Meeting the Challenges of Malignancies in People with HIV/AIDS

Mark Polizzotto
HIV/AIDS Malignancy Branch
Center for Cancer Research, National Cancer Institute
Slides developed by the National Cancer Institute, and the NIH Clinical Center Nursing Department and used with permission.
Outline

Cancers in People with HIV/AIDS

Human Tumor Viruses

Targeting Viral Malignancies
Evolution

PCP Pneumonia in young gay men, San Francisco
June 1981

Kaposi Sarcoma, New York and San Francisco
July 1981

Non-Hodgkin Lymphoma
May 1982

Primary CNS Lymphoma
January 1983

Anal Cancer
January 1986

AZT shown to be effective
August 1986

Primary Effusion Lymphomas
January 1989

Castlemann Disease
January 1990

Hodgkin Lymphoma
July 1992

Cervical Cancer
January 1994

Kaposi Sarcoma Herpesvirus discovered
January 1994

HAART
August 1996

Plaque
August 1997
## Relative Risk of Selected Cancers

<table>
<thead>
<tr>
<th>Malignancy</th>
<th>Incidence (per 100,000 person years)</th>
<th>Standardized Incidence Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Cancer Types</td>
<td>468</td>
<td>2.1 (2.0-2.3)</td>
</tr>
<tr>
<td>AIDS Defining Cancers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kaposi sarcoma</td>
<td>173</td>
<td>1,300 (1,100-1,500)</td>
</tr>
<tr>
<td>Non Hodgkin Lymphoma</td>
<td>109</td>
<td>7.3 (6.4-8.4)</td>
</tr>
<tr>
<td>Diffuse large B-cell lymphoma</td>
<td>50</td>
<td>9.6 (7.7-12)</td>
</tr>
<tr>
<td>Burkitt lymphoma</td>
<td>7</td>
<td>15 (7.9-27)</td>
</tr>
<tr>
<td>Primary CNS lymphoma</td>
<td>15</td>
<td>250 (160-360)</td>
</tr>
<tr>
<td>Invasive cervical cancer</td>
<td>44</td>
<td>2.9 (1.9-42)</td>
</tr>
<tr>
<td>Non-AIDS Defining Cancers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anogenital</td>
<td>10</td>
<td>9.2 (5.5-15)</td>
</tr>
<tr>
<td>Hodgkin Lymphoma</td>
<td>19</td>
<td>5.6 (3.9-7.8)</td>
</tr>
<tr>
<td>Head and Neck</td>
<td>14</td>
<td>1.7 (1.1-2.5)</td>
</tr>
<tr>
<td>Hepatocellular</td>
<td>8</td>
<td>2.7 (1.5-4.6)</td>
</tr>
<tr>
<td>Lung Cancer</td>
<td>59</td>
<td>2.6 (2.1-3.1)</td>
</tr>
<tr>
<td>Acute Lymphocytic Leukemia</td>
<td>2</td>
<td>2.5 (0.7-6.4)</td>
</tr>
<tr>
<td>Pancreas</td>
<td>8</td>
<td>2.2 (1.2-3.6)</td>
</tr>
</tbody>
</table>

Engels et al. 2008 Int J Cancer
AIDS-Defining Malignancies

- Kaposi sarcoma
- "Aggressive non-Hodgkin lymphoma"
- Cervical cancer
Non AIDS-Defining Malignancies

Hodgkin lymphoma

Head and Neck Cancer

Lung Cancer

Anogenital Cancer

Liver Cancer
Immunosuppression and Risk of KS

Incidence of KS 1993-2002

Malignancies in HIV/AIDS

People Living with HIV/AIDS
Other Factors and Trends

Aging Population
Prolonged Infection
Prolonged Drug Exposure
Carcinogen Exposure
Oncovirus Exposure

Future Trends
AIDS Defining Malignancies

Kaposi Sarcoma

Non-Hodgkin Lymphoma

Cervical Cancer

Standardized Incidence Ratio

Pre HAART  | Early HAART  | Later HAART
---|---|---
60000 | 45000 | 30000

Pre HAART  | Early HAART  | Later HAART
---|---|---
80 | 60 | 20

Pre HAART  | Early HAART  | Later HAART
---|---|---
8 | 6 | 4
Non-AIDS Defining Malignancies

**Head and Neck Cancer**

- Pre HAART
- Early HAART
- Later HAART

**Anogenital Cancer**

- Pre HAART
- Early HAART
- Later HAART

**Hepatocellular Cancer**

- Pre HAART
- Early HAART
- Later HAART

**Lung Cancer**

- Pre HAART
- Early HAART
- Later HAART

**Hodgkin Lymphoma**

- Pre HAART
- Early HAART
- Later HAART
## Viral Malignancies in People with HIV

<table>
<thead>
<tr>
<th>Malignancy</th>
<th>Incidence (per 100,000 person years)</th>
<th>Standardized Incidence Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All Cancer Types</strong></td>
<td>468</td>
<td>2.1 (2.0-.23)</td>
</tr>
<tr>
<td><strong>AIDS Defining Cancers</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kaposi sarcoma</td>
<td>173</td>
<td>1,300 (1,100–1,500)</td>
</tr>
<tr>
<td>Non Hodgkin Lymphoma</td>
<td>109</td>
<td>7.3 (6.4–8.4)</td>
</tr>
<tr>
<td>Diffuse large B-cell lymphoma</td>
<td>50</td>
<td>9.6 (7.7–12)</td>
</tr>
<tr>
<td>Burkitt lymphoma</td>
<td>7</td>
<td>15 (7.9-27)</td>
</tr>
<tr>
<td>Primary CNS lymphoma</td>
<td>15</td>
<td>250 (160–360)</td>
</tr>
<tr>
<td>Invasive cervical cancer</td>
<td>44</td>
<td>2.9 (1.9-42)</td>
</tr>
<tr>
<td><strong>Non-AIDS Defining Cancers</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anogenital</td>
<td>10</td>
<td>9.2 (5.5–15)</td>
</tr>
<tr>
<td>Hodgkin Lymphoma</td>
<td>19</td>
<td>5.6 (3.9–7.8)</td>
</tr>
<tr>
<td>Head and Neck</td>
<td>14</td>
<td>1.7 (1.1–2.5)</td>
</tr>
<tr>
<td>Hepatocellular</td>
<td>8</td>
<td>2.7 (1.5–4.6)</td>
</tr>
<tr>
<td>Lung Cancer</td>
<td>59</td>
<td>2.6 (2.1–3.1)</td>
</tr>
<tr>
<td>Pancreas</td>
<td>8</td>
<td>2.2 (1.2–3.6)</td>
</tr>
</tbody>
</table>

Human Tumor Viruses

- World Health Organization estimates that worldwide:
  - 17.8% of cancer cases are caused by infection, 12% are caused by one of seven human tumor viruses

- Diverse viral types represented (DNA, RNA, retroviruses)

- Burden heaviest in resource limited settings

# Viral Etiology of Malignancies

<table>
<thead>
<tr>
<th>Malignancy</th>
<th>Virus</th>
<th>Attributable Fraction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kaposi sarcoma</td>
<td>Kaposi sarcoma herpesvirus (KSHV)</td>
<td>100%</td>
</tr>
<tr>
<td>Multicentric Castleman disease</td>
<td>Kaposi sarcoma herpesvirus</td>
<td>100%</td>
</tr>
<tr>
<td>Primary effusion lymphoma</td>
<td>KSHV (±EBV)</td>
<td>100% (80%)</td>
</tr>
<tr>
<td>Diffuse large B-cell lymphomas</td>
<td>Epstein Barr virus (EBV)</td>
<td>10-20%</td>
</tr>
<tr>
<td>Primary CNS lymphoma</td>
<td>Epstein Barr virus</td>
<td>80%</td>
</tr>
<tr>
<td>Burkitt lymphoma</td>
<td>Epstein Barr virus</td>
<td>Variable (20-90%)</td>
</tr>
<tr>
<td>Plasmablastic lymphoma</td>
<td>Epstein Barr virus</td>
<td>80%</td>
</tr>
<tr>
<td>Hodgkin lymphoma</td>
<td>Epstein Barr virus</td>
<td>30-50%</td>
</tr>
<tr>
<td>Nasopharyngeal carcinoma</td>
<td>Epstein Barr virus</td>
<td>&gt;90%</td>
</tr>
<tr>
<td>Leiomyosarcoma</td>
<td>Epstein Barr virus</td>
<td>10%</td>
</tr>
<tr>
<td>Invasive cervical carcinoma</td>
<td>Human papillomavirus</td>
<td>100%</td>
</tr>
<tr>
<td>Anogenital carcinoma</td>
<td>Human papillomavirus</td>
<td>100%</td>
</tr>
<tr>
<td>Head and neck carcinoma</td>
<td>Human papillomavirus</td>
<td>20-30%</td>
</tr>
<tr>
<td>Primary hepatocellular carcinoma</td>
<td>Hepatitis B and C</td>
<td>20-50%</td>
</tr>
<tr>
<td>Adult T cell leukemia/lymphoma</td>
<td>Human T lymphotrophic virus (HTLV)</td>
<td>100%</td>
</tr>
<tr>
<td>Merkel cell carcinoma</td>
<td>Merkel cell polyomavirus</td>
<td>&gt;90%</td>
</tr>
</tbody>
</table>
Kaposi Sarcoma Incidence 1973-82

Number of Cases

- Never Married Young Men
- Ever Married Young Men


New York State Cancer Registry
Common Features of Tumor Viruses

• Establish chronic, commonly lifelong infection

• Infection generally non-permissive (non replicating)

• Necessary but not sufficient cause of cancer
  – Cofactors include immunosuppression and other infections
  – Commonly a byproduct of viral survival strategies

• Mechanisms of oncogenesis
  – Viral proteins promoting growth and enabling immune evasion
  – Viral integration sites in host genome
  – Virally induced chronic inflammation
Common Features of Tumor Viruses

• Implications for prevention
  — Vaccination (HPV)
  — Eradication (HCV)
  — Cofactor targeting (HIV for KSHV and EBV)

• Implications for therapy
  — Not amenable to conventional antiviral drugs
  — May present unique protein targets for therapies
  — May be amenable to immune modulation
  — Burden greatest in resource limited settings -- price and scalability crucial

• Implications for basic science
  — Provide insights into important cellular and oncogenic mechanisms
KSHV Associated Diseases

- Kaposi Sarcoma
- Primary Effusion Lymphoma
- Multicentric Castleman Disease

Kaposi Sarcoma Herpesvirus (KSHV)
# Molecular Piracy by KSHV

<table>
<thead>
<tr>
<th>Viral Gene</th>
<th>Human Analog</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORF K6/vMIP1</td>
<td>Macrophage inhibitory protein (MIP)</td>
<td>Th2 chemoattractant; angiogenesis</td>
</tr>
<tr>
<td>ORF K4/vMIP2</td>
<td></td>
<td>B cell growth; angiogenesis</td>
</tr>
<tr>
<td>ORF K4.1/vMIP3</td>
<td></td>
<td>Constitutively active GPCR; proliferation and angiogenesis</td>
</tr>
<tr>
<td>ORF K2/vIL-6</td>
<td>Interleukin 6 (IL-6)</td>
<td></td>
</tr>
<tr>
<td>ORF74/vGPCR</td>
<td>IL-8 receptor</td>
<td>Inhibits interferon signaling</td>
</tr>
<tr>
<td>ORF K9/vIRF-1</td>
<td>Interferon regulatory factors (IRF)</td>
<td></td>
</tr>
<tr>
<td>ORF K11.5/vIRF-2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ORF16/vBcl-2</td>
<td>Bcl-2</td>
<td>Inhibits apoptosis</td>
</tr>
<tr>
<td>ORF72/vCYC</td>
<td>D-type cyclins</td>
<td>Cell cycle control</td>
</tr>
<tr>
<td>ORF K13/vFLIP</td>
<td>FLICE-inhibitory protein (FLIP)</td>
<td>Inhibits Fas-mediated apoptosis</td>
</tr>
<tr>
<td>ORF K5</td>
<td>Ubiquitin ligase</td>
<td>Inhibits MHC expression</td>
</tr>
</tbody>
</table>
KSHV-associated MCD

- Lymphoproliferative disorder
- Most common in HIV coinfected patients
- Intermittent symptomatic flares:
  - inflammatory symptoms and evidence of systemic inflammation
  - hematologic cytopenias
  - biochemical abnormalities
  - lymphadenopathy, organomegaly
- Historical untreated median survival <2 years, though improving
- Progression to large cell lymphoma common

Human and Viral IL-6

Targeting KSHV Lytic Cells

KSHV Lytic Genes ORF36 (Phosphotransferase) and ORF21 (Thymidine Kinase) Activate ganciclovir (GCV) and zidovudine (AZT) to cytotoxic moieties

- Together these agents may be selectively cytotoxic to lytically active KSHV-infected B-cells responsible for KSHV-MCD pathogenesis

KSHV VL and Cytokines with Therapy

KSHV Viral Load

Viral IL-6

Human IL-6

\( p = 0.02 \)

\( p = 0.03 \)

### Clinical Responses

<table>
<thead>
<tr>
<th>Symptomatic</th>
<th>Biochemical</th>
<th>Radiographic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete 7 (50%)</td>
<td>Complete 3 (21%)</td>
<td>Complete 4 (29%)</td>
</tr>
<tr>
<td>Partial 5 (35%)</td>
<td>Partial 4 (29%)</td>
<td>Partial 1 (7%)</td>
</tr>
<tr>
<td>Overall 12 (86%)</td>
<td>Overall 7 (50%)</td>
<td>Overall 5 (36%)</td>
</tr>
<tr>
<td>Stable Disease 2 (14%)</td>
<td>Stable Disease 6 (43%)</td>
<td>Stable Disease 9 (64%)</td>
</tr>
<tr>
<td>Progressive Disease –</td>
<td>Progressive Disease 1 (7%)</td>
<td>Progressive Disease 1 (7%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Clinical Responses

Kaposi Sarcoma

- Multifocal angioproliferative tumor
- Most common in HIV, other immunodeficiencies, and advancing age (‘classical’ KS)
- High burden of disease in sub-Saharan Africa, where KSHV and HIV are endemic
- Highly responsive to changes in host immune status
- Disease commonly relapses and remits over years
# Kaposi Sarcoma Therapies

<table>
<thead>
<tr>
<th>Drug</th>
<th>Type</th>
<th>Class</th>
<th>Response Rate</th>
<th>FDA Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liposomal doxorubicin and daunorubicin</td>
<td>Systemic</td>
<td>Cytotoxic (Topoisomerase inhibition)</td>
<td>40-70%</td>
<td>1995/1997</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>Systemic</td>
<td>Cytotoxic (Microtubule stabilizer)</td>
<td>55-70%</td>
<td>1997</td>
</tr>
<tr>
<td>Interferon-alpha</td>
<td>Systemic</td>
<td>Immune modulator</td>
<td>25-40%</td>
<td>1988</td>
</tr>
<tr>
<td>Alitretinoin (Panretin)</td>
<td>Local</td>
<td>Retinoic acid derivative</td>
<td>~35%*</td>
<td>1999</td>
</tr>
</tbody>
</table>

- Unmet clinical needs
  - Effective agents with less toxicity
  - Agents deliverable long-term for relapsing disease
  - Effective oral agents
  - Agents deliverable in resource-limited settings
HIV VL: 277,444 copies/mL
CD4: 53 cells/µL

HAART

HIV VL: <50 copies/mL
CD4: 274 cells/µL
HIV VL: 66 copies/mL
CD4: 176 cells/µL

Doxil+IL-12

HIV VL: <50 copies/mL
CD4: 318 cells/µL
Immunomodulatory agents (IMiDs)

- **Thalidomide and derivatives**
  - Oral agents with immunomodulatory, anti-angiogenic, and anti-proliferative activity
  - Second generation: lenalidomide
  - Third generation: pomalidomide

- **Derivatives**
  - Reduce neurotoxicity and sedation
  - Increase immunomodulatory potency

- **Mechanisms of action**
  - Likely to vary by malignancy, but common pathways
  - Target Cereblon, an E3 ubiquitin ligase
  - Modulate transcription factors including IKZF1, IKZF3, IRF4

Subject 1 (HIV associated KS)

Baseline (Left Great Toe)

Week 4 (Partial Response)

Week 24 (Complete Response)

Subject 2 (Classical KS)

Baseline (Medial Aspect Right Foot)

Week 4 (Partial Response)

Week 24 (Complete Response)
<table>
<thead>
<tr>
<th>Disease</th>
<th>Study</th>
<th>Phase</th>
<th>Key Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anal Cancer</td>
<td>ChemoRTx+MTS-01</td>
<td>1</td>
<td>Topical Antioxidant for Local Toxicity</td>
</tr>
<tr>
<td>Cervical Cancer</td>
<td>Ixabepilone</td>
<td>2</td>
<td>Novel ChemoTx</td>
</tr>
<tr>
<td>Kaposi Sarcoma</td>
<td>Bevacizumab+Doxil</td>
<td>2</td>
<td>Antiangiogenesis with ChemoTx</td>
</tr>
<tr>
<td></td>
<td>Pomalidomide</td>
<td>1/2</td>
<td>Oral Immune Modulation and Antiangiogenesis</td>
</tr>
<tr>
<td>KSHV Inflammatory Cytokine Syndrome</td>
<td>Natural History and Antiviral</td>
<td>NA</td>
<td>Natural History and Virus Activated Cytotoxic Therapy</td>
</tr>
<tr>
<td></td>
<td>Therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multicentric Castleman Disease</td>
<td>Natural History and Antiviral</td>
<td>NA</td>
<td>Natural History and Virus Activated Cytotoxic Therapy</td>
</tr>
<tr>
<td></td>
<td>Therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tocilizumab</td>
<td>2</td>
<td>Anti-IL-6 ± Antiviral Therapy</td>
</tr>
<tr>
<td>Primary CNS Lymphoma</td>
<td>Rituximab+MTX</td>
<td>2</td>
<td>Radiation-sparing ChemolImmuRx</td>
</tr>
<tr>
<td>Diffuse Large B-cell Lymphoma</td>
<td>daEPOCH-RR</td>
<td>2</td>
<td>Response-guided Infusion ChemoTx</td>
</tr>
<tr>
<td>Burkitt Lymphoma</td>
<td>daEPOCH-R</td>
<td>2</td>
<td>Infusion ChemoTx</td>
</tr>
<tr>
<td>Primary Effusion Lymphoma</td>
<td>Pomalidomide-daEPOCH-R</td>
<td>1</td>
<td>Immune modulation and ChemoTx</td>
</tr>
</tbody>
</table>
Summary Points

- Elevated risk of malignancy remains a defining feature of HIV infection
- Evolving epidemiology: AIDS-defining and non-AIDS-defining malignancies now make approximately equal contributions to burden of cancer in HIV
- Viral tumors are especially important causes of malignancy in people with HIV
- Viral tumors present unique control points
  - prevention and early intervention prior to malignancy
  - leveraging unique viral targets
  - enhancing host immune responses
Acknowledgements

- **HIV and AIDS Malignancy Branch**
  Robert Yarchoan
  Kathleen Wyvill
  Thomas Uldrick
  Karen Aleman

- **Biostatistics and Data Management Unit**
  Seth Steinberg

- **Protocol Support Office**
  Therese White

- **Laboratory of Pathology**
  Stefania Pittaluga
  Richard Lee

- **Laboratory of Cellular Oncology**
  Giovanna Tosato

- **Viral Resistance Program**
  Frank Maldarelli

- **Technology Transfer Unit**
  Bob Wagner

- **Clinical Center, National Institutes of Health**
  Margaret Bevans

- **Molecular Pharmacology Unit**
  Cody Peer
  Kathy Compton
  Douglas Figg

- **Analytical and Functional Biophotonics Section, National Institute of Child Health Research**
  Jana Kainerstorfer
  Amir Gandjbakhche

- **Viral Oncology Section, Frederick National Laboratory for Cancer Research**
  Denise Whitby
  Vickie Marshall

- **HIV Pathogenesis Unit, National Institute of Allergy and Infectious Diseases**
  Irini Sereti
  Amrit Singh
  Stig Larsen
  Stephen Kovacs

- **Celgene Corporation and Celgene Global Health**
  Jerry Zeldis and colleagues

- **Patients and their families**