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Statins in HIV-Infected Patients: Potential Beneficial Effects and Clinical Use

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Abstract

Patients living with HIV have an increased risk of cardiovascular disease that is considered to be the result of an interaction between traditional cardiovascular risk factors, particularly smoking and dyslipidemia, and persistent chronic inflammation and immune activation associated with HIV infection, along with side effects of antiretroviral therapy. In the general population, the administration of statins has been associated with a reduction in cardiovascular disease-associated mortality, and these drugs are among the most common class of medication prescribed in high-income countries. The beneficial effect of statins extends beyond reducing cholesterol levels as they have been shown to have anti- inflammatory, antithrombotic, antioxidant, immunomodulatory, and vasodilatory effects, and to improve endothelial function. Despite the widespread use of statins in the general population, cohort studies show that these drugs are underutilized in HIV-infected patients, probably due to safety concerns by clinicians and limited data evaluating clinical outcomes in patients on antiretroviral therapy. In this article we review and update the most important clinical studies of statins in HIV- infected patients, describe their side effects and interaction profiles, and discuss the anti-atherosclerotic and pleiotropic effects of these drugs. Finally, we propose recommendations for clinical use of statins in patients living with HIV. **(AIDS Rev. 2017;19:59-71)**

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Key words

Cardiovascular risk. Clinical use. HIV. Hyperlipidemia. Pleiotropic effect. Statin.

Introduction

Antiretroviral therapy (ART) has dramatically changed the natural history of HIV infection. People living with HIV who have access to therapy are expected to maintain long-term viral suppression and are unlikely to develop opportunistic infections[1]. However, cohort studies have shown that patients receiving suppressive ART experience a variety of non-infectious comorbidities, also known as non-AIDS events, that have replaced opportunistic diseases as major causes of morbidity and mortality[2-4].

Some non-AIDS events, like myocardial infarction, have been found to occur more frequently in patients living with HIV compared to age- and sex-matched HIV-uninfected populations[5,6]. Although the pathogenesis of cardiovascular disease in HIV-infected patients remains to be completely elucidated, traditional cardiovascular risk factors along with factors

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linked with HIV infection, including HIV viral replication, coinfections, associated inflammation and immune activation, and antiviral treatments, all are thought to contribute to this increased risk[2,5,7-9]. Traditional risk factors, particularly smoking and dyslipidemia, seem to play a central role in this excess in myocardial infarction risk[5,9]. Rates of smoking are generally thought to be 2-3-times higher in people living with HIV than in those uninfected[10] and smoking has recently been associated with a higher risk of myocardial infarction in the HIV-infected population than in the general population[11]. On the other hand, more than 30% of patients receiving ART show dyslipidemia consisting of increased concentrations of low-density lipoprotein cholesterol (LDL-C) and triglycerides (TG), with low levels of high-density lipoprotein cholesterol (HDL-C)[12]. HIV itself, and especially ART, has been implicated in the pathogenesis[12,13].

Hypercholesterolemia is one of the most important factors contributing to increased cardiovascular risk in these patients[13]. Despite traditional risk factors being leading contributors to cardiovascular disease, recent data suggest that HIV-infected persons are less likely to be prescribed medications appropriate for coronary artery disease risk reduction than uninfected persons[14] and the prevalence of optimal cardiac health on this population remains low[9].

Persistent chronic inflammation and immune activation associated with HIV infection is also considered to contribute to accelerated atherosclerosis in HIV-infected subjects[15,16]. The mechanism of the persistence of this immune activation is unclear, but could be the result of residual viral replication, infection with co-pathogens such as herpesvirus[8,17-21] and hepatitis C virus[22-25], and/or bacterial translocation caused by damage of the gastrointestinal lymphoid tissue[26].

Statins are a group of drugs that reduce cholesterol levels, particularly the concentrations of LDL-C, but the effect on reducing cardiovascular risk extends beyond their lipid-reducing properties as they have anti-inflammatory and immunomodulatory effects[27-29]. In the general population, these drugs have proven to reduce cardiovascular events in several patient groups and are among the most common class of medications prescribed. Given the pathogenesis of cardiovascular disease associated with HIV infection, therapy with these drugs might be particularly valuable for people living with HIV. However, prescription of statins in the HIV-infected population remains low[14,30], likely due to safety concerns by clinicians and limited data evaluating clinical outcomes in this population.

In this review, the characteristics of the main statins, their metabolism, interaction profile, adverse events, and lipid lowering effects, along with other cardiovascular and immunomodulatory potential beneficial effects in HIV-infected patients, are examined. Finally, we propose recommendations for clinical use of statins in this population.

Mechanism of action, metabolism, and type of statins

Statins are a group of drugs that have a common mechanism of action: they inhibit competitively, partially and reversibly the hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the rate-limiting enzyme in cholesterol synthesis. Currently, seven statins are approved by the European Medicines Agency (EMA) and by the US Food and Drug Administration (FDA): atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin (Table 1).

With a variable potency depending on the drug, statins reduce LDL-C effectively, which is the primary objective in patients with dyslipidemia. Cholesterol reduction is usually maximal at four weeks of treatment and remains stable over time. Statins reduce, though less, triglyceride levels due to the inhibition of cholesterol hepatic synthesis, decreasing the synthesis of very low-density lipoprotein (VLDL). They also induce moderate elevations of HDL-C. Statins are rapidly absorbed, reaching a peak concentration within four hours, and most of them show low bioavailability (5-14% for simvastatin, lovastatin and atorvastatin, 20-30% for fluvastatin, pravastatin and rosuvastatin, and 60% for pitavastatin). Elimination half-lives of the statins range from less than five hours for fluvastatin, lovastatin, pravastatin, and simvastatin, to 11 hours for pitavastatin and 20-30 hours for atorvastatin and rosuvastatin[31]. 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[31].

In addition to their effects on lipid profile, statins have other beneficial effects known as pleiotropic effects, which include, among others, anti-inflammatory, antithrombotic, antioxidant, immunomodulatory, vasodilatory,

Table 1. Statins, doses, potency, metabolism and interactions

Drug	Doses	Potency	Metabolism	Interactions
Lovastatin	10-80 mg/day	+ (20 mg) ++ (40 mg)	CYP3A4	PI (contraindicated), NNRTI
Simvastatin	5-80 mg/day	+ (10 mg) ++ (20-40 mg)	CYP3A4	PI (contraindicated), NNRTI
Pravastatin	10-80 mg/day	+ (10-20 mg) ++ (40-80 mg)	Partial hepatic (OATP1B1); Partial biliary/urinary excretion	PI
Fluvastatin	20-80 mg/day	+ (20-40 mg) ++ (40-80 mg)	CYP2C9, CYP3A4 (minor)	Efavirenz
Atorvastatin	10-80 mg/day	++ (10-20 mg), +++ (40-80 mg)	CYP3A4	PI or cobicistat (do not exceed 20-40 mg) Contraindicated with TPV/ritonavir Decrease plasma levels with efavirenz
Rosuvastatin	5-40 mg/day	++ (5-10 mg), +++ (20-40 mg)	CYP2C9 (< 10%)	PI (do not exceed 10-20 mg with boosted PI)
Pitavastatin	1-4 mg/day	+ (1 mg), ++ (2-4 mg)	Glucuronidation UGT 1A3 and 2B7, CYP2C9 and 2C8 (minimum)	Elvitegravir/cobicistat

Potency: High potency (LDL-C reduction ≥ 50% (+++), Moderate (LDL-C reduction ≥ 30- 50% (++), Low (LDL-C reduction < 30% (+)[104].
ATV: atazanavir; CYP: cytochrome P450; LPV: lopinavir; NNRTI: non-nucleoside reverse transcriptase inhibitor; OATP1B1: organic anion-transporting polypeptide 1B1; PI: protease inhibitor; TPV: tipranavir; UGT: uridine 5'-diphospho-glucuronosyltransferase.

and anti-atherosclerotic effects and improvement of endothelial function[27,32].

Lipid-lowering effect and potency of statins

Statins are effective in lowering cholesterol and have shown a good safety and tolerability profile[33]. The highest efficacy in lowering cholesterol is achieved with lower doses, so after the first dose, cholesterol decreases by 30-50%. The dose-response relationship of statins is curvilinear, so the response to a dose increase is not proportional. When the dose of a statin is doubled, the reduction of LDL-C levels is not twofold, but only an average of 6% of additional reduction is generally obtained[34].

In the general population, with equivalent doses, rosuvastatin (10 mg/day) is more effective than atorvastatin (10-20 mg/day), simvastatin (20-40 mg/day), and pravastatin (20-40 mg/day) in reducing levels of total cholesterol (TC), LDL-C and TG, and in increasing HDL-C levels (Table 1)[35,36]. Atorvastatin and rosuvastatin have also shown efficacy in lowering LDL-C in the HIV-infected population; as it occurs in the HIV-uninfected population, rosuvastatin appears to be somewhat more potent than atorvastatin and substantially more potent that pravastatin with regard to lowering LDL-C in this population[37,38]. In a randomized study of 83 HIV-infected patients with dyslipidemia treated with protease inhibitor (PI)-containing ART regimens, rosuvastatin (10 mg/day) was more effective (close to double) than pravastatin (40 mg/day) in reducing both LDL-C and TG levels after eight weeks of treatment[37]. In another trial where HIV-infected patients treated with PIs were randomized to rosuvastatin (10 mg/day), atorvastatin (10 mg/day), or pravastatin (20 mg/day), levels of LDL-C were reduced by 25, 20, and 18%, respectively, after one year of treatment[38]. In the AIDS Clinical Trials Group (ACTG) Study 5087, fluvastatin at a dose of 20-40 mg/day was more effective than pravastatin at a dose of 10-20 mg/day in reducing LDL-C in HIV-infected patients on PIs[33]. In a larger study of 174 HIV-infected patients randomized to pravastatin 40 mg daily or fenofibrate, pravastatin reduced LDL from baseline by a mean of 30 mg/dl (20% reduction), which was a similar reduction to that seen in HIV-uninfected patients at a similar dose[39].

A recent meta-analysis of statins for primary prevention in patients with HIV found that rosuvastatin (10 mg/day) and atorvastatin (10 mg/day) provided the largest reduction in TC levels, atorvastatin (80 mg/day) and simvastatin (20 mg/day) the largest reduction in LDL-C, and pravastatin (10-20 mg/day) and atorvastatin (10 mg/day) led to the largest increase in HDL-C, whereas atorvastatin (80 mg/day) and simvastatin (20 mg/day) had the largest reduction in TG[40]. Pitavastatin seems to be superior to pravastatin. In a clinical trial, 242 HIV-infected patients receiving stable ART with an LDL-C of 130-220 mg/dl were randomized to receive pitavastatin (4 mg/day) or pravastatin (40 mg/day) for 52 weeks. Pitavastatin led to a greater decrease in LDL-C (30 vs. 21% reduction) and TC (20 vs. 14% reduction)[41].

Although statins are thought to have similar effects in HIV-infected and uninfected subjects, some studies have shown a lower response in reducing LDL-C and TG levels and increasing HDL-C levels in patients with HIV compared to the general population[42-44]. It is unclear why there might be a lower response in HIV-infected patients, although factors like drug-drug interactions and the distinctive pattern of mixed dyslipidemia seen in this population could account for the differences[33]. As mentioned previously, lipid abnormalities are frequently found in patients infected with HIV, and they are often the result of the effects of HIV infection itself and of ART, mainly of PI-based regimens. Indeed, in most studies where the PI has been switched to another antiretroviral drug with an improved lipid profile, a significant reduction in the levels of total and LDL cholesterol has been achieved[45]. However, it was unknown whether this effect could be higher than that achieved with statin therapy. A recent study was conducted in HIV-infected patients with dyslipidemia and high cardiovascular risk to assess whether switching from a boosted PI to another antiretroviral agent with improved lipid profile (rilpivirine, raltegravir or unboosted atazanavir) was better than adding rosuvastatin 10 mg/day. After 12 weeks of treatment, there was a greater decrease in levels of TC, LDL-C and TC:HDL ratio in the rosuvastatin group compared to the patients that switched the ART regimen[46]. Similar results were previously reported when either pravastatin or bezafibrate was added to PI-treated patients compared to switching to efavirenz or nevirapine[47]. It follows that changing just the PI to reduce cholesterol levels and cardiovascular risk may be insufficient.

Interactions of statins with antiretroviral drugs

One of the main concerns with the use of statins in HIV-infected patients is the potential for drug-drug interaction with antiretroviral agents. Most statins are metabolized by CYP3A4 and all of them are substrate of organic anion transporter polypeptide (OATP) 1B1, an uptake transporter expressed in the hepatocyte membrane.

Protease inhibitors have generally been used boosted with low doses of ritonavir, a potent inhibitor of CYP3A4. Fluvastatin, pravastatin, and rosuvastatin are the only statins that can be used safely when combined with most PIs because they do not use the CYP3A4[31]. Nevertheless, pravastatin and rosuvastatin may have minor interactions with PIs via inhibition of OATP 1B1, which facilitates the uptake of statins in the liver[31], and some individuals experience a potentially dangerous increase in levels of pravastatin when used in combination with darunavir/ritonavir; so when pravastatin is used with darunavir, it should be started at the lowest dosage with careful monitoring for toxicity. Simvastatin, lovastatin and atorvastatin preferably use the CYP3A4 as metabolic pathway. Lovastatin and simvastatin are contraindicated when co-administered with PIs. Atorvastatin is safe if a submaximal dose of 10-20 mg/day is used[31]. Pitavastatin is metabolized by uridine 5-diphosphate glucuronosyl transferases (UGT) 1A3 and 2B7 with minimal metabolism by CYPs 2C9 and 2C8, and it is also a substrate of the hepatic transporter OATP1B1[31]. Pitavastatin has a good safety profile, even when co-administered with PIs[27]. In an open-label, parallel-arm, pharmacokinetic study in HIV-uninfected healthy volunteers, there were no significant interactions between pitavastatin and darunavir/ritonavir or efavirenz[48].

In general, non-nucleoside reverse transcriptase inhibitors (NNRTI) are inducers of CYP3A4, so co-administration with statins can reduce their plasma exposure. Plasma concentrations of simvastatin, atorvastatin, and pravastatin were reduced by 58, 34, and 40%, respectively, when combined with efavirenz[49]. Instead, co-administration of efavirenz with fluvastatin may increase the plasma levels of fluvastatin because efavirenz is an inhibitor of CYP2C9 and fluvastatin mainly uses this metabolic pathway[50]. Therefore, this combination is not recommended. Similarly, nevirapine and etravirine can induce CYP3A4 and reduce concentrations of atorvastatin, simvastatin,

and pravastatin. In contrast, nevirapine and etravirine are not expected to have interactions with rosuvastatin and pitavastatin. The combination of atorvastatin and rilpivirine has been studied, with no significant interactions observed[50]. It is not expected either to have interactions when rilpivirine is combined with other statins[50].

Data on drug-drug interactions with the co-administration of the new booster cobicistat and statins are limited, but, due to its mechanism of action (CYP3A inhibitor and substrate), cobicistat could potentially increase plasma exposure of statins. Cobicistat should not be co-administered with lovastatin or simvastatin and careful attention should be paid when co-administered with other statins, mainly atorvastatin. If the use of atorvastatin is considered strictly necessary, the lowest dose of atorvastatin should be administered with careful monitoring[50]. Regarding integrase inhibitors, statins are not expected to have significant interactions except when combined with elvitegravir, which is co-formulated with cobicistat. As mentioned, pitavastatin is metabolized by UGTs with minimal metabolism by CYP 2C9 and 2C8, but it is also a substrate of the hepatic transporter OATP1B1. The net effect of the interaction is difficult to predict as cobicistat may increase pitavastatin exposure (OATP1B1 inhibition) and elvitegravir may reduce pitavastatin exposure (induction of glucuronidation and CYP2C9). Therefore, starting with the lowest possible dose of pitavastatin and titrating up to the desired clinical effect while monitoring for safety is required if both drugs are co-administered[50].

In summary, co-administration of PIs or cobicistat with simvastatin and lovastatin is contraindicated as they are expected to markedly increase simvastatin and lovastatin concentrations. On the other hand, atorvastatin appears to be relatively safe at submaximal doses (10-20 mg/day) when combined with ritonavir-boosted PIs. Co-administration of cobicistat and atorvastatin has not been studied and is not recommended. Plasma concentrations of atorvastatin are expected to increase when co-administered with cobicistat. Overall, pitavastatin and rosuvastatin seem to be the agents with a better safety profile when co-administered with ART and do not appear to require dose adjustment[33]. Nevertheless, data on co-administration of these drugs with cobicistat are limited. Therefore, when co- administered, the lowest recommended dose should be started with, and titrated while monitoring for safety.

Side effects of statins

In general, statins used at the recommended doses in HIV-infected patients have a relatively low risk of undesirable effects[37,51-54]. In a recent systematic review and meta-analysis of statins for primary prevention in patients with HIV, the mean discontinuation rate was 0.12 per 100 person-years[40]. While higher doses may achieve better control of dyslipidemia, they increase the likelihood of side effects. The most common serious adverse event is rhabdomyolysis, which appears in the general population at about 0.1%[55], but can reach 10% in patients treated with high doses[56]. This risk seems to be similar in HIV-infected as in the general population. Throughout 96 weeks in the Stopping Atherosclerosis and Treating Unhealthy Bone with Rosuvastatin in HIV (SATURN-HIV) trial, a randomized, double-blind, placebo-controlled study evaluating rosuvastatin in 147 HIV-infected patients, there were no cases of rhabdomyolysis and only three participants (two statin and one placebo) discontinued the study because of myalgia[57]. Additionally, there was no change in creatinine kinase levels and a trend toward increased lean body mass in the rosuvastatin arm was observed.

Hepatotoxicity is not a frequent adverse event in patients with HIV treated with statins. In a retrospective study performed in 80 HIV-infected patients taking statins, including 38 patients with viral hepatitis coinfection, statins did not cause significant liver damage[58].

Statins may increase the risk of developing diabetes mellitus in the general population, an effect that is known to be dose-dependent[59]. However, overall, the benefit of decreasing LDL-C and the associated reduction in cardiovascular events outweighs the risks associated with the increased incidence of diabetes mellitus[60]. The increased risk of diabetes with statins in the HIV population is unclear[61], although some recent studies have found an association[7,62]. Thus, in an analysis of the North American HIV Outpatient Study (HOPS), including 350 episodes of incident diabetes in 4,690 HIV-infected patients, the development of diabetes was associated with the use of statins (adjusted hazard ratio, 1.14 per year of treatment)[7]. Similarly in the SATURN-HIV trial[62], patients taking rosuvastatin were more likely to develop insulin resistance evaluated by homeostasis model insulin resistance (HOMA-IR) than those receiving placebo after 48 weeks of monitoring.

Mortality, cardiovascular risk, and surrogate markers of atherosclerosis

In the general population, several studies have confirmed the beneficial effect of statins in reducing cardiovascular events and mortality[27]. However, there are no studies yet demonstrating this effect in HIV-infected patients. Most of the investigations carried out until now in the HIV population have been conducted using inflammatory and other surrogate markers of atherosclerosis.

In the Johns Hopkins HIV Clinical Cohort, Moore, et al.[63] found that in HIV-infected individuals on ART, statin therapy was associated with a lower risk of all-cause mortality (adjusted mortality rate ratio: 0.33; 95% CI: 0.14-0.76) after adjusting for CD4, HIV-1 RNA, hemoglobin and cholesterol levels at the start of ART, age, race, HIV risk group, prior use of ART, year of ART start, NNRTI vs. PI-based ART, prior AIDS-defining illness, and viral hepatitis coinfection. In the Danish cohort, statin use was also associated with a similar reduction in mortality, though non-statistically significant, among individuals with at least one comorbidity (adjusted mortality rate ratio: 0.34; 95% CI: 0.11-1.04), having a minimal or no impact on patients without comorbidities[64]. In contrast, in the analysis of the AIDS Clinical Trials Group Longitudinal Linked Randomized Trials (ALLRT) cohort, with 484 patients starting statins, no reduction in time to all non-AIDS-defining events, including cardiovascular events, or in non-accidental deaths was observed[44]. Unexpectedly, a 57% statistically significant reduction in non-AIDS-defining malignancies (adjusted hazard ratio: 0.43; 95% CI: 0.19-0.94) was found in this analysis[65].

There have been a number of studies that have investigated the effects of statins on a variety of surrogate markers of atherosclerosis, including carotid artery intima-media thickness (cIMT), arterial stiffness, and endothelial function[66]. Most of them have reported potential beneficial effects of statins on different pathways of the pathogenesis of atherosclerosis (Fig. 1).

The first clinical trials with statins in HIV-infected patients were performed a long time ago using low potency statins. Stein, et al.[67] showed that the administration of pravastatin in 20 HIV-infected patients on PI-containing ART regimens achieved a slight improvement of endothelium-dependent vasodilation measured by flow-mediated dilatation (FMD: 0.7% ± 0.6%), although it was not statistically significant when compared to placebo. These results were corroborated in a clinical trial with similar design conducted in 29 men receiving PIs with total cholesterol levels > 193 mg/dl[68]. In this study, the administration of pravastatin 40 mg daily led to a significant increase of FMD after eight weeks (from 2.0 to 3.2%). However, these data were not confirmed in another study[69].

Boccara, et al. evaluated the effect of pravastatin on the cIMT and arterial stiffness assessed by pulse wave velocity in 42 HIV-infected patients compared to a group of non-infected subjects matched by age, sex, and cardiovascular risk factors. The authors did not find any statistical difference between both groups[70]. However, more recent studies have demonstrated a beneficial effect of statins on cIMT and other validated surrogate markers of atherosclerosis[49-51]. In a prospective observational study in 36 HIV-infected patients with hypercholesterolemia and elevation of cIMT (≥ 0.9 mm) who began therapy with rosuvastatin 10 mg/day as part of their treatment, there was a significant reduction of cIMT in both carotids after 24 months of therapy[71]. Lo, et al. randomized 40 HIV-infected patients receiving ART, with subclinical coronary atherosclerosis and LDL cholesterol < 130 mg/dl, to atorvastatin (20-40 mg) or placebo. After one year of monitoring, no changes in arterial inflammation, as assessed by 18fluorodeoxyglucose (18F-FDG)-PET uptake of the aorta, were observed. There was, however, a significant reduction in non-calcified coronary plaque volume assessed with coronary computed tomography angiography, relative to placebo, and in the number of high-risk plaques[72].

In the SATURN-HIV trial, investigators evaluated the effect of rosuvastatin in the progression of carotid cIMT in HIV-infected patients on ART with LDL-C levels < 130 mg/dl and elevated markers of systemic inflammation (high sensitivity C-reactive protein ≥ 2mg/l) or activation of T lymphocytes (CD8,CD38,HLA-DR ≥ 19%). Assignment to statin was associated with 0.019 mm (95% CI: 0.002-0.037) less progression of cIMT over 96 weeks. Patients with higher baseline cIMT and coronary calcifications were the patients who benefited most[73].

Although all these studies support the beneficial effects of statins in reducing the progression of carotid atherosclerosis in patients with HIV infection with low cardiovascular risk, none of them was designed to demonstrate a reduction of cardiovascular events. Currently, a clinical trial (REPRIEVE) is being carried out in order to assess whether a statin (pitavastatin)

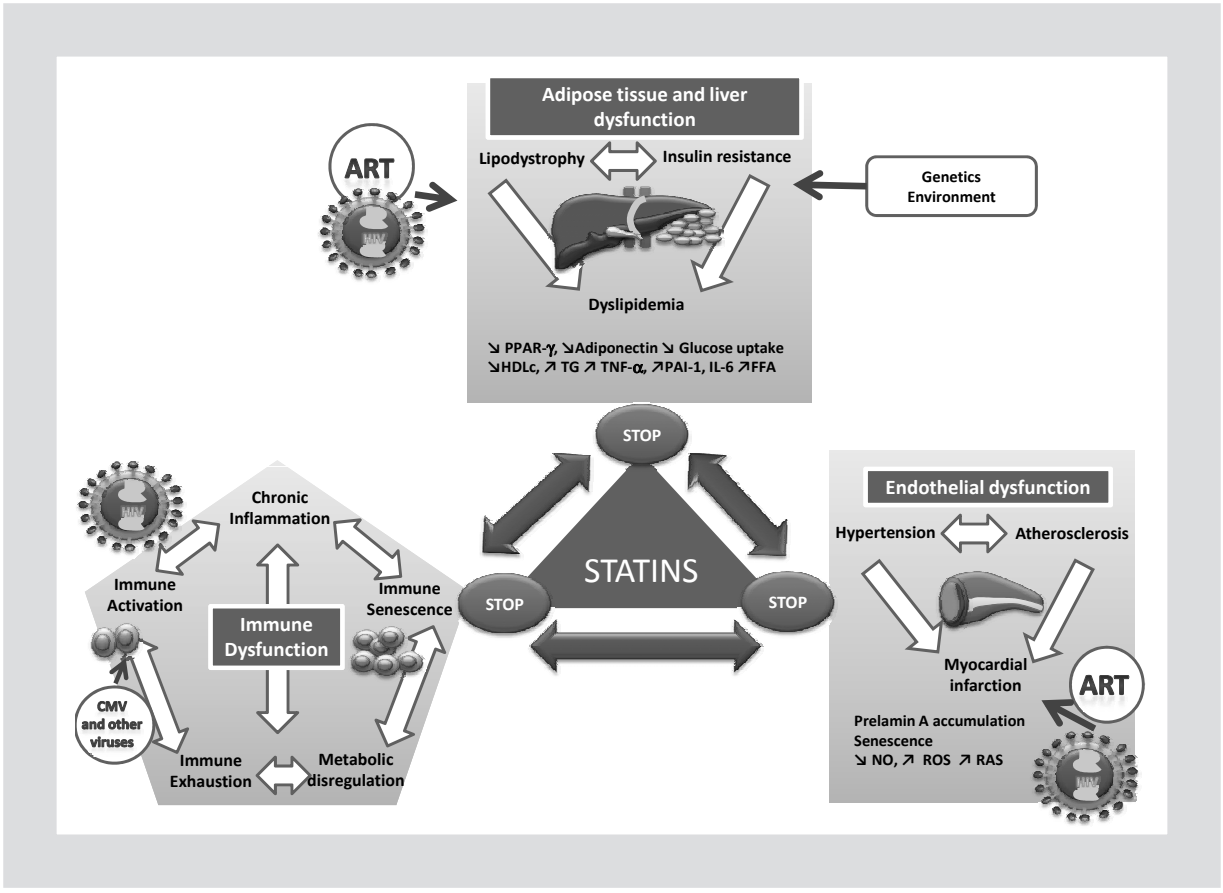

Figure 1. *Proposed mechanisms of increased cardiovascular risk in chronic HIV infection and potential beneficial actions of statins. There is a very complex interaction of various related factors. HIV and antiretroviral therapy have direct effects on adipose tissue and liver function with subsequent dyslipidemia, lipodystrophy, and insulin resistance. At this level, statins can act by reducing concentrations of LDL cholesterol, total cholesterol, and triglycerides, and increasing concentrations of HDL cholesterol. Another hypothetical mechanism to increase cardiovascular risk includes effects on endothelial cells and vascular smooth muscle cells, leading to vascular and endothelial dysfunction with subsequent hypertension, atherosclerosis and myocardial infarction. Statins may improve endothelial function and reduce the progression of atherosclerosis measured by carotid intima-media thickness. Continuous immune activation and viral replication may lead to permanent T-cell activation, which might also be affected by reactivation of other viruses, e.g. cytomegalovirus. These pathways are more or less interrelated and mediate indirect effects of HIV and antiretroviral therapy on cardiovascular disease. Statins could block inflammation and immune activation. CMV: cytomegalovirus; FFA: free fatty acids; IL6: interleukin 6; PAI-1: plasminogen activator inhibitor type 1; PPARy: peroxisome proliferator-activated receptor; NO: nitrogen oxide; RAS: renin angiotensin system; ROS: reactive oxygen species; TNF: tumor necrosis factor.*

reduces cardiovascular events in HIV patients receiving ART with cardiovascular risk at 10 years lower than 7.5%, but the results will not be available until 2020 (Table 2).

Anti-inflammatory and immunomodulatory effects of statins

Several studies support increased immune activation and inflammation in virologically suppressed HIV patients[74-76] that can contribute to the development of non-AIDS events, including cardiovascular diseases and neoplasia[16,75,77-79]. Furthermore, chronic inflammation and immune activation has been associated with an increase of all-cause mortality and progression of HIV disease[80,81]. Therefore, developing strategies targeting inflammation and immune activation are now within the AIDS scientific agenda.

It has been shown that, in the general population, statins have an immunomodulatory effect that could contribute to the reduction of cardiovascular risk, regardless of its effect in lowering cholesterol levels. Statins reduce levels of C-reactive protein, an acute-phase reactant that plays an important role in the pathogenesis of atherosclerosis[27]. Statins can also reduce other biomarkers of systemic inflammation and endothelial dysfunction[66]. There are data suggesting they are able to lessen the process of adhesion to

Table 2. Ongoing clinical trials evaluating statins in HIV-infected patients

Clinical trials gov. identifier	Estimated completion	(n)	Patients	Intervention	Phase	Primary endpoint	Duration
NCT02081638	2017	80	Elite controller or ART > 5 years with suppressed viral load > 3 years	Open label aspirin 81 mg vs. atorvastatin 40 mg	2	Changes of CD14	9 months
NCT01813357	2017	102	Stable ART and Moderate CVD risk (10-15%, 10 years)	Rosuvastatin 20 mg vs. placebo	4	Progression of cIMT	96 weeks
NCT02234492	2018	82	> 40 years; ART > 1 year; Framingham risk score = 10- 20% LDL < 4 mmol/l (< 155 mg/dl)	Open-label rosuvastatin 10 mg vs. current medical therapy	4	Correlation CFR and TBRmax	6 months
NCT02344290	2020	6,500	40-75 years; stable ART; ASCVD < 7.5%	Pitavastatin 4 mg vs. placebo	4	Time to the first event*	42-72 months

cardiovascular disease
ART: antiretroviral therapy; ASCVD: clinical atherosclerotic cardiovascular disease; CFR: coronary flow reserve; cIMT, carotid intima-media thickness; CVD: cardiovascular disease; LDL; low-density lipoprotein; sCD14: soluble factor CD14; TBR: target to background ratio.

endothelial cells and monocyte recruitment, and to redirect the migration of smooth muscle cells, and may affect favorably the metalloproteinases of the extracellular matrix, so they can help stabilize the atherosclerotic plaques[82]. Moreover, statins are thought to act on the innate and adaptive immunity and to reduce the activation of T-cells[28]. In addition, due to their immunomodulatory effect, some studies suggest they could reduce the risk of malignancies and mortality among patients with infections[83].

As previously discussed, use of statins was associated with a reduction in all-cause mortality, regardless of their action on lipid levels, in the Johns Hopkins HIV cohort[63], and a reduction in non-AIDS-defining malignancies in the ALLRT cohort [65]. Furthermore, in a case-control study among HIV-positive patients of Kaiser Permanente in California, the use of statins was associated with a reduced risk of non-Hodgkin lymphoma (hazard ratio [95% CI] forever use, < 12 months, and ≥ 12 months cumulative use was 0.55 [0.31-0.95], 0.64 [0.31-1.28], and 0.50 [0.23-1.10], respectively)[84].

Taken together, these studies suggest that statin therapy might decrease the incidence of some comorbidities associated with HIV infection and reduce mortality in HIV-infected patients, an effect that could be due to their immunomodulatory action. Though this may turn out to be true, studies conducted in this population have shown conflicting results. Thus, in a double-blind clinical trial designed to evaluate the lipid-lowering effect of pravastatin 40 mg/day compared to rosuvastatin 10 mg/day, in 58 HIV-infected patients on ritonavir- boosted PIs with dyslipidemia, only a mild decrease in C-reactive protein levels was observed with both drugs, with no significant changes in other inflammatory markers[85]. In contrast, in an observational study performed in naive patients who started treatment with tenofovir/emtricitabine/efavirenz, alone (n = 46) or in combination with rosuvastatin 10 mg/day (n = 40), greater reductions in C-reactive protein levels were observed in the group treated with rosuvastatin, along with significant decreases of other inflammatory markers (interleukin-6 and 8, tumor necrosis factor) in those receiving rosuvastatin[86]. However, other studies, including randomized clinical trials and case-control studies, have not found significant changes in C-reactive protein levels after 24 and 48 weeks of treatment with statins[52,87,88]. This discrepancy may be due to the use of different agents and/or differences among the treated HIV-infected patients. De Wit, et al.[88] conducted a case-control study to assess the effect of atorvastatin at 48 weeks

on inflammatory markers in HIV-infected patients on ART and virologically suppressed. Although they did not observe a decrease in C-reactive protein levels, there was a significant reduction in CD38 expression on $CD8^+$ T lymphocytes, suggesting that statins could reduce immune activation in those patients.

The effect of statins on immune activation has been evaluated in other studies. In the SATURN-HIV, previously discussed, there was a favorable change in the activation of CD4 and CD8 lymphocytes after 48 weeks of treatment with rosuvastatin[57]. In this study, it was also shown that plasma levels of soluble CD14 marker fell by 13.2% compared to 1.2% in the placebo group ($p = 0.002$)[89]. The soluble CD14 factor is a marker of monocyte activation and an independent predictor of mortality in HIV-infected patients[90]. A 13% reduction would be associated with an estimated 21% decrease of non-AIDS-related morbidity or death based on the risk found among virologically suppressed patients[91].

The effect of atorvastatin on immune activation was evaluated in a randomized, double-blind, placebo-controlled study performed in HIV patients not receiving ART with LDL-C levels < 130 mg/dl[65]. Atorvastatin was administered at high (80 mg/day) doses and different markers of immune activation were measured. After eight weeks of treatment, the investigators found significant reductions in levels of activated T-cells ($CD4^+$, $HLA\text{-}DR^+$ [–2.5%; $p = 0.02$], $CD8^+$, $HLA\text{-}DR^+$ [–5%; $p = 0.006$], and $CD8^+$, $HLA\text{-}DR^+$, $CD38^+$ T-cells [–3%; $p = 0.03$]) not related to lower levels of LDL-C[92]. In another placebo-controlled clinical trial performed in Uganda, atorvastatin reduced CD4 and CD8 T-cell activation, and CD4 and CD8 T-cell exhaustion[93]. A similar effect on CD8 T-cell activation and exhaustion was observed with atorvastatin, but not with pravastatin, in a retrospective study on 21 patients receiving ART[94].

In summary, in most studies a reduction in the activation of T lymphocytes and monocytes has been found with different statins, but the effect on inflammatory markers has been inconsistent. It is also noteworthy that while the effects of statins on the immune system can lead to beneficial effects on some comorbidities, they might eventually be harmful in some circumstances. It has been observed that statins can decrease the T-helper-1/T-helper-2 (Th1/Th2) lymphocyte ratio[95]. The use of statins was associated with a worse response of $CD4^+$ T-cells in patients on ART in an observational study[96], but this finding has not been confirmed in controlled clinical trials[87,97].

Other pleiotropic effects of statins

Chronic kidney disease is one of the strongest predictors of cardiovascular events in the general population[98] and in HIV-infected patients[5]. Although statins reduce cardiovascular events in the general population, they appear to have little effect on kidney function decline[99]. However, in the SATURN-HIV trial, rosuvastatin was associated with improvements in the kidney biomarker cystatin C and creatinine-based estimates of glomerular filtration rate[100]. Other analyses of secondary end points in the same trial suggest a beneficial effect on N-terminal pro-B-type natriuretic peptide[101], a biomarker of cardiac wall stress that predicts both vascular and heart failure events, but there was no effect on the expression of two well-known transcriptional mediators of vascular inflammation: Kruppel-like factors 2 and 4[102].

Figure 1 depicts hypothetical mechanisms of increased cardiovascular risk in chronic HIV infection and potential beneficial actions of statins.

Recommendations for the use of statins in patients with HIV infection

Based on the best available evidence, the indications for the use of statins among patients with HIV infection to reduce cholesterol levels for primary prevention of acute coronary disease should not differ from uninfected patients.

Current European and American guidelines on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk base their recommendations on individual risk and LDL-C levels, but they differ in the strategy. In the European guidelines[103], the target of LDL-C levels depends on the 10-year risk of cardiovascular disease of the patient. This is estimated by the SCORE charts, so in patients with very high cardiovascular risk (SCORE ≥ 10%), the objective is reaching LDL-C levels < 70 mg/dl and/or reduction of LDL-C ≥ 50% when that target cannot be achieved. On the other hand, in patients with high cardiovascular risk (SCORE ≥ 5% and < 10%), the objective is < 100 mg/dl, and finally, in patients with a moderate risk (SCORE ≥ 1% and < 5%), the objective is < 115 mg/dl. The recommended treatment of choice for patients with hyperlipidemia is with statins up to the highest recommended doses or maximum tolerated doses to achieve the target level. These guidelines do not promote one or another statin, but depending on the levels of cholesterol reduction that are needed to reach the

objective, a specific drug may be chosen according to its potency. Noteworthy, in the HIV population, the possibility of interactions of statins with other drugs, and whether the patient has impaired renal function or not, should be taken into account. Other lipid-lowering medications are recommended either as adjuvants or substitutes in case of statin intolerance. For mixed dyslipidemia, the administration of drug combinations is recommended. According to the results of the IMPROVE-IT trial[60], adding ezetimibe to statins achieves additional reductions in levels of LDL-C in patients with acute coronary syndromes, so adding ezetimibe in this clinical setting may improve control of dyslipidemia. According to the European recommendations, to optimize lipid-lowering therapy, levels of LDL-C should be periodically determined in order to achieve the target objectives.

Current American guidelines[104] have brought a change in the management of patients with dyslipidemia. Firstly, a new equation to estimate the 10-year risk of suffering an atherosclerotic cardiovascular event (death from coronary heart disease, non-fatal myocardial infarction, fatal and non-fatal stroke) based on recent epidemiological studies is used, and the cut-off to define high cardiovascular risk at 10 years is 7.5%. In addition, it takes into account the different races (African Americans and Hispanics, with different levels of risk than Caucasians). Second, they eliminate the need to achieve specific LDL-C objectives because no randomized clinical trial has evaluated the impact of different doses of statins to achieve a specific goal of LDL-C. Therefore, LDL-C is determined at baseline and after 1-3 months of statin therapy to evaluate the response, but continuous monitoring will not be necessary unless the aim is improving adherence. Based on the evidence available, these guidelines identify four groups of patients who clearly will benefit from statin therapy and propose the specific drug to be selected based on the expected response of LDL-C reduction. Thus, patients with established coronary heart disease aged ≤ 75 or LDL-C ≥ 190 mg/dl or diabetic patients (type 1 or 2) aged 40-75 with cardiovascular risk ≥ 7.5% should receive high potency statins (atorvastatin 40-80 mg/day or rosuvastatin 20-40 mg/day). However, patients with established coronary heart disease aged > 75 years or diabetic patients (type 1 or 2) aged 40-75 with cardiovascular risk < 7.5% should receive moderate potency statins (lovastatin 40 mg/day, simvastatin 20-40 mg/day, pravastatin 40-80 mg/day, fluvastatin 40-80 mg/day, atorvastatin 10-20 mg/day, rosuvastatin 5-10 mg/day or pitavastatin 2-4 mg/day). Subjects aged 40-75 with cardiovascular risk ≥ 7.5% can receive moderate or high-potency statins (Table 1).

Recommendations for HIV-infected patients vary among different scientific societies, and there is no clear consensus on when to administer drug treatment or the target level[103,105,106]. European AIDS Clinical Society (EACS) guidelines[106] recommend the calculation of cardiovascular risk using the Framingham score or any local system of risk assessment (http://www.hivpv.org). For patients with high risk, defined as established cardiovascular disease, type 2 diabetes, or 10-year cardiovascular disease risk ≥ 10%, the standard recommended goal for TC is ≤ 190 mg/dl and for LDL-C ≤ 115 mg/dl, and the optimal recommended goal for TC is ≤ 155 mg/dl and for LDL-C ≤ 80 mg/dl[106]. For persons with lower cardiovascular risk, EACS guidelines refer to the Adult Treatment Panel III Report (www.nhlbi.nih.gov/guidelines/cholesterol/atp3_rpt.htm). According to the European Society of Cardiology guidelines, HIV-infected patients with dyslipidemia should be currently considered at least as patients with high cardiovascular risk, and a therapeutic goal for LDL-C of < 100 mg/dl is recommended[103].

When choosing a statin in patients with HIV infection, it is of paramount importance to take into account the drug-drug interaction profile, in addition to potency and safety. At present, patients taking ritonavir or cobicistat-boosted PIs should probably be started with pitavastatin at an initial daily dose of 2 mg to minimize the risk of drug interactions. For those receiving NNRTI, atorvastatin, starting at an initial daily dose of 10 mg, may be the preferred agent due to its potency and proven effectiveness in this population[38,43,44]. Rosuvastatin, starting at an initial daily dose of 10 mg, is a very effective alternative agent that has few drug-drug interactions. However, caution is recommended with this drug, given its potential exacerbation of insulin resistance. Pravastatin at an initial daily dose of 20 mg is a very acceptable alternative, but it may be less effective.

Conclusions

In conclusion, the lipid-lowering effects of statins in HIV-infected patients do not differ significantly from the general population. They are effective and well tolerated with few side effects. The safest and most effective statins are rosuvastatin, pitavastatin, atorvastatin, and pravastatin. It is important to consider the drug interaction profile, especially when combined with PIs boosted with ritonavir or cobicistat. Lovastatin and

simvastatin should be contraindicated when combined with PIs or cobicistat. Although additional clinical trials and observational studies are required to define the long-term benefits more accurately, statins in HIV patients receiving ART may slow the progression of vascular disease and could reduce mortality and the incidence of non-AIDS events. This effect appears to be independent of their hypolipidemic action and may be mediated by their ability to reduce immune activation and the anti-inflammatory effect.

Declaration of interest

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