Interactions between Antiretrovirals and Drugs for Treatment of Pulmonary Arterial Hypertension

	Protease Inhibitors	Non-Nucleoside Reverse Transcriptase Inhibitors	Other Antiretrovirals
Prostaglandin (prostacyclin) analogs			
Epoprostenol (IV) • *Undergoes rapid hydrolyzation* Treprostinil (IV or SC infusion) • *substantially metabolized by the liver, but precise enzymes unknown* • *does not inhibit CYP-1A2, 2C9, 2C19, 2D6, 2E1, or 3A* Iloprost (inhalation) • *CYP enzymes play minor role in biotransformation; iloprost does not inhibit CYP450 system (in vitro)*	Significant pharmacokinetic interactions with antiretroviral agents are not anticipated.		
Endothelin receptor antagonists			
Ambrisentan (Volibris®) • *substrate of UGT1A9S, 2B7S, and 1A3S, CYP3A4 and CYP2C19, OATP, and P-gp.* • *does not inhibit UGT1A1, UGT1A6, UGT1A9, UGT2B7 or CYP450 enzymes 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1 and 3A4. Additional in vitro studies showed that ambrisentan does not inhibit P-gp, NTCP, OATP or BSEP. Furthermore, ambrisentan does not induce MRP2, P-gp or BSEP.*	Potential for ↑ ambrisentan concentrations with concomitant CYP3A4 inhibitors. Steady state administration of ketoconazole 400 mg daily increased the AUC and Cmax of ambrisentan by 35% and 20%, respectively.[1] The clinical significance of these changes is not known. Patients on 10 mg of ambrisentan while on ketoconazole or other potent CYP3A4 inhibitors including ritonavir or cobicistat should be monitored closely for any signs of adverse effects.	Monitor for potential ↓ ambrisentan concentrations. No clinically relevant effect on ambrisentan exposure by day 8, following administration of multiple doses of rifampin. No dose adjustment of ambrisentan is needed with concomitant rifampin therapy.[2]	Potential for ↑ ambrisentan concentrations with elvitegravir/cobicistat. Steady state administration of ketoconazole 400 mg daily increased the AUC and Cmax of ambrisentan by 35% and 20%, respectively.[1] The clinical significance of these changes is not known. Patients on 10 mg of ambrisentan while on ketoconazole or other potent CYP3A4 inhibitors including ritonavir or cobicistat should be monitored closely for any signs of adverse effects.
Bosentan (Tracleer®) • *substrate of*	In a healthy volunteer study involving	A recent report documented the	Potential for ↑ bosentan concentrations with

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CYP2C9 and CYP3A • *inducer of CYP2C9 and CYP3A4.*[3, 4]	coadministration of bosentan 125 mg BID and **lopinavir/ritonavir 400/100 mg BID**, bosentan concentrations increased up to 48-fold during the first 4 days, and at steady-state, the GMR for AUC was 5.22 and for Cmax was 6.12. Therefore, bosentan should only be initiated once boosted PIs have reached steady-state (i.e., at least 10 days therapy). In such patients, bosentan may be started at a dose of 62.5 mg once daily or every other day. For patients on stable bosentan therapy who require initiation of a boosted PI regimen, bosentan should be discontinued for at least 36 hours prior to starting the boosted PI, then reinstituted 10 days after PI initiation at 62.5 mg once daily or every other day.[5] Do not give bosentan with **unboosted atazanavir**, as plasma atazanavir concentrations may be decreased.[6] A case report noted a possible interaction between bosentan and unboosted **indinavir** leading to a reduction in indinavir plasma concentrations.[7]	successful, long-term coadministration of bosentan and **nevirapine**-based cART in a 51-year old HIV-positive woman with AIDS and HIV-associated PAH. Over a four-year follow-up period, the patient experienced significant clinical and hemodynamic improvement on bosentan 125 mg BID, and maintained complete viral suppression, therapeutic nevirapine trough concentrations, and excellent immunologic response.[8]	elvitegravir/cobicistat. In patients on Stribild® for at least 10 days, start bosentan at 62.5 mg once daily or q2days based on individual tolerability. If initiating Stribild® in patients already on bosentan, discontinue bosentan at least 36 hours prior, and resume at 62.5 mg once daily or q2days at least 10 days following Stribild® initiation.[9] Potential for ↓ maraviroc concentrations. Avoid combination if possible.
Macitentan (Opsumit®) • *substrate of CYP3A4, 2C9>>2C8, 2C19* • *no inhibitory or*	Potential for increased macitentan exposures. Interaction study with ketoconazole 400 mg	Potential for decreased macitentan exposures. In healthy volunteers, coadministration of	Potential for ↑ macitentan concentrations with elvitegravir/cobicistat.

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inducing effects on CYP enzymes • *no effect on transporters including P-gp, OATP1B1/1B3, OCT1, OCT2, OAT1, OAT, BCRP, MATE-1 and MATE2-K*	resulted in 2-fold increase AUC of macitentan and 26% decrease AUC of active metabolite.[10] U.S. monograph recommends avoiding coadministration with strong CYP3A4 inhibitors, and specifically recommends alternate PAH therapy for HIV patients who require antiretrovirals that are strong CYP3A4 inhibitors.[11] Canadian monograph states to use combination with caution.[12]	macitentan plus rifampin 600 mg daily resulted in 79% decrease in macitentan AUC but did not affect exposure to the active metabolite.[13] Avoid coadministration with strong CYP3A4 inducers due to the potential for reduced macitentan efficacy.	Interaction study with ketoconazole 400 mg resulted in 2-fold increase AUC of macitentan and 26% decrease AUC of active metabolite.[10] U.S. monograph recommends avoiding coadministration with strong CYP3A4 inhibitors, and specifically recommends alternate PAH therapy for HIV patients who require antiretrovirals that are strong CYP3A4 inhibitors.[11] Canadian monograph states to use combination with caution.[12]
Sitaxsentan (Thelin®; discontinued in 2010) • *substrate of CYP3A4/5 and 2C9* • *inhibitor of CYP2C9, as well as 2C19, 3A4/5, and 2C8*	Case report of an HIV-positive patient on tenofovir, 3TC and **atazanavir** with HIV-PAH who was initially well-controlled on bosentan 125 mg BID, but who required discontinuation of bosentan after 18 months due to persistent nasal/sinus congestion. Bosentan was replaced with sitaxsentan 100 mg daily, with rapid resolution of nasal congestion and continued clinical benefit.[14]	Potential for ↑ etravirine concentrations. Possible ↑ other NNRTI concentrations.	Potential for ↑/↓ sitaxsentan and ↑ elvitegravir and cobicistat concentrations. Potential for ↑ maraviroc concentrations.
Phosphodiesterase inhibitors			
Sildenafil (Revatio®) • *CYP3A4>>2C9 substrate; weak inhibitor of CYP1A2, 2C9, 2C19, 2D6, 2E1, 3A4 - unlikely to cause significant interactions*	Sildenafil exposures are ↑2-11-fold in the presence of PIs.[5] Sildenafil for treatment of PAH is **contraindicated** with all PIs.	In the presence of etravirine, sildenafil AUC ↓ 57%. Combination may be co-administered, adjust sildenafil dose according to response.[15] In healthy volunteers taking rilpivirine 75 mg	No pharmacokinetic with maraviroc is expected, but both Maraviroc and the PDE5 inhibitors have reported hypotension adverse; therefore, co-administer combination with caution.

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		once daily for 12 days, the kinetics of single dose sildenafil 50 mg were similar as compared to sildenafil alone, and rilpivirine exposures were not affected by sildenafil. The combination may be coadministered without dose modifications.[16] Potential for ↓ sildenafil concentrations with other NNRTIs.	Sildenafil for treatment of PAH is contraindicated with elvitegravir/cobicistat.[9]
Tadalafil (Adcirca®) • *CYP3A4 substrate*	Significant ↑in tadalafil concentrations with ritonavir and boosted tipranavir.[17] Recurrent priapism secondary to an interaction between tadalafil and boosted fosamprenavir has been reported.[18] For patients on stable (i.e,. greater than 7 days) PI treatment who require therapy for PAH: tadalafil may be initiated at a dose of 20 mg once daily and increased to 40 mg once daily based on tolerability. For patients already stabilized on tadalafil who require PI-based treatment: tadalafil should be discontinued at least 24 hours prior to initiating the PI, and restarted 7 days after PI initiation at a dose of 20 mg once daily, increasing to 40 mg once daily based on tolerability.[5]	Potential for ↓ tadalafil concentrations. Dose adjustment may be necessary with coadministration.	No pharmacokinetic with maraviroc is expected, but both maraviroc and the PDE5 inhibitors have reported hypotension adverse; therefore, co-administer combination with caution. Potential for ↑ tadalafil concentrations with elvitegravir/cobicistat. If already on Stribild®, start tadalafil 20 mg daily, ↑ to 40 mg daily based on tolerability. If on tadalafil and starting Stribild®, stop tadalafil at least 24 hours prior; after at least 1 week, resume tadalafil at 20 mg daily, ↑ to 40 mg daily based on tolerability.[9]

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