Pulmonary hypertension is broadly recognized as a group of disorders that share the common characteristic of an elevated mean pulmonary arterial pressure (≥25 mm Hg). Pulmonary arterial hypertension (PAH; Group 1) is a subset of the pulmonary hypertension disorders that is also characterized by pulmonary arterial remodeling, the formation of plexiform lesions, and poor clinical outcomes. When present, pulmonary hypertension is associated with a worse overall prognosis. Clinical evaluation of patients with human immunodeficiency virus (HIV) has indicated that there is a high prevalence of PAH in patients with HIV suggesting a relationship between HIV infection and the pathogenesis of PAH.

Human immunodeficiency virus is a member of the genus Lentivirus of the family Retroviridae. The primary target of HIV is the immune system; destruction of lymphocytes (mainly CD4+ T cells) by the virus induces severe damage to the host immune function, which increases patient risk for developing opportunistic infections. AIDS is a clinical syndrome representing the final stage of HIV infection and is often characterized by a CD4+ T cell count <200 cells/μL. Even in the contemporary era of immune-modulating therapies, the prevalence of HIV infection continues to grow worldwide, devastating the health of individuals, communities, regions, and entire countries. Two major types of the virus are reported: HIV type 1 (HIV-1) is related to viruses originally endemic to West African primates and is primarily responsible for the AIDS pandemic, whereas HIV type 2 (HIV-2) is comparatively less virulent. HIV infection promotes a range of cardiovascular diseases, and is an independent risk factor for the development of pulmonary vascular diseases, including severe PAH, the latter of which is the subject of this review.

First Observations of Pulmonary Vascular Disease in HIV Patients

In 1987, Kim and Factor published the first case report of a 40-year-old homosexual man with hemophilia and AIDS, who presented with dyspnea and renal insufficiency. A chest radiograph showed cardiomegaly and prominent pulmonary arteries. This radiographic finding was consistent with pulmonary hypertension, which was subsequently confirmed at right heart catheterization. The patient died 3 days after admission. At autopsy, Pneumocystis carinii pneumonia and plexogenic pulmonary arteriopathy were discovered. However, electron-dense immunoglobulin deposits, which were present in the membranoproliferative glomerulonephritis pathology examination, were not identified in the pulmonary plexogenic lesions, suggesting that the pulmonary arteriopathy did not result from direct vascular infection with HIV. Shortly thereafter, Goldsmith and associates described 5 patients with classic hemophilia, HIV infection, and pulmonary hypertension, indicating that the original description of pulmonary hypertension associated with HIV was not an isolated phenomenon. Around the same time, others described a cohort of 6 patients with AIDS and moderate or severe pulmonary hypertension, right ventricular hypertrophy, and right heart failure. All 6 patients in that series presented with rapid clinical deterioration: 2 patients died, and their autopsies revealed mediastinal hypertrophy of the small pulmonary arteries and arterioles (ie, endarteritis obliterans), intimal fibrosis of the pulmonary veins, and lymphohistiocytic infiltration of the interstitium, but no plexogenic lesions. One patient had Cytomegalovirus pneumonia, and another had Pneumocystis carinii pneumonia. In 1990, Coplan et al published data on 4 additional patients diagnosed with primary pulmonary hypertension in the setting of HIV. The first case of HIV-associated PAH in a child was in a 10-year-old African American girl referred in 1991 for evaluation of cardiomegaly, chronic nonproductive cough, and shortness of breath. In that case, vertical transmission from the patient’s mother was suspected to account for HIV disease expression. Also in 1991, Speich and colleagues prospectively studied 74 HIV-infected patients with cardiopulmonary complaints, and identified 6 patients (8.1%) with pulmonary hypertension and echocardiographic evidence of elevated right ventricular systolic pressure. The autopsies of 2 patients in that series revealed a plexogenic pulmonary arteriopathy that resembled PAH in the absence of HIV infection. Thus, in the early 1990s, the possibility of a relationship between HIV infection and the development of pulmonary vascular diseases, and consequently PAH, was established.

These early observations suggested the following clinical and pathological features for HIV-associated PAH.
1. Male predominate prevalence, which is in contrast to the high female predominance observed in non-HIV PAH.10,11
2. PAH occurs in early and late stages of HIV infection.
3. The degree of immunodeficiency does not influence the development of PAH.
4. PAH may contribute to rapid clinical decline in HIV.
5. PAH is not responsive to treatment of comorbid infection, oxygen therapy, or vasodilators.
6. The estimated incidence of PAH in hospitalized patients with HIV in developed countries is ≈1:200 (0.5%).9
7. The pathology of PAH in HIV overlaps with idiopathic PAH, including the following8,12,13:
   a. Intimal and medial hyperplasia of the small and medium-sized pulmonary arteries.
   b. Endarteritis obliterans.
   c. Some parenchymal lung disease, thickened alveolar septa, and prominent interstitial fibrosis.
   d. Inflammation with lymphohistiocytic infiltration of the interstitium and small vessel perivascular inflammatory reaction with no evidence of granulomas.
   e. Plexogenic arteriopathy is present in >80% of cases.
   f. Thrombotic pulmonary arteriopathy, either recurrent thromboembolism or in situ thrombosis, was observed in the majority of patients.
   g. Veno-occlusive disease of the pulmonary veins was observed in a minority of cases.14,15

**Pathogenesis of Pulmonary Vascular Diseases in HIV**

To better understand the role of HIV in the pathogenesis of PAH, several experimental models, including both small (eg, mice, rat, cat or rabbit) and large (eg, primates) animals, were developed to study HIV-1 infection in vivo.16–19 However, failure of these models to recapitulate the HIV-1 disease phenotype effectively prompted investigators to study various primate species infected with a form of Simian Immunodeficiency Virus (SIV) that is endemic to Africa. Although the natural history of SIV is akin to HIV, the pulmonary vasculopathy observed in SHIV-infected primates, the pulmonary vasculopathy observed in SHIV-infected mice lacks plexiform lesions or intimal fibrosis of the pulmonary arteries and is characterized mainly by vascular inflammation, which is also a component of PAH.25,27

Many early attempts were made to localize HIV-1 in the lung as an explanation for the observed pulmonary vascular pathology. These efforts focused on identifying viral particles or any other evidence of immune complex deposition in the vascular endothelium using electron microscopy, immunohistochemistry, DNA in situ hybridization, and polymerase chain reaction; yet, all failed.17,24 It was, therefore, hypothesized that a direct pathogenic role of HIV in pulmonary vascular remodeling/dysfunction was unlikely. As a result, interest shifted to examining the contribution of HIV viral proteins to the pathogenesis of HIV-associated PAH.28,29

**HIV Proteins and HIV-Related Factors That Mediate Pulmonary Vascular Remodeling**

Findings from the last 10 years suggest that the viral proteins gp120, Tat, and Nef mediate endothelial cell injury to initiate the complex pathogenesis and vascular remodeling pattern of HIV-associated PAH.29 The envelope glycoprotein 120 (gp120) is encoded by the HIV env gene, is exposed on the surface of the HIV virus, and facilitates entry of HIV into cells. With the support of coreceptors, such as CCR5 and CXCR4, gp120 is involved in the attachment of HIV to specific cell surface receptors, mainly CD4+ receptors. This attachment starts a cascade of conformational changes that leads to fusion of the virus with the host cell membrane and subsequent intracellular entry of the HIV virions.29

The Tat (Trans-Activator of Transcription) protein is encoded by the tat gene of the HIV-1 genome and it enhances HIV virus efficiency by promoting the transcription of all HIV genes (particularly in CD4+ T lymphocytes and macrophages). The Tat protein is detectable in the blood of HIV-1 infected patients and it may also be absorbed by cells that are not infected directly with HIV, such as the vascular endothelium.31,32 Tat interacts with endothelial cells via cell membrane receptors, including various integrins and the vascular endothelial growth factor receptor-2/Kinase Insert Domain Receptor. Increased levels of the cytokine interleukin (IL)-2 and the HIV-1 coreceptor CCR5 are also attributed to Tat. Exposure of isolated endothelial cells in culture to viral proteins (mainly Tat and gp120) results in the accumulation of hypoxia-inducible factor–1α protein27 that occurs concomitant with increases in platelet-derived growth factor–B (PDGF-B). In turn, both hypoxia-inducible factor–1α and PDGF-B initiate and sustain activation of metabolic and proliferation
signaling pathways that are contribute to pulmonary vascular remodeling in HIV.33

A third HIV protein relevant to pulmonary vascular disease is Nef, which was originally believed to be a negative factor for HIV replication but is now recognized as critical to the HIV virus life cycle through its actions on infected cells and depletion of T cells.34 Nef is a myristoylated protein that is predominantly cytoplasmic but has also been identified in the cell nucleus. It is expressed at high levels in the viral life cycle, causing elevated viral protein titers.35–38 Marecki et al35,36 suggested that Nef plays a vital part in the pathogenesis of PAH. Following their initial observation that pulmonary vascular plexiform lesions were present only in macaques infected with a chimeric viral construct containing the HIV nef gene, they found medial hypertrophy, perivascular cuffing by inflammatory cells, thrombosis, and pulmonary vascular lesions with recanalized lumens and complex plexiform-like lesions, which had not been reported previously in macaque monkey lungs infected with SIV nef genes.39 Endothelial cells harvested from both SHIV-nef macaques and patients with HIV-associated PAH have been shown to express Nef suggesting that it may be causative; however, Nef has not been identified in patients with idiopathic PAH.39 Despite this, it was concluded that HIV nef and the SHIV-nef genes play a key role in the development of severe complex pulmonary vascular lesions, including plexiform lesions. More recently, an association between polymorphisms involving Nef functional domains and an HIV-associated PAH phenotype has been reported in 2 separate clinical cohorts.39

Other Factors Contributing to HIV-Associated Pulmonary Arterial Hypertension

Illicit intravenous drug use such as opioids (heroin and morphine) is a bona fide risk factor for contracting HIV/AIDS, and, as such, should raise suspicion for HIV-associated PAH in the appropriate clinical circumstance.40–42 Furthermore, there is evidence that these drugs may act as disease modifiers. In 1 study, SIV macaques treated with morphine developed significant pulmonary vascular remodeling, including plexiform lesions, compared morphine-treated uninfected animals.42 Furthermore, simultaneous exposure to Tat protein and cocaine or morphine can induce endothelial cell injury that promotes the pulmonary angioproliferative remodeling process.43,44

Comorbid infection with selected pathogens also appears to be an additional contributing factor to the development of HIV-associated PAH. In fact, SIV macaques that received either morphine or a control substance were more likely to demonstrate the pulmonary arteriopathy and pulmonary hypertension in the setting of coinfection with Pneumocystis jirovecii pneumonia.42 Immune activation caused by a higher prevalence of concurrent infections has been hypothesized to be a driving factor for increased HIV-1 replication and cytokine dysregulation in African patients with HIV-1 infection.42 Therefore, there is an increasing interest in the hypothesis that chronic immune activation and inflammation may contribute to the development of pulmonary vascular diseases in HIV infection.45

In addition to Pneumocystis pneumonia, Schistosoma mansoni also appears to influence HIV replication, cell-to-cell transmission of HIV-1, and HIV disease progression as indicated by lower CD4+ T cell counts when coinfection is present. Deworming of HIV-positive individuals living in endemic areas may have an impact on HIV-1 viral loads and the CD4+ T cell count.46 Schistosomiasis can also impair the response to antiretroviral therapy among HIV-infected patients.47 A study in rural Zimbabwe reported that 57% of HIV patients were coinfected with Schistosoma mansoni, and that treatment of schistosomiasis could reduce the rate of HIV viral replication and increase CD4+ T cell count in the coinfected host.48 In turn, it is well known that schistosomiasis is a major independent cause of PAH globally.49–51 Coinfection with HIV is proposed to create an unusual but biologically plausible circumstance that would allow for severe and rapidly progressive PAH. This subject has not yet been studied, but is due for careful evaluation considering its importance, particularly in Africa where dual HIV-schistosomiasis infection is most prevalent.52

The Role of HIV in the Pathogenesis of Pulmonary Vascular Diseases: Contemporary Hypotheses

The exact mechanism(s) by which to account for pulmonary vascular disease in HIV patients is still uncertain. However, a summary of the current framework explaining the pathogenesis of HIV-associated PAH based on empirical evidence and the aforementioned observations is reviewed (Figure 1). Pulmonary vascular diseases are associated with pulmonary vasoconstriction and remodeling of the pulmonary vasculature, especially smaller (ie, distal) vessels. The process typically starts with injury to the endothelial cells.33,54 As the HIV virus does not directly infect endothelial cells, viral proteins (mainly Nef, Tat and probably gp120) are proposed to contribute to endothelial cell injury and initiate pulmonary vascular remodeling. In particular, these proteins may activate growth and survival factors, such as VEGF and PDGF, which, in turn, stimulate maladaptive vascular cell growth patterns, including proliferation, endothelial cell apoptosis, and vascular smooth muscle cell apoptosis resistance, similar to the defining features of non-HIV forms of PAH. Circulating proteins may also interact with functionally relevant vascular endothelial cell receptors to promote HIV-associated PAH. One such example is CXCR4,53 which is expressed in lung vascular endothelial cells. Additionally, Tat interacts with different types of receptors present on the surface of endothelial cells to induce VCAM-1 expression, p38 MAPK activation, nuclear factor–xB translocation, and increased expression of hypoxia-inducible factor–1α, which, collectively are involved in the pathogenesis of pulmonary vascular remodeling and dysfunction.55 Tat may also bind VEGF and PDGF to increase local concentrations of these factors and this may explain the elevated levels of PDGF seen in lung biopsies of patients with HIV-associated PAH.56 Similarly, elevated levels of PDGF have been found in patients with HIV infection and PAH, but not in HIV-infected individuals without PAH.56

Nef has been shown to induce pulmonary endothelial cell proliferation as well as apoptosis,25,26 similar to the pattern observed in human brain microvascular endothelial cells.
exposed to exogenous Nef. Changes in cell survival mediated by Nef appear to occur through caspase-related signaling pathways and changes in the redox status of the pulmonary vascular cells. Interestingly, HIV-1 Tat is reported to increase reactive oxygen species levels in endothelial cells to promote apoptosis. Additionally, HIV-1 gp120 proteins can also induce apoptosis as well as increase secretion of the potent vasoconstrictor endothelin-1 in human pulmonary microvascular endothelial cells. Removal of apoptotic cells by neighboring viable cells, likely by phagocytosis intended to maintain tissue homeostasis, may in fact cause the release of growth factors and cytokines, which, consequently, could lead to the emergence of uncontrolled vascular cell proliferation, complex vascular remodeling, plexiform lesions, and PAH.  

Inflammation, the release of cytokines and chemokines such as IL-6, or increased levels of vasoactive peptides that influence remodeling like asymmetrical dimethylarginine, may also contribute to HIV-associated PAH. Observations suggest that chronic HIV-associated inflammation leads to an accumulation of asymmetrical dimethylarginine, which is a well-known endogenous inhibitor of endothelial nitric oxide synthase, and, thus, promotes endothelial dysfunction and vascular smooth muscle cell proliferation. Additionally, Nef and Tat proteins modulate the release of IL-2 and monocyte chemotactic protein-1 (MCP-1, also known as CCL2), which stimulate pulmonary vascular remodeling, particularly in Schistosomiasis infection (Figure 2). Whether overlap in cytokine activation patterns in Schistosomiasis and HIV is responsible for PAH in coinfected patients, however, requires further investigation.  

The adverse effects of the HIV viral proteins on the pulmonary endothelium can also be potentiated by the use of intravenous illicit drugs. In the setting of HIV infection, the use of morphine enhances apoptosis and leads to a compensatory increase in pulmonary endothelial cell proliferation. This sequence of events also induces pulmonary endothelial cell autophagy, which can increase the severity of angioproliferative remodeling of the pulmonary vasculature. Cocaine exacerbates the disruption of tight junction proteins and increases the rate of permeability in the pulmonary microvasculature.
permeability of human pulmonary artery endothelial cells that have been exposed to Tat protein. Furthermore, cocaine and Tat synergize to increase the expression of miRNAs, which can potentially target BMPR protein expression in vascular smooth muscles cells (examples include miR130a, miR216, miR19a, miR301a, and miR21) to initiate vascular remodeling.\(^{43}\)

In a subset of patients, PAH in the setting of HIV infection may occur as a result of major histocompatibility complex abnormalities, suggesting an autoimmune basis for the disease. This was confirmed by the finding that Tat protein downregulates the gene encoding major histocompatibility complex class I. Morse et al.\(^{72}\) noticed that HIV patients who developed pulmonary hypertension had an increased frequency of HLA-OR6 and HLA-ORS2. These findings suggest that HIV-associated pulmonary hypertension reflects a host response to HIV-1, determined by 1 or more HLA-OR alleles located within the major histocompatibility complex. Unfortunately, the role of major histocompatibility complex abnormalities in pulmonary vascular diseases in patients without HIV has not been studied in detail. In addition, observations suggest that viral proteins are involved in the regulation of major histocompatibility complex receptors,\(^{73}\) and may regulate inflammatory cell function in HIV-related PAH through this mechanism (Figure 2).\(^{54,74}\)

**The Prevalence and Global Impact of HIV-Associated Pulmonary Arterial Hypertension**

In 2012, according to the UNAIDS program, 35.5 million adults and children were living with HIV. Countries with the highest prevalence of HIV are generally in sub-Saharan Africa, including Swaziland, Botswana, Lesotho, South Africa, Mozambique, Zimbabwe, Zambia, and Malawi. Although these countries are home to <1% of the global population, they contribute to 20% of the global burden of HIV infection (Figure 3). Sadly, despite Africa being home to a very significant proportion of individuals with the disease, the complexity of the socio-demographics, different cultures, and other endemic diseases together form barriers that limit our understanding of the dynamic forces that continue the HIV epidemic on this continent.\(^{75-77}\)

Early estimates from developed countries in the late 1980s and 1990s suggested that the prevalence of pulmonary hypertension was ≈0.5% in patients with seropositive HIV infection.\(^{9,28}\) This estimate was supported by data from a prospective study of 7648 HIV positive adults that were followed in 14 HIV clinics in France.\(^{78}\) However, Quezada and colleagues\(^{79}\) in Spain studied 392 HIV-infected individuals and found that the prevalence of HIV-related PAH was as high as 9.9% when based on echocardiography to estimate pulmonary pressures with moderate-to-severe disease occurring in ≈4% of cases. In the HIV-HEART cross-sectional study, 802 HIV patients (83.4% male; mean age 44.3±10.3 years) were evaluated for the development of cardiovascular disease. In this study, 4.7% of patients had echocardiographically-diagnosed pulmonary hypertension (defined by a pulmonary systolic pressure >35 mmHg), but only 1.7% of patients were symptomatic.\(^{80}\) Data from a cohort of 196 HIV-infected patients evaluated at San Francisco General Hospital suggested a prevalence of 35.2%, which is much higher than was reported by other groups. In that study, however, a lower pulmonary arterial systolic pressure cutoff was used to define pulmonary hypertension (>30 mmHg). This likely allowed for the inclusion of some individuals that did not have true pulmonary hypertension, which was suggested by the pulmonary hypertension diagnosis rate of 7.7% in non-HIV infected referents and is far greater than anticipated in the general population.\(^{81}\) The Study to Understand the Natural History of HIV/AIDS in the Era of Effective Therapy (SUN study),\(^{82}\) a retrospective observational multi-site study involving 7 HIV-specialty clinics in 4 U.S. cities, observed an even higher prevalence of pulmonary hypertension (57%) when patients were stratified by echocardiographic estimates of pulmonary artery pressure with 7% of patients having moderate-to-severe PAH. The observed differences in the prevalence of pulmonary hypertension between studies are likely related to methodological issues regarding the echocardiographic cutoff criteria.

It is notable that estimates of the prevalence of HIV-associated PAH from other countries, and particularly the developing world, are scant. An observational study of 207 HIV-infected patients in Brazil (94% on antiretroviral therapy) identified pulmonary hypertension in 5 patients (2.6%)
by echocardiography, which is lower than what was reported in the aforementioned studies performed in developed countries.\textsuperscript{83} It is important to consider that, generally, developing nations (particularly sub-Saharan Africa) report a high incidence of conditions that may confound the accurate diagnosis of HIV-associated PAH, such as tuberculosis, bronchiectasis, and even schistosomiasis. Furthermore, several studies indicate that there is a higher incidence of cardiac involvement in HIV patients residing in Africa, including biventricular systolic and diastolic dysfunction, that may contribute to the incidence of pulmonary hypertension attributable to left heart disease, which is reported to be as high as 12.7% in some local regions.\textsuperscript{71,84–90} Nevertheless, careful analysis of the published data suggests that the estimated prevalence of HIV-associated PAH ranges from 0.4 to 5% globally. Despite this, many studies and clinical reports involve only symptomatic patients, thereby introducing potential selection bias to these estimates and underestimating the magnitude of the disease. The true prevalence of clinical PAH in HIV patients is likely to vary according to regional differences as a result of differences in environmental, cultural, and genetic factors, as well as heterogeneity across the methods for diagnosis of pulmonary hypertension.

**Clinical Features of HIV-Associated Pulmonary Arterial Hypertension**

Unfortunately, there are no specific symptoms that indicate the diagnosis of pulmonary hypertension in HIV patients. The symptoms are nonspecific, may not differ from other cases of PAH, such as progressive dyspnea, chest discomfort, dizziness, and syncope, and may not differ from those attributable to respiratory infections in the absence of fever.\textsuperscript{4–7,9} According to the current guidelines, the clinical diagnosis and approach to an HIV patient with suspected pulmonary hypertension is similar to that used to diagnose PAH in the absence of HIV infection.\textsuperscript{91} However, in developing countries where cardiac catheterization laboratories are often unavailable, clinicians should consider the possibility of PAH when HIV patients present with suggestive symptoms. Echocardiography is useful, but an elevated pulmonary artery systolic pressure should not be considered diagnostic unless there is concomitant evidence of severe right ventricular abnormalities. Frequent intravenous drugs use is not considered an independent risk factor for HIV-associated PAH per se, but may increase the diagnostic index of suspicion. Although some researchers\textsuperscript{92–94} have observed that a lower CD4+ T cell count is associated with PAH, this relationship has not yet been confirmed by others.\textsuperscript{95,96} Other inflammatory markers, including IL-8 in sputum, and peripheral IL-8, interferon-\(\gamma\), and CD8(+) T-cell expression of CD69(+) have also been associated with increased pulmonary pressure in HIV patients but are not diagnostic for the disease.\textsuperscript{94}

**The Effect of Antiretroviral Therapy on Pulmonary Arterial Hypertension and Outcomes in HIV Patients**

The successful roll-out of highly active antiretroviral therapy (HAART) has extended the life expectancy and enhanced the overall well-being of HIV-positive individuals. The role of HAART on the prevalence and outcome of pulmonary hypertension secondary to HIV is still controversial and data are sparse, with no current prospective trial evaluating the effect of HAART on the progression of PAH associated with HIV. In the Swiss HIV Cohort Study (SHCS), the median survival period was 2.7 years and was almost twice as high in patients treated for HIV (3.0 years) than in untreated patients (1.6 years). These data suggest that the use of standard antiretroviral therapy in patients with pulmonary hypertension secondary to HIV infection may have a beneficial effect on survival.\textsuperscript{97–99} A prospective French national study\textsuperscript{93} that included 77 patients (81% patients on HAART at the time of diagnosis, 65% treated with PAH-specific therapy) demonstrated an overall survival rate of 88% at 1 year and 72% at 3 years despite no improvement of hemodynamic parameters, indicating that improved survival with HAART was likely related to CD4+ counts and better cardiac function as opposed to a direct effect on pulmonary hypertension.\textsuperscript{93}
Notwithstanding these promising findings, there are increased concerns regarding HAART-mediated metabolic derangements and the potential attendant risk for the development of cardiovascular diseases, particularly with respect to HIV protease inhibitors. Furthermore, some of the antiviral therapy has been observed to contribute to the development of PAH. The SUN study, which was designed to monitor the incidence of HIV drug therapy–related complications, found that two-thirds of patients using HAART developed some form of cardiac dysfunction. The use of current ritonavir-boosted protease inhibitors was the only factor significantly associated with PAH. Pugliese and colleagues found that PAH occurred in 0.7% of patients treated with nucleoside reverse transcriptase inhibitors, compared with 2% in the group of patients treated with HAART (P=0.048). This indicated that some standard antiretroviral therapy, in particular first-generation HIV protease inhibitors but also some HAART treatment, may facilitate the pulmonary vascular pathophysiology of HIV-associated PAH.

The mechanism underlying the relationship between ritonavir and pulmonary hypertension is incompletely characterized; however, ritonavir inhibits bradykinin-dependent vasorelaxation in a concentration-dependent manner leading to endothelial dysfunction. In fact, 5 HAART drugs (ritonavir, indinavir, lamivudine, abacavir, and zidovudine) have been shown to decrease endothelial nitric oxide synthase expression significantly and increase reactive oxygen species levels and ERK1/2 activation in human pulmonary artery endothelial cells in vitro. These deleterious effects are inhibited by nonspecific antioxidants (eg, dihydroxybenzyl alcohol) or magnesium supplementation. Conversely, some antiretroviral agents have been shown to inhibit pulmonary artery smooth muscle cell proliferation in vivo in the monocrotaline- and hypoxia-induced models of experimental pulmonary hypertension, most likely via the inhibition of Akt phosphorylation. Taken together, these findings suggest that there are dual (opposing) effects of antiretroviral therapy on pulmonary arterial remodeling, and each drug may differentially affect pulmonary hypertension in patients.

**PAH-Specific Therapy: Considerations When Used With Antiretroviral Agents**

Although the French study reported that two-thirds of their patients with HIV-associated PAH used PAH-specific therapy, none of these drugs have been studied in sufficiently powered randomized, clinical trials in this patient population. Despite this, it is now recognized that HIV patients who develop PAH have a disease process similar to non-HIV patients with PAH and are likely to require treatment with established therapies (ie, phosphodiesterase type-V inhibitors, endothelin receptor antagonists, others). The phosphodiesterase type-V drug class, in particular sildenafil, is among the first oral therapies implemented in the treatment of pulmonary hypertension secondary to HIV, but there are only a few case reports describing its use in HIV patients and proper clinical trials assessing drug efficacy in HIV patients with pulmonary hypertension are lacking. It has been observed in HIV-infected patients taking protease inhibitors (saquinavir, indinavir and particularly ritonavir) that these drugs significantly modified the pharmacokinetics of sildenafil, presumably through inhibition of CYP3A4. This resulted in increased plasma concentration of both sildenafil and its metabolite, although recent reports do not indicate that this translates into an increase in rates of significant adverse reactions. Therefore, it is advisable to consider tailoring the dosage of the drug or therapeutic drug monitoring of sildenafil after the initiation of the treatment to avoid over-dosage (Cmax values of sildenafil > 500 ng/mL) although this may not be available in all hospital clinical laboratories. Use of the nonselective endothelin receptor antagonist bosentan has also been reported in many patients with HIV-associated PAH with treated patients demonstrating significant improvement in functional and hemodynamic parameters. There are also reports of normalization of hemodynamics in some patients, even after withdrawal of the drug. Furthermore, bosentan was found to be well tolerated when combined with highly active antiretroviral therapy, with no reported significant interaction and no negative impact on HIV infection control. Similarly, the selective endothelin receptor antagonist ambrisentan is also considered an appropriate oral selective pulmonary vasodilator in patients with HIV-related PAH. Careful monitoring of liver function tests is very important when treating patients with this class of drugs due to their potential hepatotoxicity.

**Conclusion**

HIV can be considered 1 of the causative factors of PAH as patients with HIV are significantly more susceptible to developing PAH in comparison with the general population. The pathophysiology of this condition is still far from being fully understood, but is unlikely to be attributable to direct viral infection of the pulmonary vascular endothelium or vascular tissue by HIV. Products of the viral particle/proteins Nef, Tat, and gp120 are candidate contributors to vascular injury and pulmonary arteriole remodelling in HIV-associated PAH. Other relevant factors include increased inflammation, and the derivative consequences of illicit drug use and coinfection with Pneumocystis or schistosomiasis. The role of HAART therapy in PAH incident is controversial; however, HAART is of vital importance to improving outcome in HIV and, thus, should not be delayed based on a concern for HAART-associated pulmonary vascular disease alone.

Increased insight into this clinical condition is of particular importance in the developing countries, specifically Africa, where the prevalence of HIV-associated PAH is anticipated to be substantially greater than current estimates indicate. Furthermore, additional data are required to further our understanding of mechanisms underpinning the pathophysiology of HIV-associated PAH to identify disease-specific therapies for this complex and morbid form of pulmonary vascular disease.

**Disclosures**

None.

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