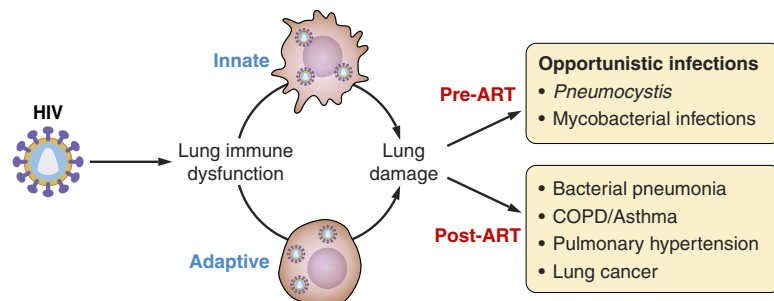# PATHOGENESIS OF HIV-RELATED LUNG DISEASE: IMMUNITY, INFECTION, AND INFLAMMATION

GRAPHICAL ABSTRACT

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## KEYWORDS

HIV; immunity; infection; inflammation; lung

CLINICAL HIGHLIGHTS

This article provides a comprehensive review on the pathogenesis of HIV-related lung diseases. The review also discusses the history of HIV-associated lung diseases from the pre-combination anti-retroviral therapy era to the present, with a focus on mechanisms and novel therapeutic targets.

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PATHOGENESIS OF HIV-RELATED LUNG DISEASE: IMMUNITY, INFECTION, AND INFLAMMATION

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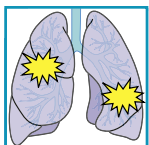
Cribbs SK, Crothers K, Morris A. Pathogenesis of HIV-Related Lung Disease: Immunity, Infection, and Inflammation. *Physiol Rev* 100: 603–632, 2020. First published October 10, 2019; doi:10.1152/physrev.00039.2018.—Despite anti-retroviral therapy (ART), human immunodeficiency virus-1 (HIV)-related pulmonary disease continues to be a major cause of morbidity and mortality for people living with HIV (PLWH). The spectrum of lung diseases has changed from acute opportunistic infections resulting in death to chronic lung diseases for those with access to ART. Chronic immune activation and suppression can result in impairment of innate immunity and progressive loss of T cell and B cell functionality with aberrant cytokine and chemokine responses systemically as well as in the lung. HIV can be detected in the lungs of PLWH and has profound effects on cellular immune functions. In addition, HIV-related lung injury and disease can occur secondary to a number of mechanisms including altered pulmonary and systemic inflammatory pathways, viral persistence in the lung, oxidative stress with additive effects of smoke exposure, microbial translocation, and alterations in the lung and gut microbiome. Although ART has had profound effects on systemic viral suppression in HIV, the impact of ART on lung immunology still needs to be fully elucidated. Understanding of the mechanisms by which HIV-related lung diseases continue to occur is critical to the development of new preventive and therapeutic strategies to improve lung health in PLWH.

HIV; immunity; infection; inflammation; lung

> This article provides a comprehensive review on the pathogenesis of HIV-related lung diseases. The review also discusses the history of HIV-associated lung diseases from the pre-combination anti-retroviral therapy era to the present, with a focus on mechanisms and novel therapeutic targets.

I. INTRODUCTION

Since human immunodeficiency virus-1 (HIV) was first discovered, pulmonary complications have been a frequent cause of morbidity and mortality (304). The advent of anti-retroviral therapy (ART) has expanded life expectancy for people living with HIV (PLWH), and consequently, the spectrum of infectious and noninfectious pulmonary complications has changed. For example, the incidence of opportunistic infections such as *Pneumocystis* pneumonia (PCP) has declined significantly while the incidence of community acquired pneumonia (CAP) has not decreased proportionately. In addition, noninfectious complications such as chronic obstructive pulmonary disease (COPD), asthma, lung cancer, and pulmonary hypertension have emerged as significant comorbidities.

Overall, the impact of HIV in the lung is significant, and alterations in lung-specific host immunity may increase the risk for HIV-related lung infections and chronic lung disease. Although effects of ART in the peripheral immune system have been studied extensively, the impact of ART on lung immunity is less well-understood. In this review, we discuss the impact of HIV on pulmonary immunity and the mechanisms of lung damage that can occur from HIV as well as review animal models that can be used to study the effect of HIV on the lung. We then consider the changing epidemiology and pathophysiology of major HIV-related lung diseases seen in the post-combination ART era. Although advances have been made in understanding how HIV affects the lung, many questions remain. Future animal

and human studies are critical to elucidating the mechanisms behind HIV-related lung damage to inform novel therapies to mitigate pulmonary complications, which are still major causes of morbidity and mortality in PLWH. Investigating the mechanisms by which these pulmonary complications occur is critical to the discovery of further preventive and treatment modalities.

II. PULMONARY IMMUNE FUNCTION IN HIV

A. Innate Immune Functions

Innate immunity involves recognition of pathogen-associated molecular patterns, which activate many cells along with a wide range of proinflammatory pathways. HIV can affect various aspects of the innate immune system in the lung spanning from the airway epithelium and surfactant proteins to alveolar macrophages, dendritic cells, and natural killer cells **(FIGURE 1)**.
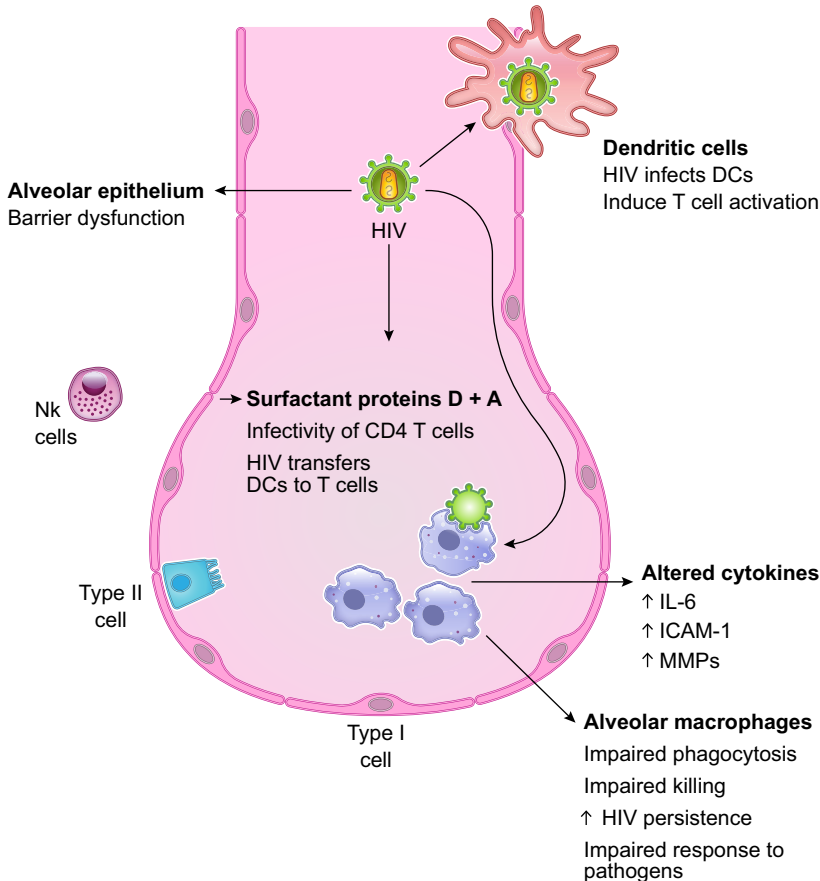
1. Airway epithelium

Situated at the interface with the external environment, the airway epithelium, made up of pseudostratified columnar

epithelial cells, lines the lumen of the airways and alveoli and serves as the initial barrier between noxious stimuli in the external environment and the lung. The barrier function of the lung epithelium depends on tight junctions that regulate paracellular permeability through coordinated activity of transmembrane proteins known as claudins (151). The initial mechanical barriers encountered by microorganisms include ciliated epithelial cells that secrete antimicrobial mucin and various inflammatory cytokines.

HIV can infect bronchial epithelial cells as these cells express HIV receptors CD4, C-C chemokine receptor type 5 (CCR5), and C-X-C chemokine receptor type 4 (CXCR-4). HIV entry into epithelial cells can impair cell-cell adhesion and increase inflammatory mediators (38). The HIV *trans*-activator of transcription (Tat) protein can suppress cystic fibrosis transmembrane conductance regulator (CFTR) functions, which are critical in modulating mucociliary clearance (52). HIV-related proteins can also cause significant alveolar epithelial barrier dysfunction, associated with changes in tight junctions (167). PLWH have shorter telomere lengths in airway epithelial cells compared with HIV-negative controls, suggestive of accelerated aging within the small airway epithelium, even after adjusting for age (308). These studies demonstrate that HIV can have significant

HIV effects on lung innate immunity

FIGURE 1. Human immunodeficiency virus-1 (HIV) effects on lung innate immunity. HIV can affect many aspects of the innate immune system. HIV can infect bronchial epithelial cells resulting in barrier dysfunction in the airway epithelium. Surfactant proteins D and A can modulate HIV, inhibiting infectivity of CD4+ T cells, but also stimulating HIV transfer from dendritic cells (DCs) to CD4+ T cells. HIV can also infect alveolar macrophages (AMs), primary innate immune cells in the lung, causing impaired phagocytosis, killing, and dysfunctional immune responses to pathogens. HIV infection of AMs can lead to HIV persistence in the lung and can result in altered cytokine release by AMs. Similar to AMs, DCs are key cells of innate immunity and can be primarily infected by HIV. IL-6, interleukin-6, ICAM-1, intracellular adhesion molecule-1; NK, natural killer cells; MMPs, matrix metalloproteinases. [Adapted from Standiford TJ, Toews GB, Huffnagle GB. Pulmonary Clearance of Infectious Agents. In: *Fishman's Pulmonary Diseases and Disorders* (5th ed.), edited by Grippi MA, Elias JA, Fishman JA, Kotloff RM, Pack AI, Senior RM, Siegel MD. New York: McGraw-Hill, 2015; with permission from McGraw-Hill Education.]

effects in both the bronchial and alveolar epithelium and could represent a novel mechanism by which HIV infection renders individuals susceptible to lung injury.

2. Surfactant

Dysfunction in pulmonary surfactant, a lipoprotein complex formed by type II alveolar cells, is seen in many diseases. Although all surfactant proteins play a role in surfactant lipid homeostasis and reducing lung surface tension, surfactant protein D (SP-D) and surfactant protein A (SP-A) have been shown to play key roles in innate immunity as well and may be altered in HIV infection.

In pre-clinical models, SP-D binds to HIV envelope glycoprotein 120 (gp120), an HIV protein that mediates binding and entry of HIV into macrophages (146). In doing so, SP-D inhibits HIV infectivity (190, 226). SP-D also inhibits direct infection of CD4+ T cells by HIV, but may enhance transfer of HIV particles from dendritic cells (DCs) to CD4+ T cells in vivo (174). In an animal model of acquired immunodeficiency syndrome (AIDS) following inoculation with *Pneumocystis* cysts, increased levels of SP-D were seen (13), resulting in increased recruitment of effector cells. Most recently, investigators from the Strategic Timing of Anti-Retroviral Treatment (START) study showed that the initiation of ART and suppression of HIV replication was associated with reduction in blood SP-D levels (160). Previous studies have shown a relationship between SP-D levels and pulmonary outcomes, such as lung function in cystic fibrosis (221) and mortality in pulmonary fibrosis (22). Thus these data suggest that SP-D levels may be associated with pulmonary outcome measures in PLWH as well.

Similar to SP-D, SP-A modulates HIV by inhibiting infection of CD4+ T cells; however, SP-A also augments transfer of HIV viral particles from DCs to CD4+ T cells (108). Increases in bronchoalveolar lavage (BAL) SP-A and SP-D have also been seen in patients with PCP (97) and non-PCP pneumonia compared with HIV-negative individuals (234), suggesting upregulation during inflammatory states. SP-A promotes attachment of *Mycobacterium tuberculosis* to alveolar macrophages (AMs) during HIV infection and augments interleukin-6 (IL-6) and HIV-1 long terminal repeat (LTR) activity (117). The evidence supports a multifaceted role of surfactant proteins in the course of HIV infection and lung infections. Further investigations into how these proteins may be utilized to potentially inhibit viral cellular entry and immune activation in the lungs of PLWH remain to be done.

3. Alveolar macrophages

AMs are the primary innate immune cells in the lung and the most plentiful cells, representing 95% of cells in BAL. AMs are lung phagocytes; they survey the lung for pathogens and are ultimately responsible for pathogen elimination. AMs perform a variety of important innate immune functions including phagocytosis, superoxide burst, proteolysis, and killing. In addition, AMs remove senescent cells, repair tissue, and intimately coordinate with T cells in adaptive immune functions. HIV can cause significant dysfunction in a variety of AM immune functions, and AM-T cell crosstalk may result in significant alterations in both innate and adaptive immunity. HIV entry into AMs is mediated by a surface CD4 molecule and two receptors, CCR5 and CXCR-4 (229), and infection of AMs occurs early in the disease.

Studies on the effects of HIV on AM phagocytic function have been variable, likely due to differences in study populations. Although several studies showed that AMs were dysfunctional in PLWH with low CD4+ cells counts, high viral loads, and opportunistic pneumonias (4, 5, 155), AM functions are impaired even in otherwise healthy asymptomatic PLWH without a decrease in CD4 counts (64, 171). Earlier studies showed increased phagocytosis of *Staphylococcus aureus* in a cohort of PLWH who were both smokers and nonsmokers, when compared with healthy controls (208). However, in a small subgroup of individuals with AIDS and pneumonia, viability of AM and phagocytic capacity were significantly reduced (208). Others have also shown reduced phagocytosis of *S. aureus* (143, 278), especially by AMs with HIV proviral DNA present (64), and reduced binding and phagocytosis of *Pneumocystis* (152). Studies suggest that two macrophage populations, small and large, exist in the alveolar space, but impaired phagocytosis seems to be specific to HIV-infected small AMs, with reduced expressions of HLA-DR and CD206 (140). HIV infection also impairs apoptosis-associated pneumococcal killing in AMs from ART-treated, virally suppressed PLWH (61).

AMs also contribute to defense against pathogens through inflammatory mediators, and HIV can diminish the lung's immune response to various pathogen challenges through dysregulation of inflammatory cytokines. HIV impairs tumor necrosis factor-α (TNF-α) release from AMs via Toll-like receptor-4 (TLR4)-mediated signaling when stimulated with lipopolysaccharide (LPS) (283). Furthermore, in vitro HIV infection of AMs from healthy people results in impaired TNF-α release and AM apoptosis in response to irradiated *M. tuberculosis* (231). The mechanisms by which HIV impairs AM immune functions are likely multifactorial and secondary to a number of factors including persistence of HIV within the AMs, local pulmonary inflammation and oxidative stress, and environmental factors (see sect. III).

4. Dendritic cells

Similar to AMs, DCs are key cells of innate immunity. As the main antigen-presenting cells in the lung, they are constantly processing proteins and presenting antigens via major histo-

compatibility complex (MHC) molecules which are recognized by T cells. Like AMs, HIV can primarily infect DCs, as these cells express high amounts of the HIV entry receptors CCR5 and CXCR4, in addition to low levels of CD4 (250). During chronic HIV infection, resting memory T cells carrying proviral DNA may interact with resident DCs in a lymphoid organ, which may induce T cell activation and transmission of reactivated HIV to DCs (292). This continuous cycle may lead to surges in plasma viral load and contribute to T cell exhaustion (248). As such, DCs are central to the integration between innate and adaptive immunity.

There are few data demonstrating how HIV affects DCs in the lung. Lung DCs are known to have an immature phenotype that is able to recognize and capture antigens, but unable to stimulate naive T cells due to a lack of costimulatory molecules (280). Mediators expressed by epithelial cells may be critical for downregulating airway DC functions (280), in addition to crosstalk between neuromediators in the intercellular spaces and DCs (156). In the absence of infection or inflammation, there is a continuous migration of DCs from the airways into draining lymph nodes (133). Under inflammatory conditions, there is a marked increase in the numbers and activation of DCs. Although there are several studies investigating the role of DCs in the course of respiratory viral infections and in antiviral immunity (166), there is a paucity of evidence on the effect of lung DCs in the setting of HIV. The ability of DCs with specific antigenic peptides to elicit a specific T cell response to HIV is very encouraging for vaccine development (47). Further study in this area may open a new research avenue for the role of DCs in HIV vaccine development.

5. Natural killer cells

Natural killer (NK) cells play a critical role in host immunity. They are key antiviral effector cells within the innate immune system, but recent studies have shown their adaptive ability to develop memory-like responses after an initial infection or vaccination (220). Studies show direct interactions between NK cells and HIV peptides (184). NK cells are additionally known to have an important role in controlling HIV infection through production of interferon-γ (IFN-γ) (287); however, there are little data on HIV infection of NK cells in the lung itself.

6. Impact of ART on innate immunity

Many innate immune deficits can be mitigated by ART; however, the impact of ART on lung immunity and on pulmonary sequelae in PLWH remains incompletely understood. Early preclinical studies showed that retaining zidovudine in AM cultures inhibited transfer of HIV to lymphocytes (126). A study of asymptomatic PLWH on ART demonstrated that phagosomal proteolysis in AMs is only impaired in individuals receiving <4 yr of ART (139). Despite ART, HIV can persist within the lung. Specifically, AMs or DCs can harbor latent HIV for extended periods of time, and HIV can resume viral replication with an inflammatory stimulus, resulting in viral load surges. Furthermore, although HIV infection of tissue macrophages is rapidly suppressed by ART, as reflected by decreases in cell-associated virus, delayed viral rebound in tissue macrophages occurs in about one-third of animals studied reinforcing the notion of established persistence of HIV infection within macrophages (134). These data suggest that despite ART and reductions in plasma viral load, the lung is a potential reservoir for HIV and viral replication within lung cells could impair innate immune functions.

B. Acquired Immune Function

The adaptive immune system, also referred to as the acquired immune system, is composed of highly specialized cells that eliminate pathogens or prevent their growth. This system is normally silent, but may be activated when a pathogen is able to overcome innate immune defenses. Adaptive immunity is highly specific to a particular antigen and is divided into cell-mediated immunity (modulated by antigen-specific cytotoxic T cells) and humoral immunity (modulated by B cells). Chronic HIV infection is characterized by chronic immune activation and immune suppression, as well as reduced proliferative and cytotoxic capacity. These effects lead to progressive loss of T cell functionality including a decreased cytokine response to antigenic stimuli, and increased B cell activation resulting in impairment of long-term serologic immunity. These changes occur not only systemically, but in the lung as well, resulting in significant pulmonary complications (FIGURE 2).

1. Cell-mediated immunity

CD4+ T lymphocytes are the primary target cells for HIV. Acute HIV infection leads to systemic depletion of gut-associated mucosal CD4+ T cells from direct infection and virus-induced apoptotic cell destruction (90) (FIGURE 3). Even in PLWH with preserved CD4+ T cell counts, there is significant compartmentalization of the immune response between BAL and blood; a higher frequency of antigen-specific CD4+ T cells tends to exist in the BAL compared with blood, suggesting recruitment of T cells to the lung in response to HIV antigens (141). However, BAL CD4+ T cell depletion does occur as HIV progresses to a more chronic phase, and is a predictor of mortality (3). In addition, chronic immune activation in the lung causes HIV-induced lymphocytic alveolitis, secondary to an influx of dysfunctional HIV-specific CD8+ T cells (213) directed at AMs or B cells expressing HIV antigens. The resulting low CD4:CD8 ratio is associated with pulmonary complications, including a loss of lung function (238) and overall increased mortality (295). In addition to accelerated destruction of CD4+ T cells and influx of CD8+ T cells,

HIV effects on
lung adaptive immunity
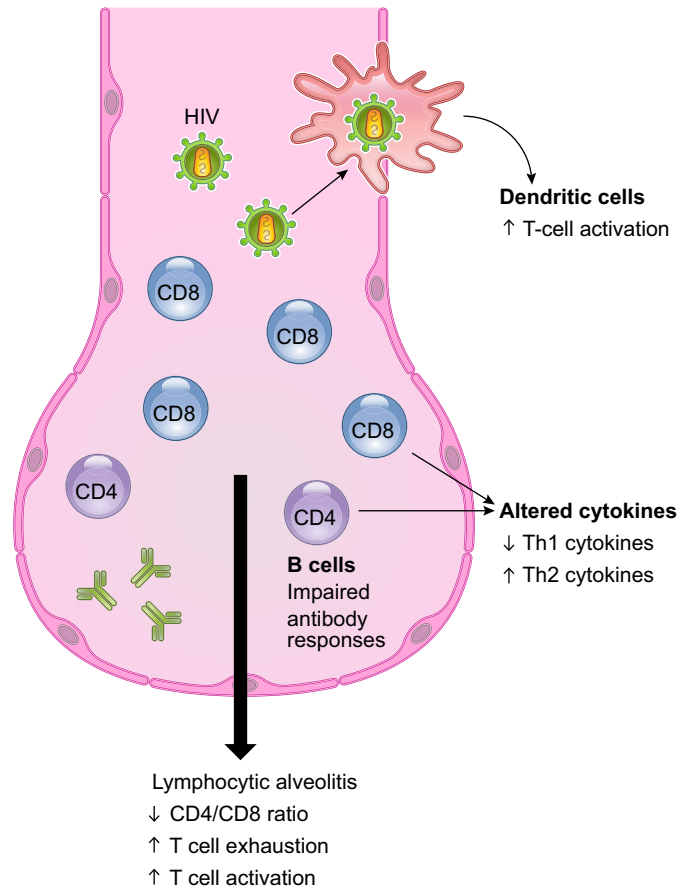
FIGURE 2. Human immunodeficiency virus-1 (HIV) effects on lung adaptive immunity. HIV affects many aspects of adaptive immune system in the lung. HIV can infect dendritic cells (DCs), primary antigen-presenting cells located in the airway epithelium, resulting in T cell activation. Chronic immune activation in the lung causes an influx of HIV-specific CD8+ T cells, resulting in a decreased CD4+/CD8+ T cell ratio, impaired proliferative responses, and T cell exhaustion. HIV can also affect the differentiation of CD4+ T cells, which is mediated by cytokines and transcription factors. HIV-induced chronic immune activation can also shift T cell immune responses, inhibiting the production of Th1 cytokines to favor a more Th2 response. In addition to alterations in cell-mediated immunity and chronic T cell activation, HIV also increases B cell activation impairing serologic response, resulting in impaired antibody responses. [Adapted from Standiford TJ, Toews GB, Huffnagle GB. Pulmonary Clearance of Infectious Agents. In: *Fishman's Pulmonary Diseases and Disorders* (5th ed.), edited by Grippi MA, Elias JA, Fishman JA, Kotloff RM, Pack AI, Senior RM, Siegel MD. New York: McGraw-Hill, 2015; with permission from McGraw-Hill Education.]

proliferative responses are also impaired in the lung. HIV-specific CD4+ and CD8+ T cells in BAL have increased expression of programmed cell death protein one (PD-1) and impaired proliferative capacity compared with T cells in the periphery, suggesting T cell exhaustion in the lung (213). Furthermore, blockade of the PD-1 pathway augments HIV-specific T cell proliferation. BAL CD8+ T cells also have impaired cytotoxicity and ultimately start to decline as HIV progresses, leading to further dissemination of secondary infections (102).

Major defects in the cytokine response are also seen during HIV infection. HIV shifts T cell immune responses, inhibiting the production of Th1 cytokines to favor a more Th2-type response, a critical change in cytokine balance that leads to HIV disease progression (25). Although ART has improved T cell cytokine responses, there continues to be significant impairment in production of IFN-γ and TNF-α, both Th1 cytokines, in response to infectious antigens and respiratory pathogens, such as *M. tuberculosis* or *S. pneumoniae* (135). Significant impairment of the BAL CD4+ T cell cytokine response remains as well with reductions in IFN-γ, TNF-α, and interleukin-2 (IL-2) (42, 141). Dysfunctional immune activation, as reflected by low CD4:CD8 ratio, high HIV

RNA levels, and chronic inflammation, contributes to lung diseases such as lung cancer (268) and COPD.

2. Humoral immunity

Chronic immune activation and suppression in HIV impairs humoral immunity and increases B cell activation, resulting in hypergammaglobulinemia. In the pre-ART era, PLWH with respiratory symptoms had increases in BAL IgG, IgM, and IgA compared with HIV-negative individuals (311). In contrast, asymptomatic PLWH have decreased BAL IgG levels, which is thought to be secondary to transforming growth factor-β1 (TGF-β1)-induced impairments in AMs (294). B cell activation also results in loss of memory B cells, which correlates with CD4+ T cell counts. The ability of HIV to impair long-term serologic immunity has important consequences when evaluating the ability of PLWH to respond to acute infections and vaccines.

3. Impact of ART on adaptive immunity

ART improves T cell functions in the lung. ART reconstitutes BAL CD4+ T cells, likely via local proliferation of memory CD4+ T cells, and results in improved immune
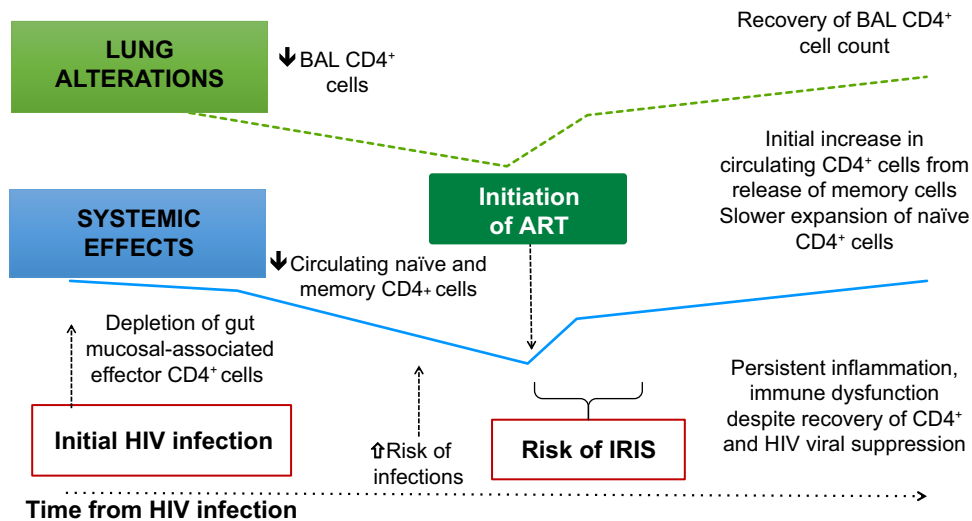
FIGURE 3. Systemic and lung alterations in T-lymphocytes with human immunodeficiency virus-1 (HIV) infection and initiation of anti-retroviral therapy (ART). After initial HIV infection, CD4$^+$ lymphocytes of the effector memory type are depleted from mucosal-associated lymphoid tissue; the CD4$^+$ cells within the alveolar space appear to be spared, but gradually decrease over time with progressive, untreated HIV. During the chronic phase of HIV infection, there is progressive decline in the systemic CD4$^+$ cell count due to decreased naive and memory T cells. Within the alveolar space, HIV-specific cytotoxic CD8$^+$ T-lymphocytes predominate, although in late-stage disease these are replaced with CD8$^+$ suppressor lymphocytes. As discussed in the text, HIV infection is also associated with abnormal function of T cells, B cell dysfunction, and, within the lung, abnormalities in several other lines of host defense. With initiation of ART, CD4$^+$ cell counts systemically and in the lung increase. However, abnormal innate and adaptive immune responses can persist over time despite recovery of CD4 cell count with ART. BAL, bronchoalveolar lavage; IRIS, immune reconstitution inflammatory syndrome. (From Crothers K, Thompson BW, Burkhardt K, Morris A, Flores SC, Diaz PT, Chaisson RE, Kirk GD, Rom WN, Huang L; Lung HIV Study. HIV-associated lung infections and complications in the era of combination antiretroviral therapy. *Proc Am Thorac Soc* 8: 275–281, 2011. Reprinted with permission of the American Thoracic Society. Copyright © 2018 American Thoracic Society. *Proceedings of the American Thoracic Society* is an official journal of the American Thoracic Society.)

functionality (150, 238). ART has also been associated with a delayed, but significant decrease in BAL CD8+ T cells, which can restore the CD4:CD8 T cell ratio in the lung to a more physiological state (238, 296). Effective viral suppression with ART reduces expression of Fas receptor and PD-1 in lung CD4+ T cells, which appears to directly correlate with increased IFN-γ function and reduced susceptibility to apoptosis (238).

ART also partially reverses B cell dysfunction induced by HIV. ART increases B cell numbers and decreases frequency of B cell subpopulations, specifically mature activated and immature transitional B cells, that are prone to apoptosis. This increase in B cell numbers is secondary to an increase in naive and resting memory B cells, both essential for functioning humoral immunity (193).

Although ART has improved humoral immunity in HIV, the effectiveness of immunizations directed at pulmonary pathogens is still variable. ART can restore effective antibody responses to influenza vaccination (158) and results in a more durable antibody response with a slower decline in IgG concentrations to pneumococcal vaccine (274). However, others studies show that despite ART, PLWH have lower circulating frequencies of memory B cells that recog-

nize the influenza vaccine (306), suggesting that revaccination is critical to maintain and reestablish B cell memory pools.

4. Immune reconstitution inflammatory syndrome: clinical implications of ART in the lung

ART can also impact the lung by causing immune reconstitution inflammatory syndrome (IRIS), a paradoxical worsening of respiratory status secondary to ART-induced immune recovery. HIV-associated IRIS may complicate ART initiation, particularly in the setting of an acute opportunistic infection or neoplasm, and has been associated with increased morbidity and mortality (207). Pulmonary IRIS is often secondary to mycobacterial infections, particularly latent or partially treated tuberculosis (TB). TB-IRIS incidence varies, but mortality is significant, especially with TB meningitis, resulting in death in ~40% of patients (187). Pathogenesis of pulmonary IRIS is likely associated with disruption of both innate and adaptive mechanisms. Reconstitution of CD4+ T cells with ART results in AM activation in the setting of mycobacterial infections (168), increased proinflammatory mediators (20) with inflammasome activation (285), and release of other tissue-injury mediators such as matrix metalloproteinases (MMPs)

(284). Although mortality can be significant with some cases of IRIS, early initiation of ART is still favored in individuals with most opportunistic infections. It is recommended that ART be initiated within 2 wk of opportunistic infection diagnosis (122). Possible exceptions to early ART initiation include cryptococcal meningitis and tuberculous meningitis, in which the risk of severe IRIS outweighs the benefits of early ART (210).

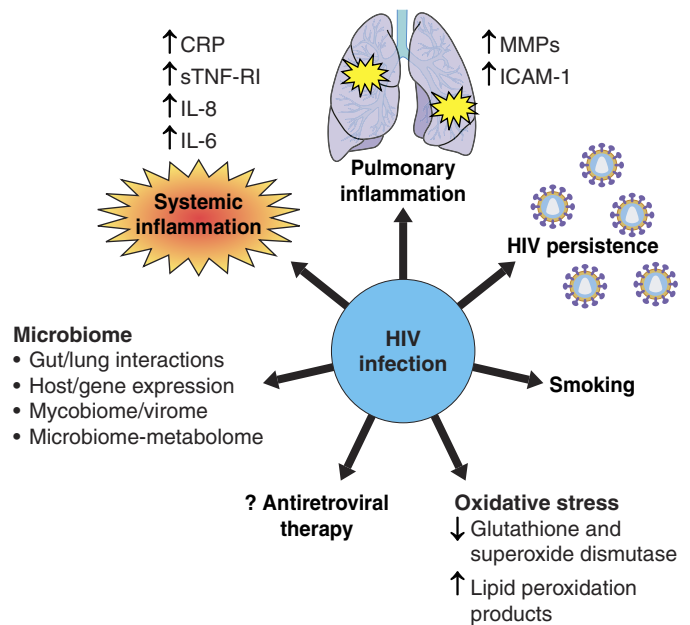## III. HIV-RELATED MECHANISMS OF LUNG DAMAGE

Beyond the immune dysfunction caused by HIV, a number of HIV-associated features may also contribute to chronic pulmonary disease. Systemic immune activation has long been recognized in HIV pathogenesis, and circulating markers of immune activation predict mortality in HIV despite ART. In the following sections, we discuss mechanisms of lung damage in HIV including systemic and pulmonary inflammation, persistence of HIV in the lung, smoking, oxidative stress, and the effects of ART itself on lung toxicity (FIGURE 4). In addition, we discuss the role of lung microbiome and the role of the metabolome in the lung.

A. Systemic Inflammation

HIV-induced chronic systemic inflammation is associated with increased risk of lung infections as well as chronic lung diseases. In PLWH treated with ART, higher levels of systemic inflammatory markers, such as C-reactive protein (CRP), have been associated with increased bacterial pneumonia risk (32). Others have shown that higher levels of plasma interleukin-8 (IL-8), lactate dehydrogenase (LDH), hydroxybutyrate dehydrogenase, and the ratio of IL-6 to IL-10 correlated with severity and mortality in AIDS PCP patients (281). Higher levels of CRP and IL-8 were also noted in PLWH with bacterial pneumonia, and an elevated admission IL-8 level predicted higher mortality (27). In addition, higher plasma baseline levels of soluble receptor of TNF-α (sTNF-RI) and soluble intercellular adhesion molecule (sICAM-1) were significantly associated with an increased risk of AIDS-defining events including recurrent bacterial pneumonia and PCP, even after adjusting for baseline CD4 count (185). Furthermore, higher plasma pre-ART CRP was significantly associated with developing a non-AIDS event, including non-PCP pneumonia (185).

B. Pulmonary Inflammation

In addition to its systemic effects, HIV can also lead to deleterious pulmonary inflammatory responses. Although CD8+ T cells in the lung are dysfunctional and express markers of functional exhaustion such as PD-1, they are still able to secrete effector cytokines in response to HIV antigens, resulting in local pulmonary inflammation and lung

FIGURE 4. Human immunodeficiency virus-1 (HIV)-related mechanisms of lung damage. HIV can induce lung damage through several mechanisms. 1) HIV can increase systemic inflammation, and increases in several inflammatory markers including C-reactive protein (CRP), interleukin-6 (IL-6), interleukin-8 (IL-8), and soluble receptor of tumor necrosis factor-α (sTNF-RI) can be seen in people living with HIV (PLWH) and have been associated with worse outcomes. 2) HIV antigens can cause significant local pulmonary inflammation and lung damage with release of matrix metalloproteinases (MMPs) and local inflammatory mediators, such as intracellular adhesion molecule-1 (ICAM-1). 3) HIV persistence in the lung can lead to impaired lung immune functions that can lead to chronic lung disease and injury over time. 4) Cigarette smoking is a significant problem among PLWH. HIV renders lung cells more susceptible to the harmful effects of cigarette smoke, suggesting that cigarette smoke results in additive risk, interacting with HIV to increase the risk for chronic lung disease. 5) PLWH have evidence of abnormal oxidant/antioxidant balance, systemically and in the lung, and oxidative stress may play a significant role in inducing lung damage. Reductions in antioxidant defenses such as glutathione, the primary antioxidant in the lung, and superoxide dismutase are seen along with increased levels of lipid peroxidation products. 6) In addition, anti-retroviral therapy itself may affect the lungs in ways that are not yet clear. 7) Finally, evidence that the changes in the gut are relevant to HIV-associated lung disease and the lung microbiome is also altered in PLWH adds to the knowledge that the gut microbiome is altered in HIV. Correlations of the lung microbiome to host gene expression and metabolomic profiles have shown that these changes to the microbiota result in dysregulation of inflammatory responses which could result in lung injury.

damage (237). IL-6, a potent inducer of acute phase responses, is released by AMs from PLWH (290). In lung interstitial macrophages, IL-6 is significantly higher in simian immunodeficiency virus (SIV)-infected non-human primates (NHP) and correlates with monocyte turnover and severity of lung-tissue damage, as evidenced by perivascular inflammation, interstitial pneumonia, and precipitation of fibrin and edema (44). HIV also impairs cell-cell adhesion within the airway epithelium and increases expression of local inflammatory mediators, such as intracellular adhesion molecule-1 (ICAM-1) (38).

Expression of inflammatory cytokines in the lung also leads to release of MMPs, a family of endopeptidases released from AMs with elastolytic and collagenolytic activity with key roles in extracellular matrix turnover. AM gene expressions of several MMPs (MMP-1, -7, -9, and -12) are elevated in smokers with HIV compared with smokers without HIV (145). Infection with *Pneumocystis* in PLWH correlates with increased expression of MMP-12 from AMs, which is modulated by IL-4 and IFN-γ. MMP-12-induced TNF-α release also mediates lung neutrophil migration (214). These data suggest that HIV-induced release of cytokine and chemokines by AMs and T cells results in neighboring lung cellular damage and dysfunction.

Dysregulation of inflammatory responses can also impair the immune response to pneumonia. Specifically, HIV-related pneumonia is characterized by higher mean alveolar levels of IL-2 and IL-1β, especially in those with opportunistic infections such as *Pneumocystis* (233). However, increased BAL IL-8 levels are seen not only in patients with *Pneumocystis* and bacterial pneumonia (157), but also in asymptomatic PLWH (80). Levels of IL-8 correlate with the percentage of neutrophils in BAL fluid and with clinical severity of pneumonia, suggesting an intact ability to attract neutrophils to the alveolar space despite immune impairments (26). Increased HIV replication in the lungs of individuals with active PCP is also linked to defective local chemokine release and an imbalance between proinflammatory and anti-inflammatory cytokine production (137). Impaired TLR4 signaling by AMs in PLWH may also contribute to the poor response of host cells to bacterial pathogens (283). HIV can also impair bronchoalveolar T cell response to mycobacteria. The resulting reduced number of cells expressing IFN-γ, TNF-α, IL-2, IL-8, and IL-1β suggests a failure of lung immune response in PLWH with TB (288). Overall, HIV-related pneumonia induces a dysfunctional inflammatory milieu in the lung that may result in cytotoxic lung injury and worse clinical outcomes.

C. Persistence of HIV in the Lung

Eradication of HIV has been difficult to achieve. Ongoing viral replication continues to occur in latently infected cells. Unfortunately, ART has been ineffective in eliminating these latent reservoirs. HIV integrates into the host DNA and can remain transcriptionally inactive for an extended period (60). The lung and gut harbor the highest viral loads of replication competent virus (165), suggesting that the lung is also a reservoir for HIV. Initial studies, using phylogenetic analysis of DNA sequences in small groups of asymptomatic PLWH, showed complete separation of HIV lineages from lung and blood (211). More recently, the C2-V5 region of HIV envelope was sequenced from a paired sampling of lung and blood and showed evidence of compartmentalization between lung and blood (127).

There is an abundance of evidence suggesting that lung myeloid cells are infected with HIV, particularly in uncontrolled HIV infection, which could impact lung immune function. HIV-infected AMs have altered HIV receptor expression, which increases further infection. AMs are also resistant to apoptosis and able to live for a long time with a low-turnover rate, making them ideal virus reservoirs in the lung. Although infected macrophages are able to replicate the virus, the amount of virus released from HIV-infected macrophages is significantly less than that of T cells. However, the virus remains sequestered from host immunity, representing a compartment for continued infection (188).

One of the first investigations in human BAL cellular components showed that the quantity of HIV DNA was higher in the lung compared with corresponding blood cells, and higher levels of HIV DNA were detected in the monocyte/macrophage cell populations (56). Other early studies showed that HIV was detected in AMs in individuals with AIDS and respiratory infections (267) and that ART reduced viral DNA in AMs (56). However, more recent studies show that HIV DNA and RNA are present in AMs, even in asymptomatic healthy HIV-infected individuals with systemic viral suppression (64). More recent investigations have investigated replication-competent viral genomes and found productively infected macrophages in BAL fluid and lung tissue (19). HIV viral replication occurs even in cell-free BAL fluid, and viral load may increase with active lung infection (153, 295). Further investigations on targeting this compartment and understanding lung macrophages as a possible reservoir for HIV are critical to eradication of the virus.

Information on HIV reservoirs in other cell types in the lung is limited. Approximately 5% of the total circulating lymphocyte pool is in the alveolar space, and T cells play critical roles in host pathogen defense. As discussed previously, PLWH have a lymphocytic alveolitis in the lung due to an influx of CD8+ T cells (295). These cells may become infected by HIV via fusion with AMs (120), resulting in significant numbers of infected T lymphocytes in the lung. In patients with AIDS-related lower respiratory tract chronic inflammation, lung CD4+ and CD8+ T cells also harbor replicating HIV (260), but further understanding of the clinical impact of the HIV-infected T cell reservoir in the lung is lacking. Human lung fibroblasts were also studied early in the course of HIV. When exposed to IFN-γ, fibroblasts express MHC class II molecules that allow them to become antigen-presenting cells to T cells (91). HIV readily infects lung-derived fibroblasts resulting in continued production of infectious virus. Furthermore, TNF-α and IL-6 stimulate HIV production in fibroblasts and release infectious virions, suggesting that inflammatory stimuli could enhance HIV transmission between infiltrating cells within the lung (91). Coculture of an HIV-infected promonocytic line with embryonic lung fibroblasts resulted in 30- to 40-

fold greater HIV reverse transcriptase activity, while an IL-6 antibody blocked HIV induction (131). These data suggest that interaction of human lung fibroblasts with macrophages may play an important role in HIV transmission within the lungs and that blocking the inflammatory stimuli may mitigate HIV transmission. Thus lung fibroblasts may also act as HIV reservoirs and may be involved in induction of inflammatory reactions.

The effect of ART on lung tissue compartments has not been well-described. In PLWH, ART can reduce lung viral load and alveolar lymphocytosis in both acellular BAL fluid and within lung cells (296), but the virus can still be detected when ART is interrupted, suggesting targeted therapies against HIV in the lung are still needed.

D. Role of Smoking

The frequency of cigarette smoking is nearly twice as high in PLWH compared with the general United States population. In a 2009 survey, ~40% of PLWH in the United States were current smokers and 20% were former smokers, compared with a 20% prevalence of current smoking in the HIV-negative population (186). Recent rates of smoking have declined in both populations, but remain twice as high in PLWH; in 2014, an estimated 34% of PLWH were current smokers compared with only 17% of the HIV-negative population (107).

Smoking is increasingly recognized as a major driver of mortality in PLWH on ART (69, 128). Smoking is also a major contributor to the development of comorbid diseases in PLWH, particularly for conditions with a longer latency of onset such as COPD. Given the prevalence of smoking in HIV and the strong associations of smoking with many lung diseases, disentangling the effects of HIV virus versus the impact of smoking on lung health is challenging. Epidemiologic studies that control for cigarette smoke exposure support an independent effect of HIV infection on lung health. Mechanistic studies further suggest that HIV infection may render lung cells more susceptible to the deleterious effects of cigarette smoke through a variety of pathways including generation of reactive oxygen species (ROS). Cigarette smoke may be a "second hit" in interacting with HIV to enhance risk for lung disease. Cigarette smoke has also been found to enhance HIV viral entry and viral replication by upregulation of CCR5 expression on bronchial epithelial cells via a TGF-β pathway (52) as well as by suppression of transcription and function of the CFTR.

Smoking also increases recovery of HIV in BAL (57), may accelerate progression of HIV (215), and impair response to ART (9, 37, 101, 307). While these associations have not always been consistently demonstrated in cohort studies and are subject to unmeasured, residual confounding (144, 305), laboratory-based studies support plausibility. For example, benzo(a)pyrene, a carcinogenic component of cigarettes, enhances HIV-1 replication in AMs in in vitro studies through a cytochrome P-450 pathway (242). Smoking can also cause systemic effects, including increased levels of CRP, sICAM, and MMP-9 in PLWH (7). Thus some of the deleterious lung effects of smoking may be related not only to oxidative stress, tissue injury, and increased inflammation directly from smoking (12), but also to direct effects on HIV replication, which may feedback to further amplify the injury from smoking. Although the exact mechanisms remain uncertain, these findings may account for the increased risk of pulmonary infections in smokers with HIV infection and the development of chronic lung diseases.

E. Role of Oxidative Stress

PLWH have an abnormal oxidant/antioxidant balance, both systemically and in the lung (18, 41, 92, 310). Oxidative stress results from an accumulation of free radicals due to oxygen metabolism and has been linked to aging and many comorbidities, including COPD (241, 255, 297). Increased oxidative stress during HIV infection persists despite ART (178) and is a predictor of all-cause mortality in PLWH (181).

PLWH have decreased antioxidant defenses, including superoxide dismutase and glutathione (40, 289). They also have elevated serum levels of lipid peroxidation products such as malondialdehyde and hydroperoxide (243, 275). HIV-related proteins, such as tat, can directly promote oxidative stress (35, 99, 106, 223), and gp120 may directly increase hydrogen peroxide production in target cells (261). HIV infection alters critical mediators of AM oxidative stress and phagocytic function such as peroxisome proliferator-activated receptor (PPAR)-γ; NADPH oxidase (Nox) isoforms Nox1, Nox2, and Nox4; TGF-β1; and respiratory burst (154), even in asymptomatic individuals with preserved CD4 counts (61, 310). HIV-related proteins can also inhibit nuclear factor (erythroid-derived 2)-like 2 (Nrf2), a master transcription factor that activates the antioxidant response within AMs, impairing phagocytic capacity (278). Oxidative stress from HIV can contribute to impaired immune function and the increased risk for lung diseases in HIV.

PLWH may be more vulnerable to additional oxidative stressors including smoke exposure, hypoxia, AM production of ROS, air pollution, and ART-related mitochondrial toxicity (124, 194, 230). In a prospective longitudinal study, BAL glutathione levels decreased to a greater degree in PLWH who were smokers compared with nonsmokers (225), and plasma glutathione levels were significantly lower in PLWH who were smokers compared with nonsmokers (59). Thus oxidative stress induced by HIV, as well as by comorbid conditions and exposures, may be a critical driver of both infectious and noninfectious lung diseases in PLWH.

F. Adverse Effects of Anti-retroviral Therapy on the Lung

A variety of adverse effects have been reported with all anti-retroviral medications and, in the early days of ART, toxicities were a major reason that ART regimens were changed. Fortunately, newer ART regimens have been associated with fewer serious side effects. Although adverse events have been observed with respect to cardiac, gastrointestinal, liver, endocrine, and renal effects, there have been no studies documenting direct toxicity of ART in the lung. Given the number of PLWH on ART and the prolonged exposure to these agents, better understanding of potential ART toxicity is needed. Studies have been done investigating interactions between ART and treatment regimens for lung cancer (176) and obstructive lung disease (249). One significant interaction is between protease inhibitors and inhaled or intranasal corticosteroids which can result in Cushing's syndrome and adrenal insufficiency (249, 251). Treatment guidelines have also been updated regarding prescribing ART in the setting of chronic lung disease (247). New drug-drug interaction tables have been included on drugs to treat chronic lung disease and pulmonary hypertension; one change includes a strong recommendation against coadministering steroids with boosted ART regimens because of an increased risk for Cushing's syndrome. These new guidelines acknowledge the increasing prevalence of pulmonary complications in this population and the potential for further drug-drug interactions with ART.

G. Role of the Lung Microbiome

With the advent of next-generation sequencing and investigation of the human microbiome, there has been increasing interest in the impact of the microbiome in HIV infection. With the profound immunosuppression that occurs in patients with AIDS, there may be alterations of the microbiome in multiple body sites, but studies in this population have been limited. Even in treated HIV, residual immune dysfunction could lead to alterations in the microbiome that could then contribute to pathogenesis of comorbidities via systemic and local inflammation, production of active metabolites, or direct pathogenic effects. Given the ability to modify microbial composition and gene expression, manipulation of the microbiome represents a novel avenue for therapeutics in HIV and its associated comorbidities.

The gut has been one of the most studied body sites in the HIV microbiome. The initial depletion of CD4+ T cells in the gut during acute HIV infection can result in bacterial translocation, which may stimulate systemic inflammation and contribute to end-organ damage. There also appears to be loss of diversity in the gut microbiome in HIV, although this finding has not been replicated in all groups (169). Several studies find increases in the proinflammatory *Prevotella* spp. and decreases in *Bacteroides* spp., which stimulate regulatory T cells (169). In general, decreased microbial diversity appears to be associated with elevated markers of microbial translocation and immune activation as well as decreased CD4+ cell counts, but causality has not been proven (217). One study found that the rectosigmoid mucosal microbiome was dysbiotic, particularly in untreated PLWH (301). In addition, the microbiome correlated with peripheral IL-6 levels and kynurenine pathway of tryptophan metabolism, which are linked to chronic inflammation (301). Effects of ART on the gut microbiome are inconsistent, and it is difficult to distinguish changes resulting from immune reconstitution versus those that occur directly from the ART agents or other factors (236). There are also changes in the gut virome such as expansion of adenovirus in advanced HIV (195), but these are less well-described.

Changes in the gut microbiome may be relevant to HIV-associated lung disease via effects on systemic inflammation, bacterial translocation, production of metabolites, or production of antimicrobials. The gut microbiome impacts lung diseases such as asthma and alters immune responses to acute infections such as influenza, but studies relating either the composition of the gut microbiome to the lung microbiome or to lung function in HIV are lacking.

There are far fewer studies of the lung microbiome in HIV. In part, lung microbiome work has lagged behind investigation of the gut microbiome given the initial debate over the presence of a normal lung microbiome. It is now generally accepted that the lung may contain bacteria that derive from aspiration of oral microbes, as well other organisms in healthy individuals (89, 198). The absolute bacterial load is much lower than in the gut, and these bacteria likely do not represent established, replicating communities as seen in the gut. Furthermore, given the low biomass in the lung, studies must be carefully controlled for environmental contamination with both procedural and sequencing controls.

Most work in the lung microbiome in HIV has come from the Lung HIV Microbiome Project (LHMP), a multi-center National Institutes of Health-sponsored study assessing the respiratory tract microbiome (24, 172, 198). Using 16S rRNA sequencing of BAL, this group identified *Tropheryma whipplei (T. whipplei)*, the agent of Whipple's disease, as a common bacteria in the lungs of PLWH, especially in those who smoke (172). The prevalence of *T. whipplei* decreased with initiation of ART, but *T. whipplei* was not associated with respiratory symptoms. This organism has also been identified in a smaller number of healthy individuals (50, 198) and NHP with and without HIV-like immunosuppression (202).

A larger study of the lung microbiome in PLWH and HIV-negative individuals from the LHMP did not find significant

differences in alpha (within sample) or beta (between sample) diversity by HIV status (24). PLWH in this cohort were either treated with ART or had intact CD4+ cell counts. Another study investigating individuals with more advanced HIV infection before and after ART initiation found that alpha diversity was decreased in the BAL of individuals with more advanced HIV before the initiation of ART (293). There were significant differences in beta diversity between PLWH and HIV-negative individuals, with greater dispersion in the communities of the PLWH. These differences generally decreased after 1 yr of ART, but PLWH continued to have greater abundance of *Veillonella* and *Prevotella*. These bacteria are considered proinflammatory and might contribute to the persistent pulmonary inflammation and lung damage seen in PLWH.

There have also been investigations assessing the lung microbiome and its relationship to host gene expression. One group found that PLWH with pneumonia in Uganda had a different lung microbiome than those from San Francisco with a higher prevalence of *Pseudomonas aeruginosa* and a greater diversity (138). Pulmonary expression of TNF-α was also positively associated with bacterial burden and negatively correlated with diversity. Expression of MMP-9, a protease involved in emphysema pathogenesis, negatively correlated with both bacterial richness and diversity. A larger follow-up study of the Ugandan cohort defined three groups of pneumonia patients based on airway microbiome composition. These groups showed differences in mortality, associations with serum metabolites and predicted bacterial metabolic function, and detection of *Aspergillus* from culture of lung specimens (263). A small study of bronchial epithelial cell microbiome and gene expression in PLWH with and without COPD found minimal differences in the microbiome based on spirometric diagnosis of COPD or emphysema on computed tomography (CT) scan, but did see relationships of *Firmicutes* with host gene expression, including genes relevant to inflammation and immunity (282).

Although these bacterial studies in general find few changes in bacterial taxonomy except in cases of pneumonia or advanced HIV, there may nonetheless be differences in the lung microbiome that have not yet been detected with current methodology. 16S sequencing does not allow identification of most bacteria down to a species or strain level, and whole genome sequencing could be more illuminating in identifying subtle differences in bacterial community structure. In addition, bacterial function, as measured by gene expression or metabolomics, could be more important than the identity of the bacteria, as discussed below. Bacterial gene expression in the lung has not been examined, but could potentially impact lung inflammation and function. Finally, although the identities of bacteria may be similar in PLWH and HIV-negative individuals, it is possible that the host response to the microbial communities differs and that an aberrant response could result in lung injury.

Alterations of the oral cavity also occur in HIV and could influence lung function. The LHMP found differences in the oral bacterial microbiome in HIV and in smokers including increased abundances of *Streptococcus* and *Actinomyces* with decreased oral microbiome alpha diversity in PLWH (14). Other studies have also found that PLWH have decreased oral alpha diversity (44). Whether these changes in the oral microbiome are related to lung infections or chronic lung diseases is not currently known, but changes in the oral microbiome could influence the lung via microaspiration or by stimulating systemic and local inflammation.

Most microbiome studies focus on bacterial communities, but fungi and viruses also contribute to the microbiome and may be altered in HIV infection. A study of BAL from PLWH and HIV-negative individuals with and without COPD demonstrated that there was greater fungal diversity in the lung than there was bacterial diversity. The mycobiome was distinct in PLWH and also varied by COPD status (73). The presence of *Pneumocystis jirovecii* was most strongly associated with both HIV and HIV-COPD, and other fungal species were also differentially abundant. These results built on prior work using polymerase chain reaction (PCR)-based techniques that identified *Pneumocystis* as associated with HIV and COPD in both human and animal studies (197). Inflammatory changes associated with colonization by *Pneumocystis* may also be connected to the development of COPD (203). In a SIV model, *Pneumocystis* coinfection resulted in a dramatic influx of IFN-γ CD8+ T cells followed by an increase in IL-8, TNF-α, and neutrophils leading to significant airflow limitation (33, 216). Interestingly, marijuana use and low CD4 cell count both seem to influence the mycobiome (73). As fungi are immunogenic, they could stimulate a host response that is detrimental to the lung. Viruses may also be important in the lung, but few studies have examined the pulmonary virome in HIV.

If the microbiome of the lung, mouth, or gut plays a role in lung disease in PLWH, it might be possible to modify the microbial communities of these sites to impact disease. Fecal microbiota transplantation (FMT) is being investigated in HIV to reduce systemic inflammation, but impact on lung disease is unknown (129, 170). Currently, ability to modify the lung microbiome is limited to antibiotics, but development of strategies to change bacterial composition or function may eventually prove beneficial in HIV-associated lung disease. Studies have found that dental cleaning can improve lung function in HIV-negative individuals with COPD (262), but manipulation of the oral microbiome has not been investigated in HIV.

H. Impact of the Lung Metabolome

Metabolomics uses small-molecule chemical profiling to support integration of host and disease in a complex biosystems approach. As downstream products of genes and proteins, metabolites provide a unique fingerprint of an individual's phenotype. The metabolome is dynamic and can reflect metabolic pathways of host and/or microorganisms. There are a paucity of studies investigating metabolomics in the HIV lung or in HIV-related lung diseases, but understanding of lung metabolites could improve biomarkers of lung disease and suggest novel therapies.

One of the first studies compared the metabolome in BAL in otherwise healthy PLWH with healthy HIV-negative controls using liquid chromatography/mass spectrometry (LC/MS) methods (65). Overall metabolic profiles were different in BAL fluid between PLWH and HIV-negative controls, even in PLWH without a history of lung disease or lung infections. Furthermore, pyochelin, a siderophore of *Pseudomonas*, was significantly higher in PLWH compared with controls, suggesting that differences in the metabolome could reflect lung bacterial colonization (65). Another study found that the lung metabolomes in PLWH compared with HIV-negative individuals differed much more than bacterial taxonomy, with enrichment of metabolites such cystine, a key product in the oxidative stress response that has been postulated to play a role in HIV-associated COPD (66).

Metabolite profiling has also been performed in plasma of individuals with HIV-COPD. PLWH and COPD had a metabolite profile that included sphingolipids and fatty acids (132). Tryptophan metabolism was also altered in HIV, but was not associated with HIV-COPD. The significance of these findings is unknown; however, these pathways may represent key mechanisms in the pathogenesis of HIV-related chronic lung diseases and may lead to future diagnostic and therapeutic targets.

Bacteria produce an array of active metabolites and also stimulate metabolite production by the host, but there have been few studies that have correlated lung microbiota with lung metabolic profiles in HIV. One of the first studies found that specific metabolic pathways and oxidative stress metabolites were increased even in the BAL fluid of asymptomatic PLWH compared with HIV-negative controls (66). Specifically, pathways related to fatty acid, glycerophospholipid, and linoleate metabolism correlated with lung microbial species. The bacterial organisms associated with the greatest number of metabolic features were organisms known to be involved in pneumonia pathogenesis, including *Staphylococcus, Streptococcus*, and *Norcardia* (66). These data suggest that HIV alters inflammatory and oxidant pathways in the lung, which may shift the functional response of the lung microbiota, even in asymptomatic PLWH. More recently, Segal et al. (257) found that increased serum short-chain fatty acids (SCFAs) predicted the risk of TB in a cohort of ART-treated PLWH. Pulmonary SCFAs correlated with increased oral anaerobes in the lung, suggesting that metabolites from anaerobic bacterial fermentation may increase the risk of TB.

IV. ANIMAL MODELS OF HIV-RELATED LUNG DISEASE

Studies in animal models of HIV have been limited by the lack of a rodent model that faithfully reproduces the immune deficits seen in HIV and by the cost and challenges of work in NHP models. Cell culture or ex vivo tissue systems are useful, but animal models are needed to more accurately model HIV infection and its systemic effects. HIV has limited tropism, only infecting humans and chimpanzees (81). Consequently, animal models must employ either related lentiviruses such as SIV or humanized animal models. Each of these systems replicates different features of HIV in humans and has different limitations.

A. Rodent Models

Rodent cells are not susceptible to HIV infection, but development of humanized mice and rat models have been useful in studying HIV. These models allow study of HIV infection and transmission, immunologic effects, viral-host interactions, viral persistence, end-organ damage, therapy, and prevention. There are several types of humanized rodents including those that are immunodeficient and transplanted with human cells or tissue, CD34+ hematopoietic cells, or some combination of these (182). Advantages of using these models include *1*) feasibility and relatively lower cost compared with large-animal models, *2*) replication of many features of HIV infection, and *3*) utility in prevention studies, as they can acquire HIV from multiple routes of infection. The presence of a human immune system allows the mice to be infected with HIV, although most systems do not mimic T cell development in a human thymus and not all features of the human immune system are replicated. Other disadvantages include the short rodent life span and the fact that the models do not reproduce all facets of organ pathology.

Other rodent models either have manufactured HIV with mouse genes that render it infectious to rodent immune cells or have developed transgenic mice that express various HIV proteins. For example, the coding region of gp120 in HIV can be replaced with gp80 from a murine leukemia virus to construct a chimeric virus that can infect murine lymphocytes (240). The virus can be transmitted sexually (123), but the model does not replicate immunodeficiency and seems to be more analogous to treated HIV infection with controlled viral replication. Transgenic models in mice and rats that express HIV proteins such as Nef, Tat, and gp120 are useful to investigate the deleterious effects of these proteins, but cannot replicate active HIV infection. Each model

has unique strengths and weaknesses, and use of particular models is dictated by the scientific question to be examined.

Rodent models have been used to study several aspects of HIV-associated pulmonary disease. For example, a recent study using the murine chimeric virus model examined development of COPD in smoke-exposed mice (113). Smoke exposure did not increase lung viral levels, but decreased CD4+ T cells in the lung. The infected, smoke-exposed mice had greater anatomic emphysema and increased airway obstruction compared with noninfected smoke-exposed animals or infected animals not exposed to cigarette smoke. In addition, these animals had increased lung cell apoptosis and increased collagenase, neutrophil elastase, and MMP-9, which have been linked to lung destruction in humans with COPD.

Studies of pulmonary arterial hypertension (PAH) have also been performed in transgenic rodent models. In one study, HIV transgenic rats had increased right ventricular systolic pressure, increased right ventricular wall thickness, increased pulmonary artery thickness and remodeling, and alterations in lung cell gene expression (173). Another study reported similar findings of increased right ventricular mass and vascular remodeling in the setting of elevated hypoxia inducible factor-α and platelet-derived growth factor-B (189). In the presence of hypoxia, HIV transgenic rats had worse pathological findings of PAH compared with controls exposed to hypoxia (239). This model has also been used to study the interactions of HIV proteins and cocaine in development of PAH with findings of worse disease in transgenic animals in the presence of cocaine (75).

Coinfection models with TB have been developed in bone marrow, liver, thymus (BLT) humanized mice (45, 218) that mimic many pathological and inflammatory aspects of TB infection in PLWH. Other models of lung pathology in mice include a transgenic mouse that is engineered to express Tat in the lung. These animals develop cellular infiltration and increased oxidative stress, and higher levels of the proinflammatory NF-κB (63). Although the authors did not find alterations in lung structure, the changes seen replicate several findings in the lung of PLWH that could contribute to lung disease.

B. Non-Human Primate Models

NHP models of HIV are more complex, expensive, and time-consuming than rodent models, but better reflect infection with the virus in humans. The advantages of using these NHP models overall include the similarities of NHP to humans: *1*) similar outbreeding with genetic and environmental variation, *2*) similar course of immunodeficiency following infection, and *3*) multiple routes of infection that mimic human transmission. These models are also quite useful for investigations of therapies and vaccines. However, there are significant difficulties with the use of NHP including cost, need for a specialized facility, small numbers in experimental groups, and the relatively long duration to develop immunodeficiency.

To create these models, cynomolgus or rhesus macaques are intravenously or intramucosally inoculated with either SIV or SHIV (SIV/HIV chimeric virus). As with the different rodent models, each viral model has advantages and disadvantages. SIV is a naturally occurring lentivirus that resembles HIV. Infection with SIV results in a course of immunodeficiency similar to humans with initial high levels of HIV replication, decreases in CD4+ T cells, and development of similar AIDS-associated infections, malignancies, and other comorbidities. Immunodeficiency is accelerated, allowing for studies of the disease course. Although SIV infection in NHP is the best model of HIV infection in humans, there are differences between SIV and HIV that may limit its utility including genetic and biological differences between the viruses and differences in response to therapies.

SHIV models have been established by developing chimeric viruses that replace certain genes and reverse transcriptase with HIV. Features of this model depend on the specific properties of the SIV-HIV chimeras and which HIV proteins they express. The SHIV model has been used to evaluate the efficacy of AIDS vaccine candidates. However, disappointing results from the STEP study1 (HVTN 502) (39), where a vaccine candidate showed efficacy against SHIV in NHP, but not in a cohort of 3,000 HIV-negative volunteers at high risk of HIV infection, have suggested that SHIV may not be the best model for evaluating vaccine efficacy.

NHP models have been useful in studying infectious lung diseases such as TB and *Pneumocystis*. NHP models develop a similar range of infection from latent infection through active TB with variability in granuloma formation in the lungs similar to that in humans (43). *Pneumocystis* infection has been modeled in NHP, contributing to our understanding of the immune response, transmission, and contributions to COPD pathogenesis. NHP develop PCP after intrabronchial inoculation with macaque-derived *Pneumocystis* (33). Interestingly, infection can also be transmitted solely by cohousing these animals (148).

NHP models can also be used to study several chronic lung diseases including COPD and PAH. These animals develop histological, radiographic, and physiological signs of COPD in the setting of *Pneumocystis* colonization as determined by PCR-based detection of the organism and mounting of an antibody response in the absence of clinical signs of pneumonia (148, 149, 266). Pulmonary outcomes can be assessed in these models by *1*) bronchoscopy, which can be repeated with greater frequency than humans to evaluate longitudinal changes; *2*) pulmonary function testing that mimics human testing; *3*) chest CT; *4*) positron emission

tomography; and *5*) pathology. NHP models also develop PAH and have been useful for studying this disease (110). Both echocardiography and survival right-heart catheterization can be performed in these animals to assess longitudinal changes in pulmonary and right ventricular hemodynamics (111).

V. LUNG DISEASE IN PEOPLE LIVING WITH HIV

A. Pre-Combination ART Pulmonary Manifestations of HIV

There are few diseases whose epidemiology has shifted as dramatically as that of HIV. Infection with HIV was a certain death sentence at the start of the epidemic in the 1980s. With the development of combination ART to suppress the virus to undetectable levels and restore CD4+ T cell counts, HIV has become a chronic disease for people who can access and are adherent to therapy. Prior to the institution of ART, lung disease was the leading cause of morbidity and mortality. The first reports of the disease that later would be known as AIDS were cases of a previously rare opportunistic pneumonia in gay men (183). PCP later became the leading serious AIDS-defining illnesses (47a). Other fungi including *Cryptococcus neoformans*, *Histoplasma capsulatum*, and *Penicillium marneffei* also caused pneumonia in PLWH, particularly those with advanced immunosuppression **(FIGURE 5)**. Tuberculosis in PLWH rapidly became a devastating epidemic, particularly in sub-Saharan Africa. Other mycobacterial infections, such as *Myocbacterium kansasii*, had a higher incidence in HIV infection (125). Bacterial pneumonia was a common complication in PLWH, even with CD4+ T cell counts greater than 500 cells/μl (130). In 1993, recurrent bacterial pneumonia was added to the Centers for Disease Control definition of AIDS-defining illnesses (1). Pulmonary malignancies including lung cancer, Kaposi sarcoma, and non-Hodgkin lymphoma were all seen more commonly in PLWH (142).

The Pulmonary Complications of HIV Study (PCHIS) was one of the first large-scale, multicenter studies to define the epidemiology of lung disease in PLWH in a cohort of primarily men, reflecting the HIV epidemic at the time. The study found that upper respiratory tract infections were the most frequent respiratory disorder and that lower respiratory tract infections increased with decreasing CD4+ cell counts (304). Noninfectious, chronic lung complications were also reported in the pre-combination ART era, but received less attention than the highly morbid opportunistic pneumonias and AIDS-associated malignancies. Performing serial pulmonary function testing, the PCHIS found that HIV infection was associated with a decrease in the lung diffusing capacity for carbon monoxide (DLCO) (162) and that duration of HIV infection was an independent predic-
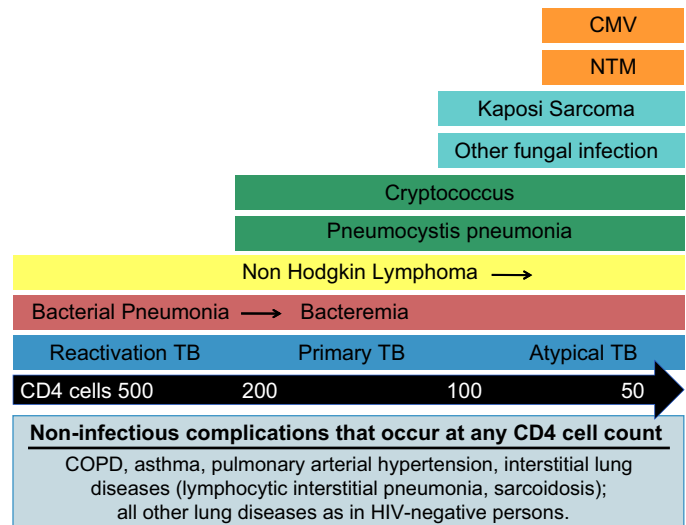
FIGURE 5. Risk of lung diseases and relationship to CD4 cell count in people living with HIV (PLWH). The risk of different infectious and noninfectious pulmonary complications varies depending on the level of immunosuppression that can be assessed by CD4+ T cell counts. Several pulmonary infections occur when the CD4+ count decreases below 200 cells/μl including *Pneumocystis* pneumonia and lung infections due to *Cryptococcus*, cytomegalovirus (CMV), and non-tuberculous mycobacteria (NTM). In contrast, bacterial pneumonia and tuberculosis (TB) can occur at any CD4+ count, but the severity of disease tends to increases as the CD4+ count declines. In addition, noninfectious pulmonary complications such as chronic obstructive pulmonary disease (COPD), asthma, and pulmonary arterial hypertension can occur at any CD4+ count. (Figure courtesy of Dr. Sudhakar Pipavath.)

tor of accelerated decline in pulmonary function (204). Other groups also reported advanced COPD and radiographic emphysema in PLWH, particularly in those who smoked (86). PAH was a highly morbid disease that was also increased in HIV (142, 276).

B. Post-Combination ART Pulmonary Manifestations of HIV

In the era of combination ART, the spectrum of lung complications affecting PLWH has shifted. With earlier initiation of ART at first diagnosis of HIV, survival has improved and PLWH are aging on effective therapy. The incidence of lung infections has decreased, and chronic lung diseases are emerging as important contributors to morbidity and mortality. HIV infection confers an increased risk for a number of chronic lung diseases, with COPD and asthma being the most prevalent. Other conditions that continue to be associated with an increased risk in PLWH include PAH and lung cancer. Links between HIV and interstitial lung diseases are less clear, but an increased incidence of certain types of interstitial lung diseases such as sarcoidosis, nonspecific interstitial pneumonia, and lymphocytic interstitial pneumonia have been associated with HIV infection (112).

1. Bacterial community-acquired pneumonia

As more PLWH are treated early with ART, the overall incidence of lung infections, particularly opportunistic infections such as PCP, has decreased. However, the incidence of lung infections remains high in populations who are without access to ART, who are not adherent to ART, or who are unaware of their HIV infection. Opportunistic infections such as PCP are more common in PLWH with CD4+ cell counts below 200 cells/μl (FIGURE 5). The frequency of different pulmonary infections, particularly those due to mycobacteria and fungi, varies depending on the spectrum of organisms encountered regionally in addition to other factors including CD4 cell count.

In PLWH on ART, the most common lung infection is bacterial community-acquired pneumonia (CAP), particularly in those with CD4+ cell counts above 200 cells/μl, in whom an opportunistic infection is less likely to occur. Bacterial CAP can occur throughout the course of HIV infection and at any CD4+ cell count, although the incidence increases with lower CD4+ cell counts. In the START study, the incidence rate of serious bacterial infections overall was 0.87 per 100 person-years of follow-up, with ~40% of infections being due to bacterial pneumonia (219). While rates of bacterial CAP decrease with ART, CAP remains more frequent in PLWH compared with HIV-negative individuals (258, 272). The most common cause of CAP in PLWH is *Streptococcus pneumonia* (55), but frequently no causative organism is identified.

Numerous factors contribute to the continued increased risk for pneumonia in PLWH, including alterations in host lung immunity, environmental risk factors, and associated comorbid conditions. Behavioral risk factors for CAP include cigarette smoking, illicit drug use, and alcohol. Risk for CAP increases with age and comorbid diseases such as COPD, as well as with obesity (16, 219), an emerging health problem in PLWH. Vaccinations against influenza and pneumococcus decrease risk for pneumonia (163); however, HIV may lower effectiveness for the vaccine.

CAP is also associated with increased morbidity and mortality, both short and long term in PLWH. However, these outcomes have improved in the ART era. In a Danish cohort study of PLWH hospitalized for pneumonia, 30-day risk of death fell from 7.9% in 1995–1996 to 5.5% in 2000–2008. Ninety-day mortality after pneumonia similarly decreased from 12.0% in 1995–1996 to 8.4% in 2000–2008 (273). In the Community Acquired Pneumonia Organization (CAPO) database from 2001 to 2006, in-hospital all-cause mortality was ~10% in PLWH (177). Although these data are encouraging, given the increasing survival of PLWH and their growing burden of comorbidities, incidence rates of CAP may see another surge as these individuals age. Investigations into novel adjunct therapeutic and preventative options for PLWH who are at continued risk for CAP are needed.

2. COPD

Although the prevalence of COPD in PLWH is in part due to greater rates of smoking in PLWH versus the general population, HIV infection has also been associated with an independent risk for COPD, even without prior AIDS-related pulmonary complications (68, 70, 86, 87, 175). A recent systematic review and meta-analysis of 30 studies on COPD in the global population of PLWH found that the prevalence of COPD was significantly higher in PLWH than in HIV-negative controls, even after adjusting for cigarette smoking (30). COPD can also present at an earlier age in PLWH (70), and PLWH may be more likely to experience acute exacerbations of COPD (82, 164). However, other studies have not found significant differences in the prevalence of COPD among those with and without HIV (246, 299). Results may differ depending on characteristics of the patients and the prevalence of exposure to other COPD risk factors in the populations studied.

When comparing pulmonary function test results by HIV status, HIV infection is an independent risk factor for a low DLCO, adjusting for smoking and other risk factors (71, 103, 162). Results of spirometry are less consistent. The forced expiratory volume in 1 s (FEV1), forced vital capacity (FVC), and their ratio (FEV1/FVC) are similar by HIV status in some studies (71), whereas in others, HIV infection is associated with a greater prevalence of airflow limitation (175). HIV infection is also associated with concurrently decreased FEV1 and FVC (246, 299). Overall, among PLWH, the prevalence of abnormal spirometry is high: 37% in the Lung HIV Study had abnormal spirometry, with 27% having airflow limitation and 10% having a restricted lung disease pattern (93).

Emphysema is a frequent sub-phenotype of COPD in PLWH (14, 87, 121) and may account for the significantly decreased DLCO in PLWH compared with HIV-negative persons. In a Veterans Affairs (VA)-based study, emphysema in PLWH was more severe and tended to be more diffuse when compared with HIV-negative veterans (14). Although HIV was not associated with an increased risk of emphysema in a recent Danish study (244), the HIV-negative individuals in this study were significantly older than those with HIV. Furthermore, the PLWH had ART initiated early and had higher CD4+ cell counts than those in the VA-based study. HIV is also associated with a greater risk of chronic bronchitis, another major sub-phenotype of COPD (88).

Poor HIV disease control (i.e., a low CD4+ cell count, high HIV viral load) is a risk factor for abnormal lung function [manifested by a low FEV1, FVC, DLCO, airflow limitation (FEV1/FVC <0.70)] or a clinical diagno-

Table 1. *Circulating soluble and HIV-related markers*

| Lung Measure	Circulating Soluble and HIV-Related Markers
Decreased airflow (low FEV1)	Inflammation (IL-6, CRP), monocyte activation (sCD163), endothelial dysfunction (ET-1), high HIV viral load (>75,000 copies/ml),* low CD4 cell count (<200 cells/μl)*
Decreased airflow (low FVC)	Inflammation (IL-6, CRP), monocyte activation (sCD163), high HIV viral load (>75,000 copies/ml),* low CD4 cell count (<200 cells/μl)*
Airflow obstruction (decreased FEV1/FVC)	Monocyte activation (sCD163)
Impaired gas exchange (low DLCO)	Inflammation (IL-6, TNF-α, CRP), monocyte activation (sCD163, sCD14, IL-2 receptor), microbial translocation (LPS), endothelial activation (ET-1)
Emphysema (by CT scan)	Monocyte activation (sCD14), immune compromise and imbalance (nadir CD4 <200 cells/μl, CD4/CD8 ratio <0.4)

*Associated with accelerated decline in forced expiratory volume in 1 s (FEV1) and forced vital capacity (FVC) over time. CRP, C-reactive protein; DLCO, lung diffusing capacity for carbon monoxide; ET-1, endothelin-1; IL-2, interleukin-2; IL-6, interleukin-6; LPS, lipopolysaccharide; sCD14, soluble CD14; sCD163, soluble CD163; TNF-α, tumor necrosis factor-α. [Data from Attia et al. (14), Drummond et al. (95), Fitzpatrick et al. (104), North et al. (216a), and Triplette et al. (291).]

sis of COPD (TABLE 1) (71, 94, 95, 246). Poorly controlled HIV also puts PLWH at risk for more rapid decline in lung function (95). A nadir CD4+ cell count below 200 cells/μl and a low CD4:CD8 ratio (<0.4) are associated with greater radiographic emphysema (14, 291). These data support that the immune deficiency from HIV is important in the development of COPD, although COPD is still seen in PLWH who have preserved immune function.

Chronic systemic inflammation, chronic innate immune activation, and abnormalities in immune function related to HIV that persist despite ART are linked to COPD in PLWH (FIGURE 6). Inflammatory markers such as CRP and IL-6 are associated with pulmonary function test abnormalities, specifically airflow limitation and diffusion impairment (72, 105). Analyses of peripheral blood leukocyte gene ex-

pression reveal upregulation of inflammatory and immune-related pathways in PLWH with impaired lung gas exchange (low DLCO) compared with HIV-negative persons, suggesting that these pathways may play a relatively greater role in HIV-related lung disease versus non-HIV-related lung disease (72). Increased levels of biomarkers reflecting monocyte activation are also correlated with lung disease in PLWH (TABLE 1). Increased soluble CD14, the LPS co-receptor, is associated with emphysema (14), and increased soluble CD163 (sCD163) is seen with a low FEV1/FVC ratio and low DLCO in PLWH (104). Taken together, these data suggest that systemic inflammation, immune activation, and dysfunction related to HIV contribute to the development of HIV-associated COPD.

Abnormalities in AM function and imbalance of protease and anti-proteases within the lung are also critical in the pathogenesis of COPD. HIV infection of AMs may contribute to enhanced susceptibility to COPD. The number of macrophages is ~10-fold higher in the lungs of smokers than nonsmokers, and emphysema develops coincident with increased macrophage influx in several mouse models. Macrophages produce a variety of proteinases that can cause extracellular matrix damage that leads to emphysema. In smokers with HIV infection, AMs upregulate MMPs (145). Specifically, AM expression of MMP-1, -7, -9, and -12 is significantly higher in smokers with emphysema if they are HIV-positive compared with HIV-negative (145). HIV infection also induces IL-23, particularly in smokers, which upregulates MMP-9 in AMs (21). Interestingly, a report that examined AIDS lung autopsy specimens detected HIV-infected AMs associated with areas of emphysema, with adjacent, uninfected (possibly epithelial) cells positive for MMP-9 (309). Furthermore, HIV infection reprograms human airway basal stem cells to induce a tissue-destructive phenotype also via increased MMP-9. In in vitro models of primary human basal cells, HIV binds to basal cells, resulting in upregulation of MMP-9 expression through mitogen-activated protein kinase signaling path-
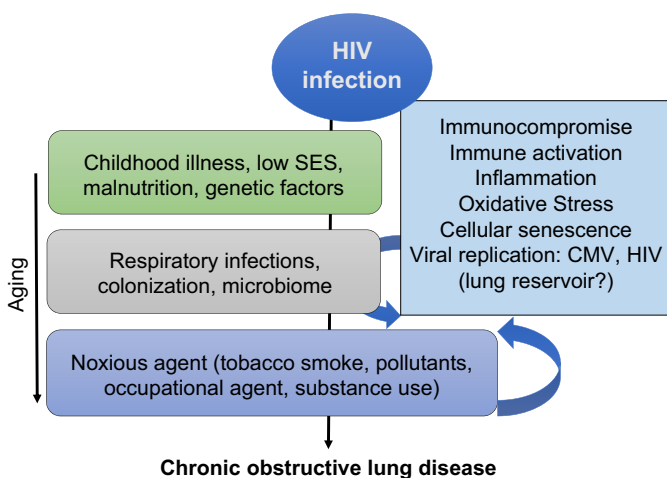
FIGURE 6. Contributors to chronic obstructive lung disease in people living with HIV (PLWH). A complex interplay between genetic, microbiologic, environmental, and other exposures during childhood and with advancing age are likely to interact with HIV-related perturbations to contribute to the development of chronic lung diseases such as chronic obstructive pulmonary disease. SES, socioeconomic status; CMV, cytomegalovirus.

ways (54). Decreased function of α-one-antitrypsin (A1AT), resulting in protease/anti-protease imbalance, may also play a role in HIV-associated COPD. In one recent study, anti-elastase activity was decreased, and levels of oxidized A1AT were higher in BAL from PLWH; however, total A1AT levels were actually increased in BAL in PLWH (279). These findings highlight how alterations may be compartmentalized within the lung, as systemic levels of A1AT did not differ between PLWH and HIV-negative persons. Overall, infection with HIV may result in dysfunction of AMs and imbalance of proteases and anti-proteases including A1AT within the lungs of PLWH.

Cellular senescence has also been linked to HIV-associated COPD. HIV infection can confer a phenotype of premature frailty (84) and has been associated with senescence-related changes in the immune system and other organ systems (11, 46, 76, 77, 286). Airflow limitation has been associated with shorter peripheral blood mononuclear cell telomeres, indicative of replicative senescence (105). Furthermore, PLWH have significantly shorter telomeres in small airway bronchial epithelial cells compared with HIV-negative individuals, controlling for smoking, age, and sex (308). Postulated mechanisms of these senescent changes include HIV-driven increases in small airway epithelial cell turnover or alterations in the telomere length in the basal stem cells that give rise to the small airway epithelium (308). These studies provide intriguing data on the role of senescence in HIV-associated COPD.

The role of ART in HIV-associated COPD has been debated. Earlier cross-sectional studies found associations of ART with a greater likelihood of airflow limitation or COPD (115). However, in the longitudinal pulmonary substudy to START, no difference was seen in spirometry results over time between groups randomized to early versus delayed ART. ART did not impact change in lung function, at least in a relatively young cohort with low prevalence of smoking and fairly well-preserved CD4+ cell counts (159). In another cohort of HIV-infected injection drug users, higher CD4 cell count and ART use were associated with a greater risk of COPD exacerbations (164). Thus the impact of ART in lung function is not completely understood.

In summary, the abnormal immune and inflammatory milieu in HIV infection appears to drive an increased susceptibility to COPD, and potentially different endotypes of disease, in PLWH compared with HIV-negative persons. Insights gained into mechanisms can point to tailored preventative and therapeutic options for HIV-associated COPD.

3. Asthma

Asthma is another obstructive lung disease that is prevalent in PLWH, although whether HIV is an independent contributor to asthma is undetermined. A study of 1,201 HIV-positive youth found that asthma incidence increased significantly from 2008 to 2014 compared with the period from 2004 to 2007 (192). In a study of HIV-positive adults, ~10–20% had been told by their doctor that they had asthma (114). Although frequency of asthma did not differ by HIV status, another study found that many PLWH had been diagnosed as an adult after HIV infection, rather than during childhood (116). In addition, asthma in the HIV population was more common in women, and the prevalence increased with higher body mass index.

Mechanisms by which HIV influences the development or clinical course of asthma remain uncertain. ART use has been associated with a decreased risk for asthma, whereas chemokines released by CD8+ T cells and HIV suppressive factors have been associated with a greater risk (116). These chemokines have been associated with asthma-related airway inflammation in the HIV-negative population (31), suggesting that chronic HIV infection may stimulate an immune response that could contribute to asthma pathogenesis, but such a link remains speculative. Airway wall thickness, as measured on CT scan, is associated with subcutaneous adipose volume, lower peripheral adiponectin (an anti-inflammatory adipokine), and higher levels of CRP in PLWH (23). Such an "obese asthma phenotype" has been reported in adult-onset asthma, but whether this phenotype in PLWH is related to independent effects of HIV or its therapies remains to be determined.

4. Pulmonary hypertension

Although still rare, PAH also occurs more frequently in PLWH than in the HIV-negative population. The estimated prevalence is 0.5%, which has not changed significantly with introduction of ART; however, wide-scale studies to diagnose and systematically assess for primary and secondary causes of pulmonary hypertension (PH) are limited (78, 270). Physiologically, PAH is defined by right heart catheterization with mean pulmonary artery pressure of at least 25 mmHg with a pulmonary capillary wedge pressure of <15 mmHg. The typical female predominance of PAH in HIV-negative individuals is not seen in HIV-PAH. HIV-PAH is more common in intravenous drug users and appears less related to CD4+ cell count or HIV viral levels, although treatment with ART may result in improvement. Hepatitis C co-infection may be associated with increased risk for HIV-PAH, possibly secondary to increases in systemic inflammation (252). Histologically, HIV-PAH is marked by proliferative vasculopathy with intimal fibrosis and development of plexiform lesions, similar to the pathology seen in idiopathic PAH.

Although the reliability of echocardiography alone to make the diagnosis of PAH is debated, studies of PLWH using echocardiography in research cohorts find a high prevalence of elevated right ventricular systolic pressure above 30 mmHg (57%) (196), and pulmonary artery systolic pres-

sures greater than or equal to 40 mmHg (16%) (36, 200). The extent of echocardiographic findings of PAH is likely influenced by the age, immune status, and clinical characteristics of the populations including rates of illicit drug use, cardiovascular disease, and pulmonary disease in the populations studied. Whether these elevated pressures represent true PAH, secondary causes of PH, a preclinical form of the disease, or an incidental finding are unclear. Nonetheless, elevations of pulmonary artery pressures detected by echocardiography in PLWH have been linked to greater respiratory symptoms, lower DLCO, and greater systemic inflammation, underscoring the clinical significance of these echocardiographic findings and the need for further investigation (200, 201).

Direct effects of HIV itself may stimulate the development of PAH. The virus does not directly infect pulmonary vascular or endothelial cells (48, 180), but HIV-associated proteins have been postulated to play a role in the endothelial dysfunction that is seen in HIV-PAH. Release of endothelin-1, a potent vasoconstrictor, from macrophages and pulmonary arterial endothelial cells can be stimulated by envelope glycoprotein gp120 (146). The HIV protein tat is secreted by cells that have been infected with HIV and can therefore have distant effects. Tat stimulates release of reactive oxygen species and activation of platelet-derived growth factor that can lead to changes of PAH (189). The HIV protein Nef has also been investigated in HIV-PAH. In a NHP model, plexiform pulmonary vascular lesions were only detected in animals infected with SHIV containing human nef, and not in animals infected with SIV alone, lacking any human virus (180). Nef has also been found in the pulmonary endothelium in PLWH with PAH (10). Nef may act through stimulation of various signaling pathways in immune cells or via effects on Golgi dysfunction (10, 259). Nef does not seem to be required for HIV-PAH, as another group detected PAH and pulmonary vascular lesions in SIV and SHIV NHP models without Nef (110).

Inflammatory and proliferative pathways stimulated by the virus, even in well-treated PLWH, may also play a role in HIV-PAH. Perivascular inflammation including follicle lymphocytic infiltration has been seen in pulmonary arteries in NHP models of HIV (111). Other infections that occur commonly in PLWH have been postulated to stimulate an inflammatory response that predisposes to PAH. Human herpes virus-8 (HHV-8), the agent of Kaposi sarcoma, has been reported in the lungs of HIV-negative individuals with PAH (62), but this association has not been found in HIV-PAH despite increased risk of HHV-8 in HIV (136). Mutations in bone morphogenetic protein receptor type 2 (BMPR-2), a TGF-β family receptor, have been associated with PAH in the HIV-negative population. Although mutations in this gene have not been reported in HIV-PAH, it is possible that downregulation of the protein may play a role in pathogenesis. BMPR2 expression in macrophages is decreased by HIV Tat; and Tat, Nef, and gp120 decrease BMPR2 protein expression in human pulmonary arterial smooth muscle cells (74, 79). Cell culture experiments also find downregulation of BMPR2 and increased cell proliferation in human pulmonary arterial smooth muscle cells exposed to HIV-Tat and cocaine (74).

MicroRNAs (miRNAs) have been postulated to play a role in HIV-PAH. miRNAs are short, non-protein coding molecules that bind mRNAs to negatively regulate gene expression and can stimulate inflammation. HIV can induce or repress specific human miRNAs and may also produce HIV-specific miRNAs that can influence disease processes (49, 253, 254). Pulmonary vascular stiffness seen in early PAH activates signaling pathways that induce the miR-130/301 family, leading to extracellular matrix remodeling and cellular proliferation, which can contribute to PAH pathology (29).

Use of opiates and cocaine may have an additive effect in HIV-PAH. Cell culture experiments demonstrate that exposure to morphine and HIV proteins leads to endothelial cell proliferation and death (277). Cocaine exposure may also increase the damage caused by HIV. In a pulmonary endothelial cell model, cocaine exposure in the setting of HIV Tat resulted in increased endothelial cell permeability as well as increased pulmonary artery smooth muscle cell proliferation compared with either Tat or cocaine alone (85). In a SIV NHP model, animals exposed to opiates had a greater degree of pulmonary vascular remodeling and medial hypertrophy than SIV-infected or morphine-exposed alone (277). Interestingly, miR-216a, a miRNA that targets the BMPR-2 receptor, is upregulated in response to cocaine and Tat in human pulmonary arterial smooth muscle cells and mediates smooth muscle proliferation (53). Similar findings of enhanced pulmonary vascular remodeling with elevations in mean pulmonary arterial pressure were also seen in an HIV transgenic rat model exposed to cocaine (75).

Multiple biomarkers have been studied in parallel to investigations on pathogenesis of HIV-PAH. In a cohort of PLWH, levels of endothelin-1 were associated with increased pulmonary artery systolic pressures (PASP) by echocardiography (100, 227), higher values of mean pulmonary artery pressures, and presence of PAH on right heart catheterization (227). Asymmetric dimethylarginine (ADMA) is another mediator of endothelial dysfunction that inhibits nitric oxide synthase. Higher ADMA and IL-6 levels have been associated with increased PASP on echocardiography and increased mean pulmonary artery pressures on right heart catheterization among PLWH (228). However, only ADMA was associated with PAH in this cohort of PLWH. Other studies have found associations of inflammatory markers such as IL-8 and IFN-γ, indicating a potential inflammatory component to the disease (200). Although biomarker associations with the disease provide

some insight into potential mechanisms of HIV-PAH, the pathogenesis of HIV-PAH is still largely unknown. Further investigations in the multi-faceted contribution of various pathways to the development of HIV-PAH including effects of HIV proteins, detrimental effects of inflammation and matrix remodeling stimulated by HIV, abnormalities in BMPR2, and illicit drug use in combination with HIV-associated factors are needed in the future.

5. Lung cancer

Lung cancer is emerging as a leading source of cancer mortality in PLWH in the ART era. With greater use of ART, AIDS-defining cancers related to immunosuppression have declined (256, 265, 269). In contrast, non-AIDS defining cancers (NADC) have increased primarily among PLWH greater than 50 yr of age (265, 269). Lung cancer is now the most common infection-unrelated NADC in PLWH (2, 96, 265, 269). Increased lung cancer incidence in PLWH, controlling for greater rates of smoking, has been demonstrated in multiple studies, with incidence rate ratios ranging from 1.7 to 4.7 (51, 58, 96, 125, 147). PLWH develop lung cancer at younger ages compared with HIV-negative individuals (median of 50 vs. 54 yr) (264). There are a number of factors shown to predispose PLWH to lung cancer such as prior pneumonia, immune suppression and dysregulation, and increased inflammation (34, 179, 268).

C. Pulmonary Diseases in People Living with HIV in Low- and Middle-Income Countries

The changes in lung diseases impacting PLWH are based on data from high income countries; however, the epidemiology of pulmonary disease in PLWH differs in other areas of the world. The burden of HIV is disproportionate in low- and middle-income countries (LMIC). The vast majority (≥70%) of PLWH in the world live in sub-Saharan Africa (307a), where they are more likely to have delayed ART initiation, advanced immunodeficiency, and repeated lower respiratory tract infection (LRTI). Despite these factors, survival has improved with expansion of free ART to treat millions of PLWH in LMIC. However, as these individuals age, they are at higher risk for noncommunicable diseases compared with HIV-negative individuals (206, 212), and the prevalence of chronic comorbidities and disability in PLWH in LMIC is increasing dramatically (28, 271).

Emerging data suggest that the risk of chronic lung disease, particularly COPD, is also greater in LMIC in PLWH compared with HIV-negative adults. Several cross-sectional African studies demonstrate a greater risk of COPD in PLWH, although many of these studies have limitations such as lack of spirometry to define COPD (206); no HIV-negative control group (8); and use of self-reported, rather than measured, exposure to household air pollutants (8, 222, 232). While some studies have incorporated spirometry, no pub-

lished studies have reported on chest CT abnormalities in adult populations of PLWH in sub-Saharan Africa. The lack of radiographic data makes it challenging to identify the structural causes of chronic lung disease (emphysema, bronchiectasis, fibrosis, etc.). Children and adolescents living with HIV also have a high prevalence of respiratory symptoms and pulmonary function abnormalities (15, 17). Investigations from countries including Malawi, Zimbabwe, and Kenya utilizing spirometry, chest radiographs, and chest CT scans suggest that constrictive obliterative bronchiolitis and bronchiectasis may be the most common manifestations of chronic lung disease in this younger population, who often have pre- or perinatally acquired HIV infection (17, 83, 209).

A notable difference in the global population is that HIV infection is more common in women in many LMIC settings. Gender influences on the pathogenesis and manifestations of HIV-associated chronic lung diseases is not known. Female sex may be a risk factor for pulmonary disease not only due to biological differences (235), but because women in these settings are more likely to have been exposed to household air pollution from use of indoor stoves (98, 205). Exposure to fuel smoke has been consistently associated with chronic lung disease as well as lung infections and is a significant problem in many LMICs, including sub-Saharan Africa (119, 161). Ongoing studies may help elucidate the burden and types of chronic lung disease in PLWH in sub-Saharan Africa and other LMICs globally.

VI. FUTURE PERSPECTIVES: GAINING FURTHER INSIGHTS INTO MECHANISMS AND TAILORING TREATMENT OF HIV-ASSOCIATED LUNG DISEASES

There is no question that ART has changed the landscape of HIV forever, shifting it from an acute deadly illness to a chronic disease, but there are still many questions to be answered. Although some mechanisms by which HIV impairs lung immunity and causes lung injury and disease have been elucidated, there are still knowledge gaps in how HIV affects various lung cells. Further investigations of the bronchial epithelium, various innate and adaptive immune cells, and differentiating the effects of specific HIV-infected lung cells versus the effects of the lung milieu in HIV infection are still lacking. The lung is a known reservoir for HIV, but investigations on replication competency virus in the lung and therapeutic cure strategies targeting the lung are missing. In addition, more longitudinal studies determining the impact of HIV on the lung need to be done; for example, investigations targeting HIV-specific responses on lung immunity over time and studies evaluating biomarkers that can predict lung disease and lung function decline. Furthermore, the epidemiology of tobacco use is changing with the

advent of electronic cigarettes (e-cigarettes) that have increased in popularity among young people worldwide.

Given the large and growing burden of chronic lung disease in PLWH globally in the era of effective ART, therapies specifically targeted to this population are needed. In general, drugs that are given in HIV-negative individuals have not been tested in PLWH, so the efficacy and safety are not known, especially in the context of ART. Interactions with ART agents may have unique risks or may impact the benefit of these medications for lung disease. Unique pathways may be involved in common lung diseases such as COPD and asthma in PLWH; therefore, improved understanding of lung disease mechanisms should be used to develop and test novel therapeutics.

For example, the pronounced inflammation seen in HIV-associated COPD suggests that anti-inflammatory mediators may be of particular benefit, and a small pilot study of rosuvastatin showed that its pleiotropic anti-inflammatory effects might slow decline in lung function (199). The Statins for Pulmonary Complications of Chronic HIV (SPARC) trial investigated the use of rosuvastatin for COPD in HIV (199). Statin therapy has been shown to reduce circulating inflammatory markers, such as IL-6 and CRP, and previously showed a trend to improvement in the decline of FEV1 in non-HIV-COPD patients (67). The SPARC study found that 6 mo of statin therapy stabilized FEV1 and increased DLCO in a small group of PLWH with COPD (199). However, the absolute difference in these parameters was not different between the groups, and larger studies are needed to confirm these results.

Others are investigating azithromycin in HIV-related chronic lung disease in children (118), as azithromycin has anti-inflammatory properties and also affects airway epithelial cells to reduce mucus secretion (300). In addition, there are ongoing trials in PLWH of other anti-inflammatory medications such as 5-aminosalicylic acid, chloroquine, sirolimus, and versions of more common drugs such as aspirin. The rationale for these clinical trials includes the association of HIV with mucosal and T cell inflammation resulting in persistence of viral replication and HIV compartmentalization that could be improved by anti-inflammatory medications.

Other novel therapies that are being tested in HIV that might be used for HIV-associated lung disease in the future include new immune checkpoint inhibitors such as anti-PD-1. HIV can persist even in PLWH on effective ART and chronic HIV antigen stimulation upregulates inhibitor co-receptors such as PD-1, resulting in immune exhaustion and downregulation of HIV-specific immune responses. Antibodies against PD-1 have been investigated in SIV-infected NHP, reducing SIV RNA and immune activation markers and prolonging survival (298). Although potentially beneficial, reversing immune exhaustion and improving immunity may also increase the risk of immune-related adverse events such as hepatitis, pneumonitis, and emergence of other autoimmune diseases such as myasthenia gravis (191). A recent phase I trial did not report any treatment-related grade 3 or higher adverse events in a small group of PLWH on suppressive ART (109), suggesting promise for the future. In addition to these medications, fecal microbiota transplantation is also being investigated in HIV as a strategy to decrease immune activation and improve the persistent inflammatory state (302). It remains to be seen what effects these novel therapeutic strategies will have on chronic lung diseases in HIV. Chronic pulmonary diseases may be seen more frequently in PLWH, and it is critical to investigate the mechanisms by which HIV causes these diseases, define optimal approaches for screening and diagnosis, and develop targeted therapeutic strategies for HIV-related lung disease.

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DISCLOSURES

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