**Introduction**

Pulmonary arterial hypertension (PAH) is a term used to classify a variety of conditions sharing similarities in the pathogenesis, clinical presentations, and therapeutic options, and results from chronic obstruction of small pulmonary arteries, leading to right ventricular failure, and, ultimately, death. HIV infection is an established risk factor for the development of PAH. In comparison with the incidence of idiopathic PAH in the general population (1-2 per million), HIV-infected patients have a 2500-fold risk of developing PAH. 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. HIV-associated PAH (HIV-PAH) occurs at all stages of disease and does not seem to be related to the stage of HIV infection, the degree of immune deficiency or CD4 T-lymphocyte count. Since highly effective therapies for PAH are now available, allowing an amelioration of symptoms and a better prognosis, clinicians should be aware that the appearance and progression of shortness of breath and other cardiopulmonary symptoms in HIV-infected patients may be suggestive of HIV-PAH. This paper will focus on HIV-PAH with special considerations to epidemiology, pathogenesis, clinical features and diagnosis, and treatment.

**Keywords:** pulmonary arterial hypertension, HIV, pathogenesis, diagnosis, treatment, HAART

**ABSTRACT**

Pulmonary arterial hypertension (PAH) is a rare but severe disease that results from chronic obstruction of small pulmonary arteries, leading to right ventricular failure, and, ultimately, death. HIV infection is an established risk factor for the development of PAH. In comparison with the incidence of idiopathic PAH in the general population (1-2 per million), HIV-infected patients have a 2500-fold risk of developing PAH. 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. HIV-associated PAH (HIV-PAH) occurs at all stages of disease and does not seem to be related to the stage of HIV infection, the degree of immune deficiency or CD4 T-lymphocyte count. Since highly effective therapies for PAH are now available, allowing an amelioration of symptoms and a better prognosis, clinicians should be aware that the appearance and progression of shortness of breath and other cardiopulmonary symptoms in HIV-infected patients may be suggestive of HIV-PAH. This paper will focus on HIV-PAH with special considerations to epidemiology, pathogenesis, clinical features and diagnosis, and treatment.
affected by HIV-PAH, possibly reflecting the high prevalence of men in HIV population (12).

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 (13).

In a study by Opravil et al, the median survival of HIV-PAH patients was significantly lower than HIV-infected patients without PAH (1.3 versus 2.6 years, respectively; p<0.05) (14). Although these data are more than ten years old, they are best representative of the natural history of the effect of PAH on mortality in patients with HIV infection, because only a small proportion of patients were treated with antiretrovirals (zidovudine or didanosine only) and no patients received HAART-specific therapy.

More recently, studies conducted in the current era of HAART and specific PAH therapies showed an improved survival of HIV-PAH patients; in the Swiss HIV Cohort Study the median survival period of HIV-PAH patients was 3.6 years with 84% of patients survived to one year (15). Prognosis remains particularly poor for patients in New York Heart Association (NYHA) functional class III-IV, with a three-year survival rate of only 28% (16). Also data from the French Reference Centre for PAH showed overall survival rates of HIV-PAH patients of 88% and 72% at one and three years, respectively (17).

Pathogenesis

Different factors could be responsible for the pathophysiological modifications of pulmonary vasculature in HIV-PAH, such as HIV infection itself, increased adrenergic stimulation, liver diseases, toxic substances, and genetic predisposition (Table 1).

Role of HIV

There is no evidence that HIV infects the pulmonary vascular endothelium, and any attempt to isolate HIV-1 nucleic acid (18), and HIV-1 p24 antigen (19) in the pulmonary lesions of HIV-PAH patients by in situ hybridization and immunochemistry, respectively, has failed.

However, HIV proteins are known to be noxious to endothelial cells. 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 (20).

In recent years, Marecki and colleagues have reported complex plexiform-like pulmonary vascular lesions in macaques infected with a chimeric viral construct containing the HIV nef gene in a Simian Immunodeficiency Virus backbone. Moreover, the HIV-1 Nef protein was detected in the alveolar mononuclear cells and in the endothelial cells of the lungs of two HIV-PAH patients, but not in the lungs of a HIV uninfected individual and of two patients with idiopathic PAH, suggesting that nef gene could play a role in the development of HIV-PAH (21).

Furthermore, HIV-1 nef signature sequences were identified in patients with HIV-PAH, compared to counterparts without PAH (22). These studies suggest a role of Nef in the pathogenesis of HIV-PAH.

In human monocye-derived macrophages, Nef activates the signal transducer and activator of transcription 1 pathway and the secretion of macrophage inflammatory protein-1 (MIP-1), interleukin-1 (IL-1) α, interleukin-6 (IL-6), and tumor necrosis factor-α (23).

An increase in IL-1 and IL-6 serum concentrations has been demonstrated in patients with PAH suggesting a role of these cytokines in the pathogenesis of the disease (24). The effects of these cytokines on pulmonary vascular vessels could be direct or partly indirect and mediated by platelet-derived growth factor (PDGF). Elevated PDGF expression has been found in lung biopsies from patients with PAH, and in one patient with HIV-PAH, but not in HIV-infected patients without overt PAH (25).

Other HIV proteins seem to be involved in the development of HIV-PAH. The envelope glycoprotein-120 (gp-120) stimulates pro-inflammatory cytokine production from monocytes/macrophages, increases the secretion of endothelin-1 (ET-1) (ET-1), and induces apoptosis of endothelial cells (26). ET-1 is a potent vasoconstrictor, which has inotropic and mitogenic properties and stimulates the renin-angiotensin-aldosterone system and the sympathetic nervous system. The overall effect of ET-1 is to increase vascular tone and blood pressure. Increased ET-1 levels have been found in the plasma of HIV-infected patients and in the cerebrospinal fluid of HIV-infected patients with encephalopathy (27).

HIV protein Tat (transactivator of transcription) also activates endothelial cells and has angiogenic properties. Chronic exposure to Nef, Tat, and gp-120, as well as deficiency in regulatory T cells and altered production of chemokines/cytokines might contribute to pulmonary vascular dysfunction (28).

α1-adrenergic hypothesis

The pulmonary vasculature expresses α adreno-receptors and β adreno-receptors, both of which help to regulate pulmonary vascular tone by producing vasoconstriction or vasodilatation. In normal pulmonary circulation, there is a balance that favors vasodilatation and the inhibition of proliferation of smooth muscle cells, which is maintained by a predominantly β-adrenergic effect (29).

In HIV-infected patients different factors can induce a chronic stimulation of α1 adrenoreceptors of pulmonary vasculature, including chronic hypoxia, high circulating levels of norepinephrine, appetite suppressant agents or cocaine use, pulmonary pressure or volume overload, commonly associated with HIV-correlated cardiac disease.

Chronic hypoxia can up-regulate α1-adrenoreceptors by activation of a hypoxia inducible factor 1 (HIF-1) localized in smooth muscle cells of pulmonary circulation (30). HIF-1 induces the production of vasoactive substances including vascular endothelial growth factor (VEGF) and ET-1 (31).

Role of human herpes virus 8 (HHV8)

The role of HHV8 in the development of PAH is still controversial and less definite than that of HIV. In favor of an involvement of HHV-8 are the results of the study by Cool and colleagues that demonstrated by polymerase chain reaction (PCR) and immunohistochemical analysis, the presence of HHV8 genome and HHV8-encoded latency-associated nuclear antigen-1 in pulmonary plexiform lesions of patients with PAH (33).

Since then, however, seven independent research groups, using sophisticated immunohistochemical and PCR tech-
Table 1- Pathogenesis of HIV-associated pulmonary arterial hypertension

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<tr>
<th>Role of HIV</th>
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<td>HIV not detected in endothelium of pulmonary arteries</td>
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<td>HIV-1 Nef protein detected in the alveolar mononuclear cells and in the endothelial cells of the lungs of HIV-PAH patients</td>
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<th>Role of HIV</th>
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<td>Secretion of MIP-1, IL-1α, IL-6, and TNF-α</td>
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<td>Increased secretion of ET-1, production of pro-inflammatory cytokines, apoptosis of endothelial cells induced by gp-120 protein</td>
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<td>Activation of endothelial cells induced by HIV Tat protein</td>
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<th>Chronic stimulation of α1-adrenoreceptors</th>
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<td>chronic hypoxia (by activation of HIF-1)</td>
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<td>increased levels of norepinephrine</td>
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<td>appetite suppressant agents or cocaine use</td>
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<td>pulmonary overload</td>
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| Role of HHV8 | Controversial and still under investigation |

| Genetics | Increased frequency of HLA DR52 and DR6 |
| Liver disease | Enhanced synthesis and reduced metabolism of ET-1 |
|             | Over expression of proliferative and angiogenetic mediators |
|             | Imbalance between the vasodilator/antiproliferative mediators and vasoconstrictor/growth mediators |
|             | Use of β-blockers |

HIV-PAH: HIV-associated pulmonary arterial hypertension; MIP-1: macrophage inflammatory protein-1; IL-1α: interleukin-1α; IL-6: interleukin-6; TNF-α: tumor necrosis factor-α; ET-1: endothelin-1; gp-120: glycoprotein-120; Tat: trans-activator of transcription; HIF-1: hypoxia inducible factor 1; HHV8: human herpes virus 8; HLA: human leukocyte antigen.

HIV-PAH patients have been shown to have increased frequency of HLA DR52 and DR6, and of the linked alleles HLA-DRB1 1301/2, DRB3 0301, DQB1 0603/4, which has been found in HIV-PAH patients, compared with the frequencies of the same alleles in normal Caucasian control subjects (36). HLA DR6 and its DRB1 1301/2 subtypes were also significantly increased in HIV-PAH patients compared with the respective frequencies of racially diverse HIV positive control subjects (37). These data could suggest a role of different major histocompatibility complex alleles in the susceptibility to HIV-PAH.

**Host genetics**

A significant increase in the frequency of human leukocyte antigen (HLA) class II DR52 and DR6, and of the linked alleles HLA-DRB1 1301/2, DRB3 0301, DQB1 0603/4, has been found in HIV-PAH patients, compared with the frequencies of the same alleles in normal Caucasian control subjects (36). HLA DR6 and its DRB1 1301/2 subtypes were also significantly increased in HIV-PAH patients compared with the respective frequencies of racially diverse HIV positive control subjects (37). These data could suggest a role of different major histocompatibility complex alleles in the susceptibility to HIV-PAH.

No mutations of the bone morphogenetic protein receptor type 2 (BMPR2), that have been associated with both familial and sporadic idiopathic PAH (38), were found in patients with HIV-PAH (39). Of note, the HIV-1 Tat protein represses BMPR2 gene expression in human macrophages in vitro, thus interfering with transcriptional regulation of bone morphogenetic protein and BMPR2 (40). It might therefore be possible that the BMPR2 downregulation may participate in the development of HIV-PAH (41).

**Liver disease and porto-pulmonary hypertension**

Porto-pulmonary hypertension is a condition characterized by an elevated PAP, increased PVR, and a normal pulmonary capillary wedge pressure (PCWP) in the setting of underlying portal hypertension (portal pressure >10 mmHg) (42). Liver disease is not uncommon in HIV-infected patients due to their frequent coinfection with hepatitis C virus and/or hepatitis B virus. The pathogenesis of PH in cirrhotic patients remains incompletely understood. Almost all patients with advanced liver disease and portal hypertension have high cardiac output and hyperdynamic circulation. The shear stress from increased pulmonary blood flow may result in endothelial injury and subsequent proliferation of these cells. Overexpression of proliferative and angiogenetic mediators such as VEGF and HIF may sustain the endothelial cells proliferation. An imbalance between the vasodilator/antiproliferative mediators and vasoconstrictor/growth mediators (ET-1, thromboxane) normally secreted by endothelial cells has also been invoked (43). Various studies have demonstrated that enhanced synthesis and reduced metabolism of ET-1 in cirrhotic hepatocytes could be an important mechanism associated with elevated ET-1 plasma concentration in cirrhotic patients (44).

**Toxic substance**

The use of cocaine has been associated with PH and various contractile vascular responses (45). The action of cocaine is primarily dependent on α1-adrenoreceptors stimulation (46), suggesting that PH associated with cocaine could be due to stimulation of the α1-adrenergic receptors in the pulmonary artery.
Appetite suppressant agents are associated with a six-fold greater risk for the development of PH. A multicenter prospective case control study reported that the use of appetite suppressant agents increased by 23-fold the risk of developing PH when these drugs were used for more than 3 months (47). Abenham (1996). Assumption of these agents should be excluded when diagnosing HIV-PAH.

Clinical presentation and diagnosis

Most symptoms of HIV-PAH result from right ventricular dysfunction. In a review of 131 cases of HIV-PAH, progressive shortness of breath was the most common presenting symptom (85% of cases), followed by pedal edema (30%), non-productive cough (19%), fatigue (13%), syncope or near syncope (12%), and chest pain (7%) (48).

Since early detection is essential for diagnosis and clinical interventions before quality of life is compromised, clinical suspicion of PAH is crucial in the diagnosis of this disease. The occurrence of dyspnea unexplained after proper exclusion of infectious causes, should prompt further evaluation of PAH.

HIV-PAH can be detected and further diagnosed by a sequential approach that practically includes four steps, as summarized in Table 2.

On physical examination the most frequent findings are 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 edema (49).

Chest x-ray generally shows enlarged central pulmonary arteries and clear lung fields; moreover, it is helpful in excluding some causes of pulmonary hypertension, such as chronic obstructive pulmonary diseases (COPD) and interstitial pneumonia. However, in the initial phases of the disease, chest x-ray could not detect early changes of pulmonary arteries.

The electrocardiogram (ECG) usually reveals right axis deviation and right ventricular hypertrophy. P waves are tall and most prominent in standard leads II, III, and aVF because of right atrial enlargement. R waves are tall in V1, with abnormal S waves in V6 and V4. Complete or incomplete right bundle branch block may be present. Nevertheless, a normal ECG does not exclude the presence of severe PH (50).

Transthoracic echocardiography has been proved to be an extremely useful tool for diagnosis of HIV-PAH (51); moreover, it is extremely helpful in ruling out congenital, valvular, and myocardial disease. The most frequent bidimensional echocardiographic features are: systolic flattening of the interventricular septum, an enlarged right atrium and ventricle and a reduction in both left ventricular systolic and diastolic dimensions. Percardial effusion and patent foramen ovale are also frequently detected by echocardiography (52).

Doppler echocardiography may be used to estimate systolic PAP, by estimating the peak velocity of the tricuspid valve regurgitant jet (53).

Assessment of hemodynamic measures by right heart catheterization (RHC) is however mandatory to diagnose HIV-PAH, and to assess its severity and response to therapy. PAH is defined by a mean PAP ≥25 mmHg with a mean PCWP ≤15 mmHg, and a normal or reduced cardiac output (54).

As patients with HIV infection have frequently a history of viral hepatitis, measurement of portal pressure should be performed during RHC to exclude porto-pulmonary hypertension secondary to liver cirrhosis.

Acute vasodilator testing is an important component of the haemodynamic assessment, since the responses to acute challenge with vasodilators (e.g. inhaled nitric oxide or intravenous epoprostenol or adenosine) is predictive of the long-term response to oral vasodilator therapy with calcium channel blockers (CCBs). In HIV-PAH however acute vasodilator testing rarely has a positive response (55).

Other possible causes of PH in HIV-infected patients should be excluded.

Pulmonary function test and thoracic computed tomography (CT) should be done to exclude COPD. A ventilation/perfusion lung scan and a contrast enhanced CT may be helpful in order to evidence PH secondary to chronic thromboembolic pulmonary embolism (CTEPH).

In case of CTEPH a pulmonary angiography should be performed in search of proximal obstructions that may necessitate surgical interventions (56).

Exercise tolerance is commonly assessed in PH 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 (57).

Treatment

Even though considerable progress in therapy has been made in the last few years, no study has yet established a single agent of choice for the treatment of HIV-PAH that still remains a progressive disease for which there is no cure (58).

Treatment of HIV-PAH includes supportive treatments, and disease-specific treatments. In many patients pharmacotherapy for right ventricular failure is also necessary.

Supportive therapy

Supportive therapy includes oxygen administration, diuretics, digoxin, and oral anticoagulants.

Supplemental oxygen therapy is of benefit in patients who are hypoxic. Chronic hypoxemia is due to impaired cardiac output, which results in desaturation of mixed venous blood. Because hypoxemia is a potent pulmonary vasoconstrictor, most expert recommend oxygen supplementation when arterial blood oxygen pressure is consistently ≤60 mmHg (59).

Patients with overt right ventricular failure should be treated with diuretics, which reduces right ventricular preload (60).

Digoxin has been shown to improve cardiac output acutely in patients with right ventricular dysfunction due to PH (61). However, the role of cardiac glycosides in treating isolated right heart dysfunction is controversial.

Most experts recommend long term oral anticoagulant therapy in patients with idiopathic PAH, but there is little evidence to support its use in HIV-PAH, although in situ thrombosis is occasionally found in these patients (62). Moreover, increased risk of bleeding, also in relation to frequently associated liver diseases, compliance issues, and interactions with antiretrovirals should be considered. In the absence of contraindications, however, treatment with anticoagulants may be given.

Specific therapy

Vasodilators

Vasodilators have been extensively used in the treatment of PAH, since vasoconstriction is a determin-
nant characteristic of this disease. Recent data suggest that, although less frequent than in other forms of PAH, long term response to CCBs may be present in HIV-PAH (63). However, it is essential to identify the responders by acute pulmonary vasodilator testing before long-term CCB therapy is undertaken (64). Moreover, the potential for interactions with antiretroviral therapy, in particular with protease inhibitors (PIs), should be considered (65).

**Prostanoids**

The beneficial effects of the prostacyclin analogue epoprostenol have been demonstrated in patients with HIV-PAH, with a significant long-term decrease in mean PAP and PVR, and a significant increase in mean cardiac output (66). The principal limitation of the use of epoprostenol is its short half-life, i.e. 3-5 minutes after intravenous administration. For this reason a portable infusion pump attached to a permanent indwelling central venous catheter (CVC) is needed for continuous administration of epoprostenol. Thus, concern exists about the long term use of epoprostenol, and the risk of CVC-related infectious complications, particularly important in immunocompromised HIV-infected patients (67). Prostacyclin analogues that can be administered non parenterally, including subcutaneous treprostinil and inhaled iloprost, have been investigated, but there are few data regarding the use of these compounds in HIV-PAH patients (68).

**Endothelin receptor antagonists.**

Bosentan is an oral non selective ET-1 receptor blocking agent that has demonstrated to considerably improve clinical and hemodynamic parameters in patients with HIV-PAH and NYHA class III-IV (69). A recent retrospective study confirmed the long-term benefit of bosentan therapy in HIV-PAH.
patients, without impacting control of HIV infection (70). During bosentan therapy monitoring of liver and hematologic functions is necessary. Increases in hepatic enzymes to >3 times the upper limit of normal have been observed in about 11% of patients treated with bosentan in clinical trials (71).

Newer selective endothelin A receptor antagonists sitaxsentan and ambrisentan have been investigated for the treatment of PAH and demonstrated improvements in exercise tolerance and hemodynamics (72). However, sitaxsentan has recently been withdrawn by the manufacturer due to cases of fatal liver toxicity (73).

**Phosphodiesterase-5 inhibitors.**

Sildenafil is a phosphodiesterase-5 (PDE5) inhibitor that enhance nitric oxide dependent cyclic guanosine monophosphate (cGMP)-mediated pulmonary vasodilatation through inhibition of the breakdown of cGMP, and demonstrated to improve exercise capacity, functional class and hemodynamics also in patients with HIV-PAH (74).

However, the experience with PDE5 inhibitors, including sildenafil, in HIV-PAH is preliminary, and no controlled studies currently exist to determine their efficacy and safety. Moreover, caution should be used in HIV-infected patients in HAART regimen containing PIs since saquinavir and particularly ritonavir significantly modified the pharmacokinetics of sildenafil resulting in increased plasma concentration of both drug and metabolite (75).

**Role of HAART**

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, based on improvements in pressure gradient over time in HIV-PAH patients receiving zidovudine or didanosine, compared to an increased gradient in untreated HIV-PAH patients (76).

However, there is no current objective trial evaluating the effect of antiretroviral therapy on the progression of HIV-PAH and its efficacy is still controversial. Recent data (77) suggested that HAART does not prevent the development of PAH in HIV-infected patients since most of patients from these studies were on HAART at diagnosis of PAH. However, HAART could delay or attenuate the development of PAH in HIV-infected patients (78).

A study of 47 patients with HIV-PAH within the Swiss Cohort Study found that patients receiving HAART had a significantly decrease of the pressure gradient compared to patients who did not receive antiretroviral therapy (79); moreover, HAART significantly reduced the risk of death in patients with HIV-PAH (hazard ratio 0.075; 95%CI, 0.02-0.28; p<.001) (80), 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 (81).

In a retrospective study of 82 patients, patients in NYHA functional class III-IV treated with epoprostenol plus HAART had a better survival than those receiving conventional therapy plus HAART, suggesting that HAART alone does not influence the progression of PAH (82). An analysis of the HIV-PAH cases reported in the literature (January 1987- January 2009) showed a more favorable outcome in patients treated with PAH-specific therapy rather antiretroviral therapy only (83).

More recently, long-term HAART without PAH-specific therapy improved 6MWD, but not the hemodynamic parameters in most patients (84).

**Conclusions**

HIV-PAH is a severe manifestation in the course of HIV disease. The occurrence of dyspnoea in a patient with HIV infection which is unexplained after appropriate evaluation of infectious causes should prompt further evaluation of PAH, 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 may be suggestive of HIV-PAH.

Since specific PAH—therapies that may favorably influence the prognosis and survival of HIV-PAH patients are now available, early detection is essential for the diagnosis and clinical interventions before quality of life is compromised.

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.

**Ongoing research initiatives directed at a better understanding of HIV-PAH: the Pulmonary Vascular Research Institute**

Authors of this article are members of the Pulmonary Vascular Research Institute (PVRI).

PVRI is an international academic medical centre that incorporates the traditional triad of research, education, and clinical care. Its research effort are focused on pulmonary vascular disease and heart failure, and the education and clinical care are targeted to countries with underserved populations. Specifically, the PVRI seeks to better determine the epidemiology of HIV-PAH in the affected regions by working with local health authorities, to study the pathobiology of the disease by established and making available patient databases and bio-repositories to international research centres with appropriate expertise, and to increase the number of clinics where the patients can be screened to eventually conduct clinical trials to determine the most appropriate and cost-effective treatments.

The PVRI task force on pulmonary hypertension associated with HIV infection is working on developing and validating screening algorithms that can be accessible to developing countries (85)

Also, efforts are directed to investigate the influence of antiretroviral therapy on the natural history of PAH, as well as co-infections, co-morbidities, and molecular signature of HIV as risk factors for PAH in HIV-infected patients.
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