Cancer risk and prevention in persons living with HIV/AIDS (PLWHA)

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Main collaborators

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- Janet Tate
- Amy Justice
- Michael Silverberg
- Li Qin
- Haiqun Lin
Cancer risk and prevention in PLWHA

• Cancer is a major cause of morbidity and mortality in PLWHA

• PLWHA have elevated risk for many cancer types, especially those with a viral etiology, due to
  – HIV infection itself
  – High prevalence of non-HIV cancer risk factors

• Cancer prevention among PLWHA
  – Early antiretroviral therapy (ART) to preserve/restore immune function
  – Reduction in prevalence of non-HIV cancer risk factors
  – Screening for selected cancer types
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Cancer is a major cause of morbidity and mortality in the general US population
Proportionate mortality, US, 2010
Classification of cancers in HIV

• AIDS-defining cancers (ADC)
  – Kaposi sarcoma (KS)
  – Non-Hodgkin lymphoma (NHL)
  – Invasive cervical cancer (ICC)

• Non-AIDS-defining cancers (NADC)
AIDS: end stage of HIV infection

• HIV seropositivity
  
  AND

• CD4 cell count <200 cells/ml blood
  
  OR

• One or more AIDS-defining condition
  – Opportunistic infections
  – Cancers
  – Other

• In the pre-ART era, most PLWHA died of AIDS
AIDS-Defining Conditions: Other

- Encephalopathy, HIV-related
- HIV wasting syndrome
AIDS-Defining Conditions: opportunistic infections (1)

- Candidiasis of bronchi, trachea, or lungs
- Candidiasis, esophageal
- Coccidioidomycosis, disseminated or extrapulmonary
- Cryptococcosis, extrapulmonary
- Cryptosporidiosis, chronic intestinal (> 1 month duration)
- Cytomegalovirus disease (other than liver, spleen, or lymph nodes)
- Cytomegalovirus retinitis (with loss of vision)
AIDS-Defining Conditions: opportunistic infections (2)

- Herpes simplex virus: chronic ulcer(s) (> 1 month duration) or bronchitis, pneumonitis, or esophagitis
- Histoplasmosis, disseminated or extrapulmonary
- Isosporiasis, chronic intestinal (> 1 month duration)
- *Mycobacterium avium* complex or *M. kansasii*, disseminated or extrapulmonary
AIDS-Defining Conditions: opportunistic infections (3)

- *Mycobacterium tuberculosis*, any site
- *Mycobacterium*, other species or unidentified species, disseminated or extrapulmonary
- *Pneumocystis jirovecii* pneumonia
- Pneumonia, recurrent
- Progressive multifocal leukoencephalopathy
- *Salmonella* septicemia, recurrent
- Toxoplasmosis of brain
AIDS-Defining Conditions: cancers

• KS
  – Caused by KS-associated herpesvirus (KSHV)
• NHL
  – Lymphoma, Burkitt’s
  – Lymphoma, immunoblastic
  – Lymphoma, primary, of brain
  – HIV-associated subtypes caused by Epstein-Barr virus (EBV)
• ICC
  – Caused by human papillomavirus (HPV)
HIV in the ART era (1996 onward)

• Substantial increase in life expectancy
• Substantial increase in non-AIDS co-morbidities
• Shift in cause of death spectrum toward non-AIDS-defining causes, including NADC
Time trends of cancer mortality among men in the Veterans Aging Cohort Study (VACS) Virtual Cohort
VACS Virtual Cohort

• Assembled from national VA databases
  – No contact with patients
  – Linkage accomplished using scrambled Social Security Number as personal identifier

• Periodically updated open cohort with earliest enrollment in 1996

• ~48,000 HIV-infected veterans

• ~96,000 HIV-infected veterans, matched to HIV-infected veterans by age, sex, race/ethnicity, and VA site
Time trends of cancer mortality among men in the VACS Virtual Cohort

- Linked VACS with the National Death Index to obtain causes of death, 1996-2009
- Median observation time
  - HIV-infected: 6.4 years
  - HIV-uninfected: 8.3 years
- 27,195 deaths
Time trends in cancer proportionate mortality (deaths with cancer/all deaths [%])
Time trends in ADC proportionate mortality (deaths with ADC/all deaths [%])

- HIV-infected
- HIV-uninfected
Time trends in NADC proportionate mortality (deaths with NADC/all deaths [%])

- **1996-98**: HIV-infected (25%) vs HIV-uninfected (15%)
- **1999-2002**: HIV-infected (22%) vs HIV-uninfected (10%)
- **2003-2006**: HIV-infected (20%) vs HIV-uninfected (12%)
- **2007-2009**: HIV-infected (18%) vs HIV-uninfected (15%)
Time trends in underlying cause cancer mortality rates (age- and race/ethnicity standardized)

HIV-infected (●)
HIV-uninfected (○)
Time trends in underlying cause ADC mortality rates (age- and race/ethnicity standardized)

HIV-infected (●)  
HIV-uninfected (○)
Time trends in underlying cause NADC mortality rates (age- and race/ethnicity standardized)

HIV-infected (●)
HIV-uninfected (○)
Time trends of cancer mortality among men in the VACS: conclusions

- Cancer proportionate mortality among PLWHA is approaching that in the HIV-uninfected population
- Cancer mortality rates are about 1.7-fold higher in HIV-infected persons compared to HIV-uninfected persons
Cancer risk and prevention in PLWHA

• Cancer is a major cause of morbidity and mortality in PLWHA

• PLWHA have elevated risk for many cancer types, especially those with a viral etiology, due to
  – HIV infection itself
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• Cancer prevention among PLWHA
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  – Reduction in prevalence of non-HIV cancer risk factors
  – Screening for selected cancer types
Cancer incidence in HIV-infected compared to HIV-uninfected veterans in the VACS Virtual Cohort

- Linked VACS with VA Central Cancer Registry to obtain cancer diagnoses
- Age-, sex-, race/ethnicity- and calendar-period-standardized incidence rate ratios (IRR) (HIV-infected vs. HIV-uninfected)
IRRs (HIV-infected vs. HIV-uninfected) for specific cancer types (1)

<table>
<thead>
<tr>
<th>Cancer</th>
<th>IRR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>1.93</td>
<td>1.82, 2.05</td>
</tr>
<tr>
<td>Oral cavity &amp; pharynx</td>
<td>1.30</td>
<td>1.03, 1.64</td>
</tr>
<tr>
<td>Esophagus</td>
<td>0.89</td>
<td>0.59, 1.34</td>
</tr>
<tr>
<td>Stomach</td>
<td>1.03</td>
<td>0.62, 1.72</td>
</tr>
<tr>
<td>Colorectal</td>
<td>1.22</td>
<td>0.97, 1.52</td>
</tr>
<tr>
<td>Cancer</td>
<td>IRR</td>
<td>95% CI</td>
</tr>
<tr>
<td>----------</td>
<td>-------</td>
<td>-------------</td>
</tr>
<tr>
<td>Anal</td>
<td>28.14</td>
<td>16.06, 49.32</td>
</tr>
<tr>
<td>Liver</td>
<td>3.27</td>
<td>2.50, 4.29</td>
</tr>
<tr>
<td>Pancreas</td>
<td>1.31</td>
<td>0.84, 2.03</td>
</tr>
<tr>
<td>Larynx</td>
<td>1.37</td>
<td>0.98, 1.91</td>
</tr>
<tr>
<td>Lung</td>
<td>1.87</td>
<td>1.63, 2.14</td>
</tr>
</tbody>
</table>
IRRs (HIV-infected vs. HIV-uninfected) for specific cancer types (3)

<table>
<thead>
<tr>
<th>Cancer</th>
<th>IRR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melanoma</td>
<td>2.21</td>
<td>1.40, 3.49</td>
</tr>
<tr>
<td>Prostate</td>
<td>0.96</td>
<td>0.85, 1.07</td>
</tr>
<tr>
<td>Testicular</td>
<td>4.59</td>
<td>1.38, 15.27</td>
</tr>
<tr>
<td>Bladder</td>
<td>1.04</td>
<td>0.71, 1.54</td>
</tr>
<tr>
<td>Kidney</td>
<td>1.11</td>
<td>0.82, 1.49</td>
</tr>
<tr>
<td>Brain</td>
<td>0.81</td>
<td>0.36, 1.82</td>
</tr>
</tbody>
</table>
IRRs (HIV-infected vs. HIV-uninfected) for specific cancer types (4)

<table>
<thead>
<tr>
<th>Cancer</th>
<th>IRR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thyroid</td>
<td>0.62</td>
<td>0.32, 1.20</td>
</tr>
<tr>
<td>Hodgkin lymphoma</td>
<td>9.08</td>
<td>5.09, 16.19</td>
</tr>
<tr>
<td>NHL</td>
<td>6.68</td>
<td>5.57, 8.00</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>1.40</td>
<td>0.86, 2.27</td>
</tr>
<tr>
<td>Leukemia</td>
<td>2.02</td>
<td>1.33, 3.08</td>
</tr>
<tr>
<td>KS</td>
<td>519.61</td>
<td>229.02, 1178.90</td>
</tr>
</tbody>
</table>
Cancer incidence in HIV-infected compared to HIV-uninfected veterans: conclusions

• Overall cancer incidence is about 2-fold higher in HIV-infected than in HIV-uninfected veterans
• PLWHA have elevated ADC incidence
• PLWHA have elevated incidence of a variety of NADC cancer types, many of which have viral etiologies
Cancer risk and prevention in PLWHA

• Cancer is a major cause of morbidity and mortality in PLWHA

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  – HIV infection itself
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Immune system and cancer: a double-edged sword

• Immune system protects against cancer
  – Clears/suppresses oncogenic virus infections
  – Cancer immunosurveillance: recognition and destruction of cancer cells

• Chronic immune activation and inflammation promotes cancer development
  – Stimulation of cell proliferation
  – Generation of genotoxic reactive oxygen and nitrogen species
  – Production of procarcinogenic cytokines and growth factors
Grulich et al. Incidence of cancers in people with HIV/AIDS compared with immunosuppressed transplant recipients: a meta-analysis
(Lancet 2007;370:59-67)

- Lifestyle-related risk factors probably differ substantially between these 2 groups
- Immunodeficiency is the risk factor these 2 groups have in common
- Similar cancer incidence patterns would suggest immunodeficiency as the cause
- Combined data from population-based cohort studies that compared cancer incidence in the cohort with cancer incidence in the general population
<table>
<thead>
<tr>
<th></th>
<th>HIV/ AIDS</th>
<th>Transplant</th>
</tr>
</thead>
<tbody>
<tr>
<td># of studies</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Aggregate cohort size</td>
<td>444,172</td>
<td>31,977 (97% renal)</td>
</tr>
</tbody>
</table>
Cancer types with significant ($p<.05$) standardized incidence ratios (SIRs) in both HIV and transplant patients, by SIR magnitude

<table>
<thead>
<tr>
<th>SIR</th>
<th>Cancer types</th>
</tr>
</thead>
<tbody>
<tr>
<td>Both &gt;8</td>
<td>KS (KSHV), non-Hodgkin lymphoma (EBV)</td>
</tr>
<tr>
<td>Both &gt;4</td>
<td>Hodgkin lymphoma (EBV), anus (HPV), vulva and vagina (HPV), penis (HPV), non-melanoma skin (HPV)</td>
</tr>
<tr>
<td>Both &gt;2</td>
<td>Liver (HCV/HBV), cervix (HPV), oral cavity &amp; pharynx (HPV), lip (HPV), larynx (HPV), eye (HPV), lung, multiple myeloma, leukemia</td>
</tr>
<tr>
<td>Both &gt;1.5</td>
<td>Esophagus (HPV), stomach (\textit{H pylori}), kidney</td>
</tr>
<tr>
<td>Both &gt;1.2</td>
<td>Melanoma</td>
</tr>
</tbody>
</table>

KSHV, KS-associated herpesvirus; EBV, Epstein-Barr virus; HPV, human papillomavirus; HCV, hepatitis C virus; HBV, hepatitis B virus
Grulich et al.: conclusions

• Many cancer types had increased incidence in both groups
• Most are of known or suspected viral origin
• Lack of increased incidence of breast and prostate cancers argues against increased medical surveillance as the explanation of increased incidence
• Immunodeficiency is the most likely explanation for the elevated risk
Epidemiologic measures of immune function in HIV infection

• CD4 cell count: measure of immunodeficiency
• HIV viral load (i.e., HIV RNA copies in blood)
  – Rough measure of chronic immune activation and inflammation
CD4 and HIV RNA in relation to KS risk in the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD)
NA-ACCORD

• Consortium of >20 HIV cohorts
• Validated cancer diagnoses for each cohort by chart review or cancer registry linkage
• Data center standardizes variables among cohorts to create a combined analytic dataset
CD4 and HIV RNA in relation to KS risk in NA-ACCORD

• 15 cohorts
• N = 64,693
• KS cases = 689
• Median follow-up: 6.2 years
• Calculated hazard ratios (HRs) using Cox proportional hazards models
• Models adjusted for age, sex, race/ethnicity, cohort, calendar-period of entry into cohort, HIV risk group, baseline ART
### Baseline CD4 in relation to KS risk

<table>
<thead>
<tr>
<th>CD4 (cells/µl)</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>500+</td>
<td>1.0 (ref)</td>
<td>--</td>
</tr>
<tr>
<td>350-499</td>
<td>1.4</td>
<td>1.2-1.7</td>
</tr>
<tr>
<td>200-349</td>
<td>1.7</td>
<td>1.3-2.1</td>
</tr>
<tr>
<td>100-199</td>
<td>2.1</td>
<td>1.6-2.8</td>
</tr>
<tr>
<td>50-99</td>
<td>3.0</td>
<td>2.1-4.3</td>
</tr>
<tr>
<td>&lt;50</td>
<td>1.6</td>
<td>1.1-2.4</td>
</tr>
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</table>
## Time-updated CD4 (6-month lag) in relation to KS risk

<table>
<thead>
<tr>
<th>CD4 (cells/µl)</th>
<th>HR</th>
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<td>200-349</td>
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<td>3.6-7.3</td>
</tr>
<tr>
<td>100-199</td>
<td>12.2</td>
<td>8.6-17.4</td>
</tr>
<tr>
<td>50-99</td>
<td>28.4</td>
<td>19.9-40.7</td>
</tr>
<tr>
<td>&lt;50</td>
<td>45.7</td>
<td>32.8-63.7</td>
</tr>
</tbody>
</table>
Baseline HIV RNA in relation to KS risk

<table>
<thead>
<tr>
<th>HIV RNA (copies/ml)</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;500</td>
<td>1.0 (ref)</td>
<td>--</td>
</tr>
<tr>
<td>500-9,999</td>
<td>1.9</td>
<td>1.2-3.0</td>
</tr>
<tr>
<td>10,000-99,999</td>
<td>3.6</td>
<td>2.3-5.5</td>
</tr>
<tr>
<td>100,000+</td>
<td>3.5</td>
<td>2.2-5.4</td>
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Time-updated HIV RNA (6-month lag) in relation to KS risk

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</tr>
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<tr>
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<td>1.0 (ref)</td>
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</tr>
<tr>
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<td>2.7</td>
<td>1.8-4.3</td>
</tr>
<tr>
<td>10,000-99,999</td>
<td>11.0</td>
<td>7.5-16.1</td>
</tr>
<tr>
<td>100,000+</td>
<td>38.5</td>
<td>28.7-55.6</td>
</tr>
</tbody>
</table>
Time-updated CD4 and HIV RNA (6-month lags) (simultaneous adjustment) in relation to KS risk

<table>
<thead>
<tr>
<th>CD4 (cells/µl)</th>
<th>500+</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>350-499</td>
<td>2.0</td>
<td>1.4-3.0</td>
<td></td>
</tr>
<tr>
<td>200-349</td>
<td>3.5</td>
<td>2.4-5.0</td>
<td></td>
</tr>
<tr>
<td>100-199</td>
<td>6.8</td>
<td>4.7-9.8</td>
<td></td>
</tr>
<tr>
<td>50-99</td>
<td>13.3</td>
<td>9.1-19.5</td>
<td></td>
</tr>
<tr>
<td>&lt;50</td>
<td>18.7</td>
<td>13.0-27.1</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HIV RNA (copies/ml)</th>
<th>&lt;500</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>500-9,999</td>
<td>1.9</td>
<td>1.2-3.0</td>
<td></td>
</tr>
<tr>
<td>10,000-99,999</td>
<td>5.1</td>
<td>3.4-7.5</td>
<td></td>
</tr>
<tr>
<td>100,000+</td>
<td>9.0</td>
<td>6.0-13.4</td>
<td></td>
</tr>
</tbody>
</table>
CD4 and HIV RNA in relation to KS risk in NA-ACCORD: conclusions

• Time-updated measures of CD4 and HIV RNA must be used to assess these covariates in relation to risk of KS (and of other cancer types)

• Both recent CD4 count and recent HIV RNA level were strong, independent predictors of KS risk
Natural history of HIV infection

- Primary infection
- ± Acute HIV syndrome
- Wide dissemination of virus
- Seeding of lymphoid organs

Clinical Latency

- Constitutional symptoms
- Opportunistic diseases

AIDS

Death

CD4+ T Lymphocyte Count (cells/mm³) vs HIV RNA Copies per ml Plasma

Days

0 3 6 9 12 1 2 3 4 5 6 7 8 9 10 11

10^2 10^3 10^4 10^5 10^6 10^7
HIV infection, immunodeficiency, viral replication, and the risk of cancer

• Kaiser Permanente (KP) Northern California cohort
• 20,775 HIV-infected
• 215,158 HIV-uninfected
• Mean observation time
  – HIV-infected: 4.4 years
  – HIV-uninfected: 5.3 years
• Rate ratios from Poisson regression
• Time-updated recent (6-month lag) CD4 and HIV RNA
• Adjusted for age, sex, race/ethnicity, calendar period, KP region, smoking, alcohol/drug abuse, overweight/obesity
Time-updated CD4 and HIV RNA (simultaneous adjustment) in relation to risk of selected NADC

<table>
<thead>
<tr>
<th>Cancer type</th>
<th>Adjusted Rate Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CD4 (&lt;200 vs. 500+ cells/µl)</td>
</tr>
<tr>
<td>Anal</td>
<td>3.1 (1.6-6.1)</td>
</tr>
<tr>
<td>Hodgkin lymphoma</td>
<td>3.7 (1.8-7.8)</td>
</tr>
<tr>
<td>Oral cavity/pharynx</td>
<td>5.9 (1.8-19.4)</td>
</tr>
<tr>
<td>Liver</td>
<td>4.3 (1.2-15.0)</td>
</tr>
<tr>
<td>Prostate</td>
<td>0.7 (0.3-1.6)</td>
</tr>
<tr>
<td>Lung</td>
<td>2.0 (0.9-4.1)</td>
</tr>
<tr>
<td>Colorectal</td>
<td>4.8 (1.9-12.3)</td>
</tr>
<tr>
<td>Melanoma</td>
<td>1.8 (0.6-6.0)</td>
</tr>
</tbody>
</table>
HIV infection, immunodeficiency, viral replication, and the risk of cancer: conclusions

• Low recent CD4 count was associated with increased risk of a variety of NADC after adjustment for HIV RNA, demographic variables, and non-HIV cancer risk factors

• No compelling evidence that high recent HIV RNA was independently associated with increased NADC risk
Cancer risk and prevention in PLWHA

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  – HIV infection itself
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  – Screening for selected cancer types
## Modifiable cancer risk factors and associated cancer types

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Cancer types</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking</td>
<td>Oral cavity/pharynx, esophagus, stomach, pancreas, larynx, lung, cervix, bladder, kidney, acute myeloid leukemia</td>
</tr>
<tr>
<td>Alcohol</td>
<td>Oral cavity/pharynx, esophagus, colorectal, liver, larynx, breast</td>
</tr>
<tr>
<td>Obesity</td>
<td>Adenocarcinoma of esophagus/gastric cardia, colorectal, pancreas, breast (postmenopausal), endometrial, kidney</td>
</tr>
<tr>
<td>HPV</td>
<td>Oral cavity/pharynx, anal, cervix, vagina, vulva, penis</td>
</tr>
<tr>
<td>HCV and HBV</td>
<td>Liver</td>
</tr>
</tbody>
</table>
## Prevalence of cancer risk factors in PLWHA and general population

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>General pop.</th>
<th>PLWHA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current smoking</td>
<td>19%</td>
<td>38%-84%</td>
</tr>
<tr>
<td>Hazardous alcohol</td>
<td>3%-32%</td>
<td>11%-20%; IDU: 74%</td>
</tr>
<tr>
<td>Obesity</td>
<td>32%-36%</td>
<td>12%-29%</td>
</tr>
<tr>
<td>Cervical HPV</td>
<td>27%</td>
<td>44%-79%</td>
</tr>
<tr>
<td>Anal HPV</td>
<td>MSM: 57%-70%</td>
<td>59%-98%</td>
</tr>
<tr>
<td>Oral HPV</td>
<td>4%-10%</td>
<td>20%-47%</td>
</tr>
<tr>
<td>Hepatitis B virus</td>
<td>0.3%</td>
<td>1%-33%</td>
</tr>
<tr>
<td>Hepatitis C virus</td>
<td>2%</td>
<td>3%-50%; IDU: 90%</td>
</tr>
</tbody>
</table>
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• Cancer is a major cause of morbidity and mortality in PLWHA

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  – Screening for selected cancer types
Does early ART reduce cancer risk?

• Biologic evidence: effects of ART
  – Suppresses viral load
  – Increases CD4 count
  – Reduces (but does not normalize) immune activation and inflammation

• Increasing evidence from observational epidemiology

• No data available from randomized controlled trials

• Question may be viewed as academic: US Dept. of Health and Human Services guidelines recommend ART for all PLWHA, regardless of CD4 count
“For those with high CD4 cell counts, whose short-term risk for death may be low, the recommendation to initiate ART is based on growing evidence that untreated HIV infection or uncontrolled viremia is associated with development of non-AIDS-defining diseases, including cardiovascular disease, kidney disease, liver disease, neurologic complications, and malignancies. Furthermore, newer ART regimens are more effective, more convenient, and better tolerated than regimens used in the past.”
Reduction in prevalence of non-HIV cancer risk factors

• Targeted interventions needed
• Behavioral and pharmacologic interventions for smoking and alcohol
• Vaccination for HPV, HBV
• Treatment of HBV, HCV
Cancer screening in PLWHA

• Beneficial for patients with sufficient life expectancy
  – Cervical cancer: pap smear
  – Breast cancer: mammography
  – Colorectal cancer: fecal occult blood testing, sigmoidoscopy, colonoscopy

• More research needed to determine benefits vs. harms
  – Anal cancer: cytology, high-resolution anoscopy
  – Lung cancer: low dose CT scan
  – Liver cancer: ultrasonography
Cancer risk and prevention in PLWHA

• Cancer is a major cause of morbidity and mortality in PLWHA

• PLWHA have elevated risk for many cancer types, especially those with a viral etiology, due to
  – HIV infection itself
  – High prevalence of non-HIV cancer risk factors

• Cancer prevention among PLWHA
  – Early ART to preserve/restore immune function
  – Reduction in prevalence of non-HIV cancer risk factors
  – Screening for selected cancer types