Pulmonary hypertension and human immunodeficiency virus infection: epidemiology, pathogenesis, and clinical approach

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Abstract

In recent years, the pathogenic role of human immunodeficiency virus (HIV) and the clinical manifestations of HIV-associated pulmonary arterial hypertension (HIV-PAH), which currently represents one of the most severe complications of HIV infection, have received more attention. HIV-PAH occurs at all stages of the disease, and does not seem to be related to the degree of immune deficiency. Many of the symptoms in HIV-PAH result from right ventricular dysfunction: the first clinical manifestation is effort intolerance and exertional dyspnoea that will progress to the point of breathlessness at rest. Echocardiography is an extremely useful tool for the diagnosis of HIV-PAH, and Doppler echocardiography can be used to estimate systolic pulmonary artery pressure. Assessment of haemodynamic measures by catheterization remains, however, the best test for evaluating the response to therapy. Cardiac catheterization is mandatory to definitively diagnose the disease and exclude any underlying cardiac shunt as the aetiology. Recently, effective therapies for pulmonary arterial hypertension (PAH) have been available, including prostanoids, endothelin receptor antagonists, and phosphodiesterase-5 inhibitors, allowing amelioration of symptoms and a better prognosis. However, HIV-PAH remains a progressive disease for which treatment is often unsatisfactory and there is no cure. As new efficient antiretroviral treatment is introduced, clinicians should expect to encounter an increasing number of cases of PAH in HIV-infected patients in the future.

Keywords: Clinical, HIV proteins, human immunodeficiency virus, pathogenesis, pulmonary hypertension, review, treatment

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Introduction

Although the introduction of highly active antiretroviral therapy (HAART) 15 years ago transformed human immunodeficiency virus (HIV) infection into a chronic infectious disease, HIV remains an intractable pathogen at the clinical and basic science levels worldwide.

While the search for a cure continues, long-term cardiovascular complications of HIV infection have now become significant contributors to morbidity and mortality. Pulmonary arterial hypertension (PAH) was probably undetected before the advent of HAART, because patients succumbed to immunodeficiency and opportunistic infections. PAH results from chronic obstruction of small pulmonary arteries, leading to right ventricular failure, and death. HIV infection is one established risk factor for PAH [1–3].

The first case of PAH in an HIV-infected subject was described in 1987 [4]. Recently, more attention has been paid to the pathogenic role of HIV and the clinical manifestations of HIV-associated PAH (HIV-PAH) [5–7], one of the most severe complications of HIV disease.

Epidemiology of PAH in HIV-infected Patients

In 1991, the prevalence of HIV-PAH in developed countries was estimated to be 0.5% [8]; this prevalence remains the same [5,6,9,10] regardless of HAART.
However, the actual prevalence of HIV-PAH could be higher, as most published studies evaluating HIV-PAH are not able to include the asymptomatic patients [11].

Furthermore, the epidemiology of HIV-PAH could be different in developing countries. For example, in an echocardiographic study conducted in Burkina Faso (West Africa), the prevalence of pulmonary hypertension (PH) was found to be 5% [12].

Nevertheless, data from the Swiss HIV Cohort Study showed that the incidence of newly diagnosed cases of PAH in HIV-infected patients decreased from 0.24% in 1993 to 0.03% in 2006 [5,9]. This decrease was related to changes in modes of HIV infection transmission, HAART-induced increases in CD4 cell counts, and a decrease in immune activation [5].

The average age of HIV-PAH patients is 33 years [13]. The male/female ratio is about 1.5 : 1 [3,13–15]. This ratio is different from that of uninfected patients with idiopathic PAH, in whom the female/male ratio is 1.7 : 1. This finding may reflect the higher frequency of HIV infection among male patients. More recently, however, a slightly marked female predominance in HIV-PAH patients has been suggested [11].

HIV-PAH occurs at all stages of HIV infection, and does not seem to be related to the immune deficiency [14]. No specific risk factors for HIV infection are associated with this disease, although HIV-PAH is more frequent in intravenous drug users, who represented 59% of cases of HIV-PAH in a French cohort study [15]. However, patients with HIV-PAH acquired via intravenous drug use have no clinical, functional or haemodynamic differences from patients with HIV-PAH acquired via another transmission route [7]. The role of intravenous drug use as an independent risk factor for PAH was recently ruled out [2]. The presence of PAH is an independent risk factor for mortality in patients with HIV infection, and, in most cases, death is causally related to PAH rather than to other complications of HIV infection [14,15].

In a study by Opravil et al. [1], the median survival of HIV-PAH patients was significantly lower than that of HIV-infected patients without PAH (1.3 vs. 2.6 years, respectively; p <0.05). These data reflect the independent contribution of PAH to mortality in HIV-infected patients, because only a small proportion of patients were treated with antiretrovirals (zidovudine or didanosine only) and no patients received PAH-specific therapy.

Data on the characteristics and outcomes of patients with PAH-HIV in the current era of HAART and specific PAH therapies are scanty. In the Swiss HIV Cohort Study, the median survival period for 66 patients with HIV-PAH (43 of 66 patients on HAART) was 3.6 years, with 84% surviving to 1 year [5]. The prognosis is particularly poor for patients in NYHA functional class III–IV, with a 3-year survival rate of only 28% [15]. A recent study of 77 HIV-PAH patients from the French Reference Centre for PAH (most patients on HAART at PAH diagnosis and 50 of 77 patients on PAH-specific therapy) showed overall survival rates of 88% and 72% at 1 and 3 years, respectively [7]. A cardiac index of >2.8 L/min per m² and a CD4 T-lymphocyte count of >200 cell/mm³ were the only independent predictors of increased survival [7].

**Clinical Presentation**

Most symptoms of HIV-PAH result from right ventricular dysfunction. As the predominant symptom is progressive shortness of breath, which can be present in many other clinical manifestations, the disease is typically diagnosed late in its course, when the clinical and laboratory findings of severe PH are generally present.

In a review of 131 cases of HIV-PAH, Mehta et al. [13] found that progressive shortness of breath was the most common presenting symptom (85% of cases), followed by pedal oedema (30%), non-productive cough (19%), fatigue (13%), syncope or near syncope (12%), and chest pain (7%).

Usually, about 6 months elapse between the onset of symptoms and the diagnosis of HIV-PAH [13]. This period is shorter than that seen in idiopathic PAH, in which this period is, on average, 2.5 years [15]. One likely explanation for this difference is the fact that HIV-infected patients are more closely followed up, starting soon after initial HIV diagnosis. However, a more aggressive type of PAH in HIV-infected patients could not be ruled out.

**Diagnosis**

The diagnosis of PAH in HIV-infected patients requires a sequential approach that, in practice, includes four steps: the clinical suspicion of PH, the detection of PH, the exclusion of other possible causes of PH, and the PAH evaluation (Fig. 1).

**Clinical suspicion of PH**

The clinical suspicion of PH should arise in any case of breathlessness without overt signs of heart-specific or lung-specific disease in patients with underlying cardiopulmonary disease whenever there is increasing dyspnoea unexplained by the underlying disease itself.

The physical examination may reveal increased intensity of pulmonic second heart sound (P₂), with P₂ louder than aortic
second heart sound, right-sided third and fourth heart sound gallop, murmurs of tricuspid and pulmonic regurgitation, increased jugular venous pressure, and peripheral oedema [13], and may also provide clues as to the cause of PH (e.g. the stigmata of liver disease, such as spider naevi and palmar erythema, in liver cirrhosis and portal hypertension).

**Detection of PH**

The detection of PH requires investigations that are able to confirm the diagnosis of PH, and includes the electrocardiogram, chest X-ray, and transthoracic Doppler echocardiography.

The ECG usually reveals right axis deviation, right ventricular hypertrophy, and right atrial abnormalities [13]. Complete and incomplete right bundle branch block may be present.

As electrocardiography has insufficient sensitivity (55%) and specificity (70%) [16], it should be not considered to be a screening tool for the detection of significant PH. Indeed, a normal electrocardiogram does not exclude the presence of severe PH.

Chest X-ray generally shows enlarged central pulmonary arteries and clear lung fields. Moreover, it helps to exclude some causes of PH, such as chronic obstructive pulmonary diseases and interstitial lung diseases. However, chest X-ray cannot detect early changes in pulmonary arteries.

Transthoracic Doppler echocardiography is an extremely useful tool for the diagnosis of HIV-PAH [16]; moreover, it is extremely helpful in ruling out congenital, valvular and myocardial disease.

The most frequent echocardiographic features are systolic flattening of the interventricular septum, enlargement of both the right atrium and ventricle, and a reduction in both left ventricular systolic and diastolic dimensions. Pericardial effusion and patent foramen ovale are also frequently detected [13].

Doppler echocardiography may be used to estimate systolic pulmonary arterial pressure (PAP) on the basis of the peak velocity of the tricuspid valve regurgitant jet [16]. However, the false-positive rate from Doppler echocardiography for PAH diagnosis in HIV-infected patients has been recently reported to be as high as 72% [6].

**Exclusion of other causes of PH**

The next step to the diagnosis of HIV-PAH is the exclusion of other possible causes of PH, as shown in Fig. 1.

**PAH evaluation**

Assessment of haemodynamic measures by right heart catheterization remains the reference standard for diagnosing HIV-PAH, as well as for assessing its severity and response to therapy. PAH is defined by a mean PAP (mPAP) ≥25 mmHg with a mean pulmonary capillary wedge pressure ≤15 mmHg, and a normal or reduced cardiac output [16].

Acute vasodilator testing is an important component of the haemodynamic assessment, as the response to acute...
challenge with vasodilators (e.g. inhaled nitric oxide or intravenous epoprostenol or adenosine) is predictive of the long-term response to oral therapy with calcium channel blockers (CCBs).

A positive response is defined as decrease of ≥10 mmHg in mPAP, to reach an absolute mPAP value of ≤40 mmHg, with either unchanged or increased cardiac output [16]. In HIV-PAH, however, acute vasodilator testing rarely has a positive response [17].

Exercise tolerance in PAH is commonly assessed by means of the 6-minute walking distance (6MWD). Although the test is not sufficiently validated in HIV-PAH, it is predictive of survival in idiopathic PAH, and correlates inversely with NYHA functional status severity [16]. Moreover, it represents an entry criterion and primary endpoint of many clinical trials of therapeutic agents for PAH [16].

**Treatment**

Guidelines are not currently available for PAH therapy in HIV-PAH, and no study has yet established a single agent of choice for the treatment of HIV-PAH. Therefore, treatment of HIV-PAH relies on PAH-specific therapy, and includes supportive treatments and disease-specific treatments.

The therapeutic options for HIV-PAH are not well established in comparison with other forms of PAH [16], and there are still conflicting data on the role of HAART in the management of patients with HIV-PAH.

**Supportive therapy**

Supportive therapy includes oxygen administration, diuretics, digoxin and oral anticoagulants. Supplemental oxygen therapy may benefit patients who are hypoxic. Most experts recommend oxygen supplementation when arterial blood oxygen pressure is consistently ≤60 mmHg [16].

Patients with overt right ventricular failure should be treated with diuretics, which reduce right ventricular pre-load [16]. Digoxin has been shown to improve cardiac output acutely in patients with right ventricular dysfunction attributable to PH [18]. However, the role of cardiac glycosides in treating isolated right heart dysfunction is controversial. These agents are most useful in cor pulmonale, when left ventricular failure is also present. However, as neurohormonal sympathetic activation has been demonstrated in PH, digoxin may be of value because of its sympatholytic properties [19].

Most experts recommend long-term anticoagulant therapy with warfarin in patients with PAH. The rationale for anticoagulant therapy is based on the identification of in situ thrombosis of the small arterioles on post-mortem examination in patients with idiopathic PAH [20]. However, no data actually support anticoagulant therapy specifically in patients with PAH. In a systematic review of studies evaluating the effectiveness of anticoagulant therapy in improving the survival of patients with idiopathic PAH, five observational studies were found to suggest a survival benefit associated with warfarin [21]. On the basis of these limited studies, a target International Normalized Ratio between 1.5 and 2.5 is recommended.

There is not enough supporting evidence for the use of anticoagulants in HIV-PAH, although in situ thrombosis is occasionally found. Increased risk of bleeding, also in relation to frequently associated hepatic disease, anticipated compliance issues, and drug–drug interactions, should be also considered.

**Specific therapy**

CCBs. Recent data suggest that a long-term response to CCBs may be present in HIV-PAH, although less frequently than in other forms of PAH [7]. However, it is essential to identify the responders by acute pulmonary vasodilator testing before long-term CCB therapy is undertaken [7]. Moreover, the potential for drug–drug interactions should be considered, especially for patients receiving antiretroviral therapy with protease inhibitors (PIs) [22].

Prostanoids. The beneficial effects of epoprostenol have been demonstrated in patients with HIV-PAH, with a significant long-term decrease in mPAP and pulmonary vascular resistance, and a significant increase in mean cardiac output [23].

However, concern exists about the long-term use of epoprostenol, which requires a permanent central venous catheter for continuous infusion, adding the risk of infectious complications, which is particularly important in HIV-infected patients who are immune compromised [23,24].

Subcutaneous administration or nebulized prostacyclin analogues may overcome the limitations of intravenous administration, but there are few data regarding the use of these compounds in HIV-PAH patients [25,26]. Subcutaneous treprostinil enhanced functional parameters in three patients with HIV-PAH [26]. Inhaled iloprost improved NYHA functional capacity and 6MWD in four patients with severe HIV-PAH, although the effect was not statistically significant [25].

Endothelin receptor antagonists. Bosentan is an oral, non-selective endothelin-1 receptor antagonist that has been shown to considerably improve all clinical and haemodynamic parameters in PAH, and also in patients with HIV-PAH and NYHA class III–IV [27]. In particular, significant improvements were
observed in 6MWD, cardiac index, pulmonary vascular resistance, and right atrial area and eccentricity index at echocardiography, all of which are considered to be prognostic indicators for survival in patients with idiopathic PAH. A recent retrospective study confirmed the long-term benefit of bosentan therapy in HIV-PAH patients without impacting on the control of HIV infection [28].

The newer selective endothelin A receptor antagonists sitaxsentan and ambrisentan have been investigated for the treatment of PAH, and have demonstrated improvements in exercise tolerance and haemodynamics [16]; however, only a single case of an HIV-PAH patient switching from bosentan to sitaxsentan has been reported so far [29].

**Phosphodiesterase-5 inhibitors.** No controlled trials of the phosphodiesterase-5 inhibitor sildenafil in HIV-PAH currently exist, and data on its beneficial effects in HIV-PAH patients derive from case studies, which have reported improvements in dyspnoea and functional class [30–32].

Moreover, caution should be used in HIV-infected patients receiving a HAART regimen containing PIs, as saquinavir and, particularly, ritonavir have been shown to significantly modify the pharmacokinetics of sildenafil, resulting in increased plasma concentrations of both drug and metabolite [33].

**Antiretroviral therapy.** There is no current objective trial evaluating the still controversial effect of HAART on the progression of HIV-PAH. Recent data [5,7] suggested that HAART does not prevent the development of PAH in HIV-infected patients, as most of patients from these studies were receiving HAART at the time of diagnosis of PAH. However, HAART could delay or attenuate the development of PAH in HIV-infected patients [7].

Since the first studies on HIV-PAH, the initiation of antiretroviral therapy has been recommended in all HIV-PAH patients, irrespective of their CD4+ T-lymphocyte counts, on the basis of improvements in pressure gradient over time in HIV-PAH patients receiving zidovudine or didanosine as compared with an increased gradient in untreated HIV-PAH patients [1].

A study of 47 patients with HIV-PAH within the Swiss Cohort Study found that patients receiving HAART had a significantly decreased median right ventricular systolic pressure over right atrial pressure gradient (~21 mmHg) as compared with patients who did not receive antiretroviral therapy (+25 mmHg) [9]; moreover, HAART significantly reduced the risk of death in patients with HIV-PAH (hazard ratio 0.075; 95% CI 0.02–0.28; p <0.001) [9], suggesting a beneficial effect of HAART in patients with HIV-PAH. By contrast, two patients with HIV-PAH who were treated with a PI-including HAART regimen experienced an accelerated course of PAH, with worsening systolic PAP [34].

In a retrospective study of 82 patients, those in NYHA functional class III–IV treated with epoprostenol plus HAART had better survival than those receiving conventional therapy plus HAART, suggesting that HAART alone does not influence the progression of PAH [15]. An analysis of the HIV-PAH cases reported in the literature (January 1987 to January 2009) showed a more favourable outcome in patients treated with PAH-specific therapy than in those treated with antiretroviral therapy only [35].

More recently, long-term HAART without PAH-specific therapy improved 6MWD, but not the haemodynamic parameters, in most patients [7].

**New Pathogenetic Insights into HIV-PAH.**

Infectious pathogens in the lung are known inducers of vasculitis; whether this is a consequence of persistent viral infection, exposure to toxic viral proteins or viral-induced immune activation remain unknown. There is a significant evidence for vascular involvement in HIV/simian immunodeficiency virus infection, including arteriopathy with severe intimal and smooth muscle hyperplasia in AIDS patients and in simian immunodeficiency virus-infected macaques. As in the brain and intestinal mucosa, HIV-1 may exhibit differential evolution in the lungs and periphery. The latest efforts to characterize the HIV-1 envelope gene in matched blood and lung samples from 18 HIV-infected subjects suggest continuous reseeding of viral forms between the peripheral blood and lung tissues in most patients [36].

Histologically, HIV-infected patients do not differ from uninfected counterparts with PAH; 80% of HIV-infected patients also exhibit the concentric laminar intimal fibrosis, medial hypertrophy and plexiform lesions that are hallmarks of PAH [14]. Additional landmarks include augmented expression of smooth muscle cell/fibroblast growth factors such as platelet-derived growth factor.

Just as in severe PAH, macrophages, lymphocytes and dendritic cells are important inflammatory cellular components in the perivascular of HIV tissues. Hence, HIV-induced chronic inflammation and immune hyperactivation may enrich the proinflammatory milieu implicated in HIV-PAH.

**HIV affects the dynamics of the endothelial cell (EC) microenvironment.**

The endothelium is a dynamic entity that constantly communicates with cellular components in blood and with the extracellular matrix. Monocytes/macrophages migrate through the
endothelium to ensure immune surveillance and replenishment of myeloid cells.

Westhorpe et al. [37] showed that chronic exposure of monocytes/macrophages to HIV significantly decreased the emigration of macrophages from tissues, by 67%. Their in vitro system measured forward and reverse transmigration, and suggested that HIV-infected macrophages are capable of migration through the endothelium but not re-entry into the bloodstream. These studies suggest that the presence of ‘trapped’ macrophages in tissues may result in defective monocyte/macrophage-mediated immune responses, as well as the establishment of tissue HIV reservoirs. The mechanisms that account for this differential impairment in transendothelial migration remain to be outlined.

There is no evidence that HIV infects the pulmonary vascular endothelium, but HIV proteins are known to be noxious to ECs; viral proteins and their interactions with molecular partners in the infected host are strong candidates for cause–effect relationships, because they may promote apoptosis, growth and proliferation [38]. PAH has been linked with viral proteins in infections with hepatitis B virus and human herpes virus-8, although the latter is not statistically associated with PAH [2,39].

At least three of the HIV proteins are implicated in the pathology of PAH. For example, HIV attaches and fuses through the host cell membrane, thanks to the envelope glycoprotein-120 (gp-120) present on the surface of HIV virions. Cell-free HIV-1 gp-120, which has been detected in the

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**FIG. 2.** Pathogenetic views of human immunodeficiency virus (HIV)-associated pulmonary arterial hypertension (HIV-PAH). The presence of HIV in the pulmonary vasculature may trigger several aberrant responses at the subcellular level that are translated to the macrovasculature and microvasculature. Established risk factors for HIV-PAH are shown in circles outlined in red; additional factors that merit consideration are shown in circles outlined in grey. For example, cardiovascular complications have been ascribed to iatrogenic metabolic effects of prolonged exposure to protease inhibitors in the antiretroviral regimens. Considering that, with the advent of antiretrovirals, HIV-infected patients live longer, antiretroviral drugs add to the complex interplay between the virus and the cells, as older HIV-infected patients may experience the effects of accelerated vascular ageing and distress. Also, known comorbidities in HIV infection (e.g. other viral infections, hypertension and diabetes) might exacerbate the insults to the pulmonary vasculature. Each one of the aspects presented in this figure offers a niche to search for biomarkers of HIV-PAH, to expedite the screening and diagnosis. EC, endothelial cell.
blood, cerebrospinal fluid and brains of HIV/AIDS patients, stimulates proinflammatory cytokine production from monocytes/macrophages [40], increases the secretion of endothelin-1, and induces apoptosis of human lung ECs [41]. The HIV protein Tat (transactivator of transcription) also activates ECs, and has angiogenic properties.

These HIV proteins may contribute to HIV cardiomyopathy. Post-mortem studies in HIV patients with cardiomyopathy showed that HIV infection was restricted to inflammatory cells, but no virus was found in ECs or cardiomyocytes. Extended observations in vitro demonstrated that the HIV proteins gp-120 and Tat generated proapoptotic signals that induced apoptosis in bystander cardiomyocytes [42].

HIV transgenic murine models show that elevated proinflammatory cytokines reduce sodium channel function, which may lead to arrhythmias [43]. In addition, HIV gp-120 exerts a negative inotropic effect in ventricular myocytes, via phosphorylation of p38 mitogen-activated protein kinase and troponin I, upon binding to the CXCR4 receptor [44]. Finally, expression of HIV Tat in the heart induces oxidative stress [45]. HIV-induced cardiomyopathy is a recognized clinical problem that remains to be investigated.

HIV-1 Nef co-localizes to ECs. Nef, originally thought to be a negative factor, because it is dispensable for viral replication and cytopathicity in vitro, is expressed early during viral infection and is a strategic player in HIV pathogenesis. The association between Nef and obliterative PAH-like vascular lesions in macaque lungs (similar to those in end-stage human PAH) was demonstrated previously [46].

Furthermore, HIV-1 nef signature sequences were identified in patients with HIV-PAH, as compared with counterparts without PAH (FASEB J 2009; Abstract 331.1). Nef crosses cellular membranes and enters target cells via chemokine receptors such as CXCR4. This receptor is expressed on ECs, which may take up Nef as innocent bystander cells. In addition, Nef complexes with several host cell proteins, and recruits host adaptor proteins to commandeering trafficking of intracellular vesicles participating in secretory and endocytic pathways [47].

These studies support the concept that Nef perturbs the subcellular environment.

On the Quest for Biomarkers and Early Identification

HIV evolutionary patterns in the lungs may be playing a role in HIV-PAH. The high mutational profile of HIV is the main hurdle in the development of vaccines to prevent and/or cure this infection. However, this feature of HIV may set the stage for selection of specific HIV quasispecies at specific anatomical sites such as the lung, where virus presence may translate into a disease phenotype.

Research and clinical efforts should be driven by the imperative to understand HIV-PAH, so that reliable therapeutic targets can be pinpointed. Itemization of established risk factors playing strongest roles in HIV-PAH, as well as additional views that merit consideration, reveals the complexity of this disease (Fig. 2).

A wealth of data suggest that HIV-1 Nef is a broad-spectrum modulator that may impact on both infected and uninfected cells. The finding of nef signature sequences in patients with HIV-PAH as compared with normotensives, together with the tight sequence–function relationship intrinsic to Nef, offers the potential use of mutations in Nef as a screening tool for HIV-PAH. Basic science techniques coupled with bioinformatics approaches may redirect efforts to understand the consequences of such mutations in HIV Nef in the context of pulmonary vascular biology.

Conclusions

HIV-PAH is a severe manifestation in the course of HIV disease. The occurrence of dyspnoea in a patient with HIV infection that is unexplained after appropriate evaluation of infectious causes should prompt further evaluation of PH, particularly if there is evidence of right ventricular dysfunction. Clinicians should be aware that the appearance and rapid progression of shortness of breath and other cardiopulmonary symptoms in HIV-infected individuals should suggest HIV-PAH.

A systematic cardiopulmonary evaluation and follow-up should be incorporated in the clinical management of HIV-infected patients. Furthermore, improved awareness should lead to increased referral to specialized centres to initiate specific management and therapies in order to enhance quality of life, exercise capacity, and survival.

Transparency Declaration

Conflicts of interest: none.

References


