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Chronic Lung Disease in HIV Patients

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Abstract

This narrative review discusses literature on chronic obstructive pulmonary disease (COPD) in people living with HIV (PLWH). Existing data indicate that HIV itself, independent of smoking, constitutes a pathogenic agent implicated in this disease condition. COPD can be viewed not exclusively as a pulmonary disease but rather as a systemic syndrome sparked and fueled by a persistent low-grade HIV-attributable inflammatory state. We speculate that even in the absence of airflow obstruction on spirometry, HIV-related lung disease can manifest with respiratory symptoms and structural lung derangement. Although not fully satisfying the global initiative for obstructive lung disease criteria for COPD, this phenotype of small airways lung disease is related to significant impairment of lung health and is associated with a high comorbidity burden. Within the specific context of the aging epidemic affecting HIV patients characterized by a high burden of comorbidities, frailty, and disabilities HIV-related lung disease has to be fit into the framework of the general comorbidity burden that PLWH experience, due to both HIV infection and to incidental HIV-unrelated risk factors. In this review, we will also provide a list of research gaps and an agenda for future studies in HIV patients. **(AIDS Rev. 2018;20:150-157)**

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Key words

HIV. Chronic obstructive disease. Aging. Inflammation

Introduction

The contemporary clinical picture of HIV infection in the highly active antiretroviral therapy era (HAART) is characterized by non-infectious diseases sometimes called HIV-associated non-AIDS (HANA) conditions that affect people living with HIV (PLWH). Importantly, HANA conditions are universally age-related diseases and typically associated with traditional risk factors such as smoking and parenteral drug use. Given the increased life expectancy of PLWH and the higher rates of traditional risk factors in HIV-infected patients than in general population[1], it is not surprising that several modeling studies have forecast an epidemic burden of multimorbidity in years to come[2]. Moreover, even after matching for smoking and substance abuse, Schouten et al. demonstrated a higher prevalence of non-communicable disease among HIV-infected patients compared to same age controls[3]. The unique contribution of HIV itself to these diseases may explain

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their higher burden and sometimes premature onset in comparison to what is observed in HIV-negative cohorts exposed to similar traditional risk factors.

With the growing recognition that chronic lung disease affects a significant portion of PLWH, also routine assessment of lung function, at least in patients with important risk factors such as smoking or with respiratory symptoms, has been suggested by European HIV management guidelines[4].

Several reviews have recently described chronic obstructive pulmonary disease (COPD) in HIV, many acknowledging the higher prevalence of disease even after adjusting for cigarette smoking habits.

In this updated review, we summarize the literature on COPD within the specific context of the aging epidemic affecting HIV patients, characterized by a high burden of comorbidities, frailty, and disabilities, providing a list of research gaps and an agenda for future studies.

We will not include a specific section regarding treatment in consideration of a substantial lack of data regarding any difference in the clinical management of this disease condition in PLWH in comparison with general population.

Methods

Relevant articles pertaining to HIV-associated COPD were identified up to May 31, 2017, through a literature search through the PubMed and Google Scholar research engines. The following key words were used: COPD, HIV, airflow limitation, emphysema, and comorbidities. We restricted our search to English language papers published from 1999, identifying a total of 75 works, of which 54 were original research papers and 21 were reviews.

Epidemiology

COPD as per the 2017 global initiative for obstructive lung disease (GOLD) guidelines is defined as a "common, preventable, and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases"[5], where airflow limitation is defined by a forced expiratory volume in the first second (FEV1)/forced vital capacity (FVC) <70%.

Table 1 summarizes the data from available studies on COPD prevalence among PLWH, especially where an HIV-negative control group was available.

The largest spirometry study ever performed in PLWH was conducted by the INSIGHT Strategic Timing of AntiRetroviral Treatment (START) trial[6]. This study assessed HAART-naive PLWH with CD4 counts > 500 cells/mL and found an overall prevalence of COPD of 5.5% using a fixed ratio definition (6.8% using the lower limit of normal for FEV1/FVC), also providing a regional distribution of COPD prevalence: 7.8% in Africa, 2% in Asia, 9.1% in Europe/Israel/Australia, 3.3% in South America, and 8.2% in North America. Regional differences persisted even after adjustment for smoking status and other COPD risk factors in a regression analysis.

Smoking status was the major predictor of COPD in multivariate regression analysis, with current smokers demonstrating a prevalence of COPD of 12%, but at the same time among those with COPD, a high proportion (48%) also reported being lifelong non-smokers. These data suggest that in PLWH, factors other than tobacco may play a role in COPD pathogenesis.

Pathogenesis

Although there is growing evidence that an innate predisposition to airways obstruction may exist through prebirth smoke exposure, smaller native bronchial diameter[7], and preexistent lower than normal FEV1[8], classical features of the pathogenic process of COPD can be summarized into a highly interdependent "pathogenic triad:" persistent inflammation, oxidative stress, and protease-antiprotease imbalance[9]. In this context, COPD in PLWH can be viewed not exclusively as a pulmonary disease but rather as a systemic syndrome sparked and fueled by a persistent low-grade HIV-attributable inflammatory state.

Inflammation

The exact nature of the interaction between HIV and the lung epithelium is an open field for research. In one study, HIV was shown to enter (yet not replicate in) the airway epithelium by promoting the breakdown of cell junctions and the expression of pro-inflammatory mediators[10]. Consistent with these findings, increased activated CD8 lymphocytes have been described both in the peripheral blood and in bronchoalveolar lavage (BAL) fluid of PLWH[11], and increased expression of cellular senescence markers such as CD57 in both HIV-specific and unspecific CD8 lymphocytes has also been described[12]. Lower than normal peripheral blood CD4/CD8 ratio, usually considered a sign of pathologic immune system activation, has also been found to be linked to HIV-related emphysema[13]. Although on

Table 1. COPD prevalence in HIV versus non-HIV in different studies

Kendall	Crothers	Gingo	Agkun	Crothers	Mugisha	Campo	Brown	Study
2014	2011	2013	2016	2006	2016	2014	2017	Year
Canada	US	US	US	US	Uganda	US	UK	Country
14005	33420	4505	3568	1014	244	180	197	HIV+Sample size
ICD	ICD	Patient-reported	ICD	ICD	Patient-reported	fixed ratio	fixed ratio	COPD diagnosis
7.9	4.6	0.4	4.3	10.3	8.6	29	11	COPD prevalence (%)
45	45	33	49	50	57	55 (49,58)	50 (42,55)	Age (years)
NA	65	31	83	16	90	89	94	ART use (%)
71410	66480	4595	3606	713	227	160	97	HIV- Sample size
6.5	4	0.3	5	9	1.8	20	9	COPD prevalence, HIV-
NA	80	39	53	46	NA	65	30	Current smokers (%)
NA	NA	33	24	29	NA	21	27	Former smokers (%)
NA	20	28	23	25	NA	14	41	Never smokers

COPD: chronic obstructive pulmonary disease

a small sample size, activation of inflammatory pathways in PLWH with reduced DLCO has been shown to significantly differ from that detected in DLCO-impaired HIV subjects[14].

Pneumocystis jirovecii (PJP)

PJP infection has a potentially important role in COPD pathogenesis and progression. From an epidemiological point of view, pneumocystis colonization, assessed by nested PCR performed on lung tissue sample, was found to be associated with worse lung function tests in both terms of GOLD staging and intracohort rating independent of smoking history[15]. Second, in a large cohort study of over 1000 patients, PJP pneumonia was found to be associated with permanent decreases in FEV1, FVC, and FEV1/FVC[16]. Furthermore, primate models of PJP exhibit the development of airway obstruction and emphysema as the result of the inflammatory response to pneumocystis colonization[17].

Oxidative stress

Indirect measures of redox activity, such as BAL glutathione levels, suggest that active viral replication in HAART-naive patients is linked to a decreased glutathione level reflecting an enhanced oxidative environment[18]. Furthermore, regional distribution of glutathione has been observed to match regional emphysema distribution, suggesting that glutathione may concentrate where oxidative stress is most intense[19].

The role of HAART

Although mainly cited for its protective role in immune reconstitution, some authors have speculated that HAART could also contribute to some extent to the progression of lung damage[20]. Possible explanations for this link include the potential oxidative stress effect associated with antiretroviral regimens[21] and immune restoration following the introduction of HAART that may result in a clinically silent chronic immune response ("modified IRIS") against microorganisms and self-antigens[20]. The susceptibility of HIV-infected individuals on HAART to developing autoimmunity in the setting of immune restoration[22] combined with the findings supporting an autoimmune pathogenesis in COPD[23], suggests that autoimmune mechanisms may be important in HIV-related lung disease. Some authors on the other hand argue that findings of autoan-

tibodies in COPD may be a consequence rather than the cause of widespread parenchymal tissue destruction[24]. In fact, the previously mentioned START trial failed to demonstrate any relationship between lung function declines in PLWH and immediate versus delayed HAART initiation[25].

Protease-antiprotease imbalance

Multiple immunological studies have suggested that HIV-infected macrophages may display altered production of matrix metalloproteinases (MMPs)[26], with possible implications for the pathogenesis of many multimorbidities. Alveolar macrophage expression of MMP is also upregulated in HIV-infected smokers with early emphysema[27] resulting in a protease imbalance within the lung.

A new study by Chung et al.[28] seems to introduce a whole new pathogenetic mechanism, as they demonstrated *in vitro* that HIV may upregulate MMP-9 production through non-productive infection of lung basal stem cells.

The role of the microbiome

The observation of the beneficial effect of dietary fiber on lung function has brought to speculate the existence of a gut–liver–lung bacterial axis, integrating the knowledge of the role of the gut microbiome and the liver as a source of inflammatory cytokines[29]. HIV, due to the well-documented effects on promoting gut microbial translocation, may interfere as well with such a system[30].

A recent review from Twigg postulated that the lung microbiome may play a significant role in normal lung function and disease in HIV patients. This new pathogenic perspective appears to be particularly interesting in patients with a low CD4 count, who exhibit a wider range of variability in microbiome composition and an imbalance in microbial populations[31]. Similar studies from Becket al., however, failed to confirm this finding[32], leaving this an open field for future research.

Disease description

Functional lung abnormalities

While the relative risk of fixed airways obstruction due solely to HIV infection is still a matter of debate[33], different studies tend to agree on the relationship between HIV and impaired DLCO. Crothers's case–control cross-sectional study was among the first in the HAART era to highlight a significantly higher prevalence of DLCO < 60% predicted in HIV-infected individuals[34] after adjusting for smoking status, sex age, and ethnicity. In addition, a recent CD4+ count < 200 cell/μl was found to increase the risk of DLCO impairment.

Furthermore, a Danish prospective study, though in a small sample, was able to document longitudinal DLCO impairment at baseline and after 4-year follow-up in PLWH smokers and never smokers[35].

Subsequent studies have postulated a correlation between low DLCO and low CD4 count[34], Stage C HIV infection[36], and PJP[37].

Two recent studies, however, have shifted the focus of research from viral or acute immune-mediated damage to the role of chronically activated immune system, identifying in one case changes in mRNA expression in peripheral blood leukocytes toward a pro-inflammatory pattern in HIV-infected patients with reduced DLCO[14], and in another, a positive correlation between DLCO impairment and sputum neutrophil count in HIV-infected never smokers[38], suggesting that a mild grade inflammatory process may persist even in the lungs of these subjects.

Structural lung abnormalities

Emphysematous changes in lung of PLWH have been linked to HIV-specific parameters: nadir CD4 cell count, markers of bacterial translocation[39], and CD4/CD8 ratio in blood[40]. The strong association between emphysema and DLCO impairment in PLWH may be regarded as the manifestation of a common underlying pathogenic drive: in particular, simian models suggest that a possible chronic immune response to lung colonizing microbes such as PJP may be implicated[17].

PLWH are known to harbor a wider range of incidental pulmonary findings with unknown clinical significance. Park et al. were able to identify 129 incidental pulmonary findings of unknown clinical significance, in 147 computed tomography (CT) scans from asymptomatic HIV patients[41]. A study from Modena HIV Metabolic Clinic showed a prevalence of radiologic subclinical bronchiolitis and emphysema as high as 50%[42].

Another similar study from Sigel et al., however, found no significant difference in the prevalence of abnormal CT findings between HIV-infected and uninfected participants[43].

To this day, no review is currently available on the baseline radiologic presentation of lungs in PLWH. Given the growing interest in tailored screening programs for the lung health of PLWH, this constitutes a

necessary step in defining a population-specific "normal presentation."

Respiratory symptoms

While smoking habits remain a major risk factor for respiratory symptoms independent from COPD diagnosis or HIV status[44,45], PLWH tend to demonstrate a higher burden of symptoms, with a significantly higher rate of cough, phlegm, and dyspnea compared to HIV-negative individuals[34]. Data from the Modena HIV Metabolic Clinic point out a disproportionately high prevalence of respiratory symptoms compared to what would normally be expected for the same degree of airflow obstruction in an HIV-negative population: in 133 patients who were evaluated with the St. George's Respiratory Questionnaire, cough was reported in 22%, shortness of breath in 16%, phlegm production in 14%, and wheezing in 8%[2]. In a paper published by Leung et al.[46], SGRQ scores were correlated in multivariate regression with FEV1 reduction, CD4 nadir inferior to 350 cells/µl, and interleukin-6 levels, showing that along with pulmonary function decline immunological impairment and inflammatory state independently influenced respiratory symptoms and respiratory-related functional impairment.

Comorbidities

From a clinical perspective, HIV and COPD share the common trait of not presenting as single diseases but rather clustering together with other comorbid conditions. The relationship between COPD and other diseases simultaneously affecting an individual is still a debated topic, as it is unclear whether these conditions are the consequence of the disease or the sequelae of shared risk factors such as old age, cigarette smoke, and a sedentary lifestyle. The presence of commonly described comorbidities that occur in association with COPD, i.e., hypertension, diabetes, heart failure, ischemic heart disease, cancer, osteoporosis, depression, and anemia, is one of the main determinants of patient health outcomes[47].

In a similar way, granted access to HAART, the health status of PLWH greatly depends on the accumulation of HANA conditions that determine disability and mortality of these patients[48]. Given the higher risk of COPD-like disease in HIV, the study of the interplay between these systemic diseases is not only a matter of scientific research but also a real clinical question that concerns a significant proportion of PLWH.

Cardiovascular disease

The underlying mechanisms linking COPD to atherosclerosis, ischemic heart disease, and stroke are not fully elucidated. Persistent low-grade inflammation is believed to be the common underlying pathogenic factor linking these disease conditions[49]. Both diseases lead to early signs of vascular atherosclerosis[50,51] and cardiovascular disease accounts for the majority of deaths in both conditions[52,53]. It should be noted, however, that the START trial conducted on over 4500 participants, showed very little benefit to cardiovascular risk profile in deferring HAART treatment initiation[54]. Paradoxically, a direct cardiovascular toxicity induced by HAART exists, particularly associated with current abacavir or darunavir exposure[55] or secondary to metabolic derangements induced by protease inhibitors (PI)[56].

Osteoporosis

A systematic literature review reported a pooled prevalence of osteoporosis in COPD in 35.1% of patients, related to several underlying mechanisms including malnutrition, sedentary life, smoking, steroid treatment, and systemic inflammation[57]. The prevalence of osteoporosis increases with more severe disease, and both osteoporosis and osteopenia are invariably present in patients with the low body mass index and fat-free mass that can also be observed in end-stage COPD[58]. PLWH are as well at risk of osteoporosis progression due to a coincidence of similar risk factors, such as those mentioned above, as well as HIV-related and HAART-related risk factors. In particular, HIV proteins have been demonstrated to have a pro-osteoclastic effect[59] and commonly used HIV medications such as tenofovir disoproxil fumarate and PI are known to affect bone mineral density and have been linked to an increased risk of osteoporotic fractures[60]. In PLWH with COPD, it has also been speculated that drug-drug interactions between PI and systemic steroids may lead to the onset of Cushing syndrome, with further toxic effect on bone metabolism[61].

Depression

Depression represents an emerging comorbidity in COPD patients[62]. Patients with severe COPD are at even greater risk of developing depression, which, in turn, further diminishes their functional performance, impairs their quality of life, and increases their risk of death[63]. While psychosocial factors remain the major

determinants of the development of depression among PLWH, it should be noted that a recent study points out that systemic inflammation may as well play a role in the onset of depression[64]. Hypogonadism and concomitant disruption of endocrine pathways caused by the infection may as well be implicated[65].

Frailty

Geriatric medicine has taught us that neither chronologic age nor comorbidities completely describe the complexity of aging and the capacity of each single individual to experience a healthy aging process. Frailty is recognized as a condition of increased vulnerability to stressors, associated with an impaired homeostatic response, and increased likelihood of multiple adverse health outcomes including falls, delirium, disability, and death[66]. The frailty phenotype is a widely used tool to assess frailty in clinical practice.

One single study[67] examined the association between COPD and frailty in HIV patients. Justice et al. performed a cross-sectional study of the veterans aging cohort study participants between 2002 and 2012. The sample included 3538 HIV-infected and 3606 uninfected participants; 4% and 5% had COPD, respectively. COPD was independently associated with frailty measures that accounted for limitations in physical activity. The authors suggested that optimizing COPD management may be an important priority to minimize frailty and maintain physical function for individuals aging with HIV.

Longitudinal studies are needed to characterize trajectories in frailty and physical limitations for PLWH with COPD and to develop interventions to maintain physical function in this population.

Research gaps and agenda for future studies

To this day, the pathogenesis of HIV-related lung health deterioration needs to be fully elucidated, possibly adopting new animal models.

From a clinical point of view, this may provide better clinical significance to abnormal pathogen colonization as *Tropheryma whipplei*[68] in HIV-associated COPD, but even more, identifying a mechanistic link between chronic lung disease and lung cancer in HIV, the driver of non-AIDS defining neoplastic condition in PLWH[69].

In consideration that chronic HIV infection is related to profound depletion of T-memory cells in COPD patients,[70] HIV may turn to be a unique model to study anti-PD1 agents for lung cancer immunotherapy.

Experimental observations that blockade of PD-1-ligand interaction contributes to immune restoration in HIV[71] may provide models of delayed lung senescence.

On top of HIV-induced lung senescence, aging itself contributes to the development of paraphysiological changes in lung function: older age is associated with a reduction in DLCO regardless of fitness status[72], systemic multiorgan senescence leads to a variety of paraphysiological changes that can mimic symptoms of airway obstruction and so contribute to COPD misclassification[73], and finally old age is also associated with derangements in lung structure[74].

Further studies are needed to better identify the patients in which a high-resolution lung CT will allow to integrate structural and functional changes in the identification of specific phenotypes who may benefit for treatment opportunities.

More work is needed to establish the potential mechanisms and causal pathways that link HIV and COPD with comorbidities. A hierarchical view of comorbidities as consequences of a primary disease is challenged by the frequent coexistence of two primary conditions such as HIV and COPD in the same individual.

A typical feature of geriatric medicine is to evaluate functional assessment rather than specific organ diseases, an approach which may better describe patient disability status and quality of life of elderly patients. Nevertheless, in a clinical setting, where small airways dysfunction may precede by many years the onset of spirometric-defined COPD, it is worth exploring other functional tests which may identify patients at higher risk for a rapid FEV1 decline. In a small sample of 45 never smoker Danish PLWH, small airways dysfunction was evaluated using the lung clearance index (LCI), a measure of lung physiology derived from multiple nitrogen breath washout which identifies preclinical airways dysfunction. 41% of HIV patients (95% confidence interval [CI] 27-56%) had an LCI greater than the upper limit of normal, whereas only 5% (95% CI 1-24%) of the 20 HIV-negative controls had an abnormal LCI ($p < 0.01$)[75].

Conclusions

This narrative review has described putative pathogenic mechanisms, structural lung abnormalities, physiological lung function changes, symptoms, and comorbidities associated with chronic lung disease in PLWH.

Existing data indicate that HIV itself, independent of smoking, constitutes a pathogenic agent implicated in this disease condition.

We speculate that even in the absence of airflow obstruction on spirometry, HIV-related lung disease can manifest with respiratory symptoms and structural lung derangement. Although not fully satisfying the GOLD criteria for COPD, this phenotype of small airways lung disease is related to significant impairment of lung health and is associated with a high comorbidity burden.

Further, research is needed to clarify how this disease progresses from its early signs to a COPD-like disease, the need for a systematic screening for lung disease in HIV, obviously in heavy smokers but offered also in never smokers.

Finally, HIV-related lung disease has to be fit into the framework of the general comorbidity burden that PLWH experience, due to both HIV infection and to incidental HIV-unrelated risk factors.

References

1. Reynolds NR. Cigarette smoking and HIV: more evidence for action. AIDS Educ Prev. 2009;21:106-21.
2. Santoro A, Scaglioni R, Besutti G, et al. Chronic lung disease in HIV never smokers. Top Antivir Med. 2017;25:276-7.
3. Schouten J, Wit FW, Stolte IG, et al. Cross-sectional comparison of the prevalence of age-associated comorbidities and their risk factors between HIV-infected and uninfected individuals: the AGEhIV cohort study. Clin Infect Dis. 2014;59:1787-97.
4. EACS Society. European guidelines for treatment of HIV-infected adults in Europe. Eur AIDS Clin Soc. 2017;102. Available from: http://www.eacsociety.org/files/guidelines_9.0-english.pdf%0A; http://www.eacsociety.org/guidelines/eacs-guidelines/eacs-guidelines.html. [Last accessed on 2018 Mar 16].
5. Barnes PJ. GOLD 2017: A New report. Chest. 2017;151:245-6.
6. Kunisaki KM, Niewoehner DE, Collins G, et al. Pulmonary function in an international sample of HIV-positive, treatment-naïve adults with CD4 counts >500 cells/μL: a substudy of the INSIGHT strategic timing of antiRetroviral treatment (START) trial. HIV Med. 2015;16 Suppl 1: 119-28.
7. Diaz AA, Rahaghi FN, Ross JC, Harmouche R, Tschirren J, San José Estépar R, ***et al.*** Understanding the contribution of native tracheobronchial structure to lung function: CT assessment of airway morphology in never smokers. Respir Res. 2015;16:23.
8. Lange P, Celli B, Agustí A, et al**.** Lung-function trajectories leading to chronic obstructive pulmonary disease. N Engl J Med. 2015;373:111-22.
9. Fischer BM, Pavlisko E, Voynow JA. Pathogenic triad in COPD: oxidative stress, protease-antiprotease imbalance, and inflammation. Int J Chron Obstruct Pulmon Dis. 2011;6:413-21.
10. Brune KA, Ferreira F, Mandke P, et al. HIV impairs lung epithelial integrity and enters the epithelium to promote chronic lung inflammation. PLoS One. 2016;11:e0149679.
11. Barry SM, Johnson MA, Janossy G. Increased proportions of activated and proliferating memory CD8+ T lymphocytes in both blood and lung are associated with blood HIV viral load. Acquir Immune Defic Syndr. 2003;34:351-7.
12. Papagno L, Spina CA, Marchant A, et al. Immune activation and CD8+ T-cell differentiation towards senescence in HIV-1 infection. PLoS Biol. 2004;2:E20.
13. Triplette M, Attia EF, Akgün KM, et al. A low peripheral blood CD4/CD8 ratio is associated with pulmonary emphysema in HIV. PLoS One. 2017; 12:e0170857.
14. Crothers K, Petrache I, Wongtrakool C, et al. Widespread activation of immunity and pro-inflammatory programs in peripheral blood leukocytes of HIV-infected patients with impaired lung gas exchange. Physiol Rep. 2016;4:e12756.
15. Morris A, Sciurba FC, Lebedeva IP, et al. Association of chronic obstructive pulmonary disease severity and pneumocystis colonization. Am J Respir Crit Care Med. 2004;170:408-13.
16. Morris AM, Huang L, Bacchetti P, et al. Permanent declines in pulmonary function following pneumonia in human immunodeficiency virus-infected persons. The pulmonary complications of HIV infection study group. Am J Respir Crit Care Med. 2000;162:612-6.
17. Norris KA, Morris A, Patil S, Fernandes E. Pneumocystis colonization, airway inflammation, and pulmonary function decline in acquired immunodeficiency syndrome. Immunol Res. 2006;36:175-87.
18. Cribbs SK, Guidot DM, Martin GS, Lennox J, Brown LA. Anti-retroviral therapy is associated with decreased alveolar glutathione levels even in healthy HIV-infected individuals. PLoS One. 2014;9:e88630.
19. Diaz PT, Wewers MD, King M, et al. Regional differences in emphysema scores and BAL glutathione levels in HIV-infected individuals. Chest. 2004;126:1439-42.
20. Morris A, George MP, Crothers K, et al**.** HIV and chronic obstructive pulmonary disease: is it worse and why? Proc Am Thorac Soc. 2011; 8:320-5.
21. Blas-Garcia A, Apostolova N, Esplugues JV. Oxidative stress and mitochondrial impairment after treatment with anti-HIV drugs: clinical implications. Curr Pharm Des. 2011;17:4076-86.
22. Roszkiewicz J, Smolewska E. Kaleidoscope of autoimmune diseases in HIV infection. Rheumatol Int. 2016;36:1481-91.
23. Lee SH, Goswami S, Grudo A, et al. Antielastin autoimmunity in tobacco smoking-induced emphysema. Nat Med. 2007;13:567-9.
24. Toyoshima M, Chida K, Suda T, Sato M. Is autoimmunity really related to the pathogenesis of COPD? Am J Respir Crit Care Med. 2011; 184:1212-3.
25. Kunisaki KM, Niewoehner DE, Collins G, et al. Pulmonary effects of immediate versus deferred antiretroviral therapy in HIV-positive individuals: a nested substudy within the multicentre, international, randomised, controlled strategic timing of antiretroviral treatment (START) trial. Lancet Respir Med. 2016;4:980-9.
26. Webster NL, Crowe SM. Matrix metalloproteinases, their production by monocytes and macrophages and their potential role in HIV-related diseases. J Leukoc Biol. 2006;80:1052-66.
27. Kaner RJ, Santiago F, Crystal RG. Up-regulation of alveolar macrophage matrix metalloproteinases in HIV1(+) smokers with early emphysema. J Leukoc Biol. 2009;86:913-22.
28. Chung NPY, Ou X, Khan KM, et al. HIV reprograms human airway basal stem/progenitor cells to acquire a tissue-destructive phenotype. Cell Rep. 2017;19:1091-100.
29. Young RP, Hopkins RJ, Marsland B. The gut-liver-lung axis. Modulation of the innate immune response and its possible role in chronic obstructive pulmonary disease. Am J Respir Cell Mol Biol. 2016;54:161-9.
30. Dinh DM, Volpe GE, Duffalo C, et al. Intestinal microbiota, microbial translocation, and systemic inflammation in chronic HIV infection. J Infect Dis. 2015;211:19-27.
31. Twigg HL 3rd, Knox KS, Zhou J, et al**.** Effect of advanced HIV infection on the respiratory microbiome. Am J Respir Crit Care Med. 2016; 194:226-35.
32. Beck JM, Schloss PD, Venkataraman A, et al. Multicenter comparison of lung and oral microbiomes of HIV-infected and HIV-uninfected individuals. Am J Respir Crit Care Med. 2015;192:1335-44.
33. Lalloo UG, Pillay S, Mngqibisa R, Abdool-Gaffar S, Ambaram A. HIV and COPD: a conspiracy of risk factors. Respirology. 2016;21:1166-72.
34. Crothers K, McGinnis K, Kleerup E, et al**.** HIV infection is associated with reduced pulmonary diffusing capacity. J Acquir Immune Defic Syndr. 2013;64:271-8.
35. 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;32:288-95.
36. Sampériz G, Guerrero D, López M, et al. Prevalence of and risk factors for pulmonary abnormalities in HIV-infected patients treated with antiretroviral therapy. HIV Med. 2014;15:321-9.
37. Gingo MR, George MP, Kessinger CJ, et al**.** Pulmonary function abnormalities in HIV-infected patients during the current antiretroviral therapy era. Am J Respir Crit Care Med. 2010;182:790-6.
38. Gingo MR, He J, Wittman C, et al. Contributors to diffusion impairment in HIV-infected persons. Eur Respir J. 2014;43:195-203.
39. Attia EF, Akgün KM, Wongtrakool C, et al. Increased risk of radiographic emphysema in HIV is associated with elevated soluble CD14 and nadir CD4. Chest. 2014;146:1543-53.
40. Leung JM, Malagoli A, Santoro A, et al**.** Emphysema distribution and diffusion capacity predict emphysema progression in human immunodeficiency virus infection. PLoS One. 2016;11:e0167247.
41. Park MS, Hileman CO, Sattar A, Gilkeson R, McComsey GA. Incidental findings on chest computed tomography are common and linked to inflammation in HIV-infected adults. Antivir Ther. 2017;22:127-33.
42. Guaraldi G, Besutti G, Scaglioni R, et al. The burden of image based emphysema and bronchiolitis in HIV-infected individuals on antiretroviral therapy. PLoS One. 2014;9:e109027.
43. Sigel K, Wisnivesky J, Shahrir S, et al. Findings in asymptomatic HIV-infected patients undergoing chest computed tomography testing: implications for lung cancer screening. AIDS. 2014;28:1007-14.
44. Regan EA, Lynch DA, Curran-Everett D, et al. Clinical and radiologic disease in smokers with normal spirometry. JAMA Intern Med. 2015; 175:1539-49.

45. Woodruff PG, Barr RG, Bleecker E, et al. Clinical significance of symptoms in smokers with preserved pulmonary function. N Engl J Med. 2016; 374:1811-21.
46. Leung JM, Liu JC, Mtambo A, et al. The determinants of poor respiratory health status in adults living with human immunodeficiency virus infection. AIDS Patient Care STDS. 2014;28:240-7.
47. Mannino DM, Watt G, Hole D, et al. The natural history of chronic obstructive pulmonary disease. Eur Respir J. 2006;27:627-43.
48. Smit M, Brinkman K, Geerlings S, et al. Future challenges for clinical care of an ageing population infected with HIV: a modelling study. Lancet Infect Dis. 2015;15:810-8.
49. Ross R. Atherosclerosis – an inflammatory disease. N Engl J Med. 1999;340:115-26.
50. Eickhoff P, Valipour A, Kiss D, et al. Determinants of systemic vascular function in patients with stable chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2008;178:1211-8.
51. Francisci D, Giannini S, Baldelli F, et al. HIV Type 1 infection, and not short-term HAART, induces endothelial dysfunction. AIDS. 2009;23:589-96.
52. Huiart L, Ernst P, Suissa S. Cardiovascular morbidity and mortality in COPD. Chest. 2005;128:2640-6.
53. Rodger AJ, Lodwick R, Schechter M, et al. Mortality in well controlled HIV in the continuous antiretroviral therapy arms of the SMART and ESPRIT trials compared with the general population. AIDS. 2013;27:973-9.
54. Baker JV, Sharma S, Achhra AC, et al. Changes in cardiovascular disease risk factors with immediate versus deferred antiretroviral therapy initiation among HIV-positive participants in the START (Strategic timing of antiretroviral treatment) trial. J Am Heart Assoc. 2017;6:e004987.
55. Choi AI, Vittinghoff E, Deeks SG, et al. Cardiovascular risks associated with abacavir and tenofovir exposure in HIV-infected persons. AIDS. 2011;25:1289-98.
56. Friis-Møller N, Weber R, Reiss P, et al. Cardiovascular disease risk factors in HIV patients – association with antiretroviral therapy. Results from the DAD study. AIDS. 2003;17:1179-93.
57. Graat-Verboom L, Wouters EF, Smeenk FW, et al. Current status of research on osteoporosis in COPD: a systematic review. Eur Respir J Off J Eur Soc Clin Respir Physiol. 2009;34:209-18.
58. Corlateanu A, Covantev S, Mathioudakis AG, Botnaru V, Siafakas N. Prevalence and burden of comorbidities in chronic obstructive pulmonary disease. Respir Investig. 2016;54:387-96.
59. Chew N, Tan E, Li L, Lim R. HIV-1 tat and rev upregulates osteoclast bone resorption. J Int AIDS Soc. 2014;17:19724.
60. Bedimo R, Maalouf NM, Zhang S, Drechsler H, Tebas P. Osteoporotic fracture risk associated with cumulative exposure to tenofovir and other antiretroviral agents. AIDS. 2012;26:825-31.
61. Chung WS, Chen YF, Hsu JC, Yang WT, Chen SC, Chiang JY. Inhaled corticosteroids and the increased risk of pulmonary tuberculosis: a population-based case-control study. Int J Clin Pract. 2014;68: 1193-9.
62. Connolly MJ, Yohannes AM. The impact of depression in older patients with chronic obstructive pulmonary disease and asthma. Maturitas. 2016;92:9-14.
63. Salte K, Titlestad I, Halling A. Depression is associated with poor prognosis in patients with chronic obstructive pulmonary disease - A systematic review. Dan Med J. 2015;62:A5137.
64. Rivera-Rivera Y, Vázquez-Santiago FJ, Albino E, Sánchez MD, Rivera-Amill V. Impact of depression and inflammation on the progression of HIV disease. J Clin Cell Immunol. 2016;7:423.
65. Rochira V, Guaraldi G. Hypogonadism in the HIV-infected man. Endocrinol Metab Clin North Am. 2014;43:709-30.
66. Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. Lancet. 2013;381:752-62.
67. Akgün KM, Tate JP, Oursler KK, et al. Association of chronic obstructive pulmonary disease with frailty measurements in HIV-infected and uninfected veterans. AIDS. 2016;30:2185-93.
68. Lozupone C, Cota-Gomez A, Palmer BE, et al. Widespread colonization of the lung by tropheryma whipplei in HIV infection. Am J Respir Crit Care Med. 2013;187:1110-7.
69. Sigel K, Wisnivesky J, Gordon K, et al. HIV as an independent risk factor for incident lung cancer. AIDS. 2012;26:1017-25.
70. Popescu I, Drummond MB, Gama L, et al. Activation-induced cell death drives profound lung CD4(+) T-cell depletion in HIV-associated chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2014;190: 744-55.
71. Velu V, Shetty RD, Larsson M, Shankar EM. Role of PD-1 co-inhibitory pathway in HIV infection and potential therapeutic options. Retrovirology. 2015;12:14.
72. Coffman KE, Carlson AR, Miller AD, Johnson BD, Taylor BJ. The effect of aging and cardiorespiratory fitness on the lung diffusing capacity response to exercise in healthy humans. J Appl Physiol (1985). 2017; 122:1425-34.
73. Fragoso CA. Epidemiology of chronic obstructive pulmonary disease (COPD) in aging populations. COPD. 2016;13:125-9.
74. Copley SJ. Morphology of the aging lung on computed tomography. J Thorac Imaging. 2016;31:140-50.
75. Ronit A, Mathiesen IH, Gelpi M, et al. Small airway dysfunction in well-treated never-smoking HIV-infected individuals. Eur Respir J. 2017;49:1602186.