Most common causes of death in people with HIV. D:A:D study of 49,731 participants

Age-standardized incidence rating for specific causes of death in 49,731 D:A:D participants

AIDS-defining vs non-AIDS defining cancers
Data Collection on Adverse Events of Anti-HIV Drugs
D : A : D Study

23,000 HIV-positive patients followed since 1999

305/1246 (~ 25%) of total deaths due to cancer

- 37% AIDS-defining (ADC)
- 63% non-AIDS-defining

FATAL AIDS-DEFINING CANCERS
- Lymphoma
- Kaposi Sarcoma
- Cervical Cancer

FATAL NON-AIDS DEFINING CANCERS
- Lung Cancer
- GI (Liver)
- Anal
- Hodgkins

Median CD4 at death
- 75 cells/mm³
- 211/mm³

Age at cancer diagnosis
- 43 years
- 52 years

- Lung CA → Associated with tobacco use
- Liver CA → Associated with active Hepatitis B infection

Ref: D’Arminio Monforte A, et al. CROI 2007; Abstract #84.
Non-AIDS-defining cancers are significantly increased in HIV-infected persons (~2-fold over general population), despite use of HAART

HIV-infected persons with NAD cancers are significantly LESS likely to receive cancer treatment

Studied 3045 HIV+ with cancer and 1,087,648 HIV- with cancer 1996 - 2010

Risks of NO cancer treatment in HIV-infected

<table>
<thead>
<tr>
<th>Cancer</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>2.18</td>
<td>1.80 – 2.64</td>
</tr>
<tr>
<td>Prostate</td>
<td>1.79</td>
<td>1.31 – 2.46</td>
</tr>
<tr>
<td>Colorectal</td>
<td>2.27</td>
<td>1.38 – 3.72</td>
</tr>
</tbody>
</table>

LUNG CANCER
Epidemiology in USA /Globally

• Most common cause of death from cancer globally

• In USA, leading cause of death from cancer in men and women (170,000 deaths/year) — more deaths than breast, colorectal, and prostate cancers combined

• 75% of patients diagnosed in USA will have locally advanced or metastatic disease at diagnosis

• In USA, only 18% of patients with lung cancer are alive 5 years after diagnosis

Etiology of lung cancer among people with HIV / AIDS (PWHA)

Smoking / Tobacco Use

High likelihood of smoking among HIV-infected persons

- 4,217 HIV+ adults (Medical Monitoring Project) and 27,731 participants in National Health Interview Survey in 2009

<table>
<thead>
<tr>
<th></th>
<th>HIV+</th>
<th>HIV-</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current smoker</td>
<td>42.4%</td>
<td>20.9%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prior smoker</td>
<td>20.3%</td>
<td>22%</td>
<td></td>
</tr>
<tr>
<td>Quit ratio</td>
<td>32.4%</td>
<td>51.7%</td>
<td></td>
</tr>
<tr>
<td>Never smoked</td>
<td>37.3%</td>
<td>58%</td>
<td></td>
</tr>
</tbody>
</table>

Etiology of lung cancer among people with HIV / AIDS (PWHA)

Chronic Antigenic Stimulation

• Chronic lung disease
  - Asthma
  - Recurrent pneumonia
  - Other
• Chronic inflammation

Etiology of lung cancer among people with HIV / AIDS (PWHA)

**HIV itself??**

**NO / IMPROBABLE**
- Viral sequences absent in lung cancer cells
- Estimated 55% – 90% of HIV patients with lung cancer on HAART at diagnosis
- Lung cancer the most frequent NADC in HAART era
- Median CD4 counts 300 – 350/μL
- Viral load often ND at diagnosis

**YES / POSSIBLE**
- HIV-1 tat protein modulates proto-oncogene expression in bronchoalveolar carcinoma cell lines
- Microsatellite alterations and loss of heterozygosity in lung cancer tissue from HIV / AIDS
- Lung cancer increased in HIV/AIDS patients

# Characteristics of lung cancer in HIV-infected patients

<table>
<thead>
<tr>
<th></th>
<th>HIV</th>
<th>No HIV</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>61</td>
<td>90</td>
<td>NS</td>
</tr>
<tr>
<td>Male</td>
<td>82%</td>
<td>83%</td>
<td>NS</td>
</tr>
<tr>
<td>Age</td>
<td>48 (41 – 53)</td>
<td>66 (58 - 72)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Active smokers</td>
<td>97%</td>
<td>58%</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Hx prior lung infection</td>
<td>48%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Histology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Squamous cell</td>
<td>39%</td>
<td>59%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>38%</td>
<td>13%</td>
<td>&lt; 0.002</td>
</tr>
<tr>
<td>Stage III / IV</td>
<td>80%</td>
<td>88%</td>
<td>NS</td>
</tr>
</tbody>
</table>

Can we prevent death from lung cancer?

- Early screening
- Smoking cessation
National Lung Screening Trial (NLST)
Enrolled 53,000 persons in 33 US centers

Participants
- 55 to 74 years old
- > 30 PY smoking history
- Current smoker or quit < 15 years prior

Randomization
- 3 years of annual low-dose chest CT
- vs
- 3 years of annual CXR

Exposure to radiation
- 1.5 mSu in CT group (usual annual exposure in USA)

RESULTS
- A minimum of 20% reduction in lung cancer death in CT arm (study stopped in 11/2010 when 20% endpoint reached)

Caveats:
- 39% in CT group had > 1 finding; 95% of these were false positives
- 1% had > 1 complication from invasive tests, but only 20% of complications were in patients without cancer
- No difference in anxiety levels or QOL in patients with false positive vs negative results
- 1 patient now reported to have died of complications of biopsy in USA to date

Cost effectiveness of low-dose CT scanning for lung cancer

COST = $81,000 / quality adjusted life year (QALY) gained and $52,000 / life-year gained

Threshold of $100,000 / QALY gained is considered a reasonable value in the USA
Guidelines for lung cancer screening with low-dose CT scanning

• Age 55 – 74 (or 77)
• Smoking history ≥ 30 PYs
• If quit, < 15 years ago

Guidelines recommended by

• USPSTF
• NCCN
• Am Lung Assn
• ASCO
• Am Cancer Society
• Etc., etc.
Who pays for low-dose CT screening of lung cancer?

• REQUIRED to be covered as an essential health benefit without co-pay under Affordable Care Act
  – Grade B recommendation by USPSTF mandates this

• Centers for Medicare & Medicaid Services (CMS) released final coverage decision (February 2015) to pay for 55 – 77 year olds, with same smoking history as USPSTF and NLST
  – Also require shared decision-making (with documentation of same) and participation in a clinical registry
SMOKING CESSATION

Cytisine = Plant-based alkaloid (leguminosae family) partial agonist of nicotinic acetylcholine receptors, with affinity for α4β2 receptor
Generic: made by Sopharma (Tabex™) and Aflofarm Pharma (Desmoxan™)
Used in Eastern Europe since 1960s for smoking cessation
Inexpensive: $20 to $30 for a 25-day course vs $112 to $685 for 8 to 10 weeks of nicotine replacement

TRIAL OF CYTISINE vs NICOTINE REPLACEMENT IN 1,310 SMOKERS
QUIT RATE

<table>
<thead>
<tr>
<th></th>
<th>CYTISINE</th>
<th>NICOTINE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 week</td>
<td>41%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>1 month</td>
<td>42%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>2 months</td>
<td>38%</td>
<td>0.020</td>
</tr>
<tr>
<td>6 months</td>
<td>31%</td>
<td>NS</td>
</tr>
</tbody>
</table>

Time to relapse

- 127 days
- 20 days

Day 1 – 3 = 1 tab q 2 hrs (up to 6/day)
Day 4 – 12 = 1 tab q 2.5 hrs (up to 5/day)
Day 13 – 16 = 1 tab q 3 hrs (up to 4/day)
Day 17 – 20 = 1 tab q 4.5 hrs (3/day)
Day 21 – 25 = 1 tab q 6 hrs (2/day)

PROSTATE CANCER

- Risk NOT increased in HIV
- But most common cancer in men
- Recent controversies in value of screening (PSA / DRE) and in treatment (vs active surveillance) of low-risk prostate cancer
Gleason’s Pattern Scoring System

1° grade = dominant pattern (≥ 50%)
2° grade = next most frequent (< 50%)
Risk categories in prostate cancer

LOW RISK
(35% - 70% of all patients)
- Gleason $\leq 6$
- Pretreatment PSA $< 10$ ng/mL
- Clinical stage $T_1 - T_{2a}$

HIGH RISK
- Black race
- Family history prostate cancer
- Use of alpha-reductase inhibitors
Screening of Prostate Cancer

HOW → DRE and PSA testing annually

Potential Benefit
• Lower stage and grade of cancer at time of diagnosis

Potential Harm / No Benefit
• Early definitive Rx (surgery, XRT) of low-risk prostate cancer shows no survival benefit at 10 years
• 2 large studies show no survival benefit to screening (at 10 years)
• BUT European study shows survival benefit at ≥ 11 years f/u

May be differences in survival at longer f/u times

BUT, toxicities of Rx

Active surveillance in men with low-risk prostate cancer

- PSA testing every 3 - 6 - 12 months
- Repeat prostate biopsies every 1 - 2 years

ISSUES / PROBLEMS

- Frequent visits
- Risk of infection, pain from biopsies
- Cumulative costs
Long-term F/U of active surveillance

N = 993, median F/U = 6.4 years (0.2 – 19.8 years)

METHODS

PSA every 3 mos x 2 yrs → then every 6 mos. If stable confirmatory biopsy within 12 mos, then PSA every 3 – 4 years until 80 years

Patients reclassified as higher risk if:

- PSA doubling time < 3 yrs
- Histologic upgrade on repeat biopsy
- Clinical progression

RESULTS

- Metastatic disease in 2.8%
- Death secondary to prostate cancer = 1.5%
- Cumulative risk of non-prostate: prostate cancer mortality = 9 : 2
- Follow-up data

<table>
<thead>
<tr>
<th></th>
<th>5 yr</th>
<th>10 yr</th>
<th>15 yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cause-specific OS</td>
<td>98%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>% on surveillance</td>
<td>76%</td>
<td>64%</td>
<td>55%</td>
</tr>
</tbody>
</table>

Prostate cancer mortality in 162,388 European men at 13-year follow-up


Rate Ratio of Prostate Death

<table>
<thead>
<tr>
<th>Time</th>
<th>Rate Ratio</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yr 1 – 9</td>
<td>0.85</td>
<td>(p = NS)</td>
</tr>
<tr>
<td>Yr 1 – 11</td>
<td>0.78</td>
<td>(p = .002)</td>
</tr>
<tr>
<td>Yr 1 – 13</td>
<td>0.79</td>
<td>(p = 0.001)</td>
</tr>
</tbody>
</table>
## Acute and long-term complications and AEs in prostate cancer patients with life expectancy < 10 years

<table>
<thead>
<tr>
<th>Complications</th>
<th>Surveillance</th>
<th>Radical Prostatectomy</th>
<th>p Value</th>
<th>Radiation</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood transfusion</td>
<td></td>
<td>13%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30-day complications</td>
<td></td>
<td>22%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stricture</td>
<td>5%</td>
<td>11%</td>
<td>.004</td>
<td>6%</td>
<td>NS</td>
</tr>
<tr>
<td>Long-Term Toxicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>52%</td>
<td>79%</td>
<td>&lt; 0.001</td>
<td>65%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Urinary</td>
<td>41%</td>
<td>59%</td>
<td>&lt; 0.001</td>
<td>50%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Bowel</td>
<td>11%</td>
<td>7%</td>
<td>NS</td>
<td>18%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Erectile</td>
<td>13%</td>
<td>48%</td>
<td>&lt; 0.001</td>
<td>20%</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Source</th>
<th>Recommendation</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>USPSTF (2012)</td>
<td>No routine screening</td>
<td>No routine screening</td>
</tr>
<tr>
<td>NCCN (2012)</td>
<td>No routine screening</td>
<td>Begin risk-benefit talk re: baseline DRE/PSA at age 40</td>
</tr>
<tr>
<td>Am Soc Clin Oncology (2012)</td>
<td>Discourage for men with life expectancy ≤ 10 yrs</td>
<td>Shared decision-making in others</td>
</tr>
<tr>
<td>Am Cancer Society (2013)</td>
<td>No routine screening</td>
<td>Shared decision-making in those with life expectancy &gt; 10 years</td>
</tr>
<tr>
<td>Am College of Physicians (2013)</td>
<td>No routine screening for average risk men &lt; 50 yrs; men &gt; 69 yrs; or men with life expectancy &lt; 10 or 15 yrs</td>
<td>MD should inform men 50 – 69 of limited benefits and substantial harm</td>
</tr>
<tr>
<td>American Urological Assn (2013)</td>
<td>No routine screening</td>
<td>Individualized decisions for men &lt; 55 at high risk</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Shared decision-making in men 55 to 69 yrs</td>
</tr>
</tbody>
</table>
Tool for shared decision-making re: screening for prostate cancer

KEY FACTS

- Prostate cancer is common; most men will get it.
- Only a small % of men die of prostate cancer, but screening will decrease the risk.
- Screening detects many low-risk, indolent cancers.
- In the USA, most low-risk patients get treatment, which can lead to complications.

KEY TAKE HOME MESSAGES

- Goal of screening is to find aggressive cancer and treat early.
- Most cancers found by screening can be managed by active surveillance.
- If you choose screening and low-risk cancer found, you may be pressured to treat (by MD or by family/friends).

DECISION

- If you would be uncomfortable knowing you had cancer but not treating it, screening may NOT be the answer for you.
- If you would only accept treatment for aggressive cancer and could be comfortable living with a diagnosis of low-risk cancer, screening is probably the answer for you.

Prostate cancer screening in HIV-infected men

• Prostate cancer risk is NOT increased in HIV

• Manage HIV+ men in same way as HIV-negative
  A. High risk → Screened
  B. Average risk → Shared decision-making

  ↓

  FUTURE
  Precision / Personalized Medicine

Decisions based on: genomic characteristics of tumor, sophisticated imaging techniques
BREAST CANCER

- Risk NOT increased in HIV
- Risk MAY be decreased in HIV

Binding of HIV CXCR4 to CXCR4 receptor on breast cancer cells leads to apoptosis.

Study of 19 HIV-infected cancer patients and 55 controls in WIHS studied for CXCR4 or CCR5 tropism.

Odds of breast cancer = 90% lower with HIV-X4 vs exclusive HIV-R5.

Refs: Luker KE, Luker GD: Cancer Letter 2006; 238:30–41
Efficacy of annual mammogram starting at age 40, in preventing death from breast cancer ~ 30 year experience

Relative Risk Reduction of Death

- Age 40 - 49: 15%
- Age 60 - 69: 35%

### Recommendations for Breast Cancer Screening in Average Risk Women

<table>
<thead>
<tr>
<th>Society</th>
<th>Imaging</th>
<th>Clinical Breast Exam</th>
</tr>
</thead>
<tbody>
<tr>
<td>Am Cancer Society (2013)</td>
<td>Age ≥ 40 yrs Annual</td>
<td>Age 20 – 39: every 1-3 yrs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Age ≥ 40: annually</td>
</tr>
<tr>
<td>NCCN (2013)</td>
<td>Age ≥ 40 yrs Annual</td>
<td>Age ≥ 25 - &lt; 40: every 1-3 yrs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Age ≥ 40: annually</td>
</tr>
<tr>
<td>Am College of Ob/Gyn (2011)</td>
<td>Age ≥ 40 yrs Annual</td>
<td>Age 20 – 39: every 1-3 yrs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Age ≥ 40: annually</td>
</tr>
<tr>
<td></td>
<td>Age ≥ 75: insufficient evidence</td>
<td></td>
</tr>
</tbody>
</table>
Women at Higher Risk for Breast Cancer

- Very dense breasts
- Heterogeneously dense breasts
- First-degree relative with breast cancer
- Second-degree relatives with breast cancer
- Prior breast biopsy
- Current oral contraceptive use
- Nulliparous
- First child at age ≥ 30 years
- BRCA-1 or BRCA-2 mutation
- Receipt of chest radiation, age 10 – 30
- Peutz-Jeghers Syndrome
- Cowan Syndrome
- Lynch Syndrome
Recommendations for mammographic screening of HIV-infected women

• Incidence of breast cancer is not increased, and may be decreased

• Follow standard guidelines
  – Annual mammogram starting at age ≥ 40
  – May choose to adopt USPSTF guideline, starting at age 50 – 74, and performed every 2 years
SUMMARY

• 25% of total deaths in HIV = cancer

• Non-AIDS-defining cancers are most common (63%)

• Lung cancer associated with smoking and history of pulmonary infections or inflammation. Screening indicated with low-dose CT: (1) age 55 – 74 or 77 (CMS); (2) > 30 PY; (3) quit < 15 years ago

• Prostate cancer not increased, but be aware of recent trends in screening

• Breast cancer may be decreased; screen in usual manner