Drug-Drug Interactions: Treatment Considerations for Pulmonary Hypertension Patients With Human Immunodeficiency Virus and/or Hepatitis C

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Managing pulmonary arterial hypertension (PAH) treatment is a complex balance of achieving the desired medication effect versus maintaining safe and tolerable side effects for the patient. The "balancing act" intensifies when PAH patients are faced with multiple disease states that require treatment medication. This article will focus on the drug-drug interactions that must be considered in PAH patients with concomitant human immunodeficiency virus (HIV) and/or hepatitis C virus (HCV) infection.

Both HIV and HCV are infections that are treated with medications that can cause significant and noteworthy drug-drug interactions with PAH medication therapies. The incidence of PAH, as a cardiovascular complication of HIV, is higher in the HIV population than the incidence of PAH for the normal population.[1] The first recognized case of HIV-associated PAH was published in 1987,[2] and the prevalence of this HIV complication was estimated in the early 1990s to be 0.5%.[3] Over time, reported prevalence estimates have varied[4]; however, the development of highly active antiretroviral therapy (HAART) for the treatment of HIV has not changed the incidence of PAH for this patient population.[5-8] PAH associated with HCV occurs as the result of an HCV treatment effect, rather than from the disease itself. A published case series by Renard et al[9] suggests that sofosbuvir, an interferon-α medication and mainstay treatment for HCV, may be linked to the new or worsening development of PAH in sofosbuvir-treated HCV patients with other risk factors. Further studies are warranted for this patient population.

Currently approved medications to treat PAH include endothelin receptor antagonists (ERAs), phosphodiesterase-5 (PDE-5) inhibitors, prostacyclin analogs, a prostaglandin I2 receptor agonist, and a soluble guanylate cyclase (sGC) stimulator. Pathophysiologically, these medications undergo hepatic metabolism and thus drug-drug interactions in patients requiring medication for concomitant disease states must be carefully evaluated. PAH patients with HIV and/or HCV are particularly complex as many of the medications used to treat these diseases display drug-drug interactions as a result of how they are metabolized in the body. Table 1 identifies all systemic PAH, HIV, and HCV medications by class.

PATHOPHYSIOLOGY

Drug-drug interactions occur as a result of pharmacokinetic mechanisms that affect absorption, distribution, metabolism, and/or elimination of a medication. Understanding how these principles are affecting the incidence and intensity of a drug-drug interaction is vital to safely administering multiple medications to a single patient.

Many of the PAH-, HIV-, and HCV-specific medications are metabolized by various hepatic cytochrome P-450 (CYP-450) enzymes, P-glycoproteins (Pgp), and organic anion transporting polypeptides (OATPs), or may cause induction or inhibition of the CYP-450 enzyme.

To define what is being described in the context of this statement:

Hepatic enzymes are the catalysts within the liver that bind to a substrate to activate a chemical reaction. Examples of hepatic enzymes would include CYP3A4 and CYP2C9, but there are many others.

Substrates are the medications that are metabolized by a specific enzyme. For example, a medication metabolized by CYP3A4 would be called a CYP3A4 substrate.

Induction occurs when a medication undergoes hepatic metabolism and it results in increased metabolic activity of the enzyme. The metabolizing enzyme is working overtime, which results in a decrease of the substrate level available to the body. For example, a medication that increases the CYP3A4 enzyme would be called a CYP3A4 inducer. If a patient is taking a CYP3A4 inducer concomitantly with a CYP3A4 substrate, the substrate medication level would be decreased compared to what is expected.

Inhibition occurs when a medication undergoes hepatic metabolism and it results in decreased metabolic activity of the enzyme. The metabolizing enzyme's activity is hindered, which results in an increase of the substrate level available to the body. For example, a medication that decreases the CYP3A4 enzyme would be called a CYP3A4 inhibitor. If a patient is taking a CYP3A4 in-

Table 1. List of Systemic PAH, HIV, and HCV Medications by Class

PAH Medications	Antiretroviral (ARV)[10]	HCV Medications[11]
ERAs	Nucleoside reverse transcriptase inhibitors (NRTIs)	Direct-acting antivirals (DAAs)
Ambrisentan Bosentan Macitentan	Abacavir (ABC) Didanosine (ddI) Emtricitabine (FTC) Lamivudine (3TC) Stavudine (d4T) Tenofovir (TDF/TAF) Zidovudine (AZT/ZDV)	NS5A/NS5B inhibitors Daclatasvir Dasaburvir Elbasvir Glecaprevir Grazoprevir Ledipasvir Ombitasvir Pribentasvir Sofosbuvir Velpatasvir NS3/4 protease inhibitors (PIs) Paritaprevir Simeprevir Voxilaprevir
PDE-5 inhibitors	Non-nucleoside reverse-transcriptase inhibitors (NNRTIs)	Miscellaneous agents
Sildenafil Tadalafil	Efavirenz (EFV) Etravirine (ETR) Nevirapine (NVP) Rilpivirine (RPV)	Interferon/peginterferon Ribavirin
Prostacyclin analogs	PIs	
Treprostinil (PO/IV/SC/INH) Epoprostenol (IV) Iloprost (INH)	Atazanavir (ATV) Darunavir (DRV) Fosamprenavir (FPV) Indinavir (IND) Lopinavir (LPV) Nelfinavir (NFV) Ritonavir (r or RTV) Saquinavir (SQV) Tipranavir (TPV)	
IP receptor agonist	Integrase strand transfer inhibitors (INSTIs)	
Selexipag	Bictegravir (BIC) Dolutegravir (DTG) Elvitegravir (EVG) Raltegravir (RAL)	
sGC stimulator	Entry inhibitors	
Riociguat	Enfuviritide (T20) Maraviroc (MVC)	
	Pharmacokinetic boosters	
	Cobicistat (c or COBI) Ritonavir (r or RTV)	

hibitor concomitantly with a CYP3A4 substrate, the substrate medication level would be increased compared to what is expected.

The majority of PAH medications undergo metabolism via the CYP-450 enzyme system. Among the ERAs, bosentan is also a potent inducer of CYP2C9, CYP3A4, and to a certain extent CYP2C19, which potentiates the risk for significant drug-drug interactions with HIV protease inhibitors (PIs) and HCV direct-acting antivirals (DAAs). Ambrisentan and macitentan, on the other hand, do not induce CYP enzymes. However, they are metabolized by CYP3A4 and CYP2C19, thereby requiring close monitoring of therapy when coadministered with CYP-inhibitors.[12-14] The PDE-5 inhibitors are predominantly metabolized via CYP3A4, thereby leading to contraindications with coadministration of sildenafil and PIs.[15,16] Amongst the prostacyclin analogs, epoprostenol does not undergo hepatic metabolism while treprostinil is primarily metabolized by CYP2C8.[17,18] The IP receptor agonist selexipag is metabolized by CYP3A4 and CYP2C8, and therefore contraindicated with strong CYP2C8 inhibitors.[19] And finally the sGC stimulator riociguat is metabolized by various CYP enzymes, including CYP3A4, as well as Pgp and the breast cancer resistance protein (BCRP).[20] Agents that are metabolized

Table 2. Clinically Significant Drug-Drug Interactions Between PAH and HIV Medications

	NRTI	NNRTI	PI	INSTI	Maraviroc
ERAs	-	++	++	+	++
PDE-5 inhibitors	-	+	++	++	-
Prostacyclin analogs	-	+	+	-	-
IP receptor agonist	-	-	-	-	-
sGC stimulator	-	+	+	+	-

+ close monitoring; ++ dose adjustment recommended and/or alternative therapy considerations (see Table 3).

Table 3. Interaction Details Between PAH and HIV Medications[2,10]

PAH Medications	ARV	Interaction	Comments
ERAs[12-14]			
Ambrisentan, Bosentan, Macitentan	NNRTI	• EFV and ETR may ↓ bosentan exposure • EFV, ETR, and NVP may decrease macitentan exposure • Bosentan may ↓ RPV exposure • No interactions expected with ambrisentan	• Coadministration of bosentan with NVP is NOT recommended due to concerns for cumulative hepatotoxicity • Close monitoring recommended if coadministered with EFV, ETR, or RPV
	All PIs	• ↑ ambrisentan concentrations due to OATP inhibition • ↑ macitentan concentrations due to CYP3A4 inhibition • LPV/r may increase bosentan concentrations 48-fold by Day 4, and 5-fold by Day 10 • Bosentan may decrease ATV concentrations	• Start ambrisentan at a low dose and increase based on tolerability • No dose adjustments required but caution is advised when coadministered with macitentan • DO NOT coadminister bosentan with unboosted ATV <u>Initiating bosentan while on a PI or ATV/r:</u> • Ensure patient has been on PI or ATV/r for >10 days prior to initiating bosentan • Start at bosentan 62.5 mg once daily or every other day <u>Initiating a PI or ATV/r while on bosentan:</u> • Stop bosentan ≥36 hours before PI or ATV/r initiation • After 10 days of PI or ATV/r, resume bosentan at 62.5 mg once daily or every other day
	• INSTI (particularly EVG/c)	• ↑ bosentan and macitentan concentrations due to CYP3A4 inhibition by COBI • No interactions expected with ambrisentan	• No dose adjustment recommended for macitentan <u>Initiating bosentan while on EVG/c:</u> • Ensure patient has been on EVG/c for ≥10 days prior to initiating bosentan • Start at bosentan 62.5 mg once daily or every other day based on tolerability <u>Initiating EVG/c while on bosentan:</u> • Stop bosentan ≥36 hours before EVG/c initiation • After 10 days of EVG/c, resume bosentan at 62.5 mg once daily or every other day based on tolerability • Coadministration with DTG and BIC-containing regimens have not been studied. Potential for interaction is expected to be low. No dose adjustments are recommended
	MVC	• Bosentan may ↓ MVC concentrations via moderate CYP3A4 induction • No interaction expected with ambrisentan or macitentan	<u>If coadministering with bosentan</u> • Consider increasing MVC to 600 mg BID when coadministering <u>without</u> a PI or other potent CYP3A4 inhibitor • Consider decreasing MVC to 150 mg BID when coadministering along <u>with</u> a PI or other potent CYP3A4 inhibitor
PDE-5 Inhibitors[15,16]			
Sildenafil, Tadalafil	NNRTI (particularly EFV, ETR, NVP)	• ↓ PDE-5 inhibitor concentrations via induction of CYP3A4 • ETR can ↓ sildenafil exposure by 57%	• Monitor PDE-5 inhibitor therapy and consider dose increase based on clinical effect • Coadministration of RPV and tadalafil has not been studied, but no interaction or dose adjustment expected with RPV and sildenafil
	All PIs	• RTV can ↑ PDE-5 inhibitor exposure by 124%-1000% • Coadministration of DRV/r with sildenafil 25 mg is similar to sildenafil 100 mg alone	• Coadministration of sildenafil and a PI is contraindicated for treatment of PAH • May consider tadalafil with the following precautions <u>Initiating tadalafil while on a PI:</u> • Initiate if patient has been on PI >7 days • Start at tadalafil 20 mg once daily and increase to 40 mg once daily based on tolerability <u>Initiating a PI while on tadalafil:</u> • Stop tadalafil ≥24 hours before PI initiation • After 7 days of PI, resume tadalafil at 20 mg once daily • May increase tadalafil dose to 40 mg once daily based on tolerability
	INSTI (particularly EVG/c)	• ↑ PDE-5 inhibitor concentrations due to PK booster (COBI)	• Coadministration of a PDE-5 inhibitor with EVG/c is contraindicated. Consider an alternative INSTI agent without COBI

Table 3. Interaction Details Between PAH and HIV Medications[2,10] ***Continued***

PAH Medications	ARV	Interaction	Comments
Prostacyclin Analogs[17,18]			
Epoprostenol, Treprostinil	NNRTI	• No interactions expected with epoprostenol • Potential weak interaction with EFV (↑ treprostinil) due to CYP2C8 and 2C9 inhibition	• No dose adjustments recommended. Monitor therapy
	PI	• No interactions expected with epoprostenol • Potential weak interaction with RTV (↑ treprostinil) due to CYP2C8 inhibition	• No dose adjustments recommended. Monitor therapy
sGC Stimulator[20]			
Riociguat	NNRTI	• EFV, ETR, and NVP may ↓ riociguat exposure • No interaction expected with RPV	• Monitor clinical effects of riociguat
	PI	• ↑ riociguat exposure expected	• Initiate riociguat at 0.5 mg TID, adjust dose based on clinical effects
	INSTI (particularly EVG/c)	• COBI may ↑ riociguat exposure	• Initiate riociguat at 0.5 mg TID, adjust dose based on clinical effects • Consider an alternative INSTI agent without COBI

via multiple pathways may carry a weaker potential for interactions due to the ability to bypass the primary CYP-mediated pathways.

Metabolic pathways for PAH medications may result in varying degrees of interaction with HIV antiretrovirals (ARVs) and HCV DAAs, particularly the non-nucleoside reverse transcriptase inhibitors (NNRTIs), which are potent CYP-enzyme inducers and the protease inhibitors (PIs), which are potent CYP-enzyme inhibitors. Tables 2–5 highlight the most notable drug-drug interactions between PAH medications and ARVs and HCV DAAs, and provide therapy adjustment recommendations, if needed.

Table 4. Clinically Significant Drug-Drug Interactions Between PAH and HCV Medications

	NS5A/NS5B Inhibitors	NS3/4 PIs	Interferons	Ribavirin
ERAs	++	++	-	-
PDE-5 inhibitors	-	++	n/a	n/a
Prostacyclin analogs	-	-	-	-
IP receptor agonist	-	-	-	-
sGC stimulator	-	++	-	-

+ close monitoring; ++ dose adjustment recommended and/or alternative therapy considerations (see Table 5).

CONCLUSION

In summary, treatment of PAH in patients with HIV and/or HCV requires the additional consideration of the potential for drug-drug interactions. Utilizing specialist pharmacists and resources such as the University of Liverpool's HIV and HCV drug interaction websites provide guidance for practitioners prescribing concomitant medications in these patient populations.[21,22] That being said, the key to managing these patients is a robust collaboration among the patient, treating PH physician, PH coordinator, pharmacists, and infectious diseases and/or hepatology medical specialists.

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Table 5. Interaction Details Between PAH and HCV Medications[2,11]

PAH Medications	HCV Medication	Interaction	Comments
ERAs[12-14]			
Ambrisentan, Bosentan, Macitentan	NS5A/NS5B Inhibitors	• Bosentan may ↓ NS5A/NS5B inhibitor concentrations via CYP-enzyme induction • Coadministration of bosentan with ledipasvir and sofosbuvir has not been studied • NS5A/NS5B inhibitors may ↑ ambrisentan concentrations due to mild inhibition of Pgp and CYP enzymes	• Do NOT coadminister bosentan with NS5A/NS5B inhibitors if possible • If coadministering with ambrisentan or macitentan, consider initiating ERA at low dose and titrating based on clinical effects
	NS3/4 PIs	• ↑ bosentan exposure due to OATP1B1 inhibition • Coadministration with ambrisentan and macitentan has not been studied	• Do NOT coadminister bosentan with NS3/4 PIs • If coadministering with ambrisentan or macitentan, consider initiating ERA at low dose and titrating based on clinical effects
PDE-5 Inhibitors[15,16]			
Sildenafil, Tadalafil	NS3/4 PIs	• Simeprevir may ↑ PDE-5 inhibitor concentrations via CYP-enzyme inhibition • No interaction expected with voxilaprevir	• Do NOT coadminister sildenafil with paritaprevir/ritonavir-containing regimens • If coadministering with simeprevir, consider initiating PDE-5 inhibitor at low dose and titrating based on clinical effects
	Interferons, Ribavirin	• No clear data	• No clear data
sGC Stimulator[20]			
Riociguat	NS3/4 PIs	• ↑ exposure expected with paritaprevir/ritonavir-containing regimens due to inhibition of CYP, Pgp, BCRP, and UGT pathways • No interactions expected with simeprevir or voxilaprevir	• Do NOT coadminister with paritapravir/ritonavir-containing regimens

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