Lung disease in HIV: Causes and consequences

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Pulmonary co-morbidities in HIV?

Younas M et al, HIV Med, 2015

- HIV residual production
- HIV ongoing infection
- Co-infections
- Microbial translocation
- Lymphopaenia
- Treg/Th17
- Genetics
- Senescence

Immune activation

- Senescence
- Cell death
- Anergy

Immune deficiency

non AIDS-linked morbidities: metabolic syndrome, neurocognitive disorders, atherothrombosis, liver steatosis, cancer, osteoporosis, kidney failure, frailty
Outline

• Scope of the problem
  – Pre-ART
  – Post-ART

• Phenotypes of COPD
  – Epidemiology
  – Contribution of HIV
  – Biomarkers

• Potential role of the microbiome

• Approach to therapy
Lung disease leading cause of mortality in early HIV epidemic

*Infections:*
*Pneumocystis* pneumonia
Tuberculosis
Bacterial pneumonia

*Neoplasms:*
Kaposi sarcoma
Lymphoma
COPD and HIV Pre-ART: Increased prevalence even in those without AIDS, primarily emphysema

Pulmonary Complications of HIV Study (PCHIS)

- >1,300 HIV+ and HIV- men
- HIV+ individuals:
  - More common respiratory symptoms
  - Abnormal diffusing capacity (DLco)
  - Progressive COPD-like changes after pneumonia (PCP & bacterial)
  - HIV independent risk

What do we know about COPD in the ART era?
COPD is more common in HIV+ Veterans

COPD prevalence

- Based on self report or chart review

COPD incidence per 1,000 person-yrs

Crothers et al. Chest, 2006
Crothers et al. AJRCCM, 2011
Multicenter AIDS Cohort Study (MACS)

Women’s Interagency HIV Study (WIHS)

Pittsburgh Clinical Trials Unit

University of Washington
Respiratory symptoms and inhaler use common in HIV+ outpatients

Only 15% had prior PFTs

Gingo, M et al. AJRCCM, 2010
Pulmonary function abnormalities are common
Increased risk of pneumonia in HIV+ COPD

CAP, TB, and PCP in all ART eras

Attia EF et al, JAIDS, 2015
Pulmonary function independently predicts walk distance in HIV

<table>
<thead>
<tr>
<th>Variable</th>
<th>Beta (95%CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caucasian</td>
<td>28.7 (12.1-45.4)</td>
<td>0.001</td>
</tr>
<tr>
<td>Weight kg</td>
<td>-0.9 (-1.4- -0.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Height cm</td>
<td>1.4 (0.4- 2.3)</td>
<td>0.004</td>
</tr>
<tr>
<td>Pack-years</td>
<td>-0.9 (-1.4- -0.4)</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>FEV% post-BD</strong></td>
<td><strong>0.6 (0.01- 1.1)</strong></td>
<td><strong>0.047</strong></td>
</tr>
<tr>
<td><strong>DLco %</strong></td>
<td><strong>0.7 (0.2-1.3)</strong></td>
<td><strong>0.006</strong></td>
</tr>
<tr>
<td><strong>SGRQ</strong></td>
<td><strong>-0.8 (-1.3- -0.3)</strong></td>
<td><strong>0.001</strong></td>
</tr>
<tr>
<td>IL-6 (square root)</td>
<td>-22.9 (-42.9- -2.9)</td>
<td>0.025</td>
</tr>
<tr>
<td>IL-2 (square root)</td>
<td>14.8 (3.9- 25.6)</td>
<td>0.008</td>
</tr>
<tr>
<td>Constant</td>
<td>207.3 (40.6-374.1)</td>
<td>0.012</td>
</tr>
</tbody>
</table>

Robertson T et al, JAIDS, in review
Survival worse in HIV+ COPD

Gingo MR et al, Ann Am Thor Soc, 2018
Sub-Phenotypes of COPD

Adapted from F. Sciurba
HIV phenotypes

- Emphysema
- DLco impairment
- Fixed airway obstruction/COPD
- Asthma
- Pulmonary hypertension
- Cardio-pulmonary
Why are phenotypes important?

• Functional consequences
• Different pathways and biomarkers
• Different response to treatment
Airway obstruction

• Several definitions
• FEV1/FVC<70%, FEV1< 80% predicted
• Below LLN
• Primarily in smokers
Airway obstruction risk factors

- Age
- Pack-year smoking
- Intravenous drug use
- ART
- History of bacterial pneumonia or use of PCP prophylaxis

George MP et al, PLoS One, 2009; Gingo et al. AJRCCM 2010
Lung HIV predictors of airway obstruction

- Age: OR 1.75 (p<0.001)
- Current smoking: OR 1.77 (p=0.004)
- >20 pack-years: OR 1.68 (p=0.003)
- History of asthma: OR 1.81 (p=0.005)
- History of *Pneumocystis*: OR 1.97 (p=0.005)

Drummond MB, et al. JAIDS, 2015
Airway obstruction increases by lower CD4 in MACS/VACS

Crothers K et al, JAIDS, 2013
Diffusing capacity

• Measures multiple aspects of lung and cardiac function
• Noted to be low in HIV in pre-ART era
• Important phenotype in HIV
• *Persist in ART era*
DLco is abnormal in majority of HIV+ individuals

-85% of cohort have DLco<80% predicted
-35% are below 60% predicted
-24% of never smokers are below 60% predicted
Different risk factors for DLco in smokers and never smokers

Multivariable regression models showing independent associations for \( DL_{CO} \% \) predicted in ever smokers and never smokers.

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Ever Smokers*</th>
<th>Never Smokers</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( \beta )-coefficient</td>
<td>p-value</td>
</tr>
<tr>
<td>Post-FEV(_1) % predicted</td>
<td>0.3940</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Post-BD FVC % predicted</td>
<td>-0.0423</td>
<td>0.001</td>
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<tr>
<td>Log Fraction &lt;950 HU</td>
<td></td>
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<tr>
<td>Sputum % Neutrophils</td>
<td></td>
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<tr>
<td>Sputum % Lymphocyte (square root)</td>
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</tbody>
</table>

Clinical risk factors and DLco

- Smoking
- CD4 cell count < 200
- HIV viral load > 500 copies
- Hepatitis C co-infection

Crothers K et al, JAIDS, 2013; Fitzpatrick M, Gingo M et al, JAIDS, 2013
Does HIV contribute to these phenotypes?

Presti RM et al. Chest 2017
HIV associated with lower pre-BD FEV1 although no difference in COPD

HIV independent predictor of lower FEV1 and FVC in ALIVE cohort

Drummond MB et al, AIDS, 2013; Ronit A et al, Thorax, 2018
No difference in obstruction by HIV status if preserved CD4 count
HIV is independent predictor of DLco in MACS/VACS

Effect seen in smokers and non-smokers, high and low CD4 although worse in risk groups

Crothers K et al, JAIDS, 2013
DLco lower in HIV+ women and more have moderately reduced DLco (<60%)
Progression of pulmonary deficits in HIV

• 285 HIV+ individuals
• Median follow-up 6.3 years
• FEV1 declined 1%/62 ml per year
  – Older age, GOLD stage predicted decline
  – Female sex protective
• Rapid FEV1 decline
  – Age, marijuana
  – Female sex protective
• No decline in DLco
  – Smoking, history of pneumonia predicted decline
• No relationship to HIV-associated variables

Li Y et al, JAIDS, in press
HIV not an independent predictor of decline except in those with viral load >75,000

Drummond MB et al, AIDS 2013
Slow progression in HIV in START study

- 1,026 participants
- No impact of early or delayed ART on lung function
- FEV1 -24 to -29 ml per year
- Smokers had faster average FEV1 decline
  - -38.3 mL/yr vs -25.1 mL/yr
  - More likely to be rapid decliners

Kunisaki K et al, Lancet Resp Med, 2017; McDonald DM et al, JAIDS, 2018
## Biomarkers suggest potential pathways

<table>
<thead>
<tr>
<th>Lung measure</th>
<th>Circulating soluble and HIV-related markers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased airflow (low FEV1)</td>
<td>• Inflammation (IL-6, CRP)</td>
</tr>
<tr>
<td></td>
<td>• Monocyte activation (sCD163)</td>
</tr>
<tr>
<td></td>
<td>• Endothelial dysfunction (endothelin-1)</td>
</tr>
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<td></td>
<td>• Shortened PBMC telomere length</td>
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<td>Airflow obstruction (decreased FEV1/FVC)</td>
<td>• Monocyte activation (sCD163)</td>
</tr>
<tr>
<td>Impaired gas exchange (low DLCO)</td>
<td>• Inflammation (IL-6, TNFα, CRP)</td>
</tr>
<tr>
<td></td>
<td>• Monocyte activation (sCD163, sCD14, IL-2 receptor)</td>
</tr>
<tr>
<td></td>
<td>• Microbial translocation (LPS)</td>
</tr>
<tr>
<td></td>
<td>• Endothelial activation (endothelin-1)</td>
</tr>
<tr>
<td>Emphysema (by CT scan)</td>
<td>• Monocyte activation (sCD14)</td>
</tr>
<tr>
<td></td>
<td>• Shortened PBMC telomere length</td>
</tr>
</tbody>
</table>

Cribbs S et al, Phys Rev, in press
Lung microbiome has local and systemic effects

COPD, asthma, cystic fibrosis, pulmonary fibrosis
Lung HIV Microbiome Project

- 6 clinical sites and data coordinating center
- Focus on normal lung (non-smokers and smokers) and HIV
- Bronchoscopy with 16S rRNA analyses
No significant difference by HIV status in lung bacterial communities

Beck J et al, AJRCCM, 2015
Why do we not see differences?

- Wrong populations
- Difficulty with detecting bacteria in BAL
- Longitudinal studies may be needed
- Taxonomy less important: metabolites or gene function
- Other sites may influence lung function
- Need to look at all organisms
What about fungus (mycobiome)?
Mycobiome likely shapes the immune response

-Lung could be affected by local mycobiome, GI tract mycobiome, or translocation of fungus

Cui L, et al. Genome Medicine, 2013
Lung HIV Mycobiome Study

• 56 HIV+ and HIV- individuals from Lung HIV Microbiome Program
• Oral wash (OW), induced sputum (IS) and bronchoalveolar lavage (BAL), environmental controls
• Analyzed by sample type, HIV status, and lung function

Courtesy of L. Cui
HIV+ and HIV- differ in communities: Primarily *Pneumocystis*
Fungal microbiome in HIV COPD: Primarily *Pneumocystis*
Host response to *Pneumocystis jirovecii* colonization: Th1 inflammatory gene expression, increases in MMP-12, and IL-6

Fitzpatrick M et al, Microbiology and Immunology, 2014; Morris et al., J Clin Micro, 2010
Airway obstruction increases in Pc-colonized monkeys, but not in SHIV infection alone

Peak expiratory flow

FEV 0.4

Shipley et al, *JID*, 2010
No therapies tested in HIV

- *Pneumocystis* treatment
- Anti-inflammatories
- Endothelin antagonists
TMP-SMX did not influence lung function in NHP model

(A) PEF (Pc-colonized/TMP-SMX+)

(B) PEF (Pc-colonized/TMP-SMX−)

(C) FEV0.4 (Pc-colonized/TMP-SMX+)

(D) FEV0.4 (Pc-colonized/TMP-SMX−)
Why not?

- Microbial community may be important
- Damage already done
- Perpetuation of inflammation

Tipton L et al, 2017
Statins in HIV COPD: Rationale

• Reductions in circulating inflammatory markers (IL-6, CRP, and MMPs) pertinent to HIV COPD
• General population COPD statin RCT disappointing, but trend to improvement in decline in lung function (FEV$_1$ % predicted) over time
• COPD in chronic HIV, with enhanced immune activation, may be more likely to derive benefit

Kinlay et al Circ 2003 (108); Balk et al Ann Int Med 2003 (189); Bellosta et al Arterioscler Thromb Vasc Biol 1998 (18); Criner et al; NEJM 2014 (370)
Trend for effect on rate of decline in HIV+ statin users

McLaughlin M et al, ATS, 2015
Statin initiation slowed decline in $FEV_1$

- Pre-statin rate of decline -1.2% /100 days (p=0.002)
- Post-statin rate of decline -0.2% (p=0.3)
- p=0.002 for comparison

McLaughlin M et al, ATS, 2015
Statins for Pulmonary Complications of Chronic HIV (SPARC Trial)

- HIV+ participants from 2 sites (Pitt, UCSF)
- Inclusion: FEV$_1$/FVC<0.7 or DL$_{CO}$ < 0.8
- Exclusion: Pre-existing indication for statin, contraindication to study drug, plans to change ART or smoking status
- Adaptive randomization to placebo vs. rosuvastatin, double-blinded
- PFTs and biomarkers collected at 0, 12, and 24 weeks
- Comparisons performed using paired t-tests and Wilcoxon rank-sum
FEV$_1$ % predicted declined significantly in placebo group, stable in those receiving rosuvastatin

- Median decline in absolute FEV$_1$ 70 mL over 6 months

Morris A et al, AIDS, 2017
DLco % predicted unchanged in placebo, but increased in those receiving rosuvastatin

Change in DLCO %

Morris A et al, AIDS, 2017
**Decreases in IL-6 and endothelin-1 in rosuvastatin group**

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n = 11)</th>
<th>Rosuvastatin (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median</td>
<td>(Q1, Q3)</td>
</tr>
<tr>
<td>hs-CRP</td>
<td>-0.02</td>
<td>(-0.14, 0.08)</td>
</tr>
<tr>
<td>IL-6</td>
<td>-0.01</td>
<td>(-0.12, 0.08)</td>
</tr>
<tr>
<td>ET-1</td>
<td>-0.16</td>
<td>(-0.44, 0.10)</td>
</tr>
</tbody>
</table>

*Signed Rank Test to determine if the median differs from zero
**Wilcoxon test to determine if the change in the placebo group equals the change in the statin group*
Statins for lung disease?

• Need bigger trial, absolute difference not significant between groups

• Indications?
  – FEV\textsubscript{1} decline prevented even in those without airway obstruction
  – Non-smokers
  – DLco abnormalities
Summary

• COPD is a common problem in HIV
• Associated with morbidity and mortality
• Different phenotypes of lung disease
• Potential role of the microbiome
• Optimal therapy undefined
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