HHS Public Access

Author manuscript

Curr Infect Dis Rep. Author manuscript; available in PMC 2019 May 26.

Published in final edited form as:

Curr Infect Dis Rep. ; 20(8): 20. doi:10.1007/s11908-018-0628-7.

Benefits and risks of statin therapy in the HIV infected population

Mosepele Mosepele[1,2], **Julia O. Molefe-Baikai**[1], **Steven K. Grinspoon**[3], and **Virginia A. Triant**[4]

[1]Department of Internal Medicine, Faculty of Medicine, University of Botswana, Gaborone, Botswana

[2]Department of Botswana-Harvard AIDS Institute Partnership, Gaborone, Botswana

[3]Program in Nutritional Metabolism, Harvard Medical School & Massachusetts General Hospital, Boston, Massachusetts, USA

[4]Divisions of Infectious Diseases and General Internal Medicine, Harvard Medical School & Massachusetts General Hospital, Boston, Massachusetts, USA

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 (6,500 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

Corresponding Author: Mosepele Mosepele MD, MSc, Sir Ketumile Masire Teaching Hospital, 3rd Floor, Block F, Room F4069, Faculty of Medicine, University of Botswana, Gaborone, BOTSWANA, mosepelemosepele@gmail.com, mosepelem@ub.ac.bw, Contact Number: +267 355 5589, Fax: +267 310 5979.

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 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 80mg 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 10mg 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 cholesterol, 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 10mg 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 that 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 are 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 is 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 prescription of statin therapy for primary prevention of CVD was assessed in a clinical setting, there was no association of statin therapy 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 there was 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 1,738 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 4mg was significantly more likely to lower soluble CD14 (sCD14) compared with pravastatin 40mg (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 10mg decreased sCD14 by 10%, lipoprotein-associated phospholipase A2 by 12%, 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 10mg 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 10mg, atorvastatin 10mg and pravastatin 40mg all induced similar decreases in high-sensitivity C-reactive protein (hsCRP) and tumor necrosis factor- alfa (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 US [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 10mg 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], statin therapy has been evaluated address these problems. For instance, in a study of 147 HIV-infected adults on ART followed for 96 weeks, rosuvastatin 10mg 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.

Non-alcoholic 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 10mg 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 under prescription 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 6,195 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 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 in 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 17737 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 toxicity 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 4mg [91], on major cardiovascular events and all-cause mortality among 6,500 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 end-points.

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.

REFERENCES:

1. Endo A, The discovery and development of HMG-CoA reductase inhibitors. J Lipid Res, 1992 33(11): p. 1569–82. [PubMed: 1464741]
2. Sirtori CR, The pharmacology of statins. Pharmacol Res, 2014 88: p. 3–11. [PubMed: 24657242]

3. Brunengraber H, New mechanisms by which statins lower plasma cholesterol. J Lipid Res, 2016 57(8): p. 1325–6. [PubMed: 27338872]
4. Schonewille M, et al., Statins increase hepatic cholesterol synthesis and stimulate fecal cholesterol elimination in mice. J Lipid Res, 2016 57(8): p. 1455–64. [PubMed: 27313057]
5. Gili S, et al., Comparative safety and efficacy of statins for primary prevention in human immunodeficiency virus-positive patients: a systematic review and meta-analysis. Eur Heart J, 2016 37(48): p. 3600–3609. [PubMed: 26851703]
6. Banach M, et al., A PRISMA-compliant systematic review and meta-analysis of randomized controlled trials investigating the effects of statin therapy on plasma lipid concentrations in HIV-infected patients. Pharmacol Res, 2016 111: p. 343–356. [PubMed: 27350264]
7. Stein JH, Management of Lipid Levels and Cardiovascular Disease in HIV-Infected Individuals: Just Give Them a Statin? Top Antivir Med, 2016 23(5): p. 169–73. [PubMed: 27398770]
8. Wongprikorn A, et al., Effects of Pitavastatin on Lipid Profiles in HIV-Infected Patients with Dyslipidemia and Receiving Atazanavir/Ritonavir: A Randomized, Double-Blind, Crossover Study. PLoS One, 2016 11(6): p. e0157531. [PubMed: 27304841]
9. Longenecker CT, et al., Rosuvastatin slows progression of subclinical atherosclerosis in patients with treated HIV infection. Aids, 2016 30(14): p. 2195–203. [PubMed: 27203715]
10. Nixon DE, et al., Effects of atorvastatin on biomarkers of immune activation, inflammation, and lipids in virologically suppressed, human immunodeficiency virus-1-infected individuals with low-density lipoprotein cholesterol <130 mg/dL (AIDS Clinical Trials Group Study A5275). J Clin Lipidol, 2017 11(1): p. 61–69. [PubMed: 28391912]
11. Stone NJ, 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, 2014 63(25 Pt B): p. 2889–934. [PubMed: 24239923]
12. Limsreng S, et al., Dyslipidemias and Elevated Cardiovascular Risk on Lopinavir-Based Antiretroviral Therapy in Cambodia. PLoS One, 2016 11(8): p. e0160306. [PubMed: 27579612]
13. Lee FJ, et al., Rosuvastatin vs. protease inhibitor switching for hypercholesterolaemia: a randomized trial. HIV Med, 2016 17(8): p. 605–14. [PubMed: 26987376]
14. Wangpatharawanit P and Sungkanuparph S, Switching Lopinavir/Ritonavir to Atazanavir/Ritonavir vs Adding Atorvastatin in HIV-Infected Patients Receiving Second-Line Antiretroviral Therapy With Hypercholesterolemia: A Randomized Controlled Trial. Clin Infect Dis, 2016 63(6): p. 818–20. [PubMed: 27402817]
15. Saeedi R, et al., Lipid lowering efficacy and safety of Ezetimibe combined with rosuvastatin compared with titrating rosuvastatin monotherapy in HIV-positive patients. Lipids Health Dis, 2015 14: p. 57. [PubMed: 26087958]
16. Hileman CO, et al., Changes in oxidized lipids drive the improvement in monocyte activation and vascular disease after statin therapy in HIV. Aids, 2016 30(1): p. 65–73. [PubMed: 26731754]
17. Aberg JA, et al., Pitavastatin versus pravastatin in adults with HIV-1 infection and dyslipidaemia (INTREPID): 12 week and 52 week results of a phase 4, multicentre, randomised, double-blind, superiority trial. Lancet HIV, 2017 4(7): p. e284–e294. [PubMed: 28416195]
18. Joshi PH, et al., Greater remnant lipoprotein cholesterol reduction with pitavastatin compared with pravastatin in HIV-infected patients. Aids, 2017 31(7): p. 965–971. [PubMed: 28121706]
19. Nou E, et al., Serum oxidized low-density lipoprotein decreases in response to statin therapy and relates independently to reductions in coronary plaque in patients with HIV. Aids, 2016 30(4): p. 583–90. [PubMed: 26558731]
20. Calza L, et al., Statin therapy decreases serum levels of high-sensitivity C-reactive protein and tumor necrosis factor-alpha in HIV-infected patients treated with ritonavir-boosted protease inhibitors. HIV Clin Trials, 2012 13(3): p. 153–61. [PubMed: 22592095]
21. Singh S, et al., Comparative Effectiveness and Toxicity of Statins Among HIV-Infected Patients. Clin Infect Dis, 2011 52(3): p. 387–95. [PubMed: 21189273]
22. Adams SP, Tsang M, and Wright JM, Lipid-lowering efficacy of atorvastatin. Cochrane Database Syst Rev, 2015(3): p. Cd008226. [PubMed: 25760954]

23. Hileman CO, et al., Baseline Vitamin D Deficiency Decreases the Effectiveness of Statins in HIV-Infected Adults on Antiretroviral Therapy. J Acquir Immune Defic Syndr, 2017 74(5): p. 539–547. [PubMed: 28045766]
24. Hileman CO and McComsey GA, The Effect of Rosuvastatin on Vascular Disease Differs by Smoking Status in Treated HIV Infection. AIDS Res Hum Retroviruses, 2017.
25. Phan BAP, et al., Utility of 2013 American College of Cardiology/American Heart Association Cholesterol Guidelines in HIV-Infected Adults With Carotid Atherosclerosis. Circ Cardiovasc Imaging, 2017 10(7).
26. Zanni MV, et al., 2013 American College of Cardiology/American Heart Association and 2004 Adult Treatment Panel III cholesterol guidelines applied to HIV-infected patients with/without subclinical high-risk coronary plaque. Aids, 2014 28(14): p. 2061–70. [PubMed: 25265074]
27. Krsak M, et al., Myocardial Infarction, Stroke, and Mortality in cART-Treated HIV Patients on Statins. AIDS Patient Care STDS, 2015 29(6): p. 307–13. [PubMed: 25855882]
28. Lang S, et al., Is Impact of Statin Therapy on All-Cause Mortality Different in HIV-Infected Individuals Compared to General Population? Results from the FHDH-ANRS CO4 Cohort. PLoS One, 2015 10(7): p. e0133358. [PubMed: 26200661]
29. Moore RD, Bartlett JG, and Gallant JE, Association between use of HMG CoA reductase inhibitors and mortality in HIV-infected patients. PLoS One, 2011 6(7): p. e21843. [PubMed: 21765919]
30. Rasmussen LD, et al., Statin therapy and mortality in HIV-infected individuals; a Danish nationwide population-based cohort study. PLoS One, 2013 8(3): p. e52828. [PubMed: 23469159]
31. Overton ET, et al., Effect of statin therapy in reducing the risk of serious non-AIDS-defining events and nonaccidental death. Clin Infect Dis, 2013 56(10): p. 1471–9. [PubMed: 23386631]
32. Bernal E, et al., Statins in HIV-Infected Patients: Potential Beneficial Effects and Clinical Use. AIDS Rev, 2017 19(2): p. 59–71. [PubMed: 28182617]
33. Tousoulis D, et al., Innate and adaptive inflammation as a therapeutic target in vascular disease: the emerging role of statins. J Am Coll Cardiol, 2014 63(23): p. 2491–2502. [PubMed: 24613322]
34. Elahi S, Weiss RH, and Merani S, Atorvastatin restricts HIV replication in CD4+ T cells by upregulation of p21. Aids, 2016 30(2): p. 171–83. [PubMed: 26645604]
35. Aslangul E, et al., High-sensitivity C-reactive protein levels fall during statin therapy in HIV-infected patients receiving ritonavir-boosted protease inhibitors. Aids, 2011 25(8): p. 1128–31. [PubMed: 21422984]
36. Fichtenbaum CJ, Evans SE, and Aberg JA, High-sensitivity C-reactive protein levels do not decrease with the use of statins in all persons with HIV infection. Aids, 2011 25(16): p. 2053. [PubMed: 21997492]
37. Toribio M, et al., Effects of pitavastatin and pravastatin on markers of immune activation and arterial inflammation in HIV. Aids, 2017 31(6): p. 797–806. [PubMed: 28252528]
38. Funderburg NT, et al., Rosuvastatin reduces vascular inflammation and T-cell and monocyte activation in HIV-infected subjects on antiretroviral therapy. J Acquir Immune Defic Syndr, 2015 68(4): p. 396–404. [PubMed: 25514794]
39. Yadav A, Betts MR, and Collman RG, Statin modulation of monocyte phenotype and function: implications for HIV-1-associated neurocognitive disorders. J Neurovirol, 2016 22(5): p. 584–596. [PubMed: 27021071]
40. Dirajlal-Fargo S, et al., Statin therapy decreases N-terminal pro-B-type natriuretic peptide in HIV: randomized placebo-controlled trial. Aids, 2015 29(3): p. 313–21. [PubMed: 25686680]
41. Eckard AR, et al., Kallistatin levels in HIV-infected patients and effects of statin therapy. Biomarkers, 2017 22(1): p. 55–62. [PubMed: 27326658]
42. Lo J, et al., Effects of statin therapy on coronary artery plaque volume and high-risk plaque morphology in HIV-infected patients with subclinical atherosclerosis: a randomised, double-blind, placebo-controlled trial. Lancet HIV, 2015 2(2): p. e52–63. [PubMed: 26424461]
43. Weijma RG, et al., The Effect of Rosuvastatin on Markers of Immune Activation in Treatment-Naive Human Immunodeficiency Virus-Patients. Open Forum Infect Dis, 2016 3(1): p. ofv201. [PubMed: 26835476]

44. Zanni MV, et al., Effects of Antiretroviral Therapy on Immune Function and Arterial Inflammation in Treatment-Naive Patients With Human Immunodeficiency Virus Infection. JAMA Cardiol, 2016 1(4): p. 474–80. [PubMed: 27438325]
45. Allen SC and Mamotte CDS, Pleiotropic and Adverse Effects of Statins-Do Epigenetics Play a Role? J Pharmacol Exp Ther, 2017 362(2): p. 319–326. [PubMed: 28576976]
46. El-Far M and Tremblay CL, Gut microbial diversity in HIV infection post combined antiretroviral therapy: a key target for prevention of cardiovascular disease. Curr Opin HIV AIDS, 2018 13(1): p. 38–44. [PubMed: 29045253]
47. Bandera A, et al., Altered gut microbiome composition in HIV infection: causes, effects and potential intervention. Curr Opin HIV AIDS, 2018 13(1): p. 73–80. [PubMed: 29045252]
48. Funderburg NT, et al., Rosuvastatin Decreases Intestinal Fatty Acid Binding Protein (I-FABP), but Does Not Alter Zonulin or Lipopolysaccharide Binding Protein (LBP) Levels, in HIV-Infected Subjects on Antiretroviral Therapy. Pathog Immun, 2016 1(1): p. 118–128. [PubMed: 27500282]
49. Thurn M and Gustafson DR, Faces of Frailty in Aging with HIV Infection. Curr HIV/AIDS Rep, 2017 14(1): p. 31–37. [PubMed: 28210943]
50. Grant PM, et al., Long-term body composition changes in antiretroviral-treated HIV-infected individuals. Aids, 2016 30(18): p. 2805–2813. [PubMed: 27662545]
51. Erlandson KM, et al., Antiretroviral initiation is associated with increased skeletal muscle area and fat content. Aids, 2017 31(13): p. 1831–1838. [PubMed: 28590329]
52. Oliveira VH, et al., Muscle strength is impaired in men but not in women living with HIV taking antiretroviral therapy. Antivir Ther, 2017.
53. Erlandson KM, et al., Effects of 96 Weeks of Rosuvastatin on Bone, Muscle, and Fat in HIV-Infected Adults on Effective Antiretroviral Therapy. AIDS Res Hum Retroviruses, 2016 32(4): p. 311–6. [PubMed: 26477698]
54. Angulo P, GI epidemiology: nonalcoholic fatty liver disease. Aliment Pharmacol Ther, 2007 25(8): p. 883–9. [PubMed: 17402991]
55. Moyle G and Carr A, HIV-associated lipodystrophy, metabolic complications, and antiretroviral toxicities. HIV Clin Trials, 2002 3(1): p. 89–98. [PubMed: 11894812]
56. Joshi D, et al., Increasing burden of liver disease in patients with HIV infection. Lancet, 2011 377(9772): p. 1198–209. [PubMed: 21459211]
57. Causes of death in HIV-1-infected patients treated with antiretroviral therapy, 1996–2006: collaborative analysis of 13 HIV cohort studies. Clin Infect Dis, 2010 50(10): p. 1387–96. [PubMed: 20380565]
58. Lo J, et al., Statin Effects to Reduce Hepatosteatosis as Measured by Computed Tomography in Patients With Human Immunodeficiency Virus. Open Forum Infect Dis, 2016 3(2): p. ofw062. [PubMed: 27419149]
59. Foster T, et al., Atorvastatin and antioxidants for the treatment of nonalcoholic fatty liver disease: the St Francis Heart Study randomized clinical trial. Am J Gastroenterol, 2011 106(1): p. 71–7. [PubMed: 20842109]
60. Longenecker CT, et al., Rosuvastatin preserves renal function and lowers cystatin C in HIV-infected subjects on antiretroviral therapy: the SATURN-HIV trial. Clin Infect Dis, 2014 59(8): p. 1148–56. [PubMed: 25015912]
61. Williams DW, et al., Monocytes mediate HIV neuropathogenesis: mechanisms that contribute to HIV associated neurocognitive disorders. Curr HIV Res, 2014 12(2): p. 85–96. [PubMed: 24862333]
62. Todd JV, et al., Underutilization of Statins When Indicated in HIV-Seropositive and Seronegative Women. AIDS Patient Care STDS, 2017 31(11): p. 447–454. [PubMed: 29087746]
63. Mosepele M, et al., Cholesterol Screening and Statin Prescription is Low Among HIV-Infected Patients on Protease-Inhibitor Regimens in Botswana. Open AIDS J, 2017 11: p. 45–51. [PubMed: 28839514]
64. Guo F, et al., Cardiovascular disease risk among Chinese antiretroviral-naive adults with advanced HIV disease. BMC Infect Dis, 2017 17(1): p. 287. [PubMed: 28427339]
65. Clement ME, et al., Statin Utilization and Recommendations Among HIV- and HCV-infected Veterans: A Cohort Study. Clin Infect Dis, 2016 63(3): p. 407–13. [PubMed: 27143663]

66. van Zoest RA, et al., Suboptimal primary and secondary cardiovascular disease prevention in HIV-positive individuals on antiretroviral therapy. Eur J Prev Cardiol, 2017 24(12): p. 1297–1307. [PubMed: 28578613]

67. De Socio GV, et al., Statins and Aspirin use in HIV-infected people: gap between European AIDS Clinical Society guidelines and clinical practice: the results from HIV-HY study. Infection, 2016 44(5): p. 589–97. [PubMed: 27048184]

68. Ladapo JA, et al., Disparities in the Quality of Cardiovascular Care Between HIV-Infected Versus HIV-Uninfected Adults in the United States: A Cross-Sectional Study. J Am Heart Assoc, 2017 6(11).

69. Maggi P, et al., Use of statins and aspirin to prevent cardiovascular disease among HIV-positive patients. A survey among Italian HIV physicians. New Microbiol, 2017 40(2): p. 139–142. [PubMed: 28072892]

70. Boccara F, et al., Statin therapy and low-density lipoprotein cholesterol reduction in HIV-infected individuals after acute coronary syndrome: Results from the PACS-HIV lipids substudy. Am Heart J, 2017 183: p. 91–101. [PubMed: 27979047]

71. Monroe AK, et al., Low-Density Lipoprotein Cholesterol Levels and Statin Treatment by HIV Status Among Multicenter AIDS Cohort Study Men. AIDS Res Hum Retroviruses, 2015 31(6): p. 593–602. [PubMed: 25664922]

72. Drechsler H, et al., Current use of statins reduces risk of HIV rebound on suppressive HAART. PLoS One, 2017 12(3): p. e0172175. [PubMed: 28249009]

73. Feinstein MJ, et al., A Systematic Review of the Usefulness of Statin Therapy in HIV-Infected Patients. Am J Cardiol, 2015 115(12): p. 1760–6. [PubMed: 25907504]

74. Wiggins BS, et al., Recommendations for Managing Drug-Drug Interactions with Statins and HIV Medications. Am J Cardiovasc Drugs, 2017 17(5): p. 375–389. [PubMed: 28364370]

75. Blonk M, et al., Pharmacokinetic Drug-Drug Interaction Study Between Raltegravir and Atorvastatin 20 mg in Healthy Volunteers. J Acquir Immune Defic Syndr, 2015 69(1): p. 44–51. [PubMed: 25942458]

76. Chauvin B, et al., Drug-drug interactions between HMG-CoA reductase inhibitors (statins) and antiviral protease inhibitors. Clin Pharmacokinet, 2013 52(10): p. 815–31. [PubMed: 23703578]

77. Custodio JM, et al., Pharmacokinetics of cobicistat boosted-elvitegravir administered in combination with rosuvastatin. J Clin Pharmacol, 2014 54(6): p. 649–56. [PubMed: 24375014]

78. Suttels V, et al., A 68-year old male presenting with rhabdomyolysis-associated acute kidney injury following concomitant use of elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate and pravastatin/fenofibrate: a case report. J Med Case Rep, 2015 9: p. 190. [PubMed: 26347243]

79. Lichtenstein KA, et al., Statin Use Is Associated With Incident Diabetes Mellitus Among Patients in the HIV Outpatient Study. J Acquir Immune Defic Syndr, 2015 69(3): p. 306–11. [PubMed: 26181706]

80. Erlandson KM, et al., Rosuvastatin Worsens Insulin Resistance in HIV-Infected Adults on Antiretroviral Therapy. Clin Infect Dis, 2015 61(10): p. 1566–72. [PubMed: 26157049]

81. Spagnuolo V, et al., Associations of statins and antiretroviral drugs with the onset of type 2 diabetes among HIV-1-infected patients. BMC Infect Dis, 2017 17(1): p. 43. [PubMed: 28061820]

82. Calza L, et al., No correlation between statin exposure and incident diabetes mellitus in HIV-1-infected patients receiving combination antiretroviral therapy. HIV Med, 2016 17(8): p. 631–3. [PubMed: 27028348]

83. Ou HT, et al., Intensive statin regimens for reducing risk of cardiovascular diseases among human immunodeficiency virus-infected population: A nation-wide longitudinal cohort study 2000–2011. Int J Cardiol, 2017 230: p. 592–598. [PubMed: 28062146]

84. Byrne DD, et al., Risk of Acute Liver Injury After Statin Initiation by Human Immunodeficiency Virus and Chronic Hepatitis C Virus Infection Status. Clin Infect Dis, 2017 65(9): p. 1542–1550. [PubMed: 29020184]

85. Silverberg MJ, et al., Response to newly prescribed lipid-lowering therapy in patients with and without HIV infection. Ann Intern Med, 2009 150(5): p. 301–13. [PubMed: 19258558]

86. Calza L, et al., Significant association between statin-associated myalgia and vitamin D deficiency among treated HIV-infected patients. Aids, 2017 31(5): p. 681–688. [PubMed: 28060020]

87. Avis HJ, et al., A systematic review and meta-analysis of statin therapy in children with familial hypercholesterolemia. Arterioscler Thromb Vasc Biol, 2007 27(8): p. 1803–10. [PubMed: 17569881]

88. Melvin AJ, et al., Safety and Efficacy of Atorvastatin in Human Immunodeficiency Virus-infected Children, Adolescents and Young Adults With Hyperlipidemia. Pediatr Infect Dis J, 2017 36(1): p. 53–60. [PubMed: 27749649]

89. Kakafika A, et al., Effect of atorvastatin on serum creatinine levels. Curr Med Res Opin, 2001 17(3): p. 230–1. [PubMed: 11900317]

90. Gilbert JM, Fitch KV, and Grinspoon SK, HIV-Related Cardiovascular Disease, Statins, and the REPRIEVE Trial. Top Antivir Med, 2015 23(4): p. 146–9. [PubMed: 26713505]

91. Malvestutto CD, et al., Lack of pharmacokinetic interactions between pitavastatin and efavirenz or darunavir/ritonavir. J Acquir Immune Defic Syndr, 2014 67(4): p. 390–6. [PubMed: 25202920]