

# CASE REPORT

## Successful Bosentan and Nonnucleoside Reverse Transcriptase Inhibitor–Based Therapy in a Patient with Acquired Immunodeficiency Syndrome and Pulmonary Arterial Hypertension

Helene Hardy, Pharm.D., Elke S. Backman, Pharm.D., and Harrison W. Farber, M.D.

Pulmonary arterial hypertension (PAH), which can be a complication of human immunodeficiency virus (HIV) infection, is characterized by increased pulmonary arterial pressure and peripheral vascular resistance, subsequently leading to right heart failure. In HIV-infected patients, the management of PAH is challenging given the potential drug interactions between PAH-specific vasodilators and antiretroviral drugs. We describe a 51-year-old female with acquired immunodeficiency syndrome (AIDS) and HIV-associated PAH. She was treated with the oral endothelin receptor antagonist bosentan while taking a nevirapine (a nonnucleoside reverse transcriptase inhibitor)–based antiretroviral regimen. Due to concerns about potential drug interactions with the antiretroviral therapy, her nevirapine plasma concentration, as well as CD4<sup>+</sup> cell count and viral load, were continuously monitored. We observed no interaction between bosentan and nevirapine during a 4-year period. To our knowledge, this report is the first to demonstrate successful, long-term coadministration of bosentan and a nonnucleoside reverse transcriptase inhibitor.

**Key Words:** human immunodeficiency virus, HIV, pulmonary hypertension, bosentan, nevirapine, therapeutic drug monitoring, antiretrovirals.  
(*Pharmacotherapy* 2010;30(4):139e–144e)

Pulmonary arterial hypertension (PAH) is defined as a mean pulmonary arterial pressure of 25 mm Hg or greater, a pulmonary capillary wedge pressure or a left ventricular end-diastolic pressure of 15 mm Hg or lower, and a pulmonary vascular resistance greater than 3 Wood units ( $\geq 240 \text{ dyn}\cdot\text{sec}/\text{cm}^5$ ). Human immunodeficiency virus (HIV)–infected individuals are at much greater risk for development of PAH than the general population. In fact, the occurrence of

PAH is approximately 0.5% in HIV-infected patients whereas it is only 0.02% in the general population.<sup>1, 2</sup> Although the etiology of this increased occurrence of PAH in HIV-infected individuals is not clear, it has been suggested that the induction of a chronic inflammatory state combined with a persistent activation of the immune system participates in the dysregulation of endothelial and vascular smooth muscle cell growth, leading to an imbalance of endogenous vasodilators and constrictors.<sup>3, 4</sup> Intravenous drug abusers infected with HIV appear to be at increased risk for developing PAH.<sup>4</sup> Pulmonary arterial hypertension develops independently of the degree of immunodeficiency (i.e., CD4<sup>+</sup> cell count), HIV viral load, or previous opportunistic infections, but appears to be related to the duration of HIV infection.<sup>5, 6</sup>

---

From the Center for HIV/AIDS Care and Research, Boston Medical Center (Drs. Hardy and Backman), and Boston University School of Medicine (Dr. Farber), Boston, Massachusetts.

For reprints, visit <http://www.atypon-link.com/PPI/loi/phco>. For questions or comments, contact Elke Backman, Pharm.D., Boston Medical Center, Center for HIV/AIDS Care and Research, 771 Albany Street, Dowling Building, Room G-114, Boston, MA 02118; e-mail: [elke.backman@bmc.org](mailto:elke.backman@bmc.org).

Table 1. Agents Approved for the Treatment of Pulmonary Arterial Hypertension

Class, Agent, Route of Administration	Mechanism of Action	Primary Metabolic Pathway	Implications for HAART
Prostaglandin (prostanoid) analogs			
Epoprostenol Continuous intravenous infusion	Activates intracellular adenylate cyclase, resulting in cAMP-mediated vasodilation of the pulmonary vasculature and inhibition of platelet aggregation <sup>11</sup>	Rapidly hydrolyzed; subject to some enzymatic degradation; forms one active metabolite and 13 inactive metabolites <sup>11</sup>	None known
Treprostinil Continuous intravenous or subcutaneous infusion	Same as epoprostenol, although considerably longer acting; activates intracellular adenylate cyclase, resulting in cAMP-mediated vasodilation of the pulmonary vasculature and inhibition of platelet aggregation <sup>12</sup>	Substantial hepatic metabolism, although the precise enzymes responsible are unknown; based on the results of in vitro human hepatic CYP studies, treprostinil does not inhibit CYP1A2, 2C9, 2C19, 2D6, 2E1, or 3A; whether treprostinil induces these enzymes has not been studied <sup>12</sup>	None known
Iloprost Inhalation	Aerosolized analog of epoprostenol; vasodilator; selectively acts on the pulmonary vascular bed <sup>13</sup>	Metabolized predominantly through $\beta$ -oxidation of the carboxyl side chain; CYP enzymes play only a minor role in biotransformation of iloprost; in vitro studies demonstrate that iloprost does not inhibit the CYP enzyme system <sup>13</sup>	None known
Endothelin receptor antagonists			
Bosentan Oral	Competitive antagonist of ET-1 at both ET <sub>A</sub> and ET <sub>B</sub> receptors on vascular endothelium and smooth muscle leading to reductions in vasoconstriction and vascular remodeling <sup>13-15</sup>	Bosentan is a substrate of OATP, CYP3A4 and 2C9 and is also an inducer of CYP3A4 and 2C9; auto-induction of metabolism may occur; multiple doses of bosentan may decrease plasma concentrations to 50-65% after single-dose administration <sup>14, 15</sup>	Coadministration with lopinavir-ritonavir has been shown to result in a 5-fold increase in bosentan trough concentration; ritonavir is a potent inhibitor of OATP and CYP3A4; patients who have received ritonavir for at least 10 days should start bosentan at a dosage of 62.5 mg once/day or every other day; patients receiving bosentan should discontinue the drug at least 36 hrs before starting ritonavir; after at least 10 days, bosentan should be resumed at 62.5 mg once/day or every other day based on tolerability
Ambrisentan Oral	Competitive antagonist of ET-1 predominantly at the ET <sub>A</sub> receptor (77:1 ET <sub>A</sub> :ET <sub>B</sub> selectivity) <sup>14, 16</sup>	Studies with human liver tissue indicate that ambrisentan is metabolized by CYP3A4, CYP2C19, and UGTs 1A9S, 2B7S, and 1A3S; in vitro studies show that ambrisentan is a substrate but not an inhibitor of P-glycoprotein <sup>14, 16</sup>	Not known; drug interaction studies with strong inhibitors CYP3A4 have not been conducted; increased exposure to ambrisentan could be expected when given in combination with antiretrovirals

The symptoms of PAH are typically insidious in onset and include progressive dyspnea,

lethargy, and fatigue. Due to the nonspecific nature of these symptoms, diagnosis of PAH in

Table

## I. Agents Approved for the Treatment of Pulmonary Arterial Hypertension (continued)

Class, Agent, Route of Administration	Mechanism of Action	Primary Metabolic Pathway	Implications for HAART
Endothelin receptor antagonists (continued) Sitaxentan Oral	Competitive antagonist of ET-1 predominantly at the ET <sub>A</sub> receptor (6500:1 ET <sub>A</sub> :ET <sub>B</sub> selectivity) <sup>14,17</sup>	In vitro data indicate that sitaxentan is an inhibitor of CYP2C9 and, to a lesser extent, CYP2C19, CYP3A4/5, and CYP 2C8; sitaxentan is metabolized by CYP2C9 and CYP3A4/5 <sup>14,17</sup>	Not available in the United States; no information is available on coadministration with inhibitors of CYP3A4; increased exposure to sitaxentan could be expected when given in combination with antiretrovirals
Phosphodiesterase inhibitors Sildenafil Oral	Inhibits phosphodiesterase type 5 in smooth muscle of pulmonary vasculature where this enzyme is responsible for degradation of cGMP; increased cGMP results in pulmonary vasculature relaxation; vasodilation in the pulmonary bed and the systemic circulation (to a lesser degree) may occur <sup>13,18</sup>	Sildenafil is a substrate of CYP2C8/9 (minor) and 3A4 (major); sildenafil inhibits CYP1A2 (weak), 2C8/9 (weak), 2C19 (weak), 2D6 (weak), 2E1 (weak), and 3A4 (weak) <sup>13,18</sup>	A 2–11-fold increase in sildenafil's AUC can occur in patients receiving protease inhibitors, <sup>19</sup> so this combination is not recommended <sup>18</sup> ; when given in combination with etravirine, there is a 57% decrease in sildenafil's AUC, and the sildenafil dose may need to be increased based on clinical effect <sup>20</sup>

HAART = highly active antiretroviral therapy; cAMP = cyclic adenosine monophosphate; CYP = cytochrome P450; ET = endothelin; OATP = organic anion transport protein; UGT = uridine 5'-diphosphate glucuronosyl transferase; cGMP = cyclic guanosine monophosphate; AUC =

HIV-infected patients is often delayed, with 70–80% of patients presenting with New York Heart Association (NYHA) class III–IV disease at the time of diagnosis. In addition, the impact of antiretroviral therapy on the prevalence and severity of HIV-associated PAH is conflicting and controversial.<sup>7</sup> Furthermore, limited data are available on potential drug-drug interactions between PAH-specific therapies and antiretroviral drugs.<sup>8–10</sup>

Three classes of drugs are approved by the United States Food and Drug Administration for treatment of PAH (Table 1). The prostaglandin (prostaglycin) analogs—epoprostenol, treprostinil, and iloprost—are potent vasodilators and inhibitors of both platelet aggregation and smooth muscle proliferation; however, their modes of administration (intravenous infusion, inhalation, or subcutaneous) may render long-term use problematic. In addition, the risk of infection associated with continuous intravenous infusion may be a consideration in immunocompromised individuals. The phosphodiesterase type 5 inhibitor sildenafil slows the breakdown of nitric oxide metabolites and is effective in the management of PAH. However,

all protease inhibitors increase sildenafil plasma concentration 2–11-fold.<sup>20</sup> Given this interaction and the lack of clinical experience with this combination, concurrent use, if attempted, requires cautious titration as well as decreased doses of sildenafil. Etravirine decreases sildenafil's area under the concentration-time curve by 57%; however, we know of no data on the combined use of efavirenz and sildenafil.<sup>20</sup> The third class of drugs, the oral endothelin receptor antagonists, inhibits the actions of endothelin-1 and its clearance by the pulmonary arterial endothelium. Currently, bosentan is the only endothelin receptor antagonist that has been investigated in HIV-infected patients with PAH.

We describe a patient with acquired immunodeficiency syndrome (AIDS) who was taking a nevirapine-based antiretroviral regimen, and bosentan was started for PAH; we observed no drug interaction during the next 4 years of concurrent therapy.

### Case Report

A 51-year-old, black, Haitian woman presented with simultaneous pulmonary infections with

Table 2. Laboratory and Hemodynamic Parameters for Pulmonary Arterial Hypertension

Parameter	Normal Values	Our Patient	
		At Baseline	After 3 Years of Bosentan Treatment
6-minute walk distance (meters)	> 600	341	427
Mean pulmonary arterial pressure (mm Hg)	< 25	47	36
Cardiac index (L/min/m <sup>2</sup> )	2.5–4	2.7	2.8
Cardiac output (L/min)	4–8	5.5	5.6
Pulmonary vascular resistance (dyn•sec/cm <sup>5</sup> )	< 240	505	343
Systemic vascular resistance (dynes•sec/cm <sup>5</sup> )	800–1200	1497	1356
Pulmonary capillary wedge pressure (mm Hg)	< 15	10	12
Right atrial pressure (mm Hg)	2–6	8	10
Right ventricular pressure, systolic/diastolic (mm Hg)	15–25/0–8	82/0	58/3
Left ventricular ejection fraction (%)	55–75	60	66

*Mycobacterium tuberculosis*, *avium*, and *xenopi* when she was diagnosed with AIDS. At that time, her CD4<sup>+</sup> count was 10 cells/mm<sup>3</sup> (3%) (normal range 800–1200 cells/mm<sup>3</sup>) and HIV viral load was greater than 500,000 copies/ml. The concurrent mycobacterial infections were successfully treated, and antiretroviral therapy with lamivudine 150 mg–zidovudine 300mg twice/day and nevirapine 200 mg twice/day was initiated 3 years later (the patient initially refused HIV treatment).

The patient was well controlled virologically when she presented with dyspnea 3 years after starting antiretroviral therapy. An echocardiogram was performed that demonstrated normal left ventricular size and systolic function, with a left ventricular ejection fraction (LVEF) of 60% (Table 2). Her right ventricle was moderately dilated with moderate-to-severe reduction in systolic function: mild biatrial enlargement, 1+ mitral regurgitation, 2+ tricuspid regurgitation, and an estimated pulmonary arterial systolic pressure of 74 mm Hg. Right heart catheterization at that time demonstrated PAH, with a mean pulmonary arterial pressure of 47 mm Hg; pulmonary vascular resistance of 505 dyn•sec/cm<sup>5</sup>, and pulmonary capillary wedge pressure (PCWP) of 10 mm Hg. As no other risk factors were demonstrated, she was diagnosed with HIV-associated PAH. A 6-minute walk distance test was performed, which showed 341 meters (normal > 600 meters). The patient was clinically diagnosed with NYHA–World Health Organization (WHO) functional class III PAH. Her CD4<sup>+</sup> count was 674 cells/mm<sup>3</sup> (26%), and

her HIV viral load was < 50 copies/ml. At the time of her HIV-associated PAH, the patient was reluctant to receive therapeutic intervention and was able to continue with her activities of daily living, albeit with slowly progressive symptoms.

Two years later, the patient's dyspnea had markedly progressed. Right heart catheterization demonstrated right atrial pressure 8 mm Hg, right ventricular pressure 82/0 mm Hg, pulmonary artery pressure 89/29 mm Hg, pulmonary capillary wedge pressure 8 mm Hg, cardiac output/cardiac index 5.5/2.7 m<sup>2</sup>, pulmonary vascular resistance 625 dyn•sec/cm<sup>5</sup>, and systemic vascular resistance 1497 dyn•sec/cm<sup>5</sup>. Bosentan 62.5 mg twice/day was started, titrated to 125 mg twice/day after 1 month. The patient's CD4<sup>+</sup> count, CD4%, HIV viral load, and nevirapine plasma trough concentration, as well as liver function tests and clinical status, were monitored (Table 3). Processing and quality control analysis of nevirapine plasma concentrations were performed by the Pharmacotherapy Research Center Core Analytical Laboratory at the University of Buffalo (Buffalo, NY). Nevirapine trough plasma concentrations were approximately 5–6.5 µg/ml during the 4-year follow-up period (Table 3). The therapeutic trough level of nevirapine against wild-type HIV-1 is estimated to be greater than 3 µg/ml.<sup>20</sup> Significant clinical and hemodynamic improvement was noted during the follow-up period. The 6-minute walk distance improved by 86 meters to 427 meters.

Right heart catheterization performed after 3 years of bosentan treatment demonstrated right

**Table 3. CD4<sup>+</sup> Cell Count, CD4%, HIV Viral Load, and Nevirapine Plasma Trough Levels During the 4-Year Follow-up Period After Starting Bosentan**

Time Relative to Starting Bosentan (mo)	CD4 <sup>+</sup> Cell Count (cells/mm <sup>3</sup> ) <sup>a</sup>	CD4%	HIV Viral Load (copies/ml)	Nevirapine Plasma Trough Level (µg/ml) <sup>b</sup>
Bosentan started	667	24	< 75	
4	934	30	< 75	
7	866	25	< 75	5.68
11	575	17	< 75	
12				5.13
17	731	21	< 75	
22	1110	24	< 75	
25	694	21	< 75	
28				6.34
29	951	24	< 75	
33	760	22	< 75	
37	772	22	< 75	5.73
40	756	24	< 75	
43	785	22	< 75	
46	1179	27	< 75	5.94
49	878	25	< 75	
54	1124	27	< 75	

HIV = human immunodeficiency virus.

<sup>a</sup>Normal range for CD4<sup>+</sup> cell count is 800–1200 cells/mm<sup>3</sup>.

<sup>b</sup>Nevirapine therapeutic trough level is greater than 3 µg/ml.

atrial pressure 10 mm Hg, right ventricular pressure 58/3 mm Hg, pulmonary artery pressure 60/22 mm Hg, pulmonary capillary wedge pressure 12 mm Hg, cardiac output/cardiac index 5.6/2.8 m<sup>2</sup>, pulmonary vascular resistance 343 dyn•sec/cm<sup>5</sup>, and systemic vascular resistance 1356 dyn•sec/cm<sup>5</sup>. In addition, an echocardiogram demonstrated normal left ventricular wall thickness, size, and systolic function, with an LVEF of 66%. No evidence of right ventricular hypertrophy was noted; the patient's right ventricle was only mildly dilated with normal systolic function. Normal biatrial size was also noted. Estimated pulmonary arterial systolic pressure was 68 mm Hg with a normal inferior vena cava. Finally, the patient's NYHA–WHO functional class had decreased in severity from III to II.

## Discussion

Our patient's case of HIV-associated PAH, treated with bosentan and the nonnucleoside reverse transcriptase inhibitor nevirapine, was clinically successful, and no untoward virologic effects of the concurrent administration of the two drugs could be demonstrated. This is important because bosentan is both a substrate

and inducer of the hepatic cytochrome P450 (CYP) isoenzymes 2C9 and 3A4. It causes autoinduction of both of these isoenzymes with repeated dosing; likewise, nevirapine is also a known substrate and inducer of CYP3A4 and CYP2B6.<sup>16, 21</sup> Although bosentan has been shown to be safe and effective in studies of patients with HIV-associated PAH,<sup>6, 22, 23</sup> serum concentrations of antiretroviral agents concomitantly administered with bosentan have not been reported. We were concerned about a possible clinically significant interaction between bosentan and nevirapine. Indeed, although the mechanism(s) of the drug interaction between bosentan and antiretrovirals has not been clearly elucidated, it may be due to both inhibition and/or induction of the CYP3A4 pathway and the organic anion transport protein (OATP) transporters.<sup>15</sup> In animal models, nevirapine has not been shown to affect OATP transporters, but it is a known inducer of CYP3A4.<sup>23</sup> The stability of nevirapine plasma trough concentrations observed in our patient over a 4-year period, despite an increase in bosentan dose from 62.5 mg twice/day to 125 mg twice/day, argues against a clinically significant interaction mediated through induction of CYP3A4. Moreover, the absence of clinically significant changes in CD4<sup>+</sup> count, CD4%, or

HIV viral load further strengthen the hypothesis that no clinically significant drug-drug interaction occurred between nevirapine and bosentan. Other studies have suggested that bosentan is a safe drug to administer in patients with HIV-associated PAH. The authors of one study reported a significant improvement in exercise capacity in 18 antiretroviral-naïve patients with HIV-associated PAH after 12 weeks of bosentan and antiretroviral therapy and concluded that there was no negative impact on control of HIV infection.<sup>22</sup> Two of their patients were taking nevirapine and seven were taking efavirenz, yet no plasma concentrations of bosentan or antiretrovirals were measured. In another study, the authors reported on the long-term benefits of bosentan therapy in HIV-associated PAH and described improved symptoms, hemodynamic parameters, and survival in their cohort.<sup>24</sup> Forty-nine of their 59 HIV-infected patients were receiving antiretrovirals, but no drug-drug interaction between bosentan and the antiretrovirals was evaluated. Similar safety findings were reported in a 16-week, prospective cohort study of 16 HIV-infected patients with PAH. Antiretroviral drug plasma concentrations were not measured in that study, but the absence of deleterious changes in clinical outcomes after 8 weeks of concomitant administration of bosentan with antiretrovirals led the authors to conclude that bosentan did not reduce the efficacy of antiretroviral therapy.<sup>21</sup>

## Conclusion

To our knowledge, this is the first case report suggesting a lack of a pharmacokinetic interaction between bosentan and the nonnucleoside reverse transcriptase inhibitor nevirapine. Our clinical findings concur with observations in larger cohorts suggesting that bosentan is safe to use in HIV-associated PAH and helps improve symptoms and hemodynamic parameters. Further studies are needed to determine if other antiretrovirals, in particular CYP3A4 inhibitors or inducers, are significantly affected by bosentan or can significantly affect bosentan plasma concentrations.

## References

1. Grubb JR, Moorman AC, Baker RK, Masur H, for the HOPS Investigators. The changing spectrum of pulmonary disease in patients with HIV infection on antiretroviral therapy. *AIDS* 2006;20:1095–107.
2. Barnett C, Hsue P, Machado R. Pulmonary hypertension: an increasingly recognized complication of hereditary hemolytic anemias and HIV infection. *JAMA* 2008;299(3):324–31.
3. Kanmonge GD. Noninfectious pulmonary complications of HIV/AIDS. *Curr Opin Pulm Med* 2005;11:208–12.
4. Nunes H, Humbert M, Sitbon O, et al. Prognostic factors for survival in human immunodeficiency virus–associated pulmonary arterial hypertension. *Am J Respir Crit Care Med* 2003;167:1433–9.
5. Farber HW, Loscalzo J. Pulmonary arterial hypertension. *N Engl J Med* 2004;351(16):1655–65.
6. Sitbon O, Lascoux-Combe C, Delfraissy JF, et al. Prevalence of HIV-related pulmonary arterial hypertension in the current antiretroviral therapy era. *Am J Respir Crit Care Med* 2008;177:108–13.
7. Sitbon O. HIV-related pulmonary arterial hypertension: clinical presentation and management. *AIDS* 2008;22(suppl 3):S55–62.
8. Zuber JP, Calmy A, Evison JM, et al. Pulmonary arterial hypertension related to HIV infection: improved hemodynamics and survival associated with antiretroviral therapy. *Clin Infect Dis* 2004;38:1178–85.
9. Pugliese A, Isnardi D, Saini A, Scarabelli T, Raddino R, Torre D. Impact of highly active antiretroviral therapy in HIV-positive patients with cardiac involvement. *J Infect* 2000;40:282–4.
10. Badesch DB, Abman SH, Simonneau G, Rubin LJ, McLaughlin VV. Medical therapy for pulmonary arterial hypertension: updated ACCP evidence-based clinical practice guidelines. *Chest* 2007;131:1917–28.
11. GlaxoSmithKline. Flolan (epoprostenol sodium) package insert. Research Triangle Park, NC; January 2008.
12. United Therapeutics Corp. Remodulin (treprostinil sodium) package insert. Research Triangle Park, NC; September 2008.
13. Hackman AM, Lackner TE. Pharmacotherapy for idiopathic pulmonary arterial hypertension during the past 25 years. *Pharmacotherapy* 2006;26(1):68–94.
14. Price LC, Howard LS. Endothelin receptor antagonists for pulmonary arterial hypertension. *Am J Cardiovasc Drugs* 2008;8(3):171–85.
15. Actelion Pharmaceuticals US, Inc. Tracleer (bosentan) package insert. South San Francisco, CA; August 2009.
16. Gilead Sciences Inc. Letairis (ambrisentan) package insert. Foster City, CA; October 2008.
17. Encysive Pharmaceuticals Inc., CSL Limited. Thelin (sitaxentan sodium) package insert. Parkville, Australia; March 2008.
18. Pfizer Inc. Revatio (sildenafil citrate) package insert. New York, NY; December 2007.
19. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. December 1, 2009. Available from <http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf>. Accessed December 7, 2009.
20. Boehringer Ingelheim Pharmaceuticals, Inc. Viramune (nevirapine) package insert. Ridgefield, CT; 2008.
21. Barbaro G, Lucchini A, Pellicelli AM, Grisorio B, Giancaspro G, Barbarini G. Highly active antiretroviral therapy compared with HAART and bosentan in combination in patients with HIV-associated pulmonary hypertension. *Heart* 2006;92: 1164–6.
22. McRae M, Lowe C, Tian X, et al. Ritonavir, saquinavir, and efavirenz, but not nevirapine, inhibit bile acid transport in human and rat hepatocytes. *J Pharmacol Exp Ther* 2006; 318:1068–75.
23. Sitbon O, Gressin V, Speich R, et al. Bosentan for the treatment of human immunodeficiency virus–associated pulmonary arterial hypertension. *Am J Respir Crit Care Med* 2004;170:1212–17.
24. Degano B, Yaici A, Le Pavec J, et al. Long-term effects of bosentan in patients with HIV-associated pulmonary arterial hypertension. *Eur Respir J* 2009;33:92–8.