RESEARCH ARTICLE

Inflammatory mediators and lung abnormalities in HIV: A systematic review

**Breanne M. Head**[1]☉, **Ruochen Mao**[1]☉, **Yoav Keynan**[1]‡, **Zulma Vanessa Rueda**[1,2]‡*

1 Department of Medical Microbiology and Infectious Diseases, University of Manitoba, Winnipeg, Manitoba, Canada, **2** Facultad de Medicina, Universidad Pontificia Bolivariana, Medellín, Antioquia, Colombia

☉ These authors contributed equally to this work.
‡ These authors also contributed equally to this work.
* zulmaruedav@gmail.com
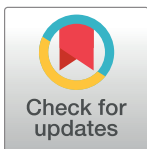
Abstract

HIV and pneumonia infections have both been shown to negatively impact lung function. However, evidence of the role of inflammation on lung dysfunction in HIV and pneumonia co-infected individuals remains limited. We aimed to systematically review the association of inflammatory markers and lung abnormalities in HIV and pneumonia co-infected individuals. This systematic review was registered with the International Prospective Register of Systematic Reviews on August 15, 2017 (registration number CRD42017069254) and used 4 databases (Cochrane Central Register of Controlled Trials, PubMed Central, Clinical Trials.gov and Google Scholar). All clinical trial, observational, and comparative studies targeting adult (> 18 years old) populations with HIV, pneumonia, or both, that report on immune response (cytokine, chemokine, or biomarker), and lung abnormality as an outcome were eligible. Data selection, risk of bias and extraction were performed independently by 2 blinded reviewers. Due to heterogeneity among the articles, a qualitative synthesis was performed. Our search strategy identified 4454 articles of which, 7 met our inclusion criteria. All of the studies investigated the ability of circulating biomarkers to predict lung damage in HIV. None of the articles included patients with both HIV and pneumonia, nor pneumonia alone. Markers of inflammation (IL-6, TNF-α, CRP), innate defense (cathelicidin), monocyte and macrophage activation (sCD14, sCD163 and, IL-2sRα), endothelial dysfunction (ET-1) and general immune health (CD4/CD8 ratio) were associated with lung abnormalities in HIV. This review highlights the lack of available information regarding the impact of inflammatory mediators on lung function in HIV and pneumonia populations, therefore opportunities to prevent lung damage with available anti-inflammatory treatment or to investigate new ones still remain.

Introduction

Since the introduction of combination antiretroviral therapy (cART), HIV infection has transitioned from a fatal infection to a chronic and manageable disease, with patient life expectancy approaching that of the general population [1]. However, despite treatment, individuals

with HIV continue to have higher rates of morbidity and mortality compared to the general population.

The lungs are a common site of complication during HIV infection, with pneumonia as a leading cause of hospitalization [2–4]. Following HIV establishment within the lungs, there is an increase in monocyte and macrophage activation, inflammatory markers (interleukin [IL]-1, IL-6, IL-8, IL-15, tumor necrosis factor [TNF]-α, granulocyte-macrophage colony-stimulating factor [GM-CSF], and macrophage inflammatory protein [MIP]-lα) [5], and, in contrast to the gut, an increase in CD4+ T cell concentrations [4,6–9]. An efflux of Interferon (IFN)-γ also occurs and functions as a leukocyte chemoattractant, affecting cell differentiation, B cell regulation and natural killer activity [10]. Together, these processes lead to continuous local inflammation and activation, endothelial dysfunction, altered coagulation, and cell destruction [4,6–9,11]. Persistent immune activation can also lead to impaired immunity and lung function decline.

Due to viral replication, a chronic inflammatory state, and impaired immunity, individuals with HIV have significantly greater lung disease compared to healthy individuals [12–17]. In a recent meta-analysis, HIV-infected individuals had a higher prevalence of chronic obstructive pulmonary disease (COPD) compared to HIV-negative individuals (odds ratio, OR 2.58, 95% confidence interval, CI 1.05, 6.35), even after adjusting for tobacco smoking [18]. In addition, Gingo and colleagues [13] found that a forced expiratory volume in 1 second/forced vital capacity (FEV_1/FVC) ratio <0.7 and a lung diffusing capacity (DLCO) <60% associated with an increase in all-cause mortality in HIV-infected individuals. Decreased diffusing capacity has also been reported in other studies as well [19].

Similarly, in pneumonia, individuals can also experience immune dysregulation and lung damage. Following pathogen invasion within the lungs, neutrophils are recruited to the site of infection where they act as first responders, initiating the release of local and systemic cytokines such as IL-4, IL-6, IL-10, IL-8, IL-1β, TNF-α, and transforming growth factor (TGF)-β, a process which is largely dependant on the invading microbe [20,21]. However, if left unchecked, excessive inflammation can lead to severe disease, tissue remodeling, lung fibrosis, and pulmonary dysfunction [20,22].

A history of pneumonia has been listed as a risk factor for airway obstruction and although information remains limited, researchers have begun to associate pneumonia-causing agents with lung function decline [22–26]. In Ralph *et al*, airflow obstruction (FEV_1 <60% predicted) was seen in approximately half of the individuals with tuberculosis, with only a 14.8% improvement in FEV_1 following treatment [23]. Rhee *et al* showed that patients cured of tuberculosis had a mean FEV_1 decline of 38 mL/year, rates that were similar to those seen among COPD patients without tuberculosis [24]. In addition, persistent *Chlamydophila pneumoniae* infection has also been linked to decreased FEV_1 (6 mL/year) and FVC (7 mL/year) in women [25].

Looking at individuals who have both HIV and pneumonia, Nelsing *et al* noted persistent reduction in DLCO up to 9 months post pneumonia infection [27] while Morris and coworkers observed that HIV-infected individuals who had either *Pneumocystis jirovecii* or bacterial pneumonia had a permanent decrease in FEV_1, FVC, and FEV_1/FVC ratio [28]. Although the underlying mechanisms behind these decreases have yet to be elucidated, investigations have attempted to correlate immune markers with lung damage and poor clinical outcomes. In a recent publication by Wang *et al*, 8 biomarkers including markers of inflammation (soluble TNF receptor [sTNFR]-1, sTNFR-2, C-reactive protein [CRP]), coagulation (D-dimer), T cell activation (sCD27), interferon response (IP-10), monocyte and macrophage activation (sCD14), and fibrosis (hyaluronan) were found to be elevated among HIV and pneumonia co-infected individuals, even after adjusting for pneumonia severity [11]. Moreover, these

cytokines were predictive of short-term mortality after pneumonia. Since tuberculosis is often the main cause of pneumonia among HIV patients, and IFN pathways have been reported as one of the most important pathways in tuberculosis [29], it would be interesting to study the role that this immune marker plays in lung abnormality in further studies.

Collectively, studies suggest a potential role for a variety of immune markers in lung dysfunction in individuals with HIV and/or pneumonia. Consequently, the aim of this systematic review was to provide an overview of inflammatory markers associated with lung abnormalities in HIV, pneumonia or HIV and pneumonia to gain insight into lung disease among HIV and pneumonia co-infected individuals and to suggest potential targets for anti-inflammatory treatment.

Materials and methods

This systematic review was registered with the International Prospective Register of Systematic Reviews (PROSPERO) on August 15, 2017 (registration number CRD42017069254- S1 File).

Search strategy and information sources

Following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, we performed an exhaustive search using 4 databases: Cochrane Central Register of Controlled Trials, PubMed Central, Clinical Trials.gov and Google Scholar [30,31] (see S2 File). Search terms included the following MeSH terms and keywords: cytokines, chemokines, biomarkers, lung function, lung function decline, lung injury, lung inflammation, pneumonia, community-acquired pneumonia, and HIV.

Studies were included if they reported on: (i) adult populations (>18 years old); (ii) HIV, pneumonia (caused by any pathogen), or HIV with pneumonia; (iii) cytokines, chemokines, or biomarkers; (iv) lung abnormalities; and were (v) clinical trials, observational or comparative studies. The exposure of interest was cytokine exposure, while the study outcome was lung abnormality (not mortality which could be attributable to a variety of reasons). Lung abnormality includes structural and functional abnormalities and was defined using lung function tests, diffusion capacity, or imaging (looking for emphysema or fibrosis). For cohort and clinical trials, we verified that the paper described that the outcome was not present at the time of enrolment. The main covariates of interest were HIV serostatus and the presence of infectious pneumonia. Studies that focused on patients with lung cancer, cystic fibrosis, COPD, hospital-acquired pneumonia, and acute respiratory distress syndrome (ARDS) were excluded. Non-HIV causes of immunosuppression (organ transplant, autoimmune disorders, neutropenia) were also excluded, as were descriptive studies, case reports and series, reviews and conference abstracts.

For Cochrane, PubMed, and Clinical Trials, all studies published before June 2018 were eligible for review. For Google Scholar, due to the extensive number of abstracts that were returned during our search, only studies published after 2014 were sought. There were no setting restrictions, however, only articles published in English were reviewed.

Study selection and data extraction

To identify which studies met our inclusion criteria, abstracts/summaries retrieved during the search strategy were screened independently by 2 reviewers (BMH and RM). All disagreements regarding study eligibility were resolved using a third reviewer. The full text of each of the identified studies was then assessed for eligibility. A pre-determined extraction table was used for data extraction and quality assessment (S3 File). Extracted information included: year of publication, the country in which the research took place, study design (cohort, clinical or

cross-sectional), population, duration of follow-up, total number and age of participants, techniques and samples used for cytokine measurement, etiology of lung disease, cytokines which were deemed significant, smoking and HIV history (whether on cART, if/when diagnosed, CD4+ T cell count, viral load), and any previous hospitalization for lung infection/disease.

To ensure completeness of our review, a manual search on all of the references from each screened article was also conducted.

Assessment of risk of bias

Both reviewers independently assessed the risk of bias of the exposure, outcome, and comparisons of each included study using previously established quality assessment scales (the Jadad and the Newcastle-Ottawa Quality Assessment Scales and the National Institutes of Health Cross-Sectional Quality Assessment Tool) [32–34]. Cohort studies were evaluated based on selection (representativeness of the cohort, ascertainment of exposed individuals, demonstration that the outcome was not present at study initiation), comparability (cohorts are comparable in design or analysis), and outcome (assessment of the outcome and follow-up). Clinical trials were assessed for randomization (whether mentioned and appropriate), concealment, blinding (whether mentioned and appropriate), and patient accountability (all patients accounted for including withdrawals and dropouts). Lastly, cross-sectional studies were evaluated based on their research question, objective and population (whether specified and well-defined); selection (representativeness of the population), participation rate, blinding (whether mentioned and appropriate), exposure and outcome (well defined, reliable and consistent across the study participants), and statistical analyses (whether appropriate and if they controlled for confounding variables).

Summary measures

Due to heterogeneity in study design and method of cytokine measurement between the identified studies, a qualitative synthesis was performed.
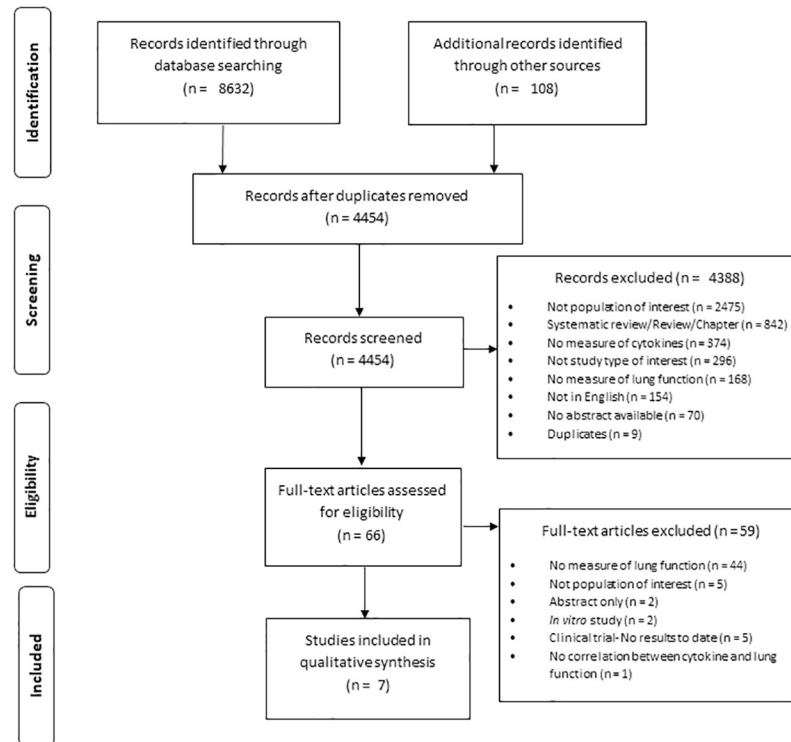
Results

Study selection

The search strategy identified 8632 records while the manual search identified an additional 108 records that had not appeared using the search strategy (Fig 1). After removing the duplicates, 4454 unique records remained. Of those, 66 full texts were assessed for eligibility from which 59 were excluded for not meeting our inclusion criteria (S3 File).

Seven articles met our criteria and were included for review [35–41]. The articles included 6 cross-sectional studies and 1 cohort study, all of which investigated the association between circulating biomarkers and lung abnormality among HIV-infected individuals. None of the included articles reported on patients with HIV and pneumonia nor pneumonia alone.

Critical appraisal of the included studies

Following the risk of bias assessment, studies were scored based on high, moderate or low risk of bias due to methodological limitations (S4 File). In several of the included studies, sample size or power calculations are not included, limiting the external validity of their findings. Four of the included studies were at risk of observer bias due to the lack of reported blinding of the investigators, radiologists or interpreters [36,38–40]. In addition, several studies are at risk of sampling bias [35,36,40]. In North *et al*, groups were chosen by convenience sampling [40], while in Attia and Triplette [35,37], patients were chosen from a veteran population,

Fig 1. PRISMA flow diagram of the search and review process.

https://doi.org/10.1371/journal.pone.0226347.g001

which limits the generalizability of these results [35,37]. The study by Crothers *et al* is at risk of confounding since they had limited ability to adjust for multiple covariates and confounders within their groups [41]. Lastly, in Fitzpatrick *et al*, inclusion and exclusion criteria were not specified, therefore it is unknown whether the sample population is representative of the general population making their investigations at risk for selective reporting [38].

Patient characteristics

Seven studies involving 1737 patients examined biomarkers and their association with lung structure or function (Table 1). Altogether, 1089 HIV-infected individuals and 648 controls were compared. Patients were primarily male, of black ethnicity, and were either current or former smokers.

Immunological markers

Eleven biomarkers were analyzed in the 7 studies (see Table 2) with IL-6 and sCD14 assessed the most frequently (n = 5). Majority of the studies consisted of cross-sectional assessments and measured cytokines in blood (plasma or serum) using an enzyme-linked immunosorbent assay (ELISA).

Nine biomarkers, including IL-6, TNF-α, CRP, cathelicidin, sCD14, sCD163, IL-2 receptor α chain (IL-2sRα), endothelin-1 (ET-1), and CD4/CD8 ratio had significant associations with lung abnormality, however findings were discordant as there was little overlap reported amongst the cytokines that had significant associations (Table 3). Nonetheless, cytokines can be grouped based on pathways, such as markers involved in general inflammation (IL-6, TNF-α, CRP), innate defense (cathelicidin), monocyte and macrophage activation (sCD14, sCD163

Table 1. Demographic characteristics of patients from each included study.

	Attia 2014 [35]	Fitzpatrick 2014 [39]	Lambert 2014 [36]	Crothers 2016 [41]	Fitzpatrick 2016 [38]	Triplette 2017 [37]	North 2018 [40]
Number of participants	203	147	650	39	274	190	234
Country	USA	USA	USA	USA	USA	USA	Uganda
Age (years)	55(50–58)[b]	45.6(9.4)[a]	48.6(8.0)[a]	40–57[c]	54(48–61)[b]	55(49–59)[b]	52(48–55)[b]
Sex (n, %)							
Female	21(10)	49(33)	227(35)	-	0(0)	4(2)	107(46)
Male	182(90)	98(67)	423(65)	-	274(100)	186(98)	127(54)
Ethnicity (n, %)							
White	42(21)	-	N/A	-	213(78)	24(13)	-
Black	136(67)	82(56)	592(91)	30 (77)	47(17)	135(71)	234(100)
Other	22(11)[¶]	5(3.4)[*]	N/A	-	14(5)[¶]	31(16)[¶]	-
Smoking status (n, %)							
Current	46(23)	84(57.1)	556(85.5)	39(100)	-	120(63)	35(15)
Former	-	-	60(9.2)	-	-	40(21)	80(34)
Never	36(18)	25(17)	34(5.2)	-	-	29(15)	119(51)
Smoking, pack years	-	10(1.4–22)[b]	23.8(16.9)[a]	8–40[c]	1.9(0–22.1)[b]	3–42[c]	0(0–18)[b]

N/A: Not applicable;—not mentioned

[a] mean (standard deviation)

[b] median (interquartile range)

[c] range

[*] Hispanic

[¶] Hispanic and other

and, IL-2sRα), endothelial dysfunction (ET-1) or general biomarkers of immune system health (CD4/CD8 ratio). Below we summarize the results for each of the 9 cytokines.

Markers of inflammation (IL-6, TNF-α, and CRP). Five studies looked at the relationship between IL-6 and lung abnormality among HIV-infected populations [35,38–41]. In each of the studies, IL-6 concentrations were higher among people living with HIV and in 4 of the studies, increased IL-6 associated with decreased lung function [38–41]. Crothers et al [41] reported that HIV patients that had low DLCO (≤60% predicted value) had plasma IL-6 concentrations twice that of those with preserved DLCO (4 and <2 pg/mL, respectively, $P<0.005$). Similarly, Fitzpatrick 2014 [39] found that plasma IL-6 concentrations correlated negatively with DLCO and FEV_1%-predicted (correlation coefficients of -0.075, $P = 0.005$ and -0.074, $P = 0.03$, respectively). In addition, individuals that had IL-6 levels >3.3 pg/mL had 3.7 times greater odds of having DLCO% predicted <60 ($P = 0.006$). In keeping with these findings, Fitzpatrick 2016 et al [38] reported that IL-6 associated with significantly worse FEV_1%-predicted and DLCO values among the HIV-infected participants. North et al also reported that per IQR increase in IL-6 in individuals with HIV, FEV_1 and FVC saw a significant decrease by 18.1 ml (95% CI -29.1, -7.1) and 17.1 (95% CI -28.2, -5.9), respectively [40]. In contrast, studies by Attia et al reported no significant association between IL-6 and emphysema severity.

Only one study looked at TNF-α and its association with lung function decline [38]. In Fitzpatrick 2016 et al, TNF-α had a significant association with lower DLCO%-predicted values in HIV-infected individuals, with similar trends also seen among the uninfected controls.

Two studies assessed the relationship between CRP and lung dysfunction in the HIV-infected population, both of which reported higher CRP levels among HIV-infected

Table 2. Characteristics and descriptions of the included articles.

Author	Study Type	Population (n)	Sample type	Immunological markers assessed/ Method	Lung function methodology
Attia 2014 [35]	Cross-sectional	HIV-positive (114) HIV-negative (49)	Blood (serum)	**IL-6, D-dimer, sCD14**: Immunoassay (NM)	PFT Radiograph
Fitzpatrick 2014 [39]	Cross-sectional	HIV-positive (147)	Blood (plasma)	**hsCRP**: ELISA (Phoenix Pharmaceuticals, Burlingame, CA, USA) **IL-6, IL8**: ELISA (R&D, Minneapolis, MN, USA)	PFT
Lambert 2014 [36]	Cross-sectional	HIV-positive (370) HIV-negative (280)	Blood (plasma)	**Cathelicidin**: ELISA (Hycult Biotech, Uden, Netherlands)	PFT
Crothers 2016 [41]	Cross-sectional	HIV-positive (19) HIV-negative (20)	Blood (plasma/serum*)	**IL-6**: Immunoassay (R&D, Minneapolis, MN, USA) **sCD14**: Immunoassay (R&D, Minneapolis, MN, USA)	PFT Radiograph
Fitzpatrick 2016 [38]	Cohort	HIV-positive (124) HIV-negative (150)	Blood (serum)	**IL-8, sCD14, sCD163, IL- 2sRa, ET-1**: ELISA (R&D, Minneapolis, MN, USA) **IL-6, TNFa**: Luminex (Luminex corporation, Texas, USA)	PFT
Triplette 2017 [37]	Cross-sectional	HIV-positive (190)	Blood (plasma)	**sCD14, CD4/CD8 ratio**: Flow cytometry	PFT Radiograph
North 2018 [40]	Cross-sectional	HIV-positive (125) HIV-negative (109)	Blood (serum- hsCRP; plasma-IL-6, sCD14, sCD163)	**hsCRP**: Latex immunoturbidimetry (LabCorp, Burlington, NC, USA) **IL-6**: ELISA (MesoScale Discovery, Rockville, MD, USA); **sCD14, sCD163**: ELISA (R&D, Minneapolis, MN, USA)	PFT

ELISA: Enzyme-linked immunosorbent assay, NM: Not mentioned; PFT: Pulmonary function test;

*Crothers *et al* [41] describes the use of serum IL-6 in their methods but report on plasma in their results

individuals [39,40]. Fitzpatrick *et al* found that plasma CRP (>1 mg/L) associated with significantly lower FEV1%-predicted values and higher odds (2.5 times) of airflow obstruction (FEV_1/FVC ratio <0.7, OR 2.545, $P = 0.06$) [39]. In addition, individuals who had elevated CRP (>1 mg/L) had lower DLCO ($P = 0.001$) and had 3.7 times greater odds of having impaired DLCO ($P = 0.006$). In *post-hoc* analyses controlling for undetectable HIV viral load, elevated CRP retained an association with worse DLCO.

In the second study, median CRP concentrations were higher among individuals with HIV compared to uninfected controls ($P<0.001$) however, elevated CRP (>3 mg/L) associated with reduced FEV_1 and FVC in both patient groups [40]. HIV-infected individuals that had elevated CRP had a 39.3 mL reduction in FEV_1 (95% CI -61.7, -16.9) and a 44 ml decrease in FVC (95% CI -48.4, -6.4). Uninfected controls exhibited similar results (FEV_1: 37.9 ml [95% CI -63.2, -12.6]; and FVC 58.0 ml [95% CI -88.4, -27.5]).

Innate antimicrobial peptides (cathelicidin). Cathelicidin was the only peptide that was investigated for its role in lung disease among our study populations. In Lambert *et al* [36], no association between HIV serostatus and median cathelicidin levels was observed ($P = 0.12$), however, individuals with low cathelicidin (<28.8 ng/mL) demonstrated a 115 mL decrease in FEV_1 (95% CI -221, -8; $P = 0.035$) compared to individuals with high cathelicidin.

Markers of monocyte activation (sCD14, sCD163 and IL-2sRα). Five studies measured sCD14 in HIV-infected individuals, 4 of which found no significant association between

Table 3. Study findings of the included articles, stratified by immune marker.

Immune marker	Author	Sample size with data	Immunological markers		Method of lung assessment	Associations between immunological markers and lung findings
			Assessment method	Findings		
IL-6	Attia 2014 [35]	203	Immunoassay	**Median (IQR), pg/mL:** *** HIV-positive: 1.81 (1.28–3.43) HIV-negative: 1.23 (0.94–2.07)	PFT Radiograph	• No significant association between IL-6 and emphysema severity
	Crothers 2016 [41]	40	Immunoassay	**Median, pg/mL:** *** HIV-positive with low DLCO: 4 HIV-negative with low DLCO: < 2	PFT Radiograph	• HIV+ subjects with low DLCO ($\leq$60% predicted value) had higher IL-6 concentrations (4 and <2 pg/mL) ***
	North 2018 [40]	234	ELISA	**Results:** HIV-positive: higher (exact values NM) HIV-negative: lower (exact values NM)	PFT	• HIV-infected individuals with IL-6 levels in the 4th quartile, had lower FEV_1 (-18.1 ml [95% CI -29.1, -7.1] and FVC (-17.1 [95% CI -28.2, -5.9]) ***
	Fitzpatrick 2014 [39]	123	ELISA	**Median (IQR), pg/mL:** HIV: 2.0 (1.1–3.3)	PFT	• IL-6 negatively correlated with DLCO (r -0.075) and FEV_1%-predicted (r -0.074) *** • Individuals with elevated IL-6 had greater odds of impaired DLCO (<60% predicted values; OR 3.758) ***
	Fitzpatrick 2016 [38]	259	Luminex	**Median (IQR), pg/mL:** HIV-positive: 10.9 (1.7–21.1) HIV-negative: 7.0 (1.2–20.8)	PFT	• IL-6 associated with worse FEV_1%-predicted and DLCO values among HIV-infected participants***
TNF-α	Fitzpatrick 2016 [38]	260	Luminex	**Median (IQR), pg/mL:** HIV-positive: 33.4 (5.0–69.4) HIV-negative: 35.9 (3.8–62.0)	PFT	• TNF-α associated with lower DLCO%-predicted values in HIV-infected individuals with similar trends seen among the control group***
CRP	North 2018 [40]	234	Latex immunoturbidimetry	**Results:** *** HIV-positive: higher (exact values NM) HIV-negative: lower (exact values NM)	PFT	• HIV-infected individuals that had CRP >3 mg/L had lower FEV_1 (-39.3mL [95% CI -61.7, -16.9]) and FVC (-44 mL, [95% CI -48.4, -6.4]) compared to individuals with CRP levels <3 mg/L ***
	Fitzpatrick 2014 [39]	123	ELISA	**Median (IQR), mg/L:** HIV: 1.6 (0.1–6.8)	PFT	• CRP (>1 mg/L) associated with FEV_1% predicated and DLCO *** • CRP (>1 mg/L) associated with greater odds of impaired DLCO (OR 3.758) ***
Cathelicidin	Lambert 2014 [36]	650	ELISA	**Median (IQR), ng/mL:** HIV-positive: 35.5 (28.4–44.6) HIV-negative: 36.4 (29.2–47.0)	PFT	• Low cathelicidin (< 28.8 ng/mL) associated with decreased levels of FEV_1 (-115 mL [95% CI -221, -8]) ***

(*Continued*)

Table 3. (Continued)

Immune marker	Author	Sample size with data	Immunological markers		Method of lung assessment	Associations between immunological markers and lung findings
			Assessment method	Findings		
sCD14	Attia 2014 [35]	203	Immunoassay	**Median (IQR), ng/mL:** *** HIV-positive: 1671 (1472–2128) HIV-negative: 1386 (1171–1569)	PFT Radiograph	• High sCD14 (>1883 ng/mL) associated with increased (>10%) emphysema *** • HIV-infected individuals with nadir CD4+ T cell count <200 cells/mL had increased odds of emphysema (OR 2.39, 95% CI 1.02, 5.62) ***
	Crothers 2016 [41]	40	Immunoassay	**Mean, ng/mL:** *** HIV-positive: 1681 HIV-negative: 1367	PFT Radiograph	• No significant association between sCD14 and DLCO status
	Triplette 2017 [37]	190	Flow cytometry	**Median (IQR), ng/mL:** HIV-positive: 1674 (1487–2164) HIV-negative: 1626 (1364–1953)	PFT Radiograph	• No significant association between sCD14 and emphysema severity or decreased lung function
	Fitzpatrick 2016 [38]	263	ELISA	**Median (IQR), pg/mL:** *** HIV-positive: 2128.6 (1831.2–2522.9) HIV-negative: 1782.5 (1607.2–2075.3)	PFT	• No significant association between sCD14 and lung abnormalities in either group
	North 2018 [40]	234	ELISA	**Results:** *** HIV-positive: higher (exact values NM) HIV-negative: lower (exact values NM)	PFT	• No significant association between sCD14 and lung function
sCD163	North 2018 [40]	234	ELISA	**Results:** HIV-positive: higher (exact values NM) HIV-negative: lower (exact values NM)	PFT	• In the HIV group, sCD163 associated with lower FVC (-14.3 ml [95% CI -26.9 to -1.7]) ***
	Fitzpatrick 2016 [38]	274	ELISA	**Median (IQR), ng/mL:** *** HIV-positive: 862.5 (640.1–1099.9) HIV-negative: 649.5 (499.2–847.0)	PFT	• sCD163 associated with lower FEV$_1$/FVC ratios and lower DLCO %-predicted ***

(*Continued*)

Table 3. (Continued)

Immune marker	Author	Sample size with data	Immunological markers		Method of lung assessment	Associations between immunological markers and lung findings
			Assessment method	Findings		
IL-2sRα	Fitzpatrick 2016 [38]	274	ELISA	**Median (IQR), pg/mL:** *** HIV-positive: 942.9 (694.6–1256.9) HIV-negative: 814.7 (646.0–1022.0)	PFT	• In both populations, IL-2sRα associated with lower DLCO%-predicted***
ET-1	Fitzpatrick 2016 [38]	268	ELISA	**Median (IQR), pg/mL:** HIV-positive: 1.4 (1.1–1.7) HIV-negative: 1.3 (1.3–1.6)	PFT	• ET-1 associated with lower FEV$_1$%-predicted and increased odds of reduced FEV$_1$/FVC ratios (OR 4.8) among HIV-infected individuals *** • ET-1 associated with lower FEV$_1$%-predicted over time in HIV-infected individuals ***
CD4/CD8 Ratio	Attia 2014 [35]	190	Flow cytometry	**CD4/CD8 ratio < 0.4** **CD4/CD8 ratio 0.4–1.0** **CD4/CD8 ratio > 1.0**	PFT Radiograph	• CD4/CD8 ratio <0.4 associated with increased odds of having >10% emphysema compared to those with a CD4/CD8 ratio >1.0 (OR 7.4; 95% CI 1.5, 35) *** • Patients with low CD4/CD8 ratio (<0.4) had reduced DLCO% (51 [IQR 41–58] vs 59 [IQR 49–71]) ***

ELISA: Enzyme-linked immunosorbent assay; FEV$_1$: Forced expiratory volume in 1 second; FVC: Forced vital capacity; DLCO% predicted: % predicted of carbon monoxide diffusion capacity; NM: Not mentioned; PFT: Pulmonary function test; r: correlation coefficient

*** indicates a significant result ($P \leq 0.05$).

https://doi.org/10.1371/journal.pone.0226347.t003

sCD14 and lung abnormality [35,37,38,40,41]. Crothers and colleagues reported significantly higher concentrations of sCD14 in HIV patients (1681 vs. 1367 ng/mL), however, their populations did not differ by DLCO status [41]. Triplette and coworkers write that median sCD14 concentrations were similar among individuals with HIV and controls (1674, IQR 1487–2164; vs 1626, IQR 1364–1953 ng/mL; $P = 0.13$) and did not associate with decreased lung function nor disease severity [37], a view which was also supported by North [40] and Fitzpatrick [38]. In contrast, Attia *et al* [35] observed that HIV-infected individuals had significantly higher median serum sCD14 concentrations compared to controls (1671, IQR 1472–2128; vs 1386, IQR 1171–1569 ng/mL) and that individuals who had >10% emphysema had higher sCD14 compared to those with <10% emphysema (1883 vs 1648 ng/mL; $P<0.05$). Additionally, they found that patients with a nadir CD4+ T cell count <200 cells/mL had 2 times greater odds of having increased emphysema (OR 2.39; 95% CI 1.02, 5.62).

Two studies looked at the association between sCD163 and lung abnormalities in the HIV-infected population, both of which reported decreased lung function among individuals with elevated sCD163 [38,40]. North *et al* found that although median sCD163 levels were similar among study populations, sCD163 associated with a 14.3 ml decrease in FVC (95% CI -26.9, -1.7) in the HIV group. Fitzpatrick and colleagues come to similar conclusions in their HIV population, stating that elevated sCD163 associated with significantly lower FEV$_1$/FVC ratios and DLCO during follow-up [38].

Only 1 study, Fitzpatrick 2016, reported on IL-2sRα in lung function studies among HIV-infected individuals [38]. In their analysis, investigators found that IL-2sRα concentrations were significantly higher among those with HIV (942.9, IQR 694.6–1256.9; vs 814.7, IQR 646.0–1022.0 pg/mL) however, in both populations, IL-2sRα associated with lower DLCO %-predicted ($P = 0.005$ and $P = 0.004$). Interestingly, this association was lost over time.

Markers of endothelial dysfunction (ET-1). Fitzpatrick et al [38] was the only study that investigated the association between ET-1 and lung abnormality among the HIV-infected population. ET-1 concentrations were similar among the HIV group and the uninfected controls (1.4, IQR 1.1–1.7; and 1.3, IQR 1.3–1.6 pg/mL, respectively; $P = 0.4$), however HIV-infected individuals who had higher ET-1 had significantly lower FEV_1%-predicted values, and had 4.8 greater odds of having lower FEV_1/FVC ratios (OR 4.8, $P = 0.04$) compared to controls.

When looking at the relationship between ET-1 and lung function over time, baseline levels of ET-1 associated with decreased FEV_1%-predicted, and DLCO in HIV-infected individuals [38]. However, ET-1 was not able to predict a greater rate of decline of FEV_1 or DLCO.

Markers of general immune health (CD4/CD8 ratio). One study which set out to determine the relationship between plasma CD4/CD8 ratio and lung abnormality found that low CD4/CD8 ratio (<0.4) associated with increased emphysema (>10% involvement) [37]. After adjusting for CD4 count and HIV viral load, individuals with a CD4/CD8 ratio <0.4 had 7.4 times the odds of >10% emphysema compared to those with a CD4/CD8 ratio >1.0 (OR 7.4, 95% CI 1.5, 35). Patients with low CD4/CD8 ratio also had reduced DLCO% (51, IQR 41–58; vs 59, IQR 49–71 for low and high CD4/CD8 ratio, respectively; $P = 0.008$).

Discussion

The present review assessed cytokines associated with lung abnormalities among HIV and/or pneumonia-infected individuals. Seven studies [35–41] were identified in our search from which 11 cytokines were studied for their association with lung abnormalities among HIV-infected individuals. Interestingly, none of the articles reported on biomarkers and lung structure or function among individuals with HIV and pneumonia co-infection, nor pneumonia alone, reflecting a gap in knowledge regarding the pathogenesis of lung disease among these populations.

Although 9 immune markers (IL-6, TNF-α, CRP, cathelicidin, sCD14, sCD163, IL-2sRα, ET-1, and CD4/CD8 ratio) associated with decreased lung function or lung abnormalities, there was discordance in markers studied and differences identified between the studies. For example, of the 5 studies that reported on IL-6, Attia *et al* did not find a significant association between IL-6 and lung abnormality among their HIV-infected population [35]. However, more prevalent smoking has been associated with both IL-6 and lower lung function [42] and as Attia *et al* reported a lower percentage of cigarette smokers among their study cohort, this may have contributed to their result. Attia *et al* also reported a relationship between sCD14 and emphysema with greater odds of emphysema among their HIV patients, results that differ from those seen in the other 4 studies which looked at sCD14 [37,38,40,43]. This divergence could be attributable to the fact that Attia *et al* measured biomarkers in serum while the others looked at plasma since detectability and measurability differences between serum and plasma have been documented [44]. Conversely, different methods of immunological assessment that have different sensitivity levels may also be a contributing factor. Another potential and very important confounder that many publications did not report, is cART and CD4 count, both of which could reflect different stages of immunosuppression and could affect cytokine production. In addition, HIV patients often have multiple coinfections, for example, sexually transmitted blood-borne infections, which can affect cytokines results however, many of the included studies did not mention this information.

Nonetheless, similar trends among the studies were that people living with HIV have higher concentrations of IL-6, CRP, sCD14, sCD163, IL-2sRα and ET-1 and lower concentrations of cathelicidin and CD4/CD8 ratio, with similar concentrations of TNF-α seen in HIV-positive individuals and controls, and that IL-6, TNF-α, CRP, cathelicidin, sCD14, sCD163, IL-2sRα,

ET-1, and CD4/CD8 ratio associated with lung abnormalities. Since several of these cytokines represent similar pathways, i.e. inflammation, innate defense, macrophage activation, endothelial dysfunction, and general immune health, this discussion will focus on candidate pathways of inflammation and/or immune activation, how these biomarkers relate to one another and how their presence in HIV and pneumonia co-infected individuals may lead to increased lung abnormality.

Within a normal and healthy lung, the innate and adaptive immune systems work together to maintain a homeostatic state. The airway epithelium and residential macrophages serve as the first-lines of defense, able to sense the environment and react to external dangers and cues through initiation or suppression of the adaptive immune response [45]. If no danger is present, the immune system remains immune quiescent [45,46]. However, in the case of HIV, immune activation and improper regulation of the immune network are a hallmark of disease. Systemic and local inflammatory markers such as TNF-α, IL-6, and CRP have been shown to be overexpressed in HIV infection, pneumonia and other diseases [5,21,47–49], with Fitzpatrick *et al* 2016 reporting a strong association between IL-6 and TNF-α (r = 0.87) [38]. High concentrations of TNF-α can cause localized cell damage and epithelial channel disruption leading to barrier dysfunction within the lungs [47]. Moreover, TNF-α, along with ET-1, can cause eosinophilic recruitment and fibrinogenic cytokine production, all of which can contribute to lung damage [50,51]. Although IL-6 and TNF-α can be produced by fibroblasts, lymphoid, and endothelial cells, monocytes and macrophages are their main source [52] thus, it is not surprising that markers of monocyte and macrophage activation, such as sCD14, sCD163, and IL-2sRα, were also elevated in Fitzpatrick *et al* [38]. sCD14, sCD163, and IL-2sRα are biomarkers that aid in pathogen surveillance and phagocytosis, inducing immune activation and amplification of subsequent host responses [53–55]. Among HIV-infected individuals, moderate associations between and sCD163 and IL-2sRα have been reported [38]. Increased activation of these markers and their downstream effects is what we hypothesize led to the increased emphysema seen in Attia *et al* [35]. sCD14 responses, although beneficial, can affect the lung through excessive inflammation and pathogen dissemination. sCD14 present in the bronchoalveolar space of *Streptococcus pneumoniae*-infected mice was shown to cause invasive pneumonia [56]. In serum of HIV-infected individuals, elevated sCD14 associated with the occurrence of immune activation-induced end-organ dysfunction and poor prognosis despite cART [57–59]. Similar results in HIV patients and in individuals with pneumonia have also been seen with sCD163 [38,60].

An association between low cathelicidin levels and history of bacterial pneumonia has also been observed [36]. Cathelicidin, an innate response protein that acts as a cell signaling and chemotaxis molecule, serves as a natural antimicrobial against viruses, bacteria and fungi [61]. Although it can be expressed by numerous cell types (macrophage, mast cells, and airway epithelial cells), it is perpetually available within neutrophils [62–64]. Upon stimulation of the exterior of the neutrophil, cathelicidin is released into the extracellular milieu triggering a cascade of events including induction of incoming neutrophils, recruitment of monocytes, eosinophils, mast cells and T lymphocytes and initiation of epithelial regeneration and remodeling [61,62,65]. High concentrations of cathelicidin can contribute to epithelial injury and destruction through overstimulation and overproduction of structural cells [62]. Conversely, at low levels, it was also correlated with lung dysfunction among individuals with HIV [36]. Although these findings are contradictory and need to be explored further, cathelicidin may play a role in lung disease.

Elevated levels of markers of inflammation, and monocyte and macrophage activation have been documented in both individuals with HIV and individuals with pneumonia [5,8,21,38,40,47–49,55,66]. Likewise, innate response markers are also affected [36,63]. Since
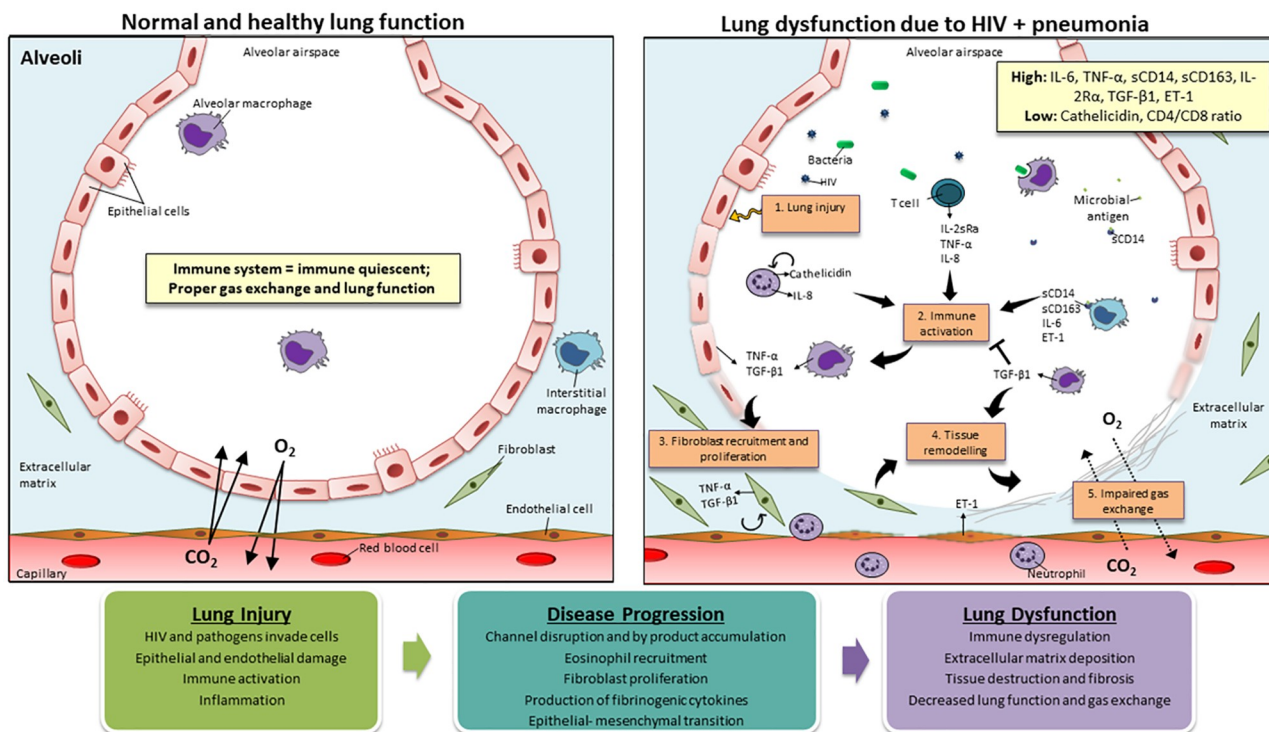
Fig 2. A proposed framework for the hypothesized pathogenesis of lung abnormality among individuals with HIV and pneumonia co-infection.
In a normal and healthy alveolus, the immune system works together to maintain an immune quiescent state (top left panel) [45]. However, in individuals with HIV and in those with pneumonia, innate response markers are affected [36,63] and elevated levels of markers of inflammation (IL-6, TNF-α and CRP) [5,21,35,40,41,48,49,68,69], macrophage activation (sCD14, sCD163, and IL-2sRα) [35,37,40,41,55,66,69] and endothelial dysfunction (ET-1) [69] have been reported. HIV alters the immune environment and affects the host response [67], therefore it is hypothesized that HIV-infected individuals who contract pneumonia will have a decreased ability to clear the invading pathogen, leading to increased fibroblast activation, extracellular matrix deposition and tissue remodeling resulting in impaired gas exchange and greater lung abnormality (top right panel).

https://doi.org/10.1371/journal.pone.0226347.g002

HIV alters the immune environment and affects alveolar macrophage response to bacteria [67], it is logical to think that HIV-infected individuals who contract pneumonia will have a decreased ability to clear the invading pathogen, leading to increased damage and lung abnormality. A proposed framework for the hypothesized pathogenesis of lung abnormality among individuals with HIV and pneumonia co-infection can be seen in Fig 2.

Although this review identified cytokines associated with lung abnormalities and found more lung function decline among people living with HIV compared to uninfected controls, it could not identify a causal relationship between these factors. There may be several pathways to the low pulmonary function observed in the HIV-infected population. Li *et al* examined the progression of pulmonary function measurements in an HIV cohort over a 6-year period [70]. They found that a history of pneumonia was significantly associated with DLCO% decline. Similar results were also reported by Gupte and colleagues who found that prior TB infection associated with an excess loss of FEV_1, and that although older age, smoking and higher CRP associated with obstructive lung disease, CD4 count and ART did not [71]. Similarly, Kunisaki and coworkers found no difference in lung dysfunction between HIV patients on early or deferred cART in their study which followed patients for 2 years [72]. Likewise, in one of the largest cohorts which looked at pulmonary function in people living with HIV and uninfected controls, Ronit *et al* found that HIV was a risk factor for decreased FEV_1 and FVC despite being on cART (n = 1064, 98.5%) and having a viral load <50 copies/mL (n = 1015, 94.6%)

[12]. Similar findings were also reported in a cynomolgus macaques model which used sim-ian-adapted HIV [73]. In contrast to expert opinion, these studies suggest that cART does not prevent lung dysfunction nor does it have much of an impact on lung function in HIV. Although most agree that there is not enough data on ART and its relationship with lung func-tion, this hypothesis is intriguing and hints that other factors might be at play. Perhaps it is not the virus itself but rather the associated systemic immune activation, microbial translocation or dysbiosis. Studies aimed at better understanding lung dysfunction in the HIV-infected pop-ulation are warranted and will be required to determine the role that ART, the virus, the microbiome, and inflammation have on lung function decline.

In this review, we could not do a quantitative analysis of the data due to heterogeneity in the methodologies used for quantifying cytokines (immunoassays, ELISA, Luminex, and flow cytometry) and lung abnormality (PFT and radiograph) and since many of the included publi-cations relied on different statistical outputs, such as the correlation coefficient, odds ratio, percent predicted, confidence intervals, *P* values etc.. Additionally, each of the inflammatory markers were measured in blood, however circulating cytokines can be confounded by coin-fections, and also may not truly reflect what is occurring locally in the lungs. Lastly, cytokine concentrations vary during infection which may potentially affect the interpretation of the results depending on when samples are collected [74–76]. Consequently, cross-sectional stud-ies, like the ones identified herein which only sample at a single time point, are less desirable to evaluate causality than studies that sample repeatedly over time. Ideally, simultaneous sam-pling of blood and lung, in a prospective and longitudinal study may provide a better ability to understand the processes leading to lung abnormalities.

We are also aware that there are limitations at the review level. Since there were a small number of scientific publications available for this topic, we, unfortunately, were not able to find any information pertaining to lung dysfunction in HIV and pneumonia co-infected indi-viduals nor individuals with pneumonia alone, highlighting the importance of having new studies to evaluate our hypothesis.

Conclusions

The immune response and its role in lung disease is complex. This systematic review identified several biomarkers that were elevated among HIV-infected individuals with lung abnormality, however, the cross-sectional data preclude linking these biomarkers as the cause of the associ-ated lung disease. This review highlights the lack of information available on the association of cytokines and lung disease in the adult HIV and pneumonia populations, a finding which reflects an opportunity for further research. Studying markers of immune activation and how cytokine profiles impact lung structure and function in HIV and pneumonia is important as it may provide candidate biomarkers for future studies to ascertain their predictive utility and may lead to potential targets for immunomodulatory intervention thereby improving patient outcomes for individuals with these types of coinfections.

Supporting information

S1 File. PROSPERO protocol.
(PDF)

S2 File. Search strategy.
(DOCX)

S3 File. Data extraction tables.
(XLSX)

S4 File. Study quality assessment.
(XLSX)

S5 File. PRISMA checklist.
(DOC)

Author Contributions

Conceptualization: Breanne M. Head, Ruochen Mao, Yoav Keynan, Zulma Vanessa Rueda.

Data curation: Breanne M. Head, Ruochen Mao.

Formal analysis: Breanne M. Head, Ruochen Mao.

Funding acquisition: Yoav Keynan, Zulma Vanessa Rueda.

Investigation: Breanne M. Head, Ruochen Mao.

Methodology: Breanne M. Head, Ruochen Mao, Zulma Vanessa Rueda.

Supervision: Yoav Keynan, Zulma Vanessa Rueda.

Validation: Yoav Keynan, Zulma Vanessa Rueda.

Writing – original draft: Breanne M. Head, Ruochen Mao.

Writing – review & editing: Yoav Keynan, Zulma Vanessa Rueda.

References

1. Nakagawa F, May M, Phillips A. Life expectancy living with HIV: Recent estimates and future implications. Curr Opin Infect Dis. 2013; 26(1):17–25. https://doi.org/10.1097/QCO.0b013e32835ba6b1 PMID: 23221765

2. Cilloniz C, Torres A, Polverino E, Gabarrus A, Amaro R, Moreno E, et al. Community-acquired lung respiratory infections in HIV-infected patients: Microbial aetiology and outcome. Eur Respir J. 2014; 43 (6):1698–708. https://doi.org/10.1183/09031936.00155813 PMID: 24525448

3. Head BM, Trajtman A, Rueda Z V, Vélez L, Keynan Y. Atypical bacterial pneumonia in the HIV-infected population. Pneumonia. 2017; 9(12):1–7.

4. Brune KA, Ferreira F, Mandke P, Chau E, Aggarwal NR, D'alessio FR, et al. HIV Impairs Lung Epithelial Integrity and Enters the Epithelium to Promote Chronic Lung Inflammation. PLoS One. 2016; 11(3): e0149679. https://doi.org/10.1371/journal.pone.0149679 PMID: 26930653

5. Agostini C, Semenzato G. Immunologic effects of HIV in the lung. Clin Chest Med. 1996; 17(4):633–45. https://doi.org/10.1016/s0272-5231(05)70337-3 PMID: 9016369

6. Kristoffersen US, Lebech A-M, Mortensen J, Gerstoft J, Gutte H, Kjaer A. Changes in lung function of HIV-infected patients: A 4·5-year follow-up study. Clin Physiol Funct Imaging. 2012; 32(4):288–95. https://doi.org/10.1111/j.1475-097X.2012.01124.x PMID: 22681606

7. Saksena NK, Wang B, Zhou L, Soedjono M, Shwen Ho Y, Conceicao V. HIV reservoirs in vivo and new strategies for possible eradication of HIV from the reservoir sites. HIV/AIDS—Res Palliat Care. 2010; 2:103–22.

8. Mascolini M. Faster lung function decline with HIV linked to sCD14 activation marker. Conf Reports NATAP [Internet]. 2014; https://www.thieme-connect.com/DOI/DOI?10.1055/s-2004-822307

9. Crothers K, Thompson BW, Burkhardt K, Morris A, Flores SC, Diaz PT, et al. HIV-associated lung infections and complications in the era of combination antiretroviral therapy. Proc Am Thorac Soc. 2011; 8:275–81. https://doi.org/10.1513/pats.201009-059WR PMID: 21653528

10. Schroder K, Hertzog PJ, Ravasi T, Hume DA. Interferon-y: an overview of signals, mechanisms and functions. J Leukoc Biol [Internet]. 2004; 75(February):163–89. Available from: http://www.jleukbio.org/content/75/2/163.long%0A http://www.ncbi.nlm.nih.gov/pubmed/14525967

11. Wang RJ, Moore J, Moisi D, Chang EG, Byanyima P, Kaswabuli S, et al. HIV infection is associated with elevated biomarkers of immune activation in Ugandan adults with pneumonia. PLoS One. 2019; 14 (5):1–14.

12. Ronit A, Lundgren J, Shoaib A, Benfield T, Roen A, Mocroft A, et al. Airflow limitation in people living with HIV and matched uninfected controls. Thorax. 2018; 0:1–8.

13. Gingo MR, Nouraie M, Kessinger CJ, Greenblatt RM, Huang L, Kleerup EC, et al. Decreased lung function and all-cause mortality in HIV-infected individuals. Ann Am Thorac Soc. 2018; 15(2):192–9. https://doi.org/10.1513/AnnalsATS.201606-492OC PMID: 29313714

14. Drummond MB, Merlo CA, Astemborski J, Marshall M, Kisalu A, Mcdyer JF, et al. The effect of HIV infection on longitudinal lung function decline among injection drug users: A prospective cohort. AIDS. 2013; 27(8):1303–11. https://doi.org/10.1097/QAD.0b013e32835e395d PMID: 23299176

15. Crothers K, Rodriguez C V, Wongtrakool C, Hoo GS, Kim J, Brown ST, et al. Association of HIV infection and immune activation with decline in lung function. Top Antivir Med. 2014; 22:397–8.

16. Drummond MB, Lambert AA, Hussien AF, Lin CT, Merlo CA, Wise RA, et al. HIV infection is independently associated with increased CT scan lung density. Acad Radiol. 2017; 24(2):137–45. https://doi.org/10.1016/j.acra.2016.09.019 PMID: 27876271

17. Popescu I, Drummond MB, Gama L, Lambert A, Hoji A, Coon T, et al. HIV suppression restores the lung mucosal CD4+T-cell viral immune response and resolves CD8+T-cell alveolitis in patients at risk for HIV-associated chronic obstructive pulmonary disease. J Infect Dis. 2016; 214(10):1520–30. https://doi.org/10.1093/infdis/jiw422 PMID: 27613775

18. Bigna JJ, Kenne AM, Asangbeh SL, Sibetcheu AT. Prevalence of chronic obstructive pulmonary disease in the global population with HIV: A systematic review and meta-analysis. Lancet Glob Heal. 2018; 6:e193–202.

19. Drummond MB, Kirk GD. HIV-associated obstructive lung diseases: Insights and implications for the clinician. Lancet Respir Med. 2014; 2(7):583–92. https://doi.org/10.1016/S2213-2600(14)70017-7 PMID: 24831854

20. Rendon A, Rendon-Ramirez EJ, Rosas-Taraco AG. Relevant Cytokines in the Management of Community-Acquired Pneumonia. Curr Infect Dis Rep. 2016; 18(3):1–9.

21. Fernandez-Botran R, Uriarte SM, Arnold FW, Rodriguez-Hernandez L, Rane MJ, Peyrani P, et al. Contrasting inflammatory responses in severe and non-severe community-acquired pneumonia. Inflammation. 2014; 37(4):1158–66. https://doi.org/10.1007/s10753-014-9840-2 PMID: 24557760

22. Ravimohan S, Kornfeld H, Weissman D, Bisson GP. Tuberculosis and lung damage: from epidemiology to pathophysiology Eur Respir Rev [Internet]. 2018; 27(147):170077. Available from: http://err.ersjournals.com/lookup/doi/10.1183/16000617.0077-2017 PMID: 29491034

23. Ralph AP, Kenangalem E, Waramori G, Pontororing GJ, Sandjaja Tjitra E,, et al. High morbidity during treatment and residual pulmonary disability in pulmonary tuberculosis: Under-recognised phenomena. PLoS One. 2013; 8(11):1–11.

24. Rhee CK, Yoo KH, Lee JH, Park MJ, Kim WJ, Park YB, et al. Clinical characteristics of patients with tuberculosis-destroyed lung. 2013; 17(August 2012):67–75.

25. Gislason T, Gudnason V, Benediktsdottir B, Olafsson I, Aspelund T, Thjodleifsson B, et al. Persistent Chlamydia Pneumoniae serology is related to decline in lung function in women but not in men. Effect of persistent Chlamydia pneumoniae infection on lung function. BMC Pulm Med. 2010; 10.

26. George MP, Kannass M, Huang L, Sciurba FC, Morris A. Respiratory symptoms and airway obstruction in HIV-infected subjects in the HAART era. PLoS One. 2009; 4(7):1–7.

27. Nelsing S, Jensen B, Backer V. Persistent reduction in lung function after Pneumocystis carinii pneumonia in AIDS patients. Scand J Infect Dis [Internet]. 1995; 27(4):351–5. Available from: https://www.ncbi.nlm.nih.gov/pubmed/8658069

28. Morris AM, Huang L, Bacchetti P, Turner J, Hopewell PC, Wallace JM, et al. Permanent declines in pulmonary function following pneumonia in Human Immunodeficiency Virus-infected persons. Am J Respir Crit Care Med. 2000; 162:612–6. https://doi.org/10.1164/ajrccm.162.2.9912058 PMID: 10934095

29. Pai M, Denkinger CM, Kik S V., Rangaka MX, Zwerling A, Oxlade O, et al. Gamma interferon release assays for detection of Mycobacterium tuberculosis infection. Clin Microbiol Rev. 2014; 27(1):3–20. https://doi.org/10.1128/CMR.00034-13 PMID: 24396134

30. Moher D, Liberati A, Tetzlaff J, Altman DG, Altman D, Antes G, et al. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. PLoS Med. 2009; 6(7):e1000097. https://doi.org/10.1371/journal.pmed.1000097 PMID: 19621072

31. Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis (PRISMA) protocols 2015 checklist. Br Med J. 2015; 349(Jan02 1):g7647.

32. Halpern SH, Douglas MJ. Jadad scale for reporting randomized controlled trials. Evidence-based Obstet Anesth. 2005;237–8.

33. Wells G, Shea B, O'Connell D, Peterson J. Newcastle-Ottawa Quality Assessment Scale. In: Coding Manual for Cohort Studies [Internet]. p. 1–2. http://www.ohri.ca/programs/clinical_epidemiology/nosgen.pdf

34. National Institute of Health. Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies—NHLBI, NIH [Internet]. 2014. p. 1–4. https://www.nhlbi.nih.gov/health-pro/guidelines/in-develop/cardiovascular-risk-reduction/tools/cohort

35. Attia EF, Akgün KM, Wongtrakool C, Goetz MB, Rodriguez-Barradas MC, Rimland D, et al. Increased Risk of Radiographic Emphysema in HIV Is Associated With Elevated Soluble CD14 and Nadir CD4. Chest [Internet]. 2014; 146(6):1543–53. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4251616/pdf/chest_146_6_1543.pdf

36. Lambert AA, Kirk GD, Astemborski J, Neptune ER, Mehta SH, Wise RA, et al. A cross sectional analysis of the role of the antimicrobial peptide cathelicidin in lung function impairment within the ALIVE cohort. PLoS One. 2014; 9(4):e95099. https://doi.org/10.1371/journal.pone.0095099 PMID: 24743155

37. Triplette M, Attia EF, Akgün KM, Hoo GWS, Freiberg MS, Butt AA, et al. A low peripheral blood CD4/CD8 ratio is associated with pulmonary emphysema in HIV. PLoS One. 2017; 12(1):1–15.

38. Fitzpatrick ME, Nouraie M, Gingo MR, Camp D, Kessinger CJ, Sincebaugh JB, et al. Novel relationships of markers of monocyte activation and endothelial dysfunction with pulmonary dysfunction in HIV-infected persons. Aids. 2016; 30(9):1327–39. https://doi.org/10.1097/QAD.0000000000001092 PMID: 26990629

39. Fitzpatrick ME, Singh V, Bertolet M, Lucht L, Kessinger C, Michel J, et al. Relationships of pulmonary function, inflammation, and T-cell activation and senescence in an HIV-infected cohort. AIDS. 2014; 28(17):2505–15. https://doi.org/10.1097/QAD.0000000000000471 PMID: 25574956

40. North CM, Muyanja D, Kakuhikire B, Tsai AC, Tracy RP, Hunt PW, et al. Systemic inflammation, immune activation, and impaired lung function among people living with HIV in rural Uganda. J Acquir Immune Defic Syndr [Internet]. 2018; 78(5):543–8. Available from: http://dx.doi.org/10.1097/QAI.0000000000001711

41. Crothers K, Petrache I, Wongtrakool C, Lee PJ, Schnapp LM, Gharib SA. 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(8):1–10.

42. Golpe R, Martín-Robles I, Sanjuán-López P, Pérez-de-Llano L, González-Juanatey C, López-Campos JL, et al. Differences in systemic inflammation between cigarette and biomass smoke-induced COPD. Int J COPD. 2017; 12:2639–46.

43. Crothers K, Butt AA, Gibert CL, Rodriguez-Barradas MC, Crystal S, Justice AC. Increased COPD among HIV-positive compared to HIV-negative veterans. Chest. 2006; 130(5):1326–33. https://doi.org/10.1378/chest.130.5.1326 PMID: 17099007

44. O'Neal WK, Anderson W, Basta PV., Carretta EE, Doerschuk CM, Barr RG, et al. Comparison of serum, EDTA plasma and P100 plasma for luminex-based biomarker multiplex assays in patients with chronic obstructive pulmonary disease in the SPIROMICS study. J Transl Med. 2014; 12(1):1–9.

45. Vitenberga Z, Pilmane M. Inflammatory, anti-inflammatory and regulatory cytokines in relatively healthy lung tissue as an essential part of the local immune system. Biomed Pap. 2017; 161(2):164–73.

46. Esposito S, Droghetti R, Bosis S, Claut L, Marchisio P, Principi N. Cytokine secretion in children with acute Mycoplasma pneumoniae infection and wheeze. Pediatr Pulmonol. 2002; 34(2):122–7. https://doi.org/10.1002/ppul.10139 PMID: 12112778

47. Mukhopadhyay S, Hoidal JR, Mukherjee TK. Role of TNF α in pulmonary pathophysiology. Respir Res. 2006; 7(125):1–9.

48. Antunes G, Evans SA, Lordan JL, Frew AJ. Systemic cytokine levels in community-acquired pneumonia and their association with disease severity. Eur Respir J. 2002; 20(4):990–5. https://doi.org/10.1183/09031936.02.00295102 PMID: 12412694

49. Paats MS, Bergen IM, Hanselaar WEJJ, Van Zoelen ECG, Hoogsteden HC, Hendriks RW, et al. Local and systemic cytokine profiles in nonsevere and severe community-acquired pneumonia. Eur Respir J. 2013; 41(6):1378–85. https://doi.org/10.1183/09031936.00060112 PMID: 23258791

50. Liu R-M. Oxidative stress, plasminogen activator inhibitor 1, and lung fibrosis. Antioxidants Redox Signal. 2008; 10(2):303–19.

51. Zhang K, Gharaee-Kermani M, McGarry B, Remick D, Phan SH. TNF-a-Mediated Lung Cytokine Networking and Eosinophil Recruitment in Pulmonary Fibrosis. J Immunol. 1997; 158(2):954–9. PMID: 8993016

52. Duque GA, Descoteaux A. Macrophage cytokines: involvement in immunity and infectious diseases. Front Immunol. 2014; 5(October):1–12.

53. Marcos V, Latzin P, Hector A, Sonanini S, Hoffmann F, Lacher M, et al. Expression, regulation and clinical significance of soluble and membrane CD14 receptors in pediatric inflammatory lung diseases. Respir Res. 2010; 11:1–13. https://doi.org/10.1186/1465-9921-11-1 PMID: 20047687

54. Quon BS, Ngan DA, Wilcox PG, Paul Man SF, Sin DD. Plasma sCD14 as a biomarker to predict pulmonary exacerbations in cystic fibrosis. PLoS One. 2014; 9(2):e89341. https://doi.org/10.1371/journal.pone.0089341 PMID: 24586701

55. Anas A, Poll T Van Der, Vos AF De. Role of CD14 in lung inflammation and infection. Crit Care. 2010; 14(209):1–8.

56. Dessing MC, Knapp S, Florquin S, De Vos AF, Van Der Poll T. CD14 facilitates invasive respiratory tract infection by Streptococcus pneumoniae. Am J Respir Crit Care Med. 2007; 175(6):604–11. https://doi.org/10.1164/rccm.200606-824OC PMID: 17185649

57. Sandler NG, Wand H, Roque A, Law M, Nason MC, Nixon DE, et al. Plasma levels of soluble CD14 independently predict mortality in HIV infection. J Infect Dis. 2011; 203(6):780–90. https://doi.org/10.1093/infdis/jiq118 PMID: 21252259

58. Castley A, Williams L, James I, Guelfi G, Berry C, Nolan D. Plasma CXCL10, sCD163 and sCD14 levels have distinct associations with antiretroviral treatment and cardiovascular disease risk factors. PLoS One. 2016; 11(6):1–14.

59. CASTILLO-MANCILLA JR, MORROW M, BOUM Y, BYAKWAGA H, HABERER JE, MARTIN JN, et al. Higher ART adherence is associated with lower systemic inflammation in treatment-naïve Ugandans who achieve virologic suppression. JAIDS J Acquir Immune Defic Syndr. 2018; 1.

60. Møller HJ, Moestrup SK, Weis N, Wejse C, Nielsen H, Pedersen SS, et al. Macrophage serum markers in pneumococcal bacteremia: Prediction of survival by soluble CD163. Crit Care Med. 2006; 34 (10):2561–6. https://doi.org/10.1097/01.CCM.0000239120.32490.AB PMID: 16915112

61. Polcyn-Adamczak M, Niemir ZI. Cathelicidin–Its Structure, Function and the Role in Autoimmune Diseases. Adv Cell Biol. 2014; 4(2):83–96.

62. Seiler F, Bals R, Beisswenger C. Function of Antimicrobial Peptides in Lung Innate Immunity. In: Harder J, Schröder J-M, editors. Antimicrobial Peptides: Role in Human Health and Disease [Internet]. Springer International Publishing Switzerland; 2016. p. 33–52. http://link.springer.com/10.1007/978-3-319-24199-9

63. Rivas-Santiago B, Hernandez-Pando R, Carranza C, Juarez E, Contreras JL, Aguilar-Leon D, et al. Expression of cathelicidin LL-37 during Mycobacterium tuberculosis infection in human alveolar macrophages, monocytes, neutrophils, and epithelial cells. Infect Immun. 2008; 76(3):935–41. https://doi.org/10.1128/IAI.01218-07 PMID: 18160480

64. Bals R, Wang X, Zasloff M, Wilson JM. The peptide antibiotic LL-37/hCAP-18 is expressed in epithelia of the human lung where it has broad antimicrobial activity at the airway surface. Proc Natl Acad Sci. 1998; 95(16):9541–6. https://doi.org/10.1073/pnas.95.16.9541 PMID: 9689116

65. Nijnik A, Pistolic J, Filewod NCJ, Hancock REW. Signaling pathways mediating chemokine induction in keratinocytes by cathelicidin LL-37 and flagellin. J Innate Immun. 2012; 4(4):377–86. https://doi.org/10.1159/000335901 PMID: 22516952

66. Hoheisel G, Zheng L, Teschler H, Striz I, Costabel U. Increased soluble CD14 levels in BAL fluid in pulmonary tuberculosis. Chest. 1995; 108(6):1614–6. https://doi.org/10.1378/chest.108.6.1614 PMID: 7497770

67. Gingo MR, Morris A. Pathogenesis of HIV and the lung. Curr HIV/AIDS Rep. 2013; 10(1):42–50. https://doi.org/10.1007/s11904-012-0140-x PMID: 23079728

68. Fitzpatrick M, Singh V, Bertolet M, Lucht L, Kessinger C, Michel J, et al. Relationships of pulmonary function, inflammation, and T-cell activation and senescence in an HIV-infected cohort. AIDS. 2014; 28 (17):2505–15. https://doi.org/10.1097/QAD.0000000000000471 PMID: 25574956

69. Fitzpatrick ME, Nouraie M, Gingo MR, Camp D, Kessinger CJ, Sincebaugh JB, et al. Novel relationships of markers of monocyte activation and endothelial dysfunction with pulmonary dysfunction in HIV-infected persons. AIDS. 2016; 30(9):1327–39. https://doi.org/10.1097/QAD.0000000000001092 PMID: 26990629

70. Li Y, Nouraie SM, Kessinger C, Weinman R, Huang L, Greenblatt RM, et al. Factors Associated With Progression of Lung Function Abnormalities in HIV- Infected Individuals. J Acquir Immune Defic Syndr. 2018; 79(4):501–9. https://doi.org/10.1097/QAI.0000000000001840 PMID: 30142142

71. Gupte AN, Wong ML, Msandiwa R, Barnes GL, Golub J, Chaisson RE, et al. Factors associated with pulmonary impairment in HIV-infected South African adults. PLoS One [Internet]. 2017; 12(9):1–15. Available from: http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L618265558

72. Kunisaki KM, Niewoehner DE, Collins G, Aagaard B, Atako NB, Bakowska E, et al. Pulmonary eff ects 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. 2016; 4(December):980–9.

73. Chand HS, Vazquez-Guillamet R, Royer C, Rudolph K, Mishra N, Singh SP, et al. Cigarette smoke and HIV synergistically affect lung pathology in cynomolgus macaques. J Clin Invest. 2018; 128(12):5428–33. https://doi.org/10.1172/JCI121935 PMID: 30277472

74. Calbo E, Alsina M, Rodríguez-Carballeira M, Lite J, Garau J. The impact of time on the systemic inflammatory response in pneumococcal pneumonia. Eur Respir J. 2010; 35(3):614–8. https://doi.org/10.1183/09031936.00052709 PMID: 19608588

75. Fernández-Serrano S, Dorca J, Coromines M, Carratalà J, Gudiol F, Manresa F. Molecular inflammatory responses measured in blood of patients with severe community-acquired pneumonia. Clin Diagn Lab Immunol. 2003; 10(5):813–20. https://doi.org/10.1128/CDLI.10.5.813-820.2003 PMID: 12965910

76. Calbo E, Alsina M, Rodríguez-Carballeira M, Lite J, Garau J. Systemic expression of cytokine production in patients with severe pneumococcal pneumonia: Effects of treatment with a β-lactam versus a fluoroquinolone. Antimicrob Agents Chemother. 2008; 52(7):2395–402. https://doi.org/10.1128/AAC.00658-07 PMID: 18426893