GIFIL

CORSO EDUCAZIONALE

GRUPPO LINFOMI IN PAZIENTI CON IMMUNODEFICIT

Milano, Starhotels Anderson

24 maggio 2024

Innovative Treatment and Preventive Strategies in Persons Living with HIV and Lymphomas

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Dichiaro che negli ultimi due anni
NON ho avuto rapporti,
anche di finanziamento, con soggetti
portatori di interessi commerciali
in campo sanitario.

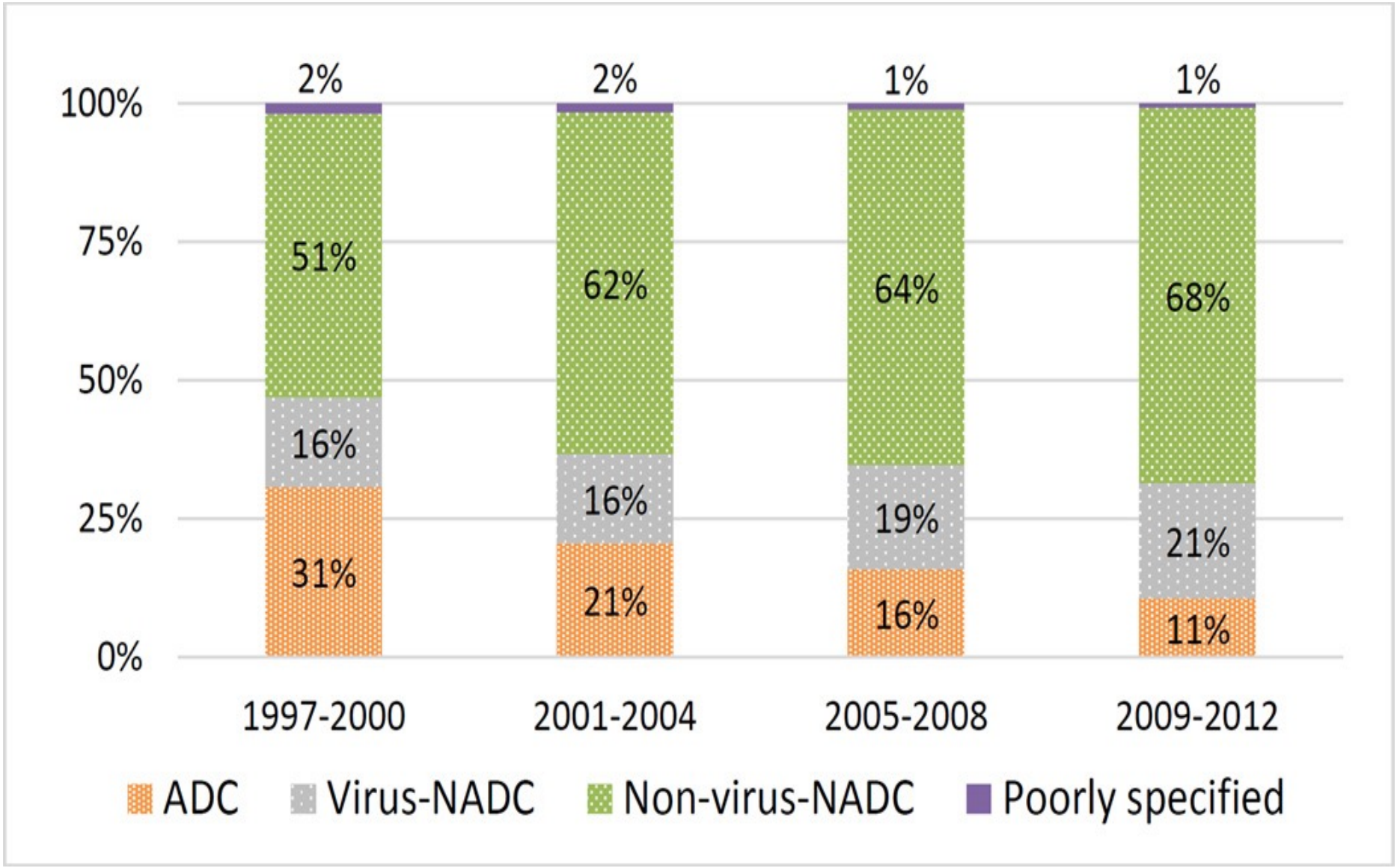
HIV-related Lymphoma

Background

- The epidemiology of HIVdisease has evolved in the cART era
- The incidence and morbidity of AIDS-defining cancers has decreased, whereas morbidity and mortality of NADCs (including Hodgkin Lymphoma) has increased
- However, NHLs remain the main cause of death in Persons Living with HIV.
- PLWH survivors after lymphoma diagnosis are at increased risk for subsequent primary cancers, suggesting the need for long-term surveillance programs.

Proportion of Cancer Cases among HIV-infected Patients by Cancer Group in each Calendar Period (VA System 1997-2012)

Park LS et al AIDS 2016



Standardized Incidence Ratio (SIR) of AIDS-defining cancers in 99.309 pts with HIV/AIDS from French registry-linkage study in different cART periods (mean Follow-up 6.9 yrs)

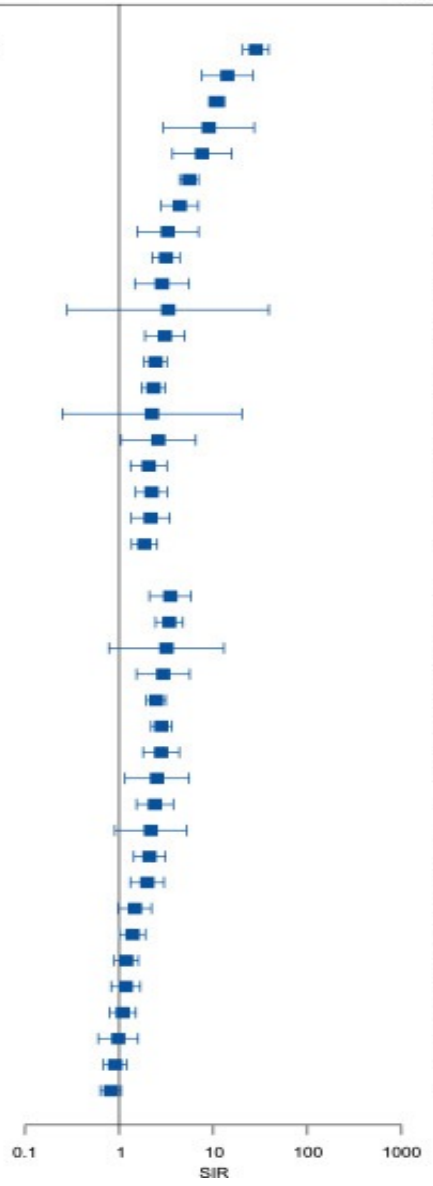
Cancer	Pre-cART (1992-96) SIR (95%CI	Early cART (1997-2000) SIR (95%CI)	Intermediate (2001-2004) SIR (95%CI	Late cART (2005-2009) SIR (95%CI
KS All pts	787.0 (754-821)	388.1 (353 -425.)	408.6 (370-451)	304.5 (274-338)
MSM	1399.9 (1334 -1467)	534.5 (476-599)	531.6 (468-602)	414.1 (365-474)
NHL	116.7 (110-124)	33.6 (31-37)	15.4 (14-17)	9.1 (8-10)
Cervical cancer	12.2 (9-17)	9.3 (7-12)	5.4 (4-8)	5.4 (4-7)

Message. The risk for all AIDS-cancers continued to fall, including invasive cervical cancer, but it remained higher than in the general popoulation in late cART era

Hleyhel M. et al. CID 2013

Meta-analysis of Standardized Incidence Ratio (SIR) for non-AIDS-defining Cancers among People Living with HIV(PLWH) (1992-2022)

Type of Cancer	SIR (95%CI)	Number of studies	Number of effect sizes	Number of observed cancers	Heterogenity I^2(%)
A. Infection related cancers					
Anus and anal canal	28.33 (20.30-38.96)	27	82		
Vulva and vagina	14.13 (7.58-26.36)	14	26		
Hodgkin lymphoma	10.93 (9.05-13.20)	32	81		
Eye and adnexa	8.97 (2.95-27.28)	9	20		
Penis	7.60 (3.68-15.70)	11	17		
Liver	5.54 (4.39-7.00)	34	69		
Skin nonmelanoma	4.41 (2.80-6.92)	22	36		
Nasal cavity, middle ear, and accessory sinuses	3.29 (1.55-6.98)	7	10		
Lip, oral cavity and pharynx	3.15 (2.25-4.41)	26	112		
Lip	2.85 (1.47-5.54)	6	16		
Salivary glands	3.32 (0.28-39.12)	4	5		
Nasopharynx	3.06 (1.88-4.97)	13	13		
Tongue	2.44 (1.84-3.22)	8	12		
Tonsil	2.32 (1.74-3.09)	3	3		
Oropharynx	2.23 (0.25-20.18)	3	5		
Uterus	2.61 (1.05-6.52)	12	18		
Head and neck	2.06 (1.32-3.22)	12	23		
Larynx	2.21 (1.50-3.24)	15	29		
Esophagus	2.16 (1.35-3.46)	17	27		
Stomach	1.86 (1.36-2.54)	24	52		
B. Non-infection related cancers					
Mesothelial and soft tissue	3.50 (2.10-5.81)	14	36		
Multiple myeloma	3.41 (2.44-4.77)	18	42		
Biliary tract	3.19 (0.78-13.02)	5	7		
Bone and joints	2.94 (1.53-5.64)	12	18		
Trachea, bronchus, and lung	2.48 (1.94-3.16)	38	99		
Leukaemia	2.81 (2.18-3.62)	22	77		
Brain and central nervous system	2.80 (1.80-4.37)	23	50		
Small intestine	2.53 (1.15-5.54)	8	12		
Ovary	2.40 (1.53-3.77)	15	24		
Thymus, heart, mediastinum, and pleura	2.17 (0.90-5.21)	7	9		
Testis	2.10 (1.43-3.11)	18	47		
Pancreas	1.99 (1.32-3.01)	19	35		
Kidney and renal pelvis	1.47 (0.98-2.21)	20	40		
Gallbladder	1.39 (1.01-1.90)	3	3		
Melanoma of skin	1.19 (0.89-1.61)	25	55		
Bladder	1.18 (0.82-1.68)	25	48		
Colon and rectum	1.09 (0.79-1.51)	25	75		
Thyroid	0.98 (0.60-1.59)	20	33		
Breast	0.91 (0.68-1.20)	29	56		
Prostate	0.81 (0.63-1.05)	28	61		



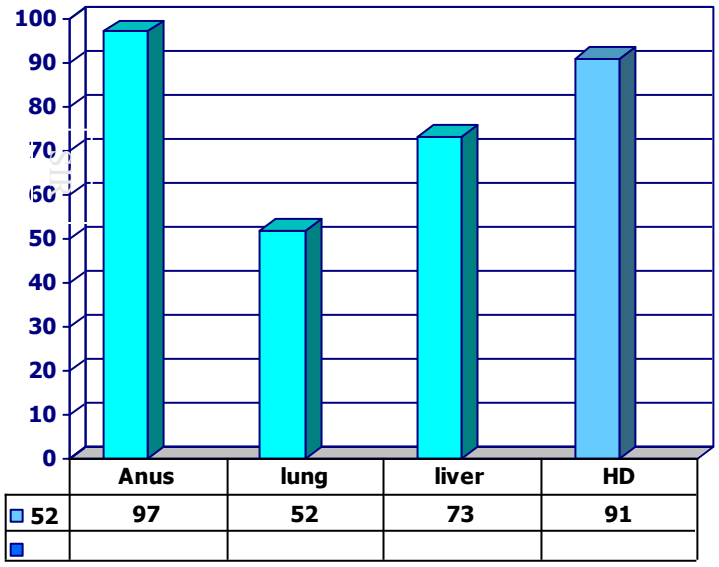
Virus-related Cancer	SIR (95%CI)
Anus	**28 (**20.3-38.9)
Vulva-Vagina	**14 (**7.6-26.4)
Penis	**7.6** (3.4-15.7)
Hodgkin L.	**10.8** (8.9-13.7)
Eye and Adnexa	**8.9** (2.9-27.3)
Liver	**5.5** (4.4-7.2)
Skin nonmelanoma	**4.4** (2.8-6.9)
Lung	**2.48** (1.94-3.16)
Oropharynx	**2.23** (0.25-20.1)
Larynx	**2.21** (1.50-3.2)

Yuan T et al Thelancet.com 2022

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

NADCs

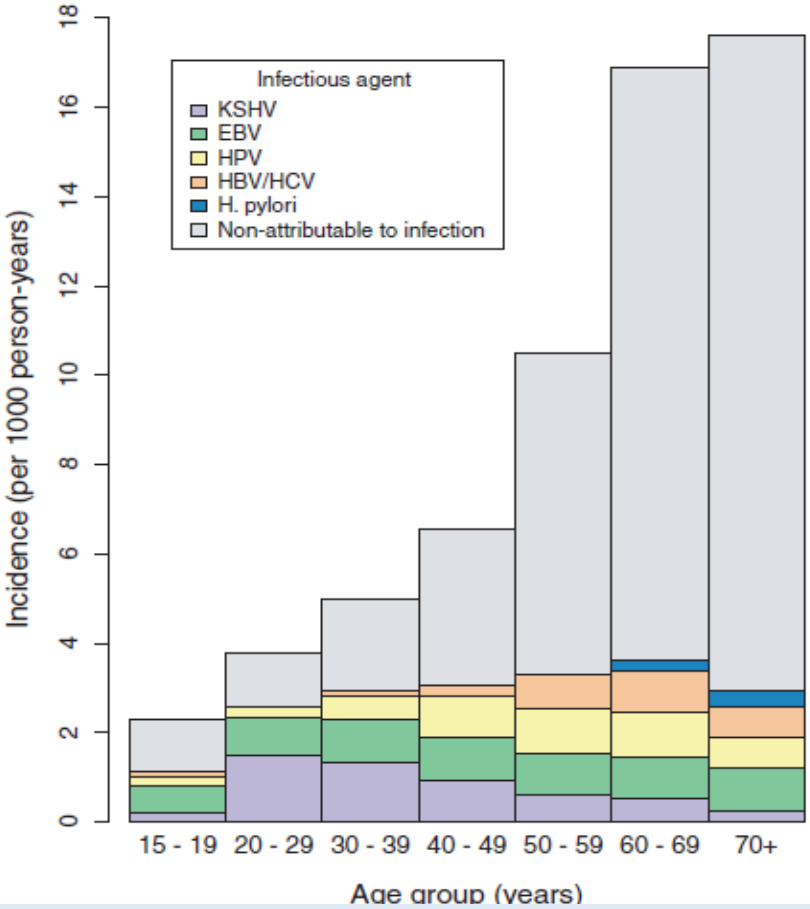
Excess of Non-AIDS-Defining Cancers %



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)



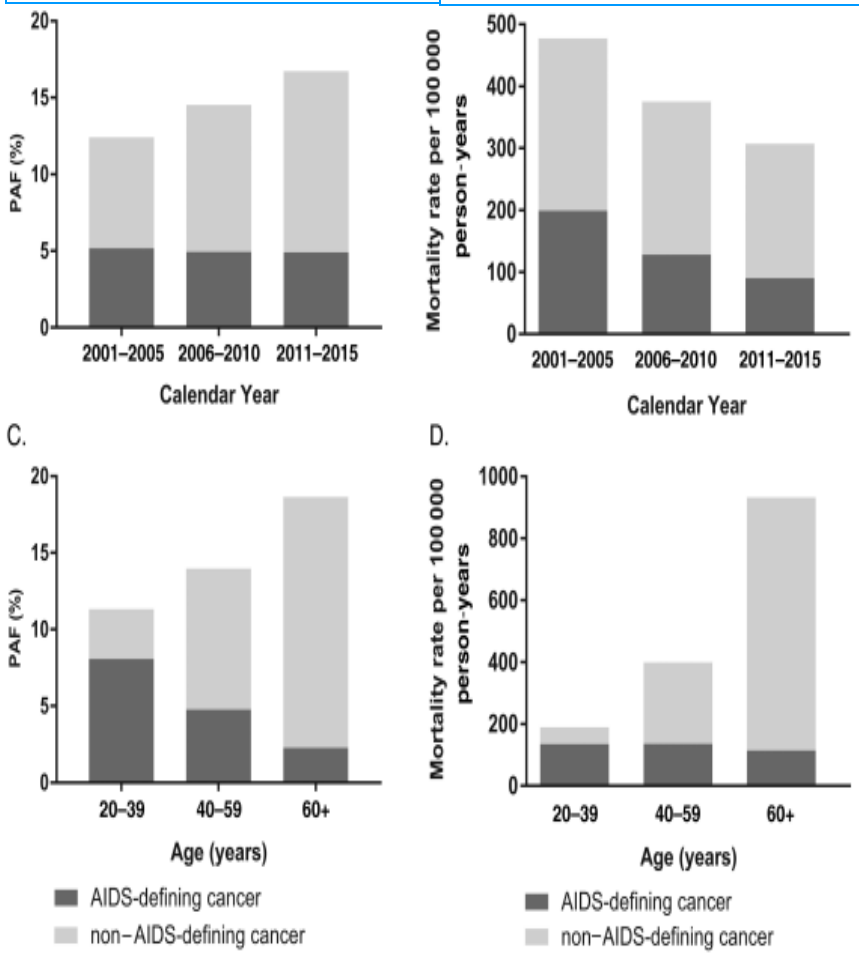
The incidence rate of cancer non-attributable to infection, including breast and prostate cancers steeply increased with age,.

de Martel C et al AIDS 2015

Deaths Attributable to Cancer in the US HIV Population (2001-2015)

Horner MJ et al CID 2021

PAF (%) | **Mortality Rate per 100.000 py**

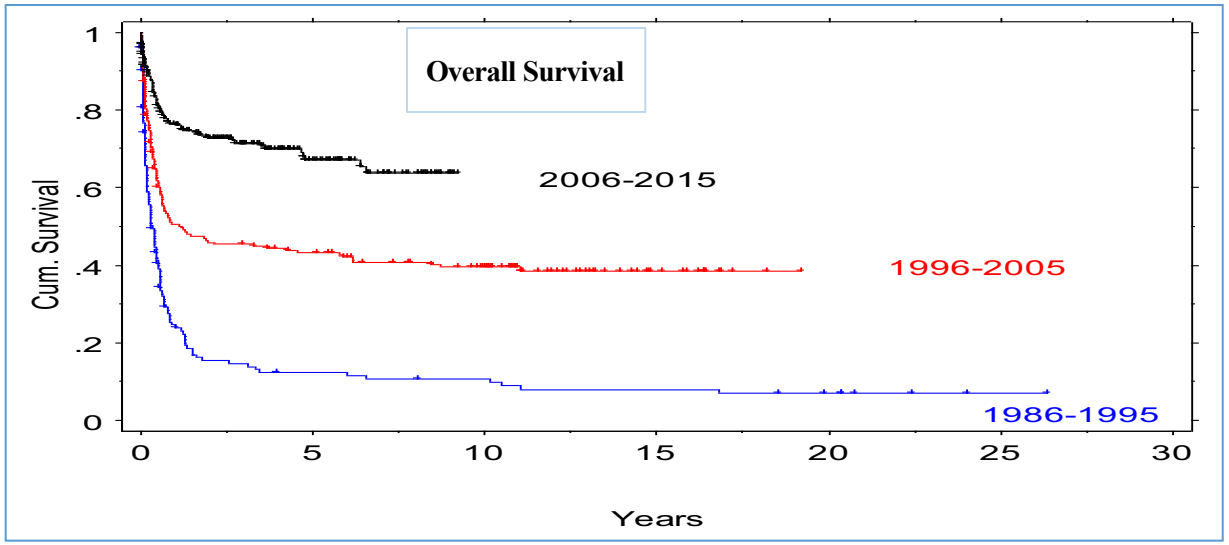


Cancers	PAF (%) (95% CI)
All cancers	**14.5** (13.6-15.4)
AIDS-Defining Cancers	**5** (4.4-5.6)
Non-AIDS Def Cancers	**9.2** (8.5-9.9)
Cancer Site	
NHL	**3.5** (3.0-3.9)
Lung	**2.4** (2.0-2.7)
Cervix	**2.0** (1.0-4.0)
Kaposi Sarcoma	**1.3** (8.5-9.9)
Liver	**1,1** (0.9-1.6)

Population-Attributable Fractions (PAF):proportional contributions of cancer to mortality

Although cancer mortality is declined over time, it remains high and represents a growing fraction of deaths in the US HIV population. NHL is a leading cause of cancer-attributable deaths

Change in Treatment Paradigm and Outcome of HIV-Lymphoma



	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

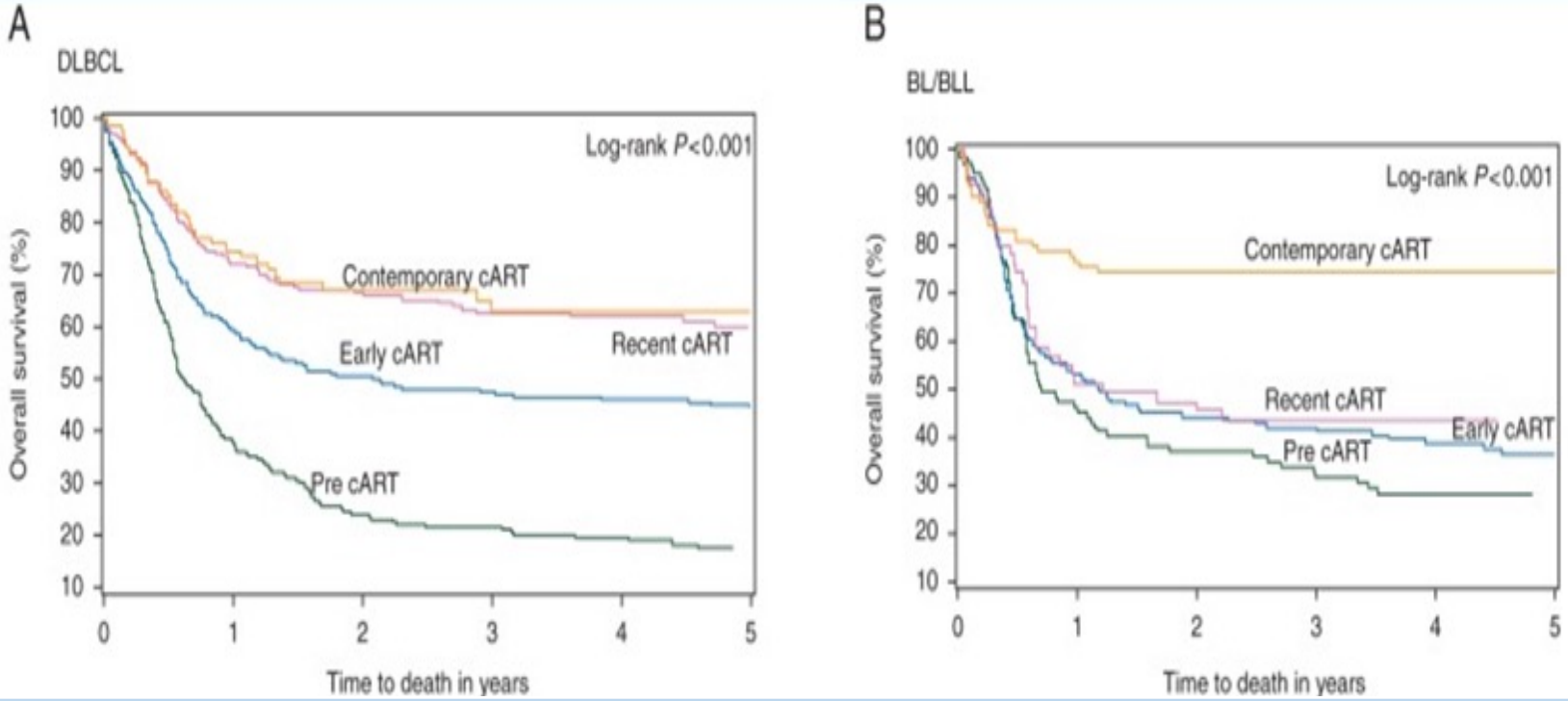
Risk-adjusted CT regimens

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)

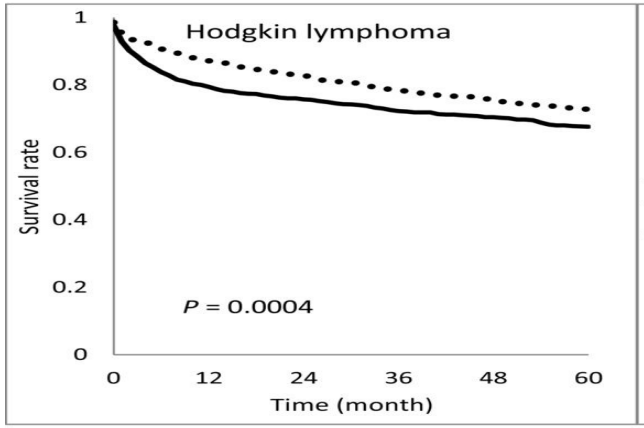


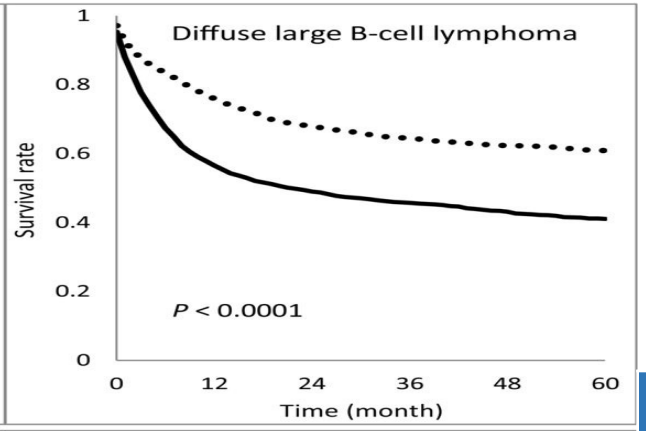
Major Prognostic Factors over time

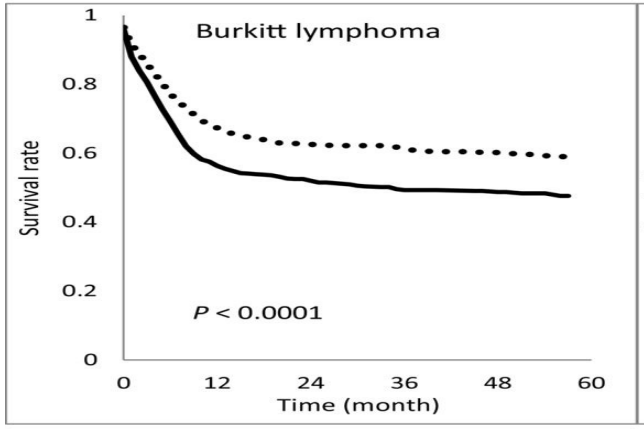
Pre/early cART era	Early cART era	Contemporary cART
CD4 count< 100 /µL	CD4 count< 100/µL	aa-IPI score
Prior AIDS diagnosis	aa-IPI score	Failure to achieve CR
Performance Status	BL subtype	
	Failure to achieve CR	

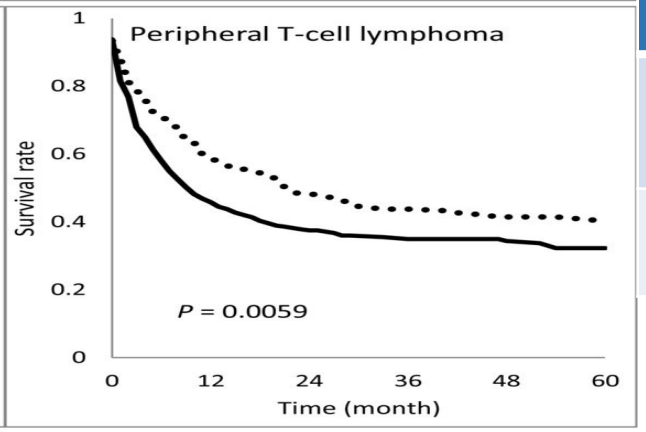
Mounier N et al Blood 2006, Castillo JJ Am J Hematol 2012, Barta SK et al Ann Oncol 2015

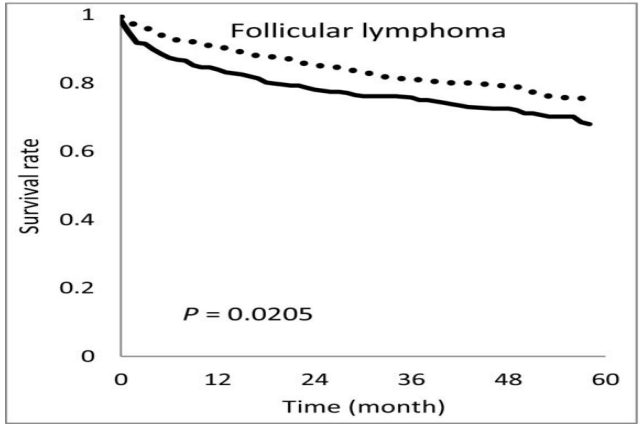
Overall Survival by HIV status among 179.520 Patients with Lymphoma - (USA-National Cancer Database 2004-2011)











	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

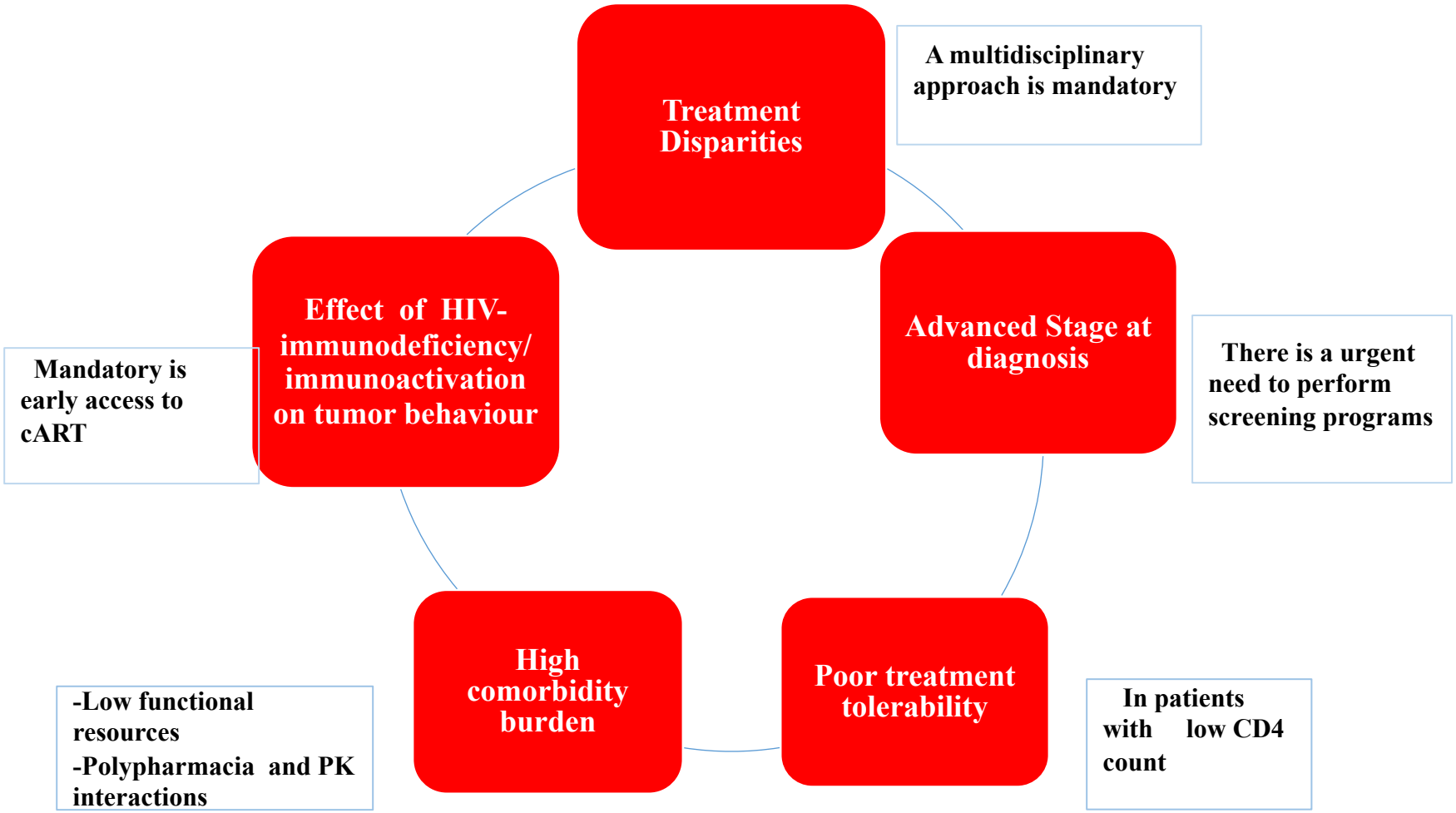
Outcomes after Cancer Diagnosis for HIV-Infected Patients compared to the General Population (1996-2010)

Coghill A et al J clin Oncol 2021

Cancer	Overal Death HR (95%CI	Cancer Specific Death HR (95%CI
Lung	**1.85** (1.73-1.97)	**1.28** (1.17-1.39)
Prostate	**2.59** (2.14-3.14)	**1.57** (1.02-2.41)
Breast	**4.62** (3.92-5.45)	**2.61** (2.06-3.31)
Colorectal	**2.26** (1.95-2.61)	**1.49** (1.21-1.84)
Liver	**1.50** (1.32-1.70)	1.17 (0.99-1.39)
Anal	**1.86** (1.60-2.16)	0.97 (0.75-1.25)
Head Neck	**2.46** (2.09-2.88)	1.31 (0.94-1.83)
Hodgkin L.	**4.19** (3.65 -491)	0.86 (0.61.21)1
DLBCL	**3.55** (3.31-3.81)	0.88 (0.76-1.01)

HIV was associated with increased cancer-specific mortality for lung, prostate,breast and colorectal cancer cancer.

Major Causes of Poor Cancer Outcomes in HIV Population



Treatment Guidelines for HIV-related Cancers

Treatment Strategies	HIV-Specific Issues
The treatment strategy for cancers in patients receiving effective cART should not be influenced by HIV status	Potential pharmacokinetic interactions between cART and anticancer or supportive care drugs
All PLWH with cancer must receive cART during antineoplastic treatment	The need to maximize supportive care, particularly prophylaxis against opportunistic infections and support with hematopoietic growth factor, in high risk patients
PLWH with cancer should not be excluded from cancer clinical trials of the general population.	The management of comorbity in aging PLWH (Alert: higher comorbidity rate in PLWH compared to general population

New Treatment Strategies for HIV-NHL (2012-2019)

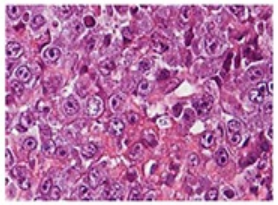
Oncolytic strategy

Bortezomid plus ICE/R

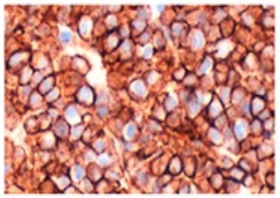
Oncolytic treatment is designed to induce oncolysis through viral replication and immune-mediated cell death of cancer cells latently infected with EBV or KSHV.

-Vorinostat (HDAC inhibitor) plus R-EPOCH
-Bortezomid (proteasome and HDAC inhibitor) plus ICE/R
-

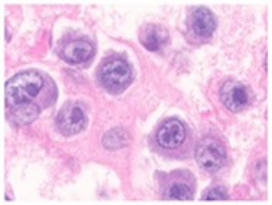
DLBCL



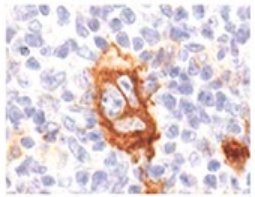
PBL



PEL



HL



Ceckpoint Inhibitors

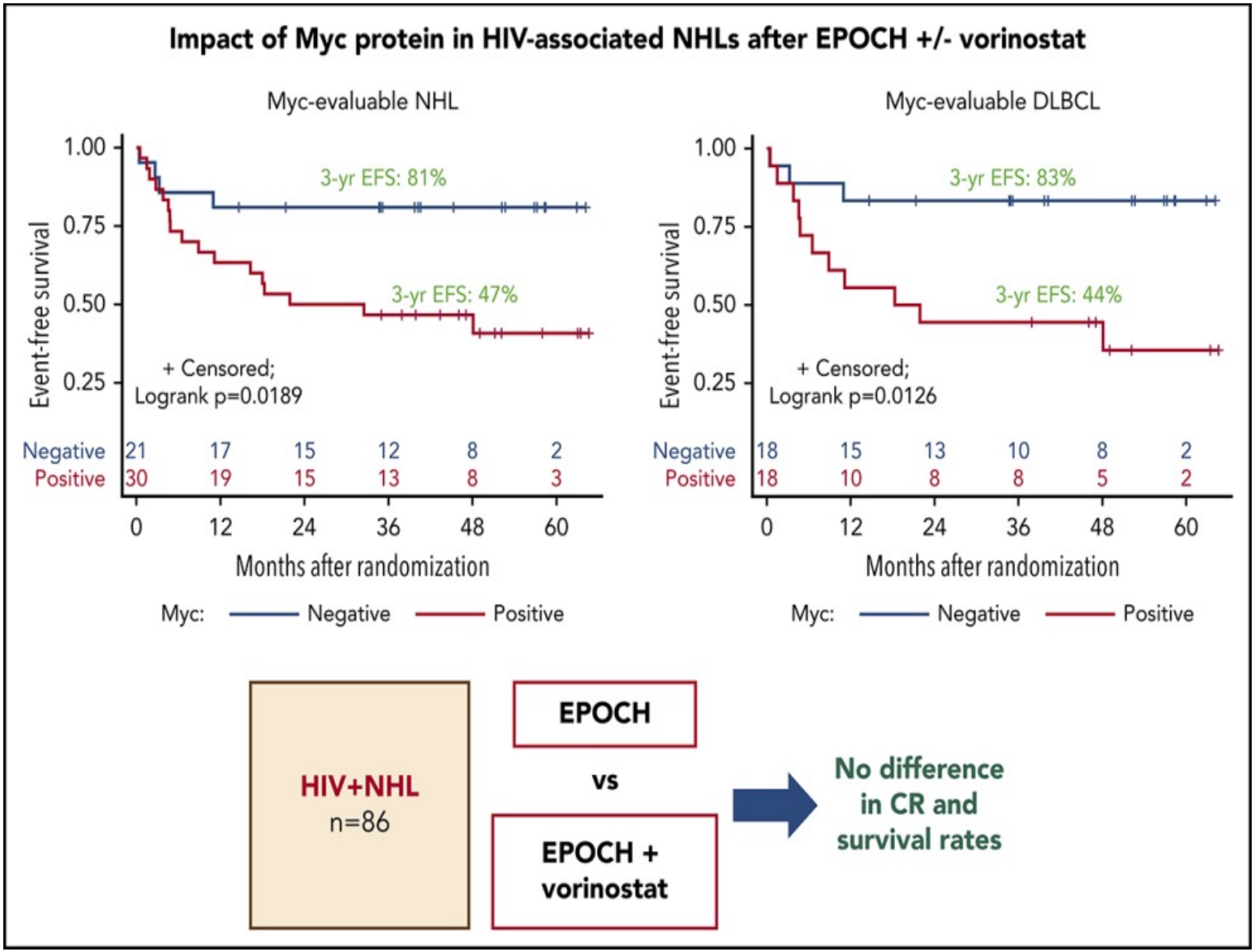
Brentuximab Vedotin (anti-CD30 monoclonal antibody plus microtubule-disrupting agent, MMAE) plus AVD

Immunomodulatory Strategy
Pembrolizumab
/Nivolumab- Pomalidomide

Target therapy strategy

Brentuximab plus AVD

Impact of Myc in HIV-associated Highly Aggressive NHL* treated with EPOCH +/- Vorinostat
Phase 2 Randomized Study (AMC-075 Trial)



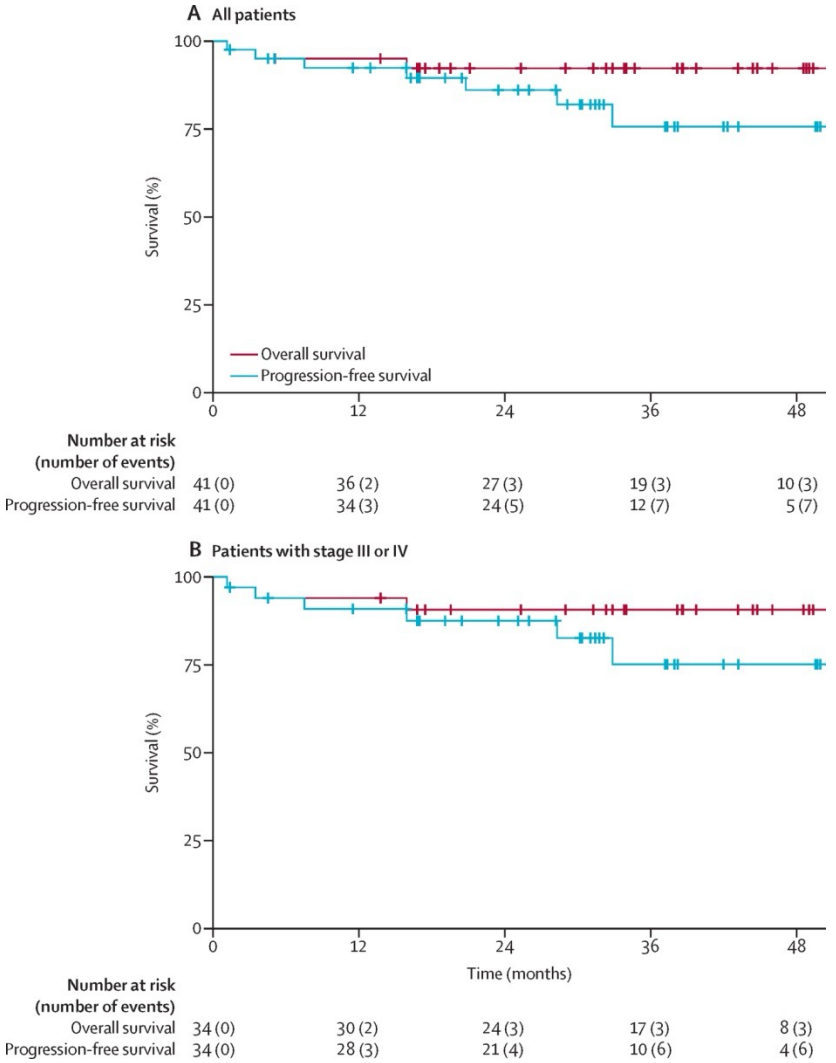
*non-GCB DLCL,PBL, PEL subtype ,high aa-IPI score

Ramos JC et al Blood 2020

Brentuximab Vedotin with AVD for Stage II-IV HIV-related Hodgkin Lymphoma: Phase 2 Results from a Multicenter Phase 1/2 Trial (AMC-085 Trial)

Previously untreated patients with HIV-cHL on cART: unfavourable II stage (17%), III-IV (83%),histology: NS 41%, MC 37%, LD 2%,NOS 20%; IPI score ≥3 73%; median CD4 count 258/µcL- median followup: 29 mos

	Results n° (%)
Total PTS n°	41
Pts with complete therapy	37 (90)
CR Rate	37 (100)
Major grade 3-4 Toxicity:	
- Neutropenia	18/41 (44)
-Febrile Neutropenia	5/41 (12)
- peripheral sensory neuropathy	4/41 (10)
-Neutropenia	
Toxic Death	1/41 (2)
2-yr PFS % (95% CI)	
- Entire cohort Pts	87 (71-94)
- PTS with III-IV stage cHL	87 (71-94)
2-yr OS % (95% CI)	
Entire cohort Pts	92 (78-97)
- PTS with III-IV stage cHL	90 (74-97)



Rubinstein PG et al Lancet Haematol 2023

CRO 2024

Innovative Treatment Strategies for HIV-NHL
Focus on Gammaherpesvirus-related Lymphpomas (2020-2024)

Targeted Therapy

Bortezomib+ Chemotherapy
.-CDK4/CDK6 Inhibitors
-Daratumumab
Ibrutinib +/-Chemotherapy
Pacritinib

Immunomodulatory Therapy

-Lenalidomide-Pomalidomide +/- Rituximab and Chemotherapy-
-Pomalidomide+Nivolumab

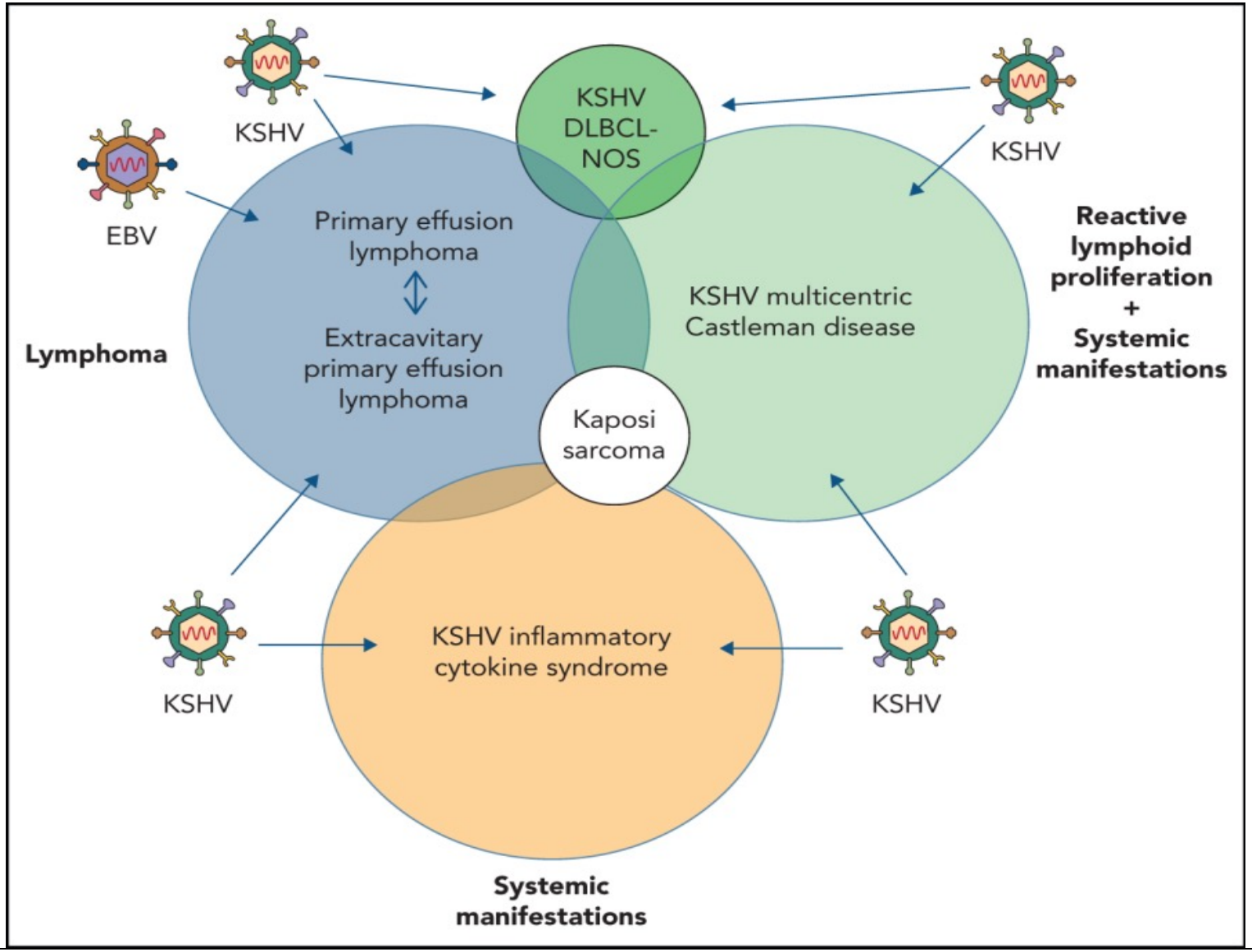
Cellular Therapy

-CART-T
-EBV-Specific Adoptive Immunotherapy*
-KS HV-Specific Adoptive Immunotherapy*
(* with epigenetic modulation)

CRO 2024

KSHV/HHV8-related Hematologic Disease

Cesarman E et al Blood 2022



The clinical and molecular phenotypes of the KSHV disease depend on the cellular targets as well as host environment, including HIV infection, degree of host immunodeficiency/immune dysregulation

Major Clinico-Pathological Features of KSHV and/or EBV-associated Lymphoproliferative Disorders

	Classic PEL	EC-PEL	HHV8+ DLBCL-NOS	MCD	PBL
Clinical Evolution	Aggressive	Aggressive	Aggressive	Aggressive	Agressive
Site Involvement	Serous cavities	Extra cavities	Nodal/extranodal	Nodal	Extranodal Nodal
HIV Infection %	>90	>90	>90	>95%	>90%
HHV8 (LANA) %	100	100	100	100	-
EBV (EBER) %	90 (latency I)	90 (Latency I)	-	-	70-80 (Latency I)
Phenotype: CD20 CD 38 -CD138 -MUM1 -CD30 -EBER	 - + + + + +	 - + + + + +	 - - - + - -	 microenvironment + + + - -	 - + + + +/- +/-
Ig	IgG	IgG	IgM	IgM	K, lambda
IgVH status	Mutated	Mutated	Non mutated	Non mutated	Mutated

CRO 2024

Cesarman E et al Blood 2022;Carbone A et al Blood Advances 2024

Primary Effusion Lymphoma: Major Series

	Castillo JJ (2012)	Guillet S (2016
N° Pts (yr of study)	301 (2001-2012)	51 (1996-2013)
PEL %	76	67
EC-PEL	24	33
Age median yrs	55	45
HIV %	67	100
cART%		100
CD4/µL median	NA	204 (90-370)
EBV %	50	66
KS %	28	49
MCD %	4	35

	Castillo JJ (2012)	Guillet S (2016
Receiving CT %	86	88
CT Type	various	CHOP-like
CR Rate %	NA	62 classic 41 EC
OS median mo	6	10
OS Rate 5-y %	NA	43 classic 39 EC
DFS 2-yr %	NA	71 classic 100 EC

Castillo JJ et al Leuk Lymphoma 2012; Guillet S et al Am J Hematol 2016

Primary Effusion Lymphoma in Persons Living With HIV: Major Series

	Guillet	Boulanger	Simonelli	Chadburn	**Lurain**	**Ramos**	**Lurain**
N° Pts (yr of study)	51 1996-2013	28 1993-2003	11 1987-2002	8 1987-2001	20 2000-2013	7 2010-2017	8
PEL %	76	100	100	0	98	100	67
EC-PEL	24			100	2		33
Age median yrs	55	44	41	40	44	NA	38
cART %	100	78	NA	20	100	100	100
CD4/µL median	204	133	140	NA	125	NA	231
EBV %	66	71	NA	NA	73	60	NA
KS %	49	67	27	25	75	NA	66
MCD %	35	32	NA		30	NA	27
Chemotherapy %	88 CHOP	79 CHOP	73 CHOP	75 CHOP	95 DA-EPOCH	100 DA-EPOCH	100 DA-EPOCH
CR Rate %	62 C 43 EC	41	42	NA	53	71	50
OS median mo	10	6	6	11	22	NA	Data non mature
OS Rate %	at 5-yr 43 C, 39 EC	at 1-yr 39	NA	at 5-yr 40	at 3-yr CSS 47	71 3-yr EFS	at 2-yr 67

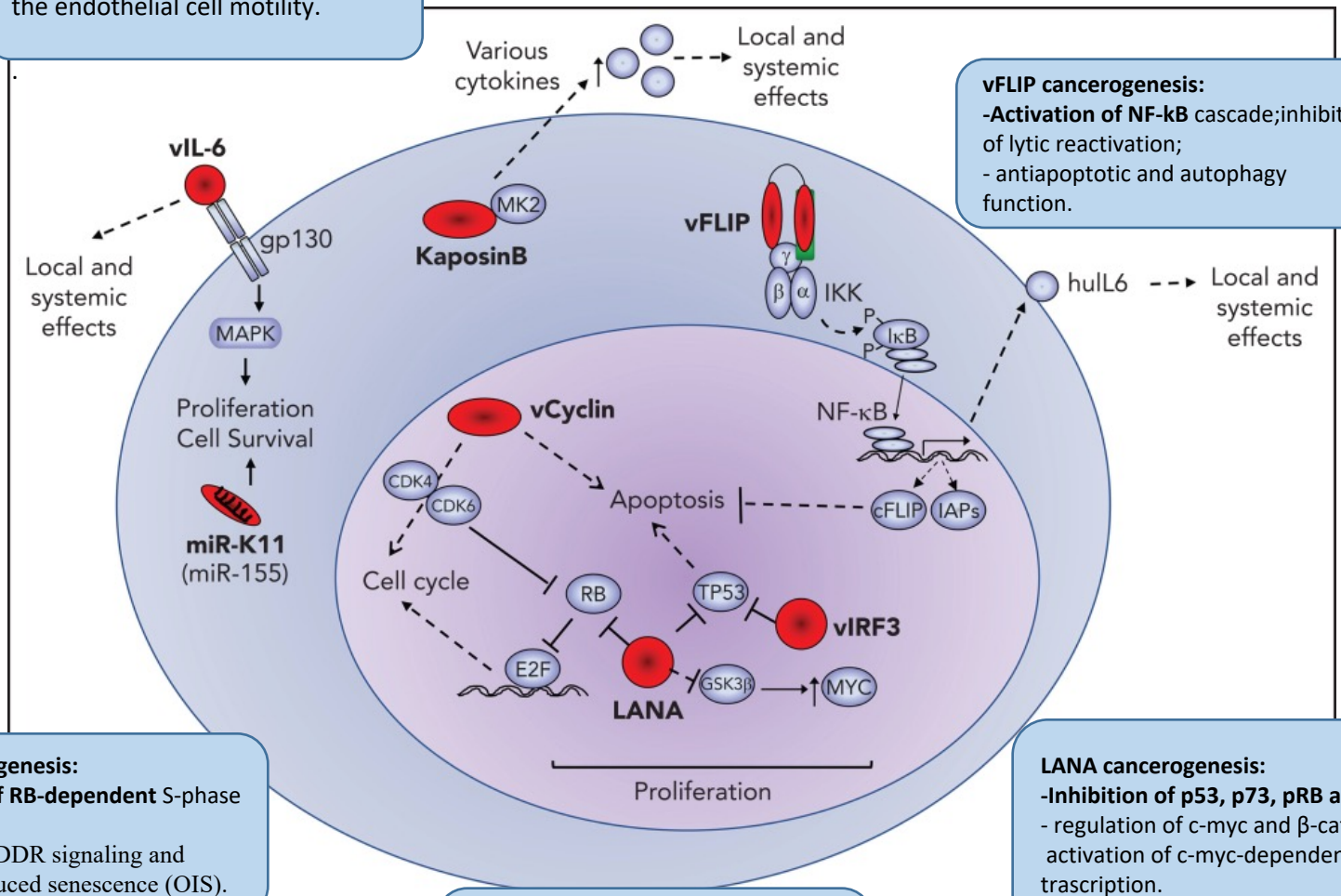
Cesarman E et al Blood 2022

KSHV/HHV8 Oncogenesis

K

aposinB cancerogenesis:
Angiogenesis and promotion of the endothelial cell motility.

Cesarman E et al Blood 2022



vFLIP cancerogenesis:
-Activation of NF-kB cascade;inhibition of lytic reactivation;
- antiapoptotic and autophagy function.

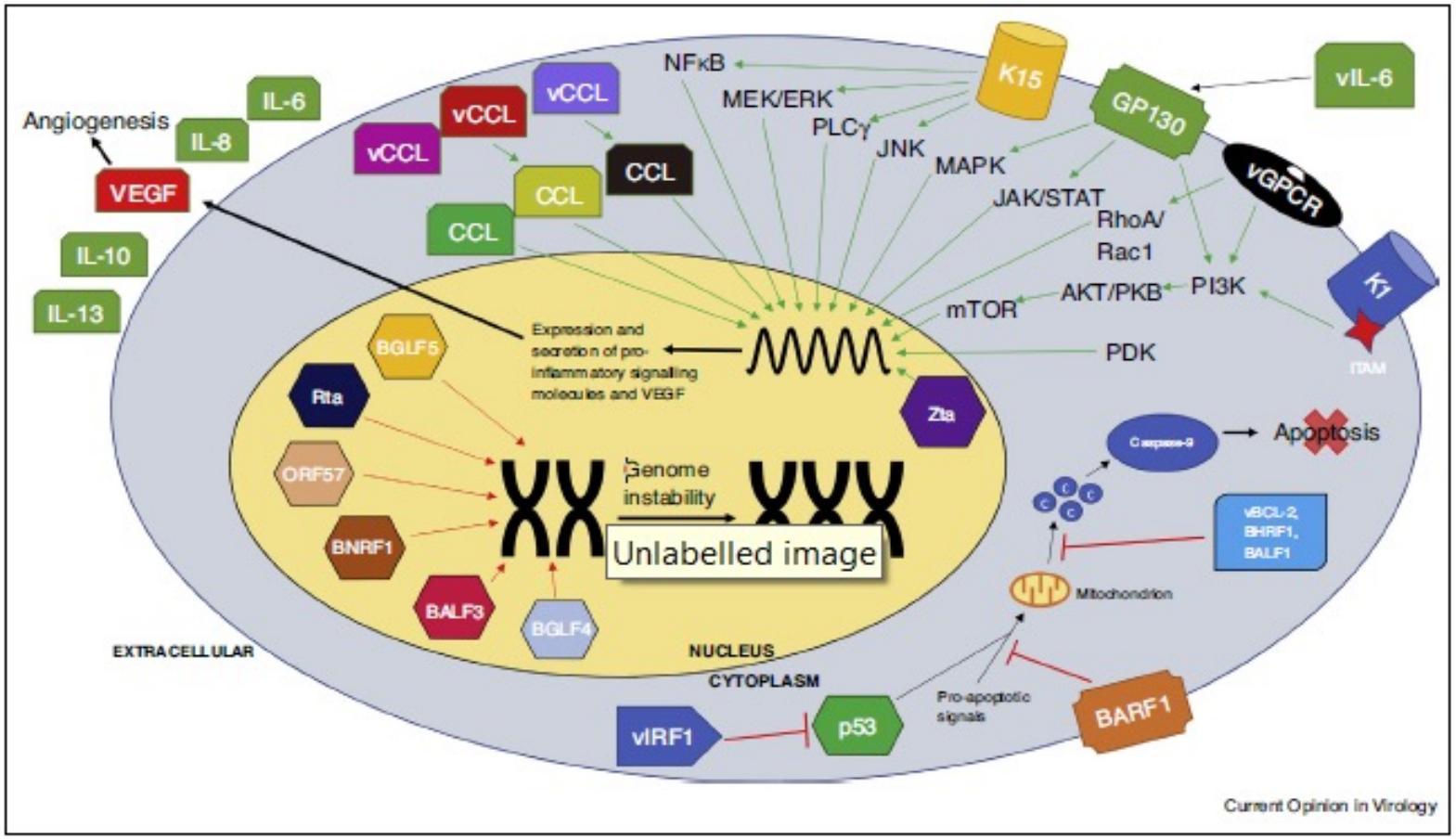
vCYC cancerogenesis:
-Promotion of RB-dependent S-phase entry;
-induction of DDR signaling and oncogene-induced senescence (OIS).

vIRF3 cancerogenesis:
-modulation of p53 function and PKR- and IFN-mediated apoptosis; - promotion PEL cell survival.vIRF4: p53 degradation.

LANA cancerogenesis:
-Inhibition of p53, p73, pRB activity;
- regulation of c-myc and β-catenin, activation of c-myc-dependent trascription.

Contribution of the KSHV and EBV Lytic Cycles to Tumourigenesis

Manners O et al Curr Opin Virol 2018



Schematic representation how KSHV and EBV lytically expressed proteins augment the pathogenesis of KSHV and EBV-associated malignancies.

Innovative Treatment Strategies for HIV/Gammaherpesvirus (GHV)-related lymphoma

Drug	Mechanism of Action	Potential Targets	Study	Major Risks
Targeted Therapies				
Bortezomib (Proteosoma and HDAC inhibitor)	Potent activator of EBV/HHV8 lytic cycle.Citotoxicity, Inductor of apoptosis, Sinergistic/additive activity with CT.AZT	GHV-malignancies	-Preclinical -Ongoing trial (B+DA-EPOCH)	Infections of other cells Cytokine syndrome
CDK4/6 Inhibitors (inhibition of cyclineD-CD4/6 complex formation: cycle arrest from G1 to S phase)	Inhibitor of cell growth. Potent activator of immunological control by blocking virus-induced downregolation of MCH-1, ICAM -1, CD86.	GHV-malignancies	Preclinical	Myelotoxicity, Gastrointestinal toxicity
Daratumumab (anti-CD38 monoclonal antibody)	Cytotoxicity by ADCC-mediated lysis Inductor of apoptosis	GHV-malignancies	Preclinical (PEL cell lines) Ongoing trial (DARA+CT)	Severe infusional reaction HBV reactivation
Ibrutinib (BTK inhibitor)	Inhibitor of B cell receptor signaling and downstream activation of NF-kB pathway	EBV-lymphoma (eg R/R PCNSL)	Ongoing trial (I plus CT)	Myelotoxicity
Pacritinib (JAK/STAT inhibitor)	Inhibitor of vIl-6,hIL-6 signaling, Inductor of apoptosis and cytotoxicity	GHV-malignancies	Preclinical	

Innovative Treatment Strategies for HIV/Gammaherpesvirus (GHV)-related lymphoma

Drug	Mechanism of Action	Potential Targets	Study	Major Risks
Immunomodulatory Therapies				
Pomalidomide (inhibitor of cereblon, E3ubiquitin ligase = inhibition of NF-kB)	Potent activator of immunological control by blocking virus-induced downregolation of MCH-1, ICAM -1, CD86. T-cell,NK cell activation. Cytoxic activity (targeting IRF4) Antiangiogenic/anti-inflammatory activity	GHV-malignancies	Preclinical Ongoing trials (Poma+Nivo in R/R NHL)	Myelotoxicity Thromboembolic events, Neuropathy

Innovative Treatment Strategies
Conclusions

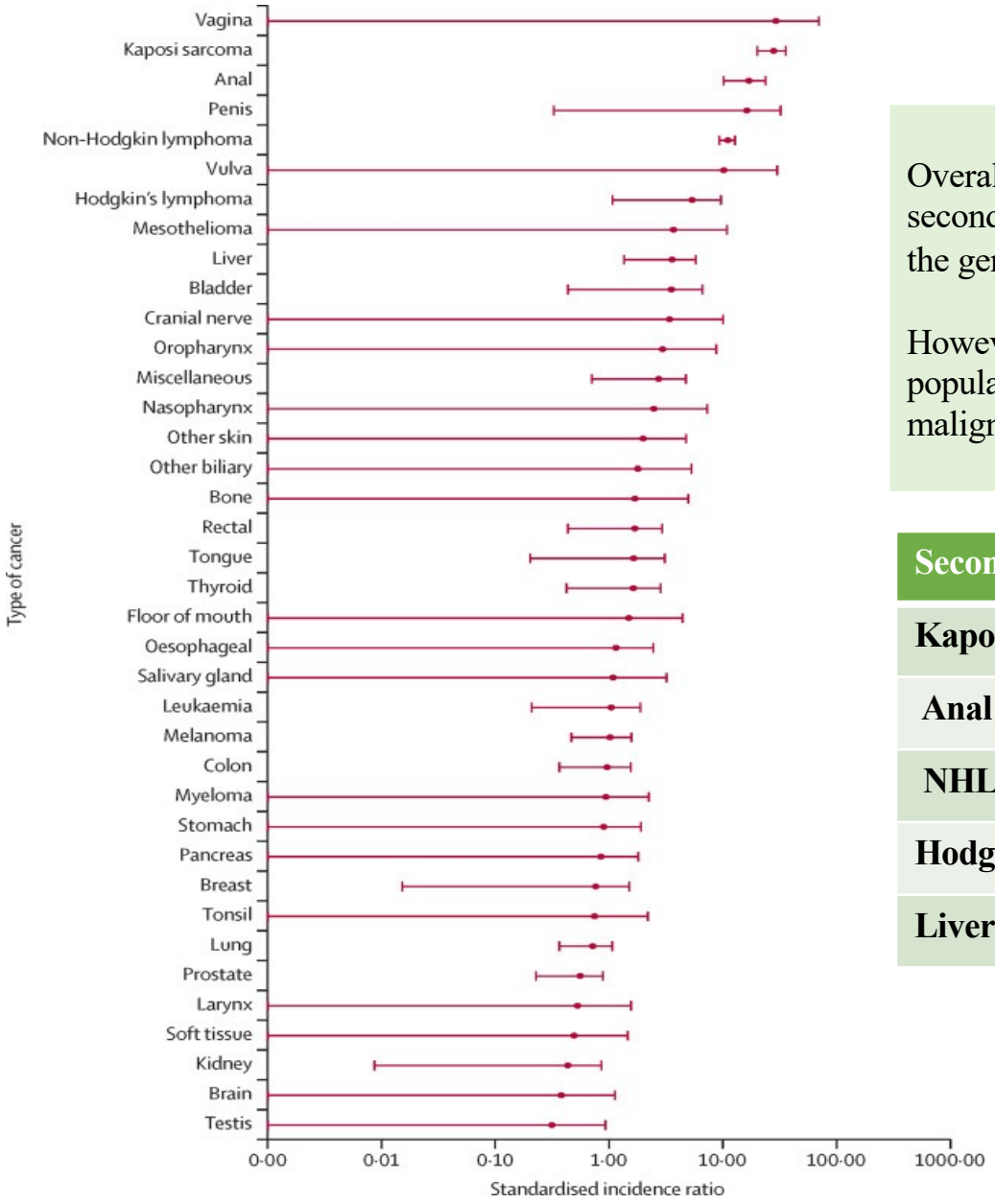
Persons living with HIV remain at higher risk of a variety of aggressive lymphomas with worse overall survival than the general population.

Restoration of immune system by cART is the core of all treatments providing benefit for treatrment outcomes.

Understanding the distinct pathogenesis of HIV-related lymphoma affords opportunities to develop novel therapies targeting the specific role of EBV and HHV8 in immunodeficiency-related lymphomagenesis.

Preventive Measures

Incidence of Second Primary Cancers among 22.623 People with HIV Infection in the USA: a Population-based Registry Linkage Study (1985-2013)



Overall, 9% of 4545 incident primary cancers were second or later cancers, a proportion similar to that in the general population of people aged 20-64 years.

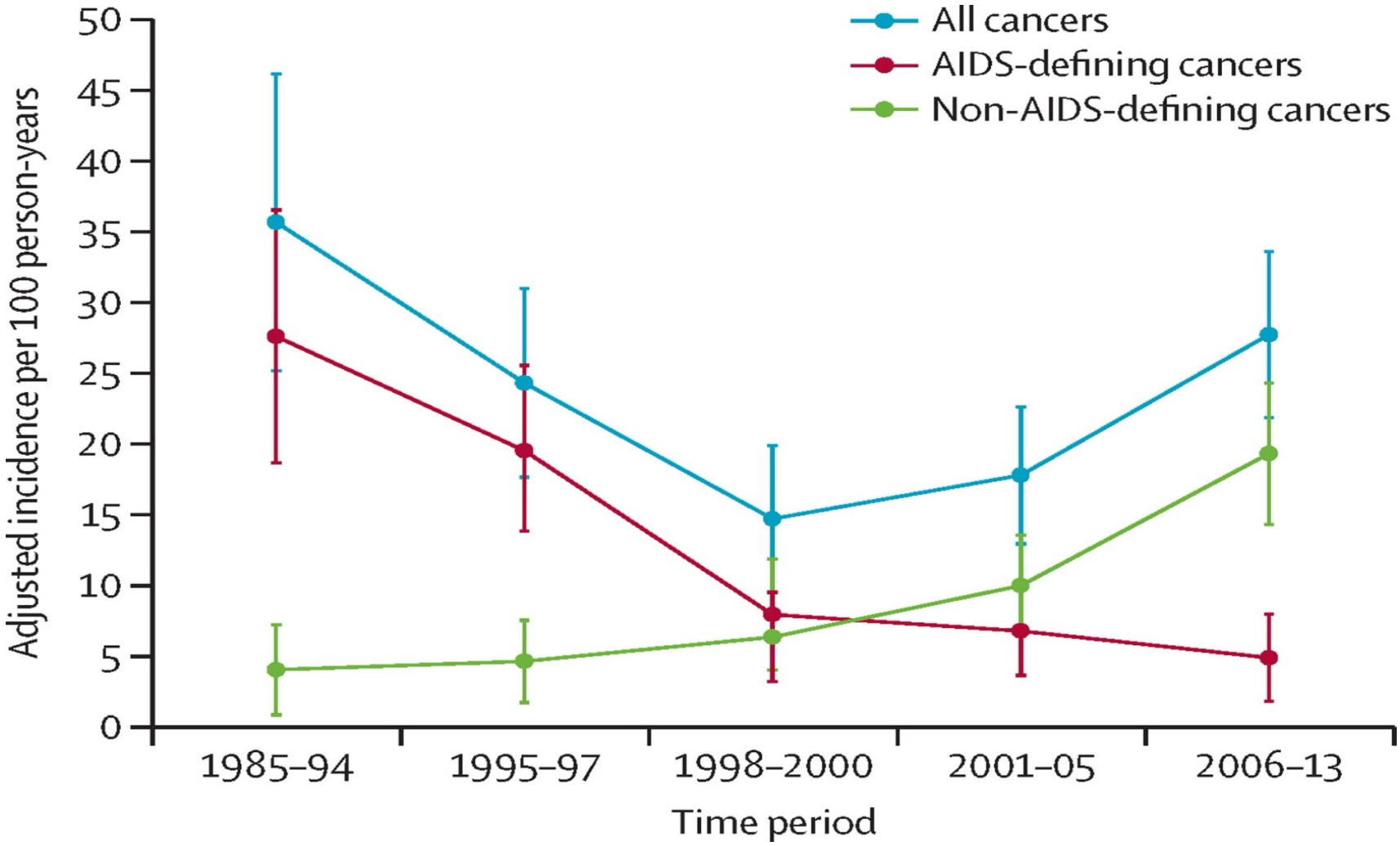
However, the incidence was higher than in the general population for both first and second primary malignancies among people with HIV.

Second Primary Cancer	SIR (95% CI
Kaposi Sarcoma	**28.0** (20.2-35.9)
Anal Cancer	**17.0** (10.2-23.8
NHL	**11.1** (9.3-12.8)
Hodgkin Lymphoma	**5.4** (1.1-9.7)
Liver Cancer	**3.6** (1.4-5.8)

Hessol NA et al Lancet HIV 2018

Incidence of Second Primary Cancers among People with HIV Infection in the USA: a Population-based Registry Linkage Study (1985-2013)

Age,race and sex adjusted second primary cancer incidence per 100 person-years by calendar period



Hessol NA et al Lancet HIV 2018

Cancer Risk following Lymphoid Malignancies among 531.460 HIV-infected People Case-Control Study (USA 1996-2015)

Cancers	aHR (95%CI) Model 1	aHR (95% CI) Model 2
Any non-Lymphoid Cancers	**2.7** (2.3-3.2)	**1.7** (1.5-2.0)
Kaposi Sarcoma	**4.6** (3.4-6.2)	**2.0** (1.5-2.7)
Rectum **Rectal SCC** **Rectal non-SCC**	**3.6** (1.9-6.7) **5.5** (2.3-13.5) **2.7** (1.1-6.4)	**2.7** (1.5-5.1) **4.1** (1.7-10.1) 2.0 (0.8-4.9)
Anus	**3.6** (2.5-5.1)	**2.6** (1.8-3.6)
Oral cavity	**2.6** (1.2-5.5)	1.9 (0.9-4.0)
Colon	**2.4** (1.1-5.0)	2.0 (1.0-4.3)
Liver	**2.0** (1.2-3.5)	1.7 (1.0-3.0)
Lung	**1.6** (1.1-2.4)	1.2 (0.8-1.8)
Myeloid Malignancies	**9.7** (6.1-15.4)	**7.1** (4.5-11.3)
Miscellaneous	**3.4** (2.1-5.3)	**2.5** (1.6-3.9)

aHR: adjusted Hazard Ratio; Model 1: adjusted for sex, risk group, race, calendar year; Model 2 additional adjustment for prior AIDS and time since HIV diagnosis

Mahale P et al AIDS 2020

HIV-related Solid Tumours
focus on
Screening Programs and Preventive Strategies

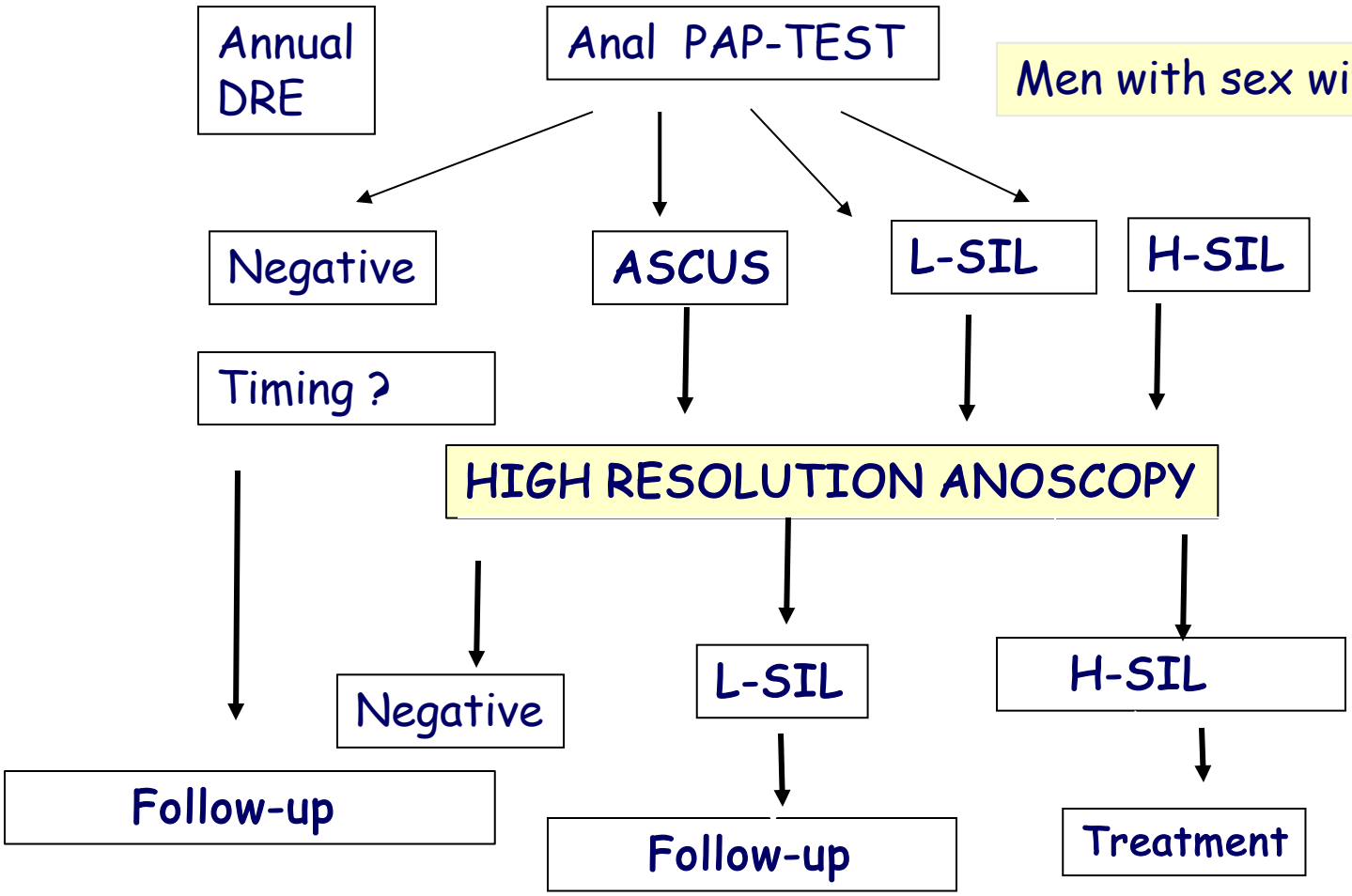
Major Features:

-Few trials for cancer prevention have be done to provide guidance on HIV-specific surveillance programs for patients with solid tumours.

-European and US guidelines recomended cancer screening that is appropriates for age and risk factors

-New target population: Long-term survivor patients with prior malignancies

Guidelines for diagnosis and Treatment of Anal Precancerous Lesions in HIV-infected Patients



Palefsky JM et al Semin Oncol 2000, Lam JM AIDS 2011; Mathews WC PLoSONE 2011; Deshmkh AA* Cancer 2018

Cervical Cancer Screening Guidelines of Various Organizations in the General Population

Organization	Age Group	Screening Test	Screening Interval	Recommendations
WHO	30-49	**Cytology**	3-5 yrs	If HPV test unvailable
		HPV test	5 yrs	Preferred
European Guidelines	<30 yrs	**Cytology**	3-5 yrs	Cytology alone
	35-65	**HPV Test**	5-10 yrs	HPV testing alone; cytology triage if HPV test+
US Preventive Task Force	21-29	**Cytology**	3 yrs	-HPV testing not recommended
NCCN	30-65	**Cytology**	3 yrs	Cytology alone
		HPV test	5 yrs	Alone or Cotesting with Cytology

Screening Programs for Anogenital Cancer in Persons Living with HIV: Provocative Questions

hr-HPV Prevalence		
Site	HIV-pos Pts %	HIV-neg Pts %
Cervix	46-64	29
Anus		
MSM	74-94	14- 37
MSW	27	7
Women	16-76	42
Head-Neck	16-28	4

High-risk HPV test in anal/cervical smears: can it optimize the screening for anal/cervical cancers?

What is the impact of cART on the natural history of anogenital HPV infection among persons living with HIV?

Machalek DA Lancet Oncol 2012;Park LS AIDS 2016, Poljak M Expert Rev anti-Infected Therapy Wei F Lancet HIV 2021;Gupta R HIV Med 2022

Anal Screening Programs Controversial Issues

	* Sensitivity %	* Specificity
Anal Pap test	69-93	32-52
HPV test	80-100	16-18

*for HGAIN in MSM

- High Resolution Anoscopy is the gold standard test for anal cancer screening
- Limited n°of clinicians with necessary expertise
- Paucity of cost-effectiveness data on anal screening approaches

HRA:limited expertise
and equipment availability

There are no formalized anal screening programs

Clinical Performance for Anal Precancer Detection of Major Biomarker Testing in Person Living with HIV (Pooled Meta-Analysis)

Test	Sensibility %	Specificity %	Immediate AIN2 risk% if Test pos	Immediate AIN2 risk% If Test neg
Cytology (ASCUS+)	84	60	37	6
Cytology H-SIL	23	96	64	20
HPV-testing	94	35	31	5
Cytology+HPV testing (co-testing)	92	32	27	6
HPV16 genotyping	44	92	36	14
HPV 16/18 genotyping	46	69	24	16

Clark MA Int J Cancer 2022

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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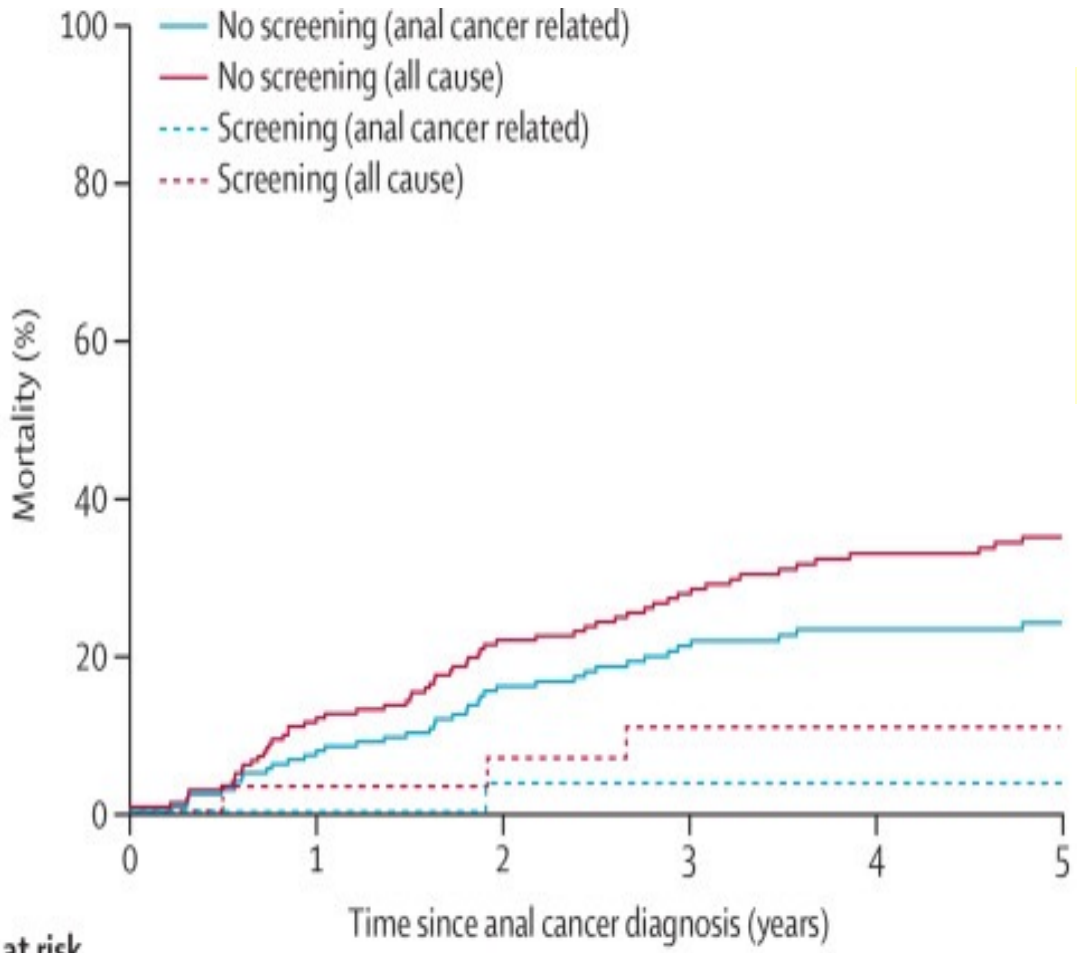
Effect of the Introduction of Anal Screening among 16.817 MSM with HIV: a Nationwide Cohort Study

Van der Zee RP et al Lancet HIV 2023



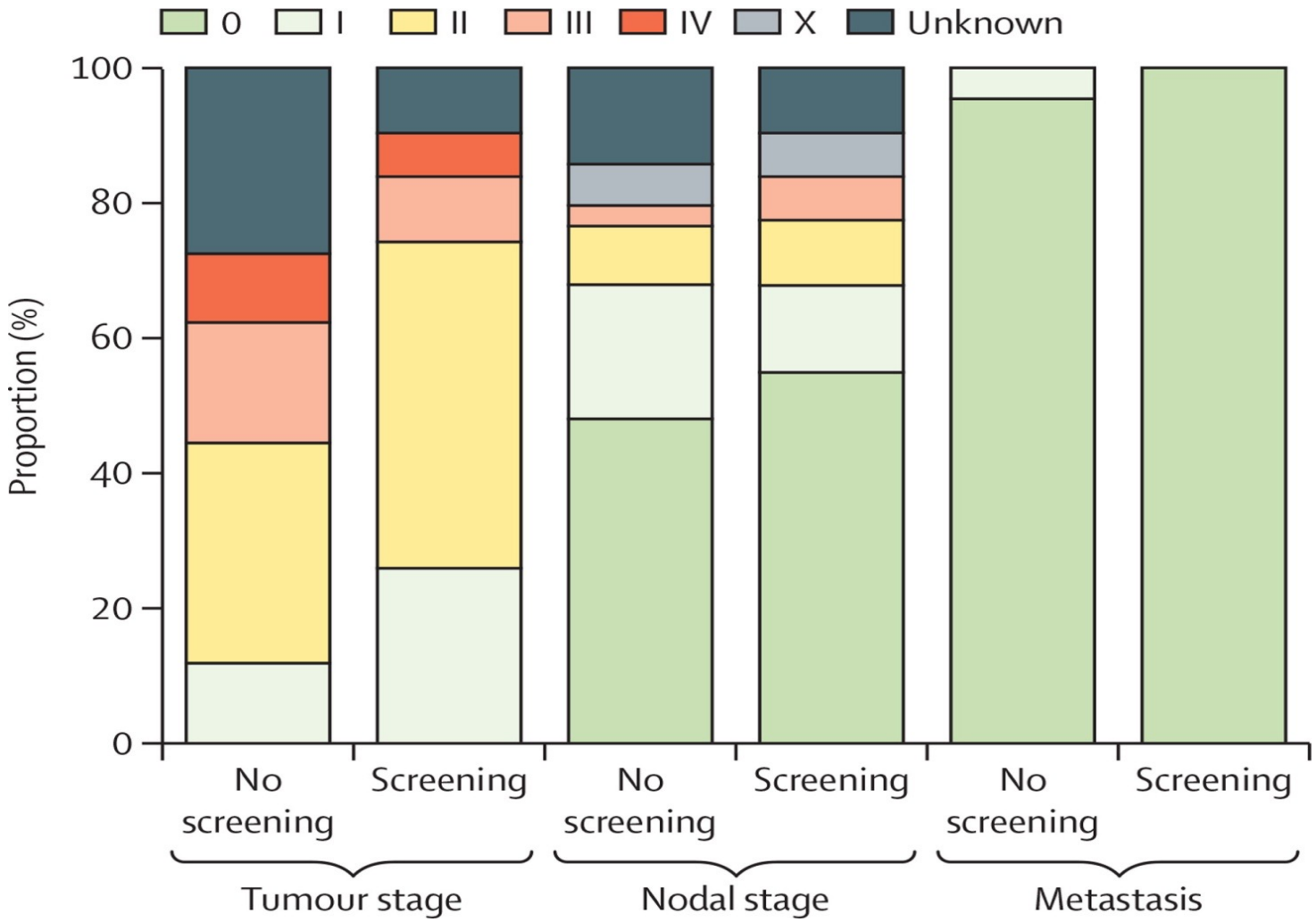
Number at risk

No screening (anal cancer related)	187 (0)	163 (11)	141 (18)	120 (31)	100 (48)	88 (147)
No screening (all cause)	187 (0)	163 (3)	141 (6)	120 (17)	100 (29)	88 (126)
Screening (anal cancer related)	30 (0)	29 (1)	26 (3)	22 (7)	17 (12)	12 (29)
Screening (all cause)	30 (0)	29 (0)	26 (2)	22 (5)	17 (10)	12 (27)

Crude anal cancer-associated 5-yr mortality in People living with HIV decreased from 30% (1996-2005) to 18% (2013-2020);
Odd Ratio 0.48

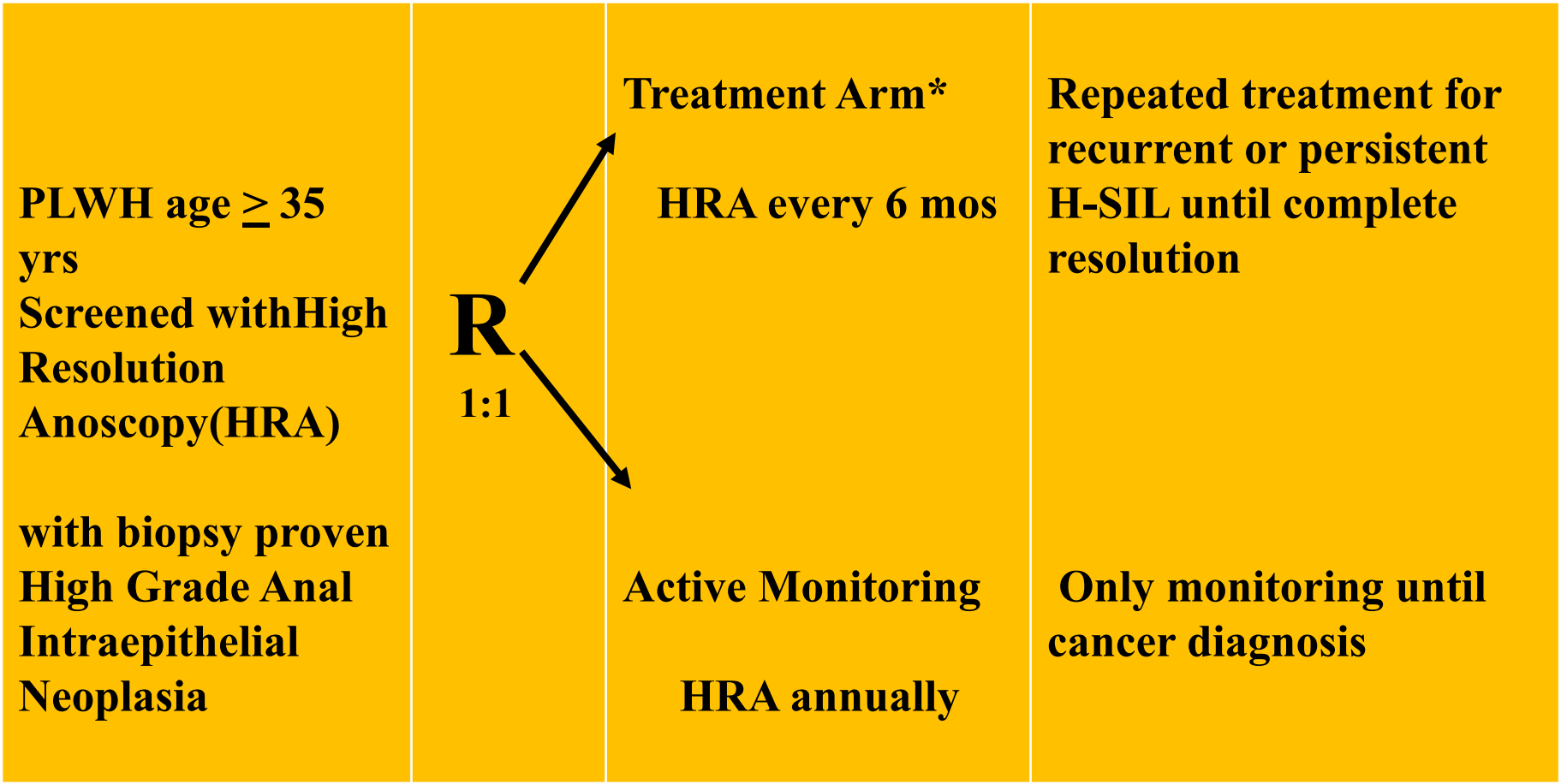
In men, screening participation and cumulative exposure to CD4 count <200/mL were independently associated with anal cancer-related mortality

Effect of the Introduction of Anal Screening on Cancer Stage in Persons Living with HIV: a Nationwide Cohort Study



van der Zee RP Lancet HIV 2023

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



* electrocautery in most cases

Palefsky J CROI 2022

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

Palefsky NEJM 2022

	Treatment Arm n°2227	Active Monitoring Arm n°2219
Median Age	51 (44-57)	51 (44-57)
Gender Identify n° (%)		
Male	1793 (81)	1782 (80)
Female	346 (16)	365 (17)
Transgender	85 (4)	68 (3)
Unknown	3	4
Risk Group n°(%):		
MSM	1738 (78)	1742 (79)
Heterosex.	532 (24)	510 (23)
IVDU	152 (7)	177 (8)
Other	84	78
Median Duration HIV (yrs)	17	17
Median CD4 count µ/mL	602 (393-827)	607 (410-837)
HIV-RNA cp/mL		
<50	1852 (84)	1800 (82)
51-199	155 (7)	160 (7)
200-1000	83 (4)	93 (4)
>1000	122 (6)	148 (7)

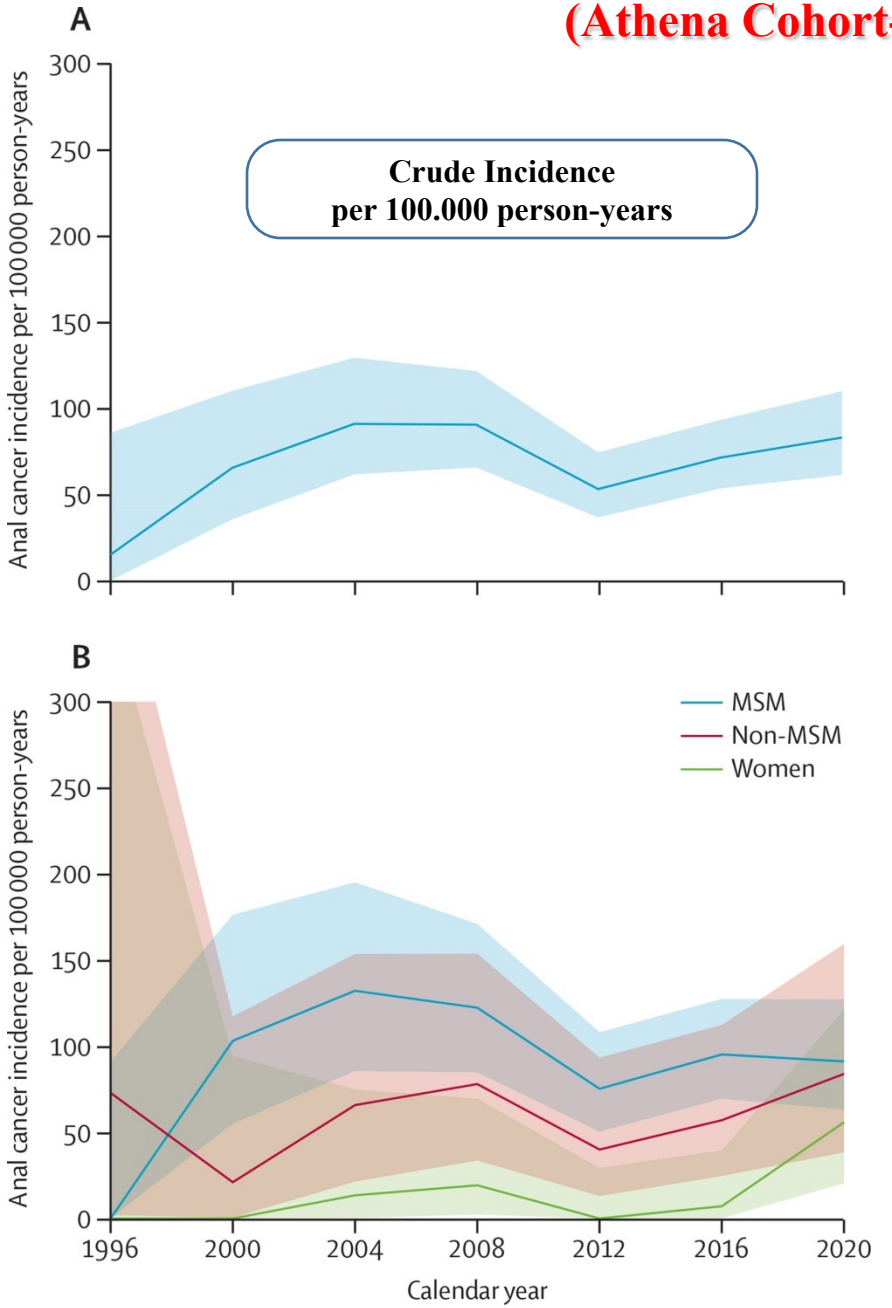
Anal Cancer/H-SIL Outcomes Research (ANCHOR) Study in Persons Living With HIV (PLWH) (USA 2014-2021)

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 CROI 2022

Anal Cancer Incidence among 28.175 Persons Living with HIV in the Netherlands (Athena Cohort-1996-2020)



Crude Incidence per 100.000 person-years

Age-adjusted Incidence Rate Ratios (RR) (95% CI) over time

	MSM	Men non-MSM	Women
1996-2005	1 (ref)	1 (ref)	1(ref)
2006-2012	**0.75** (0.49-1.14)	**0.98** (0.38-2.55)	**1.03** (0.09-11.53)
2013-2020	**0.62** (0.41-0.92)	**1.03** (0.42-2.55)	**1.94** (0.22-16.98)

As anal cancer incidence is slowly declining in MSM but not in non.MSM and women, health-care professionals should not focus only on MSM for anal cancer prevention

van der Zee RP Lancet HIV 2023

Screening Carcinoma Cervice Uterina in HIV- Linee Guida

Popolazione	Procedura Screening	Tempistica
Donne sessualmente attive. Lo screening deve iniziare all'età ≥ 21 aa e continuare per tutta la vita	Solo Pap test PAP test convenzionale PAP test su base liquida - Co-testing (Pap test+HPV test) - Colposcopia	Età < 30 aa: il secondo° esame a 12 mesi; -ogni 3 aa se 3 Pap test annuali negativi. Età ≥ 30 aa: il secondo° esame a 12 mesi; - ogni 3 aa se 3 Pap test annuali negativi o se Co-test negativo°° - Co-test annuale se Pap test normale ed HPV test positivo Se Pap test patologico o HPV test positivo per ceppi alto rischio

http://clinicainfo.hiv.gov./en/guidelines/adult-and-adolescent-opportunistic-infection/human-papillomavirus-disease.

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Screening Specifici per HIV- Update Linee Guida Italiane

Tumore	Popolazione	Procedura Screening	Tempistica	Forza Raccomandazione
Fegato	-HCV coinfetti con cirrosi; -Tutti HBV con viremia rilevabile -Tutti HBV/HCV aviremici se con cirrosi -Tutti HCV aviremici (post-DAAs) con pregresso epatocarcinoma	Ecografia addome +/- α-fetoproteina	Ogni 6-12 mesi	
Polmone	-Fumatori con storia di ≥ 30(A), >20 (E) pacchi di sigarette/anno; -se ex-fumatori entro 10 (E)-15(A) anni dalla cessazione - Età≥ 40 aa**	TAC spirale a basso dosaggio senza mdc	Annuale	Elevata (categoria 1) Per età di inizio Debole (C)
Cute	- Pelle chiara; - Razza bianca non-ispanica	Esame della cute Dermatoscopia	Annuale	

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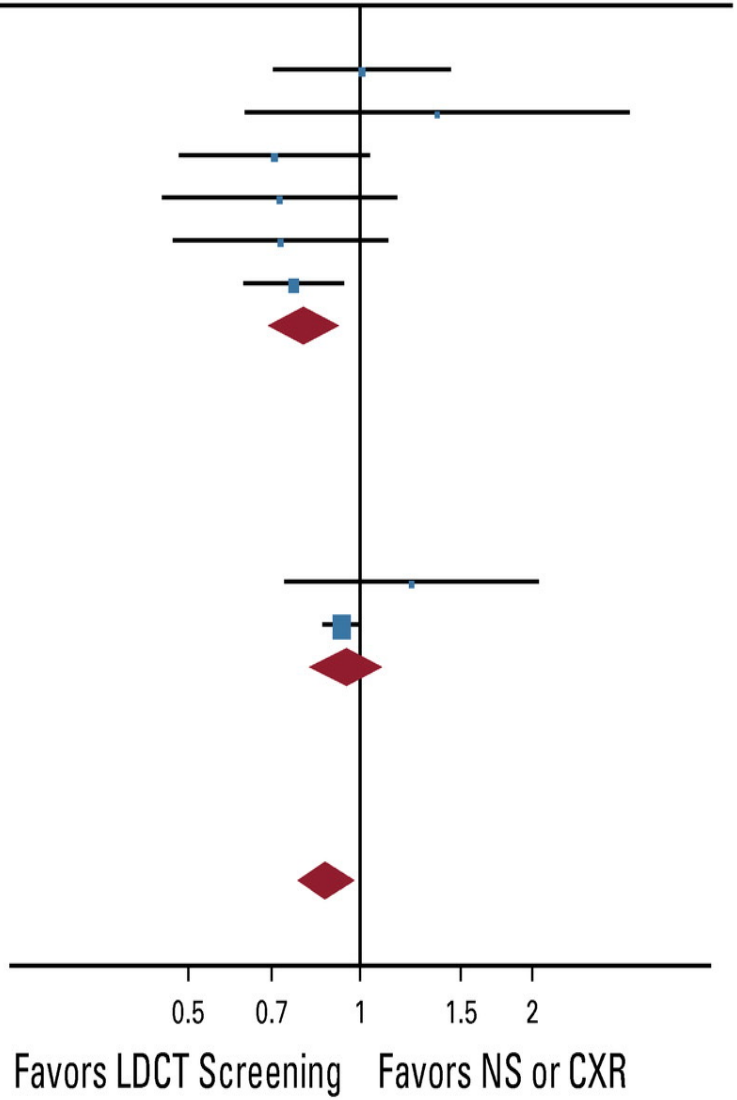
Benefits and Harms of Lung Cancer Screening by Low Dose CT in the General Population
A Meta-Analysis

Passiglia F et al J Clin Oncol 2021

Study or Subgroup	LDCT Screening Events	LDCT Screening Total	NS or CXR Events	NS or CXR Total	Weight (%)	RR M-H, Random (95% CI)
LDCT *v* NS						
DANTE	59	1,264	55	1,186	8.8	1.01 (0.70 to 1.44)
DLCST	15	2,052	11	2,052	2.2	1.36 (0.63 to 2.96)
ITALUNG	43	1,613	60	1,593	7.8	0.71 (0.48 to 1.04)
LUSI	29	2,029	40	2,023	5.4	0.72 (0.45 to 1.16)
MILD	40	2,376	40	1,723	6.3	0.73 (0.47 to 1.12)
NELSON	160	6,583	210	6,612	20.6	0.77 (0.62 to 0.94)
Subtotal (95% CI)		**15,917**		**15,189**	**51.1**	**0.80 (0.69 to 0.92)**
Total events	346		416			
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 4.33$, $df = 5$ ($P = .50$); $I^2 = 0\%$						
Test for overall effect: $Z = 3.16$ ($P = .002$)						
LDCT *v* CXR						
LSS	32	1,660	26	1,658	4.7	1.23 (0.74 to 2.05)
NLST	1,147	26,722	1,236	26,730	44.2	0.93 (0.86 to 1.00)
Subtotal (95% CI)		**28,382**		**28,388**	**48.9**	**0.95 (0.82 to 1.10)**
Total events	1,179		1,262			
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 1.13$, $df = 1$ ($P = .29$); $I^2 = 11\%$						
Test for overall effect: $Z = 0.71$ ($P = .48$)						
Total (95% CI)		**44,299**		**43,577**	**100.0**	**0.87 (0.78 to 0.98)**
Total events	1,525		1,678			
Heterogeneity: $\tau^2 = 0.01$; $\chi^2 = 9.21$, $df = 7$ ($P = .24$); $I^2 = 24\%$						
Test for overall effect: $Z = 2.30$ ($P = .02$)						
Test for subgroup differences: $\chi^2 = 2.83$, $df = 1$ ($P = .09$); $I^2 = 64.6\%$						



Low Dose CT benefits outweigh harms including overdiagnosis (38%).
Better lung nodule management is mandatory

Benefits and Harms of Lung Cancer Screening by Low Dose CT in the HIV Population
Major Studies on Lung Cancer Screening

- **Simulation model-** For HIV-infected patients with CD4 count at least 500/µL and 100% cART adherence, lung cancer screening using the old criteria (age 55-80 yrs,30 pack-year of smoking, current smokers or quit within 15 years) would reduce lung cancer mortality by 19%, similar to the mortality reduction on the general population. (*Kong CY et al AIDS 2018)*

- **Baltimore study** (2006-2013): Elegibilty criteria: age at least 25 yrs, 20 pack-year of smoking, current smokers or quit within 15 years) . Low adherence: only 1 TC scan:8%, 2 TC:46%, 3 TC :20%, 4 TC :17%, 5 TC 9%- (*Hulbert A J Thorac Oncol 2014*)

ANRS Study (2011-2012)- Elegibilty criteria: at least 40 yrs, 20 pack-year of smoking, current smokers or quit within 3 years) and CD4 count at least 100.Lung cancer:10/442 (2%) patients ;false positive rate 21% (*Makinson A AIDS 2016*)

Programmi di screening per la popolazione generale .

Tumore	Popolazione	Procedure di screening	Tempistiche dello screening	commenti
Mammella	Donne 50-70 aa (E) Donne ≥ 40 aa (A)	Mammografia	1-2 aa (E) Annuale (A)	Autopalpazione dopo i 20 aa Esame clinico fra 20-30 aa, minimo ogni 3 aa
Colon-retto	Tutti tra 50-75 aa (E) ≥50 aa (A)	°Ricerca sangue occulto feci °°Rettosigmoidoscopia §Rettocolonscopia	°ogni 2 aa °°ogni 5 aa §ogni 10 aa	Particolare attenzione nel monitoraggio dei pazienti a rischio (familiarità per ca colon-retto, poliposi intestinale e malattie infiammatorie del grosso intestino).
Prostata	Uomini ≥ 50 aa	Esame rettale + PSA test	Annuale	- Beneficio ancora controverso - Candidati se spettanza di vita ≥10 aa

E: linee guida europee; A: linee guida americane

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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 ≤26 yrs)

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Estimated Hazard Ratio for serious Events in Immediate-Initiation vs Deferred-Inititation Groups- (The INSIGHT START Study Group)

Serious Endpoints	Hazard Ratio	(95 % CI)
AIDS events	0.28	(0.15-0.50)°
Non-AIDS events	0.61	(0.38-0.97)°
Kaposi Sarcoma	0.09	(0.01-0.71)*
Infectious-related Cancers	0.26	(.11-.64)•
Infectious-unrelated Cancers	0.49	(0.21-1.15) ••

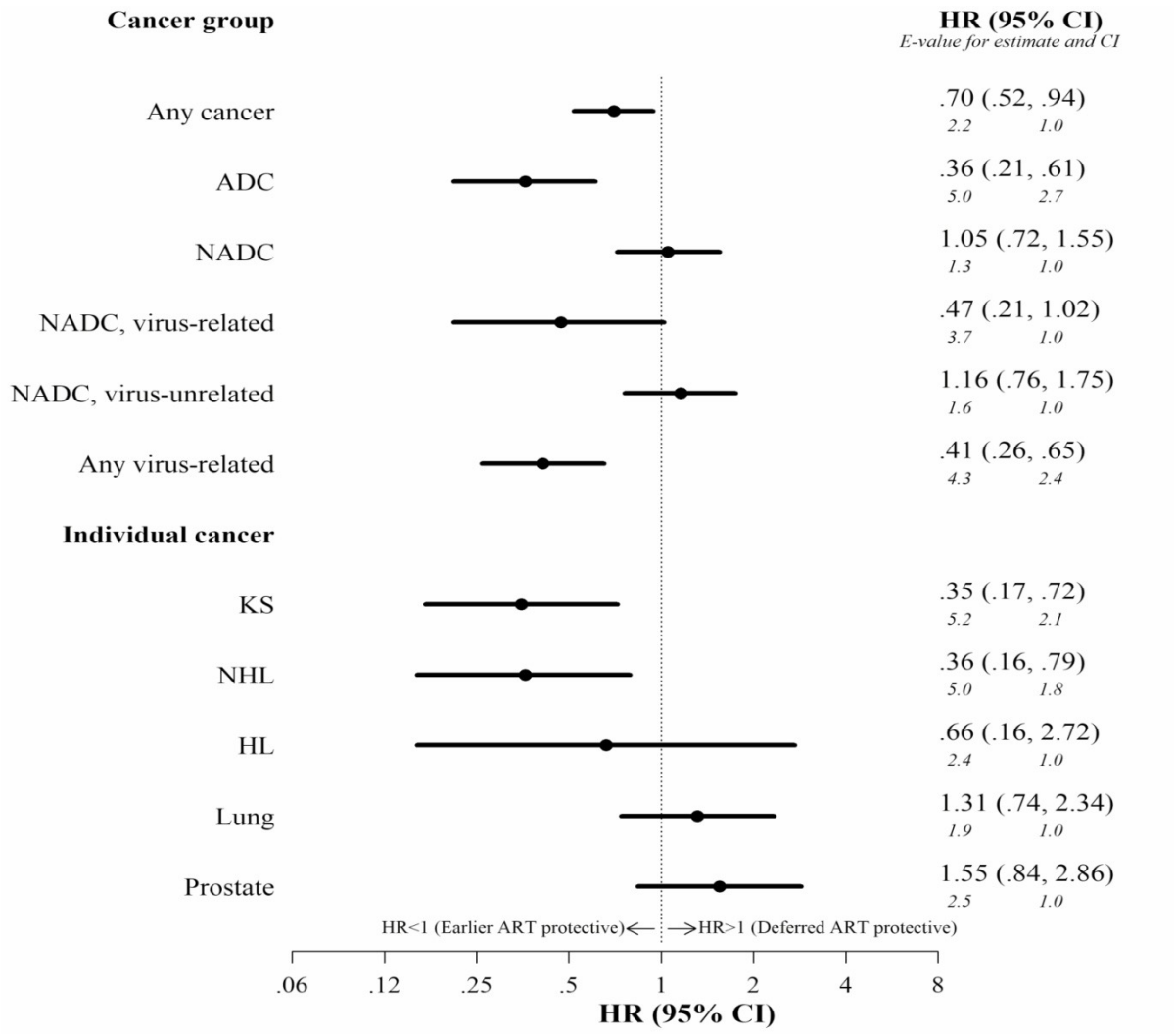
°p>0.001,*p=0.05; •0.003 ••0.10

The initiation of cART in HIV-Infected adults with CD4>500/µL provided net benefits over starting therapy after the CD4 had declined to 350/µL

Borges AM et al CID 2016

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

HPV Vaccination in HIV Infection

Although the evidence base to support the immunogenicity of HPV vaccines in HIV-infected persons is high, the evidence base to support the efficacy of HPV vaccines in all HIV-infected individuals is a controversial issue.

In one recent study, 18-26-yrs old HIV-positive MSM naïve to HPV vaccine types were protected against incident HPV16 associated LSILs/HSILs compared with those previously exposed to HPV.

Therefore, there is an urgent need to vaccinate young individuals, before exposure to HPV vaccine-type, before initiating sexual activity.

Several studies in HIV-infected individuals have shown superior immunogenicity of Bivalent Vaccines (which uses a TLR4 agonist adjuvant) compared to 4-valent vaccines. Therefore,questions remain as to optimal HPV vaccine regimens in HIV and further clinical trials are urgently needed