# Epoprostenol (Prostacyclin) Therapy in HIV-associated Pulmonary Hypertension

ROBIN V. AGUILAR and HARRISON W. FARBER

The Pulmonary Center, Boston University School of Medicine, Boston, Massachusetts

Although HIV-associated pulmonary hypertension and primary pulmonary hypertension (PPH) are clinically and histologically similar, treatment options for the former are limited. Treatment with calcium channel blockers (CCB), proven to be beneficial in a subset of patients with PPH, has been disappointing in HIV-associated pulmonary hypertension and there are no data examining the effects of long-term epoprostenol in this entity. Six patients with severe HIV-associated pulmonary hypertension were treated with continuous intravenous epoprostenol infusions. Acute infusion of epoprostenol resulted in a significant ($p < 0.05$) decrease in mean pulmonary artery pressure (PAP) and pulmonary vascular resistance (PVR) of 16.4 and 32.7%, respectively, and a significant ($p < 0.05$) increase in mean cardiac output (CO) of 36.9%. At 1 yr, mean PAP and PVR had decreased by 21.7 and 54.9% ($p < 0.05$), respectively, and mean CO had increased by 51.4% ($p < 0.05$) when compared with baseline values. Repeat catheterizations of three patients at 2 yr and one patient at 40 mo demonstrated further improvement or maintenance of hemodynamics. In addition, NYHA functional class improved in all patients. We conclude that epoprostenol infusion is effective in improving hemodynamic and functional status in this cohort of six patients with HIV-associated pulmonary hypertension acutely and long-term.

The association between pulmonary hypertension and human immunodeficiency virus (HIV) infection is well established (1–11). However, despite a report of cytomegalovirus endothelialitis in the lung of a patient with AIDS and pulmonary hypertension (1), a direct cause and effect relationship between HIV infection and pulmonary hypertension has not been established. Moreover, neither HIV nor its proteins has been identified in the pulmonary vascular endothelium (2). Whether HIV infection itself causes secondary pulmonary hypertension or whether it is a trigger, similar to appetite suppressants, for development of primary pulmonary hypertension (PPH) in susceptible individuals is not clear; however, tissue sections have revealed lung pathology similar to that of patients with PPH, that is, plexiform/plexogenic lesions (3–8, 10, 11).

There are suggestions that the incidence of pulmonary hypertension in patients with HIV infection may be greater than the incidence of PPH (3, 5, 10), but severity is not related to the level of immunodeficiency (5). Despite the increased reports of HIV-associated pulmonary hypertension, as well as the longer life span of HIV-infected patients, there have been few studies examining therapeutic options in HIV-associated pulmonary hypertension. One study reported that calcium channel blocker therapy was ineffective but antiretroviral therapy may have a salutory effect on right heart pressure gradients in some patients (10). Because of the similarity between the pathology of HIV-associated pulmonary hypertension and PPH, epoprostenol (prostacyclin) might be beneficial in the treatment of patients with the former. Therapy with this agent in patients with PPH improves right ventricular function and structure, quality of life, and survival (12–19). More importantly, there appears to be sustained efficacy or continued reductions in pulmonary vascular resistance (20, 21). In one study of patients with HIV-associated pulmonary hypertension, acute epoprostenol infusion resulted in a significant decrease in pulmonary vascular resistance in 58% of patients (18). Another study reported modest decreases in mean pulmonary artery pressure (PAP) and pulmonary vascular resistance (PVR) with the use of inhaled prostacyclin in patients with this disorder (22). However, no data are available examining the long-term use or effects of epoprostenol in patients with this form of pulmonary hypertension. In the current study, we report the effects of acute and long-term infusions of epoprostenol in six patients with HIV-associated pulmonary hypertension.

## METHODS

Six consecutive patients with HIV infection and pulmonary hypertension (NYHA class III or IV) were referred for evaluation and treatment. The diagnosis of pulmonary hypertension was established according to the PPH diagnostic criteria from the National Institutes of Health Registry on Primary Pulmonary Hypertension (23). Informed consent for right heart catheterization, intravenous adenosine trial, and oral calcium channel blocker trial was obtained from all patients. Risks and benefits of epoprostenol infusion for this non-FDA approved indication were explained to all patients and consent obtained prior to initiation of treatment. Permission for compassionate use of epoprostenol was obtained from each patient's medical insurer. No patient offered therapy refused. The patients were admitted to the Medical Intensive Care Unit at Boston Medical Center for insertion of a pulmonary artery catheter (right internal jugular or left subclavian vein approach) and for continuous hemodynamic monitoring.

After insertion, baseline hemodynamics (central venous pressure [CVP], right atrial pressure [RAP], pulmonary artery pressure, mean pulmonary artery pressure, pulmonary capillary wedge pressure [PCWP], cardiac output by thermodilution technique, cardiac index, systemic vascular resistance, and pulmonary vascular resistance) were obtained. Trials with adenosine and calcium channel blockers (oral nifedipine or diltiazem) were performed per prior guidelines (12, 13); they were terminated if there was no response to therapy or if the patients experienced intolerable side effects, such as hypotension (systolic blood pressure [SBP] < 90 mm Hg or greater than 20% decrease in SBP).

Epoprostenol (Flolan; Glaxo Wellcome Inc., Research Triangle Park, NC) infusion was initiated after washout of previous medications of ≥ 3 half-lives and return to baseline hemodynamics. The starting dose of 2 ng/kg/min was titrated (1–2 ng/kg every 15 min) until side effects (headache, jaw pain, nausea, or vomiting) were experienced. The dose was then decreased to the prior dose where no side effects were experienced. Hemodynamics were measured after each change in dosage and hourly. The dose was then slowly titrated to the maximally tolerated level. After reaching a stable dose, all patients underwent insertion of a permanent intravenous catheter.

All patients have been followed regularly in the Boston Medical Center Immunodeficiency Clinic and the dosage of epoprostenol increased according to symptoms (especially exertional dyspnea) or oxygen desaturation on a standardized exercise course (flat, uphill, and

## TABLE 1
### PATIENT DEMOGRAPHICS

| Patient No. | Age/Sex | HIV Risk Factors | Date of HIV Positivity | CD4 Count* | ARV Therapy | EPO Start Date |
|---|---|---|---|---|---|---|
| 1 | 40/F | IVDU | 1988 | 409 | 3TC/d4T | April 1996 |
| 2 | 35/F | IVDU | 1987 | 232 | 3TC/d4T | July 1997 |
| 3 | 34/F | IVDU | 1987 | 100 | 3TC/d4T | July 1997 |
| 4 | 45/F | IVDU | 1987 | 208 | None | March 1998 |
| 5 | 50/M | IVDU/HSX | 1988 | 410 | HAART | June 1998 |
| 6 | 32/M | IVDU | 1991 | 84 | HAART | March 1999 |

*Definition of abbreviations*: ARV = antiretroviral; d4T = stavudine; EPO = epoprostenol; HAART = highly active antiretroviral therapy; HSX = homosexual; IVDU = intravenous drug user; PAP = pulmonary artery pressure (mm Hg); 3TC = lamivudine.
* CD4 count and antiretroviral therapy prior to initiation of epoprostenol.

downhill walking and stair climbing). Repeat right heart catheterization has been performed on five patients at least 12 mo after initiation of epoprostenol.

### Statistics

The one-tailed Wilcoxon paired-sample test was used to compare means. Differences were considered significant when $p < 0.05$.

### RESULTS

#### Patients

The demographics of the patients treated with epoprostenol are presented in Table 1. The mean age was 39.3 yr; four of the six were women. All had been HIV positive for extended periods prior to the diagnosis of pulmonary hypertension and initiation of therapy. Risk factors for HIV infection were intravenous drug injection in all six patients and homosexual activity in one patient. Therapy for HIV infection before and during treatment with epoprostenol included standard nucleoside analogue (3TC/d4T) medications in Patients 1–3. Highly active antiretroviral therapy with a nonnucleoside reverse transcriptase inhibitor and two nucleoside analogues was used in Patients 5 and 6. Patient 4 did not receive any specific treatment for HIV infection due to severe side effects from these medi-

cations. CD4 counts ranged from 84 to 410 and did not correlate with the short- or long-term response to epoprostenol. HIV viral loads on these regimens remained below detectable limits and CD4 counts rose in all patients except Patient 4 whose CD4 counts and HIV viral load remained stable. None of the patients has had an opportunistic infection since the initiation of epoprostenol. All patients had additional risk factors for development of pulmonary hypertension: intravenous drug use and hepatitis B and/or C viral infection. Antibodies to the hepatitis C virus were found in Patients 1, 2, 5, and 6 whereas hepatitis B core antibody was positive in Patients 3, 4, and 5. Patients 3 and 5 had undergone liver biopsy demonstrating histological evidence of hepatitis and/or cirrhosis.

#### Acute Hemodynamic Data

Baseline hemodynamic data are presented in Table 2. At initial measurement, mean RAP was $10.5 \pm 3.5$ mm Hg and mean PCWP was $12.5 \pm 1.8$ mm Hg and there was no evidence for an atrial septal defect or patent foramen ovale. None of the six patients exhibited improvement in hemodynamics to either intravenous adenosine (up to 200 μg/kg; data not shown) or high-dose oral calcium channel blockers (cumulative dose of nifedipine was 60–200 mg/24 h; diltiazem 720–960 mg/24 h; data not shown). After administration of the maximum toler-

## TABLE 2
### HEMODYNAMIC MEASUREMENTS AT BASELINE AND AFTER ACUTE AND CHRONIC EPOPROSTENOL INFUSIONS

| | Patient 1 | Patient 2 | Patient 3 | Patient 4 | Patient 5 | Patient 6 | Mean ± SD |
|---|---|---|---|---|---|---|---|
| **PAP (mean)** | | | | | | | |
| Baseline | 93/40 (58) | 112/49 (74) | 74/29 (44) | 74/14 (34) | 81/31 (50) | 89/34 (51) | 51.8 ± 13.5 |
| Acute infusion | 81/33 (49) | 94/39 (61) | 65/30 (42) | 43/21 (28) | 59/22 (35) | 84/26 (45) | 43.3 ± 11.4* |
| 12 mo | 77/28 (47) | 85/40 (58) | 53/23 (36) | 75/22 (40) | 30/22 (26) | — | 41.4 ± 12.0* |
| 24 mo | 75/75 (42) | 57/32 (42) | 45/22 (30) | — | — | — | 38.0 ± 11.0 |
| **PVR** | | | | | | | |
| Baseline | 1,128 | 1,072 | 380 | 378 | 333 | 672 | 660.5 ± 361.6 |
| Acute infusion | 779 | 833 | 269 | 297 | 121 | 366 | 444.2 ± 292.0* |
| 12 mo | 427 | 562 | 163 | 253 | 84 | — | 297.8 ± 195.2* |
| 24 mo | 373 | 412 | 210 | — | — | — | 331.7 ± 107.2 |
| **CO** | | | | | | | |
| Baseline | 3.4 | 4.4 | 8.2 | 7.4 | 8 | 4.4 | 5.97 ± 2.13 |
| Acute infusion | 4 | 4.7 | 11 | 7.8 | 13.2 | 8.3 | 8.17 ± 3.55* |
| 12 mo | 5.8 | 6.4 | 10.8 | 7.9 | 10.5 | — | 8.28 ± 2.28* |
| 24 mo | 6.8 | 6.6 | 5.7 | — | — | — | 6.37 ± 0.59 |
| **CI** | | | | | | | |
| Baseline | 1.9 | 2.8 | 4.9 | 4.5 | 4.5 | 2.2 | 3.47 ± 1.32 |
| Acute infusion | 2.4 | 3 | 6.2 | 4.7 | 7.1 | 4.1 | 4.58 ± 1.81* |
| 12 mo | 3.5 | 4.1 | 6.1 | 5 | 6 | — | 4.94 ± 1.15* |
| 24 mo | 4.1 | 4.2 | 3.4 | — | — | — | 3.90 ± 0.44 |

*Definition of abbreviations*: CI = cardiac index (L/min/m²); CO = cardiac output (L/min); PAP = pulmonary artery pressure (mm Hg); PVR = pulmonary vascular resistance (dyn/s/cm⁻⁵); SD = standard deviation.
* $p < 0.05$ compared with baseline (there were not enough patients at 24 mo to determine significance).
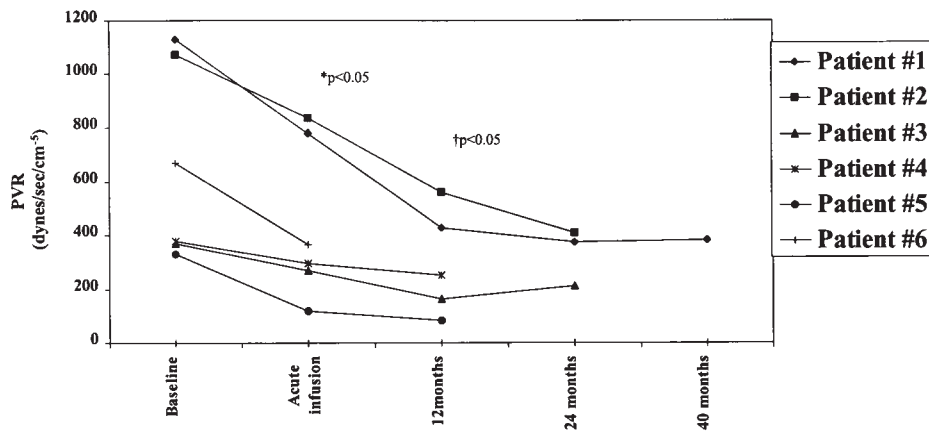
*Figure 1.* Pulmonary vascular resistance at baseline and after long-term infusion of epoprostenol. The patients underwent right heart catheterization at the points cited and pulmonary vascular resistance was calculated. PVR = pulmonary vascular resistance. *p < 0.05 compared with PVR at baseline. †p < 0.05 compared with PVR after acute infusion of epoprostenol. There were not enough patients at 24 mo to determine significance.

ated acute dose of epoprostenol, there was a decrease in mean PAP ($-16.4\%$, $p < 0.05$) and PVR ($-32.7\%$, $p < 0.05$) and an increase in mean cardiac output (CO) ($+36.9\%$, $p < 0.05$) and cardiac index (CI) ($+32.0\%$, $p < 0.05$) in all patients (Table 2 and Figure 1). There were no significant oxygen desaturations during any of the trials. Mean dose of epoprostenol at discharge was $9.5 \pm 2.1$ ng/kg/min.

### Long-term Hemodynamic Data

Duration of epoprostenol therapy has ranged from 12 to 47 mo. The current mean dose of epoprostenol is $27.5 \pm 7.9$ ng/kg/min. Hemodynamic data for the five patients who have had repeat pulmonary artery catheterizations are presented in Table 2 and Figure 1. After 1 yr of continuous intravenous infusion, five patients (Patients 1–5) underwent repeat catheterization. Patients 1, 2, 3, and 5 demonstrated further improvement in PAP, PVR, and CO. Patient 4 demonstrated an elevation of mean PAP at repeat catheterization but there was a continued reduction in PVR and maintenance of CO and CI. Compared with baseline hemodynamic data prior to epoprostenol therapy, there was an overall decrease in mean PAP and PVR of 21.7 and 54.9% ($p < 0.05$), respectively, and an increase in mean CO and CI of 51.4 and 42.4% ($p < 0.05$), respectively. Compared with hemodynamic data after initiation of epoprostenol, there was a decrease in mean PAP and PVR of 3.7 and 35.2% ($p < 0.05$), respectively, and a further increase in mean CO and CI of 1.7 and 5.5%, respectively.

Patients 1–3 had a third catheterization after approximately 24 mo of continuous epoprostenol therapy. Compared with baseline hemodynamic data prior to epoprostenol therapy, there was an overall decrease in mean PAP and PVR of 35.3 and 61.4%, respectively, and an increase in mean CO and CI of 16.3 and 17.9%, respectively. Compared with hemodynamic data after 1 yr of epoprostenol infusion, there was a decrease in mean PAP and PVR of 19.1 and 13.6% although absolute PVR increased in Patient 2 (Table 2 and Figure 1). CO and CI improved in Patient 1, remained stable in Patient 2, and decreased in Patient 3. Patient 1 underwent a fourth catheterization after 40 mo of therapy. Mean PAP (45 mm Hg) and PVR (384 dyn/s cm$^{-5}$) remained similar to values from the previous catheterization whereas CO and CI decreased from 6.8 to 5.8 L/min and 4.1 to 3.5 L/min/m$^2$, respectively (Figure 1).

New York Heart Association Functional Class before and after long-term epoprostenol therapy is presented in Figure 2. All six patients receiving long-term infusion of epoprostenol demonstrated an improvement in functional class (from class III–IV to I–II) compared with their functional class prior to initiation of therapy.

### Morbidity and Mortality

Complications included jaw pain, intermittent headache, and flushing especially with dosage increases. Central line infection requiring intravenous antibiotics and changing of the permanent catheter occurred in Patients 1 and 3. No patient has incurred significant epoprostenol-associated thrombocytopenia. Patient 6 died from nucleoside analog-induced lactic acidosis after 12 mo of epoprostenol treatment and marked clinical improvement.

### DISCUSSION

In our patient population with HIV-associated pulmonary hypertension, acute infusion of epoprostenol resulted in marked improvements in pulmonary artery pressure, pulmonary vascular resistance, and/or cardiac output. Repeat catheterization in five patients after 1 yr of therapy demonstrated continued benefit and improvement in hemodynamics and further benefit was seen after 2 yr in three patients and after 40 mo in one patient. Changes in hemodynamics were accompanied by improvements in NYHA functional class. These results are comparable to data for long-term epoprostenol infusion for PPH (21) (a mean reduction in PVR of 53 versus 54.9% in our study; a decrease in mean PAP of 22 versus 21.7%; an increase in CO of 67 versus 51.4%; and 96% of patients in NYHA functional class I or II compared with 100% in our study). The mean dose of epoprostenol at long-term follow up in the PPH trial was $40 \pm 15$ versus $27.5 \pm 7.9$ ng/kg/min in our patients. The complications observed in these HIV-positive patients were similar to and no greater than those reported for patients with PPH treated with epoprostenol (15–17, 21).
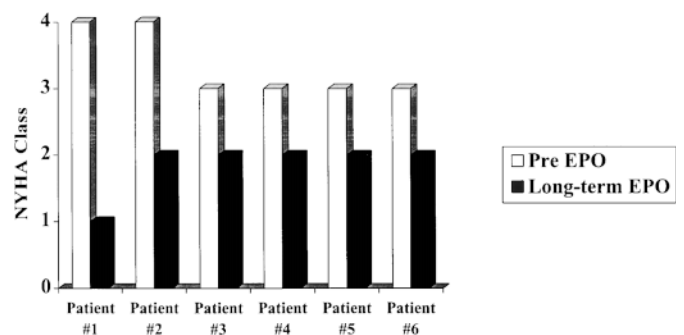


*Figure 2.* New York Heart Association Class before and after long-term epoprostenol therapy. NYHA = New York Heart Association; EPO = epoprostenol.

Use of epoprostenol in HIV-associated pulmonary hypertension has not been extensively evaluated. In one report of two patients with HIV-associated pulmonary hypertension (22), treatment with inhaled prostacyclin (of 7 mo duration) resulted in modest decreases in mean PAP (from 73 to 62 mm Hg and 53 to 47 mm Hg) and in PVR (from 1,093 to 945 dyn/s cm$^{-5}$ and from 860 to 837 dyn/s cm$^{-5}$). There was no change in cardiac index and no adverse effects. NYHA functional class improved from IV to II. In comparison, our study showed similar reductions in PAP but much greater reductions in PVR, marked improvement in CO/CI, and significant improvement in NYHA functional class.

Another study (8) used short-term epoprostenol infusions in 19 patients with HIV-associated pulmonary hypertension only to assess the capacity of the pulmonary vasculature to vasodilate, not for long-term therapy. There was a 20% reduction in total pulmonary vascular index in those patients compared with a 30.1% reduction in PVR in our patient series, but only one-half of the patients in that study were NYHA class III or IV; the remainder were class I or II. In the current study all patients were NYHA class III or IV, similar to patients in the PPH/epoprostenol trials.

This is the initial report of the use of intravenous epoprostenol as long-term therapy for HIV-associated pulmonary hypertension. In these patients, treatment appears to be as effective as in patients with PPH and the morbidity experienced was similar. Thus, these results are encouraging, especially in an era in which patients with HIV infection are living longer due to improved medical therapy. Although treatment with epoprostenol has been primarily reserved for patients with primary pulmonary hypertension, treatment of secondary pulmonary hypertension with this agent is not without precedent and has showed success (24–32). Because of the similarity in the histopathology of HIV-associated pulmonary hypertension and PPH, it is not unreasonable to expect epoprostenol infusion to have similar effects in these patients with HIV-associated pulmonary hypertension as compared with patients with PPH. Of note in this study was the universal lack of response to adenosine, used to predict the response to epoprostenol, yet subsequent improvement with epoprostenol infusion. This study suggests that adenosine may not be effective in predicting response to epoprostenol in HIV-associated pulmonary hypertension and that in addition to its vasodilator effect, the effect of epoprostenol may be mediated by a decrease in platelet aggregation and release of platelet products (26).

Despite the impressive clinical response in our patients, there are obvious limitations with the current study. First, the number of patients is very small. Second, there is no control group as in the PPH/epoprostenol trials. None of our patients nor patients in another study (10) had a response to oral calcium channel blockers; thus, dissimilar to the PPH/epoprostenol trials, it may be difficult to identify an appropriate control group. Third, although there was a marked improvement in exercise tolerance in all patients, a definite effect on survival cannot be ascertained, although the survival rate of our patients appears better than that of patients with HIV-associated pulmonary hypertension who were not treated with epoprostenol. One study of 20 HIV-infected patients with pulmonary hypertension reported a 46% survival rate at 2 yr, which was similar to their control group of patients with PPH (53%) (8). A second study of 19 HIV-infected patients with pulmonary hypertension reported a median survival of 1.3 yr with survival rates of 58% at 1 yr, 32% at 2 yr, and 21% at 3 yr (10).

Further study of long-term therapy with epoprostenol with a greater number of patients will be needed to assess these questions as well as the continued benefit and safety of this treatment. Development of central venous line infection and sepsis remains a concern in these immunosuppressed patients and the benefits and risks of chronic epoprostenol therapy should be weighed. However, with the life expectancy of patients with HIV infection increasing, the use of intravenous epoprostenol should be considered in patients with HIV-associated pulmonary hypertension, NYHA class III or higher, who demonstrate no significant response to acute vasodilator testing and whose morbidity and mortality from pulmonary hypertension may exceed that of HIV infection alone.

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