What is the statin of choice in patients infected with human immunodeficiency virus (HIV) taking protease inhibitors?

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Several sources assert that there is a potential for drug-drug interactions between protease inhibitors (PIs) and lipid-lowering therapies, particularly the 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase inhibitors, also known as statins.[1-3] In a recent drug safety communication, the Food and Drug Administration (FDA) states that concomitant use of PIs and certain statins may raise blood levels of the statins, increasing the risk for myopathy.[4] There does not appear to be a clear consensus regarding a statin of choice in patients infected with human immunodeficiency virus (HIV) who are taking PIs.

The potential for drug interactions between statins and PIs may be explained by their pharmacokinetic characteristics.[1] Most of the statins undergo extensive hepatic metabolism by cytochrome P450 (CYP) 3A4.[5] A summary of statin pharmacokinetic characteristics may be seen in Table 1. All of the PIs are metabolized by CYP enzymes, primarily CYP 3A4, and have either inducing or inhibitory effects. Additionally, however, it has been proposed that there may be multiple mechanisms of drug interactions involved, based on differences in the degree to which statin concentrations are changed when co-administered with the PIs.[6]

Table 1. Pharmacokinetic Characteristics of Available Statins.[7-13]

Statin	Absorption	Distribution	Metabolism	Elimination
Atorvastatin	14%	≥98% protein bound	CYP 3A4, extensive	$T_{1/2}$ 14 h; biliary excretion, <2% in urine
Fluvastatin	24%	98% protein bound	CYP 2C9 and 3A4, extensive	$T_{1/2}$ <3 h; 90% fecal, 5% in urine
Lovastatin	<5%	>95% protein bound	CYP 3A4, extensive	$T_{1/2}$ 3-4 h; 83% fecal, 10% in urine
Pitavastatin	51%	>99% protein bound	CYP 2C9, marginal	$T_{1/2}$ 12 h; 79% fecal, 15% in urine
Pravastatin	34%; 17% absolute bioavailability	50% protein bound	Sulfation, extensive	$T_{1/2}$ 77 h; 70% fecal, 20% in urine
Rosuvastatin	20%	88% protein bound	CYP 2C9, minor	$T_{1/2}$ 19 h; 90% fecal
Simvastatin	<5%	95% protein bound	CYP 3A4, extensive	$T_{1/2}$ not specified; 60% fecal, 13% in urine

CYP=cytochrome P450; $T_{1/2}$=half life

The National Institutes of Health (NIH) issue guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents in which they list medications that should not be used with PIs.14 This list was last updated in October of 2011 and may be found on page 134 of the document. Of note, the PIs include amprenavir, atazanavir, darunavir, fosamprenavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, and

tipranavir. Information from these guidelines on interactions between each statin and the PIs is summarized in Table 2.

Table 2. Data on Interactions between Statins and PIs.[14]

Statin	PI	Effect on PI or Statin	Dosing and Clinical Recommendations
Atorvastatin	All PIs	Darunavir/r + atorvastatin 10 mg similar to using atorvastatin 40 mg alone Fosamprenavir ± ritonavir increased atorvastatin AUC by 130-153% Lopinavir/r increased atorvastatin AUC by 488% Saquinavir/r increased atorvastatin AUC by 79% Tipranavir/r increased atorvastatin AUC by 836%	Use lowest possible starting dose with careful monitoring for toxicities or consider other statins with less potential for interaction
Lovastatin	All PIs	Significant increase in lovastatin expected	**Contraindicated. Do NOT administer.**
Pitavastatin	Atazanavir	Pitavastatin AUC increased by 31%, Cmax by 60%; no significant effect on atazanavir	No dosage adjustment needed for atazanavir without ritonavir
	All ritonavir-boosted PIs	Pitavastatin AUC may be increased	**Do NOT co-administer** due to possible increase in pitavastatin concentration and risk of rhabdomyolysis.
Pravastatin	Darunavir/r	Pravastatin AUC increased by 81%	Use lowest possible starting dose with careful monitoring.
	Lopinavir/r	Pravastatin AUC increased by 33%	No dosage adjustment necessary.
	Saquinavir/r	Pravastatin AUC decreased by 47-50%	No dosage adjustment necessary.
Rosuvastatin	Atazanavir/r	Rosuvastatin AUC increased by 213%, Cmax by 600%	Use lowest possible starting dose with careful monitoring or consider other statins with less potential for interaction.
	Darunavir/r, Fosamprenavir ± ritonavir, Saquinavir/r	Rosuvastatin AUC may increase	
	Lopinavir/r	Rosuvastatin AUC increased by 108%, Cmax by 366%	
	Tipranavir/r	Rosuvastatin AUC increased by 26%, Cmax by 123%	
Simvastatin	All PIs	Significant increase in simvastatin; Saquinavir/r 400 mg/400 mg twice daily increased simvastatin AUC by 3059%	**Contraindicated. Do NOT administer.**

PI=protease inhibitor; PI/r=PI boosted with ritonavir; AUC=area under the curve; Cmax=maximum concentration

The NIH guidelines suggest that use of lovastatin, pitavastatin, and simvastatin are contraindicated with most PIs.[14] As alternatives, they state that pravastatin and fluvastatin have the least potential for drug-drug interactions with the PIs, except for pravastatin and darunavir boosted with ritonavir. Atorvastatin and rosuvastatin may also be used with caution, starting at the lowest possible dosage and titrating based on lipid levels and tolerability.

In addition to the NIH, the Infectious Diseases Society of America (IDSA) put forth guidelines for the management of dyslipidemia in HIV-infected patients, in which they address use of statins.[15] In patients taking PIs, the IDSA recommends starting with low doses of statins and titrating upward while carefully monitoring the patient's virologic status and development of liver or skeletal muscle toxicities. The statins they recommend and initial doses include pravastatin 20-40 mg daily or atorvastatin 10 mg daily. Fluvastatin 20-40 mg daily is suggested as an alternative. Simvastatin and lovastatin are not recommended. The IDSA notes that these recommendations are based on a small number of studies involving HIV-infected patients taking PIs that had been published to date. Of note, these guidelines were published in 2003, at which time rosuvastatin and pitavastatin were not available.

In February of 2012, the FDA required labeling changes of all statins, including removal of routine monitoring of liver enzymes from the safety section.[16] Healthcare providers are advised to perform liver function tests prior to initiation of statin therapy and as clinically indicated. The prescribing information for lovastatin in particular has been extensively revised to include new contraindications and dose limitations. In the revised label, the manufacturer clearly states that the combination of protease inhibitors with lovastatin is contraindicated.[17]

From a search of the literature, there are few studies evaluating the comparative efficacy and safety of statins in patients infected with HIV. Also of note, while there are studies of the reduction in cardiovascular risk associated with statin use in non-HIV infected patients, such studies in HIV-infected patients are lacking. Most evaluate changes in low density lipoprotein cholesterol (LDL-c).[18] For example, Aslangul et al recently conducted a trial which compared the LDL-lowering effect of pravastatin and rosuvastatin in HIV-infected patients taking a ritonavir boosted PI for at least 2 months.[19] Patients with exposure to a statin or fibrate within 2 months of enrollment were excluded. Patients were randomized to receive either rosuvastatin 10 mg daily or pravastatin 40 mg daily for 45 days. The primary endpoint was percent change in LDL-c from baseline to study endpoint. A total of 83 patients participated of which 41 received rosuvastatin and 42 received pravastatin. At baseline, the median LDL-c was 4.93 mmol/L (190 mg/dL); by the study endpoint, the investigators observed a median reduction in LDL-c of 37% in the rosuvastatin group vs. 19% for the pravastatin group. Changes in serum creatinine, liver transaminases, creatine phosphokinase, and proteinuria were also documented; these were not significantly different between groups although the values were not specified. No renal, hepatic, or musculoskeletal adverse events were reported. The authors concluded that rosuvastatin was more effective than pravastatin in lowering LDL-c in patients taking PIs and that both statins were well-tolerated.

Calza et al performed an open-label study in which they compared the cholesterol lowering effects of rosuvastatin, pravastatin, and atorvastatin in HIV-infected patients who had PI-associated hypercholesterolemia.[20] Patients included in the study had been taking a stable PI-based regimen for at least 12 months prior to enrollment. Patients were randomized to receive rosuvastatin 10 mg daily, pravastatin 20 mg daily, or atorvastatin 10 mg daily. The primary endpoint was decrease in LDL-c and total cholesterol from baseline to 12 months. A total of 85 patients completed the study, 26 in the rosuvastatin group, 31 in the pravastatin group, and 28 in the atorvastatin group. All patients were taking ritonavir-boosted PIs. Mean decreases in total cholesterol from baseline to the study endpoint were appreciated in all treatment groups; however, the reductions were significantly greater in the rosuvastatin group compared to the pravastatin group (25.2% vs. 17.6%, p=0.01) and compared to the atorvastatin group (25.2% vs. 19.8%, p=0.03). Mean LDL-c levels were also significantly reduced in the rosuvastatin group compared to the pravastatin and atorvastatin groups (26.3% [rosuvastatin] vs. 18.1% [pravastatin], p=0.04, and 26.3% vs. 20.3% [atorvastatin], p=0.02). Commonly reported adverse events included nausea, dyspepsia, and diarrhea, and these occurred at similar incidences among the treatment groups. There were no reports of myopathy or hepatotoxicity. The authors concluded that all statins used in the study were effective in lowering LDL and total cholesterol levels in patients taking PIs and were well-tolerated. Among the statins used, rosuvastatin demonstrated the greatest cholesterol-lowering effect.

It is important to note that while the literature suggests that pravastatin carries the lowest potential for drug interactions, use of pravastatin is not without risks. Mikhail et al described a case in which an HIV-infected patient who had been taking atazanavir boosted with ritonavir, emtricitabine, and tenofovir developed rhabdomyolysis 4 months after increasing his pravastatin dose.[21] He had been virologically stable on this regimen and had been taking pravastatin 40 mg as well for 18 months. The dose of pravastatin was increased to 80 mg daily in an effort to attain his LDL goal of <100 mg/dL. The patient had symptoms consistent with myopathy beginning shortly after the dose increase and the resulting rhabdomyolysis resolved within 10 days of pravastatin discontinuation.

In a recent review, Martinez et al state that it may be beneficial to initiate a statin with high potency and low risk of clinically significant drug interactions, and to administer the statin at higher doses than used in HIV-uninfected patients.[18] They justify the latter recommendation based on data indicating a lower efficacy of lipid-lowering therapies in general in patients infected with HIV compared to that reported in uninfected patients. Statins of higher potency include atorvastatin and rosuvastatin, both of which may be safe to use in HIV-infected patients. While the authors state that pravastatin may be associated with the least amount of drug interactions compared to the other statins, it is of low potency. Similarly, fluvastatin may have a low potential for drug interactions but is also of low potency.

Jimenez-Nacher et al also suggest that while interactions may occur with atorvastatin and PIs, the effect of CYP 3A4 inhibition is more modest compared to that of simvastatin or lovastatin; thus, atorvastatin may be a viable treatment option.[22] Regarding rosuvastatin, Jimenez-Nacher et al state that the drug may compete with

PIs for uptake in the liver and lead to an increase in plasma concentrations of rosuvastatin but decreases in liver concentrations, possibly diminishing the efficacy of the statin.

In summary, based on the current literature, no one statin appears to be clearly superior in the management of dyslipidemia in HIV-infected patients taking PIs. There is agreement on the recommendation to avoid use of simvastatin or lovastatin based on a higher propensity to interact with the PIs. Healthcare providers should closely monitor HIV-infected patients who are taking statins and be conservative with the dosing, both at initiation and with titration.

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