

Interactions between Antiretrovirals and Drugs for Treatment of Pulmonary Arterial Hypertension

	Protease Inhibitors	Non-Nucleoside Reverse Transcriptase Inhibitors	Other Antiretrovirals
Prostaglandin (prostacyclin) analogs			
<p>Epoprostenol (IV)</p> <ul style="list-style-type: none"> • <i>Undergoes rapid hydrolyzation</i> <p>Treprostinil (IV or SC infusion)</p> <ul style="list-style-type: none"> • <i>substantially metabolized by the liver, but precise enzymes unknown</i> • <i>does not inhibit CYP-1A2, 2C9, 2C19, 2D6, 2E1, or 3A</i> <p>Iloprost (inhalation)</p> <ul style="list-style-type: none"> • <i>CYP enzymes play minor role in biotransformation; iloprost does not inhibit CYP450 system (in vitro)</i> 	<p>Significant pharmacokinetic interactions with antiretroviral agents are not anticipated.</p>		
Endothelin receptor antagonists			
<p>Bosentan</p> <ul style="list-style-type: none"> • <i>substrate of CYP2C9 and CYP3A</i> • <i>inducer of CYP2C9 and CYP3A4.^{1,2}</i> 	<p>In a healthy volunteer study involving 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 C_{max} 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</p>	<p>A recent report documented the 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.⁶</p>	<p>Potential for ↓ maraviroc concentrations. Avoid combination if possible.</p>

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	<p>boosted PI regimen, bosentan should be discontinued for at least 36 hours prior to starting the boosted PI, then reinstated 10 days after PI initiation at 62.5 mg once daily or every other day.³</p> <p>Bosentan is contraindicated with unboosted atazanavir, as plasma atazanavir concentrations may be decreased.⁴</p> <p>A case report noted a possible interaction between bosentan and unboosted indinavir leading to a reduction in indinavir plasma concentrations.⁵</p>		
<p>Ambrisentan</p> <ul style="list-style-type: none"> • <i>substrate of UGT1A9S, 2B7S, and 1A3S, CYP3A4 and CYP2C19, OATP, and P-gp.</i> • <i>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.</i> 	<p>Potential for ↑ ambrisentan concentrations with concomitant CYP3A4 inhibitors.</p>	<p>Monitor for potential ↓ ambrisentan concentrations.</p> <p>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.</p>	
<p>Sitaxsentan</p> <ul style="list-style-type: none"> • <i>substrate of CYP3A4/5 and 2C9</i> • <i>inhibitor of CYP2C9, as well as 2C19, 3A4/5, and 2C8</i> 	<p>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,</p>	<p>Potential for ↑ etravirine concentrations. Possible ↑ other NNRTI concentrations.</p>	<p>Potential for ↑ maraviroc concentrations.</p>

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	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. ⁷		
Phosphodiesterase inhibitors			
Sildenafil <ul style="list-style-type: none"> • <i>CYP3A4</i> >> <i>2C9</i> substrate; weak inhibitor of <i>CYP1A2</i>, <i>2C9</i>, <i>2C19</i>, <i>2D6</i>, <i>2E1</i>, <i>3A4</i> - unlikely to cause significant interactions 	Sildenafil exposures are ↑2-11-fold in the presence of PIs. ³ 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. ⁸ In healthy volunteers taking rilpivirine 75 mg 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. ⁹ Potential for ↓ sildenafil concentrations with other NNRTIs.	No pharmacokinetic with maraviroc is expected, but both Maraviroc and the PDE5 inhibitors have reported hypotension adverse; therefore, co-administer combination with caution.
Tadalafil <ul style="list-style-type: none"> • <i>CYP3A4</i> substrate 	Significant ↑ in tadalafil concentrations with ritonavir and boosted tipranavir. ¹⁰ Recurrent priapism secondary to an interaction between tadalafil and boosted fosamprenavir has been reported. ¹¹ For patients on stable (i.e., greater than 7	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.

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	<p>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.</p> <p>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.³</p>		

References:

1. Acetelion Pharmaceuticals Ltd. Tracleer (bosentan) Product Monograph. Laval, QC 2010.
2. Weiss J, Herzog M, Haefeli WE. Differential modulation of the expression of important drug metabolising enzymes and transporters by endothelin-1 receptor antagonists ambrisentan and bosentan in vitro. *Eur J Clin Pharmacol* 2011;660(2-3):298-304.
3. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents. Department of Health and Human Services. Federal register 2011. p. 1-166.
4. Bristol-Myers Squibb Canada. Reyataz (atazanavir) Product Monograph. Montreal, QC 2011.
5. Beau-Salinas F, Garot D, Le Guellec C, et al. Possible reduction in indinavir serum concentrations by bosentan. *Ther Drug Monitor* 2005;27(6):822-3.
6. Hardy H, Backman ES, Farber HW. Successful bosentan and nonnucleoside reverse transcriptase inhibitor-based therapy in a patient with acquired immunodeficiency syndrome and pulmonary arterial hypertension. *Pharmacotherapy* 2010;30(4):139e-44e.
7. Zacà V, Metra M, Danesi R, et al. Successful switch to sitaxsentan in a patient with HIV-related pulmonary arterial hypertension and late intolerance to nonselective endothelin receptor blockade. *Ther Adv Respir Dis* 2009;3(1):11-4.
8. Kakuda TN, Schöller-Gyüre M, Hoetelmans RM. Pharmacokinetic interactions between etravirine and non-antiretroviral drugs. *Clin Pharmacokinet* 2011;50(1):25-39.
9. Crauwels HM, Van Heeswijk R, Stevens M, et al. TMC278, a next-generation non-nucleoside reverse transcriptase inhibitor (NNRTI), does not alter the pharmacokinetics of sildenafil [abstract

- P_22]. 10th International Workshop on Clinical Pharmacology of HIV Therapy, April 15-17, 2009, Amsterdam.
10. Durant J, Dellamonica P, Garraffo R, et al. The effect of tipranavir/ritonavir on the pharmacokinetics of tadalafil in healthy volunteers [abstract 61]. 8th International Workshop on Clinical Pharmacology of HIV Therapy, April 16-18, 2007, Budapest, Hungary.
 11. Louergue P, Gaillard R, Mir O. Interaction involving tadalafil and CYP3A4 inhibition by ritonavir. *Scand J Infect Dis* 2011;43(3):239-40.