Terapia e Prevenzione dell'Infezione da HIV e Microrganismi Emergenti

XVI Workshop Nazionale

Virus-related Malignancies In Persons Living with HIV

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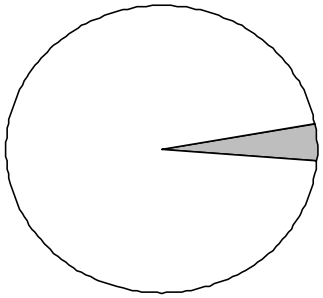
Firenze 2023

Cancer attributable to Infection in the General Population and HIV-infected People (USA 2008)

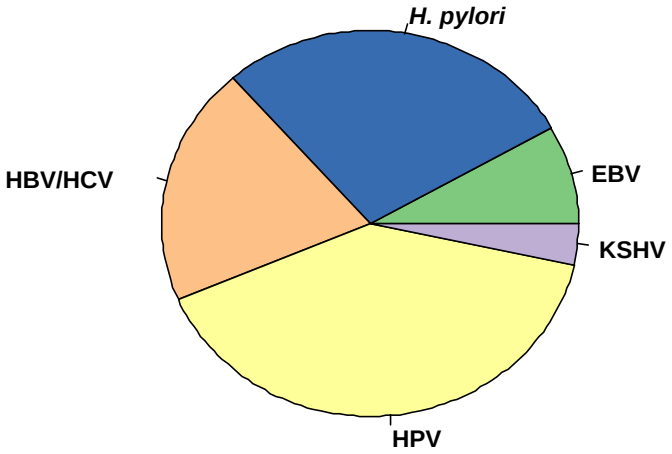
de Martel C et al AIDS 2015

General population



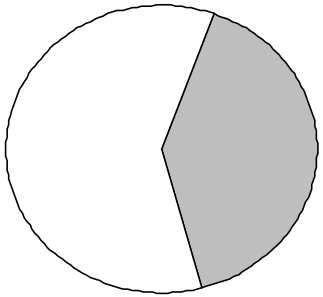
AF = 4%

Total cancers
N=1,437,199



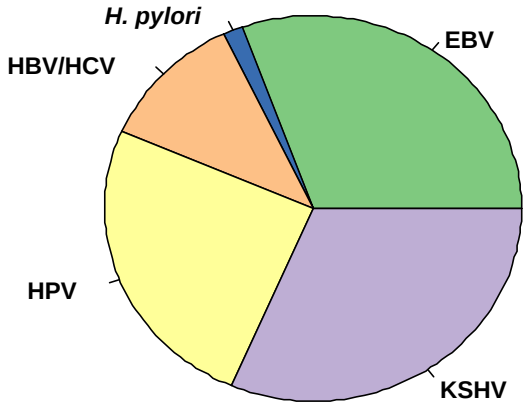
Total cancers attributable to infection
N=58,264

HIV-infected people



AF = 40%

Total cancers
N=6,231



Total cancers attributable to infection
N=2,512

AIDS-defining and associated Oncogenic Viruses

AIDS-defining Cancers	Associated Oncogenic Viruses
Kaposi Sarcoma (KS)	100% KSHV (HHV8)
Primary CNS Lymphoma	100% EBV
Burkitt's Lymphoma (BL)	40-60 % EBV
Diffuse Large Cell Lymphoma (DLCL)	Centroblastic 30% EBV Immunoblastic 90% EBV
Primary Effusion Lymphoma (PEL)	100% KSHV 80-90% EBV
Plasmoblastic Lymphoma of oral cavity Castleman-associated Plasmoblastic L.	80% EBV 100% KSHV
Invasive Cervical Cancer	HPV

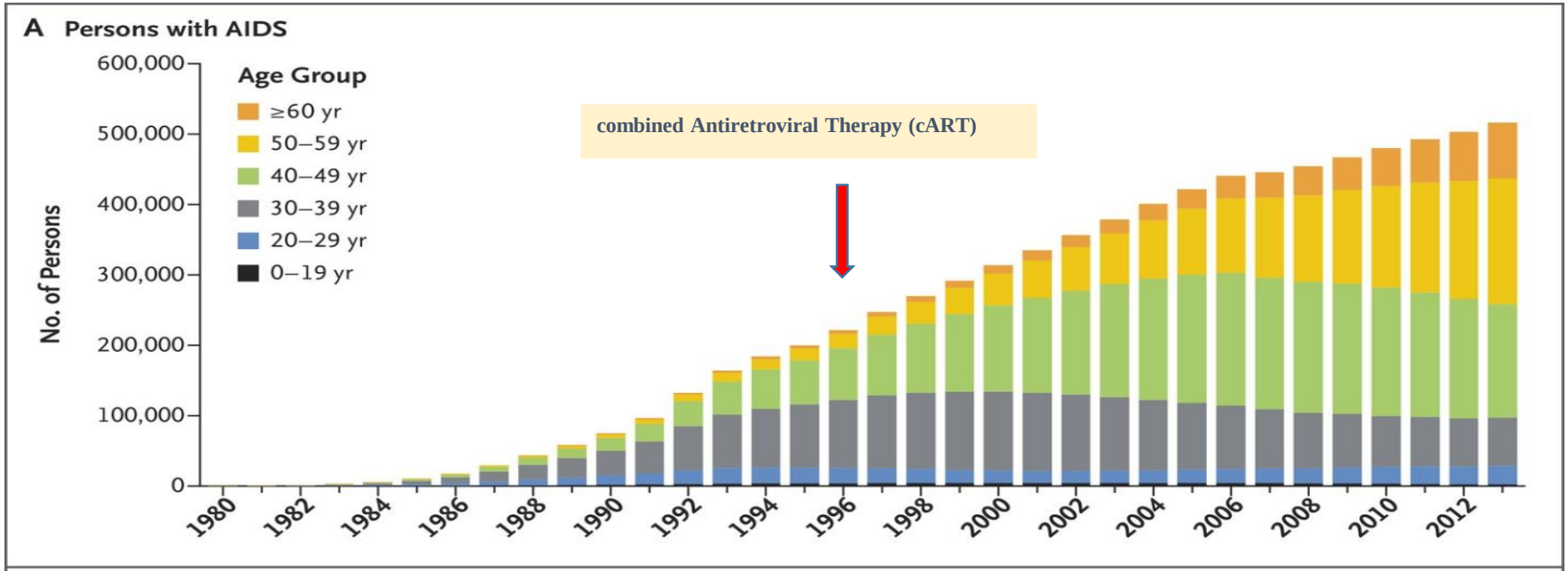
Gloghini et al. Semin Cancer Biol 2013, Carbone A et al Nat Rev Clin Oncol 2014, Rubinstein PG et al AIDS 2014, Yarchoan R and Uldrick TS NEJM 2018

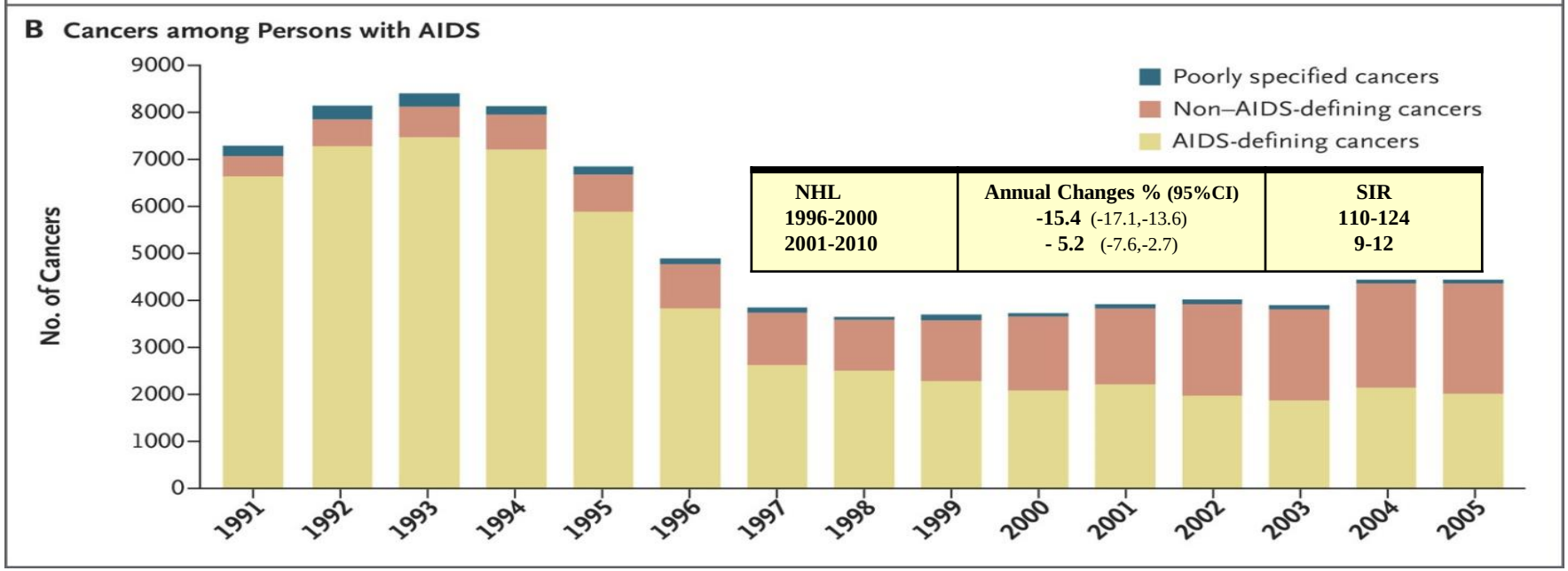
Non-AIDS defining Cancers (NADCs) and associated Oncogenic Viruses

Non-AIDS-defining Cancers	Associated Oncogenic Viruses
Hodgkin Lymphoma	100% EBV
Anal Cancer	100% HPV
Hepatocellular Carcinoma	HCV/HBV
Head-Neck Carcinoma (Oropharynx)	HPV
Lung Carcinoma	--------- (Smoking)
Non-Melanoma Skin Cancers	β-HPV cofactor (sun light exposure)

Gloghini et al. Semin Cancer Biol 2013, Carbone A et al Nat Rev Clin Oncol 2014, Rubinstein PG et al AIDS 2014, Yarchoan R and Uldrick TS NEJM 2018

Trends in AIDS and in Cancers among Persons with AIDS.





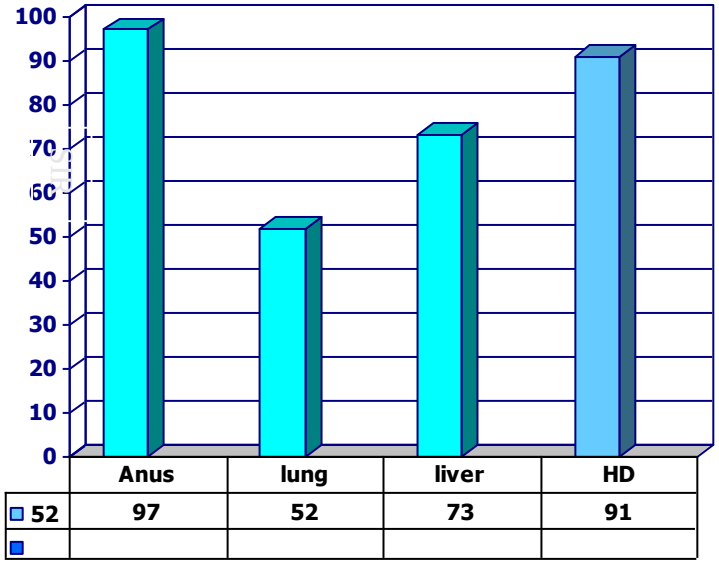
NHL	Annual Changes % (95%CI)	SIR
1996-2000	-15.4 (-17.1,-13.6)	110-124
2001-2010	- 5.2 (-7.6,-2.7)	9-12

Hleyhel M. et al. CID 2013, Shiels MS et al Natl Cancer Inst 2011, Robbins H.A et al. AIDS 2015, R. Yarchoan, TS Uldrick. N Engl J Med 2018

Excess Cancers Among 859.522 people living with HIV in the United States (2010)

NADCs

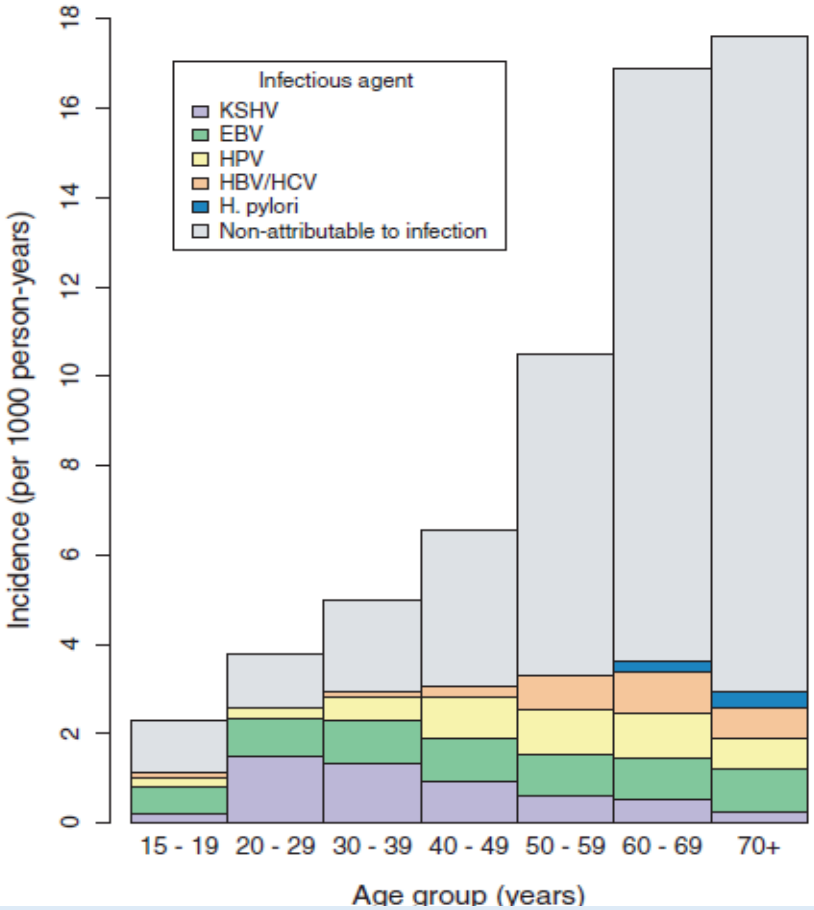
Excess of Non-AIDS-Defining Cancers %



NADCs	DEFICIT %	(95% CI)
Breast	- 42	(-42 to -14)
Prostate	- 41	(-53 to -26)

Robbins H. Br J Nat Cancer Inst 2015

Cancers attributable and non-attributable to infections among adults with HIV in the United States (2008)



The incidence rate of cancer non-attributable to infection, including breast and prostate cancers steeply increased with age,.

de Martel C et al AIDS 2015

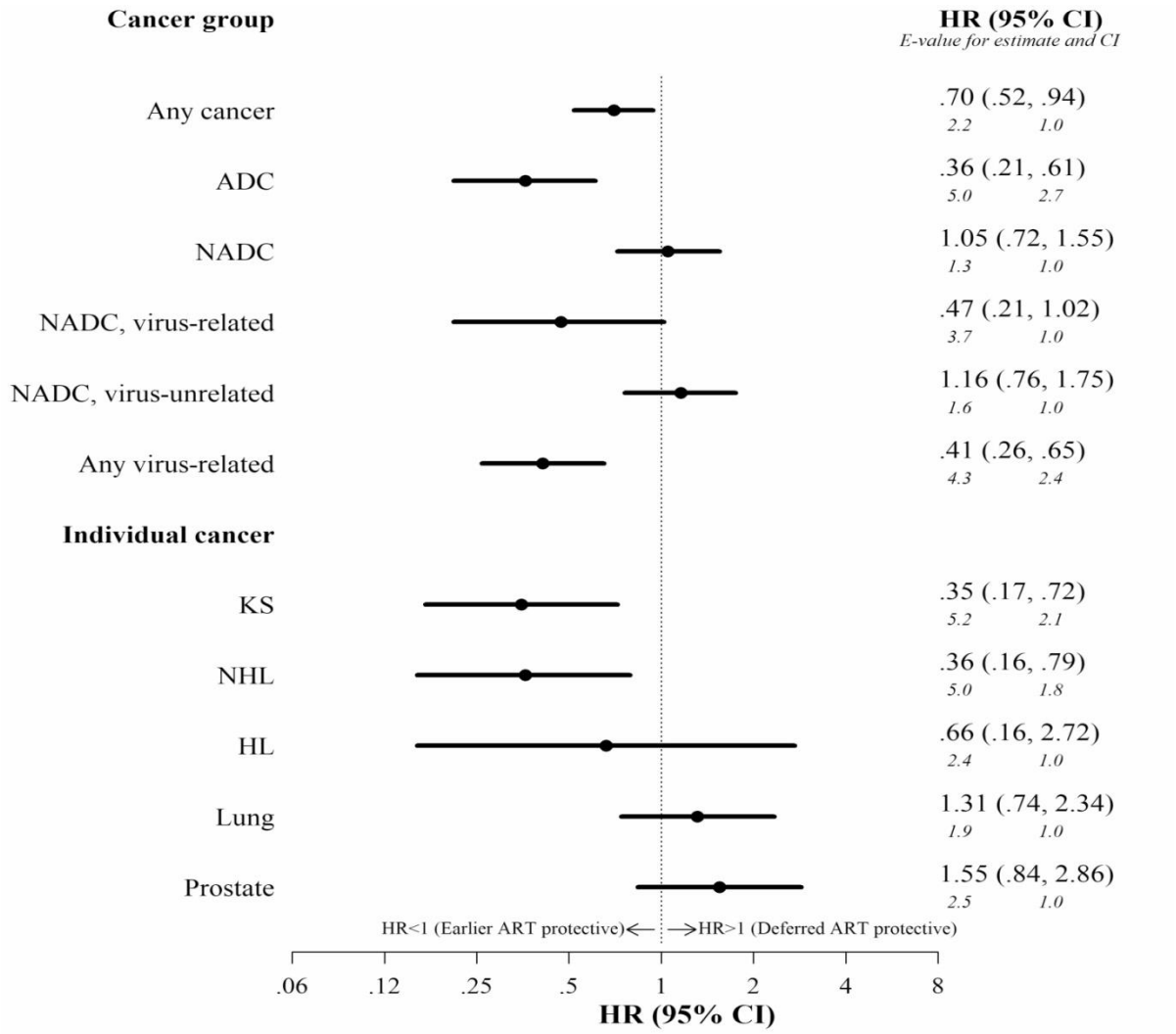
Standardized Incidence Ratios (SIRs) for cancer in 448.258 HIV-infected Patients by AIDS status. (Linkage study-USA 1996-2012)

Hernandez-Ramirez RU et al Lancet HIV 2018

	SIR (95%CI)		adjusted SIR Ratio AIDS vs HIV	
Cancer Type	**HIV only**	**AIDS**	**Ratios (95% CI)**	**pvalue**
All cancers	**1.24** (1.20-1.28)	**1,88** (1.85-1.91)	**1.83** (1.77-1,89)	<0.0001
Kaposi Sarcoma	**277** (249-307)	**586** (560-613)	**3.21** (2.86-3.60)	<0.0001
NHL	**5.90** (5.43-6.40)	**14** (13.5-14,5)	**3.12** (2.85-3.42)	<0.0001
DLBCL	**5.05** (4.53-5.62)	**12.6** (12.1-13,2)	**3.32** (2.94-3.73)	<0.0001
BL	**17.5** (14.5-20,9)	**21.5** (19,2-24,0)	**1.63** (1.31- 2.03)	<0.0001
CNS NHL	**30.04** (20.08-43.0)	**207** (189-225)	**10.1** (7.02-14.5)	<0.0001
Cervix	**2.04** (1.66-2.48)	**3.94** (3.53-4.39)	**2.20** (1.74-2.76)	<0.0001
NADCs	0.99 (0.96-1.02)	**1.30** (1.27-1.32)	**1.45** (1.39-1.51)	<0.0001
Virus-rel. NADCs	**3.25** (3.02-3.50)	**6.27** (6.06-6.49)	**2.21** (2.03-2.40)	<0.0001
Anus	**7.41** (6.39-8.56)	**24.2** (22.9-25.5)	**3.49** (2.98-4.08)	<0.0001
Hodgkin Lymphoma	**4.64** (4.00-5.35)	**9.42** (8.72-10.1)	**2.12** (1.80-2.51)	<0.0001
Liver	**2.81** (2.48-3.17)	**3.36** (3.14-3.59)	**1.25** (1.08-1.44)	<0.003
Lung	**1.57** (1.45-1.71)	**2.13** (2.03-2.22)	**1.51** (1.37-1.66)	<0.0001
Vulva	**4.00** (2.54-6.00)	**12.3** (10.3-14.6)	**3.22** (2.04-5.08)	<0.0001
Vagina	0.84 (0.10-3.02)	**4.95** (3.14-7.43)	**6.76** (1.58-28.9)	0.01

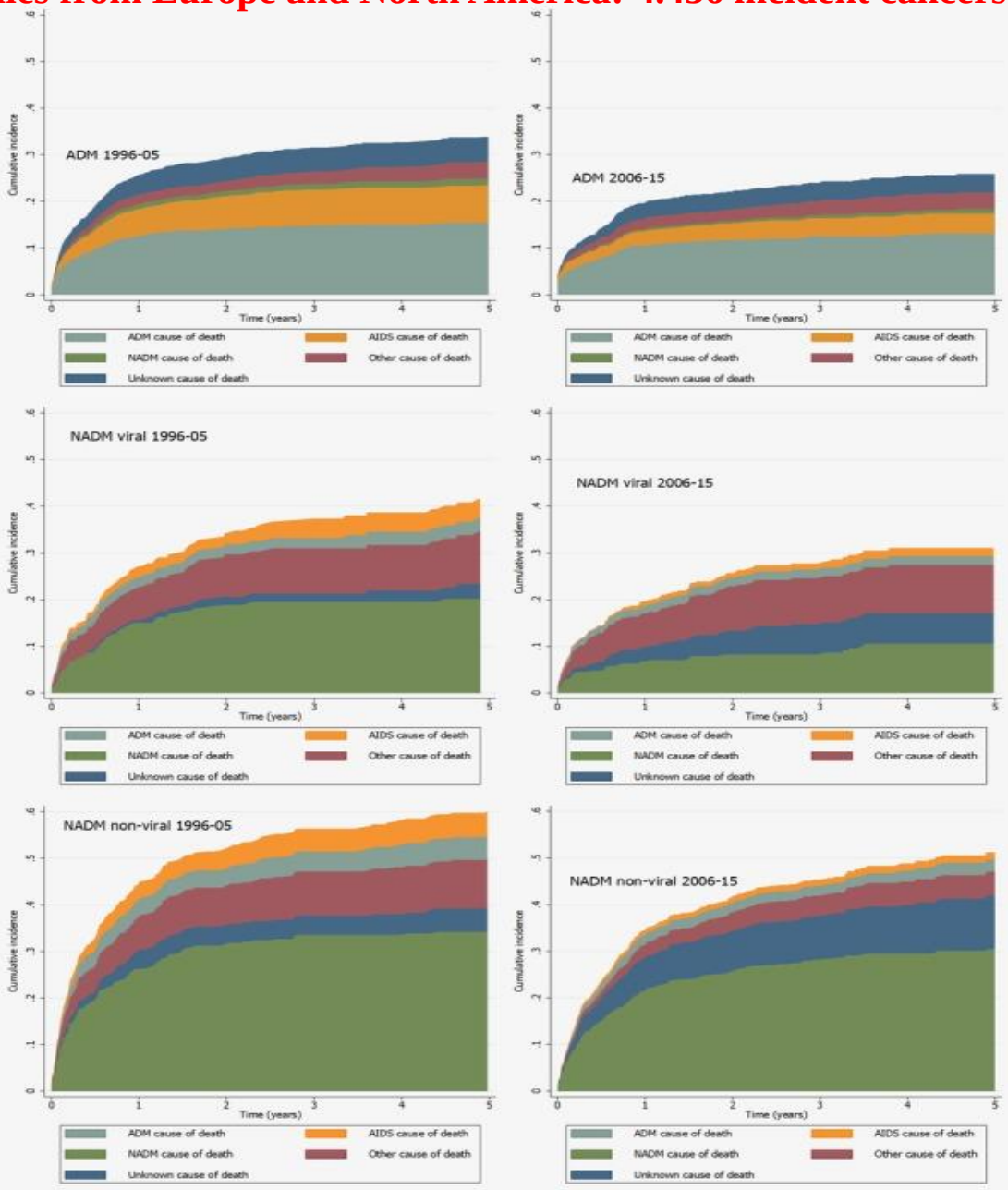
Risk of Cancer among 119.543 HIV-infected Patients (baseline CD4 350-500/µL): Adjusted hazard ratios of earlier versus deferred antiretroviral therapy (USA 1996-2014)

Silverberg MJ et al CID 2020



Earlier cART initiation has potential to reduce the burden of virus-related cancers but non-AIDS-defining Cancers (NADCs) without known or suspected viral etiology

Cause-specific Mortality after Diagnosis of Cancer among 83,585 HIV-positive Patients: 10 Cohort Studies from Europe and North America: 4.436 incident cancers (Mortality Rate Ratio, MRR)



2006-2015 vs 1996-2005

Cancer	Adjusted MRR (95% CI)
ADM	**0.77** (0.61-0.86)
Viral NADCS	**0.76** (0.54-1.07)
Nonviral-NADCs	**0.84** (070-1.00)

adjusted for sex, risk group,age,CD4 count,HIV viral load at cancer diagnosis

Trickey A Int J Cancer 2020

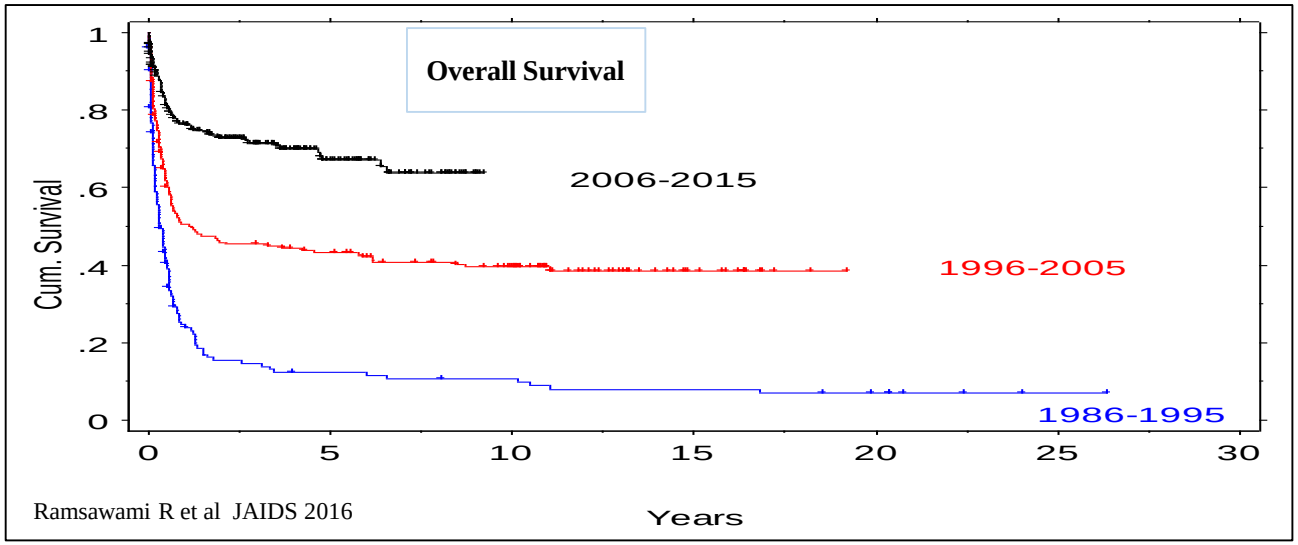
HIV-related Lymphoma

Major Features:

-Advanced stage and B symptoms at diagnosis
-Aggressive clinical course complicated by opportunistic infections and/or other cancer
-Poor Prognosis

-NHLs remain the leadying cause of death in the cART era

Change in Treatment Paradigm and Outcome of HIV-Lymphoma



Ramsawami R et al JAIDS 2016

	2-yr OS %	5-yr OS %
1986-1995	**20**	**13**
1996-2005	**48**	**45**
2006-2015	**74**	**70**

USA

Standard CT regimens

Low-dose CT regimens in all pts

-Infusional CT
-sequential cART

-DA-EPOCH
-Rituximab –EPOCH

-AutoSCT
-AlloSCT

1984-1986

1987-1995

1996-2005

2006-2014

≥2015

EUROPE

Standard CT regimens

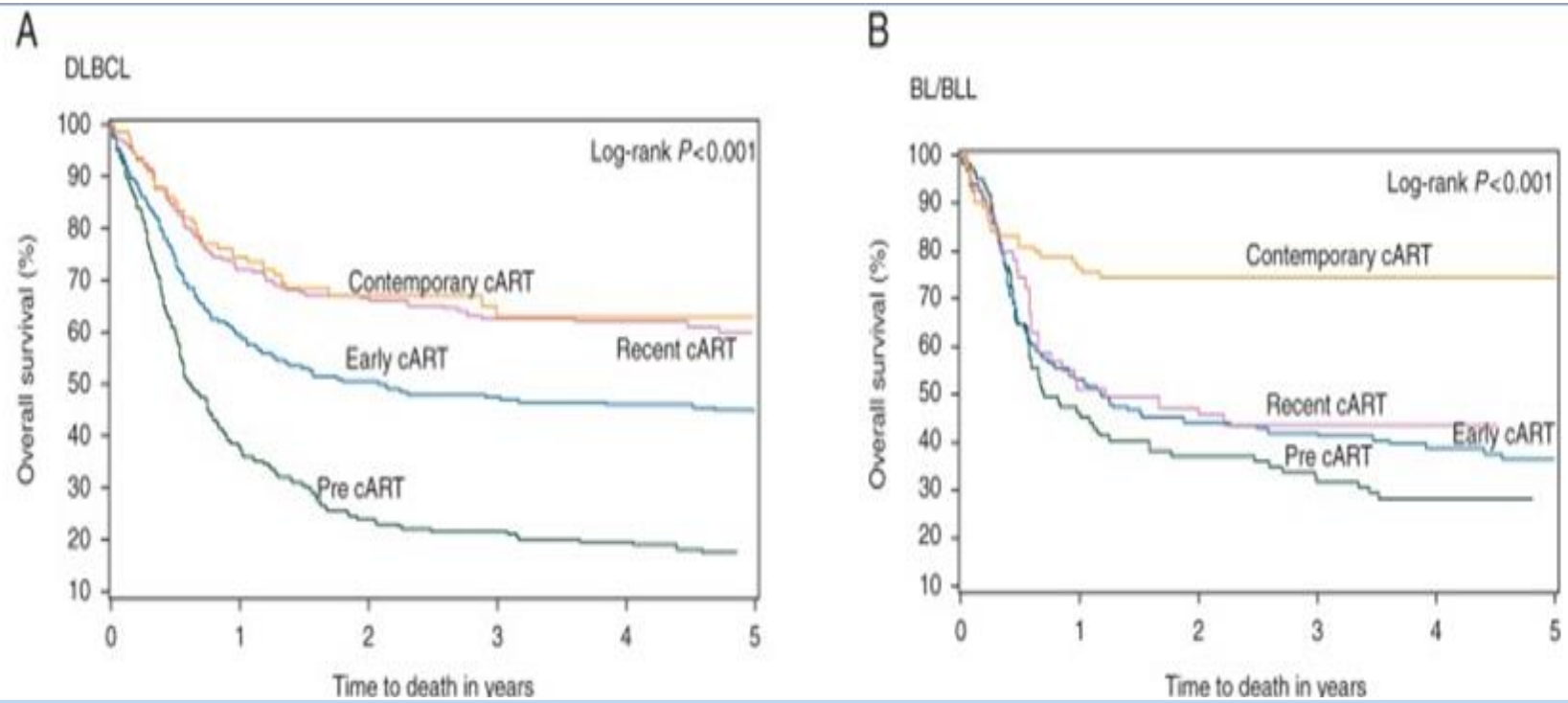
Risk-adjusted CT regimens

Rituximab-CHOP

Concurrent cART-CT

Autologous Stem Cell Transplant (ASCT) in relapsed/refractory disease

Overall Survival of HIV-NHL by Histological subtypes in different eras: pre-cART (1986-1995),early (1996-2000), recent (2001-2004),contemporary (2005-2010)

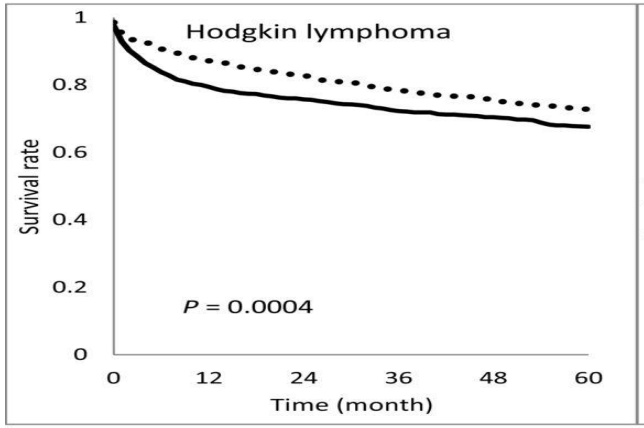


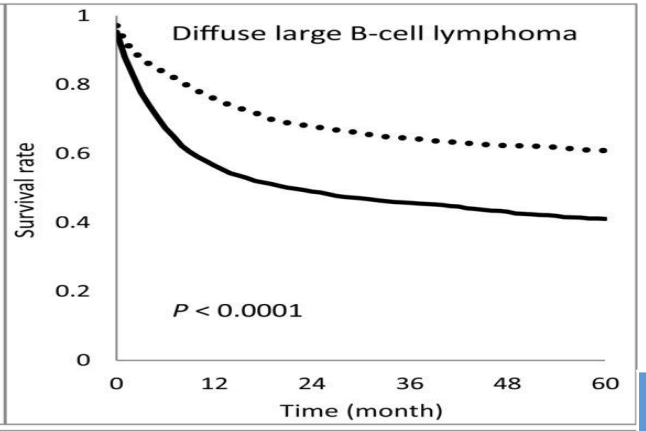
Major Prognostic Factors over time

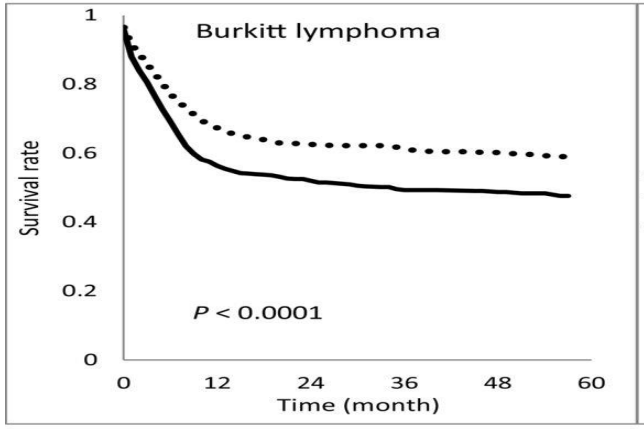
Pre/early cART era	Recent cART era	Contemporary cART
CD4 count< 100 /µL	CD4 count< 100/µL	aa-IPI score
Prior AIDS diagnosis	aa-IPI score	Failure to achieve CR
Performance Status	BL subtype	
	Failure to achieve CR	

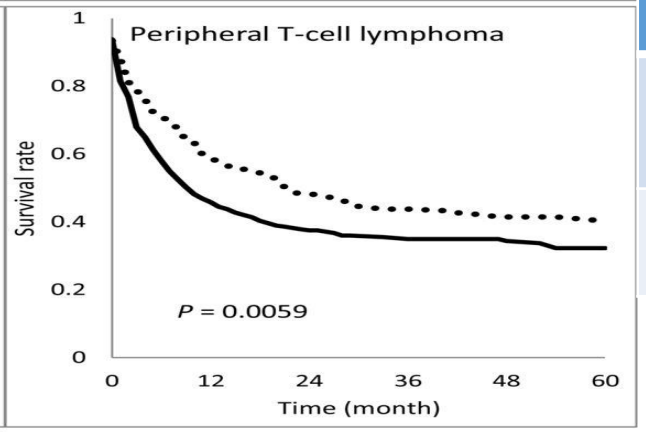
Mounier N et al Blood 2006, Castillo JJ Am J Hematol 2012, Barta SK et al Ann Oncol 2015

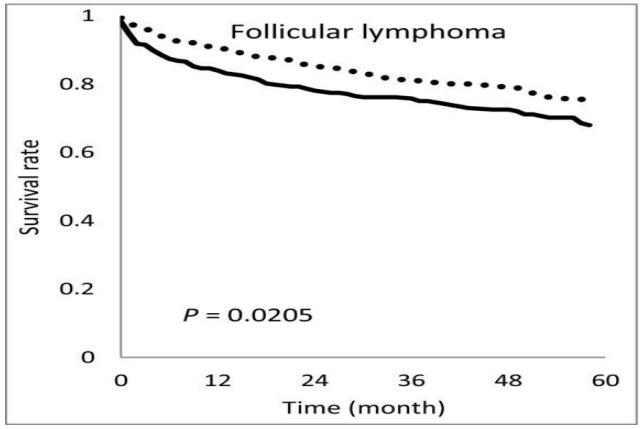
Overall Survival by HIV status among 179.520 Patients with Lymphoma - (USA-National Cancer Database 2004-2011)











	HIV-pos Pts	HIV-neg Pts
No Therapy %	16*	8
CT use %	82*	87

*p<0.0001

Han X et al Cancer Epidemiol Biomarkers Prevention 2016

Treatment Guidelines for HIV-related Cancers in the cART era

Treatment Guidelines of Cancer in HIV-infected Patients need to be similar to those applied in the General Population,

except for those with unfavorable immunological and virological features

cART should be administered concurrently to antineoplastic treament including chemotherapy

cARTregimens should be adjusted

to avoid drug-drug interactions

Common Questions in the Management of HIV-NHL-I

QUESTIONS	COMMENTS
Should Rituximab be included within the regimen in CD20+ HIV-NHL?	-The combination of Rituximab and chemotherapy results in significant clinical benefit for all CD20+ HIV-NHL patients compared to chemotherapy alone (higher CR rates and better PFS and OS), as in the general population. -There is need to maximize opportunistic infection prophylaxis in patients with CD4 count $\leq$ 50/µL, according current guidelines on HIV management*.
What is the best chemotherapy regimen (infusional vs bolus chemotherapy)?.	-In the cART era, the standard treatments of HIV-associated lymphomas (infusional or bolus chemotherapy) mirror that of HIV-negative patients, but controversy remains regarding the optimal chemotherapy regimen.
Should antiretroviral therapy be suspended during chemotherapy?	-All HIV-infected patients with cancer must be mainteined on cART during antineoplastic treatment. -Ritonavir or Cobicistat-based antiretroviral regimens must be avoided because of drug-drug interactions.

;* https://aidsinfo.nih.gov/guidelines/html/4/adult and adolescent-oi-prevention-and treatment guidelines)

Vaccher E,Curr Opin Oncol 2022;Carbone A, Vaccher E, Gloghini A Blood 2022

Common Questions in the Management of HIV-NHL-II

QUESTIONS	COMMENTS
Are there subtypes of lymphomatous disease that should be treated differently from others?.	- The best therapy for HIV-associated Burkitt's Lymphoma (BL) still remains unclear, but CHOP chemotherapy backbone is not recommended. -HIV-infected patients with Plasmablastic Lymphoma (PBL) or Primary Effusion Lymphoma (PEL) continue to be characterized by a dismal prognosis and should be included in clinical trials. - HD-methothrexate-based chemotherapy is recommended for selected** HIV-positive patients with PCNSL, based on general consensus. For patients inelegible for chemotherapy, WBRT remains a useful palliative treatment.
Is the approach with intensive chemotherapy and peripheral stem cell rescue feasible?	-HIV infection should not preclude lymphoma patients from undergoing HDC-ASCT, according to the same eligibility criteria adopted for the general population.

**patients responsive to cART, with good performance status and without opportunistic infections

Vaccher E,Curr Opin Oncol 2022;Carbone A, Vaccher E, Gloghini A Blood 2022

HIV-related Kaposi Sarcoma

Major Features

Clinically, Ks most commonly involves adults with a male predilection, and lesions evolve from early macules (patch stage) to plaques (plaque stage) and larger nodules (tumour stage). They typically involve mucocutaneous sites but may also involve visceral locations (gastrointestinal tract >50%, lung 20%).All organs may be affected by KS

Heterogeneous clinical course ranging from an indolent state to a severe, progressive disease leading to significant morbidity and mortality

Prospective validation of ACTG staging system in 211 KS pts enrolled in two prospective studies of the cART era (GICAT-ICONA study)

Nasti G et al J Clin Oncol 2003

HR (95% CI)		
Stage	**So**	**S1**
To	**1**	**1.70** (0.46-6.33)
T1	**2.4** (0.77-6.49)	**5.68** (1.97-16.38)

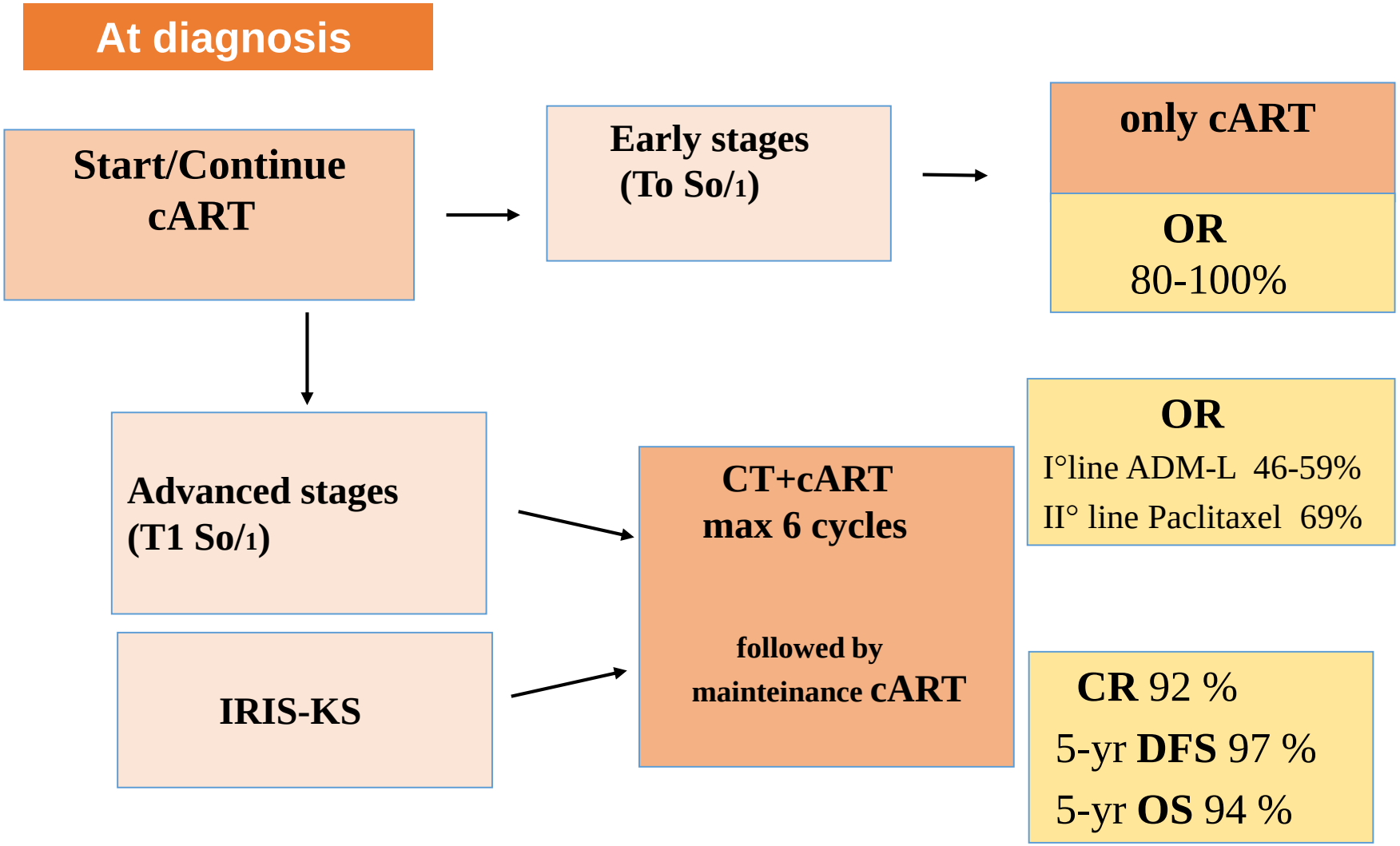
Stage	**3-yr Overall Survival %**
ToSo	**88**
T_oS_1	**81**
T1So	**80**
T1S1	**53**
T1 Lung **T1 no-Lung**	**46** **77**

- CD4 cell count does not provide prognostic information in the cART era.

-Two different risk categories are identified: a good risk (T0S0, T1S0, T0S1) and a poor risk (T1S1) group.

Lung involvment predicts survival better than Tumor extension,independent of S stage and identifies the poorest category.

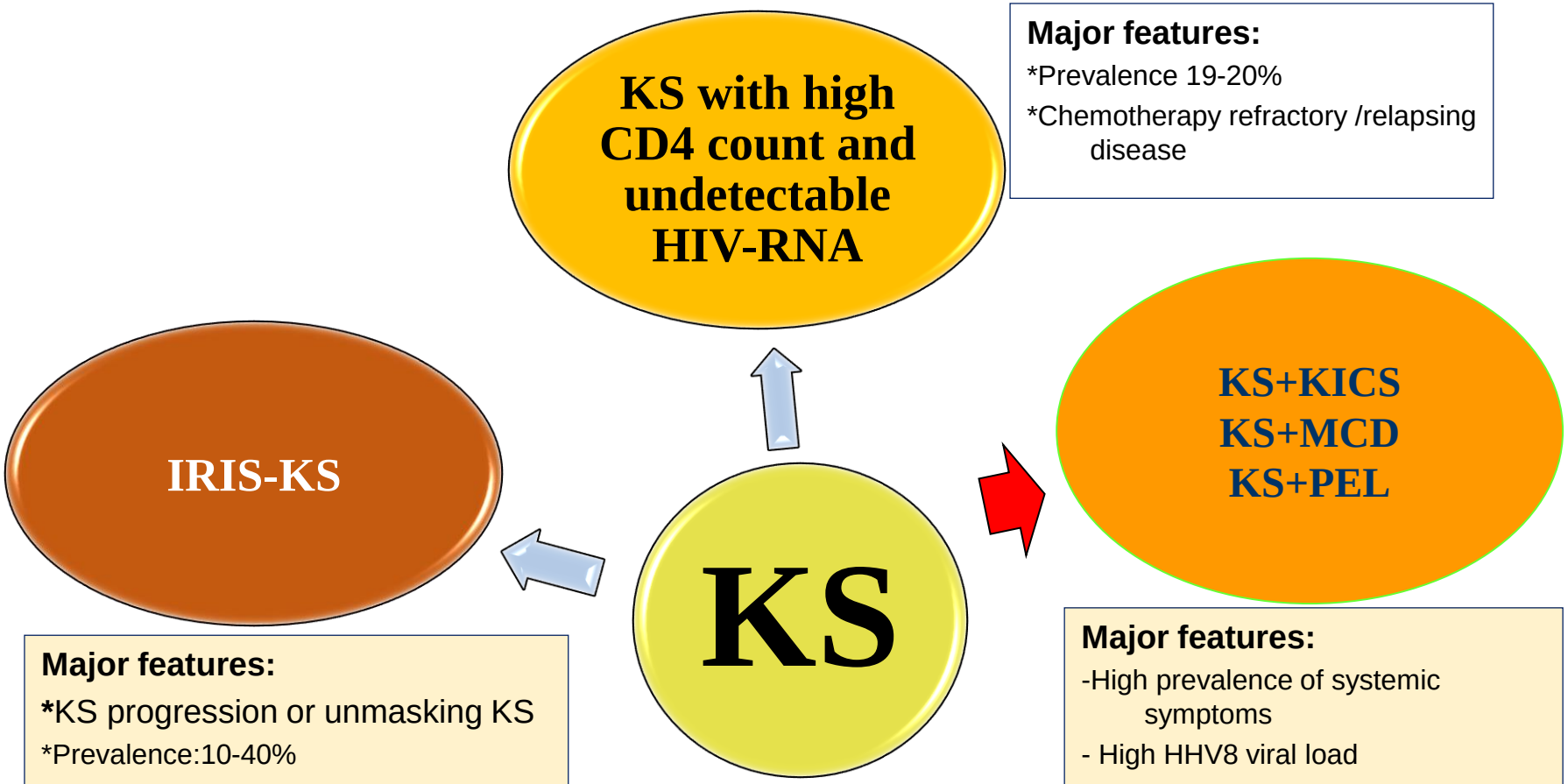
Treatment Guidelines for HIV-related KS



cART: combined Antiretroviral Theraphy; OR:Objective response; CR:Complete Remission; DFS: Disease Free Survival; OS:Overall Survival

CRO 2023

Evolving Spectrum of Kaposi Sarcoma (KS) in the cART era



Major features:

*Prevalence 19-20%

*Chemotherapy refractory /relapsing disease

Major features:

*****KS progression or unmasking KS

*Prevalence:10-40%

*Agressive clinical course

*High mortality

*Treatment: immediate chemotherapy +cART

Major features:

-High prevalence of systemic symptoms

- High HHV8 viral load

- Rapidly progressive KS

-High mortality

-Treatment: chemotherapy and/or immunotherapy +cART

Kaposi Sarcoma in HIV-infected Pts with high CD4 count

The proportion of KS cases occurring of high CD4 count is rising in the cART era

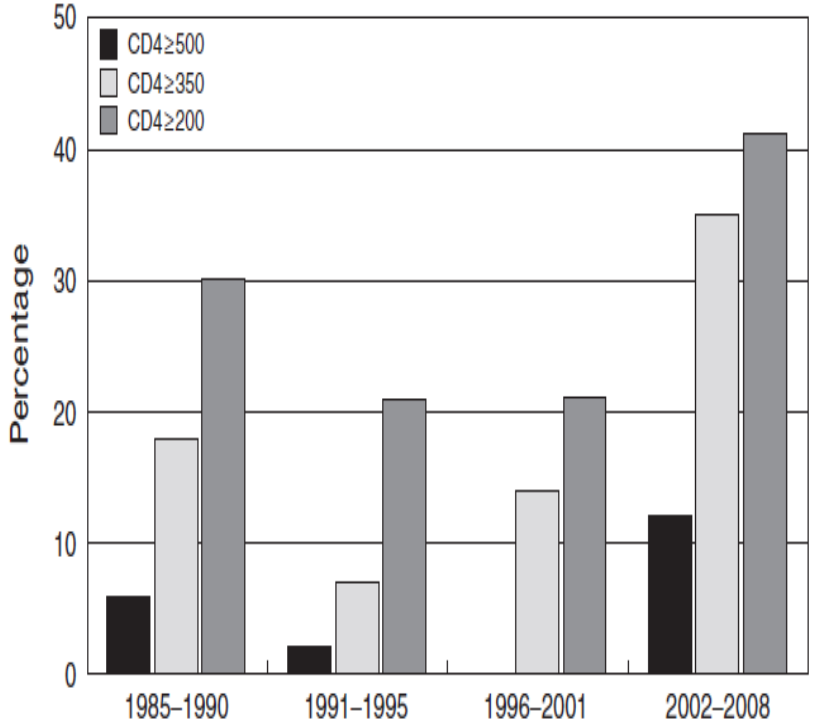


Fig. 1. CD4 cell count at diagnosis of Kaposi's sarcoma during the course of the HIV epidemic (1985–2008).

CD4 cells	Cluster KS % (N°19)	HIV+ Controls % (n°47)	P value°
CD57+	41.5	27.7	0.005
CD28-	60.5	51.3	0.04
CD27+CD28+ CD45RA*	11.3	20.7	0.02
CCR5	43.1	28.3	<0.001

Increased frequency of T cells with Immunosenecence phenotype and lower naive T cells* are associated with Kaposi's Sarcoma among effectively treated patients

Crum-Cianflone NF et al, AIDS, 2010;Unemor P AIDS 2013

Major Cancer Preventive Strategies in the cART era

- Early Initiation of cART
- Treatment of HCV/HBV Infections
- Stop Smoking and/or alchool use
- HPV Vaccination (age <30 yrs)

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Screening Carcinoma Anale in HIV- Update Linee Guida

Popolazione	Procedura Screening	Tempistica	Livelli Raccomandazione
-MSM; -Tutti con storia di condilomi ano-genitali; -Donne con istologia genitale patologica ∞∞∞∞∞∞∞∞∞ MSM*	-PAP test convenzionale -PAP test su base liquida Anoscopia ad alta risoluzione ∞∞∞∞∞∞∞∞∞ Anoscopia ad alta risoluzione	*Annuale, se 2 esami consecutivi neg Se Pap test patologico	Elevata (categoria 1)

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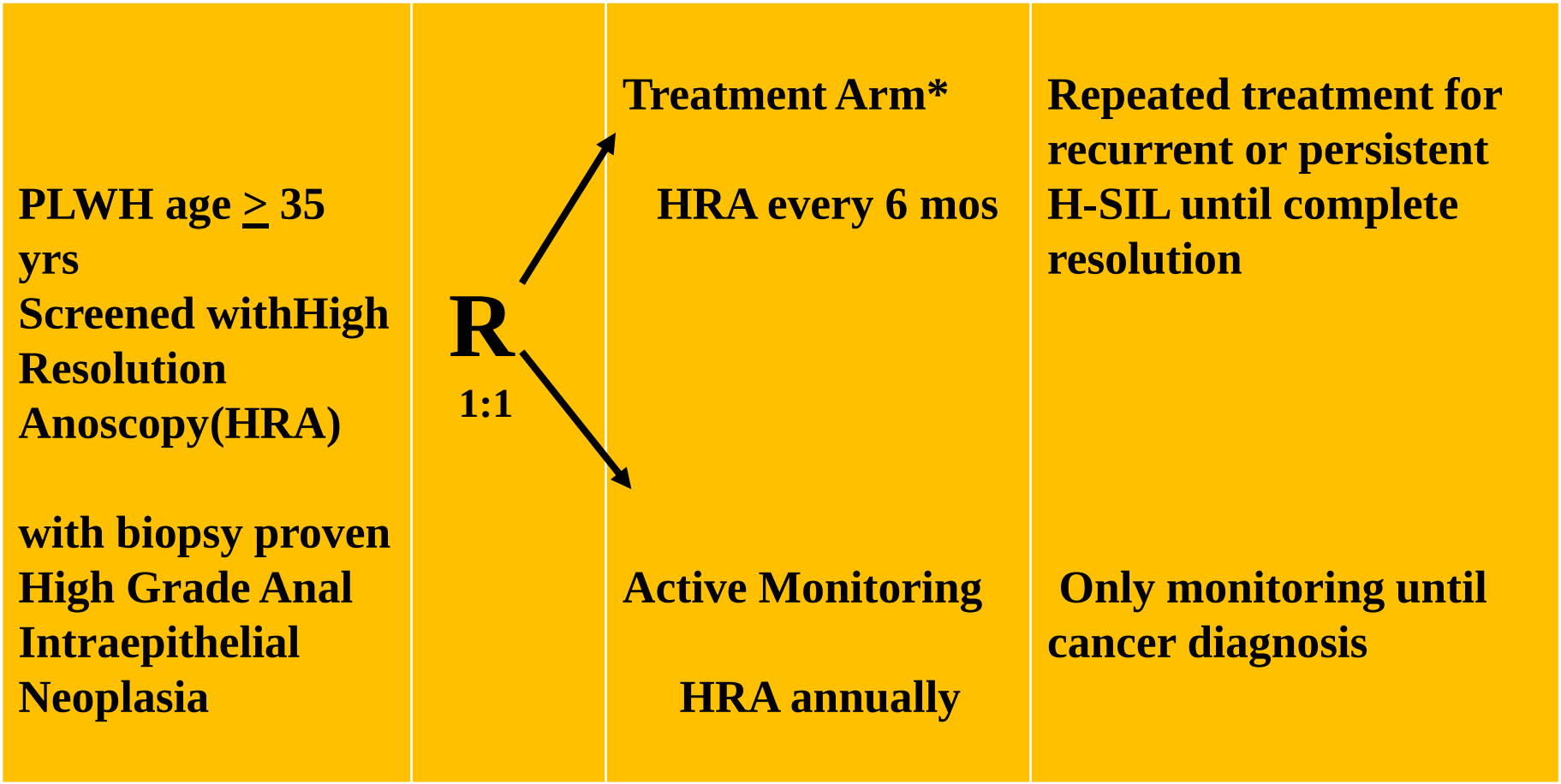
Anal Cancer/H-SIL Outcomes Research (ANCHOR) Study in Persons Living With HIV (PLWH) (USA 2014-2021)



* electrocautery in most cases

Palefsky J NEJM 2022

Anal Cancer/H-SIL Outcomes Research (ANCHOR) Study in Persons Living With HIV (PLWH) (USA 2014-2021)

Median Followup: 26 months

	Treatment Arm n°2227	Active Monitoring Arm n°2219
Anal cancer n° cases	9	21
Incidence/100.000 PY	173	402
REDUCTION 57% (95% CI 6-80%) p 0.03		
Adverse Events n° (%)	683	635

Palefsky J NEJM 2022

Change in Treatment Paradigm of HIV-Malignancies
Conclusions

- 1. Treatment of HIV-malignancies has evolved over time, in line with better control of HIV replication and recovery of immune function by cART. The overall survival for these patients has dramatically improved in the modern cART era.

2. However, data from large population-based studies have shown that HIV infection remains associated with higher risk of death in patients with all malignancies compared to general population
Disparities in practice pattern based on HIV status may influence outcomes in this population that is still excluded from prospective clinical trials of the general population.

3. Dissemination of effective management strategies is mandatory to improve patient outcome.

4. HIV infection alone should no longer be an exclusion criterion in any clinical trial.