National Cancer Institute

Meeting the Challenges of Malignancies in People with HIV/AIDS

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

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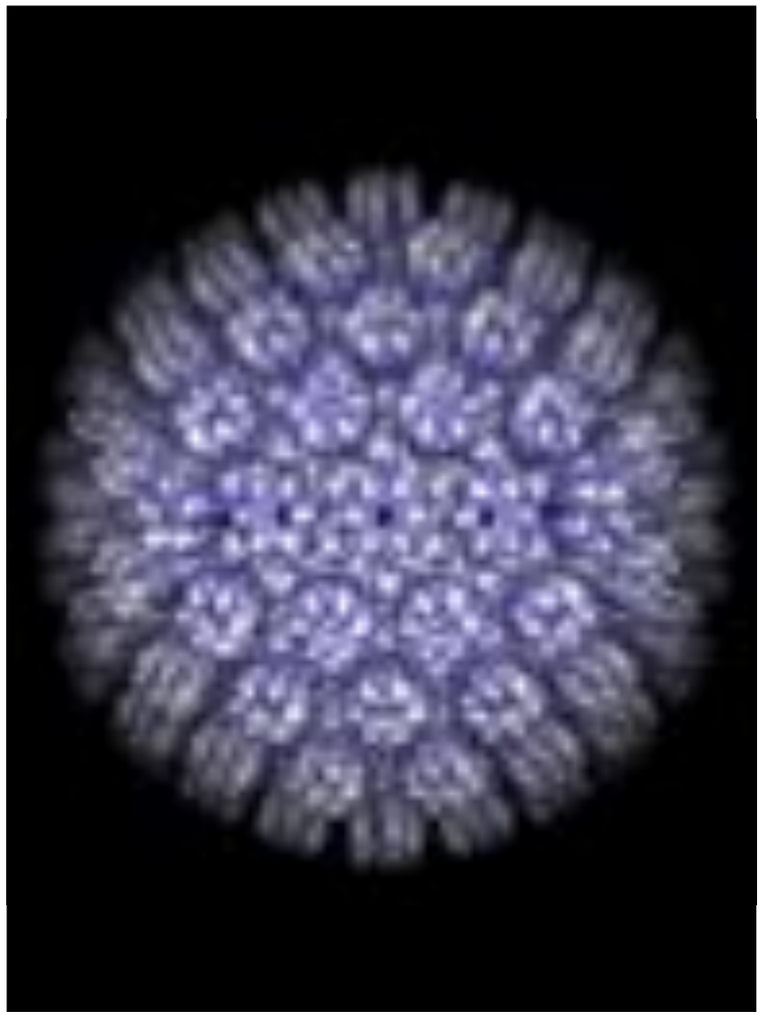
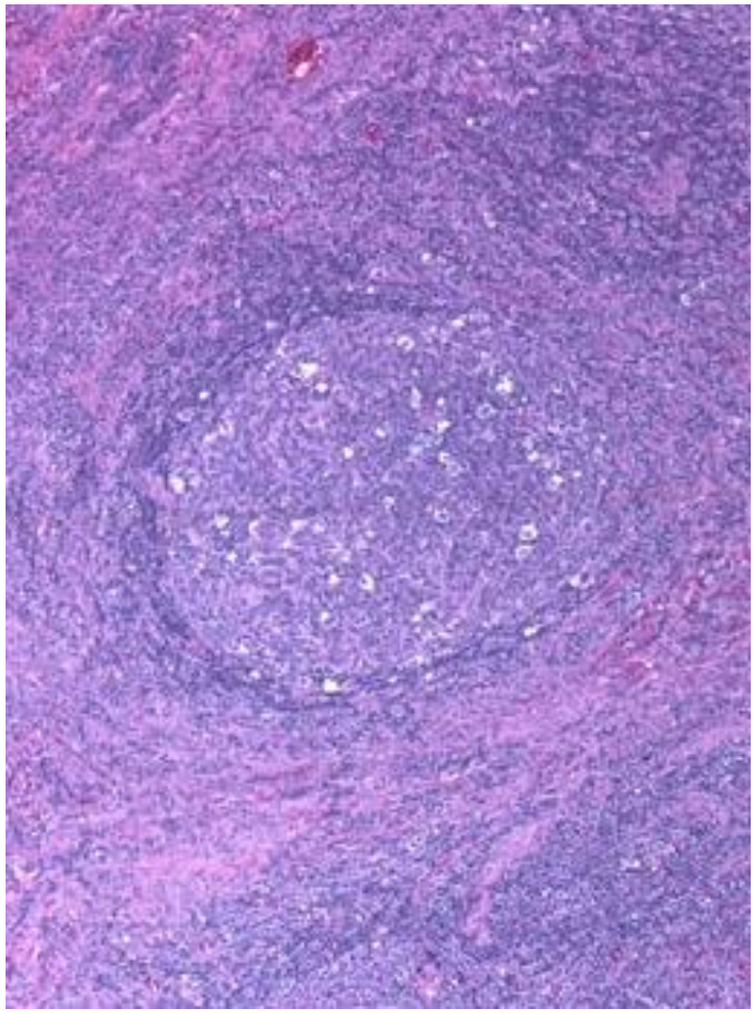
Outline

Cancers in People with HIV/AIDS



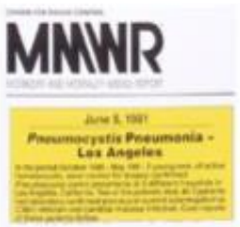
Human Tumor Viruses



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

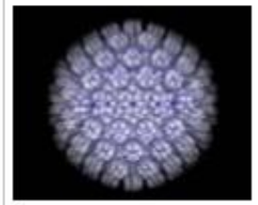
Primary Effusion Lymphomas
January 1989

Castleman Disease
January 1990

Hodgkin Lymphoma
July 1992

Cervical Cancer
January 1994

Kaposi Sarcoma Herpesvirus discov
January 1994



Pla
Aug

HAART
August 1996

1981 1982 1983 1984 1985 1986 1987 1988 1989 1990 1991 1992 1993 1994 1995 1996 1997 19

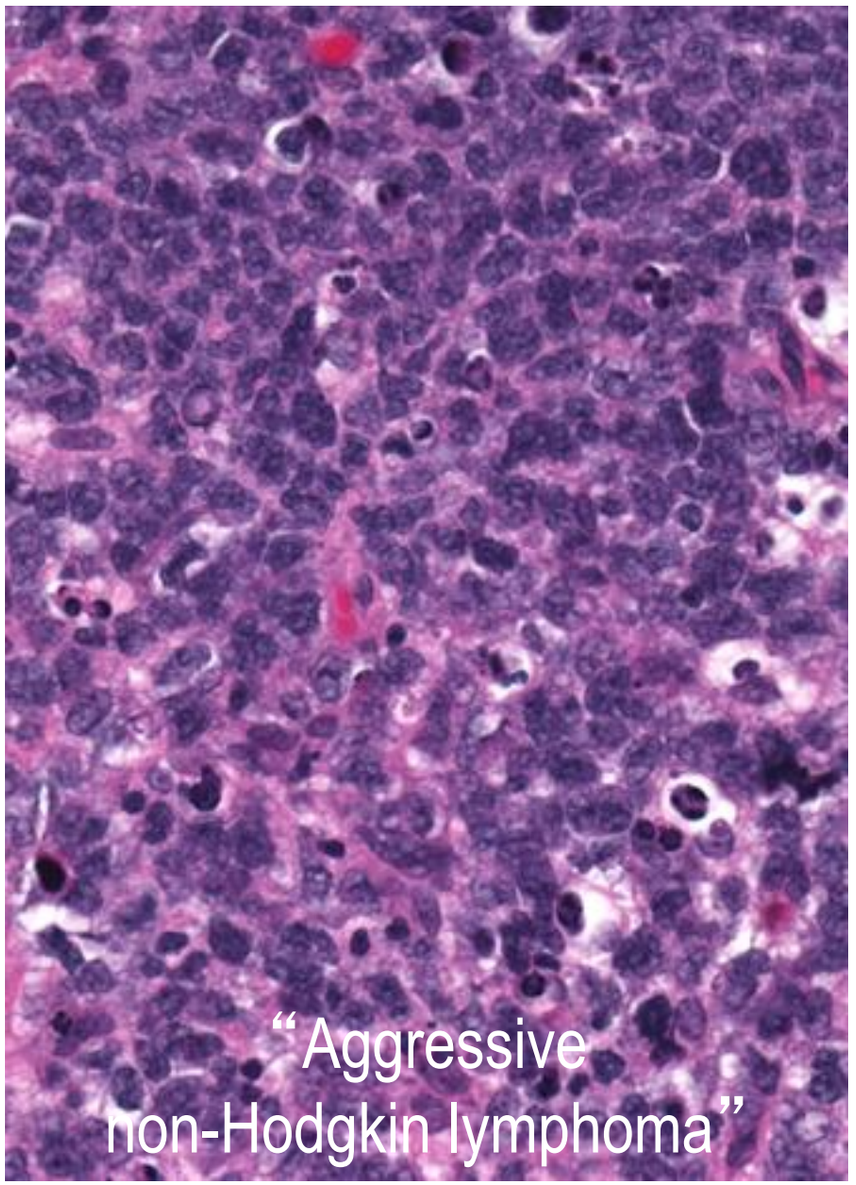
Relative Risk of Selected Cancers

Malignancy	Incidence (per 100,000 person years)	Standardized Incidence Ratio
All Cancer Types	468	2.1 (2.0-.23)
AIDS Defining Cancers		
Kaposi sarcoma	173	1,300 (1,100–1,500)
Non Hodgkin Lymphoma	109	7.3 (6.4–8.4)
Diffuse large B-cell lymphoma	50	9.6 (7.7–12)
Burkitt lymphoma	7	15 (7.9-27)
Primary CNS lymphoma	15	250 (160–360)
Invasive cervical cancer	44	2.9 (1.9-42)
Non-AIDS Defining Cancers		
Anogenital	10	9.2 (5.5–15)
Hodgkin Lymphoma	19	5.6 (3.9–7.8)
Head and Neck	14	1.7 (1.1–2.5)
Hepatocellular	8	2.7 (1.5–4.6)
Lung Cancer	59	2.6 (2.1–3.1)
Acute Lymphocytic Leukemia	2	2.5 (0.7–6.4)
Pancreas	8	2.2 (1.2–3.6)

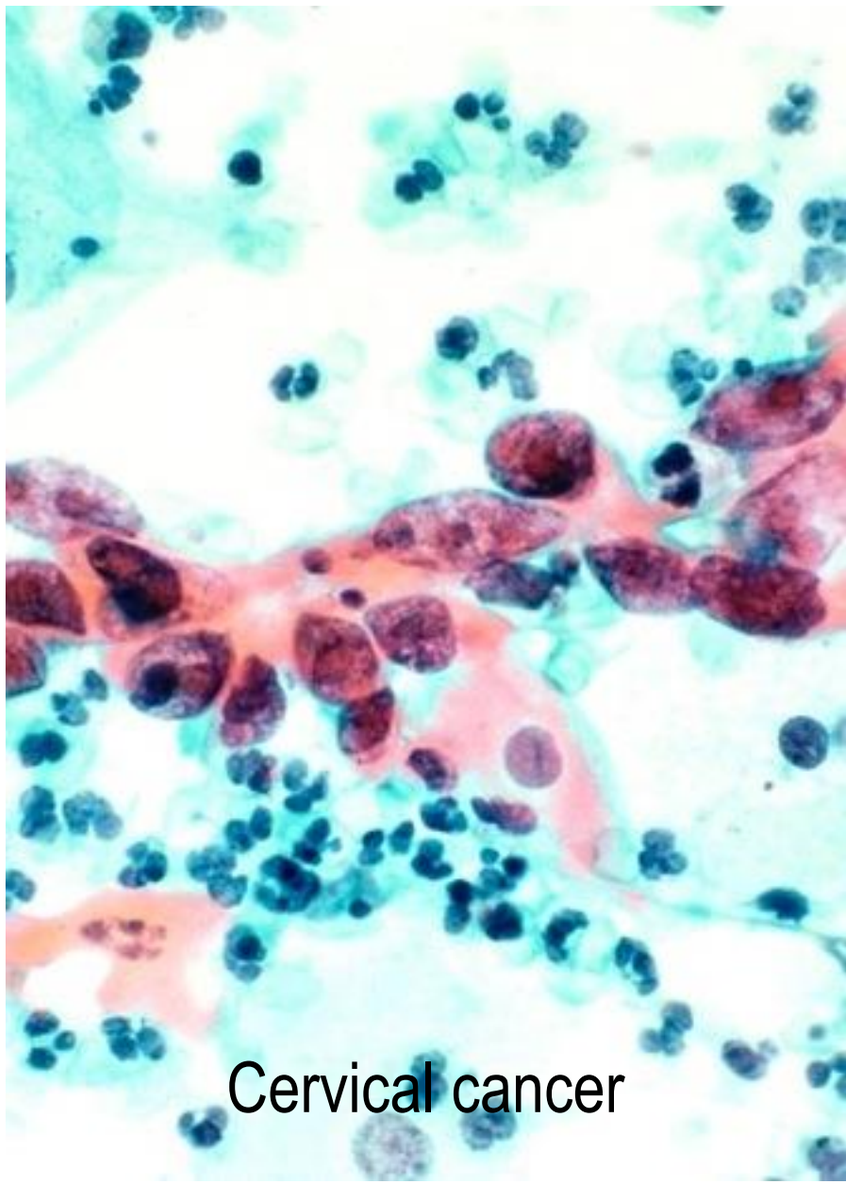
Engels et al. 2008 Int J Cancer

AIDS-Defining Malignancies

Kaposi sarcoma

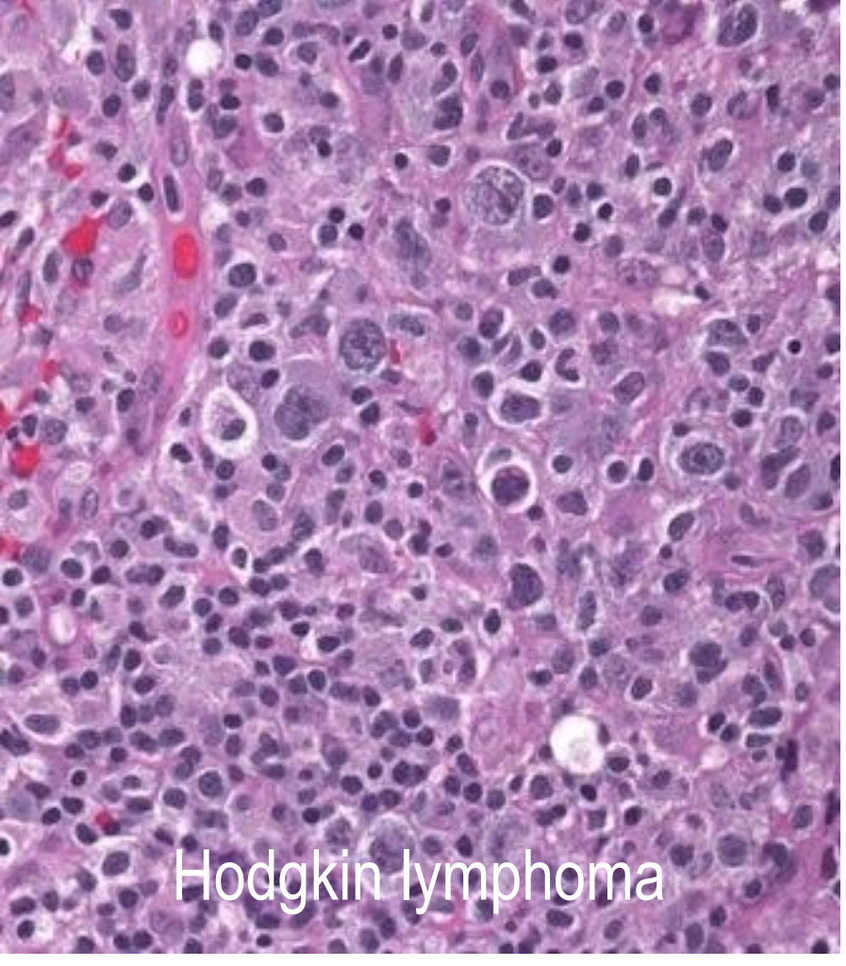


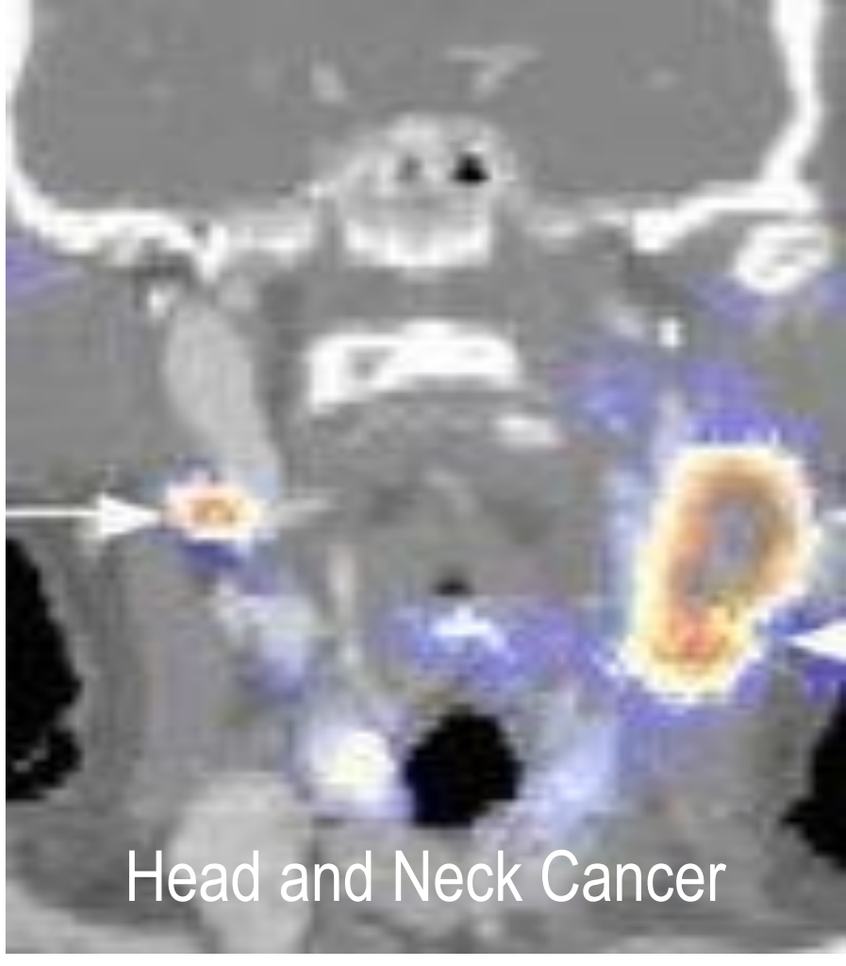
“Aggressive non-Hodgkin lymphoma”

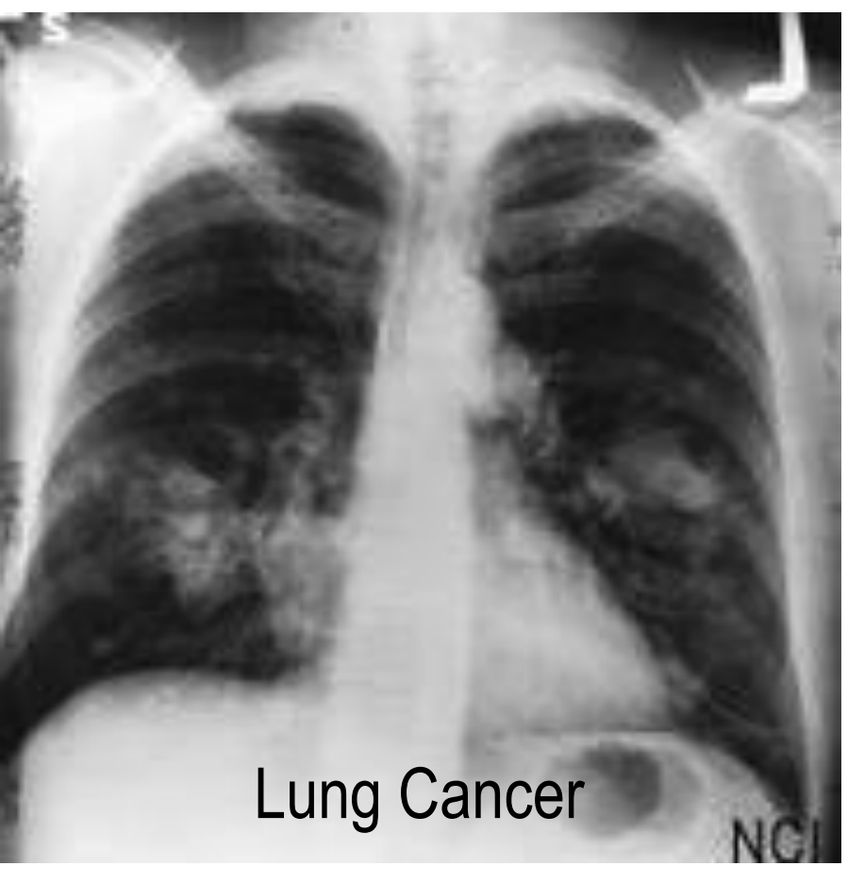


Cervical cancer

Non AIDS-Defining Malignancies

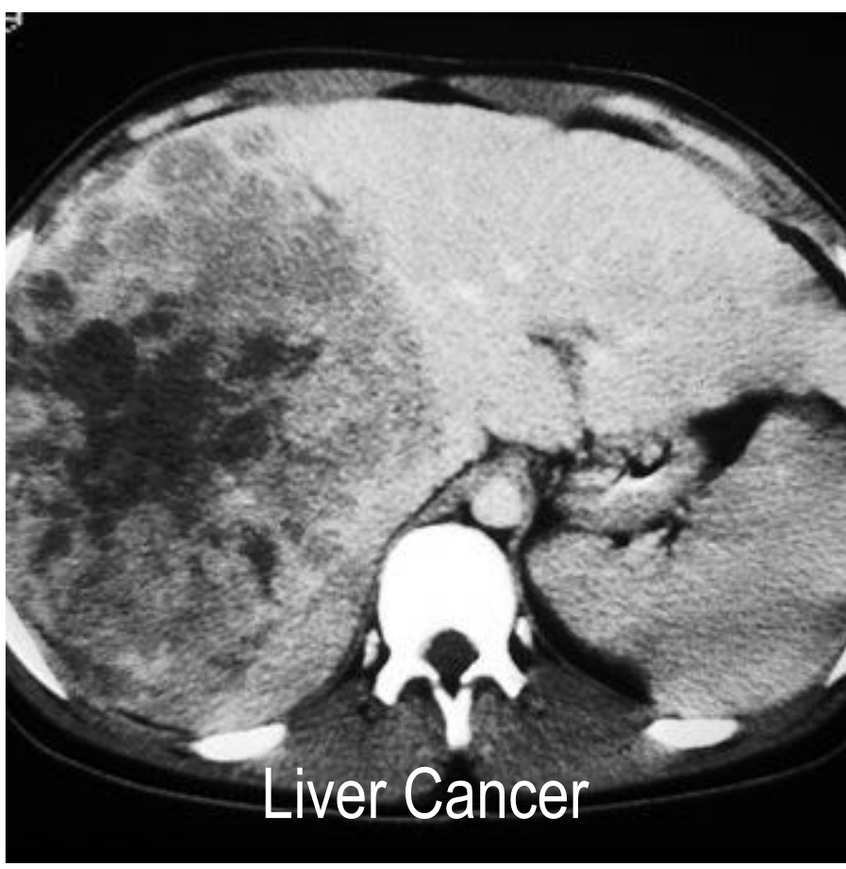

Hodgkin lymphoma


Head and Neck Cancer

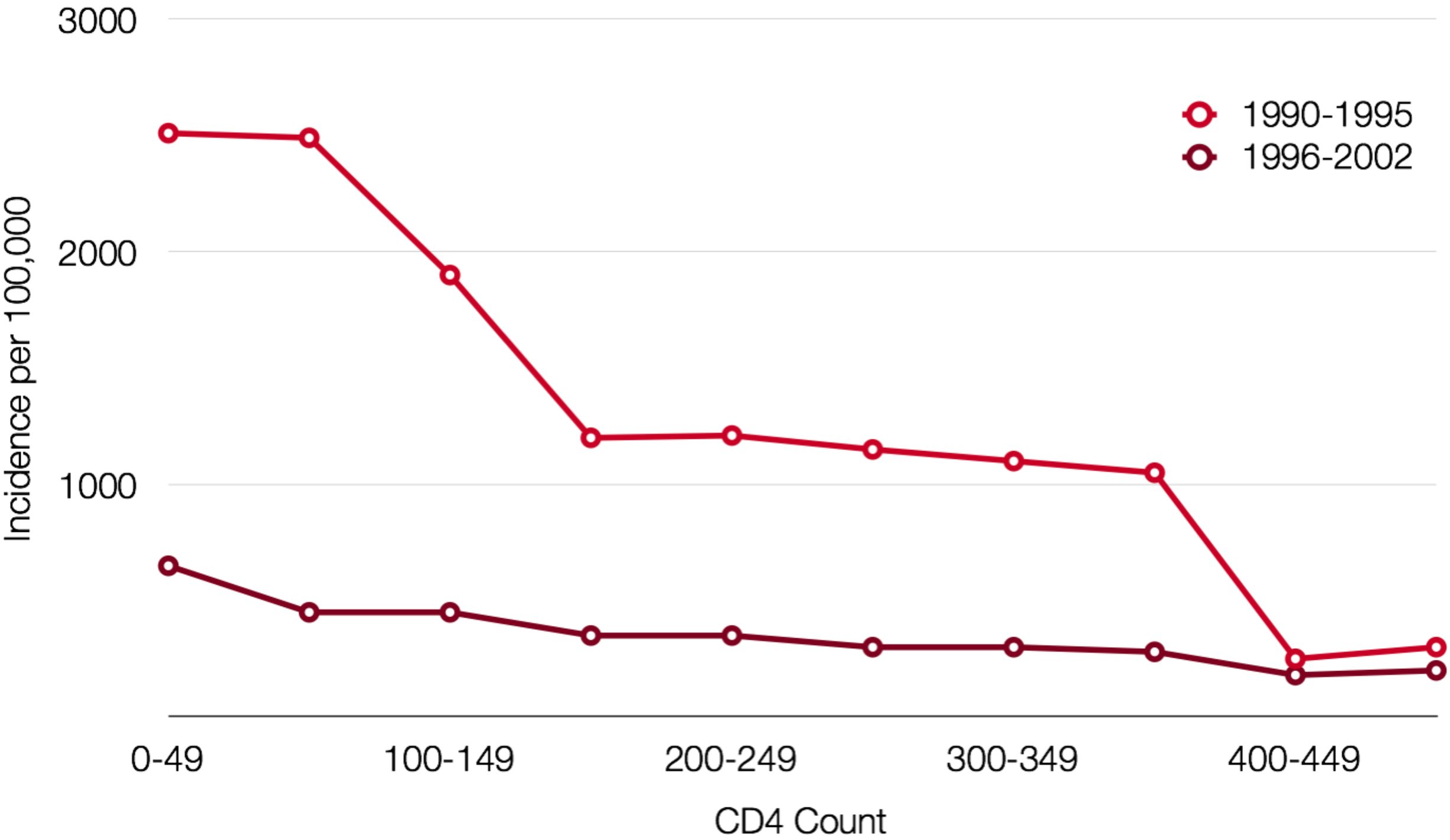


Lung Cancer


Anogenital Cancer

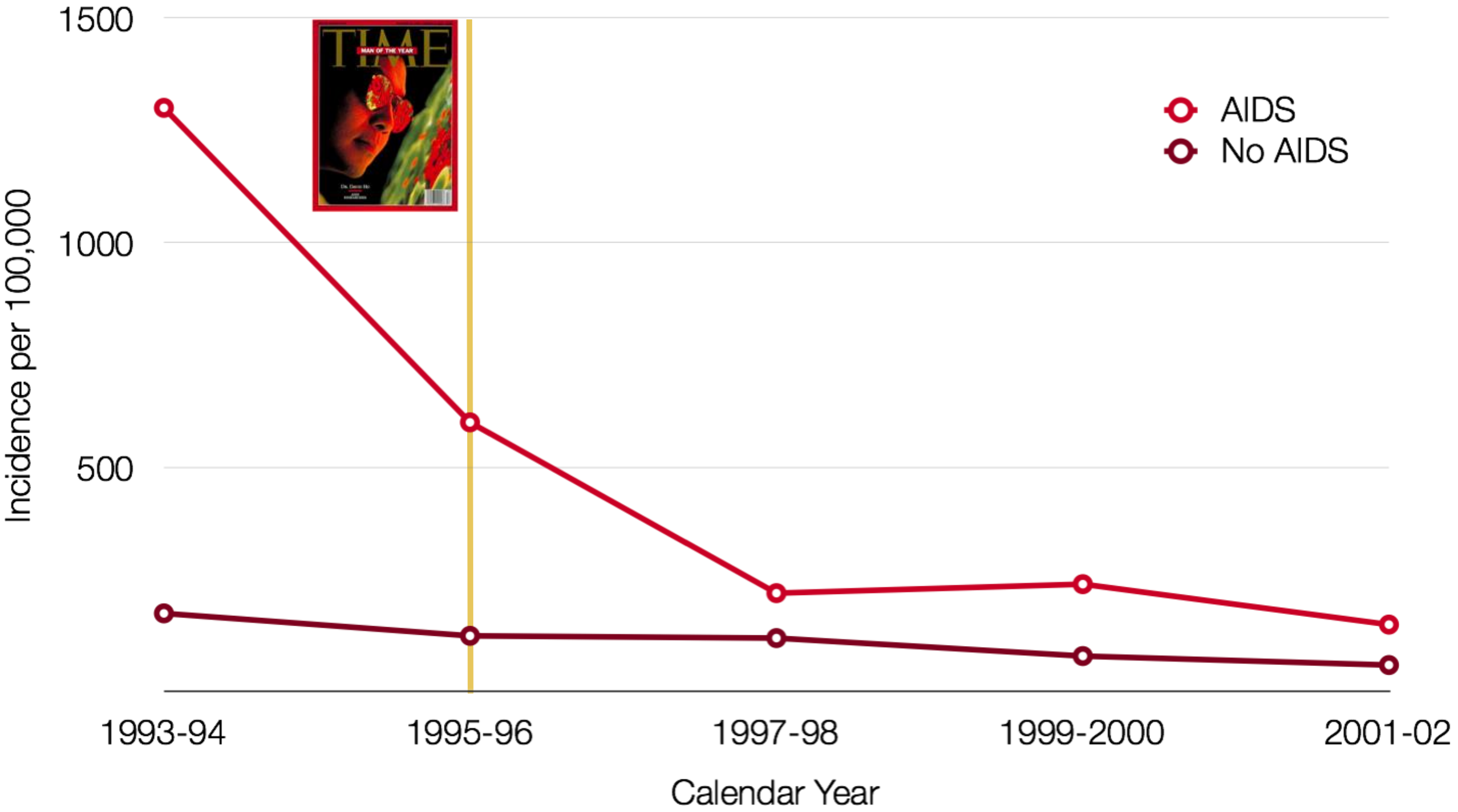

Liver Cancer

Immunosuppression and Risk of KS



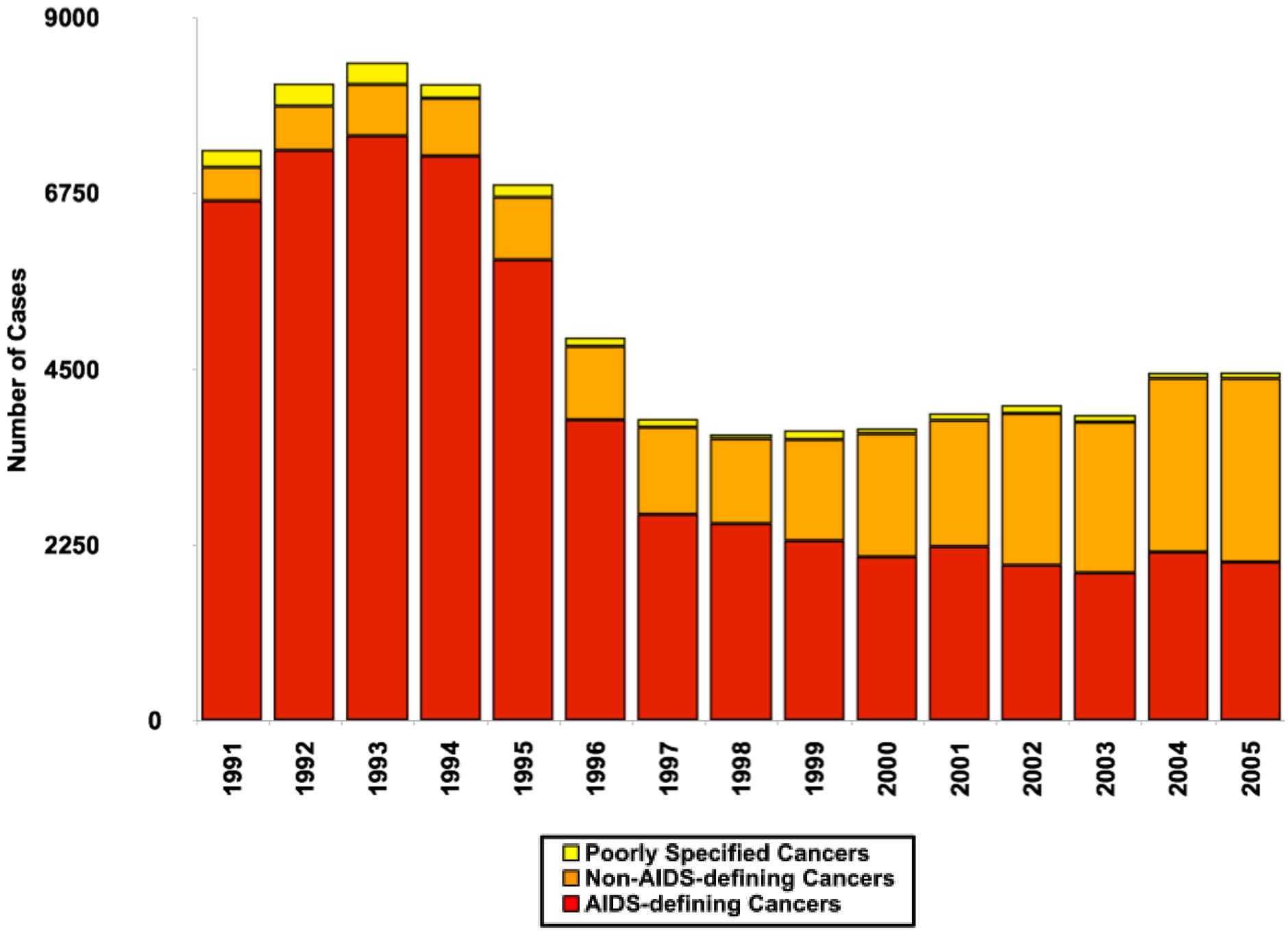
Adapted from Biggar, R.J et al. J Natl Cancer Inst (2007).

Incidence of KS 1993-2002



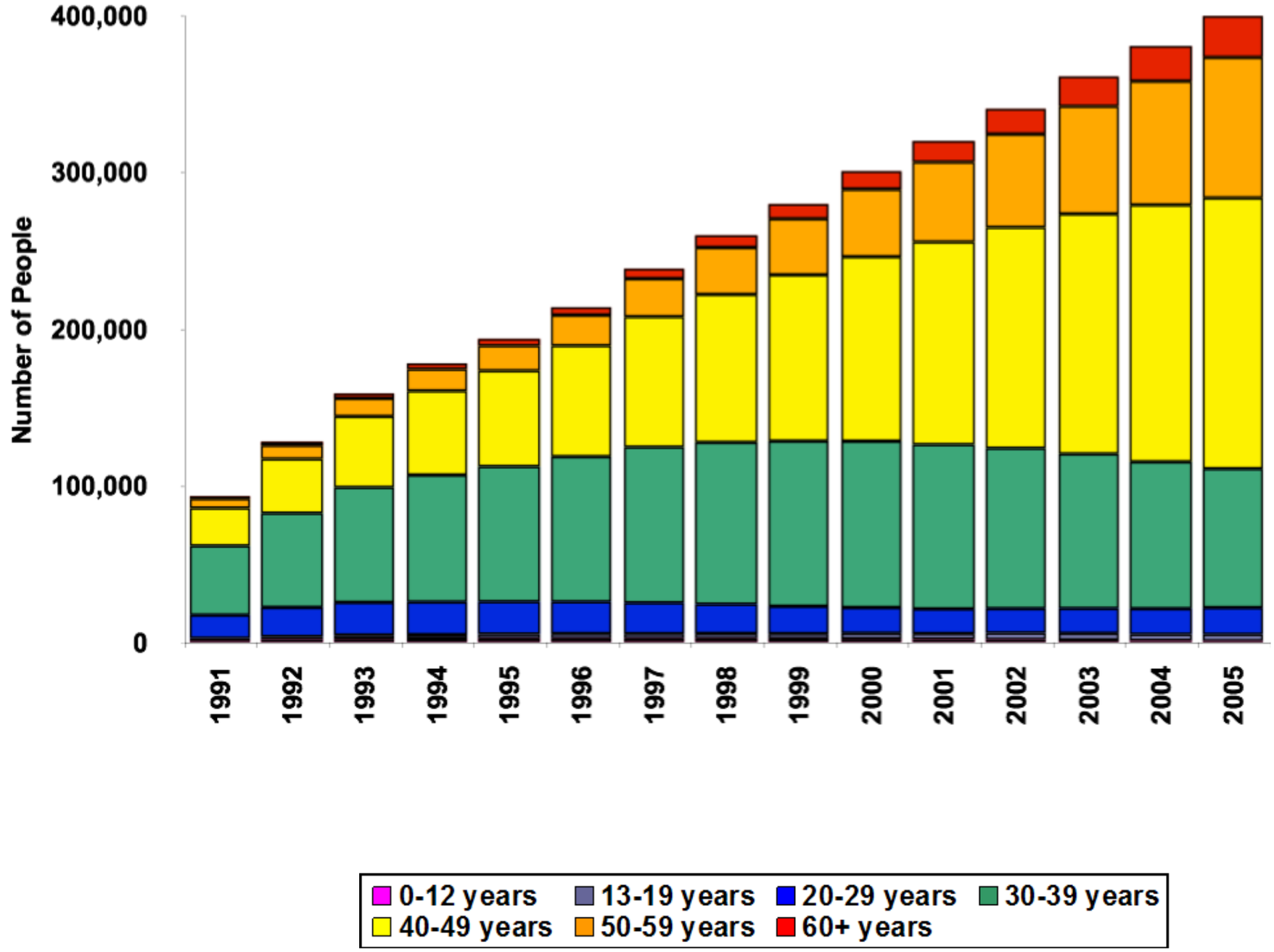
Adapted from Engels E.A. et al. Int J Cancer Inst (2008).

Malignancies in HIV/AIDS

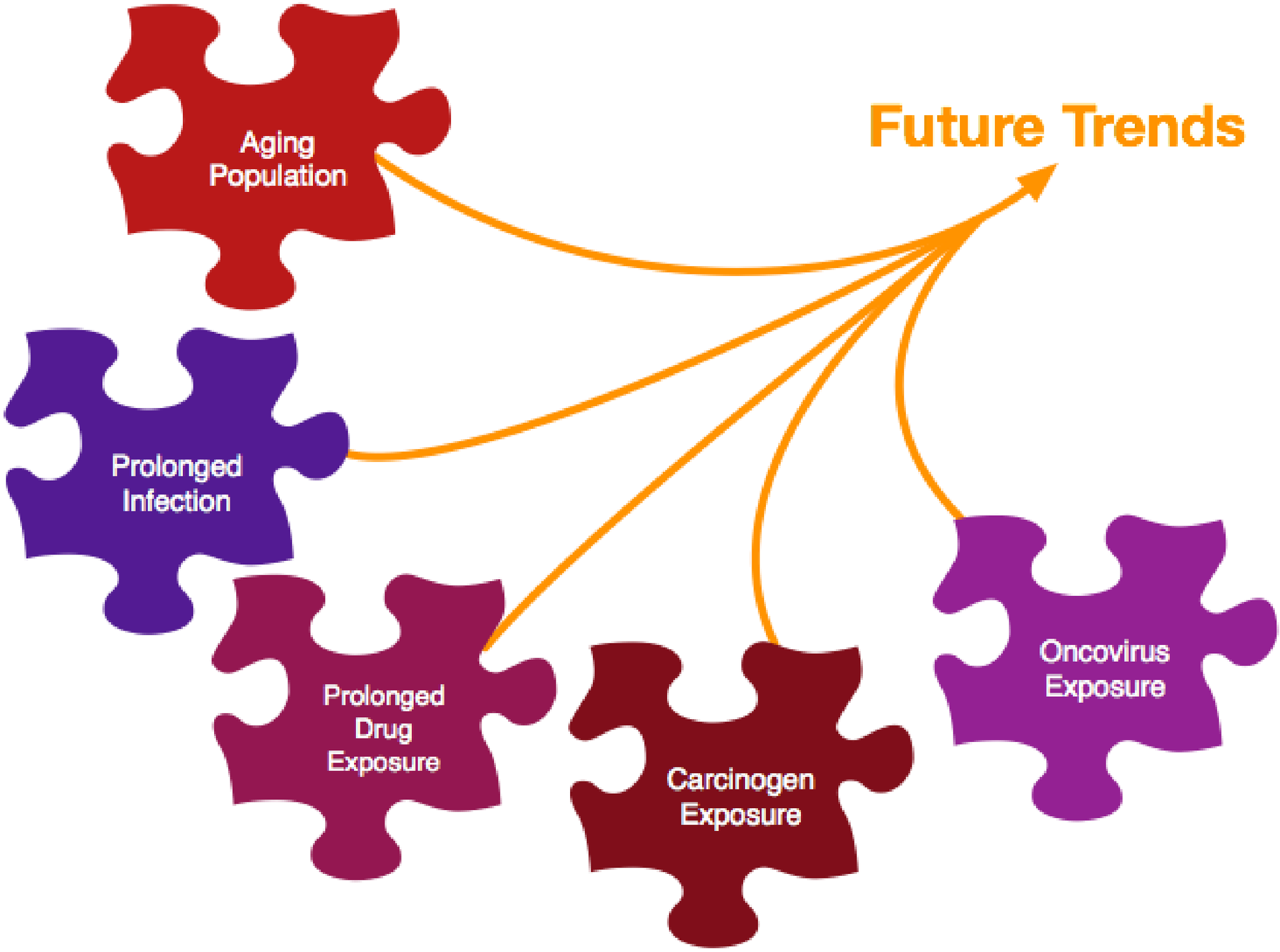


Shiels M.S., et al., *JNCI*, 2011.

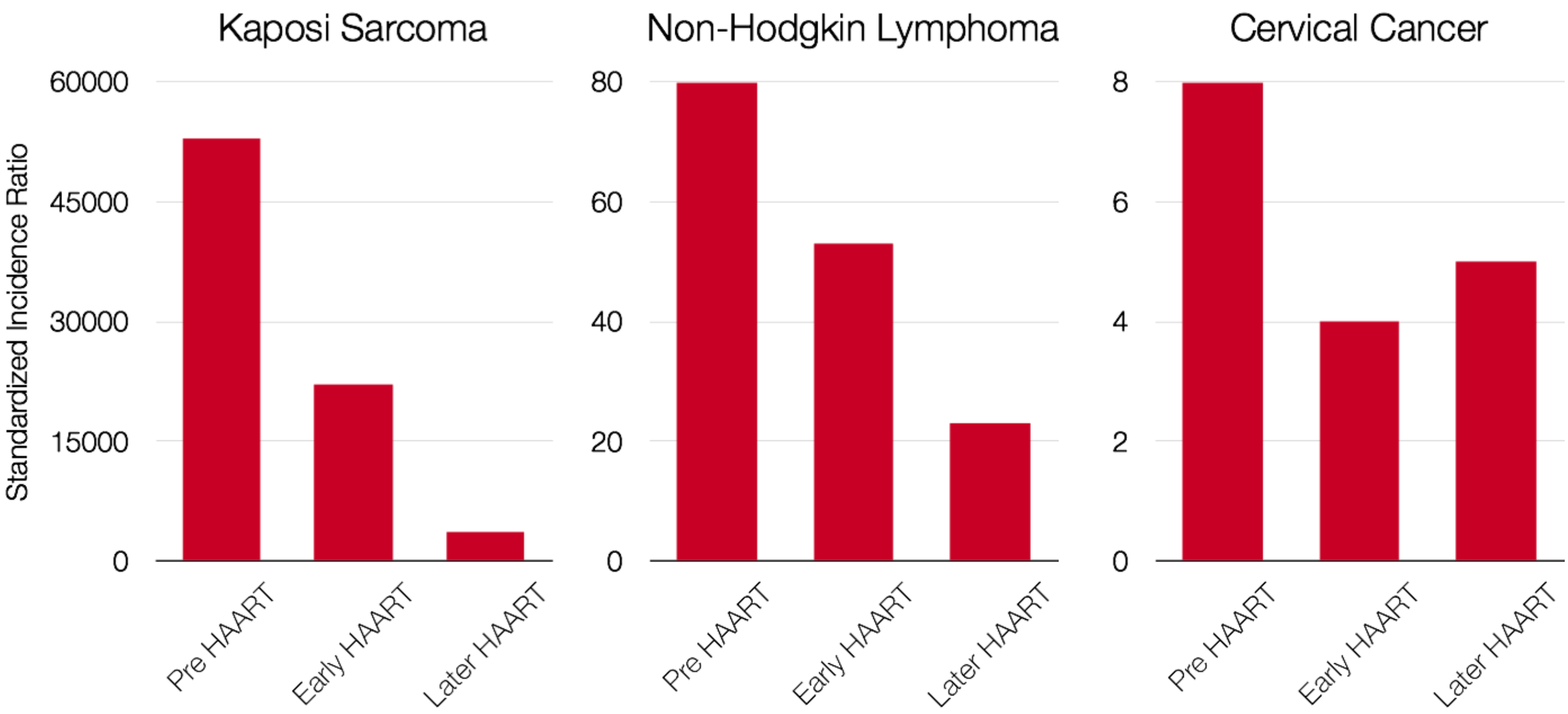
People Living with HIV/AIDS



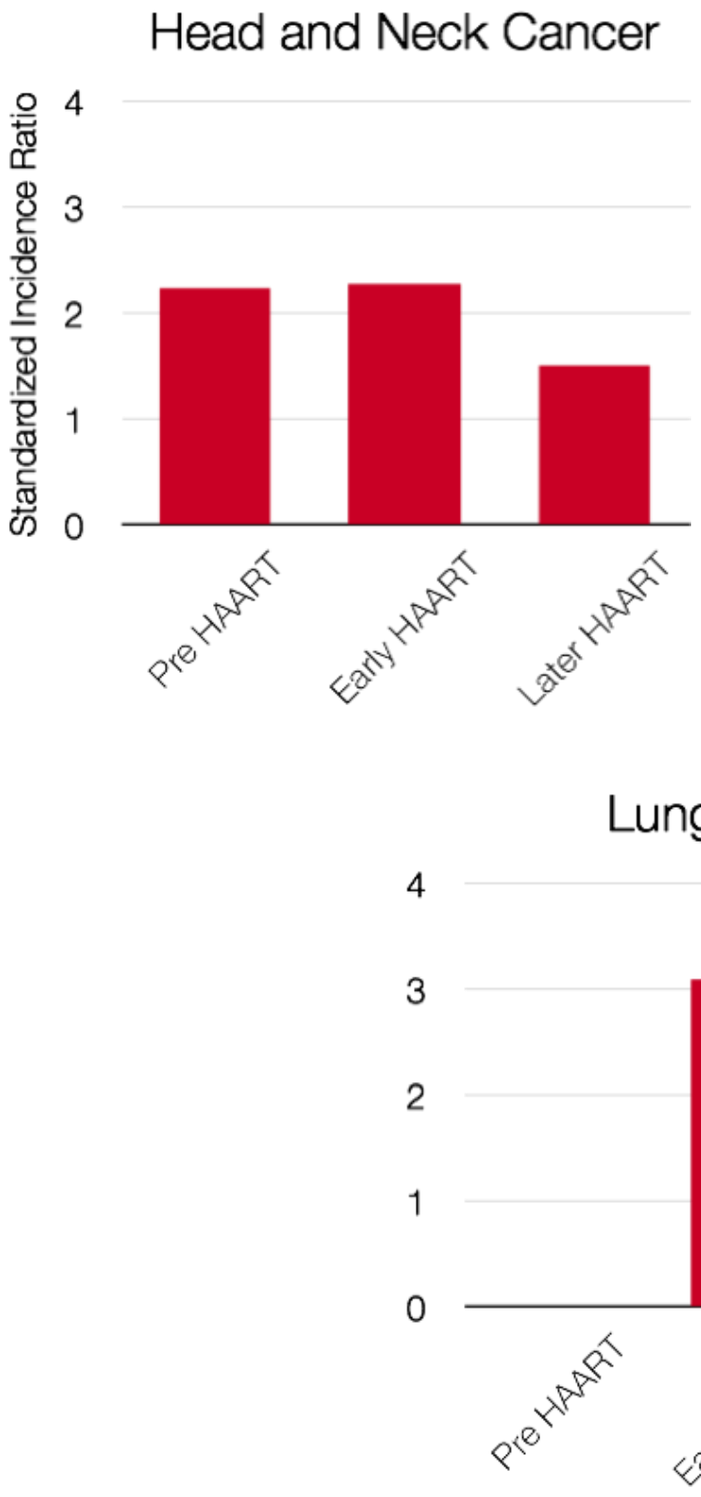
Other Factors and Trends

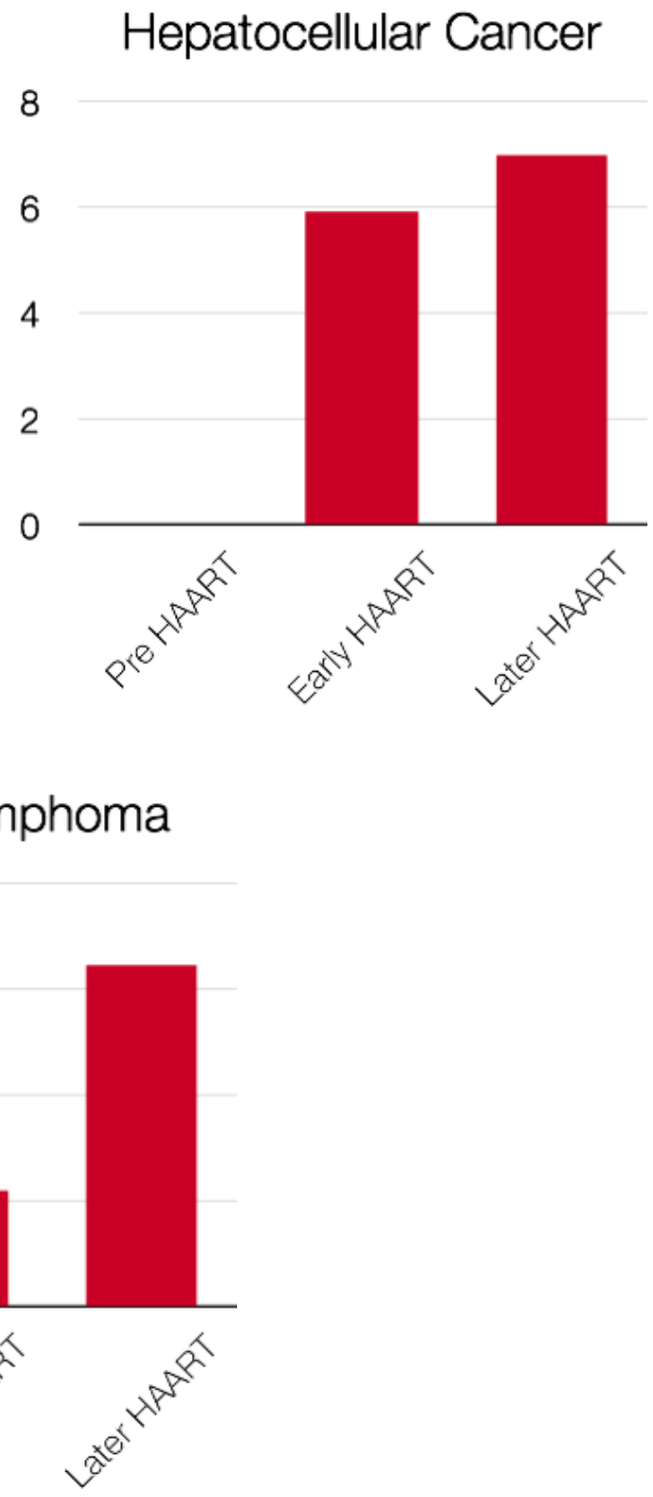


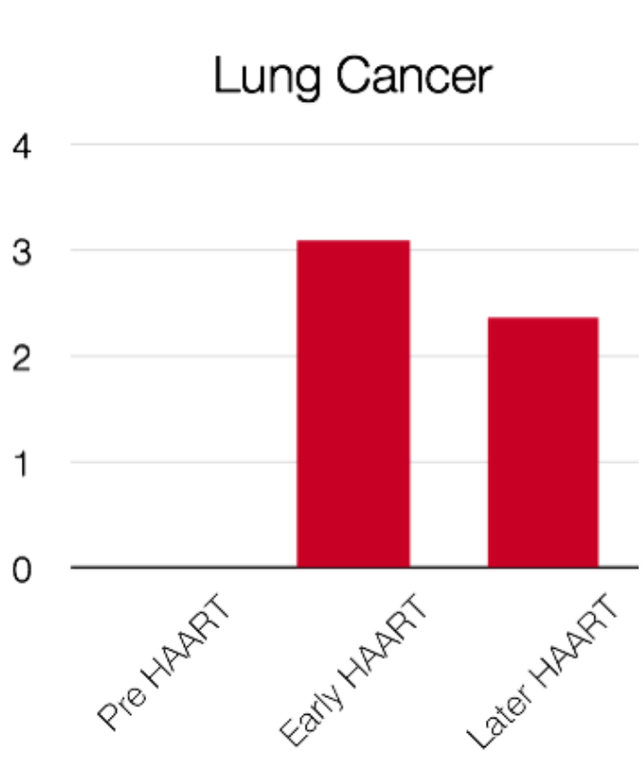
AIDS Defining Malignancies

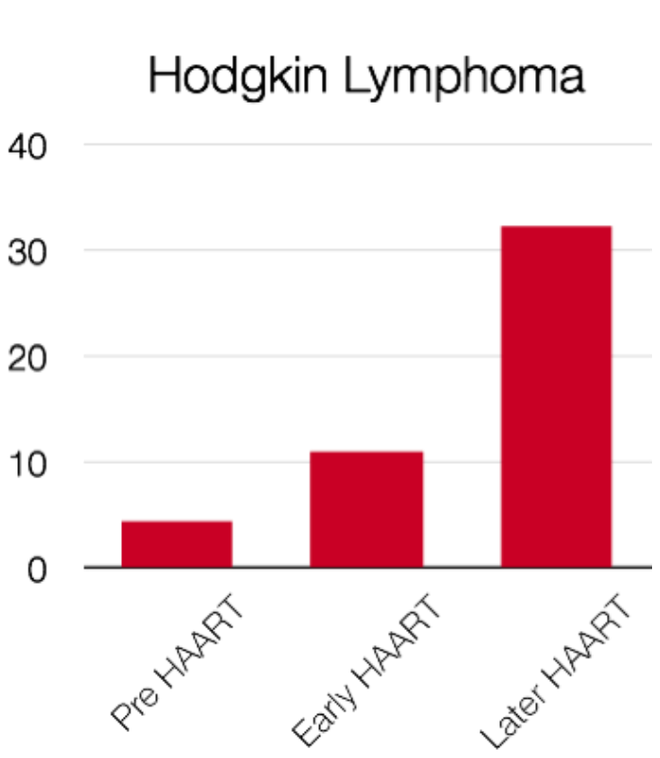


Non-AIDS Defining Malignancies









Viral Malignancies in People with HIV

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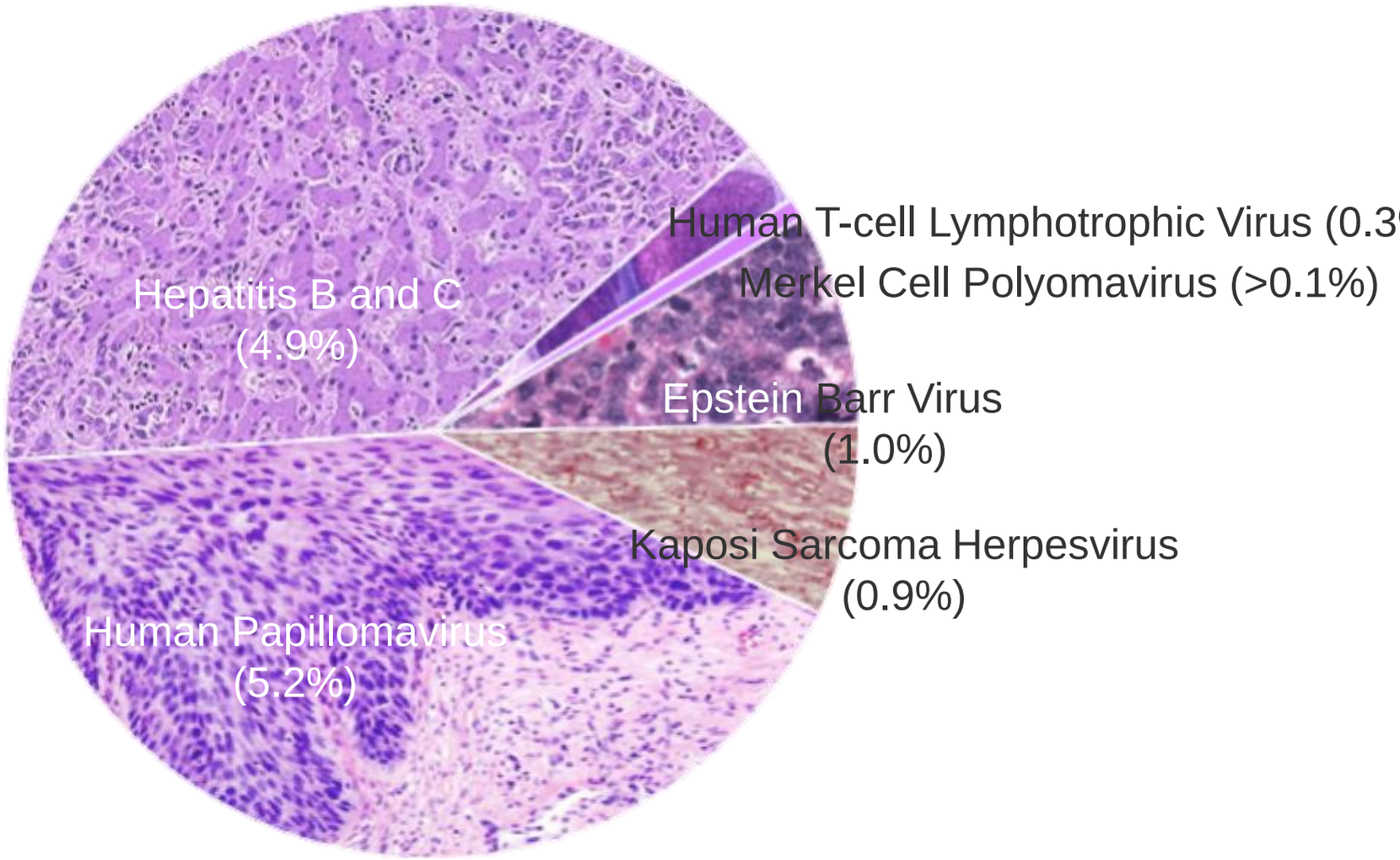
Engels et al. *Int J Cancer* 123: 187-94 (2008).

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

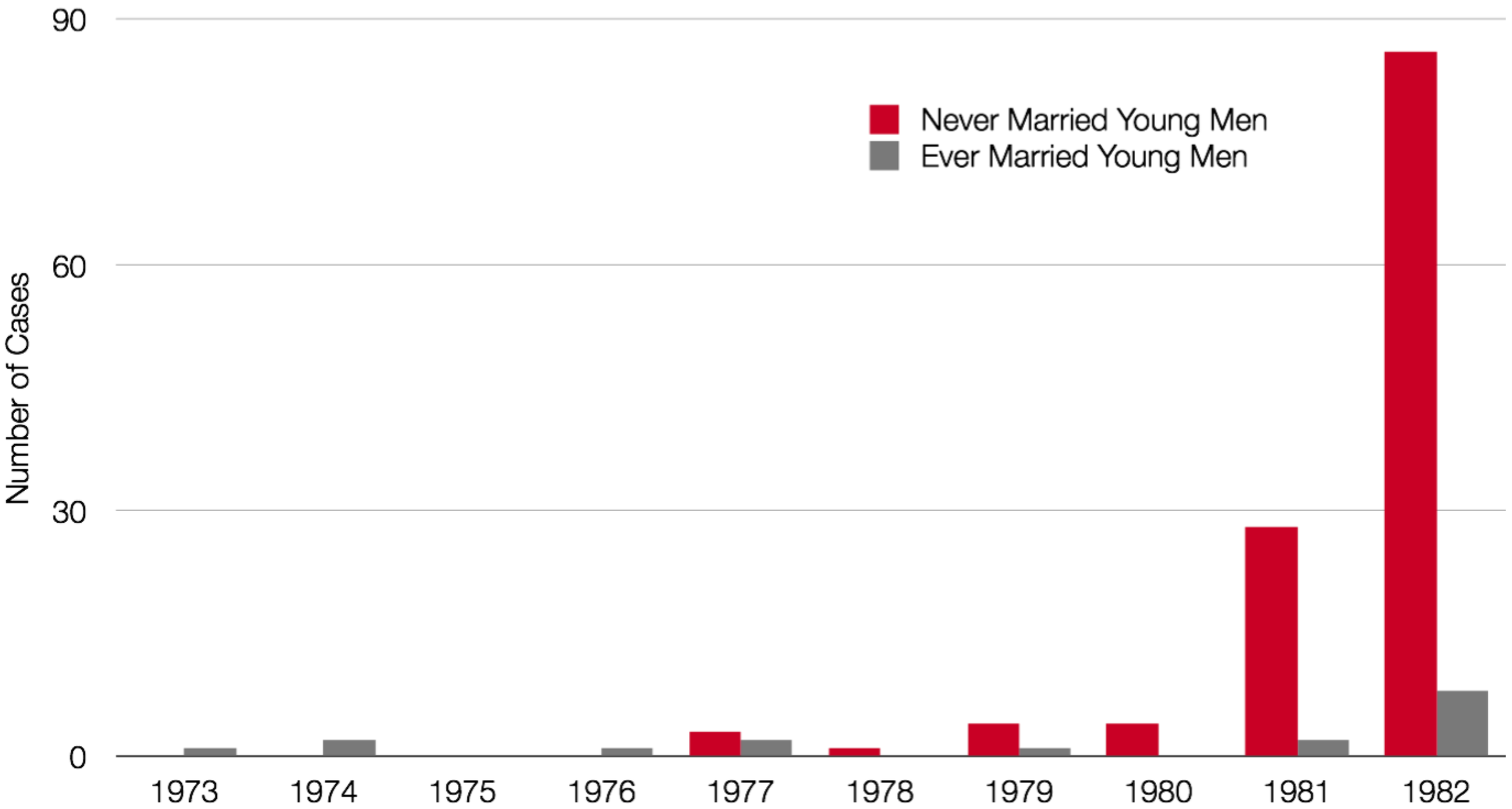
Parkin, *Int J Cancer* 2006:118, 3030–3044.

Viral Etiology of Malignancies

Malignancy	Virus	Attributable Fraction
Kaposi sarcoma	Kaposi sarcoma herpesvirus (KSHV)	100%
Multicentric Castleman disease	Kaposi sarcoma herpesvirus	100%
Primary effusion lymphoma	KSHV (±EBV)	100% (80%)
Diffuse large B-cell lymphomas	Epstein Barr virus (EBV)	10-20%
Primary CNS lymphoma	Epstein Barr virus	80%
Burkitt lymphoma	Epstein Barr virus	Variable (20-90%)
Plasmablastic lymphoma	Epstein Barr virus	80%
Hodgkin lymphoma	Epstein Barr virus	30-50%
Nasopharygeal carcinoma	Epstein Barr virus	>90%
Leiomyosarcoma	Epstein Barr virus	10%
Invasive cervical carcinoma	Human papillomavirus	100%
Anogenital carcinoma	Human papillomavirus	100%
Head and neck carcinoma	Human papillomavirus	20-30%
Primary hepatocellular carcinoma	Hepatitis B and C	20-50%
Adult T cell leukemia/lymphoma	Human T lymphotrophic virus (HTLV)	100%
Merkel cell carcinoma	Merkel cell polyomavirus	>90%

Parkin, *Int J Cancer* 118: 3030–3044 (2006).

Kaposi Sarcoma Incidence 1973-82



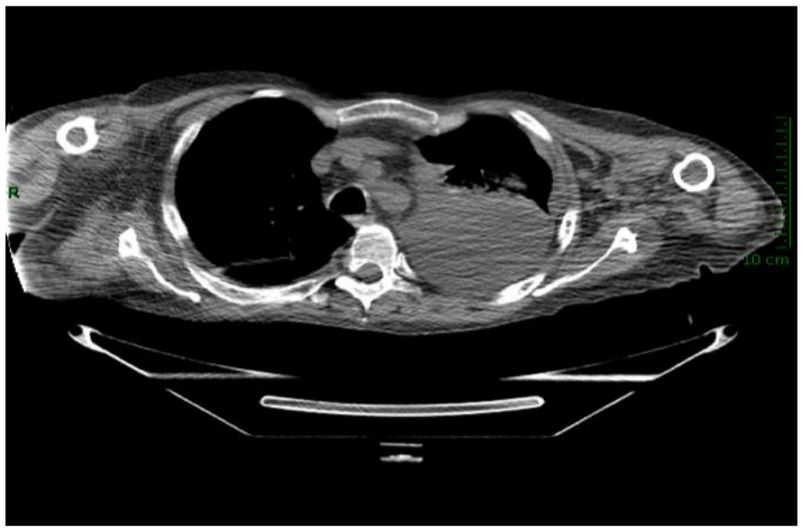
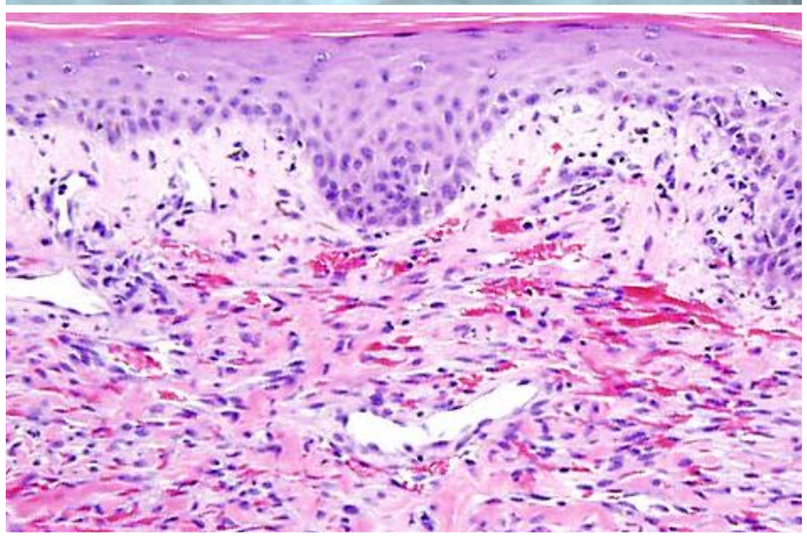
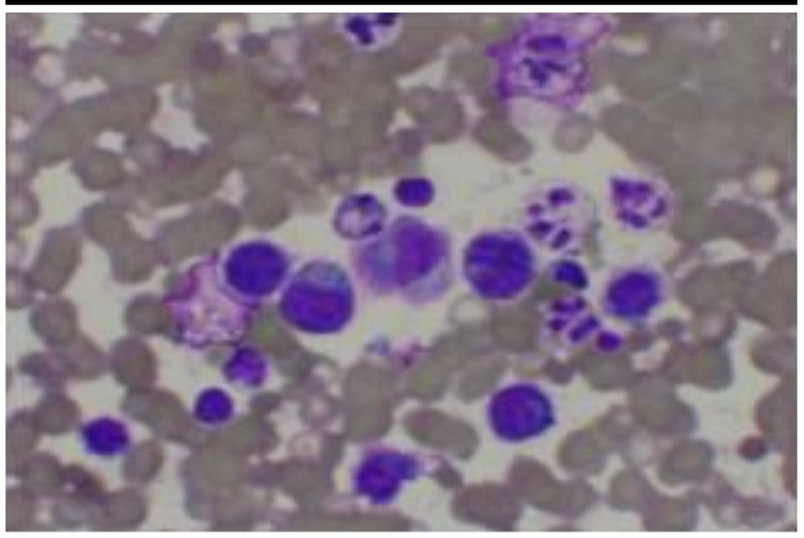
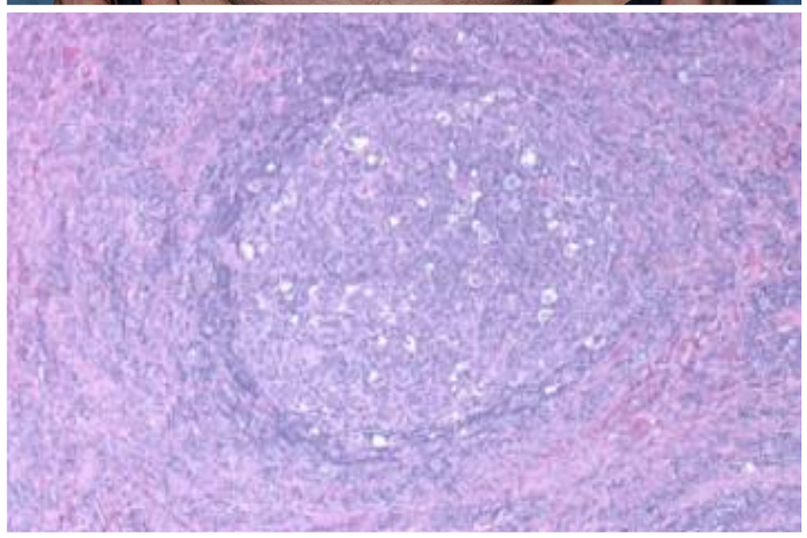
Common Features of Tumor Viruses

- 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 oncogeneis
  - Viral proteins promoting growth and enabling immune evasion
  - Viral integration sites in host genome
  - Virally induced chronic inflammation

Common Features of Tumor Viruses

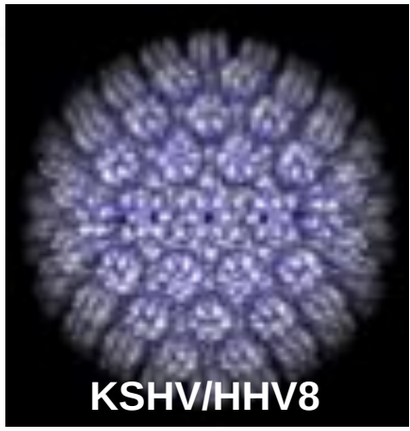
- Implications for prevention
  - Vaccination (HPV)
  - Eradication (HCV)
  - Cofactor targeting (HIV for KSHV and EBV)
- Implications for therapy
  - Not amenable to conventional antiviral drugs
  - May present unique protein targets for therapies
  - May be amenable to immune modulation
  - Burden greatest in resource limited settings -- price and scalability crucial
- Implications for basic science
  - Provide insights into important cellular and oncogenic mechanisms

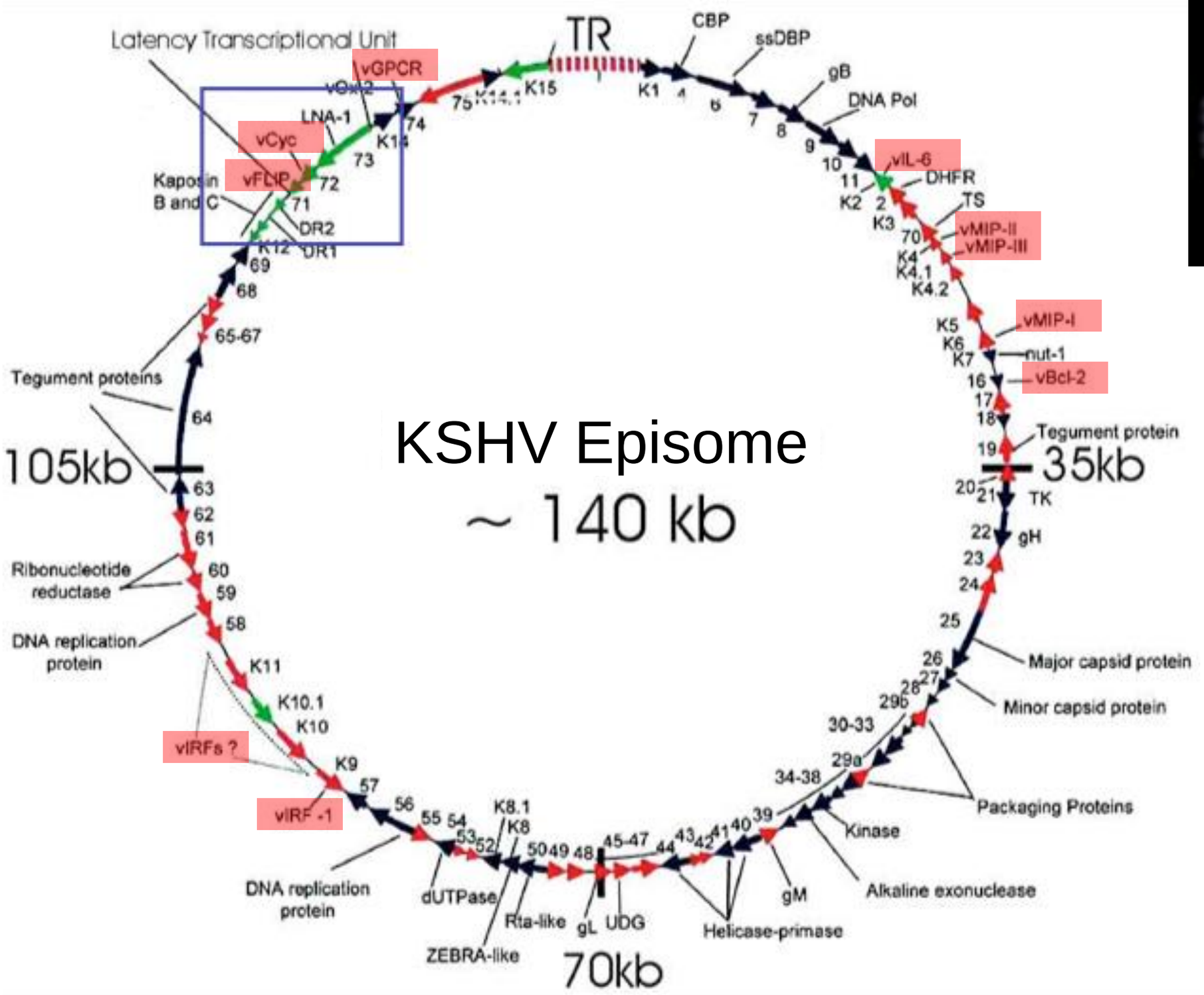
KSHV Associated Diseases

Kaposi Sarcoma	Primary Effusion Lymphoma	Multicentric Castleman Disease
		
		
Endothelial	Lymphoid	Lymphoid

Chang Y., et al. *Science* 1994. Cesarman E., et al. *N Engl J Med* 1995. Soulier, J., et al. *Blood* 1995.

Kaposi Sarcoma Herpesvirus (KSHV)





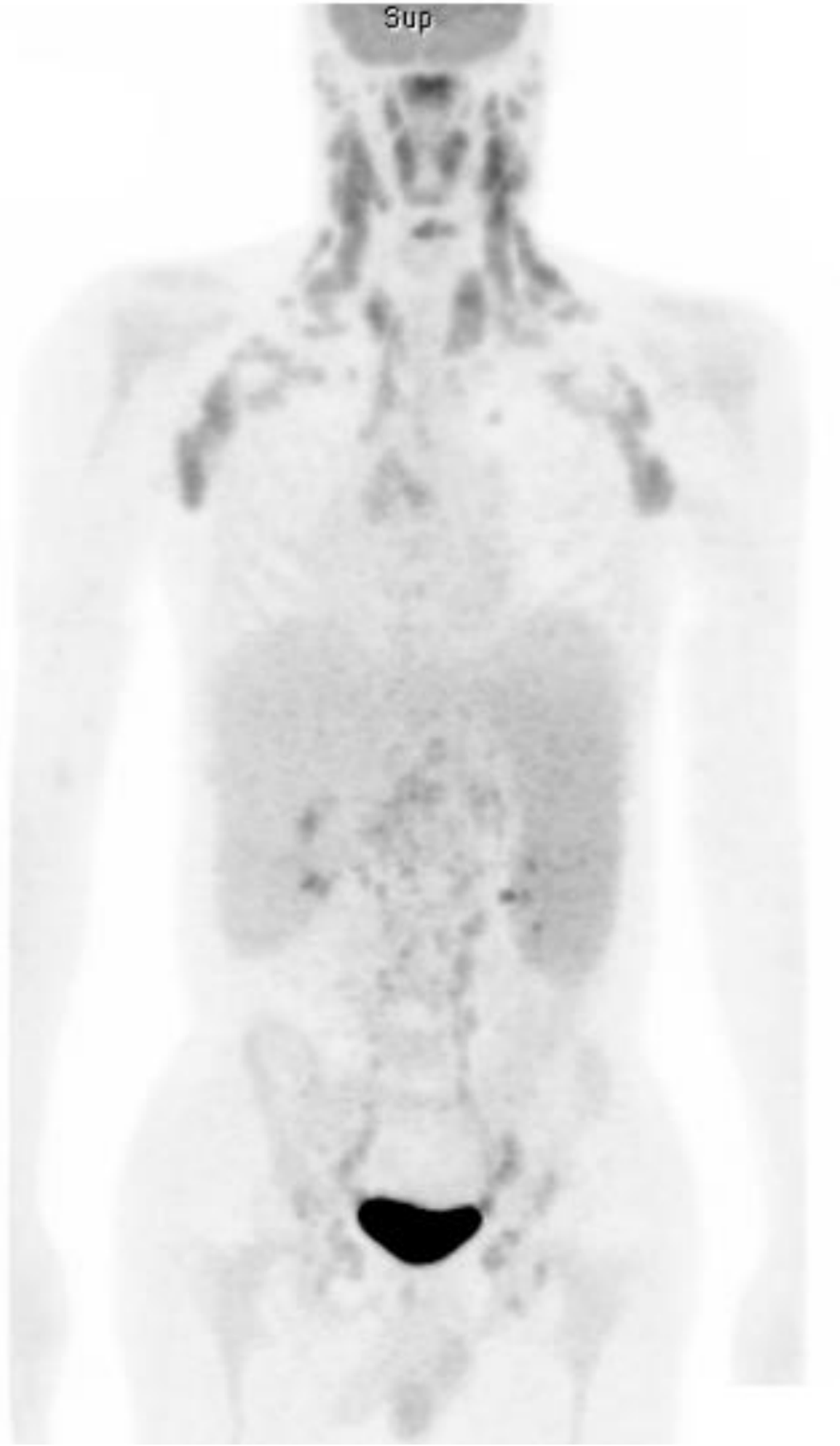
Molecular Piracy by KSHV

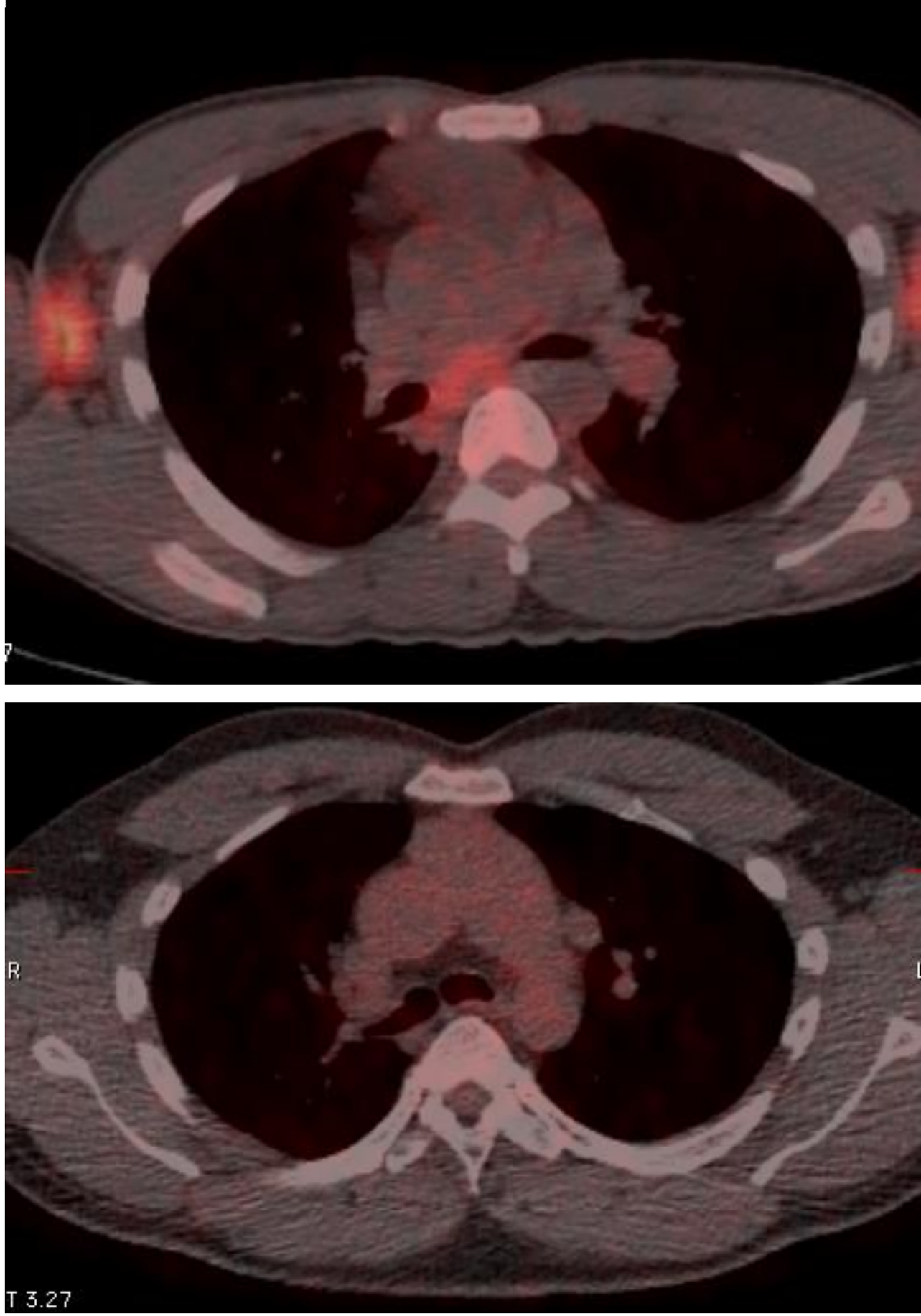
Viral Gene	Human Analog	Function
ORF K6/vMIP1 ORF K4/vMIP2 ORF K4.1/vMIP3	Macrophage inhibitory protein (MIP)	Th2 chemoattractant; angiogenesis
ORF K2/vIL-6	Interleukin 6 (IL-6)	B cell growth; angiogenesis
ORF74/vGPCR	IL-8 receptor	Constitutively active GPCR; proliferation and angiogenesis
ORF K9/vIRF-1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

KSHV-associated MCD

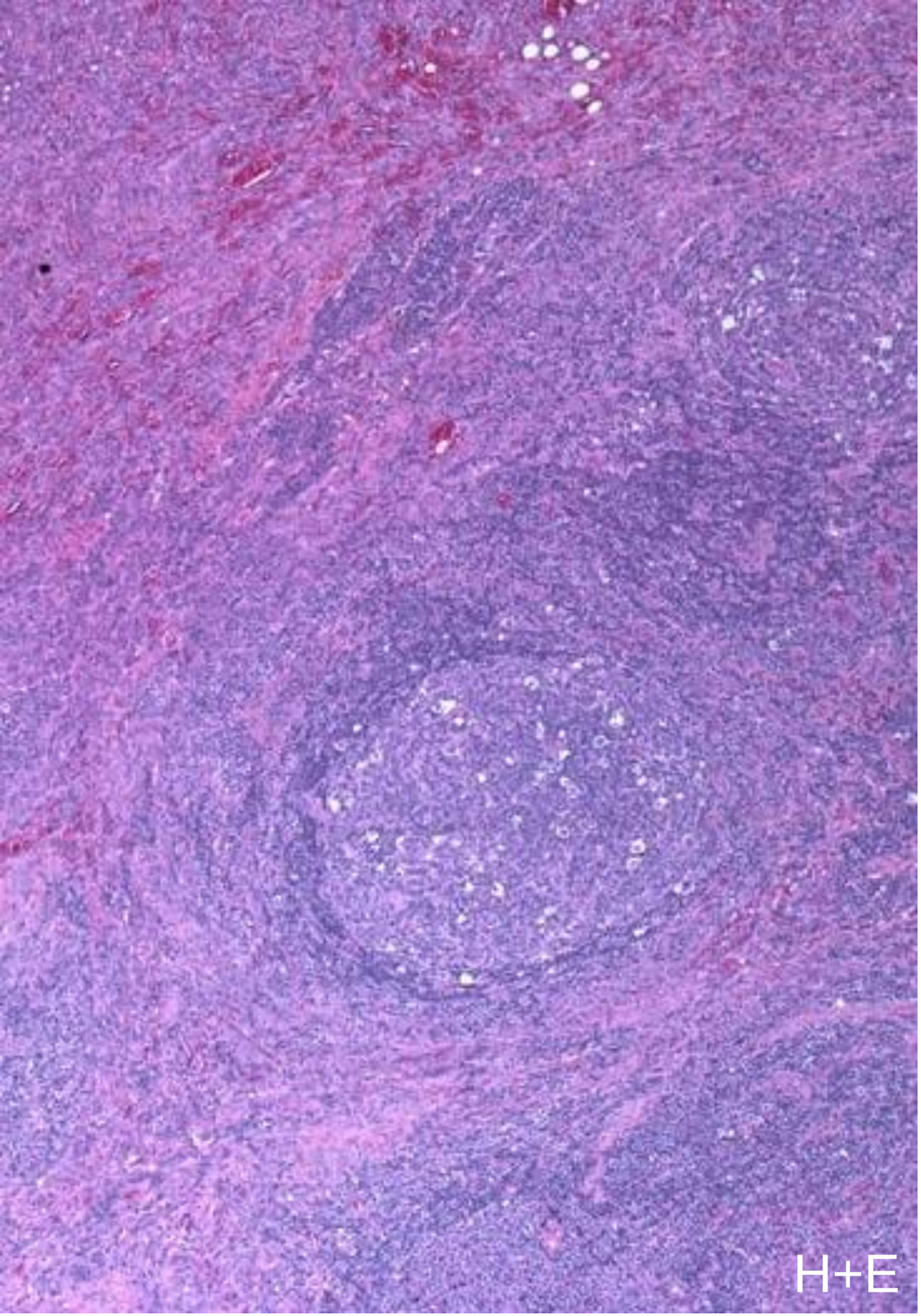
- Lymphoproliferative disorder
- Most common in HIV coinfected patients
- Intermittent symptomatic flares:
  - inflammatory symptoms and evidence of systemic inflammation
  - hematologic cytopenias
  - biochemical abnormalities
  - lymphadenopathy, organomegaly
- Historical untreated median survival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

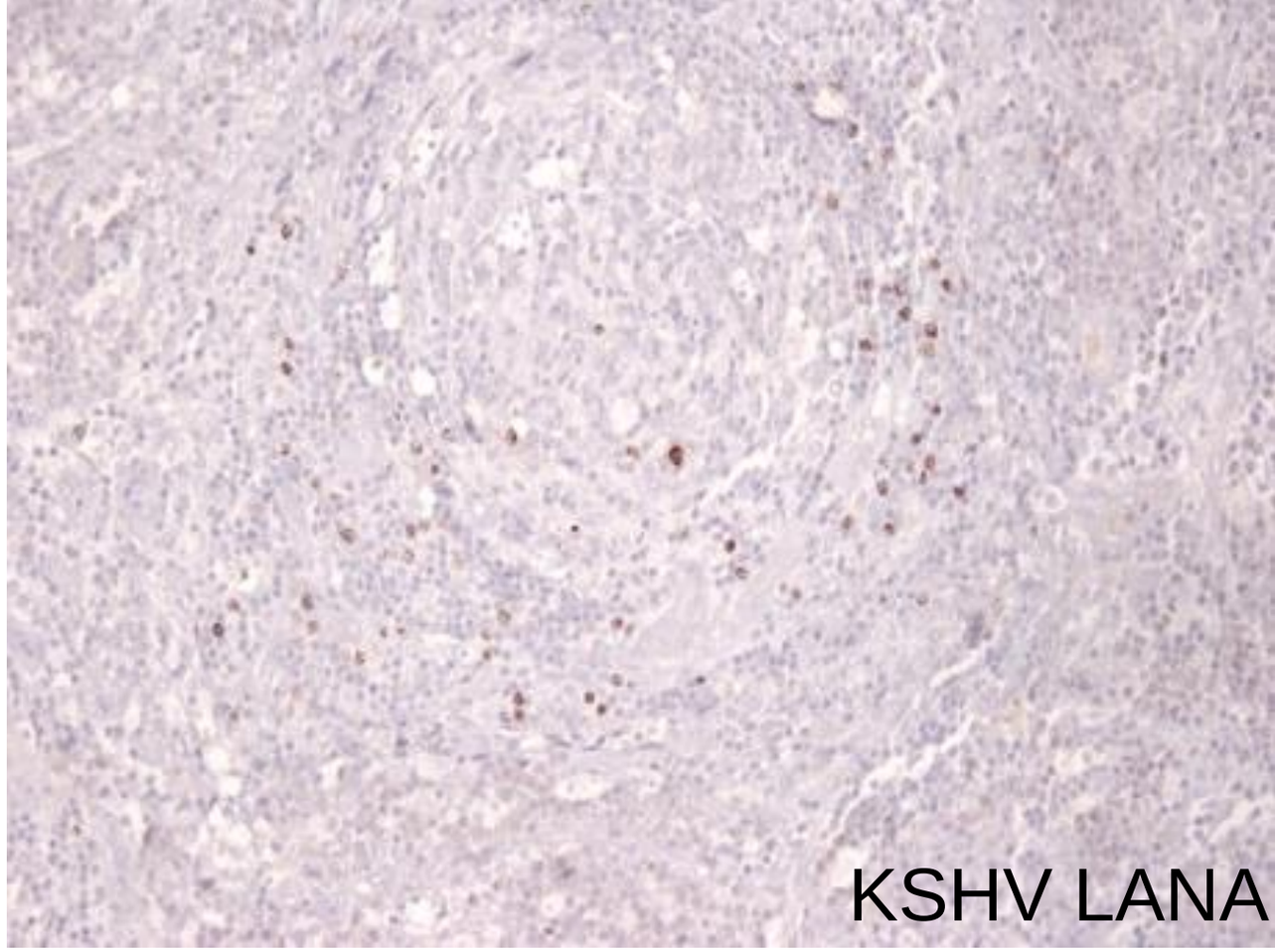
Oksenhendler E., et al. Blood 2000.

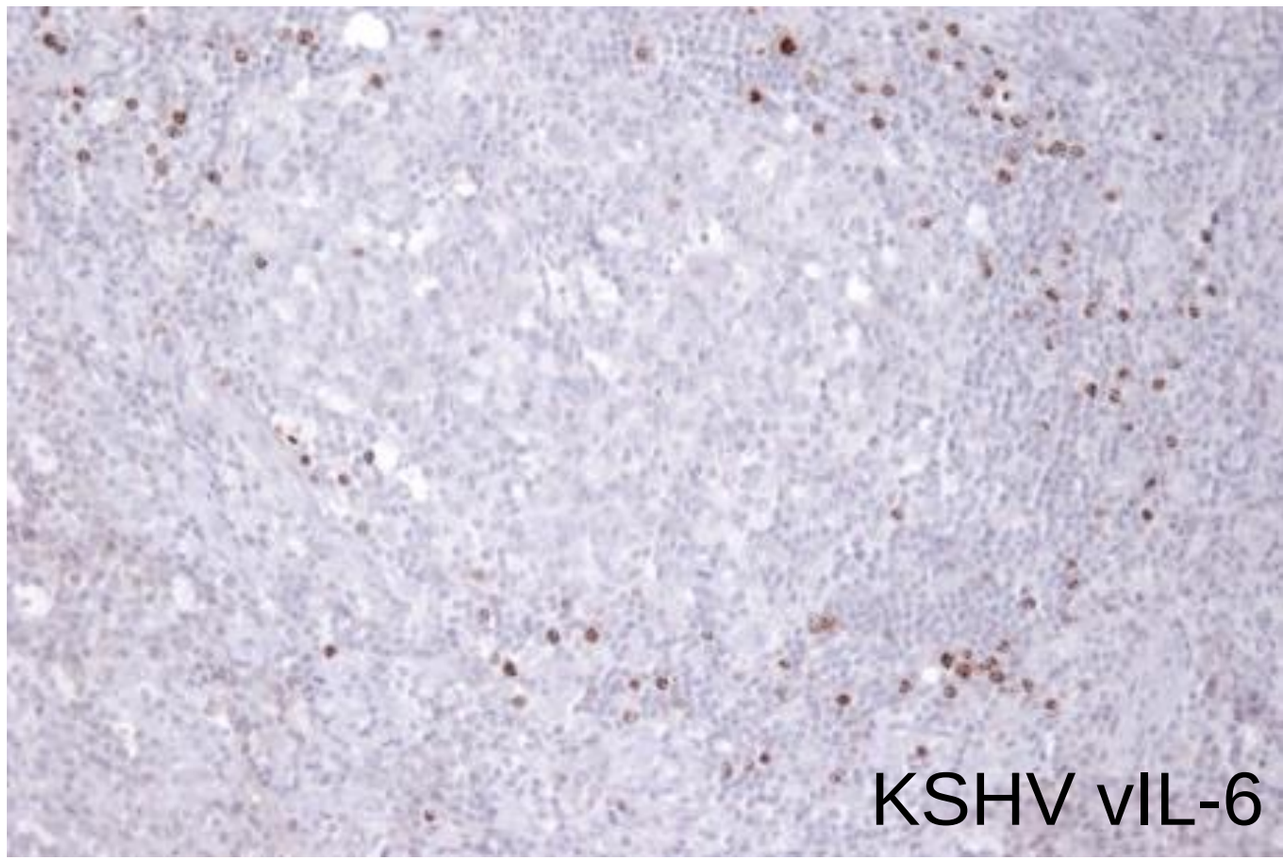




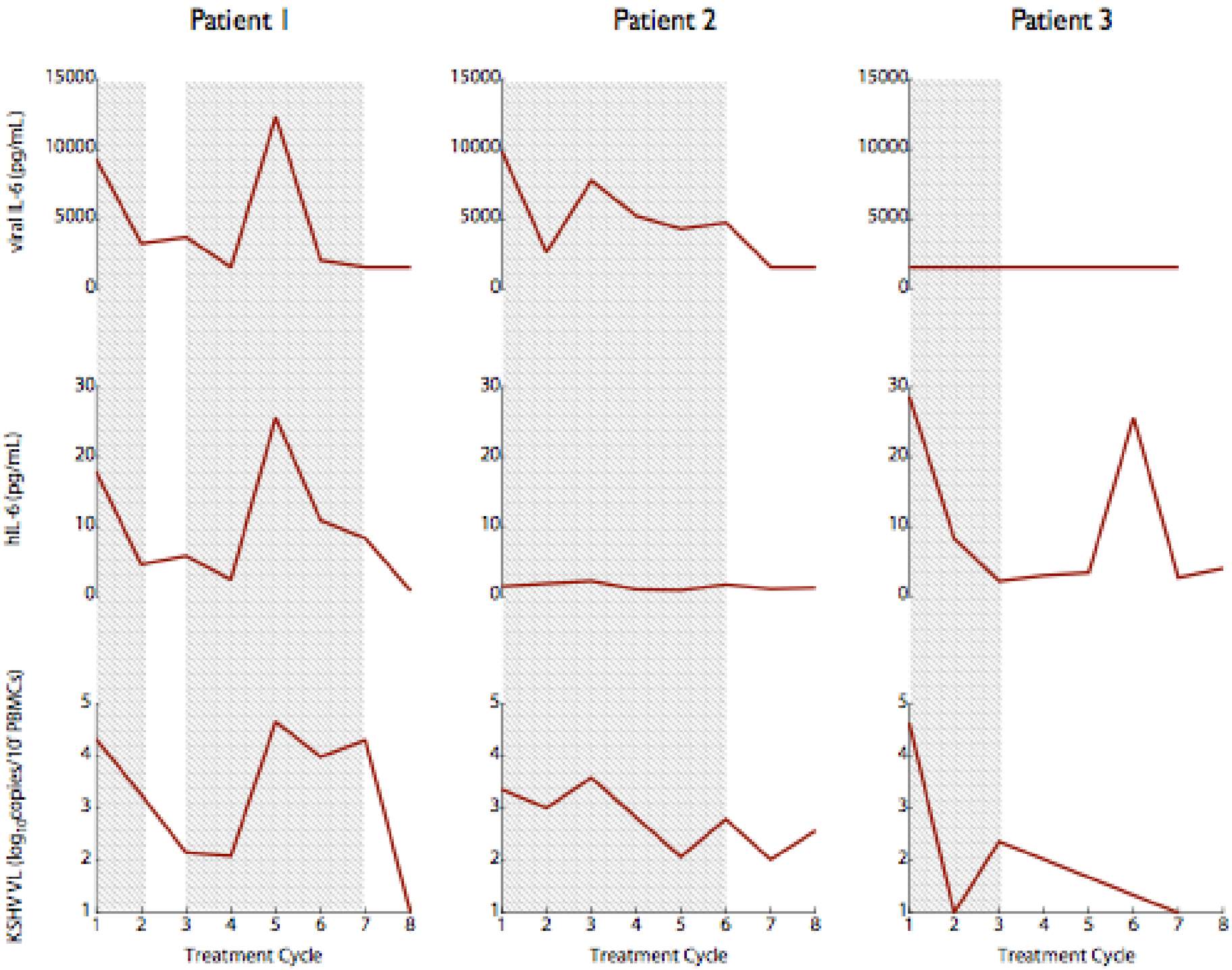
Polizzotto, Millo et al. *Clinical Cancer Research* In Press (2014).


H+E


KSHV LANA


KSHV vIL-6

Human and Viral IL-6



Polizzotto, Uldrick, et. al. *Blood* 122: 4189-4198 (2013).

Targeting KSHV Lytic Cells

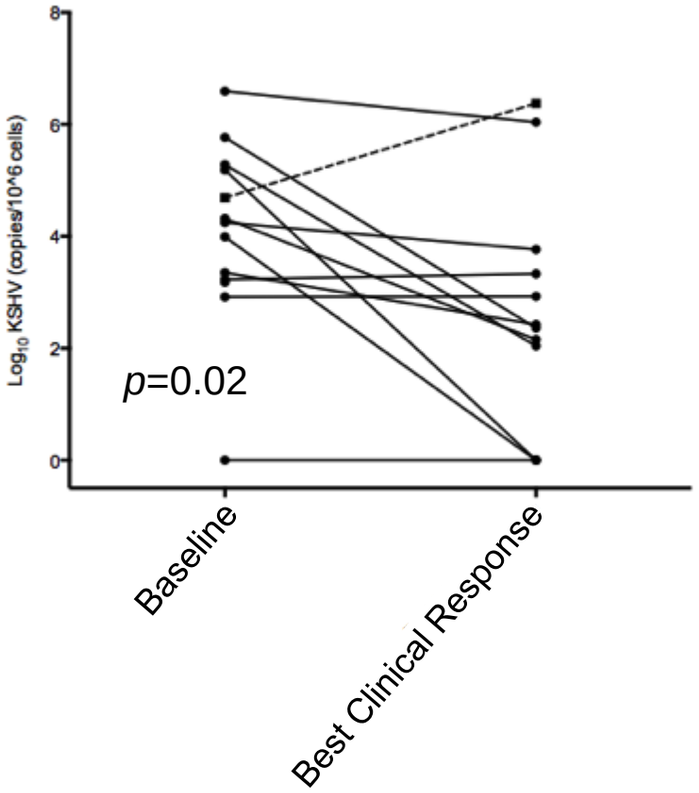
KSHV Lytic Genes ORF36 (Phosphotransferase) and ORF21 (Thymidine Kinase) Activate ganciclovir (GCV) and zidovudine (AZT) to cytotoxic moieties

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

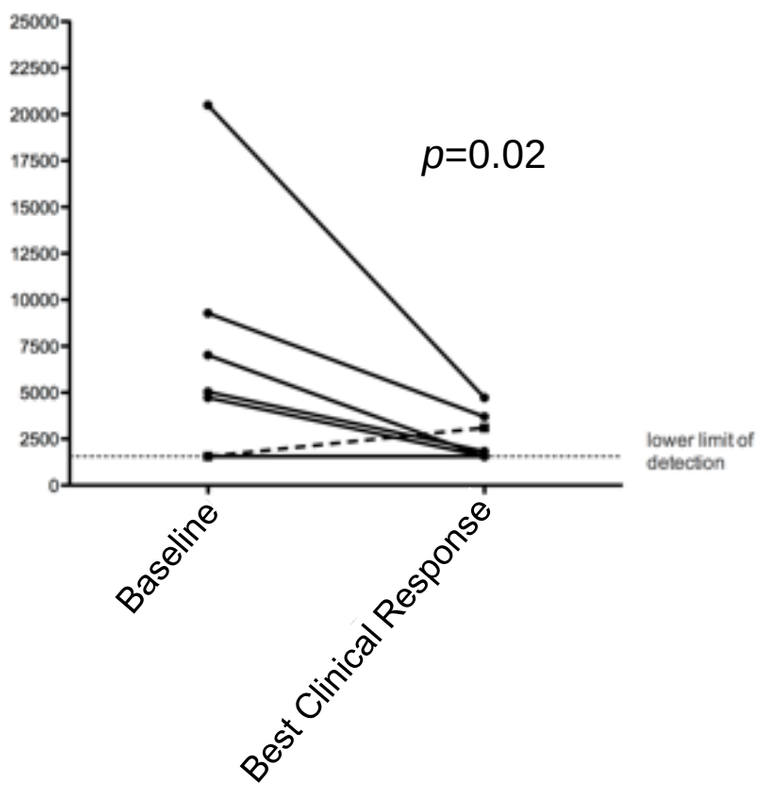
Cannon et al., *J Virol.* 73:4786-93 (1999); Gustafson et al., *J Virol* 74, 684-92 (2000)

KSHV VL and Cytokines with Therapy

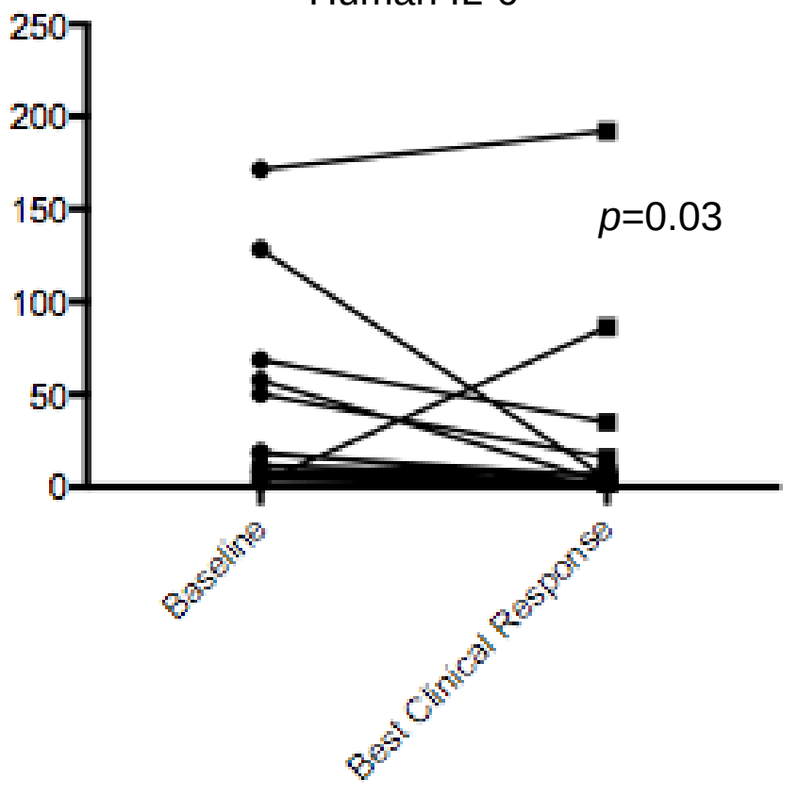
KSHV Viral Load



Viral IL-6



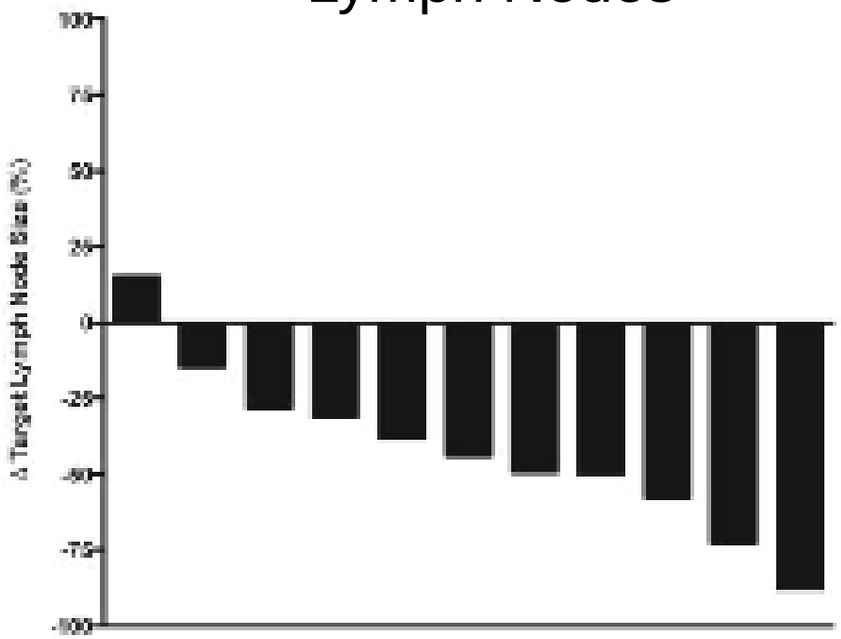
Human IL-6



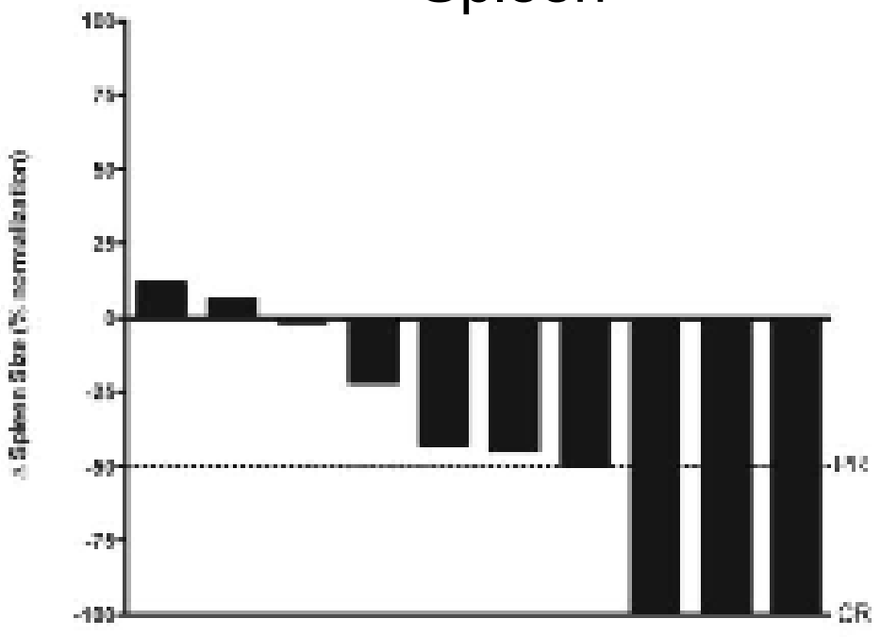
Clinical Responses

Symptomatic	Biochemical	Radiographic
Complete 7 (50%)	Complete 3 (21%)	Complete 4 (29%)
Partial 5 (35%)	Partial 4 (29%)	Partial 1 (7%)
Overall 12 (86%)	Overall 7 (50%)	Overall 5 (36%)
Stable Disease 2 (14%)	Stable Disease 6 (43%)	Stable Disease 9 (64%)
Progressive Disease –	Progressive Disease 1 (7%)	Progressive Disease 1 (7%)

Lymph Nodes

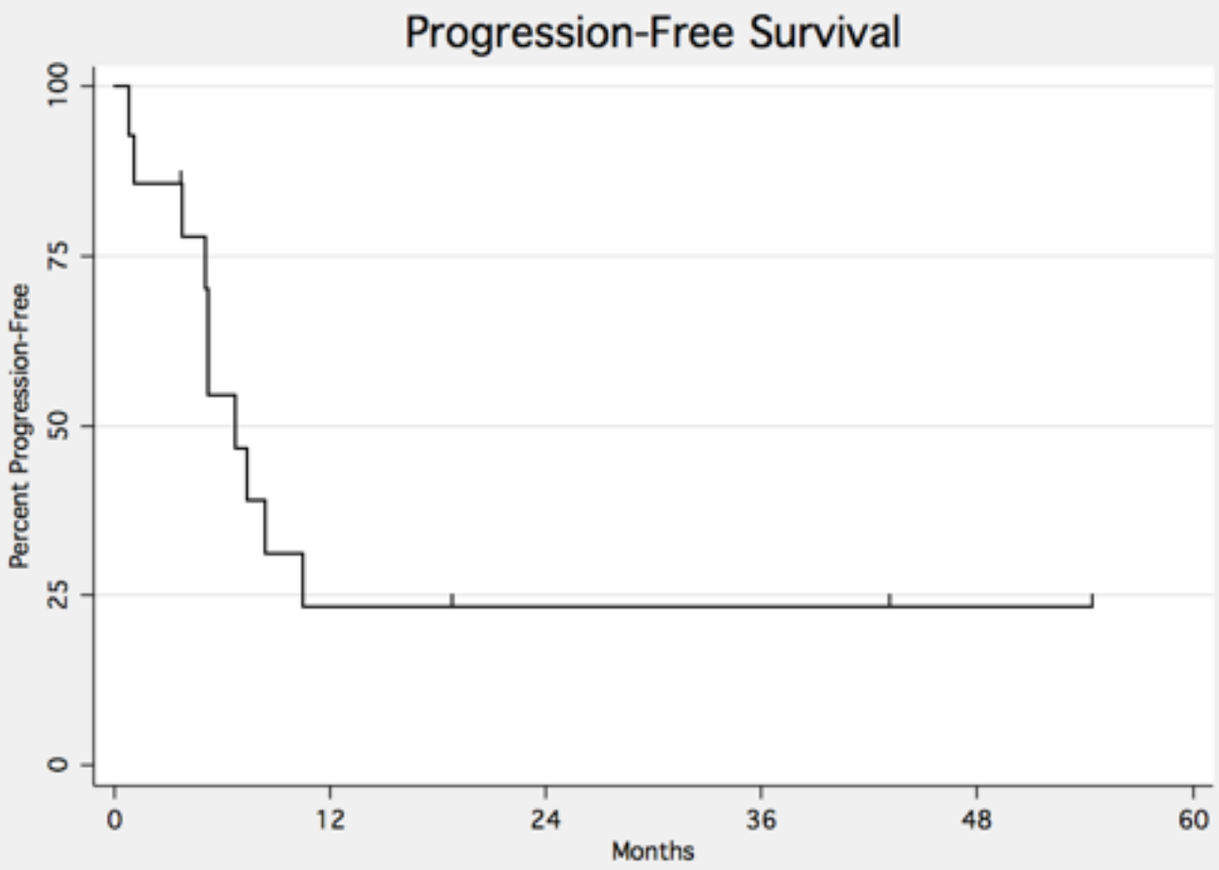


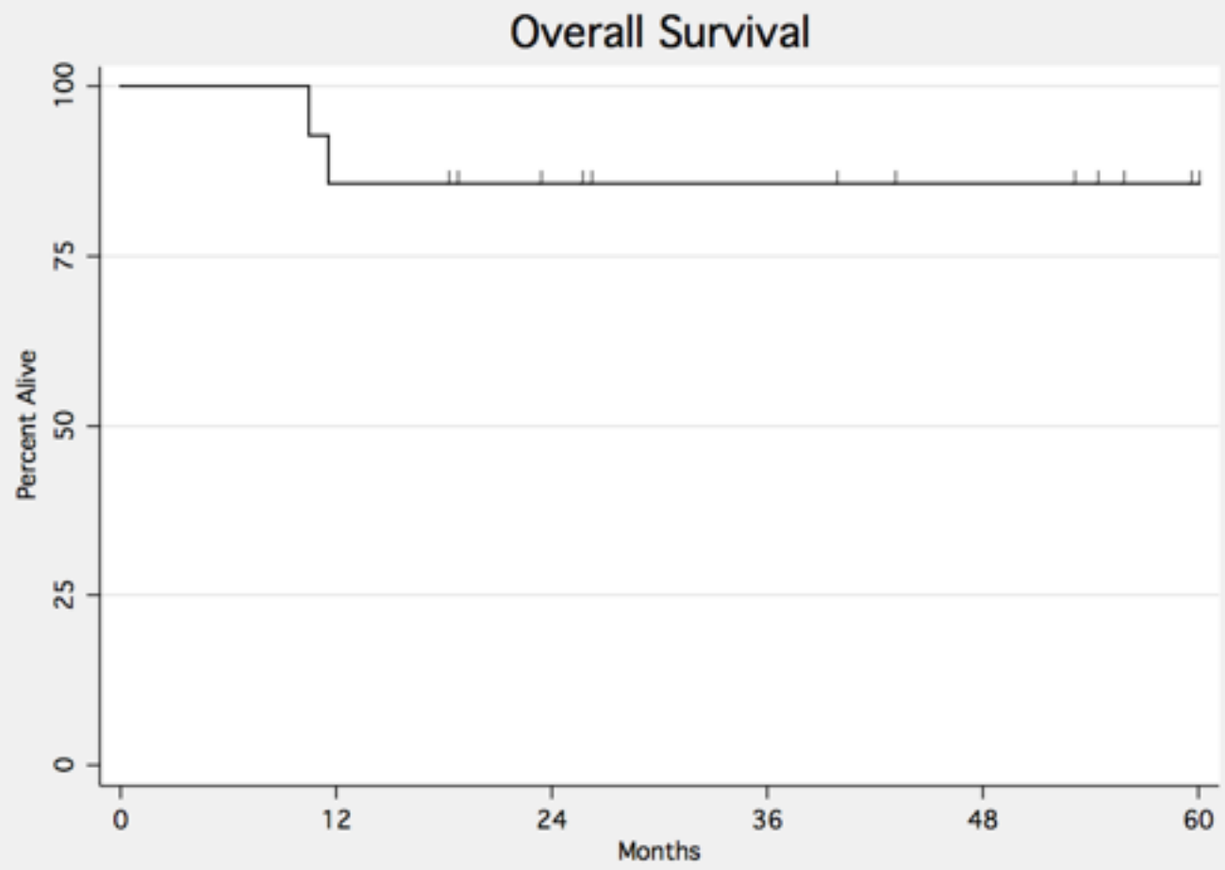
Spleen



Uldrick, Polizzotto, et. al. *Blood* 122: 4189-4198 (2013).

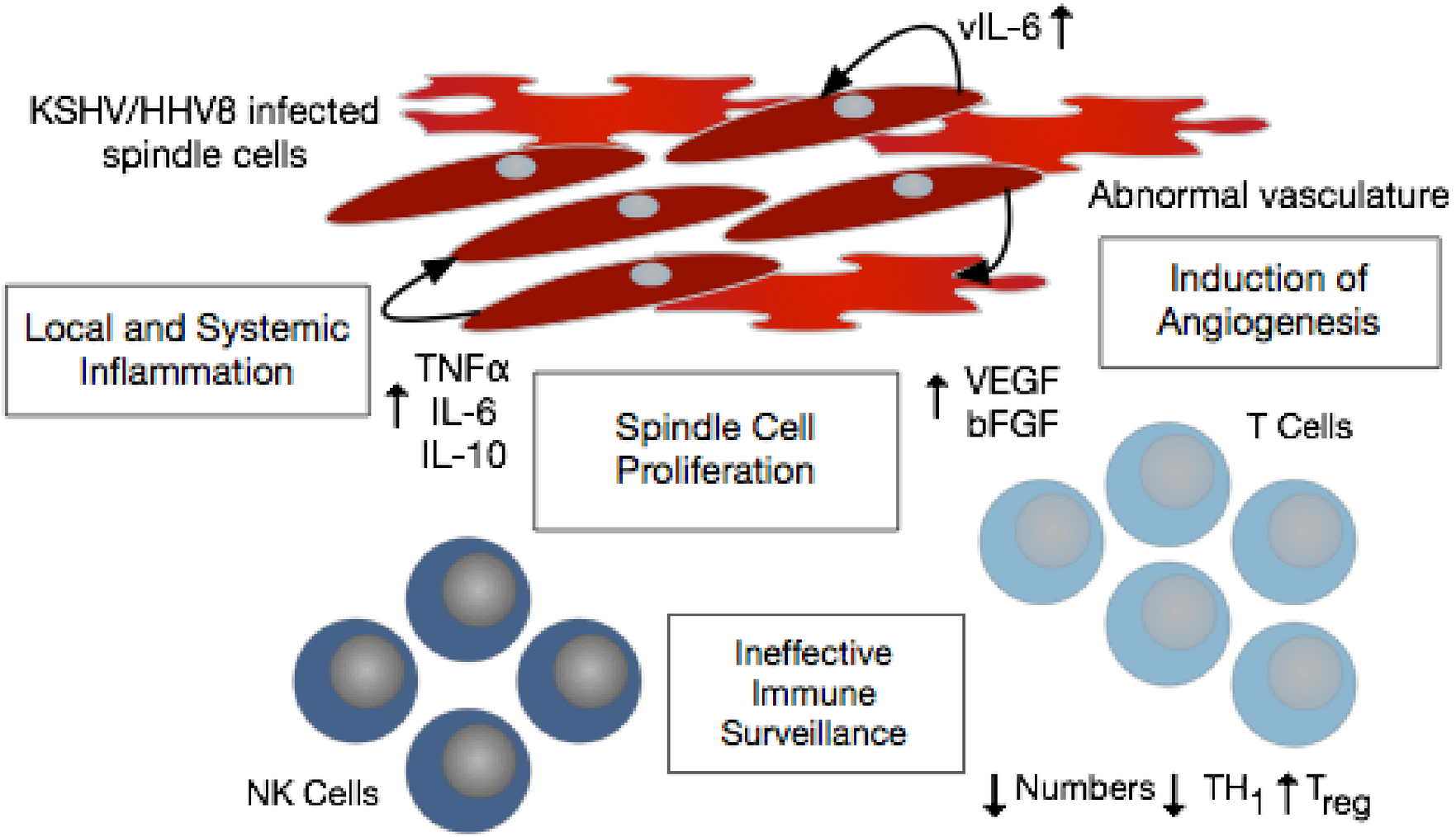
Clinical Responses





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

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

- 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

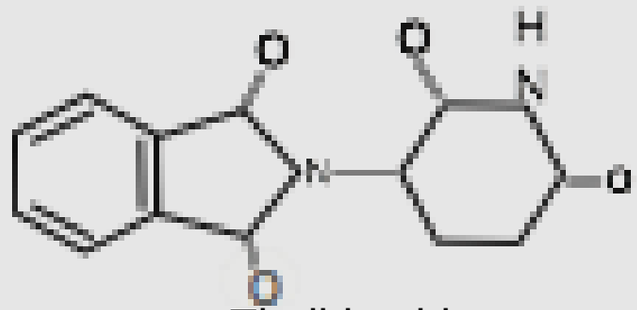
Doxil+IL-12

HIV VL: <50 copies/mL

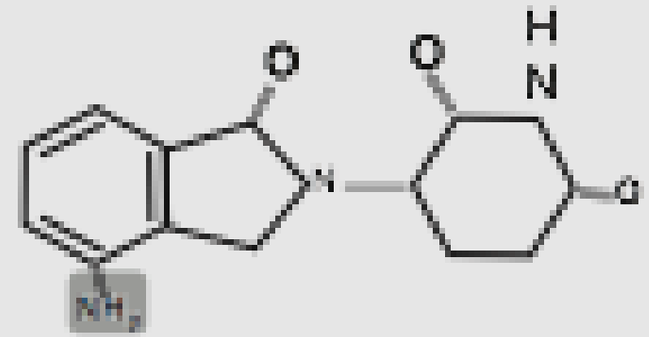
CD4: 318 cells/µL

Immunomodulatory agents (IMiDs)

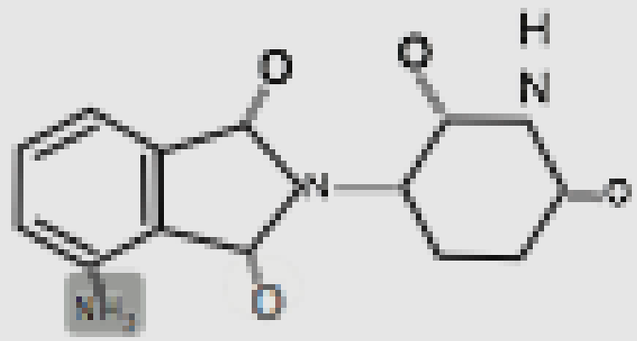
- Thalidomide and derivatives
  - Oral agents with immunomodulatory, anti-angiogenic, and anti-proliferative activity
  - Second generation: lenalidomide
  - Third generation: pomalidomide
- Derivatives
  - Reduce neurotoxicity and sedation
  - Increase immunomodulatory potency
- Mechanisms of action
  - Likely to vary by malignacy, but common pathways
  - Target Cereblon, an E3 ubiquitin ligase
  - Modulate transcription factors including IKZF1, IKZF3, IRF4



Thalidomide



Lenalidomide



Pomalidomide

Ito et al. *Science* 327:1345-7 (2010); Zhu et al Blood 118:4771-4779 (2011).

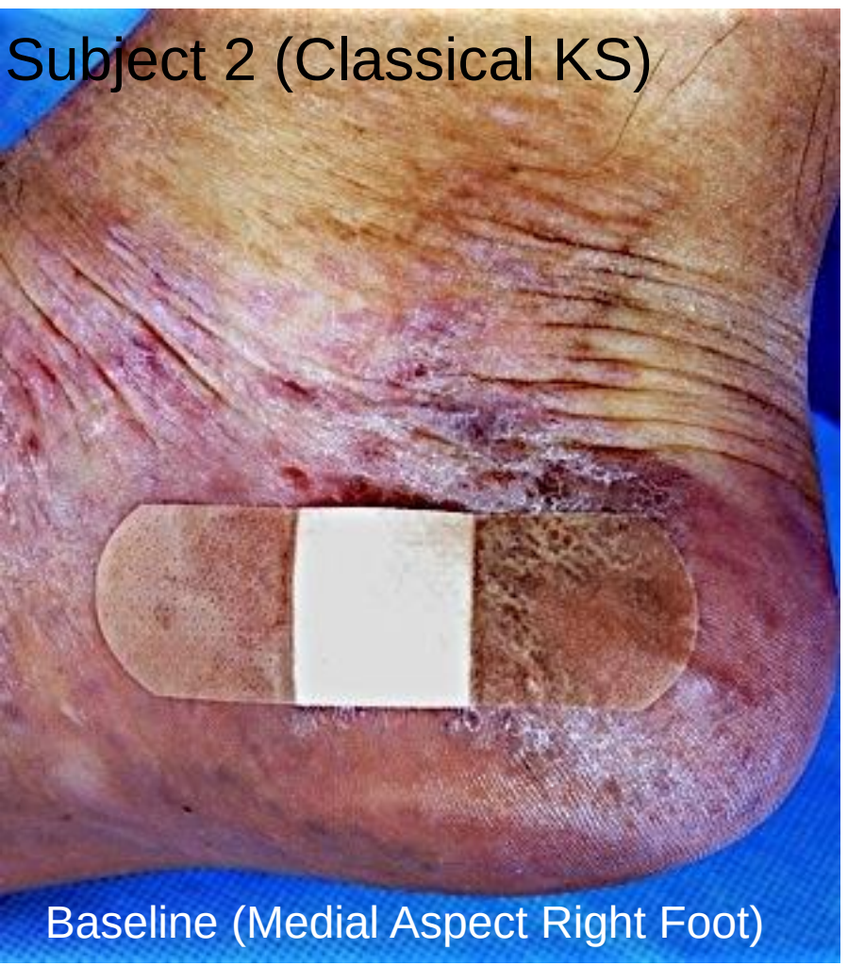
Subject 1 (HIV associated KS)

Baseline (Left Great Toe)

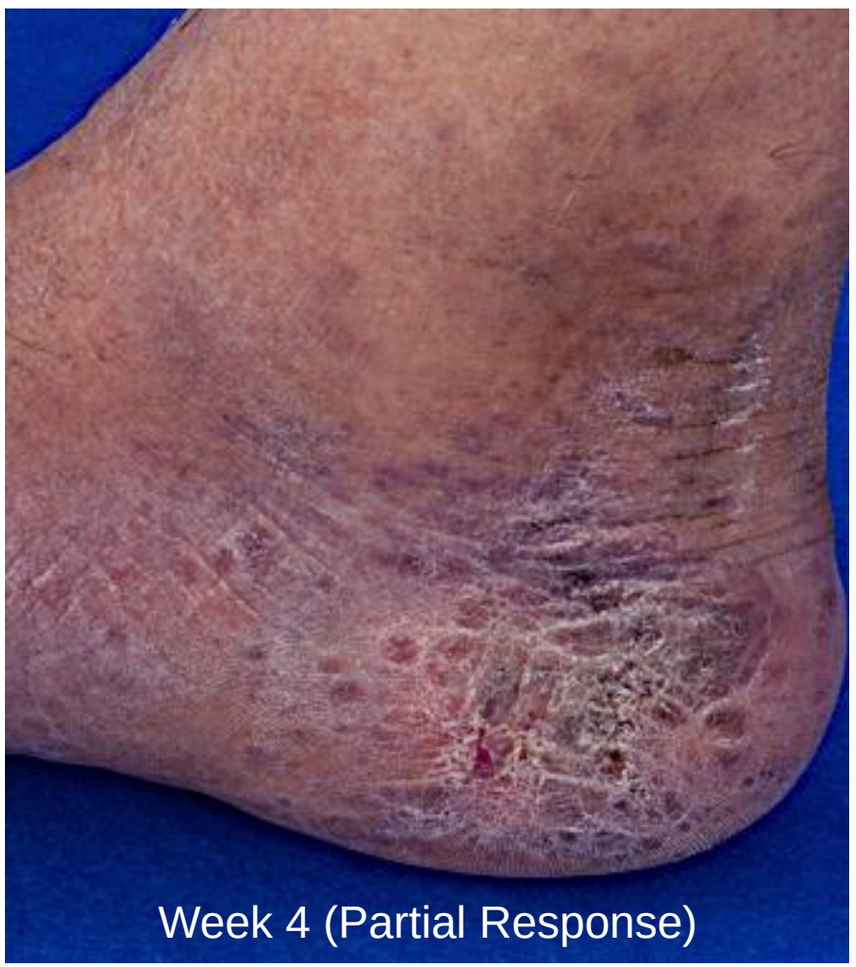
Week 4 (Partial Response)

Week 24 (Complete Response)

Subject 2 (Classical KS)



Baseline (Medial Aspect Right Foot)



Week 4 (Partial Response)

Week 24 (Complete Response)

Current NCI Studies

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

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

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