

HIV and HAART-Associated Dyslipidemia

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Abstract: Effective highly active antiretroviral therapy (HAART) for human immunodeficiency virus-1 (HIV) infection has led to marked improvement in life-expectancy for those infected with HIV. Despite reductions in the incidence of AIDS with effective treatment, patients continue to experience considerable morbidity and mortality from non-AIDS illness such as premature cardiovascular disease, liver failure and renal failure. These morbidities, particularly premature cardiovascular disease, are thought to be related to a combination of the effects of an ageing HIV-infected population coupled with long-term effects of HIV infection and antiretroviral therapy (ART). One of the principle drivers behind the well documented increase in the risk of cardiovascular disease in HIV-infected patients is dyslipidemia.

This review will focus on the clinical presentation of HIV and ART-associated dyslipidemia, what is known of its pathophysiology, including associations with use of specific antiretroviral medications, and suggest screening and management strategies.

Keywords: HIV, HAART, dyslipidemia, cholesterol, triglycerides, lipids.

INTRODUCTION

The introduction of effective highly active antiretroviral therapy (HAART) in the mid-1990s led to a marked reduction in morbidity and mortality from human immunodeficiency virus (HIV) infection [1, 2]. Increasing life-expectancy [3], an aging population [4], and high rates of smoking [5] have led to concerns over the cardiovascular health of HIV-infected individuals in the long term. Metabolic effects of HIV infection such as hypertriglyceridemia are long recognised [6], and side effects of HAART such as dyslipidemia and insulin resistance were described very soon after its introduction [7]. Initial concerns of increased rates of myocardial infarction arising as a result of dyslipidaemia in HIV-infected patients on antiretrovirals (ARV) [8, 9, 10] have been confirmed by studies such as the D:A:D study, a large, prospective, multi-cohort study that showed associations between exposure to antiretroviral therapy and an increased risk of myocardial infarction [11]. In multivariate analyses, for every mmol/L increase in total cholesterol, the relative risk of myocardial infarction increased by a factor of 1.26 [12]. In another analysis from D:A:D which included stroke, acute myocardial infarction and invasive cardiovascular procedures there was a similar effect of hypercholesterolemia, with every mmol/L increase in total cholesterol associated with a relative risk of 1.11 of the combined endpoint [13]. There are little other data on associations between lipid profiles and other markers of vascular disease such as peripheral arterial disease.

Additional well-established cardiovascular risk factors are more commonly found in HIV-infected individuals such as high smoking rates [5], diabetes and insulin resistance [14] and hypertension [15]. Also, although dyslipidemia is a common problem encountered in delivering care to HIV-infected individuals, it is not the only described adverse effect of antiretroviral medications on the cardiovascular system. HIV-infected individuals have increased carotid artery intermediate thickness compared to HIV-negative controls, and those on HAART have further disturbances in vascular distensibility and compliance [16]. Endothelial function is also abnormal in HIV-infected individuals compared to negative controls, with higher serum levels of markers of endothelial dysfunction such as soluble P-selectin, von Willebrand factor and others [17]. Changes in platelet reactivity among HIV-infected individuals have been reported¹, and increased insulin resistance and higher prevalence of diabetes is a well described side effect of exposure to some ARV [7, 18]. All of these factors likely act in combination with dyslipidemia to increase overall cardiovascular risk for those infected with HIV.

THERAPY FOR HIV INFECTION

Conventional HAART consists of a combination of three medications drawn from three main drug classes; nucleoside reverse transcriptase inhibitors (NRTIs - nucleoside [or nucleotide] analogues which inhibit the viral reverse tran-

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¹Satchell C, Cotter A, O'Connor E, *et al.* A Case Control Assessment of Platelet Function in HIV-1+ and HIV-1- Individuals. Abstract 737, Sixteenth Conference on Retroviruses and Opportunistic Infections, Montreal, 2009.

scriptase (RT) enzyme) [19], non-nucleoside reverse transcriptase inhibitors (NNRTIs - which also inhibit the RT enzyme) and protease inhibitors (PIs - which act on the HIV protease) [20]. Traditionally HAART combines two NRTIs with either a NNRTI, or a PI [21]. The decision on which dual NRTI combination or 'backbone' to use, and which agent to combine it with, is dependent on numerous factors, including CD4+ T-cell count, HIV viral load, potential toxicities, drug interactions, pill burden and viral resistance.

PATTERNS OF DYSLIPIDEMIA IN HIV

HIV Infection

Prior to the introduction of HAART, it was recognised that HIV infection itself caused dyslipidemia [6]. Declines in total cholesterol, low density lipoprotein cholesterol (LDL-C) and high density lipoprotein cholesterol (HDL-C) have been shown in men who seroconverted from HIV-negative to HIV-positive [22]. HIV-infected, untreated patients (particularly those with more advanced disease) are more likely to have low total, LDL-C and HDL-C and elevated serum triglyceride (TGs) than HIV-negative controls [23, 24, 25], with lower HDL-C concentrations associated with higher circulating HIV RNA levels and longer duration of HIV infection [26, 27].

Antiretroviral Therapies

A summary of the overall effects of antiretrovirals on serum lipids are listed in Table 1. Effective HAART sup-

presses HIV RNA to undetectable levels, allowing immune recovery, measured by increases in CD4+ T-cell counts, in the majority of patients. This is usually accompanied by some increases in total cholesterol and LDL-C [22, 28] which some have suggested may be a return to norm. However, with some PI based therapies, HDL-C levels remain low [22, 29], and hypertriglyceridemia may in fact worsen [30], giving rise to a distinctly atherogenic lipid profile [31]. In contrast, initiation of NNRTI based HAART regimens has been shown to result in *increases* in HDL-C of approximately 40% depending on the agent used, with increases in total cholesterol, LDL-C and triglycerides also seen, although the triglyceride increases are usually not as severe as those seen with some PIs [32].

Many ARVs have dyslipidemic properties. Use of PIs has been associated with hypertriglyceridemia and hypercholesterolemia. Ritonavir, a PI, is a potent inhibitor of the hepatic cytochrome P4503A4 enzyme [33] used at a low dose with other PIs for its ability to 'boost' the drug concentrations of the PI, resulting in increased total drug exposure and half-life, allowing for improved dosing regimens and reduced pill burden [34]. In healthy volunteer studies, even when used at a boosting dose (100mg twice daily), exposure to ritonavir increased triglycerides by 26% and LDL-C by 16% after only 2 weeks of therapy [35]. When combined with other protease inhibitors such as lopinavir, serum triglycerides increased by 83%, free fatty acids by 30% and VLDL-C by 33% in HIV-negative subjects after 4 weeks exposure [36]. Similar effects have also been seen in cohorts of HIV-

Table 1. Overall Effects of Main Antiretrovirals on Lipid Profiles

Currently Recommended First-Line Agents are in Bold				
Antiretroviral	Total Cholesterol	LDL-C	HDL-C	Triglycerides
PIs (boosted)				
Lopinavir	↑↑	↑↑	↔/↓	↑↑↑
Atazanavir	↑	↔/↑	↔/↓	↔
Fosamprenavir	↑	↑	↔/↓	↑↑
Saquinavir	↑↑	↑↑	↔/↓	↑
Darunavir	↑	↑	↔/↓	↑
Tipranavir	↑↑	↑↑	↔/↓	↑↑↑
NNRTIs				
Efavirenz	↑	↑	↑	↑
Nevirapine	↑	↑	↑↑	↔/↑
NRTIs				
Tenofovir	↔/↑	↔/↑	↔/↑	↔/↑
Abacavir	↔/↑	↑	↑	↑
Lamivudine	↔	↔	↔	↔
Zidovudine	↑	↑	↑	↑↑
Stavudine	↑↑	↑↑	↑	↑↑
CCR5 Inhibitors				
Maraviroc	↔	↔	↔/↑	↔
Integrase Inhibitors				
Raltegravir	↔/↑	↔/↑	↔/↑	↔

infected patients treated with PIs, including newer drugs such as tipranavir [29, 37, 38]. Induction of dyslipidaemia does not occur with all PIs however. Atazanavir is an azapeptide PI with relatively few effects on serum lipids [39], while other newer PIs such as darunavir have also been shown to induce less dyslipidaemia [40].

Although NNRTIs induce less dyslipidemia than PIs it does appear that efavirenz, one of two commonly prescribed NNRTIs, has a deleterious effect on lipids when compared to the other commonly used NNRTI, nevirapine. The 2NN study compared HAART comprising efavirenz, nevirapine or both in combination with 2 NRTI (stavudine and lamivudine) and demonstrated greater increases in triglycerides in the efavirenz arm compared to the nevirapine arm (49% versus 20% at 48 weeks) [41]. In addition, the AIDS Clinical Trials Group (ACTG) 5142 trial, comparing therapy with lopinavir (PI) or efavirenz (NNRTI) or both with 2 NRTI, demonstrated significant increases in serum triglycerides and total cholesterol in both arms. The combination of lopinavir and efavirenz led to greater increases in serum triglycerides, non-HDL-C, and HDL-C than with either agent alone. Between lopinavir and efavirenz there was no significant difference in cholesterol levels, and only triglycerides were significantly higher in the lopinavir arm [32]. In the Swiss HIV Cohort, triglycerides tended to *decrease* in those treated with nevirapine but increase with efavirenz [42]. Overall, these data point to significant potential for efavirenz-induced dyslipidaemia, with increases in total cholesterol similar to some PI, but triglyceride increases that are less than observed with use of some PI.

Use of NRTI is not free of dyslipidaemia. Use of the NRTI stavudine has been associated with a worse lipid profile than the nucleotide reverse transcriptase inhibitor (NtRTI) tenofovir, with significantly larger increases in total cholesterol, LDL-C and triglycerides [43]. Similar effects were seen when tenofovir was compared to zidovudine, with significantly smaller increases in total cholesterol and LDL-C observed with tenofovir use [44]. It is for reasons of toxicities such as these that tenofovir and abacavir are now the preferred first line NRTIs compared to zidovudine or stavudine [21]. Recent data from the ACTG 5202 study in which abacavir-containing HAART was compared to tenofovir-containing HAART suggested that abacavir use was associated with significantly greater increases in median triglycerides (25mg/dl vs 3 mg/dl) and total cholesterol (34mg/dl vs 26mg/dl) than tenofovir at 48 weeks². Similar results were observed in the HEAT study, which also compared abacavir and tenofovir-containing HAART in treatment-naïve patients; those on abacavir had greater increases in serum triglycerides (64mg/dl vs 38 mg/dl) and total cholesterol (32 mg/dl vs 23mg/dl) at 48 weeks³, though the difference between arms was less at 96 weeks [45].

Although these data point to dyslipidaemia induced by ARV from all of the three commonly used drug classes, not all patients respond similarly to antiretroviral regimens (ARV). Cohorts of treatment experienced patients tend to have had more exposure to various classes of ARVs and have greater adverse effects compared to treatment naïve patients. For example, in the ARTEMIS trial, treatment naïve patients started on darunavir at 96 weeks had relatively small (12-15%) increases in total cholesterol, LDL-C and triglycerides [40]. Contrast this to the POWER studies, which used darunavir in heavily pretreated patients, where 15% of patients had TG levels of greater than 8.4mmol/L (744mg/dL) [46].

Metabolic Syndrome and HIV-Associated Lipodystrophy

A possible explanation for the differences in dyslipidaemia upon HAART initiation observed in antiretroviral naïve versus heavily pre-treated HIV-infected patients is the changes in lipid metabolism induced by medium to long term exposure to antiretroviral therapy. While direct dyslipidemia induced by protease inhibitors can develop rapidly, other more chronic metabolic changes affecting lipid metabolism can occur with HAART. Shortly after the introduction of combination antiretroviral therapy, a syndrome of subcutaneous lipoatrophy, central adiposity, dyslipidemia, and insulin resistance, termed HIV-associated lipodystrophy (HIVLD) was noted [7]. This was initially associated with PI exposure [7], but subsequently exposure to NRTIs [47], particularly thymidine analogue NRTIs (tNRTIs) such as stavudine [48] and zidovudine [49] were also recognised as being central to the development of this syndrome. Compared to HIV-infected controls without lipodystrophy, individuals with HIVLD tend to have higher total cholesterol, total cholesterol:HDL ratios, LDL-C and triglyceride levels [50, 51].

In addition to HIVLD, in the general population there is concern about the increasing prevalence of the metabolic syndrome among HIV infected individuals. The pattern of abdominal obesity, low HDL-C, high triglycerides, and insulin resistance, all seen in HIVLD, are also components of the metabolic syndrome [52]. The prevalence of the metabolic syndrome in HIV-infected populations has been reported at 4.4% at enrolment in the D:A:D cohort [53], 17-25% in other studies, and as with the general population, prevalence increases with age and BMI [54, 55, 56]. However, the most common features present in HIV-infected individuals are hypertriglyceridemia and low HDL-C [53, 54] and studies that have matched patients for age and BMI have estimated the prevalence of the metabolic syndrome to be similar among HIV-infected and HIV negative individuals [54, 55].

PATHOPHYSIOLOGY OF DYSLIPIDEMIA IN HIV HIV Infection

Hypertriglyceridemia in untreated HIV-infected patients may be a response to a systemic inflammatory response against persistent viral infection. TG concentrations, and TG clearance time in untreated HIV-infected patients have been shown to correlate with serum interferon-alpha (IFN- α) [23], which is overproduced in HIV infection [57]. In these untreated patients the activity of lipoprotein lipase (LPL) and hepatic lipase, which are both involved in TG clearance from

²Sax P, Tierney C, Collier AC, et al. ACTG 5202: shorter time to virologic failure (VF) with abacavir/lamivudine (ABC/3TC) than tenofovir/emtricitabine (TDF/FTC) as part of combination therapy in treatment-naïve subjects with screening HIV RNA >100,000 c/mL. Abstract THAB0303, XVII International AIDS Conference, Mexico City, 2008.

³Smith K, Fine D, Patel P, et al. Efficacy and Safety of Abacavir/Lamivudine Compared to Tenofovir/Emtricitabine in Combination with Once-daily Lopinavir/Ritonavir through 48 Weeks in the HEAT Study. Abstract 774, Fifteenth Conference on Retroviruses and Opportunistic Infections, Boston, 2008.

the circulation, are decreased compared to controls. Treatment of hepatocytes *in vitro* with IFN- α (and other cytokines such as IL-1) causes increases in lipogenesis [58], and hepatic lipogenesis *in vivo* is higher in HIV-infected individuals [59]. In hepatitis C virus (HCV) infected individuals receiving IFN- α therapy hypertriglyceridemia combined with low HDL-C levels have also been reported [60, 61], with levels returning to normal upon cessation of IFN- α therapy.

The activity of cholesterol ester transfer protein (CETP), which transfers cholesterol esters from HDL-C to apolipoprotein-B containing proteins [62], is elevated in HIV infection, and its activity correlates inversely with serum HDL concentrations [63]. This may help explain why HDL-C levels are lower in HIV infection. Although the reason for elevated CETP activity is still to be determined, CETP functions more efficiently in the setting of high TG levels [64], and this could help explain the increased activity in HIV-infected patients.

Antiretroviral Therapies

Direct Effect

PIs affect different tissues to cause dyslipidemia. In the liver of mice exposed to PI, excess fatty acid synthesis and hepatic steatosis occur after ritonavir exposure, which is associated with intra-nuclear accumulation of sterol response element binding proteins (SREBP), a nuclear transcription factor important for regulation of expression of many lipid metabolism genes [65, 66]. This effect has been replicated in hepatocytes *in vitro*, with an increase in SREBP-1 nuclear localisation [67]. Also in the liver, PIs appear to inhibit the proteasomal degradation of pre-secretory apolipoprotein B (the protein component of LDL particles) in cultured hepatocytes [68]. Inhibition of proteasomal degradation of SREBP could also explain its accumulation in hepatic nuclei.

An interesting finding which points towards a hepatic cause of dyslipidemia is the fact that hepatitis C virus (HCV) co-infection appears to protect against the development of HAART-associated dyslipidemia [69-71]. This may be due to alterations in hepatocyte lipid secretion – mono-infection with HCV genotype 3a is associated with a lower serum cholesterol but a marked increase in hepatic steatosis [72].

The effect of PIs in adipose tissue is different to their effect in liver. In adipocytes, PIs inhibit lipolysis by impairing LPL activity, which impairs TG uptake into adipocytes, which may contribute to elevated plasma TG levels [73]. PIs also *inhibit* SREBP-1 nuclear localisation in adipocytes [74], which leads to decreased adipocyte differentiation and which may also inhibit the ability of adipose tissue to store lipids removed from the circulation. In adipocytes PIs have also been shown to reduce expression of peroxisome proliferator-activated receptor gamma (PPAR γ) [75], an nuclear receptor important for adipocyte differentiation. As PPAR γ is a transcriptional target of SREBP-1, impaired nuclear localisation of SREBP-1 in adipose tissue may contribute to reduced PPAR γ activity.

Indirect Effect

At a cellular level, individuals with HIVLD have atrophic subcutaneous fat with smaller adipocytes, macrophage infiltration and evidence of adipocyte apoptosis [76]. It is known

that tNRTIs can accumulate within adipocytes [77]. Adipocytes from patients exposed to tNRTIs demonstrate mitochondrial dysfunction, manifested by depletion of mitochondrial DNA (mtDNA) [76, 78] and reduced mitochondrial RNA (mtRNA) expression [79]. This is felt to be due in part to the ability of tNRTIs to inhibit DNA polymerase- γ , the enzyme responsible for replication of mtDNA [80]. Compared to protease inhibitors, which induce dyslipidemia within a short period of time, the effect of NRTIs on serum lipids takes longer. 6 weeks exposure to tNRTIs did not significantly alter lipid parameters in healthy volunteers, though a reduction in mtRNA expression were seen as early as 2 weeks, without reductions in mtDNA [81]. As with PIs, a downregulation of PPAR γ expression in adipose tissue was also observed. The effect of this downregulation is potent as it cannot be overcome with the PPAR γ agonist rosiglitazone in the presence of ongoing tNRTI use [79]. These molecular effects may explain how NRTIs can inhibit preadipocyte differentiation [82], reduce triglyceride accumulation [83] and increase adipocyte apoptosis [84] *in vitro*.

As well as their effects on lipid metabolism outlined above, PIs also affect adipose tissue. PIs can accumulate in adipocytes [77], and ritonavir, lopinavir and saquinavir inhibit adipocyte differentiation [85], an effect not seen with atazanavir, a PI associated with less dyslipidaemia [86]. Nelfinavir has also been shown to induce adipocyte apoptosis [87].

The ultimate result of abnormally functioning subcutaneous adipose tissue is reduced storage capacity for circulating lipids resulting in increased circulating free fatty acids [88], reduced adiponectin secretion [89], and lipid accumulation in non-adipose tissues such as liver (hepatic steatosis [90] and hepatic triglyceride accumulation [91]). This, combined with the effects of PIs on lipid metabolism as mentioned in the previous section, likely underlie the hypertriglyceridemia and hypercholesterolemia observed in HIVLD. Clinical studies have shown that a combination of a PI with NRTIs are a greater risk than PIs alone for the development of lipodystrophy and dyslipidemia [92].

MANAGEMENT STRATEGIES

Although dyslipidaemia in HIV-infected patients is common, not all patients with dyslipidemia require lipid lowering therapy. The goal of therapy, as in the HIV negative population, is to reduce an individual's cardiovascular risk. Therefore treatment of HIV-associated dyslipidemia should be an integral part of a general attempt to improve cardiovascular health, with advice on diet and exercise, smoking cessation, management of hypertension and diabetes where present, and the use of anti-platelet agents where warranted.

Despite this, in a recent retrospective review, HIV-infected veterans in the USA who met NCEP/ATPIII guidelines for dyslipidemia were half as likely to be receiving lipid lowering therapies as HIV-negative controls [93]. HIV-infected patients should be screening for dyslipidemia at HIV diagnosis, annually, and upon starting HAART. An individual's cardiovascular risk should be assessed by standardised scoring systems such as the Framingham or Joint British Societies score, and treatment instituted for those

with previous cardiovascular disease or a high (>20% in 10 year) risk of cardiovascular disease (Fig. 1).

Current European Aids Clinical Society (EACS) guidelines recommend target LDL-C levels dependent on an estimated 10 year cardiovascular risk. The Infectious Diseases Society of America guidelines use a similar estimate of risk. These are summarised in Table 2.

EACS guidelines recommend only treating severe isolated hypertriglyceridemia (TGs >10mmol/L), or combined hyperlipidemia (LDL-C elevated and TG 2.3-10mmol/L) with lipid lowering therapy, while treating isolated hypertriglyceridemia with TG<10mmol/L with dietary and lifestyle advice. IDSA recommend treatment of isolated TGs>5.6mmol/L (500mg/dL) or elevated LDL-C and TGs of 2.2-5.6mmol/L (200-500mg/dL).

The treatment options available for the management of dyslipidemia in HIV-infection are similar to those in the general population; dietary and lifestyle modification and the use of lipid lowering medications. An additional option in

those on HAART is the ability to switch antiretrovirals away from those that may exacerbate the dyslipidemia. Although all these options have been studied in HIV-associated dyslipidemia, many studies are open-label, few are randomised and even fewer placebo-controlled. While many of these studies have shown beneficial effects of switching HAART components or lipid lowering therapy on dyslipidemia, there are no data available on the impact of these effects on cardiovascular disease endpoint and any perceived benefit is derived from corresponding beneficial effects on CVD of lipid lowering in the general population.

Dietary / Lifestyle Modification

As in the management of dyslipidemia in HIV-negative subjects, counselling on ‘therapeutic lifestyle changes’ such as reducing fat and cholesterol intake, increasing physical activity, weight reduction and adjusting diet to reduce LDL-C are also important components of managing HIV-associated dyslipidemia [94], although the data on a beneficial result are inconsistent. Despite similar caloric intake,

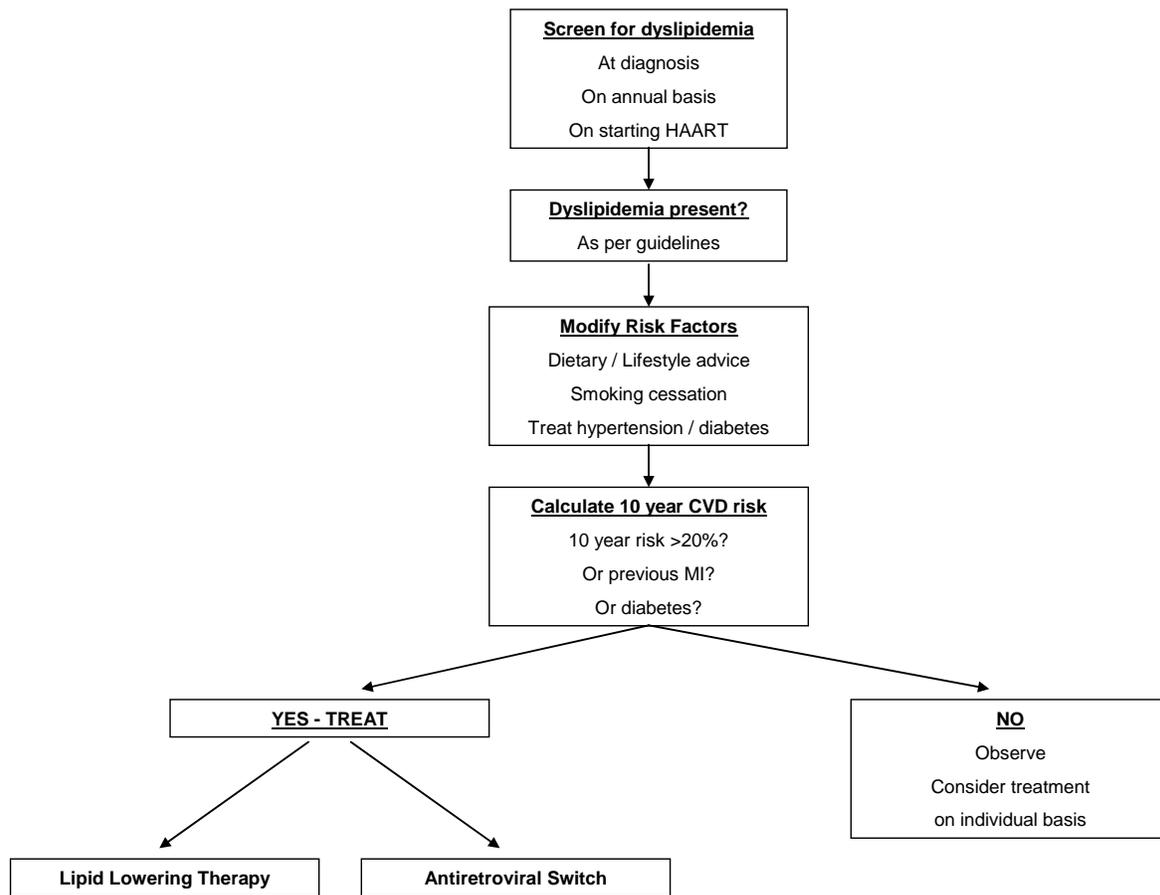


Fig. (1). Screening and treatment algorithm.

Table 2. LDL-C Treatment Goal Recommendations

Recommending Group	Risk <10%	Risk 10-20%	Risk >20% Previous CV Disease Diabetes
EACS	<5.0mmol/L (<190mg/dL)	<4.0mmol/L (<155mg/dL)	<3.0mmol/L (<115mg/dL)
IDSA/ACTG	<4.1mmol/L (<160mg/dL)	<3.3mmol/L (<130mg/dL)	<2.6mmol/L (<100mg/dL)

HIV-infected individuals have been shown to ingest more saturated fat than HIV-negative matched controls, and dietary saturated fat intake correlates with serum triglyceride concentrations [95]. In an early study in PI-treated patients with dyslipidemia, a diet and exercise program led to an 11% reduction in total-C, and a 21% reduction in TG [96]. However, in a study examining the effect of fish oil on serum lipids in HAART treated subjects with hypertriglyceridemia, those randomised to dietary and exercise counselling alone only reduced TG levels by 6%, with no change in LDL cholesterol at 16 weeks despite decreased caloric and total fat intake [97]. In another study of individuals with hypertriglyceridemia on HAART, only 4 of 49 individuals achieved normal TG levels at any stage within an 18 month period with diet and exercise alone [98]. It is therefore unlikely that lifestyle modifications alone will suffice in correcting HAART-induced dyslipidemia in the presence of ongoing exposure to the antiretrovirals precipitating the problem.

Switch Strategies

An approach available to some HAART-treated patients with dyslipidemia is to switch away from the presumed offending agent to another ARV with less propensity to induce dyslipidemia [99]. Studies examining this strategy are summarised in Table 3. These options should only be considered when there is a viable alternate antiretroviral agent or regimen, the new regimen is likely to induce less dyslipidemia than the original and is likely to possess similar or enhanced antiretroviral potency compared to the original regimen. At all times, maintenance of an effective ARV regimen capable of durable viral suppression is of paramount importance. Switching therapy needs careful discussion with patients about potential risks and benefits of changing what may be a virologically successful ARV regimen.

PI Switches

Within Class Switching

Switching from one PI to another has the advantage of maintaining the same class of drug whilst preserving future treatment options. Atazanavir is a potent PI with once-daily dosing and relatively favourable effects on serum lipids [39], making it an attractive option to switch to from other PIs. The need to “boost” atazanavir by using boosting doses of ritonavir [100], may reduce the beneficial effects on lipids. However, even when ritonavir-boosted, atazanavir induces less dyslipidemia than other boosted PIs [101], with the possible exception of the newer agent darunavir, which appears to have similar effects on lipid parameters to atazanavir in HIV-negative individuals [102].

Many studies examining switching to atazanavir did not actively recruit patients with dyslipidemia [103, 104, 105, 106]. However there appears to be a consistent reduction in triglycerides and cholesterol among those who switched compared to those who remained on other PIs (Table 3). This appears to hold true even for those who switch to boosted atazanavir, though the margin of reduction in lipids is smaller [104]. Atazanavir can also be used ‘un-boosted’. One study that examined the effect of switching to un-boosted atazanavir in patients with hypercholesterolemia

demonstrated reductions in triglycerides and total cholesterol without concomitant lipid-lowering therapy [107]. However only 37% of patients achieved LDL-C \leq 130mg/dL.

Switching to a Different ARV Class

Until recently, the options for switching away from protease inhibitors had been confined to NRTI or NNRTI switches. Switching a PI to a NNRTI such as efavirenz or nevirapine makes virological sense, as the combination of 2 NRTIs and one NNRTI is a well studied and effective antiviral combination [99]. However NNRTI have a low genetic barrier to resistance, with only one mutation required to induce high level resistance, raising concerns regarding the efficacy of this approach, particularly in patients who have been previously exposed to NNRTIs. It appears that switching to nevirapine compared to efavirenz has a better effect on lipids [108, 109]. Studies have shown that switching a PI to nevirapine has a minor effect on lipids and is virologically safe [109, 110, 111], though the magnitude of the lipid-lowering effect has been shown to be inferior to lipid lowering therapy alone [109].

Switching a PI to a NRTI such as abacavir, leaving patients on a triple combination of NRTIs, while well-tolerated and beneficial from a lipid perspective, has been shown to be virologically inferior to conventional HAART comprising drugs from more than one drug class [112, 113] and is now not generally recommended.

NRTI Switches

As previously discussed, thymidine analogue NRTIs (tNRTIs) are associated with subcutaneous fat loss, adipose tissue dysfunction, and increases in cholesterol and triglycerides (HIV-associated lipodystrophy). Switching away from tNRTIs to other NRTIs such as abacavir and tenofovir has been investigated as a therapeutic option for HIVLD and have resulted in both increases in subcutaneous fat [114] and improvements in dyslipidemia [115].

Switching from tNRTI to tenofovir appears to have more favourable effects on lipids than switching from tNRTI to abacavir, though the overall lipid improvements are often slight [115, 116, 117]. In one comparative randomised trial, switching from stavudine to tenofovir rather than abacavir resulted in significantly greater improvements in total cholesterol (median reduction of 0.45mmol/L) and LDL-C (median reduction of 0.25 mmol/L) [114]. Similarly in the BI-COMBO study, in which patients were randomised to switch from any NRTI to either tenofovir or abacavir, those switching to tenofovir had lower fasting total cholesterol, LDL-C, HDL-C and triglycerides at week 48 than those switching to abacavir [118]. However the between group differences were relatively small and there was no difference in the use of lipid lowering agents at the end of the study. One study has examined dose reduction of stavudine compared to switching to tenofovir. Despite most patients having normal lipids at baseline, switching to tenofovir resulted in greater lipid improvements than stavudine dose reduction [119]. The SWEET study examined the effect of switching from zidovudine to tenofovir. Although those switching to tenofovir

Table 3. Antiretroviral Switch Studies and Effect on Lipids

Study	Patient Group	N	Switch From	Switch to (N)	Weeks	LLT* in use	Outcome	Notes
PI Switch								
Sension <i>et al.</i> [107]	PI based HAART LDL- C \geq 130mg/dL	246	PI	ATV Immediate vs delayed	48	No	↓35% TG ↓18% LDL-C 37% achieved LDL-C \leq 130mg/dl	Tenofovir not used Unboosted atazanavir
Soriano <i>et al.</i> [104] (SLOAT)	LPV/r based HAART	189	LPV/r	ATV(49) or ATV/r (53) <i>vs no switch (87)</i>	48	Yes (More in LPV/r arm)	↓9.5% total-C (↓0.2% LPV/R) ↓43.7% TG (↓3.4% LPV/R) No significant change LDL-C 4% ATV LDL-C \geq 160mg/dL 16% LPV/r LDL-C \geq 160mg/dL	ATV/r if tenofovir in NRTI backbone Previous PI failure permitted 12 virologic failures on ATV – all had previously failed PI ↓21.9% TG , ↓6.2% total-C ATV/r (boosted) ↓48.7 TG, ↓12.9% ATV (unboosted)
Gatell <i>et al.</i> [103] (SWAN)	PI-based HAART	419	PI	ATV (252) or ATV/r (26) <i>or no switch (141)</i>	48	Yes	↓33% TG ↓18% total-C ↓12% LDL-C	Previous PI failure not permitted ATV/r if tenofovir in NRTI backbone
Nguyen <i>et al.</i> [105]	PI-based HAART	36	PI	ATV/r	24	Yes	↓23% TG ↓9% total-C ↓13% LDL-C	Retrospective review 47% patients met NCEP III guidelines at 6months
Wood <i>et al.</i> [106]	NFV / d4T / 3TC	63	NFV	ATV	24	Yes	↓25% TG ↓16% total-C ↓20% LDL-C	
NNRTI Switch								
Negredo <i>et al.</i> [110]	PI-based HAART	77	PI	NVP (26) EFV (25) <i>Vs no switch (26)</i>	52	Yes	↓21% TG, ↓10% total-C NVP group	No significant change EFV group or no switch group
Estrada <i>et al.</i> [108]	PI-based HAART Lipodystrophy	28	PI	EFV	48	Yes	No significant change	No improvement lipodystrophy
Calza <i>et al.</i> [109]	PI-based HAART TGs \geq 200mg/dL Total-C >250mg/dL	130	PI	NVP (29) EFV (34) <i>Vs lipid lowering (67)</i>	52	No (comparator)	↓25% TG, ↓27% total-C NVP group ↓9.4% TG, ↓24% total-C EFV group	Lipid lowering therapies (statin / fibrate) better than switch
Martinez <i>et al.</i> [112]	PI-based HAART	460	PI	NVP (155) EFV (156) ABC (162)	52	Yes	No difference in median TG levels Total-C lower in ABC group Fewer patients in ABC group: with TG \geq 400mg/dL with total-C \geq 240mg/dL	Higher virologic failure in abacavir group
Martinez <i>et al.</i> [150]	PI based HAART Lipodystrophy	20	PI	EFV	24	Yes	↓25% TG No change total-C	No improvement lipodystrophy
Carr <i>et al.</i> [151]	PI-based HAART Lipodystrophy	81	PI	NVP+ABC (49) +hydroxyurea +adefovir <i>vs no switch (32)</i>	24	Yes	Switch group: ↓34.6% TG ↓25% total-C	Significant between group difference in total-C and TG 37% discontinuation rate in switch group at 24 weeks
Petit <i>et al.</i> [111]	PI-based HAART	55	PI	NVP	24	Yes	↓17.8% TG No change in total cholesterol ↑16.8% HDL-C	Significant change in TG only seen in men Men had higher TG at baseline

Table 3. contd....

Study	Patient Group	N	Switch From	Switch to (N)	Weeks	LLT* in use	Outcome	Notes
NRTI Switch								
Llibre <i>et al.</i> [116]	On d4T with toxicity (172 with dyslipidemia)	352	d4T	Tenofovir	48	Yes	In patients with baseline dyslipidemia: ↓26.9% TG ↓14.1% total-C ↓17.8% LDL-C	77% of patients had lipodystrophy
Madruca <i>et al.</i> [115]	d4T+3TC+EFV	85	d4T	Tenofovir	144	Yes	↓78mg/dL TG ↓22mg/dL total-C	
Ananworanich <i>et al.</i> [117]	d4T+ddI+SQV/r	35	d4T ddI	Tenofovir + Lamivudine	48	Yes	↓17% TG ↓4.5% total-C ↓6.7% LDL-C	Some improvement in lipoatrophy
Martin <i>et al.</i> [152]	tNRTI-containing HAART Lipoatrophy	85	d4T/ AZT	Abacavir (42) <i>vs no switch</i>	104	Yes	No improvement in lipid parameters	Some improvement in lipoatrophy
Moyle <i>et al.</i> [114]	tNRTI-containing HAART Lipoatrophy	105	d4T/ AZT	Tenofovir (52) Abacavir (53)	48	Yes	Tenofovir: ↓8% total-C, ↓16.5% TG, ↓7.5% LDL-C Abacavir ↑3.9% total-C, ↑4.1% TG, ↑3% LDL-C	Significant differences in total-C and LDL-C between arms Both arms had increase in limb fat Small rises in cholesterol in both arms when switching from AZT
Schwede <i>et al.</i> [153]	d4T containing HAART	66	d4T	Tenofovir	72 (mean)	Yes	↓36mg/dL total-C No significant ↓TG at 72 weeks	Retrospective analysis Initial 84mg/dL decrease in TGs at 12 weeks
Milinkovic <i>et al.</i> [119]	d4T containing HAART Lipoatrophy	58	d4T	Tenofovir (17) Low dose d4T (19) <i>vs continue d4T</i> (22)	24	None used	Low dose d4T ↓8% TG ↑0.6% total-C Tenofovir ↓28.7% TG ↓15.6% total-C	Most patients had normal lipids at baseline
Martinez <i>et al.</i> [118] (BICOMBO)	HAART with 2 NRTIs	333	NRTI	Tenofovir / FTC (166) Abacavir / 3TC (167)	48	Yes	Total-C, LDL-C, HDL-C, TGs lower in tenofovir arm	Lipid lowering agent use similar in both arms
Fisher <i>et al.</i> [120] (SWEET)	AZT with 3TC+EFV	234	AZT	Tenofovir (117) <i>vs no switch</i> (117)	48	Yes	Greater decrease in total-C, TGs in tenofovir arm at week 24	No significant difference at week 48 Reduction greatest in those with higher levels at baseline

*LLT = lipid lowering therapy.

had lower total cholesterol and triglycerides at 24 weeks (with the greatest reductions occurring in those with the highest baseline values), there were no statistically significant between group differences at 48 weeks between each arm [120].

Treatment Interruption

Cessation of HAART has been proposed as a therapeutic option in dyslipidemia, and does result in improvements in TG, total-C and LDL-C even after a short period of time [121]. However, clinical studies have shown excess morbidity and mortality, including increased major cardiovascular, renal and hepatic events in those undergoing treatment interruption [122]. As a result this strategy should not be considered as therapy for dyslipidemia.

Lipid Lowering Therapies

Many lipid lowering therapies have been investigated in HIV infection (summarised in Table 4). The treatment of dyslipidemia in HIV infection is often complicated by potential drug interactions between ARV and lipid-lowering medications. In addition, other medications used in the treatment of HIV-infection such as macrolide antibiotics [123], azole antifungals [124] or the rifamycin antimycobacterials [125] may also have significant interactions with lipid-lowering agents.

Fish Oils

Fish oils, rich in omega-3 fatty acids, can help lower triglycerides and have been studied in HIV-infected patients.

Table 4. Trials of Lipid Lowering Agents in HIV Infection

Study	Patient Group	N	Intervention (N)	Followup	Outcome	Notes
Fish Oils						
Wohl <i>et al.</i> [97]	On HAART TG \geq 200mg/dl	52	3g fish oil / day (26) <i>vs diet and exercise alone</i>	16	↓19.5% TG (↓5.7% TG in diet/ exercise)	No significant difference at week 16 Approximately 20% increase LDL cholesterol both arms
Gerber <i>et al.</i> [126]	On HAART TG \geq 400mg/dl, LDL- C \leq 160mg/dL	100	6g fish oil / day (50) <i>vs fenofibrate</i>	8	↓46% TG ↑37% LDL-C	8.5% achieved TG \leq 200mg/dL Addition of fenofibrate allowed 22.1% to achieve TG \leq 200mg/dL at 18 weeks
Manfredi <i>et al.</i> [98]	On HAART TG 200-500mg/dl on 2 occasions	156	2g polyunsaturated ethyl esters of n-3 fatty acids / day (54) <i>vs fibrates vs diet and exercise</i>	72	↓11.6% TG	25.9% achieved target TG \leq 172mg/dL at any stage Superior to diet and exercise alone
Fibrates						
Palacios <i>et al.</i> [129]	On HAART TG \geq 400mg/dl	20	Fenofibrate 200mg/day	24	↓53.6% TG ↓14.1% total-C	70% achieved TG \leq 400mg/dl
Badiou <i>et al.</i> [127]	On HAART TG \geq 175mg/dL	36	Fenofibrate 200mg/day (18) <i>vs Vitamin E</i>	12	↓40% TG ↓14% total-C ↑15% HDL-C	
Aberg <i>et al.</i> [131]	On HAART Combined dyslipidemia	88	Fenofibrate 200mg/day	12		1% achieved NCEP guidelines on fenofibrate alone
Gerber <i>et al.</i> [126]	On HAART TG \geq 400mg/dl, LDL- C \leq 160mg/dL	100	Fenofibrate 160mg/day (50) <i>vs fish oil</i>	8	↓58% TG ↓46% LDL-C ↓10% total-C	16.7% achieved TG \leq 200mg/dL Addition of fish oil allowed 22.1% to achieve TG \leq 200mg/dL at 18 weeks
Manfredi <i>et al.</i> [98]	On HAART TG 200-500mg/dl on 2 occasions	156	Bezafibrate / Gemfibrozil / Fenofibrate (53)	72	34% achieved target TG \leq 172mg/dL at any stage	Superior to fish oil & diet and exercise
Miller <i>et al.</i> [154]	On PI-containing HAART TG \geq 263mg/dL	37	Gemfibrozil 600mg/day (17) <i>Vs placebo</i>	12	↓100mg/dL TG	Did not achieve significance
Calza <i>et al.</i> [128]	On PI-containing HAART TG \geq 300mg/dl +/- total-C \geq 290mg/dl	106	Bezafibrate 400mg / day (25) Gemfibrozil 600mg / day (22) Fenofibrate 200mg / day (22) <i>vs pravastatin / fluvastatin</i>	52	↓40.7% TG ↓21.9% total-C	Statins / fibrates achieved similar reductions
Calza <i>et al.</i> [109]	On PI-containing HAART TG \geq 200mg/dl Total-C \geq 250mg/dl	130	Bezafibrate 400mg/day (31) <i>Vs NNRTI switch</i> <i>Vs pravastatin</i>	52	↓46.6% TG ↓37.6% total-C	Statins / fibrates similar efficacy Statin / fibrates superior to NNRTI switch
Statins						
Calza <i>et al.</i> [132]	On PI-containing HAART Total-C \geq 240mg/dL (TG \geq 500mg/dl excluded)	16	Rosuvastatin 10mg/day	24	↓30.1% TG ↓21% total-C ↓22.4% LDL-C ↑28.5% HDL-C	
Bonnet <i>et al.</i> [136]	On PI-containing HAART Total-C \geq 210mg/dL LDL-C \geq 130mg/dL	21	Pravastatin 40mg/day (12) <i>Vs placebo</i>	12	No change in TG ↓23% total-C ↓24% LDL-C	
Mallon <i>et al.</i> [134]	On PI-containing HAART Total-C \geq 253mg/dL		Pravastatin 40mg/day (16) <i>Vs placebo</i>	12	Greater TWAUC change in cholesterol in pravastatin arm	No difference in time weighted-change in cholesterol between arms Increased limb fat in pravastatin arm

Table 4. contd....

Study	Patient Group	N	Intervention (N)	Followup	Outcome	Notes
Statins						
Calza <i>et al.</i> [128]	On PI-containing HAART TG \geq 300mg/dl +/- total-C \geq 290mg/dl	106	Pravastatin 20mg/day (19) Fluvastatin 20mg/day (18) <i>Vs fibrates</i>	52	↓36.1% TG ↓26.9% total-C	Statins / fibrates achieved similar reductions
Calza <i>et al.</i> [109]	On PI-containing HAART TG \geq 200mg/dl Total-c \geq 250mg/dl	130	Pravastatin 20mg/day (36) <i>Vs NNRTI switch</i> <i>Vs bezafibrate</i>	52	↓41.2% TG ↓45.8% total-C	Statins / fibrates similar efficacy Statin / fibrates superior to NNRTI switch
Palacios <i>et al.</i> [130]	On HAART Total-C \geq 240mg/dl	20	Atorvastatin 10mg/day	24	↓40% TG ↓27% total-C ↓37% LDL-C	
Baldini <i>et al.</i> [133]	On HAART Hyperlipidemia	19	Pravastatin 20mg/day	8	↓37% TG ↓19% total-C	
Niacin						
Gerber <i>et al.</i> [143]	On HAART TG \geq 200mg/dL +/- LDL \geq 130mg/dL	14	ER-Niacin up to 2000mg/day	14	↓34% TG ↓14% total-C	Concern over glucose intolerance
Dube <i>et al.</i> [144]	On HAART TG \geq 200mg/dL non-HDL-C \geq 180mg/dl	33	ER-Niacin up to 2000mg/day	48	↓32% TG ↓3% total-C	Transient increases in insulin resistance
Ezetimibe						
Wohl <i>et al.</i> [141]	On HAART LDL-C \geq 75mg/dL, TG \leq 800mg/dL	48	Ezetimibe 10mg/day	6	↓5.3% total-C TG unchanged	
Negredo <i>et al.</i> [142]	On / off HAART LDL-C \geq 130mg/dL despite pravastatin 20mg/day	19	Ezetimibe 10mg/day + Pravastatin 20mg/day	24	Significant ↓ in LDL-C, total-C Significant ↑HDL-C No change TG	61.5% achieved LDL-C \leq 130mg/dl

They are generally well tolerated and have few side-effects. Although a randomised study of 3g of fish oil daily together with diet and exercise resulted in a 19.5% mean decrease in TGs at 16 weeks (though this was not statistically significant compared to diet and exercise alone), LDL-C concentrations actually increased by 22% [97]. In a further study (ACTG 5186), comparing 6g of fish oil per day to fenofibrate in HIV-infected patients on HAART with isolated severe hypertriglyceridemia, those on fish oil experienced a 46% reduction in median TG at 8 weeks, but only 8.5% achieved TG levels \leq 200mg/dL and LDL-C concentrations increased. Combining fish oil with fenofibrate achieved normal TG levels in 22% of patients [126]. Treatment of HIV-infected patients with moderate HAART-related hypertriglyceridemia with polyunsaturated ethyl esters of n-3 fatty acids resulted in a 11.6% reduction in TG levels at 18 months, with 25.9% of patients achieving normal TG levels at some stage over the 18 months follow-up [98]. Given the rises in LDL-C observed in these studies, it is unclear if use of fish oils in this clinical setting will have an overall clinical benefit in terms of cardiovascular risk reduction.

Fibrates

Fibrates are an attractive therapeutic option in HIV-infected patients, as hypertriglyceridemia is common and

fibrates lack significant pharmacologic interactions with ARV. Fibrates reduce triglycerides by approximately 40-50% in HIV-infected patients with hypertriglyceridemia [109, 127, 128, 129], with larger reductions in those with higher baseline TG levels [126, 130]. These effects appear to be similar to the effect of statins [128] (see below) and in one study were superior to switching PI to NNRTI [109]. In studies fibrates appear to be well tolerated, with gastrointestinal upset being the most frequently reported side effect. Proportions of patients achieving target goals vary, with one study reporting 70% achieving a target TG \leq 200mg/dL, but most others report much lower proportions ranging from 1-40% [98, 126, 131]. Despite these benefits, it is still unclear if reductions in triglyceride concentrations alone will be sufficient to significantly alter overall cardiovascular risk in HIV-infected patients.

Statins

HMG CoA reductase inhibitors, or "statins" have been shown to be an effective method of treating hypercholesterolemia in HIV-negative individuals and are also effective in HIV-infected individuals, reducing total cholesterol by approximately 30% and triglycerides by similar amounts [128, 130, 132, 133]. As with use of fibrates for hypertriglyceridaemia, the percentage of patients achieving LDL-

C targets with statin use vary, with some studies reporting 50-60% patients reaching NCEP targets [128, 130, 132], while others report far lower percentages [131, 134]. Interactions between statins and antiretrovirals (ARVs) are very common. PIs inhibit the CYP3A4 metabolism of statins, and increase overall exposure to statins, in the case of simvastatin by over 3000% [135]. This has led to concerns regarding the potential for statin toxicity with PI use and for this reason simvastatin is contraindicated with concurrent PI use. However atorvastatin (at 10-80mg qd) and pravastatin (at 20-80mg qd) are less affected by this interaction and have been extensively studied with PIs [109, 128, 130, 136]. Conversely, the NNRTI efavirenz induces hepatic metabolism of statins, leading to a marked reduction in the AUC for simvastatin, pravastatin and atorvastatin [137]. The newer statin rosuvastatin is only marginally metabolised by the CYP3A4 system, with most of the drug being excreted unchanged, and has been used to treat dyslipidaemia in HIV-infected patients [132]. Despite this, both lopinavir/ritonavir [138, 139] and atazanavir/ritonavir [140] increase both the C_{max} and AUC of rosuvastatin. This may be due to blockage of the OATP-1B1 membrane transporter for rosuvastatin, of which ritonavir is a known inhibitor [138]. This transporter is involved in the hepatic uptake of rosuvastatin, therefore ritonavir inhibition may reduce the effect of rosuvastatin on lowering cholesterol despite inducing higher circulating concentrations of the drug [124].

Ezetimibe

Ezetimibe, which blocks cholesterol absorption in the intestine and is metabolised independent of the CYP3A4 pathway, appears to have minor effects in HAART-induced dyslipidemia as monotherapy [141]. However when added to pravastatin it allowed 62% of patients with hyperlipidemia to achieve a target LDL-C concentration of ≤ 130 mg/dl [142]. Its effects seem confined to LDL-C reduction as effects on triglycerides in HAART-induced dyslipidemia appear minor [141, 142].

Niacin

Niacin has been investigated in two small studies, and appears to be well-tolerated, reducing TG levels by approximately 30% with a smaller effect on total cholesterol [143, 144]. A concern is the increase in insulin resistance seen in both studies. Given the concern over insulin resistance and diabetes in HIVLD the role for routine use of niacin in this setting is unclear.

Combination Therapies

There are few data reporting the efficacy or safety of combination therapies in HIV-infected individuals. One open label study allowed the addition of pravastatin or fenofibrate to those who had failed to reach NCEP guidelines on either agent as monotherapy for 12 weeks [131]. Combination therapy was well tolerated and led to reductions in TG levels particularly, but only allowed 4% of patients to achieve combined NCEP guidelines. The increased risk of rhabdomyolysis in HIV-negative individuals from the combination of statins and fibrates [124] would advise their concurrent use in HIV positive patients only be undertaken with strict caution.

CONCLUSION / FUTURE DIRECTIONS

As the ongoing roll-out of antiretroviral treatment programs in resource poor settings is continuing, use of older medications such as tNRTIs is common [145]. As a result dyslipidemia and lipodystrophy will continue to be major issues for many HAART treated patients for years to come [146]. The recent introduction of new medications with more lipid friendly profiles within existing classes such as darunavir (PI) [46], and etravirine (NNRTI) [147] will broaden the options available to clinicians. In addition, entirely new classes of drugs, such as integrase inhibitors (raltegravir) [148] and CCR5 inhibitors (maraviroc) [149] should allow more options both for antiretroviral-naïve patients starting therapy and those needing to switch therapies to avoid dyslipidaemia. Furthermore, the development of newer, selective boosting agents to replace ritonavir that lack dyslipidaemia is continuing⁴. Such advances could reduce the requirement for ritonavir as a boosting agent, further reducing the potential for ARV to induce dyslipidemia. Despite early data showing much less effects on lipids with these new agents, long term safety data is required and clinicians will need to remain vigilant for treatment-related toxicities as HIV-infected individuals continue to live longer and healthier lives.

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REFERENCES

- [1] Bhaskaran K, Hamouda O, Sannes M, *et al.* Changes in the risk of death after HIV seroconversion compared with mortality in the general population. *JAMA* 2008; 300: 51-9.
- [2] Palella FJ, Jr., Delaney KM, Moorman AC, *et al.* Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators. *N Engl J Med* 1998; 338: 853-60.
- [3] Lohse N, Hansen AB, Pedersen G, *et al.* Survival of persons with and without HIV infection in Denmark, 1995-2005. *Ann Intern Med* 2007; 146: 87-95.
- [4] Mack KA, Ory MG. AIDS and older Americans at the end of the Twentieth Century. *Journal of acquired immune deficiency syndromes (1999)*. 2003; 33 Suppl 2: S68-75.
- [5] Mamary EM, Bahrs D, Martinez S. Cigarette smoking and the desire to quit among individuals living with HIV. *AIDS Patient Care STDS* 2002; 16: 39-42.
- [6] Grunfeld C, Kotler DP, Hamadeh R, *et al.* Hypertriglyceridemia in the acquired immunodeficiency syndrome. *Am J Med* 1989; 86: 27-31.
- [7] 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: F51-8.
- [8] Passalaris JD, Sepkowitz KA, Glesby MJ. Coronary artery disease and human immunodeficiency virus infection. *Clin Infect Dis* 2000; 31: 787-97.
- [9] Holmberg SD, Moorman AC, Williamson JM, *et al.* Protease inhibitors and cardiovascular outcomes in patients with HIV-1. *Lancet* 2002; 360: 1747-8.

⁴Mathias A, Lee M, Callebaut C, *et al.* GS-9350 : A Pharmacoenhancer without Anti-HIV activity. Abstract 40, Sixteenth Conference on Retroviruses and Opportunistic Infections, Montreal, 2009.

- [10] Currier JS, Taylor A, Boyd F, *et al.* Coronary heart disease in HIV-infected individuals. *J Acquir Immune Defic Syndr* 2003; 33: 506-12.
- [11] 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.
- [12] Friis-Moller N, Reiss P, Sabin CA, *et al.* Class of antiretroviral drugs and the risk of myocardial infarction. *N Engl J Med* 2007; 356: 1723-35.
- [13] d'Arminio A, Sabin CA, Phillips AN, *et al.* Cardio- and cerebrovascular events in HIV-infected persons. *AIDS* 2004; 18: 1811-7.
- [14] Brown TT, Cole SR, Li X, *et al.* Antiretroviral therapy and the prevalence and incidence of diabetes mellitus in the multicenter AIDS cohort study. *Arch Intern Med* 2005; 165: 1179-84.
- [15] Hadigan C, Meigs JB, Corcoran C, *et al.* Metabolic abnormalities and cardiovascular disease risk factors in adults with human immunodeficiency virus infection and lipodystrophy. *Clin Infect Dis* 2001; 32: 130-9.
- [16] van Vonderen MG, van Agtmael MA, Hassink EA, *et al.* Zidovudine/lamivudine for HIV-1 infection contributes to limb fat loss. *PLoS One*. 2009; 4: e5647.
- [17] Francisci D, Giannini S, Baldelli F, *et al.* HIV type 1 infection, and not short-term HAART, induces endothelial dysfunction. *AIDS* 2009; 23: 589-96.
- [18] Walli R, Herfort O, Michl GM, *et al.* Treatment with protease inhibitors associated with peripheral insulin resistance and impaired oral glucose tolerance in HIV-1-infected patients. *AIDS* 1998; 12: F167-73.
- [19] Sarafianos SG, Marchand B, Das K, *et al.* Structure and function of HIV-1 reverse transcriptase: molecular mechanisms of polymerization and inhibition. *J Mol Biol* 2009; 385: 693-713.
- [20] Danner SA, Carr A, Leonard JM, *et al.* A short-term study of the safety, pharmacokinetics, and efficacy of ritonavir, an inhibitor of HIV-1 protease. European-Australian Collaborative Ritonavir Study Group. *N Engl J Med* 1995; 333: 1528-33.
- [21] Hammer SM, Eron JJ, Jr., Reiss P, *et al.* Antiretroviral treatment of adult HIV infection: 2008 recommendations of the International AIDS Society-USA panel. *JAMA* 2008; 300: 555-70.
- [22] Riddler SA, Smit E, Cole SR, *et al.* Impact of HIV infection and HAART on serum lipids in men. *JAMA* 2003; 289: 2978-82.
- [23] Grunfeld C, Pang M, Doerrler W, *et al.* Lipids, lipoproteins, triglyceride clearance, and cytokines in human immunodeficiency virus infection and the acquired immunodeficiency syndrome. *J Clin Endocrinol Metab* 1992; 74: 1045-52.
- [24] Shor-Posner G, Basit A, Lu Y, *et al.* Hypocholesterolemia is associated with immune dysfunction in early human immunodeficiency virus-1 infection. *Am J Med* 1993; 94: 515-9.
- [25] Anastos K, Lu D, Shi Q, *et al.* Association of serum lipid levels with HIV serostatus, specific antiretroviral agents, and treatment regimens. *J Acquir Immune Defic Syndr* 2007; 45: 34-42.
- [26] El-Sadr WM, Mullin CM, Carr A, *et al.* Effects of HIV disease on lipid, glucose and insulin levels: results from a large antiretroviral-naive cohort. *HIV Med* 2005; 6: 114-21.
- [27] 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: 90-5.
- [28] Berthold HK, Parhofer KG, Ritter MM, *et al.* Influence of protease inhibitor therapy on lipoprotein metabolism. *J Intern Med* 1999; 246: 567-75.
- [29] 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: 700-5.
- [30] Mulligan K, Grunfeld C, Tai VW, *et al.* Hyperlipidemia and insulin resistance are induced by protease inhibitors independent of changes in body composition in patients with HIV infection. *J Acquir Immune Defic Syndr* 2000; 23: 35-43.
- [31] Mercie P, Tchamgoue S, Thiebaut R, *et al.* Atherogen lipid profile in HIV-1-infected patients with lipodystrophy syndrome. *Eur J Intern Med* 2000; 11: 257-63.
- [32] Haubrich RH, Riddler SA, DiRienzo AG, *et al.* Metabolic outcomes in a randomized trial of nucleoside, nonnucleoside and protease inhibitor-sparing regimens for initial HIV treatment. *AIDS* 2009; 23: 1109-18.
- [33] Acosta EP. Pharmacokinetic enhancement of protease inhibitors. *J Acquir Immune Defic Syndr* 2002; 29 Suppl 1: S11-8.
- [34] Zeldin RK, Petruschke RA. Pharmacological and therapeutic properties of ritonavir-boosted protease inhibitor therapy in HIV-infected patients. *J Antimicrob Chemother* 2004; 53: 4-9.
- [35] Shafran SD, Mashinter LD, Roberts SE. The effect of low-dose ritonavir monotherapy on fasting serum lipid concentrations. *HIV Med* 2005; 6: 421-5.
- [36] Lee GA, Seneviratne T, Noor MA, *et al.* The metabolic effects of lopinavir/ritonavir in HIV-negative men. *AIDS* 2004; 18: 641-9.
- [37] Walmsley S, Bernstein B, King M, *et al.* Lopinavir-ritonavir versus nelfinavir for the initial treatment of HIV infection. *N Engl J Med* 2002; 346: 2039-46.
- [38] 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.
- [39] Murphy RL, Sanne I, Cahn P, *et al.* Dose-ranging, randomized, clinical trial of atazanavir with lamivudine and stavudine in antiretroviral-naive subjects: 48-week results. *AIDS* 2003; 17: 2603-14.
- [40] Mills AM, Nelson M, Jayaweera D, *et al.* Once-daily darunavir/ritonavir vs. lopinavir/ritonavir in treatment-naive, HIV-1-infected patients: 96-week analysis. *AIDS* 2009; 23(13): 1679-88.
- [41] van Leth F, Phanuphak P, Stroes E, *et al.* Nevirapine and efavirenz elicit different changes in lipid profiles in antiretroviral-therapy-naive patients infected with HIV-1. *PLoS Med* 2004; 1: e19.
- [42] Young J, Weber R, Rickenbach M, *et al.* Lipid profiles for antiretroviral-naive patients starting PI- and NNRTI-based therapy in the Swiss HIV cohort study. *Antivir Ther* 2005; 10: 585-91.
- [43] Gallant JE, Staszewski S, Pozniak AL, *et al.* Efficacy and safety of tenofovir DF vs stavudine in combination therapy in antiretroviral-naive patients: a 3-year randomized trial. *JAMA* 2004; 292: 191-201.
- [44] Gallant JE, DeJesus E, Arribas JR, *et al.* Tenofovir DF, emtricitabine, and efavirenz vs. zidovudine, lamivudine, and efavirenz for HIV. *N Engl J Med* 2006; 354: 251-60.
- [45] Smith KY, Patel P, Fine D, *et al.* Randomized, double-blind, placebo-matched, multicenter trial of abacavir/lamivudine or tenofovir/emtricitabine with lopinavir/ritonavir for initial HIV treatment. *AIDS* 2009; 23: 1547-56.
- [46] Clotet B, Bellos N, Molina JM, *et al.* Efficacy and safety of darunavir-ritonavir at week 48 in treatment-experienced patients with HIV-1 infection in POWER 1 and 2: a pooled subgroup analysis of data from two randomised trials. *Lancet* 2007; 369: 1169-78.
- [47] Madge S, Kinloch-de-Loes S, Mercey D, Johnson MA, Weller IV. Lipodystrophy in patients naive to HIV protease inhibitors. *AIDS* 1999; 13: 735-7.
- [48] Mallal SA, John M, Moore CB, James IR, McKinnon EJ. Contribution of nucleoside analogue reverse transcriptase inhibitors to subcutaneous fat wasting in patients with HIV infection. *AIDS* 2000; 14: 1309-16.
- [49] Bogner JR, Vielhauer V, Beckmann RA, *et al.* Stavudine versus zidovudine and the development of lipodystrophy. *J Acquir Immune Defic Syndr* 2001; 27: 237-44.
- [50] Carr A, Samaras K, Thorisdottir A, *et al.* Diagnosis, prediction, and natural course of HIV-1 protease-inhibitor-associated lipodystrophy, hyperlipidaemia, and diabetes mellitus: a cohort study. *Lancet* 1999; 353: 2093-9.
- [51] Carr A, Emery S, Law M, *et al.* An objective case definition of lipodystrophy in HIV-infected adults: a case-control study. *Lancet* 2003; 361: 726-35.
- [52] Grundy SM, Brewer HB, Jr., Cleeman JI, Smith SC, Jr., Lenfant C. Definition of metabolic syndrome: Report of the National Heart, Lung, and Blood Institute/American Heart Association conference on scientific issues related to definition. *Circulation* 2004; 109: 433-8.
- [53] Worm SW, Sabin CA, Reiss P, *et al.* Presence of the metabolic syndrome is not a better predictor of cardiovascular disease than the sum of its components in HIV-infected individuals: data collection on adverse events of anti-HIV drugs (D: A: D) study. *Diabetes Care* 2009; 32: 474-80.

- [54] Jerico C, Knobel H, Montero M, *et al.* Metabolic syndrome among HIV-infected patients: prevalence, characteristics, and related factors. *Diabetes Care* 2005; 28: 132-7.
- [55] Mondy K, Overton ET, Grubb J, *et al.* Metabolic syndrome in HIV-infected patients from an urban, midwestern US outpatient population. *Clin Infect Dis* 2007; 44: 726-34.
- [56] Jacobson DL, Tang AM, Spiegelman D, *et al.* Incidence of metabolic syndrome in a cohort of HIV-infected adults and prevalence relative to the US population (National Health and Nutrition Examination Survey). *J Acquir Immune Defic Syndr* 2006; 43: 458-66.
- [57] 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.
- [58] Grunfeld C, Dinarello CA, Feingold KR. Tumor necrosis factor-alpha, interleukin-1, and interferon alpha stimulate triglyceride synthesis in HepG2 cells. *Metabolism* 1991; 40: 894-8.
- [59] 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.
- [60] Fernandez-Miranda C, Castellano G, Guijarro C, *et al.* Lipoprotein changes in patients with chronic hepatitis C treated with interferon-alpha. *Am J Gastroenterol* 1998; 93: 1901-4.
- [61] Hamamoto S, Uchida Y, Wada T, *et al.* Changes in serum lipid concentrations in patients with chronic hepatitis C virus positive hepatitis responsive or non-responsive to interferon therapy. *J Gastroenterol Hepatol* 2005; 20: 204-8.
- [62] Lewis GF, Rader DJ. New insights into the regulation of HDL metabolism and reverse cholesterol transport. *Circ Res* 2005; 96: 1221-32.
- [63] Rose H, Hoy J, Woolley I, *et al.* HIV infection and high density lipoprotein metabolism. *Atherosclerosis* 2008; 199: 79-86.
- [64] Guerin M, Le Goff W, Lassel TS, *et al.* Atherogenic role of elevated CE transfer from HDL to VLDL(1) and dense LDL in type 2 diabetes : impact of the degree of triglyceridemia. *Arterioscler Thromb Vasc Biol* 2001; 21: 282-8.
- [65] Bengoechea-Alonso MT, Ericsson J. SREBP in signal transduction: cholesterol metabolism and beyond. *Curr Opin Cell Biol* 2007; 19: 215-22.
- [66] Riddle TM, Kuhel DG, Woollett LA, Fichtenbaum CJ, Hui DY. HIV protease inhibitor induces fatty acid and sterol biosynthesis in liver and adipose tissues due to the accumulation of activated sterol regulatory element-binding proteins in the nucleus. *J Biol Chem* 2001; 276: 37514-9.
- [67] Zhou H, Gurley EC, Jarujaron S, *et al.* HIV protease inhibitors activate the unfolded protein response and disrupt lipid metabolism in primary hepatocytes. *Am J Physiol Gastrointest Liver Physiol* 2006; 291: G1071-80.
- [68] 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.
- [69] Di Giambenedetto S, Baldini F, Cingolani A, *et al.* The influence of hepatitis C virus coinfection on the risk of lipid abnormalities in a cohort of HIV-1-infected patients after initiation of highly active antiretroviral therapy. *J Acquir Immune Defic Syndr* 2004; 36: 641-2.
- [70] Cooper CL, Mills E, Angel JB. Mitigation of antiretroviral-induced hyperlipidemia by hepatitis C virus co-infection. *AIDS* 2007; 21: 71-6.
- [71] Floris-Moore M, Howard AA, Lo Y, *et al.* Increased serum lipids are associated with higher CD4 lymphocyte count in HIV-infected women. *HIV Med* 2006; 7: 421-30.
- [72] Hofer H, Bankl HC, Wrba F, *et al.* Hepatocellular fat accumulation and low serum cholesterol in patients infected with HCV-3a. *Am J Gastroenterol* 2002; 97: 2880-5.
- [73] den Boer MA, Berbee JF, Reiss P, *et al.* Ritonavir impairs lipoprotein lipase-mediated lipolysis and decreases uptake of fatty acids in adipose tissue. *Arterioscler Thromb Vasc Biol* 2006; 26: 124-9.
- [74] Caron M, Auclair M, Sterlingot H, Kornprobst M, Capeau J. Some HIV protease inhibitors alter lamin A/C maturation and stability, SREBP-1 nuclear localization and adipocyte differentiation. *AIDS* 2003; 17: 2437-44.
- [75] Caron M, Auclair M, Vigouroux C, *et al.* The HIV protease inhibitor indinavir impairs sterol regulatory element-binding protein-1 intranuclear localization, inhibits preadipocyte differentiation, and induces insulin resistance. *Diabetes* 2001; 50: 1378-88.
- [76] Nolan D, Hammond E, Martin A, *et al.* Mitochondrial DNA depletion and morphologic changes in adipocytes associated with nucleoside reverse transcriptase inhibitor therapy. *AIDS* 2003; 17: 1329-38.
- [77] Janneh O, Hoggard PG, Tjia JF, *et al.* Intracellular disposition and metabolic effects of zidovudine, stavudine and four protease inhibitors in cultured adipocytes. *Antivir Ther* 2003; 8: 417-26.
- [78] Shikuma CM, Hu N, Milne C, *et al.* Mitochondrial DNA decrease in subcutaneous adipose tissue of HIV-infected individuals with peripheral lipoatrophy. *AIDS* 2001; 15: 1801-9.
- [79] Mallon PW, Sedwell R, Rogers G, *et al.* Effect of Rosiglitazone on Peroxisome Proliferator-Activated Receptor gamma Gene Expression in Human Adipose Tissue Is Limited by Antiretroviral Drug-Induced Mitochondrial Dysfunction. *J Infect Dis* 2008; 198: 1794-803.
- [80] Cote HC. Possible ways nucleoside analogues can affect mitochondrial DNA content and gene expression during HIV therapy. *Antivir Ther* 2005; 10 Suppl 2: M3-11.
- [81] Mallon PW, Nemorini P, Sedwell R, *et al.* *In vivo*, nucleoside reverse-transcriptase inhibitors alter expression of both mitochondrial and lipid metabolism genes in the absence of depletion of mitochondrial DNA. *J Infect Dis* 2005; 191: 1686-96.
- [82] Stankov MV, Schmidt RE, Behrens GM. Zidovudine impairs adipogenic differentiation through inhibition of clonal expansion. *Antimicrob Agents Chemother* 2008; 52: 2882-9.
- [83] Saillan-Barreau C, Tabbakh O, Chavoïn JP, Casteilla L, Penicaud L. Drug-specific effect of nelfinavir and stavudine on primary culture of human preadipocytes. *J Acquir Immune Defic Syndr* 2008; 48: 20-5.
- [84] Caron M, Auclair M, Lagathu C, *et al.* The HIV-1 nucleoside reverse transcriptase inhibitors stavudine and zidovudine alter adipocyte functions *in vitro*. *AIDS* 2004; 18: 2127-36.
- [85] Vernochet C, Azoulay S, Duval D, *et al.* Human immunodeficiency virus protease inhibitors accumulate into cultured human adipocytes and alter expression of adipocytokines. *J Biol Chem* 2005; 280: 2238-43.
- [86] Jones SP, Waitt C, Sutton R, Back DJ, Pirmohamed M. Effect of atazanavir and ritonavir on the differentiation and adipokine secretion of human subcutaneous and omental preadipocytes. *AIDS* 2008; 22: 1293-8.
- [87] Dowell P, Flexner C, Kwitrovich PO, Lane MD. Suppression of preadipocyte differentiation and promotion of adipocyte death by HIV protease inhibitors. *J Biol Chem* 2000; 275: 41325-32.
- [88] Meininger G, Hadigan C, Laposata M, *et al.* Elevated concentrations of free fatty acids are associated with increased insulin response to standard glucose challenge in human immunodeficiency virus-infected subjects with fat redistribution. *Metabolism* 2002; 51: 260-6.
- [89] Vigouroux C, Maachi M, Nguyen TH, *et al.* Serum adipocytokines are related to lipodystrophy and metabolic disorders in HIV-infected men under antiretroviral therapy. *AIDS* 2003; 17: 1503-11.
- [90] Sutinen J, Hakkinen AM, Westerbacka J, *et al.* Increased fat accumulation in the liver in HIV-infected patients with antiretroviral therapy-associated lipodystrophy. *AIDS* 2002; 16: 2183-93.
- [91] Moreno-Torres A, Domingo P, Pujol J, *et al.* Liver triglyceride content in HIV-1-infected patients on combination antiretroviral therapy studied with ¹H-MR spectroscopy. *Antivir Ther* 2007; 12: 195-203.
- [92] van der Valk M, Gisolf EH, Reiss P, *et al.* Increased risk of lipodystrophy when nucleoside analogue reverse transcriptase inhibitors are included with protease inhibitors in the treatment of HIV-1 infection. *AIDS* 2001; 15: 847-55.
- [93] Freiberg MS, Leaf DA, Goulet JL, *et al.* The association between the receipt of lipid lowering therapy and HIV status among veterans who met NCEP/ATP III criteria for the receipt of lipid lowering medication. *J Gen Intern Med* 2009; 24: 334-40.
- [94] National Cholesterol Education Program. Third Report of the National Cholesterol Education Program (NCEP) expert panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). 2004 [cited 2010 March 10]; Available from: <http://www.nhlbi.nih.gov/guidelines/cho-lesterol/atp3full.pdf>.

- [95] Joy T, Keogh HM, Hadigan C, *et al.* Dietary fat intake and relationship to serum lipid levels in HIV-infected patients with metabolic abnormalities in the HAART era. *AIDS* 2007; 21: 1591-600.
- [96] Henry K, Melroe H, Huebesch J, Hermundson J, Simpson J. Atorvastatin and gemfibrozil for protease-inhibitor-related lipid abnormalities. *Lancet* 1998; 352: 1031-2.
- [97] 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.
- [98] 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.
- [99] Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. November 3, 2008; 1-139. Available at <http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf>. Accessed 23rd December 2009.
- [100] Taburet AM, Piketty C, Chazallon C, *et al.* Interactions between atazanavir-ritonavir and tenofovir in heavily pretreated human immunodeficiency virus-infected patients. *Antimicrob Agents Chemother* 2004; 48: 2091-6.
- [101] Molina JM, Andrade-Villanueva J, Echevarria J, *et al.* Once-daily atazanavir/ritonavir versus twice-daily lopinavir/ritonavir, each in combination with tenofovir and emtricitabine, for management of antiretroviral-naïve HIV-1-infected patients: 48 week efficacy and safety results of the CASTLE study. *Lancet* 2008; 372: 646-55.
- [102] Tomaka F, Lefebvre E, Sekar V, *et al.* Effects of ritonavir-boosted darunavir vs. ritonavir-boosted atazanavir on lipid and glucose parameters in HIV-negative, healthy volunteers. *HIV Med* 2009; 10: 318-27.
- [103] Gatell J, Salmon-Ceron D, Lazzarin A, *et al.* Efficacy and safety of atazanavir-based highly active antiretroviral therapy in patients with virologic suppression switched from a stable, boosted or unboosted protease inhibitor treatment regimen: the SWAN Study (AI424-097) 48-week results. *Clin Infect Dis* 2007; 44: 1484-92.
- [104] Soriano V, Garcia-Gasco P, Vispo E, *et al.* Efficacy and safety of replacing lopinavir with atazanavir in HIV-infected patients with undetectable plasma viraemia: final results of the SLOAT trial. *J Antimicrob Chemother* 2008; 61: 200-5.
- [105] Nguyen ST, Eaton SA, Bain AM, *et al.* Lipid-lowering efficacy and safety after switching to atazanavir-ritonavir-based highly active antiretroviral therapy in patients with human immunodeficiency virus. *Pharmacotherapy* 2008; 28: 323-30.
- [106] 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.
- [107] Sension M, Neto JL, Grinsztejn B, *et al.* Improvement in Lipid Profiles in Antiretroviral-Experienced HIV-Positive Patients With Hyperlipidemia After a Switch to Unboosted Atazanavir. *J Acquir Immune Defic Syndr* 2009; 51(2): 153-62.
- [108] Estrada V, De Villar NG, Larrad MT, *et al.* Long-term metabolic consequences of switching from protease inhibitors to efavirenz in therapy for human immunodeficiency virus-infected patients with lipotrophy. *Clin Infect Dis* 2002; 35: 69-76.
- [109] 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: 1051-8.
- [110] Negro E, Cruz L, Paredes R, *et al.* Virological, immunological, and clinical impact of switching from protease inhibitors to nevirapine or to efavirenz in patients with human immunodeficiency virus infection and long-lasting viral suppression. *Clin Infect Dis* 2002; 34: 504-10.
- [111] Petit JM, Duong M, Masson D, *et al.* Serum adiponectin and metabolic parameters in HIV-1-infected patients after substitution of nevirapine for protease inhibitors. *Eur J Clin Invest* 2004; 34: 569-75.
- [112] Martinez E, Arnaiz JA, Podzamczar D, *et al.* Substitution of nevirapine, efavirenz, or abacavir for protease inhibitors in patients with human immunodeficiency virus infection. *N Engl J Med* 2003; 349: 1036-46.
- [113] Gulick RM, Ribaldo HJ, Shikuma CM, *et al.* Triple-nucleoside regimens versus efavirenz-containing regimens for the initial treatment of HIV-1 infection. *N Engl J Med* 2004; 350: 1850-61.
- [114] Moyle GJ, Sabin CA, Cartledge J, *et al.* A randomized comparative trial of tenofovir DF or abacavir as replacement for a thymidine analogue in persons with lipotrophy. *AIDS* 2006; 20: 2043-50.
- [115] Madruga JR, Cassetti I, Suleiman JM, *et al.* The safety and efficacy of switching stavudine to tenofovir df in combination with lamivudine and efavirenz in hiv-1-infected patients: three-year follow-up after switching therapy. *HIV Clin Trials* 2007; 8: 381-90.
- [116] 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.
- [117] Ananworanich J, Nuesch R, Cote HC, *et al.* Changes in metabolic toxicity after switching from stavudine/didanosine to tenofovir/lamivudine--a Staccato trial substudy. *J Antimicrob Chemother* 2008; 61: 1340-3.
- [118] Martinez E, Arranz JA, Podzamczar D, *et al.* A simplification trial switching from nucleoside reverse transcriptase inhibitors to once-daily fixed-dose abacavir/lamivudine or tenofovir/emtricitabine in HIV-1-infected patients with virological suppression. *J Acquir Immune Defic Syndr* 2009; 51: 290-7.
- [119] Milinkovic A, Martinez E, Lopez S, *et al.* The impact of reducing stavudine dose versus switching to tenofovir on plasma lipids, body composition and mitochondrial function in HIV-infected patients. *Antivir Ther* 2007; 12: 407-15.
- [120] Fisher M, Moyle GJ, Shahmanesh M, *et al.* A Randomized Comparative Trial of Continued Zidovudine/Lamivudine or Replacement With Tenofovir Disoproxil Fumarate/Emtricitabine in Efavirenz-Treated HIV-1-Infected Individuals. *J Acquir Immune Defic Syndr* 2009; 51: 562-8.
- [121] Hatano H, Miller KD, Yoder CP, *et al.* Metabolic and anthropometric consequences of interruption of highly active antiretroviral therapy. *AIDS* 2000; 14: 1935-42.
- [122] El-Sadr WM, Lundgren JD, Neaton JD, *et al.* CD4+ count-guided interruption of antiretroviral treatment. *N Engl J Med* 2006; 355: 2283-96.
- [123] 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.
- [124] Neuvonen PJ, Niemi M, Backman JT. Drug interactions with lipid-lowering drugs: mechanisms and clinical relevance. *Clin Pharmacol Ther* 2006; 80: 565-81.
- [125] Backman JT, Luurila H, Neuvonen M, Neuvonen PJ. Rifampin markedly decreases and gemfibrozil increases the plasma concentrations of atorvastatin and its metabolites. *Clin Pharmacol Ther* 2005; 78: 154-67.
- [126] Gerber JG, Kitch DW, Fichtenbaum CJ, *et al.* Fish oil and fenofibrate for the treatment of hypertriglyceridemia in HIV-infected subjects on antiretroviral therapy: results of ACTG A5186. *J Acquir Immune Defic Syndr* 2008; 47: 459-66.
- [127] Badiou S, Merle De Boever C, Dupuy AM, *et al.* Fenofibrate improves the atherogenic lipid profile and enhances LDL resistance to oxidation in HIV-positive adults. *Atherosclerosis* 2004; 172: 273-9.
- [128] Calza L, Manfredi R, Chiodo F. Statins and fibrates for the treatment of hyperlipidaemia in HIV-infected patients receiving HAART. *AIDS* 2003; 17: 851-9.
- [129] Palacios R, Santos J, Gonzalez M, *et al.* Efficacy and safety of fenofibrate for the treatment of hypertriglyceridemia associated with antiretroviral therapy. *J Acquir Immune Defic Syndr* 2002; 31: 251-3.
- [130] Palacios R, Santos J, Gonzalez M, *et al.* Efficacy and safety of atorvastatin in the treatment of hypercholesterolemia associated with antiretroviral therapy. *J Acquir Immune Defic Syndr* 2002; 30: 536-7.
- [131] 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.
- [132] Calza L, Colangeli V, Manfredi R, *et al.* Rosuvastatin for the treatment of hyperlipidaemia in HIV-infected patients receiving protease inhibitors: a pilot study. *AIDS* 2005; 19: 1103-5.

- [133] Baldini F, Di Giambenedetto S, Cingolani A, *et al.* Efficacy and tolerability of pravastatin for the treatment of HIV-1 protease inhibitor-associated hyperlipidaemia: a pilot study. *AIDS* 2000; 14: 1660-2.
- [134] 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.
- [135] 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.
- [136] 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.
- [137] 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.
- [138] van der Lee M, Sankatsing R, Schippers E, *et al.* Pharmacokinetics and pharmacodynamics of combined use of lopinavir/ritonavir and rosuvastatin in HIV-infected patients. *Antivir Ther* 2007; 12: 1127-32.
- [139] Kiser JJ, Gerber JG, Predhomme JA, *et al.* Drug/Drug interaction between lopinavir/ritonavir and rosuvastatin in healthy volunteers. *J Acquir Immune Defic Syndr* 2008; 47: 570-8.
- [140] Busti AJ, Bain AM, Hall RG, 2nd, *et al.* Effects of atazanavir/ritonavir or fosamprenavir/ritonavir on the pharmacokinetics of rosuvastatin. *J Cardiovasc Pharmacol* 2008; 51: 605-10.
- [141] Wohl DA, Waters D, Simpson RJ, Jr., *et al.* Ezetimibe alone reduces low-density lipoprotein cholesterol in HIV-infected patients receiving combination antiretroviral therapy. *Clin Infect Dis* 2008; 47: 1105-8.
- [142] 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.
- [143] 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.
- [144] Dube MP, Wu JW, Aberg JA, *et al.* Safety and efficacy of extended-release niacin for the treatment of dyslipidaemia in patients with HIV infection: AIDS Clinical Trials Group Study A5148. *Antivir Ther* 2006; 11: 1081-9.
- [145] World Health Organisation. Antiretroviral therapy for HIV infection in adults and adolescents. Recommendations for a public health approach. (2006 revision). Available at 2006 [cited 2010 Mar 10]; Available from: <http://www.who.int/hiv/pub/guidelines/artadultguidelines.pdf>.
- [146] Mutimura E, Stewart A, Rheeder P, Crowther NJ. Metabolic function and the prevalence of lipodystrophy in a population of HIV-infected African subjects receiving highly active antiretroviral therapy. *J Acquir Immune Defic Syndr* 2007; 46: 451-5.
- [147] Johnson LB, Saravolatz LD. Etravirine, a next-generation nonnucleoside reverse-transcriptase inhibitor. *Clin Infect Dis* 2009; 48: 1123-8.
- [148] Steigbigel RT, Cooper DA, Kumar PN, *et al.* Raltegravir with optimized background therapy for resistant HIV-1 infection. *N Engl J Med* 2008; 359: 339-54.
- [149] Gulick RM, Lalezari J, Goodrich J, *et al.* Maraviroc for previously treated patients with R5 HIV-1 infection. *N Engl J Med* 2008; 359: 1429-41.
- [150] Martinez E, Garcia-Viejo MA, Blanco JL, *et al.* Impact of switching from human immunodeficiency virus type 1 protease inhibitors to efavirenz in successfully treated adults with lipodystrophy. *Clin Infect Dis* 2000; 31: 1266-73.
- [151] 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.
- [152] Martin A, Smith DE, Carr A, *et al.* Reversibility of lipodystrophy in HIV-infected patients 2 years after switching from a thymidine analogue to abacavir: the MITOX Extension Study. *AIDS* 2004; 18: 1029-36.
- [153] Schewe CK, Maserati R, Wassmer G, Adam A, Weitner L. Improved lipid profiles and maintenance of virologic control in heavily pretreated HIV-infected patients who switched from stavudine to tenofovir treatment. *Clin Infect Dis* 2006; 42: 145-7.
- [154] 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.

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