



Evidence-based review of statin use in patients with HIV on antiretroviral therapy



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ABSTRACT

Introduction: As a result of improved safe and effective therapeutic options for human immunodeficiency virus (HIV), life expectancy of those living with HIV is increasing leading to new challenges (e.g., management of chronic diseases). Some chronic diseases (e.g., cardiovascular disease [CVD]), are up to two times more prevalent in patients with HIV. Statins are a mainstay of therapy for prevention of CVD; but, clinicians should be aware that not all statins are appropriate for use in the HIV population, especially those receiving antiretroviral therapy (ART). The purpose of this article is to review the pharmacokinetic and clinical data for statin therapy in HIV-infected patients receiving ART.

Methods: A systematic literature search using PubMed and MEDLINE databases was performed using each statin drug name combined with HIV, pharmacokinetics, AIDS, and/or human immunodeficiency virus. English language trials published from 1946 to November 2016 were considered, and results were limited to clinical efficacy trials.

Results: In general, atorvastatin and pravastatin are safe and effective for patients treated with protease-inhibitor (PI) or non-nucleoside reverse transcriptase inhibitor-based ART. Rosuvastatin is generally considered safe if started at a low dose, but should be avoided if possible in patients receiving PI-based ART. Pitavastatin has limited supporting evidence, but appears safe for use based on its pharmacokinetic properties and low number of drug interactions. Fluvastatin, lovastatin, and simvastatin should be avoided in patients receiving ART due to drug interactions, adverse events, and/or limited clinical data.

Conclusion: Clinicians need to be familiar with the intricacies of statin selection for the prevention of CVD in patients with HIV on ART.

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Introduction

Epidemiology of human immunodeficiency virus

Globally, 36.9 million persons are living with human immunodeficiency virus (HIV) [1]. Alarming, only 53% have been diagnosed, 41% are on antiretroviral therapy (ART), and 32% are virologically suppressed with HIV RNA viral loads <1000 copies/mL. In the United States at the end of 2012, an estimated 1.2 million individuals 13 years of age and older were living with HIV, of which 12.8% were undiagnosed [2]. The rate of virologic suppression in the US is poor at best at 30%, despite advancements in medical treatment [3]. This is comparable to sub-Saharan Africa (32%), but much lower than Switzerland or France (68% and 52%, respectively).

Life expectancy of HIV-infected individuals

The life expectancy of an HIV-infected patient has increased significantly over the past 30 years [4], from less than 40 years in the late 1990's to over 50 years by the end of 2011 [5]. Unfortunately, a 13.8 year gap in life expectancy persists between HIV-positive and HIV-negative people. Lower rates of life expectancies have been observed in blacks, individuals co-infected with hepatitis B virus (HBV) or hepatitis C virus (HCV), intravenous drug abusers, and smokers. Earlier initiation of ART, particularly in patients with CD4+ T-helper cells ≥ 500 cells/mL, increases life expectancy. The median age of patients receiving ART is expected to increase from 43.9 years in 2010, to 56.6 years in 2030, according to data from the ATHENA cohort [6]. Furthermore, the percentage of HIV positive patients aged 50, 60, and 70 years and older is expected to increase from 28% to 73%, 8% to 39%, and 8% to 12%, respectively. The cause of death in HIV-infected patients has shifted for those treated with ART, however. While some continue to die of acquired immunodeficiency syndrome (AIDS), an increasing percentage is due to non-AIDS-defining malignancies, cardiovascular, and hepatic diseases [7].

Incidence of cardiovascular disease

As of 2010, 19% of HIV-infected patients in the Netherlands were diagnosed with cardiovascular disease (CVD); this is expected to increase to up to 78% by 2030 [6]. The increasing incidence of CVD is likely the result of higher rates of CVD risk factors, ART-related metabolic complications, and a longer life expectancy.

The prevalence of CVD morbidity and mortality in HIV-infected patients has consistently been observed to be 1.5- to 2-times greater than negative controls, particularly in those greater than 45 years of age [8–11]. Furthermore, infection with HIV is independently associated with an increased risk of CVD due to inflammation, activation and dysfunction of the immune system, and immunosenescence [12,13].

Significance of drug interactions and metabolic consequences of use

Despite virologic suppression, the higher incidence of CVD persists [14], prompting many studies on the association between ART and CVD [11,15,16]. Overall, the extent to which ART contributes to the increased risk of CVD is largely unknown, but likely differs with individual ART drugs. Metabolic changes, including lipodystrophy, insulin resistance, and dyslipidemia, are typically associated with protease inhibitors (PIs), but recent evidence suggests that this may no longer be the case with newer PIs [8]. Neither nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), nor integrase strand transfer inhibitors (INSTIs) appear to have an association with deleterious lipid abnormalities or CVD.

Dyslipidemia occurs in up to 80% of HIV-infected patients, and <10% of these patients receive statin therapy [17,18]. One barrier that may explain low rates of statin use is the significance of drug interactions with ART and concomitant statin therapy [19,20]. Most drug interactions with ART occur via the cytochrome P (CYP) 450 system, with PIs inhibiting CYP3A4, while the majority of NNRTIs induce this isoenzyme [21]. Pharmacokinetic properties of statins vary significantly between individual drugs [8,22]. Most statins are primarily metabolized through CYP3A4, with minimal CYP2C9 involvement, to produce pharmacologically active metabolites. The potential for drug interactions exists because many statins are substrates for CYP3A4. Depending on the concomitant medication, serum concentrations of statins may vary, leading to higher rates of adverse events or decreased lipid lowering properties.

Benefits of statin use for CV disease

Statin competitively inhibit hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase impairing cholesterol biosynthesis and decreasing hepatic cholesterol concentrations [14,22]. These actions result in decreased cholesterol in plasma and cell membranes, explaining their widespread use in the primary and secondary prevention of CVD. Statins also have anti-inflammatory effects by decreasing circulating concentrations of pro-inflammatory cytokines, improving endothelial function, and stabilizing coronary plaques [22].

The Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults was released by the American College of Cardiology/American Heart Association (ACC/AHA) in November 2013, to replace the outdated Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (ATP III) [23,24]. The new guidelines eliminated LDL-cholesterol (LDL-C) targets, and created 4 groups of patients that could benefit most from statin therapy: patients with atherosclerotic cardiovascular disease (ASCVD), patients with LDL-C ≥ 190 mg/dL, patients age 40–75 years with diabetes mellitus and LDL-C of 70–189 mg/dL without ASCVD, and patients age 40–75 years with LDL-C of 70–189 mg/dL and an estimated 10 year ASCVD risk of $\geq 7.5\%$ without ASCVD or diabetes mellitus. Based on these changes, statin therapy is now recommended for a much larger percentage of the general patient population.

Direct extrapolation and application of these recommendations to HIV-infected patients would result in up to 74% of individuals with subclinical high risk morphology coronary plaque not receiving statin therapy [25]. Unfortunately, these guidelines do not account for specific risk factors among HIV-infected patients, including HIV infection itself, ART, and the effects of the immune system, in combination with traditional cardiovascular risk factors. Previous data confirm that conventional cardiovascular risk equations underestimate the risk of myocardial infarction among HIV-infected patients [26].

Efficacy of statin therapy in HIV-infected patients is primarily derived from observational or retrospective data evaluating surrogate biomarkers [14]. These markers of CVD, including carotid, femoral, or iliac intima-media thickness, are greater and progress earlier in the HIV-infected patient population [27–29]. Limited data exist on clinical outcomes of statin therapy in HIV-infected patients. A Danish nationwide population-based cohort study of HIV-infected individuals starting ART after January 1, 1998, revealed decreased all-cause mortality among those receiving statin therapy with at least one comorbidity [30]. Contrary to the ACC/AHA guidelines, the National Lipid Association (NLA) emphasized statin therapy to achieve cholesterol targets [31,32]. Among their recommendations was to include HIV as a major risk factor for CVD to ultimately identify the appropriate risk category and treatment target. As a result, statin use is expected to increase due to the increasing prevalence of dyslipidemia, CVD, and reduction in surrogate markers associated with CVD among this population [17,18].

The statin drug class is made up of a heterogeneous group of individual compounds that differ in bioavailability, solubility, hepatic metabolism, and cellular transfer [22]. These pharmacokinetic differences determine the lipid lowering potency, and potential toxicities, including hepatic dysfunction, myopathy, cognitive dysfunction and memory loss. Clinicians must carefully select a statin for HIV-infected patients receiving ART by navigating potential drug-drug interactions.

The purpose of this article is to review the available pharmacokinetic and clinical data for statin therapy in HIV-infected patients receiving ART to assist clinicians in determining the most appropriate choice.

Methods/search strategy

A systematic literature search using PubMed and MEDLINE databases was performed using each statin drug name combined with HIV, pharmacokinetics, AIDS, and/or human immunodeficiency virus. An additional search was performed including MESH terms HIV, CVD, mortality, and antiretroviral therapy. English language trials published from 1946 to November 2016 were considered, and results were limited to clinical efficacy trials. Articles were screened by title and abstract for possible inclusion, and references within articles of interest were scanned to capture additional sources. Google Scholar was used as a secondary source for information with the same criteria.

Results

Atorvastatin

Atorvastatin is rapidly absorbed following oral administration with subsequent extensive first-pass metabolism [33]. It is metabolized to active metabolites via CYP3A4, and is also a substrate for this isoenzyme and organic anion-transporting polypeptide (OATP) 1B1. Although the elimination half-life is only 14 h, the presence of active metabolites extends the inhibitory activity half-life to

approximately 20–30 h. These features allow atorvastatin to be administered without regard to time of day.

Atorvastatin area under the curve (AUC) is significantly increased with concomitant use of PIs due to CYP3A4 inhibition [34]. Overall atorvastatin exposure increased by 343% in patients receiving saquinavir (SQV)/ritonavir (RTV), but active atorvastatin, including parent drug and its two active metabolites, increased by only 79% [35]. Administration of atorvastatin with lopinavir (LPV)/RTV resulted in a 5-fold increase in atorvastatin, but a decrease in the formation of active metabolites [36]. Similar to PIs, cobicistat (COBI) is a potent CYP3A4 inhibitor that may increase the systemic concentration of atorvastatin [37]. The United States Department of Health and Human Services (DHHS) guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents recommend using the lowest dose of atorvastatin required and increasing the dose carefully [38]. In patients treated with darunavir (DRV)/RTV-containing ART, concomitant use of atorvastatin 10 mg per day is equivalent in lipid lowering efficacy to 40 mg per day in patients not receiving PIs. Doses should be titrated carefully not to exceed 20 mg per day in combination with all RTV or COBI boosted-PIs, except tipranavir (TPV) and LPV/RTV.

Alternatively, most non-nucleoside reverse transcriptase inhibitors (NNRTIs), including efavirenz (EFV), etravirine (ETV), and nevirapine (NVP), may induce the metabolism of atorvastatin via CYP3A4, decreasing overall lipid reductions [34]. ETV and EFV may decrease atorvastatin AUC by 32% and 43%, respectively, necessitating the need for higher atorvastatin doses, not to exceed 80 mg per day [38]. No dose adjustment is required with concomitant use of rilpivirine (RPV)-containing ART.

Multiple studies evaluating atorvastatin therapy in HIV-infected patients have been published (See Table 1) [39–42]. Concomitant use of atorvastatin is considered safe in patients treated with either PI- or NNRTI-based ART.

Pravastatin

Pravastatin is absorbed 60–90 min following oral administration with low bioavailability (17%) [43]. Pravastatin undergoes extensive first-pass extraction in the liver, and its radioactive elimination half-life is only 1.8 h without active metabolites [43]. Pravastatin AUC is primarily metabolized by glucuronidation and is only minimally impacted by the CYP3A system [34]. Pravastatin exposure decreases by 50% in patients receiving SQV/RTV [35], although this decrease does not appear with microdoses of SQV/RTV [44]. DHHS guidelines recommend no dose adjustment for pravastatin with co-administration of SQV/RTV [38], but a higher than usual starting dose could be warranted. Administration of pravastatin with LPV/RTV results in a 33% increase in pravastatin AUC which also merits no dose adjustment [38]. Pravastatin has not demonstrated a difference in 1-h co-administration exposure concentrations at 24 weeks of various PIs (e.g., indinavir, RTV, SQV) [45]. Pravastatin has elicited a decrease in 12-h post-dose PI concentrations when compared to placebo over 12 weeks, particularly with LPV/RTV; however, this post-dose effect has demonstrated no impact on virologic failure [46]. Despite lacking data, the DHHS guidelines for the use of atazanavir (ATV)-containing regimens in HIV-1-infected adults and adolescents recommend using the lowest dose of pravastatin and monitoring for efficacy and adverse effects [38]. DRV/RTV-containing ART will increase AUC of concomitant pravastatin by 81% following a single dose and 23% at steady state; therefore, the lowest necessary dose of pravastatin is recommended, as well as careful monitoring of statin-related adverse effects [38]. There are no reported dose adjustments necessary for pravastatin in combination with COBI-boosted PIs; however, there has been a report of rhabdomyolysis

Table 1
Trials evaluating statins in HIV patients.

Trial	Number of patients	Primary Outcome	Results	Comments
<i>Atorvastatin</i>				
Atorvastatin 10-20 mg/day in patients treated with PI-containing ART with severe dyslipidemia [39]	15	Efficacy of atorvastatin in the treatment of dyslipidemia for 12 weeks	TC: 25% decrease TG: 35% decrease	No cases of myopathy One patient experienced transaminitis that resolved within 3 months Decreased lipid values observed at 12 weeks and maintained through 15 months
Prospective study of atorvastatin 10 mg/day in patients receiving ART \geq 12 weeks with TC \geq 240 mg/dL, with or without increased TG despite therapeutic lifestyle changes [40]	20	Efficacy of atorvastatin in the treatment of dyslipidemia for 24 weeks	TC: 27% decrease TG: 41% decrease LDL-C: 37% decrease HDL: 1.3 mg/dL increase	No cases of myalgia, myositis, or increased CK Significant decrease in TC and LDL-C with atorvastatin
Open-label, randomized, prospective study of atorvastatin 10 mg/day, pravastatin 20 mg/day, or rosuvastatin 10 mg/day in HIV-infected patients treated with PI-containing regimens \geq 12 months and dyslipidemia $>$ 3 months despite therapeutic lifestyle changes [41]	85	Evaluation of different statins in the management of PI-associated dyslipidemia	Overall:TC: 21% decrease LDL-C: 24% decrease Atorvastatin: TC: 20% decrease Pravastatin: TC: 18% decrease Rosuvastatin: TC: 25% decrease	Favorable tolerability profile with significant efficacy among all statins Rosuvastatin more effective than atorvastatin or pravastatin in decreasing TC and LDL-C
Randomized, double-blind, placebo-controlled trial of HIV-infected patients on ART \geq 6 months with subclinical coronary atherosclerosis, arterial inflammation in the aorta, and LDL-C $<$ 130 mg/dL treated with either atorvastatin 20-40 mg/day or placebo [42]	40 (atorvastatin [n = 21] versus placebo [n = 19])	Efficacy of statin treatment to reduce arterial inflammation regression of coronary atherosclerosis for 12 months	TC: 48% decrease TG: unchanged LDL-C: 39% decrease HDL: 1% increase	Similar rates of myalgia, transaminitis, and CK elevation in atorvastatin group vs. placebo, 5 vs. 6, 2 vs. 3, 0 vs. 0, respectively Significant decreases in TC and LDL-C with atorvastatin vs. placebo
<i>Pravastatin</i>				
Pilot study of HIV patients receiving PI-containing regimens treated with pravastatin [50]	19	Efficacy of pravastatin 20 mg at bedtime in the treatment of dyslipidemia for 16 weeks	TC: 19% decrease TG: 37% decrease	No adverse effects noted CD4 and HIV RNA has no significant change with pravastatin treatment
Randomized, open-label comparative study of HIV patients receiving PI-containing regimens treated with pravastatin or diet only [51]	31	Efficacy of pravastatin 40 mg/day versus diet only in the treatment of dyslipidemia for 24 weeks	Pravastatin TC: 17% decrease LDL-C: 19% decrease Diet Only TC: 4% increase LDL-C: 6% decrease	Despite numerical change, TC differences did not reach statistical significance There was no difference in HDL or TG All patients were male
Open-label, randomized, prospective study of HIV patients receiving PI-containing regimens treated with pravastatin, fluvastatin, or fibrates [52]	106 (pravastatin [n = 19] versus fluvastatin [n = 18] versus fibrate [n = 69])	Efficacy and safety of pravastatin, fluvastatin or fibrates in the treatment of diet-resistant hypertriglyceridemia for 12 months	Statin (either) TC: 25% decrease TG: 35% decrease LDL-C: 26% decrease HDL: 24% increase	Cholesterol changes versus baseline were significant, but no when compared to each other
Placebo-controlled, double-blind, crossover study of HIV patient receiving PI-containing regimens with pravastatin [53]	20	Efficacy of pravastatin 40 mg/day versus placebo in the treatment of dyslipidemia	Fibrates (any) TC: 22% decrease TG: 41% decrease LDL-C: 23% decrease HDL: 20% increase TC: 18% decrease LDL-C: 21% decrease	All agents demonstrated favorable tolerability Significant decreases in TC and LDL-C with pravastatin vs. placebo No significant difference in flow-mediated dilation
Randomized, crossover, double-blind placebo-controlled study of HIV-infected patients with dyslipidemia receiving PI-containing regimens with pravastatin [54]	29	Efficacy of pravastatin 40 mg/day versus placebo in the treatment of dyslipidemia for 8 weeks	Data only reported as median +/- interquartile ranges	Significant decreases in TC, LDL-C, and TG with pravastatin vs. placebo Significant increase in flow-mediated dilation with pravastatin
Randomized, open-label study of HIV-infected patients with dyslipidemia receiving PI-containing regimens with pravastatin or fibrates versus switching to NNRTI [55]	130 (pravastatin [n = 36] or bezafibrate [n = 31] versus nevirapine [n = 29] or efavirenz [n = 34] switch)	Efficacy of pravastatin or bezafibrate versus switching ART to NNRTI (NVP or EFV) in the treatment of mixed hyperlipidemia for 12 months	Nevirapine TG: 25% decrease LDL-C: 25% decrease Efavirenz TG: 9% decrease LDL-C: 9% decrease Pravastatin TG: 41% decrease LDL-C: 40% decrease Bezafibrate TG: 47% decrease LDL-C: 35% decrease	Significant decreases in TG and LDL-C with lipid medication versus switching to NNRTI Comparable viral efficacy Switching to NVP demonstrated greater TG reduction than switching to EFV

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Table 1 (continued)

Trial	Number of patients	Primary Outcome	Results	Comments
Randomized, open-label, study of HIV-infected patients with dyslipidemia receiving ART with pravastatin, fenofibrate or both [56]	174 (pravastatin [n = 86] or fenofibrate [n = 88])	Efficacy of pravastatin or fenofibrate or both in the treatment of combined dyslipidemia for 48 weeks	Pravastatin (12 weeks) LDL-C 20% decrease TG 13% decrease Fenofibrate (12 weeks) LDL-C 8% increase TG 35% decrease HDL 11% increase	Pravastatin significantly reduced LDL-C versus baseline and fenofibrate at 12 weeks Fenofibrate significantly reduced TG and increased HDL versus baseline and pravastatin at 12 weeks Over 75% of patients enrolled were initiated on dual-therapy
Randomized, placebo-controlled study of HIV-infected patients with dyslipidemia receiving PI-containing regimens with pravastatin [57]	33 (pravastatin [n = 16] versus placebo [n = 17])	Efficacy of pravastatin 40 mg/day in the treatment of hypercholesterolemia for 12 weeks	Time-weighted change in TC decreased and subcutaneous fat increased with pravastatin	No change in TG versus placebo
Randomized, placebo-controlled study of HIV-infected patients with dyslipidemia receiving PI-containing regimens with pravastatin [46]	21 (pravastatin [n = 12] versus placebo [n = 9])	Efficacy of pravastatin 40 mg/day in the treatment of TC \geq 213 mg/dL for 12 weeks	Data only reported as medians	TC and LDL-C decreased significantly with pravastatin No virological failure
Placebo-controlled, 2 \times 2 factorial study of HIV patients receiving ART with pravastatin +/- Lisinopril without compelling indication [58]	34 (pravastatin +/- lisinopril [n = 18] versus placebo +/- lisinopril [n = 16])	Efficacy of pravastatin 20 mg/day with or without lisinopril with no statin indication for 4 months	No change in TC, LDL-C or inflammatory markers with pravastatin	No meaningful adverse effects Lisinopril reduced blood pressure
Randomized, open-label, crossover study of HIV patients on ART with pravastatin, +/- phytosterols [59]	36	Efficacy of pravastatin 40 mg/day +/- phytosterols 2 g/day in patients with LDL-C \geq 130 mg/dL for 12 weeks including a 4 week washout	Pravastatin LDL-C: 29% Phytosterols LDL-C: 9% Both LDL-C: 27%	Adding phytosterols to pravastatin does not add any LDL-C benefit
Randomized, prospective comparator study of HIV-infected patients with dyslipidemia receiving PI-containing regimens with pravastatin versus ezetimibe + fenofibrate [60]	42	Efficacy of pravastatin 40 mg/day versus ezetimibe 10 mg/day + fenofibrate 200 mg/day in the treatment of dyslipidemia for 6 months	Pravastatin TC: 6% decrease LDL-C: 18% decrease Ezetimibe + Fenofibrate TC: 11% decrease LDL-C: 17% decrease	Similar lipid parameter changes with combination non-statin therapy as with moderate-intensity statin Both arms were well tolerated
<i>Rosuvastatin</i>				
Rosuvastatin reduces vascular inflammation and T cell and monocyte activation in HIV-infected subjects on ART [65]	147 (Rosuvastatin [n = 72] vs. placebo [n = 75])	Assess changes in baseline to 48 weeks in plasma inflammatory and coagulation indices and markers of lymphocyte and monocyte activation	LDL-C: 23.4% decrease HDL: 0.7% increase TG: 5.5% increase	Significant reduction in LDL-C with rosuvastatin vs. placebo No significant changes in HDL or TG Significant decrease in sCD14, Lp-PLA2, and markers of monocyte and lymphocyte activation in rosuvastatin vs. placebo
Rosuvastatin versus pravastatin in dyslipidemic HIV-1 infected patients receiving PIs: a randomized trial [66]	83 (Rosuvastatin [n = 41] vs. Pravastatin [n = 42])	Compare the efficacy of rosuvastatin and pravastatin on plasma lipid levels in HIV-1 infected patients on at least one PIs after 45 days	Rosuvastatin: LDL-C: 37% decrease TG: 19% decrease HDL: 2.5% increase TC: 28% decrease Pravastatin: LDL-C: 19% decrease TG: 7% decrease HDL: no change TC: 14% decrease	Significant reduction in LDL-C, TG, and TC with rosuvastatin vs. pravastatin No difference in HDL No renal, hepatic, or muscular events in either group
Rosuvastatin for the treatment of hyperlipidaemia in HIV-infected patients receiving protease inhibitors: a pilot study [67]	16	Evaluate rosuvastatin for the management of PI-related dyslipidemia in HIV-positive patients over 24 weeks	TC: 21.7% decrease TG: 30.1% decrease LDL-C: 22.4% decrease HDL: 28.5% increase	Significant decreases in TC, LDL-C, and TG and significant increase in HDL with rosuvastatin No significant clinical or laboratory adverse effects
Two-year treatment with rosuvastatin reduces carotid IMT in HIV type 1-infected patients receiving highly ART with asymptomatic atherosclerosis and moderate cardiovascular risk. AID Res Hum Retroviruses [68]	36	Assess changes in carotid IMT and evaluate effect on lipid parameters with rosuvastatin for 24 months	TC: 25.3% decrease LDL-C: 29.8% decrease HDL: 11.6% increase TG: 16.5% decrease Right internal carotid IMT: 23.7% decrease Left internal carotid IMT: 25.6% decrease Right carotid bifurcation IMT: 18.7% decrease Left carotid bifurcation IMT: 21.4% decrease	Significant reductions in TC, LDL-C, TG, IMT with rosuvastatin No serious adverse events reported

Table 1 (continued)

Trial	Number of patients	Primary Outcome	Results	Comments
Other statins				
<i>Fluvastatin</i>				
Placebo-controlled, double-blind, randomized cross-over study of HIV-infected patients with dyslipidemia receiving PI-containing regimens treated with fluvastatin [78]	16	Safety and efficacy of fluvastatin 40 mg/day in the management of dyslipidemia for 4 weeks	TC: 54% decrease TG: 18% decrease	Significant reduction in TC with fluvastatin vs. placebo
Prospective, non-randomized, open-label study of treatment-experienced HIV-infected patients on ART \geq 2 years with hypercholesterolemia despite therapeutic lifestyle changes [79]	25 (fluvastatin [n = 12] vs. pravastatin [n = 13])	Compare the effectiveness of fluvastatin and pravastatin for the treatment of hypercholesterolemia and potential interactions with ART for 12 weeks	Fluvastatin: TC: 19% decrease LDL-C: 30% decrease Pravastatin: TC: 14% decrease LDL-C: 14% decrease	Greater reductions in TC and LDL-C with fluvastatin compared to pravastatin No changes in ART serum concentrations
<i>Pitavastatin</i>				
After 52 weeks, pitavastatin is superior to pravastatin for LDL-C lowering in patients with HIV [84]	252 (Pitavastatin [n = 126] vs. Pravastatin [n = 126])* *99 vs. 91 patients completed 52 weeks	Evaluate long-term (52 weeks) safety and efficacy of pitavastatin vs. pravastatin in HIV-infected adults with dyslipidemia	Pitavastatin LDL-C: 29.7% decrease TC: 19.1% decrease TG: 2.0% decrease HDL: 8.9% increase Pravastatin LDL-C: 20.5% decrease TC: 13.7% decrease TG: 6.3% decrease HDL: 7.2% increase	Safety profiles were similar between agents Pitavastatin displayed a significantly greater decrease in LDL-C and TC at 52 weeks No difference in changes in TG or HDL
Effects of pitavastatin on lipid profiles in HIV-infected patients with dyslipidemia and receiving ATV/RTV: a randomized, double-blind, crossover study [85]	24 (Pitavastatin [n = 12] vs. placebo [n = 12])	Determine efficacy and safety of pitavastatin in HIV-infected patients with dyslipidemia who are receiving ATV/RTV at 12 weeks	TC: 13.7% decrease LDL-C: 21.8% decrease TG: 24.6% increase HDL: 5.3% increase	Significant decrease in TC and LDL-C at 12 weeks with pitavastatin vs. placebo No difference in TG or HDL No adverse events reported in pitavastatin group
<i>Simvastatin</i>				
Retrospective chart review of HIV-infected men receiving EFV-based ART and concomitant simvastatin 20 mg/day [92]	13	Evaluate the safety and efficacy of simvastatin for treatment of dyslipidemia for up to 6 months	TC: 20% decrease TG: 21% decrease LDL-C: 36% decrease	No cases of myalgia, myositis, or increased CK Reduction in TC, TG, and LDL-C values with simvastatin

PI, protease inhibitor; ART, antiretroviral therapy; TC, total cholesterol; TG, triglycerides; LDL, low-density lipoprotein; HDL, high-density lipoprotein; CK, creatinine kinase; HIV, human immunodeficiency virus; NNRTI, nonnucleoside reverse transcriptase inhibitor; NVP, nevirapine; EFV, efavirenz; sCD14, soluble CD14; Lp-PLA2, Lipoprotein-associated phospholipase A2; carotid IMT, carotid intima-media thickness; ATV/RTV, atazanavir/ritonavir.

with pravastatin/fenofibrate in a patient prescribed a COBI-boosted PI regimen [47].

Generally, NNRTIs appear to induce the metabolism of pravastatin, minimizing the effectiveness of pravastatin's moderate LDL reduction potential. Pravastatin has no effect on the AUC of NVP or its active metabolite [35]. EFV significantly decreases pravastatin exposure by 40%, but pravastatin has no effect on non-steady state EFV concentrations [48]. ETV and RPV generally lack interaction data with pravastatin, but no significant effect is expected [38]. Co-administration with raltegravir does not impact pravastatin exposure, and raltegravir AUC is only minimally affected (13% increase) making dose adjustments unnecessary [49].

Multiple studies evaluating efficacy of pravastatin therapy on lipid parameters in HIV-infected patients have been published (See Table 1) [46,50–60]. Concomitant use of pravastatin is considered safe in patients treated with either PI- or NNRTI-based ART. Consideration may be given to higher starting doses of pravastatin in patients on EFV or SQV-based ART, whereas the lowest pravastatin dose necessary should be used in ATV or DRV-based ART.

Rosuvastatin

Rosuvastatin is not extensively metabolized, but the 10% of the dose that is recovered as a moderately active metabolite occurs as a result of CYP2C9 [61]. Rosuvastatin is 90% excreted in the feces, with an elimination half-life of 19 h. There is no difference in the absorption (AUC) of rosuvastatin based on time of administration,

which allows it to be administered without regard to time of day [61].

Because of the minimal metabolism of rosuvastatin, drug-drug interactions that significantly alter the concentrations of PIs that treat HIV-1 have been limited in the extensive studies performed [8,62]. However, in one study, rosuvastatin co-administration with ATV/RTV was independently associated with a significant increase in ATV concentrations above therapeutic threshold of 800 ng/mL, potentially increasing the risk of adverse drug reactions [63]. In other studies, the rosuvastatin AUC and maximum concentration (C_{max}) increased when co-administered with ATV or LPV (213%, 600% for ATV and 108%, 366% for LPV, respectively) [62]. In combination with other PIs (nelfinavir [NfV], RTV, DRV, fosamprenavir, TPV), rosuvastatin AUC may increase in varying degrees, but to a lesser extent than ATV and LPV [62,64]. If rosuvastatin will be co-administered with PIs, caution is warranted. The rosuvastatin should be started at a low dose (5 mg daily), and titrated slowly [38]. If using with ATV or LPV, the maximum dose should be 10 mg daily [38,62]. No significant drug-drug interactions have been reported between rosuvastatin and the NNRTIs [8,61].

Several studies have evaluated the efficacy of rosuvastatin in HIV-infected patients (See Table 1) [65–68]. In addition, rosuvastatin may have other added benefits in HIV, including decreased inflammatory markers, decreased N-terminal pro-B-type natriuretic peptide, preserved renal function, decreased monocyte and T-cell activation, and increased bone mineral density [65,69–73]. Rosuvastatin is generally considered safe in patients treated with

ART if started at a low dose and closely monitored for adverse effects. Considering the reliability of other statins at doses classified as moderate-intensity, the DHHS guidelines recommend that concomitant use of rosuvastatin should be avoided if possible in HIV patients receiving PI-based ART [38]. In contrast, the European AIDS Clinical Society (EACS) suggests that rosuvastatin use is generally safe, if started with a low dose and using no more than a maximum dose of 20 mg [74].

Other statins

Fluvastatin

The primary metabolic pathway for fluvastatin is via CYP2C9 to inactive metabolites [75]. Interactions with most PIs are unlikely, although RTV is a known inducer of CYP2C9 and may lead to decreased fluvastatin efficacy [76]. Alternatively, ETV, an inhibitor of CYP2C9, may increase serum concentrations of fluvastatin [77]. No recommendations are provided in the DHHS guidelines on ART [38]. Furthermore, limited data are available evaluating the use of fluvastatin in HIV-infected with dyslipidemia (See Table 1) [78,79]. Administration of fluvastatin in patients treated with ART is likely safe; however, due to the paucity of data, lower potential effectiveness with RTV, and cost-effective availability of safer statins, concomitant fluvastatin should be avoided. If administered, the EACS recommends consideration of higher doses if combined with ART [74].

Pitavastatin

Pitavastatin has similar pharmacokinetic properties as pravastatin [62]. Similar to some of the other statins, the absorption of pitavastatin did not differ based on morning or evening doses, allowing for administration without regard to time of day [80]. Pitavastatin is metabolized marginally by CYP2C9 and minimally by CYP2C8, and excreted 79% in the feces. Because the major metabolite of pitavastatin is formed through glucuronidation, clinically relevant interactions with ART have not been documented at this time [81–83].

Although there is favorable information regarding interactions, there is still limited information regarding clinical efficacy of pitavastatin in HIV. Initial results from the INTREPID trial are promising (See Table 1) [84,85]. The REPRIEVE trial, started in April 2015 and slated to end in 2019, should provide additional valuable information on pitavastatin use in HIV [81]. Although generally considered safe to use with ART, the paucity of data with pitavastatin to date has limited its inclusion in the recommendations for statins in the HIV treatment guidelines [38]. If pitavastatin is used, it is recommended to start with the currently approved initial dose and titration [62].

Simvastatin

Simvastatin, a prodrug, requires *in vivo* non-CYP related hydrolysis to active hydroxymetabolites [86]. Simvastatin is extensively metabolized via intestinal and hepatic CYP3A4 to further active and inactive metabolites. Inhibition of CYP3A4 through RTV or COBI boosted-PI regimens may result in increased concentrations of lactone prodrug available for non-CYP related hydrolysis. Pharmacokinetic studies revealed a 6-fold and 30-fold increase in simvastatin AUC when administered with NFV and SQV/RTV, respectively [35,87]. Hare and colleagues reported the first fatal case of a 70 year-old HIV-infected man receiving treatment with NFV-containing ART, who presented with rhabdomyolysis secondary to concomitant simvastatin [88]. Multiple cases of

rhabdomyolysis following the introduction of simvastatin have been reported in patients treated with various PI-containing ART [89–91]. As a result, co-administration of simvastatin and PIs are contraindicated [38].

EFV, via CYP3A4 induction, may decrease simvastatin AUC by up to 58% [34]. Due to similar pharmacokinetic properties, the same effect is expected when simvastatin is administered with NVP. Simvastatin doses may need to be increased, not to exceed the maximum daily dose, to achieve target lipid goals [38].

Only one clinical trial evaluating the use of simvastatin in HIV-infected patients has been conducted to date (See Table 1) [92]. Due to limited data, significant drug-drug interactions, and safer statins available, simvastatin should not be concomitantly administered to patients treated with ART.

Lovastatin

Lovastatin has similar pharmacokinetic properties compared to simvastatin [86]. It is administered as an inactive lactone prodrug that requires non-CYP hydrolysis to its active hydroxymetabolites. Lovastatin undergoes intestinal and hepatic CYP3A4 metabolism. As with simvastatin, inhibition of CYP3A4 significantly increases concentrations of lactone prodrug that can be converted via non-CYP hydrolysis into active drug. Alternatively, induction of CYP3A4 may decrease lovastatin concentrations. Concomitant use of lovastatin and PIs are contraindicated, while use with NNRTIs may warrant lovastatin dose increases to reach desired lipid lowering effects [38]. Lovastatin should not be used in patients treated with ART due to significant drug interactions and lack clinical data.

Non-statin lipid lowering therapies

Several other medications approved for use in the treatment of dyslipidemia in HIV patients, specifically fibrates, ezetimibe, niacin, and omega-3 fatty acids [93]. Fibrates should be considered when triglycerides (TG) are >400 mg/dL. Fenofibrate and fenofibric acid are preferred over gemfibrozil due to less risk of drug interactions with ART. Omega-3 fatty acids should be considered when TG are >500 mg/dL, particularly in combination with fibrates due to synergistic TG lowering [94]. Niacin can also be used when TG are elevated, but should be reserved after fibrates and omega-3 fatty acids. Ezetimibe is used as a safe adjunct to statin therapy for modest LDL reduction in HIV patients [93]. Other medications that have been studied but lack approval for treatment of dyslipidemia include thiazolidinediones, acipimox, growth hormone, tesamorelin, leptin, and glutathione [93].

Conclusion

Clinicians need to be familiar with the intricacies of statin selection for the prevention of CVD in patients with HIV on ART. Based on pharmacokinetic and clinical data, atorvastatin and pravastatin are generally considered safe for HIV patients receiving ART. Rosuvastatin is generally safe if started at a low dose and a maximum 20 mg per day. Fluvastatin, lovastatin, and simvastatin should be avoided in patients with HIV receiving ART. In general, individualizing lipid therapy for a patient and starting with the lowest possible statin dose are best practices in the management of dyslipidemia in HIV.

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