The Complexity of HIV Persistence and Pathogenesis in the Lung Under Antiretroviral Therapy: Challenges Beyond AIDS

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Abstract

Antiretroviral therapy (ART) represents a significant milestone in the battle against AIDS. However, we continue learning about HIV and confronting challenges 30 years after its discovery. HIV has cleverly tricked both the host immune system and ART. First, the many HIV subtypes and recombinant forms have different susceptibilities to antiretroviral drugs, which may represent an issue in countries where ART is just being introduced. Second, even under the suppressive pressures of ART, HIV still increases inflammatory mediators, deregulates apoptosis and proliferation, and induces oxidative stress in the host. Third, the preference of HIV for CXCR4 as a co-receptor may also have noxious outcomes, including potential malignancies. Furthermore, HIV still replicates cryptically in anatomical reservoirs, including the lung. HIV impairs bronchoalveolar T-lymphocyte and macrophage immune responses, rendering the lung susceptible to comorbidities. In addition, HIV-infected individuals are significantly more susceptible to long-term HIV-associated complications. This review focuses on chronic obstructive pulmonary disease (COPD), pulmonary arterial hypertension, and lung cancer. Almost two decades after the advent of highly active ART, we now know that HIV-infected individuals on ART live as long as the uninfected population. Fortunately, its availability is rapidly increasing in low- and middle-income countries. Nevertheless, ART is not risk-free: the developed world is facing issues with antiretroviral drug toxicity, resistance, and drug–drug interactions, while developing countries are confronting issues with immune reconstitution inflammatory syndrome. Several aspects of the complexity of HIV persistence and challenges with ART are discussed, as well as suggestions for new avenues of research.

Introduction

THE ENTIRE RESPIRATORY TRACT is exposed to a myriad of innocuous and pathogenic particles, including carbon monoxide, dust, pollen, oxidants, gastric contents, live pathogenic and nonpathogenic bacteria, bacterial endotoxins, fungi, and viruses. Together, these represent relentless challenges to the respiratory immune system, which relies in physical aerodynamic and immune barriers to maintain the lungs in good health. This ensures an undisturbed gas exchange process, which is the ultimate physiologic goal of the lung. In addition, systemic diseases such as infection with HIV may affect the lung. This review focuses on the impact of HIV in pulmonary immunology and the new challenges in both developed and developing countries, focusing on the noninfectious complications of HIV disease. Figure 1 summarizes the concepts discussed in this article and their interrelationships.

HIV: The Portrait of a Challenging Virus

Co-discovered by Barre-Sinoussi *et al.* and Gallo *et al.* three decades ago (8,55), HIV is the etiologic agent of AIDS and the topic of more than 270,000 research articles in the biomedical literature. HIV produces more than 10 billion virions per day and has an extensive genetic variability, compelled by the error-prone viral transcription (139,156), rapid HIV turnover (new generation every 2.6 days) (130), genetic recombination (126), and host selective immune pressures. Due to such genetic variability, the main group of HIV type 1 is subtyped into nine genetic variants (A, B, C, D, F, G, H, J, and K), all of which recombine, which may introduce differences in mutation rates and fitness. HIV mutation rates do not seem to vary among host cell types, at least in embryonic kidney cell lines, T-lymphoblasts, and glioblastoma (77). Whether this holds true in primary cells, especially in tissue-resident cell types with different metabolic demands, remains to be addressed.

FIG. 1. Interrelationship between concepts of HIV persistence and pathogenesis and challenges in the era of antiretroviral therapy. The outcomes of HIV infection may be influenced by downregulation of critical host cell receptors (i.e., CD4 and MHC-1), the subtype of the infecting virion and the co-receptor usage. The advent of highly active antiretrovirals has brought an end to AIDS. Antiretrovirals decrease HIV viral loads to levels below the limits of clinical detection and restores the overall immunity. While the reconstituted immune system protects the host from opportunistic pathogens, the vigorous response to residual pathogens (i.e., IRIS) is concerning low- and middle-income countries where antiretrovirals are increasingly available. However, long-term use of antiretrovirals causes several side effects; additional issues include drug–drug interactions and drug resistance. Even under suppressive pressures of antiretrovirals, HIV still replicates at low levels and evolves in anatomical reservoirs; efforts are aimed at the functional eradication of these reservoirs. HIV is present in the lung, where the HIV virions and/or proteins compromise the innate immunity and induce oxidative stress and chronic inflammation, leading to vasculopathies. People living with HIV are significantly more susceptible to pulmonary complications, including lung cancer, pulmonary hypertension, and COPD. MHC-1, major histocompatibility complex-1; IRIS, immune reconstitution inflammatory syndrome; COPD, chronic obstructive pulmonary disease.

Understanding HIV interactions with the host is essential to learn how the viral machinery induces pathogenicity and to identify potential therapeutic targets. Key concepts on HIV entry, persistence, and pathogenesis are discussed.

HIV receptors

HIV enters the cells via interactions with the CD4 receptor in the host cell and the C-C chemokine receptor-5 (CCR5) and C-X-C chemokine receptor-4 (CXCR4). The CCR5 is a receptor for RANTES/CCL5, MIP- α /CCL3, and MIP- β /CCL4 in primary macrophages (42). The CCR5 receptor is expressed in microglia, T-lymphocytes, macrophages, and dendritic cells (DC). CXCR4, initially known as “fusin,” is a

7-transmembrane G protein-coupled receptor used by HIV as a co-receptor for preferential entry to T-cell lines (53). Its natural ligand is stromal derived factor-1 (SDF-1/CXCL12) (10). Conventionally, HIV virions that use CCR5 as a portal of entry are designated as “R5,” while virions using CXCR4 are referred to as “X4.” The HIV preference for CCR5 co-receptor switches to a preference for CXCR4 over the course of HIV infection; this co-receptor switch predicts progression to AIDS in ~50% of HIV+ individuals (29).

HIV-mediated evasion of immune surveillance

Shotgun proteomic analyses of the bronchoalveolar lavage fluid (BALf) in HIV+ versus HIV– patients confirmed

down-modulation of innate and adaptive immune responses such as lymphocyte-mediated immunity, activation of complement, and humoral responses (122). Furthermore, HIV may hide in cells by downregulation of key host receptors to evade immune surveillance (67). For example, HIV-Nef is a key player in HIV pathogenesis by enhancing infectivity and downregulating critical molecules such as major histocompatibility complex-1 (MHC-1) and CD4 receptors (115). It is known that Nef downregulates the CD4 receptor by targeting it to the endocytic degradation pathway in clathrin-coated vesicles. CD4 downregulation stimulates viral replication in primary T-cells (107). HIV-Nef also downregulates MHC-1 by sequestering it in the trans-Golgi, and hence it prevents the recycling of this receptor from the Golgi to the membrane. Nef has highly conserved protein–protein interaction domains essential for these functions (57). In addition, the Nef signature motifs used to downregulate MHC-1 are also used to downregulate CXCR4 and CCR5, which decreases the chances of HIV superinfection (18,171).

HIV reservoirs

HIV-infected individuals who are compliant to antiretroviral therapy (ART) show an apparent clearance of the virus in the peripheral blood shortly after initiating therapy. Nevertheless, viral particles can be detected after interruption of antiretrovirals (30,64,183). Moreover, there is genetic HIV evolution over time in patients with undetectable viremia. In addition, Buzon *et al.* used deep sequencing and statistics to demonstrate that in the presence of suppressive ART, the integrated HIV (i.e., archival, proviral HIV) and extrachromosomal HIV (episomal, surrogate for recent infection) belong to different viral populations (14), confirming continuous low-level replication of HIV.

Where does the virus hide? At the cellular level, resting T-lymphocytes (memory cells) or long-lived myeloid cells (macrophages and DC) remain transcriptionally silent for long periods of time while having integrated copies of the HIV genome, especially in the presence of potent antiretrovirals (22,23,41,71). The activation of these cells resumes the production of infectious particles, and hence the story repeats itself by [infection of new cells] ↔ [reseeding of the reservoir] ↔ [return to resting state] and perpetuation of the persistence of HIV. At the organ/system level, anatomic compartments that may serve as reservoirs of HIV include the central nervous system (28,96), the genitourinary tract (32,125), and the gut-associated lymphoid tissue (24,133). In the respiratory system, the lung can embrace high levels of HIV replication. Early studies showed that bronchoalveolar cells of AIDS patients may host at least 7.6-fold more HIV proviral DNA than cells in the peripheral blood (25). More than a decade later, Brechley's group found that the frequency of HIV-infected BALc was comparable to that in blood cells (12). Studies with rhesus macaques infected with simian immunodeficiency virus (the simian homolog of HIV) showed that the lungs and the intestines harbored the highest levels of viremia, second to lymph nodes, even during the ART-induced suppression of blood viral loads (78).

In the alveoli, lymphocytes are more susceptible to HIV infection than macrophages. HIV infects 1 in 100 CD4+ alveolar lymphocytes (82) and 1 in 1,000 alveolar macro-

phages (AM) (26). The alveolar space harbors small and large subpopulations of macrophages, which differ not only in morphology but also in cell surface markers (54,178). HIV preferentially infects the small macrophages, which display features of highly active inflammatory cells (81). Although at lower levels than blood monocytes, alveolar macrophages express CD4, CCR3, CCR5, and CXCR4, which are receptors required for HIV infection and can be infected by several HIV isolates but not by CXCR4-utilizing viruses (175). HIV also infects CD8 T-cells and fibroblasts (105,143).

May the lungs act as anatomical reservoirs for HIV? Studies in the 1990s showed significantly less HIV sequence variability in AM leading to complete phylogenetic separation of the HIV lineages in the lung and the blood (121). Further genetic studies of the third variable domain (V3) of the HIV envelope showed tissue-specific quasiespecies in the lungs, brain, and testis of AIDS patients (168). In the same studies, HIV isolates from the lung clustered with macrophage-tropic/nonsyncytium-inducing (NSI) variants in the blood, while isolates from the lymph nodes clustered with lympho-tropic/syncytium-inducing (SI) variants in the blood. Because both NSI and SI variants were detected in different tissues, the existence of tissue reservoirs apart from the brain was discounted, and the presence of HIV in nonlymphoid tissues was seen as a late-stage event secondary to lymphocyte infiltration (168). By using functional env clones from primary isolates, Singh's group (151) examined the HIV co-receptor utilization patterns in the lung and showed that the lung isolates used CCR5 as exclusive co-receptor, while the blood isolates may use either CCR5 or CXCR4. Furthermore, lung and blood isolates were undistinguishable regarding the use of secondary co-receptors, including CCR2b, CCR3, CCR8, and CX3CR1 and orphan receptors GPR1, GPR15, and STRL33, suggesting that co-receptor utilization does not determine HIV compartmentalization in the lung, despite the biological differences between HIV quasiespecies in the blood and the lung.

Later studies that compared HIV env sequences spanning the second constant and the fifth variable region (C2–V5) from matched blood and lung samples (either lung sputa or BALc) found lung-specific evolution in up to 56% of HIV-infected individuals (74). In this study, HIV compartmentalization in the lung was supported by significant statistical comparisons but not by phylogenetic tree inspections, which showed only modest compartmentalization. This study also found almost identical sequences in BALc samples of a single patient with the greatest compartmentalization; the authors attributed these observations to localized clonal expansions of the viral quasiespecies (74).

The lung is a macrophage-rich tissue, and hence myeloid cells represent strong candidates as cellular sources of HIV in the lungs. The idea that AM differentiate from precursor peripheral blood monocytes has been used as a basis in several HIV molecular evolution studies. Itescu *et al.* performed phylogenetic analyses of HIV envelope V3 loop sequences from circulating monocytes and lung macrophages of four HIV-infected individuals with diverse pulmonary diseases. They found highly homogeneous sequences in the BALc compared to the peripheral blood, suggesting a lack of unrestricted bidirectional trafficking of HIV quasiespecies in the lung and therefore independent evolution (80). In the

blood, HIV quasiespecies in dendritic cells have different phylogenetic clustering patterns than those in their precursor blood monocytes (170). In both cases, the authors concluded that viral forms in either the lung macrophages or blood dendritic cells evolved independently from their blood monocytic putative ancestries. One caveat that might account for these observations, at least in part, is molecular sampling. At the time of sample collection, precursor monocytes in the blood and their differentiated versions of lung AM or blood dendritic cells may not correspond to the same generation of cells or, even more likely, the differentiated versions of the monocytes collected previously may have ended up in anatomical sites other than the lung or the blood. Also, the HIV infection of macrophages may have occurred postdifferentiation, especially in the presence of ART (3). Importantly, cell-to-cell contact between lymphocytes, dendritic cells, and macrophages that cohabit in the lung may certainly facilitate the spread of HIV quasiespecies within the intrapulmonary neighborhood.

The existence of HIV reservoirs demonstrates that ART does not eliminate from the host. Although evidence points to lung-specific viral evolution, the lung is not as anatomically enclosed as the brain, and hence some viral leakiness is most likely to occur due to the active blood flow through the cardiopulmonary system. Although this shakens the notion of the lung as a HIV reservoir, cryptic replication of HIV in the lung might contribute to immune disturbances leading to pulmonary complications, and hence, deserves close attention.

Evidence of HIV as a *Silent Pathogen* in the Lung

HIV is present in the alveolar compartment, but how much of it is detected and resented by the lung? Alveolar macrophages from HIV-infected individuals are classically activated and are fully competent to respond to *Streptococcus pneumoniae* (61,63), an etiologic agent for recurrent pneumonias in the HIV group. HIV-challenged AM but not blood monocytes or peritoneal macrophages also retain normal antifungal activity against *Cryptococcus neoformans*, as per findings by Cameron *et al.* (16). HIV itself may not impair the phagocytic activity of AM unless combined with cigarette smoking (48). AM from smokers exhibit a decreased internalization of *C. neoformans*, regardless of HIV disease stage (136), suggesting that smoking, which is a prevailing problem in the HIV-infected population (75), certainly complicates the immunologic landscape in the lungs.

While these studies suggest that AM are fairly resilient to HIV in the lungs, contrasting evidence suggest that HIV alters the pulmonary cell biology. Compared to HIV-uninfected counterparts, HIV-infected individuals have lower secretion of interferon-gamma (IFN- γ) and tumor necrosis factor-alpha (TNF- α) in the lung, significantly increased RANTES and lysozyme in the BALf (62), and marked cellular activation and accumulation of inflammatory mediators in the alveolar space, including increased HIV-specific CD8⁺ T-cells.

Transgenic expression of HIV in a rat model showed decreased expression of the beta subunit of the GM-CSF receptor in AM and impaired bacterial phagocytosis *in vitro* potentially mediated by pulmonary zinc deficiency (85). HIV also impairs the innate antifungal activity and toll-like receptor-4 (TLR-4) signaling in alveolar macrophages and significantly decreases the microbicidal effector cell func-

tion against *Pneumocystis carinii* (79,95,157), probably mediated by a significant reduction of mannose receptor-mediated binding (94). Nicol's group found decreased TLR-1 and TLR-4 surface expression in U1 monocyte cells *in vitro* and in AM *ex vivo*, accompanied by decreased production of TNF- α , supporting the notion that HIV predisposes the host to co-infections (124).

The presence of HIV in the lungs may also impact bystander pulmonary residence cells such as endothelial cells. Pivotal studies by Kanmogne *et al.* showed that endothelial cells in the pulmonary microvasculature do not express CD4, CXCR4, or CCR5 receptors on their surface, although the presence of CXCR4 and CCR5 mRNA, but not CD4, was demonstrated in human microvascular endothelial cells (87). Despite being resistant to HIV infection, EC remain susceptible to apoptosis when exposed to HIV proteins (65,87, 128,172). Later, it was demonstrated that the lung endothelial cells strictly regulate the CXCR4 surface expression, which can be significantly induced by erythromycin in human lung microvascular endothelial cells *in vitro* and lung capillary endothelial cells *in vivo* (158). While EC may not represent a cellular source of HIV in the lung, they certainly remain susceptible to the cytopathic effects of HIV.

The impact of HIV on the pulmonary cell biology can also be exemplified by the interactions with co-receptors. While CCR5 may have protective roles in lung inflammation (66,93,127). CXCR4 and its natural ligand CXCL12 are linked to malignant outcomes such as progression and metastasis of osteosarcomas (104,182), breast cancer (118), colon cancer (119), prostate cancer (1), ovarian cancer (6), and non-small cell lung cancer (NSCLC) (21,36,179). Whether HIV interactions with the CXCR4 receptor in lung cells mediate similar outcomes warrants further studies.

In summary, the mere presence of HIV in the lung translates to decreased antimicrobial cytokines, increased inflammatory and cell activation markers, and impaired responsiveness of bronchoalveolar T-lymphocytes and macrophages, all of which may ease the colonization and persistence of potential pathogens. Additionally, interaction of HIV with CXCR4 receptors may invoke noxious outcomes beyond cell infection (e.g., malignant phenotypes). Together, these take us to the arena of HIV-associated pulmonary complications.

HIV-associated challenges in the lung

The lung is a frequent target organ for disorders associated with HIV infection, including chronic obstructive pulmonary disease (COPD), lung cancer, pulmonary arterial hypertension (PAH), fibrosis, and infections, as indicated by echocardiographic abnormalities, which are usually accompanied by systemic and/or pulmonary inflammation (34,117). The following section will focus on COPD, pulmonary arterial hypertension, and lung cancer as three main pulmonary complications associated with HIV infection.

COPD. COPD is characterized by limited expiratory airflow, and represents the fourth cause of death worldwide (176). With a complex pathophysiology, COPD is overrepresented in HIV-infected patients compared to uninfected counterparts, and represents a significant risk factor for hospitalization in this population (2,46,108). A study that followed a HIV-infected cohort for 4.5 years in Rigshospitalet,

Denmark, reported that the HIV group presented decreased forced expiratory volume in one second, alveolar volume, and carbon monoxide diffusion capacity over time, with modest signs of COPD at the time of the report (97). This observation was predicted by smoking and not associated with ART in separate studies in Sassari, Italy, and Ontario, Canada (35,108). Another study suggested that HIV-COPD co-exists with increased pulmonary artery systolic pressures (PASP) or tricuspid regurgitant jet velocity (TRV), in association with inflammatory markers (sputum interleukin-8, peripheral interleukin-8, peripheral IFN- γ levels) and peripheral T-cell activation (117). Conversely, studies using a considerable large data set from the Multicenter AIDS Cohort Study and the Women's Interagency HIV Study reported that noninfectious diseases were more frequent in the pre-ART era, but authors did not find a significant risk for COPD (odds ratio [OR] = 1.61) or lung cancer (OR = 2.65) post-ART (58). This study relied on self-reported pulmonary diagnoses, which were not confirmed clinically, and hence findings from this study might have been masked by the presence of unrecognized COPD.

COPD patients display abnormal accumulation of CD8+ T-cells in the lungs, which triggers the release of inflammatory cytokines and growth factors from macrophage and neutrophils (7,69). Lassitier *et al.* showed that transgene expression of HIV depleted glutathione (the most abundant free radical scavenger in the cells) and increased oxidative stress in the alveolar compartment, linked to alterations in the expression of tight junction proteins and impaired barrier functions of the epithelial cells in the alveoli (99). Further studies by Fan *et al.* pointed to inhibition of the nuclear factor (erythroid-derived 2)-like 2/antioxidant response element (Nrf2/ARE) pathway as mechanistic insights into HIV-mediated barrier functions and oxidative status (51). HIV-associated COPD also features low levels of glutathione in the lungs and in the peripheral blood (33). Together, this suggests that the presence of infectious pathogens such as HIV, coupled with abnormal inflammatory responses and oxidative stress, all contribute mechanistically to HIV-COPD.

Emphysema is a COPD characterized by apoptosis of epithelial and alveolar cells, with various degrees of inflammation. While cigarette smoking is a major cause of COPD/emphysema (38), HIV is another risk factor for COPD, independent of smoking. Patients with HIV, including non-smokers, are susceptible to accelerated forms of emphysema that develops significantly earlier than smoking-associated emphysema (45). Alveolar macrophages in HIV+ smokers display upregulated matrix metalloproteinases, which may

contribute to the development of emphysema at a younger age and with higher incidence than HIV + nonsmokers (66). Histologically, HIV is mostly found in the emphysematous regions of the lung, while very rare HIV+ cells are present in normal lung areas (180), suggesting a direct role of HIV and/or HIV proteins in emphysema. Clauss's group proposed the upregulation of the inflammatory cytokine endothelial monocyte activating polypeptide II (EMAP II) as a mechanistic explanation for the lung endothelial cell apoptosis (27) and that such upregulation is induced by gp120 signaling through the CXCR4 receptor and activation of p38 MAPK (65).

Relevant to chronic bronchitis, CXCR4 and HIV-X4 viruses are implicated in the overproduction of mucus and mucous cell metaplasia in human bronchial epithelial cells *in vitro*, via the CXCR4/ α 7-nicotinic acetylcholine receptor/ γ -aminobutyric acid (GABA)-A receptor axis (70). These results further support a potential role of HIV in the higher incidence of COPD.

Pulmonary arterial hypertension. Pulmonary arterial hypertension (PAH) is a rare disease in the general population, affecting one to two people per million individuals, but it occurs significantly more frequently in the HIV-infected population, regardless of gender, age, sociodemographic characteristics, duration of HIV diagnosis, or interventions with ART.

PAH is characterized by elevation of circulating inflammatory cytokines, atypical pulmonary vascular remodeling featured quasi-malignant phenotype of pulmonary endothelial cells (i.e., "cancer paradigm" of PAH) (101,135), and highly glycolytic pulmonary artery vascular cells (60,161). In addition, a signature of PAH is the presence of cells that obliterate the lumina of pulmonary arteries (plexiform lesions) (162). Therefore, the mean pulmonary artery pressures increase (mPAP > 25 mmHg), ending fatally due to right heart failure. PAH can be screened by echocardiography, which measures PASP and diagnosed by right heart catheterization (RHC), which measures mPAP; final diagnosis is made based on mPAP > 25 mmHg.

The prevalence of PAH in the HIV-infected population is usually reported to be 1 in 200 (0.5%) individuals. Nonetheless, the awareness of HIV-PAH has increased in medical communities worldwide, as evidenced by the coordination of taskforces aimed to screen patients who are asymptomatic for PAH. PAH has been recently reported to affect 0.2–12.7% of HIV-infected individuals in several countries (Table 1), based on either echocardiographic PASP or RHC. Noteworthy, Vazquez *et al.* found a single HIV+ patient in

TABLE 1. RECENT REPORTS ON THE PREVALENCE OF HIV-ASSOCIATED PULMONARY ARTERIAL HYPERTENSION

Cohort	Country	N	% HIV-PAH	Reference
Mayo Clinic (3 centers)	United States	445	0.2%	(119)
Infectious Diseases Unit, Virgen de la Victoria University Hospital	Malaga, Spain	194	2.6%	(50)
Jos University Teaching Hospital	Nigeria	200	4%	(177)
Registry to Evaluate Early and Long-term PAH Disease Management (REVEAL; 55 centers)	United States	1,506	4.4%	(49)
Hospital Carlos III	Madrid, Spain	394	9.9%	(145)
Muhimbili National Hospital	Dar es Salaam, Tanzania	102	12.7%	(173)

a cohort of 445 individuals with PAH (0.2%) and posed the question of whether all patients with PAH should undergo HIV testing (169). The opposite is also valid: should all patients with HIV undergo screening for PAH?

A study comparing pressures measured by Doppler-based echocardiography versus right heart catheterization showed that 19.7% of the Doppler-based measurements were inaccurate, missing the PAH phenotype in one out of three patients (142). Despite this, the reality is that many patients may just decline the RHC procedure, are ineligible, or it may just not be available, especially in low-resource settings. Hence, the best scenario in many instances is to retrieve echocardiography data and use PASP 30–35 mmHg as a cutoff for echocardiographic abnormalities associated with PAH, with the caveat that some of these data may still be underestimated but are at least accounted for.

The increased prevalence of HIV-PAH (whether accurate or underestimated) has been documented by several studies worldwide, but have we refreshed the hints for mechanisms and targets for therapy? Do we really know what in HIV increases the chances of PAH? There is no definitive proof that HIV causes PAH and no evidence that HIV infects lung endothelial cells (62). However, viral proteins and their interactions with molecular partners in the infected cells may damage endothelial cells, induce inflammation, and deregulate apoptosis and proliferation of vascular endothelial cells in the lung, resulting in pulmonary vascular remodeling featured in PAH patients (65,88,106,113,172). Previous studies have shown that HIV Nef protein co-localized with EC in PAH-like plexiform lesions in rhesus macaques infected with the SHIV_{nefSF33} chimera (expressing human Nef) (110,111). Subcellular analyses showed increased cellular content of giantin and p115 (Golgi tethers) in cells in plexiform lesions, particularly in Nef-positive cells (141), suggesting a Nef-Golgi dysfunction duet in PAH. After translating the animal studies to humans, Nef signature sequences were found to be associated with the PAH phenotype (4). Separate studies in two macaque models (rhesus macaques infected with SIV_{AB670} and cynomolgous monkeys infected with chimeric SHIV_{89.6P-env}) also showed intimal and medial hyperplasia along with elevated pulmonary pressures resembling human PAH (56). Together, these studies suggest that HIV proteins play key roles in the pathogenesis of HIV-PAH.

The combination of HIV—and/or its proteins—and recreational drugs such as cocaine exacerbates pulmonary arteriopathies. Dhillon *et al.* showed that HIV Tat or cocaine disrupted tight junction proteins, increased the expression of platelet-derived growth factor, and increased the proliferation of pulmonary smooth muscle cells; additive effects were observed with combined Tat and cocaine (44). HIV Tat also increased the basal inflammatory status and oxidative stress in a murine model (31). Additionally, macaques exposed to the simian immunodeficiency virus (simian homologue of HIV) and morphine also showed significant pulmonary vascular remodeling and oxidative-stress mediated apoptosis of endothelial cells followed by proliferation of apoptosis-resistant cells (153). In the framework of pulmonary artery vascular smooth muscle cells, Goncharov *et al.* recently showed that the balance tilts toward increased proliferation and decreased apoptosis when the mammalian target of rapamycin complex-2 (mTORC2) downregulates the energy sensor AMP activated protein kinase (AMPK) (60).

In light of the absolute presence of inflammation in PAH, Tcherakian *et al.* proposes that a lack of CD4 T-cell restoration in the gut is followed by translocation of lipopolisaccharides, which induces the overproduction of interleukin yielding to chronic inflammation (159).

PAH remains incurable. Current therapeutic approaches aim to prevent further pulmonary damage by using parenteral, inhaled, and oral combinations of prostaglandins (e.g., prostanoids), endothelin receptor antagonists, diuretics, calcium channel blockers, and phosphodiesterase-5 inhibitors (19,112,134). Hopes of reversing established PAH via regenerative approaches, including the use of endothelial progenitor cells and mesenchymal stem cells, await extensive clinical testing (155). Riociguat is a soluble guanylate cyclase stimulator that belongs to a new class of vasodilators currently in clinical development, which reversed right heart hypertrophy and ventricular remodeling associated with PAH in rats and mice (5). Moreover, telmisartan improved pulmonary artery EC dysfunction and remodeling in a monocrotaline rat model of PAH through the peroxisome proliferator-activated receptor γ (PPAR- γ)-dependent P13K/Akt/eNOS pathway (103).

The unquestioned success of ART in controlling HIV and the impact of ART on PAH remains a dichotomy because some studies suggest that ART does not protect but rather accelerates the development of PAH (129,138) on top of drug–drug interactions (discussed below).

HIV-associated malignancies. HIV-associated malignancies that define AIDS (e.g., Kaposi's sarcoma, non-Hodgkin lymphoma, and cervical cancer) have decreased in the post-ART era. Nonetheless, the incidence of non-AIDS-defining cancers (NADC) have tripled. In a retrospective study at Casey House, Toronto, Canada, up to 52% of deaths in the post-ART era were ascribed to NADC, including liver, gastric, colorectal, and lung malignancies, which occurred in patients with fairly well-controlled HIV disease (154). In Cologne/Bonn, NADC accounted for the death of about one in six HIV-infected people (47). Post-ART, people living with HIV in California have a high cancer risk, as shown by significantly higher rate ratio (RR) for anal (RR=56), liver and melanoma (RR=2), lung (RR=1.2), and prostate and colorectal (RR=1) cancers (150). In patients across Europe, Israel, and Argentina (EuroSIDA), lung cancer (9%) was the second most common NADC after anal cancer (19% vs. 9% respectively) (137).

Globally, lung cancer is the most common cancer (59). In turn, lung cancer is more frequent among HIV-infected individuals in the era of suppressive ART (72). A study that encompassed 15 years pre- and post-ART documented increases in NADC including prostate cancer (11% increase), anal cancer (13% increase), liver (20% increase), and lung cancer (46% increase) (148). The most common type of lung cancer in the HIV-infected population is the adenocarcinoma (149), although NSCLC was found in 88% of cases with HIV-associated lung cancer (72). Compared to the HIV-uninfected population, patients with HIV present with a younger age (mean 50 years) at the time of diagnosis with lung cancer (40). In addition, most of the affected patients are smokers and unfortunately present with symptoms of advanced cancer (144). HIV itself is an independent

risk factor for lung cancer, regardless of smoking, COPD, and bacterial pneumonia (149).

One of the mechanisms proposed for HIV-associated lung cancer is immunosuppression (68,137,150). Meta-analyses from Shiels's group reported an increased incidence of lung cancer among patients with AIDS-related immunosuppression (146). Separate studies found a 2.2 relative risk of lung cancer in HIV-infected immunosuppressed patients (with CD4 counts <200 cells/mL) compared to uninfected individuals (150). Contrasting data from several groups show that lung cancer in HIV-infected individuals is not associated with CD4 counts (20,91,147), despite the inverse relationship with HIV viral load (50). Results from the D:A:D Study group, which followed >40,000 HIV-infected individuals over 200 clinics in Europe, the United States, and Australia from 2004 to 2010 also identified lung cancer as the most common NADC, with the highest mortality rate, regardless of CD4 counts (177).

Additional mechanistic views into lung malignancies associated with HIV infection are provided by respiratory infections and genomic instability. The HIV-infected population is particularly prone to bacterial pneumonia, in addition to mycobacterial pneumocystis, and viral respiratory infections. Pulmonary infections, in turn, may increase the risk of lung malignancies in the HIV-infected population (49,91,145). In addition, genomic instability, reflected by microsatellite alterations, has been hypothesized to increase the risk of lung cancer in HIV. Microsatellite alterations, but not the loss of heterozygosity, were significantly increased (sixfold higher) in HIV-associated lung carcinomas (173). What produces this HIV-related genomic instability? A previously unrecognized interaction between HIV and endogenous retrotransposable elements has been uncovered with the finding that HIV infection results in accumulation of type 1 long-interspersed nuclear elements (L1s) DNA in primary CD4+ lymphocytes (84).

Inflammation is also an ingredient in the recipe for HIV-associated cancers. A study that evaluated activated inflammatory pathways (IL-6 and C-reactive protein) and coagulation pathways (D-dimer) in HIV-infected patients found that individuals with higher levels of IL-6 had a significantly higher risk for cancer (11).

Despite the potential underestimations due to calculations based on self-reported disorders, the use of screening tools for diagnosis, or even undocumented patient cohorts, the higher susceptibility of HIV+ patients to serious lung complications including COPD, PAH, and lung cancers is evident. Inflammation, oxidative stress, deregulated apoptosis and proliferation, and malignant phenotypes are common denominators in the quest for mechanistic hints. Many of the specifics regarding the direct and indirect role of the virus in these diseases remain undetermined.

Success and Challenges of Antiretrovirals

Combinations of antiretrovirals, introduced in 1996, reformed the standard of care for HIV patients and antiretroviral drug industry. The Food and Drug Administration in the United States has 33 drugs currently approved for HIV treatment (165). Current ART targets HIV entry, fusion, reverse transcriptase, integrase, and proteases. In the setting of HIV receptors, Maraviroc is the only CCR5 re-

ceptor blocker available since 2007. Plerixafor antagonizes the CXCR4 receptor and mobilizes hematopoietic stem cells (166). It has been available as a chemotherapeutic agent since 2008, but its feasibility for anti-HIV treatment was rejected after reports of serious thrombocytopenia, premature ventricular contractions, and paresthesias (76). Other compounds, including TG-0054 (for chemotherapeutic purposes) and AMD-070 (for anti-HIV uses), are being tested in clinical trials (37). While pre-exposure prophylaxis and/or heavy postexposure prophylaxis represent robust hopes for a cure nowadays (9), research interests are now trending toward a functional eradication of HIV. This strategy aims for a profound suppression—not eradication—of the virus, particularly in reservoirs, so that patients can discontinue antiretrovirals, which will require extensive knowledge about potentially unrecognized reservoirs and reservoir modulation as a solid platform.

ART significantly decreases the HIV viral load in the bronchoalveolar lavage fluid to undetectable levels in >80% patients; it also decreases IFN- γ , IL-6, and CD8+ lymphocytes while increasing CD4+ cells in the alveolar space, returning the BAL differential toward normal values (92,163,164). The reconstitution of the CD4+ cell pool appears to occur via proliferation of lung resident CD4 cells rather than recruited from the periphery (92), which might have implications in the reseeding of the HIV reservoirs in the lung. Together, ART significantly decreases the HIV viral load and cell activation in the lungs and decreases inflammatory cytokines. However, other studies report that HIV impairs TLR-mediated TNF- α production in the alveolar compartment, decreases in TLR-1 and TLR-4, leading to deficiencies in innate immune response in the presence of ART (124). In addition, measurements of glutathione and cysteine levels in BAL as surrogate markers of oxidative stress in the lung showed no significant differences between HIV-infected and uninfected subjects and that HIV-infected patients without ART had significantly decreased alveolar glutathione levels, suggesting increased oxidative stress in that population (33).

Given the significant reduction in mortality accomplished by ART, the HIV-infected population lives as long as the noninfected. A 15-year longitudinal study by Moore *et al.* (116) in Maryland reported that the expected longevity of HIV-infected patients is now 73 years. A separate study using a stochastic computer simulation model of HIV infection in the United Kingdom calculated that HIV-infected individuals have a life expectancy of 72 years nowadays in the ART era (120). Given that the global life expectancy at birth in 2011 was 70 years (range of 56 years in Africa and 76 years in America, Europe, and Western Pacific) (176), these studies confirm that antiretrovirals have rendered HIV as a chronic disease, especially in developed countries (39).

Nevertheless, the benefits of ART come with side effects, including insulin resistance (52), lypodystrophy (43), osteoporosis (140), subfertility (98), and atherogenic chances including EC dysfunction, neointimal hyperplasia, and mitochondrial damage (83). ART also has an impact at the pharmacodynamic level via interactions with antituberculosis agents, antimalarials, anticoagulants, chemotherapeutic agents, and pulmonary antihypertensive agents, especially when co-administered with newer antiretrovirals, including darunavir (protease inhibitor), raltegravir (integrase inhibitor),

maraviroc (CCR5 antagonist), and etravirine (non-nucleoside reverse transcriptase inhibitor) (89,131,132,152). Given the number of comorbidities along with HIV disease, it is almost inevitable to avoid the co-administration of medications and the complexity that it involves in the developed world.

According to the World Health Organization, 9.7 million HIV+ people were receiving the life-saving ART in low- and middle-income countries at the end of 2012, 77% of whom live in the African region. This means that the current HIV ART coverage in Africa has tripled since 2008 (176). Now that the ART era is being extended geographically to Africa, noninfectious complications of HIV infection would be a foreseeable challenge, just like in the developed world. Here is a different one though: immune reconstitution inflammatory syndrome (IRIS). IRIS occurs in response to residual pathogens including, but not limited to, *Cryptococcus*, nontuberculous mycobacteria, pneumocystis, and tuberculosis (15). The sub-Saharan African population is facing high rates of mortality within months of initiating ART, with 73% of the cases due to IRIS (174), while other studies report high morbidity that is easy to manage therapeutically, but low mortality (15,100). In view of this, timing for therapeutic interventions and dose adjustments are being considered to resolve this dilemma. Current considerations involve starting antiretrovirals 2 weeks postinitiation of antimycobacterials in patients with CD4 counts >50 cells/ μ L (100,102).

Another aspect to contemplate is the fact that most of the antiretrovirals known have been developed and tested in subtype B HIV strains, which prevail mostly in America, Western/Central Europe, Southeast Asia, Northern Africa, the Middle East, and Australia (13). Non-B subtypes of HIV exhibit resistance to drugs effective on subtype B (73). For instance, a study on antiretroviral-naïve HIV-infected individuals with subtypes F, G, and K/F, A/F, and J/F recombinants in Romania found resistance mutations in the pol gene in up to 50% of cases (160). In Tanzania, 12% of antiretroviral naïve HIV+ pregnant women infected with subtype A and C presented primary drug resistance (167). After exposure to ART, up to 51% of cases had a positive drug resistance genotyping in KwaZulu-Natal, South Africa, where subtype C predominates (109). In Cote d'Ivoire, West Africa, up to 25% patients infected mostly with A/G recombinants acquired mutations to at least one drug in the antiretroviral cocktail (114). In Spain, up to 19% of the patients infected with non-subtype B recombinants displayed resistance mutations in the pol gene (181). On the other hand, a study in France found that patients infected with B and non-B subtypes of HIV have similar virologic (HIV RNA levels <50 copies/mL) and immunologic responses (CD4 counts) to antiretrovirals (17). Viruses of different subtypes may also be comparable in terms of antiretroviral drug susceptibility. For instance, studies using structural models of the HIV integrase enzyme showed that subtype B viruses and recombinant A/G viruses (prevalent recombinant form in West Africa) have comparable susceptibility to integrase inhibitors (123). Kenya seems to have a very promising drug resistance profile: drug resistance mutations were detected in <2% of antiretroviral-naïve individuals (90). Hence, the expanded availability of ART must be accompanied by initial HIV subtyping and profiling of primary and acquired drug resistance mutations

as much as possible so that efficient antiretroviral therapies can be tailored accordingly.

Viewpoints and Potential Avenues for New Research

While ART has been a significant milestone in the battle against AIDS, we are still learning about HIV and facing challenges 30 years after its discovery. Figure 1 outlines key concepts discussed in this review. This review illustrated key concepts of HIV persistence and focused on how the lung resents HIV, echoing HIV-associated pulmonary complications such as COPD, pulmonary arterial hypertension, and lung malignancies.

A systematic epidemiological surveillance is strongly desirable to document HIV-associated pulmonary complications. Therefore, cross-talk between pulmonologists and HIV specialists is essential to document the true prevalence of these diseases, which otherwise would go unnoticed and untreated before the patient's quality of life has seriously deteriorated. Antiretroviral drug toxicity, resistance, and drug-drug interactions are issues affecting both the developed and the developing world, which certainly require extensive research and implementation of revised therapeutic strategies.

This article also presented empirical data that will hopefully generate new hypotheses for new research enterprises. In the first instance, the increased production of mucus and the risk for cancers implicated in the HIV-X4/CXCR4 axis evidence a profound impact of HIV in the pulmonary cell biology and invoke the notion that HIV-X4 viruses are worth investigation in the context of COPD and lung cancer. Second, further studies to dissect the role of HIV and HIV proteins in PAH, particularly at the subcellular level and the impact in cellular cross-talk (e.g., EC, macrophages, T-cells, SMC) are warranted to identify novel therapeutic targets. Third, it is necessary to develop antiretroviral compounds that are more suitable to non-B subtypes of HIV. Fourth, the identification of potentially unrecognized anatomical reservoirs for HIV, as well as knowledge about the modulation of cellular sources of viruses within reservoirs, are absolutely required to strategize for a functional eradication of HIV reservoirs. Functional eradication of HIV reservoirs in the lung would increase alveolar macrophage and bronchoalveolar lymphocyte responsiveness and decrease the likelihood of co-infections with potential pathogens. Finally, the role of chronic inflammation in HIV-associated pulmonary diseases is certainly a unifying, hypothesis-generating topic that will take us to the next level.

Author Disclosure Statement

No competing financial interests exist.

References

1. Akashi T, Koizumi K, Tsuneyama K, *et al.* Chemokine receptor CXCR4 expression and prognosis in patients with metastatic prostate cancer. *Cancer Sci* 2008;99: 539–542.
2. Akgün KM, Gordon K, Pisani M, *et al.* Risk factors for hospitalization and medical intensive care unit (MICU) admission among HIV-infected Veterans. *J Acquir Immune Defic Syndr* 2013;62:52–59.
3. Almodovar S, Del CC, Maldonado IM, *et al.* HIV-1 infection of monocytes is directly related to the success of HAART. *Virology* 2007;369:35–46.

4. Almodovar S, Knight R, Allshouse AA, *et al.* Human Immunodeficiency Virus nef signature sequences are associated with pulmonary hypertension. *AIDS Res Hum Retroviruses* 2012;28:607–618.
5. Bailey SJ. Riociguat, a novel therapy for pulmonary hypertension? *Thorax* 2013 Nov 12. doi: 10.1136/thoraxjnl-2013-204664. [Epub ahead of print]
6. Barbolina MV, Kim M, Liu Y, *et al.* Microenvironmental regulation of chemokine (C-X-C-motif) receptor 4 in ovarian carcinoma. *Mol Cancer Res* 2010;8:653–664.
7. Barnes PJ, Shapiro SD, and Pauwels RA. Chronic obstructive pulmonary disease: molecular and cellular mechanisms. *European Respir J* 2003;22:672–688.
8. Barre-Sinoussi F, Chermann JC, Rey F, *et al.* Isolation of a T-lymphotropic retrovirus from a patient at risk for acquired immune deficiency syndrome (AIDS). *Science* 1983;220:868–871.
9. Blanco J. Child cured of HIV: can this be repeated? *Expert Opin Pharmacother* 2013;14:2307–2309.
10. Bleul CC, Farzan M, Choe H, *et al.* The lymphocyte chemoattractant SDF-1 is a ligand for LESTR/fusin and blocks HIV-1 entry. *Nature* 1996;382:829–833.
11. Borges AH, Silverberg MJ, Wentworth D, *et al.* Predicting risk of cancer during HIV infection: the role of inflammatory and coagulation biomarkers. *AIDS* 2013;27:1433–1441.
12. Brenchley JM, Knox KS, Asher AI, *et al.* High frequencies of polyfunctional HIV-specific T cells are associated with preservation of mucosal CD4 T cells in bronchoalveolar lavage. *Mucosal Immunol* 2008;1:49–58.
13. Buonaguro L, Tornesello ML, and Buonaguro FM. Human immunodeficiency virus type 1 subtype distribution in the worldwide epidemic: pathogenetic and therapeutic implications. *J Virol* 2007;81:10209–10219.
14. Buzon MJ, Codoner FM, Frost SD, *et al.* Deep molecular characterization of HIV-1 dynamics under suppressive HAART. *PLoS Pathog* 2011;7:e1002314.
15. Calligaro G, Meintjes G, and Mendelson M. Pulmonary manifestations of the immune reconstitution inflammatory syndrome. *Curr Opin Pulm Med* 2011;17:180–188.
16. Cameron ML, Granger DL, Matthews TJ, and Weinberg JB. Human immunodeficiency virus (HIV)-infected human blood monocytes and peritoneal macrophages have reduced anticryptococcal activity whereas HIV-infected alveolar macrophages retain normal activity. *J Infect Dis* 1994;170:60–67.
17. Chaix ML, Seng R, Frange P, *et al.* Increasing HIV-1 non-B subtype primary infections in patients in France and effect of HIV subtypes on virological and immunological responses to combined antiretroviral therapy. *Clin Infect Dis* 2013; 56:880–887.
18. Chandrasekaran P, Moore V, Buckley M, *et al.* HIV-1 Nef down-modulates C-C and C-X-C chemokine receptors via ubiquitin and ubiquitin-independent mechanism. *PLoS One* 2014;9:e86998.
19. Channick R, Preston I, and Klinger JR. Oral therapies for pulmonary arterial hypertension: endothelin receptor antagonists and phosphodiesterase-5 inhibitors. *Clin Chest Med* 2013;34:811–824.
20. Chaturvedi AK, Pfeiffer RM, Chang L, *et al.* Elevated risk of lung cancer among people with AIDS. *AIDS* 2007;21: 207–213.
21. Choi YH, Burdick MD, Strieter BA, *et al.* CXCR4, but not CXCR7, discriminates metastatic behavior in non-small cell lung cancer cells. *Mol Cancer Res* 2014;12:38–47.
22. Chun TW, Carruth L, Finzi D, *et al.* Quantification of latent tissue reservoirs and total body viral load in HIV-1 infection. *Nature* 1997;387:183–188.
23. Chun TW, Finzi D, Margolick J, *et al.* *In vivo* fate of HIV-1-infected T cells: quantitative analysis of the transition to stable latency. *Nat Med* 1995;1:1284–1290.
24. Chun TW, Nickle DC, Justement JS, *et al.* Persistence of HIV in gut-associated lymphoid tissue despite long-term antiretroviral therapy. *J Infect Dis* 2008;197:714–720.
25. Clarke JR, Gates AJ, Coker RJ, *et al.* HIV-1 proviral DNA copy number in peripheral blood leucocytes and bronchoalveolar lavage cells of AIDS patients. *Clin Exp Immunol* 1994;96:182–186.
26. Clarke JR, and Israel-Biet D. Interactions between opportunistic micro-organisms and HIV in the lung. *Thorax* 1996;51:875–877.
27. Clauss M, Voswinckel R, Rajashekhar G, *et al.* Lung endothelial monocyte-activating protein 2 is a mediator of cigarette smoke-induced emphysema in mice. *J Clin Invest* 2011;121:2470–2479.
28. Clements JE, Gama L, Graham DR, *et al.* A simian immunodeficiency virus macaque model of highly active antiretroviral treatment: viral latency in the periphery and the central nervous system. *Curr Opin HIV AIDS* 2011;6: 37–42.
29. Connor RI, Sheridan KE, Ceradini D, *et al.* Change in coreceptor use correlates with disease progression in HIV-1-infected individuals. *J Exper Med* 1997;185:621–628.
30. Costiniuk CT, Kovacs C, Routy JP, *et al.* Short communication: human immunodeficiency virus rebound in blood and seminal plasma following discontinuation of antiretroviral therapy. *AIDS Res Hum Retroviruses* 2013;29: 266–269.
31. Cota-Gomez A, Flores AC, Ling XF, *et al.* HIV-1 Tat increases oxidant burden in the lungs of transgenic mice. *Free Radic Biol Med* 2011;51:1697–1707.
32. Craig JK, Patterson BK, Paranjpe S, *et al.* Persistent HIV type 1 infection in semen and blood compartments in patients after long-term potent antiretroviral therapy. *AIDS Res Hum Retroviruses* 2004;20:1196–1209.
33. Cribbs SK, Guidot DM, Martin GS, *et al.* Anti-retroviral therapy is associated with decreased alveolar glutathione levels even in healthy hiv-infected individuals. *PLoS One* 2014;9:e88630.
34. Crothers K, Huang L, Goulet JL, *et al.* HIV infection and risk for incident pulmonary diseases in the combination antiretroviral therapy era. *Am J Respir Crit Care Med* 2011;183:388–395.
35. Cui Q, Carruthers S, McIvor A, *et al.* Effect of smoking on lung function, respiratory symptoms and respiratory diseases amongst HIV-positive subjects: a cross-sectional study. *AIDS Res Ther* 2010;7:6.
36. Dai X, Mao Z, Huang J, *et al.* The CXCL12/CXCR4 autocrine loop increases the metastatic potential of non-small cell lung cancer *in vitro*. *Oncol Lett* 2013;5:277–282.
37. Debnath B, Xu S, Grande F, *et al.* Small molecule inhibitors of CXCR4. *Theranostics* 2013;3:47–75.
38. Decramer M, Janssens W, and Miravittles M. Chronic obstructive pulmonary disease. *Lancet* 2012;379:1341–1351.
39. Deeks SG, Lewin SR, and Havlir DV. The end of AIDS: HIV infection as a chronic disease. *Lancet* 2013;382: 1525–1533.

40. Demopoulos BP, Vamvakas E, Ehrlich JE, and Demopoulos R. Non-acquired immunodeficiency syndrome-defining malignancies in patients infected with human immunodeficiency virus. *Arch Pathol Lab Med* 2003;127:589–592.
41. Demoustier A, Gubler B, Lambotte O, *et al.* In patients on prolonged HAART, a significant pool of HIV infected CD4 T cells are HIV-specific. *AIDS* 2002;16:1749–1754.
42. Deng H, Liu R, Ellmeier W, *et al.* Identification of a major co-receptor for primary isolates of HIV-1. *Nature* 1996;381:661–666.
43. de Waal R, Cohen K, and Maartens G. Systematic review of antiretroviral-associated lipodystrophy: lipoatrophy, but not central fat gain, is an antiretroviral adverse drug reaction. *PLoS One* 2013;8:e63623.
44. Dhillon NK, Li F, Xue B, *et al.* Effect of cocaine on human immunodeficiency virus-mediated pulmonary endothelial and smooth muscle dysfunction. *Am J Respir Cell Mol Biol* 2011;45:40–52.
45. Diaz PT, King MA, Pacht ER, *et al.* Increased susceptibility to pulmonary emphysema among HIV-seropositive smokers. *Ann Intern Med* 2000;132:369–372.
46. Drummond MB, Kirk GD, Astemborski J, *et al.* Prevalence and risk factors for unrecognized obstructive lung disease among urban drug users. *Int J Chron Obstruct Pulmon Dis* 2011;6:89–95.
47. Ehren K, Hertenstein C, Kummerle T, *et al.* Causes of death in HIV-infected patients from the Cologne–Bonn cohort. *Infection* 2014;42:135–140.
48. Elssner A, Carter JE, Yungler TM, and Wewers MD. HIV-1 infection does not impair human alveolar macrophage phagocytic function unless combined with cigarette smoking. *Chest* 2004;125:1071–1076.
49. Engels EA. Inflammation in the development of lung cancer: epidemiological evidence. *Expert Rev Anticancer Ther* 2008;8:605–615.
50. Engels EA, Biggar RJ, Hall HI, *et al.* Cancer risk in people infected with human immunodeficiency virus in the United States. *Int J Cancer* 2008;123:187–194.
51. Fan X, Staitieh BS, Jensen JS, *et al.* Activating the Nrf2-mediated antioxidant response element restores barrier function in the alveolar epithelium of HIV-1 transgenic rats. *Am J Physiol Lung Cell Mol Physiol* 2013;305:L267–277.
52. Feeney ER, and Mallon PW. Insulin resistance in treated HIV infection. *Best Pract Res Clin Endocrinol Metab* 2011;25:443–458.
53. Feng Y, Broder CC, Kennedy PE, and Berger EA. HIV-1 entry cofactor: functional cDNA cloning of a seven-transmembrane, G protein-coupled receptor. *Science* 1996;272:872–877.
54. Frankenberger M, Menzel M, Betz R, *et al.* Characterization of a population of small macrophages in induced sputum of patients with chronic obstructive pulmonary disease and healthy volunteers. *Clin Exp Immunol* 2004;138:507–516.
55. Gallo RC, Sarin PS, Gelmann EP, *et al.* Isolation of human T-cell leukemia virus in acquired immune deficiency syndrome (AIDS). *Science* 1983;220:865–867.
56. George MP, Champion HC, Simon M, *et al.* Physiologic changes in a nonhuman primate model of HIV-associated pulmonary arterial hypertension. *Am J Respir Cell Mol Biol* 2013;48:374–381.
57. Geyer M, Fackler OT, and Peterlin BM. Structure—function relationships in HIV-1 Nef. *EMBO Rep* 2001;2:580–585.
58. Gingo MR, Balasubramani GK, Kingsley L, *et al.* The impact of HAART on the respiratory complications of HIV infection: longitudinal trends in the MACS and WIHS cohorts. *PLoS One* 2013;8:e58812.
59. GLOBOCAN. GLOBOCAN 2008 database (version 1.2).
60. Goncharov DA, Kudryashova TV, Ziai H, *et al.* Mammalian target of rapamycin complex 2 (mTORC2) coordinates pulmonary artery smooth muscle cell metabolism, proliferation and survival in pulmonary arterial hypertension. *Circulation* 2014;129:864–874.
61. Gordon SB, Jagoe RT, Jarman ER, *et al.* The alveolar microenvironment of patients infected with human immunodeficiency virus does not modify alveolar macrophage interactions with *Streptococcus pneumoniae*. *Clin Vaccine Immunol* 2013;20:882–891.
62. Gordon SB, Janoff EN, Sloper D, *et al.* HIV-1 infection is associated with altered innate pulmonary immunity. *J Infect Dis* 2005;192:1412–1416.
63. Gordon SB, Molyneux ME, Boeree MJ, *et al.* Opsonic phagocytosis of *Streptococcus pneumoniae* by alveolar macrophages is not impaired in human immunodeficiency virus-infected Malawian adults. *J Infect Dis* 2001;184:1345–1349.
64. Goujard C, Emilie D, Roussillon C, *et al.* Continuous versus intermittent treatment strategies during primary HIV-1 infection: the randomized ANRS INTERPRIM Trial. *AIDS* 2012;26:1895–1905.
65. Green LA, Yi R, Petrusca D, *et al.* HIV envelope protein gp120-induced apoptosis in lung microvascular endothelial cells by concerted upregulation of EMAP II and its receptor, CXCR3. *Am J Physiol Lung Cell Mol Physiol* 2014;306:L372–382.
66. Grommes J, Drechsler M, and Soehnlein O. CCR5 and FPR1 mediate neutrophil recruitment in endotoxin-induced lung injury. *J Innate Immun* 2014;6:111–116.
67. Guha D, and Ayyavoo V. Innate immune evasion strategies by human immunodeficiency virus type 1. *ISRN AIDS* 2013;2013:954806.
68. Guiguet M, Boue F, Cadranel J, *et al.* Effect of immunodeficiency, HIV viral load, and antiretroviral therapy on the risk of individual malignancies (FHDH-ANRS CO4): a prospective cohort study. *Lancet Oncol* 2009;10:1152–1159.
69. Guillon JM, Autran B, Denis M, *et al.* Human immunodeficiency virus-related lymphocytic alveolitis. *Chest* 1988;94:1264–1270.
70. Gundavarapu S, Mishra NC, Singh SP, *et al.* HIV gp120 induces mucus formation in human bronchial epithelial cells through CXCR4/alpha7-nicotinic acetylcholine receptors. *PLoS One* 2013;8:e77160.
71. Gunthard HF, Frost SD, Leigh-Brown AJ, *et al.* Evolution of envelope sequences of human immunodeficiency virus type 1 in cellular reservoirs in the setting of potent antiviral therapy. *J Virol* 1999;73:9404–9412.
72. Hakimian R, Fang H, Thomas L, and Edelman MJ. Lung cancer in HIV-infected patients in the era of highly active antiretroviral therapy. *J Thorac Oncol* 2007;2:268–272.
73. Hamers RL, Sigaloff KC, Kityo C, *et al.* Emerging HIV-1 drug resistance after roll-out of antiretroviral therapy in sub-Saharan Africa. *Curr Opin HIV AIDS* 2013;8:19–26.
74. Heath L, Fox A, McClure J, *et al.* Evidence for limited genetic compartmentalization of HIV-1 between lung and blood. *PLoS One* 2009;4:e6949.
75. Helleberg M, Afzal S, Kronborg G, *et al.* Mortality attributable to smoking among HIV-1-infected individuals:

- a nationwide, population-based cohort study. *Clin Infect Dis* 2013;56:727–734.
76. Hendrix CW, Collier AC, Lederman MM, *et al.* Safety, pharmacokinetics, and antiviral activity of AMD3100, a selective CXCR4 receptor inhibitor, in HIV-1 infection. *J Acquir Immune Defic Syndr* 2004;37:1253–1262.
 77. Holtz CM, and Mansky LM. Variation of HIV-1 mutation spectra among cell types. *J Virol* 2013;87:5296–5299.
 78. Horiike M, Iwami S, Kodama M, *et al.* Lymph nodes harbor viral reservoirs that cause rebound of plasma viremia in SIV-infected macaques upon cessation of combined antiretroviral therapy. *Virology* 2012;423:107–118.
 79. Jeong MH, Reardon CC, Levitz SM, and Kornfeld H. Human immunodeficiency virus type 1 infection of alveolar macrophages impairs their innate fungicidal activity. *Am J Respir Crit Care Med* 2000;162:966–970.
 80. Itescu S, Simonelli PF, Winchester RJ, and Ginsberg HS. Human immunodeficiency virus type 1 strains in the lungs of infected individuals evolve independently from those in peripheral blood and are highly conserved in the C-terminal region of the envelope V3 loop. *Proc Natl Acad Sci U S A* 1994;91:11378–11382.
 81. Jambo KC, Banda DH, Kankwatira AM, *et al.* Small alveolar macrophages are infected preferentially by HIV and exhibit impaired phagocytic function. *Mucosal Immunol* 2014 Jan 29. doi: 10.1038/mi.2013.127. [Epub ahead of print]
 82. Jeffrey AA, Israel-Biet D, Andrieu JM, *et al.* HIV isolation from pulmonary cells derived from bronchoalveolar lavage. *Clin Exp Immunol* 1991;84:488–492.
 83. Jiang B, Khandelwal AR, Rogers LK, *et al.* Antiretrovirals induce endothelial dysfunction via an oxidant-dependent pathway and promote neointimal hyperplasia. *Toxicol Sci* 2010;117:524–536.
 84. Jones RB, Song H, Xu Y, *et al.* LINE-1 retrotransposable element DNA accumulates in HIV-1-infected cells. *J Virol* 2013;87:13307–13320.
 85. Joshi PC, Raynor R, Fan X, and Guidot DM. HIV-1 transgene expression in rats decreases alveolar macrophage zinc levels and phagocytosis. *Am J Respir Cell Mol Biol* 2008;39:218–226.
 86. Kaner RJ, Santiago F, and Crystal RG. Up-regulation of alveolar macrophage matrix metalloproteinases in HIV1(+) smokers with early emphysema. *J Leukoc Biol* 2009;86:913–922.
 87. Kanmogne GD, Kennedy RC, and Grammas P. Analysis of human lung endothelial cells for susceptibility to HIV type 1 infection, coreceptor expression, and cytotoxicity of gp120 protein. *AIDS Res Hum Retroviruses* 2001;17:45–53.
 88. Kanmogne GD, Primeaux C, and Grammas P. Induction of apoptosis and endothelin-1 secretion in primary human lung endothelial cells by HIV-1 gp120 proteins. *Biochem Biophys Res Commun* 2005;333:1107–1115.
 89. Kigen G, Kimaiyo S, Nyandiko W, *et al.* Prevalence of potential drug–drug interactions involving antiretroviral drugs in a large Kenyan cohort. *PLoS One* 2011;6:e16800.
 90. Kiptoo M, Brooks J, Lihana RW, *et al.* HIV-1 drug resistance-associated mutations among HIV-1 infected drug-naïve antenatal clinic attendees in rural Kenya. *BMC Infect Dis* 2013;13:517.
 91. Kirk GD, Merlo C, O'Driscoll P, *et al.* HIV infection is associated with an increased risk for lung cancer, independent of smoking. *Clin Infect Dis* 2007;45:103–110.
 92. Knox KS, Vinton C, Hage CA, *et al.* Reconstitution of CD4 T cells in bronchoalveolar lavage fluid after initiation of highly active antiretroviral therapy. *J Virol* 2010;84:9010–9018.
 93. Kohlmeier JE, Miller SC, Smith J, *et al.* The chemokine receptor CCR5 plays a key role in the early memory CD8+ T cell response to respiratory virus infections. *Immunity* 2008;29:101–113.
 94. Koziel H, Eichbaum Q, Kruskal BA, *et al.* Reduced binding and phagocytosis of *Pneumocystis carinii* by alveolar macrophages from persons infected with HIV-1 correlates with mannose receptor downregulation. *J Clin Invest* 1998;102:1332–1344.
 95. Koziel H, Li X, Armstrong MY, *et al.* Alveolar macrophages from human immunodeficiency virus-infected persons demonstrate impaired oxidative burst response to *Pneumocystis carinii* *in vitro*. *Am J Respir Cell Mol Biol* 2000;23:452–459.
 96. Kramer-Hämmerle S, Rothenaigner I, Wolff H, *et al.* Cells of the central nervous system as targets and reservoirs of the human immunodeficiency virus. *Virus Res* 2005;111:194–213.
 97. Kristoffersen US, Lebech AM, Mortensen J, *et al.* Changes in lung function of HIV-infected patients: a 4.5-year follow-up study. *Clin Physiol Funct Imaging* 2012;32:288–295.
 98. Kushnir VA, and Lewis W. Human immunodeficiency virus/acquired immunodeficiency syndrome and infertility: emerging problems in the era of highly active antiretrovirals. *Fertil Steril* 2011;96:546–553.
 99. Lassiter C, Fan X, Joshi PC, *et al.* HIV-1 transgene expression in rats causes oxidant stress and alveolar epithelial barrier dysfunction. *AIDS Res Ther* 2009;6:1.
 100. Laureillard D, Marcy O, Madec Y, *et al.* Paradoxical tuberculosis-associated immune reconstitution inflammatory syndrome after early initiation of antiretroviral therapy in a randomized clinical trial. *AIDS* 2013;27:2577–2586.
 101. Lee SD, Shroyer KR, Markham NE, *et al.* Monoclonal endothelial cell proliferation is present in primary but not secondary pulmonary hypertension. *J Clin Invest* 1998;101:927–934.
 102. Lee SS, Meintjes G, Kamarulzaman A, and Leung CC. Management of tuberculosis and latent tuberculosis infection in human immunodeficiency virus-infected persons. *Respirology* 2013;18:912–922.
 103. Li H, Lu W, Cai WW, *et al.* Telmisartan attenuates monocrotaline-induced pulmonary artery endothelial dysfunction through a PPAR gamma-dependent PI3K/Akt/eNOS pathway. *Pulm Pharmacol Ther* 2013 Nov 20. doi: 10.1016/j.pupt.2013.11.003. [Epub ahead of print]
 104. Liao YX, Zhou CH, Zeng H, *et al.* The role of the CXCL12-CXCR4/CXCR7 axis in the progression and metastasis of bone sarcomas (Review). *Int J Mol Med* 2013;32:1239–1246.
 105. Linnemann CC Jr, Baughman RP, Frame PT, and Floyd R. Recovery of human immunodeficiency virus and detection of p24 antigen in bronchoalveolar lavage fluid from adult patients with AIDS. *Chest* 1989;96:64–67.
 106. Liu K, Chi DS, Li C, *et al.* HIV-1 Tat protein-induced VCAM-1 expression in human pulmonary artery endothelial cells and its signaling. *Am J Physiol Lung Cell Mol Physiol* 2005;289:L252–260.
 107. Lundquist CA, Tobium M, Zhou J, *et al.* Nef-mediated downregulation of CD4 enhances human immunodeficiency

- virus type 1 replication in primary T lymphocytes. *J Virol* 2002;76:4625–4633.
108. Madeddu G, Fois AG, Calia GM, *et al.* Chronic obstructive pulmonary disease: an emerging comorbidity in HIV-infected patients in the HAART era? *Infection* 2013;41:347–353.
 109. Manasa J, Lessells RJ, Skingsley A, *et al.* High-levels of acquired drug resistance in adult patients failing first-line antiretroviral therapy in a rural HIV treatment programme in KwaZulu-Natal, South Africa. *PLoS One* 2013;8:e72152.
 110. Marecki JC, Cool CD, Parr JE, *et al.* HIV-1 Nef is associated with complex pulmonary vascular lesions in SHIV-nef-infected macaques. *Am J Respir Crit Care Med* 2006;174:437–445.
 111. Marecki J, Cool C, Voelkel N, *et al.* Evidence for vascular remodeling in the lungs of macaques infected with simian immunodeficiency virus/HIV NEF recombinant virus. *Chest* 2005;128:621S–622S.
 112. McLaughlin VV, and Palevsky HI. Parenteral and inhaled prostanoid therapy in the treatment of pulmonary arterial hypertension. *Clin Chest Med* 2013;34:825–840.
 113. Mermis J, Gu H, Xue B, *et al.* Hypoxia-inducible factor-1 alpha/platelet derived growth factor axis in HIV-associated pulmonary vascular remodeling. *Respir Res* 2011;12:103.
 114. Messou E, Chaix ML, Gabillard D, *et al.* Increasing rate of TAMs and etravirine resistance in HIV-1-infected adults between 12 and 24 months of treatment: the VOLTART cohort study in Cote d'Ivoire, West Africa. *J Acquir Immune Defic Syndr* 2013;64:211–219.
 115. Miller MD, Warmerdam MT, Gaston I, *et al.* The human immunodeficiency virus-1 nef gene product: a positive factor for viral infection and replication in primary lymphocytes and macrophages. *J Exper Med* 1994;179:101–113.
 116. Moore RD, Keruly JC, and Bartlett JG. Improvement in the health of HIV-infected persons in care: reducing disparities. *Clin Infect Dis* 2012;55:1242–1251.
 117. Morris A, Gingo MR, George MP, *et al.* Cardiopulmonary function in individuals with HIV infection in the anti-retroviral therapy era. *AIDS* 2012;26:731–740.
 118. Mukherjee D, and Zhao J. The role of chemokine receptor CXCR4 in breast cancer metastasis. *Am J Cancer Res* 2013;3:46–57.
 119. Murakami T, Kawada K, Iwamoto M, *et al.* The role of CXCR3 and CXCR4 in colorectal cancer metastasis. *Int J Cancer* 2013;132:276–287.
 120. Nakagawa F, Lodwick RK, Smith CJ, *et al.* Projected life expectancy of people with HIV according to timing of diagnosis. *AIDS* 2012;26:335–343.
 121. Nakata K, Weiden M, Harkin T, *et al.* Low copy number and limited variability of proviral DNA in alveolar macrophages from HIV-1-infected patients: evidence for genetic differences in HIV-1 between lung and blood macrophage populations. *Mol Med* 1995;1:744–757.
 122. Nguyen EV, Gharib SA, Crothers K, *et al.* Proteomic landscape of bronchoalveolar lavage fluid in human immunodeficiency virus infection. *Am J Physiol Lung Cell Mol Physiol* 2014;306:L35–42.
 123. Ni X, Abdel-Azeim S, Laine E, *et al.* In silico and in vitro comparison of HIV-1 subtypes B and CRF02_AG integrases susceptibility to integrase strand transfer inhibitors. *Adv Virol* 2012;2012:548657.
 124. Nicol MQ, Mathys JM, Pereira A, *et al.* Human immunodeficiency virus infection alters tumor necrosis factor alpha production via Toll-like receptor-dependent pathways in alveolar macrophages and U1 cells. *J Virol* 2008;82:7790–7798.
 125. Nunnari G, Leto D, Sullivan J, *et al.* Seminal reservoirs during an HIV type 1 eradication trial. *AIDS Res Hum Retroviruses* 2005;21:768–775.
 126. Onafuwa-Nuga A, and Telesnitsky A. The remarkable frequency of human immunodeficiency virus type 1 genetic recombination. *Microbiol Mol Biol Rev* 2009;73:451–480, Table of Contents.
 127. Park EJ, Roh J, Kim SN, *et al.* CCR5 plays an important role in resolving an inflammatory response to single-walled carbon nanotubes. *J Appl Toxicol* 2013;33:845–853.
 128. Park IW, Ullrich CK, Schoenberger E, *et al.* HIV-1 Tat induces microvascular endothelial apoptosis through caspase activation. *J Immunol* 2001;167:2766–2771.
 129. Pellicelli AM, D'Ambrosio C, Vizza CD, *et al.* HIV-related pulmonary hypertension. From pathogenesis to clinical aspects. *Acta Cardiol* 2004;59:323–330.
 130. Perelson AS, Neumann AU, Markowitz M, *et al.* HIV-1 dynamics in vivo: virion clearance rate, infected cell life-span, and viral generation time. *Science* 1996;271:1582–1586.
 131. Peyriere H, Eiden C, Macia JC, and Reynes J. Anti-hypertensive drugs in patients treated with antiretrovirals. *Ann Pharmacother* 2012;46:703–709.
 132. Pham PA, and Flexner C. Emerging antiretroviral drug interactions. *J Antimicrob Chemother* 2011;66:235–239.
 133. Poles MA, Boscardin WJ, Elliott J, *et al.* Lack of decay of HIV-1 in gut-associated lymphoid tissue reservoirs in maximally suppressed individuals. *J Acquir Immune Defic Syndr* 2006;43:65–68.
 134. Pugh ME, Hemnes AR, and Robbins IM. Combination therapy in pulmonary arterial hypertension. *Clin Chest Med* 2013;34:841–855.
 135. Rai PR, Cool CD, King JA, *et al.* The cancer paradigm of severe pulmonary arterial hypertension. *Am J Respir Crit Care Med* 2008;178:558–564.
 136. Reardon CC, Kim SJ, Wagner RP, *et al.* Phagocytosis and growth inhibition of *Cryptococcus neoformans* by human alveolar macrophages: effects of HIV-1 infection. *AIDS* 1996;10:613–618.
 137. Reekie J, Kosa C, Engsig F, *et al.* Relationship between current level of immunodeficiency and non-acquired immunodeficiency syndrome-defining malignancies. *Cancer* 2010;116:5306–5315.
 138. Reinsch N, Buhr C, Krings P, *et al.* Effect of gender and highly active antiretroviral therapy on HIV-related pulmonary arterial hypertension: results of the HIV-HEART Study. *HIV Med* 2008;9:550–556.
 139. Roberts JD, Bebenek K, and Kunkel TA. The accuracy of reverse transcriptase from HIV-1. *Science* 1988;242:1171–1173.
 140. Schafer JJ, Manlangit K, and Squires KE. Bone health and human immunodeficiency virus infection. *Pharmacotherapy* 2013;33:665–682.
 141. Sehgal PB, Mukhopadhyay S, Patel K, *et al.* Golgi dysfunction is a common feature in idiopathic human pulmonary hypertension and vascular lesions in SHIV-nef-infected macaques. *Am J Physiol Lung Cell Mol Physiol* 2009;297:L729–737.
 142. Selby VN, Scherzer R, Barnett CF, *et al.* Doppler echocardiography does not accurately estimate pulmonary

- artery systolic pressure in HIV-infected patients. *AIDS* 2012;26:1967–1969.
143. Semenzato G, Agostini C, Ometto L, *et al.* CD8+ T lymphocytes in the lung of acquired immunodeficiency syndrome patients harbor human immunodeficiency virus type 1. *Blood* 1995;85:2308–2314.
144. Shcherba M, Shuter J, and Haigentz M Jr. Current questions in HIV-associated lung cancer. *Curr Opin Oncol* 2013;25:511–517.
145. Shebl FM, Engels EA, Goedert JJ, and Chaturvedi AK. Pulmonary infections and risk of lung cancer among persons with AIDS. *J Acquir Immune Defic Syndr* 2010;55:375–379.
146. Shiels MS, Cole SR, Kirk GD, and Poole C. A meta-analysis of the incidence of non-AIDS cancers in HIV-infected individuals. *J Acquir Immune Defic Syndr* 2009;52:611–622.
147. Shiels MS, Cole SR, Mehta SH, and Kirk GD. Lung cancer incidence and mortality among HIV-infected and HIV-uninfected injection drug users. *J Acquir Immune Defic Syndr* 2010;55:510–515.
148. Shiels MS, Pfeiffer RM, Gail MH, *et al.* Cancer burden in the HIV-infected population in the United States. *J Natl Cancer Inst* 2011;103:753–762.
149. Sigel K, Wisnivesky J, Gordon K, *et al.* HIV as an independent risk factor for incident lung cancer. *AIDS* 2012;26:1017–1025.
150. Silverberg MJ, Chao C, Leyden WA, *et al.* HIV infection, immunodeficiency, viral replication, and the risk of cancer. *Cancer Epidemiol Biomarkers Prev* 2011;20:2551–2559.
151. Singh A, Besson G, Mobasher A, and Collman RG. Patterns of chemokine receptor fusion cofactor utilization by human immunodeficiency virus type 1 variants from the lungs and blood. *J Virol* 1999;73:6680–6690.
152. Soodalter J, Sousa M, and Boffito M. Drug–drug interactions involving new antiretroviral drugs and drug classes. *Curr Opin Infect Dis* 2009;22:18–27.
153. Spikes L, Dalvi P, Tawfik O, *et al.* Enhanced pulmonary arteriopathy in simian immunodeficiency virus-infected macaques exposed to morphine. *Am J Respir Crit Care Med* 2012;185:1235–1243.
154. Stewart A, Chan Carusone S, To K, *et al.* Causes of death in HIV patients and the evolution of an AIDS hospice: 1988–2008. *AIDS Res Treat* 2012;2012:390406.
155. Suen CM, Mei SH, Kugathasan L, and Stewart DJ. Targeted delivery of genes to endothelial cells and cell- and gene-based therapy in pulmonary vascular diseases. *Compr Physiol* 2013;3:1749–1779.
156. Svarovskaia ES, Cheslock SR, Zhang WH, *et al.* Retroviral mutation rates and reverse transcriptase fidelity. *Front Biosci* 2003;8:d117–134.
157. Tachado SD, Li X, Bole M, *et al.* MyD88-dependent TLR4 signaling is selectively impaired in alveolar macrophages from asymptomatic HIV+ persons. *Blood* 2010;115:3606–3615.
158. Takagi Y, Hashimoto N, Phan SH, *et al.* Erythromycin-induced CXCR4 expression on microvascular endothelial cells. *Am J Physiol Lung Cell Mol Physiol* 2009;297:L420–431.
159. Tcherakian C, Couderc LJ, Humbert M, *et al.* Inflammatory mechanisms in HIV-associated pulmonary arterial hypertension. *Semin Respir Crit Care Med* 2013;34:645–653.
160. Temereanca A, Ene L, Duiculescu D, and Ruta S. Major HIV resistance mutations in untreated Romanian patients. *J Med Life* 2011;4:151–157.
161. Tudor RM, Davis LA, and Graham BB. Targeting energetic metabolism: a new frontier in the pathogenesis and treatment of pulmonary hypertension. *Am J Respir Crit Care Med* 2012;185:260–266.
162. Tudor RM, Groves B, Badesch DB, and Voelkel NF. Exuberant endothelial cell growth and elements of inflammation are present in plexiform lesions of pulmonary hypertension. *Am J Pathol* 1994;144:275–285.
163. Twigg 3rd HL, and Knox KS. Impact of antiretroviral therapy on lung immunology and inflammation. *Clin Chest Med* 2013;34:155–164.
164. Twigg III HL, Weiden M, Valentine F, *et al.* Effect of highly active antiretroviral therapy on viral burden in the lungs of HIV-infected subjects. *J Infect Dis* 2008;197:109–116.
165. U.S. Food and Drug Administration. Antiretroviral drugs used in the treatment of HIV infection. 2013. www.fda.gov/ForConsumers/ByAudience/ForPatientAdvocates/HIVandAIDSActivities/ucm118915.htm (accessed November 2013).
166. Uy GL, Rettig MP, Motabi IH, *et al.* A phase 1/2 study of chemosensitization with the CXCR4 antagonist plerixafor in relapsed or refractory acute myeloid leukemia. *Blood* 2012;119:3917–3924.
167. Vairo F, Nicastrì E, Liuzzi G, *et al.* HIV-1 drug resistance in recently HIV-infected pregnant mother's naive to antiretroviral therapy in Dodoma urban, Tanzania. *BMC Infect Dis* 2013;13:439.
168. van't Wout AB, Ran LJ, Kuiken CL, *et al.* Analysis of the temporal relationship between human immunodeficiency virus type 1 quasispecies in sequential blood samples and various organs obtained at autopsy. *J Virol* 1998;72:488–496.
169. Vazquez AA, Aduen JF, Aduen P, *et al.* Should all patients with pulmonary hypertension undergo HIV serologic testing? *South Med J* 2011;104:589–592.
170. Vazquez M, Maldonado IM, Almodovar S, *et al.* Short communication: Human blood dendritic cells are infected separately from monocytes in HIV type 1 patients. *AIDS Res Hum Retroviruses* 2010;26:471–479.
171. Venzke S, Michel N, Allespach I, *et al.* Expression of Nef downregulates CXCR4, the major coreceptor of human immunodeficiency virus, from the surfaces of target cells and thereby enhances resistance to superinfection. *J Virol* 2006;80:11141–11152.
172. Wang T, Green LA, Gupta SK, *et al.* Transfer of intracellular HIV nef to endothelium causes endothelial dysfunction. *PLoS One* 2014;9:e91063.
173. Wistuba II, Behrens C, Milchgrub S, *et al.* Comparison of molecular changes in lung cancers in HIV-positive and HIV-indeterminate subjects. *JAMA* 1998;279:1554–1559.
174. Wong EB, Omar T, Setlhako GJ, *et al.* Causes of death on antiretroviral therapy: a post-mortem study from South Africa. *PLoS One* 2012;7:e47542.
175. Worgall S, Connor R, Kaner RJ, *et al.* Expression and use of human immunodeficiency virus type 1 coreceptors by human alveolar macrophages. *J Virol* 1999;73:5865–5874.
176. World Health Organization. Life expectancy by WHO Region. Global Health Observatory. 2013. <http://apps.who.int/gho/data/view.main.690?lang=en> (accessed November 2013).

177. Worm SW, Bower M, Reiss P, *et al.* Non-AIDS defining cancers in the D:A:D Study—time trends and predictors of survival: a cohort study. *BMC Infect Dis* 2013;13:471.
178. Wright AK, Rao S, Range S, *et al.* Pivotal advance: expansion of small sputum macrophages in CF: failure to express MARCO and mannose receptors. *J Leukoc Biol* 2009;86:479–489.
179. Yan L, Cai Q, and Xu Y. The ubiquitin-CXCR4 axis plays an important role in acute lung infection-enhanced lung tumor metastasis. *Clin Cancer Res* 2013;19:4706–4716.
180. Yearsley MM, Diaz PT, Knoell D, and Nuovo GJ. Correlation of HIV-1 detection and histology in AIDS-associated emphysema. *Diagn Mol Pathol* 2005;14:48–52.
181. Yebra G, de Mulder M, del Romero J, *et al.* HIV-1 non-B subtypes: high transmitted NNRTI-resistance in Spain and impaired genotypic resistance interpretation due to variability. *Antiviral Res* 2010;85:409–417.
182. Zhang P, Dong L, Yan K, *et al.* CXCR4-mediated osteosarcoma growth and pulmonary metastasis is promoted by mesenchymal stem cells through VEGF. *Oncol Rep* 2013;30:1753–1761.
183. Zugna D, Geskus RB, De Stavola B, *et al.* Time to virological failure, treatment change and interruption for individuals treated within 12 months of HIV seroconversion and in chronic infection. *Antivir Ther* 2012;17:1039–1048.

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