LIPID-LOWERING AGENTS

Drug	Dose	Metabolism[1]	Efficacy	Onset	Interactions	Side Effects	Cost
FIBRIC ACID DERIVATIVES							
bezafibrate Bezalip® (Roche)	400 mg SR once daily or 200 mg tid with meals	Clrenal (50% unchanged, 20% glucuronides) - hydroxylation and glucuronidation	↓ 20% total cholesterol, ↓ (50%) TG, ↓ 20% LDL, variable ↑ 20% HDL	Decrease in TG within 1-2 months, increase HDL in 3-6 months	Decrease dose in renal failure; ritonavir, nelfinavir and efavirenz may ↑ clearance via GT induction	GI disturbances, rash, headache, insomnia, myositis, elevated CPK	usual: $1.60/day (ODB) $1.60/400 mg $0.6183/200 mg
clofibrate Atromid-S® (Ayerst)	1 g bid with food	Esterase to CPIB (active form), then GT	↓ 20% total cholesterol, ↓ 45% TG, ↓ variable LDL, variable ↑ HDL	Effect within 2-5 days, max response in 21 days	Caution with ritonavir; ritonavir, nelfinavir and efavirenz may ↑ clearance via GT induction	GI disturbances, potential carcinogenicity, rash, headache, myositis, elevated CPK	not covered by ODB
fenofibrate Lipidil®, Lipidil Micro® (Fournier)	200 mg daily with food (max. 300 mg/day)	Prodrug, - hydrolyzed to fenofibric acid and GT; Clrenal	↓ 30% total cholesterol, ↓↓ 50%TG, ↓ 20% LDL, ↑ 15% HDL	Effect within 6-8 weeks	Decrease dose in renal failure; ritonavir, nelfinavir and efavirenz may ↑ clearance via GT induction. In healthy volunteers, **ritonavir 100 mg BID or lopinavir/ritonavir 400/100 mg BID** did not have significant effects on the pharmacokinetics of single-dose fenofibrate 145 mg: fenofibrate AUC ↓ 11%, Cmax ↓ 1% with ritonavir and fenofibrate AUC ↓ 14% and Cmax ↓ 3% with lopinavir/ritonavir.[2]	GI disturbances, rash, headache, myositis, elevated CPK	usual: $1.21/day (ODB) $0.4325/100 mg $1.21/200 mg
gemfibrozil Lopid® (Parke Davis)	600 mg BID (max. 1200 mg/day)	30-50% GT, CYP (?)	↓ 10% total cholesterol, ↓ 45% TG, ↓ variable LDL, ↑ 15% HDL	Max. response in 4weeks	Ritonavir, nelfinavir and efavirenz may ↑ clearance via GT induction. In a healthy volunteer	GI distress and rash	usual: $1.19/day (ODB) $0.2964/300 mg

Drug	Dose	Metabolism[1]	Efficacy	Onset	Interactions	Side Effects	Cost
					study, subjects received single dose gemfibrozil 600 mg before and after 14 days of **LPV 400/rtv 100 mg BID**. In the presence of steady-state LPVr, gemfibrozil AUC was ↓ 41%.[3]		
HMG-COA-REDUCTASE INHIBITORS							
atorvastatin Lipitor® (Parke Davis)	10 mg qhs, max. 80 mg/day; make dose changes q4 weeks	CYP3A4, P-gp, OAT1B1, OAT2B1	↓ 28-40% total cholesterol, ↓ 13-32% TG, ↓ 38-51% LDL, ↑ 5-6% HDL	Effect within 2 weeks, maximum response at 2-4 weeks	Pharmacokinetic studies in HIV-negative subjects: a) **saquinavir** 400 mg/ritonavir 400 mg BID plus 40 mg atorvastatin resulted in a 4.5-fold ↑ AUC atorvastatin.[4] Do not exceed 20 mg atorvastatin daily with saquinavir.[5] b) **nelfinavir** 1250 mg BID plus 10 mg atorvastatin resulted in 74% ↑ AUC atorvastatin.[6] Do not exceed 40 mg atorvastatin daily with nelfinavir.[5] c) **lopinavir** 400 mg/ritonavir 100 mg BID plus 20 mg atorvastatin resulted in 5.9-fold ↑ AUC.[4, 7] Use lowest atorvastatin dose necessary.[5] d) **fosamprenavir** 1400 mg BID or fosamprenavir 700 mg/ritonavir 100 mg	Abdominal cramps, nausea, myalgia, thrombocytopenia, ↑CPK, ↑LFTs	usual: $2.00/day (ODB) $1.60/10 mg $2.00/20 mg $2.15/40 mg

Drug	Dose	Metabolism[1]	Efficacy	Onset	Interactions	Side Effects	Cost
					BID plus atorvastatin 10 mg resulted in significant ↑ in atorvastatin Cmax (404% and 284%, respectively) and AUC (230% and 253%, respectively); APV levels were not affected.[8] Do not exceed 20 mg atorvastatin daily with boosted or unboosted fosamprenavir.[5] e) **tipranavir** 500 mg/ ritonavir 200 mg BID led to 9-fold ↑ atorvastatin AUC.[9] Avoid atorvastatin use with tipranavir.[5] f) Combination of atorvastatin 10 mg daily plus **darunavir 300/ritonavir** 100 mg BID led to 15% ↓ atorvastatin AUC vs. atorvastatin 40 mg QD alone. Do not exceed 20 mg atorvastatin daily with darunavir.[5] With **efavirenz** 600 mg/d and atorvastatin 10 mg/d: - significant ↓ **atorvastatin** AUC by 43% (total active atorvastatin exposure ↓ 34%);		

Drug	Dose	Metabolism[1]	Efficacy	Onset	Interactions	Side Effects	Cost
					EFV concentrations not affected. Patients on combination should be closely monitored for anti-lipid activity; statin dose may need to be titrated.[10] In healthy volunteers, atorvastatin 40 mg QD plus **etravirine** 800 mg BID (old formulation) led to 37% ↓ AUC of atorvastatin and 27% ↑ AUC atorvastatin active metabolite. Etravirine exposures were not affected. Combination may be coadminstered.[11] In healthy volunteers, atorvastatin 40 mg QD plus **rilpivirine 150 mg QD** did not lead to significant alterations in plasma exposures of either rilpivirine or atorvastatin. A modest increase in exposure to atorvastatin hydroxylated metabolites (via mild induction of CYP3A activity by rilpivirine) resulted in an increase in the total lipid-lowering activity of atorvastatin during rilpivirine coadministration; this was considered clinically relevant. Combination may be coadministered without dose		

Drug	Dose	Metabolism[1]	Efficacy	Onset	Interactions	Side Effects	Cost
					adjustment.[12] Potential for ↑ atorvastatin concentrations with **elvitegravir/cobicistat**; initiate with lowest starting dose of atorvastatin and titrate to response.[13] In healthy volunteers, coadministration of **raltegravir** 400 mg BID plus atorvastatin 20 mg daily did not change the pharmacokinetics of either drug in a clinically meaningfull way. The combination can be safely administered without dose adjustments.[14]		
fluvastatin Lescol® (Novartis)	20 mg qhs (max. 40 mg qhs or 20 mg BID)	extensive 1st-pass; CYP2C9 >>3A4 (minor), OATP1B1, OAT1B3, OAT2B1, BCRP (intestinal); weak inhibitor of 2C9	↓ 13-23% total cholesterol, ↓ 5-15% TG, ↓ 17-34% LDL, ↑ 1-7% HDL	maximum response within 4 weeks	May be less likely to interact with PIs; caution with ritonavir (induces 2C9 but inhibits 3A). Potential for ↓ concentrations with **elvitegravir/cobicistat** via 2C9 induction (clinical significance unknown). Potential for increased concentrations with **efavirenz and etravirine** via 2C9 inhibition (clinical significance unknown).	Same as above - dyspepsia and lupus-like syndrome	(ODB) $0.75/20 mg $1.05/40 mg
lovastatin	10-20 mg cc	hydrolysis to active	↓ 21-36% total	Effect within 3	Elevated liver function	Same as	(ODB)

Drug	Dose	Metabolism[1]	Efficacy	Onset	Interactions	Side Effects	Cost
Mevacor® (Merck)	(max. 40 mg BID or 80 mg cc)	form, CYP3A4, also 2D6, 2C9, OATP1B1, P-gp, BCRP	cholesterol, ↓ 12-13% TG, ↓ 29-48% LDL, ↑ 7-8% HDL	days, maximum response at 4-6 weeks	tests, myalgias reported with concomitant use of lovastatin and PI therapy.[15] **Lovastatin** is contraindicated with all HIV protease inhibitors and elvitegravir/cobicistat.[5, 13]	atorvastatin -lupus-like syndrome and ↑LFTS 3x normal	$1.2985/20 mg $2.3951/40 mg
Pitavastatin (Livalo® - not available in Canada)		Primarily via UGT1A3, UGT2B7 and OAT1B1. Minimal CYP450 metabolism (mostly CYP2C9, 2C8).			In healthy volunteers, administration of pitavastatin 4 mg daily in the presence of steady-state **lopinavir/ritonavir 400/100 mg BID** did not result in clinically significant changes in pharmacokinetic exposures of either drug.[16] In healthy volunteers, coadministration of pitavastatin 4 mg and **darunavir 800/100 mg** QD resulted in 26% ↓ AUC of pitavastatin, and no significant changes in darunavir exposures compared to either drug administered alone.[17] In healthy volunteers, coadministration of pitavastatin 2 mg daily with **darunavir/ritonavir 800/100 mg daily or efavirenz 600 mg daily** did not result in significant interactions. Pitavastatin AUC ↓ 9% and Cmax ↓ 7% in the		

Drug	Dose	Metabolism[1]	Efficacy	Onset	Interactions	Side Effects	Cost
					presence of darunavir/r; pitavastatin AUC ↓ 11% and Cmax ↑ 20% in the presence of efavirenz.[18] **Pitavastatin** may be used without dose limitations with boosted or unboosted atazanavir, darunavir/ritonavir and lopinavir/ritonavir.[5]		
pravastatin Pravachol® (Squibb)	10-20 mg qhs (max. 40 mg qhs)	40-54% Clrenal; substrate of CYP3A (minor), P-glycoprotein, OATP1B1, OATP1B3, OATP2B1, BCRP (intestinal)	↓ 13-24% total cholesterol, ↓ 10-15% TG, ↓ 19-34% LDL, ↑ 3-10% HDL	Effect within 3 days, maximum response at 4-6 weeks	Pharmacokinetic studies in HIV-negative subjects: a) **saquinavir 400 mg/ritonavir 400 mg BID** plus 40 mg pravastatin resulted in a 35% ↓ AUC of pravastatin.[4] b) **lopinavir 400 mg/ ritonavir 100 mg BID** + pravastatin 20 mg: 30% ↑ pravastatin AUC[7] c) **darunavir 600 mg/ rtv 100 mg BID** plus single-dose pravastatin 40 mg led to 81% ↑ pravastatin AUC.[19] d) **Nelfinavir 1250 mg BID** + pravastatin 40 mg QD: 46.5% ↓ pravastatin AUC.[20] Addition of pravastatin 40 mg daily to either **indinavir, saquinavir, or ritonavir**-containing regimens (n=15) did not	Same as atorvastatin	(ODB) $1.0593/10 mg $1.2495/20 mg $1.505/40 mg

Drug	Dose	Metabolism[1]	Efficacy	Onset	Interactions	Side Effects	Cost
					result in any significant changes to PI concentrations.[21] **Pravastatin** may be used without dose limitations with darunavir/ritonavir and lopinavir/ritonavir.[5] With **efavirenz** 600 mg/d and pravastatin 40 mg/d, **pravastatin** AUC ↓ 40%; EFV concentrations not affected. Patients on combination should be closely monitored for anti-lipid activity; statin dose may need to be titrated.[10] In healthy adults who received pravastatin 40 mg QD plus **raltegravir** 400 mg BID for 4 days, pravastatin exposures were not significantly affected in the presence of raltegravir. Raltegravir AUC ↑ 13%, Cmax ↑ 31% and C12 ↓ 41% when coadministered with pravastatin; however, since raltegravir efficacy is better correlated with AUC, this interaction is not likely to be clinically significant, and no dose adjustments are required.[22]		

Drug	Dose	Metabolism[1]	Efficacy	Onset	Interactions	Side Effects	Cost
					Potential for ↓/↑ concentrations with **elvitegravir/cobicistat.**		
rosuvastatin Crestor® (Astra Zeneca)	5-20 mg once daily (max. 40 mg daily). May be given with/ without food at any time of day.	Minimal (10%) hepatic metabolism, mostly through CYP2C9. Substrate of OATP1B1, OATP1B3, BCRP (intestinal). Mostly excreted in bile.	28-30%↓ total cholesterol, ↓ 40-58%↓ LDL, 12-15% ↓ TG, 7-12% ↑ HDL	Within 2 weeks, maximal response at 6-12 weeks.	Prospective study with 6 healthy adult volunteers of **ATV/r 300mg/100mg daily** for 7 days and rosuvastatin 10mg single dose led to 213% ↑ rosuvastatin AUC, 600% ↑ Cmax vs. rosuvastatin alone. Rosuvastatin-lactone AUC ↑ 61%, no change in N-desmethyl rosuvastatin levels.[23] **Limit rosuvastatin dose to 10 mg once daily** with boosted or unboosted atazanavir.[5] In healthy volunteers who received rosuvastatin 10 mg daily alone or with **darunavir 600/100 mg BID** for 7 days, mean rosuvastatin AUC ↑ 48% and Cmax ↑ 144% in the presence of darunavir/ritonavir. Darunavir kinetics were not significantly affected by rosuvastatin. Lipid-lowering effects of rosuvastatin were not significantly altered in the presence of darunavir/ritonavir.[24] In a prospective study of	Headache, asthenia, upper respiratory infections, gastrointestinal symptoms, and myalgia have been reported; myopathy has occurred rarely	(ODB) $1.36/10 mg $1.70/20 mg $1.99/40 mg

Drug	Dose	Metabolism[1]	Efficacy	Onset	Interactions	Side Effects	Cost
					healthy volunteers, **FPV/r 700mg/100mg BID** for 7 days did not affect the AUC or Cmax of rosuvastatin 10mg (single dose) or N-desmethyl Rosuvastatin levels (metabolite). FPV/r ↑ rosuvastatin-lactone AUC (metabolite) by 76%. Based on PK data, no dose adjustments required when combination is used.[23] In a prospective cohort of HIV-positive subjects (n=14) on **lopinavir/r** regimens, LPV Cmin were not changed during 12 weeks of rosuvastatin therapy;[25] however, rosuvastatin concentrations were 1.5-2-fold higher compared to historical data.[26] In an open-label, 3-phase pharmacokinetic study in healthy volunteers, the combination of **rosuvastatin 20 mg/day plus LPV/r 400/100 mg BID** for 7 days led to a 2.1-fold ↑ AUC and 4.7-fold ↑ Cmax of rosuvastatin, compared to rosuvastatin alone ($p<0.0001$). LPV levels were not changed in the		

Drug	Dose	Metabolism[1]	Efficacy	Onset	Interactions	Side Effects	Cost
					presence of rosuvastatin.[27] Case report of rhabdomyolysis in a patient on lopinavir/ritonavir after switching from pravastatin to rosuvastatin.[28] **Limit rosuvastatin dose to 10 mg once daily** with lopinavir/ritonavir.[5] In 16 healthy volunteers, **tipranavir 500/ritonavir 200 mg BID** plus single dose rosuvastatin 10 mg led to 37% ↑ AUC and 123% ↑ Cmax of rosuvastatin; TPV and RTV levels were not changed in the presence of rosuvastatin. Use lowest dose of rosuvastatin (5 mg/day) and titrate slowly to treatment response.[9] Randomized, crossover study in healthy subjects of **elvitegravir 150mg/ cobicistat 150 mg daily** alone or with rosuvastatin 10 mg. Elvitegravir kinetics were unaffected with coadministration, while rosuvastatin Cmax ↑ 89%, AUC ↑ 38%. Dose adjustment likely not necessary.[29]		

Drug	Dose	Metabolism[1]	Efficacy	Onset	Interactions	Side Effects	Cost
simvastatin Zocor® (Merck Frosst)	5-10 mg before supper or hs (max. 20 mg BID or 40 mg before supper or hs)	hydrolysis to active form, CYP3A	↓ 21-30% total cholesterol, ↓ 12-15% TG, ↓ 28-39% LDL, ↑ 7-10% HDL	Effect within 3 days, maximum response at 4-6 weeks	Pharmacokinetic studies in HIV-negative subjects: a) saquinavir 400 mg/ritonavir 400 mg BID plus 40 mg simvastatin resulted in a 31.6 fold ↑ AUC simvastatin.[4] b) nelfinavir 1250 mg BID plus 20 mg simvastatin resulted in 506% ↑ AUC simvastatin [6] **Simvastatin** is contraindicated with all HIV protease inhibitors and elvitegravir/cobicistat.[5, 13] Severe toxicity including rhabdomyolysis and hepatic toxicity have been reported with combination.[30] With **efavirenz** 600 mg/d and simvastatin 40 mg/d: - significant ↓ **simvastatin** AUC by 58% (active HMG-CoA reductase inhibitory activity ↓ 60%); EFV concentrations not affected. Patients on combination should be closely monitored for anti-lipid activity; statin dose may need to be titrated.[10]	Same as atorvastatin - lupus-like syndrome and thrombocytopenic purpura	(ODB) $0.90/5 mg $1.78/10 mg $2.20/20 mg $2.20/40 mg $2.20/80 mg

Drug	Dose	Metabolism[1]	Efficacy	Onset	Interactions	Side Effects	Cost
CHOLESTEROL ABSORPTION INHIBITORS							
Ezetimibe (Ezetrol®)	10 mg once daily +/- food	Glucuronidated in gut wall to active metabolite	Monotherapy: 18%↓ LDL, 5% ↓ TG, 4%↑ HDL; Combined with atorvastatin: 54.5%↓ LDL, 33%↓ TG, 7%↑ HDL (all parameters sig. > vs. atorvastatin alone)	Onset within 1 week, peak ↓ LDL within 2-4 weeks	**Fibrates:** ezetimibe concentrations ↑ 1.7-fold with gemfibrozil, ↑ 1.5-fold with fenofibrate; fibrates ↑ cholesterol excretion into bile, leading to ↑ risk cholelithiasis. Avoid co-administration, may need to ↑ ezetimibe dose. **Cyclosporine**: 12-fold ↑ ezetimibe levels reported in renal transplant patient, mechanism unknown. Co-administer with caution. **Lopinavir/rtv:** Ezetimibe 10 mg QD for 12-18 weeks did not affect steady-state kinetics of lopinavir/ritonavir in HIV-infected subjects.[31, 32] **Raltegravir:** Steady-state kinetics of raltegravir 400 mg BID were not affected by ezetimibe 10 mg QD for 10 days in healthy subjects.[33]	GI: dyspepsia, diarrhea	(ODB): $1.58/10 mg
BILE ACID SEQUESTRANTS							
cholestyr-amine Questran® (Bristol)	4 g 30-60 min before 1-2 main meals (max. 8g before 2-3 meals)	not metabolized	↓ (15-30%) LDL; may ↑ (15-25%) TG (via compensatory ↑ hepatic	Effect within 24-48 hrs and cont'd up to 12 months	May ↓ absorption of other drugs (e.g., thiazides, propranolol, thyroxine, warfarin, cardiac glycosides, fat-soluble vitamins); take	GI: dyspepsia, N/V, abdominal discomfort, bloating, constipation; no systemic s/e	(ODB) $19.92/42 doses $0.6407/ pouch

Drug	Dose	Metabolism[1]	Efficacy	Onset	Interactions	Side Effects	Cost
			synthesis of VLDL?)		other drugs 1 hr before or 4-6 hrs after bile acid resin		
colestipol HCl Colestid® (Pharmacia & Upjohn)	5 g 30-60 min before 1-2 main meals (max. 10 g before 2-3 meals)	not metabolized	↓ LDL; may ↑ TG (via compensatory ↑ hepatic synthesis of VLDL?)	Effect within 24-48 hrs, maximum response at 1 month	as above	GI: dyspepsia, N/V, abdominal discomfort, bloating, constipation; no systemic side effects	(ODB) $0.8183/5g $0.8183/7.5 g $46.00/60 doses
OTHER							
niacin/ nicotinic acid/vitamin B3	250-500 mg BID after meals (max. 1-2 g BID-TID pc); use immediate-release form to ↓ risk liver toxicity	Metabolized to active metabolite niacinamide	↓ (20-35%) LDL, ↓(20-40%) TG,↑ (10-20%) HDL, ↓ lipoprotein a	Effect within 3-5 weeks	Increased effect of insulin and oral hypoglycemics -increased myopathy when administered with statins or fibric acid derivatives. Potential for overlapping toxicities with PIs, especially ritonavir.	flushing, pruritus, N/ GI discomfort, gastritis, blurred vision; alters serum glucose, uric acid levels; Long term: hyperuricemia, hepatotoxicity, PUD; rhabdomyolysis (in combination with HMG-CoA reductase inhibitors)	$0.0295/100 mg

Please note: This chart summarizes some of the major drug interactions identified to date, based on current available data; other drug interactions may exist. Please use caution whenever adding/modifying therapy. The information in this table is intended for use by experienced physicians and pharmacists. It is not intended to replace sound professional judgment in individual situations, and should be used in conjunction with other reliable sources of information. Due to the rapidly changing nature of information about HIV treatment and therapies, users are advised to recheck the information contained herein with the original source before applying it to patient care.

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