REGULAR ARTICLE

Human Immunodeficiency Virus–Associated Pulmonary Arterial Hypertension

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Human immunodeficiency virus (HIV) attacks the immune system and can cause acquired immunodeficiency syndrome. Thankfully, antiretroviral therapy is highly effective, and people infected with HIV can live long lives with proper adherence to therapy. One of the important noninfectious complications of HIV is the development of pulmonary arterial hypertension (PAH). This review will cover the epidemiology, pathogenesis, and clinical characteristics of HIV-associated PAH. It will also cover the current knowledge on use of vasodilator therapy in this population.

INTRODUCTION

The human immunodeficiency virus (HIV) is a retrovirus, primarily transmitted via genital fluid or blood, which attacks the immune cells of the human body.[1,2] If left unchecked, HIV can lead to fulminant immune failure and the development of acquired immunodeficiency syndrome (AIDS).[3] The most recent estimates indicate that 38.4 million people are infected with HIV globally, and 1.5 million new infections occurred in 2021.[4] Treatment of HIV with antiretroviral therapy is quite successful and has led to a 32% decline in the annual incidence of new infections over the last decade. Further, regular use of antiretroviral therapy has limited the development of infectious complications and AIDS in those living with HIV, essentially turning a once almost universally fatal disease into a chronic one, the effects of which can be mitigated with good adherence to therapy.[5] As such, patients with HIV are living longer, and the noninfectious complications of HIV require escalating clinical focus.

The development of pulmonary arterial hypertension (PAH) is one of the important potential noninfectious complications of HIV.[6,7] PAH is a disorder of the pulmonary vasculature characterized by a rise in the pulmonary circulatory pressures. The hemodynamic definition of PAH requires an elevation in the mean pulmonary artery pressure to greater than 20 mmHg and an elevation in the pulmonary vascular resistance to greater than or equal to 3 Wood units. Increasingly, evidence of prognostic value exists with even mildly abnormal hemodynamics, and recently published guidelines advocate to diagnose PAH at a pulmonary vascular resistance threshold greater than 2 Wood units.[8,9] Clinically, patients with pulmonary hypertension can be classified into subgroups based on etiology. Patients with HIV-associated PAH (HIV-PAH) fall under the Group 1 classification, with a subgrouping under Group 1.4 (associated PAH).[6] When advanced, PAH can lead to right ventricular failure, respiratory distress, impaired health-related quality of life, and attenuated survival.[10]

EPIDEMIOLOGY OF HIV-PAH

The true prevalence of HIV-PAH is unknown; however, it is estimated to be at least 0.5% among HIV-positive individuals. Preliminary reports of the association between HIV and PAH came from the prospective evaluation of cardiopulmonary limitations in patients who complained of dyspnea within a large cohort of Swiss patients living with HIV.[11] The cohort consisted of 1,200 patients, and of the 74 patients who complained of cardiopulmonary limitations, 6 had echocardiographic evidence of PAH, which accounts for 0.5% of the total cohort. Authors of various other echocardiography-based studies confirmed a higher prevalence of elevations in the pulmonary artery systolic pressure (PASP) in patients living with HIV than the known estimates in the general population.[12-17] While some have postulated that the prevalence of HIV-PAH may be higher in sub-Saharan Africa due to a greater proportion of patients with uncontrolled HIV, a meta-analysis assessing echocardiography estimates of elevations in the pulmonary artery pressures found no regional difference across 25 studies from 17 different countries.[16]

The most comprehensive study, for which authors assessed the prevalence of HIV-PAH with invasive hemodynamics, came in 2008 from a large prospective cohort of 7,648 HIV positive patients living in France.[18] Patients were screened for unexplained dyspnea, and if they met criteria, an echocardiogram was obtained, followed by a right heart catheterization for those with suspicious findings. The study yielded a total of 35 patients with right heart

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catheterization-confirmed PAH or an estimated prevalence of 0.46% (95% CI = 0.32-0.64). Notably, this study was performed after the widespread adoption of antiretroviral therapy, and only 13% of the cohort had a CD4 count <200 cells/μL. As such, even though it is an older study, it is informative on the current state because the HIV control was relatively high in this cohort. Another notable aspect of this study is that it was performed before the 2018 World Symposium on Pulmonary Hypertension hemodynamic change, which lowered the mPAP criteria for diagnosis; thus, a 0.5% estimate may underestimate the current prevalence of HIV-PAH based on the contemporary hemodynamic definition.[6] The prevalence would also rise further based on the recent recommendations from the European Society of Cardiology and European Respiratory Society to reduce the pulmonary vascular resistance threshold for diagnosis of PAH.[8,9] Compiling the evidence together, even using conservative estimates, the prevalence of PAH in HIV-positive individuals is likely many thousand times that of idiopathic PAH in the general population.[19]

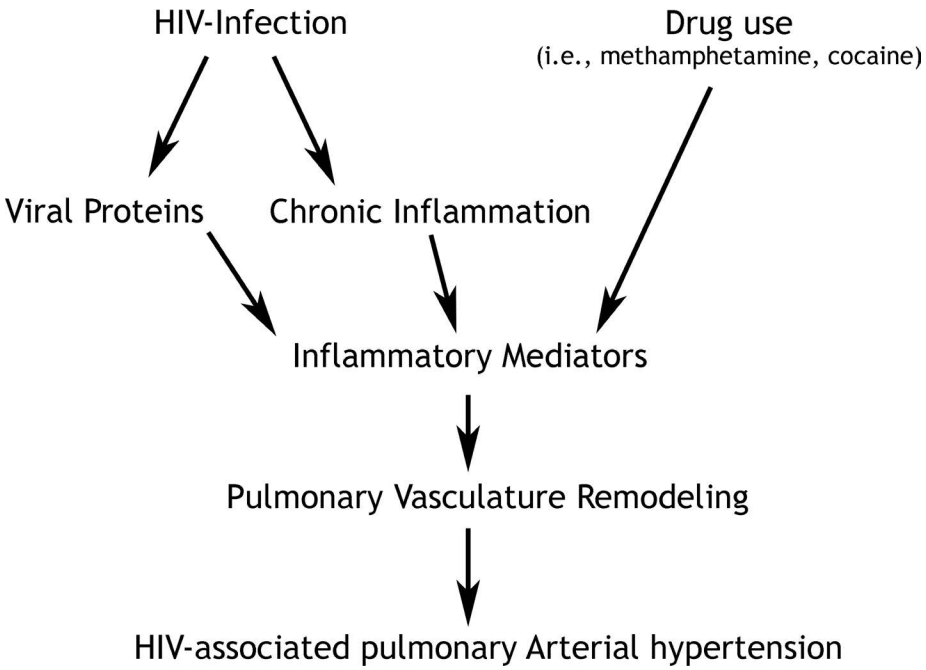

Figure 1: Pathogenesis of the development of human immunodeficiency virus (HIV)-associated pulmonary arterial hypertension (PAH). HIV viral infection of pulmonary vascular endothelial cells has not been seen. However, HIV viral proteins and chronic inflammation are believed to lead to elaboration of inflammatory mediators which cause pulmonary vascular remodeling including plexiform lesions characteristic of Group 1 PAH.

PATHOGENESIS OF HIV-PAH

The pathologic changes found in the pulmonary vasculature of patients with HIV-PAH are the same as those found in other patients with Group 1 PAH. Histopathologic findings in HIV-PAH demonstrate evidence of plexogenic pulmonary arteriopathy, medial hypertrophy, intimal fibrosis, and thrombotic arteriopathy.[20] Indeed, the explants or autopsies of most patients with HIV-PAH are impossible to differentiate from those with idiopathic PAH. Notably, however, some case reports have also demonstrated evidence of pulmonary veno-occlusive disease in HIV-positive individuals.[21,22] It is unclear if these cases represent comorbid conditions or if HIV can drive pulmonary veno-occlusive disease in addition to precapillary PAH.

The pathogenesis of HIV-PAH is believed to be multifactorial (Figure 1). Early investigation into the pathogenesis of precapillary PAH in patients with HIV led to the hypothesis of a direct viral infection of the pulmonary vasculature as the culprit, yet authors of in vitro studies of human lung microvascular endothelial cells have demonstrated a lack of expression of the HIV coreceptors CXCR4 and CCR5.[23] Further, adding HIV to the cell culture of these human lung microvascular endothelial cells demonstrated no active viral infection. Although direct cellular infection does not appear to be involved in the pathogenesis, it does appear that HIV viral proteins may be contributory. A transgenic HIV rat model, which is noninfectious but expresses HIV RNA and HIV proteins, demonstrated increased vascular oxidative stress as well as pathologic changes consistent with PAH.[24] Histology on the transgenic rats showed evidence of pulmonary vascular remodeling with medial thickening and right ventricular hypertrophy.

One potential mechanism by which these proteins lead to PAH is via increased production of vasoconstrictors. HIV envelope glycoprotein gp120, expressed on the surface of the HIV envelope, was shown to induce apoptotic cell death and also increase secretion of the pulmonary vasoconstrictor endothelin-1.[23,25] Circulating monocytes of HIV-infected individuals also demonstrate expression of the endothelin-1 gene, a finding which was not present in healthy controls.[26] Increased endothelin-1 expression is likely a strong driver of HIV-PAH, as higher levels are independently associated with worse hemodynamics assessed by right heart catheterization in HIV-infected patients.[27]

Another potential pathway through which HIV may lead to PAH is via the bone morphogenic protein receptor signaling pathway. Mutations in the gene bone morphogenic protein receptor 2 (BMPR2) account for the most common form of hereditable PAH.[28,29] Loss of BMPR2 signaling leads to increased production of pro-inflammatory cytokines as well as pulmonary vascular remodeling.[30-32] Rebalancing of this pathway is also a potential therapeutic target for the treatment of PAH.[33] Inhibition of BMPR2 expression was found in macaque models infected with a chimeric strain of the simian immunodeficiency virus, which coexpressed the HIV protein Nef.[34] These animals, but not controls exposed to wild type simian immunodeficiency virus, went on

to develop plexiform lesions and cardiac hypertrophy. Further evidence of the Nef protein being involved in HIV-PAH pathogenesis comes from 2 human cohorts, where polymorphisms in Nef were overrepresented in patients with HIV-PAH as compared with HIV-positive controls without PAH.[35]

Chronic inflammation due to immune dysregulation may also play a role. Patients with HIV-PAH had an increased frequency of HLA-DR6 and HLA-DR52 as compared with HIV-positive patients without PAH and noninfected controls, potentially implicating the immune response to HIV as a mechanism.[36] The cardiovascular risks of chronic inflammation persist, even in patients with well-controlled HIV.[37] Markers potentially linking HIV and PAH via inflammation include asymmetric dimethylarginine, an inhibitor of nitric oxide synthase, hypoxemia-inducible factor-1, platelet-derived growth factors, and vascular endothelial growth factor.[24,38,39]

Behavioral factors may also play a role in the development of HIV-PAH. Injection drug use is a known comorbid condition for many infected with HIV.[40] While cocaine is still considered a probable cause of drug and toxin-associated PAH, methamphetamine is now considered a definite cause PAH.[6,41,42] The double hit of HIV viral proteins combined with drug use may potentiate the risk of pulmonary vascular disease.[43] In cell culture, coexposure of HIV viral proteins and cocaine led to a down regulation of the BMPR2 signaling pathway as well as proliferation of smooth muscle cells and increased pulmonary endothelial cell permeability.[44,45] In animal models, early plexiform lesions developed in simian immunodeficiency virus-infected macaques who were also treated with intravenous morphine, whereas lesions were not found in infected macaques not exposed to morphine, or in noninfected macaques exposed to morphine.[46] Evidence for a 2-hit hypothesis between HIV viral proteins and drug use is also found in human cohort studies, as patients with a diagnosis of HIV-PAH reported a higher rate of methamphetamine use than patients with idiopathic PAH.[47]

EFFECT OF ANTIRETROVIRAL THERAPY ON HIV-PAH

Some data exist on the potential beneficial effect of antiretroviral therapy on the pathogenesis of HIV-PAH. Certainly, active viral infection presents greater exposure to the viral proteins implicated in the development of PAH, so many have postulated that HIV-PAH would be associated with poorer control of infection. Authors of various studies assessing the association of HIV-PAH with antiretroviral therapy have demonstrated a benefit of therapy, with a lower rate of HIV-PAH in treated patients.[48,49] Authors of a recent large-scale study of US Veterans demonstrated that noninvasive elevations in the PASP were more likely in HIV-infected veterans who had lower CD4 counts and higher viral loads than uninfected veterans and HIV-infected veterans with good viral control.[50]

One notable exception to the notion of better control leading to less HIV-PAH was a retrospective study in which authors compared the effect of nucleoside reverse transcriptase inhibitors alone versus combination antiretroviral therapy.[51] In this study, increased rate of cardiac complications such as arrhythmias, ischemia, cardiomyopathy, pericarditis, and endocarditis occurred in patients treated with nucleoside reverse transcriptase inhibitors alone. However, an increased rate of PAH occurred in those treated with combination antiretroviral therapy (2.0% versus 0.7%, $P = 0.048$). It does not seem plausible that the driver of PAH was due to better control of the HIV; rather, it likely represents better screening for PAH in providers who chose to use combination antiretroviral therapy instead of nucleoside reverse transcriptase inhibitors alone.

Authors of another important study looked at the effect of antiretroviral therapy on HIV-PAH via invasive hemodynamics.[52] In this study, 77 patients with HIV-PAH were followed longitudinally. Of those patients, 62 were on antiretroviral therapy at diagnosis, and 15 were not. Most patients (65%) were put on PAH-specific therapy and had improvements in functional class, 6-minute walk distance, pulmonary vascular resistance, and cardiac index. Of interest, 8 of the 15 patients who were not on any therapy at the time of PAH diagnosis were treated with initiation of antiretroviral therapy alone and no vasodilators. In those patients, antiretroviral therapy alone improved 6-minute walk distance, with no benefit in functional class, pulmonary vascular resistance, or invasive hemodynamics. Authors of another study that assessed invasive hemodynamics in 62 HIV-infected patients demonstrated that the presence of HIV-PAH was more likely in patients with a detectable viral load and lower CD4 counts than in those with good viral control.[53] Ultimately, without large-scale prospective studies, the true effect of antiretroviral therapy on HIV-PAH is unclear. Based on the evidence, antiretroviral therapy seems to have some utility in controlling the virus, as an association between HIV-PAH and immune dysfunction seems to exist. However, antiretroviral therapy alone does not appear to be enough to control PAH. Regardless, all patients with HIV should be put on antiretroviral therapy based on current guidelines, irrespective of CD4 count, viral load, or presence of PAH.[54]

CLINICAL CHARACTERISTICS AND DIAGNOSIS OF PATIENTS WITH HIV-PAH

Patients with HIV-PAH present in a manner like those with other forms of Group 1 PAH. Literature review of 131 reported HIV-PAH cases demonstrated that the most common clinical features were progressive dyspnea, pedal edema, cough, fatigue, chest pain, and syncope.[20] The interval time between diagnosis of HIV and the diagnosis of HIV-PAH was 33 months. Notably, this was an older study, so it is possible that the time course may be longer in the contemporary era, with more patients being on antiretroviral therapy. Chest radiographs in this review demonstrated that the most common features were cardiomegaly and an enlarged pulmonary arterial prominence. Ventilation or perfusion scans were normal. Electrocardiograms demonstrated features of right ventricular hypertrophy, right axis deviation, and sinus tachycardia. Echocardiograms were notable for the presence of right

ventricular enlargement, tricuspid regurgitation, and paradoxical septal motion. In this group of patients, the PAH was advanced, with a mean pulmonary vascular resistance of 12.2 Wood units. These data highlight the nonspecific nature of symptoms, signs, and routine diagnostic testing so that a high index of suspicion and low threshold to perform an echocardiogram and invasive right heart catheterization is required to detect HIV-PAH.

When PAH is suspected, the most effective noninvasive initial diagnostic test is an echocardiogram.[55] In addition to performing echocardiography in patients living with HIV in patients who have unexplained symptoms, the most recent World Symposium on Pulmonary Hypertension Proceedings propose screening echocardiography in selected asymptomatic patients.[19] In the general population, the echocardiogram has a good sensitivity and specificity for the diagnosis of PAH; however, no substitute for performing a right heart catheterization exists.[6] The necessity of a right heart catheterization in the diagnosis of HIV-PAH is also clear. While the echocardiogram is still a useful test to detect HIV-PAH, it has limitations. Direct comparison of PASP via paired echocardiograms and right heart catheterizations in patients with HIV demonstrated that, while only a mild average bias existed, 1.75 mmHg greater via echocardiogram, 20% of patients had a more than 10 mmHg discrepancy between the 2 modalities so that echo estimated pulmonary artery pressure may miss patients who have HIV-PAH.[56] Patients with HIV are also at an increased risk of left ventricular diastolic dysfunction, which can lead to PASP elevations in the absence of PAH, further confounding echocardiogram results and validating the need for invasive right heart catheterization in the diagnosis of HIV-PAH.[57]

The most contemporary assessment of the clinical characteristics of HIV-PAH comes from the Pulmonary Hypertension Association Registry.[47] While the number of patients assessed with HIV-PAH was small, this study was unique because, in it, authors compared the clinical characteristics between 23 patients with HIV-PAH and 563 patients with idiopathic PAH. As compared with those with idiopathic PAH, patients with HIV-PAH were younger, had a lower body mass index, and had worse renal function. Pulmonary vascular resistance was higher in patients with HIV-PAH than those with idiopathic PAH (12.8 Wood units versus 10.4 Wood units), and a trend for a lower cardiac output, cardiac index, and stroke volume index existed. The authors of the study did not find any difference in generic health-related quality of life as measured by the Short Form-12 instrument or in PAH-specific health-related quality of life as measured by the emPHasis-10 instrument. HIV-PAH patients also had rates of hospitalizations and emergency department visits like those with idiopathic PAH. When assessed by PAH-specific vasodilator class, patients with HIV-PAH were treated in a manner like those with idiopathic PAH.

TREATMENT OF HIV-PAH

HIV-PAH falls in the Group 1 PAH category, and treatment guidelines for Group 1 PAH should be followed in HIV-PAH patients.[8-10] In those patients with low or intermediate risk Group 1 PAH, recommendations include upfront oral combination therapy with an endothelin receptor antagonist and an agent targeting the nitric oxide pathway.[58] If patients do not achieve a low-risk status after 2-drug therapy has been initiated, it is recommended that a prostacyclin pathway agent is started.[10] In those with high-risk disease, parenteral prostacyclin is the standard of care. Because HIV-PAH patients may have multiple comorbidities, it is important these comorbidities be enumerated and well characterized so that decisions about PAH therapies can be tailored to each individual patient.

In the real world, patients with HIV-PAH are generally treated in a manner like those with idiopathic PAH.[47] However, it is important to consider the potential for drug-drug interactions between HIV and PAH medications when choosing therapy for patients with HIV-PAH. Collaboration between the PAH and HIV providers is important to ensure that important drug-drug interactions are identified and appropriately managed (Table 1).[59]

The most notable interaction occurs between antiretroviral therapy and drugs in the nitric oxide pathway. The metabolism of the phosphodiesterase-5 inhibitors tadalafil and sildenafil occurs via the cytochrome P450 enzymes CYP3A4 and CYP2C9. Notably, these enzymes are inhibited by protease inhibitors, and authors of pharmacokinetic studies have demonstrated higher plasma levels of sildenafil when coingested with the HIV drugs ritonavir, indinavir, and saquinavir.[60,61] Despite the known interaction, most patients seem to tolerate coingestion without significant adverse effects.[62,63] Similar findings were seen for tadalafil with protease inhibitors.[64] While trials studying the guanylate cyclase stimulator riociguat excluded patients with HIV-PAH, the interaction is generally considered low risk because riociguat is metabolized via multiple CYP enzymes. Authors of one study assessing the pharmacokinetics between riociguat and 5 different HIV regimens demonstrated tolerability across all the regimens; however, a threefold increase in riociguat exposure occurred when patients coingested riociguat with abacavir, dolutegravir, and lamivudine.[65] Given the potential for higher plasma concentrations of the phosphodiesterase-5 inhibitors and riociguat in patients with HIV-PAH, we recommend starting at lower doses, titrating slowly, and monitoring for adverse effects closely.

The nonselective endothelin receptor antagonist bosentan was assessed for safety and tolerability in a small study of 16 patients with HIV-PAH.[66] The rationale behind this study was that bosentan induces CYP3A, so it could increase metabolism of antiretroviral therapy.[67] In the study, bosentan yielded improvements in PAH-related clinical parameters, and no change in HIV viral control at both the 16-week period and in long-term follow up occurred.[66,68] The newer endothelin receptor antagonists ambrisentan and macitentan have less potential for interaction. Indeed, HIV-PAH patients were included in the various clinical trials of both agents.[58,69,70]

Arguably, the most important pathway in PAH management is the prostacyclin

Table 1. Effects of HIV medication coadministration on PAH medication kinetics and clinical effectsa

PAH medications	HIV medications	Effect on PAH medication	Recommendation
Sildenafil	All PIs	• Darunavir/ritonavir plus sildenafil 25 mg like sildenafil 100 mg alone. • Ritonavir 500 mg twice daily ↑sildenafil AUC 1,000%	• Consider alternative therapy. • Initiate sildenafil at a low dose (i.e., 20 mg every other day), increase slowly with close monitoring for side effects.
	Efavirenz Nevirapine	• ↓ sildenafil possible	• Titrate sildenafil dose based on clinical effect.
	Etravirine	• Sildenafil AUC ↓ 57%	• Titrate sildenafil dose based on clinical effect.
	Elvitegravir/ cobicistat	• ↑ sildenafil expected	• Consider alternative therapy. • Initiate sildenafil at a low dose (i.e., 20 mg every other day), increase slowly with close monitoring for side effects.
Tadalafil	All PIs	• Ritonavir 200 mg twice daily ↑ tadalafil AUC 124%	In patients on a PI > 7 d: • Start tadalafil 20 mg once daily and increase to tadalafil 40 mg once daily based on tolerability. In patients on tadalafil who require a PI: • Stop tadalafil ≥24 h before PI initiation. 7 d after PI initiation, restart tadalafil at 20 mg once daily and increase to tadalafil 40 mg once daily based on tolerability. In patients switching between cobicistat and ritonavir: • Maintain tadalafil dose.
	Efavirenz Etravirine Nevirapine	• ↓ tadalafil possible.	• May need to titrate tadalafil dose based on clinical effect.
	Elvitegravir/ cobicistat	• ↑ tadalafil expected.	In patients on elvitegravir/cobicistat >7 days: • Initiate tadalafil 20 mg once daily. Increase to tadalafil 40 mg once daily based on tolerability. In patients on tadalafil who require elvitegravir/cobicistat: Stop tadalafil ≥24 h before elvitegravir/cobicistat initiation. 7 d after elvitegravir/cobicistat initiation, restart tadalafil at 20 mg once daily and increase to tadalafil 40 mg once daily based on tolerability.
Riociguat	Abacavir	• Riociguat ↑ AUC200%.	• Initiate riociguat at 0.5 mg 3 times daily and monitor for adverse effects.
Bosentan	All PIs	With lopinavir/ritonavir: • ↑ bosentan 48-fold (Day 4) and ↑ 5-fold (Day 10). With other PIs: • ↑ bosentan expected.	• Do not coadminister bosentan and unboosted atazanavir. In patients on a PI (other than unboosted atazanavir) > 10 d: • Start bosentan at 62.5 mg once daily or every other day. In patients on bosentan who require a PI (other than unboosted atazanavir): • Stop bosentan ≥36 h before PI initiation and restart bosentan 10 d after PI initiation at 62.5 mg once daily or every other day. When switching between cobicistat and ritonavir: • Maintain same bosentan.
	Efavirenz Etravirine Nevirapine	• ↓ bosentan possible.	If coadministration is necessary, monitor bosentan efficacy.
	Elvitegravir/ cobicistat	• ↑ bosentan possible.	In patients on elvitegravir/cobicistat ≥10 d: • Start bosentan at 62.5 mg once daily or every other day based on individual tolerability. In patients on bosentan who require elvitegravir/cobicistat: • Stop bosentan ≥36 h before elvitegravir/cobicistat initiation. At least 10 d after initiation of elvitegravir/cobicistat, resume bosentan at 62.5 mg once daily or every other day based on individual tolerability.

Abbreviations: AUC, area under the curve; HIV, human immunodeficiency virus; PAH, pulmonary arterial hypertension; PI, protease inhibitor.

[a]Adapted from Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV.[59]

pathway. While the initial trials which established the efficacy of the parenteral prostacyclins epoprostenol and treprostinil did not include patients with HIV, these drugs seem to be well tolerated in HIV-PAH without significant drug interactions.[71-75] Prostacyclins can also be administered in oral and inhaled routes, and patients with HIV-PAH were included in the various clinical trials of these agents.[76-78] Additionally, authors of the study investigating the drug selexipag, an oral selective IP prostacyclin-receptor agonist, included patients with HIV-PAH.[79] Given their inclusion in the various clinical trials and the real-world data, the prostacyclin pathway agents are generally considered safe and effective in HIV-PAH.

CONCLUSIONS

HIV-PAH is a unique subset of pulmonary vascular disease. The prevalence of HIV-PAH is at least 0.5% of all people living with HIV. The mechanism by which HIV leads to PAH is felt to be mediated via viral proteins leading to increased endothelin-1-related vasoconstriction, inhibition of BMPR2 signaling, chronic inflammation, and an increased rate of drug and toxin exposure. These patients have clinical characteristics like others with Group 1 PAH. Treatment is also like other types of PAH; however, caution is necessary when starting the nitric oxide pathway agents to avoid potentially dangerous drug-drug interactions.

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