Malignancies in HIV: A Growing Concern

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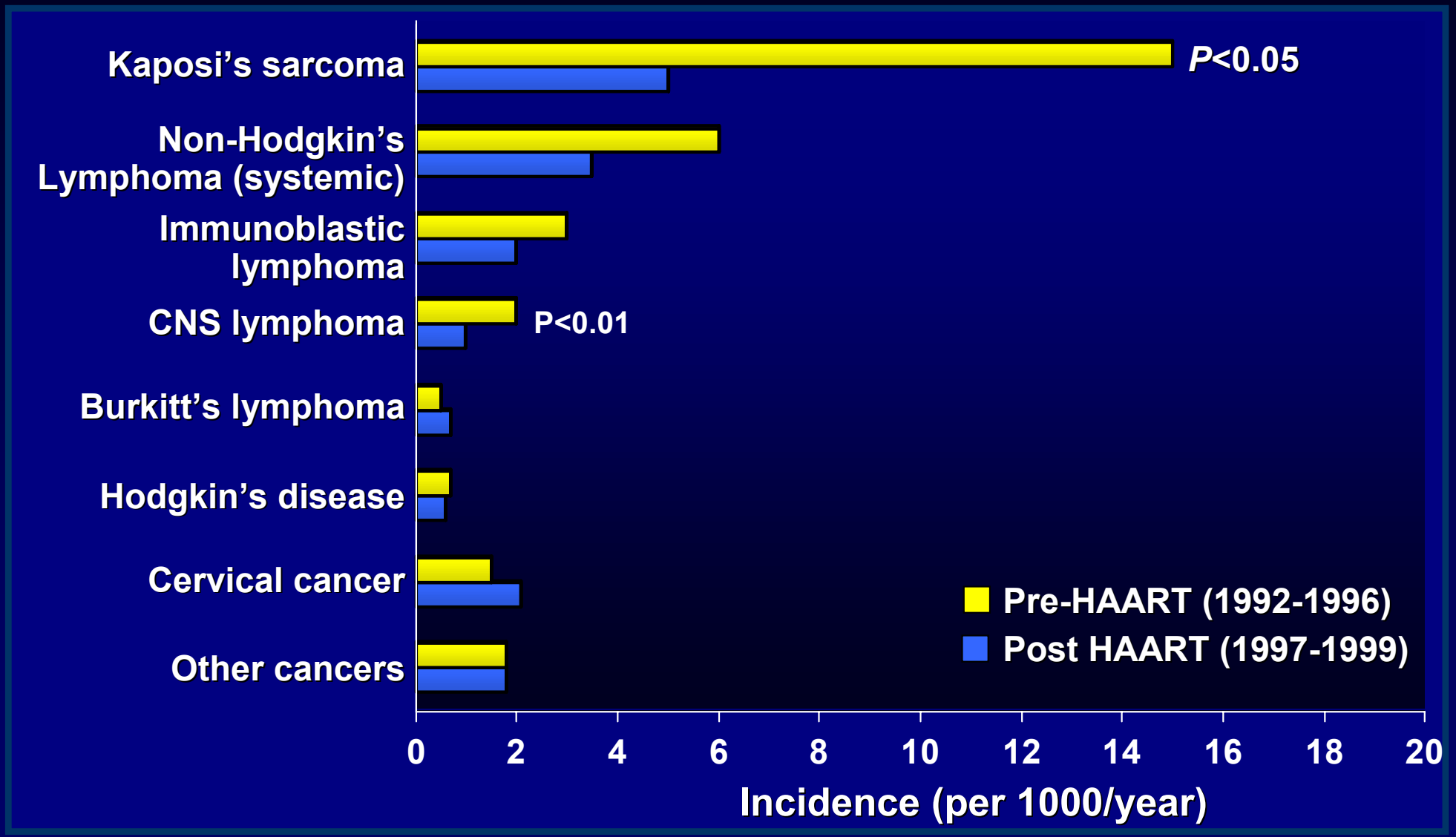
Cancers in HIV Disease

AIDS-Defining	Virus
• Kaposi's Sarcoma	HHV-8
• Non-Hodgkin's Lymphoma (systemic and CNS)	EBV, HHV-8
• Invasive Cervical Carcinoma	HPV
Non-AIDS Defining	
• Anal Cancer	HPV
• Hodgkin's Disease	EBV
• Leiomyosarcoma (pediatric)	EBV
• Squamous Conjunctival Carcinoma	HPV (?)
• Hepatoma	HBV, HCV

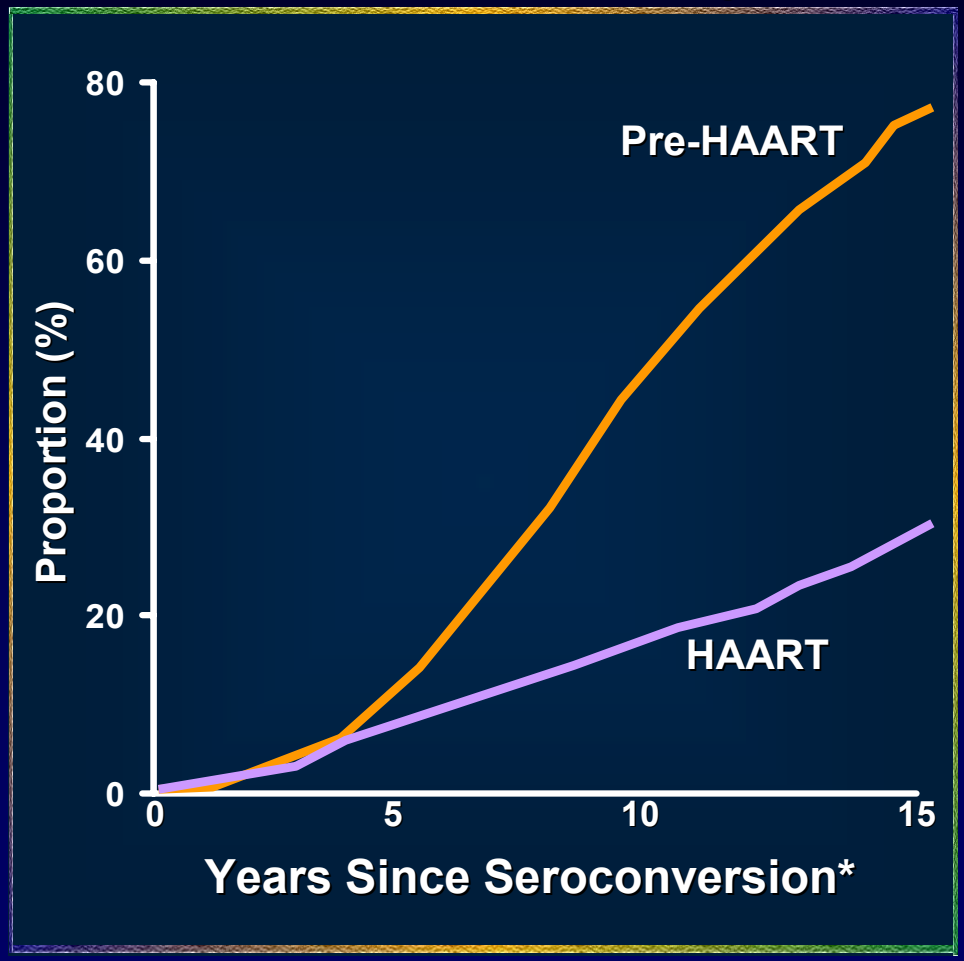
HIV-Associated Cancers: Incidence Pre and Post HAART



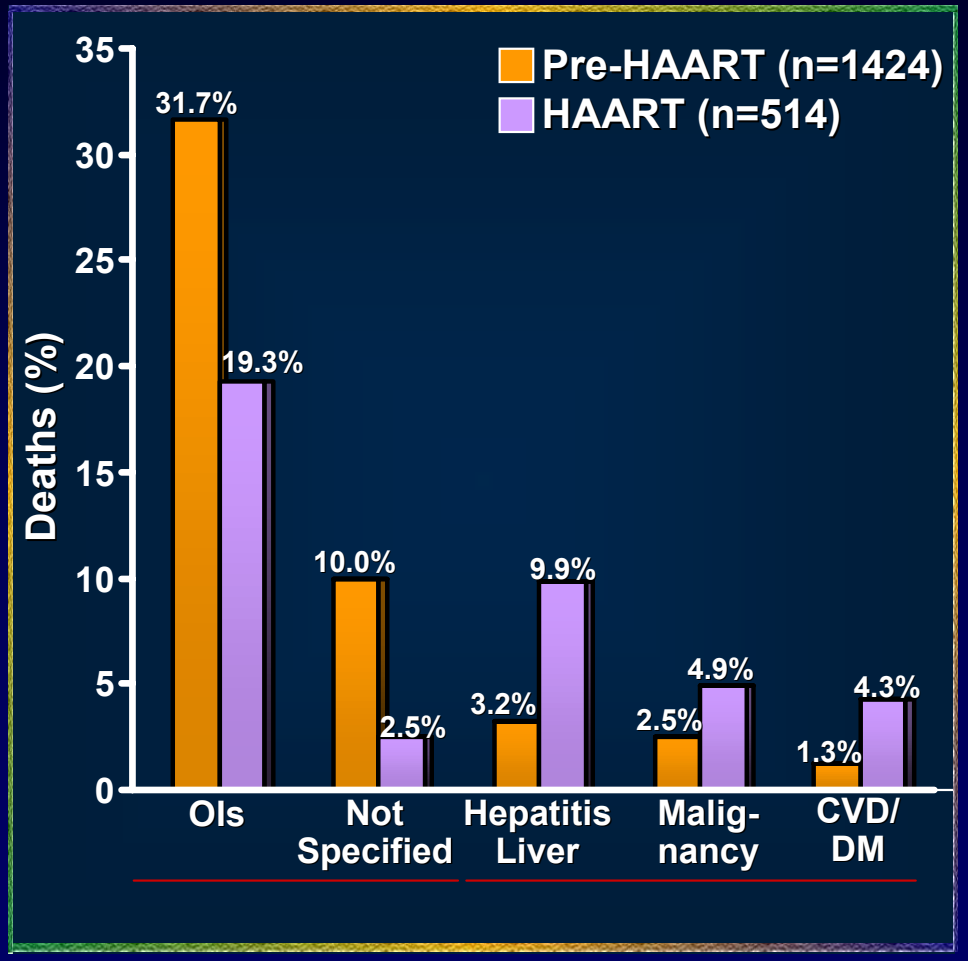
International Collaboration on HIV and Cancer. *J Natl Cancer Inst*. 2000;92:1823-1830.

CASCADE Collaboration: Overall Mortality and Causes of Death

Overall Mortality*



Causes of Death†



*n=7680 seroconverters, of whom 1938 died (26%; 1424 pre-HAART and 514 during HAART).

†no change in the following causes of death: AIDS-related malignancy, other infections, organ failure, and unknown causes.

Smit C, et al. *AIDS.* 2006;20:741-749.

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

Endpoint	Number	%
CVD	79	42
Hepatic	17	12
Renal	11	10
NA Cancer	60*	36

*25% Fatal

Silverberg et al. AIDS 2007, 21:1957-1963

HIV-Cancers: Overview

- Non-AIDS defining malignancies
- Anogenital neoplasia
- Lymphomas
- Kaposi's Sarcoma

Non-AIDS Defining Cancers
NADC

Pathogenesis of NADC

- 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 HIV (e.g 6 fold higher number of MA in HIV lung CA over non-HIV)[1]
- Increase susceptibility to effects of carcinogens (tobacco)
- Population differences based on genetics and exposure to carcinogens
- Decreased immune surveillance

[1]Wistuba, AIDS 1999;13:415-26

Relative Risk for Malignancies in AIDS in USA

Strong Association

	Relative Risk
Kaposi's sarcoma	
Overall	73,000
MSM	106,000
non-MSM	13,000
Non-Hodgkin's lymphoma	165
Anal	31.7
Squamous cell carcinoma	13.0

Possible Association

	Relative Risk
Hodgkin's	7.6
Multiple myeloma	4.5
Lip	4.1
Brain	3.5
Seminoma	2.9
Cervical cancer	2.9

Goedert J. *Semin Oncol.* 2000;4:390-401.

Incidence of Non-AIDS-Defining Malignancies 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

Clifford J Natl Cancer Inst 2005; 97:425; Engels CROI 2005 Abstract 908; Phelps Int J Cancer 2001; 94:753; Serraino AIDS 2000; 14:553; Giordano Clin Infect Dis 2005; 40:490. Patel, CROI 2004.

Summary of NADCs 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, RR 1915 (1 in 5000, 8-14% of all cancers in kids)

Chiao EY and Krown SE. Curr Opin Oncol 15:389-97, 2003

NADCs: 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 NADCs perhaps due to
  - Underdiagnosis
  - Deaths due earlier from infections

Chaio EY and Krown SE Curr Opin Onc 15:389-97, 2003

Why does lung CA do so badly?

	HIV-	Age-Matched HIV-	Pre HAART HIV+	Post HAART HIV+
Number	192	102	97	18
Age	69	45	42	45
Stage 1-IIIA	32%	10%	25%	6%
PS 0-2	51%	52%	42%	40%
Survival (months)	>10	4	4.5	4
Adenocarcinoma	28%	66%	45%	27%

Powels, Br J Cancer 2003;89:457-9

Anogenital Cancers

Anogenital Cancers

- Invasive cervical carcinoma
  - Considered an AIDS-defining condition
- Anal cancer[1]
  - Not AIDS defining but very common
- HPV involvement[1-2]
  - Both derive from premalignant dysplastic lesions due to HPV
  - Most oncogenic strains: 16, 18, 31, 33, 35, 45
  - Repeated infections and infection with multiple HPV strains increase the risk of developing neoplasia

[1]Phelps RM, et al. *Int J Cancer*. 2001;94:753-757.
[2]Martin F, et al. *Sex Transm Infect*. 2001;77:327-331.

Guidelines for assessment of CIN in HIV+ women

- Pap smear at initial evaluation
- Repeat Pap smear 6 months later
- If both negative, can do annual Pap
- Low threshold for colposcopy
- Role of HPV testing
  - Screening for women over 18

Treatments for Cervical SIL and Invasive Cervical Cancer

Local Disease HSIL

- Cryoablation
- Laser therapy
- Cone biopsy
- Loop electrosurgical excision procedure (LEEP)
- Topical 5-FU
- Trans-retinoic acid
- Podophyllin cream
- Imiquimod cream
- Antiretroviral Therapy (?)

Invasive Disease[1,2]

- Surgery (stage I)
- Radiation therapy
- Cisplatin or carboplatin

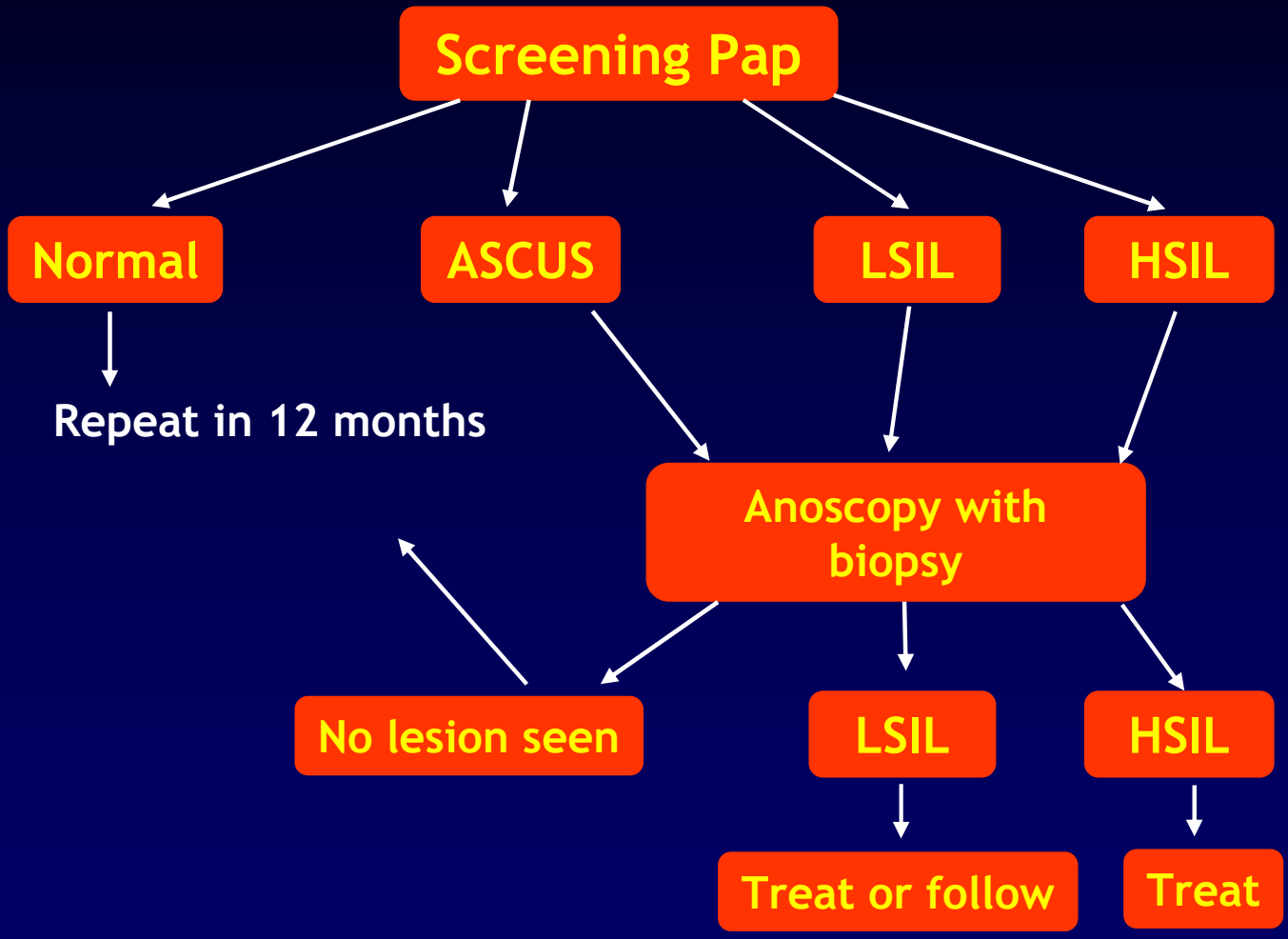
[1]Mitsuyasu RT, et al. *Cancer Management.* 2006:609-632.
[2]Martin F, et al. *Sex Transm Infect.* 2001;77:327-331.

Relative risk of anal cancer in U.S.A. AIDS-cancer registry match study

Age	HIV+ women	HIV+ men
<30	134	163
30-39	12.2	40
≧40	2.6	32
All ages	6.8	37

Frisch et al, JNCI, 2000;92:1500-1510.

Anal Cytology Screening for AIN in HIV-positives



Chin-Hong PV et al. *J Infect Dis.* 2004;90:2070-2076.

Treatments for Anal SIL and Carcinoma

Anal SIL[1]

- Low grade
  - Repeat high resolution anoscopy every 6 months
- High grade
  - Surgery
  - Laser, IRC or electrocautery
  - 80% Trichloroacetic acid
  - Investigational agents
    - Cidofovir cream (AMC 046)
    - Imiquimod

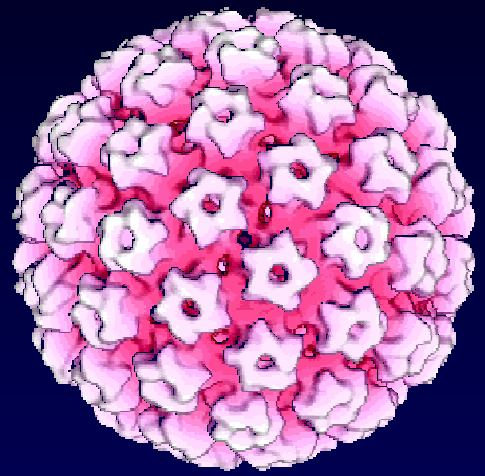
Carcinoma[1,2]

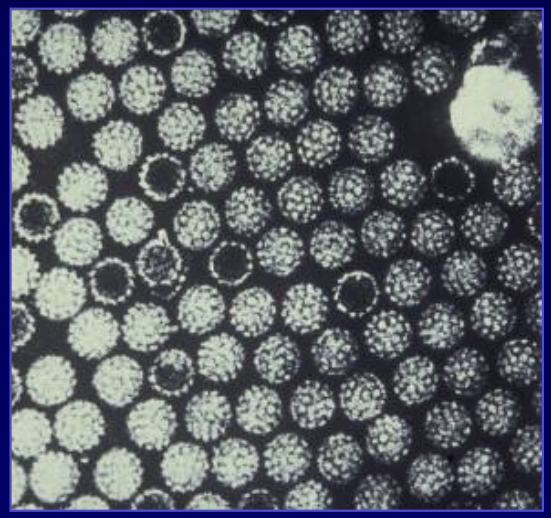
- Combination chemoradiotherapy
  - Mitomycin + 5-fluorouracil/RT
  - Cisplatin ± 5-fluorouracil/RT
- Investigational
  - Combined chemoradiotherapy + Cetuximab (AMC 045)

[1]Mitsuyasu RT, et al. *Cancer Management.* 2005:-632.
[2]Martin F, et al. *Sex Transm Infect.* 2001;77:327-331.

Immunization Against HPV

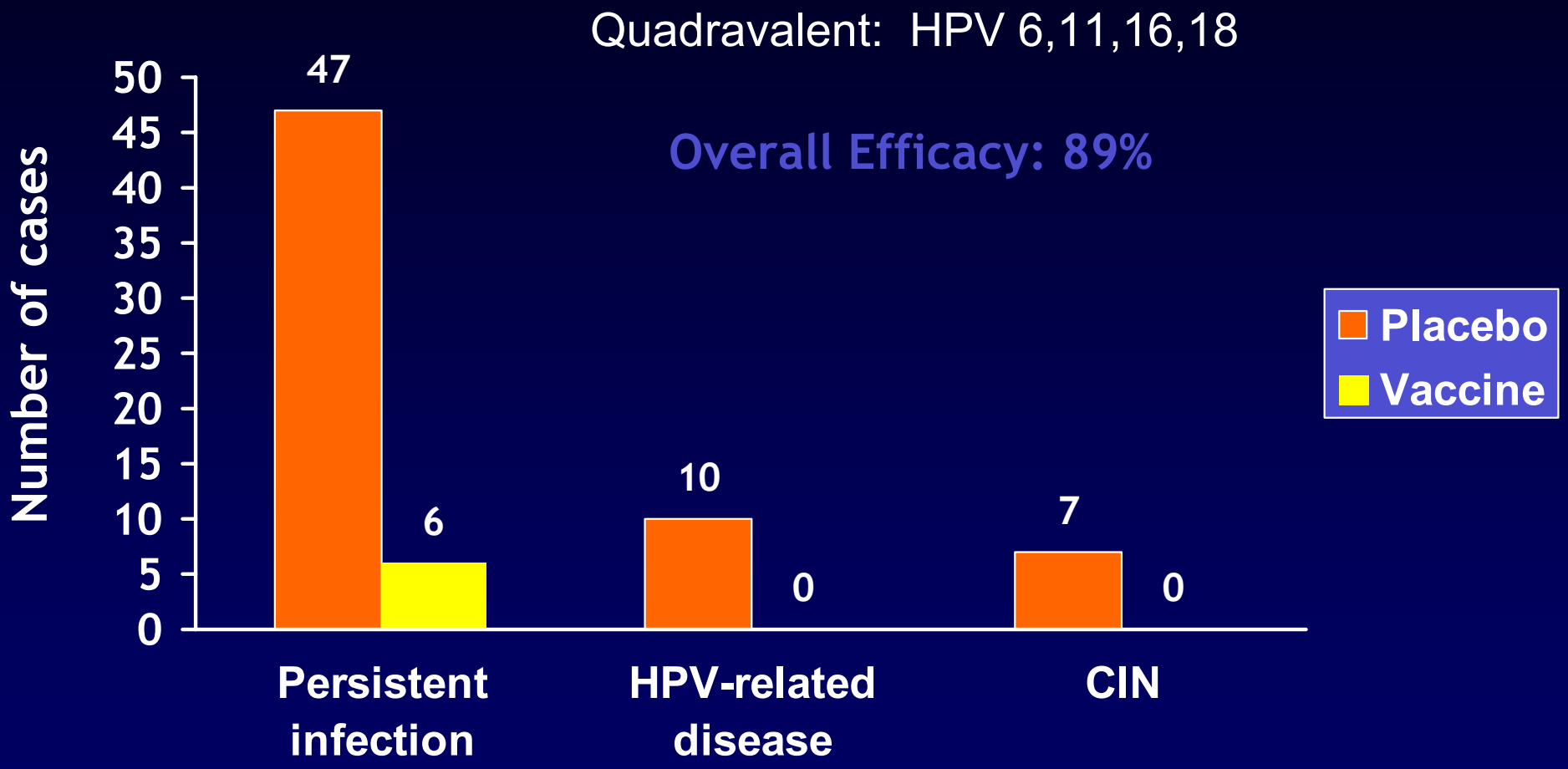
- HPV infection induces type-specific immune responses
- Promising vaccine candidate:
  - Virus-like particles (VLP) are recombinant viral capsids that induce type-specific neutralizing antibodies
- VLPs are nontoxic and highly immunogenic
- Both bivalent (HPV 16,18) and quadravalent (HPV 6,11,16,18) vaccines available





Schiller JT et al. *Nat Rev Cancer*. 2004;2:343-347.

Phase II Trial of a Quadrivalent HPV Vaccine: Modified Intention-to-Treat (MITT) Efficacy



Villa LL et al. *Lancet Oncol.* 2005;6:271-278.

Lymphomas

Pathology of AIDS-Related Non-Hodgkin's Lymphoma

- 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

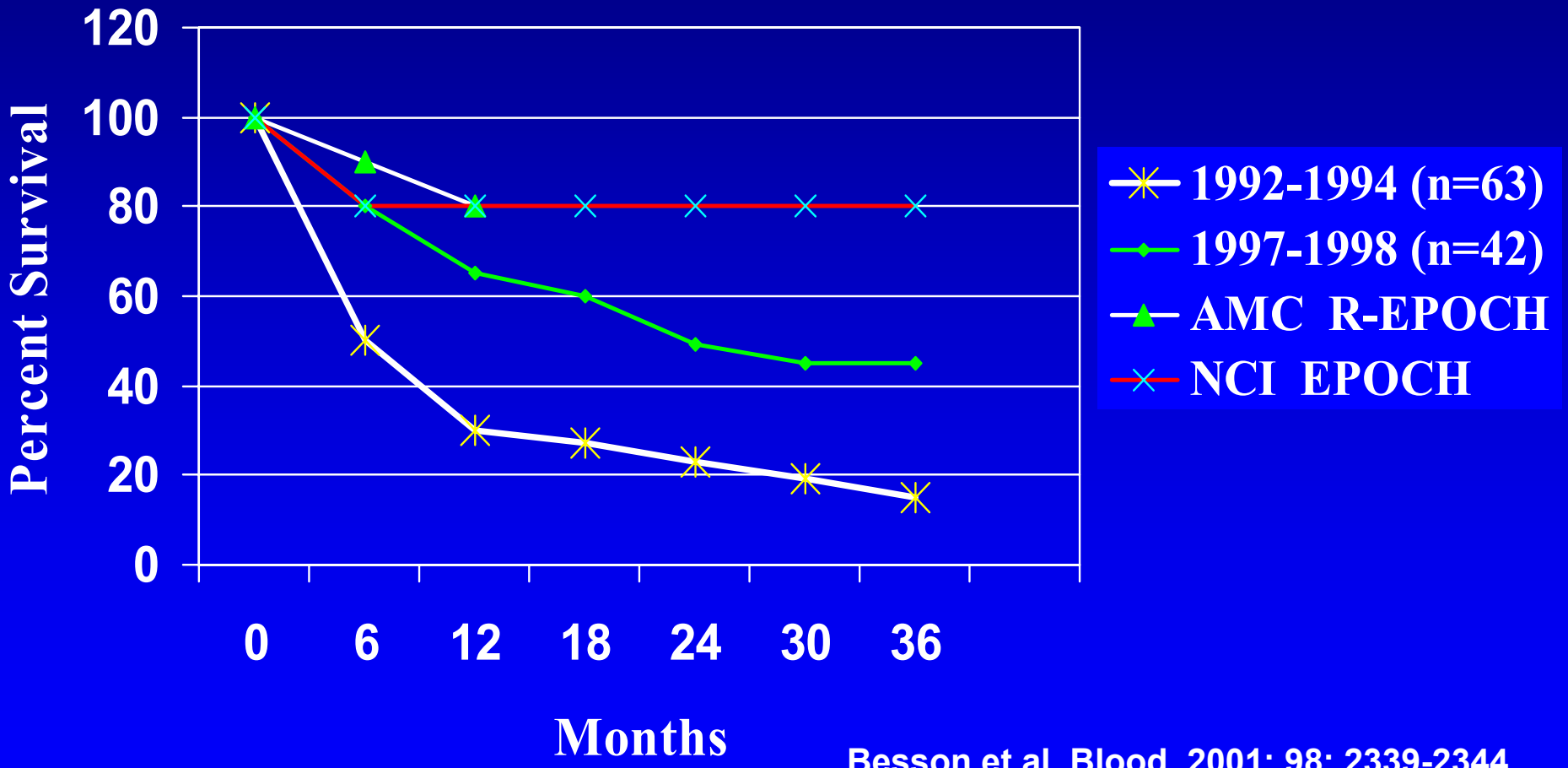
Tirelli U, et al. *AIDS*. 2000;14:1675-1688.

Therapeutic Approaches for AIDS-Related Non-Hodgkin's Lymphoma

- 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 HAART
- Use of monoclonal antibodies (rituximab) AMC 010 and 034
- High dose chemotherapy with ASCT

AIDS-NHL Survival:

Impact of HAART and EPOCH



Besson et al. Blood. 2001; 98: 2339-2344
Little et al Blood. 2003; 101: 4653-4659
Sparano et al: 2006,10th ICMAOAI, Bethesda

AIDS Malignancies Consortium Study 010: CHOP With or Without Rituximab

- Phase II trial
  - 149 patients
  - Median CD4 count: 133 cells/mm^3
- Regimens
  - Rituximab (day 1) + CHOP (day 3)
  - CHOP
- Patients restaged every 2 cycles
- Median F/U 137 wk

	CHOP + Rituximab	CHOP Alone
Number of patients	99	51
Complete response (%)	58	48
Median time to response (weeks)	11.0	10.5
Median event-free survival (weeks)	52	51
Death due to infection	13*	1
Median overall survival (weeks)	139	110

**P*=0.035 vs CHOP alone.

Kaplan LD, et al. Blood 2005;106:1538-1543

Dose-Adjusted EPOCH (NCI) in HIV-Infected Patients

- Dose-adjusted EPOCH chemotherapy
  - Etoposide 200 mg/m^2 (96-hour infusion)
  - Vincristine 1.6 mg/m^2 (96-hour infusion)
  - Doxorubicin 40 mg/m^2 (96-hour infusion)
  - Prednisone 60 mg po on days 1–5
  - Cyclophosphamide IV on day 5
    - CD4 <100 cells/mm^3: 187 mg/m^2
    - CD4 >100 cells/mm^3: 375 mg/m^2
    - Dose adjusted in cycles 2 through 6 to a maximum of 750 mg/m^2

Little RF, et al. *Blood.* 2003;101:4653-4659.

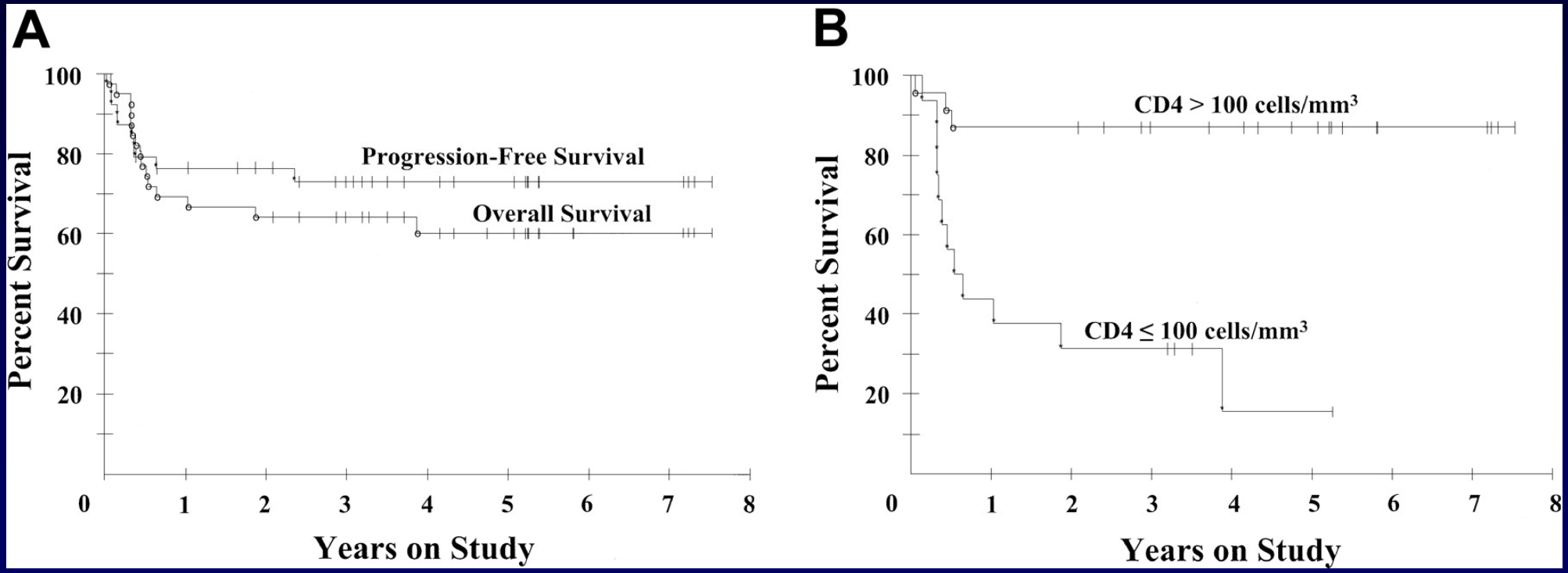
Response to Dose-Adjusted EPOCH in HIV-Infected Patients

- Median follow-up
  - 53 months
- Median CD4
  - 190 cells/mm^3
- Not prognostic
  - Tumor proliferation
  - p53 overexpression

	CD4 (cells/mm^3)		
	<100	≥100	Total
Number of patients	16	23	39
Complete response (%)	56	87	79
Relapse	2	0	2
Progression-free survival (%)	73	93	87
Overall survival (%)	36	87	60

Little RF, et al. *Blood.* 2003;101:4653-4659.

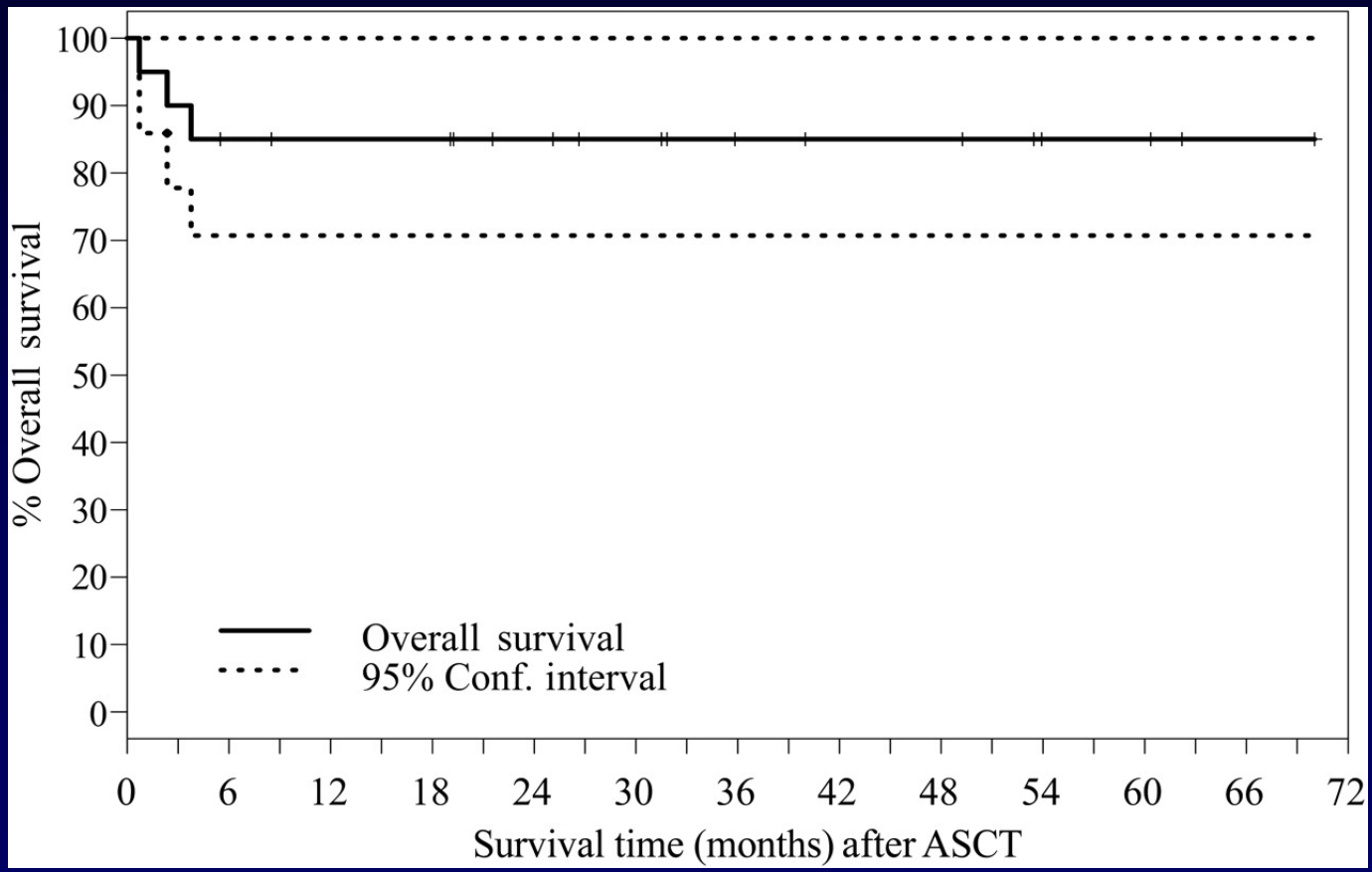
Progression-Free and Overall Survival with EPOCH



Little, R. F. et al. Blood 2003;101:4653-4659

Kaplan-Meier analysis of Overall Survival in 20 patients after ASCT

Median Followup: 32 (5.5-70) mos



Krishnan, A. et al. Blood 2005;105:874-878

Primary CNS Lymphomas in HIV-Infected Patients

- Incidence: <5% of AIDS patients. Now very rare
- Diagnostic approaches
  - Cranial CT or MRI scan
    - Most important differential diagnosis: toxoplasmosis
  - Stereotatic brain biopsy essential for diagnosis
    - When biopsy not possible, EBV-PCR of CSF is useful, 100% sensitive, 80% specific
- Therapeutic approaches
  - Traditional: radiation (4000-5000 cGy)- 10% 1yr survival
  - High-dose methotrexate based chemotherapy
    - Non-AIDS patients: shows promise
  - High-dose ZDV + GCV +/- IL-2 may have benefit (JAIDS 1999;15:713-19)

Primary Effusion Lymphomas in HIV-Infected Patients

- B-cell non-Hodgkin's lymphoma
  - Most cases are dually infected with HHV8 and EBV
  - Median survival: 6 months
- Traditional treatment: 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

Boulanger E, et al. *Am J Hematol.* 2003;73:143-148.

Hodgkin's Disease

- Association with HIV-infection
  - Hodgkin's disease: RR: 5 to 30
  - Non-Hodgkin's disease: RR: 24 to 165
- Patients with HIV present with:
  - B symptoms (70% to 96%), worse histology, higher-stage tumor (74% to 92% are III or IV), bone marrow involvement (40% to 50%), pancytopenia
- Good response to MOPP/ABV
  - Complete response: 74.5%
  - 2-year disease-free survival: 62%
  - Early better results with Stanford V and BEACOPP

Gerard L, et al. *AIDS*. 2003;17:81-87.

Kaposi's Sarcoma

Kaposi's Sarcoma

- One of the first recognized AIDS-defining illnesses
- Vascular tumor that may involve mucocutaneous, lymphatic, gastrointestinal, and pulmonary sites
  - Human herpesvirus-8 (HHV8) or KSHV
- HHV8
  - DNA virus found in both HIV+ and HIV- KS.
  - Tropism for B cells and endothelial cells, high titers in saliva
  - Also associated with primary effusion lymphoma, Castleman's disease, and angioimmunoblastic lymphadenopathy in HIV
  - Genome codes for viral homologs of human proteins involved in cell cycle regulation and signaling
- HIV- and Kaposi's sarcoma-induced angiogenic and inflammatory cytokines also stimulate Kaposi's sarcoma cell growth

Pulmonary KS has Poor Prognosis

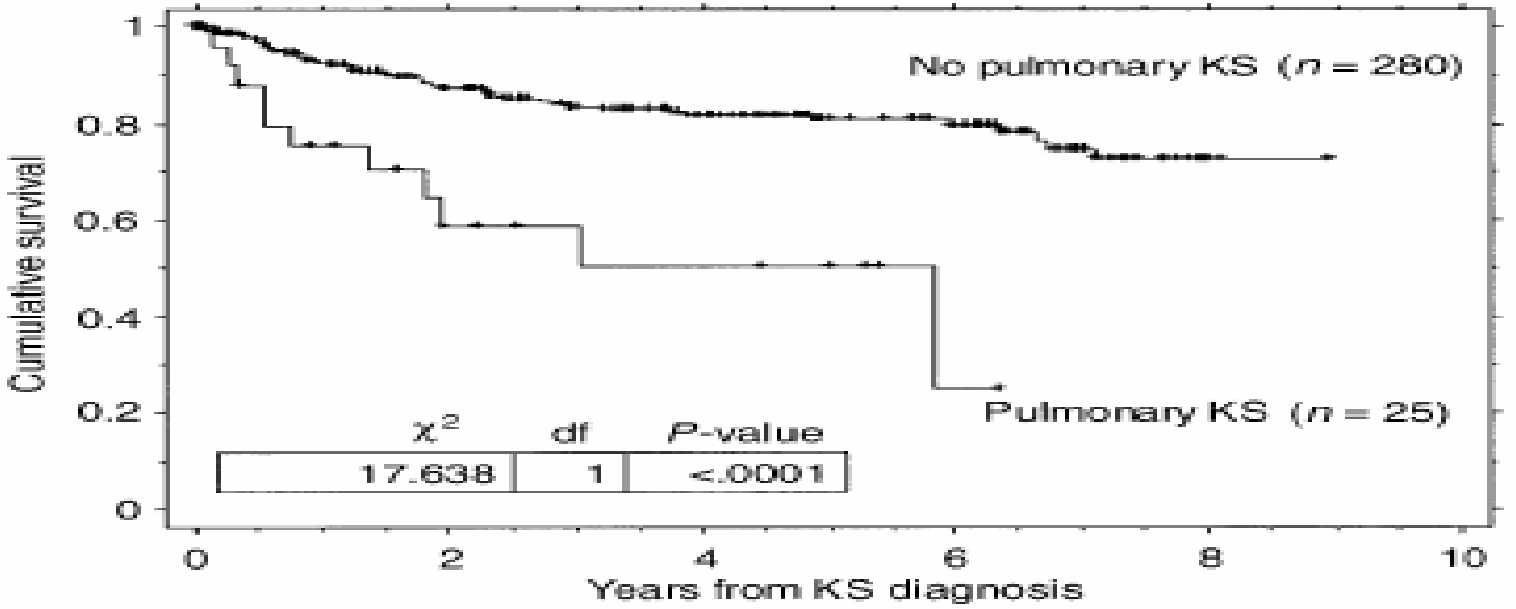


Fig. 1 Kaplan–Meier overall survival duration curves (all causes of death) for patients with Kaposi sarcoma (KS) diagnosed in the era of highly active antiretroviral therapy, comparing those with ($n = 25$) and without ($n = 280$) pulmonary KS. df, degrees of freedom.

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[1]

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

Systemic[1,2]

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

[1]Levine AM, et al. *Eur J Cancer*. 2001;37:1288-1295.
[2]Mitsuyasu RT, et al. *Cancer Management. 9th Ed.* 2005:609-632.

Indication for Systemic Therapy

- Widespread skin involvement (usually more than 25 lesions)
- Extensive cutaneous KS unresponsive to local treatment or HAART
- Extensive edema
- Symptomatic visceral involvement
- Patients request for rapid tumor control

KS Response to HAART

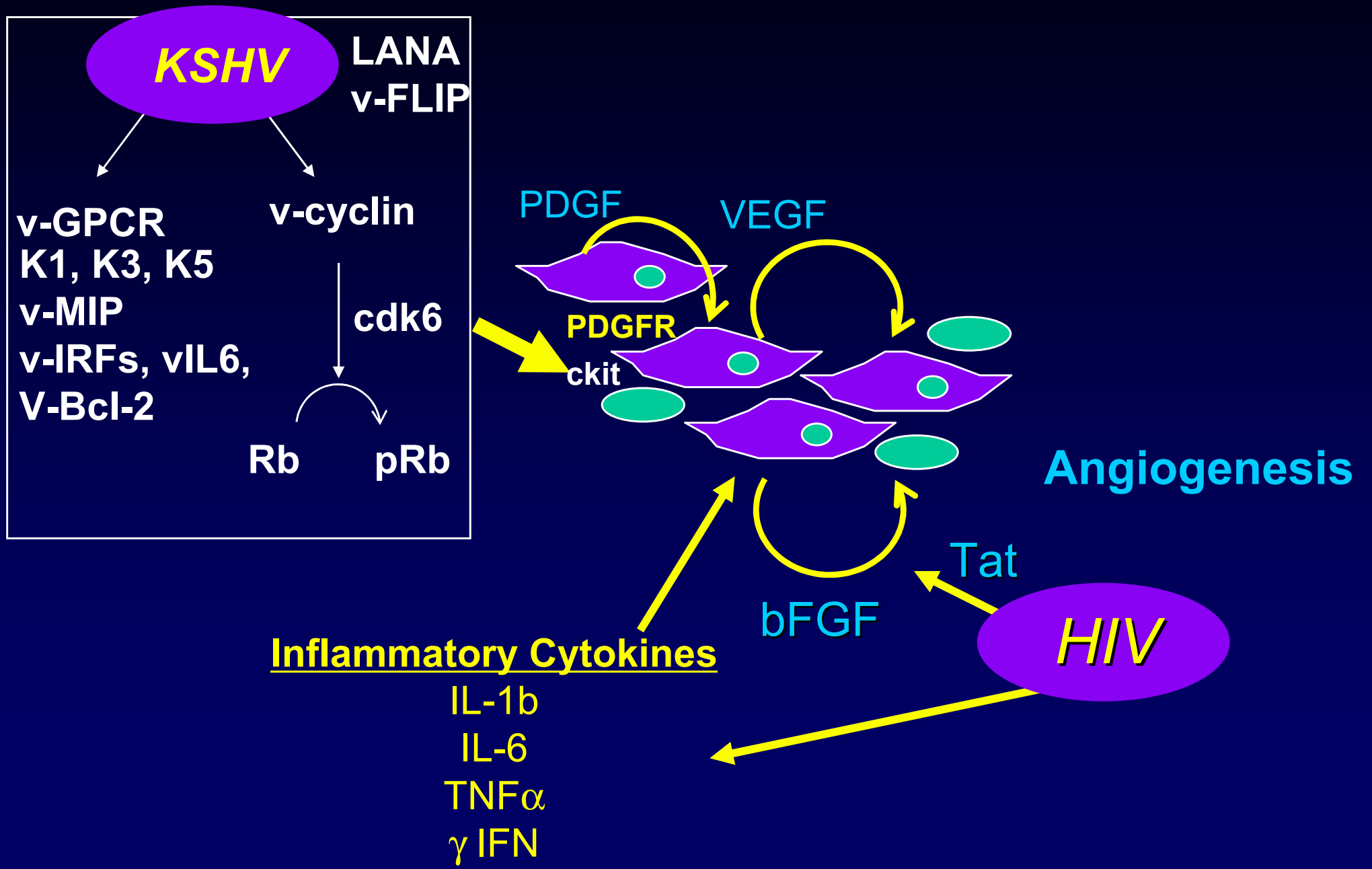
Study	N	Response	Survival
Leitch et al			
HAART+	20	14(71%)	31 mo
HAART-	28	3(13%)	7 mo
Gill J et al			
HAART+	21	10(48%)	
Paparizos	26	22(85%)	
Cattelan et al	14	12(86%)	
Dupont et al	19	10(53%)	

Potential for HHV8-Directed Therapy for Kaposi's Sarcoma

- Gamma herpes viruses (eg, HHV8 and Epstein-Barr) 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[1]
  - 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
- Bortezimib (Velcade) +/- Ganciclovir

[1]Little RF, et al. *J Infect Dis.* 2003;187:149-153.

Pathogenesis of KS



Summary

- As patients live longer with HIV, morbidity and mortality from cancers are increasing
- We must be able to quantify and characterize cancers in HIV, as it may vary in different populations around the world
- Treatment of malignancies in HIV should be vigorously and appropriate to the situation
- Side effects associated with HAART and cancer therapy should be treated/prevented
- Prevention strategies for virally-associated malignancies need to be investigated
- Effective and feasible treatments are under development and need to be tested worldwide

Prevention and Treatment of Malignancies in HIV

Thank you

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