Dyslipidemia in HIV-Infected Patients

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Introduction

Since the advent of effective combination antiretroviral therapy (ART), patterns of mortality in HIV infection have changed and the rates have fallen, with the acquired immunodeficiency syndrome (AIDS) now overtaken by non-AIDS events [1]. Cardiovascular disease is a common cause of death in this population, and will become increasingly so as these patients age [2, 3].

This is partly because some traditional risk factors, notably smoking, are more common amongst HIV-infected individuals, placing them at risk of events at ages younger than their HIV-negative peers [4, 5]. Additionally, both the infection and especially ART are significantly associated with the development of an abnormal metabolic milieu that can promote cardiovascular risk. The resulting derangements in plasma lipids are believed to be a key pathway by which accelerated atherosclerosis may occur in HIV-infected individuals [6].

In this chapter, we review the phenotypic changes in lipid metabolism observed in both untreated ('treatment-naïve') and treatment-experienced HIV infection, the current state of knowledge about their respective pathogenic mechanisms and the approach to management. All the information presented relates to HIV-1, by far the dominant cause of HIV cases, and not the less virulent HIV-2, for which very little metabolic data are available.

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Dyslipidemia Associated with HIV Viremia

Observations in HIV-Infected, Treatment-Naïve Populations

Derangements in lipid metabolism have long been a recognized feature of untreated HIV infection, predating the advent of ART [7]. The precise time course in the untreated setting is unknown, but the key early change is a fall in cholesterol fractions [8]. A fall in high-density lipoprotein (HDL) cholesterol levels appears to be the initial change, followed by a fall in low-density lipoprotein (LDL) cholesterol levels somewhat later.

The first prospective description of evolving dyslipidemia was made via a subgroup analysis of the Multicenter AIDS Cohort Study. In 50 HIV-infected but treatment-naïve men, mean plasma HDL and LDL cholesterol (and triglyceride levels) fell between seroconversion and initiation of ART [9]. As this was documented by comparing paired samples (preseroconversion vs. pre-ART, median separation 99 months), an accurate illustration of the time course does not exist. The net effect may be pro-atherogenic as HDL cholesterol remains a strong inverse predictor of cardiovascular events even with

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concurrently low levels of LDL cholesterol [10]. This is likely compounded because HDL cholesterol loses its efficacy as an antioxidative agent in the setting of active infection and inflammation [11]. These changes to HDL and LDL cholesterol were corroborated in a later prospective study of HIV-infected adults prior to treatment [12].

Data from the Strategies for Management of Antiretroviral Therapy (SMART) study provide a striking illustration of the relationship between lipid metabolism and HIV infection [13]. In this study, patients received CD4-guided intermittent ART with the aim of limiting dyslipidemia and other metabolic toxicities. While total and LDL cholesterol levels fell during periods of treatment interruption, there was a proportionally greater decline in HDL cholesterol, such that the total-to-HDL cholesterol ratio actually increased, consistent with a higher cardiovascular risk. This was borne out in the clinical outcomes, where the group receiving intermittent therapy had more frequent cardiovascular events and deaths.

With advanced disease, there is a significant elevation in triglycerides and very low-density lipoprotein (VLDL) cholesterol levels, with the latter further increasing cardiovascular risk [8]. The rise in triglycerides appears related to the HIV viral load; in an early study of the antiretroviral drug zidovudine, used as monotherapy in patients with AIDS, mean triglyceride levels fell only in those patients receiving zidovudine [14]. Correlations also exist between falling HDL cholesterol levels, high plasma viral load and low CD4 counts of late disease. However, this lipid profile is now uncommon in developed countries, where there is access to combination ART.

A limitation of the aforementioned studies is that the participants were almost exclusively male and sourced from resource-rich populations. Subsequent studies confirm that dyslipidemia is also a prominent metabolic feature in untreated women and non-Caucasians, although no data directly comparing different ethnicities are available. One large cross-sectional study of 12,513 adults pre-ART in Tanzania (65% female) showed a high prevalence of dyslipidemia as defined by the US National Cholesterol Education Program (NCEP) guidelines, with decreased HDL cholesterol (<1 mmol/L) in 67%, and elevated triglycerides (>1.7 mmol/L) in 28% [15]. Interestingly, males had significantly lower total, HDL, and LDL cholesterol levels; the reasons for this are unclear. As observed in other studies, triglyceride levels were positively associated with more advanced HIV disease. In a smaller Nigerian study, active tuberculosis infection (a marker for advanced disease and inflammation) was associated with a significantly higher mean LDL cholesterol level [16].

A very small minority (<0.5%) of HIV-infected individuals remain clinically well for decades without developing AIDS despite not receiving ART. There are no data on circulating lipid levels in these long-term nonprogressors and so-called 'elite controllers', although some suggestion of increased cardiovascular risk exists [17].

Mechanisms of Dyslipidemia Associated with HIV Viremia

A number of possible mechanisms have been identified to explain the dyslipidemia of untreated HIV infection, although none are definitive. Broadly, they may be categorized as:

- Direct viral effects
- Consequences of the inflammatory response triggered by the infection

These mechanisms act to disrupt existing metabolic pathways, and in some cases the effects feed back to exacerbate the initial insult.

HIV infection appears to directly interfere with steps in the reverse cholesterol transport pathway, whereby HDL cholesterol facilitates clearance by the liver of cholesterol from the extrahepatic tissues. The HIV protein *nef* is a virulence factor expressed to enhance viral replication that has been shown to block the efflux of cholesterol from macrophages mediated by the adenosine triphosphate (ATP)-binding cassette protein A1 (ABCA1). *Nef* induces a post-transcriptional downregulation of the normal expression of ABCA1 as well as redistributing it to the plasma membrane [18]. In doing so, lipid accumulates in macrophages, promoting their conversion into the foam cells involved in the genesis of atherosclerotic plaques.

HIV infection also upregulates expression of the cholesterylester transfer protein (CETP), a later step in reverse cholesterol transport. CETP exchanges triglycerides from LDL and VLDL particles for cholesterol esters from HDL particles [19]. This leads to the HDL particles becoming saturated with triglycerides, and their accelerated clearance by hepatic lipases.

Although not directly related to lipid metabolism, another HIV protein, *tat,* in concert with tumour necrosis factor (TNF)-α can induce endothelial proliferation and activation, permitting adhesion and translocation of leukocytes into the vasculature, creating a pro-inflammatory, pro-atherogenic state [20]. The HIV envelope protein gp120 may also increase endothelial activation and monocyte adhesion [21]. Such dysfunction promotes local thrombosis as well as inflammation.

But it must be remembered that most of these findings are from in vitro studies; it remains unclear which of these, if any, play the predominant role in causing dyslipidemia in untreated HIV infection. For instance, there is no clear in vivo evidence to demonstrate that the HIV virus directly reduces circulating levels of HDL cholesterol, although that is what is observed clinically. Persons with noninfective, chronic inflammatory diseases such as systemic lupus erythematosus and rheumatoid arthritis display lipid derangements similar to those found in untreated HIV; furthermore, these lipid changes correlate well with disease activity [22, 23]. This suggests that the state of active inflammation in untreated HIV may play a greater role in generating dyslipidemia (and subsequently, increased cardiovascular risk) than direct effects of the virus. Inflammation stimulates endothelial phospholipase A2, which reduces HDL cholesterol, and in turn attenuates cholesterol efflux from macrophages in the arterial wall [24]. Hypertriglyceridemia results from increased hepatic fatty acid synthesis, activation of adipose tissue lipolysis, and suppression of ketogenesis. This is mediated by multiple cytokines—TNF-α, interleukin (IL)-1, IL-2, and IL-6 [25].

The strong association between serum triglyceride levels and the degree of inflammation is seen in AIDS, which is marked by increased levels of interferon (IFN)-α and TNFα [26]. As seen with noninfective chronic inflammatory states, IFN-α decreases lipoprotein lipase activity, impairing the clearance and/or storage uptake of lipoproteins, raising the circulating levels of triglycerides and VLDL cholesterol [27]. Levels of TNF-α further rise during opportunistic infections, and permits lipolysis by attenuating the anabolic effect of insulin and interfering with free fatty acid metabolism [28]. In the resulting lipoprotein-rich environment, HDL cholesterol becomes enriched with triglycerides, marking it for clearance by hepatic lipase. This complements the aforementioned enhanced activity of CETP.

These mechanisms (and their interplay with metabolic disturbances generated by ART, discussed below) are summarized in Fig. 9.1.

Whether the reduction of HDL cholesterol levels and modest increase in serum triglyceride concentrations, when associated with a fall in LDL cholesterol levels, will increase risk of atherosclerosis or coronary heart disease in treatment-naïve HIV-infected patients remains unknown. In the pre-ART era, most HIV-infected patients died of AIDS and its complications, and not from coronary heart disease.

Dyslipidemia Associated with ART

The metabolic derangements associated with ART are ultimately of greater clinical relevance than those attributed to HIV viremia alone. This is because in the current absence of a cure, ART requires a high degree (>90 %) of lifelong adherence to maintain its efficacy. Furthermore, guidelines are trending towards a 'test-and-treat' approach, whereby ART is initiated progressively earlier [29].

Although the first clinical trial of zidovudine was in 1986, the current era of effective combination ART began in 1996 [30]. Currently, there are almost 30 drugs in six classes with widespread regulatory approval for use as ART:

- Nucleoside reverse transcriptase inhibitors (NRTI)
- Nonnucleoside reverse transcriptase inhibitors (NNRTI)

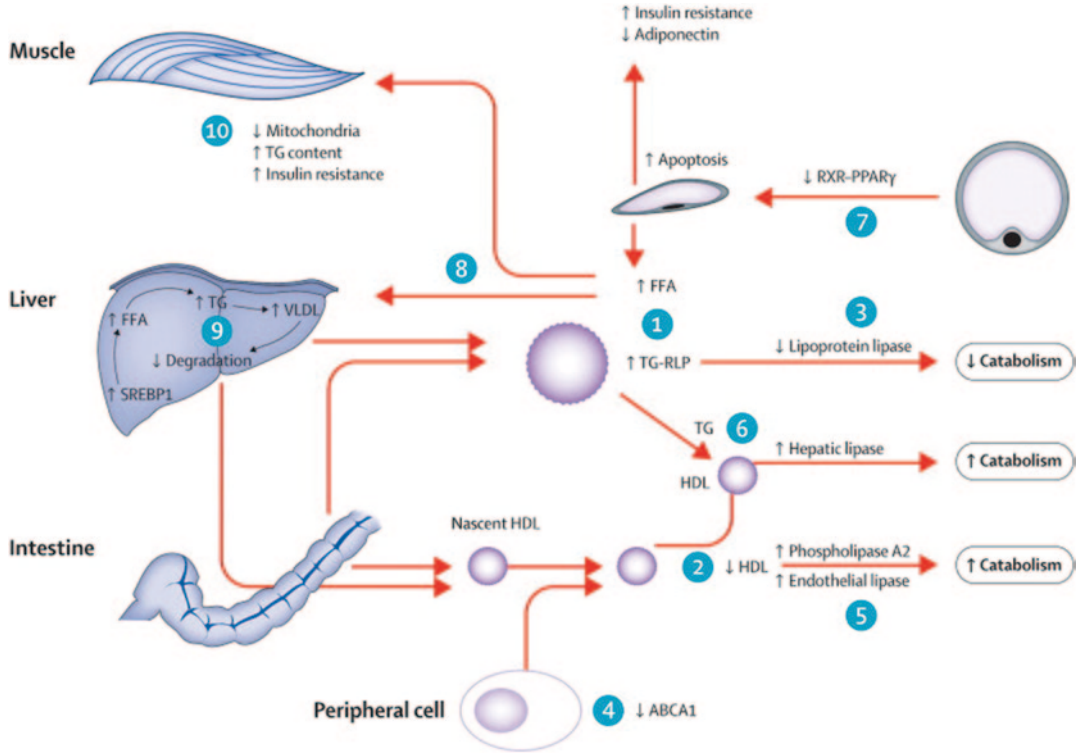

Fig. 9.1 Schematic representation of possible mechanisms underlying HIV-associated dyslipidemia. Derangements of lipid metabolism are a result of direct effects of the HIV itself, the inflammatory response to infection. The addition of antiretroviral therapy (ART) further adds to the complexity. *1* Increased triglyceride (TG)-rich lipoproteins (RLP), particularly very low-density lipoprotein (VLDL cholesterol; and *2* decreased high-density lipoprotein (HDL) cholesterol. The inflammatory cytokine response to HIV infection: *3* decreases lipoprotein lipase activity, which results in accumulation of triglycerides; *4* decreases cholesterol efflux from peripheral cells via the ATP-binding cassette protein A1 (ABCA1), which results in decreased formation of HDL cholesterol; and *5* increases activity of phospholipase A2 and endothelial lipase, which results in increased catabolism of HDL cholesterol. Increased plasma TG results in *6* abnormal TG-enrichment of HDL cholesterol, which increases catabolism via hepatic lipase. ART causes redistribution of adipose tissue as a result of *7* decreased retinoid X receptor-peroxisome proliferator-activated receptor γ (RXR-PPAR-γ) activity. *8* Free fatty acid (FFA) spills over from apoptotic peripheral adipocytes, increasing 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 (SREBP) 1c 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*, ART is associated with mitochondrial depletion, which in turn compromises FFA oxidation; as a result, intra- and intermyocellular TG content increases. Insulin resistance in liver and skeletal muscle compounds the metabolic disturbances, including dyslipidemia. *HIV* human immunodeficiency virus, *ATP* adenosine triphosphate. (Reproduced with permission from: Oh J and Hegele RA. HIV-associated dyslipidemia: pathogenesis and treatment. Lancet Infect Dis. 2007;7:787–796. Copyright ©2007 ScienceDirect)

- Protease inhibitors (PI)
- Integrase strand transfer inhibitors (INSTI)
- CC chemokine receptor 5 (CCR5) entry antagonists
- Viral fusion blockers

The therapeutic targets of the ART classes within the HIV-1 lifecycle are represented in Fig. 9.2. Initial therapy is usually a combination of three medications: Typically, to a 'backbone' of two NRTIs is added a third agent, drawn from the NNRTI, PI or INSTI classes. The role of CCR5 entry antagonists is still being defined, while viral fusion blockade is reserved for 'salvage' therapy in cases of multiresistant virus. Considering the

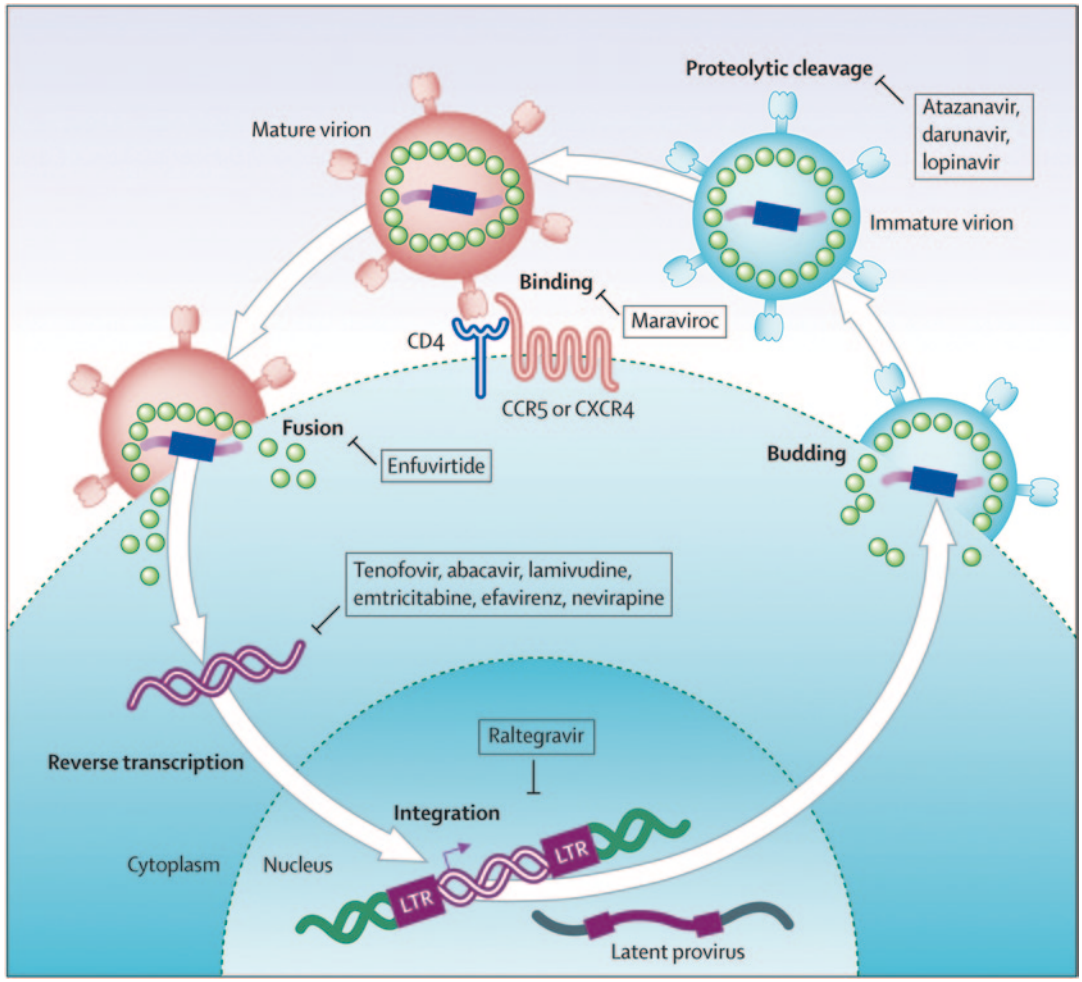

Fig. 9.2 HIV life cycle and antiretroviral targets. Present antiretroviral drugs span six classes that target five unique steps in the HIV life cycle (binding, fusion, reverse transcription, integration, and proteolytic cleavage). The most common drugs currently used in resource-rich regions to target each step are shown. Extracellular virions enter their target cell through a complex three-step process, which is (1) attachment to the CD4 receptor, (2) binding to the CCR5 or CXCR4 co-receptors, or both, and (3) membrane fusion. Maraviroc blocks CCR5 binding and enfuvirtide blocks fusion. The HIV reverse transcriptase enzyme catalyses transcription of HIV RNA into double-stranded HIV DNA, a step inhibited by nucleoside analogues and nonnucleoside reverse transcriptase inhibitors (NNRTIs). The HIV integrase enzyme facilitates incorporation of HIV DNA into host chromosomes, and this step is inhibited by raltegravir and other integrase inhibitors. After transcription and translation of the HIV genome, immature virions are produced and bud from the cell surface. The HIV protease enzyme cleaves polypeptide chains, allowing the virus to mature. This last step is inhibited by HIV protease inhibitor. *HIV* human immunodeficiency virus, *CD4* cluster of differentiation 4, *CCR5 C-C* chemokine receptor type 5, *CXCR4 C-X-C* chemokine receptor type 4. (Reproduced with permission from: Volberding PA and Deeks SG. Antiretroviral therapy and management of HIV infection.Lancet. 2010;376:49–62. Copyright ©2010 ScienceDirect) Dietary factors can also play an important role in advanced disease. Patients with AIDS are frequently malnourished, with protein depletion being a particular problem, and this may contribute to lipid metabolism derangements [7, 26].

number of possible permutations, it is not helpful to attempt to define any single lipid profile as being representative of ART-associated dyslipidemia. Rather, individual drugs, and where possible, different classes need to be considered separately. The possible mechanisms of ART-associated dyslipidemia are outlined in Table 9.1. It is also useful to examine the evolution of observed phenotypes concurrent with developments in ART, starting with HIV lipodystrophy.

Table 9.1 Proposed possible mechanisms of ART-associated dyslipidemia

Mechanism	Effect
Protease inhibitors	
Fall in activated retinoic acid levels	Blocks activity of activity of peroxisome proliferator-activated receptor (PPAR)-γ, inhibiting adipocyte differentiation and promoting apoptosis (and therefore lipodystrophy) [34]
	FFA from apoptotic adipocytes flux to the liver and skeletal muscle, leading to insulin resistance
Protease inhibitor binding to CRABP1 (60% homology between HIV-1 protease and CRABP1)	Stops activation of retinoic acid, blocking PPAR-γ activity [34]
Cytochrome P450 (CYP) 3A4 inhibition (particularly by ritonavir)	Reduces amount of activated retinoic acid synthesized [118]
Proteasome blockage (demonstrated with lopinavir and ritonavir)	Retards degradation of the sterol-regulatory element-binding protein (SREBP) 1c, leading to increased hepatic production of lipoproteins [119, 120]
Accumulation of intramyocellular fat	Insulin resistance, and elevated levels of triglycerides and apolipoprotein B [121]
PIs binding to the LDL-receptor-related protein (LRP)-1 (LRP 1 shares homology with HIV-1 protease)	Blocks LRP 1 from binding to endothelial lipoprotein lipase. Stops hydrolysis of free fatty acids from circulating triglycerides [122]
Inhibition of the expression of lipoprotein lipase (indinavir)	Reduced clearance of lipids, particularly by the liver [123]
Possible decreased expression of LDL receptors	Reduced uptake of LDL cholesterol particles with resulting higher plasma levels [124]
Decreased lipid intake by adipocytes, increased lipolysis in adipocytes (demonstrated at supratherapeutic levels with nelfinavir, saquinavir, and ritonavir, but not amprenavir or indinavir)	Increased plasma triglyceride levels [125]
Elevated expression of lipogenic genes in cultured hepatocyte models (may not occur at therapeutic plasma concentrations)	Increased production of VLDL cholesterol [119, 125]
Reduced CD36 expression in human monocytes	Lipid accumulation in macrophages, promoting apoptosis and conversion into atherogenic foam cells [126]
Inhibition of the zinc metalloproteinase ZMPSTE24	Dysregulation of nuclear lamin A processing, leading to prelamin A accumulation within fibroblasts and adipocytes [38]
Nucleoside reverse transcriptase inhibitors	
Inhibition of mitochondrial DNA polymerase γ (particularly by thymidine analogues, stavudine, and zidovudine)	Depletion of mitochondrial DNA and suppression of the respiratory chain [127]
	Leads to lipoatrophy in adipocytes, and insulin resistance in skeletal muscle
CCR5 entry antagonists and integrase strand transfer inhibitors	
No described mechanisms	

ART antiretroviral therapy, *FFA* free fatty acid, *CRAPB1* cytoplasmic retinoic acid binding protein I, *CYP* cytochrome P-450A, *LDL* low-density lipoprotein, *HIV* human immunodeficiency virus, *VLDL* very-low-density lipoprotein, *CD4* cluster of differentiation 4

HIV Lipodystrophy and Dyslipidemia

HIV lipodystrophy was first described in 1998 [31]. The hallmarks are a loss of subcutaneous fat (lipoatrophy) in the face and limbs, and the accumulation of fat (lipohypertrophy) centrally, especially intra-abdominally. Both lipoatrophy and lipohypertrophy may occur independently, to varying degrees and in an anatomically localized fashion (Fig. 9.3). As it remains a clinical diagnosis without a validated case definition, the reported prevalence of HIV lipodystrophy can

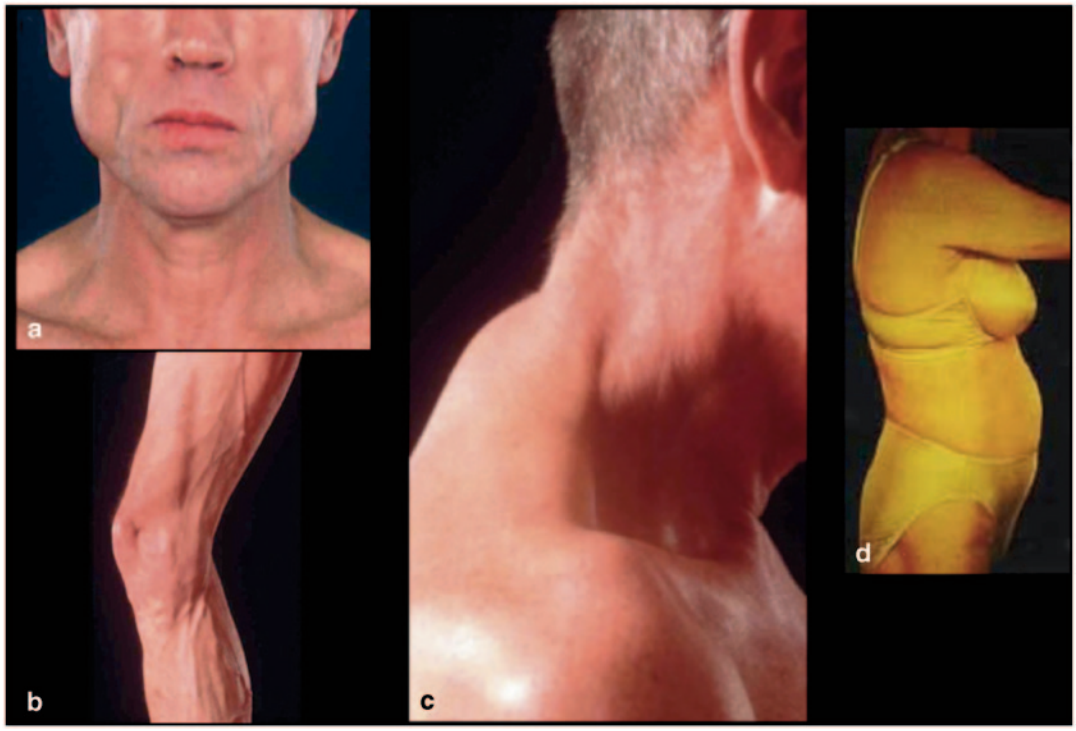

Fig. 9.3 Morphological changes of HIV lipodystrophy. Examples of lipodystrophy, most strongly associated with the use of thymidine analogues. Typical features include a prominent, hollowed-out facial appearance due to lipoatrophy of buccal fat (**a**) and appendicular fat (**b**), causing leg and arm veins to become prominent. Enlargement of the cervico-dorsal fat, commonly referred to as a 'buffalo hump' (**c**) is another typical feature. Concurrent deposition of fat intra-abdominally leads to central obesity. Computed tomography and dual-energy X-ray absorptiometry can be used to quantify the extent of lipodystrophy. These imaging modalities show that both superficial and deep fat is affected. HIV human immunodeficiency virus. (Photos courtesy of A. Carr)

vary significantly—studies from the late 1990s describe rates of 20–35% at 12–18 months post-ART initiation [32, 33].

Insights into the pathogenesis of this complex syndrome remain few and unclear, particularly as an appropriate biomarker is lacking. The first case descriptions and early clinical studies identified PI use as a strong predictor of lipodystrophy [34–36]. There is certainly some in vitro study evidence supporting a role for PIs. Indinavir may inhibit adipocyte differentiation, probably acting via the sterol-regulatory element-binding protein (SREBP) [37]. Lopinavir and tipranavir inhibit the zinc metalloproteinase ZMPSTE24, disrupting the processing of nuclear lamin A; this is significant because genetic defects in lamin A metabolism result in syndromes that feature lipodystrophy [38]. However, accumulated clinical trial data appears to implicate use of thymidine analogue NRTIs (stavudine, zidovudine) as the major causative factor, rather than PIs [33, 39, 40]. Lipodystrophy may occur without exposure to thymidine analogues, suggesting that other patient or disease factors, presently unidentified, are involved. Although assessing the contribution of PIs to lipodystrophy is confounded because almost all participants of early ART studies also received concurrent zidovudine or stavudine, they may act synergistically with thymidine analogues to potentiate its development [41].

Dyslipidemia is a very common feature of lipodystrophy; up to 70% of affected individuals will have a lipid profile conferring an increased risk of cardiovascular disease [31, 42]. Greater proportions of lipodystrophic patients have elevated triglycerides (up to 57%), total cholesterol (up

to 57%) and LDL cholesterol (up to 22%), and low levels of HDL cholesterol (up to 46%) when compared to those without lipodystrophy [43]. Nascent insulin resistance (up to 25%) and type 2 diabetes mellitus (8–10%) are also common findings. These metabolic changes are unlikely to be solely due to the changes in body fat distribution, as direct effects of ART drugs also play a role, not to mention diet and premorbid body habitus. A number of nonmedication risk factors for developing HIV lipodystrophy have been identified, mainly from large cross-sectional studies [32, 33, 44]. These are older age, lower body weight pre-ART, previous diagnosis of AIDS, and a lower nadir CD4 cell count. Women may be more susceptible to central adiposity than men [45].

With currently preferred ART regimens, which use an NRTI backbone of tenofovir and emtricitabine, and anchored with later-generation drugs such as efavirenz (NNRTI) and raltegravir (INSTI), new-onset cases of lipodystrophy are very uncommon. Where possible, patients affected with lipoatrophy should be switched from thymidine analogues. This slows progression, and any subsequent gains in fat volume are modest and not usually clinically evident, making lipoatrophy effectively irreversible [46]. Nor does the lipid profile significantly improve—depending upon the replacement ART drug, the dyslipidemia may actually be exacerbated [47]. Injectable temporary facial fillers are the mainstay of treating lipoatrophy but are solely cosmetic and have no effect on lipid metabolism; poly-L-lactic acid and calcium hydroxylapatite are approved by the US Food and Drug Administration (FDA) for this purpose [48, 49]. The thiazolidinedione pioglitazone was demonstrated to significantly increase HDL cholesterol (0.04 mmol/L) and limb fat (0.38 kg), although the improvement in lipoatrophy was insufficient to be clinically perceived [50]. Its use in lipodystrophy remains investigational.

Accumulation of intra-abdominal fat in HIV lipodystrophy is largely visceral and not amenable to liposuction. The growth hormone-releasing factor analogue tesamorelin is an effective medical treatment, producing significant reductions in visceral adipose tissue (15%), triglycerides (0.57 mmol/L) and total cholesterol (0.2 mmol/L) without affecting glycemic control [51]. It does not significantly alter HDL cholesterol or the total-to-HDL cholesterol ratio, however [52]. Although FDA-approved for the treatment of excess abdominal fat in HIV lipodystrophy, fat rapidly re-accumulates after discontinuation [53]. Long-term safety data are lacking, and cost can be a limiting factor, so it is best reserved for patients who have not responded to regular exercise and dietary modifications. Metformin has been shown to reduce insulin resistance and both subcutaneous and visceral fat, but has no significant effects upon lipids [54]. It should be regarded as investigational in nondiabetic HIV-infected patients, and be used in caution in those with significant lipoatrophy.

Data from Clinical Trials: 1996 to the Present

The majority of lipid ART data come from prospective, randomized trials that directly compare two or more regimens. These trials fall into one of two categories:

- Initial treatment
- Changing ART in treatment-experienced patients (so-called switch studies)

Important ancillary data are derived from large observational cohorts, such as the Danish Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D Study), and systematic analyses of pooled prospective trials that allow comparisons between individual drugs and classes for a variety of risk and safety outcomes.

Of all the ART classes, PIs are the most strongly associated with dyslipidemia—typically proatherogenic increases in total, LDL and VLDL cholesterol, as well as hypertriglyceridemia, with minimal effect upon HDL cholesterol levels [55–57]. This association was founded largely upon studies of early-generation PIs; patients receiving indinavir, nelfinavir or saquinavir were reported to have a significantly higher prevalence of dyslipidemia (38–70%) compared to PI-naïve individuals (5 to 25%) [58]. Treatment with indinavir is associated with significant median increases from baseline of total, LDL cholesterol and triglycerides (17, 21, and 27%, respectively), while saquinavir may result in smaller, but still-

significant rises (8, 6, and 12%, respectively) [59]. These increases are evident even after only 4 weeks of treatment and maintained at 48 weeks. Similar results have been described for nelfinavir and full-dose ritonavir when compared to non-PI controls, with mean increases in total cholesterol of 0.8–2.0 mmol/L, depending upon the PI [56]. Apart from the particular PI used, factors associated with greater dyslipidemia are duration of PI exposure and use of dual-PI therapy [60].

Switching away from full-dose ritonavir improves the lipid profile, suggesting at least a partial reversibility [56]. Recent switch studies have borne out this principle in clinical practice, positioning it as a feasible treatment option for dyslipidemia in those patients receiving a ritonavir-boosted PI [61, 62].

Early-generation PIs are no longer favoured for first-line therapy (although low-dose ritonavir remains as a pharmacokinetic booster of other PIs); nor is lopinavir, which causes similar lipid derangements. In large prospective studies, the present first-line PIs, atazanavir and darunavir, both display a significantly favourable lipid effect compared to lopinavir, with relatively modest increases in all lipid fractions, including HDL cholesterol, of between 11 and 19% from baseline after 96 weeks [63, 64]. As the mean lipids for both PIs remained within NCEP target ranges for optimal lipids, these increases are of doubtful clinical relevance. The only trial directly comparing these two PIs showed greater increases of all lipid fractions with darunavir, although the differences were all nonsignificant [65]. Studies conducted in vitro with atazanavir demonstrate no effect upon adipocyte metabolism, suggesting that it may be altogether lipid neutral [66].

Results from the D:A:D Study analysis provide a useful illustration of the differences between the individual PIs by examining the impact upon cardiovascular risk. When compared to patients not exposed to any PIs, early-generation PI-based ART regimens were associated with a 1.16 times per year increased risk of myocardial infarction, of which approximately 50% could be attributed to PI-associated dyslipidemia [67]. Further analysis implicated cumulative exposure to indinavir and lopinavir (and the NRTIs, didanosine and abacavir), but not nelfinavir or saquinavir, as being independently associated with a statistically significant increased risk of myocardial infarction [68]. Atazanavir-based therapies are. however, not associated with increased risk of stroke or myocardial infarction [69]. Similar data for darunavir are yet to be reported. While the risk reduction seen with atazanavir may be driven by greater awareness and thence more aggressive treatment of cardiovascular risk, including lipid-lowering therapies, it may also suggest a progressive diminution of lipid derangement with newer agents.

While NNRTIs are not as well known for their dyslipidemic properties, they do exert lipid effects. The key difference compared to the early-generation PIs appears to be that pro-atherogenic shifts are offset by increases in anti-atherogenic HDL cholesterol. For instance, nevirapine is linked with increases in LDL cholesterol (to levels similar to the PI indinavir). Yet it is also associated with significant increases in HDL cholesterol of up to 50% from baseline, conferring a favourable decrease in the total-to-HDL cholesterol ratio, as well as a decline in triglycerides [60]. The first-line NNRTI, efavirenz, is associated with significant increases in triglycerides and lesser increases in HDL cholesterol, similar to the lipid effects of lopinavir [70]. Interestingly, there is no association between the NNRTIs and increased risk of myocardial infarction [67, 68], emphasising that the expectation of neither particular lipid profiles nor cardiovascular risk can be deduced simply based upon the drug class.

Amongst the NRTIs, stavudine and zidovudine are associated with dyslipidemia [71, 72]. This is in part due to their strong link with lipodystrophy. The currently preferred NRTI for first-line therapy, tenofovir, and the alternate agent, abacavir, both have significantly less lipid effects than their predecessors [73]. In studies of initial ART, tenofovir is associated with modest elevations of total (0.7 mmol/L), HDL (0.3 mmol/L), LDL cholesterol (0.2–0.4 mmol/L), and triglycerides (0.1–0.5 mmol/L), as well as a fall in the total-to-HDL cholesterol ratio (0.4–0.9). In comparison, abacavir shows a similar pattern of changes when used in initial treatment, although the elevations in total, LDL cholesterol and triglycerides tend to be significantly higher than with tenofovir, while

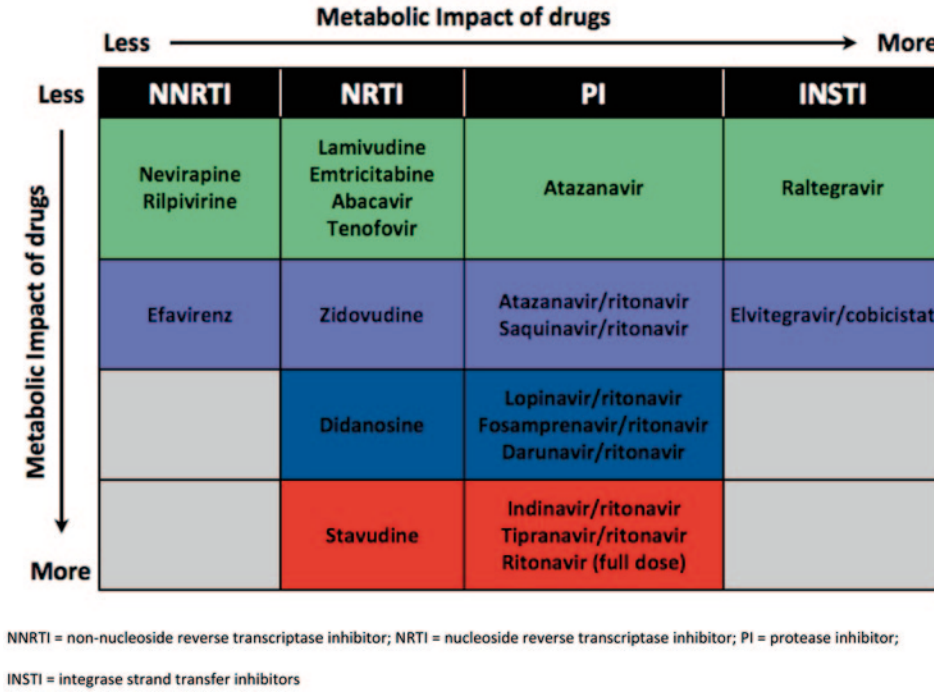

Fig. 9.4 Estimated lipid and metabolic changes associated with ART drugs and classes. Limited data from use of fusion blockers (enfuvirtide) and CCR5 entry antagonists (maraviroc) suggest these drugs to have little metabolic impact, but length of experience with these agents is limited. *ART* antiretroviral therapy, *NNRTI* nonnucleoside reverse transcriptase inhibitor, *NRTI* nucleoside reverse transcriptase inhibitor, *PI* protease inhibitor, *INSTI* integrase strand transfer inhibitors. (Adapted with permission from: Lundgren JD, Battegay M, Behrens G et al. European AIDS Clinical Society (EACS) on the prevention and management of metabolic diseases in HIV. HIV Med. 2008;9:72–81. Copyright ©2010 Wiley-Blackwell)

the fall in total-to-HDL cholesterol ratio is smaller but nonsignificant [74–76]. In treatment-experienced patients, switching to a tenofovir-based regimen, either from abacavir or a thymidine analogue, results in significantly greater falls in total and LDL cholesterol [77, 78].

A 2008 D:A:D Study analysis reported that abacavir was associated with a significantly increased risk of myocardial infarction that was not associated with dyslipidemia [79]. Rather, IL-6 and high-sensitivity C-reactive protein levels were found to be higher in patients receiving abacavir, fuelling speculation that it caused vascular inflammation, triggering coronary artery disease. Cessation of abacavir may revert risk to the pre-abacavir baseline [80]. More recent systematic analyses have failed to replicate the D:A:D Study results [81, 82], leaving this an area of uncertainty; abacavir remains an accepted alternate agent in current treatment guidelines.

There are insufficient data on emerging classes of ART agents (INSTIs, CCR5 entry antagonists) and the viral fusion blocker, enfuvirtide, to make definitive assessments of their long-term metabolic effects. Thus far, phase 2 –4 clinical trials indicate that these drugs have minimal effects upon lipid levels [83–87]. Results of in vitro studies indicate that like atazanavir, the INSTI raltegravir may be lipid neutral [66]. Cobicistat (GS-9350) is a recently approved, potent inhibitor of human cytochrome P450 (CYP) 3A isoforms intended as an alternate pharmacokinetic booster to low-dose ritonavir. It is not a PI, and devoid of anti-HIV activity. However, compared to low-dose ritonavir in prospective studies, there appears to be no significant difference in lipid effects [88].

The relative effects of individual ART agents on lipid metabolism are summarized in Fig. 9.4.

ART-Associated Dyslipidemia: The Risk and Clinical Relevance

Determining the metabolic effects of ART drugs remains of particular clinical relevance when deciding which agents to recommend as components of a preferred initial regimen. However, a number of considerations make assessing the clinical impact potentially confusing. Firstly, there are the number of available ART agents and the mandatory requirement for combination treatment to consider. As we have seen, there can also be considerable heterogeneity in the lipid effects of individual ART drugs, both between and within classes. Even amongst different drugs with similar lipid effects (for instance, lopinavir and efavirenz), it is particularly curious that the downstream impact on cardiovascular risk diverges significantly. The reasons for this are unknown, but it does serve to demonstrate that the dyslipidemia is ultimately but a component of and not the sole arbiter of the clinical endpoint.

Secondly, it is important to remember that many patients initiating combination ART already have varying degrees of dyslipidemia due to viremia and inflammation, while ART trials report metabolic changes relative to the point of ART initiation. In contrast, prospective data for lipids relative to preinfection are limited to one study; triglycerides and LDL cholesterol rose following ART, to levels, respectively, greater and similar to preseroconversion levels, with no significant change in HDL cholesterol [9]. But it is worth noting that these data were collected from patients initiating therapy before 1997, with now nonpreferred PIs. Part of the seemingly proatherogenic lipid changes seen post ART may in fact reflect a 'return to health', or at least the premorbid baseline, rather than being wholly due to metabolic derangement. Making an assessment of the net effect upon cardiovascular risk solely attributable to ART is therefore difficult. Pilot studies in HIV-negative healthy volunteers have demonstrated that individual drugs—mainly PIs—have effects upon fasting and postprandial lipid profiles even after very short periods [89, 90]. Typically, these are limited by the small number of participants and that the findings are based solely on monotherapy, not a full therapeutic regimen. While it could reasonably be expected that the impact of untreated infection on lipids will be negated because of progressively earlier ART initiation, this is a relatively recent shift in the management paradigm.

Finally, the dyslipidemia of ART is a mixed, heterogeneous entity; not all patients will develop disturbances to the same extent on the same regimen; many have only minimal disturbances. This suggests that genetic factors may play a role in the metabolic response to ART. Examples include polymorphisms of the *APOA5* and *APOC3* genes being associated with greater hypertriglyceridemia in PI-treated patients [91, 92]. Polymorphisms of the CYP enzymes can affect ART pharmacokinetics, leading to variable lipid effects with efavirenz and nevirapine [93, 94]. Study design is also an influence. In trials of darunavir, treatment-experienced participants developed greater lipid derangements compared to studies in treatment-naïve participants [95].

Management of ART-associated Dyslipidemia

Diagnosis and Evaluation

Dyslipidemia in HIV-infected patients is essentially a variable, mixed hyperlipidemia—isolated elevations of lipid fractions are uncommon and warrant other diagnostic consideration. Hence, there are no formal criteria for its diagnosis. It is therefore important that clinicians be familiar with the components of a patient's ART and their possible actions (and interactions). HIV-infected individuals are subject to the same vascular risk factors as the noninfected population, and these comorbidities should be assessed for, and treated, or excluded before attributing the dyslipidemia to the HIV or the ART (Table 9.2). D:A:D Study data indicate that the incidence of diabetes mellitus has increased with cumulative exposure to ART, and the European AIDS Clinical Society guidelines recommend that all HIV-infected persons be screened for diabetes mellitus at diagnosis, prior to initiating ART and annually thereafter [96].

Table 9.2 Secondary causes of dyslipidemia to consider in HIV-infected individuals

Condition	Relevant assessments
Lipodystrophy	Use of thymidine analogues (stavudine, zidovudine)
	Use of protease inhibitors
Smoking	Medical history
Type 2 diabetes mellitus	Fasting glucose regularly in all patients
	Consider oral glucose tolerance testing
	Glycoslyated hemoglobin (HbA1c)
Obesity	Body-mass index
	Waist-to-hip circumference ratio
Hypothyroidism	Thyroid function testing
Medications (nonantiretroviral)	Medications history:
	Thiazide diuretics
	β-blockers
	Corticosteroids
	Oral contraceptive pill
	Atypical antipsychotics (clozapine, olanzapine)
Hepatic or biliary disease	History of excessive alcohol intake
	Viral hepatitis serology
	Serum transaminases, bilirubin levels
Chronic renal disease	Proteinuria
	Elevated serum creatinine
Familial hyperlipiademias (rare)	Known family history
	Presence of corneal arcus, xanthelasmata, and xanthomata

HIV human immunodeficiency virus

Guidelines issued by the Infectious Diseases Society of America and the AIDS Clinical Trials Group recommend that the NCEP targets be used as the basis for evaluating and treating HIV-infected patients [97, 98]. This means that the goals of treatment are currently no different than for an HIV-negative individual.

These guidelines recommend that HIV-positive individuals undergo screening of their fasting lipid profile (total, HDL, LDL cholesterol and triglycerides) prior to initiating ART and within 3–6 months of starting or switching an established regimen. While the utility of postprandial lipid measurements have been assessed in pilot studies, there are insufficient data to recommend their use.

The NCEP targets aim to tailor the intensity of any lipid-lowering intervention(s) to a patient's overall risk. Factors assessed for risk stratification include cigarette smoking, systolic hypertension (≥140 mmHg), depressed HDL cholesterol (<1 mmol/L), family history of premature coronary heart disease, age (men >45 years, women >55 years), and the calculated risk score. Several algorithms are available to quantify risk, but the Framingham Risk Score (FRS), which provides a percentage risk at 10 years, is the most widely used. However, clinicians should note that although the FRS is a useful tool for conventional risk factors, it likely underestimates the risk in the HIV-infected population [99].

The only risk-scoring algorithm to cater specifically for HIV-infected persons is the D:A:D risk equation, which produces a 5-year risk score (rather than 10-year score, pending longer follow up of the cohort) [100]. The D:A:D algorithm factors in traditional risk factors (age, family history, gender, diabetes mellitus, blood pressure, total and HDL cholesterol, smoking) as well as current and prior exposure to particular ART drugs associated with increased risk of myocardial infarction (indinavir, lopinavir, abacavir), thereby countering a key shortcoming of the FRS. The D:A:D algorithm has the additional advantage of being derived from a much larger population than the FRS.

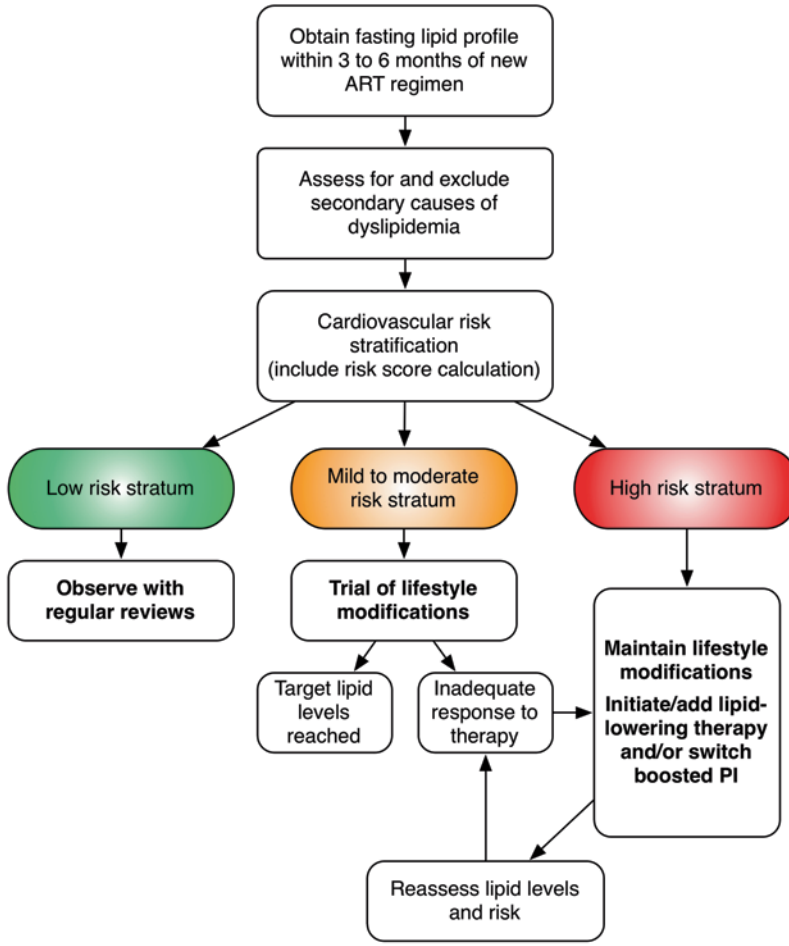

Fig. 9.5 Management approach for ART-associated dyslipidemia. *ART* antiretroviral therapy, *PI* protease inhibitor

Those with the highest risk, such as those with established heart disease, diabetes mellitus, or a calculated risk score >20% are targeted for the most aggressive therapy. Some HIV physicians may choose to intervene at a lower-risk score of 10–15%, taking the view that it may be an underestimate of the actual risk.

Management Approach

The overall management approach (including screening) is outlined in Fig. 9.5.

As with assessment, the management and goals of treatment are derived from the studies of HIV-negative cohorts. This is tacit acknowledgement that there are no randomized trial data on the benefits of lipid lowering in HIV-infected populations, although the D:A:D study reports that the cardiovascular event rate stabilized between 1999 and 2006 despite the greater risk of an aging population, perhaps due to more aggressive management of risk factors, including prescription of lipid-lowering drugs, and the use of newer ART drugs [101].

For all patients, treatment should begin with the same nonpharmacological strategies as those employed in HIV-negative patients—namely dietary modification and regular exercise prescription as lifestyle changes. For the former, review by a dietician may be of value. Attempts at smoking cessation are mandatory, as it is the modifiable factor with the single greatest impact on calculated risk scores.

The success of nonpharmacological therapies is dependent upon the patient's long-term adherence. For those patients in which this is achieved, these measures alone may prove sufficient; and they may be half as likely to require pharmacological intervention [102].

In those patients with established coronary heart disease or a risk equivalent, such as diabetes mellitus, concomitant use of pharmacotherapy is usually required. But for mild-to-moderate risk individuals, it is not clear how long lifestyle alterations should be trialled before proceeding to pharmacological therapies. The NCEP guidelines simply state that they should be 'given a thorough trial'—and how this should be interpreted for HIV-infected patients is not known in the absence of prospective data.

For HIV-infected patients on ART, the pharmacological options are:

- Switching to an alternate ART combination with a more favourable lipid profile, or
- Lipid-lowering drugs

Both methods have their respective advantages and disadvantages (Table 9.3). To date, there has only been one prospective study directly comparing these two strategies [103]. While statin and fibrate therapy appeared to have a modest advantage over switching to an NNRTI for lipids, the study was limited by using efavirenz as a switch option, and examining now nonpreferred PIs (indinavir, nelfinavir, saquinavir). As yet, there are no clinical data comparing these two approaches for the endpoint of risk reduction.

Switching ART

Switching assumes that the ART is the source of dyslipidemia. It should be considered firstly for those patients receiving a ritonavir-boosted PI. Switching to another PI has the advantage of maintaining the same drug class, thus preserving future non-PI treatment options—atazanavir can be used unboosted, and with its favourable lipid profile, may be a feasible option.

Switching must be done only after careful consideration, taking into account the pill burden, patient lifestyle, and possible effects on adherence, and the availability of switch options due to previous treatment failures and resistance mutations. Too broad a selection of patients as switch candidates may prove suboptimal, resulting in higher rates of virological failure, as was seen in the SWITCHMRK study [104]. In contrast, patients switched in the course of the SPIRAL study maintained suppression of HIV viral loads, while improving lipid levels [62]. Both studies used the INSTI raltegravir as the switch drug. Switching

Table 9.3 Comparison of switching and statin strategies for ART-associated dyslipidemia

Advantages	Disadvantages
Statin therapy	
Proven efficacy in reducing cardiovascular risk in the general population both as primary and secondary prevention	Potential side effects (hepatitis and myopathy/rhabdomyolysis
Well tolerated	Using a drug to treat another drug toxicity
Several statins (pravastatin, atorvastatin or rosuvastatin) can be used safely with PI therapy, although dose adjustment may be required	Increases pill burden and treatment costs indefinitely; both undesirable in a disease in which pill burden associates with ART efficacy
Possible anti-inflammatory effects independent of their lipid-lowering effects that may incur additional cardiovascular benefit	
Minimal risk of virological failure	
Switching ART	
Removes cause of the hypercholesterolemia	Boosted PI therapy may not be the cause of dyslipidemia in many patients
Less likely to increase pill burden or costs	Virological failure
	Drug toxicity from the new ART drug
	Reduces available ART choices

ART antiretroviral therapy, *PI* protease inhibitor

Table 9.4 Potential switch ART options for patients receiving a ritonavir-boosted protease inhibitor

Baseline regimen	Switch options (as per DHHS guidelines)	Notes
2 NRTIs + rPI	rPI → NNRTI	Efavirenz may lead to lipid changes similar to that of some boosted PIs
	rPI → INSTI	
	rPI → unboostedatazanavir	Unboostedatazanavir should not be used if NRTI backbone includes tenofovir[a]
NNRTI + rPI	rPI → 2 NRTIs	
INSTI + rPI	rPI → NNRTI	

ART antiretroviral therapy, *DHHS* Department of Health and Human Services (USA), *NRTI* nucleoside reverse transcriptase inhibitor, *NNRTI* nonnucleoside reverse transcriptase inhibitor, *INSTI* integrase strand transfer inhibitor, *rPI* ritonavir-boosted protease inhibitor

[a]Tenofovir decreases the bioavailability of unboosted atazanavir

of boosted PIs to NNRTIs has also demonstrated favourable changes in both total cholesterol and triglycerides with both nevirapine and rilpivirine [105, 106]. Even the switching of efavirenz to nevirapine has been associated with significant decreases in LDL cholesterol levels [107].

For suitable patients not receiving novel or salvage ART regimens, potential switch options are outlined in Table 9.4.

Statin Therapy

The 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, or statins, are the best known and most effective pharmacotherapy for treating hypercholesterolemia. They are the first choice for reducing elevated LDL cholesterol in HIV-negative individuals, thereby improving cardiovascular risk. Statins show similar efficacy in HIV-infected individuals, with a mean reduction in total and LDL cholesterol levels of up to 50% from baseline. The actual risk reduction, however, is unknown [108].

The mechanisms and additional benefits of statin therapy are described in greater detail elsewhere in this book. For HIV-infected patients receiving ART, however, the main issue is not a lack of efficacy, but the potential for drug-to-drug interactions with PIs (Table 9.5) [109]. Some of the statins are metabolized by the same CYP 3A4 isoform inhibited by PIs, leading to increased exposure to statins. This can predispose to a greater risk of statin-induced myopathy. In the case of simvastatin, the exposure can increase by as much as 3000% [110]. For this reason, simvastatin (and lovastatin) are contraindicated with PI use. Other commonly prescribed PIs are less affected by this interaction and may be used in conjunction with PIs, but still require dose reduction (atorvastatin, rosuvastatin).

In prospective studies of HIV-infected patients, rosuvastatin has proven to be the most effective statin, reducing LDL cholesterol significantly higher than the least-potent agent, pravastatin (37 vs. 20%) [111]. Both rosuvastatin and atorvastatin are significantly more likely to achieve NCEP target goals for total and LDL cholesterol than pravastatin, with similar toxicity rates of between 5% and 7% [112].

Other Hypolipidemic Agents

Other lipid-lowering options include fibrates, ezetimibe, omega-3 fatty acids (found in fish oil supplements), niacin, and bile–acid sequestering resins.

Fibrates (gemfibrozil, fenofibrate, bezafibrate) are agonists of peroxisome proliferator-activated receptor α, and are well tolerated in HIV-infected patients and have few interactions with ART. Their principal action is reduction of triglycerides. Their utility in HIV is limited, however, by the presence of mixed dyslipidemia; in hypertriglyceridemic states, relatively common in HIV, fibrates can lead to increases in LDL cholesterol of up to 0.5 mmol/L, potentially blunting their

Table 9.5 Statin–protease inhibitor interactions[a]

Statin	Affected PIs	Pharmacokinetic interaction	Prescribing recommendations
Atorvastatin	Tipranavir/r	Moderate inhibition of statin metabolism	Avoid
	Lopinavir/r		
	Darunavir/r	Mild inhibition of statin metabolism	Use with caution, use lowest dose necessary
	Fosamprenavir/r		
	Saquinavir/r		
Fluvastatin	Nelfinavir	Limited data available (possible induction of statin metabolism via non-CYP mechanism)	Alternative to rosuvastatin, pravastatin and atorvastatin
	Ritonavir (full-dose)		
Lovastatin	All PIs	Marked inhibition of statin metabolism	Avoid
Pravastatin	Darunavir/r	Induction of statin metabolism, with possible reduced statin effect	No special limitations to dose
	Lopinavir/r		
Rosuvastatin	Atazanavir	Inhibition of statin metabolism (via non-CYP mechanisms)	Limit to 10 mg daily (5 mg daily in Asians[b])
	Atazanavir/r		
	Lopinavir/r		
Simvastatin	All PIs	Marked inhibition of statin metabolism	Avoid

PI protease inhibitor, *r* with ritonavir-boosting, *CYP* cytochrome P450
[a]Drug interactions are regularly updated at the University of Liverpool's online database (http://www.hiv-druginteractions.org/)
[b]Includes individuals of SouthEast and South Asian ethnicity

reduction of cardiovascular risk [113]. Combined statin–fibrate therapy can be considered where the triglyceride level is >5.6 mmol/L (500 mg/dL), but should be generally cautioned against because of the potential for myopathy [98].

Eicosapentaenoic acid and docosahexaeneoic acid—the omega-3 fatty acids—significantly lower triglycerides in HIV-infected patients with dyslipidemia by up to 20% [114]. However, fish oil is also associated with a >20% rise in LDL cholesterol. It is therefore unclear if omega-3 fatty acids will have an overall benefit for cardiovascular risk.

Ezetimibe blocks cholesterol absorption in the gastrointestinal tract and is free of interactions via the CYP pathway. As monotherapy in HIV-uninfected persons, it can reduce circulating LDL cholesterol by >20% and by up to 50% in combination with statins [115]. As a relatively recent addition to lipid-lowering therapies, data in HIV-infected persons are limited, but it is associated with reductions in LDL cholesterol [116]. Risk reduction is yet to be demonstrated, but using a statin–ezetimibe combination may prove to be useful and preferable to increasing statin doses.

Niacin (nicotinic acid) is well-known for its side effects of flushing and headaches, and can be effective for reducing triglycerides and LDL cholesterol in HIV-infected patients [117]. Other common self-limiting side effects include cutaneous rash and pruritus. But importantly for cardiovascular risk, one study reported the nascent onset of insulin resistance and glucose intolerance. It should therefore be avoided as a first-line option. Hepatotoxicity is uncommon, but can be severe. Bile–acid sequestering resins such as cholestyramine are known to decrease the serum concentration of many orally administered drugs by limiting gastrointestinal absorption. Although no such interactions with any of the ART drug classes have been reported, no studies to assess this question have been performed, so clinicians should be mindful of the potential for interaction.

Conclusions

Dyslipidemia in HIV-infected patients is a product of viremia and ART; both contribute independently to an increase in cardiovascular risk. The

precise pathogenesis is unclear, being a highly complex portmanteau of direct and inflammatory effects, and no predominant mechanism has hitherto been identified.

As ART is initiated ever earlier, patients spend less time in a state of active viral replication following diagnosis, diminishing the relative contribution of viremia to dyslipidemia. ART is therefore ultimately of greater long-term clinical relevance on lipid levels. As the full metabolic profile of the newer ART classes remains to be determined, dyslipidemia will continue to be a commonly encountered problem by HIV physicians.

It is important to remember that HIV-infected patients have a greater likelihood of cardiovascular disease even after correcting for traditional risk factors. The management of HIV-associated dyslipidemia may therefore require a lower threshold for intervention, and should be aimed at the reduction of overall cardiovascular risk, not just restitution of a normal lipid profile. Statins remain the first choice for pharmacotherapy, but may require dose reduction. Switching of ART is a treatment option in carefully selected patients.

Further studies are required to assess the most efficacious intervention to reduce cardiovascular risk attributable to HIV-related dyslipidemia. Elucidating pathogenic mechanisms, particularly those of each class of ART drugs, may also identify future therapeutic targets.

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