Challenges of Statins in HIV Hyperlipidemia

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Abstract

As a result of access to potent antiretroviral therapy (ART), HIV-infected adults with virologic suppression are living longer, but unfortunately are at increased risk for developing comorbid conditions. It is postulated that this increased risk seen at all ages is partly due to the effects of viral-mediated chronic inflammation in addition to the traditional risk factors. One of the more common traditional risk factors, hyperlipidemia, may be worsened by ART. However, the benefits of ART greatly outweigh the possible negative effects of ART agents on lipid parameters. As the HIV-infected patient population ages, it is critical to control hyperlipidemia in ART-treated patients in order to reduce the risk for long-term cardiovascular complications. If hyperlipidemia cannot be managed through lifestyle modifications, clinical guidelines recommend the use of lipid-lowering medication, particularly HMG Co-A reductase inhibitors (statins), to reduce low-density lipoproteins-cholesterol. However, many ART agents inhibit or induce major metabolic pathways of statins, creating potentially serious drug–drug interactions. In this article, we present a review of the various challenges in managing hyperlipidemia with a focus on drug–drug interactions.

Keywords

Antiretroviral therapy, drug–drug interactions, HIV, statins

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As a result of advanced medication regimens, particularly protease inhibitors (PIs), the life expectancy of HIV-infected adults has risen considerably. As a result, non-AIDS comorbidities of chronic illness, such as cardiovascular disease (CVD), non-AIDS cancer, and liver disease, now account for the majority of deaths.[1–3] While traditional risk factors such as age, smoking, diabetes, and dyslipidemia influence the development of CVD in HIV-infected individuals, infection with HIV may be considered an independent risk factor for CVD.[1] The risk for CVD is elevated in HIV-infected individuals even when traditional risk factors are taken into account: a cohort study found a significant difference in rates of acute myocardial infarction between HIV and non-HIV infected adults, with a relative risk (RR) of 1.75 (95 % confidence interval [CI] 1.51–2.02; p<0.0001), adjusting for age, gender, race, hypertension, diabetes, and dyslipidemia.[3] Furthermore, traditional calculators of risk for CVD may significantly underestimate the likelihood of CV events in HIV-infected individuals,[4,5] By 2015, approximately 50 % of adults infected with HIV will be over the age of 50,[6] thus adding another risk factor for CVD.[7] CVD has become one of the most common causes of mortality in HIV-positive individuals in resource-rich countries.[8]

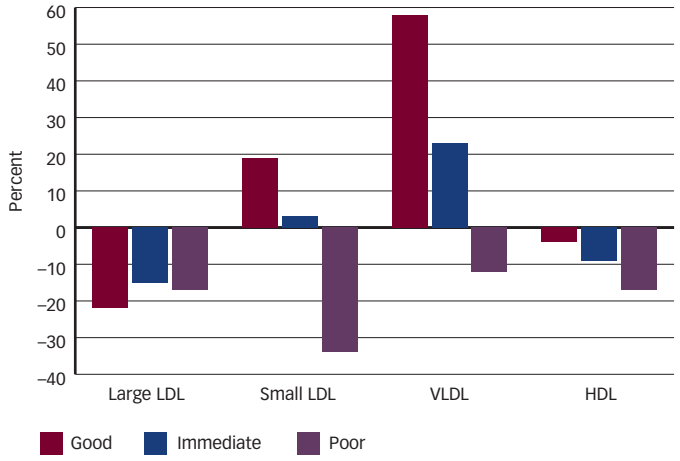
The risk for CVD in HIV is increased through numerous mechanisms that affect the atherosclerotic process. HIV infection itself causes a state of chronic inflammation that promotes atherosclerosis via immune activation.[9] Concomitant infections such as cytomegalovirus (CMV) may also promote atherosclerosis.[10,11] Furthermore, rates of smoking are high among HIV-infected individuals compared with the general population.[12] Other traditional risk factors such as insulin resistance,[13] hypertension,[14] and hyperlipidemia[15] are major contributors to the excess CVD risk observed in HIV-infected patients. There is evidence that traditional risk factors contribute to the formation of calcified plaque, while immune activation and other non-traditional risk factors are associated with non-calcified plaque, which may be more prone to rupture.[9] Clinical data suggest that the observed lipid abnormalities among people with HIV may be the result of the viral infection,[16] and its induced cytokine dysregulation,[9] antiretroviral therapy (ART),[17,18] or, most likely, both.[19] Hyperlipidemia is now a common clinical feature of ART-treated patients[20] and has therefore become an important therapeutic target to reduce CVD risk in these patients.[21]

Table 1: Mean Change in Blood Lipids for 50 Seroconverters Initiating HAART

Lipid Measurement	Level (mg/dL [95 % CI])	Mean Change in Lipid Level (mg/dL [95 % CI])				
	Pre-seroconversion (n=50)	Last Visit Before HAART (n=50)	First Visit After HAART (n=49)	Second Visit After HAART (n=49)	Third Visit After HAART (n=43)	Fourth Visit After HAART (n=438)
Total cholesterol	201 (179 to 222)	–30 (–52 to –9)	–4 (–17 to 25)	9 (–16 to 34)	20 (–1 to 41)	18 (–7 to 42)
HDL-C	51 (46 to 57)	–12 (–19 to –6)	–11 (–16 to –6)	–11 (–16 to –6)	–9 (–16 to –2)	–10 (–16 to –3)
LDL-C	122 (102 to143)	–22 (–45 to 1)	–6 (–29 to 17)	–1 (–24 to 22)	–1 (–25 to 22)	5 (–20 to 30)

Data taken from the Multicenter AIDS Cohort Study. This was a prospective study in which homosexual and bisexual men were enrolled, and from which 50 of 517 HIV seroconverters were drawn for the analysis herein, who later initiated highly active antiretroviral therapy (HAART), involving measurements of stored serum samples obtained between 1984 and 2002. CI = confidence interval; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol. Source: Riddler et al., 2010.[17]

Figure 1: Percent Difference in Median Lipoprotein Particle Concentrations Among HIV-infected HAART-treated Men in the Multicenter AIDS Cohort Study



Percent differences in the estimates of the four categories of lipoproteins for HIV-infected, highly active antiretroviral therapy (HAART)-treated men compared with HIV-seronegative men. Patients were classified by current clinical status: good (n=220), intermediate (n=160), or poor (n=16). HDL = high-density lipoprotein; LDL = low-density lipoprotein; VLDL = very low-density lipoprotein. Source: Riddler et al., 2008.[25]

Most clinical providers are reluctant to modify ART regimens with the purpose of controlling hyperlipidemia due to the potential risk for virologic failure or drug intolerance. Consequently, the use of lipid-modifying therapies that can be used in combination with ART is preferred. While statin therapy has been associated with reduced mortality in HIV-infected patients in one clinical cohort,[22] no randomized clinical trials have been conducted to confirm these findings. Thus some have raised concerns regarding toxicity secondary to drug interactions between statins and ART. This article will discuss the challenges of statin therapy in HIV-infected patients on ART with hyperlipidemia.

Hyperlipidemia in HIV-infected Individuals

HIV infection has been associated with abnormalities in lipid profiles even in the absence of ART, increasing the risk for CVD.[1,23] The natural history of HIV infection is associated with a characteristic evolving pattern of lipid parameters. There is an initial decrease in high-density lipoprotein cholesterol (HDL-C) followed by a decrease in low-density lipoprotein cholesterol (LDL-C). In more advanced disease, there is an increase in triglycerides (TG) and in very LDL cholesterol (VLDL-C).[24] Initiation of ART causes lipid levels to return to baseline levels and subsequently increase above pre-seroconversion levels, except for HDL-C, which remains persistently low (see *Table 1*).[15,25] Decreased HDL-C levels resulting from altered HDL metabolism is a typical feature of HIV-infection even after ART is initiated.[26,27] The magnitude of these changes varies widely among patients depending on individual characteristics such as ethnicity/race, or mitochondrial haplotypes.[28]

Antiretroviral Therapy and Hyperlipidemia

Conventional ART consists of a combination of three medications drawn from multiple drug classes: nucleoside reverse transcriptase (RT) inhibitors (NRTIs—nucleoside [or nucleotide] analogs, which inhibit the viral RT enzyme); non-NRTI inhibitors (NNRTIs), which also inhibit the RT enzyme; PIs, which act on the HIV protease; integrase inhibitors, which block the action of the viral enzyme integrase; and CCR5 inhibitors, which block the CCR5 co-receptor on CD4+ T-cells. The use of ART produces negative changes on lipid parameters including total cholesterol (TC), LDL-C, and TG.[17] HIV itself also contributes to these detrimental effects on lipids, most notably via a persistent decrease in HDL-C. The typical lipid pattern is one of low HDL-C levels, excess TC, and increased levels of small LDL particles (see *Figure 1*).[18,29] This creates deleterious alterations in the lipid profiles of HIV patients that require attention and management.

In HIV-infected individuals treated with ART agents, differences in serum lipids have been observed between and within drug classes.[30] PIs generally increase levels of LDL-C and TG (see *Table 2*).[30] Ritonavir inhibits the cytochrome P450 3A4 isoenzyme and is co-administered with PIs to boost their plasma concentrations, resulting in improved efficacy and reduced pill burden.[31] Ritonavir-boosted PIs generally result in similar lipid profiles in HIV-infected patient cohorts. However, tipranavir, which must be boosted with a higher ritonavir dose than other PIs, is associated with substantial elevations in TC and TG.[32] A review of clinical trials of first-line ARTs with available lipids data found that fosamprenavir/ritonavir and lopinavir/ritonavir in combination with NRTIs other than tenofovir caused the highest lipid elevations at 48 weeks.[33] Atazanavir and darunavir cause modest increases in lipids compared with other PIs.[34–36] A recent study comparing ritonavir with cobicistat, when used as a booster of atazanavir, plus an NRTI, showed no significant differences in lipid levels at 48 weeks.[37]

Non-NRTI inhibitors increase lipids only modestly (see *Table 3*). The addition of the NNRTI efavirenz to a NRTI backbone results in small increases in all lipids including HDL-C.[38] A head-to-head comparison of nevirapine and efavirenz demonstrated that nevirapine had the most favorable effects on lipid profile.[39] The addition of etravirine to a PI+NRTI regimen does not result in additional lipid elevations.[40] Rilpivirine appears to have even more modest effects on lipids compared with efavirenz.[41,42]

Table 2: Lipid Changes Associated with Protease Inhibitor Use

Protease Inhibitor	Lipids			
	Total Cholesterol	HDL-C	LDL-C	Triglycerides
Atazanavir	↔	↔	↔ by 16 %	↓ by 12 %
Atazanavir+ritonavir and Atazanavir/cobicistat	↔	↔	↑	↑
Darunavir+ritonavir	↔	↔	↑	↑
Fosamprenavir+ritonavir	↑↑	↔	↑	↑↑
Lopinavir/ritonavir (co-formulated)	↑↑ (additional increase over ritonavir alone)	↔ (no change)	↑ (no additional increase over ritonavir alone)	↑↑ (no additional increase over ritonavir alone)
Nelfinavir	↑	↔	↑↑	↑
Ritonavir (low dose for boosting)	↑ by 10 %	↓ by 5 %	↑ by 16 %	↑↑ by 26 %
Saquinavir+ ritonavir	↑↑	↔	↑	↑
Tipranavir+ritonavir	↑↑	Not known	Not known	↑↑↑

↑ = some increase; ↑↑ = moderate increase; ↑↑↑ = large increase; ↓ = some decrease; ↔ = no significant change. HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol. Modified from Malvestutto and Aberg, 2010.[1]

Table 3: Lipid Changes Associated with Non-nucleoside Reverse Transcriptase Inhibitor Use

NNRTI	Lipids			
	Total Cholesterol	HDL-C	LDL-C	Triglycerides
Efavirenz	↑	↑	↑	↑
Etravirine	↔	↔	↔	↔
Nevirapine	↑	↑↑ (larger increase than with efavirenz)	↑	↑ (lower increase than with efavirenz)
Rilipivirine	↑ lower increase than with efavirenz	Not known	↑ Lower increase than with efavirenz	↑ Lower increase than with efavirenz

↑ = some increase; ↑↑ = moderate increase; ↑↑↑ = large increase; ↓ = some decrease; ↔ = no significant change. HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; NNTI = non-nucleoside reverse transcriptase inhibitor. Modified from Malvestutto and Aberg, 2010.[1]

With the exception of stavudine, which causes significant lipid elevations, NRTIs generally produce smaller lipid increases compared with PIs or NNRTIs. Tenofovir-containing regimens were associated with smaller increases in TC compared with other NRTIs.[33] Some studies suggest that tenofovir may have independent lipid-lowering properties.[43,44]

Other ART agents such as integrase inhibitors (e.g., raltegravir, dolutegravir, and elvitegravir) and the fusion inhibitors enfuvirtide have not been associated with significant lipid changes.[45–48] The CCR5 inhibitor maraviroc does not increase lipids and may be associated with lipid reductions in dyslipidemic patients.[49] A study comparing the co-formulations elvitegravir/cobicistat/tenofovir/emtricitabine with efavirenz/tenofovir/emtricitibine found lower lipid increases in the elvitegravir fixed-dose combination arm at 48 weeks.[50]

Management of Hyperlipidemia in HIV-infected Individuals

Clinical Guidelines

The HIV Medical Association (HIVMA) of the Infectious Disease Society of America (IDSA) have recently updated their HIV guidelines to reflect the increased life expectancy of patients with HIV, with a focus on preventative care, including obtaining a fasting lipid profile on initiation of care.[51] The guidelines support the management of dyslipidemia in HIV-infected patients according to the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP III) guidelines and those of the American Heart Association (AHA). More recently, the 2013 American College of Cardiology (ACC)/AHA guideline for the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk has been published. The latter emphasizes the need for physicians to discuss the risk for statin-associated side effects related to potential drug–drug interactions (DDIs), and calculates both the 10-year and lifetime risk for CVD. In young patients, the 10-year risk can be low, but the lifetime risk can be high. This can be of importance in deciding which HIV-infected patients should be treated with statins.[52] The ACC/AHA guidelines recommend statin therapy for individuals at increased CVD risk who are most likely to experience a net benefit in terms of the potential to reduce CVD events and the potential for adverse effects. They also suggest the use of statins to prevent both non-fatal and fatal CVD events.[52] The implications of these new guidelines for those with HIV infection are unclear at this time.

Both the NCEP ATP III and the ACC/AHA guidelines recommend initiation of statin therapy for elevated non-HDL-C when TG levels are between 200 and 500 mg/dL. If the TG level is higher than 500 mg/dL, initial treatment with a fibrate is recommended.[53] The International Atherosclerosis Society has also recently published their recommendations of dyslipidemia. These emphasize the importance of non-HDL cholesterol (non-HDL-C) as the major atherogenic lipoprotein and estimate lifetime risks for CVD.[54]

To date, guidelines that recommend lipid-lowering therapies for use in HIV-infected individuals defer to the recommendations for the general population as there are inadequate large randomized controlled trials with cardiac outcomes among persons with HIV infection to recommend specific lipid targets.[7] According to the IDSA guidelines, HIV-infected individuals with two or more risk factors should be evaluated for 10-year risk for CHD using the Framingham risk calculator.[55] The European AIDS Clinical Society (EACS) guidelines, on the other hand, recommend CHD risk assessment in all HIV-infected patients.[56] It must also be borne in mind that the Framingham risk calculator is likely to underestimate the true risk for CVD in HIV-infected patients and that the Framingham risk calculator was only validated for use in persons with two or more risk factors (excluding LDL-C) to determine the lipid target goal.[4,5] Current research is investigating more appropriate prediction models for this patient group.[4]

According to the HIVMA/IIDSA guidelines, treatment of HIV-associated dyslipidemia should be an integral part of a general attempt to improve cardiovascular health, with advice on lifestyle modification, management of hypertension and diabetes where present, and the use of anti-platelet agents where warranted.

Antiretroviral Therapy Interruption

Interruption of ART has been considered as an option for correcting lipid abnormality; however, this strategy was discredited as unreasonable after a clinical study among HIV-infected subjects found an increased risk for cardiovascular events observed in patients undergoing intermittent ART compared with those on continuous ART.[57] It is believed that the deleterious effect of circulating HIV greatly outweighs the potential benefit of reduced LDL-C and TC in untreated HIV infection.

Antiretroviral Therapy Modification

A strategy of switching the ART regimen to one with fewer negative effects on lipid metabolism has demonstrated benefits on lipid parameters.[49,50,58–61] In some cases, however, this strategy may not result in the desired lipid level targets. Patients with pre-existing dyslipidemia prior to initiation of ART that worsens while on ART are unlikely to achieve a normalization of lipids without the use of lipid-lowering drugs.[53] In addition, switching ART carries a risk for virologic failure, particularly in patients with an underlying drug-resistant virus.[62] Management of dyslipidemia through ART modification should be reserved only for patients with significant lipid abnormalities on the current ART regimen who cannot achieve lipid control with available lipid-lowering pharmacotherapy or do not tolerate lipid-lowering drugs.

Use of Lipid-lowering Therapy

Both the HIVMA/IDSA and EACS guidelines recommend diet, exercise, and smoking cessation as the initial lipid control strategy. However, if lifestyle changes do not result in improved lipid profiles, the first-line therapy for the management of increased LDL-C includes the use of lipid-lowering medications, particularly statins. Patient selection for statin therapy is important in HIV patients. The guidelines urge caution when prescribing statins with PIs because of the potential for DDIs.[51] Special consideration should be given to the management of dyslipidemia in HIV-infected patients with pre-existing dyslipidemia prior to initiation of ART. Attention should be paid to comorbidities, such as myopathy, co-infections such as hepatitis C, predicted effects of specific ART drugs on lipids, and possible drug interactions between ART agents and lipid-lowering medications.

Drug Interactions Between Antiretrovirals and Statins

HMG-CoA reductase inhibitors, also known as statins, are widely used for the treatment of hyperlipidemia. Seven statins are approved by the US Food and Drug Administration (FDA): atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin. Therapeutically equivalent doses have been approximated, based on the fact that fluvastatin 40 mg, lovastatin 10–20 mg, pravastatin 20–40 mg, and simvastatin 10 mg reduced LDL-C by 20–30 %, and a 30-40 % reduction was achieved by atorvastatin 10 mg, rosuvastatin 5 mg, pitavastatin 2 mg, fluvastatin 80 mg, lovastatin 40/80 mg, and simvastatin 20 mg.[63–65] Statins are rapidly absorbed, reaching a peak concentration within 4 hours and most exhibit low bioavailability (5–14 % for simvastatin, lovastatin, atorvastatin, 20–30 % for fluvastatin, pravastatin, rosuvastatin, and 60 % for pitavastatin).[66] Elimination half-lives of the statins range from less than 5 hours for fluvastatin, lovastatin, pravastatin, and simvastatin to 11 hours for pitavastatin and 20 to 30 hours for atorvastatin and rosuvastatin. Lovastatin, simvastatin, and atorvastatin are extensively metabolized by the cytochrome P450 (CYP) isoenzyme CYP3A4, while rosuvastatin, pitavastatin, and pravastatin undergo minimal metabolism via CYP isoenzymes and are eliminated primarily unchanged in bile and urine.[66]

The selection of lipid-lowering medications that are potent, effective, and safe to administer while taking into account interactions with ART agents and other drugs, such as antifungals, presents an important challenge for clinical providers treating HIV-infected patients. Data on the safety of statin use comes primarily from non-HIV-infected populations. In addition, the safety of statins has not been conclusively evaluated in patients co-infected with HIV and hepatitis C viruses, where potential statin hepatotoxicity is a safety concern. A small study suggested that statin use was safe in this patient population but recommended further evaluation with a prospective controlled trial to definitively answer this safety concern.[67]

Many ARTs inhibit or induce major metabolic pathways of statins, creating potentially serious DDIs (see *Table 4*). Failure to recognize these DDIs can result in toxicity due to excessive plasma statin concentrations, leading to myopathy or rhabdomyolysis, or in the inability to reach lipid control targets due to sub-therapeutic statin levels in blood.

Drug–Drug Interactions of Protease inhibitors Co-administered with Statins

PIs inhibit CYP3A4: ritonavir is the most potent CYP3A4 inhibitor, which has led to its use as a pharmacologic booster for other PIs. Cobicistat, another pharmacokinetic booster that is devoid of anti-HIV activity, is believed to be more selective than ritonavir as it does not induce non-CYP3A4 drug-metabolizing pathways.[68] Several statins also depend on CYP3A4 for metabolic clearance. The co-administration of PIs is therefore a cause for concern in terms of side effects and DDIs, and can result in elevated plasma levels of statins.[69] In 2012, the FDA released a safety announcement, recommending dose restrictions on rosuvastatin and atorvastatin when combining statins with PIs.[9]

Simvastatin and Lovastatin

The most serious DDI between statins and PIs involve simvastatin and lovastatin. The simvastatin area under the curve (AUC) increases sixfold when co-administered with the unboosted PI nelfinavir and 30-fold when co-administered with ritonavir-boosted saquinavir.[69] Cases of rhabdomyolysis have been described with the concomitant use of simvastatin and boosted indinavir[69] and also with unboosted atazanavir when another CYP3A4 inhibitor (amiodarone) was inadvertently administered.[70] As a result of these data, lovastatin, which has similar pharmacokinetic properties to simvastatin, is contraindicated for patients taking PIs.[9] This contraindication can be extended to patients taking other CYP3A inhibitors, including any ARV combined with cobicistat, such as the fixed-dose combination elvitegravir/cobicistat/tenofovir/emtricitabine.

Atorvastatin

The co-administration of atorvastatin and PIs results in increases in its AUC. A fourfold increase in atorvastatin AUC has been reported with ritonavir-

Table 4: Interactions between Antiretroviral Therapy and Statins

Statins	Antiretroviral Therapy Drug Class	
	Protease Inhibitor	Non-nulceoside Reverse Transcriptase Inhibitor
Atorvastatin	Atorvastatin AUC ↑↑. Use lowest starting atorvastatin and titrate carefully. Do not exceed 20 mg atorvastatin daily with DRV/r, FPV/r, SQV/r. Atorvastatin AUC ↑↑ 488 % with LPV/r. Atorvastatin AUC ↑↑↑ 836 % with TPV/r and should not be co-administered	Atorvastatin AUC ↓ 43 % with efavirenz. Atorvastatin AUC ↔ but C_{max} ↓ 37 % with etravirine. No data for nevirapine. May need higher atorvastatin starting dose with efavirenz and etravirine. No dose adjustments for rilpivirine
Fluvastatin	Use not recommended with nelfinavir	Fluvastatin AUC ↑ with etravirine may require higher fluvastatin starting dose with etravirine
Lovastatin	Contraindicated with all PIs (lovastatin AUC ↑↑↑)	Lovastatin AUC ↓↓ with efavirenz. May require higher lovastatin starting dose. No dose adjustment needed for rilpivirine
Pitavastatin	Modest ↑ AUC with ATV/r (31 %) and modest ↓ AUC with DRV/r (20–26 %) and LPV/r (20 %). No dose adjustment required	↔ with efavirenz and no dose adjustment needed. No dose adjustment needed for rilpivirine
Pravastatin	↓ AUC of pravastatin except with DRV/r and LPV/r which ↑ AUC of pravastatin by 81 % and 33 %, respectively Use lowest possible pravastatin starting dose	Pravastatin AUC ↓ 40 % with efavirenz but ↔ with etravirine May need higher pravastatin starting dose
Rosuvastatin	Rosuvastatin AUC ↑↑ 213 % and C_{max} ↑↑↑ 600 % with LPV/r Rosuvastatin AUC ↑↑ 108 % and C_{max} ↑↑↑ 366 % with ATV/r Rosuvastatin AUC ↑ 48 % and C_{max} ↑ 139 % with DRV/r Rosuvastatin AUC ↔ and C_{max} ↑ 123 % with TPV/r Rosuvastatin AUC ↔ with FPV/r Titrate rosuvastatin dose carefully with LPV/r or ATV/r and do not exceed 10 mg daily. With DRV/r, use lowest necessary rosuvastatin dose	Allowed. ↔. No reported interactions
Simvastatin	Contraindicated (simvastatin AUC ↑↑↑)	Simvastatin AUC ↓ 58 % with efavirenz and ↓ with etravirine. No data for nevirapine. May require higher simvastatin starting dose

↑ = some increase; ↑↑ = moderate increase; ↑↑↑ = large increase; ↓ = some decrease; ↔ = no significant change. ATV/r = atazanavir/ritonavir; AUC = area under the concentration-time curve; C_{max} = maximum drug concentration; DRV/r=darunavir/ritonavir; FPV/r = fosamprenavir/ritonavir; LPV/r = lopinavir/ritonavir; SQV/r = saquinavir/ritonavir. Modified from Malvestutto and Aberg, 2010.[1]

boosted saquinavir.[66] Tipranavir co-administration results in a 4.4-fold increase in the AUC of atorvastatin.[71] Fosamprenavir induces an increase of atorvastatin AUC of 130–153 %.[72] Co-administration of atorvastatin 10 mg with twice-daily darunavir 300 mg boosted with ritonavir 100 mg resulted in a 3.4-fold increase in the atorvastatin AUC.[73] Therefore, the FDA has recommended avoiding the use of atorvastatin with tipranavir, using atorvastatin with caution at the lowest possible dose with lopinavir/ritonavir, and not exceeding an atorvastatin dose of 20 mg when combined with saquinavir, fosamprenavir, or darunavir.[9]

Rosuvastatin

Rosuvastatin is not a substrate, inhibitor, or inducer of CYP3A4. However, it is a substrate of organic anion-transporting polypeptide 1B1 (OATP1B1) and breast cancer-resistance protein (BCRP). PI-induced inhibition of OATP1B1 can cause a decrease in hepatocyte uptake of rosuvastatin while inhibition of BCRP decreases hepatobiliary excretion and increases rosuvastatin absorption, leading to possible DDIs when rosuvastatin is co-administered with PIs.[71] When co-administered with lopinavir, the rosuvastatin AUC increases only slightly but the maximum concentration of drug in serum (maximum drug concentration [C_{max}]) increases 3.6-fold.[74] When co-administered with atazanavir, increases in the AUC and C_{max} of rosuvastatin of 213 % and 600 %, respectively, have been reported. Co-administration of rosuvastatin with ritonavir-boosted darunavir increases the rosuvastatin AUC by 48 %.[74] The concomitant use of rosuvastatin and tipranavir leads to a modest increase in rosuvastatin AUC of 37 % but a significant increase in rosuvasatin C_{max} of 223 %.[71] Therefore, this combination should be avoided or used cautiously starting with the lowest dose possible of rosuvastatin of 5 mg daily.[71] The FDA recommends a maximum rosuvastatin dose of 10 mg daily when co-administered with boosted atazanavir or lopinavir.[9]

Fluvastatin

There is a lack of data on DDIs between ART drugs and fluvastatin. Since this statin is metabolized primarily via CYP2C9, DDIs are unlikely with most PIs. Ritonavir is a known CYP2C9 inducer and could, theoretically, cause a reduction in the fluvastatin AUC when co-administered.[66] Due to this lack of empirical data, it would seem more prudent to use other statins with better-studied pharmacokinetics when co-administered with ART agents.

Pravastatin

Pravastatin is metabolized mostly by glucuronidation and only minimally by CYP3A4,[69] and can therefore be used safely with most PIs.[51] However, when co-administered with nelfinavir[75] or saquinavir[66] the pravastatin AUC is reduced by about 50 %, thus limiting its potential lipid lowering effectiveness. On the other hand, pravastatin AUC is practically unaffected by co-administration with lopinavir/ritonavir and is increased non-significantly by 81 % in the presence of boosted darunavir. Of note, subjects with low functioning haplotype forms of the *SLCO1B1* drug transporter gene had significantly increased pravastatin AUC compared with those with wild-type forms—an effect that was maintained in the presence of boosted darunavir.[76] It is recommended that the lowest-possible dose of pravastatin, atorvastatin, or rosuvastatin be used in patients taking darunavir.[73]

Pitavastatin

Like pravastatin, pitavastatin is metabolized mostly by glucuronidation and minimally by CYP.[77] As a result, pitavastatin does not interact with CYP34A inhibitors and therefore undergoes few DDIs compared with other statins.[78,79] In healthy volunteers, pitavastatin in combination with lopinavir/ritonavir, darunavir/ritonavir, and atazanavir has shown modest DDIs, requiring no

dose adjustment. The concomitant use of pitavastatin 4 mg daily or 2 mg daily with darunavir/ritonavir 800 mg/100 mg once daily resulted in modest reductions in pitavastatin AUC of about 20 %[80] and 11 %,[81] respectively, without significant adverse effects. Co-administration of lopinavir/ritonavir 400 mg/100 mg twice daily with pitavastatin 4 mg daily also resulted in a modest reduction in pitavastatin AUC of 24 %.[82]

Drug–Drug Interactions of Non-nucleoside Reverse Transcriptase Inhibitors with Statins

Some NNRTIs can also interact with statins. Nevirapine is a selective inducer of CYP3A4 and efavirenz is a mixed inducer/inhibitor of CYP3A4. Owing to its status as a preferred first-line agent, efavirenz is one of the most widely prescribed ART drugs. Efavirenz decreases the simvastatin AUC by 58 % and atorvastatin AUC by 43 %. Efavirenz also reduces the pravastatin AUC by 40 % even though pravastatin is only minimally metabolized by CYP3A4. Since pravastatin is substrate of the organic anion transporters OTAP-C and MRP-2, efavirenz may be an inducer of these transporters, resulting in increased hepatic elimination of pravastatin.[83] Therefore, higher doses of these statins may be required for use with efavirenz. No dose adjustment is required for pitavastatin when co-administered with efavirenz. Pharmacokinetic data showed no significant changes in pitavastatin AUC and C_{max} in the presence of efavirenz.[81]

Data on statin DDIs with second-generation NNRTIs (etravirine and rilpivirine) are limited. Etravirine is metabolized via several CYP enzymes including CYP3A4, CYPC2C9, and CYP2C19. It is an inducer of CYP3A and inhibits CYP2C9 and CYP2C19. When etravirine was co-administered with atorvastatin 40 mg, the atorvastatin AUC was unchanged but the C_{max} was reduced by 37 %.[84] Since lovastatin and simvastatin are CYP3A4 substrates, co-administration with etravirine may result in lower concentrations of these statins and may require higher doses. Fluvastatin and pitavastatin are metabolized at least in part by CYP2C9 and co-administration with etravirine may result in increased AUC of these statins although actual pharmacokinetic data are lacking.[84] No dose adjustments are required when rilpivirine is co-administered with simvastatin, lovastatin, atorvastatin, rosuvastatin, pravastatin, or pitavastatin.[85]

Drug–Drug Interactions between Other Antiretrovirals and Statins

The integrase inhibitor raltegravir is metabolized through uridine diphosphate-glucuronosyltransferase 1A1 (UGT1A1) glucuronidation and does not inhibit or induce CYP450 isoenzymes such as CYP3A4.[86] Therefore, it is not expected to interact significantly with statins. A study has confirmed the lack of significant interaction between pravastatin and raltegravir.[87] Another integrase inhibitor, elvitegravir, is co-formulated with cobicistat, which is an inhibitor of CYP3A and CYP2D6, and also inhibits numerous transporter proteins including (P-gp), BCRP, OATP1B1, and OATP1B3. Thus, co-administration of this fixed-dose combination with statins that are primarily metabolized by CYP3A, or are substrates of P-gp, BCRP, OATP1B1, or OATP1B3, may result in increased plasma concentrations of such drugs. Elvitegravir is a modest inducer of CYP2C9 and may decrease the plasma concentrations of CYP2C9 substrates, such as pravastatin. Co-administration of the four drug fixed-dose combinations (containing elvitegravir, cobicistat, tenofovir, and emtricitabine) with rosuvastatin 10 mg resulted in an increase of the rosuvastatin AUC and C_{max} by 89 % and 38 %, respectively.[88] The manufacturer's prescribing information recommends that atorvastatin should be initiated at the lowest starting dose and titrated carefully while monitoring for safety. Simvastatin and lovastatin are contraindicated when using this fixed-dose combination. Dolutegravir is primarily metabolized by UDP-glucuronosyltransferase 1-1 (UGT1A1).[89] It is also not considered an inducer or inhibitor of CYP450 isoenzymes and is not expected to have significant DDIs with statins although data have not been published. The CCR5 receptor inhibitor, maraviroc, is a CYP3A substrate but it does not seem to inhibit or induce CYP450 isoenzymes including CYP3A4.[90] Therefore, it is not expected to have significant DDIs with statins.

In summary, DDIs should be considered before prescribing statins in HIV-infected individuals. Current HIVMA/IDSA guidelines support the use of pitavastatin and pravastatin due to their low potential for DDIs compared with other statins.[51]

Effectiveness of Statins in Managing Dyslipidemia in HIV-infected Patients

In general, lipid-lowering drugs, including statins, produce similar or somewhat reduced lipid declines in HIV-infected patients compared with those achieved in the general population. Data from a retrospective cohort study (n=829) showed that statin use was associated with reductions in LDL-C of 25.6 % for HIV-infected patients versus 28.3 % for HIV-uninfected patients (p=0.01).[91] Lipid-lowering therapies other than statins have shown similar lipid reductions for HIV-infected and uninfected cohorts.[92,93] However, HIV-infected patients are more likely to present with mixed lipid derangements (i.e. increased TG and LDL-C and decreased HDL-C) at different stages of their HIV disease, requiring the use of multiple pharmacologic agents compared with the general population.[53] Therefore, lipid-lowering study results should be interpreted with caution.

Although clinical trial experience in the HIV-infected population is limited for some lipid-lowering agents, extensive study data is available for statins in this population. Due to its favorable safety profile and limited interactions with PIs and NNRTIs, most early statin interventional studies used pravastatin. An open-label, randomized trial of bezafibrate, gemfibrozil, fenofibrate, pravastatin, and fluvastatin for treatment of PI-associated dyslipidemia showed that fibrate and statin use reduced TG and LDL-C to a similar extent. HDL-C was increased by 20 % in those who used fibrates and 24 % in those using statins, but differences were not statistically significant. A randomized trial comparing the use of pravastatin 40 mg/day to fenofibrate 200 mg/day for the treatment of mixed dyslipidemia in 174 HIV-infected patients showed that NCEP targets were achieved at week 12 for LDL-C, HDL-C, and TG in 9 %, 66 %, and 48 % of patients on fenofibrate compared with 36 %, 49 %, and 18 % of those on pravastatin, respectively.[92] Markers of inflammation and platelet activation including plasminogen-activator inhibitor type 1 (PAI-1), P-selectin, and high-sensitivity C-reactive protein (hs-CRP) did not change significantly.[94]

Data from a retrospective cohort at two large HIV clinics found that the most commonly prescribed statins were atorvastatin and pravastatin, followed by rosuvastatin. One year after starting statin therapy, patients taking atorvastatin or rosuvastatin had significantly greater decreases in TC, LDL-C, and non-HDL-C than patients on pravastatin. The likelihood of reaching non-HDL-C NCEP targets was higher for rosuvastatin compared with pravastatin (odds ratio [OR]=2.3; p=0.45) but not with atorvastatin (OR=1.5; p=0.1).[95]

Few head-to-head prospective clinical trials have compared the efficacy of different statins in HIV-infected patients. In an open-label, randomized, prospective study, 94 HIV-infected patients with hypercholesterolemia were randomized to rosuvastatin 10 mg/day, pravastatin 20 mg/day, or atorvastatin 10 mg/day. The mean decrease in TC was significantly higher with rosuvastatin (25.2 %) than with atorvastatin (19.8 %; p=0.03) and pravastatin (17.6 %; p=0.01) at 12 months. Similarly, the reduction in LDL-C was greater with rosuvastatin (26.3 %) than with atorvastatin (20.3 %; p=0.02) and pravastatin (18.1 %; p=0.04) at 12 months. Changes in TG and mean HDL were similar for all statins.[96] In a randomized, double-blind multicenter open-label study, 42 HIV-infected patients with dyslipidemia were randomized to receive rosuvastatin 10 mg/day or pravastatin 40 mg/day. After 45 days, rosuvastatin reduced LDL-C by 37 % versus 19 % for pravastatin (p<0.001). Levels of TG were reduced by 19 % versus 7 % for rosuvastatin and pravastatin, respectively (p=0.035). Increases in HDL-C did not differ significantly between the two statins.[97] A recent study demonstrated that pitavastatin 4 mg was also superior to pravastatin 40 mg in LDL-C reduction in HIV-infected patients with dyslipidemia. At 12 weeks, patients on pitavastatin achieved a decrease in LDL-C of 49.4 mg/dL (31 %) versus 33.6 mg/dL (21 %) (p<0.001) for those on pravastatin.[98]

Diabetes and Statin Use

Several recent general population studies, including two meta-analyses[99,100] and an analysis from the Women's Health Initiative study,[101] showed an association between statin use and new-onset diabetes. However, the absolute risk appears to be low and is likely offset by the benefit in reduction of CHD resulting from statin use.[99,102] This finding is of concern as HIV infection and ART are associated with increased insulin resistance and diabetes,[103] but confirmatory studies are needed in the HIV-infected population. However, the benefits of lipid control with the use of statins are still likely to outweigh the possible increase in risk for diabetes onset. Addressing other risk factors for diabetes, such as obesity through lifestyle modification and regular glucose monitoring, is warranted.

Additional Benefits of Statins in HIV

Statins are known to have pleiotropic beneficial effects that are independent of their lipid-lowering properties. Their anti-inflammatory and non-lipid-associated cardioprotective properties have been demonstrated in non-HIV infected populations. Statin therapy is associated with reductions in CRP in the general population.[104,105] However, most studies exploring statins in the HIV-infected population have failed to note such a decrease, which may be due to the lack of sensitivity and specificity of the assay in those with underlying inflammation and immune activation.[53] *In vitro* studies suggest that statin use is also associated with improvements in vascular senescence markers in HIV-infected patients taking PIs.[106] The identification of appropriate markers of inflammation to be used as surrogate markers of CVD risk in HIV-infected patients presents a special challenge due to the persistent state of inflammation caused by HIV disease. A cross-sectional analysis of virologically suppressed HIV-infected subjects enrolled in the Stopping Atherosclerosis and Treating Unhealthy Bone With Rosuvastatin in HIV (SATURN-HIV) trial who had LDL-C <130 mg/dL and increased T-cell activation or hs-CRP showed an association between the inflammatory markers TNF receptor I (TNFRI) and fibrinogen and subclinical vascular disease.[107]

Statin use has also been recently associated with reduced cancer incidence and mortality in both the general population and among HIV-infected subjects,[108–110] although reduced cancer incidence has not been reported in all statin studies.[111] A clinical endpoint trial in HIV-infected patients without dyslipidemia may be required to assess the effect of statins on morbidity and mortality in this population.

Conclusion

As HIV has evolved to become a chronic disease, the HIV population is aging and becoming increasingly vulnerable to CVD. Management of dyslipidemia in this population presents special challenges due to multiple DDIs between specific antiretrovirals and lipid-lowering drugs, most notably, statins. Statins are considered safe and effective in the treatment of dyslipidemia in HIV-infected patients but must be selected and dosed carefully in order to achieve lipid targets without toxicity. Clinical trial data comparing statins suggest that rosuvastatin, atorvastatin, and pitavastatin are superior to pravastatin in lipid reductions in this patient population. As a result of its lack of DDIs with ART agents, pitavastatin presents an attractive option for HIV-infected patients on ART. While recent data suggest a possible association of diabetes with statin use in the general population, this potential complication has not been adequately studied in the HIV population but warrants astute clinical observations in practice. At present, the cardiovascular benefits of statin use in HIV-infected patients justify continuing their use following conventional lipid management guidelines. Pleiotropic anti-inflammatory and cardioprotective benefits of statins independent of their lipid lowering benefits are suggested in various studies but need to be confirmed in HIV-infected patients. ■

1. Malvestutto CD, Aberg JA, Coronary heart disease in people infected with HIV, *Cleve Clin J Med*, 2010;77:547–56.
2. 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.
3. Triant V, Lee H, Hadigan C, et al., Increased acute myocardial infarction rates and cardiovascular risk factors among patients with human immunodeficiency virus disease, *J Clin Endocrinol Metab*, 2007;92:2506–12.
4. Friis-Moller N, Ryom L, Smith C, et al., An updated prediction model of the global risk of cardiovascular disease in HIV-positive persons; The Data Collection on Adverse Effects of Anti-HIV Drugs (D:A:D) Study, presented at the European AIDS Clinical Society 14th European AIDS Conference, October 17, 2013, abstract no PS1/3.
5. D'Agostino RB, Sr, Cardiovascular risk estimation in 2012: lessons learned and applicability to the HIV population, *J Infect Dis*, 2012;205(Suppl. 3):S362–7.
6. Vance D, McGuinness T, Musgrove K, et al., Successful aging and the epidemiology of HIV, *Clin Interv Aging*, 2011;6:181–92.
7. National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, 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) final report, *Circulation*, 2002;106:3143–421.
8. Data Collection on Adverse Events of Anti HIVdSG, Smith C, Sabin CA, et al., Factors associated with specific causes of death amongst HIV-positive individuals in the D:A:D Study, *AIDS*, 2010;24:1537–48.
9. Lo J, Plutzky J, The biology of atherosclerosis: general paradigms and distinct pathogenic mechanisms among HIV-infected patients, *J Infect Dis*, 2012;205(Suppl. 3):S368–74.
10. Hsue PY, Hunt PW, Sinclair E, et al., Increased carotid intima-media thickness in HIV patients is associated with increased cytomegalovirus-specific T-cell responses, *AIDS*, 2006;20:2275–83.
11. Sacre K, Hunt PW, Hsue PY, et al., A role for cytomegalovirus-specific CD4+CX3CR1+ T cells and cytomegalovirus-induced T-cell immunopathology in HIV-associated atherosclerosis, *AIDS*, 2012;26:805–14.
12. 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.
13. Stanley TL, Grinspoon SK, Body composition and metabolic changes in HIV-infected patients, *J Infect Dis*, 2012;205 (Suppl. 3):S383–90.
14. 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.
15. Saves M, Chene G, Ducimetire P, et al., Risk factors for coronary heart disease in patients treated for human immunodeficiency virus infection compared with the general population, *Clin Infect Dis*, 2003;37:292–8.
16. 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.
17. Riddler SA, Smit E, Cole SR, et al., Impact of HIV infection and HAART on serum lipids in men, *JAMA*, 2003;289:2978–82.
18. Stein JH, Komarow L, Cotter BR, et al., Lipoprotein changes in HIV-infected antiretroviral-naive individuals after starting antiretroviral therapy: ACTG Study A5152s Stein: lipoprotein changes on antiretroviral therapy, *J Clin Lipidol*, 2008;2:464–71.
19. Dau B, Holodniy M, The relationship between hiv infection and cardiovascular disease, *Curr Cardiol Rev*, 2008;4:203–18.
20. Grinspoon S, Carr A, Cardiovascular risk and body-

fat abnormalities in HIV-infected adults, *N Engl J Med*, 2005;352:48–62.
21. Giannarelli C, Klein RS, Badimon JJ, Cardiovascular implications of HIV-induced dyslipidemia, *Atherosclerosis*, 2011;219:384–9.
22. Moore RD, Bartlett JG, Gallant JE, Association between use of HMG CoA reductase inhibitors and mortality in HIV-infected patients, *PLoS One*, 2011;6:e21843.
23. Klein D, Hurley LB, Quesenberry CP, Jr., et al., Do protease inhibitors increase the risk for coronary heart disease in patients with HIV-1 infection?, *J Acquir Immune Defic Syndr*, 2002;30:471–7.
24. 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.
25. Riddler S, Li X, Otvos J, et al., Antiretroviral therapy is associated with an atherogenic lipoprotein phenotype among HIV-1-infected men in the Multicenter AIDS Cohort Study, *J Acquir Immune Defic Syndr*, 2008;48:281–8.
26. Mujawar Z, Rose H, Morrow M, et al., Human immunodeficiency virus impairs reverse cholesterol transport from macrophages, *PLoS Biology*, 2006;4:e365-e.
27. Rose H, Hoy J, Woolley I, et al., HIV infection and high density lipoprotein metabolism, *Atherosclerosis*, 2008;199:79–86.
28. Hulgan T, Haubrich R, Riddler SA, et al., European mitochondrial DNA haplogroups and metabolic changes during antiretroviral therapy in AIDS Clinical Trials Group Study A5142*, *AIDS*, 2011;25(1):37–47.
29. Riddler SA, Li X, Otvos J, et al., Antiretroviral therapy is associated with an atherogenic lipoprotein phenotype among HIV-1-infected men in the Multicenter AIDS Cohort Study, *J Acquir Immune Defic Syndr*, 2008;48:281–8.
30. Fontas E, van Leth F, Sabin CA, et al., Lipid profiles in HIV-infected patients receiving combination antiretroviral therapy: are different antiretroviral drugs associated with different lipid profiles?, *J Infect Dis*, 2004;189:1056–74.
31. Shafran SD, Mashinter LD, Roberts SE, The effect of low-dose ritonavir monotherapy on fasting serum lipid concentrations, *HIV Med*, 2005;6:421–5.
32. Temesgen Z, Feinberg J, Tipranavir: a new option for the treatment of drug-resistant HIV infection, *Clin Infect Dis*, 2007;45:761–9.
33. Hill A, Sawyer W, Gazzard B, Effects of first-line use of nucleoside analogues, efavirenz, and ritonavir-boosted protease inhibitors on lipid levels, *HIV Clin Trials*, 2009;10:1–12.
34. Malan DR, Krantz E, David N, et al., Efficacy and safety of atazanavir, with or without ritonavir, as part of once-daily highly active antiretroviral therapy regimens in antiretroviral-naive patients, *J Acquir Immune Defic Syndr*, 2008;47:161–7.
35. Overton ET, Arathoon E, Baraldi E, et al., Effect of darunavir on lipid profile in HIV-infected patients, *HIV Clin Trials*, 2012;13:256–70.
36. Aberg JA, Tebas P, Overton ET, et al., Metabolic effects of darunavir/ritonavir versus atazanavir/ritonavir in treatment-naive, HIV type 1-infected subjects over 48 weeks, *AIDS Res Hum Retroviruses*, 2012;28:1184–95.
37. Gallant JE, Koenig E, Andrade-Villanueva J, et al., Cobicistat versus ritonavir as a pharmacoenhancer of atazanavir plus emtricitabine/tenofovir disoproxil fumarate in treatment-naive HIV type 1-infected patients: week 48 results, *J Infect Dis*, 2013;208:32–9.
38. Shikuma C, Yang Y, Glesby M, et al., Metabolic effects of protease inhibitor-sparing antiretroviral regimens given as initial treatment of HIV-1 Infection (AIDS Clinical Trials Group Study A5095), *J Acquir Immune Defic Syndr*, 2007;44:540–50.
39. 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.
40. Katlama C, Haubrich R, Lalezari J, et al., Efficacy and safety of etravirine in treatment-experienced, HIV-1 patients: pooled 48 week analysis of two randomized, controlled trials, *AIDS*, 2009;23:2289–300.
41. Nelson MR, Elion RA, Cohen CJ, et al., Rilpivirine versus efavirenz in HIV-1-infected subjects receiving emtricitabine/tenofovir DF: pooled 96-week data from ECHO and THRIVE Studies, *HIV Clin Trials*, 2013;14:81–91.
42. Cohen C, Wohl D, Henry K et al, STaR study: association of efficacy outcomes with baseline HIV-1 RNA and CD4 count and adherence rate for the single-tablet regimens rilpivirine/emtricitabine/tenofovir DF and efavirenz/emtricitabine/tenofovir DF in ART-naïve adults. Presented at ID Week 2013, October 2–6, 2013. San Francisco, abstract no 671.
43. Tungsiripat M, Kitch D, Glesby M, et al., A pilot study to determine the impact on dyslipidemia of adding tenofovir to stable background antiretroviral therapy: ACTG 5206, *AIDS*, 2010;24:1781–4.
44. Randell P, Jackson A, Zhong L, et al., The effect of tenofovir disoproxil fumarate on whole-body insulin sensitivity, lipids and adipokines in healthy volunteers, *Antivir Ther*, 2010;15:227–33.
45. Lennox J, Dejesus E, Berger D, et al., Raltegravir versus efavirenz regimens in treatment-naive HIV-1-infected patients: 96-week efficacy, durability, subgroup, safety, and metabolic analyses, *J Acquir Immune Defic Syndr*, 2010;55:39–48.
46. Raffi F, Rachlis A, Stellbrink HJ, et al., Once-daily dolutegravir versus raltegravir in antiretroviral-naive adults with HIV-1 infection: 48 week results from the randomised, double-blind, non-inferiority SPRING-2 study, *Lancet*, 2013;381:735–43.
47. Mir O, Garrabou G, Lopez S, et al., Short communication metabolic and mitochondrial effects of switching antiretroviral-experienced patients to enfuvirtide, tenofovir and saquinavir/ritonavir, *Antivir Ther*, 2006;11:625–30.
48. Markowitz M, Nguyen B-Y, Gotuzzo E, et al., Rapid and durable antiretroviral effect of the HIV-1 Integrase inhibitor raltegravir as part of combination therapy in treatment-naive patients with HIV-1 infection: results of a 48-week controlled study, *J Acquir Immune Defic Syndr,* 2007;46:125–33.
49. MacInnes A, Lazzarin A, Di Perri G, et al., Maraviroc can improve lipid profiles in dyslipidemic patients with HIV: results from the MERIT trial, *HIV Clin Trials*, 2011;12:24–36.
50. Sax PE, DeJesus E, Mills A, et al., Co-formulated elvitegravir, cobicistat, emtricitabine, and tenofovir versus co-formulated efavirenz, emtricitabine, and tenofovir for initial treatment of HIV-1 infection: a randomised, double-blind, phase 3 trial, analysis of results after 48 weeks, *Lancet*, 2012;379:2439–48.
51. Aberg JA, Gallant JE, Ghanem KG, et al., Executive summary: primary care guidelines for the management of persons infected with HIV: 2013 update by the HIV medicine association of the Infectious Diseases Society of America, *Clin Infect Dis*, 2014;58:1–10.
52. Stone NJ, Robinson J, Lichtenstein AH, et al., 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines, *J Am Coll Cardiol*, 2013; Epub ahead of print.
53. Malvestutto CD, Aberg JA, Management of dyslipidemia in HIV-infected patients, *Clin Lipidol*, 2011;6:447–62.
54. Expert Dyslipidemia P, Grundy SM, An International Atherosclerosis Society Position Paper: global recommendations for the management of dyslipidemia, *J Clin Lipidol*, 2013;7:561–5.
55. Kirchner JT, Clinical management considerations for dyslipidemia in HIV-infected individuals, *Postgrad Med*, 2012;124:31–40.
56. Lundgren JD, Battegay M, Behrens G, et al., European AIDS Clinical Society (EACS) guidelines on the prevention and management of metabolic diseases in HIV, *HIV Med*, 2008;9:72–81.
57. Phillips AN, Carr A, Neuhaus J, et al., Interruption of antiretroviral therapy and risk of cardiovascular disease in persons with HIV-1 infection: exploratory analyses from the SMART trial, *Antivir Ther*, 2008;13:177–87.
58. 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.
59. Martinez E, The NEFA study: results at three years, *AIDS Rev*, 2007;9:62.
60. 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 lipoatrophy, *AIDS*, 2006;20:2043–50.
61. Tebas P, Palella F, Ruane P, et al., SPIRIT: simplification to rilpivirine/emtricitabine/tenofovir DF single-tablet regimen from boosted protease inhibitor maintains HIV-1 suppression and improves fasting lipids at week 48. Presented at ID Week 2013, October 2–6, 2013. San Francisco, abstract no 672.
62. Eron J, Young B, Cooper D, et al., Switch to a raltegravir-based regimen versus continuation of a lopinavir-ritonavir-based regimen in stable HIV-infected patients with suppressed viraemia (SWITCHMRK 1 and 2): two multicentre, double-blind, randomised controlled trials, *Lancet*, 2010;375:396–407.
63. Ose L, Budinski D, Hounslow N, et al., Comparison of pitavastatin with simvastatin in primary hypercholesterolaemia or combined dyslipidaemia, *Curr Med Res Opin*, 2009;25:2755–64.
64. Lee SH, Chung N, Kwan J, et al., Comparison of the efficacy and tolerability of pitavastatin and atorvastatin: an 8-week, multicenter, randomized, open-label, dose-titration study in Korean patients with hypercholesterolemia, *Clin Ther*, 2007;29:2365–73.
65. Weng TC, Yang YH, Lin SJ, et al., A systematic review and meta-analysis on the therapeutic equivalence of statins, *J Clin Pharm Ther*, 2010;35:139–51.
66. Chauvin B, Drouot S, Barrail-Tran A, et al., Drug-drug interactions between HMG-CoA reductase inhibitors (statins) and antiviral protease inhibitors, *Clin Pharmacokinet*, 2013;52:815–31.
67. Stroup JS, Harris B, Is statin therapy safe in patients with HIV/hepatitis C coinfection?, *Proc (Bayl Univ Med Cent)*, 2010;23:111–3.
68. Mathias AA, German P, Murray BP, et al., Pharmacokinetics and pharmacodynamics of GS-9350: a novel pharmacokinetic enhancer without anti-HIV activity, *Clin Pharmacol Ther*, 2010;87:322–9.
69. Fichtenbaum C, Gerber J, Rosenkranz S, et al., Pharmacokinetic interactions between protease inhibitors and statins in HIV seronegative volunteers: ACTG Study A5047, *AIDS*, 2002;16:569–77.
70. Schmidt GA, Hoehns JD, Purcell JL, et al., Severe rhabdomyolysis and acute renal failure secondary to concomitant use of simvastatin, amiodarone, and atazanavir, *J Am Board Fam Med*, 2007;20:411–6.
71. Pham PA, la Porte CJ, Lee LS, et al., Differential effects of tipranavir plus ritonavir on atorvastatin or rosuvastatin pharmacokinetics in healthy volunteers, *Antimicrob Agents Chemother*, 2009;53:4385–92.
72. Lexiva: Highlights of prescribing information, 2009. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/021548s021,022116s005lbl.pdf (accessed January 7, 2014).
73. Prezista (darunavir): Highlights of prescribing information, 2013. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/021976s030,202895s007lbl.pdf (accessed January 7, 2014).
74. Samineni D, Desai PB, Sallans L, et al., Steady-state pharmacokinetic interactions of darunavir/ritonavir with lipid-lowering agent rosuvastatin, *J Clin Pharmacol*, 2012;52:922–31.
75. Aberg J, Rosenkranz S, Fichtenbaum C, et al., Pharmacokinetic interaction between nelfinavir and pravastatin in HIV-seronegative volunteers: ACTG Study A5108, *AIDS*, 2006;20:725–9.
76. Influence of SLCO1B1 polymorphisms on pharmacokinetic (PK) variability in the drug-drug interaction between darunavir/ritonavir (DRV/r) and pravastatin (PRA). Presented at the 50th Interscience Conference on Antimicrobials and Chemotherapy, 2010.
77. Saito Y, Pitavastatin: an overview, *Atheroscler Suppl*, 2011;12:271–6.
78. Corsini A, Ceska R, Drug-drug interactions with statins: will pitavastatin overcome the statins' Achilles' heel?, *Curr Med Res Opin*, 2011;27:1551–62.
79. Ando H, Tsuruoka S, Yanagihara H, et al., Effects of grapefruit juice on the pharmacokinetics of pitavastatin and atorvastatin, *Br J Clin Pharmacol*, 2005;60:494–7.
80. Morgan RE, Campbell SE, Suehira K, et al., Effects of steady-state lopinavir/ritonavir on the pharmacokinetics of pitavastatin in healthy adult volunteers, *J Acquir Immune Defic Syndr*, 2012;60:158–64.
81. Malvestutto C, Ma Q, Morse GD, et al., Pharmacokinetic study assessing drug interactions of pitavastatin with darunavir/ritonavir and pitavastatin with efavirenz in healthy volunteers. Presented at the 53rd Interscience Conference on Antimicrobials and Chemotherapy (ICAAC), Denver, September 10–13, 2013, abstract no A-1577c, 2013.
82. Yu C, Campbell SE, Sponseller CA, et al., Steady-state pharmacokinetic interactions of darunavir/ritonavir with pitavastatin in healthy adult volunteers. Presented at the 19th International AIDS Conference, July 22–27, 2013, Washington DC, Abstract no. TUPE053.
83. Gerber J, Rosenkranz S, Fichtenbaum C, 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.
84. Intelence (Etravirine) Package Insert, 2008 (Revised 2/2013). Available at: http://www.intelence.com/shared/product/intelence/prescribing-information.pdf; date last accessed 7 January 2014).
85. Edurant (rilpivirine) package insert, 2011. Available at: http://pharmacy.hsc.wvu.edu/wvcdhi/MediaLibraries/Pharmacy-WVCDHI/Media/Documents/PDF/Monographs/Edurant(rilpivirine).pdf (accessed January 7, 2014).
86. Isentress (raltegravir) highlights of prescribing information, Revised 8/2013. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/022145s029lbl.pdf (accessed January 7, 2014).
87. van Luin M, Colbers A, van Ewijk-Beneken Kolmer EW, et al., Drug-drug interactions between raltegravir and pravastatin in healthy volunteers, *J Acquir Immune Defic Syndr*, 2010;55:82–6.
88. STRIBILD prescribing information, 2012. Available at: http://hivdb.stanford.edu/pages/linksPages/EVG_INI.pdf (accessed January 7, 2014).
89. Tivicay (dolutegravir) prescribing information, 2013. Available at: http://www.viivhealthcare.com/media/58599/us_tivicay.pdf (accessed January 7, 2014).
90. Selzentry (maraviroc) prescribing information, 2007. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2007/022128lbl.pdf (accessed January 7, 2014).
91. Silverberg M, Leyden W, Hurley L, et al., Response to newly prescribed lipid-lowering therapy in patients with and without HIV infection, *Ann Intern Med*, 2009;150:301–13.
92. Aberg J, Zackin R, Brobst S, 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.
93. Wohl D, Waters D, Simpson R, et al., Ezetimibe alone reduces low-density lipoprotein cholesterol in HIV-infected patients receiving combination antiretroviral therapy, *Clin Infect Dis*, 2008;47:1105–8.
94. Fichtenbaum C, Yeh T-M, Evans S, et al., Treatment with pravastatin and fenofibrate improves atherogenic lipid profiles but not inflammatory markers in ACTG 5087, *J Clin Lipidol*, 2010;4:279–87.
95. Singh S, Willig JH, Mugavero MJ, et al., Comparative Effectiveness and toxicity of statins among HIV-infected patients, *Clin Infect Dis*, 2011;52:387–95.

96. Calza L, Manfredi R, Colangeli V, et al., Rosuvastatin, pravastatin, and atorvastatin for the treatment of hypercholesterolaemia in HIV-infected patients receiving protease inhibitors, *Curr HIV Res*, 2008;6:572–8.
97. Aslangul E, Assoumou L, Bittar R, et al., Rosuvastatin versus pravastatin in dyslipidemic HIV-1-infected patients receiving protease inhibitors: a randomized trial, *AIDS*, 2010;24:77–83.
98. Sponseller C, Morgan, RE, Campbell, SE, et al., Pitavastatin 4 mg provides greater ldl-c reduction compared to pravastatin 40 mg over 12 weeks of treatment in hiv-infected adults with dyslipidemia. Poster presented at the 20th Conference on Retroviruses and Opportunistic Infections, March 3–6, 2013, Atlanta, GA, USA, 2013.
99. Sattar N, Preiss D, Murray HM, et al., Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials, *Lancet*, 2010;375:735–42.
100. Preiss D, Sattar N, McMurray JJ, Event rates in trials of patients with type 2 diabetes, *JAMA*, 2010;303:732–3, author reply 3.
101. Culver AL, Ockene IS, Balasubramanian R, et al., Statin use and risk of diabetes mellitus in postmenopausal women in the Women's Health Initiative, *Arch Intern Med*, 2012;172:144–52.
102. Athyros VG, Mikhailidis DP, Pharmacotherapy: statins and new-onset diabetes mellitus—a matter for debate, *Nat Rev Endocrinol*, 2012;8:133–4.
103. Worm SW, De Wit S, Weber R, et al., Diabetes mellitus, preexisting coronary heart disease, and the risk of subsequent coronary heart disease events in patients infected with human immunodeficiency virus: the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D Study), *Circulation*, 2009;119:805–11.
104. Ridker P, Danielson E, Fonseca FAH, et al., Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein, *N Engl J Med*, 2008;359:2195–207.
105. Albert MA, Danielson E, Rifai N, et al., Effect of statin therapy on C-reactive protein levels: the pravastatin inflammation/CRP evaluation (PRINCE): a randomized trial and cohort study, *JAMA*, 2001;286:64–70.
106. Lefevre C, Auclair M, Boccara F, et al., Premature senescence of vascular cells is induced by HIV protease inhibitors: implication of prelamin A and reversion by statin, *Arterioscler Thromb Vasc Biol*, 2010;30:2611–20.
107. Longenecker CT, Jiang Y, Yun CH, et al., Perivascular fat, inflammation, and cardiovascular risk in HIV-infected patients on antiretroviral therapy, *Int J Cardiol*, 2013;168:4039–45.
108. Nielsen SF, Nordestgaard BG, Bojesen SE, Statin use and reduced cancer-related mortality, *N Engl J Med*, 2012;367:1792–802.
109. Chao C, Xu L, Abrams DI, et al., HMG-CoA reductase inhibitors (statins) use and risk of non-Hodgkin lymphoma in HIV-positive persons, *AIDS*, 2011;25:1771–7.
110. Overton ET, Kitch D, Benson CA, et al., Effect of statin therapy in reducing the risk of serious non-AIDS-defining events and nonaccidental death, *Clin Infect Dis*, 2013;56:1471–9.
111. Cholesterol Treatment Trialists C, Baigent C, Blackwell L, et al., Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials, *Lancet*, 2010;376:1670–81.