Pulmonary Hypertension (PH) is defined by the presence of elevated pulmonary artery (PA) pressures, with a commonly employed threshold being a mean PA pressure greater than 25 mmHg. Many different types of patients can present with PH, including those with left-sided heart disease, chronic intrinsic lung disease and chronic thromboembolic disease. However, a much more discrete group of patients, said to have pulmonary arterial hypertension (PAH) has been found to share common pathophysiological features directly involving the pulmonary arterial tree, and to lack evidence of elevated left-heart filling pressures, intrinsic lung disease or thromboembolism. Such patients also tend to share a positive response to PAH-specific therapies. This group of patients includes those with idiopathic (IPAH) and familial (FPAH) forms of PAH, as well as those with PAH associated with connective tissue diseases, chronic hepatic or congenital heart disease, hemoglobin disorders, HIV infection and selected toxic exposures.

Pulmonary arterial structural and functional abnormalities frequently seen in PAH include vasoconstriction, medial hypertrophy, fibrosis, inflammation, cellular proliferation, in situ thrombosis and formation of plexiform lesions. These combine to increase pulmonary vascular resistance and right ventricular afterload. Without therapy, right heart failure and early morbidity and mortality are inevitable.

PAH remains relatively rare and its presenting signs and symptoms are notoriously non-specific. Accordingly, it is often confused with other diagnoses, and proper diagnosis and therapy are unacceptably delayed. It is the hope that increased awareness on the part of health professionals and the general public will help rectify this.
HIV-PAH (History): The first case of pulmonary hypertension (PH) in an HIV-infected individual was reported in 1987. Since that case, approximately 150 patients with HIV infection and otherwise unexplained pulmonary hypertension (HIV-PAH) have been reported; however, there are certainly many more patients with HIV-PAH who have not been reported. Interestingly, the first several cases reported occurred in patients with classic hemophilia; because of this, researchers theorized that the etiology of HIV-PAH was the hemophilia itself or perhaps the lyophilized factor VIII. Since these early cases, however, most subsequent cases of HIV-PAH have been identified in patients without hemophilia. In fact, it has been found in patients with all other reasons to incur HIV infection. Thus, it seems that development of pulmonary hypertension is, in some way, related to the HIV infection itself.

HIV-PAH (Demographics/Incidence): Although still an uncommon complication of HIV infection, HIV-PAH may become more prevalent as improved medical management increases life expectancy of HIV-infected patients. Yet, compared with IPAH, pulmonary hypertension occurs more frequently in the HIV-infected population: 1 case of HIV-PAH per 200 HIV-infected individuals (0.5%) or approximately 6-to-12 fold the occurrence in the uninfected general population. In IPAH, there is a marked female predominance (female-to-male ratio ~3:1) whereas in HIV-PAH, there is still a male predominance (male-to-female ratio ~1.6:1.0). The mean age at diagnosis of pulmonary hypertension is slightly older in individuals with IPAH than in HIV-PAH (42yrs vs. 32yrs). In studies of HIV-PAH, intravenous drug use (~45%), homosexual contact (~25%), hemophilia (~12%) and heterosexual contact (~10%) are the most frequently identified risk factors for HIV infection. Smaller numbers of cases have been identified in which the risk for HIV infection is blood transfusion, maternally acquired congenital infection, or a combination of homosexual contact and intravenous drug use. Intravenous drug use is also associated with development of pulmonary hypertension independent of HIV infection; likewise many HIV-infected individuals have other entities independently associated with an increased risk of pulmonary hypertension, such as chronic liver disease from hepatitis B or C and coagulation abnormalities. However, by convention, patients with concomitant PAH and HIV infection are considered to have HIV-PAH.

HIV-PAH (Clinical Aspects): No correlation has been demonstrated between the development of HIV-PAH and either the degree of immunodeficiency nor previous opportunistic infections. For example, CD4 counts at time of diagnosis of PH have ranged from 0–900 cells/mm3 with a mean CD4 count of ~300 cells/mm3. Presentation of HIV-PAH is similar to that in individuals with IPAH; the main complaint being dyspnea. However, individuals with HIV-PAH have somewhat lower pulmonary artery pressures; despite this, their survival rate appears worse. Likewise, the median survival in HIV-PAH is 1.3 years versus 2.6 for PPH patients. Thus, it remains unclear whether the increased mortality in HIV-infected patients is a reflection of increased severity of their pulmonary hypertension or the effect of HIV or another co-morbid condition on their general health.

HIV-PAH (Etiology): Although the precise etiology of HIV-PAH is unknown, many theories have been advanced to explain this complication of HIV infection. As noted, many HIV-infected individuals have confounding factors independently associated with development of pulmonary hypertension. Importantly, a direct cause and effect relation between HIV infection and pulmonary hypertension has never been established. Furthermore, neither HIV nor any of its proteins has been found in pulmonary vascular endothelium. Thus, whether HIV infection itself can cause pulmonary hypertension or whether it is a trigger for development of IPAH in susceptible individuals is not yet clear. A potential role of HIV itself in the development of pulmonary hypertension is supported by two animal models of HIV infection, one murine and the other simian, in which pulmonary hypertension develops and an arteriopathy characterized by endothelial proliferation is observed. However, given the absence of the virus or its proteins in the pulmonary vasculature of HIV-infected patients with pulmonary hypertension, many theories have emerged regarding the role of HIV infection in the development of pulmonary hypertension. In some, however, development of HIV-PAH is likely a complex interplay of specific stressors (abnormal vasomotor tone, dysregulated angiogenesis, direct or indirect viral infection, alterations in the expression of cytokines, growth factors and vasoactive peptides) and a genetic or other predisposition.
Importance of Screening for PH

HIV patients are typically under care for other clinical problems related to their underlying HIV infection; thus, it is fairly easy to ascertain their level of physical activity, if it has changed, and, if so, their associated symptoms. In addition, unexplained peripheral edema or an increased P2 (pulmonic valve closure) on auscultation should prompt further investigation. Doppler echocardiography is a useful screening tool; unfortunately, its accuracy is not sufficient to establish the diagnosis definitively (>30% false positive rate). Likewise, an elevated serum BNP (brain natriuretic peptide) or NT-proBNP should raise the possibility of either right or left ventricular pressure overload, but is also not definitive. Right heart catheterization remains the only definitive diagnostic test and is essential for excluding left ventricular dysfunction or significant left-sided valvular disease.

Treatment of HIV-Associated PAH

Despite increased reports of HIV-PAH, as well as the longer life span of HIV-infected individuals, few studies have examined therapeutic options in this population. But, because of the similar pathology of HIV-PAH and IPAH, it has been theorized that treatments for IPAH might be effective in patients with HIV-PAH; however, this has not been extensively evaluated—only prostacyclin and bosentan have been studied. In patients with HIV-PAH, calcium channel blockers are ineffective and no study has evaluated oral anticoagulation. The role of antiretroviral therapy in the treatment of HIV-PAH is currently controversial. Some studies have found improvement in cardiopulmonary pressures during treatment with ART or HAART; others have found no salutory effect on right heart pressures and, in some studies, there even appears to be an increased incidence of HIV-PAH in patients treated with HAART whereas in others HAART seems to decrease the incidence of HIV-PAH.

Despite reported beneficial acute and long-term results, especially with epoprostenol or bosentan, in HIV-PAH, there are obvious limitations to the available studies. First, the total number of patients is still very small. Second, there have been no control (placebo) groups (there will likely never be such a trial with intravenous prostacyclin but such a trial could occur with oral agents and patients who are more stable). Third, despite the marked clinical improvement in these patients and the suggestion, at least in one study, that survival is improved by epoprostenol, a definite effect on survival has not as yet been demonstrated. Larger patient cohorts studied with scientific rigor are needed to address these issues.
The mission of the Pulmonary Hypertension Association is to find ways to prevent and cure pulmonary hypertension, and to provide hope for the pulmonary hypertension community through support, education, advocacy and awareness. PHA's members stand as part of a community that is fighting back against this terrible illness.

Under the leadership of the Scientific Leadership Council (SLC), a group of approximately 30 global leaders in the field of pulmonary hypertension, PHA proactively facilitates the development of new knowledge about pulmonary hypertension, develops educational resources for medical and public audiences and advocates to raise awareness about pulmonary hypertension. PHA’s professional membership bodies enhance the care and support of PH patients by enabling interaction among PH colleagues and providing opportunities for professional advancement. Just a few of the many benefits of membership available to clinicians and researchers include listing your practice in the Find A Doctor section of PHA’s website, discounted registration fees for PHA’s International PH Conference and Scientific Sessions and a free subscription to an online email group, offering peer-to-peer education and information sharing. To learn more about membership, visit www.PHAssociation.org/MedicalProfessionals/PHANetworks.

PHA’s Medical Education fund was founded in 2009 and provides ongoing educational information on PAH by nationally recognized and experienced medical leadership. The fund currently supports three professional education initiatives: PHA Online University, 30-City Program and Preceptorship Program, and one for patients, PHA on the Road. To learn more and get involved today, visit www.PHAssociation.org/MedicalEducationFund.

PHA fulfills its mission through:

- Funding for research
- Quarterly medical journal Advances in Pulmonary Hypertension (www.phaonlineuniv.org/Journal)
- Professional membership sections:
  - PH Clinicians and Researchers (PHCR) — for physicians and doctorate-level researchers (www.PHAssociation.org/PHCR)
  - PH Resource Network — for nurses and allied health professionals (www.PHAssociation.org/PHResourceNetwork)
- PHA Online University offering free CME credits and the latest information on pulmonary hypertension (www.PHOnlineUniv.org)
- Educational conferences and materials for medical professionals and patients
- 300+ page book Pulmonary Hypertension: A Patient’s Survival Guide
- PH patient support groups
- Quarterly newsletter Pathlight
- Advocacy and awareness campaigns
- Toll-free Patient-to-Patient Helpline (1-800-748-7274)
- PHA website with PH discussion boards, email groups and online support chats (www.PHAssociation.org/ConnectOnline)

PHA’s website is a comprehensive source of information for patients, caregivers, and medical professionals. Please visit us at www.PHAssociation.org.

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