HIV and the lung

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Board Member of ViiV PAGW
Outline

• Epidemiology of chronic lung disease (CLD)

• Spectrum of chronic lung disease (CLD)

• Future research direction

Not talking about

• Acute respiratory disease/ Infections
Lung disease the ART era

- Substantial mortality declines with ART → increased life-expectancy

- Drop in absolute incidence of respiratory tract infections: TB, PCP and pneumonia

- Increase in incidence of non-opportunistic lung disease in HIV-infected as a result of increased life-expectancy:
  - $3 \times$ increase in mortality from obstructive airways disease from pre-ART era

--- increase greater than in the background population
--- does ART use reduce the burden of HIV-associated lung disease?

Pallela et al NEJM 1998; Grubb et al AIDS 2006
Louie et al J Infect Dis 2002; Crothers AJRCCM 2011
HIV Infection and Risk for Incident Pulmonary Diseases in the Combination Antiretroviral Therapy Era

Kristina Crothers1,2, Laurence Huang3, Joseph L. Goulet2, Matthew Bidwell Goetz4, Sheldon T. Brown5, Maria C. Rodriguez-Barradas6, Krisann K. Oursler7, David Rimland8, Cynthia L. Gibert9, Adeel A. Butt10, and Amy C. Justice2,11

A

![Graph A](image1)

B

![Graph B](image2)

Crothers AJRCCM 2011
Confounders

- Age
- Survival effect
- Smoking status (past and present)
- Recreational drug use
- Exposure to biomass fuels
- Frequency and spectrum of infections: TB, PCP, bacterial pneumonia
No of people living with AIDS, USA: 2001 vs 2008

Centers for Disease Control HIV Surveillance Report 2011
Adapted from Dubrow et al Curr Opin Oncol 2012
Chronic obstructive pulmonary disease (COPD)

- 3\textsuperscript{rd} leading cause of death; 5\textsuperscript{th} leading cause of lost DALYS
- “Expiratory airflow limitation PLUS chronic airway inflammation”
- FEV1 declines with age, smoking, infections
- HIV independently increases the risk of COPD
  - High viral load associated with faster decline rate
- ART and COPD risk:
  - 2 studies suggest no effect or an increased risk with ART\textsuperscript{1,2,3}
  - Small studies, observational, selection bias, rely on reported symptoms

Drummond Thorax 2012
\textsuperscript{1}Crothers AJRCCM 2011; \textsuperscript{2}George PloS One 2009 \textsuperscript{3}Gingo 2010 AJRCCM
HIV

Substance use

Smoking

HIV persistence & immune dysregulation

Resp infection/colonisation (TB, PJP)

Oxidative stress

Chronic inflammation

Chronic lung disease

HOST FACTORS

Chronic lung disease

Host Factors

AGING

Chronic inflammation

HIV persistence & immune dysregulation

Resp infection/colonisation (TB, PJP)

Oxidative stress

Chronic lung disease

Crothers AJRCCM 2011; Van Zyl Smit Eur Resp Journal 2010
Pathogenic mechanisms

- Colonisation with Pneumocystis jirovecii: induce MMP activity and lung tissue destruction
- Altered microbiome
- Abn accumulation of CD8 cells – interact with macrophages to release chemokines, cytokines, Growth factor
- Systemic inflammation
- Oxidative stress—low levels of glutathione
- Immunesenescence

→ correlation with clinical findings and spirometry

Twigg Clin Chest Med 2013; Morris AJRCCM 2000; Almovodar Viral Immunology 2014
Therapeutic considerations

• Ritonavir and inhaled corticosteroid interaction $\rightarrow$ hypercortisolism
  – FLUTICASONE $>$ BUDESONIDE $>$ (BECLOMETHASONE)
  – Systemic steroids: levels of PI may be reduced
  – Increased risk of infection

$\rightarrow$ Long-acting muscarinic antagonists as first-line inhaled therapy

• PAF risk of death assoc with smoking double in HIV+ : special effort on smoking cessation

• Pulmonary rehabilitation increased importance:
  – synergistic effect of COPD and HIV on physical disability

?role and optimal type of exercise training

Nici et al Am J Resp Crit Care Med 2006
# Lung Cancer & HIV

- Most common non-AIDS defining cancer (NADC): leading source of NADC mortality
- In **most** cohorts: incidence higher in people with HIV compared to HIV-uninfected, **AFTER adjusting for smoking and age**

<table>
<thead>
<tr>
<th>Study</th>
<th>Cohort Details</th>
<th>Incidence Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sigel AIDS 2012</td>
<td>VACS cohort 37294 HIV+; 75,750 HIV-</td>
<td>IRR: 1.7 (1.5- 1.9)</td>
</tr>
<tr>
<td>Shiels JAIDS 2010</td>
<td>ALIVE cohort: IVDU 1072 HIV+ ; 1423 HIV-</td>
<td>HR: 2.3 (1.1-5.1)</td>
</tr>
<tr>
<td>Engels J Clin Onc 2006</td>
<td>JHH cohort 5238 HIV+ (cf gen pop)</td>
<td>SIR: 2.5 (1.6-3.5)</td>
</tr>
<tr>
<td>Gingo PloS One 2013</td>
<td>MACS cohorts 1706 HIV+; 1774 HIV-</td>
<td>HR: 2.65 (0.29-24.4)</td>
</tr>
</tbody>
</table>
No association with stage and morphology

Overall prognosis: 10% at 24 months

Hypothesised mechanisms:
- Decreased immune surveillance or impaired immune function
- Enhanced susceptibility to carcinogens
- Lung injury (2Y infections)
  - ? Screening and early detection in HIV-infected smokers

### Smoking strata

<table>
<thead>
<tr>
<th>Smoking strata</th>
<th>HIV+ Lung cancer</th>
<th>HIV-ve Lung cancer</th>
<th>IRR</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never smoker</td>
<td>19</td>
<td>30</td>
<td>1.6 (0.9-3.0)</td>
<td>0.08</td>
</tr>
<tr>
<td>Former smoker</td>
<td>55</td>
<td>91</td>
<td>1.7 (1.2-2.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Current smoker</td>
<td>262</td>
<td>370</td>
<td>1.5 (1.3-1.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Missing data</td>
<td>121</td>
<td>114</td>
<td>2.1 (1.6-2.7)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Adjusted for age, sex, race, COPD, prev pneumonia

Sigel et al AIDS 2012
## Lung disease: children

<table>
<thead>
<tr>
<th></th>
<th>HIV-ve (n=150)</th>
<th>ART naive (n=379)</th>
<th>ART-experienced (n=201)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (IQR) Age (y)</td>
<td>11 (9-13)</td>
<td>11 (8-13)</td>
<td>11 (9-13)</td>
</tr>
<tr>
<td>Age at diagnosis (y)</td>
<td></td>
<td>11.2 (8-13)</td>
<td>5.2 (IQR 2.9-8.2)</td>
</tr>
<tr>
<td>Time on ART (y)</td>
<td></td>
<td>0</td>
<td>5.6 (4.1-7.2)</td>
</tr>
<tr>
<td>CD4 count (cells/µl)</td>
<td>375 (215-599)</td>
<td>710 (458-904)</td>
<td></td>
</tr>
<tr>
<td>MRC Dyspnoea score &gt;1</td>
<td>0 (0%)</td>
<td>46 (16%)</td>
<td>30 (15%)</td>
</tr>
<tr>
<td>Desaturation exercise</td>
<td>5 (6%)</td>
<td>24 (10%)</td>
<td>22 (11%)</td>
</tr>
<tr>
<td>FEv1 z-score &lt;-1.64</td>
<td>1 (0.8%)</td>
<td>23 (10%)</td>
<td>7 (4%)</td>
</tr>
<tr>
<td>FVC z-score &lt;-1.64</td>
<td>14 (11%)</td>
<td>43 (18%)</td>
<td>36 (20%)</td>
</tr>
<tr>
<td>Stunted (HFA z-score &lt;-2)</td>
<td>12 (8%)</td>
<td>91 (23%)</td>
<td>36% (35)</td>
</tr>
</tbody>
</table>
Chronic Lung disease: children

**Young children**
Lymphoid Intestinal Pneumonitis
Diagnosed easily
Responds to corticosteroids / ART

**Older children**
Airways disease
Mostly un- or mis-diagnosed
Poor response to steroids/ ART

_Ferrand et al Clin Infect Dis 2012_
Predicted \( \text{FEV}_1 / \text{FVC} \) ratio and \( \text{FEV}_1 \) mean values for males at ages 11, 16 and 22 years by length-adjusted infant \( V' \text{max} \) FRC quartile groups using random effects models. Predicted values were standardized to the mean height and weight for males at 11, 16 and 22 years.

*Stern et al Lancet 2007*
Tracking of lung function 6 weeks to 1 year: matched unsedated 6 week and 1 year tests; n=279

A. Respiratory rate/min

B. Tidal volume

C. Functional residual capacity

D. Ratio of peak tidal expiratory flow over total expiratory time

Slide: Lauren Willemse
Lung function at 1 yr: effect of maternal HIV infection

Infants of HIV infected mothers had increased minute ventilation compared to unexposed infants: 2.8 L.min⁻¹ vs. 2.6 L.min⁻¹; p<0.001, 95% CI 2.6 to 2.7): **ALL INFANTS HIV-NEGATIVE**

*Slide: Lauren Willemse*
Global variation in epidemiology

• Coverage of HIV treatment and prevention

• Early life events
  – Nutritional deprivation
  – Smoke exposure
  – IUGR and pre-term delivery

• Environmental factors
  – Inorganic and organic dusts, metals etc
  – Household air pollution

• Health systems and the wider context
  – Public health approach to treatment
  – Capacity to diagnose and treat chronic conditions
  – Urban development
  – Tobacco control frameworks, political/economic stability

Rylance et al Semin Resp Crit Care Med 2016
Summary

• Transition from acute to chronic lung disease- adults and children

• HIV a independent risk factor for chronic lung disease-COPD /cancer

• Screening and management strategies need incorporating into management of an increasing cohort of ageing HIV-infected patients

• Future Research:
  – Epidemiological data: impact of ART
  – Pathogenesis of lung disease: respiratory microbiome/immunology
  – Optimal screening and management strategies
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