HHS Public Access

Author manuscript

Curr HIV/AIDS Rep. Author manuscript; available in PMC 2016 September 01.

Published in final edited form as:

Curr HIV/AIDS Rep. 2015 September ; 12(3): 305–312. doi:10.1007/s11904-015-0273-9.

The Role of Statins in the Setting of HIV Infection

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Abstract

HIV-infected individuals are at an increased risk of cardiovascular disease (CVD) and other HIV-related co-morbidities. This is due in part to dyslipidemia associated with antiretroviral therapy and increased inflammation and immune activation from chronic HIV infection. Statins not only have potent lipid-lowering properties but are also anti-inflammatory and immunomodulators. Studies suggest that statin therapy in the HIV-infected population may decrease the risk of CVD and other non-AIDS-defining co-morbidities. This review summarizes the recent literature on statin use in the HIV setting.

Keywords

HIV; Statins; Hydroxy-3-methylglutaryl coenzyme A reductase inhibitors; Cardiovascular disease; Inflammation; Immune activation

Introduction

HIV-infected patients have a high prevalence of dyslipidemia secondary to antiretroviral therapy (ART), particular protease inhibitors (PIs). This dyslipidemia, as well as heightened immune activation and inflammation due to the independent effects of HIV infection, contributes to an increased risk of cardiovascular disease (CVD) in this population [1–4]. Statins are potent lipid-lowering drugs that are used increasingly more in the HIV setting to reduce blood cholesterol levels, particularly low-density lipoprotein (LDL), in an attempt to reduce CVD risk. The potential benefit of using statins in the HIV-infected population, however, extends beyond its lipid-lowering properties. Statins also have anti-inflammatory and immunomodulatory effects that may be particularly beneficial in the HIV-infected population for CVD risk reduction as well as attenuation of other HIV-related co-

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Compliance with Ethics Guidelines

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

Conflict of Interest Allison Ross Eckard declares a grant from NIH for work related to the article, grants from Cubist Pharmaceuticals, GlaxoSmithKline, and Bristol–Myers Squibb to her institution, and personal consulting fees from Gilead Sciences. Grace A. McComsey declares a grant from NIH for work related to the article and grants and personal fees from Bristol-Myers Squibb, ViiV/GlaxoSmithKline, Gilead, ICON, and Merck for serving as a consultant, speaker, and for receiving research funding.

morbidities. This review discusses the most recent literature on the use of statins in the setting of HIV.

Overview of Statins

Statins are a class of prescription drugs that, as their main mechanism of action, inhibit hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the rate-limiting enzyme in the cholesterol biosynthetic pathway. Statins were developed as a means of reducing plasma levels of cholesterol, particularly LDL cholesterol, as evidence mounted that elevated cholesterol was a major risk factor for the development of coronary heart disease (CHD) in the general population [5]. The first statin, lovastatin, was approved by the FDA and came to the market in 1987, and, currently, there are seven statin drugs available by prescription in the USA.

The first in a series of landmark clinical trials demonstrated that simvastatin use in the general population drastically reduced all-cause mortality by 30 %, owing mostly to a 42 % reduction in coronary deaths [6]. The largest, placebo-controlled 5-year statin study ever conducted followed a few years later, which confirmed these results and expanded their effectiveness to include reduction in the risk of stroke and comprised additional patient groups, such as women, patients over 70 years old, diabetics and patients with cerebrovascular or peripheral vessel disease but without CHD, and patients with LDL cholesterol <100 mg/dL [7].

Use of Statins for Dyslipidemia in HIV-infected Patients

While the introduction of highly active antiretroviral therapy (HAART) has allowed HIV-infected individuals to live for decades longer than before, it has also caused a dramatic increase in the incidence of dyslipidemia in this population, particularly among those taking PIs, and to a lesser extent, those taking non-nucleoside reverse transcriptase inhibitors (NNRTI). Given statins' drastic lipid-lowering properties, the practice of prescribing statins to HIV-infected individuals has increased dramatically. With the release of the 2013 American Heart Association/American College of Cardiology guidelines for CVD risk reduction, which expands the use of statin therapy [8•], this number will likely increase further.

The use of statins in the HIV-infected population, however, is complicated by their interactions with some antiretrovirals. Most statins are metabolized by the P450 3A4 cytochrome enzyme system (CYP3A4) and/or are substrates of the organic anion-transporting polypeptide (OATP) 1B1. Protease inhibitors and other antiretrovirals, such as efavirenz, interact with statins because they potentially inhibit CYP3A4 or transporters or both. Protease inhibitors are almost always used with a boosting agent, frequently low-dose ritonavir, which is the most powerful CYP3A4 inhibitor of all the PIs. Fluvastatin, pravastatin, and rosuvastatin generally are considered the safer statins because their metabolism does not utilize CYP3A4. However, pravastatin and rosuvastatin may have some interactions with PIs via inhibition of OATP 1B1 that facilitates statin update into the liver. There are no known interactions between rosuvastatin and NNRTIs [9–13]. While the drug–

drug interactions can be cumbersome, one study has suggested that it is more effective to add a statin to an existing antiretroviral regimen than to switch regimens [14]. The potential interactions with antiretrovirals can be managed with careful selection of the appropriate statin, often at a lower dose than what is used in the general population [12, 15].

Another factor to consider in choosing a statin for an HIV-infected individual is the lipid-lowering potency of a particular statin. In the general population, at 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 total cholesterol (TC), LDL cholesterol, and triglyceride (TG) levels and in raising high-density lipoprotein (HDL) cholesterol levels [16, 17]. This also seems to be true in the HIV-infected population. For example, in a randomized controlled trial including 83 HIV-infected subjects with dyslipidemia on a boosted PI regimen, 10 mg/kg rosuvastatin was more effective that 40 mg/day pravastatin in reducing both LDL cholesterol (−37 vs. −19 %, $P<0.001$) and TG (−19 vs. −7 %, $P=0.035$) after 8 weeks of therapy [9]. High-density lipoprotein cholesterol did not change significantly in either group. This lack of significant change in HDL cholesterol demonstrates the challenge in treating dyslipidemia in HIV-infected patients. While dyslipidemia does improve with statin therapy, the overall decrease in LDL cholesterol and TG levels appears to be less than what is observed in the general population [18–22]. In the aforementioned trial by Aslangul et al., for instance, the mean percentage changes were 13 % lower than observed in a similar study of HIV-uninfected individuals [18]. Likewise, the impact of statin therapy on HDL cholesterol also appears to be less, as studies in the general population have reported increases of 9 % [19]. These attenuated responses do not appear to be linked to the issue of drug interaction with PIs, as they have also been repeated in other studies, including among HIV-infected individuals on NNRTI regimens [23].

The etiology of this attenuated response with statin therapy in HIV-infected individuals is indeed unclear but may be due in part to the mixed dyslipidemia pattern seen among this population. Dyslipidemia in HIV-infected patients on HAART usually consists of hypertriglyceridemia, decreased HDL cholesterol, elevated LDL cholesterol, and a decrease in the size of the LDL particles. The hypertriglyceridemia also contributes to the formation of small dense LDL (sdLDL) particles that are very atherogenic because of their ability to infiltrate the arterial wall and link to the LDL receptors and their high oxidizability [24].

The effects of statins are dose-dependent; therefore, increasing the statin dose may improve its efficacy in correcting dys-lipidemia in the HIV-infected population. However, such dose increases may come at the expense of increased toxicity, including possible increased risk of diabetes. In general, statins used at recommended doses in HIV-infected individuals have a relatively low risk of side effects in most studies [9, 15, 25•]. The most serious side effect is rhabdomyolysis, which occurs in the general population at an excess risk of about 0.1 % [26]. This risk seems to be similar in the HIV-infected population. The increased diabetes risk with statins in the HIV population is unclear, albeit concerning, in a population known for a heightened risk of diabetes [27]. In the general population, high-dose statins are more likely to be associated with diabetes risk than lower doses [28]. In the HIV population, a single study investigated changes in insulin resistance with rosuvastatin in HIV-infected

subjects; in this study, we showed a >50 % increase in insulin resistance, as measured by the homeostasis model assessment of insulin resistance (HOMA-IR), after as early as 48 weeks into the study [29•].

There have been a few studies that have investigated changes in surrogate measures of CVD in dyslipidemic HIV-infected subjects. For example, Boccara et al. compared the differences in common carotid artery (CCA) intima-media thickness (IMT) as a measure of subclinical atherosclerosis and pulse wave velocity (PWV) and as a measure of arterial stiffness, in 42 pravastatin-treated HIV-infected patients and 42 sex-, age-, and smoking status-matched hypercholesterolemic HIV-infected patients not on lipid-lowering treatment. The authors did not find any differences between the two groups for CCA IMT or PWV [30].

However, in a randomized, crossover, double-blind, placebo-controlled interventional trial investigating pravastatin 40 mg daily and matching placebo for 8 weeks each, Hürlimann et al. [22] observed a significant improvement in endothelial function as measured by flow-mediated vasodilation in 29 HIV-infected dyslipidemic subjects. The differing results in these two studies may be due to the lack of a randomized design and lower pravastatin doses in the former study. The effect of statins on carotid IMT in HIV-uninfected patients is related to the degree of LDL cholesterol reduction, which was less in this study than what is observed in the general population. Additionally, in a population of HIV-infected subjects on ART with an LDL cholesterol <130 mg/dL, we recently reported the results of a randomized, double-blind, placebo-controlled trial of rosuvastatin (Stopping Atherosclerosis and Treating Unhealthy Bone with Rosuvastatin in HIV (SATURN-HIV)) [31••]. After 96 weeks, rosuvastatin successfully halted the progression of carotid IMT. This effect was independent of the lipid-lowering effect of the statin, and the subjects with higher baseline IMT levels and baseline coronary calcifications appeared to benefit the most from this protective cardiovascular effect.

Anti-Inflammatory and Immunomodulatory Properties of Statins

As shown in the SATURN-HIV study, some of statins' ability to reduce the risk of CVD events is independent of cholesterol effects and is owed to their capacity to reduce inflammation, with the most studied inflammatory marker in the general population being C-reactive protein (CRP) [32, 33], an acute-phase reactant that appears to play a role in the pathogenesis of atherosclerosis [34]. Statins reduce not only levels of CRP, but they also affect other biomarkers of systemic inflammation and endothelial dysfunction to reduce CVD risk. For example, by reducing inflammatory cell adhesion and monocyte recruitment to endothelial cells, changing smooth muscle migration in developing plaques, and favorably affecting matrix metalloproteinases, statins help stabilize atherosclerotic plaques [33, 35–38].

Indeed, statins exert wide-reaching anti-inflammatory and immunomodulatory effects that extend well beyond CVD prevention. They influence both the innate and adaptive immune responses, including decreasing T cell activation [39, 40]. Studies from the general population have shown evidence that statins reduce the risk of malignancy and mortality from such conditions as pneumonia, sepsis, and influenza [41–45].

Implications of Immunological Effects of Statins in the HIV-infected Population

Notably, inflammation, as measured by CRP and other inflammatory markers, is increased in HIV-infected individuals even with virologic suppression [46]. Similarly, these patients also have heightened levels of immune activation (both monocyte and lymphocyte activation). The increased inflammation and heighted immune activation contribute not only to an increased CVD risk beyond that seen in the general population but also to other HIV-related co-morbidities, such as non-AIDS-defining malignancies, osteoporosis, and neurocognitive impairment [47]. Notably, increased inflammation and immune activation is associated with increased all-cause mortality and HIV disease progression [3, 48]. Thus, statins are a natural choice to investigate whether their anti-inflammatory properties and immunological effects could attenuate the co-morbidity risk associated with HIV.

There have been several studies investigating whether statins affect levels of inflammation or immune activation in the HIV-infected population, with somewhat conflicting data. C-reactive protein levels decreased after 45 days of either 40 mg pravastatin or 10 mg rosuvastatin from 3.0 to 2.4 mg/L (P<0.001) in 58 dyslipidemic HIV-infected patients with good virologic control on a ritonavir-boosted PI regimen, but the authors observed no significant changes in other inflammatory markers, including soluble tumor necrosis factor-α receptors I and II, intercellular adhesion molecule-1, and vascular cell adhesion molecule-1 [49]. The CRP results are similar to a longitudinal, observational study of ART-naïve patients who were followed up for 48 weeks after starting either tenofovir/emtricitabine/efavirenz alone (N=46) or tenofovir/emtricitabine/efavirenz with 10 mg rosuvastatin for concomitant dyslipidemia (N=40) [50•]. The group that also received rosuvastatin had significantly greater reductions in CRP, but they also had a decrease in the other measured inflammatory markers (interleukin-6, interleukin-8, and tumor necrosis factor-α). However, not all studies, including randomized controlled trials, have shown any significant change in CRP after 24 [25•] and 48 weeks [51] of statin therapy, as well as in a case–control study [52]. Some of the discrepancy may be related to different statins studied and/or differences among the HIV-infected subjects.

In De Wit et al., while they did not observe a significant change in CRP after at least 48 weeks of atorvastatin in their case–control study, they did see a reduction in CD8+ T cell CD38 expression, which is a marker of immune activation [52]. This may suggest that statins affect inflammation and immune activation via different mechanisms. Similarly, Ganesan et al. [53] found significant reductions in levels of activated T cells after 8 weeks of high-dose atorvastatin vs. placebo among 22 HIV-infected individuals not on ART and with an LDL cholesterol <130 mg/dL (CD4+HLA–DR+ T cells: −2.5 %, P=0.02; CD8+HLA–DR+ T cells: −5 %, P= 0.006; CD8+HLA–DR+CD38+ T cells: −3 %, P=0.03).

In a more clinically relevant population, in subjects on ART, the previously mentioned randomized, placebo-controlled trial (SATURN-HIV) that randomized 147 subjects to 10 mg rosuvastatin vs. placebo also showed favorable changes in CD4+ and CD8+ activation, but only after 48 weeks of treatment [54•]. The SATURN-HIV trial also showed that as little as 24 weeks of treatment, rosuvastatin led to decreases in soluble CD14 (sCD14) by 13.4 vs.

1.2 % in the placebo group (P=0.002) [55•]. Soluble CD14, a marker of monocyte activation, is an independent predictor of mortality in HIV-infected subjects [56], and a reduction of this magnitude in sCD14 levels may be clinically important, as a 13 % decrease in sCD14 was associated with an estimated 21 % decrease in non-AIDS morbidity or death, based on risk findings from a study among virologically suppressed subjects [57].

Consistent with a decrease in immune activation, the SATU RN-HIV trial has also reported significant decreases in both proportions of tissue factor (TF)-positive patrolling (CD14DimCD16+) monocytes (−39 vs −12 %, P=0.04) [54•] and in lipoprotein-associated phospholipase A_2 (Lp-PLA_2) concentrations (−10 vs. −2 %, P<0.01) among rosuvastatin-treated subjects compared to placebo-treated subjects [25•]. Changes in these two parameters may have particular importance to HIV-related CVD risk. For example, TF can initiate the extrinsic clotting pathway [58] and patrolling monocytes home in to the vascular endothelium [59], where they may initiate clot formation. Tissue factor expression is increased on circulating monocytes in HIV-uninfected persons with recent acute coronary events [60].

Likewise, increased Lp-PLA_2 concentration or activity predicts both primary and recurrent future coronary or cardiovascular events in the general population [61]. Thus, decreasing Lp-PLA_2 concentrations with statin therapy may result in CVD risk reduction among HIV-infected individuals. However, STABILITY, a placebo-controlled phase III trial to evaluate the Lp-PLA_2 inhibitor, darapladib, in 15,828 subjects with stable CHD, showed no benefit for the primary endpoint of time to the first major CVD event in general population [62]. More data are needed specifically in the HIV-infected population to determine if statin therapy by way of decreasing inflammation, immune activation, or Lp-PLA_2 concentrations or perhaps even via another mechanism, may prevent clinical cardiovascular events.

There have only been a few studies investigating whether statins affect clinical outcomes in HIV-infected individuals [63••, 64, 65•, 66]. Moore et al. [64] conducted a retrospective analysis using data from the Johns Hopkins HIV Clinical Cohort of eligible patients who achieved virologic suppression within 180 days of starting a new HAART regimen after January 1, 1998. There were 85 deaths (7 in statin users, 78 in non-users) among the 1538 eligible HIV-infected patients. By multivariate Cox regression, statin use was associated with a relative hazard of 0.33 (95 % confidence interval (CI): 0.14, 0.76; P=0.009) after adjusting for a large number of clinical and demographic confounders. While there were a number of significant limitations to this observational analysis, the results are intriguing. Likewise, in a Danish nationwide cohort of 1738 HIV-infected patients, statin use significantly reduced all-cause mortality in patients who also had a co-morbidity diagnosis [63••].

Similarly, Overton et al. performed an exploratory analysis to evaluate whether statin therapy decreased the risk of non-AIDS-defining events and non-accidental death among 3601 subjects not on a statin from the AIDS Clinical Trials Group Longitudinal Linked Randomized Trials (ALLRT) cohort [65•]. Over 15,135 person-years of follow-up were evaluated, including 484 subjects who initiated statins and 616 subjects who experienced an event (cardiovascular event, renal or hepatic disease, incident diabetes, thrombotic/embolic

event, non-traumatic fracture, non-AIDS-defining malignancy, serious bacterial infection, or non-accidental death). The results did not show a significant reduction in time for combined non-AIDS-defining events or non-accidental deaths (adjusted hazard ratio (AHR), 0.81 [95 % CI, 0.53, 1.24]), or for individual clinical events, except for non-AIDS-defining malignancies (AHR, 0.43 [95 % CI, 0.19, 0.94]), where the authors demonstrated a 57 % reduction. The authors point out, however, that although not statistically significant, there was a 19 % reduction in non-AIDS-defining events with statin use, which was not driven specifically by cardiovascular events, providing support that statins' anti-inflammatory properties may provide benefit for HIV-related co-morbidities beyond CVD. Further evidence is provided by a nested case–control study of 259 cases and 1295 controls that showed that statin use was associated with a reduced risk of non-Hodgkin's lymphoma in HIV-infected subjects (hazard ratio and 95 % CI for every 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) [67].

Interestingly, Overton et al. also demonstrated a significant increase in bacterial infections (AHR, 1.30 [95 % CI, 0.64, 2.65]) and a non-significant increase in AIDS-defining events (AHR, 1.24 [95 % CI, 0.44, 3.52]). The authors suggest that this association could have been attributed to non-adherence to both HIV and statin therapy or possibly to statin-induced reductions in innate immune activation. While statin-induced reductions in innate immunity would have a beneficial effect on some co-morbidities, it could be harmful in other circumstances. This possible negative effect was also expressed as a concern in a letter to the editor to *JAIDS* by Corrales-Medina et al. in 2005 in response to a study showing that statin therapy decreases the T-helper-1 (Th1)/T-helper-2 (Th2) lymphocyte ratio [68, 69], the reverse of what is observed in the course of HIV infection. Indeed, the authors point out that cross-modulation and cross-regulation between Th1 and Th2 cytokines appear to be necessary in the maintenance of adequate anti-HIV CD8+ T cell responses in HIV-infected chronic non-progressors [70].

In addition, in small retrospective cohort studies, the data suggested that the use of statins was associated with lower CD4+ T cell responses in patients on HAART [70, 71]. In contrast, however, randomized controlled trials have not observed any changes in CD4 counts with statin therapy [54•, 72]. Similarly, a number of studies have shown in vitro HIV inhibition with statins [73–77], but this has not played out in vivo [53, 71, 72].

Taken together, these data indicate that further studies, particularly long-term, randomized, placebo-controlled trials are needed to fully assess the possible effects that statins may have on CVD and non-CVD-related co-morbidities and immunological parameters in the HIV-infected population. Further analyses are planned for the SATURN-HIV trial to understand the mechanisms of the beneficial effect of statins on halting vascular disease. Likewise, the AIDS Clinical Trials Network is currently enrolling in the REPRIEVE (Randomized Trial to Prevent Vascular Events in HIV) study, which is a large-scale randomized trial to investigate daily pitavastatin vs. placebo for the primary prevention of cardiovascular-related events in HIV-infected patients who would not normally qualify for statin initiation based on the 2013 ACC/AHA guideline thresholds. Investigators plan to enroll 6500 participants with a 72-

month follow-up period, the largest trial of its kind ever to be conducted and the first study to date that includes clinical cardiovascular endpoints rather than surrogate markers.

Conclusions

Statins have potent lipid-lowering capacity, as well as anti-inflammatory and immunomodulatory properties, and have been recently shown to reduce progression of vascular disease in HIV-infected subjects on ART. Thus, given the current data, statins appear to hold particular promise for HIV-infected individuals. Additional randomized controlled trials and mechanistic studies are needed to further define the long-term safety and benefits for reducing both CVD risk and HIV-related co-morbidities in this population.

Acknowledgments

The work was supported by the National Institute of Child Health and Development at the National Institutes of Health [K23 HD069199 to ARE and R01 NR012642 and HD070490 to GAM]. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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•• Of major importance

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