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Benefits and Risks of Statin Therapy in the HIV-Infected Population

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Abstract

Purpose of Review HIV-infected patients face an increased risk for cardiovascular disease (CVD), estimated at 1.5- to 2-fold as compared to HIV-uninfected persons. This review provides a recent (within preceding 5 years) summary of the role of statin therapy and associated role in CVD risk reduction among HIV-infected patients on anti-retroviral therapy.

Recent Findings Statins remain the preferred agents for reducing risk for CVD among HIV-infected populations based on guidance extrapolated from general population (HIV-uninfected) cholesterol treatment guidelines across different settings globally. However, HIV-infected patients are consistently under prescribed statin therapy when compared to their HIV-uninfected counterparts. The most commonly studied statins in clinical care and small randomized and cohort studies have been rosuvastatin and atorvastatin. Both agents are preferred for their potent lipid-lowering effects and their favorable or neutral pleotropic effects on chronic inflammation, renal function, and hepatic steatosis among others. However, growing experience with the newer glucuronidated pitavastatin suggests that this agent has virtually no adverse drug interactions with ART or effects on glucose metabolism—all marked additional benefits when compared with rosuvastatin and atorvastatin while maintaining comparable anti-lipid effects. Pitavastatin is therefore the statin of choice for the ongoing largest trial (6500 participants) to test the benefits of statin therapy among HIV-infected adults.

Summary Statins are underutilized in the prevention of CVD in HIV-infected populations based on criteria in established cholesterol guidelines. There is a potential role for statin therapy for HIV-infected patients who do not meet guideline criteria which will be further delineated through ongoing clinical trials.

Keywords Statin · Atherosclerotic cardiovascular disease · Inflammation · HIV · Prevention

Statin Therapy and Atherosclerotic Cardiovascular Disease

Statin Therapy and Lipid Indices Among HIV-Infected Populations

Statins are competitive inhibitors of hydroxyl-3-methylglutaryl coenzyme A (HMG-CoA) reductase that were first derived from fungal species such as *Pythium* sp., *Penicillium* sp., and *Aspergillus* sp. in the 1970s [1]. The original target of statin therapy was cholesterol reduction—both total cholesterol and low-density lipoprotein (LDL) cholesterol. Inhibition of HMG-CoA reductase results in reduced hepatic cholesterol synthesis and stores, with resultant upregulation of the LDL receptor, both of which results in lower cholesterol levels in plasma [2]. Recently, statins were newly observed to lower plasma cholesterol levels by enhancing fecal excretion of cholesterol in mice models [3, 4]. This newly elucidated mechanism of statins may be particularly relevant

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to the HIV-infected population whose underlying disease is associated with gut dysbiosis.

When prescribed to HIV-infected patients, statin therapy is associated with decreases in serum lipid indices [5••, 6•] albeit somewhat attenuated when compared to HIV-uninfected persons [7–9]. For example, in a 98-person AIDS Clinical Trials Group (ACTG) study, A5275, high-intensity statin therapy (atorvastatin dosed at an equivalent of 80 mg daily) among HIV-infected adults resulted in a 38% drop in LDL [10•], somewhat lower than the expected > 50% decrease in LDL based on general population studies [11]. To the extent that ritonavir-boosted protease inhibitor therapy has been associated with elevated cholesterol [12], initiating statin therapy yielded superior total cholesterol and LDL decreases compared with switching ART from a ritonavir-containing regimen (lopinavir, darunavir, atazanavir) to either raltegravir or etravirine [13] or with switching lopinavir/ritonavir to atazanavir/ritonavir [14]. This observation is important in instances where switching ART is not an option due to underlying HIV drug resistance or prior ART toxicity issues. Interestingly, addition of ezetimibe to rosuvastatin 10 mg results in improved lipid indices with no adverse effects compared with doubling the dose of rosuvastatin [15].

Beyond their original targets of total and LDL cholesterols, statins are associated with decreases in other atherogenic lipid particles. In A5275, oxidized LDL and lipoprotein-associated phospholipase A2 were both decreased by approximately one-third [10•]. In another randomized controlled trial of 147 HIV-infected adults on ART, rosuvastatin 10 mg was associated with in initial statistically significant drop in oxidized LDL cholesterol that was no longer apparent at 48 weeks [16], prompting questions about the long-term impact of statin therapy on cholesterol homeostatis among this group. In a post hoc analysis of the randomized INTREPID trial [17], statin therapy (pitavastatin) was associated with reduction in intermediate-density lipoprotein and very low-density lipoprotein cholesterols in addition to lowering the ratio of apolipoproteins B/apolipoproteins A1 [18]. In the HIV population, a statin-mediated decrease in oxidized LDL was also independently associated with decreases in important markers of preclinical atherosclerosis such as coronary plaque [19] and carotid intima media thickness [16] but not with changes in coronary calcium [9].

Despite the well-described beneficial effects of statin therapy on lipid indices, several biologic and pharmacologic factors may moderate the efficacy of statin therapy among HIV-infected adults. For instance, rosuvastatin seems more potent than atorvastatin [20, 21] in the HIV-infected population, yet atorvastatin appears to be more efficacious among women than men [22]. This important sex difference is yet to be studied among HIV-infected adults, especially in resource-limited settings where women face an increased risk of HIV when compared to their male counterparts. There is also new data indicating that rosuvastatin may be less efficacious among HIV-infected adults with baseline vitamin D deficiency at the time of statin initiation [23]. Further, HIV-infected adults who smoke cigarettes do not experience regression of carotid intima media thickness when prescribed rosuvastatin [24]. Whether these exposures and biological factors will ultimately guide statin selection in the HIV-infected population remains an open question. At this time, it may be reasonable to take into consideration such factors when selecting a statin.

Statin Therapy for Primary and Secondary Prevention of CVD Endpoints and Reduction in All-Cause Mortality in the HIV-Infected Population

There are no guidelines on statin therapy that have been specifically developed for primary prevention of CVD among HIV-infected patients. When the 2013 American College of Cardiology/American Heart Association cholesterol guidelines [11] were applied to HIV-infected patients, these guidelines did not identify the majority of HIV-infected patients with carotid plaque [25] or those with high-risk morphology coronary plaque [26]. This highlights a significant gap in the HIV-infected population that would not be recommended statin therapy despite being at increased risk for CVD. When statin therapy for primary prevention of CVD was assessed in a clinical setting, there was no association of statin therapy with stroke, myocardial infarction, or death among 881 HIV-infected adults after controlling for confounding via propensity scores [27]. However, only 438 participants had sufficient data to be included in the final analysis, and among these 438, only 67 were on statin therapy [27]. These low numbers, coupled with potential confounding by indication, may have precluded the ability to adequately assess statin effect for primary CVD prevention. Several studies have evaluated the effect of statins on mortality. While several studies have demonstrated reductions in mortality associated with statin use in HIV populations [28, 29] and a small, but non-statistically significant reduction in all-cause mortality following statin use among HIV-infected patients in a Danish nationwide population-based cohort study of 1738 adults [30], other studies have not shown an association [31].

Pleotropic Effects of Statin Therapy in HIV-Infected Population

Statin Therapy and Inflammation

Statin therapy may confer additional protection against CVD beyond lipid-lowering by decreasing biomarkers of arterial inflammation and thrombosis and exerting anti-oxidant and vasodilatory effects [32, 33]. Moreover, there may be a role in limiting HIV viral replication [34]. Like statin effect on

lipid indices, the immunomodulatory effects of statins have not been uniformly consistent across studies and may also differ based on the specific statin evaluated or duration of follow-up [35, 36]. In a randomized controlled trial of 256 HIV-infected adults on ART in the INTREPID trial, pitavastatin 4 mg was significantly more likely to lower soluble CD14 (sCD14) compared with pravastatin 40 mg (both moderate intensity statin therapy doses) [37]. Similarly, in the Stopping Atherosclerosis and Treating Unhealthy bone with Rosuvastatin in HIV (SATURN-HIV) trial among HIV-infected adults on ART, rosuvastatin 10 mg significantly decreased sCD14 by 10%, lipoprotein-associated phospholipase A2 by 12%, and IP-10 by 27% (versus 0.5%, 1.7 and 8.2% for placebo respectively) [38]. As in the ex vivo trial of atorvastatin and simvastatin, rosuvastatin 10 mg reduced intermediate profile monocytes, CD14++CD16+ [38, 39] and N-terminal pro-B-type natriuretic peptide (a marker of increased risk of death in HIV) [40]. However, in a retrospective cohort study of 151 HIV-infected adults on ritonavir-boosted protease inhibitors in Italy, rosuvastatin 10 mg, atorvastatin 10 mg, and pravastatin 40 mg all induced similar decreases in high-sensitivity C-reactive protein (hsCRP) and tumor necrosis factor alpha (TNF-α), unrelated to changes in lipid indices [20]. These decreases in inflammatory markers merit long-term study as some studies did not report this association [36, 41]. However, taken together, statins seem to confer a favorable inflammatory profile in the HIV-infected population.

While statin therapy did not decrease arterial inflammation as measured by FDG PET-CT in a randomized controlled trial of 40 HIV-infected adults in the USA [42], it was associated with a decrease in the volume of non-calcified coronary plaque. Among HIV-infected ART-naïve adults, the effect of statins on inflammatory markers was essentially nonexistent or minimal [43•], perhaps highlighting the overwhelming pro-inflammatory effect of ongoing HIV viral replication. Given recent data to suggest that initiation of ART does not reduce arterial inflammation [44•], concomitant adjunctive therapies to ART, to reduce inflammation, are needed and statins may be useful in this regard.

Statin Therapy and End-organ Dysfunction

Because of their pleotropic effects [45], statins have been studied in treating organ dysfunction beyond the cardiovascular system.

HIV-infected patients experience widespread gut dysbiosis, which in turn is associated with excess CVD [46, 47]. When assessed for their impact on gut dysbiosis in HIV populations, however, statin therapy has had limited benefits. In the SATURN-HIV trial, rosuvastatin 10 mg was associated with a decrease in a marker of enterocyte death, intestinal fatty binding protein (I-FABP), but not with changes in gut epithelial integrity or gut microbial translocation [48]. However, given the recent animal model of enhanced cholesterol excretion in the gut following statin therapy exposure [4], it is likely that future additional studies in the interaction between statin and gut dysbiosis in the HIV-infected population will ensue. Because HIV infection is also associated with increased frailty [49], and particularly decrease in lean body mass [50, 51] and physical strength [52], a reduction in inflammation with statin therapy has been evaluated to address these problems. For instance, in a study of 147 HIV-infected adults on ART followed for 96 weeks, rosuvastatin 10 mg was associated with a non-statistically significant increase in lean body mass [53], indicating a potential role of statin therapy in decreasing muscle frailty and its associated complications in this population. Indications for statin therapy in the HIV-infected population may expand beyond the traditional lipid-lowering role.

Nonalcoholic fatty liver disease is prevalent in the general population and among HIV-infected patients [54–56] and is related to mortality among HIV-infected patients in high-income countries [57]. To this end, a small interventional study on hepatic steatosis suggested that atorvastatin reduced hepatic steatosis [58] as has been demonstrated in the general population [59]. In relation to renal impairment, rosuvastatin 10 mg among HIV-infected adults on ART has been shown to slow down decline in renal dysfunction as assessed using cystatin C [60]. Because monocyte activation plays a significant role in the development of HIV-associated neurocognitive disorders (HANDs) [61], ex vivo experiments in which treatment with simvastatin or atorvastatin induced a reduction in intermediate monocyte profile (CD14++CD16+) that has been implicated in the development/pathogenesis of HANDs [39] suggest a possible future role of statin therapy for this condition. Nontraditional effects of statin therapy will likely be the focus of many future studies in the HIV-infected population.

Statin Prescription in Routine HIV Care

Globally, multiple HIV clinical cohorts have reported widespread underuse of statin therapy among HIV-infected patients who would otherwise be recommended statin by established general population cholesterol guidelines for both primary and secondary prevention [62–67]. For instance, in a nationally representative survey representing 2.2 million HIV-infected adults' clinic visits versus 602 million clinic visits for HIV-uninfected adults, statin prescription rates were significantly lower (23.6 versus 35.8%, $p < 0.01$) among HIV-infected versus HIV-uninfected [68]. In Botswana, a resource-limited setting, only 1% of the estimated 14% HIV-infected adults recommended statin therapy by the 2013 ACC/AHA guidelines were actually prescribed statin therapy [63]. With regard to actual physician-reported behavior towards statin prescription, 43%

of Italian physicians reported prescribing statins to HIV-infected patients who were recommended statin therapy as per the European AIDS Clinical Society recommendations [69]. However, in a US observational multicenter study of 282 acute coronary syndrome (ACS) patients, HIV-infected patients with ACS were more likely to be prescribed moderate intensity statin therapy (66 versus 45%) and less likely to be prescribed high-intensity statin therapy (15 versus 45%) as compared to HIV-uninfected controls as per the 2013 ACC/AHA cholesterol guidelines [11, 70]. Similarly, HIV-infected adults were less likely to attain LDL targets among 543 HIV-infected men in the Multicenter AIDS Cohort Study (MACS) despite statin prescription [71]. The reasons for the comparatively lower statin prescription rates among HIV-infected adults remain unclear and require further study; patient, provider, and health system/local factors may contribute to lower statin prescription rates. Of note, statin prescription in a clinical setting is associated with lower risk of HIV virologic failure [72], indicating potential benefits of statin therapy on management of underlying chronic HIV infection, and providing re-assurance regarding the neutral effects of statins in maintaining viral suppression among patients on effective ART.

Risks Associated with Statin Therapy in the HIV-Infected Population

Statin therapy is associated with increased risk for toxicity when co-prescribed with ritonavir-boosted protease inhibitors, and less so with other ART agents [73–76]. In contrast, there is no clinically significant interaction between statin therapy and integrase inhibitors with or without cobicistat [75, 77]. However, when statins are combined with fibrates in the context of cobicistat-boosted integrase inhibitors, rhabdomyolysis has been reported, in one recent case report [78].

Data on statin therapy and risk of insulin resistance and diabetes mellitus is mixed, with some studies suggesting an increased risk [79, 80] while others not [81, 82]. More recently, in a large retrospective cohort study involving 6195 HIV-infected patients on ART, statin use was not associated with increased risk for diabetes mellitus, but rather, diagnosis of diabetes mellitus was associated with the presence of other traditional risk factors for CVD and prior use of stavudine [81]. In contrast, a national observational study of 945 HIV-infected adults in Taiwan followed for 11 years revealed that high-intensity statin therapy (atorvastatin) was associated with more incident diagnoses of type II diabetes mellitus (DM II) compared with low-intensity statin therapy (pravastatin) (15.3 versus 8.3% respectively) [83]. The fact that data remain mixed may reflect the higher prevalence of insulin resistance compared with overt DM II or low statin prescription rates, factors which may influence the ability of a study to detect an association. Additionally, the association between statins and insulin resistance may not represent a class effect. For instance, pitavastatin seems to have no effect on glucose metabolism at 52 weeks in a trial setting [17]. Taken together, there is an important signal of increased insulin resistance and diabetes among HIV-infected patients on statins that merits further evaluation.

While there has been concern about risk of statin-induced liver injury among HIV-infected adults based on older studies among HIV-uninfected adults, a new large Veterans Aging Cohort Study conducted between 2000 and 2012 revealed that statin exposure among 17,737 HIV-monoinfected and 7686 HIV/HCV-coinfected adults was associated with decreased risk of acute liver injury and death when compared with statin nonusers followed for 18 months [84]. In relation to muscle toxicity, data from HIV-infected adults is mixed, with some studies reporting increased muscle toxicity among HIV-infected than HIV-uninfected adults [85] and other studies failing to detect this association [83]. This toxicity has been linked to underlying vitamin D deficiency in more recent HIV cohorts [86•]. Studies on effect of statins on cognitive function have not reported dementia as a result of statin exposure among HIV-infected adults [83]. Taken together, the benefits of statin therapy seem to outweigh the rare, often predictable, liver or muscle toxicity and other toxicities from statin therapy. These effects are likely to occur even less frequently with widespread use of integrase inhibitors and newer statins such as pitavastatin.

In the pediatric and adolescent HIV-infected population, concern for statin toxicity is focused on those on combination statin therapy and ritonavir-containing ART as this toxicity has been observed in adults. Among HIV-uninfected adolescents, the most commonly observed adverse effect is a rise in ALT, AST, or CK [87]. In a more recent trial of 28 pediatric and adolescent HIV-infected participants (10–24 years old, 79% on ritonavir-containing ART), only 2 had their statin discontinued due to toxicity [88]. The first patient experienced new grade 3 creatinine (relatively rare toxicity from atorvastatin [89]) while the other had grade 4 drug-induced liver injury. Of note, despite lowering cholesterol levels (pre-cursor for steroid production), exposure to statin therapy among HIV-uninfected children and adolescents has not been associated with delayed reproductive development [87]. There are no published studies on the risk of insulin resistance or DM II among HIV-infected children and adolescents on statin therapy. More studies are needed to explore this link given the significant morbidity associated with DM II.

Future Studies on Statin Therapy and HIV-Infected Population

The much anticipated results of randomized controlled trial to prevent vascular events in HIV (REPRIEVE) will provide the most robust evidence on the use of statins among HIV-infected adults globally [90]. Key findings to be reported by

this trial include the effect of a relatively well-tolerated glucuronidated statin with essentially no adverse drug interactions with ART, pitavastatin 4 mg [91], on major cardiovascular events and all-cause mortality among 7500 HIV-infected adults followed for approximately 4 years in both low- and high-income settings (see www.REPRIEVEtrial.org for current trial status and updates). In keeping with findings of the smaller studies that have assessed effect of statin therapy on other end-organ dysfunction, REPRIEVE (and associated nested sub-studies) will assess the impact of pitavastatin on inflammation, renal outcomes, and liver outcomes and evaluate sex-specific effects of pitavastatin on CVD risk among other secondary endpoints.

Conclusion

Statin therapy lowers LDL and oxidized LDL cholesterol among HIV-infected patients and demonstrates pleotropic effects including likely beneficial effects on inflammation, hepatic fatty infiltration, and frailty. These drugs generally have few side effects in the context of appropriate statin-ART dosing. Preliminary observational data suggests a potential CVD morbidity and all-cause mortality benefit in routine care. However, a large gap exists in the prescription of statin therapy in the HIV-infected population when compared with HIV-uninfected groups, with an estimated 50% or more HIV-infected patients who are recommended statin therapy according to the general population cholesterol guidelines not prescribed statins. The REPRIEVE trial will provide the first large randomized controlled trial data on the potential benefits of statin therapy beyond lipid-lowering in the HIV-infected population.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflicts of interest.

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.

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