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Maintaining lung health with longstanding HIV

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Abstract

Purpose of review—Human immunodeficiency virus (HIV) is now managed as a chronic disease. Non-infectious pulmonary conditions have replaced infection as the biggest threat to lung health, particularly as HIV cohorts age, but there is no consensus on how best to maintain long-term lung health. We review the epidemiology and pathogenesis of chronic obstructive pulmonary disease (COPD), pulmonary arterial hypertension (PAH) and lung cancer in HIV-seropositive individuals.

Recent Findings—Diagnoses of COPD are now up to 50% more prevalent in HIV-seropositive individuals than HIV-uninfected controls, and prospective pulmonary function studies find significant impairment in 7%–>50% of HIV-seropositive individuals. The prevalence of HIV-PAH is 0.2%–0.5%, and lung cancer is 2–3 times more prevalent in HIV-seropositive individuals. Although host factors such as age and smoking have a role, HIV is an independent contributor to the pathogenesis of COPD, PAH and lung cancer. Chronic inflammation, immune senescence, oxidative stress and direct effects of viral proteins are all potential pathogenetic mechanisms. Despite their prevalence, non-infectious lung diseases remain under-recognized and evidence for effective screening strategies in HIV-seropositive individuals is limited.

Summary—COPD, PAH and lung cancer are a growing threat to lung health in the HAART era necessitating early recognition.

Keywords

HIV; chronic obstructive pulmonary disease; pulmonary arterial hypertension; lung cancer

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Introduction

In countries with well-resourced health care systems, and increasingly in low and middle-income countries (LMIC), human immunodeficiency virus (HIV) infection has become a chronic illness. The focus of care has shifted from management of AIDS-associated illnesses to maintaining long-term health through optimal disease control and the prevention of secondary, non-AIDS complications. Primary prevention of cardiovascular disease, for example, is now a routine activity in the HIV clinic. This practice followed epidemiological studies showing the increased risk of coronary artery disease with HIV and guidelines that supported primary prophylaxis (1, 2). Neurocognitive, bone and renal health are similarly monitored. By contrast, long-term respiratory health receives less attention in the clinic, yet there is significant increased risk of non-AIDS lung disease in HIV-seropositive individuals (3–8). This review focuses on the most prevalent of these, namely chronic obstructive pulmonary disease (COPD), pulmonary arterial hypertension (PAH) and lung cancer, discusses current thinking on how HIV contributes to their pathogenesis and sets out what evidence exists to guide the promotion of long-term lung health in the HIV clinic.

COPD in HIV

It had become apparent by the 1990s that HIV was associated with both impaired diffusion capacity and COPD (9). Both case-control and prospective longitudinal studies in largely therapy-naïve HIV-seropositive cohorts showed reduced forced expiratory volume (FEV₁), impaired diffusing capacity for carbon monoxide (DL_{CO}) and emphysema on computed tomography (CT) scan of the thorax, even when matched for smoking, sex and age (9–11). Self-reported COPD was almost 3 times more common in HIV-seropositive individuals (12). Either or both COPD and impaired DL_{CO} were associated with lower CD4 counts, pulmonary and non-pulmonary AIDS-associated conditions and non-HIV factors; principally age, smoking and injecting drug use (IDU) (10, 13–15).

The association has persisted into the highly active antiretroviral therapy (HAART) era. A 47% increased risk for COPD was seen in HIV-seropositive individuals of the prospective Veterans Aging Cohort (VACs), even after adjustment for known COPD risk factors (16). The same group have since reported data from the VACs and the 1999 Large Health Survey of Veteran Enrollees (LHS) and found the prevalence of COPD was 15% higher in HIV with a higher incidence rate ratio in individuals <50 years old (1.17 (95% confidence interval 1.11–1.24) and younger non-smokers (1.25 (1.08–1.45)) compared with seronegative controls (5). Most recently, COPD has been identified as an increasing cause of death in the San Francisco HIV/AIDS registry (17). Incident COPD diagnoses have again been reported as higher in those with HIV in the Multicenter AIDS Cohort Study (MACS), although incident COPD was not higher in HIV-seropositive individuals in the Women's Interagency HIV Study (WIHS) cohort, possibly reflecting a diagnostic bias away from investigating chronic respiratory illness (18). This study also suggests that HIV clinicians might be under-diagnosing obstructive lung disease given that those with HIV report more cough, dyspnea and wheeze than HIV-seronegative individuals, but are not more likely to have had pulmonary function testing (4, 18).

These studies relied on diagnostic codes or self-report which may miss undiagnosed cases or incorrectly categorize lung disease. A more precise estimate of COPD prevalence and rates can be drawn from prospective clinic-based cohort-studies, typically involving 100–300 individuals who undergo pulmonary function testing (PFT). These studies find Global Initiative for Chronic Obstructive Lung Disease (GOLD)-defined COPD ($FEV_1/FVC < 70\%$ or $<$ lower limit of normal (LLN) and $FEV_1 < 80\%$ predicted) in 7% to 23% of HIV-seropositive individuals, 2 to 5-fold that of HIV-seronegative controls or reference populations, even in never-smokers (3, 4, 19–21). Impaired DL_{CO} is even more prominent; 30–64% of HIV-seropositive individuals record DL_{CO} below predicted values (22–24). The prevalence of DL_{CO} impairment is significantly greater than in HIV-seronegative controls and while higher in smokers, it is also raised in HIV-seropositive non-smokers (22, 23).

HIV in the pathogenesis of COPD

Several lines of evidence suggest that HIV is an independent contributor to COPD. Airflow obstruction and DL_{CO} impairment continue to be associated with prior history of pulmonary infection (e.g. *Pneumocystis pneumonia*), smoking exposure, injecting drug use (IDU) and increasing age, as in the pre-HAART era (3, 19) (Figure 1). New work confirms that disease is more pronounced in older HIV-seropositive individuals (over 40 years) who smoke more, showing 17–25% prevalence of COPD, diffusion impairment in more than a third and CT-confirmed emphysema in 26–37% (20, 21, 25, 26). Yet HIV, despite HAART, appears to remain as a driver; impairments in DL_{CO} and airflow continue to progress over time in those receiving HAART (23, 27) and among IDU with established COPD, HIV is independently associated with increased acute exacerbations (28). Also new among the literature are studies from LMIC, where cohorts are typically younger with low rates of smoking providing further insight into the contribution of HIV, age and smoking to COPD. In Cameroon, COPD was 2.85 times more common in HIV-seropositive individuals and 90% were GOLD stage 2 or 3, yet the mean age was 42.6 and more than 80% were never-smokers (29). COPD was, however, associated with moderate to heavy biomass exposure and prior pulmonary TB. This prevalence is similar to the 7.8% prevalence among a similar population of African participants of the Pulmonary Substudy of the Strategic Timing of AntiRetroviral Treatment (START) trial where 50% of COPD was in never-smokers (30).

The potential role of HIV as an independent factor in COPD development (figure 1) is also supported by associations between COPD and measures of HIV severity. Recent studies still find a correlation between lower CD4 and worse FEV_1 (20, 21, 31), DL_{CO} (22) or emphysema scores on CT (32), similar to associations reported in the pre-HAART era (13–15). Meanwhile, undetectable viral load and the use of HAART are both protective factors (22, 27).

It is possible that the immune activation that persists with HAART is implicated in COPD pathogenesis. The observation by Diaz et al. that emphysema in HIV was associated with increased numbers of cytotoxic T cells in the lung (10) has been followed by new associations between PFT abnormalities and measures of immune activation including CD8 T cell activation, CD4 T cell death receptor expression and levels of IL-6, sCD14, D-Dimer and IL-8 in the BAL, sputum or blood (31, 33–35). The importance of HIV-induced

inflammation in parenchymal damage is supported by a study in which smokers and never-smokers were analyzed separately; impaired DL_{CO} was found in the never-smokers and, in this group, it correlated with airway inflammation but not FEV₁/FVC or CT measures of emphysema as seen in the smokers (26). The dysregulated immune phenotypes of HIV and COPD share some common CD8 T cell features (36, 37) and have both been described as having features of accelerated immune senescence (5, 38), a hypothesis reinforced by the recent findings that reduced leukocyte telomere length is associated with PFT abnormalities and CT emphysema scores in HAART-treated HIV-seropositive cohorts (35, 39).

It is well documented that HIV is associated with oxidative stress (reviewed in (40)) and oxidant/antioxidant imbalance in the lung is a likely mechanism of airway damage; HIV, and specifically gp120 and tat, cause oxidative stress and alveolar epithelial barrier dysfunction in the lungs of animal models (41, 42) while the antioxidant glutathione (GSH) is reduced in both the plasma (43, 44) and the lungs (45, 46) of HIV seropositive individuals and may not return to normal with ART (47). Meanwhile, there is a compensatory GSH response in more emphysematous upper lobes of HIV-seropositive smokers and non-smokers (48). Oxidative stress also contributes to the pathogenesis of COPD; for instance GSH is reduced and linked to impaired nuclear factor (erythroid-derived 2)-like (NRF)-2 responses (reviewed in (49)), which are also documented in HIV (40). Confirming the relevance of oxidative stress, antioxidant N-acetylcysteine has been demonstrated to reduce COPD exacerbations (50).

The HIV virus and its secreted proteins may also act directly to cause lung damage. gp120 can induce mucus production from and cause damage to bronchial epithelial cells (51, 52), and greater levels of HIV RNA have been detected in more emphysematous regions of the lung (53). This finding is not solely relevant in the HAART naïve lung, as new evidence from HAART-treated macaques and virally-suppressed individuals indicates that the alveolar space may be a distinct compartment with persistent viral replication (54–57).

Finally, new data from the US Lung HIV Microbiome Program demonstrate that those with HIV and COPD have overrepresentation of fungal species (58), while there is an altered lung microbiome in HIV in general, in one series with increased *T. whipplei*, although the microbiome may be restored with HAART (59, 60). It is at least plausible that the lung microbiome could have a role, as it is well-established that bacterial microbiota in the lung are altered in COPD. The exact mechanism by which the microbiome contributes to disease progression is not yet known (61).

Pulmonary Arterial Hypertension in HIV

The prevalence of pulmonary arterial hypertension in HIV (HIV-PAH) is reported at 0.2% to 0.5% (6, 7, 62); however, prospective screening studies that use transthoracic echo to measure pulmonary artery pressure (PAP), rather than right heart catheterization (RHC), tend to report higher prevalence (63–66). PAH is defined as an elevated mean (m) PAP on RHC whereas echo estimates systolic (s) PAP as a surrogate for mPAP. sPAP is derived from measurements of the tricuspid valve regurgitant jet velocity, which may either under- or overestimate true mPAP (67). Furthermore, age- and weight-based reference values must

be used as sPAP increases with age and body mass index. For example, 6% of individuals aged over 50 have sPAP>40mmHG (68). Finally, left ventricular diastolic dysfunction, which can alter sPAP and is common in HIV, must be accounted for (69). Nevertheless, even on RHC studies, the prevalence is still some hundred-fold that of the normal population (70), and the VACs database study that relied on much less sensitive diagnostic coding of HIV-PAH still reported a significantly increased prevalence of 0.2% and incident rate ratio of 1.57(5).

These studies span the current and pre-HAART eras and, overall, show no clear change in HIV-PAH prevalence. In fact, two studies have found that HAART use correlates with HIV-PAH prevalence (64, 66). However, HIV-PAH has also been associated with higher HIV viral load (VL) and lower CD4 cell counts (33, 65); and longitudinal follow-up of pressure gradients and 6-minute walk tests in HIV-PAH shows that progression can be slowed by HAART (71, 72). Additionally, both HAART and PAH-specific therapy are associated with better outcomes in HIV-PAH patients (73, 74).

Pathogenesis of HIV-PAH

PAH prevalence in HIV-seropositive individuals is likely to be increased, in part by the co-occurrence of other PAH risk factors such as venous thromboembolic disease, IDU and hepatitis C virus (HCV) infection (75) (figure 2). HIV does appear to be an independent risk factor for PAH, and simian immunodeficiency virus (SIV)-infected macaque studies demonstrate a high frequency of PAH development (76). HIV-PAH shares the histopathological features of hypertrophy and proliferation of the arterial wall and plexiform lesions with idiopathic PAH, despite not directly infecting pulmonary endothelial cells (77), which has led to suggestions that the two have common pathogenic mechanisms, albeit with different triggers (78). Chief among these are the HIV proteins; Nef may contribute to pulmonary vascular remodeling in a primate model and is found in human endothelial cells (79, 80). Distinct nef polymorphisms are associated with HIV-PAH, although the causal relationship cannot be determined (81). HIV tat suppresses bone morphogenic protein receptor 2 (BMPR-2), implicated in idiopathic PAH. Tat can induce oxidative stress in pulmonary endothelial cells and has recently been found to act synergistically with cocaine to induce reactive oxygen species (ROS)-mediated endothelial damage (82–85). Finally, gp120 can cause apoptosis and oxidative stress in pulmonary endothelial cells (77, 86), with the latter also resulting in HIF-1 α -mediated upregulation of platelet derived growth factor, implicated in PAH (84). Further evidence of the importance of gp120, and perhaps a potential therapeutic approach, come from a new study that prevented gp120-induced pulmonary artery smooth muscle cell hypertrophy by blocking chemokine receptor 5 (CCR5) engagement using Maraviroc (ViiV Healthcare, Middlesex, UK) in a mouse model of hypoxia-induced PAH (87). gp120 also increases secretion of another important PAH factor, endothelin-1 (88). Endothelin-1 levels are higher in HIV-seropositive individuals and correlate with HIV-PAH severity (89).

Reports of associations between markers of systemic and pulmonary inflammation with HIV-PAH severity, including interleukin (IL)-8, interferon (IFN)- γ and, most recently, IL-6 and the endogenous inhibitor of endothelial nitric oxide synthase asymmetric

dimethylarginine (ADMA)(33, 90), support the hypothesis that HIV-PAH is also driven by inflammation, even during HAART (91).

Lung cancer in HIV

Lung cancer, a non-AIDS defining cancer (NADC), is 2–3 times more common (8) and carries a higher mortality in HIV-seropositive individuals than in the general population (92–94). This higher mortality may result from lung cancer presenting at a more advanced stage in HIV-seropositive individuals (95), rather than due to any difference in the subtypes, which are broadly similar to the general population (96). As the HAART era continues, the number of HIV-seropositive individuals with lung cancer is growing in proportion. In France, it is now the leading cause of death in HIV (97).

The pathogenesis of lung cancer in HIV

Smoking is more common in HIV-seropositive individuals and continues to be the major contributing factor to lung cancer in this population (98, 99). Recent data emphasize that smoking is central to the risk of non-virological cancers (100, 101). However, lower CD4 and higher VL are also relevant to cancer mortality and the association with HIV is independent after adjustment for other factors (96, 99). Additionally, Sigel et al. have reported that CD4 counts < 500 cells/mm³ and reduced CD4/CD8 ratios were associated with increased lung cancer risk (102). While the pathogenic mechanism linking HIV to lung cancer is not understood, these latter studies implicate immunosuppression, similar to its role in the pathogenesis of other malignancies in HIV (103, 104). HIV-associated inflammation is also likely to be relevant, as markers of inflammation (IL-6, D-dimer and C-reactive protein) have been linked to both infection-related and non-infection-related cancers in HIV (105) and more specifically to lung cancer (106). Finally, inflammation may also underlie the contribution of recurrent bacterial pneumonia to an increased risk of lung cancer in HIV (107).

Screening for Lung Disease in HIV

Given the disparity between COPD diagnoses and rates of respiratory symptoms or PFT abnormalities in prospective studies, the current approach is inadequate to identify COPD in the HIV clinic (4, 18). Whether this lack of detection is due to poor physician awareness is not clear, but one barrier may be that screening often requires referral and evaluation elsewhere (108). The use of readily-available screening tools like peak flow, with or without symptom questionnaires, may be an approach that identifies those who need spirometry (109), but there remains a lack of prospective trials to guide an evidence-based approach to COPD screening in the HIV clinic.

Screening for HIV-PAH is more difficult. Prevalence is lower than COPD and symptoms of fatigue, dyspnea and cough may initially be absent (64). Echo-based screening may both over and under-diagnose PAH depending on sPAP cut-offs used (110, 111). These observations lead some to conclude screening asymptomatic HIV-seropositive patients for PAH should not be performed (69). The invasiveness and availability of RHC limit its use as a screening tool; however, growth differentiation factor (GDF)-15 and N-terminal pro-B-

type natriuretic peptide (NT-proBNP) in serum are strongly associated with increased sPAP (63, 111), so could have potential as biomarkers in a screening protocol.

Radiographically, the appearance of lung cancer in HIV is similar to that of HIV-seronegative individuals (112) and given the success of lung cancer screening trials in high-risk groups (113), the use of CT screening has been investigated in HIV. Due to the presence of other lung pathology in HIV-seropositive individuals, such as scarring from previous infection (25), there might be unacceptably high rates of false positive scans resulting in significant over-investigation. This concern is borne out by Hulbert et al. (114) who found pulmonary nodules in more than 20% of participants, but detected only a single lung cancer in 678 person-years' screening of a high-smoking HIV cohort. They concluded that screening might not be worthwhile except in older age groups. In contrast, the Examinations of HIV Associated Lung Emphysema (EXHALE) study investigators found no difference in rates of abnormal CT screening scans compared with HIV-seronegative individuals, albeit only in those with a CD4 > 200 cells/mm³ (115). Initial reports from the French HIV CHEST study, targeting HIV-seropositive individuals over 40 years of age with significant recent smoking history, suggest that using low dose CT thorax for early lung cancer diagnosis and nodule follow-up may be feasible in HIV-seropositive smokers (116). Currently, lung cancer screening of HIV-seropositive populations with CT is not recommended beyond the guidelines for the general population (117).

Conclusions

Non-infectious pulmonary complications are more common in HIV-seropositive individuals, and their prevalence and severity will likely increase as the HIV-seropositive population ages. To maintain lung health in long-standing HIV, these complications have to be prevented, recognized and managed. Starting all individuals with HIV on HAART, as now advocated by guidelines (118), and promoting smoking cessation will undoubtedly aid prevention. However, the evidence base for effective strategies to identify COPD, PAH and lung cancer in HIV clinics is weak. Furthermore, the risk factors for each condition may be different, and there is much still to learn about the underlying mechanisms.

An individualized, patient-centered approach should be taken. HIV clinicians must be alert to the early symptoms of respiratory disease, particularly exertional breathlessness, and have a low threshold (and tenacious insistence) for organizing basic spirometry and DL_{CO} measurement. Echocardiography and CT of the thorax are readily available and can detect emphysema, HIV-PAH and lung cancers, but may lack specificity for the latter two. In the absence of HIV-specific evidence, the screening for these conditions should follow guidelines for HIV-seronegative individuals.

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Key Points

- Chronic obstructive pulmonary disease (COPD), pulmonary arterial hypertension (PAH) and lung cancer are all more common in HIV-seropositive individuals than in the general population in the era of highly active antiretroviral therapy (HAART).
- Chronic HIV-associated lung diseases are driven by the virus itself, non-HIV risk factors that are more prevalent in HIV-seropositive individuals such as smoking and injecting drug use (IDU) and ageing of the HIV-seropositive population.
- Clinicians caring for HIV-seropositive patients should be alert to these conditions, but current evidence does not indicate that screening and diagnostic approaches should differ from the general population.

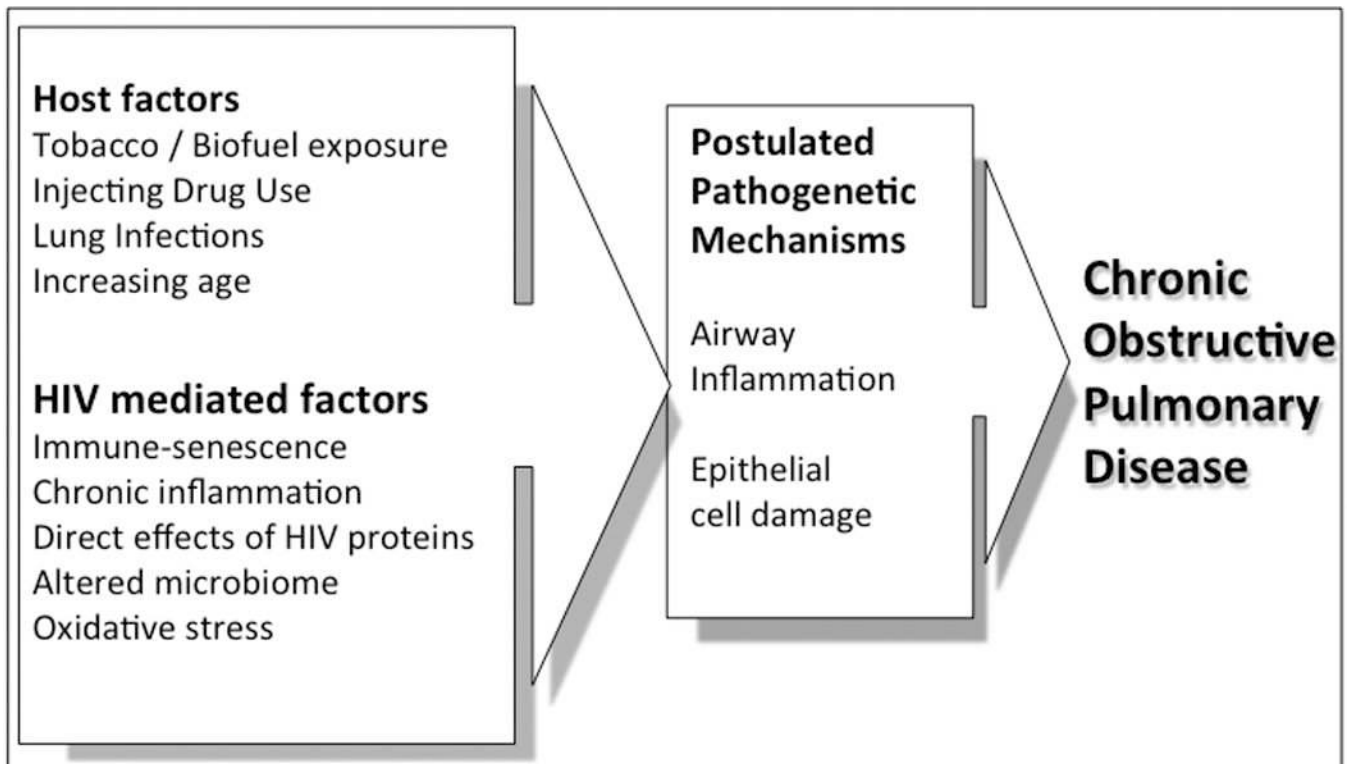


Figure 1.
The potential contribution of host factors and HIV to the development of COPD in HIV-seropositive individuals

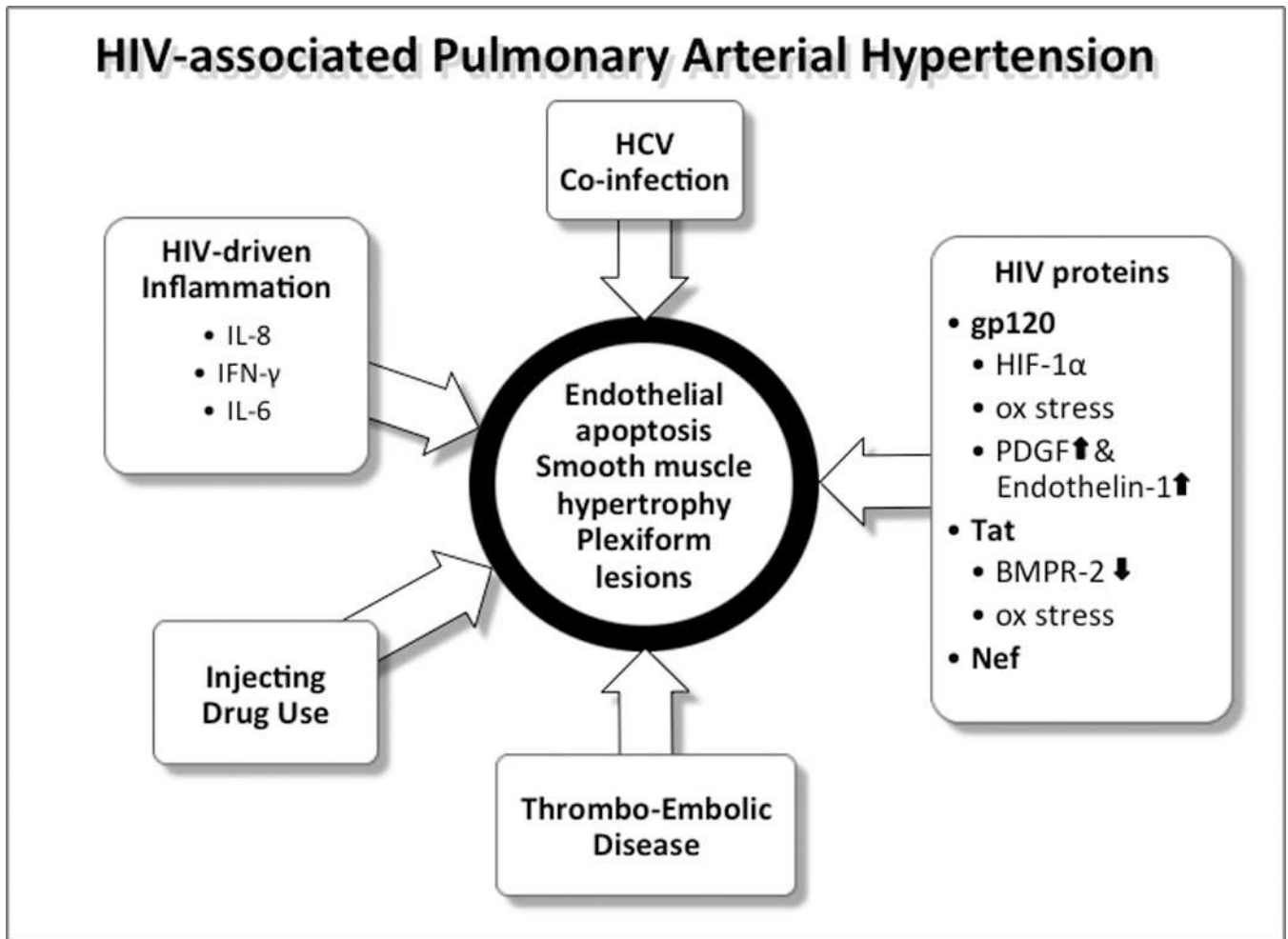


Figure 2.

The role of viral and other factors in HIV-PAH pathogenesis

IL – interleukin, IFN – interferon, HIF – hypoxia inducible factor, PDGF – platelet derived growth factor, BMPR - bone morphogenic protein receptor, HCV – hepatitis C virus