

# AIDS-defining cancers

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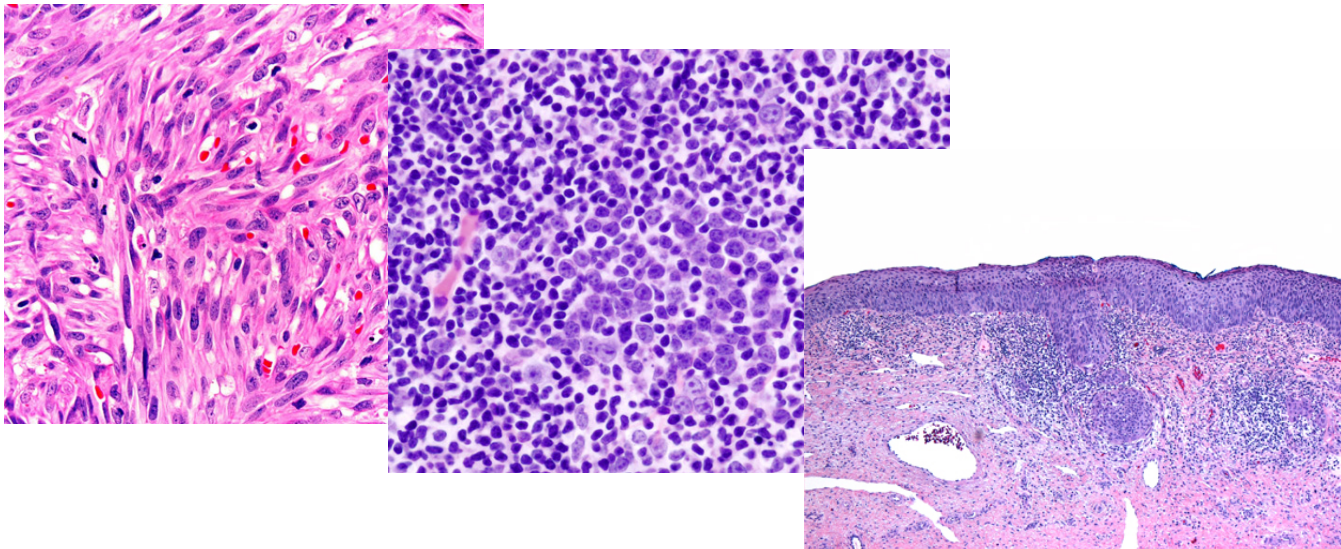
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# Objectives

- Identify the AIDS-defining cancers (ADC)
- ADC etiology/viral associations
- ADC epidemiology
- ADC risk factors
- Disproportionate, unfavorable characteristics of ADC in HIV+ population
- General diagnosis and treatment of ADC
- ADC screening guidelines, if available

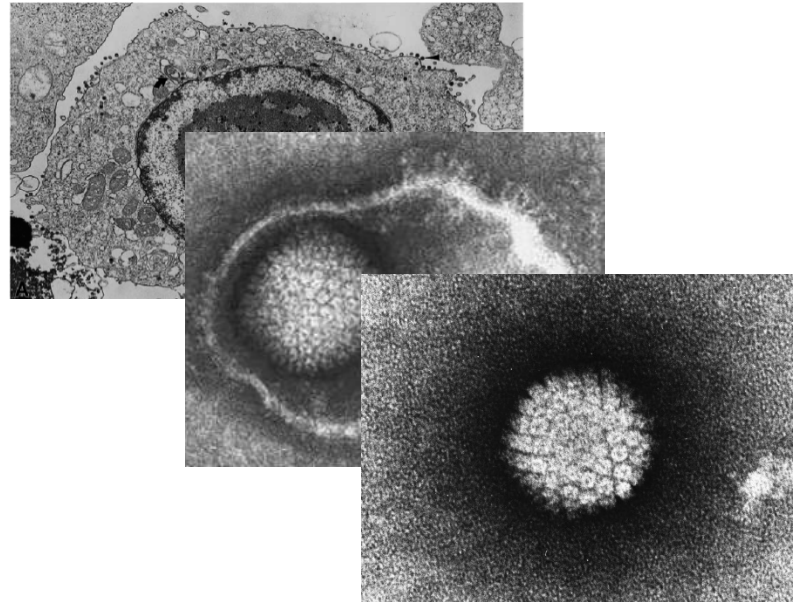
# AIDS-defining cancers

- Kaposi Sarcoma (KS)
- Non-Hodgkin Lymphoma (NHL)
- Invasive Cervical Cancer

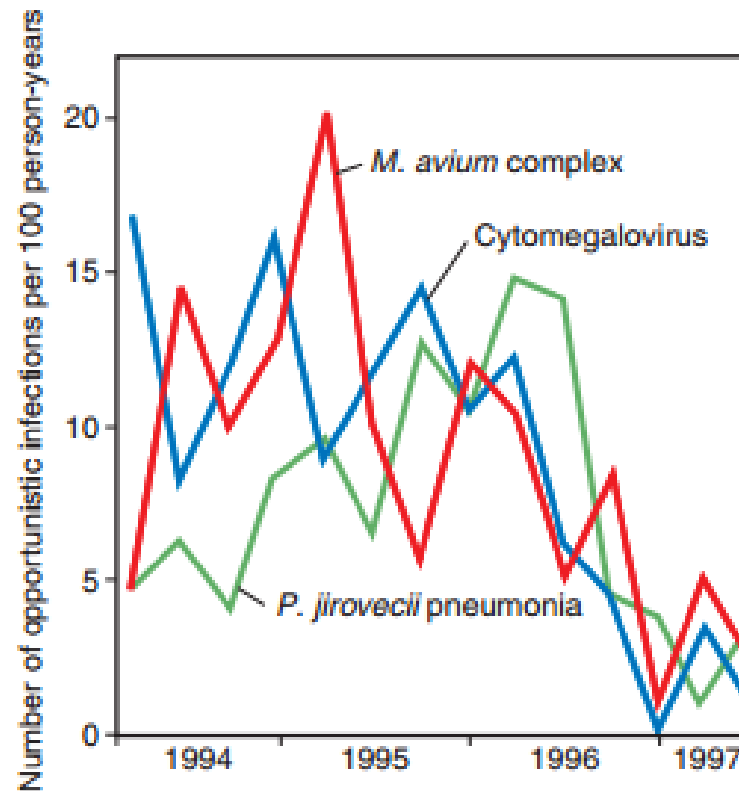


# AIDS-defining cancers

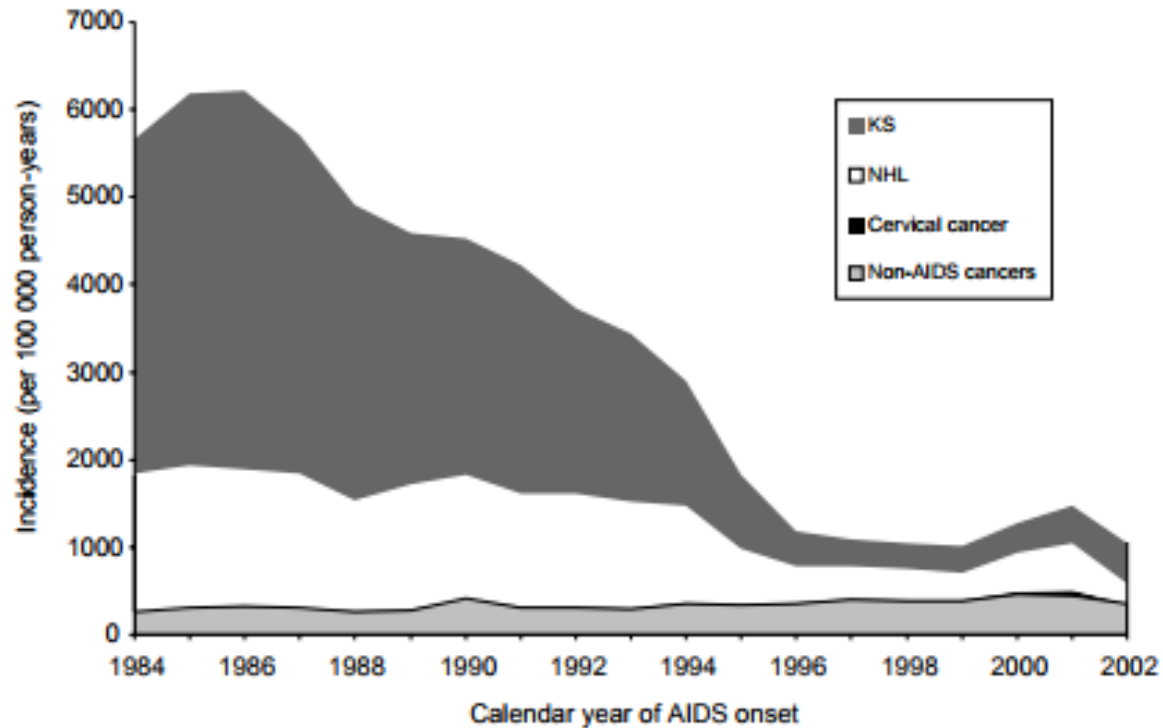
- AIDS-defining cancers are opportunistic diseases
- Viral culprits
  - HHV-8
  - EBV
  - HPV



# Opportunistic infections



# AIDS-defining cancers



# HHV8-associated cancers and conditions

- Kaposi Sarcoma (KS)
- Primary Effusion Lymphoma
- Multicentric Castleman's Disease
- Inflammatory Cytokine Syndrome



# HHV8-associated cancers

- KS described by Moritz Kaposi (Kohn), a Hungarian-born dermatologist in 1872
- Regarded as an indolent disease in elderly men of Mediterranean and Eastern European descent
- Recognized among MSM in 1980s
- Kaposi Sarcoma-associated herpesvirus (HHV-8) discovered in 1994



# HHV8-associated cancers

- In USA, 15%-20% of HIV- and 40% of HIV+ MSM are HHV-8 seropositive
- 99-100% of individuals with KS are HHV-8 seropositive

# Kaposi Sarcoma

- Classic
  - Indolent, usually on lower extremities, affects elderly men of Mediterranean/Eastern European descent
- Endemic
  - Certain African countries (prior to HIV pandemic)
  - Indolent in adults (resembles classic variant), but aggressive in children
- Epidemic
  - Affects HIV-infected individuals
  - Aggressive, often affects skin (not confined to lower extremities), oral cavity, GI, respiratory tracts
- Iatrogenic
  - Affects HIV-negative, immunosuppressed individuals
  - Aggressive



# Kaposi Sarcoma

- Risk factors in HIV infection
  - HHV-8 infection
  - CD4
    - Can occur at ANY CD4 count, but risk is substantially higher if  $<200$  cells/ $\mu\text{L}$
  - Low CD4 nadir
  - Absence of ART
  - Further immune suppression
    - Corticosteroid use (such as with *Pneumocystis pneumonia*)
  - Pro-inflammatory states
    - Opportunistic infection

Lodi S, Guiguet M, Costagliola D, Fisher M, de Luca A, Porter K, CASCADE Collaboration. Kaposi sarcoma incidence and survival among HIV-infected homosexual men after HIV seroconversion.. J Natl Cancer Inst. 2010;102(11):784.

Yanik EL, Napravnik S, Cole SR, Achenbach CJ, Gopal S, Olshan A, Dittmer DP, Kitahata MM, Mugavero MJ, Saag M, Moore RD, Mayer K, Mathews WC, Hunt PW, Rodriguez B, Eron JJ. Incidence and timing of cancer in HIV-infected individuals following initiation of combination antiretroviral therapy. Clin Infect Dis. 2013;57(5):756. Epub 2013 Jun 4.

# Kaposi Sarcoma

- Cutaneous
- Non-cutaneous (visceral)
  - Oral cavity
  - Lymph nodes
  - Intestines
  - Respiratory tract
  - Liver
  - Pancreas
  - Heart
  - Skeletal muscle
  - Testicles
  - Bone marrow

# Kaposi Sarcoma



Bruce Dezube, MD

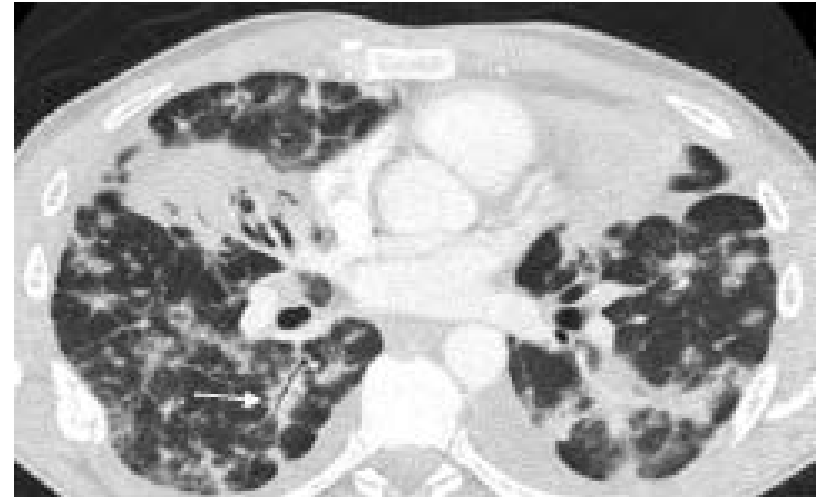


Bruce Dezube, MD

# Kaposi Sarcoma



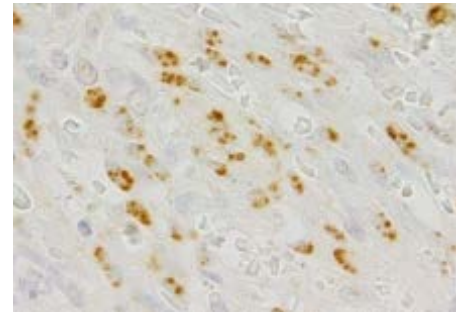
Shetty, KV MD



Hoskote, SS MD and Patel VP, MD

# Kaposi Sarcoma

- Highly vascular
  - Poorly-organized vascular spaces
- Malignant spindle cells
- Monocyte/macrophage infiltration
- Positive LANA (Latency Associated Nuclear Antigen-1) stain for HHV-8



# Kaposi Sarcoma

- Staging
  - T (tumor)
    - Minimal disease (confined to skin/node) – T0
    - Extensive disease (multiple sites, non-nodal viscera) – T1
  - I (immune system)
    - CD4 >200 – I0
    - CD4 <200 – I1
  - S (systemic illness)
    - Absent (no OIs, no B symptoms, Karnofsky performance score >70 ) – S0
    - Present (OI, B symptoms, Karnofsky performance score <70, other HIV/AIDS-related condition) – S1



# Kaposi Sarcoma

- Important considerations
  - HIV clinical status
  - GI involvement
    - FOBT, endoscopy
  - Pulmonary involvement
    - CXR, bronchoscopy

# Kaposi Sarcoma

- Treatment
  - ART
    - Usually all that's needed for T0 disease
  - IRIS can occur, and can be severe, especially in extensive disease or high baseline HIV viral load

# Kaposi Sarcoma

- Treatment
  - Local therapy
    - Cryotherapy
    - Intralesional chemotherapy
      - Vinblastine
      - Often several treatments needed
  - Radiation
    - When lesions are too big for intralesional chemotherapy

Epstein JB. Treatment of oral Kaposi sarcoma with intralesional vinblastine. *Cancer*. 1993;71(5):1722.

Donato V, Guarnaccia R, Dognini J, de Pascalis G, Caruso C, Bellagamba R, Morrone A. Radiation therapy in the treatment of HIV-related Kaposi's sarcoma. *Anticancer Res*. 2013 May;33(5):2153-7.



# Kaposi Sarcoma

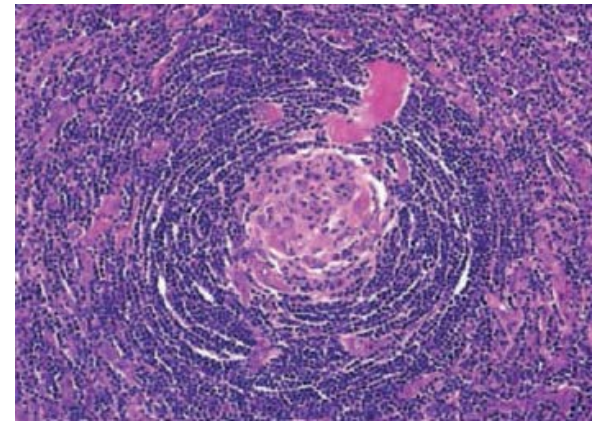
- Systemic chemotherapy
  - Indications
    - Extensive or refractory cutaneous disease
    - Symptomatic non-cutaneous disease
    - Extensive edema
    - IRIS
  - Agents
    - Doxorubicin/daunorubicin
    - Paclitaxel

# Primary Effusion Lymphoma

- HHV8-related, but it's one of the AIDS-related lymphomas. Stay tuned.....

# Multicentric Castleman's Disease

- Aggressive lymphoproliferative disorder
- Symptoms: fevers, weight loss, night sweats, generalized lymphadenopathy, splenomegaly
- Can progress to B cell plasmablastic lymphoma (and can co-exist with KS)
- High HHV-8 viral load
- Diagnosis: lymph node biopsy
- Treatment: Ganciclovir, rituximab, chemotherapy
  - *Treatment involves targeting HHV-8!*



# Kaposi Sarcoma-Associated Herpesvirus Inflammatory Cytokine Syndrome (KICS)

- Features of MCD (fevers, inflammation, high HHV8 viral load) but without characteristics of MCD on pathology
- Can overlap with other HHV8-associated cancers/conditions

# AIDS-Related Lymphomas

- Non-Hodgkin Lymphoma (Systemic) – 85%
- Primary CNS Lymphoma (non-systemic NHL) – 15%
- Primary Effusion Lymphoma – 1-4%

*Incidence is 25 – 150-fold higher than among the general population!*

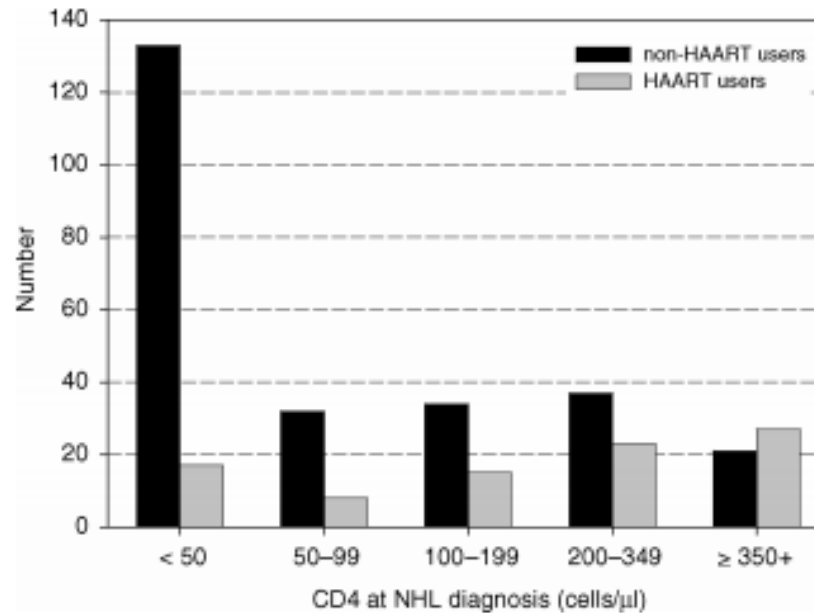


# Non-Hodgkin Systemic Lymphoma

- AIDS-related systemic NHL subtypes
  - Diffuse Large B-cell Lymphoma (75%)
  - Burkitt Lymphoma (25%)
  - Other (Plasmablastic Lymphoma, NHL-NOS)

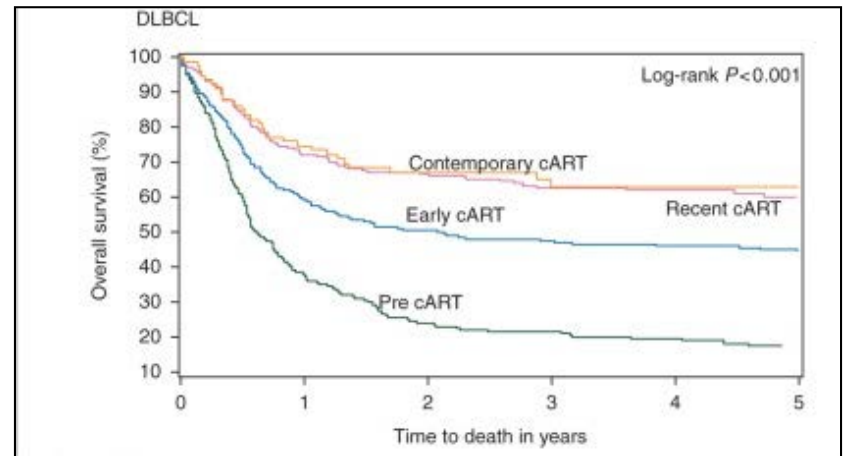
# Non-Hodgkin Systemic Lymphoma

- Risk factors:
  - Low CD4 count (and low CD4 nadir)



# Non-Hodgkin Lymphoma

- Risk factors:
  - Low CD4 count (and low CD4 nadir)
  - High HIV viral load (>100,000 copies/mL)
  - Absence of ART



Ann Oncol. 2015 May; 26(5): 958–966.

Guiguet M et al. Effect of immunodeficiency, HIV viral load, and antiretroviral therapy on the risk of individual malignancies (FHDH-ANRS CO4): a prospective cohort study. Lancet Oncol. 2009;10(12):1152

Silverberg MJ, Neuhaus J, Bower M, et al. Epidemiology and Social Risk of cancers during interrupted antiretroviral therapy in the SMART study. AIDS 2007;21(14):1957–63..

# Non-Hodgkin Systemic Lymphoma

- Risk factors:
  - Low CD4 count (and low CD4 nadir)
  - High HIV viral load (>100,000 copies/mL)
  - Absence of ART
    - ART interruption associated with 6-fold increase in cancer incidence
    - HIV viremia is thus an important risk factor
  - History of AIDS
  - Co-infection with EBV
    - Up to 80% of DLBCL are EBV-positive

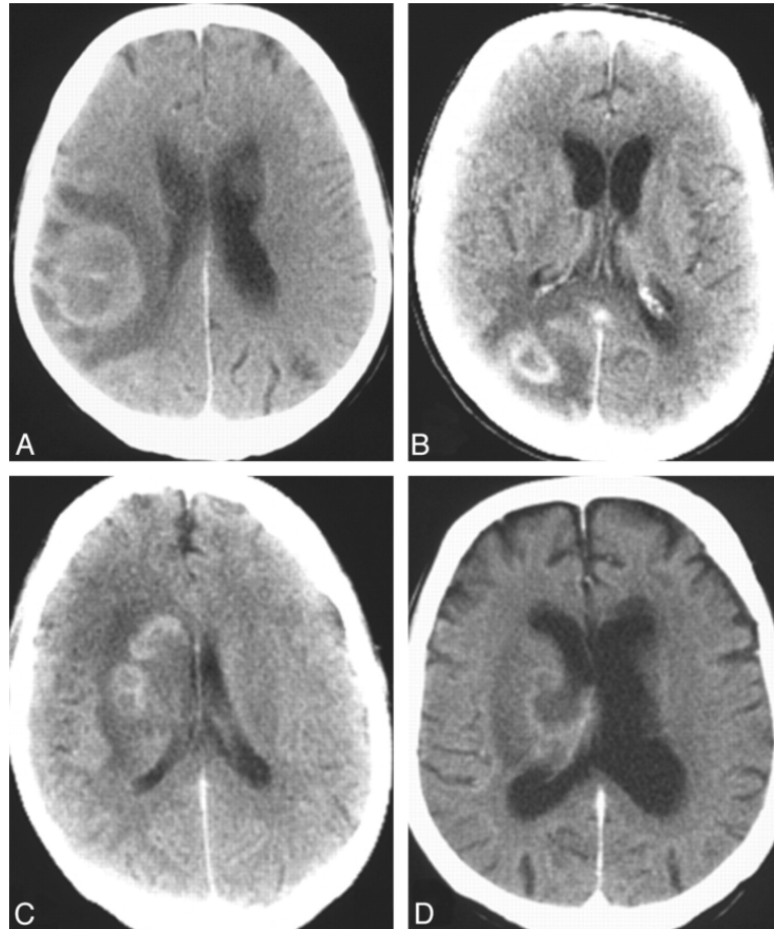
# Non-Hodgkin Systemic Lymphoma

- Clinical presentation
  - Since most are aggressive, B-cell lymphomas...
    - B symptoms (fevers, night sweats, weight loss)
    - Lymphadenopathy
    - Atypical locations (i.e. GI, CNS involvement)

# Primary CNS Lymphoma

- B-cell lymphoma
- Strong EBV association (virtually all are EBV+)
- Focal symptoms
  - Seizure
  - Altered mental status
- Non-focal symptoms
  - B symptoms

# Primary CNS Lymphoma





# Primary CNS Lymphoma

- Diagnosis
  - Establish presence of brain mass
  - Distinguish between PCL and CNS toxoplasmosis
    - Lumbar puncture with cytology and EBV DNA
    - Serologic Toxoplasma testing
    - Empiric Toxoplasma-directed antibiotics
    - Brain biopsy
- Treatment
  - Not well-defined, but ART is of substantial benefit





# Primary Effusion Lymphoma

- The HHV-8-related, AIDS-related lymphoma
- B-cell origin, often with EBV co-infection
- Usually occurs in pleural, pericardial or peritoneal body cavities
- Malignant cells are without a solid/mass component
- Can be extra-cavitary (solid-tumor variant, usually involving GI tract)
- Poor prognosis

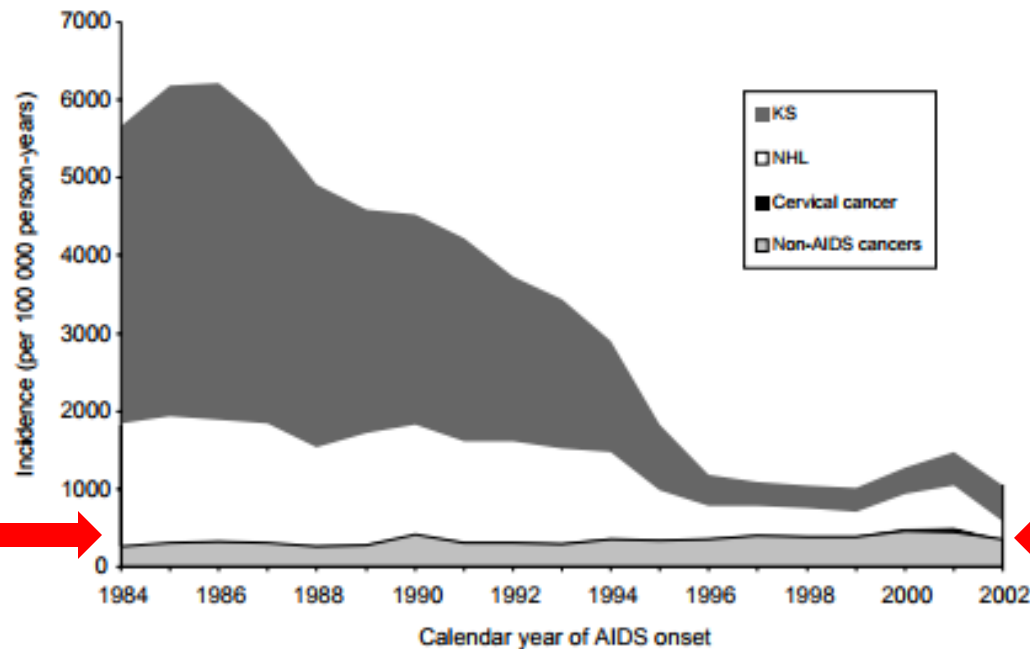
# Primary Effusion Lymphoma



Hara N, et al. Lymphoproliferative disorder in pleural effusion in a subject with past asbestos exposure. *Respiratory Medicine Case Reports*. 2015;16:169-171

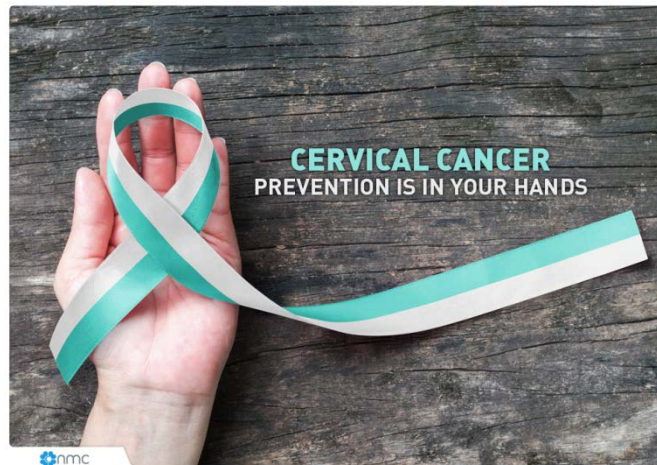
# Invasive Cervical Cancer

- Unlike KS and NHL, incidence has NOT decreased in the contemporary ART era



# Invasive Cervical Cancer

- Risk is 1.5 – 8 times that of general population
- Majority of burden is in developing countries
  - Lack of cervical cancer screening programs
  - Lack of quadrivalent HPV vaccine



# Invasive Cervical Cancer

- HIV+ women
  - are more likely to be **infected with HPV** (and have multiple HPV types)
  - are less likely to *clear* **HPV or atypical cells** (*independent of CD4 count!*)
  - are more likely to **develop intraepithelial neoplasia**
  - develop **higher grade lesions at faster rates**
  - have more **advanced disease at diagnosis** (higher grade tumors, metastases)
  - have **poorer response to therapy**
  - have **higher recurrence rates**
  - have **higher mortality rates**
- Strong correlation with immune status
  - Women with CD4 count >500 cells/uL have significantly higher remission and survival rates than women with CD4 count <500 cells/uL

Franceschi S, et al. Changing patterns of cancer incidence in the early- and late-HAART periods: the Swiss HIV Cohort Study. Br J Cancer. 2010;103(3):416.

Maiman M. Management of cervical neoplasia in human immunodeficiency virus-infected women. J Natl Cancer Inst Monogr 1998;23:43–9.

Maiman M, Fruchter RG, Serur E, et al. Human immunodeficiency virus infection and cervical neoplasia. Gynecol Oncol 1990;38:377–82.

Korn AP, Abercrombie PD, Foster A. Vulvar intraepithelial neoplasia in women infected with human immunodeficiency virus-1. Gynecol Oncol 1996;61:384–6.



# Cervical Cancer Screening

## *caveats in HIV infection*

- Initiate within first year after HIV diagnosis, but not later than age 21
- Screening should continue throughout a woman's lifetime (not stopping at 65)
- In women <30, screening should occur every 12 months. If 3 consecutive screens are normal, screening can occur every 3 years
- In women >30 and have had 3 normal consecutive annual screens with cytology alone, or 1 normal cotest screen (cytology and HPV testing), screening can occur every 3 years

# Anal Cancer

- Similar to cervical cancer, incidence has not decreased in the contemporary ART era
- The quadrivalent HPV vaccine has been shown to reduce anal HPV infection and neoplasia in men

# Anal Cancer

- There are no national recommendations for routine anal cancer screening, but should be strongly considered in HIV-infected MSM and women (especially if history of other HPV-related lesions)
- Anal cancer screening should NOT be performed without the availability of high-resolution anoscopy (HRA)



# Anal cancer

- Appropriate screening would include both cytology, HPV cotesting and DRE
- Abnormal cytology (ASCUS and LSIL), should get high-resolution anoscopy
- Any palpable masses on DRE or HSIL – Referral to colorectal surgery
- Consider annual screening after normal cytology

# Conclusion

- ADCs are opportunistic diseases
- KS and NHL have decreased in incidence, but remain leading causes of mortality and morbidity in HIV-infection
- While much more likely to occur in advanced disease, ADCs can occur in HIV regardless of immune status
- Cervical cancer incidence remains high
- Cervical (and anal) cancer screening are key components of HIV primary care

Thank you!