RETROSPECTIVE STUDY

Pulmonary arterial hypertension related to human immunodeficiency virus infection: A case series

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Abstract

AIM: To present 18 new cases of human immunodeficiency virus (HIV)-related pulmonary arterial hypertension (PAH) with presenting features, treatment options and follow-up data.

METHODS: This is a single-centre, retrospective, observational study that used prospectively collected data, conducted during a 14-year period on HIV-related PAH patients who were referred to a pulmonary hypertension unit. All patients infected with HIV were consecutively admitted for an initial evaluation of PAH during the study period and included in our study. Right heart catheterisation was used for the diagnosis of PAH. Specific PAH treatment was started according to the physician's judgment and the recommendations for idiopathic PAH. The data collected included demographic characteristics, parameters related to both HIV infection and PAH and disease follow-up.

RESULTS: Eighteen patients were included. Intravenous drug use was the major risk factor for HIV infection. Risk factors for PAH, other than HIV infection, were present in 55.5% patients. The elapsed time between HIV infection and PAH diagnoses was 12.2 ± 6.9 years. At PAH diagnosis, 94.1% patients had a CD4 cell count > 200 cells/μL. Highly active antiretroviral therapy (present in 47.1% patients) was associated with an accelerated onset of PAH. Survival rates were 93.8%, 92.9% and 85.7% at one, two and three years, respectively. Concerning specific therapy, 33.3% of the patients were started on a prostacyclin analogue, and the rest were on oral drugs, mainly phosphodiesterase-5 inhibitors. During the follow-up period, specific therapy was de-escalated to oral drugs in all of the living patients.

CONCLUSION: The survival rates of HIV-related PAH patients were higher, most likely due to new aggressive specific therapy. The majority of patients were on oral specific therapy and clinically stable. Moreover, sildenafil appears to be a safe therapy for less severe HIV-related PAH.

Key words: Human immunodeficiency virus infection; Pulmonary arterial hypertension; Treatment

Core tip: Human immunodeficiency virus (HIV)-related

pulmonary arterial hypertension (PAH) is a rare disease, and HIV-infected patients are seldom included in clinical trials. Therefore, case reports are crucial to better understand this disease and its response to specific therapies. In this retrospective, observational study, 18 HIV-related PAH patients were included. Highly active antiretroviral therapy was associated with an accelerated onset of PAH. The survival rates of HIV-related PAH patients were higher, most likely due to new aggressive specific therapy. The majority of patients were on specific oral therapy and were clinically stable. Furthermore, sildenafil appears to be a safe option for less severe disease.

INTRODUCTION

Pulmonary arterial hypertension (PAH) is a progressive disease that is caused by the chronic obstruction of small pulmonary arteries, leading to right ventricular failure and potential death[1]. Idiopathic and inherited forms have been described. However, this condition is associated with connective tissue diseases, portal hypertension, congenital heart disease, drugs, toxins and human immunodeficiency virus (HIV) infection[2].

Before the introduction of highly active antiretroviral therapy (HAART), HIV-related PAH was underdiagnosed due to the patients' short survival, which was primarily caused by opportunistic infections. After the introduction of this novel antiretroviral therapy scheme, long-term cardiovascular complications, such as PAH, have emerged[3].

The first case of HIV-related PAH was described in 1987 in an HIV-infected subject with haemophilia and membranoproliferative glomerulonephritis[4]. Subsequently, several other cases have been reported. Nonetheless, HIV-related PAH is a rare disease: in 1991, prior to the introduction of HAART, the prevalence of HIV-related PAH was estimated to be 0.5% in developed countries[5]. This rate is 25-fold higher than the prevalence of PAH in the general population[6].

Recent studies have shown that prevalence has not changed in recent years. As described by Sitbon *et al*[7], the prevalence is 0.46%, suggesting that HAART does not prevent HIV-related PAH. However, because most published studies do not include asymptomatic patients, the actual prevalence could be higher. In 2008, Reinsch *et al*[8] found that the prevalence in asymptomatic patients is 4.8%, although the diagnosis of PAH was only based on echocardiographic parameters. HIV-related PAH is clinically and histologically similar to idiopathic PAH[3].

The aim of this study is to present 18 new cases of HIV-related PAH with presenting features, treatment options and follow-up data.

MATERIALS AND METHODS

This is a single-centre, retrospective, observational study using prospectively collected data that was conducted over a 14-year period between June 1998 and June 2012.

All HIV-infected patients consecutively admitted to the Pulmonary Hypertension Unit of Hospital 12 De Octubre for an initial evaluation of PAH during the study period were included in our study.

PAH was diagnosed with right heart catheterisation and defined by a resting mean pulmonary arterial pressure of more than 25 mmHg and a pulmonary capillary wedge pressure of less than 15 mmHg. Poor prognostic factors included a right atrium pressure (RAP) > 15 mmHg and a cardiac output $\leqslant$ 2.0 mL/min[2,9].

No specific recommendations for the treatment of PAH-HIV have been made thus far; therefore, specific PAH treatment was initiated according to the physician's judgment and the recommendations for idiopathic PAH treatment. HAART is a combination of at least 3 antiretroviral drugs, such as 3 nucleoside reverse transcriptase inhibitors, 2 nucleoside reverse transcriptase inhibitors and 1 protease inhibitor or 2 nucleoside reverse transcriptase inhibitors and 1 non-nucleoside reverse transcriptase inhibitor.

All patients received nonspecific supportive therapy as recommended, unless such therapy was contraindicated or not necessary: oral anticoagulation to maintain an international normalised ratio of 2.0-3.0, long-term oxygen therapy if there was evidence of hypoxemia and diuretic therapy for right heart failure symptomatic control.

Baseline evaluation included an assessment of the NYHA functional class, 6-Minute Walk Distance (6MWD) and echocardiogram. A re-evaluation of right heart catheterisation was only performed if clinical worsening occurred. Follow-up was conducted indefinitely for alive patients or until death.

The data collected included demographic characteristics (age, gender), parameters related to both HIV infection and PAH and disease follow-up. The date of PAH diagnosis was used as the baseline for survival estimates.

Because patients had already consented to be included in the PAH national registry, no additional informed consent was needed for this sub-study.

Statistical analysis

Standard descriptive statistics were used. Variables such as New York heart association (NYHA) functional class and 6MWD were compared using the paired-sample *t*-test. Due to the small population size, univariate analysis was not possible.

All statistical tests were performed using SPSS for Windows (version 16.0: SPSS, Chicago, IL, United States).

Case No.	Age, yr	Gender	HIV risk factor	Duration of HIV infection previous to PAH, yr	CD4 count, cells/μL	HIV viral load, copies/mL	CDC stage	HAART	History of viral hepatitis	Other PAH risk factors	NYHA FC
Table 1 Patients' demographic and clinical characteristics at pulmonary hypertension diagnosis											
1	25	F	IVDU	12	339	< 50	B3	No	Hep C	None	IV
2	39	F	IVDU	4	700	< 50	A1	No	Hep B + C	None	II
3	39	M	IVDU	11	460	< 50	B3	Yes	No	ASD	III
4	32	M	IVDU	12	500	< 50	B2	No	Hep C	ASD	III
5	43	M	UK	7	397	< 50	B3	Yes	No	Splenectomy without CTEPH	III
6	45	M	IVDU	8	332	< 50	B3	Yes	Hep B+C	Portal Hypertension	II
7	40	F	IVDU	22	517	< 50	C3	UK	Hep C	None	II
8	31	F	Hetero-sexual	1	444	< 50	A2	Yes	No	None	III
9	40	M	IVDU	22	900	3000	A1	No	Hep C	None	II
10	41	M	IVDU	21	772	308	A2	No	Hep C	None	II
11	40	M	IVDU	10	460	359810	A1	Yes	Hep C	Portal Hypertension	III
12	40	F	UK	5	46	114	C3	No	Hep C	Portal Hypertension	III
13	39	M	IVDU	10	1234	< 50	B1	Yes	Hep C	None	III
14	46	M	IVDU	14	411	< 50	A2	Yes	Hep C	Portal Hypertension	II
15	47	F	IVDU	14	800	< 50	A1	No	Hep C	ASD	III
16	47	M	IVDU	4	450	< 20	A2	Yes	Hep C	None	II
17	47	F	IVDU	23	760	< 20	C2	No	Hep B + C	Portal Hypertension	II
18	43	M	UK	19	NA	NA	A2	No	No	Portal Hypertension	III

ASD: Atrial septal defect; CDC: Centers for disease control; CTEPH: Chronic thromboembolic pulmonary hypertension; F: Female; M: Male; HAART: Highly active anti-retroviral therapy; HIV: Human immunodeficiency virus; IVDU: Intravenous drug use; NA: Not accessible; NYHA FC: New York heart association functional class; PAH: Pulmonary arterial hypertension; UK: Unknown.

RESULTS

Eighteen patients were admitted to our centre during the study period, and their baseline characteristics are listed in Table 1. Male gender was predominant (61.1%), and the mean age was 40.2 years (range 25-47 years).

Concerning HIV infection, intravenous drug use was the major risk factor for infection (77.8%). At PAH diagnosis, only 16.7% were in Centers for Disease Control and Prevention stage C. The mean CD4 cell count was 554 ± 267 cells/μL, with only one patient having a CD4 cell count < 200 cells/μL. The viral load was undetectable in 76.5% of the patients.

The mean time interval between HIV infection diagnosis and PAH diagnosis was 12.2 ± 6.9 years (range 1-23 years). Approximately half of the patients were on HAART; among those who were not on HAART, only three patients had an indication for HIV treatment before the diagnosis of PAH (one was not under treatment at all due to poor adherence, and the other two took only two drugs: a non-nucleoside reverse transcriptase inhibitor and a protease inhibitor). There is a statistically significant acceleration in the onset of PAH in patients on HAART (P = 0.012).

Concomitant viral hepatitis (either C or C and B) was present in 77.8% of the patients. In 55.5% of the patients, other risk factors for PAH were identified (Table 1), including portopulmonary hypertension, splenec-

tomy and congenital heart defects. An atrial septal defect (ASD) was present in three patients: two patients had the ostium secundum type with a bidirectional shunt and a diameter of 1.8 and 0.7 cm, and the other patient had Eisenmenger's syndrome due to a sinus venosus type ASD with a 3.0 cm diameter. At PAH diagnosis, 55.6% of the patients were in the NYHA functional classes III-IV. Shortness of breath was the most prevalent symptom (present in all patients), followed by chest pain (27.8%), syncope (22.2%) and peripheral oedema and ascites (5.6%).

Exercise capacity was assessed by the 6MWD (Table 2), with a mean achieved distance of 436 ± 113 m. All but one patient walked 300 m or more at diagnosis. There was an overall improvement in the test, but no significant difference was found among the patients with or without HAART (P = 0.401).

Hemodynamic parameters, as assessed by right heart catheterisation, showed a mean pulmonary artery pressure (mPAP) of 52.6 ± 12.2 mmHg (17.6% of patients had a mPAP between 35-40 mmHg, 23.5% were between 41-45 mmHg and 58.8% were > 45 mmHg), a RAP of 6.1 ± 3.8 mmHg (none of the patients were > 15 mmHg) and a cardiac output of 4.6 ± 1.4 mL/min (11.7% of the patients with a cardiac output ≤ 2.0 mL/min).

The mean follow-up period was 5.8 ± 4.2 years, with a minimum of 0.3 and a maximum of 11.8 years (Table 2). Overall, the patients had an improved NYHA functional class, with a reduction of approximately half a functional

Case No.	Actual status	Period of follow-up, yr	Year of PAH diagnosis	Initial specific therapy	Last visit specific therapy	Initial 6MWT (m)	Final 6MWT (m)	Variation on NYHA FC
Table 2	Patients' follow-up data							
1	Dead (cause: heart failure)	2.8	1998	Epoprostenol	Epoprostenol	211	463	0
2	Alive	11.3	2001	Treprostinil	Sildenafil	NA	669	-1
3	Alive	10.8	2001	Sildenafil	Sildenafil + Ambrisentan	512	630	-1
4	Alive	9.9	2002	Sildenafil	Sildenafil + Ambrisentan + Iloprost	516	570	-2
5	Alive	11.3	2001	Treprostinil	Sildenafil	313	414	0
6	Dead (cause: liver disease)	0.3	2005	Sildenafil	Sildenafil	400	NA	NA
7	Alive	7.0	2005	Ambrisentan	Ambrisentan + Sildenafil	435	473	0
8	Missing	3.9	2006	Sildenafil	Sildenafil	300	511	-2
9	Alive	5.3	2006	Sildenafil	Sildenafil	455	546	0
10	Alive	4.5	2007	Sildenafil	Tadalafil	650	703	0
11	Alive	8.5	2003	Treprostinil	Tadalafil	510	570	-2
12	Alive	8.8	2003	Iloprost	Ambrisentan	NA	450	-1
13	Alive	11.8	2000	Treprostinil	Bosentan	327	489	-1
14	Missing	0.4	2005	Sildenafil	Sildenafil	500	NA	0
15	Alive	3.5	2008	Sildenafil + Bosentan	Sildenafil + Bosentan + Iloprost	350	420	0
16	Alive	1.6	2010	Tadalafil	Tadalafil	525	570	0
17	Alive	1.4	2011	Ambrisentan	Ambrisentan	439	423	0
18	Alive	0.5	2011	Sildenafil	Sildenafil	537	600	0

6MWT: 6 min walk test; NYHA FC: New York heart association functional class; NA: Not accessible; PAH: Pulmonary arterial hypertension.

class per patient ($P = 0.008$) and an improvement of 85 m on the 6MWD ($P = 0.002$). Functional class improvement was not dependent on HAART therapy ($P = 0.343$).

At PAH diagnosis, six (33.3%) patients were started on prostacyclin analogues. One patient was started on epoprostenol but died due to right heart failure. Recurrent infections of the Hickman catheter, which the patient used for drug abuse, might have played a role. At the last registered visit, the other five patients had clinically improved and reduced the specific therapy to oral drugs, such as phosphodiesterase-5 inhibitors and endothelin receptor antagonist (Table 2).

All but one of the remaining patients were started on specific oral monotherapy. On their most recent follow-up, these patients were on the same therapy, except for four patients who needed other specific drugs (two were started on dual combined therapy, and the other two were started on triple combined therapy). An improvement in NYHA functional class and 6MWD was observed in half and all of these patients, respectively. Specific oral therapy was well tolerated in all patients, without any major documented adverse reactions, except elevated liver enzymes in one patient on sildenafil, in whom the specific therapy was changed to tadalafil.

Concerning survival during the follow-up period, two patients died (11.1%), but only one death was related to PAH (right heart failure); this patient had one of the lowest CD4 cell counts (339 cells/μL). The other, as already discussed, had the worst NYHA functional class at PAH diagnosis; this death was related to chronic liver disease, and the patient died soon after PAH diagnosis. Two patients were lost to follow-up (Table 2). At 1, 2 and

3 years, the survival rates were 93.8%, 92.9% and 85.7%, respectively.

DISCUSSION

This study reports data on 18 HIV-infected patients diagnosed with PAH. HIV-infected patients are at a higher risk of developing PAH compared with the general population. Nevertheless, the global prevalence of this disease is low, and HIV-infected patients are rarely included in clinical trials because of the risk of interaction between PAH therapies and anti-retrovirals and the presence of multiple comorbidities in HIV-infected patients. Therefore, case reports and case series have become crucial to determine the characteristics of the disease and the efficacy of therapy. Despite our small number of patients, a major contribution with regard to survival rates and specific therapy can be made. In our study group, male gender was predominant, which is concordant with other authors and may reflect the high prevalence of men in the HIV population[10-12]. However, in a recent cross-sectional study of 802 HIV-infected patients, 14 patients had symptomatic PAH, and women were more affected, with a male: female ratio of 1:1.4[8]. Age at diagnosis did not differ from other studies that have reported a mean age ranging from 32 to 43 years[6,10-14].

Intravenous drug use was the most prevalent risk factor among HIV-infected patients with PAH (77.8% of the patients). This high prevalence was also described in other studies[10,12,13,15]. Nonetheless, patients with PAH related to HIV infection acquired *via* intravenous drug abuse have no clinical, functional or hemodynamic speci-

ficities, compared with patients with PAH related to HIV infection from any other route of transmission[15].

The mean CD4 count at the time of PAH diagnosis was somewhat higher than those observed in other studies, with only one patient (5.8%) having a CD4 cell count < 200 cells/μL; the viral load was undetectable in the majority of patients. A CD4 cell count < 200 cells/μL was observed in 59.6% and 52% of patients in the studies of Zuber *et al*[12] and Nunes *et al*[15], respectively. This difference may reflect the efficacy of the actual antiretroviral therapy. Hence, HIV-related PAH occurs in the early and late stages of HIV infection and may not be related to viral load or immune status, partially demonstrating that HAART does not prevent PAH[6,8,15].

The median time interval between the diagnoses of HIV disease and PAH, as described in literature, has ranged from 2.8 to 7.7 years[6,10-12,15], which is much shorter than the time interval determined in our study (11.5 years). Degano *et al*[13] also described a more prolonged time interval (11 years), suggesting that HAART does not prevent but may delay the development of PAH in HIV-infected patients. However, in our study, HAART was found to accelerate the onset of PAH, and this finding has been corroborated by Reinsch *et al*[8] and Pellicelli *et al*[16]. This may be due to a closer monitoring of patients on HAART, enabling an earlier PAH diagnosis.

In our population, 55.5% of the patients had another PAH risk factor other than HIV infection, including atrial septal defect, splenectomy and portal hypertension, which differs from the results of other papers. In the study by Humbert *et al*[17], approximately 4% of PAH patients presented with two co-existing risk factors, mainly HIV infection with portal hypertension. Mesa *et al*[18] reported that 13% of the HIV-related PAH patients had coexistent liver disease. Other causes of PAH and chronic thromboembolic pulmonary hypertension were not reported in our patients and have been rarely reported in HIV-infected patients[19].

The majority of the patients in our study were in a high NYHA functional class, which is consistent with other authors who have reported 71%-81% of patients in the NYHA classes Ⅲ-Ⅳ at diagnosis[15,17].

The survival rates were far better than those described in the literature. During the follow-up period of 5.8 ± 4.2 years, 12.5% patients died, and the survival rates at one, two and three years was 93.8%, 92.9% and 85.7%, respectively. In the study by Degano *et al*[13], the survival rates were closely related to our findings: 88%, 84%, 72% and 63% at one, two, three and five years, respectively, but others have reported lower survival rates[14,15,20]. Mortality in patients with HIV-related PAH is usually due to right heart failure, rather than other complications of HIV infection, and PAH is considered an independent predictor of death in HIV-infected patients[10,15]. This finding may relate to the fact that most of these individuals present in the later stages of PAH. In our study, the patient who died due to right heart failure had the worst NYHA functional class and showed no functional or hemodynamic improvement despite aggressive therapy.

Apart from the effect on PAH development, HAART has been described to influence prognosis. In our population, the improvement in NYHA functional class did not differ between the groups, nor did exercise capacity, as measured by 6MWD. Concerning mortality, the patient who died due to right heart failure was not on HAART; the other patient who died was on HAART, but the cause of death was liver failure. HAART has been associated with an improvement in exercise capacity, NYHA functional class, right ventricular systolic pressure over right atrial pressure gradient and overall survival[11-14,21,22]. However, there is also contradictory data stating that patients without HAART have no reduction in survival[23]. No current trial has been designed to evaluate the effect of HAART on the progression of HIV-PAH, but due to the weight of scientific information favouring HAART, patients with HIV-related PAH should be treated with HAART, irrespective of their CD4 cell counts[14]. This suggestion is also supported by our study.

An analysis of the cases of HIV-related PAH reported in the literature (from January 1987 to January 2009) showed a better outcome in patients treated with PAH-specific therapy than in those treated with just antiretroviral therapy[24]. Regardless of the substantial progress in therapy over the last few years, no randomised study has established a drug of choice for the treatment of HIV-related PAH. The evidence for the use of bosentan and prostaglandin therapies comes from cohort studies, case-control studies or case series. Therefore, the treatment of HIV-related PAH relies on PAH-specific therapy and includes supportive treatments and disease-specific treatments.

In our population, six of the 18 patients were started on prostacyclin analogues. These were patients with worse functional status who were diagnosed between 1998 and 2003, when prostacyclin analogues were the only recommended specific therapy for PAH. Only one of these patients was on epoprostenol due to advanced disease. The other patients were started on either iloprost or treprostinil. The beneficial effects of this drug class have been demonstrated in patients with HIV-related PAH. Our patients on iloprost and treprostinil have shown an improvement in NYHA functional class, and treatment was de-escalated to oral drugs. De-escalation to specific oral therapy can be attempted in stable patients with good long-term progress. Favourable results have been noted when switching from prostacyclin and its analogues to bosentan, with the clinical stability and pulmonary pressure measurements being maintained[25]. Similarly, transitioning from subcutaneous treprostinil to sildenafil was safely demonstrated in patients with PAH of varied aetiologies[26].

Sildenafil was the most commonly used drug among our patients (61.1%), though tadalafil was also used (16.6%). In the majority of patients, the clinical results were satisfactory. However, the experience with phosphodiesterase-5 inhibitors in HIV-related PAH is preliminary, and no controlled studies exist. Beneficial effects derived

from case studies have been reported, including improvements in dyspnoea, NYHA functional class, exercise capacity and mPAP[27-29]. However, because sildenafil is largely metabolised by cytochrome P450 3A4, there is a potential for drug interactions when it is co-administered with several antiretroviral therapies, particularly protease inhibitors. Therefore, sildenafil is rarely used. In a review of 154 case reports by Janda *et al*[11], phosphodiesterase-5 inhibitors were the least commonly used therapy and were only an option for patients who did not tolerate bosentan. Our study reinforces the benefits of sildenafil HIV-related PAH therapy, and few adverse events were reported.

This study has some limitations. This is a retrospective study conducted in a single centre, with possible biases. However, it would be ethically impossible to perform a prospective study designed to compare novel therapies such as prostacyclin analogues with less active treatments in a cohort of patients with HIV-related PAH. Because HIV-related PAH is a rare disease, few patients were included in this study, thus any analyses should be considered cautiously.

To summarise, this study adds important information to what has been reported in the literature. Survival rates of HIV-related PAH patients tend to be higher, which may be due to new aggressive specific therapies, such as prostanoids, but not to HAART. The majority of the patients were treated with specific oral therapy, even those primarily treated with prostacyclin analogues.

The onset and rapid progression of shortness of breath and other cardiopulmonary symptoms in HIV-infected individuals should suggest HIV-related PAH. A systematic cardiopulmonary evaluation and follow-up in specialised centres should be incorporated into the clinical management of HIV-infected patients to enhance quality of life, exercise capacity and survival through the delivery of HAART and specific therapy.

COMMENTS

Background
Pulmonary arterial hypertension (PAH) is a progressive disease that is caused by the chronic obstruction of small pulmonary arteries, leading to right ventricular failure and potential death. Idiopathic and inherited forms have been described.

Research frontiers
After the introduction of this novel antiretroviral therapy scheme, long-term cardiovascular complications, such as PAH, have emerged. The first case of human immunodeficiency virus (HIV)-related PAH was described in 1987 in an HIV-infected subject with haemophilia and membranoproliferative glomerulonephritis. Subsequently, several other cases have been reported. Nonetheless, HIV-related PAH is a rare disease: in 1991, prior to the introduction of highly active antiretroviral therapy (HAART), the prevalence of HIV-related PAH was estimated to be 0.5% in developed countries. This rate is 25-fold higher than the prevalence of PAH in the general population.

Innovations and breakthroughs
Recent studies have shown that prevalence has not changed in recent years. This study was designed to present 18 new cases of HIV-related PAH with presenting features, treatment options and follow-up data.

Applications
In this series, the survival rates of HIV-related PAH patients tended to be higher,

but this difference was not related to HAART. The majority of patients were treated with specific oral therapy, even in those who were primarily treated with prostacyclin analogues. The onset and rapid progression of shortness of breath and other cardiopulmonary symptoms in HIV-infected individuals can suggest HIV-related PAH, and its prompt identification and treatment can improve quality of life, exercise capacity and survival.

Term explanation
HAART: the use of multiple drugs that act on different viral targets to decrease the patient's total burden of HIV, to maintain the immune system's function and to prevent opportunistic infections. Prostacyclin analogues (epoprostenol, iloprost and treprostinil): drugs used in pulmonary arterial hypertension that reduce pulmonary pressure and improve right ventricular stroke work.

Peer review
This is an excellent review of 18 cases about PAH related to HIV infection. The authors have stated the differences with previous studies, including the time interval between the HIV and PAH diagnoses, PAH risk factors other than HIV infection, HAART, specific therapy and survival rates.

REFERENCES

1   **Chin KM**, Rubin LJ. Pulmonary arterial hypertension. *J Am Coll Cardiol* 2008; **51**: 1527-1538 [PMID: 18420094 DOI: 10.1016/j.jacc.2008.01.024]

2   **Task Force for Diagnosis and Treatment of Pulmonary Hypertension of European Society of Cardiology (ESC)**; European Respiratory Society (ERS); International Society of Heart and Lung Transplantation (ISHLT), Galiè N, Hoeper MM, Humbert M, Torbicki A, Vachiery JL, Barbera JA, Beghetti M, Corris P, Gaine S, Gibbs JS, Gomez-Sanchez MA, Jondeau G, Klepetko W, Opitz C, Peacock A, Rubin L, Zellweger M, Simonneau G. Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Respir J* 2009; **34**: 1219-1263 [PMID: 19749199 DOI: 10.1183/09031936.00139009]

3   **Cicalini S**, Chinello P, Petrosillo N. HIV infection and pulmonary arterial hypertension. *Expert Rev Respir Med* 2011; **5**: 257-266 [PMID: 21510735 DOI: 10.1586/ers.11.10]

4   **Kim KK**, Factor SM. Membranoproliferative glomerulonephritis and plexogenic pulmonary arteriopathy in a homosexual man with acquired immunodeficiency syndrome. *Hum Pathol* 1987; **18**: 1293-1296 [PMID: 3679202 DOI: 10.1016/S0046-8177(87)80417-3]

5   **Speich R**, Jenni R, Opravil M, Pfab M, Russi EW. Primary pulmonary hypertension in HIV infection. *Chest* 1991; **100**: 1268-1271 [PMID: 1935280 DOI: 10.1378/chest.100.5.1268]

6   **Petitpretz P**, Brenot F, Azarian R, Parent F, Rain B, Herve P, Simonneau G. Pulmonary hypertension in patients with human immunodeficiency virus infection. Comparison with primary pulmonary hypertension. *Circulation* 1994; **89**: 2722-2727 [PMID: 8205687 DOI: 10.1161/01.CIR.89.6.2722]

7   **Sitbon O**, Lascoux-Combe C, Delfraissy JF, Yeni PG, Raffi F, De Zuttere D, Gressin V, Clerson P, Sereni D, Simonneau G. Prevalence of HIV-related pulmonary arterial hypertension in the current antiretroviral therapy era. *Am J Respir Crit Care Med* 2008; **177**: 108-113 [PMID: 17932378 DOI: 10.1164/rccm.200704-541OC]

8   **Reinsch N**, Buhr C, Krings P, Kaelsch H, Kahlert P, Konorza T, Neumann T, Erbel R. Effect of gender and highly active antiretroviral therapy on HIV-related pulmonary arterial hypertension: results of the HIV-HEART Study. *HIV Med* 2008; **9**: 550-556 [PMID: 18557952 DOI: 10.1111/j.1468-1293.2008.00602.x]

9   **Khan MG**, Lynch JP III. Pulmonary Disease Diagnosis and Therapy: A Practical Approach. Lippincott Williams and Wilkins, 1997

10 **Mehta NJ**, Khan IA, Mehta RN, Sepkowitz DA. HIV-Related pulmonary hypertension: analytic review of 131 cases. *Chest* 2000; **118**: 1133-1141 [PMID: 11035689 DOI: 10.1378/chest.118.4.1133]

11   **Janda S**, Quon BS, Swiston J. HIV and pulmonary arterial hypertension: a systematic review. *HIV Med* 2010; **11**: 620-634 [PMID: 20408888 DOI: 10.1111/j.1468-1293.2010.00829.x]

12   **Zuber JP**, Calmy A, Evison JM, Hasse B, Schiffer V, Wagels T, Nuesch R, Magenta L, Ledergerber B, Jenni R, Speich R, Opravil M. Pulmonary arterial hypertension related to HIV infection: improved hemodynamics and survival associated with antiretroviral therapy. *Clin Infect Dis* 2004; **38**: 1178-1185 [PMID: 15095226 DOI: 10.1086/383037]

13   **Degano B**, Guillaume M, Savale L, Montani D, Jaïs X, Yaici A, Le Pavec J, Humbert M, Simonneau G, Sitbon O. HIV-associated pulmonary arterial hypertension: survival and prognostic factors in the modern therapeutic era. *AIDS* 2010; **24**: 67-75 [PMID: 19770696 DOI: 10.1097/QAD.0b013e328331c65e]

14   **Opravil M**, Pechère M, Speich R, Joller-Jemelka HI, Jenni R, Russi EW, Hirschel B, Lüthy R. HIV-associated primary pulmonary hypertension. A case control study. Swiss HIV Cohort Study. *Am J Respir Crit Care Med* 1997; **155**: 990-995 [PMID: 9117037 DOI: 10.1164/ajrccm.155.3.9117037]

15   **Nunes H**, Humbert M, Sitbon O, Morse JH, Deng Z, Knowles JA, Le Gall C, Parent F, Garcia G, Hervé P, Barst RJ, Simonneau G. Prognostic factors for survival in human immunodeficiency virus-associated pulmonary arterial hypertension. *Am J Respir Crit Care Med* 2003; **167**: 1433-1439 [PMID: 12615632 DOI: 10.1164/rccm.200204-330OC]

16   **Pellicelli AM**, Palmieri F, D'Ambrosio C, Rianda A, Boumis E, Girardi E, Antonucci G, D'Amato C, Borgia MC. Role of human immunodeficiency virus in primary pulmonary hypertension--case reports. *Angiology* 1998; **49**: 1005-1011 [PMID: 9855375 DOI: 10.1177/000331979804901206]

17   **Humbert M**, Sitbon O, Chaouat A, Bertocchi M, Habib G, Gressin V, Yaici A, Weitzenblum E, Cordier JF, Chabot F, Dromer C, Pison C, Reynaud-Gaubert M, Haloun A, Laurent M, Hachulla E, Simonneau G. Pulmonary arterial hypertension in France: results from a national registry. *Am J Respir Crit Care Med* 2006; **173**: 1023-1030 [PMID: 16456139 DOI: 10.1164/rccm.200510-1668OC]

18   **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 [PMID: 9443676 DOI: 10.1016/S0025-6196(11)63616-1]

19   **Heron E**, Laaban JP, Capron F, Quieffin J, Brechot JM, Rochemaure J. Thrombotic primary pulmonary hypertension in an HIV+ patient. *Eur Heart J* 1994; **15**: 394-396 [PMID: 8013515]

20   **Opravil M**, Sereni D. Natural history of HIV-associated pulmonary arterial hypertension: trends in the HAART era. *AIDS* 2008; **22** Suppl 3: S35-S40 [PMID: 18845920 DOI: 10.1097/01.aids.0000327514.60879.47]

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**: 1164-1166 [PMID: 16844879 DOI: 10.1136/hrt.2005.076794]

22   **Speich R**, Jenni R, Opravil M, Jaccard R. Regression of HIV-associated pulmonary arterial hypertension and long-term survival during antiretroviral therapy. *Swiss Med Wkly* 2001; **131**: 663-665 [PMID: 11835116]

23   **Zinkernagel AS**, von Overbeck J, Opravil M, Jenni R, Speich R, Mueller NJ. Long-term survival and interruption of HAART in HIV-related pulmonary hypertension. *Eur J Clin Microbiol Infect Dis* 2005; **24**: 153-155 [PMID: 15711784 DOI: 10.1007/s10096-005-1289-7]

24   **Cicalini S**, Chinello P, Grilli E, Petrosillo N. Treatment and outcome of pulmonary arterial hypertension in HIV-infected patients: a review of the literature. *Curr HIV Res* 2009; **7**: 589-596 [PMID: 19929793 DOI: 10.2174/157016209789973583]

25   **Flox Camacho A**, Escribano Subías P, Tello de Meneses R, Delgado Jiménez J, Gómez Sánchez MA, Sáenz de la Calzada C. [Transition from prostacyclin to bosentan in five patients with severe pulmonary hypertension: the switch is possible]. *Rev Esp Cardiol* 2006; **59**: 737-739 [PMID: 16938217 DOI: 10.1157/13091376]

26   **Keogh AM**, Jabbour A, Weintraub R, Brown K, Hayward CS, Macdonald PS. Safety and efficacy of transition from subcutaneous treprostinil to oral sildenafil in patients with pulmonary arterial hypertension. *J Heart Lung Transplant* 2007; **26**: 1079-1083 [PMID: 18022071 DOI: 10.1016/j.healun.2007.07.040]

27   **Schumacher YO**, Zdebik A, Huonker M, Kreisel W. Sildenafil in HIV-related pulmonary hypertension. *AIDS* 2001; **15**: 1747-1748 [PMID: 11546958 DOI: 10.1097/00002030-200109070-00026]

28   **Carlsen J**, Kjeldsen K, Gerstoft J. Sildenafil as a successful treatment of otherwise fatal HIV-related pulmonary hypertension. *AIDS* 2002; **16**: 1568-1569 [PMID: 12131202 DOI: 10.1097/00002030-200207260-00021]

29   **Alp S**, Schlottmann R, Bauer TT, Schmidt WE, Bastian A. Long-time survival with HIV-related pulmonary arterial hypertension: a case report. *AIDS* 2003; **17**: 1714-1715 [PMID: 12853763 DOI: 10.1097/00002030-200307250-00025]

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