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Review

Pulmonary Hypertension in HIV

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ABSTRACT

Human immunodeficiency virus–associated pulmonary arterial hypertension (HIV-PAH) is important to recognize given its association with significant morbidity and mortality. With the introduction of antiretroviral therapy, the focus of disease management has largely shifted from treating immunodeficiency-related opportunistic infections to managing chronic cardiopulmonary complications. Symptoms are nonspecific, and a high index of clinical suspicion is needed to avoid significant delay in the diagnosis of HIV-PAH. Although several viral proteins have been implicated in the pathogenesis of HIV-PAH, the exact mechanism remains uncertain. Further studies are needed to elucidate precise pathogenic mechanisms, early diagnostic tools, and novel therapeutic targets to improve prognosis of this severe complication.

RÉSUMÉ

Il est important de reconnaître l'hypertension artérielle pulmonaire (HTAP) associée au virus de l'immunodéficience humaine (VIH) compte tenu de son lien avec une morbidité et une mortalité élevées. L'arrivée des antirétroviraux a fait en sorte que l'attention se porte désormais bien plus sur la prise en charge des complications cardiopulmonaires chroniques que sur le traitement des infections opportunistes imputables à une immunodéficience. Les symptômes étant aspécifiques, l'indice de suspicion clinique doit être élevé pour éviter des retards indus dans le diagnostic de l'HTAP associée au VIH. Bien que plusieurs protéines virales aient été incriminées dans la pathogenèse de cette affection, son mécanisme exact reste nébuleux. Il faudra réaliser de nouvelles études pour élucider les processus pathologiques en cause, pour trouver des outils permettant un diagnostic précoce et découvrir de nouvelles cibles thérapeutiques afin d'améliorer le pronostic de cette grave complication.

Human immunodeficiency virus–associated pulmonary arterial hypertension (HIV-PAH) was first described in 1987 by Kim and Factor[1] in an HIV-infected patient with haemophilia and membranoproliferative glomerulonephritis. Since then, it has become an increasingly recognized complication of HIV infection.[2] With the introduction of antiretroviral therapy (ART), survival of HIV-infected patients has markedly improved with less deaths from consequences of immunodeficiency and opportunistic infections.[3] HIV has gradually become a chronic condition, and long-term cardiopulmonary complications including HIV-PAH have emerged as the primary source of morbidity and mortality.[4,5]

Pulmonary hypertension (PH) has historically been defined hemodynamically by a mean pulmonary artery pressure (mPAP) $\geq$ 25 mm Hg measured during right heart catheterization (RHC) and PAH by an mPAP $\geq$ 25 mm Hg and a pulmonary artery wedge pressure (PAWP) of $\leq$ 15 mm Hg.[6] However, it is important to note that the recommendations from the 2018 6th World Symposium of Pulmonary Hypertension include a revised definition of PAH; the concomitant presence of mPAP $>$ 20 mm Hg, PAWP $\leq$ 15 mm Hg, and pulmonary vascular resistance (PVR) of $\geq$ 3 Wood units.[7] Implementation of this definition will result in reclassification of HIV-PAH. Many patients who would not have previously met the diagnostic criteria will meet the revised criteria. The effects of this new definition of PAH on diagnosis and treatment of HIV-PAH will undoubtedly have significant effects on the epidemiology and treatment of HIV-PAH that will emerge in the next decade.

PH is classified clinically into 5 different categories based on pathologic similarities and hemodynamic characteristics (Table 1).[7] HIV-PAH is the most common form of PH in HIV-infected patients. However, PH associated with left heart disease and lung disease are expected to increase with the expected increase in common chronic cardiac[8] and respiratory[9] diseases in an aging population with concurrent HIV. It is important to note that the hemodynamics profile of group 1 PAH is identical to groups 3, 4, and in some cases 5 and even 2.[10] It is also common that patients with PAH have comorbid conditions (ie, a patient with HIV-PAH who has comorbid smoking-related obstructive lung disease with hypoxemia) that may also contribute to elevated pulmonary artery pressures (PAPs). Therefore, it is critically important that each patient

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Table 1. Classification of pulmonary hypertension

Clinical classification of PH
1. PAH
1.1 Idiopathic
1.2 Heritable
1.3 Drug and toxin induced
1.4 Associated with
1.4.1 Connective tissue disease
1.4.2 HIV infection
1.4.3 Portal hypertension
1.4.4 Congenital heart disease
1.4.5 Schistosomiasis
1.5 Long-term responders to calcium channel blockers
1.6 With overt features of venous/capillary (pulmonary veno-occlusive disease or pulmonary capillary hemangiomatosis) involvement
1.7 Persistent PH of the newborn
2. PH due to left heart disease
2.1 Heart failure with preserved left ventricular ejection fraction
2.2 Heart failure with reduced left ventricular ejection fraction
2.3 Valvular disease
2.4 Congenital/acquired cardiovascular conditions leading to postcapillary PH
3. PH due to lung disease or hypoxia
3.1 Obstructive lung disease
3.2 Restrictive lung disease
3.3 Other lung diseases with mixed restrictive/obstructive pattern
3.4 Hypoxia without lung disease
3.5 Developmental lung disease
4. Chronic thromboembolic PH
4.1 Chronic thromboembolic PH
4.2 Other pulmonary artery obstructions
5. PH with unclear or multifactorial mechanisms
5.1 Hematologic disorders
5.2 Systemic disorders and metabolic disorders
5.3 Others
5.4 Complex congenital heart disease

HIV, human immunodeficiency virus; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension.

undergoing evaluation for possible HIV-PAH undergo a complete diagnostic evaluation to identify all causes of elevated PAP and that the hemodynamic profile of the patient be considered in this context to determine the correct diagnosis and the appropriate course of treatment.[11]

Epidemiology

The generally accepted prevalence of HIV-PAH is 0.5% of HIV-infected individuals. The initial prevalence estimate of 0.5% came from a large Swiss cohort of 1200 untreated patients with HIV who were evaluated with transthoracic echocardiography for unexplained respiratory symptoms.[12] This was a hypothesis-generative prospective cohort study of consecutive patients with HIV infection who presented with respiratory symptoms over a 9-month period. Of the 74 patients with respiratory symptoms, echocardiography was performed in 12 patients, and 6 were found to have right ventricular systolic pressure of between 49 and 64 mm Hg plus right atrial pressure, as well as other echocardiography findings of right heart failure. RHC was not performed in this cohort. Despite the significant limitations of this study design, the estimated 0.5% prevalence of HIV-PAH was remarkably high in comparison with the prevalence of PAH in the general population, which has been estimated to be 5 to 25 cases per million.[13]

The 0.5% prevalence estimate was later confirmed in a prospective study of 7648 patients with HIV in France.[14] In this study, patients with unexplained dyspnea were evaluated with echocardiography and, if found to have a tricuspid regurgitant velocity (TRV) greater than 2.5 m/s, subsequent RHC was performed. A total of 18 patients underwent RHC, and PAH was confirmed in 5. When added to the 30 patients in the cohort previously diagnosed with HIV-PAH, this led to a prevalence of 0.46% (95% confidence interval, 0.32-0.64). Of note, this well-designed study was performed from 2004 to 2005 after introduction of ART. The estimate of 0.5% is unchanged from the initial Swiss cohort supporting a conclusion that treatment of HIV-infected patients with ART did not change the prevalence of HIV-PAH. Also, patients in this study underwent RHC and met the rigorous invasive hemodynamic criteria for a diagnosis of PAH, so the estimate of 0.5% does not include patients with elevated PAP secondary to other non-PAH processes.

At the end of 2016, there were approximately 36.7 million people living with HIV and acquired immunodeficiency syndrome worldwide. By using the estimated prevalence of 0.5%, there may be as many as 183,500 patients with HIV-PAH worldwide.

Other studies using echocardiography to estimate the prevalence of HIV-PAH have reported rates of HIV-PAH as high as 2.6% to 14%.[15-18] However, echocardiographic estimates of PAP are known to be inaccurate when compared with RHC-measured PAP, so it is possible that echocardiographic studies overestimate the prevalence of HIV-PAH. For example, in the French study described,[14] of 18 patients with elevated PAP on the echocardiogram, PAH was confirmed during RHC in only 5 (28%). However, it is also possible that differences in prevalence in the studies described next are related to differences in population studies, genetic susceptibilities, use of stimulants, or mode of HIV transmission.

A study of 196 HIV-infected patients in San Francisco found a pulmonary artery systolic pressure (PASP) $>$ 30 mm Hg in 35.2% of patients compared with 7.7% of controls. After adjustment for injection drug use, stimulant use, smoking, age, and gender, HIV-infected patients had a 7.0-fold greater odds of having a PASP $>$ 30 mm Hg ($P <$ 0.001).[19] Another echocardiography study of 656 patients with HIV from Rhode Island, Colorado, Minnesota, and Missouri showed that 23% had PASP $>$ 30 mm Hg. However, there was also a high rate of left heart abnormalities including systolic and diastolic dysfunction and left atrial enlargement, all of which suggest a diagnosis of group 2 PH from left heart disease might be contributing to elevated PASP in this cohort.[20] Two cohort studies of HIV-infected patients in Spain reported a echocardiographically estimated PASP $>$ 35 mm Hg in 9.9%[16] and 9.8%[15] of subjects. A retrospective study in patients attending an HIV clinic at the National Institutes of Health Clinical Center found that 9.3% patients had TRV 2.5 m/s or higher (PASP 30 mm Hg) and 0.4% had a TRV of at least 3 m/s (PASP 41 mm Hg).[2] It has been hypothesized that HIV-PAH may be particularly important in Africa, where there may be a growing population of HIV infection at risk for cardiovascular complications of HIV. A meta-analysis of 3 studies performed in South Africa, Tanzania, and Cameroon found a prevalence of echocardiography-estimated PASP $>$ 35 mm Hg of 14% (95% confidence interval, 6-23) in a pooled sample of 664 individuals.[18]

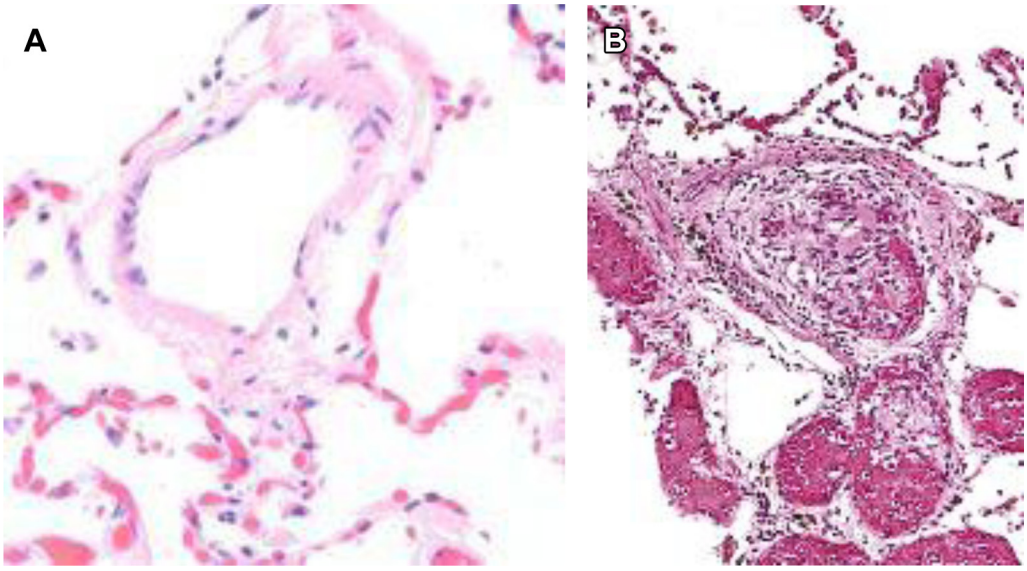

Figure 1. Pathologic appearance of a normal pulmonary arteriole compared with a pulmonary arteriole in pulmonary arterial hypertension (PAH). (**A**) Normal pulmonary arteriole. (**B**) Pulmonary arteriole from a patient with PAH demonstrating vascular endothelial cell proliferation and smooth muscle cell hypertrophy and a plexiform lesion. Reproduced from Barnett and De Marco[10] with permission from Elsevier.

Pathogenesis

Patients with HIV-PAH have histological manifestations indistinguishable from those found in patients with idiopathic PAH. All forms of PH have common pathologic features indicative of pulmonary vascular remodelling, which include medial hypertrophy of muscular and elastic arteries, dilation, and intimal atheromas of elastic pulmonary arteries.[21] PAH is characterized by the additional findings of constrictive and complex arterial lesions. The hallmark of PAH is the plexiform lesion, a complex arterial lesion, characterized by focal proliferation of endothelial cells lined by myofibroblasts, smooth muscle cells, and connective tissue matrix (Fig. 1).[22] In patients with pulmonary veno-occlusive disease, pathologic changes in the pulmonary venules are found in addition to typical arteriolar pathology, and several case reports have described findings of pulmonary veno-occlusive disease in HIV-infected patients.[23]

The mechanisms by which HIV causes PAH remain poorly understood. There is no evidence that HIV directly infects pulmonary artery endothelial cells, and HIV nucleic acids are not found in pulmonary vessels of human lung tissues.[24,25] Instead, HIV viral proteins probably play key roles in PAH-associated vascular remodelling by causing proliferation of vascular endothelial cells, induction of inflammation, oxidative stress, and deregulation of apoptosis (Fig. 2). In support of this, pulmonary vascular remodelling was shown to develop in the presence of HIV-1 proteins without an active infection, leading to PH in a noninfectious HIV-transgenic rat model.[26] The presence of viral proteins, coupled with hypoxia, also has been shown to synergistically increase the PAPs in a transgenic animal model.[27]

HIV-1 gp 120 envelope glycoprotein, a protein detected in screening tests for HIV, contributes to the development of HIV-PAH by induction of apoptosis, increased endothelial cell permeability, and increased secretion of endothelin.[28,29] Endothelins are potent vasoconstricting peptides that are also responsible for inflammation, cell proliferation, and fibrosis, with isoform endothelin-1 being a well-established mediator of pulmonary vascular homeostasis.[30] Plasma levels of endothelin-1 have been shown to be higher among HIV-infected patients with elevated PASP than among uninfected controls and were independently associated with higher values of PASP by echocardiography and RHC.[31]

The Nef protein is a viral protein important for in vivo viral replication. Several studies suggest that Nef plays a key role in the pathogenesis of HIV-PAH. Complex plexiform-like lesions were found in macaques infected with chimeric virions expressing human HIV Nef in a simian immunodeficiency virus (SIV) genetic backbone (SHIV) Nef but not in animals infected with SIV. The same study also showed co-localization of HIV Nef protein in the pulmonary endothelial cells.[32] Specific Nef signature sequences have been

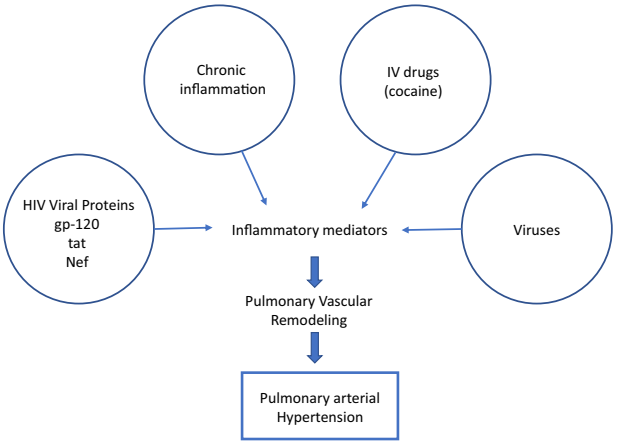

Figure 2. Pathogenesis of human immunodeficiency virus (HIV)-associated PAH. IV, intravenous; Tat, transactivator of transcription.

associated with PAH in 2 different HIV cohorts.[33] Further, a recent analysis of SHIV Nef-infected macaques showed findings that included cardiac hypertrophy, increased interleukin (IL)-2 and granulocyte macrophage colony-stimulating factor, and inhibition of bone morphogenic protein receptor-2 (BMPR2).[34]

Bone morphogenic proteins signal through BMPR2 to regulate cellular differentiation, proliferation, and apoptosis. Mutations leading to loss of function or reduction in BMPR2 expression are known to cause PAH.[35] HIV viral proteins alter the BMPR signalling pathway leading to PAH. Transactivator of transcription (Tat) is an HIV viral protein that has been shown to repress transcription of BMPR2 in macrophages with downstream decreased phosphorylation of receptor-associated SMAD causing overall repression of BMPR2-SMAD signalling cascade.[36] Tat is also implicated in significantly increasing levels of the proinflammatory cytokine, IL-6, which causes deleterious smooth muscle proliferation and adverse remodelling of the pulmonary vascular architecture.

Injection drug use has been implicated in the pathogenesis of HIV-PAH.[37] Rhesus macaques infected with SIV that were concurrently treated with intramuscular morphine developed adverse vascular remodelling, including plexiform lesions that typify PAH. Control animals that received morphine or were infected with SIV did not demonstrate pathologic endothelial proliferation or vascular obliteration.[38]

Cocaine synergizes with HIV-Tat to promote proliferation of pulmonary artery smooth muscle cells.[39] The BMPR2 axis appears to be the target of stimulant drugs as significant downregulation of BMPR expression has also been shown in the lung tissue of HIV-infected injection drug users compared with HIV-infected non-drug users or uninfected intravenous drug users.[40]

HIV infection induces a state of chronic inflammation characterized by persistent immune activation and dysregulation,[41] which likely indirectly induces release of proinflammatory cytokines and growth factors that could produce PAH.[42] Chronic inflammation persists even with effectively treated HIV infection and is independently associated with increased cardiovascular risk.[43] Asymmetric dimethyl arginine, a marker of nitric oxide—mediated endothelial dysfunction, accumulates with chronic inflammation and independently predicts HIV-PAH.[44,45] Various growth factors have been implicated in the development of HIV-PAH: Hypoxia inducible factor 1 alpha appears to mediate the response to viral proteins gp120 and Tat,[26] platelet-derived growth factor is a potent stimulus of smooth muscle cell and fibroblast growth and migration,[46] and vascular endothelial growth factor A induces vascular permeability and endothelial cell proliferation.[47] In addition, Tat protein causes increased endothelial cell permeability and injury via production of IL-6 shown to be present in lungs of patients with severe PH.

Biomarkers of fibrosis (ST-2), inflammation (high-sensitivity C-reactive protein), thrombosis (D-dimer), apoptosis (growth and differentiation factor [GDF]-15), and myocardial injury (high-sensitivity troponin I and N-terminal pro—B-type natriuretic peptide) are elevated in patients with HIV. In particular, ST-2, GDF-15, high-sensitivity C-reactive protein, and D-dimer appear to independently predict all-cause mortality irrespective of whether patients are on ART.[48] Eight biomarkers were evaluated in a cluster analysis of 332 HIV-infected patients, which showed that serum biomarkers can be used to classify patients with HIV into separate clusters that can predict structural and functional abnormalities and mortality.[49]

A role for other viruses in the pathogenesis of HIV-PAH has been hypothesized. Evidence of human herpesvirus 8 plexiform lesions of patients with PAH initially suggested a possible role for human herpesvirus 8 in the pathogenesis of PAH;[50] however, this finding was not recapitulated in other populations.[51] Upregulation of human endogenous retrovirus K could induce and perpetuate chronic immune dysfunction and endothelial dysfunction, leading to adverse remodelling related to PAH, and HIV could be a potential activator of human endogenous retroviruses.[52]

Clinical Presentation

HIV-PAH presentation is clinically indistinguishable from idiopathic PAH and presents with nonspecific and often insidious symptoms. As a result, diagnosis is often delayed because these nonspecific symptoms are often attributed to HIV infection or other common complications of HIV infection. The time from symptoms onset to diagnosis in HIV-PAH is only approximately 6 months, which is shorter than 2.5 years in patients with idiopathic PAH[53] and could be related to closer follow-up or more rapid clinical deterioration and symptom development in HIV-PAH.[54] However, a recent study of patients with HIV discharged from hospitals in the United States between 2001 and 2010 found that the reported prevalence of HIV-PAH in hospitalized HIV-infected patients was 0.04% to 0.015%, much lower than the expected prevalence of 0.5%.[55] This may indicate that the diagnosis of HIV-PAH is being missed and reinforces the importance of careful history taking to identify patients with dyspnea or exercise intolerance that is unexplained, as well as appropriate follow-up evaluation.

A meta-analysis of published cases of HIV-PAH performed in 2000 found that the most common presenting symptom in HIV-PAH was progressive shortness of breath (85%) followed by pedal edema (30%), nonproductive cough (19%), fatigue (13%), syncope or near syncope (12%), and chest pain (7%). Findings on examination may include signs of PH and right heart failure, including a loud P2 component of the second heart sound, a right sided S3 gallop, murmurs of tricuspid and pulmonic regurgitation, increased jugular venous pressure, and peripheral edema.[22] Abnormal findings on lung examination may suggest an alternative diagnosis because lung examination results are usually normal in patients with PAH. The chest radiograph may show supportive, but nonspecific findings such as cardiomegaly and prominence of the pulmonary arteries. Likewise, the electrocardiogram may show right ventricular hypertrophy, right axis deviation, right atrial abnormality, or sinus tachycardia.

Diagnosis

Until recently, it was recommended that HIV-infected patients without a clinical suspicion of PAH undergo echocardiographic screening for PAH because it is not cost-effective.[56] However, this recommendation was updated

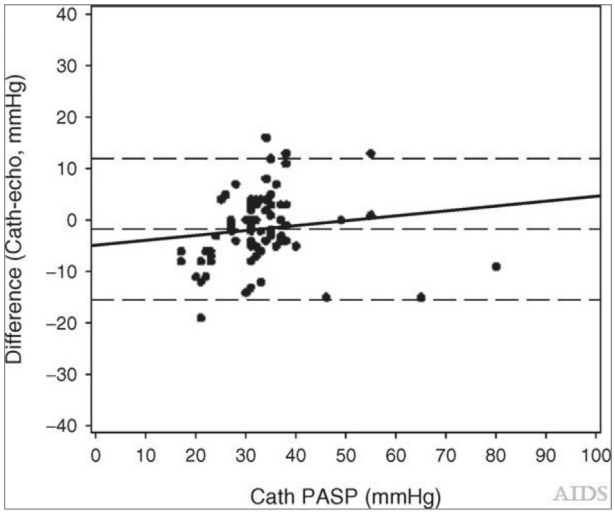

Figure 3. Bland–Altman analysis demonstrating lack of agreement between the Doppler echocardiogram-estimated pulmonary artery systolic pressure (PASP) and right heart catheterization (RHC)-measured PASP. PA, pulmonary artery; PVR, pulmonary vascular resistance. Reproduced from Selby et al.[61] with permission from Wolters Kluwer Health, Inc.

during the 2018 6th World Symposium of Pulmonary Hypertension. The new recommendation is for echocardiographic screening of HIV-infected patients with one of the following risk factors: female sex, intravenous drug use/cocaine use, hepatitis C virus infection, origin from a high-prevalence country, known Nef or Tat HIV proteins, and US African-American patients independent of symptoms.[57]

Evaluation of HIV-PAH is similar to that of HIV-negative patients with suspected PAH. All patients require a comprehensive evaluation to identify all potential contributing factors to elevated PASP, including identification of other conditions that cause group 1 PAH and any conditions that could cause group 2, 3, 4, or 5 PH according to guideline recommendations. When evaluating HIV-infected patients with respiratory symptoms, it is also important to consider and exclude all non-PAH causes of these symptoms.

Echocardiography is usually the first test to be performed if HIV-PAH is suspected. PASP is estimated from Doppler-estimated velocity of the systolic regurgitant jet across the tricuspid valve, then entering the value into the modified Bernoulli equation to estimate the pressure gradient between the right atrium and right ventricle, and then adding the estimated right atrial pressure to determine the total PASP.[58] Compared with invasive hemodynamics, Doppler estimates of PASP have been shown to be inaccurate in both the general and PAH populations[59,60] and in patients with HIV-PAH.[61] In a study of use of Doppler echocardiography to assess PASP in an HIV-infected cohort, Doppler estimates of PASP were inaccurate in 19.7% of patients and 1 in 3 patients with a diagnosis of HIV-PAH were missed (Fig. 3).[61] Thus, estimation of PASP alone by echocardiography is not sufficient to definitely rule out PAH.

In addition to PASP, echocardiography provides other important data points in the evaluation for PAH. These additional findings should be incorporated into the assessment of the clinical suspicion for PAH in HIV-infected patients. Proceeding with invasive hemodynamic evaluation is often appropriate in patients who do not have elevated echocardiographically estimated PASP but do have other echocardiographic findings that occur secondary to PAH. Pulmonary artery acceleration time as measured by pulsed-wave Doppler analysis and can be used to estimate PASP independently of tricuspid regurgitation, and it can be especially useful in cases when tricuspid regurgitation is

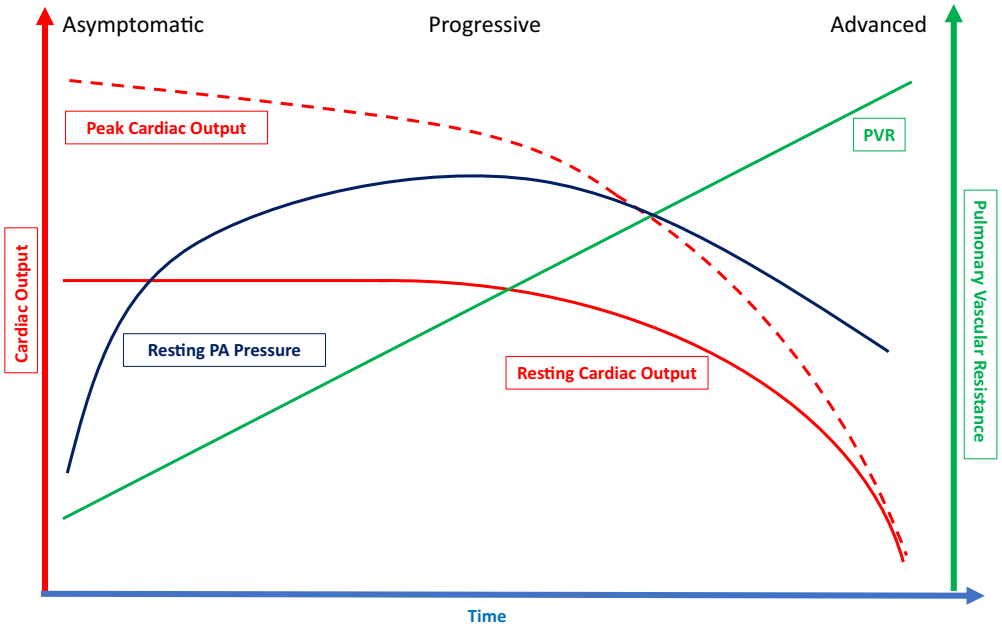

Figure 4. Schematic representation of changes in haemodynamic parameters over the course of PAH.

insufficient to estimate PASP.[62] Studies of right ventricular outflow Doppler flow velocity envelopes can provide useful insight into hemodynamics. Mid-systolic flow deceleration and notching have been associated with higher PAP, higher PVR, and worse outcomes.[63,64] Evaluation for right heart chamber enlargement, systolic dysfunction, and paradoxical septal motion are important in the evaluation of the severity and prognosis of HIV-PAH.[65] Echocardiography is also helpful to exclude secondary causes of PH, including left ventricular systolic dysfunction and clinically relevant valvular diseases.[66]

RHC is the gold standard for the hemodynamic evaluation of PH.[67] Hemodynamic assessment with RHC is mandatory before the initiation of PAH-specific therapy. It should be performed by a clinician with expertise in hemodynamic assessment and diagnostic evaluation for patients with PH to minimize complications and optimize data collection.[68] Guidelines and recommendations for the optimal performance of RHC have been published.[6,11] During RHC for suspected PAH, measurements should include the PAP, right atrial pressure, cardiac output, and PAWP, as well as the calculated cardiac index and PVR. A complete hemodynamic assessment including assessment of the cardiac output and PVR is required because the PAP in isolation is inadequate to make the diagnosis of PAH or assess prognosis. As PAH progresses and the right ventricle fails and can no longer generate pressure, PAP will decrease (Fig. 4). However, cardiac output in this case will be reduced, and the resulting PVR will be very elevated. Measurement of the PAWP is used as an estimate of left ventricular filling pressures, but it may be difficult to obtain a good-quality PAWP in some patients. Measurement of the left ventricular end-diastolic pressure (LVEDP) should be performed whenever a reliable PAWP tracing cannot be obtained or the value of the PAWP is inconsistent with the expected value based on the clinical picture. When an LVEDP is obtained, it should be substituted for the PAWP in calculation of the PVR. Routine vasodilator testing is not recommended in patients with suspected HIV-PAH because positive vasodilator testing rarely is found in patients with HIV-PAH. Additional provocative testing such as assessment of exercise hemodynamics or changes in hemodynamics after fluid challenge may be considered in patients with characteristics suggesting PH secondary to left heart disease; however, interpretation of results in this setting can be challenging.[57] In patients who are at risk for coronary artery disease, performance of coronary angiography at the time of RHC may be appropriate.

Prognosis

In patients with HIV, the development of PAH is an independent predictor of death and has often been associated with poor survival.[69] Common causes of death in HIV-PAH are attributed to consequences of PH, including right heart failure and sudden death (57%-71%).[22,53,70]

The effects of ART on the development and prognosis of HIV-PAH remain controversial, and available data are inadequate to determine clearly the effect of ART on HIV-PAH. Before the era of ART and development of PAH-specific drugs, prognosis for HIV-PAH was extremely poor with early studies showing high short-term mortality ranging from

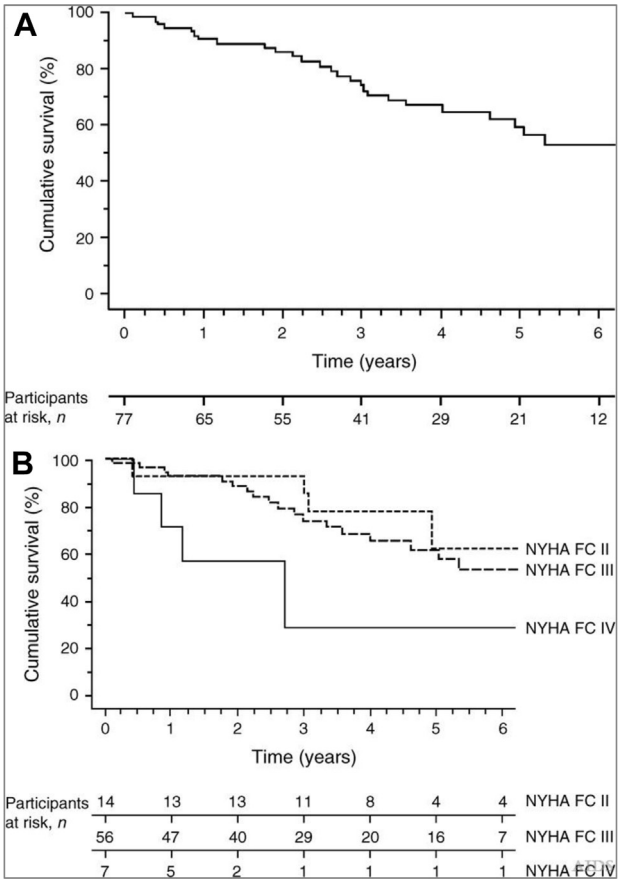

Figure 5. Kaplan–Meier estimate (**A**) of overall survival in patients with PAH-HIV and (**B**) of survival stratified by baseline New York Heart Association (NYHA) class. Survival was calculated from the time of PAH diagnosis to the end of follow-up. FC, functional class. Reprinted with permission from Degano et al.[70] with permission from Wolters Kluwer Health, Inc.

27% to 66%.[22,53,69,71] One study of 20 HIV-infected patients with PH reported survival rates of 46% at 2 years,[72] and another study of 19 patients with HIV-PAH reported survival rates of 58% at 1 year, 32% at 2 years, and 21% at 3 years with median survival of 1.3 years.[73] A larger longitudinal study of 82 consecutive patients from 1986 to 2000 showed survival rates at 1, 2, and 3 years was 73%, 60%, and 47%, respectively.[53] This study also showed that higher New York Heart Association (NYHA) functional class predicted a poor outcome. Factors associated with an improved outcomes included higher CD4 cell count, use of ART, and treatment with epoprostenol (Fig. 5).

Some recent studies have shown improved HIV-PAH survival rates that some authors have hypothesized is a result of treatment with ART in addition to treatment with PAH therapies. A retrospective review of 77 consecutive patients between 2000 and 2008 showed that overall survival rates at 1, 2, 3, and 5 years were 88%, 84%, 72%, and 63%, respectively.[70] Consistent with prior studies, survival was worse for patients in NYHA class IV. Factors related to poor HIV control (low CD4+ lymphocyte count and detectable viral load) and factors related to increased severity of PAH

(clinical right heart failure, NYHA functional class IV, and cardiac index < 2.8 L/min/m2) were associated with poor survival on univariate analysis. A low cardiac index and low CD4 count were independently related to poor survival on multivariate analysis. A recent report from the REVEAL registry showed that survival in HIV-PAH may be better than that of other forms of PAH. In this large U.S. registry of PAH, patients' survival in HIV-PAH was 93%, 75%, and 64% compared with idiopathic PAH survival of 88%, 74%, and 64% at 1, 3, and 5 years, respectively.[74] There have also been several published reports of patients with HIV-PAH who had persistently normal hemodynamics even after cessation of PAH therapy.[75]

Treatment

The approach to treatment of HIV-PAH is extrapolated from larger studies of mixed group 1 patients with PAH because there are few studies evaluating patients with HIV-PAH alone.

Antiretroviral treatment

Current guidelines recommend that all patients with HIV should be offered ART regardless of their CD4 cell count or viral load.[76] Therefore, all patients with HIV-PAH should be treated with ART. Whether or not ART confers any hemodynamic or outcomes benefits for those with HIV and PAH remains controversial.[77]

In a retrospective analysis of 1042 HIV-infected patients, PAH was significantly more frequent in patients treated with ART than in those treated only with nucleoside reverse transcriptase analogs.[78] However, this difference may be due to better knowledge of PAH as a complication of HIV infection. Indeed, other retrospective studies have shown that antiretroviral treatment is beneficial with reduced incidence of PAH in patients treated with ART.[71,78] A review of 509 cases of HIV-PAH reported in the literature from January 1987 to January 2009 showed that survival rates were higher for patients treated with ART (55% vs 22%, $P < 0.01$), patients treated with PAH-specific therapy (76% vs 32%), and patients treated with ART and PAH-specific therapy (69% vs 38%, $P < 0.01$).[77]

The effects of ART on functional and hemodynamic parameters in HIV-PAH are controversial. A retrospective analysis of 47 patients in the Swiss HIV cohort study showed significant beneficial effects on the PASP and improvement in NYHA functional class in patients with HIV-PAH treated with ART.[71] Another study reported that ART improved right ventricular systolic pressure−right atrial pressure gradient measured by echocardiography.[73] The lack of confirmatory diagnosis using RHC was a significant limitation of these studies. When RHC was used for evaluation, ART was associated with improved exercise tolerance assessed by 6-minute walk distance without change in hemodynamic parameters.[70]

The best evidence for the effects of ART on HIV-PAH comes from the large prospective French cohort study of HIV-PAH prevalence after treatment with ART became routine. The finding that the prevalence was unchanged supports a conclusion that ART does not affect the development of HIV-PAH.[14] The equipoise surrounding the effect of ART on HIV-PAH is redundant given that ART remains central in standalone HIV management.

General measures

General principles of management of PH apply to patients with HIV-PAH. Diuretics should be used for volume overload with adjustment to maintain right-sided filling pressures as near to normal as possible. Supplemental oxygen should be used to correct hypoxemia because hypoxemia can exacerbate pulmonary vasoconstriction and worsen PH. A favourable response to vasoreactivity testing in patients with HIV-PAH is rare, and calcium channel blockers should be used only in carefully selected patients with close monitoring for worsening symptoms and hemodynamics.[79]

PAH-specific therapy

Although patients with HIV are under-represented in studies of PAH-specific therapy, a systematic review of HIV-PAH treatment suggested a significant benefit to PAH-specific therapy.[77] In fact, normalization of hemodynamics with PAH-specific therapy, which is rare in PAH from other causes, has been reported.[80] The approach to using PAH-specific therapies in HIV-PAH is largely extrapolated from studies of PAH-specific therapies in other causes of group 1 PAH. PAH-specific therapies should be used in patients with HIV-PAH according to current PAH treatment guidelines.[80] Because the prognosis of HIV-PAH is poor, aggressive early treatment with parenteral prostanoids as well as upfront double or triple combination therapy may be appropriate. In patients who do not respond to PAH-specific therapies, lung transplantation may be considered.[81] Current guidelines recommend that patients with PAH be managed at or in collaboration with a PAH expert referral center.[80] This may be particularly important in patients with HIV-PAH given the potential for important drug interactions between ART and PAH-specific therapies.

Phosphodiesterase inhibitors

Experience with phosphodiesterase type 5 inhibitors in HIV-PAH comes from case reports and case series that report improvements in dyspnea, NYHA functional class, exercise capacity, and mean PAP.[82] Possible interactions with ART must be kept in mind when prescribing phosphodiesterase type 5 inhibitors. The metabolism of sildenafil and tadalafil is mediated by cytochrome P450 CYP 3A4 and CYP 2C9, which are inhibited by protease inhibitors including ritonavir. Marked increases in sildenafil levels have been observed during co-administration with indinavir, saquinavir, and ritonavir leading to the recommendation against co-administration with sildenafil. However, this finding is of uncertain clinical significance because it has not been associated with hypotension or adverse effects in pharmacokinetic studies.[83] Successful co-administration of ritonavir and sildenafil in patients with HIV-PAH have been reported.[84] Tadalafil levels are less affected by ritonavir, and guidelines suggest only close monitoring if tadalafil therapy is initiated.[85]

Endothelin receptor antagonists

Bosentan, ambrisentan, and macitentan are endothelin receptor antagonists used in the management of PAH. Endothelin receptor antagonists improve hemodynamics and exercise tolerance, and prevent worsening of PH. A prospective study of 16 patients with severely symptomatic (NYHA class III-IV) HIV-PAH showed that 16 weeks of treatment with bosentan improved clinical and hemodynamic parameters, including improvement in 6-minute walk distance by 91 $\pm$ 60 m ($P < 0.001$), NYHA functional class by at least 1 class in 14 patients, increase in cardiac index by 39%, decrease in mPAP by 21%, decrease in PVR by 43%, and improved quality of life.[86] An open-label study of bosentan with ART compared with ART alone also showed improvement in exercise capacity and cardiopulmonary hemodynamic parameters at 24 weeks.[87] These short-term improvements were found to be sustained long term in a study of bosentan in HIV-PAH that followed 59 patients over 29 months and showed long-term improvement in symptoms, exercise tolerance, and hemodynamic parameters.[88] In addition, it showed improved survival with survival rates of 93%, 86%, and 66% at 1, 2, and 3 years, respectively, with normalization of hemodynamic parameters in 10 of 59 patients. In all these studies, bosentan was observed to be safe and overall well tolerated in conjunction with ART with no adverse effects on control of HIV infection.

Large studies of ambrisentan and macitentan that resulted in Food and Drug Administration approval in PAH included only small numbers of patients with HIV.[89,90] However, use of bosentan has largely been supplanted by ambrisentan and macitentan because of the lower frequency of liver function test abnormalities and fewer drug interactions with ART.[91]

Prostacyclin analogues

Prostacyclin analogues can be administered through various routes, including intravenous, subcutaneous, inhaled, or oral. Use of short-term epoprostenol infusions was shown to reduce total PVR by 20% in a study of 19 patients with HIV-PAH.[72] Other smaller case series of 2 patients[92] and 6 patients[93] showed improvements in PAP, PVR, and cardiac output. In the latter study, the benefits were sustained over longer-term follow-up. In an uncontrolled trial of 8 patients with HIV-PAH, inhaled iloprost resulted in acute improvement of PVR and confidence interval. Hemodynamic improvement persisted and exercise capacity also improved in 4 patients who continued with long-term iloprost.[94] Selexipag is a novel prostacyclin receptor agonist that was studied in 1156 patients in a phase 3 randomized controlled trial. However, only 10 patients with HIV-PAH were included, so it is difficult to draw specific conclusions about its use in HIV-PAH.[95]

Future Directions

Diagnosing HIV-PAH and initiating treatment early are the fundamental goals in managing this condition successfully. It is possible that the high prevalence of elevated PASP in the echocardiography studies described could be early or mild HIV-PAH and might identify patients at high risk for developing HIV-PAH in whom early treatment might beneficial. However, screening for HIV-PAH is currently not recommended, and treatment of patients with HIV who have mPAP < 25 mm Hg is not recommended given the uncertain significance of mild elevations of PASP and uncertain benefits of treatment in these patients.

New diagnostic tools may better identify patients with HIV-PAH or those at risk of developing HIV-PAH. A single-center prospective observational study aims to use exercise magnetic resonance imaging in conjunction with cardiopulmonary testing to identify HIV-positive patients with elevated PASP on echocardiography who will undergo rest and exercise magnetic resonance imaging evaluation over 24 months to define longitudinal progression of disease.[96] Novel biomarkers also may aid in the identification of patients with HIV-PAH who are at risk of a poor outcome. HIV-positive patients with elevated levels, the biomarker ST2, N-terminal pro—B-type natriuretic peptide, and GDF-15 were shown to have a 67% increased risk of elevated PASP on echocardiography and 3.1-fold higher mortality compared with patients with HIV without elevations in these markers.[49] Further study is needed to determine if these approaches to diagnosis result in better outcomes for patients.

Conclusion

HIV-PAH is an important complication of HIV that results in significant mortality and mortality. Although incompletely understood, HIV proteins and chronic immune activation seem to play a significant role. Incorporating advanced imaging modalities and biomarkers may help us promptly detect and treat cases of HIV-PAH earlier. PAH-specific therapy remains the cornerstone of management, and potential for drug interactions must be kept in mind. Further studies are needed to understand the pathogenesis of HIV-PAH to find optimal targets for treatment.

Disclosures

The authors have no conflicts of interest to disclose.

References

1. Kim KK, Factor SM. Membranoproliferative glomerulonephritis and plexogenic pulmonary arteriopathy in a homosexual man with acquired immunodeficiency syndrome. Hum Pathol 1987;18:1293-6.

2. Barnett CF, Hsue PY, Machado RF. Pulmonary hypertension: an increasingly recognized complication of hereditary hemolytic anemias and HIV infection. JAMA 2008;299:324-31.

3. Thienemann F, Sliwa K, Rockstroh JK. HIV and the heart: the impact of antiretroviral therapy: a global perspective. Eur Heart J 2013;34:3538-46.

4. Boccara F. Cardiovascular complications and atherosclerotic manifestations in the HIV-infected population: type, incidence and associated risk factors. AIDS 2008;22(Suppl 3):S19-26.

5. Cannillo M, D'Ascenzo F, Grosso Marra W, et al. Heart failure in patients with human immunodeficiency virus: a review of the literature. J Cardiovasc Med (Hagerstown) 2015;16:383-9.

6. Hoeper MM, Bogaard HJ, Condliffe R, et al. Definitions and diagnosis of pulmonary hypertension. J Am Coll Cardiol 2013;62:D42-50.

7. Simonneau G, Montani D, Celermajer DS, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. Eur Respir J 2019;53(1).

8. Cerrato E, D'Ascenzo F, Biondi-Zoccai G, et al. Cardiac dysfunction in pauci symptomatic human immunodeficiency virus patients: a meta-analysis in the highly active antiretroviral therapy era. Eur Heart J 2013;34:1432-6.

9. Staitieh B, Guidot DM. Noninfectious pulmonary complications of human immunodeficiency virus infection. Am J Med Sci 2014;348:502-11.

10. Barnett CF, De Marco T. 59 - Pulmonary hypertension due to lung disease. In: Broaddus VC, Mason RJ, Ernst JD, et al., eds. Murray and Nadel's Textbook of Respiratory Medicine (Sixth Edition). Philadelphia: W.B. Saunders, 2016:1050-1065.e1055.

11. Barnett CF, Alvarez P, Park MH. Pulmonary arterial hypertension: diagnosis and treatment. Cardiol Clin 2016;34:375-89.

12. Speich R, Jenni R, Opravil M, Pfab M, Russi EW. Primary pulmonary hypertension in HIV infection. Chest 1991;100:1268-71.

13. Humbert M, Sitbon O, Chaouat A, et al. Pulmonary arterial hypertension in France. Am J Respir Crit Care Med 2006;173:1023-30.

14. Sitbon O, Lascoux-Combe C, Delfraissy JF, et al. Prevalence of HIV-related pulmonary arterial hypertension in the current antiretroviral therapy era. Am J Respir Crit Care Med 2008;177:108-13.

15. Isasti G, Moreno T, Perez I, et al. High prevalence of pulmonary arterial hypertension in a cohort of asymptomatic HIV-infected patients. AIDS Res Hum Retroviruses 2013;29:231-4.

16. Quezada M, Martin-Carbonero L, Soriano V, et al. Prevalence and risk factors associated with pulmonary hypertension in HIV-infected patients on regular follow-up. AIDS 2012;26:1387-92.

17. Schwarze-Zander C, Pabst S, Hammerstingl C, et al. Pulmonary hypertension in HIV infection: a prospective echocardiographic study. HIV Med 2015;16:578-82.

18. Bigna JJ, Nansseu JR, Um LN, et al. Prevalence and incidence of pulmonary hypertension among HIV-infected people in Africa: a systematic review and meta-analysis. BMJ Open 2016;6:e011921.

19. Hsue PY, Deeks SG, Farah HH, et al. Role of HIV and human herpesvirus-8 infection in pulmonary arterial hypertension. AIDS 2008;22:825-33.

20. Mondy KE, Gottdiener J, Overton ET, et al. High prevalence of echocardiographic abnormalities among HIV-infected persons in the era of highly active antiretroviral therapy. Clin Infect Dis 2011;52:378-86.

21. Pietra GG, Capron F, Stewart S, et al. Pathologic assessment of vasculopathies in pulmonary hypertension. J Am Coll Cardiol 2004;43:25S-32S.

22. Mehta NJ, Khan IA, Mehta RN, Sepkowitz DA. HIV-related pulmonary hypertension: analytic review of 131 cases. Chest 2000;118:1133-41.

23. Montani D, Price LC, Dorfmuller P, et al. Pulmonary veno-occlusive disease. Eur Respir J 2009;33:189-200.

24. Mette SA, Palevsky HI, Pietra GG, et al. Primary pulmonary hypertension in association with human immunodeficiency virus infection. A possible viral etiology for some forms of hypertensive pulmonary arteriopathy. Am Rev Respir Dis 1992;145:1196-200.

25. Kanmogne GD, Kennedy RC, Grammas P. Analysis of human lung endothelial cells for susceptibility to HIV type 1 infection, coreceptor expression, and cytotoxicity of gp120 protein. AIDS Res Hum Retroviruses 2001;17:45-53.

26. Mermis J, Gu H, Xue B, et al. Hypoxia-inducible factor-1 alpha/platelet derived growth factor axis in HIV-associated pulmonary vascular remodeling. Respir Res 2011;12:103.

27. Porter KM, Walp ER, Elms SC, et al. Human immunodeficiency virus-1 transgene expression increases pulmonary vascular resistance and exacerbates hypoxia-induced pulmonary hypertension development. Pulm Circ 2013;3:58-67.

28. Kanmogne GD, Primeaux C, Grammas P. Induction of apoptosis and endothelin-1 secretion in primary human lung endothelial cells by HIV-1 gp120 proteins. Biochem Biophys Res Commun 2005;333:1107-15.

29. Ehrenreich H, Rieckmann P, Sinowatz F, et al. Potent stimulation of monocytic endothelin-1 production by HIV-1 glycoprotein 120. J Immunol 1993;150:4601-9.

30. Bohm F, Pernow J. The importance of endothelin-1 for vascular dysfunction in cardiovascular disease. Cardiovasc Res 2007;76:8-18.

31. Parikh RV, Ma Y, Scherzer R, et al. Endothelin-1 predicts hemodynamically assessed pulmonary arterial hypertension in HIV infection. PLoS One 2016;11:e0146355.

32. Marecki JC, Cool CD, Parr JE, et al. HIV-1 Nef is associated with complex pulmonary vascular lesions in SHIV-nef-infected macaques. Am J Respir Crit Care Med 2006;174:437-45.

33. Almodovar S, Knight R, Allshouse AA, et al. Human immunodeficiency virus nef signature sequences are associated with pulmonary hypertension. AIDS Res Hum Retroviruses 2012;28:607-18.

34. Almodovar S, Swanson J, Giavedoni LD, et al. Lung vascular remodeling, cardiac hypertrophy, and inflammatory cytokines in SHIVnef-infected macaques. Viral Immunol 2018;31:206-22.

35. Deng Z, Morse JH, Slager SL, et al. Familial primary pulmonary hypertension (gene PPH1) is caused by mutations in the bone morphogenetic protein receptor-II gene. Am J Hum Genet 2000;67:737-44.

36. Caldwell RL, Gadipatti R, Lane KB, Shepherd VL. HIV-1 TAT represses transcription of the bone morphogenic protein receptor-2 in U937 monocytic cells. J Leukoc Biol 2006;79:192-201.

37. George MP, Champion HC, Gladwin MT, Norris KA, Morris A. Injection drug use as a "second hit" in the pathogenesis of HIV-associated pulmonary hypertension. Am J Respir Crit Care Med 2012;185:1144-6.

38. Spikes L, Dalvi P, Tawfik O, et al. Enhanced pulmonary arteriopathy in simian immunodeficiency virus-infected macaques exposed to morphine. Am J Respir Crit Care Med 2012;185:1235-43.

39. Dhillon NK, Li F, Xue B, et al. Effect of cocaine on human immunodeficiency virus-mediated pulmonary endothelial and smooth muscle dysfunction. Am J Respir Cell Mol Biol 2011;45:40-52.

40. Dalvi P, O'Brien-Ladner A, Dhillon NK. Downregulation of bone morphogenetic protein receptor axis during HIV-1 and cocaine-mediated pulmonary smooth muscle hyperplasia: implications for HIV-related pulmonary arterial hypertension. Arterioscler Thromb Vasc Biol 2013;33:2585-95.

41. Fauci AS, Pantaleo G, Stanley S, Weissman D. Immunopathogenic mechanisms of HIV infection. Ann Intern Med 1996;124:654-63.

42. Morse JH, Barst RJ, Itescu S, et al. Primary pulmonary hypertension in HIV infection: an outcome determined by particular HLA class II alleles. Am J Respir Crit Care Med 1996;153:1299-301.

43. Hsue PY, Deeks SG, Hunt PW. Immunologic basis of cardiovascular disease in HIV-infected adults. J Infect Dis 2012;205(Suppl 3):S375-82.

44. Parikh RV, Scherzer R, Grunfeld C, et al. Elevated levels of asymmetric dimethylarginine are associated with lower CD4+ count and higher viral load in HIV-infected individuals. Atherosclerosis 2013;229:246-52.

45. Parikh RV, Scherzer R, Nitta EM, et al. Increased levels of asymmetric dimethylarginine are associated with pulmonary arterial hypertension in HIV infection. AIDS 2014;28:511-9.

46. Humbert M, Monti G, Fartoukh M, et al. Platelet-derived growth factor expression in primary pulmonary hypertension: comparison of HIV seropositive and HIV seronegative patients. Eur Respir J 1998;11:554-9.

47. Ascherl G, Hohenadl C, Schatz O, et al. Infection with human immunodeficiency virus-1 increases expression of vascular endothelial cell growth factor in T cells: implications for acquired immunodeficiency syndrome-associated vasculopathy. Blood 1999;93:4232-41.

48. Secemsky EA, Scherzer R, Nitta E, et al. Novel biomarkers of cardiac stress, cardiovascular dysfunction, and outcomes in HIV-infected individuals. JACC Heart Fail 2015;3:591-9.

49. Scherzer R, Shah SJ, Secemsky E, et al. Association of biomarker clusters with cardiac phenotypes and mortality in patients with HIV infection. Circ Heart Fail 2018;11:e004312.

50. Cool CD, Rai PR, Yeager ME, et al. Expression of human herpesvirus 8 in primary pulmonary hypertension. N Engl J Med 2003;349:1113-22.

51. Montani D, Marcelin AG, Sitbon O, et al. Human herpes virus 8 in HIV and non-HIV infected patients with pulmonary arterial hypertension in France. AIDS 2005;19:1239-40.

52. Saito T, Miyagawa K, Chen SY, et al. Upregulation of human endogenous retrovirus-K is linked to immunity and inflammation in pulmonary arterial hypertension. Circulation 2017;136:1920-35.

53. Nunes H, Humbert M, Sitbon O, et al. Prognostic factors for survival in human immunodeficiency virus-associated pulmonary arterial hypertension. Am J Respir Crit Care Med 2003;167:1433-9.

54. Cicalini S, Almodovar S, Grilli E, Flores S. Pulmonary hypertension and human immunodeficiency virus infection: epidemiology, pathogenesis, and clinical approach. Clin Microbiol Infect 2011;17:25-33.

55. Henriques-Forsythe M, Annangi S, Farber HW. Prevalence and hospital discharge status of human immunodeficiency virus-associated pulmonary arterial hypertension in the United States. Pulm Circ 2015;5:506-12.

56. McGoon M, Gutterman D, Steen V, et al. Screening, early detection, and diagnosis of pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. Chest 2004;126:14S-34S.

57. Frost A, Badesch D, Gibbs JSR, et al. Diagnosis of pulmonary hypertension. Eur Respir J 2018:1801904.

58. Yock PG, Popp RL. Noninvasive estimation of right ventricular systolic pressure by Doppler ultrasound in patients with tricuspid regurgitation. Circulation 1984;70:657-62.

59. Rich JD, Shah SJ, Swamy RS, Kamp A, Rich S. Inaccuracy of Doppler echocardiographic estimates of pulmonary artery pressures in patients with pulmonary hypertension: implications for clinical practice. Chest 2011;139:988-93.

60. Fisher MR, Forfia PR, Chamera E, et al. Accuracy of Doppler echocardiography in the hemodynamic assessment of pulmonary hypertension. Am J Respir Crit Care Med 2009;179:615-21.

61. Selby VN, Scherzer R, Barnett CF, et al. Doppler echocardiography does not accurately estimate pulmonary artery systolic pressure in HIV-infected patients. AIDS 2012;26:1967-9.

62. Yared K, Noseworthy P, Weyman AE, et al. Pulmonary artery acceleration time provides an accurate estimate of systolic pulmonary arterial pressure during transthoracic echocardiography. J Am Soc Echocardiogr 2011;24:687-92.

63. Arkles JS, Opotowsky AR, Ojeda J, et al. Shape of the right ventricular Doppler envelope predicts hemodynamics and right heart function in pulmonary hypertension. Am J Respir Crit Care Med 2011;183:268-76.

64. Takahama H, McCully RB, Frantz RP, Kane GC. Unraveling the RV ejection Doppler envelope: insight into pulmonary artery hemodynamics and disease severity. JACC Cardiovasc Imaging 2017;10:1268-77.

65. Raymond RJ, Hinderliter AL, Willis PW, et al. Echocardiographic predictors of adverse outcomes in primary pulmonary hypertension. J Am Coll Cardiol 2002;39:1214-9.

66. Bossone E, Bodini BD, Mazza A, Allegra L. Pulmonary arterial hypertension: the key role of echocardiography. Chest 2005;127:1836-43.

67. Badesch DB, Champion HC, Sanchez MA, et al. Diagnosis and assessment of pulmonary arterial hypertension. J Am Coll Cardiol 2009;54:S55-66.

68. Barnett CF, Hsue PY. Human immunodeficiency virus-associated pulmonary arterial hypertension. Clin Chest Med 2013;34:283-92.

69. Opravil M, Sereni D. Natural history of HIV-associated pulmonary arterial hypertension: trends in the HAART era. AIDS 2008;22(Suppl 3):S35-40.

70. Degano B, Guillaume M, Savale L, et al. HIV-associated pulmonary arterial hypertension: survival and prognostic factors in the modern therapeutic era. AIDS 2010;24:67-75.

71. Zuber JP, Calmy A, Evison JM, et al. Pulmonary arterial hypertension related to HIV infection: improved hemodynamics and survival associated with antiretroviral therapy. Clin Infect Dis 2004;38:1178-85.

72. Petitpretz P, Brenot F, Azarian R, et al. Pulmonary hypertension in patients with human immunodeficiency virus infection. Comparison with primary pulmonary hypertension. Circulation 1994;89:2722-7.

73. Opravil M, Pechere M, Speich R, et al. HIV-associated primary pulmonary hypertension. A case control study. Swiss HIV cohort study. Am J Respir Crit Care Med 1997;155:990-5.

74. Benza RL, Miller DP, Barst RJ, et al. An evaluation of long-term survival from time of diagnosis in pulmonary arterial hypertension from the REVEAL Registry. Chest 2012;142:448-56.

75. Tcherakian C, Rivaud E, Zucman D, Metivier AC, Couderc LJ. Curing HIV-associated pulmonary arterial hypertension. Eur Respir J 2012;39:1045-6.

76. Gunthard HF, Saag MS, Benson CA, et al. Antiretroviral drugs for treatment and prevention of HIV infection in adults: 2016 Recommendations of the International Antiviral Society-USA Panel. JAMA 2016;316:191-210.

77. Cicalini S, Chinello P, Grilli E, Petrosillo N. Treatment and outcome of pulmonary arterial hypertension in HIV-infected patients: a review of the literature. Curr HIV Res 2009;7:589-96.

78. Pugliese A, Isnardi D, Saini A, et al. Impact of highly active antiretroviral therapy in HIV-positive patients with cardiac involvement. J Infect 2000;40:282-4.

79. Montani D, Savale L, Natali D, et al. Long-term response to calcium-channel blockers in non-idiopathic pulmonary arterial hypertension. Eur Heart J 2010;31:1898-907.

80. Galiè N, Corris PA, Frost A, et al. Updated treatment algorithm of pulmonary arterial hypertension. J Am Coll Cardiol 2013;62:D60-72.

81. Kern RM, Seethamraju H, Blanc PD, et al. The feasibility of lung transplantation in HIV-seropositive patients. Ann Am Thorac Soc 2014;11:882-9.

82. Barnett CF, Machado RF. Sildenafil in the treatment of pulmonary hypertension. Vasc Health Risk Manag 2006;2:411-22.

83. Muirhead GJ, Wulff MB, Fielding A, Kleinermans D, Buss N. Pharmacokinetic interactions between sildenafil and saquinavir/ritonavir. Br J Clin Pharmacol 2000;50:99-107.

84. Chinello P, Cicalini S, Pichini S, et al. Sildenafil and bosentan plasma concentrations in a human immunodeficiency virus- infected patient with pulmonary arterial hypertension treated with ritonavir-boosted protease inhibitor. Infect Dis Rep 2015;7:5822.

85. Garraffo R, Lavrut T, Ferrando S, et al. Effect of tipranavir/ritonavir combination on the pharmacokinetics of tadalafil in healthy volunteers. J Clin Pharmacol 2011;51:1071-8.

86. Sitbon O, Gressin V, Speich R, et al. Bosentan for the treatment of human immunodeficiency virus-associated pulmonary arterial hypertension. Am J Respir Crit Care Med 2004;170:1212-7.

87. Barbaro G, Lucchini A, Pellicelli AM, et al. Highly active antiretroviral therapy compared with HAART and bosentan in combination in patients with HIV-associated pulmonary hypertension. Heart 2006;92:1164-6.

88. Degano B, Yaici A, Le Pavec J, et al. Long-term effects of bosentan in patients with HIV-associated pulmonary arterial hypertension. Eur Respir J 2009;33:92-8.

89. Galie N, Olschewski H, Oudiz RJ, et al. Ambrisentan for the treatment of pulmonary arterial hypertension: results of the ambrisentan in pulmonary arterial hypertension, randomized, double-blind, placebo-controlled, multicenter, efficacy (ARIES) study 1 and 2. Circulation 2008;117:3010-9.

90. Pulido T, Adzerikho I, Channick RN, et al. Macitentan and morbidity and mortality in pulmonary arterial hypertension. N Engl J Med 2013;369:809-18.

91. Ben-Yehuda O, Pizzuti D, Brown A, et al. Long-term hepatic safety of ambrisentan in patients with pulmonary arterial hypertension. J Am Coll Cardiol 2012;60:80-1.

92. Stricker H, Domenighetti G, Mombelli G. Prostacyclin for HIV-associated pulmonary hypertension. Ann Intern Med 1997;127:1043.

93. Aguilar RV, Farber HW. Epoprostenol (prostacyclin) therapy in HIV-associated pulmonary hypertension. Am J Respir Crit Care Med 2000;162:1846-50.

94. Ghofrani HA, Friese G, Discher T, et al. Inhaled iloprost is a potent acute pulmonary vasodilator in HIV-related severe pulmonary hypertension. Eur Respir J 2004;23:321-6.

95. Sitbon O, Channick R, Chin KM, et al. Selexipag for the treatment of pulmonary arterial hypertension. N Engl J Med 2015;373:2522-33.

96. Alaiti MA, Goud A, Ramani G, et al. Design of the exercise MRI evaluation of HIV-pulmonary arterial hypertension longitudinal determinants (EXALTED) trial. J Cardiovasc Med (Hagerstown) 2017;18:888-96.