HIV and Lung Cancer

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I receive financial support from the following company or companies related to the products listed below. These relationships may lead to bias in my presentation.

<table>
<thead>
<tr>
<th>Entity</th>
<th>Type(s) of relationship(s)</th>
<th>Product name(s)</th>
<th>Relevant disease(s) or condition(s)</th>
</tr>
</thead>
</table>

“I have ZERO conflicts of interest to disclose”
Lung cancer and HIV

- Unique issues related to:
  - Risk
  - Outcomes
  - Screening
  - Treatment
CASE 2016

• 67yo man with well-controlled HIV
• PMHx: COPD, HCV, OA
• Smoker, recently quit
• 25 pack-years
• Referred for lung cancer screening in 2015
• No non-calcified nodules

Initial lung cancer screen
CASE

- Hospitalized 2016 with Legionella pneumonia

- Repeat CT Spring 2017 – 1.8 cm RUL nodule

- Biopsy: carcinoma NOS
• Referred for surgery
• VATS resection: T1N1 staging (one node+)
  – Pleiomorphic carcinoma, lean towards squamous
  – EGFR, KRAS negative; PD-L1: 1%
• 4 cycles cisplatin/taxotere
  – Rapid recurrence
  – Immunotherapy planned
  – Died unexpectedly at home
Lung cancer now the leading cause of cancer death in PWH

Proportion of total deaths in NA-ACCORD 1995-2009

Lung cancer 2-4X increased with HIV

Shiels et al. JAIDS. 2009.
Lung Cancer in HIV

- Lung cancer is the leading cause of cancer death in PWH
- PWH are at higher risk of lung cancer than similar uninfected persons
- Important/interesting questions:
  - Why is there more lung cancer in the setting of HIV?
  - How does HIV affect lung cancer outcomes?
  - Is lung cancer screening appropriate in PWH?
  - Should lung cancer treatment be modified for PWH?
Lung cancer incidence is higher in PWH vs. uninfected

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Cohort</th>
<th>#Cases</th>
<th>IRR/HR</th>
<th>95% CI</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>HIV +</td>
<td>HIV -</td>
<td>in HIV+</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Engels  | 2006 | 5238   | NA     | 33     | 2.5    | 1.6-3.5     | • Historical controls  
• Estimated smoking rate |
| Kirk    | 2007 | 480    | 1606   | 27     | 3.6    | 1.6-7.9     | • Cases by death  
• Single center |
| Shiels  | 2010 | 1072   | 1423   | 29     | 2.3    | 1.1-5.1     | • Single center |
| Sigel   | 2012 | 37,294 | 75,750 | 457    | 1.7    | 1.5-1.9     | • Smoking status, no pack-years |

Why is lung cancer risk increased in PWH?

Standard risk factors
- Smoking
- Age

Systemic / Lung
- Immune dysfunction
- Inflammation

Pulmonary injury
- Infections
- COPD/emphysema

Risks enhanced by HIV

Lung cancer
Smoking is more prevalent in PWH

4,217 HIV+ patients in MMP
27,731 US adults NHIS 2009

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- Age

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Pulmonary injury
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Risks enhanced by HIV
Increased risk of lung cancer associated with immunosuppression: HIV and transplant

Relationship between lung cancer risk and decreasing CD4 cell count has been inconsistent.

French Hospital Database on HIV Cohort

Higher CD4 = lower lung cancer risk
Low CD4/CD8 Ratio

- CD4/CD8 ratio low in early / untreated HIV, with ART improves to ~1.0 in many but not all, for unclear reasons
- Marker of abnormal immune activation, pro-inflammatory
- Prolonged low CD4/CD8 ratio associated with increased all-cause mortality, increased risk of NADCs
- Never studied specifically with lung cancer
- We used data from 21,666 VACS PWH to evaluate
## Results

<table>
<thead>
<tr>
<th>Exposure Variable</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CD4, Longitudinal Moving Average</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;100</td>
<td>1.1</td>
<td>0.6-2.3</td>
</tr>
<tr>
<td>100-200</td>
<td>2.1</td>
<td>1.4-3.1</td>
</tr>
<tr>
<td>200-500</td>
<td>1.2</td>
<td>1.2-2.1</td>
</tr>
<tr>
<td>&gt;500</td>
<td>REF</td>
<td>REF</td>
</tr>
<tr>
<td><strong>CD4/CD8, Longitudinal Moving Average</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;0.4</td>
<td>3.5</td>
<td>2.0-6.1</td>
</tr>
<tr>
<td>0.4-1.0</td>
<td>2.8</td>
<td>1.6-4.9</td>
</tr>
<tr>
<td>&gt;1.0</td>
<td>REF</td>
<td>REF</td>
</tr>
</tbody>
</table>

*Sigel, Park et al. Lancet HIV 2017*
Why is lung cancer risk increased in PWH?

Standard risk factors
- Smoking
- Age

Systemic / Lung
- Immune dysfunction
- Inflammation

Pulmonary injury
- Infections
- COPD/emphysema

Risks enhanced by HIV
### Pneumonia and Lung Cancer in PWH

<table>
<thead>
<tr>
<th>Exposure Variable</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥2 episodes</td>
<td>1.8</td>
<td>1.0-2.5</td>
</tr>
<tr>
<td>1 episode</td>
<td>1.7</td>
<td>1.2-2.4</td>
</tr>
<tr>
<td>0 episodes</td>
<td>REF</td>
<td>REF</td>
</tr>
</tbody>
</table>

** models adjusted for age, race/ethnicity, smoking, COPD, HCV, alcohol use, drug use

Sigel, Park et al. Lancet HIV 2017
Lung Cancer Risk

• Persistently low CD4, low CD4/CD8 and recurrent severe lung infections may be HIV-specific lung cancer risk factors
Lung Cancer Outcomes

• What’s going on with lung cancer outcomes in HIV+ in the “late” ART era?
• Does mild immunosuppression or dysregulation affect lung cancer natural history and/or treatment responsiveness?
Assessing Cancer Outcomes

• Lung cancer outcomes have generally been worse in PWH

• Comparing cancer outcomes in PWH versus uninfected persons complicated:
  1. Treatment disparities
  2. Competing risks
  3. Treatment intolerance / increased treatment complications?

• First: are there differences in cancer characteristics?
Similar clinical stage and tumor type

≈60% adenocarcinoma or squamous cell without difference in morphology by HIV
Worse overall survival in PWH w NSCLC despite stage appropriate treatment (Medicare 1998-2010)

Uninfected

HIV+

Sigel, Dubrow et al. British Journal of Cancer. 2013
## Is It Lung Cancer Treatment?

<table>
<thead>
<tr>
<th>Study</th>
<th># HIV</th>
<th>Cancer TX</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hakimian 2007</td>
<td>34</td>
<td>C, RT</td>
<td>35% unable to tolerate full chemotherapy</td>
</tr>
<tr>
<td>Lavole 2009</td>
<td>49</td>
<td>S, C, RT</td>
<td>Several treatment-related deaths</td>
</tr>
<tr>
<td>Makinson 2011</td>
<td>52</td>
<td>C</td>
<td>6 deaths (12%) due to grade 4 hematologic toxicity; protease inhibitor use associated with grade 4 toxicity</td>
</tr>
<tr>
<td>Hooker 2012</td>
<td>22</td>
<td>S</td>
<td>Markedly increased perioperative complications in HIV+</td>
</tr>
<tr>
<td>Bearz 2014</td>
<td>68</td>
<td>S, C, RT</td>
<td>No major complications from C but low rates of completion</td>
</tr>
</tbody>
</table>

*TX= Treatment, S = Surgery, C = Chemotherapy, RT = Radiotherapy*
Is It Treatment Disparities?

<table>
<thead>
<tr>
<th>Study</th>
<th>Lung cancer diagnosis years</th>
<th>HIV+ lung cancers (N)</th>
<th>HIV- lung cancers (N)</th>
<th>% HIV + treated</th>
<th>% HIV - treated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marcus et al. 2015 [43]</td>
<td>1996–2011</td>
<td>80</td>
<td>507</td>
<td>64%</td>
<td>76%</td>
</tr>
<tr>
<td>Suneja et al. 2016 [51]</td>
<td>2003–2011</td>
<td>1420</td>
<td>353156</td>
<td>67.3%</td>
<td>86.4%</td>
</tr>
<tr>
<td>Suneja et al. 2014 [52]</td>
<td>1996–2010</td>
<td>581</td>
<td>260652</td>
<td>65.1%</td>
<td>75.9%</td>
</tr>
<tr>
<td>Lee et al. 2013 [53]</td>
<td>1998–2007</td>
<td>174</td>
<td>3480</td>
<td>58.0%</td>
<td>59.6%</td>
</tr>
<tr>
<td>Suneja et al. 2013 [54]</td>
<td>1995–2009</td>
<td>337</td>
<td>156593</td>
<td>60.3% (lung)</td>
<td>77.5%</td>
</tr>
</tbody>
</table>

Lower rates of appropriate LC treatment
Survival Differences and Treatment Disparity Less in VA

NSCLC Survival 2009-2015

Appropriate NSCLC treatment equal by HIV status

# of patients

<table>
<thead>
<tr>
<th>HIV+ NSCLC</th>
<th>HIV- NSCLC</th>
</tr>
</thead>
<tbody>
<tr>
<td>300</td>
<td>400</td>
</tr>
</tbody>
</table>

P=0.5

Sigel et al. Conference on Retroviruses and Opportunistic Infections. 2017
Lung cancer outcomes may still lag for PWH

These differences may relate to treatment tolerability and disparities

In equal access system with much HIV experience, possibly similar outcomes
Immunotherapy

- Important emerging topic

- See next talk
Lung Cancer Screening
Harms of Lung Cancer Screening in HIV

- Lung cancer screening with LDCT now standard of care for heavy smokers
- False positivity rate of cancer screening is top determinant of safety/harm
  - Positive screen can lead to invasive procedures with possible major complications
- High rates of incidental abnormalities in chest imaging in PWH
Lung CT Findings

Total lung nodules

HIV+
N=160
29%

HIV-
N=138
23%

P>0.1

Total lung nodules

NLST+ nodules

NLST+ nodules

Sigel, Park, Justice et al. AIDS. 2014
The Lung Cancer Policy Model

- A well-validated microsimulation model of lung cancer
- Used to inform the USPSTF guidelines on lung cancer screening
- Highly complex, biologically-based state transition model (>40 interacting modules) that can be used simulate randomized control trials
- Modified to represent HIV
Lung cancer screening is likely to be safe, beneficial and effective in PWH who are smokers.

Joey Kong, MGH
Lung Cancer Treatment Decision Making

• R01: Collaboration between VACS, Kaiser, American Cancer Society, Mount Sinai to use their data to generate treatment guidelines

Modify the LCPM to simulate RCTs of lung cancer treatment for PWH based on individual characteristics
Key Questions That Remain

• Immune mechanisms related to increased lung cancer risk in PWH
• Immune microenvironment changes related to risk and tumor behavior
• Benefits of immunotherapy for PWH with lung cancer
• Screening younger PWH who smoke
• Targeted screening using factors that we have identified
• Role of HIV-specific smoking cessation
Summary

- PWH are at greater risk for developing lung cancer than HIV-uninfected patients.
- This relationship appears to be independent of smoking exposure.
- Several HIV-specific risk factors with evidence: low CD4, low CD4/CD8, lung infections
- Lung cancer outcomes may lag in PWH
- Lung cancer screening: PWH may not have altered risk-benefit profile
Thanks!!

- Juan Wisnivesky
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- Veterans Aging Cohort Study
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