Cardiac involvement and cardiopulmonary-vascular complications occur in patients with HIV infection and include pericardial effusion, myocarditis, dilated cardiomyopathy, endocarditis, coronary artery disease, malignant neoplasms, and pulmonary arterial hypertension (PAH). Patients who are infected with HIV and have HIV-related PAH (HRPAH) exhibit increased mortality compared with counterparts who are HIV-positive and normotensive; half of the deaths reported in patients with HIV infection as the only risk factor for PAH are due to cardiopulmonary complications (eg, right ventricular failure or sudden cardiac death) and not to HIV/AIDS itself. Approximately 90% of the patients with HRPAH survive 1 year, while 70% have a 3-year survival rate. This article focuses on HRPAH, with special considerations to prevalence, clinical presentation and diagnosis in the developing world, and the need for more intense research.

PAH as a Long-Term Complication of HIV Infection: What Is Known?

The antiretroviral cocktails introduced more than one decade ago have significantly improved survival for patients infected with HIV and reduced HIV-related opportunistic infections. However, 2 million lives were claimed by this infection in 2008, although deaths due to noninfectious complications of HIV infection are not accounted for in these estimates. Long-term outcomes, such as cardiovascular complications, including cardiomegaly, pericarditis, myocarditis, and PAH secondary to HIV infection, are now serious concerns.
The lung is a frequent target organ for disorders associated with HIV infection. PAH is diagnosed more frequently in the patient population infected with HIV than in the general population. The long-standing estimated prevalence of HRPAH in developed countries is 0.5%. As much as 27% of patients with suspected PAH by echocardiographic screening were diagnosed with HRPAH via right-sided heart catheterization (RHC). Based solely on echocardiographic parameters, 35% of individuals infected with HIV have been identified with “preclinical” PAH, and 5.5% of patients who are asymptomatic may be at risk for PAH. Comprehensive longitudinal studies have reported that the average age of patients with HRPAH is 38 years in a Swiss HIV study and 41 in a French study, although the range can span from infancy to old age. Men are slightly more affected by HRPAH than women (ratio of 1.2:1). There is no statistically significant association between PAH and viral loads or CD4+ T-cell counts but PAH is more severe in patients with AIDS. The role of antiretroviral therapy (ART) in PAH is still being debated; some studies suggest that HRPAH develops regardless of ART, that hemodynamic parameters by RHC remain unchanged, or that ART may accelerate the onset of HRPAH disease. On the other hand, other studies consider that therapy increases the survival and decreases the prevalence of cardiovascular diseases. In addition, there is no etiologic connection between HRPAH and the familial form of PAH ascribed to germ-line mutations in bone morphogenetic protein receptor type 2 (BMPR2).

**The Clinical Framework for HRPAH**

Patients with HRPAH are frequently misdiagnosed. Shortness of breath is the most common symptom, and although it is often ascribed to deconditioning, it usually progresses to the point of breathlessness at rest. Other symptoms include pedal and peripheral edema, nonproductive cough, fatigue, and chest pain. Right ventricular enlargement becomes evident by chest radiography and transthoracic echocardiography. The assessment of hemodynamic measures by cardiac catheterization is the gold standard for the diagnosis of PAH and the best test for evaluating the response to therapy. Cardiac catheterization, however, is not available in most health-care centers, including tertiary hospitals in sub-Saharan Africa and many other parts of the developing world.

Overall, HRPAH is typically diagnosed late in its course, when the clinical and laboratory findings of severe PAH (eg, right ventricular dysfunction) are generally present. Therefore, early detection is essential for the diagnosis, and clinical interventions are needed before quality of life is compromised.


Unfortunately, Africa has the largest number of inhabitants with HIV/AIDS worldwide (~23 of the 33 million people infected). Global efforts have yielded a 10-fold increase in availability of ART over 5 years; 43% of the African population now has access to HIV treatments. Still, pericardial and myocardial diseases associated with opportunistic infections prevail in 20% to 60% of the patients, according to pathologic and diagnostic methods and evaluation of the study population. Evidence of PAH in Africa is indirect because studies have been limited to echocardiographic measurements and anecdotes from African individuals. Echocardiographic abnormalities suggestive of PAH were found in 0.6% to 5% of the patients infected with HIV in Burkina Faso and Zimbabwe. Echocardiographic suspicions of PAH should be placed in the context of the relatively higher prevalence of pulmonary diseases (eg, TB, bronchiectasis, interstitial lung diseases), comorbidities (eg, sickle cell anemia, malnutrition, wasting syndrome, liver cirrhosis), and coinfections that are more prevalent in Africa. Cardiopulmonary pathologic conditions related to HIV infection are complicated by several additional infectious risk factors for PAH that are hyperendemic in regions like sub-Saharan Africa; these include schistosomiasis, filariasis, malaria, and chronic hepatitis B and C. In addition, human herpes virus 8, which is endemic in South America and sub-Saharan Africa, can be found in 62% of cells within and around the plexiform lesions in the lungs. Anecdotal data from centers in Africa indicate little difference between the clinical manifestations of the disease.
in Africa and the developed world.\textsuperscript{21} The fact that there are no established population studies focused on HRPAH in the African countries does not preclude judicious extrapolations from the developed world. Even if the percentage of people living with HIV who develop clinically defined HRPAH is relatively small, the disease burden in developing countries could be unbearable in the face of the high prevalence of HIV infection in these regions.

**Ongoing Research Initiatives Directed at a Better Understanding of HRPAH**

To understand any disease, cohorts of patients need to be characterized and followed up closely. The Swiss HIV Cohort Study, which followed patients for more than two decades, pioneered the determination of cumulative prevalence of HRPAH.\textsuperscript{6} The French National Registry of PAH has standardized the diagnosis of PAH by adopting an algorithm that includes self-reported dyspnea followed by echocardiographies and right-sided heart catheterization if there is clinical suspicion of PAH (eg, dyspnea in the absence of heart/lung diseases). Although not confirmed by RHC, echocardiography-based studies have focused the spotlight on subsets of patients in different cohorts worldwide. Some of these studies, such as the Swiss HIV Cohort Study, the French HIV-PAH Registry, and the Latium Registry of HRPAH, monitor the patients prospectively. Similarly, the National Heart, Lung, and Blood Institute of the National Institutes of Health in the United States has recently initiated a similar eight-site effort to understand clinically overlapping pulmonary topics related to HIV infection, including PAH, COPD, bacterial pneumonias, and emphysema.

**Mechanistic Insights Into HRPAH**

The histopathologic characteristics of HRPAH are not different from those of idiopathic PAH.\textsuperscript{17} Briefly, the pulmonary vasculature is obliterated with medial hypertrophy and increased proliferation of endothelial and smooth muscle cells. Plexiform lesions can be detected in 78% of patients with HRPAH.\textsuperscript{17} There is increased expression of smooth muscle cell/fibroblast growth factors such as platelet-derived growth factor.\textsuperscript{22} Inflammatory cells (eg, macrophages, lymphocytes, and dendritic cells) in the perivasculature in patients with severe primary PAH point to a potential role of inflammation in PAH,\textsuperscript{23,24} which is truly more evident in HRPAH. Essentially, HIV is at the center of the loop of PAH inflammation because the chronic inflammation and immune activation produced by HIV infection may lead to increased secretion of proinflammatory cytokines and growth factors that may subsequently promote PAH.

Besides the inflammatory aspect of HRPAH, Sehgal and Mukhopadhyay\textsuperscript{25} presented an alternative view that suggests that disrupted subcellular membrane trafficking in endothelial cells and smooth muscle cells is critical in the pathobiologic aspect of PAH. Observations of endothelial cells in plexiform lesions by electron microscopy revealed plump cells with enlarged endoplasmic reticulum, Golgi stacks, and vacuolation,\textsuperscript{26} suggesting defects in intracellular trafficking. Recent studies showed aberrant subcellular distribution of Golgi tethers giantin and p115 in obliterator-plexiform lesions in patients with idiopathic PAH and in macaques infected with simian-human immunodeficiency virus negative factor (SHIV nef).\textsuperscript{27} The amounts of Golgi tethers/matrix proteins were increased on a per-cell basis; together, these results suggest that subcellular trafficking and Golgi dysfunction may have important roles in the development of HRPAH.

**HIV Plays a Role in the Ethopathology of PAH**

There is no definitive evidence that HIV is a causal agent for PAH. Whether HIV infects lung vascular endothelial cells is still under discussion.\textsuperscript{22,23} The virus itself has not been detected in the lesions exhibited by patients with HRPAH.\textsuperscript{22,29} However, viral proteins and their interactions with molecular partners in the infected host are strong candidates for cause-effect relationships because they may promote apoptosis, growth, and proliferation.\textsuperscript{26} Pulmonary hypertension has been associated with viral proteins in infections with hepatitis B\textsuperscript{30} and human herpes virus-8,\textsuperscript{20} although the latter is not statistically associated with PAH.\textsuperscript{9,31} HIV proteins that damage endothelial cells and induce inflammation may result in pulmonary vascular remodeling. For example, the HIV envelope glycoprotein-120 (Env), which is essential for viral attachment and fusion through the host cellular membrane, induces apoptosis and increases the secretion of endothelin-1 from human lung endothelial cells.\textsuperscript{33} Also, HIV Env stimulates monocytes and macrophages to release proinflammatory cytokines.\textsuperscript{32} The HIV transactivator of transcription (Tat) protein activates endothelial cells and has angiogenic properties.\textsuperscript{33} Even though mutations in BMPR2 are not associated with HRPAH, the finding that Tat represses BMPR2 in monocytes\textsuperscript{34} suggests that idiopathic PAH might be biologically linked (not etiologically) to HRPAH.

HIV negative factor (Nef) is an accessory protein expressed early during viral infection, together with Tat. The Nef protein is a molecular adaptor and is a key player in HIV pathogenesis. For example, Nef interacts with several host cell proteins (including members of the p21-activated kinase family)\textsuperscript{35} and
recruits host adaptor proteins to commandeer trafficking of intracellular vesicles participating in secretory and endocytic pathways. Nef downregulates essential molecules such as the CD4 receptor by targeting the endocytic degradation pathway in clathrin-coated vesicles and major histocompatibility complex type 1 by sequestering it in the trans-Golgi and preventing its recycling from the Golgi to the membrane. Also, Nef is a migratory stimulus for monocytes and induces the release of inflammatory molecules. Capoccia and colleagues proposed a model in which Nef induces early recruitment of inflammatory monocytes, which in turn induce a secondary wave of monocytes followed by angiogenesis.

The potential role of Nef as a vascular insult is underscored by its capacity to enter lymphocytes via the human chemokine (C-X-C motif) receptor 4 (fusin) and exert apoptotic effects. Endothelial cells express this receptor, and therefore it is conceivable that Nef may be present in endothelial cells in the absence of infection. Nef localizes to vascular and perivascular cells and induces apoptosis in brain endothelial cells when expressed intracellularly or exogenously.

Recently, Lenassi and colleagues showed that nef-infected cells secrete Nef-containing exosomes that in turn induce apoptosis in resting T lymphocytes in vitro. Nef also impairs vasomotor functions in pulmonary artery cells, decreases the expression of endothelial nitric oxide synthase, and increases oxidative stress.

The use of chimeric viruses has facilitated the study of specific HIV proteins in animal models. For example, SHIV nef is a chimeric virus that preserves the backbone of simian immunodeficiency virus, the simian counterpart of HIV, but the nef gene was replaced for the HIV nef recovered from a patient with AIDS. Rhesus macaques infected with SHIV nef developed simian AIDS. Interestingly, Marecki and colleagues observed vascular remodeling in the lungs of rhesus macaques infected with SHIV nef that was similar to the remodeling exhibited by patients with PAH. Furthermore, the same research group reported plexiform lesions exclusively in banked lung samples from macaques experimentally infected with SHIV nef, but not in macaques infected with simian immunodeficiency virus. The plexiform-like lesions were characterized by luminal obliteration, endothelial cell proliferation, medial hypertrophy, thrombosis, and recanalized lumina. These data strongly suggest a role for Nef in the formation of plexiform lesions in the lung vasculature.

Is There a Diagnostic Marker of HRPAH?

The high mutational profile of HIV is the main hurdle in the design and development of vaccines to prevent and/or cure this infection. However, this feature of HIV may set the stage for the selection of specific HIV quasi-species at specific anatomic sites where virus presence may translate into a disease phenotype.

Nef Is Mutated in the Lung of a Patient With HRPAH

Nef sequences in the blood of patients with pulmonary hypertension show signature patterns that are specific to this disease phenotype, compared with their normotensive counterparts. Peripheral blood samples are the main biologic specimens analyzed in clinical research because lung tissues from these patients are extremely difficult to obtain. Nevertheless, Petrosillo et al were able to amplify and clone HIV-1 nef sequences from archived lung tissue from a patient diagnosed with HRPAH. The patient received a diagnosis of HIV infection in 2000 and of HRPAH in 2006, the same year the patient died. The lungs were collected...
during autopsy and subsequently analyzed. Sequence analyses of the HIV nef showed the presence of 4/5 Nef mutations reported in macaques infected with SHIV nef with plexiform lesions. Furthermore, this Nef sequence had six Nef functional domains mutated, all of them found only in the lung tissues collected in 2006, and interestingly, none of the mutations was found in peripheral blood mononuclear cells collected at the time of HIV diagnosis. There are clear phylogenetic differences between the quasi-species of the lung vs the periphery (Fig 1). These findings suggest either that the viral quasi-species in the lung arose later in the course of infection or that these variants are replicating more efficiently in the lung than in the periphery. These aspects warrant further research efforts in order to validate (and possibly implement) the use of Nef sequences as potential screening tools to identify subjects at risk for HRPAH, especially in a setting where resources are scarce.

CONCLUSION

Although a tight association between HIV infection and coinfections with viruses or bacterial agents in HRPAH remains to be established, interactions between HIV and other infectious diseases may result in an even higher prevalence of PAH in patients infected with HIV and influence the natural history, treatment, and outcome of HRPAH in Africa and other developing countries. Hence, increased awareness in the medical communities worldwide is an important step forward in understanding and treating this disease. Although there is no direct evidence that HIV causes PAH, it is generally accepted among the clinical-scientific community that HRPAH is more likely to occur via indirect action of HIV. Because HIV-infected cells in the lungs are sources of HIV proteins, the chronic exposure of lung endothelial cells to viral proteins has been hypothesized as one of the most important reasons for lung vascular injury in patients infected with HIV. The HIV proteins Env, Tat, and Nef have been identified as offenders of the pulmonary vasculature and, hence, key players in the pathogenesis of HRPAH. However, the understanding of the cellular and/or subcellular mechanisms and the pathways involved will be critical in unraveling the role of HIV proteins in HRPAH and research areas that need more attention (Fig 2).

The detection of elevated pulmonary artery pressures in patients infected with HIV who are asymptomatic for pulmonary complications denotes that a considerable number of these patients may be at risk for developing HRPAH and/or are exhibiting preclinical signs of HRPAH. This increases the urgency for the identification of biomarkers that will predict the likelihood of PAH in patients who are asymptomatic and in those with unexplained cardiopulmonary symptoms. A wealth of data suggests that HIV-1 Nef is a broad-spectrum modulator that may impact both infected and uninfected cells. Thus far, the potential use of mutations in Nef as a screening tool for HRPAH opens the door for further studies focused on the consequences of such mutations in HIV Nef in the context of pulmonary vascular biology.

![Figure 2. Conceptual frame of PAH as a complication of HIV infection. The connections between hypothetical events contributing to HRPAH are indicated with black arrows. Therapeutic interventions are shown by the white block arrows. Areas that warrant further research to determine molecular mechanisms and potentially unravel future therapeutic targets are indicated by triangles. PAH = pulmonary arterial hypertension. See Figure 1 for expansion of the other abbreviation.](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/22086/ on 06/27/2017)
REFERENCES


