP, Reynes J. Fenofibrate improves the atherogenic lipid profile and enhances LDL resistance to oxidation in HIV-positive adults. *Atherosclerosis* 2004; **172**: 273–79.
- 121 Bonnet E, Ruidavets JB, Tuech J, et al. Apoprotein c-III and E-containing lipoparticles are markedly increased in HIV-infected patients treated with protease inhibitors: association with the development of lipodystrophy. *J Clin Endocrinol Metab* 2001; **86**: 296–302.
- 122 Gavrilu A, Hsu W, Tsioutras S, et al. Improvement in highly active antiretroviral therapy-induced metabolic syndrome by treatment with pioglitazone but not with fenofibrate: a 2 x 2 factorial, randomized, double-blinded, placebo-controlled trial. *Clin Infect Dis* 2005; **40**: 745–49.
- 123 Normen L, Frohlich J, Montaner J, Harris M, Elliott T, Bondy G. Combination therapy with fenofibrate and rosiglitazone paradoxically lowers serum HDL cholesterol. *Diabetes Care* 2004; **27**: 2241–42.
- 124 Penzak SR, Chuck SK. Management of protease inhibitor-associated hyperlipidemia. *Am J Cardiovasc Drugs* 2002; **2**: 91–106.
- 125 Rao A, D'Amico S, Balasubramanyam A, Maldonado M. Fenofibrate is effective in treating hypertriglyceridemia associated with HIV lipodystrophy. *Am J Med Sci* 2004; **327**: 315–18.
- 126 Samson SL, Pownall HJ, Scott LW, et al. Heart positive: design of a randomized controlled clinical trial of intensive lifestyle intervention, niacin and fenofibrate for HIV lipodystrophy/dyslipidemia. *Contemp Clin Trials* 2006; **27**: 518–30.
- 127 Thomas JC, Lopes-Virella MF, Del Bene VE, et al. Use of fenofibrate in the management of protease inhibitor-associated lipid abnormalities. *Pharmacotherapy* 2000; **20**: 727–34.
- 128 Nystrom T, Bratt G, Sjöholm A. Bezafibrate-induced improvement in glucose uptake and endothelial function in protease inhibitor-associated insulin resistance. *J Intern Med* 2002; **252**: 570–74.
- 129 Huff MW, Pollex RL, Hegele RA. NPC1L1: evolution from pharmacological target to physiological sterol transporter. *Arterioscler Thromb Vasc Biol* 2006; **26**: 2433–38.
- 130 Coll B, Aragones G, Parra S, Alonso-Villaverde C, Masana L. Ezetimibe effectively decreases LDL-cholesterol in HIV-infected patients. *AIDS* 2006; **20**: 1675–77.
- 131 Negro E, Molto J, Puig J, et al. Ezetimibe, a promising lipid-lowering agent for the treatment of dyslipidaemia in HIV-infected patients with poor response to statins. *AIDS* 2006; **20**: 2159–64.
- 132 Rader DJ. Effects of nonstatin lipid drug therapy on high-density lipoprotein metabolism. *Am J Cardiol* 2003; **91**: 18E–23E.
- 133 Gerber MT, Mondy KE, Yarasheski KE, et al. Niacin in HIV-infected individuals with hyperlipidemia receiving potent antiretroviral therapy. *Clin Infect Dis* 2004; **39**: 419–25.
- 134 Hadigan C, Liebaw J, Torriani M, Andersen R, Grinspoon S. Improved triglycerides and insulin sensitivity with 3 months of acipimox in human immunodeficiency virus-infected patients with hypertriglyceridemia. *J Clin Endocrinol Metab* 2006; **91**: 4438–44.
- 135 Lee JH, Chan JL, Sourlas E, Raptopoulos V, Mantzoros CS. Recombinant methionyl human leptin therapy in replacement doses improves insulin resistance and metabolic profile in patients with lipodystrophy and metabolic syndrome induced by the highly active antiretroviral therapy. *J Clin Endocrinol Metab* 2006; **91**: 2605–11.
- 136 Woods MN. Role of n-3 fatty acids in prevention of disease complications in patients with HIV. *Nutr Clin Care* 2005; **8**: 24–30.
- 137 Wohl DA, Tien HC, Busby M, et al. Randomized study of the safety and efficacy of fish oil (omega-3 fatty acid) supplementation with dietary and exercise counseling for the treatment of antiretroviral therapy-associated hypertriglyceridemia. *Clin Infect Dis* 2005; **41**: 1498–504.
- 138 Metroka CE, Truong P, Gotto AM Jr. Treatment of HIV-associated dyslipidemia: a role for omega-3 fatty acids. *AIDS Read* 2007; **17**: 362–73.
- 139 De Truchis P, Kirstetter M, Perier A, et al. Reduction in triglyceride level with N-3 polyunsaturated fatty acids in HIV-infected patients taking potent antiretroviral therapy: a randomized prospective study. *J Acquir Immune Defic Syndr* 2007; **44**: 278–85.
- 140 Manfredi R, Calza L, Chiodo F. Polyunsaturated ethyl esters of n-3 fatty acids in HIV-infected patients with moderate hypertriglyceridemia: comparison with dietary and lifestyle changes, and fibrate therapy. *J Acquir Immune Defic Syndr* 2004; **36**: 878–80.
- 141 Fredrikson J, Ueland T, Dyroy E, et al. Lipid-lowering and anti-inflammatory effects of tetradecylthioacetic acid in HIV-infected patients on highly active antiretroviral therapy. *Eur J Clin Invest* 2004; **34**: 709–15.
- 142 Keithley JK, Swanson B, Sha BE, Zeller JM, Kessler HA, Smith KY. A pilot study of the safety and efficacy of cholestin in treating HIV-related dyslipidemia. *Nutrition* 2002; **18**: 201–04.
- 143 Loignon M, Toma E. L-Carnitine for the treatment of highly active antiretroviral therapy-related hypertriglyceridemia in HIV-infected adults. *AIDS* 2001; **15**: 1194–95.