HIV-associated dyslipidaemia: pathogenesis and treatment

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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, fibrate, 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. 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. This profile is also mechanistically linked with the insulin resistance and fat redistribution syndromes that complicate HAART therapy. However, dyslipidaemia can occur without obvious lipatrophy 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, with a relative rate of myocardial infarction of 1–2 per year of disease duration caused by HAART. 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. Viraemia-associated dyslipidaemia is characterised mainly by decreased plasma concentrations of total, LDL, and HDL cholesterol, and later elevated plasma triglyceride. Low HDL cholesterol has been correlated with immune activation early in the course of HIV infection, the repercussions of which may extend beyond atherosclerosis because of HDL’s numerous functions, including antioxidant and anti-inflammatory activities.

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. Furthermore, inflammation in general stimulates endothelial lipase and phospholipase A2, which can reduce plasma HDL. Additionally, HDL is triglyceride-enriched in hypertriglyceridaemia, becoming a more avid substrate for hepatic lipase-mediated clearance.

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

Panel 1: Clinical features associated with HIV lipodystrophy syndrome

Fat atrophy (lipodystrophy)

- 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, resulting from impaired clearance of triglyceride-rich lipoproteins. Similarly, tumour necrosis factor (TNF-α) is elevated in drug-naive HIV patients and increases further during opportunistic infections. TNFα interferes with free fatty acid metabolism and lipid oxidation, and attenuates insulin-mediated suppression of lipolysis. Finally, the nutritional state of HIV patients, including weight loss and protein depletion, 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. 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. These fundamental proatherogenic changes can be further accompanied by increases in small dense LDL particles, lipoprotein (a), and apolipoproteins B, C-III, and H.

In-vivo lipoprotein turnover studies have shown that increased plasma triglyceride-rich very low density lipoprotein (VLDL) levels result from either decreased catalysis of these particles because of HIV infection itself, or HAART-related increased production of VLDL, or protease inhibitor-mediated impaired catalysis of VLDL. Also, HAART treatment impairs hydrolysis of triglyceride-rich lipoproteins by plasma and tissue lipases, disrupts normal post-prandial free fatty acid and lipoprotein catalysis, and interferes with peripheral fatty acid trapping, all perhaps because of the interaction of these fatty acids with the master transcriptional regulator sterol regulatory element binding protein 1 (SREBP1). Protease inhibitor treatment is also associated with abnormal accumulation of intramyocellular fat, leading to insulin resistance, which further increases plasma apolipoprotein B-containing and triglyceride-rich lipoproteins. 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. Furthermore, protease inhibitor-induced lipodystrophy in HIV is associated with decreased expression of the LDL receptor and related receptors, which increases plasma LDL concentration.

Another proposed mechanism underlying the dyslipidaemia is HAART-induced mitochondrial alterations. 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. Mitochondrial respiratory chain inhibition may be responsible for abnormalities in several cell types, including adipocytes, leading to lipoatrophy. Mitochondrial dysfunction in skeletal muscle may lead to insulin resistance, with secondary dyslipidaemia. Interactions between protease inhibitors and cellular proteases acting in mitochondrial biogenesis could also underlie metabolic alterations.

Altered intracellular lipid metabolism has been attributed to the structural homology (approximately 60% at the aminoacid 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). 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-PPARγ) heterodimer, stimulating adipocyte differentiation and inhibiting apoptosis. Protease inhibitors might bind to CRABP1, thus inhibiting the formation of cis-9-retinoic acid, leading to reduced RXR-PPARγ activity and peripheral lipoatrophy, mainly on limbs and the gluteal region. Hyperlipidaemia results from impaired storage capacity and increased flux of circulating lipids. The decrease in RXR-PPARγ 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-PPARγ targets, leading to lipoatrophy and worsened dyslipidaemia.

LRP1 normally binds to lipoprotein lipase on capillary endothelium, which hydrolyses free fatty acids (FFAs) from triglyceride, promoting their accumulation in adipocytes. Protease inhibitor binding to LR1 would interfere with LR1-lipoprotein lipase complex formation, reducing adipose storage capacity and increasing plasma triglyceride-rich lipoproteins. 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.

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. Also, the –1113T>C promoter polymorphism
in the APOA5 gene was associated with hypertriglyceridaemia in protease inhibitor-treated patients. Variable responses to protease inhibitors have also been associated with other DNA polymorphisms.

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. 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

**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-peroxisome proliferator-activated receptor γ (RXR-PPARγ) 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.
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.

**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 antiretroviral agents**
- Protease inhibitor class associated with more severe dyslipidaemia, especially hypertriglyceridaemia
- Descending rank order of hyperlipidaemia induction: ritonavir-amprenavir/nelfinavir-inidinavir/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 to modest efficacy, appropriate to consider when baseline triglyceride more than 5 mmol/L
- 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

**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. Elevated plasma triglyceride in this group has also been associated with acute pancreatitis 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. Current recommendations for evaluation and treatment of dyslipidaemia in HIV-infected adults include those from the National Cholesterol Education Program Adult Treatment Panel III guidelines 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, 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.

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. A recent randomised study showed that dietary intervention in drug-naive HIV patients prevented development of dyslipidaemia after 6 and 12 months. Exercise can also help—for example, structured exercise plus diet decreased total cholesterol and triglyceride by 11% and 21%, respectively, in HIV-infected patients. Also,
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). Amprenavir and nelfinavir have intermediate effects on plasma lipids, indinavir and saquinavir have even fewer, and lopinavir has the most favourable lipid profile. Atazanavir has negligible effects on serum lipids. 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). Switching from nelfinavir to atazanavir reduced total cholesterol and triglyceride with no apparent antiviral compromise. Tipranavir, a non-peptidic protease inhibitor, is a newer option in antiretroviral-naive patients, HAART regimens and switching to an NRTI or NNRTI. For discontinuation of the protease inhibitor within HAART regimens and switching to an NRTI or NNRTI, For discontinuation of the protease inhibitor within HAART regimens and switching to an NRTI or NNRTI, the addition of fusion inhibitors, such as enfuvirtide, to existing therapies had little effect on plasma lipids.

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. 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. 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 cholesterol and a more favourable lipid profile than protease inhibitors.

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

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. Pravastatin, simvastatin, rosuvastatin, and fluvastatin were evaluated in small studies of patients with HIV-associated dyslipidaemia; each drug showed modest improvement of dyslipidaemia, with most patients not reaching targets. Although statins might have effects beyond lipid-lowering, 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, 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.

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. 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 simvastatin and atorvastatin. Fluvastatin is metabolised by cytochrome P450 3A4 (CYP3A4), 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. 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. HIV patients taking indinavir and treated with fluvastatin or pravastatin had significantly
reduced plasma total and LDL cholesterol (p<0·05). Treatment with pravastatin 40 mg daily for 12 weeks was also associated with increased subcutaneous fat in 33 HIV-infected men. 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 PPARα, 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. In general, both fibrates and statins as monotherapy have moderate effects on plasma lipids, with good tolerability. Several fibrates, including gemfibrozil, fenofibrate, and bezafibrate, 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. 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. In this study, both statins and fibrates had similar efficacy and tolerability. 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. 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.

**Ezetimibe**

Ezetimibe inhibits intestinal cholesterol absorption, without metabolism through the CYP3A4 pathway. As monotherapy, ezetimibe can reduce LDL cholesterol by 20% or more; 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. 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. 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.

**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). Recombinant methionyl human leptin was associated with improved insulin sensitivity, fasting plasma insulin, HDL cholesterol, and truncal fat mass in seven patients. Omega-3 fatty acids—namely eicosapentaenoic acid and docosahexaenoic acid—lower plasma triglyceride in HIV-associated dyslipidaemia. 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. Other studies have similarly shown benefits of omega-3 fatty acids. Polyunsaturated ethyl esters of omega-3 fatty acids plus fibrates in HAART-treated HIV patients reduced plasma triglyceride esters of omega-3 fatty acids plus fibrates in this important complication of HIV treatment. Elucidating mechanisms and optimum treatments for evaluating and clarifying the role of various agents in pharmaceutical agents. Future studies should be aimed at antiretroviral treatments, and strategic use of a variety of options include diet and exercise, control of secondary cardiovascular disease risk. Dyslipidaemia, although 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.

Conflicts of interest
We declare that we have no conflicts of interest.

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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”, “hyperlipidaemia”, “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 “fibrac acid derivative”, and “cholesterol absorption inhibitor”. All relevant identified articles were English-language papers.

http://infection.thelancet.com Vol 7 December 2007 793


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http://infection.thelancet.com Vol 7 December 2007
796

http://infection.thelancet.com Vol 7 December 2007


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