

HIV-Related Pulmonary Hypertension

ATIKUN LIMSUKON, M.D.¹, ALI IMRAN SAEED, M.D.¹, VIMALA RAMASAMY, M.D.², JHANSI NALAMATI, M.D.³,
AND SUNIL DHUPER, M.D.⁴

Abstract

With the availability of better treatment and prophylactic regimens for the infectious complications of human immunodeficiency virus (HIV), the non-infectious complications are gaining greater attention. HIV-related pulmonary arterial hypertension (HIV-PAH) is one of these. The incidence of HIV-PAH is estimated at 0.5% of HIV-infected individuals. The pathogenesis remains unclear. Patients present with symptoms as diverse as progressive shortness of breath, pedal edema, dry cough, fatigue, syncope, as well as chest pain. Chest X-ray always shows cardiomegaly and prominent pulmonary artery, and evidence of right ventricular hypertrophy can be seen from the electrocardiogram. The pulmonary arterial systolic pressure, diastolic pressure and pulmonary vascular resistance from right heart catheterization are increased.

There are a few small studies showing the benefit of prostacyclin analog (epoprostenol and iloprost) and bosentan. The role of antiretrovirals remains controversial, as do those of other agents such as calcium channel blockers and anti-coagulants. The prognosis of HIV-PAH is grave. Two thirds of HIV-PAH related mortality is usually secondary to consequences of pulmonary hypertension, with the worst survival noted in New York Heart Association (NYHA) functional class III-IV. The probability of survival in one series was 73%, 60% and 47% at one, two and three years, respectively.

Key Words: HIV-related pulmonary hypertension, AIDS-related pulmonary disease, pulmonary hypertension, epoprostenol, highly active antiretroviral therapy.

Introduction

HUMAN IMMUNODEFICIENCY VIRUS INFECTION has been associated with both infectious and non-infectious complications. With the advent of better prophylaxis against opportunistic infections, as well as longer survival secondary to new and potent antiretroviral treatments, non-infectious complications of HIV are gaining greater recognition and attention.

Many cardiovascular complications of HIV infection are well known and have been well described. These include cardiomyopathy, pericarditis and/or pericardial effusion, as well as myocarditis. Pulmonary hypertension (PH) has re-

cently also been recognized as one of the outcomes of HIV infection and is now known to be one of the most devastating non-infectious complications.

Kim and Factor (1) reported the first known case of PH in a non-hemophilic, homosexual HIV-positive subject in 1987. Since the publication of their case report, an increasing number of HIV-PAH patients have been identified. To date, more than 200 cases have been reported (2–26).

In this article, we present a comprehensive review of the epidemiology, pathogenesis, pathology, clinical features, and natural course of HIV-related pulmonary hypertension. In addition, available treatments are critically evaluated and discussed in association with the outcome and prognosis of HIV-PAH. Where relevant, recently published clinical and experimental evidence is examined and presented concisely for a comprehensive review of the topic.

Epidemiology

The prevalence of HIV-PAH has been estimated at 1:1,200 (0.5 %) of HIV-infected individuals, 8.1% of whom have cardiopulmonary complaints, as compared to 1–2:1,000,000 patients of idiopathic pulmonary hypertension (IPAH) in the

¹Department of Internal Medicine, Bronx Veterans Affairs Medical Center, Bronx, NY, and the Mount Sinai School of Medicine, New York, NY; Departments of ²Internal Medicine, ³Pulmonary and Critical Care Medicine and ⁴Medicine, North Central Bronx Hospital and the Albert Einstein College of Medicine, Bronx, New York.

Address all correspondence to Atikun Limsukon, M.D., 130 S. Flores Street, Apt. #310, Los Angeles, CA 900483489 Fort Independence Street, Apt # 6F, Bronx, NY 10463; email: atikhun@hotmail.com

Accepted for publication January 2006.

general population (2). However, it is estimated that the true prevalence of HIV-PAH is much higher, since most published studies evaluating HIV-PAH are unable to include the asymptomatic cases.

A 1992 report indicated that HIV-infected individuals had severe but significantly lower levels of PH than was common among those with non-HIV primary pulmonary hypertension (3), a phenomenon that is attributed to closer medical attention, leading to earlier diagnosis in the first group. The mean age at the time of diagnosis of HIV-PAH cases was 32, with a male-to-female ratio of 1.6:1 versus with 1:1.7 in IPAH (4).

A 1998 review by Mesa et al. (4) identified the following risk factors for HIV infection: intravenous drug abuse (IVDA) 42%, homosexuality 25%, hemophilia 13%, heterosexual transmission 10%, blood transfusions for non-hemophiliacs 4%, both homosexual and IVDA 3%, and maternally acquired congenital infection 4%. In the year 2000, Mehta et al. (5) reviewed 131 cases of HIV-PAH and found that among 82% of infected individuals, PH was related solely to HIV infection without other secondary causes.

HIV-PAH has been shown to occur in both the early and later stages of HIV infection and does not seem to be related to the degree of immunodeficiency or the CD4+ T-lymphocyte counts. However, the severity of HIV-PAH (determined by pulmonary arterial systolic pressure [PASP]) was higher in patients with full-blown AIDS than in non-AIDS HIV-infected patients (27).

Pathogenesis

The pathogenesis and exact mechanism of development of pulmonary hypertension in patients with HIV have not been clearly defined. Pathologically, HIV-PAH is characterized by significant remodeling of the pulmonary vasculatures.

In 1988, Goldsmith et al. (6) presented a case report of five HIV patients with hemophilia A that had been treated with self-administered lyophilized concentrates of Factor VIII; all of these patients developed pulmonary hypertension without other identifiable underlying cardiac or pulmonary disease. The authors concluded that the interval development of PH in this particular group of patients may have been related to the treatment with lyophilized Factor VIII. However, at that time they did not know whether the presence of antibodies to HIV could also lead to the development of pulmonary hypertension.

As subsequent non-hemophiliac cases were described, suspicion that the development of pul-

monary hypertension may relate directly to HIV infection was established. In a state-of-the-art review, for example, Mette et al. (7) could not demonstrate direct HIV infection within the pulmonary vascular endothelium, using advanced techniques such as electron microscopy, immunohistochemistry, DNA *in situ* hybridization and polymerase chain reaction in lung tissue obtained from two patients. The authors postulated that HIV-1 might play a role in the pathogenesis of PH through the release of a variety of mediators associated with retroviral infection, rather than by direct endothelial infection itself.

In a more recent publication, Humbert et al. (8) demonstrated that platelet-derived growth factor (PDGF) activity (a well-known stimulator of fibroblast and smooth muscle cell proliferation) was elevated in the lung biopsies of patients with pulmonary hypertension, irrespective of their underlying state of HIV seropositivity. Interestingly, however, they did not find similar elevations of PDGF activity in HIV-positive individuals without overt PH. These authors also did not identify HIV-1 p24 antigenemia and HIV-1 *gag* RNA in the pulmonary arteries with immuno-histochemistry and *in situ* hybridization, techniques similar to those employed earlier by Mette et al.

Several other mediators aside from the p24 antigen may be implicated in the development of PH in HIV-infected individuals. For example, an article by Ehrenreich et al. (9) reports that the envelope glycoprotein, GP-120, is a potent stimulator of the secretion of endothelin-1 (ET-1). ET-1 is produced from macrophages in a concentration-dependent fashion and is well known to be a potent vasoconstrictor. In addition, the same authors demonstrated a chronically increased expression of the ET-1 gene in the circulating monocytes of HIV-infected patients. An autoimmune etiology has also been implicated as a possible causative factor in the development of PH in patients with HIV. Thus far, studies have demonstrated that anticardiolipin IgM and anti-SS-B have been significantly elevated in patients with HIV-PAH compared to HIV patients without PH (10). However, it remains unclear with this sparse data that the autoimmune phenomenon plays a role in the development of PH.

Interestingly, the fact that only a small percentage of HIV-infected patients will actually develop HIV-PAH suggests that certain predisposing factors are necessary for the development of PH in these patients. Tending to confirm this theory, a study by Morse et al. (28) found that there were significant increases in the frequency of human leukocyte antigen (HLA) class II, HLA-DR6 (DRB1*1301/2 subtype) and of HLA-DR52

(DRB3*301 subtype) in patients with HIV-PAH, as compared to a cohort of 128 HIV negatives and 97 HIV positives without PH. The same HLA-DR6 subtype has also been associated with diffuse infiltrative lymphocytosis syndrome (DILS), previously reported as the CD8 lymphocytic host response HIV-1 infection. Although germ-line bone morphogenetic protein receptor-2 (BMPR2) gene mutation was identified as one cause of both familial and sporadic IPAH including PH patients exposed to fenfluramine derivatives, it was not found in a study of 19 patients with HIV-PAH by Nunes et al. (11).

There is an apparent need for more data and research on this particular aspect of the disease process.

Pathology

The histopathologic findings in HIV-PAH are similar to those of IPAH. These include the development of plexogenic pulmonary arteriopathy, thrombotic arteriopathy and pulmonary veno-occlusive disease, of which plexogenic pulmonary arteriopathy remains the most common finding (Fig. 1; 4). Plexogenic lesions are characterized by medial hypertrophy with concentric intimal proliferation. Mehta et al. report that among the available histopathologic findings from 46 patients, 78% showed plexogenic pulmonary arteriopathy, 11% developed medial hypertrophy and intimal fibrosis without plexiform lesions, and pulmonary veno-occlusive disease was noted in 7% (5). Thrombotic pulmonary arteriopathy remained the least frequent identified lesion, in 4% of the patients.

Clinical Features and Natural Course of the Disease

As stated earlier, the clinical course and progression of PH in HIV-infected individuals is not correlated with the stage of HIV infection or associated with the progression of the disease. The diagnosis of HIV-PAH should therefore only be entertained once all other known etiologies for pulmonary hypertension have clearly been excluded. In patients with HIV and/or AIDS, pulmonary hypertension is known to be more rapidly progressive than in IPAH, with a mean length of time from onset of symptoms to diagnosis of 6 and 30 months, respectively. Many of the known symptoms and signs of HIV-PAH result from right ventricular dysfunction, an etiology that is no different from that of patients with classical IPAH. The most common presenting symptom is progressive dyspnea (85%), followed by pedal edema (30%), non-

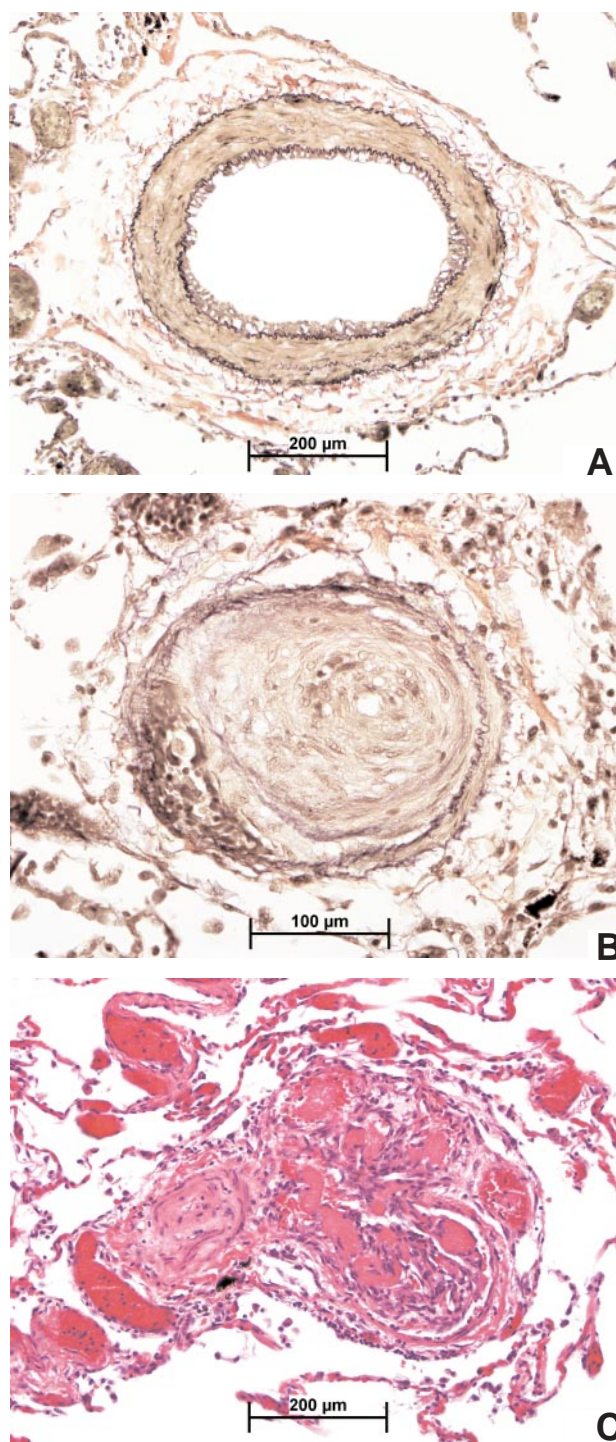
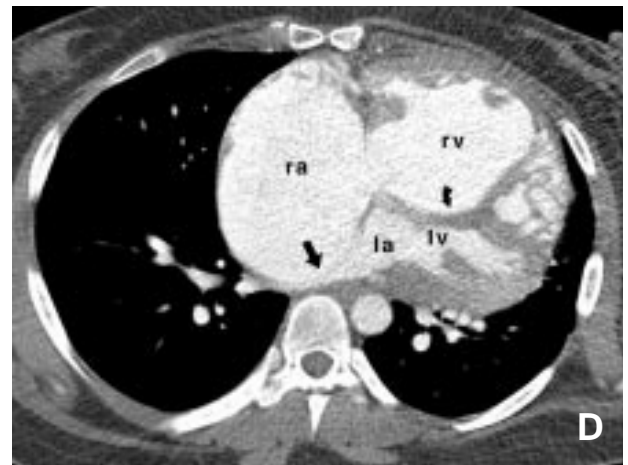
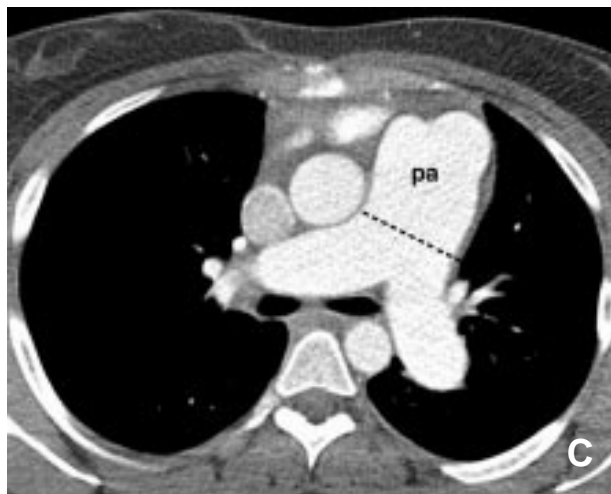
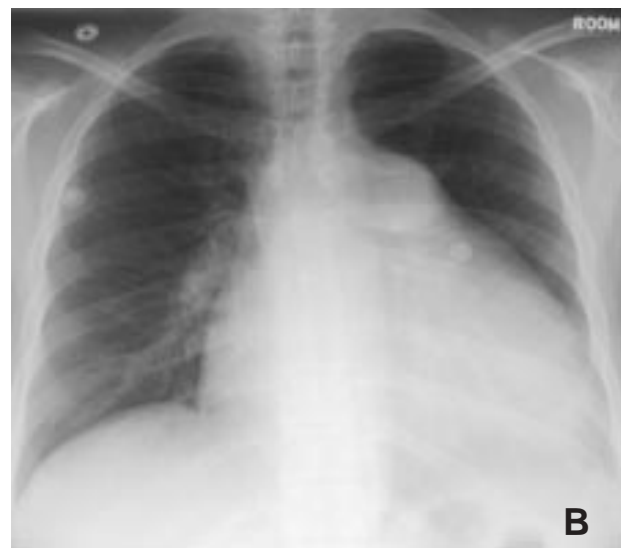
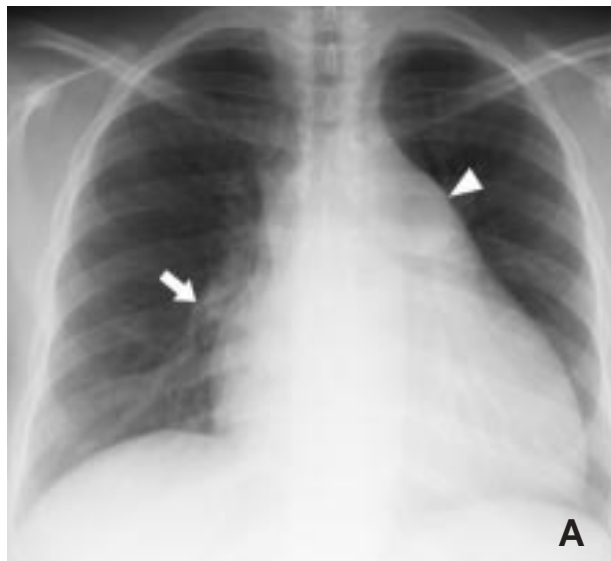


Fig. 1. Photomicrographs of muscular pulmonary arteries from a 43-year-old man with HIV-PAH. (A) Medial hypertrophy. (B) Concentric laminar intimal fibroelastosis. (C) Plexiform lesion. (A and B, Verhoeff-van Gieson; $\times 50$ and $\times 100$, respectively. C, Hematoxylin-eosin; $\times 50$.) (Courtesy of Dr. William D. Edwards, Division of Anatomic Pathology, Mayo Clinic.)

©1998 Mayo Foundation for Medical Education and Research. Reprinted with permission from Mesa RA, Edell ES, Dunn WF, Edwards WD. Human immunodeficiency virus infection and pulmonary hypertension: two new cases and a review of 86 reported cases. *Mayo Clin Proc* 1998; 73(1):37–45 (4).



productive cough (19%), fatigue (13%), syncope or near syncope (12%), and chest pain (7%) (4). Relevant physical signs include an increased pulmonary component of second heart sound (P₂), a right ventricular heave appreciated on the precordium, and the presence of the systolic murmur of tricuspid regurgitation. In advanced cases, peripheral edema, ascites and hepatomegaly from overt right heart failure may all be present (29).

Patients with pulmonary hypertension can also be functionally classified by using the NYHA classification (12). It is important to mention that no study to date has demonstrated a significant correlation between pulmonary arterial systolic pressure (PASP) and CD4 cell count. The mean CD4 count from one series (27) in patients detected with HIV-PAH was 300 ± 250 cells/mm³. A review of PASP measures in these individuals revealed a significantly higher PASP in patients with AIDS than in non-AIDS patients (mean PSAP =

85.4 ± 17 mm Hg vs. 71.8 ± 15 mm Hg, 95% CI: 2.98–24.22).

The plain chest X-ray commonly shows cardiomegaly (72%) and prominence of the pulmonary arteries (71%) with clear lung fields. An electrocardiogram frequently reveals nonspecific signs of right ventricular hypertrophy (67%), right atrial abnormality and right axis deviation. In terms of transthoracic echocardiography, findings include right heart chamber enlargement (98%), tricuspid regurgitation, and paradoxical septal motion abnormalities (Fig. 2; 30). Right heart catheterization (RHC) is the standard for confirming the diagnosis of pulmonary hypertension and for evaluating the hemodynamic status and the response to treatment. As reviewed by Mehta et al. (5), mean \pm SD of PASP was 67 ± 18 mm Hg in patients with HIV-PAH ($n = 116$). The pulmonary arterial diastolic pressure (PADP) was 40 ± 11 mm Hg ($n = 39$) with a pulmonary vascular resistance (PVR) of $983 \pm$

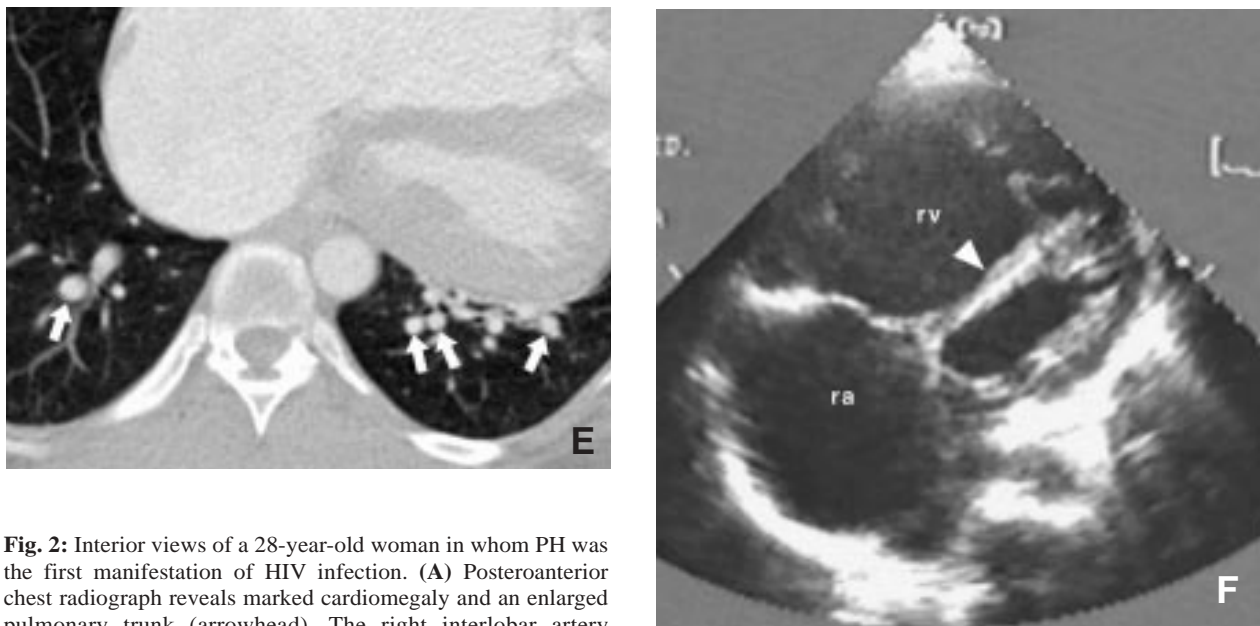


Fig. 2: Interior views of a 28-year-old woman in whom PH was the first manifestation of HIV infection. (A) Posteroanterior chest radiograph reveals marked cardiomegaly and an enlarged pulmonary trunk (arrowhead). The right interlobar artery (arrow) measures 21 mm in transverse diameter. (B) Posteroanterior chest radiograph obtained 5 years later shows interval progression of the cardiomegaly. (C–E) Electron-beam CT pulmonary angiograms (130 keV, 633 mA, 3-mm collimation, 0.2-second exposure). (C) Transverse view at the level of the bifurcation of the pulmonary artery (window width, 500 HU; window level, 40 HU) shows enlargement of the main pulmonary artery (*pa*), which measures 43 mm in transverse diameter (dashed line). (D) Transverse image obtained at a lower level (window width, 500 HU; window level, 40 HU) shows dilatation of the right ventricle (*rv*) and right atrium (*ra*) and reversal of the interatrial (straight arrow) and interventricular (curved arrow) septa. Simultaneous opacification of the right and left cardiac chambers is noted. *lv* = left ventricle, *la* = left atrium. (E) Segmental artery-to-bronchus ratios greater than 1 (arrows) in the lower lobes can be observed on this transverse image obtained at a lower level (window width, 1,400 HU; window level, 300 HU). (F) A four-chamber view from an echocardiogram shows right ventricular (*rv*) and right atrial (*ra*) dilatation. Paradoxical movement of the interventricular septum (arrowhead) was observed at real-time imaging.

©Radiological Society of North America, founded in 1915. Reprinted with permission from Bugnone AN, Viamonte M Jr., Garcia H. Imaging findings in human immunodeficiency virus-related pulmonary hypertension: report of five cases and review of the literature. *Radiology* 2002; 223(3):820–827 (30).

420 dyne·s·cm⁻⁵ (n = 29). Pulmonary function tests (PFTs) have revealed a mildly restrictive pattern with variable reductions in diffusing capacity, another phenomenon that has not been shown to correlate with the severity of PH.

Treatment Modalities and Therapeutic Considerations

It is important to remember that HIV-PAH is a progressive disease for which there is no cure. No study has yet established a single agent of choice for its treatment, even though considerable progress has been made over the past few years.

The most commonly used agents in the treatment of HIV-PAH remain PAH-specific therapy and antiretroviral medications themselves.

Stricker et al. reported two cases of HIV-PAH with NYHA class IV dyspnea treated with aerosolized prostacyclin (13). Acute responses of

reduction of mean pulmonary arterial pressure (PAP) from 73 to 62 mm Hg and 53 to 47 mm Hg, reduction of PVR from 1093 to 945 dyne·s·cm⁻⁵ and 860 to 837 dyne·s·cm⁻⁵, respectively, were noted. Based on these initial promising results, one patient was subsequently initiated on long-term treatment with inhaled epoprostenol and the other initiated on long-term inhaled iloprost treatment. After a mean of seven months' follow-up, both patients demonstrated sustained reduction of PAP and improvement of symptoms (NYHA class IV to class II), as demonstrated by increasing walking distances on treadmill tests and improvement of NYHA functional status.

In yet another prospective study (14), six patients with severe HIV-PAH were treated with continuous intravenous epoprostenol infusions. This trial demonstrated a significant acute reduction of mean PAP (16.4%) and PVR (32.7%). The mean cardiac output was also found to be significantly in-

creased (36.9%). After one year of follow-up, mean PAP and PVR had decreased by 21.7% and 54.9% ($p < 0.05$) respectively, and the mean cardiac output had increased by 51.4% ($p < 0.05$) when compared to baseline values. All patients were noted to have developed an improvement in their NYHA functional class. Further improvement and maintenance of hemodynamics was demonstrated in three patients at two years and one patient at 40 months. These sustained improvements are consistent with the trial conducted by Nunes et al. (11). However, there are some concerns about long-term epoprostenol infusion, e.g., lack of pulmonary selectivity, tachyphylaxis requiring dose escalation, inconvenient drug delivery system, catheter-related sepsis and inadvertent drug interruption, which may lead to death in 15–30 minutes. Other adverse effects typical of prostacyclin administration include jaw pain, intermittent headache, and flushing, especially with dosage increases.

Given the complicated technique associated with long-term epoprostenol infusion, the long-term effects of inhaled iloprost were studied (15). Eight patients with severe HIV-PAH (NYHA class III and IV) were monitored for hemodynamic responses with right heart catheterization while receiving oxygen, short-term nitric oxide (NO) inhalation challenges, and iloprost inhalation.

The acute vasodilatory potency was greatest for iloprost $>$ NO $>$ oxygen, with a maximum reduction (mean \pm SEM) in PVR of $30.6 \pm 3.1\%$ ($p < 0.001$), $5.9 \pm 3.9\%$ and $-0.6 \pm 3.9\%$ respectively. Iloprost was also noted to produce a significant increase in the cardiac index by $20.9 \pm 8.9\%$ ($p < 0.01$), while simultaneously beneficially decreasing the PVR to systemic vascular resistant (SVR) ratio, a fact that indicates preferential pulmonary vasodilatation. It is interesting to note, however, that none of the patients in this study cohort were found to be “NO-responders.” NO response has been widely accepted as a screening tool that helps in identifying patients who will respond favorably to long-term treatment with high doses of oral calcium channel blockers in IPAH.

Four of the eight patients in the study mentioned above underwent chronic therapy with inhaled iloprost over six months without significant changes in parameters of their HIV infection (as measured by CD4 count and viral load). However, all of these patients demonstrated clinical improvement of NYHA functional capacity, and their average 6-minute walking distance increased from 331 ± 21 m to 417 ± 40 m ($p = 0.063$), with a decrease in average PVR from $1,402 \pm 324$ dyne.s.cm⁻⁵ to 772 ± 89 dyne.s.cm⁻⁵ ($p = 0.065$).

The effect of calcium channel blockers on the course of HIV-PAH remains unclear, though they are known to be efficacious in a very selective group of IPAH patients. In one small study, for example, none of five tested patients with known HIV-PAH responded to calcium channel blockers, and four of them experienced intolerable side effects necessitating discontinuation of therapy (31).

Bosentan, an endothelin-1 receptor antagonist of proven efficacy in the treatment of primary pulmonary arterial hypertension (32), has also recently been shown to have clinical benefits in a nonrandomized clinical trial of 16 patients with HIV-PAH and in NYHA class III-IV, in terms of 6-minute walk distance ($+91 \pm 60$ m, $p < 0.001$), NYHA class (14 patients improved), hemodynamics (cardiac index: $+0.9 \pm 0.7$ L/minute/m², $p < 0.001$), Doppler echocardiographic variables, and quality of life at 16 weeks' observation (33).

Sildenafil, a specific phosphodiesterase isoform (PDE5) inhibitor, given orally, has been reported to cause a persistent reduction of PAP. It has been clinically demonstrated to improve dyspnea and exercise tolerance (16–18).

There is no current trial objectively evaluating the effect of antiretroviral therapy on the progression of HIV-PAH. In a prospective study with a median follow-up of 13 years, Opravil et al. observed that five out of eight patients who had significantly stable and decreasing estimated PASP were receiving regular antiretroviral therapy (10). Interestingly, four out of five patients with increasing estimated PASP were not receiving any antiretroviral therapy. The difference between last and first pressure gradient was $+19.0$ mm Hg and -3.2 mm Hg in the untreated and treated groups, respectively ($p = 0.026$). A retrospective study using highly active antiretroviral therapy (HAART), including the newer protease inhibitors, failed to demonstrate any significant benefit on the clinical course of PH. In fact, two patients in this study, who had low viral loads and were treated with HAART, demonstrated an accelerated course of PH with worsening PASP (34). Conversely, a study of a subgroup of 47 patients with HIV-PAH in the Swiss HIV Cohort Study found that patients who received HAART had a significantly decreased median right ventricular systolic pressure over right atrial pressure gradient (-21 mm Hg), compared with patients who received 2 nucleoside analog reverse-transcriptase inhibitors (-3 mm Hg) and those who did not receive antiretroviral therapy ($+25$ mm Hg) (35).

There is not enough supporting evidence for the use of anticoagulant in HIV-PAH, although *in situ* thrombosis is occasionally found.

Prognosis

The prognosis of HIV-PAH remains poor despite clinically significant advances in therapy. The development of PH and low CD4 counts are the two most commonly associated independent predictors of death in HIV-infected patients (10). In one study of 131 cases of HIV-PAH, two thirds of the deaths in HIV-PAH were due to direct consequences of PH itself, such as right-sided heart failure, cardiogenic shock and sudden cardiac death (5). Nunes et al. (11) studied the prognostic factors for survival among 82 patients with HIV-PAH. They also found that about two thirds of total mortality was caused by PH itself (5). The overall survival rate at one, two and three years were 73%, 60%, and 47%, respectively. Predictably, survival was dramatically worse in patients in NYHA class III-IV, when compared to patients with NYHA class I-II ($p < 0.0001$) in subgroup analysis. This fact helps emphasize the role of NYHA functional class placement as a major indicator of prognosis in HIV-PAH. The authors also specifically analyzed for the factors associated with mortality in the subgroup of patients in NYHA class III-IV. They demonstrated that CD4 count of more than 212 cell/mm³, use of combination antiretroviral therapy (CART) and treatment with epoprostenol were significantly related to a decreased risk of death. However, only CD4 count was shown to be an independent predictor of survival in multivariate analysis. CART and epoprostenol therapy were strongly linked with positive outcomes. The survival was worse in NYHA class III-IV patients who were treated with CART only, compared with those receiving CART and epoprostenol.

Summary

Physicians should be aware of possible pulmonary hypertension in patients with HIV infection who present with progressive shortness of breath and/or symptoms or signs of right-sided heart failure, as this condition increases morbidity and mortality. We recommend screening of these patients with transthoracic echocardiography. HAART may be considered for any HIV-infected patient with pulmonary hypertension, regardless of CD4 counts or viral load.

Despite major advances over the past few years, treatment options for HIV-PAH remain limited and unsatisfactory. Varieties of PAH-specific treatments have been explored, but still require larger trial(s) for better evaluation of the effects on clinical outcomes.

The prognosis for HIV-PAH remains predictably grim, with higher mortalities among patients with higher NYHA functional class. Earlier screening and a more effective application of HAART to HIV-infected individuals, in conjunction with the development of more clinically efficacious PAH-specific treatments, offer hope that the burden of disease may be reduced. Further large-scale clinical and experimental studies are clearly needed to help us better understand and manage this complex pathophysiologic disease state.

References

1. Kim KK, Factor SM. Membranoproliferative glomerulonephritis and plexogenic pulmonary arteriopathy in a homosexual man with acquired immunodeficiency syndrome. *Hum Pathol* 1987; 18(12):1293–1296.
2. Speich R, Jenni R, Opravil M, et al. Primary pulmonary hypertension in HIV infection. *Chest* 1991; 100:1268–1271.
3. Polos PG, Wolfe D, Harley RA, et al. Pulmonary hypertension and human immunodeficiency virus infection. Two reports and a review of the literature. *Chest* 1992; 101:474–478.
4. Mesa RA, Edell ES, Dunn WF, Edwards WD. Human immunodeficiency virus infection and pulmonary hypertension: two new cases and a review of 86 reported cases. *Mayo Clin Proc* 1998; 73:37–45.
5. Mehta NJ, Khan IA, Mehta RN, Sepkowitz DA. HIV-related pulmonary hypertension: analytic review of 131 cases. *Chest* 2000; 118:1133–1141.
6. Goldsmith GH Jr, Bailly RG, Brettler DB, et al. Primary pulmonary hypertension in patients with classic hemophilia. *Ann Intern Med* 1988; 108:797–799.
7. Mette SA, Palevsky HI, Pietra GG, et al. Primary pulmonary hypertension in association with human immunodeficiency virus infection: a possible viral etiology for some forms of hypertensive pulmonary arteriopathy. *Am Rev Respir Dis* 1992; 145:1196–1200.
8. Humbert M, Monti G, Fartoukh M, et al. Platelet-derived growth factor expression in primary pulmonary hypertension: comparison of HIV seropositive and HIV seronegative patients. *Eur Respir J* 1998; 11:554–559.
9. Ehrenreich H, Rieckmann P, Sinowatz F, et al. Potent stimulation of monocytic endothelin-1 production by HIV-1 glycoprotein 120. *J Immunol* 1993; 150(10):4601–4609.
10. Opravil M, Pechere M, Speich R, et al. HIV-associated primary pulmonary hypertension. A case control study. *Am J Respir Crit Care Med* 1997; 155:990–995.
11. 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(10):1433–1439.
12. Nausser TD, Stites SW. Diagnosis and treatment of pulmonary hypertension. *Am Fam Physician* 2001; 63(9):1789–1798.
13. Stricker H, Domenighetti G, Mombelli G. Prostacyclin for HIV-associated pulmonary hypertension [letter]. *Ann Intern Med* 1997; 127:1043.
14. Aguilar RV, Farber HW. Epoprostenol (prostacyclin) therapy in HIV-associated pulmonary hypertension. *Am J Respir Crit Care Med* 2000; 162:1846–1850.
15. Ghofrani HA, Friese G, Discher T, et al. Inhaled iloprost is a potent acute pulmonary vasodilator in HIV-related severe pulmonary hypertension. *Eur Respir J* 2004; 23(2):321–326.

16. Alp S, Schlottmann R, Bauer TT, et al. Long-time survival with HIV-related pulmonary arterial hypertension: a case report. *AIDS* 2003; 17(11):1714–1715.
17. Schumacher YO, Zdebek A, Huonker M, Kreisel W. Sildenafil in HIV-related pulmonary hypertension. *AIDS* 2001; 15:1747–1748.
18. Carlsen J, Kjeldsen K, Gerstoft J. Sildenafil as a successful treatment of otherwise fatal HIV-related pulmonary hypertension. *AIDS* 2002; 16:1568–1569.
19. Bray GL, Martin GR, Chandra R. Idiopathic pulmonary hypertension, hemophilia A, and infection with human immunodeficiency virus (HIV). *Ann Intern Med* 1989; 111:689–690.
20. Legoux B, Piette AM, Bouchet PF, et al. Pulmonary hypertension and HIV infection. *Am J Med* 1990; 89(1):122.
21. Himelman RB, Dohrmann M, Goodman P, et al. Severe pulmonary hypertension and cor pulmonale in the acquired immunodeficiency syndrome. *Am J Cardiol* 1989; 64:1396–1399.
22. Coplan NL, Shimony RY, Ioachim HL, et al. Primary pulmonary hypertension associated with human immunodeficiency viral infection. *Am J Med* 1990; 89:96–99.
23. Mani S, Smith GJW. HIV and pulmonary hypertension: a review. *South Med J* 1994; 87:357–362.
24. Weiss JR, Pietra GG, Schaft SM. Primary pulmonary hypertension and the human immunodeficiency virus: report of two cases and a review of the literature. *Arch Intern Med* 1995; 155:2350–2354.
25. Pellicelli AM, Palmieri F, D'Ambrosio C, et al. Role of human immunodeficiency virus in primary pulmonary hypertension. *Angiology* 1998; 49:1005–1011.
26. Recusani F, Di Matteo A, Gambarin F, et al. Clinical and therapeutic follow-up of HIV-associated pulmonary hypertension: prospective study of 10 patients. *AIDS* 2003; 17 (Suppl 1):S88–S95.
27. Pellicelli AM, Barbaro G, Palmieri F, et al. Primary pulmonary hypertension in HIV patients: a systemic review. *Angiology* 2001; 52:31–41.
28. Morse JH, Barst RJ, Itescu S, et al. Primary pulmonary hypertension in HIV infection: an outcome determined by particular HLA class II alleles. *Am J Respir Crit Care Med* 1996; 153(4 Pt 1):1299–1301.
29. Seoane L, Shellito J, Welsh D, de Boisblanc BP. Pulmonary hypertension associated with HIV infection. *South Med J* 2001; 94(6):635–639.
30. Bugnone AN, Viamonte M Jr., Garcia H. Imaging findings in human immunodeficiency virus-related pulmonary hypertension: report of five cases and review of the literature. *Radiology* 2002; 223(3):820–827.
31. Louis M, Thorens JB, Chevrolet JC. Calcium channel blockers, testing for primary pulmonary hypertension associated with HIV infection. *Am Rev Respir Dis* 1993; 147:536A.
32. Rubin LJ, Badesch DB, Barst RJ, et al. Bosentan therapy for pulmonary arterial hypertension. *N Engl J Med* 2002; 346(12):896–903.
33. 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; 170:1212–1217.
34. Pugliese A, Isnardi D, Saini A, et al. Impact of highly active antiretroviral therapy in HIV-positive patients with cardiac involvement. *J Infect* 2000; 40:282–284.
35. 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(8):1178–1185.