Meeting the Challenges of AIDS and Non-AIDS-Related Malignancies in PLWH

Hamid Shaaban, MD
Director, Regional Cancer Center
St Michael’s Medical Center

Malignancies in HIV Disease

<table>
<thead>
<tr>
<th>AIDS-Defining</th>
<th>Virus</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Kaposis’s Sarcoma</td>
<td>HHV-8</td>
</tr>
<tr>
<td>• Non-Hodgkin’s Lymphoma (systemic and CNS)</td>
<td>EBV, HHV-8</td>
</tr>
<tr>
<td>• Invasive Cervical Carcinoma</td>
<td>HPV</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Non-AIDS Defining</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Anal Cancer</td>
<td>HPV</td>
</tr>
<tr>
<td>• Hodgkin’s Disease</td>
<td>EBV</td>
</tr>
<tr>
<td>• Leiomyosarcoma (pediatric)</td>
<td>EBV</td>
</tr>
<tr>
<td>• Squamous Conjunctival Carcinoma</td>
<td>HPV (?)</td>
</tr>
<tr>
<td>• Hepatoma</td>
<td>HBV, HCV</td>
</tr>
</tbody>
</table>

A range of infection-related cancers occur at increased rates in PLWH compared to the general population. Smoking continues to be a major contributor to increased cancer risk.

AIDS-defining malignancies (ADMs):

- Kaposis’s Sarcoma (Human Herpes Virus-8)
- Non-Hodgkin’s lymphoma - now has a higher incidence than Kaposis’s Sarcoma in the US (EBV-Burkitt’s Lymphoma)
- Primary CNS lymphoma

Non-AIDS-defining malignancies (NADMs):

- Hodgkin’s Lymphoma
- Anal & Rectal Cancer
- Hepatocellular Carcinoma
- Lung cancer (smoking)
- Testicular cancer

A Grulich et al, Lancet 2007
Non-AIDS-Defining Malignancies (NADMs)

- Anal cancer (120 fold up)
- Hodgkin lymphoma (20 fold up)
- Hepatocellular cancer (5 fold up)
- Lung cancer (2 fold up)

- Note: Risk of breast cancer, prostate cancer, colon cancer is not increased in HIV (+) people in comparison to HIV (-) people

JCO 27:884, 2009

HIV-Associated Cancers: Incidence Pre and Post HAART

- Standard incidence ratios for common AIDS-defining and non-AIDS-defining cancers in the early and later HAART era and in the context of tumor-associated oncogenic viruses

- AIDs (AIDS-defining cancers), DLBCL (diffuse large B cell lymphoma), EBV (Epstein-Barr virus), HPV (human papillomavirus), N/A (not available), NADCs (non-AIDS-defining cancers), NHL (non-Hodgkin lymphoma), PCNSL (primary central nervous system lymphoma), SIR (standard incidence ratio)

CASCADE Collaboration:
Overall Mortality and Causes of Death
Non-AIDS Endpoint
SMART Study

- Randomized trial of continuous viral suppression (VS) vs drug conserving, intermittent HAART (DC), CD4 250-350
- N=5472 Study prematurely stopped due to higher deaths and other endpoints in DC

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Number</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVD</td>
<td>79</td>
<td>42</td>
</tr>
<tr>
<td>Hepatic</td>
<td>17</td>
<td>12</td>
</tr>
<tr>
<td>Renal</td>
<td>11</td>
<td>10</td>
</tr>
<tr>
<td>NA Cancer</td>
<td>60*</td>
<td>36</td>
</tr>
</tbody>
</table>

*25% Fatal


Estimated number of people living with HIV aged 50 and older by region, 1995-2013

Cancer and Ageing

- Estimated age-specific incidence rates for all cancers combined

Analysis of the Australian Cancer Database, 2016
Relative frequency of malignancy types in PLWH

E Lanoye et al, Int J Cancer, 2011

Increased malignancy cases in 2010, PLWH, USA

E Engels et al, JNCI 2015;107:dju503

Increased malignancy cases, by transmission, PLWH, USA

E Engels et al, JNCI 2015;107:dju503
Summary

- The spectrum of malignancies in PLWH has transformed as the use of potent antiretroviral therapy (ART) has become widespread.
- The incidence of KS and NHL has decreased markedly, but there has been a relative increase in malignancies that collectively are referred to as non-AIDS-defining cancers (NADCs) compared with the general population.
- NADCs now are a major factor contributing to mortality in PLWH.

### AIDS-DEFINING MALIGNANCIES

- **Kaposi Sarcoma**
  - Viral Etiology: Kaposi sarcoma herpesvirus (KSHV) 100%

- **Multicentric Castleman Disease**
  - Viral Etiology: Kaposi sarcoma herpesvirus 100%

- **Primary effusion lymphoma**
  - Viral Etiology: KSHV (± EBV) 100% (80%)

- **Diffuse large B-cell lymphomas**
  - Viral Etiology: Epstein-Barr virus (EBV) 10-20%

- **Primary CNS lymphoma**
  - Viral Etiology: Epstein-Barr virus 80%

- **Burkitt lymphoma**
  - Viral Etiology: Epstein-Barr virus Variable (20-90%)

- **Plasmablastic lymphoma**
  - Viral Etiology: Epstein-Barr virus 80%

- **Hodgkin lymphoma**
  - Viral Etiology: Epstein-Barr virus 30-50%

- **Nasopharyngeal carcinoma**
  - Viral Etiology: Epstein-Barr virus >90%

- **Leiomyosarcoma**
  - Viral Etiology: Epstein-Barr virus 10%

- **Invasive cervical carcinoma**
  - Viral Etiology: Human papillomavirus 100%

- **Anogenital carcinoma**
  - Viral Etiology: Human papillomavirus 100%

- **Head and neck carcinoma**
  - Viral Etiology: Human papillomavirus 20-30%

- **Primary hepatocellular carcinoma**
  - Viral Etiology: Hepatitis B and C 20-50%

- **Adult T cell leukemia/lymphoma**
  - Viral Etiology: Human T lymphotrophic virus (HTLV) 100%

- **Merkel cell carcinoma**
  - Viral Etiology: Merkel cell polyomavirus >90%

- **Parkin**
  - Viral Etiology: Human T lymphotrophic virus (HTLV) 100%

- **Int J Cancer**
  - Viral Etiology: Human T lymphotrophic virus (HTLV) 100%

### Viral Etiology of Malignancies
Kaposi’s Sarcoma

- Kaposi sarcoma (KS) is a low-grade soft tissue sarcoma of vascular origin that is associated with infection with human herpesvirus (HHV)-8 (also known as the KS-associated herpesvirus).
- Infection with HHV-8 precedes and is predictive of the development of KS.
- KS is primarily a disease of men; early in the HIV epidemic, KS was noted in 20 to 30 percent of HIV-infected men who have sex with men.
- With the widespread use of ART, the incidence decreased dramatically.
Pulmonary KS has Poor Prognosis

5-year overall survival: pKS—49% vs KS—82%

Median survival: Pre-HAART- 4 mos, HAART- 20 mos

Palmieri et al HIV Med 2006;7,291-293
Treatments for Kaposi’s Sarcoma

**Local**
- Radiation therapy
- Photodynamic (laser) therapy
- Intralesional chemotherapy
- Cryotherapy
- Alitretinoin gel – topical 9-cis retinoic acid

**Systemic**
- Antiretroviral therapy
- Liposomal anthracyclines
- Paclitaxel
- Bleomycin
- Vinca alkaloids
- Alpha Interferon

---

**Indication for Systemic Therapy**

- Widespread skin involvement (usually more than 25 lesions)
- Extensive cutaneous KS unresponsive to local treatment or ART
- Extensive edema
- Symptomatic visceral involvement
- Patients request for rapid tumor control
- Immune reconstitution inflammatory syndrome (ie, progressive KS within weeks after initiation of ART)

---

**KS Response to HAART**

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Response</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leitch et al HAART+</td>
<td>20</td>
<td>14(71%)</td>
<td>31 mo</td>
</tr>
<tr>
<td>Leitch et al HAART-</td>
<td>18</td>
<td>3(13%)</td>
<td>7 mo</td>
</tr>
<tr>
<td>Gill J et al HAART+</td>
<td>21</td>
<td>10(48%)</td>
<td></td>
</tr>
<tr>
<td>Pappapizos</td>
<td>26</td>
<td>22(85%)</td>
<td></td>
</tr>
<tr>
<td>Cattelan et al</td>
<td>14</td>
<td>12(86%)</td>
<td></td>
</tr>
<tr>
<td>Dupont et al</td>
<td>19</td>
<td>10(53%)</td>
<td></td>
</tr>
</tbody>
</table>

---

Potential for HHV-8-Directed Therapy for Kaposi’s Sarcoma

- Gamma herpes viruses (e.g., HHV-8 and EBV) can transform normal cells into cancerous ones
- Foscarnet
  - May induce regression of tumors in early Kaposi’s sarcoma and in multicentric Castleman’s disease
- Cidofovir
  - No activity in a small number of patients
- Valproic acid (AMC 038)
  - Upregulates lytic HHV8 genes and may enhance CTLs
- Depsipeptide, histone deacetylase inhibitor
  - Effective in inducing cell death in HHV-8 infected PEL
- Bortezomib (Velcade) +/- Ganciclovir
- Thalidomide
- MTOR inhibitors- inhibitors of the mechanistic target of rapamycin (mTOR) pathway and appear to have activity in patients with KS
- Bevacizumab
- Imatinib- c-kit is expressed on KS cells

Pathogenesis of Kaposi sarcoma

- Several viral gene products of HHV-8 affect both cell cycle regulation and the control of apoptosis, and segments of the HHV-8 genome contain viral oncopgenes that are important in the pathogenesis of tumor formation.
- Most of the spindle cells within the KS lesions show latent infection with HHV-8, although a small proportion of cells express lytic cycle genes.
- The limited number of viral genes expressed during latency are those that permit the virus to replicate within the host cell as an episome while disrupting the function of tumor-suppressor genes and avoiding recognition by the host immune system.
- On the other hand, viral genes expressed during the lytic cycle may be particularly important in increased expression of growth factors, such as vascular endothelial growth factor (VEGF), that stimulate angiogenesis and activate growth regulatory pathways, such as the phosphoinositide 3-kinase (PI3K) pathway, that lead to dysregulated cell growth.
Diffuse Large B cell Lymphoma

Pathology of AIDS-Related Non-Hodgkin’s Lymphoma (NHL)

- Small noncleaved-cell lymphoma
  - Burkitt’s lymphoma and Burkitt-like lymphoma
- Immunoblastic lymphoma (primary CNS)
- Diffuse large-cell lymphoma (90% CD20+)
  - Large noncleaved-cell lymphoma
  - CD30+ anaplastic large B-cell lymphoma
- Plasmablastic lymphoma
- Advanced stage (>75% III or IV)
- Extranodal involvement
  - Central nervous system, liver, bone marrow, gastrointestinal

**Lymphoma in PLWH**

- 50-100 fold increased incidence of aggressive NHL (in comparison to HIV-negative people)
- Some increased incidence of Hodgkin lymphoma
- Primary central nervous system lymphoma – CD4 cells < 50/µl (and often < 10/µl)

**HIV-Associated NHL: Practical Approach**

- Diffuse large B cell (most common)
- Burkitt lymphoma
- Primary CNS lymphoma (rare today)
- Plasmablastic lymphoma (rare)
- Primary effusion lymphoma (rare)

**HIV-Associated NHL**

- B symptoms common
- Often extra nodal (liver, gastric, rectum, kidney, skin involvement)
- Clinically aggressive
- Stage similarly to HIV (-) NHL
Therapeutic Approaches for AIDS-Related NHL

- Outgrowth of lymphoma treatment in general
  - Multiple agent, non-cross resistant chemotherapy
  - Increase dose intensity (infusional therapy, high dose or multiple drugs)
  - Central nervous system treatment or prophylaxis
  - Supportive antibiotics and hematopoietic growth factors
- Importance of ART
- Use of monoclonal antibodies (rituximab) AMC 010 and 034
- High dose chemotherapy with ASCT

HIV-Associated DLBCL

- Multiple studies of CHOP or EPOCH variants ± Rituximab
- EPOCH with concurrent or sequential rituximab (AMC 034)
- Concurrent better, OAS 70% at 2 years*
- Short course EPOCH with dose-dense rituximab (NCI)
- OAS 68% at 5 years
- * 23/106 patients had Burkitt lymphoma
**Meeting the Challenges of AIDS and Non-AIDS-Related Malignancies in PLWH**

---

**Short Course EPOCH with Dose-Dense Rituximab**

![Graph showing CD4+ T-cell counts](image)


---

**Treatment of HIV-Associated Diffuse Large B Cell Lymphoma**

- Dose-adjusted R-EPOCH (preferred) or R-CHOP
- Consider not using rituximab in patients with CD4 < 50/µl
- ART
- Avoid zidovudine (more cytopenias)
- Supportive care with peg-filgrastim, pneumocystis, candida, HSV-2 prophylaxis

---

**Primary CNS Lymphomas in PLWH**

- Incidence: <5% of AIDS patients. Now very rare
- Diagnostic approaches
  - Cranial CT or MRI scan
  - Most important differential diagnosis: toxoplasmosis
  - Stereotactic brain biopsy essential for diagnosis
    - When biopsy not possible, EBV-PCR of CSF is useful, 100% sensitive, 80% specific
- Therapeutic approaches
  - Traditional: whole brain radiation (4000-5000 cGy), 10% 1yr survival
  - High-dose methotrexate based chemotherapy
  - Non-AIDS patients: shows promise
  - The addition of rituximab to MTX-based regimens may provide additional benefit and is well tolerated
  - Salvage chemotherapy options include:
    - High dose cytarabine, rituximab and temozolomide, pemetrexed, temsirolimus

Primary Effusion Lymphomas in PLWH

- B-cell non-Hodgkin’s lymphoma
  - Most cases are dually infected with HHV-8 and EBV
  - Median survival: 6 months
- Traditional treatment: cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP)
- High-dose methotrexate plus CHOP
  - Retrospective series of 7 patients treated:
    - 3 in complete remission 18, 26, and 78 months after diagnosis
    - 3 died with progressive PEL
    - 1 achieved complete remission, but died with plasmablastic non-Hodgkin’s lymphoma at 9 months


Plasmablastic Lymphoma

- Rare (~3% of HIV-associated NHL)
- Mass lesion in gums/palate, but can be elsewhere (liver, GI tract, lungs, muscle)
- Often diagnosed by dentists
- Poor outcome (median survival 11 months; 5 year survival 24%), most deaths due to lymphoma

Summary

- PLWH are at increased risk for systemic non-Hodgkin lymphoma (NHL). The treatment of systemic NHL in the setting of HIV is complicated by the patient’s immunocompromised state and also requires specific treatment for the HIV.
- ART is started or modified (if already begun) to control the HIV infection and allow for the administration of chemotherapy and/or radiation therapy. As in the HIV-seronegative population, the choice of therapy is principally determined by the subtype of NHL and the stage of disease. Modifications are made based upon the degree of immunosuppression from HIV as measured by the CD4 count.
- For most patients with DLBCL who have a CD4 count >50 cells/microl, we suggest the combination of CHOP plus rituximab (R-CHOP) rather than CHOP alone.
- The decision to use rituximab in the setting of a CD4 count <50 cells/microl must be individualized. For most patients with DLBCL who have a CD4 count <50 cells/microl, we suggest CHOP chemotherapy without rituximab rather than the combination. Caution is advised if rituximab is incorporated into CHOP chemotherapy in the setting of CD4 count <50/microl.
Meeting the Challenges of AIDS and Non-AIDS-Related Malignancies in PLWH

Summary

• For DLBCL patients with >80 percent growth fraction, or plasmablastic histology in the setting of CD4 count >50/µL, we suggest the standard dose-adjusted EPOCH (etoposide, vincristine, and doxorubicin plus oral prednisone and IV bolus cyclophosphamide) regimen plus rituximab rather than R-CHOP. In such cases, we suggest concurrent rather than sequential rituximab.

• If treatment with R-EPOCH is chosen, supportive care should include prophylaxis for Pneumocystis jiroveci pneumonia (PCP, previously Pneumocystis carinii pneumonia), and antibiotic prophylaxis for enteric organisms. Given the high incidence of recurrent Herpes simplex, Herpes zoster, and Candida infections in this population, many clinicians also advise instituting antiviral and antifungal prophylaxis.

CERVICAL CANCER

World Incidence of Common Cancers

- Globally, breast cancer is the leading female cancer....
- BUT in the developing world cervical cancer is the #1 cancer killer in women
- High co-morbidity of cervical cancer with HIV
Estimated cervical cancer incidence worldwide (2012)

Global Primary Prevention:
HPV Vaccination

Global Secondary Prevention:
**Cause: Human Papillomavirus (HPV)**

- Double stranded DNA virus
- Grouped into low and high risk depending on malignant potential
- Over 150 different genotypes / 40 types infect anogenital system and oropharynx
- Infects both men and women
- Transmitted sexually (in most cases)
- Worldwide types 16/18 most common
- 80% eliminated by immune system within ± 18 months in most cases; 20% persist


**Risk Factors for HPV Infection**

- Age of first intercourse/early sexual debut
- Number of lifetime partners
- Current use of oral birth control
- Educational level/Poverty/Diet
- Smoking
- Family history
- HIV OVERRIDES ALL OF THESE TRADITIONAL RISK FACTORS
Natural history of HPV infection based on non-PLWH

- Incubation (1–8 months)
- First Lesion
- Active Growth (3–6 months)
- Immune Response
- Host Containment (3–6 months)
- About 9 months
- Late Stage
- Sustained clinical remission
- Persistent or recurrent disease

Natural history of cervical cancer in HIV negative patients

- HPV Infection
- Low-grade CIN (CIN 1)
- High-grade CIN (CIN 2/3)
- Invasive Cancer

- 60% Low-grade
- 28% High-grade
- 10–15 years?


Natural history of cervical cancer

- CIN 1
- CIN 2
- CIN 3
- Cancer

- 10–15 years?

CERVICAL CANCER: CLINICAL PROGRESSION

Normal ► HSIL (CIN2/3) ► ICC

IN NON-PLWH, THIS PROCESS CAN TAKE 15 YEARS
IN PLWH, IT IS FASTER

Cervical cancer in women living with HIV

- The risk of HPV infection – including infection with multiple high-risk HPV types – is substantially higher in HIV+ women
- HIV+ women are at 2-5x higher risk of cervical pre-cancer and cancer
- Prolonged life-expectancy on ART means they now live long enough to develop and die from cancer than OIs.
- HIV+ women present with cervical cancer at much younger ages
- Treatment of cervical cancer is also more complicated in HIV+ women, making cure more difficult to achieve


HIV / AIDS and Cervical Dysplasia Prevalence rates – higher

- USA -16.2% Dysplasia (LSIL 14.1%, HSIL 2.1%)
  - 4% Dysplasia in HIV negative
- Ireland (Europe) 28.7% had abnormal cervical cytology, 51.1% were human papillomavirus DNA-positive and 21.8% tested positive for human papillomavirus mRNA
- Brazil 23.4% Dysplasia
- Zambia 76% Dysplasia (HSIL 33%, LSIL 43%)
- Guinea 50.8% Dysplasia
- South Africa 51% Dysplasia (HSIL 18% and 23.5% LSIL)
- South Africa - rural areas (unpublished confirmed reports of 60% HSIL)
- HIV unknown status 26% Dysplasia

HIV / AIDS and Cervical Dysplasia Prevalence rates – higher

- USA -16.2% Dysplasia (LSIL 14.1%, HSIL 2.1%)
  - 4% Dysplasia in HIV negative
- Ireland (Europe) 28.7% had abnormal cervical cytology, 51.1% were human papillomavirus DNA-positive and 21.8% tested positive for human papillomavirus mRNA
- Brazil 23.4% Dysplasia
- Zambia 76% Dysplasia (HSIL 33%, LSIL 43%)
- Guinea 50.8% Dysplasia
- South Africa 51% Dysplasia (HSIL 18% and 23.5% LSIL)
- South Africa - rural areas (unpublished confirmed reports of 60% HSIL)
- HIV unknown status 26% Dysplasia

HIV / AIDS and Cervical Dysplasia Prevalence rates – higher

- USA -16.2% Dysplasia (LSIL 14.1%, HSIL 2.1%)
  - 4% Dysplasia in HIV negative
- Ireland (Europe) 28.7% had abnormal cervical cytology, 51.1% were human papillomavirus DNA-positive and 21.8% tested positive for human papillomavirus mRNA
- Brazil 23.4% Dysplasia
- Zambia 76% Dysplasia (HSIL 33%, LSIL 43%)
- Guinea 50.8% Dysplasia
- South Africa 51% Dysplasia (HSIL 18% and 23.5% LSIL)
- South Africa - rural areas (unpublished confirmed reports of 60% HSIL)
- HIV unknown status 26% Dysplasia

HIV / AIDS and Cervical Dysplasia Prevalence rates – higher

- USA -16.2% Dysplasia (LSIL 14.1%, HSIL 2.1%)
  - 4% Dysplasia in HIV negative
- Ireland (Europe) 28.7% had abnormal cervical cytology, 51.1% were human papillomavirus DNA-positive and 21.8% tested positive for human papillomavirus mRNA
- Brazil 23.4% Dysplasia
- Zambia 76% Dysplasia (HSIL 33%, LSIL 43%)
- Guinea 50.8% Dysplasia
- South Africa 51% Dysplasia (HSIL 18% and 23.5% LSIL)
- South Africa - rural areas (unpublished confirmed reports of 60% HSIL)
- HIV unknown status 26% Dysplasia

HIV / AIDS and Cervical Dysplasia Prevalence rates – higher

- USA -16.2% Dysplasia (LSIL 14.1%, HSIL 2.1%)
  - 4% Dysplasia in HIV negative
- Ireland (Europe) 28.7% had abnormal cervical cytology, 51.1% were human papillomavirus DNA-positive and 21.8% tested positive for human papillomavirus mRNA
- Brazil 23.4% Dysplasia
- Zambia 76% Dysplasia (HSIL 33%, LSIL 43%)
- Guinea 50.8% Dysplasia
- South Africa 51% Dysplasia (HSIL 18% and 23.5% LSIL)
- South Africa - rural areas (unpublished confirmed reports of 60% HSIL)
- HIV unknown status 26% Dysplasia

HIV / AIDS and Cervical Dysplasia Prevalence rates – higher

- USA -16.2% Dysplasia (LSIL 14.1%, HSIL 2.1%)
  - 4% Dysplasia in HIV negative
- Ireland (Europe) 28.7% had abnormal cervical cytology, 51.1% were human papillomavirus DNA-positive and 21.8% tested positive for human papillomavirus mRNA
- Brazil 23.4% Dysplasia
- Zambia 76% Dysplasia (HSIL 33%, LSIL 43%)
- Guinea 50.8% Dysplasia
- South Africa 51% Dysplasia (HSIL 18% and 23.5% LSIL)
- South Africa - rural areas (unpublished confirmed reports of 60% HSIL)
- HIV unknown status 26% Dysplasia

HIV / AIDS and Cervical Dysplasia Prevalence rates – higher

- USA -16.2% Dysplasia (LSIL 14.1%, HSIL 2.1%)
  - 4% Dysplasia in HIV negative
- Ireland (Europe) 28.7% had abnormal cervical cytology, 51.1% were human papillomavirus DNA-positive and 21.8% tested positive for human papillomavirus mRNA
- Brazil 23.4% Dysplasia
- Zambia 76% Dysplasia (HSIL 33%, LSIL 43%)
- Guinea 50.8% Dysplasia
- South Africa 51% Dysplasia (HSIL 18% and 23.5% LSIL)
- South Africa - rural areas (unpublished confirmed reports of 60% HSIL)
- HIV unknown status 26% Dysplasia
Primary Prevention of Cervical Cancer: HPV Vaccination

**Vaccine protects against 70% of CC**

**Dosage:** 0.5 ml given at 0, 1 and 6 months for 15-26 years old

**Efficacy of 2 doses:** study by Dobson et al (JAMA 2013) showed immunogenicity of 2 doses given to girls 9-13 yrs at 0 and 6 months was as effective against types 16 & 18 as 3 doses; now 2 doses (at times 0 and 6 months) may be given to 9-14 year olds

**TYPES:**
- Bivalent (GSK): 16, 18 HR HPV types (Cervarix)
- Quadrivalent (Merck): 6, 11, 16, 18 (Gardasil)
- Nanovalent (6, 11, 16, 18, 31, 33, 45, 52, 58) (Gardasil 9)

**ISSUES - Safety in HIV & Pregnancy**
- Safe in HIV: not live attenuated vaccine
- Safe in pregnancy, but not recommended

**ELIGIBILITY:** All genders 9-26yrs

---

**Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents**

**Recommendations for Preventing Human Papillomavirus Infections**

**Preventing First Episode of HPV Infection**
Indications for HPV Vaccination: HIV-infected; aged 9–26 years (BIII)

**Note:** Please refer to Pediatric OI guidelines for vaccination of boys and girls younger than age 13.

**Vaccination Schedules**

For Women: HPV recombinant vaccine 9 valent (Types 6, 11, 16, 18, 31, 33, 45, 52, 58) 0.5mL IM at 0, 1–2, and 6 months (BIII), or
- HPV recombinant vaccine quadrivalent (Types 6, 11, 16, 18) 0.5mL IM at 0, 1–2, and 6 months (BIII), or
- HPV recombinant vaccine bivalent (Types 16, 18) 0.5mL IM at 0, 1–2, and 6 months (BIII)

For Men: HPV recombinant vaccine 9 valent (Types 6, 11, 16, 18, 31, 33, 45, 52, 58) 0.5mL IM at 0, 1–2, and 6 months (BIII), or
- HPV recombinant vaccine quadrivalent (Types 6, 11, 16, 18) 0.5mL IM at 0, 1–2, and 6 months (BIII)

---

**TABLE. Recommended number of doses and intervals for human papillomavirus (HPV) vaccine, by age at series initiation and medical conditions — United States, 2016**

*ACIP recommends routine HPV vaccination for adolescents at age 11 or 12 years; vaccination may be given starting at age 9 years.

1. Persons with primary or secondary immunosuppressing conditions that might reduce cell-mediated or humoral immunity
2. A 6- to 2-dose schedule of HPV vaccine, the minimum interval between the first and second doses is 5 months.
3. For persons who were not adequately vaccinated previously; ACIP recommends vaccination for females through age 26 years and for males through age 21 years; males ages 22 through 26 years may be vaccinated in such as B lymphocyte antibody deficiencies, T lymphocyte complete or partial defects, HIV infection, malignant neoplasms, transplantation, autoimmune diseases, or immunosuppressive therapy because immune response to vaccination might be attenuated.

**Recommended number of doses and intervals for human papillomavirus (HPV) vaccine, by age at series initiation and medical conditions — United States, 2016**

<table>
<thead>
<tr>
<th>Population</th>
<th>Recommended number of doses</th>
<th>Recommended interval between doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persons initiating HPV vaccination at ages 9 through 16 years, except immunocompromised persons</td>
<td>3</td>
<td>0, 0–10 months*</td>
</tr>
<tr>
<td>Persons initiating HPV vaccination at ages 16 through 26 years and immunocompromised persons</td>
<td>3</td>
<td>0, 0–10 months*</td>
</tr>
</tbody>
</table>

---

**Quoted from CDC guidelines:**
1. Meites et al. MMWR. 2016;65(49);1405-8.
Recommendations for preventing HPV Infections

- HIV-infected individuals should use latex condoms during every act of sexual intercourse to reduce the risk of exposure to sexually transmitted pathogens, including human papillomavirus (HPV) (AII).
- Ideally, HPV vaccine should be administered before an individual becomes sexually active (AIII).
- HPV vaccination is recommended in HIV-infected females and males aged 11 to 12 (AIII) and 13 to 26 (BIII) years. HPV vaccination also can be administered to HIV-infected males and females aged 9 to 10 years. The bivalent and quadrivalent vaccines are approved for females and the quadrivalent vaccine is approved for males.
- Sexually active female adolescents who are HIV-infected should have routine cervical cancer screening whether or not they have been vaccinated (AIII).

Secondary Prevention of Cervical Cancer:

Screening Modalities:

1. The Papanicolaou test (Pap smear or Pap test)
   - is a routine test used to screen for cervical cancer.
   - The test looks for abnormal changes in the cells of the cervix that could indicate a precancerous condition or cervical cancer.

2. Liquid-based cytology (LBC)

3. VIA/VILI (Visual inspection with acetic acid/Lugol’s iodine)
   - “See & Treat” screening involving the application of vinegar/dye to the cervix and identifying an abnormality

4. HPV Testing
   - Molecular testing for DNA of HPV

Recommendations for Cervical Cancer Screening for HIV-Infected Women

HIV-infected Women Aged <30 Years:
- If younger than 21, known to be HIV-infected or newly diagnosed with HIV and sexually active, screen within 1 year of onset of sexual activity regardless of mode of HIV infection.
- If HIV-infected women ages 21-29 should have a Pap test following initial diagnosis.
- Pap test should be done at baseline and every 12 months (BIII).
- Results of 3 consecutive Pap tests are normal, follow-up Pap tests can be performed every 3 years (BIII).
- For Papanicolaou and HPV testing is not recommended for women younger than 18.

HIV-infected Women Aged ≥30 Years
Pap Testing (BII)
- Pap test should be done at baseline and every 12 months (BIII).
- Some experts recommend a Pap test at 6 months after the baseline test (GIII).
- Results of 3 consecutive Pap tests are normal, follow-up Pap tests can be performed every 5 years (BIII).

HPV Co-Testing:
- Pap test and HPV co-testing should be done at baseline (BII).
- If result of the Pap test is normal and HPV co-testing is negative, follow-up Pap test and HPV co-testing can be performed every 5 years (BIII).
- If one year follow-up Pap test is abnormal or HPV testing is positive, refer to colposcopy is recommended.
Treatment

Of pre-cancerous lesions:

Removal abnormal Transformation Zone(TZ):

1. Excisional treatment:
   • LEEP / LLETZ: Loop electrical excision procedure/ Large Loop Electrical Excision of the TZ
     – under colposcopic guidance, outpatient, specific criteria
   • Cold knife cone biopsy

2. Ablative treatment:
   – Cryotherapy: cryo-necrosis with N2O, specific criteria

Of cancerous lesions:

• Hysterectomy
• Chemo-radiation
• Palliative care


NON-AIDS DEFINING MALIGNANCIES (NADM)

Hodgkin's Lymphoma

Lung Cancer

Head and Neck Cancer

Hepatocellular Cancer

Anal Cancer

Pathogenesis of NADM

• Some are virally-induced cancers, but not all
• HIV-tat may transactivate cellular genes or proto-oncogenes, inhibit tumor suppressor genes
• Microsatellite alterations (MA) due to genetic instability in PLWH (eg, 6 fold higher number of MA in lung cancer of PLWH over persons without HIV)
• Increase susceptibility to effects of carcinogens (tobacco)
• Population differences based on genetics and exposure to carcinogens
• Decreased immune surveillance

Incidence of NADM in the HIV Outpatient Study (HOPS)

- 7893 HIV patients in Chicago compared to Illinois cancer registry patients
- 1992-2002
- Determined age-, race-, smoking-, and gender-adjusted rates for NADCs:
  - Increased rates for Hodgkin's (77.4), head/neck (10), anorectal (5.0), melanoma (4.1), and lung (3.6)
  - Excess lung cancers is related primarily to tobacco use
  - Cancers occur at an earlier age in HIV than non-HIV and in both men and women
  - No excess risk for breast, colon, or prostate cancer

Summary of NADMs with Increased Occurrence in USA

- Anal
- Hodgkin's Disease: mixed cellularity/lymphocyte-depleted types
- Lung – adenocarcinoma – tobacco-related
- Testicular mostly seminoma
- Skin: basal, squamous cell, melanoma
- Multiple myeloma
- Leukemia mostly M4, M5
- Leiomyosarcoma in pediatrics (1 in 5000, 8-14% of all cancers in kids)


NADMs: Other Cancers

- Lip
- Head and neck cancers
- Penile
- Conjunctival
- Little evidence for breast, colon, prostate and liver cancers occurring at higher rates, although study results vary
- In Africa, less increase in NADMs perhaps due to
  - Underdiagnosis
  - Earlier deaths (from other causes)

Cancer Risk in PLWH Over 65 Years Old

- Case-cohort study
- 5% Medicare registry sample
- All cancers in people over 65 in large cancer registry
- Association between HIV and cancer incidence
- Adjusted for age, race, sex, calendar year

Yanik EL, et al. AIDS. 2016

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Hazard Ratio Comparing HIV+ to HIV- [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kaposi sarcoma</td>
<td>79.2 (42.9-146)</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>1.01 (1.24-4.02)</td>
</tr>
<tr>
<td>Diffuse large B cell</td>
<td>5.56 (3.69-8.39)</td>
</tr>
<tr>
<td>Burkitt lymphoma</td>
<td>21.6 (6.91-68.5)</td>
</tr>
<tr>
<td>Other specified</td>
<td>1.16 (0.67-1.99)</td>
</tr>
<tr>
<td>Unspecified</td>
<td>0.78 (0.93-11.7)</td>
</tr>
<tr>
<td>Bladder</td>
<td>27.4 (22.6-34.5)</td>
</tr>
<tr>
<td>Hodgkin lymphoma</td>
<td>0.95 (4.89-10.3)</td>
</tr>
<tr>
<td>uterus</td>
<td>1.83 (1.46-5.97)</td>
</tr>
<tr>
<td>Lung</td>
<td>1.57 (1.21-1.91)</td>
</tr>
<tr>
<td>Colorectal</td>
<td>0.97 (0.69-1.36)</td>
</tr>
<tr>
<td>Breast</td>
<td>0.96 (0.56-1.65)</td>
</tr>
<tr>
<td>Prostate</td>
<td>0.78 (0.65-0.99)</td>
</tr>
</tbody>
</table>

5-year cumulative incidence (%) Yanik EL, et al. AIDS. 2016

LUNG CANCER
CD4 Count as a Predictor of Lung Cancer Risk and Prognosis

- 26,065 PLWH in VACS
- Incident non-small cell lung cancer cases
- Cox regression models for lung cancer risk, CD4 count
- Adjusted for: age, sex, race, smoking, h/o pneumonia or COPD
- Compared survival based on HIV status, CD4 +/- 200

<table>
<thead>
<tr>
<th>CD4 Analysis</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>12-month lagged value</td>
<td></td>
</tr>
<tr>
<td>&lt;200</td>
<td>1.6 (1.2-2.2)</td>
</tr>
<tr>
<td>200-500</td>
<td>1.2 (0.9-1.5)</td>
</tr>
<tr>
<td>12-month moving average</td>
<td></td>
</tr>
<tr>
<td>&lt;200</td>
<td>2.0 (1.4-2.7)</td>
</tr>
<tr>
<td>200-500</td>
<td>1.4 (1.1-1.8)</td>
</tr>
<tr>
<td>24-month moving average</td>
<td></td>
</tr>
<tr>
<td>&lt;200</td>
<td>1.7 (1.2-2.4)</td>
</tr>
<tr>
<td>200-500</td>
<td>1.3 (1.1-1.7)</td>
</tr>
</tbody>
</table>

SIGEL K et al. Abstract 728, CROI 2015

Smoking Outweighs HIV-Related Risk Factors for NADCs

- Adults in NA-ACCORD
- NADC
- HIV-related risk factors and smoking
- ≈40K adults, ≈160K person-years
- Most common cancers: lung (17%), anal (16%), prostate (10%), 9% HL, 7% liver, 7% breast

<table>
<thead>
<tr>
<th>Population-attributable risk (PAF), %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
</tr>
<tr>
<td>CD4&lt;200</td>
</tr>
<tr>
<td>200-500</td>
</tr>
<tr>
<td>200-500</td>
</tr>
</tbody>
</table>


US Preventive Services Task Force (USPSTF) Lung Cancer Screening Recommendations

**Annals of Internal Medicine**

**SCREENING FOR LUNG CANCER**

**CLINICAL SUMMARY OF U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATION**

Population: Adult men and women aged 55 to 80 who have a 30-pack-year smoking history and currently smoke or have quit within the past 15 y

Screen annually for lung cancer with low-dose computed tomography.

Lung Cancer Screening in PLWH Smokers

- 14 French clinical centers; single low-dose chest CT
- Inclusion: age ≥40, ever smoked in last 3 years, ≥20 pack-years, CD4 nadir <350, current CD4 >100
- 442 subjects:
  - Median age: 49.8, nadir CD4: 168, last CD4: 574
  - 90% with last viral load <50
  - Median smoking pack-years: 30
- 94 subjects (21%) had a significant finding
- 18 diagnostic procedures in 15 subjects


Lung Cancer Screening in HIV+ Smokers

<table>
<thead>
<tr>
<th>Patient</th>
<th>Screen Detected</th>
<th>Histology</th>
<th>Stage</th>
<th>Age</th>
<th>Pack Years</th>
<th>Viral load</th>
<th>Last CD4</th>
<th>Nadir CD4</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Yes</td>
<td>Adeno</td>
<td>IA</td>
<td>45</td>
<td>30</td>
<td>&gt;40</td>
<td>637</td>
<td>160</td>
</tr>
<tr>
<td>2</td>
<td>Yes</td>
<td>Adeno</td>
<td>IV</td>
<td>48</td>
<td>52</td>
<td>&gt;40</td>
<td>597</td>
<td>132</td>
</tr>
<tr>
<td>3</td>
<td>Yes</td>
<td>Adeno</td>
<td>IA</td>
<td>49</td>
<td>45</td>
<td>&lt;40</td>
<td>378</td>
<td>321</td>
</tr>
<tr>
<td>4</td>
<td>Yes</td>
<td>Adeno</td>
<td>IV</td>
<td>50</td>
<td>27</td>
<td>61</td>
<td>590</td>
<td>60</td>
</tr>
<tr>
<td>5</td>
<td>Yes</td>
<td>Adeno</td>
<td>IV</td>
<td>52</td>
<td>35</td>
<td>&lt;40</td>
<td>568</td>
<td>216</td>
</tr>
<tr>
<td>6</td>
<td>Yes</td>
<td>Adeno</td>
<td>IA</td>
<td>52</td>
<td>60</td>
<td>43</td>
<td>859</td>
<td>214</td>
</tr>
<tr>
<td>7</td>
<td>Yes</td>
<td>Squam</td>
<td>IA</td>
<td>54</td>
<td>26</td>
<td>&gt;40</td>
<td>345</td>
<td>72</td>
</tr>
<tr>
<td>8</td>
<td>Yes</td>
<td>Adeno</td>
<td>IIA</td>
<td>56</td>
<td>34</td>
<td>&lt;20</td>
<td>680</td>
<td>201</td>
</tr>
<tr>
<td>9</td>
<td>Yes</td>
<td>No histo</td>
<td>IA</td>
<td>58</td>
<td>21</td>
<td>&lt;20</td>
<td>573</td>
<td>218</td>
</tr>
<tr>
<td>10</td>
<td>No</td>
<td>Small cell</td>
<td>Extended</td>
<td>50</td>
<td>40</td>
<td>&lt;40</td>
<td>448</td>
<td>1</td>
</tr>
</tbody>
</table>

Conclusions: Screening is safe and effective; USPSTF guidelines may miss early CA
Questions: When to start screening? Which criteria- Age? Pack-years? CD4 nadir?


Do PLWH with lung cancer do badly?

Overall survival by HIV status: (A) All patients; (B) patients with stage I–IIIA NSCLC; (C) patients with stage IIIB-IV NSCLC; (D) patients who received stage-appropriate NSCLC treatment; (E) patients who did not receive NSCLC treatment

ANAL CANCER

Anal Anatomy: Landmarks

- Anal canal = intra-anal
  - Mucosa opposed at rest
  - Tone of external and internal sphincters
- Anal I-zone morphologically analogous to the cervical transformation zone
  - Region of squamous metaplastic
  - Variable
- Dentate line
- Anal verge = Anal opening
  - Visualized by gentle retraction of the buttocks
- Peri-anus = Anal margin
  - Extend 5 cm from verge

Cervix and Anus:
Lesions morphologically similar

Low grade

High grade

Cervix

Anus
Anal Cancer: Who is at risk? Targeted Screening

- MSM
- PLWH
- Women with HSIL/ cancer
  - Multifocal HPV-related disease
  - Vulvar/ perianal > cervix
- Other causes of immunosuppression
  - Solid organ transplantation
  - ?Other causes of immunosuppression
  - Autoimmune disease
  - Inflammatory bowel disease
  - Cancer chemotherapy

Anal Cancer: U.S. Screening Guidelines

- No national screening guidelines
- CDC: Acknowledges that some experts recommend anal cytologic screening for PLWH
- ACS: Anal cytology, sometimes called the anal Pap test, may be useful in early diagnosis of anal cancer and precancer (called anal intraepithelial neoplasia (AIN)) — some providers already recommend this test for people at high risk for anal malignancies such as PLWH
- New York State Department of Public Health AIDS Institute:
  - Clinicians should obtain anal cytology at baselines and annually in the following HIV-infected populations:
    - Men who have sex with men
    - Any patient with a history of anogenital condylomas
    - Women with abnormal cervical and/or vulvar histology

Journal of Lower Genital Tract Disease

Systmeic Review, Meta-Analysis, Narrative Review

Screening for Anal Cancer in Women

Anna Barbara Marzola, MD; Tanya W. Dornberg, MD; J. Michael Berry-Bevan, MD

Objective: The incidence of anal cancer is higher in women than men, but the reasons for this sex difference are not well understood. This article reviews the literature on anal cancer, HPV, and HPV-related disease in residents and nonresidents of the United States, to determine the incidence of anal cancer, HPV, and HPV-related disease in women.

Methods: A group of experts convened by the American Society for Colposcopy and Cervical Pathology and the International Society for the Study of Vulvar Disease evaluated the literature on anal cancer, HPV, and HPV-related disease in women.

Results: The overall prevalence of anal cancer is lower in women than men, but the relative risk is higher in women. The prevalence of HPV and anal cancer was highest among women with HIV and women who had a history of anogenital HPV infection.

Conclusion: The overall prevalence of anal cancer is higher in women than men, but the relative risk is higher in women. The prevalence of HPV and anal cancer was highest among women with HIV and women who had a history of anogenital HPV infection.

Meeting the Challenges of AIDS and Non-AIDS-Related Malignancies in PLWH
Anal Cancer and AIN: Screening and Diagnosis

HPV-related lesions of the anal canal

- Anal cytology
- **Digital anal-rectal examination (DARE)**
- High resolution anoscopy (HRA)
- HRA-directed anal biopsy

- **Link screening to treatment!**

Digital Anorectal Exam (DARE)

- Palpate for areas of:
  - Induration
  - Nodularity, etc
  - Pain
- This is the **cancer screening test!**
- Perform after anal cytology

Anal Cytology: Technique

- Use moistened Dacron swab
  - Not on wood stick!
  - Do not use pre-scored swab!
- Insert into canal until resistance
  - Above anal verge to distal rectum
- Rotate / apply pressure to walls of canal while removing sampling device
- Liquid-based cytology or direct smear
Anal Cytology: Goal

- Sample entire anal canal
- Anal transition zone
  - Analogous to cervical TZ
  - Squamous metaplasia
- Non-keratinized squamous mucosa
- Keratinized squamous mucosa

Anal Cytology: Normal Components

- Transformation Zone components:
  - Rectal columnar cells
  - Squamous metaplasia
- Nucleated squamous cells
- Anucleate squames

Anal Cytology: Organisms

- HSV
- Amoeba
- Candida
- Pinworm
John Hopkins Hospital Algorithm For Anal Cancer Screening Of High Risk Patients

- Initial abnormal anal Pap smear
  - Abnormal anal Pap smear
    - Endoscopy
    - HRA
    - HPV
  - Abnormal HRA
    - HPV
    - HRA
    - Low-grade positivity

- Refer back to HPV for viral and malignancy

Anal HPV Testing?

- No FDA-approved HPV test for anus
- Laboratories need to validate for this site

- Screening and triage?
  - Mixed reports of usefulness
  - High prevalence of HPV in at-risk populations
  - High negative predictive value
    - May be useful in post-HRA and post-treatment management
  - HPV 16 genotyping?
**Anal Cytology / Histology**

- Anal cytology used as screening test!
- Anal cytology often under-represents grade of disease
- Positive predictive value of HSIL is very good
- Anal cytology is complimentary to:
  - HRA and
  - Histology and
  - *Digital examination*
- “Gold Standard”: HRA-guided biopsy

**High-resolution Anoscopy**

- Acetowhite lesions
- Contour changes
- Vascular changes
Estimates of Anal Cancer Progression

- In PLWH with HSIL anal cytology, there is an estimated five year progression rate to invasive anal cancer of 1.7%.
- Machalek et al. calculated the theoretical progression rate to be 1 in 377 per year in HIV-infected MSM (compared with 1 in 4196 per year in HIV-uninfected MSM).

Cachay E, et al. HIV medicine. Sept 6 2014

Current Unknowns

- Is effective treatment of anal HSIL possible?
- Will anal screening and treatment of anal HSIL lower the incidence of anal cancer?
- ANCHOR: Large multisite trial in U.S.
  - HIV-infected men and women
  - Biopsy proven anal HSIL
  - Treatment vs. non-treatment (active monitoring) arms

https://anchorstudy.org/about
THE BAD NEWS

- The incidence of AIN and anal cancer is high among HIV-seropositive women and MSM (both HIV- and HIV+)
- ART has limited positive effect on HPV-related malignancy
- Evidence is mounting that the incidence of anal cancer will continue to rise among HIV+ MSM

THE GOOD NEWS

- At-risk men and women should be considered for screening and treatment of anal HSIL
  - Treatment is improving!
- At risk men and women should be screened for anal cancer with a digital rectal exam
  - Early detection of anal cancer has real benefits
- HPV vaccines have the potential to prevent anal HPV infection and ultimately, anal cancer

PREVENTION OF CANCER IN PLWH
Preventing cancer in PLWH

- Maintaining undetectable HIV viral load
- For lymphoma, detectable virus is a cause of immune stimulation that increases cancer risk
- At least some of the effect appears to be independent of immune deficiency

START: Early ART reduces cancer risk

Table 2. Primary and Secondary End Points.

<table>
<thead>
<tr>
<th>End Point</th>
<th>Immediate Initiation Group (N = 226)</th>
<th>Deferred Initiation Group (N = 225)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kaposis' sarcoma</td>
<td>1 (0.05)</td>
<td>11 (0.14)</td>
<td>0.59 (0.01-0.77)</td>
<td>0.02</td>
</tr>
<tr>
<td>Malignant lymphoma</td>
<td>3 (0.04)</td>
<td>19 (0.14)</td>
<td>0.36 (0.08-1.16)</td>
<td>0.67</td>
</tr>
<tr>
<td>Cancer not related to AIDS</td>
<td>9 (0.33)</td>
<td>18 (0.26)</td>
<td>0.50 (0.22-1.13)</td>
<td>0.09</td>
</tr>
</tbody>
</table>

J Lundgren et al, NEJM, 2015

Recommendations for Preventing and Treating Hepatitis B Virus (HBV) Infection (page 1 of 7)

Preventing HBV Infection

- Infants born to HBsAg-positive mothers should be vaccinated at birth (A).
- Infants born to HBsAg-negative mothers should receive hepatitis B immune globulin (HBIG) at birth, followed by the HBV vaccine series at age 2 months (A).

For HBV Exposed Infants

- Infants born to HBsAg-positive mothers should be vaccinated at birth (A).
- Infants born to HBsAg-negative mothers should receive hepatitis B immune globulin (HBIG) at birth, followed by the HBV vaccine series at age 2 months (A).

For HBV Exposed Adults

- Infants born to HBsAg-positive mothers should be vaccinated at birth (A).
- Infants born to HBsAg-negative mothers should receive hepatitis B immune globulin (HBIG) at birth, followed by the HBV vaccine series at age 2 months (A).
Preventing infection-related cancer in PLWH

- Treating carcinogenic infections
- Cure the HCV infection
- Treat the HBV infection
- KSHV/EBV — no current therapeutic options but risk is low if HIV treated and immune function maintained
- HPV — Screen and treat pre-invasive lesions of the cervix/anus


NIH guidelines for anal cancer screening in PLWH

- “At this time, no national recommendations exist for routine screening for anal cancer. However, some specialists recommend anal cytologic screening or high resolution anoscopy for HIV positive men and women (CIII)”
- “An annual digital anal examination may be useful to detect masses on palpation that could be anal cancer (BIII)”


Cancer in Ageing PLWH

- New patterns of cancer in ageing PLWH are beginning to develop
- Most “cancers of ageing” are not increased in this population
- Key elements of reducing risk of malignancy are
  - Achieving and maintaining a close to normal immunity and undetectable HIV viral load
  - Preventing, treating or curing oncogenic co-infections
  - Anal cancer a stand out in terms of unresolved issues
  - Addressing lifestyle risk factors (smoking, alcohol)


## Conclusion

- PLWH are living longer and hence morbidity and mortality from malignancies is on the rise.
- It is imperative to quantify and characterize malignancies in HIV, as it may vary in different populations around the world.
- The management and treatment of malignancies in PLWH should be vigorous and appropriate to the situation.
- Side effects associated with ART and chemotherapy should be treated/prevented.
- Prevention strategies for infection-associated malignancies need to be investigated.
- Effective and feasible treatment strategies are under development and need to be studied and tested worldwide.
Notes