

AGGIORNAMENTI INFETTIVOLOGICI: HIV, EPATITI &....

Congresso Nazionale

The Evolving Features of HIV-related Cancers focus on Preventive Strategies

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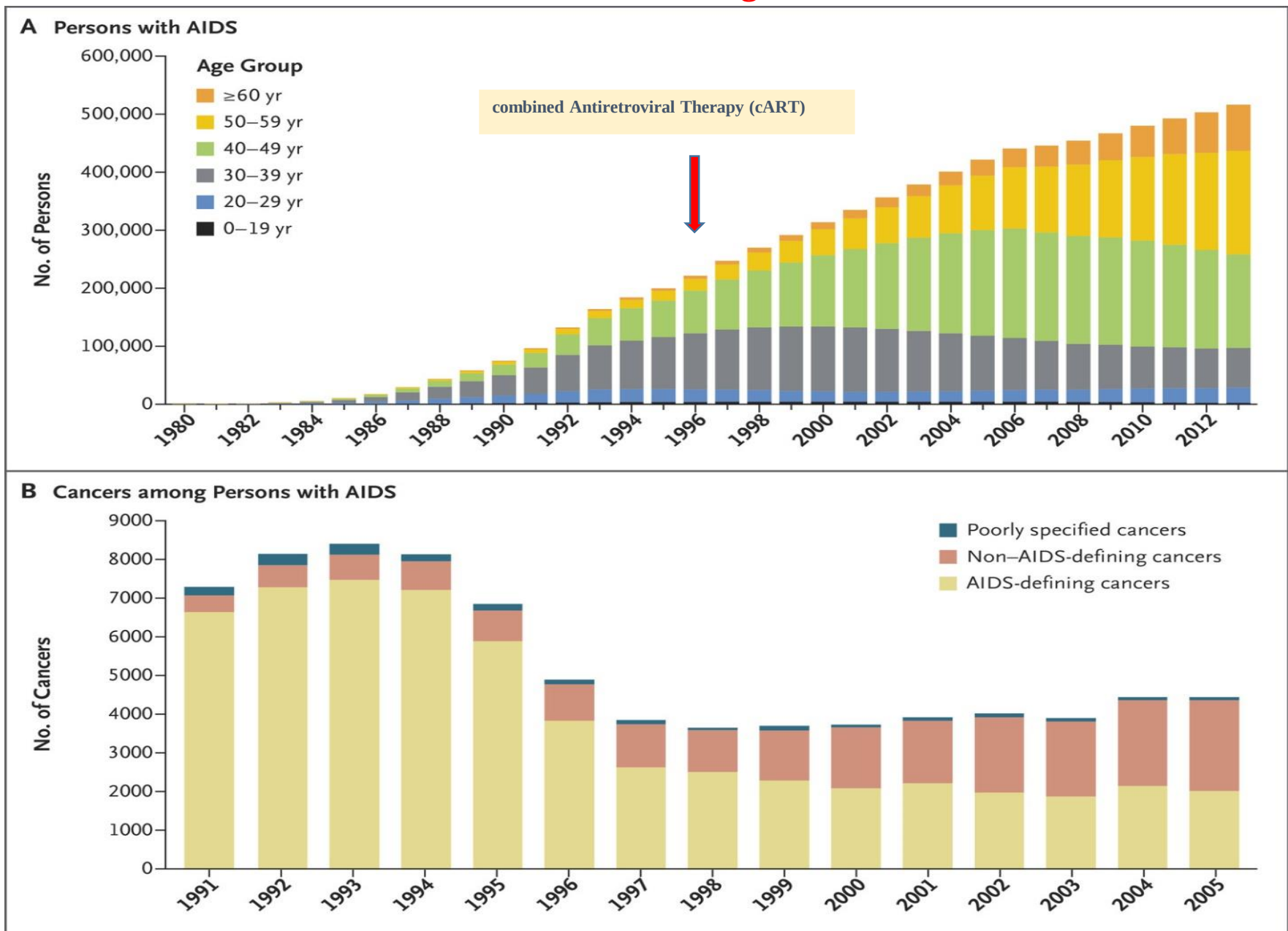
Firenze 2024

HIV-related Cancers

Background

- The epidemiology of HIV disease has evolved in the cART era
- The incidence and morbidity of AIDS-defining cancers has decreased, whereas morbidity and mortality of NADCs has increased
- People living with HIV (PLWH) have a markedly increased risk of anal, liver, lung cancer and of other HPV-associated malignancies including Head-Neck cancers
- Understanding the changing patterns of HIV-related malignancies will direct screening and treatment strategies to ensure optimal outcomes for PLWH

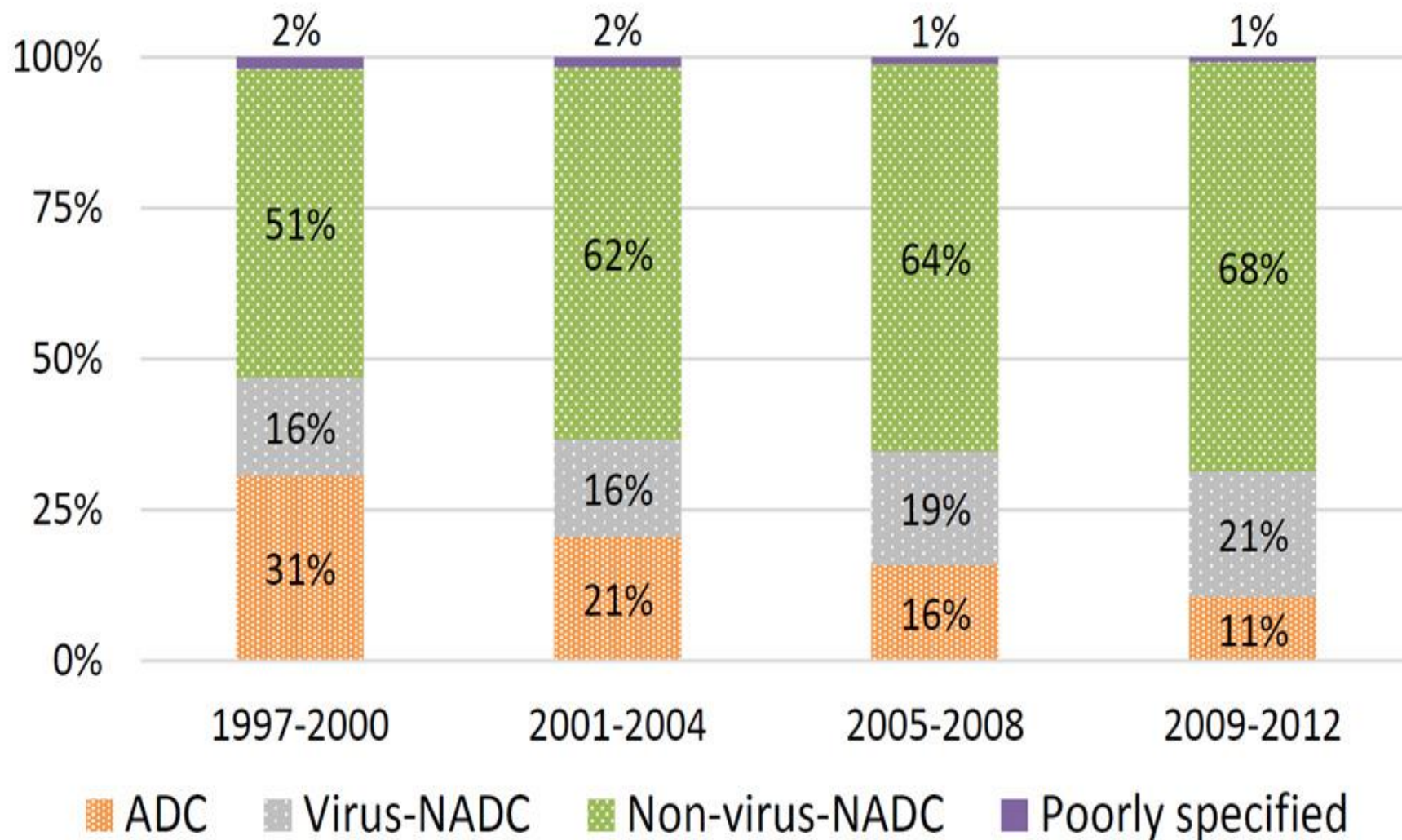
Trends in AIDS and in Cancers among Persons with AIDS.



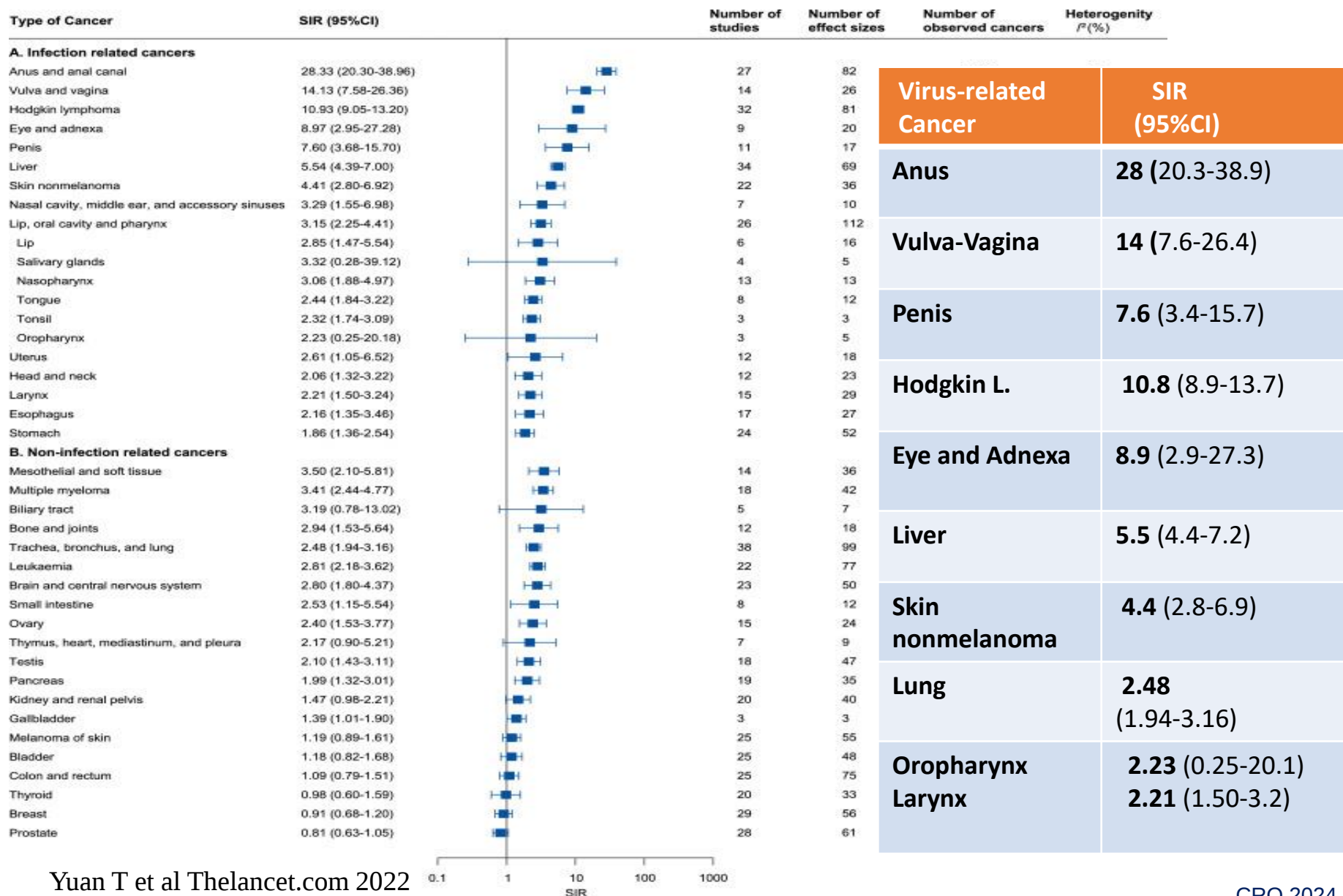
Hleyhel M. et al. CID 2013, Shiels MS et al Natl Cancer Inst 2011, Robbins H.A et al. AIDS 2015, R. Yarchoan, TS Uldrick. N Engl J Med 2018

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



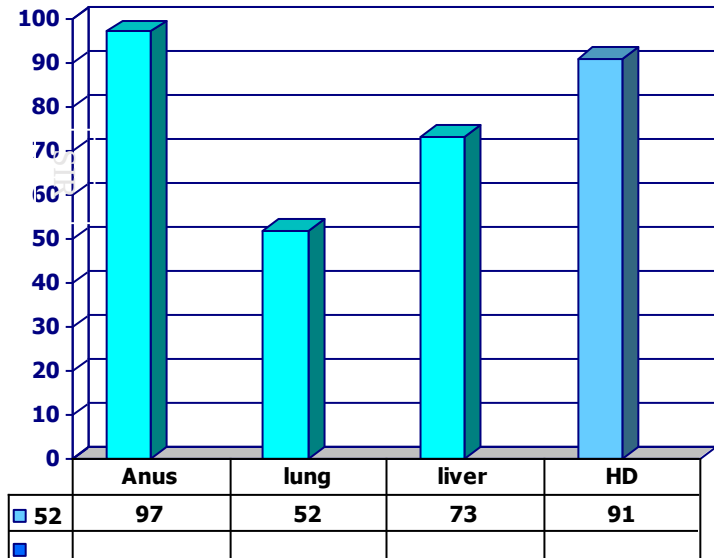
Meta-analysis of Standardized Incidence Ratio (SIR) for non-AIDS-defining Cancers among People Living with HIV(PLWH) (1992-2022)



Excess Cancers Among 859,522 people living with HIV in the United States (2010)

NADCs

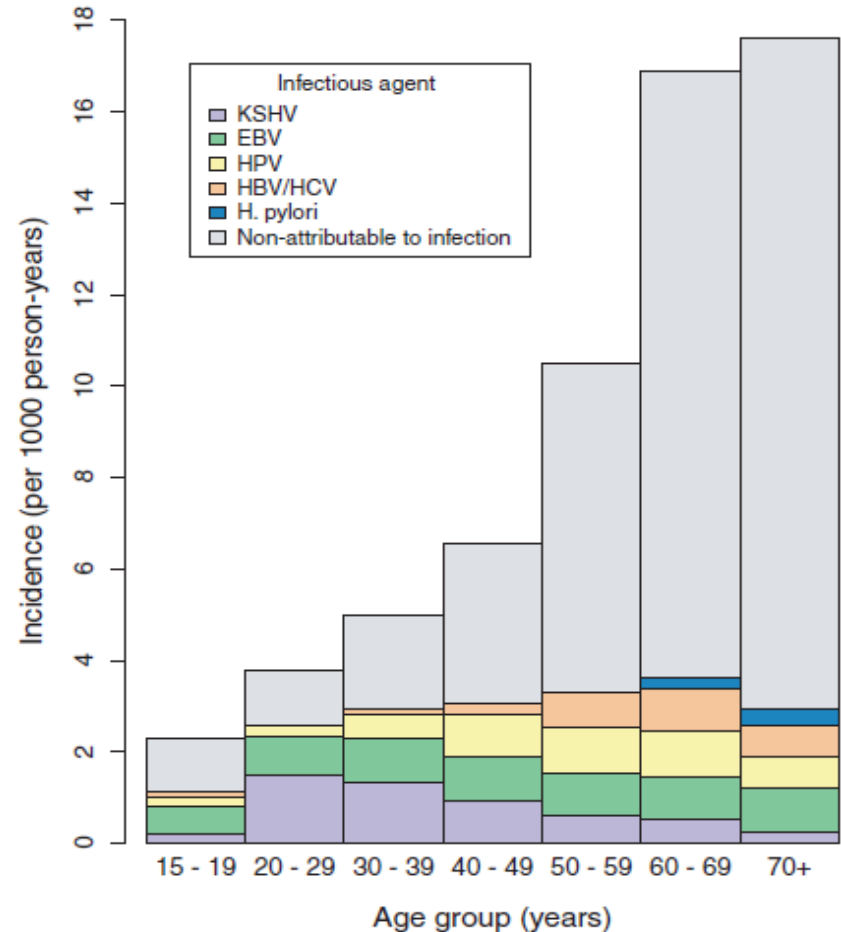
Excess of Non-AIDS-Defining Cancers %



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)

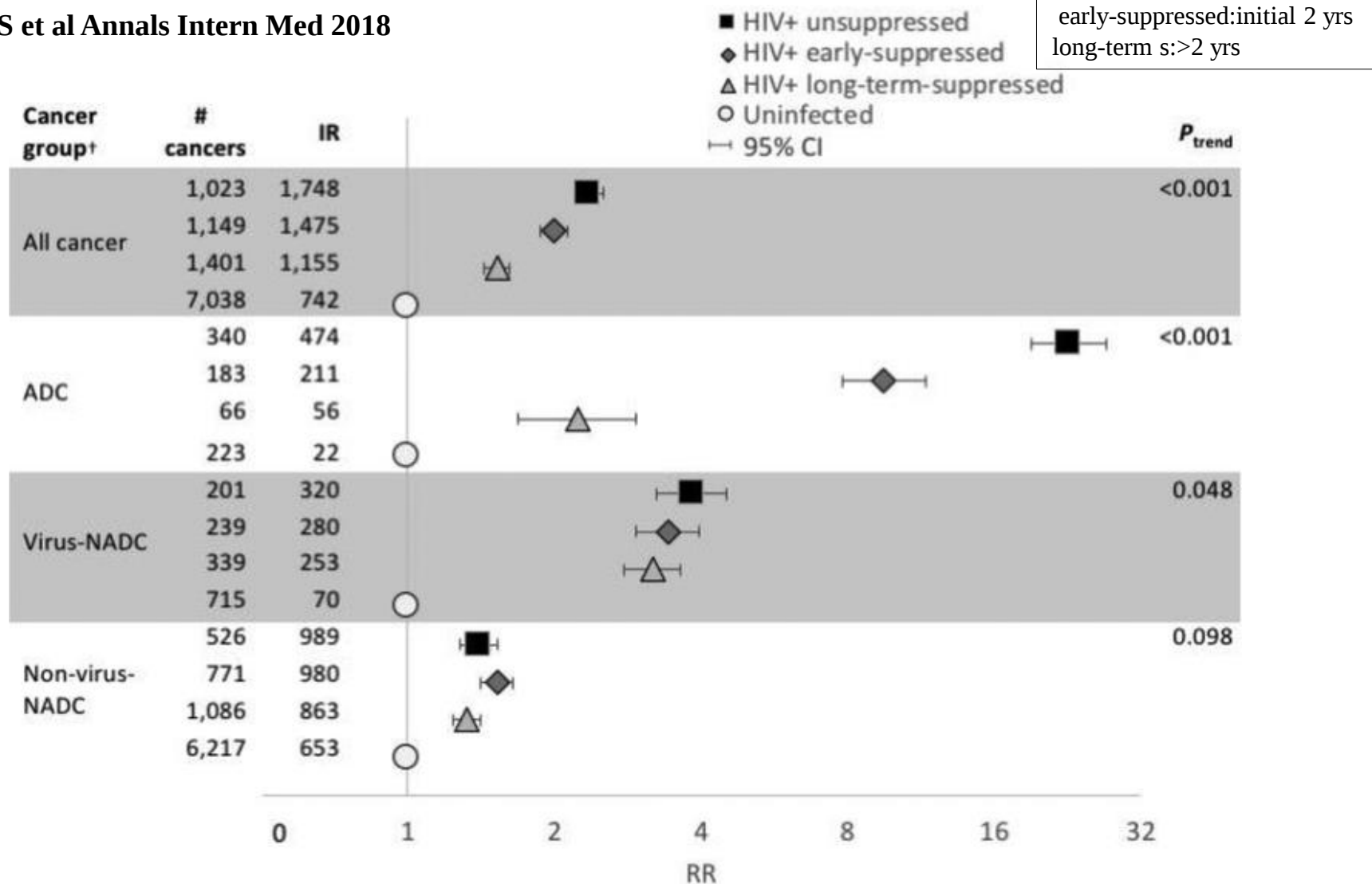


The incidence rate of cancer nonattributable to infection, including breast and prostate cancers steeply increased with age,.

de Martel C et al AIDS 2015

Viral Suppression is Associated with Decreased Cancer Incidence in the Veteran Prospective Cohort (1999-2015)

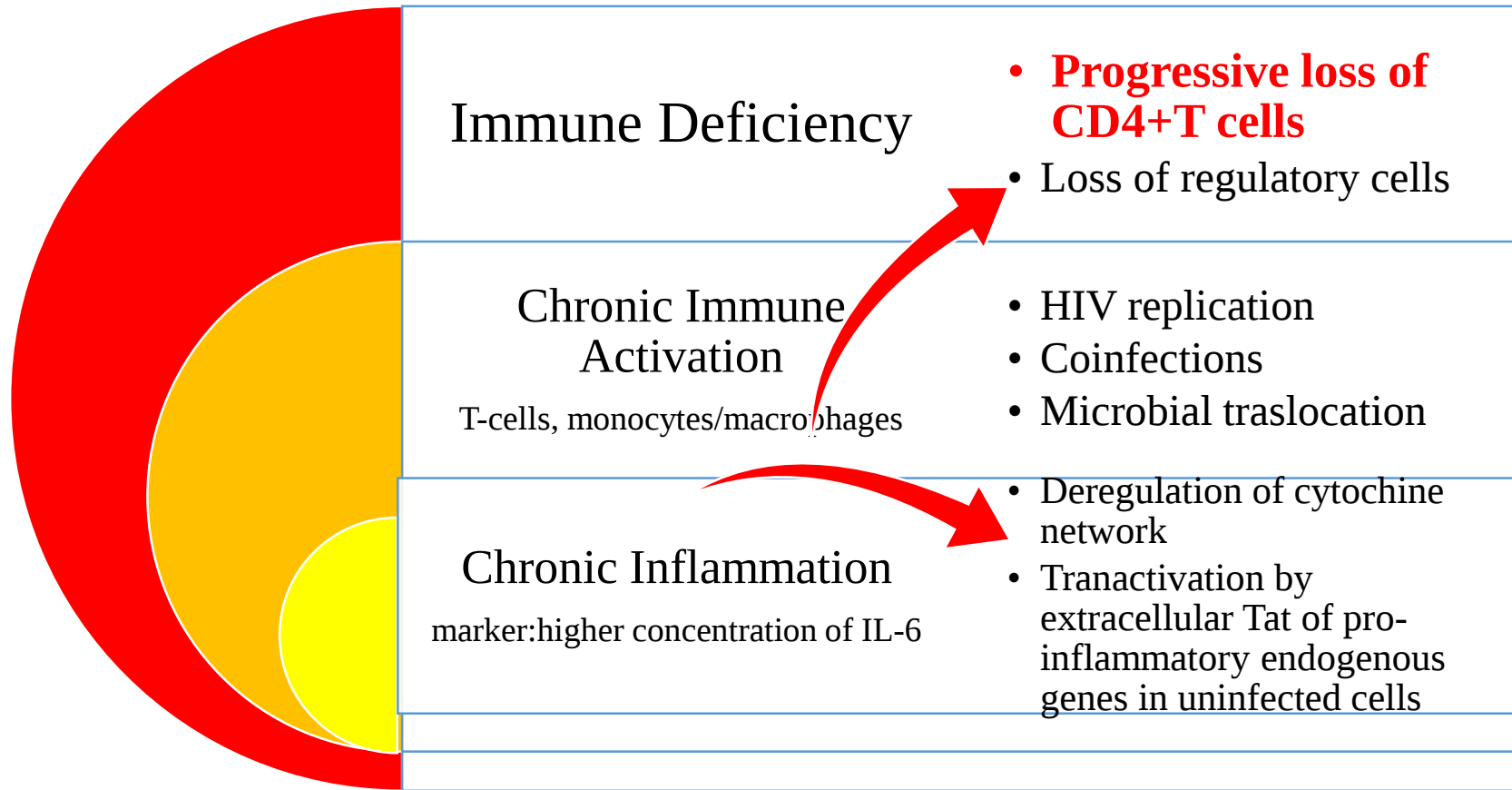
Park LS et al Annals Intern Med 2018



Long-term HIV suppression was associated with a >90% reduction in excess ADC risk, but only 20% reduction in excess virus-related NADCs and no trend for non-virus- NADCs. Excess cancer risk remained among PLWH with long-term suppression compared to HIV-negative patients.

Major Features of HIV Pathogenesis

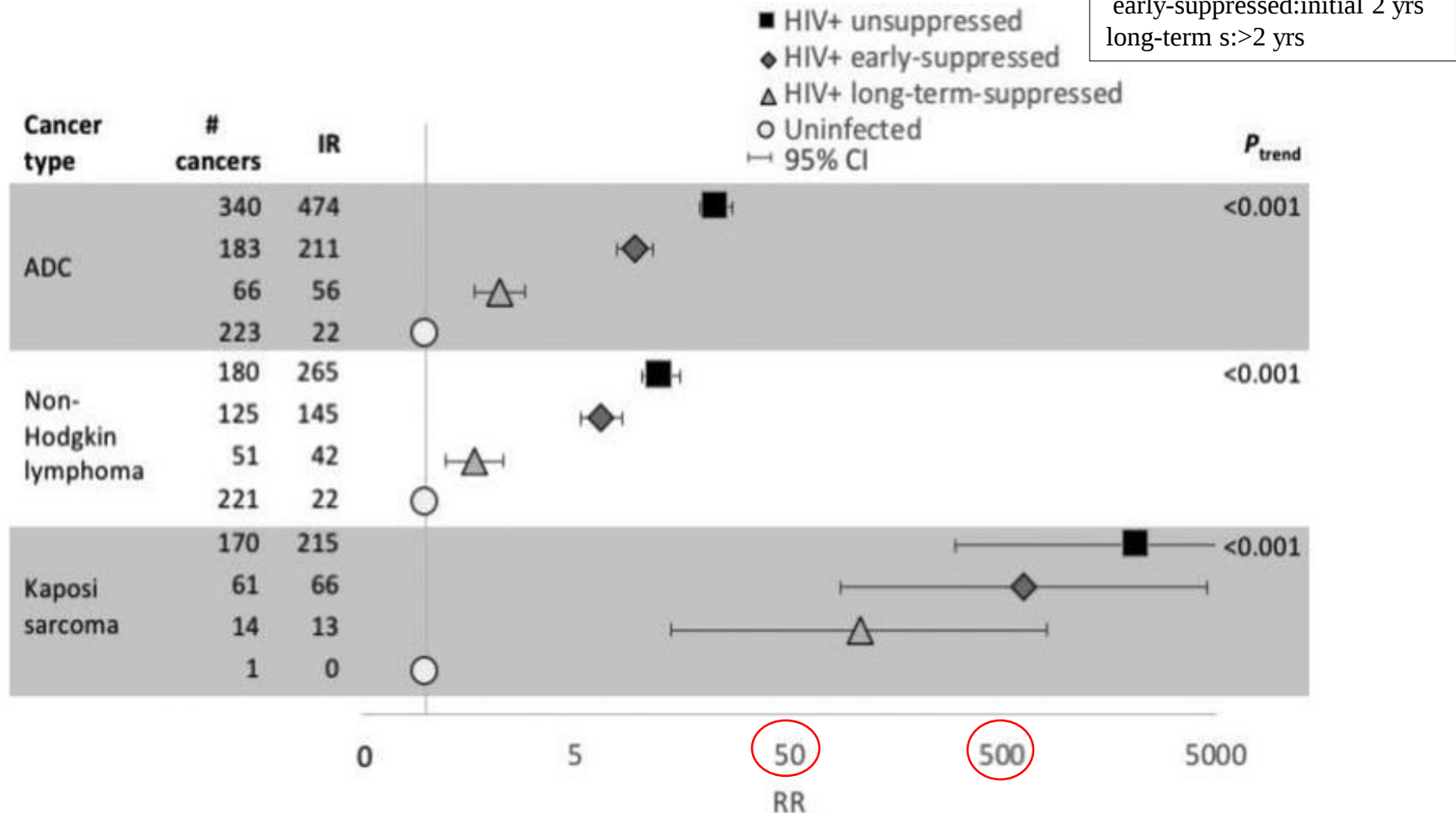
HIV primarily establishes a lytic infection in activated CD4+Tcells and a latent infection in monocytes/macrophages, dendritic cells, glial cells and resting CD4+ T cells



Deeks S et al Lancet 2013, Deeks S et al Immunity 2013, Kumar A et al Clin Epigenetics 2015, Younas M HIV Med 2016,

Viral Suppression is Associated with Decreased Cancer Incidence in the Veteran Prospective Cohort (1999-2015)

Park LS et al Annals Intern Med 2018



The risk of Kaposi Sarcoma as compared to HIV-uninfected patients was still more than 50-fold in PLWH despite long-term viral suppression and more than 500-fold in those with early-suppression.

Deleterious effects of HIV infection persist in the presence of long-term cART, such as chronic immune activation/inflammation or immune-senescence.

Standardized Incidence Ratio (SIR) for AIDS-Defining Cancers in PLWH on cART with CD4 $\geq$ 500/ μ L and Persistent ($\geq$ 2yrs) Controlled HIV Viremia

Results from the FHDH-ANRS CO4 Cohort (France 1992-2009)

Cancer Type	N° of PY o HIV Patients	IR in HIV-pos.Pts (95%CI) per 100.000 PY	IR in HIV-neg Pts (95%CI) per 100.000 PY	SIR (95 % CI)
Kaposi Sarcoma	55.633	21.6 (11.2-37.7)	0.6 (5-6)	35.4 (18.3-61.9)
NHL	56.493	15.9 (7.3-30.2)	13.8 (13.5-14.1)	1 (0.4-11.8)
Cervical cancer	14.825	20.2 (4.2-59.1)	12.9 (12.5-13.4)	

PY:person-year; IR: Incidence Rate;

In PLWH with restored immunity and persistent controlled HIV viremia, the risk remained significantly elevated for Kaposi Sarcoma and was similar to that of the general population for NHL

Hleyhel M et al CID 2013

CD4/CD8 Ratio and the Risk of Kaposi Sarcoma in 56.708 HIV-Suppressed PLWH. 20 European Cohort Studies (2000-2014)

Caby F et al CID 2021

	Whole population (221 incident KS)	PLWH with CD4>500 at baseline (65 incident KS)
Immune-Virological Factors	Adjusted °Hazard Ratio (95% CI)	Adjusted° Hazard Ratio (95% CI)
CD4/CD8 Ratio from baseline*:		
CD4/CD8:1	1	1
CD4/CD8: 0.8	1.18 (0.98-1.42)	1.38 (1.00-1.91)
CD4/CD8: 0.5	1.64 (1.10-2.45)	2.35 (1.33-4.14)
CD4/CD8: 0.3	2.02 (1.23-3.31)	3.27 (1.60-6.56)
CD4 count/μL from baseline*		
350	1.57 (1.09-2.25)	1.81 (1.04-3.14)
500	1	1
800	0.68 (0.39-1.20)	0.49 (0.22-1.09)
1000	0.74 (0.38-1.45)	0.33 (0.11-0.97)
Virological Failure from baseline	2.77 (1.90-4.06)	2.69 (1.31-5.29)

°adjusted for age,sex,risk group,calendar period of cART and virological failure; *within 6 monthsfollowing virological control

HIV-related immune activation, reflected by CD4/CD8 ratio,may contribute to Kaposi Sarcoma development in PLWH on efficient cART

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

Major features:

- High prevalence of systemic symptoms
- High HHV8 viral load
- Rapidly progressive KS
- High mortality
- Treatment: chemotherapy and/or immunotherapy +cART

Major features:

- Skin and visceral involvement
- Aggressive course
- Good prognosis in the cART era

Major features:

- *KS progression or unmasking KS
- *Prevalence:10-40%
- *Aggressive clinical course
- *High mortality
- *Treatment: immediate chemotherapy +cART

Major features:

- *Prevalence 19-20%
- *Chemotherapy refractory /relapsing disease

**KS+KICS
KS+MCD
KS+PEL**

**Low CD4 count
and/or high
HIV viremia**

IRIS-KS

**KS with high
CD4 count
and
undetectable
HIV-RNA**

Immunodeficiency

Chronic Immunoactivation

Kaposi Sarcoma in Virally Suppressed People Living with HIV and with High CD4 count

The proportion of KS cases occurring in virally suppressed PLWH and with high CD4 count is rising in the cART era

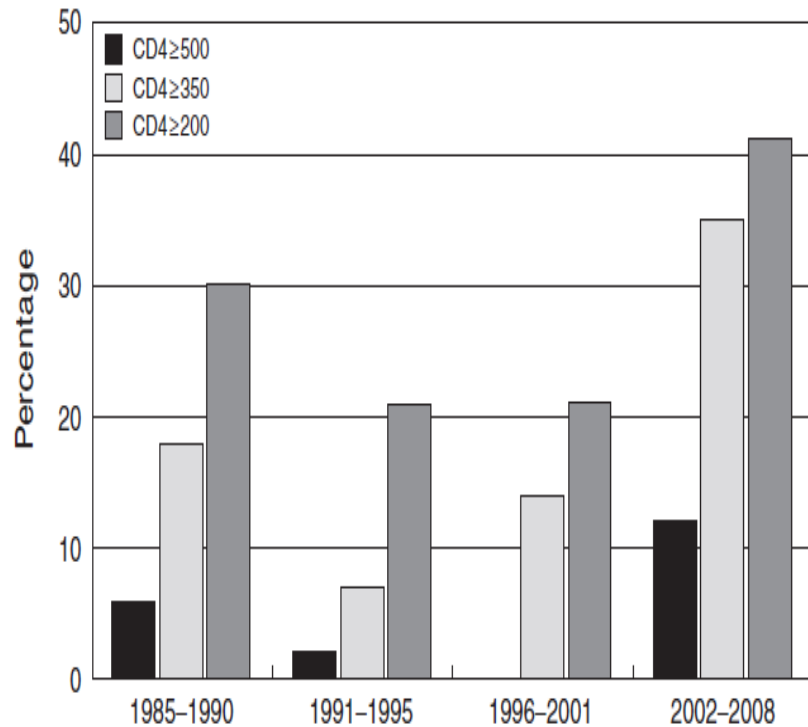


Fig. 1. CD4 cell count at diagnosis of Kaposi's sarcoma during the course of the HIV epidemic (1985-2008).

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

Kaposi Sarcoma in Virally Suppressed PLWH with High CD4 Count Major Case Series-I

	Mani D (2009)	Palich R (2020)	Severin D (2021)
Total n°	20	21	12
Sex: M/F n°	19/1	17/4	12/12
Age ,yrs, median	42 (25-69)	54 (35-61)	54 (38-60)
CD4 Count/μL (range)	483 (300-625)	449 (211-625)	723 (520-881)
CD4 /μL nadir, median	216 (4-431)	196 (81.329)	NA
cART Duration, median	5 yrs (1-12)	≥12 months	NA
Site of Disease n° (%)			
Skin	12 (60)	21 (100)	12 (100)
Lymph nodes	0	6 (27)	1 (8)
Visceral involvement	8 (40)	11 (52)	1 (8)

Mani DJ et al Int Assoc Physicians AIDS Care 2009; Palich R et al CID 2020; Severin D et al AIDS 2021

Kaposi Sarcoma in Virally Suppressed PLWH with High CD4 Count Major Case Series-II

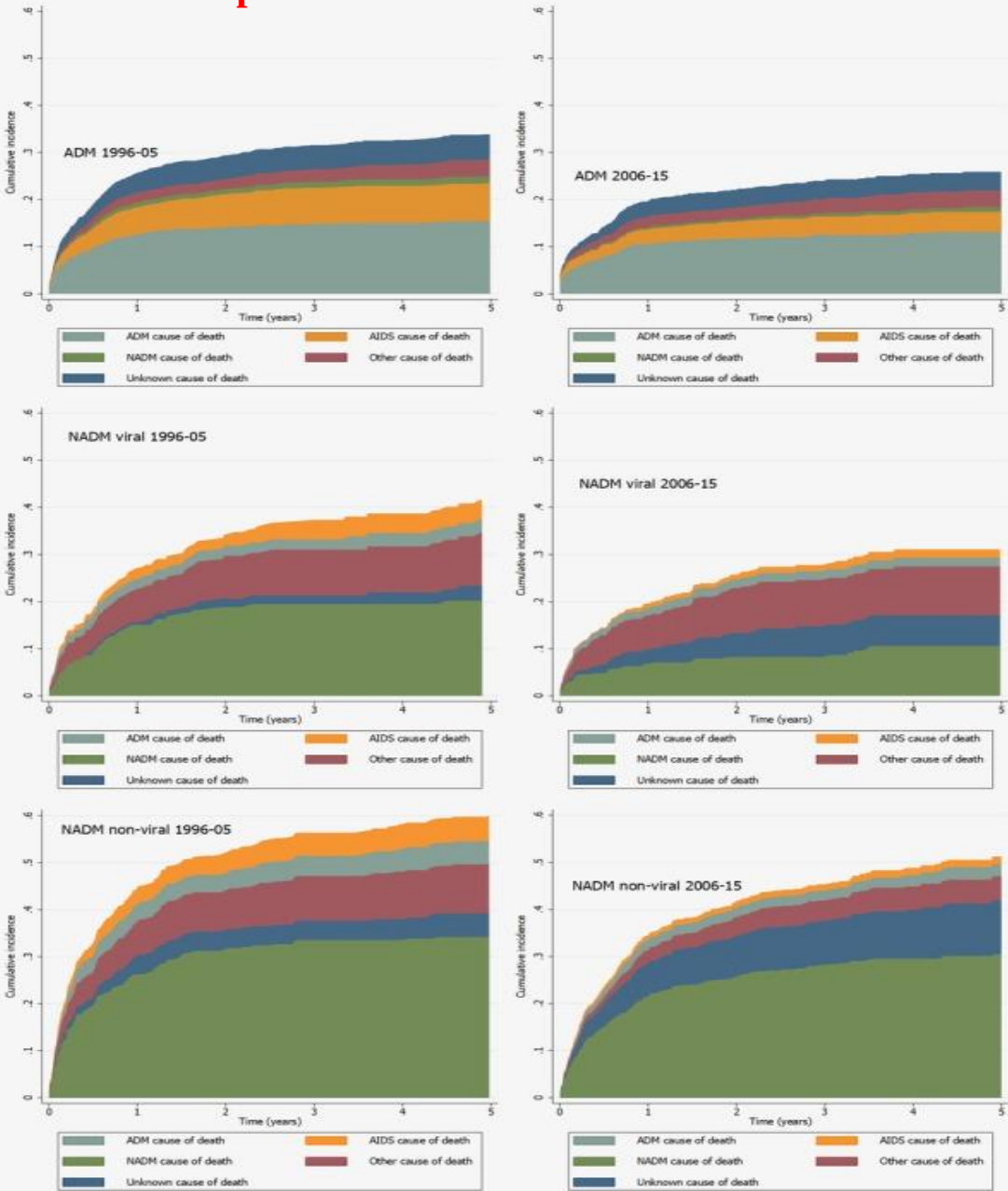
	Mani D (2009)	Palich R (2020)	Severin D (2021)
Total n°	20	21	12
Treatment: n° (%)			
Chemotherapy	14 (70)	21 (100)	2 (17)
Local Therapy	4 (20)	1 (5)	4 (33)
Response: n° (%)			
CR	13 (65)	6/16 (37)	NA
SD	4 (20)	6/16 (37)	
NR	3 (15)	4 (25)	
Followup Duration Media,mos	39 (6-120)	17 (9-20)	NA
Recurrences n° (%)	NA	13 (65)	NA

KS in virally suppressed HIV patients represents a clinical and biological entity that is still poorly understood. These clinical forms are a therapeutic challenge without short-term improvement of anti-HHV8 immunity and no active replication of HIV to control.

Survival of major HIV-Cancer

What is the natural history of cancers in HIV-suppressed PLWH on cART?

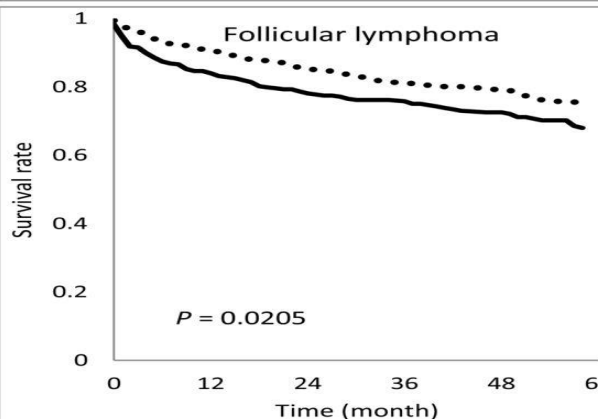
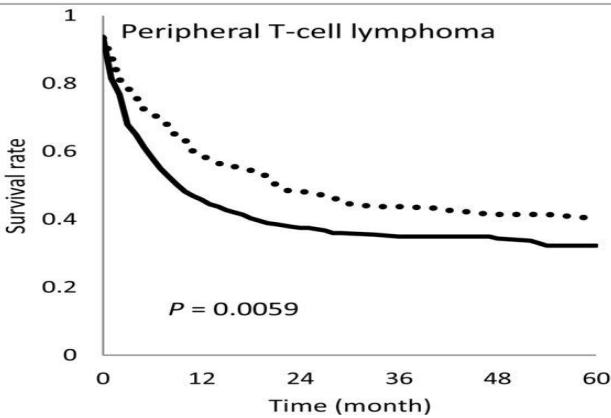
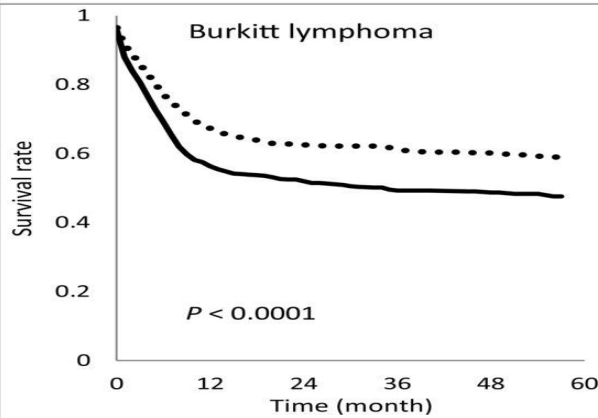
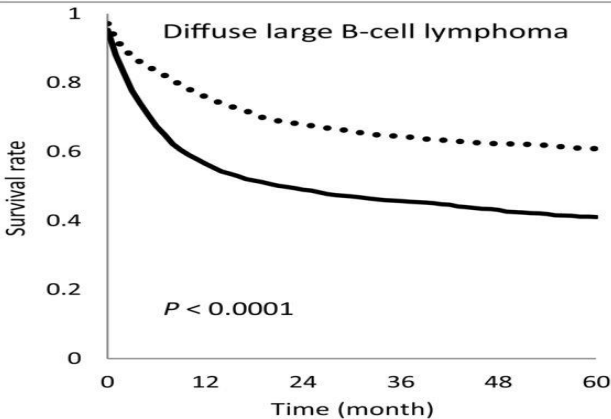
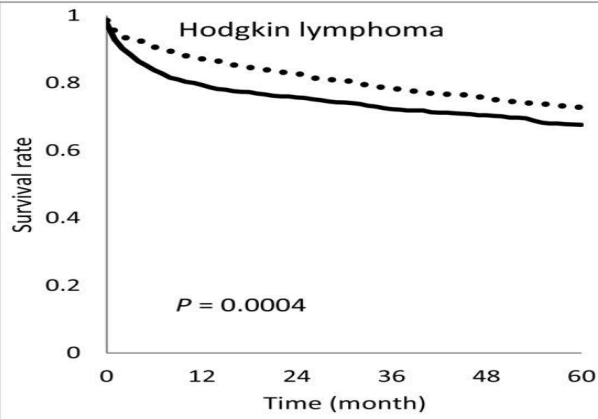
Cause-specific Mortality after Diagnosis of Cancer among 83,585 HIV-positive Patients: 10 Cohort Studies from Europe and North America: 4.436 incident cancers (Mortality Rate Ratio, MRR)



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 (0.70-1.00)

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

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

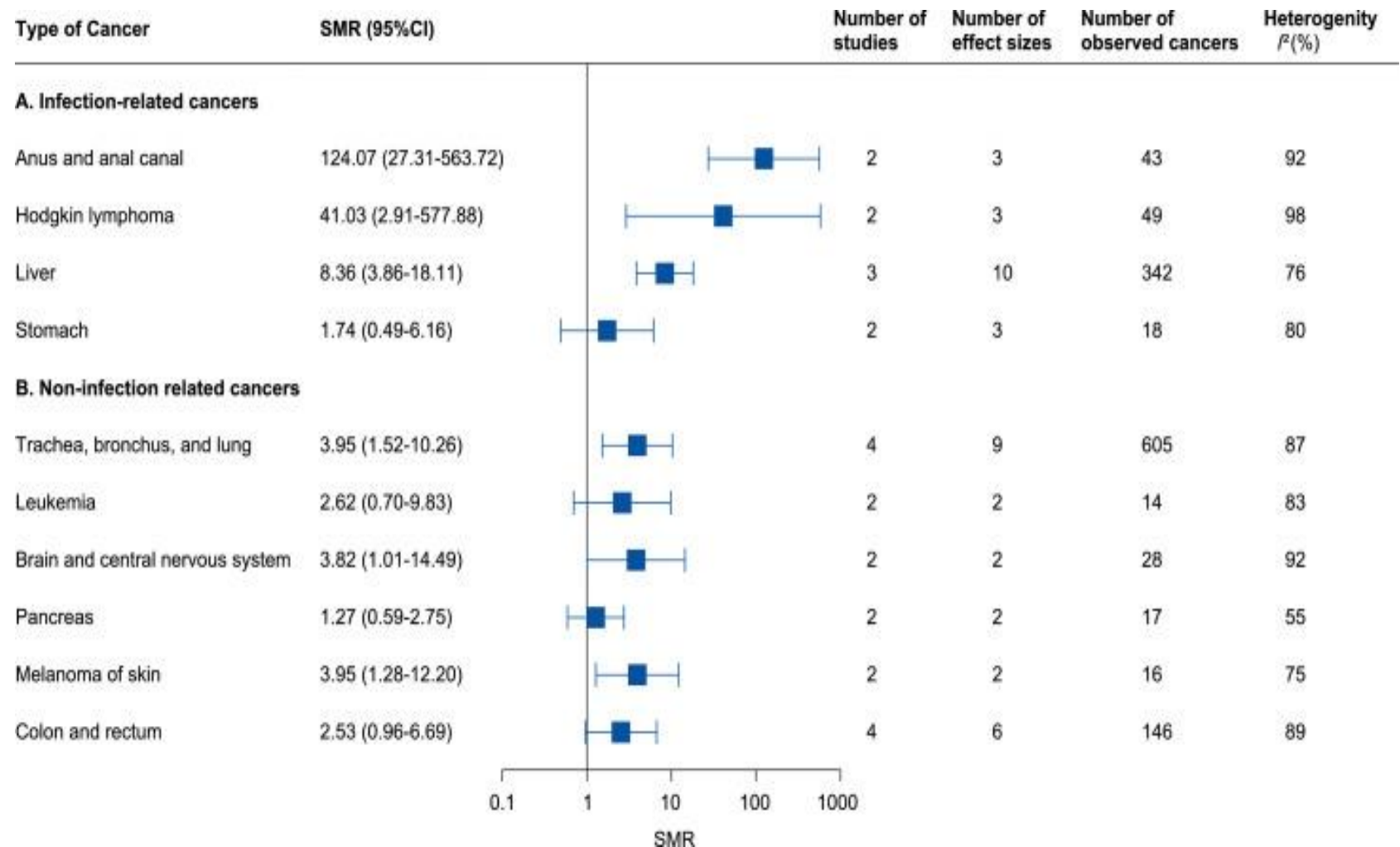


..... Non-HIV infection
—— HIV Infection

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

* $p < 0.0001$

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



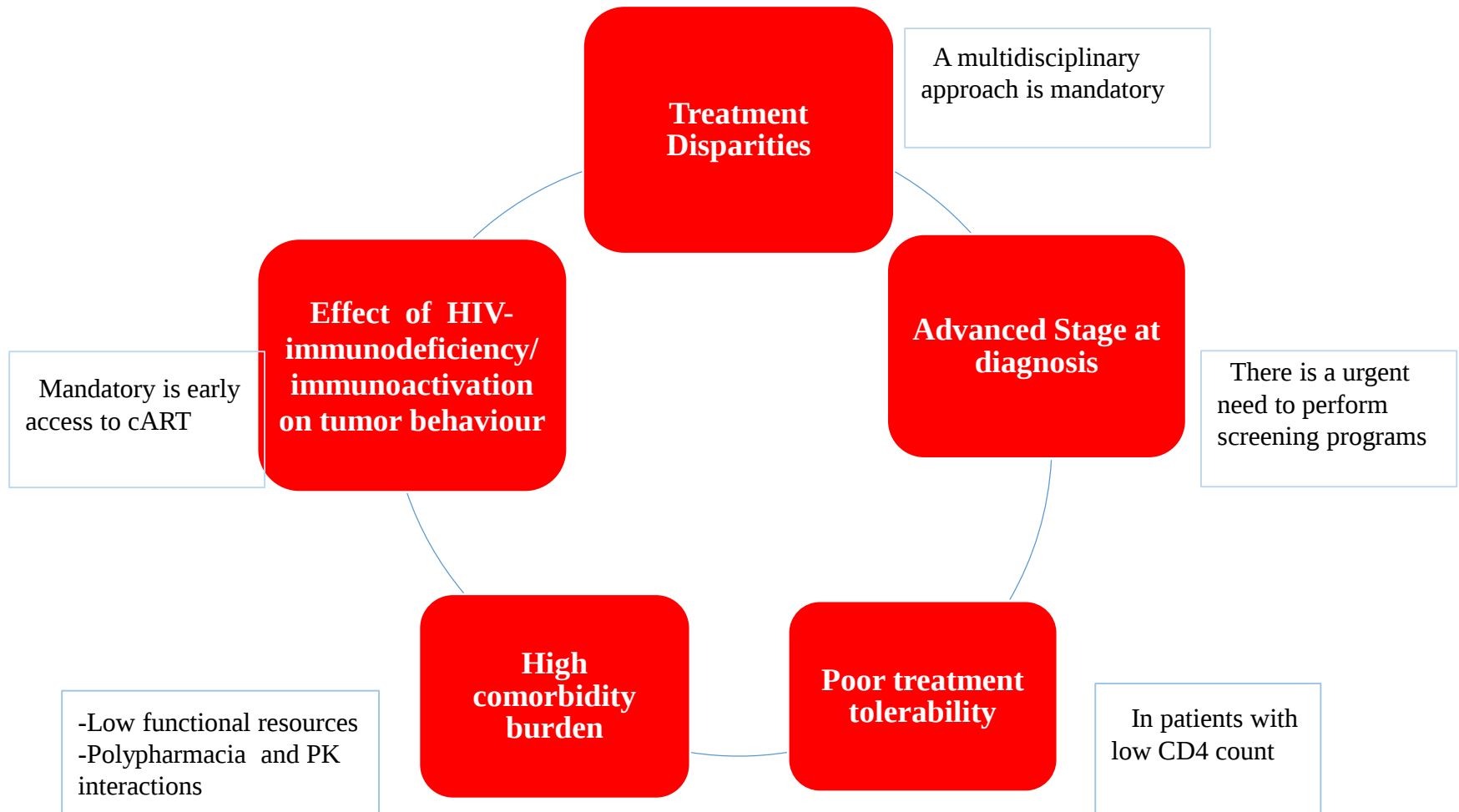
Outcomes after Cancer Diagnosis for HIV-Infected Patients
compared to the General Population

Chiao E et al Lancet Oncol 2021

Cancer	Overall 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)

HIV was not associated with increased cancer-specific mortality for Anal cancer, Liver Cancer and Head-Neck cancer.

Major Causes of Poor Cancer Outcomes in HIV Population



Treatment Guidelines for HIV-related Cancers

Treatment Strategies

The treatment strategy for cancers in patients receiving effective cART should not be influenced by HIV status

All PLWH with cancer must receive cART during antineoplastic treatment

PLWH with cancer should not be excluded from cancer clinical trials of the general population.

HIV-Specific Issues

Potential pharmacokinetic interactions between cART and anticancer or supportive care drugs

The need to maximize supportive care, particularly prophylaxis against opportunistic infections and support with hematopoietic growth factor, in high risk patients

The management of comorbidity in aging PLWH
(Alert: higher comorbidity rate in PLWH compared to general population)

HIV-related Solid Tumours

focus on

Screening Programs and Preventive Strategies

Major Features:

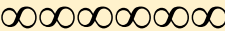
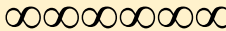
- Few trials for cancer prevention have been done to provide guidance on HIV-specific surveillance programs for patients with solid tumours.
- European and US guidelines recommended cancer screening that is appropriate for age and risk factors
- New target population: Long-term survivor patients with prior malignancies

Programmi di screening per la popolazione generale .

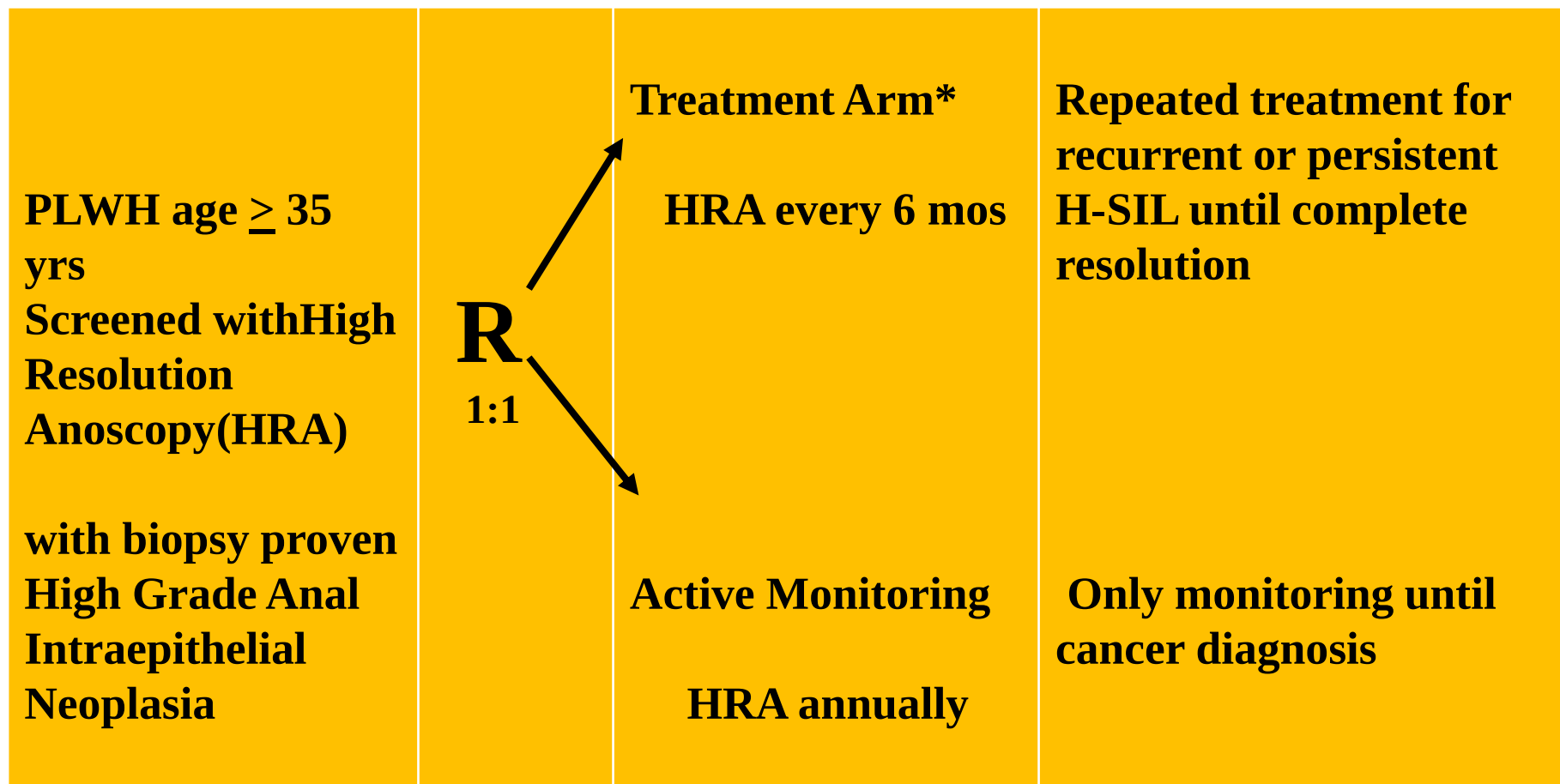
Tumore	Popolazione	Procedure di screening	Tempistiche dello screening	commenti
Mammella	Donne 50-70 aa (E) Donne ≥ 40 aa (A)	Mammografia	1-2 aa (E) Annuale (A)	Autopalpazione dopo i 20 aa Esame clinico fra 20-30 aa, minimo ogni 3 aa
Colon-retto	Tutti tra 50-75 aa (E) ≥ 50 aa (A)	°Ricerca sangue occulto feci °°Rettosigmoidosco pia §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 aspettanza di vita ≥ 10 aa

E: linee guida europee; A: linee guida americane

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	-PAP test convenzionale -PAP test su base liquida Anoscopia ad alta risoluzione	*Annuale, se 2 esami consecutivi neg Se Pap test patologico	Elevata (categoria 1)
 MSM*	 Anoscopia ad alta risoluzione		

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

Screening Carcinoma Cervice Uterina in HIV- Linee Guida

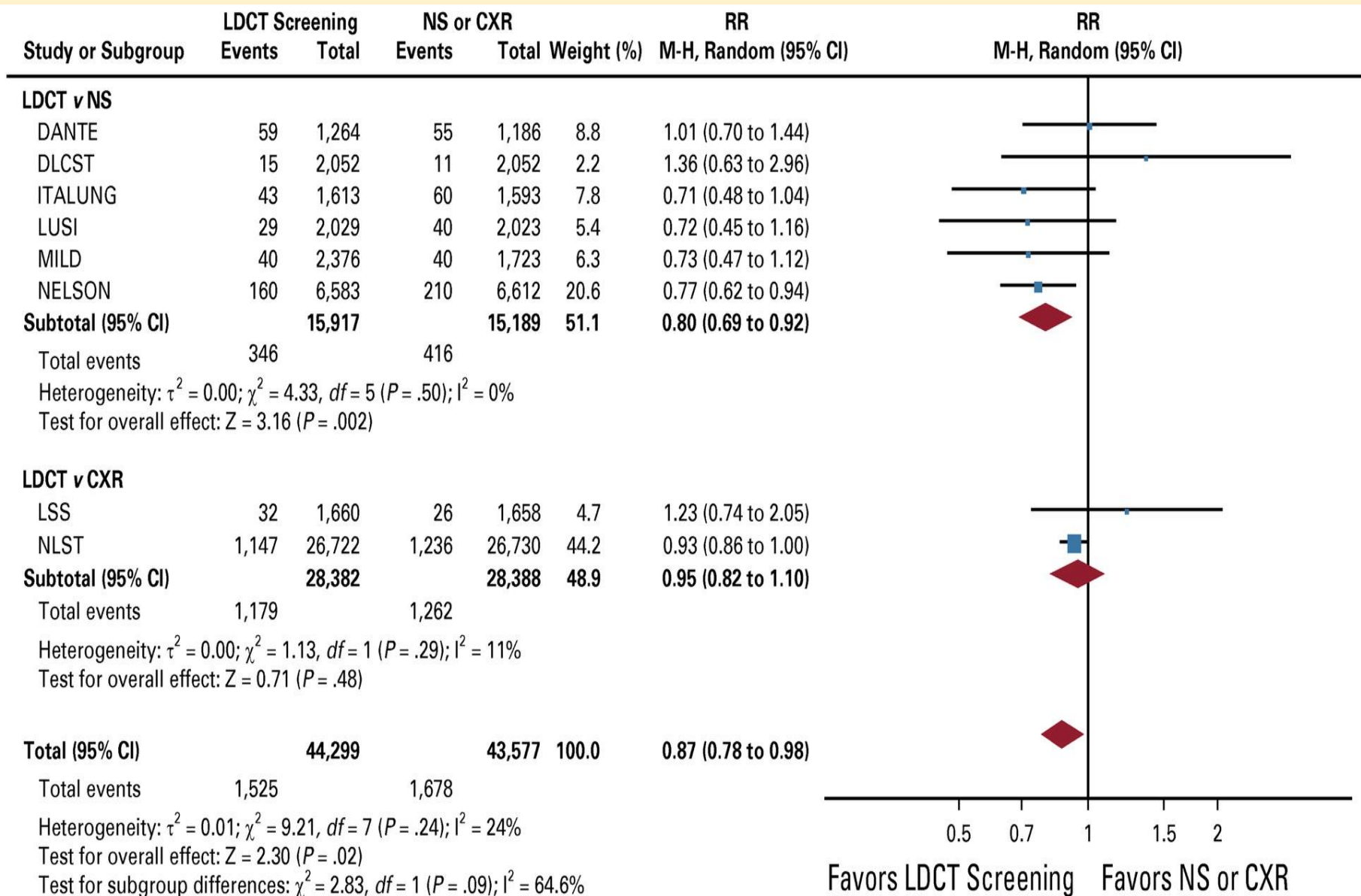
Popolazione	Procedura Screening	Tempistica
Donne sessualmente attive. Lo screening deve iniziare all'età ≥ 21 aa e continuare per tutta la vita	Solo Pap test PAP test convenzionale PAP test su base liquida - Co-testing (Pap test+HPV test) - Colposcopia	Età < 30 aa: il secondo° esame a 12 mesi; -ogni 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

Screening Specifici per HIV- Update Linee Guida Italiane

Tumore	Popolazione	Procedura Screening	Tempistica	Forza Raccomandazione
Fegato	-HCV coinfecti con cirrosi; -Tutti HBV con viremia rilevabile -Tutti HBV/HCV aviremici se con cirrosi -Tutti HCV aviremici (post-DAA) 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	

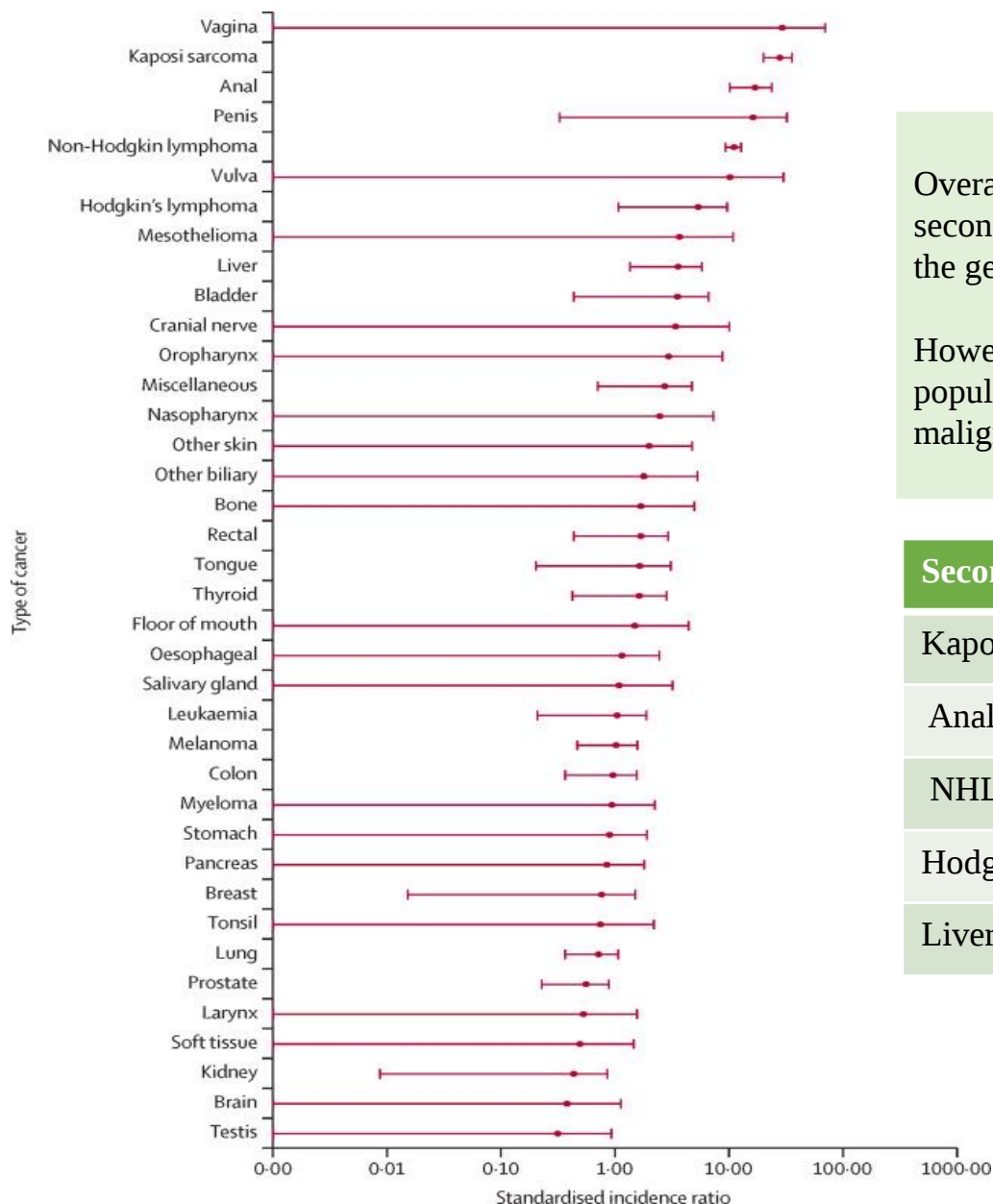
Benefits and Harms of Lung Cancer Screening by Low Dose CT in the General Population A Meta-Analysis

Passiglia F et al J Clin Oncol 2021



Low Dose CT benefits outweigh harms including overdiagnosis (38%).

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

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	3.6 (1.9-6.7)	2.7 (1.5-5.1)
Rectal SCC	5.5 (2.3-13.5)	4.1 (1.7-10.1)
Rectal non-SCC	2.7 (1.1-6.4)	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

Major Cancer Preventive Strategies in the cART era

- Early Initiation of cART
- Treatment of HCV/HBV Infections
- Stop Smoking and/or alcohol use
- HPV Vaccination (age ≤ 26 yrs)

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.