

# Chapter 7

## Pulmonary arterial hypertension in patients with HIV infection



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**SUMMARY:** With the advent of highly active antiretroviral therapy (HAART), there have been significant reductions in infectious complications with HIV; however, the prevalence of HIV-associated pulmonary arterial hypertension (HIV-PAH) has not changed. HIV-PAH can occur at any point during the disease and no definitive association with CD4 count or viral load has been observed. The aetiology and pathogenesis of HIV-PAH remains poorly characterised, although a number of observations in a simian immunodeficiency virus (SIV) model and *in vitro* studies support a pathogenic role for HIV proteins. Although there are no randomised controlled trials of treatment for HIV-PAH, therapies are currently similar to those employed for other forms of PAH; however, there are potential interactions between PAH medications and antiretrovirals and potential effects on hepatic function. Nonetheless, limited series of patients treated with epoprostenol or bosentan have demonstrated acute and chronic benefits of pulmonary vasodilators in patients. As HIV-infected patients are living longer, HIV-PAH is likely to become a more frequent complication, despite the increased access to HAART.

**KEYWORDS:** AIDS, highly active antiretroviral therapy, HIV infection, pulmonary arterial hypertension, pulmonary hypertension, pulmonary vasodilators

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Eur Respir Monogr 2012; 57: 82–93.  
Copyright ERS 2012.  
DOI: 10.1183/1025448x.10019011  
Print ISBN: 978-1-84984-025-5  
Online ISBN: 978-1-84984-026-2  
Print ISSN: 1025-448x  
Online ISSN: 2075-6674

Among the 30–40 million people infected with HIV, the primary pulmonary complications for adults are infections. However, HIV-infected persons who receive highly active antiretroviral therapy (HAART), the spectrum of pulmonary pathology is changing: there has been a decrease in the incidence of opportunistic infections and an increase in non-infectious complications [1]. HIV-associated pulmonary arterial hypertension (HIV-PAH) is among these non-infectious complications.

First described in 1987 by KIM and FACTOR [2], HIV-PAH is histologically similar to idiopathic pulmonary arterial hypertension (IPAH), although differences in disease incidence and rate of progression suggest different causative mechanisms [2–4]. In 1991, SPEICH *et al.* [5] reported a

prevalence of 0.5% for HIV-PAH in their cohort of 1,200 patients. As these patients were all characterised in 1990, it was speculated that, with the advent of HAART and the resulting improvement in viral control, there would be a change in prevalence. However, a report by SITBON *et al.* [6] in 2008 suggested that this was not the case. In a large, multicentre cohort of 7,648 HIV-infected patients, who were studied between 2004 and 2005, the prevalence of HIV-PAH was 0.46%, essentially unchanged from that found in 1990 [6]. This unchanged prevalence in HIV-PAH is in stark contrast to another pulmonary complication of HIV infection, *Pneumocystis pneumonia*, in which the total number of cases declined five-fold between 1995 and 2003 [7]. However, data from the extension of the Swiss HIV cohort study [8] suggests that although the prevalence of HIV-PAH may not have changed, the incidence of newly diagnosed cases may be declining. This may be due to differences in population mix as a result of changes in modes of transmission or possibly higher CD4 cell counts and a decrease in immune activation because of more efficient antiretrovirals.

The stable prevalence of HIV-PAH does suggest: 1) the prevalence of PAH among HIV-infected patients is, and will remain, much greater than IPAH (six- to 12-fold greater); 2) Since 30–40 million people in the world are infected with HIV and survival time is much longer, the number of HIV-PAH cases identified is certain to increase; and 3) Since the prevalence of PAH in HIV-infected people is essentially unchanged in spite of a reduced viral load, the pathogenesis of HIV-PAH is only partly dependent on the degree of HIV viraemia. The clinical implication of these observations is that current and investigative therapies used in PAH should significantly reduce the symptoms and improve the quality of life in HIV-PAH patients. The major limiting factor for the use of any PAH-modulating medication is the complicated pharmacokinetics related to concurrent antiretroviral used and the higher prevalence of hepatic impairment among HIV-infected patients [9]. Despite these limitations, it seems reasonable that, as is the case with other types of PAH, early intervention has the potential for significantly delaying disease progression.

## Pathology of HIV-PAH

HIV-PAH is included with IPAH in the World Health Organization (WHO) group 1 classification because the histology of pulmonary arterial lesions is indistinguishable from other entities in this group [10]. The original 1987 observation identified pre-capillary pulmonary arteries with endothelial cell clusters filling the lumen in a 40-year-old HIV-infected male who died of *Pneumocystis pneumonia* [2]. This initial observation was subsequently confirmed in reports of other HIV-infected patients with PAH [5, 11–15]. Interestingly, in a retrospective report of 131 published HIV-PAH cases, the majority (78%) of patients had plexiform lesions; however, other histologies were observed, including thrombotic pulmonary arteriopathy, pulmonary medial hypertrophy with intimal fibrosis, and pulmonary veno-occlusive disease (PVOD) [16]. More recently, there have been HIV-PAH cases with evidence of perivascular inflammatory cells suggesting yet another potential mechanism for the development of HIV-PAH [17, 18].

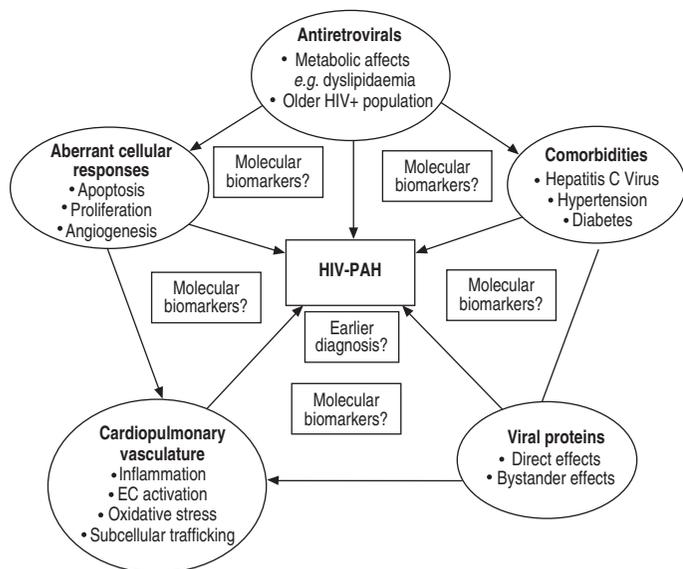
## Pathobiology of HIV-PAH

The aetiology of HIV-PAH is likely to be multifactorial, resulting from a combination of viral and host factors as shown in figure 1. A number of putative mechanisms by which an HIV infection might directly cause or elicit a cellular environment that would lead to the development of the hallmark plexogenic arteriopathy and haemodynamic pathology have been proposed. These presumed mechanisms of disease development relate directly to the virus, to the host's response to HIV-infection and/or to the consequent infections or diseases that resulted from HIV-induced immune deficiency.

## Direct effects of HIV

The proposed mechanisms that invoke a direct effect of HIV infection have, in general, focused on viral proteins being mediators. These HIV proteins are generated during viral replication and are known to be bioactive as well as being integral to HIV-induced pathogenesis [20–25]. The HIV proteins that have been studied for their potential to contribute to the development of HIV-PAH include glycoprotein (gp)120, trans-activator of transcription (Tat), negative-regulator factor (Nef) and envelope protein (Env).

Tat is an HIV protein that, in addition to being required for viral replication, interacts with a number of cytoplasmic and nuclear proteins. It mediates HIV patho-



**Figure 1.** Potential pathways and interactions in the development of HIV-associated pulmonary arterial hypertension (HIV-PAH). EC: endothelial cell. Reproduced and modified from [19] with permission from the publisher.

genesis and can cross cell membranes [25, 26]. Thus, cells that are not infected with HIV, often referred to as “bystander” cells, can be affected. Bone morphogenetic protein receptor type II (BMPR II) is a member of the transforming growth factor (TGF)- $\beta$  superfamily receptor that transduces extracellular signals through the kinases on their intracytoplasmic tail. Heritable pulmonary arterial hypertension (HPAH) is indistinguishable pathologically from IPAH and HIV-PAH. Mutations of the *BMPR2* gene are associated with increased risk of HPAH in many, but not all, individuals in these families, suggesting that compromised BMPR II signalling can contribute to the development of PAH [27]. *In vitro* studies, which used the monocyte cell line U937, demonstrate that exposure to HIV Tat protein results in decreased *BMPR2* promoter activity and transcript copy number. Thus, HIV infection and the resulting exposure to Tat may contribute to the development of PAH by compromising BMPR II signalling in a similar manner as HPAH [28]. However, small studies have not found *BMPR2* mutations in patients with HIV-PAH. Larger population studies may be necessary to address this issue completely, or, more likely, other mechanisms are more important in the majority of individuals with HIV-PAH.

Another HIV protein, gp120, which: mediates viral pathogenesis; recruits T-cells and monocytes; impairs dendritic cell maturation and antigen-presenting capacity; and induces the secretion of a number of cytokines, including endothelin-1 (ET-1). In patients with PAH, serum and pulmonary parenchymal ET-1 levels are markedly elevated; as such, endothelin receptor antagonists (ERAs) have been used clinically to mitigate the pathology of PAH. ET-1 has potent smooth muscle proliferative and vasoconstrictive effects, as well as antiproliferative and vasodilatory effects, *via* nitric oxide (NO) and prostacyclin, depending on with which of its two G-protein coupled receptors, ETA or ETB, it binds. ET-1 is produced primarily by endothelial cells but is also secreted by human macrophages [29]. Human monocytes exposed to gp120 for 24 h secrete higher amounts of ET-1. To assess the relevance of this observation to human disease, the same investigators compared monocytes isolated from HIV-infected patients at various stages of disease with healthy HIV-negative donors by real time (RT)-PCR. In eight of the 10 HIV-infected individuals, an ET-1 PCR product was clearly visible, whereas it was undetectable in the HIV-negative controls. Monocytes from other inflammatory or virus-mediated diseases were also studied as disease controls; however, none were found to have identifiable ET-1 PCR products. Finally, the investigators compared immunohistochemically stained macrophages in brain tissue

from HIV-infected patients and encephalopathy with HIV-uninfected controls. Again strong staining for ET-1 in CD68+ cells was found, consistent with brain microglia [29]. The fact that interruption of ET-1 signalling can mitigate PAH and because ET-1 is elevated in the presence of gp120 and *in vivo* HIV-infection suggest a role for gp120 in HIV-PAH. However, these studies only demonstrate association. Further studies of this HIV protein are needed to clarify its role in the pathogenesis of HIV-PAH.

The HIV proteins Nef and Env are two additional proteins that have recently been implicated in the pathogenesis of HIV-PAH. In the simian immunodeficiency virus (SIV)-infected nonhuman primates, HIV proteins can be studied by inserting the gene sequence for a specific HIV protein in place of the analogous SIV gene. Rhesus monkeys infected with simian-human immunodeficiency virus (SHIV)-*nef* develop a rapidly progressive immunodeficiency that replicates much of the pathology of HIV infection in humans, with most of the monkeys dying within 1 year [30]. In the lungs of five out of six rhesus monkeys, that had been infected with SHIV-*nef* chimaeric viruses, there was evidence of vascular remodelling with endothelial cell proliferation, compared with lungs of monkeys infected with SIV, in which no HIV Nef was present [31]. These lesions stained positive for factor VIII and muscle-specific actin. In contrast, in the SIV-infected monkeys, there was no evidence of abnormal pulmonary artery histology, suggesting that HIV Nef was associated with the vascular remodelling found in the SHIV-*nef* infected monkeys. However, whether these lesions equate to haemodynamic evidence for PAH it is not clear. MARECKI *et al.* [31] then examined lung tissue from two patients with HIV-PAH for the presence of Nef protein. In both the HIV-PAH patients and the SHIV-*nef* infected monkeys, the pulmonary artery lesions demonstrated the presence of Nef [31]. Although this provides some supportive evidence that Nef may contribute to HIV-PAH pathology, examination of lung tissue from HIV-infected patients without PAH was not performed and it is an important necessary control to bolster this hypothesis. A recent study on the proviral DNA sequences of *nef* from 12 HIV-infected patients with PAH has added to this theory. In this study, by ALMODOVAR *et al.* [32] these signature sequences were compared with the Los Alamos National Laboratory National Center for Biotechnology Information (NCBI) database of HIV-1 sequences ([www.hiv.lanl.gov/content/sequence/HIV/mainpage.html](http://www.hiv.lanl.gov/content/sequence/HIV/mainpage.html); Los Alamos National Security, Los Alamos, NM, USA ); certain residues were more frequently found among the patients with HIV-PAH compared with historical controls. Further, when compared with the *nef* sequence in the SHIV-*nef* monkeys, there was commonality in three out of five amino acid substitutions [32]. These data further support the hypothesis that HIV-infected patients who develop PAH may be infected with a particular HIV-1 mutant strain that produces a distinct and pathology-inducing Nef protein. However, against Nef as the sole mediator of PAH, another group of investigators have found pulmonary arteriopathy in 11 out of 13 SHIV-*env*-infected macaques. Furthermore, and in notable difference from the prior SHIV-*nef* report, three of the 11 SIV-infected control monkeys also demonstrated pulmonary vascular lesions, thereby arguing against an absolute requirement for an HIV protein [33].

Although a number of studies implicate HIV proteins in the development of HIV-PAH, substantial research is still required to link a specific viral protein conclusively with the development of this complication of HIV infection. However, these investigations strongly support a viral factor as contributing to the pathogenesis of PAH. Whether it is only one viral factor, the combination of many different viral factors or viral factors in combination with other variables is still unknown.

## Host response and factors

Based on the current understanding of IPAH and other associated PAH, it is very likely that during an HIV infection, the biology of the host exerts significant influence in determining the predisposition to develop PAH. Two such genomic host factors are the *BMPR2* gene and the major histocompatibility complex (MHC) human leukocyte antigen (HLA) class II allele type. There is clear association between *BMPR2* gene mutations and an increased risk of developing PAH (HPAH). In some patients with IPAH, an association with MHC HLA class II alleles of the DR and

the DQ loci has been reported [34]. Both of these associations have been tested in HIV-infected patients. In a cohort of 82 HIV-infected patients with PAH, NUNES *et al.* [35] screened 19 patients and found no *BMP2* mutations. In regard to HLA type, MORSE *et al.* [36] examined 10 racially diverse patients with HIV-PAH and identified an increased frequency of HLA-DR6-DR52, and of the linked alleles HLA-DRB1\*1301/2, DRB3\*0301 and DQB1\*0603/4 when compared with the uninfected Caucasian controls. These genotypes also differed in frequency from reports of patients with IPAH [34]. Thus, although *BMP2* mutations do not appear to contribute to HIV-PAH, there may be HLA genotypes associated with increased risk of developing PAH if infected with HIV. However, these observations are significantly limited by the number of patients included in each study and are not yet conclusive.

Beyond genomic variables, other host variables, which could possibly contribute to the pathogenesis of PAH, have also been characterised. The relevance of many of these pathways in the pathogenesis of HIV-PAH is not yet clear; however, based on the clinical response to accepted PAH therapeutics, it is clear that certain host biology is integral. Primarily this is related to the molecules of vasomotor tone, such as ET-1, phosphodiesterase type-5 (PDE-5), prostanoids and NO. Although it is clear that pulmonary arterial tone is of great relevance, the principal pathology found in PAH is the obliterating foci of endothelial cells that define the plexiform lesions; therefore, endogenous mediators of proliferation have been examined in patients with PAH. A growth factor that has been studied in both PAH and HIV-PAH is platelet-derived growth factor (PDGF). PDGF, a polypeptide composed of homo- or heterodimers and secreted by many cell types, induces proliferation and has been identified in both inflammatory and myeloproliferative disorders [37–40]. Increased PDGF isoforms and receptors have been found in lung tissue from patients with PAH compared with lung tissue from individuals without PAH [18]. Lung tissue from patients with HIV-PAH has also been examined; despite a smaller number of samples, increased expression of PDGF has been found [18]. Further, there are a small number of reports describing the use of the tyrosine kinase inhibitor (TKI) imatinib mesylate, a selective antagonist of the PDGF receptor (FDGFR), for severe pulmonary hypertension refractory to conventional medications. These case reports and a recently completed phase III trial describe significant improvement in pulmonary haemodynamics and functional class with imatinib [41–43]. Thus, it is likely that the dysregulation of host PDGF and possibly other growth factors play a role in the development of HIV-PAH.

## Clinical presentation and evaluation of HIV-PAH

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The clinical findings and the diagnostic approach to PAH have been well described [44]; in addition distinctive features for HIV-PAH have also been reported. In reviewing these reports it is important to remember that the majority of the case reports and series include patients from the pre-HAART era. Thus, these are clinical characteristics that are most applicable to cohorts with limited access to antiretrovirals; the utility of these clinical findings might be tempered in populations where HAART is widely available.

The majority of symptoms reported in HIV-PAH patients are related to right ventricular (RV) dysfunction and include dyspnoea on exertion (85%), pedal oedema (20–30%), non-productive cough (19%), fatigue (13%), syncope or near-syncope (12–30%) and chest pain (7–20%). The mean age of patients with HIV-PAH is  $33 \pm 7$  years with a female-to-male ratio of 1:1.6; this differs from IPAH in which females predominate (female-to-male ratio reported between 1.7:1 and 3:1) [45, 46]. The symptoms of HIV-PAH are similar to those of IPAH; however, the interval between symptom development and diagnosis is shorter in the HIV-PAH population (6 months *versus* 2.5 years) [46]. This may be due to the increased medical surveillance of the HIV-infected patients or is possibly a reflection of a more rapid progression of the HIV-related disease. Overall survival in patients with HIV-PAH at 1, 2, and 3 years after PAH diagnosis was reported as 73%, 60%, and 47% respectively, substantially worse than those reported for patients with IPAH [45]. As in IPAH, there is reduced survival in patients with more severe New York Heart Association (NYHA)/WHO functional class.

The most frequently identified risk factors for HIV infection in patients with HIV-PAH are intravenous drug use (58%), homosexual contact (22%), haemophilia (9%), and heterosexual contact (9.2%) [16]. There is no correlation between the CD4 count, HIV viral load, or history of opportunistic infections and the occurrence of HIV-PAH [6, 16]. However, many investigators have found that patients with lower CD4 counts have more severe PAH disease [6, 34, 46].

More recently two studies of HIV-PAH patients treated during the HAART era have been published. In a cohort of 35 French patients [6], there was no significant difference from characteristics described in prior series; compared with HIV patients with dyspnoea but no PAH, HIV-PAH patients were predominantly male (71% *versus* 53%), *i.v.* drug users (51% *versus* 22%) and more patients had a CD4 <200 (37% *versus* 18%). Overall, CD4 counts did not differ significantly between the two populations. For all patients PAH was confirmed by right heart catheterisation (RHC); it was noted that the five recently diagnosed patients had a milder disease than those patients who had less recently been diagnosed (mean  $\pm$  SD for pulmonary arterial pressure ( $P_{pa}$ )  $30 \pm 9$  *versus*  $46 \pm 13$  mmHg, and pulmonary vascular resistance (PVR) was  $4 \pm 3$  *versus*  $10 \pm 4$  Wood units, respectively) [6]. However, because of the small number of patients in this study, these observations need to be confirmed.

The Swiss HIV cohort study has been actively collecting data since 1988; it recently reported on a cohort of 19 patients diagnosed after 2001 [8]. In this cohort, in comparison with those individuals who were diagnosed before 2001, the patients were older (mean age 43 *versus* 34 years, respectively), and had a higher median CD4 cell count (215 *versus* 169 cell· $\mu$ L<sup>-1</sup>). However, by other measures, this cohort resembled pre-HAART HIV-PAH patients, more males and *i.v.* drug users. Further characterisation of HIV-PAH patients in the HAART era is clearly warranted.

Some characteristics of this population were found in a recent retrospective analysis [47], 81% patients were receiving HAART, 79% had a CD4 count >200 cells· $\mu$ L<sup>-1</sup>, and 49% had an undetectable HIV load. 22% of the patients were NYHA/WHO functional class II, 69% were NYHA/WHO functional class III and 9% were functional class IV. The mean 6-minute walking distance (6MWD) was 375 m. Mean PVR was 689 dyn·s·cm<sup>-5</sup>. In the study, all patients were treated with HAART. Patients who received PAH-specific treatment had an improvement in their 6MWD and haemodynamics. In patients who did not receive PAH-specific treatment improved, but their haemodynamic parameters did not change. Overall survival rate was 88% and 72% at 1 and 3 years, respectively. Multivariate analysis demonstrated that cardiac index >2.8 L·min<sup>-1</sup>·m<sup>-2</sup> and CD4 cell count >200 cells· $\mu$ L<sup>-1</sup> were independent predictors of survival. The authors concluded that antiretroviral therapy (ART) did not improve the haemodynamic parameters; prognosis was related to CD4+ cell counts and cardiac parameters.

Once the diagnosis of PAH is suspected in an HIV-infected person, it is essential to confirm pulmonary hypertension (PH) by RHC. Once PAH is confirmed, other comorbidities contributing to the development of PAH should be considered, for example contaminants in injected drugs, such as methylcellulose, which can induce extensive pulmonary arteriothrombosis leading to PH; likewise, chronic liver disease and portal hypertension associated with hepatitis B or C infection, commonly seen in the HIV-infected population, can lead to PH. However, by convention, HIV-infected patients with PH, even if they have a significant history of liver dysfunction or *i.v.* drug use, are considered to have HIV-PAH because it is impossible to distinguish which disease process contributed most to the development of PAH. In addition the treatment approach is the same as that for PAH.

## Treatment of HIV-PAH

Table 1 shows three selective studies of HIV-PAH patients and their therapy regimens. As with other forms of PAH, treatment of HIV-PAH is based on symptoms, NYHA/WHO functional class, the severity of PH and RV dysfunction. However, the impact of currently available PAH-specific therapies on clinical status and survival in the HIV-seropositive individual is not known [18, 49–51].

Moreover, there are no randomised, controlled studies of any PAH-specific treatment in patients with HIV-PAH.

### Calcium-channel blockers

The haemodynamic improvements with calcium channel blockers (CCBs) in IPAH have not been reproduced in HIV-PAH despite the pathological similarities of the diseases [52, 53]. Only a small subset of all IPAH patients had sufficient vasoreactivity to be considered for CCB therapy; perhaps this subset is smaller in HIV-PAH patients due to late presentation. Yet, those HIV-PAH patients with NYHA/WHO functional class I–III, who have a positive vasodilator response to NO adenosine, or prostacyclin, could be considered for CCB therapy. Oral anticoagulation to decrease *in situ* thrombosis has not been evaluated in HIV-PAH, but its use in patients with IPAH has often been extrapolated, rightly or wrongly, to those HIV-PAH patients without a contra-indication for anticoagulation (goal of an international normalised ratio (INR) 1.5–2.0).

### Prostanoids

#### Epoprostenol

Continuous *i.v.* epoprostenol (prostacyclin) improves haemodynamics, 6MWD, functional class, quality of life, and survival in NYHA/WHO functional class III and IV patients with IPAH [54–59]. In a study of 19 patients with HIV-PAH, PETITPRETZ *et al.* [3] found that acute infusion of epoprostenol resulted in a 20% decrease in the PVR index (PVRI). A subsequent study of six patients with HIV-PAH also noted a significant improvement in haemodynamics with acute infusion [49]. Five out of the six patients underwent repeat cardiac catheterisation at 12 months (the sixth patient died of nucleoside analog-induced lactic acidosis) with four of these patients having additional improvement in  $P_{pa}$ , PVR (PVR), and cardiac output with chronic epoprostenol infusion. Three of these patients had further continued benefit or improvement in their PAH at catheterisation at 24 months [50]. In one of these original patients, there has been continued benefit with epoprostenol for >15 years (unpublished data).

In the largest series to date, NUNES *et al.* [35] described a single-centre, retrospective case series of 82 HIV-PAH patients, which included 20 NYHA/WHO functional class III or IV patients treated with epoprostenol. Due to the rapidly changing therapeutic standards over the 14-year study period, only a subset of patients was treated with a protease inhibitor or HAART. While the beneficial effects of epoprostenol, as defined by an improved 6MWD and improved haemodynamic

**Table 1.** Studies on patients with HIV-associated pulmonary arterial hypertension (PAH)

|                                               | First author [ref.] |                                     |               |
|-----------------------------------------------|---------------------|-------------------------------------|---------------|
|                                               | PETITPRETZ [3]      | NUNES [35]                          | DEGANO [48]   |
| Type of study                                 | Retrospective       | Retrospective                       | Retrospective |
| Recruitment period years                      | 1987–1992           | 1986–2000                           | 2002–2007     |
| Patients included n                           | 20                  | 82                                  | 59            |
| Medication available during study             | CCB                 | Epoprostenol                        | Bosentan      |
| Number of patients on medication              | Unknown             | 20 received drug for 17 ± 13 months | All           |
| Patients on PI plus two other antiretrovirals | 0                   | 48                                  | 83            |
| Survival years                                |                     |                                     |               |
| 1                                             | NR                  | 73                                  | 93            |
| 2                                             | 46                  | 60                                  | 86            |
| 3                                             | NR                  | 47                                  | 66            |

Data are presented as %, unless otherwise stated. PI: protease inhibitor; CCB: calcium channel blocker NR: not recorded.

parameters, were durable at 17 months using multivariate analysis, only the CD4 count was independently associated with improved survival [35]. In addition to the well described adverse effects of epoprostenol, such as headache, flushing, jaw pain, nausea and thrombocytopenia, infection related to the need for chronic central venous access is a significant concern in the immunocompromised host [50, 60]. Despite this increased theoretical risk, there has been no documentation of increased incidence or severity of catheter-associated sepsis in HIV-PAH patients receiving epoprostenol. While a history of *i.v.* drug use may be a relative contra-indication to placement of a central venous catheter, we recommend epoprostenol, if appropriate, after a 6-month period of documented drug abstinence.

### **Treprostinil**

There is a single report of three patients with HIV-PAH who have been treated with subcutaneous treprostinil [61]. All patients were found to have an improvement in NYHA/WHO functional class and 6MWD (a minimum of 75 m) and all were alive at the 1 year follow-up. No adverse events requiring cessation of treatment were observed.

### **Iloprost**

There are data on a small number of patients with HIV-PAH demonstrating acute and chronic efficacy of inhaled iloprost [62–64].

## **Endothelin receptor antagonists**

### **Bosentan**

A number of newer agents have been used for IPAH and demonstrated improvement in short-term measures, such as haemodynamics and exertional capacity. Although survival data are lacking, many of these agents are now being used in HIV-PAH. The oral ERA bosentan has been studied in small cohorts of HIV-PAH patients; these studies suggest that it may be beneficial. BARBARO *et al.* [65] compared 18 patients treated with HAART with 18 patients treated with HAART and bosentan. 24 weeks after initiating treatment the bosentan-treated group had a significantly increased 6MWD and decreased mean  $P_{pa}$ , PVR, and right atrial pressure ( $P_{ra}$ ). Similar findings, increased 6MWD and haemodynamic parameters, were reported in a cohort of 16 HIV-PAH patients treated with bosentan for 16 weeks [66]. These observations have now been extended in a retrospective review of 59 patients with HIV-PAH treated with bosentan [48]. In this cohort, which included 12 of the 16 patients in the previous study [48], 56 patients were evaluated after 4 months of bosentan, and 38 were evaluated for a mean  $\pm$  SD of  $29 \pm 15$  months. Survival rates in this group at 1, 2 and 3 years were 93%, 86%, and 66%, respectively. This was in contrast to the previous data from 2003 in which survival rates were 73%, 60%, and 40% at 1, 2, and 3 years, respectively; and from 1994 in which survival rates were 46% at 2 years [2, 35]. However, it is important to differentiate the prevailing treatments available for HIV infection at the time when comparing these studies. For example, the percentage of patients receiving combination ART including a protease inhibitor was 83% in the 2009 study [48], 48% in the 2003 study [35] and 0% in the 1994 study [3].

A key limiting variable with bosentan is any active liver disease, since one of its potential side effects is transaminitis and liver injury. In Degano's cohort [47, 48], more than half of the patients ( $n=30$ ) had concurrent hepatitis C ( $n=24$ ) or B ( $n=6$ ) infection, of which 10 had mild cirrhosis (Child–Pugh A class). In a univariate analysis of the data the authors found that neither hepatitis C nor B co-infections were associated with a poorer outcome. Three patients did discontinue bosentan due to elevated transaminases, but it is not clear whether any of these were hepatitis C- or B-infected patients. However, the frequency of elevated transaminases was no higher in HIV-PAH patients than in a recently reported cohort of 4,994 PAH patients treated with bosentan, in which the incidence of elevated transaminases was 7.6% over 30 months [67].

## **Ambrisentan**

There are no peer-reviewed data available on treatment of HIV-PAH with this ERA.

## **Phosphodiesterase type-5 inhibitors**

### **Sildenafil**

Other medications for the treatment of PAH are available and have potential use in HIV-PAH, some of which have been shown to improve haemodynamics, exercise capacity and NYHA/WHO functional class in patients with IPAH. Unfortunately, there are only limited studies of these agents in the treatment of HIV-PAH. Sildenafil, a selective phosphodiesterase type-5 inhibitor (PDE 5-I), has efficacy as monotherapy and in combination treatment in several small uncontrolled studies of patients with a variety of PAH aetiologies [68]. Case reports of patients with HIV-PAH treated with sildenafil demonstrate decreased  $P_{pa}$  and improved clinical status [63, 69]. However, close consideration of potential interaction with concurrent antiretroviral medications is warranted since protease inhibitors can cause a significant increase in the levels of sildenafil and sildenafil can significantly decrease levels of protease inhibitors [70].

### **Tadalafil**

There are no peer-reviewed data available on treatment with HIV-PAH with this PDE 5-I.

## **Algorithm of PAH-specific therapy in HIV-PAH**

Due to the lack of randomised controlled trials in HIV-PAH, evidence-based guidelines are not currently available for PAH-specific therapy in HIV-PAH. As such, practitioners should follow the general guidelines for treatment for PAH. We currently recommend systemic prostanoids in NYHA/WHO functional class IV patients or in NYHA/WHO functional class III patients with a low cardiac index. In NYHA/WHO functional class II–III patients, we encourage entry into a clinical trial (if available), or treatment with an ERA (bosentan or ambrisentan) or a PDE 5-I (sildenafil or tadalafil). Ultimately, choice of these PAH-specific therapies depends on the patient's antiretroviral regime (particularly protease inhibitors), the existence of concomitant liver disease (many HIV patients are co-infected with hepatitis B and/or C), and the experience and expertise of the treating centre.

## **Antiretrovirals**

Although medical treatment of HIV-PAH has many similarities to that of treatment for IPAH, it differs significantly in that one postulated therapeutic intervention is the use of antiretrovirals that directly target what is hypothesised to be at least one of the factors in the pathogenesis of PAH in these patients. However, the impact of antiretrovirals on the clinical course of HIV-PAH is controversial. PUGLIESE *et al.* [71] reported a decreased incidence of HIV-PAH with nucleoside reverse transcriptase inhibitors (NRTI) (0.7%) compared with combination HAART therapy (2%). In a retrospective study, which included a cohort of 47 patients with HIV-PAH, it was observed that those treated with HAART had a significantly increased median duration of survival when compared with patients who had received no treatment or non-NRTIs (NNRTI) alone [72]. Small studies suggest the use of zidovudine or didanosine may have benefit on right heart function and HAART combinations including reverse transcriptase and protease inhibitors appear to decrease the mortality for HIV-related congestive heart failure [73]. There are also case reports of the benefits of protease inhibitor treatment of HIV infection on right heart function and haemodynamics [74]. However, the true effect of HAART on HIV-PAH is currently unknown; moreover, HIV-PAH is not considered as an indication for the initiation of HAART (in lieu of other indicators).

## **Statement of Interest**

None declared.

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