



8° WORKSHOP NAZIONALE CISAI

The Evolving Features of HIV-related Cancers

Emanuela Vaccher

**Medical Oncology A
National Cancer Institute Aviano**

Perugia 2017

HIV-related Cancers

TOPICS

Evolving epidemiology of HIV-cancers

Mortality and causes of death

Focus on Lymphomas and major NADCs

Prevention and Surveillance Strategies

HIV- Cancers and cART

Background

Patterns of morbidity and mortality among HIV-infected patients on cART are changing as a result of immune reconstitution, improved survival and aging.

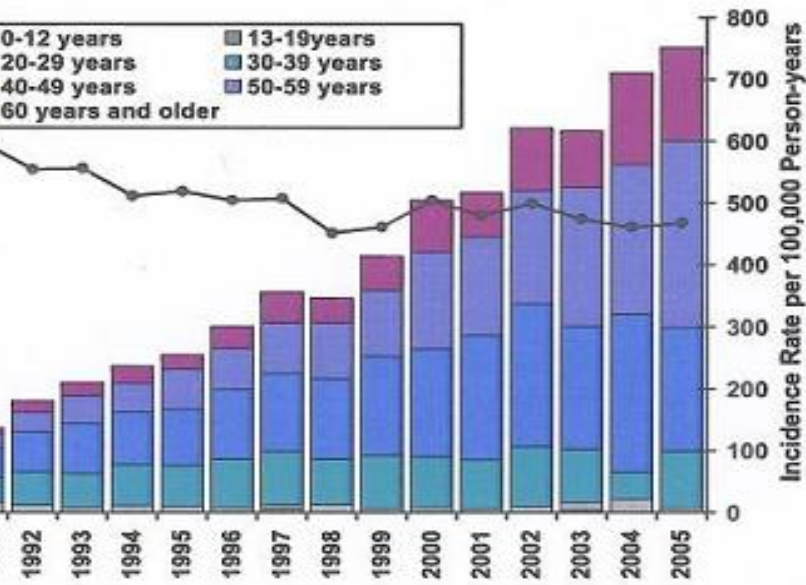
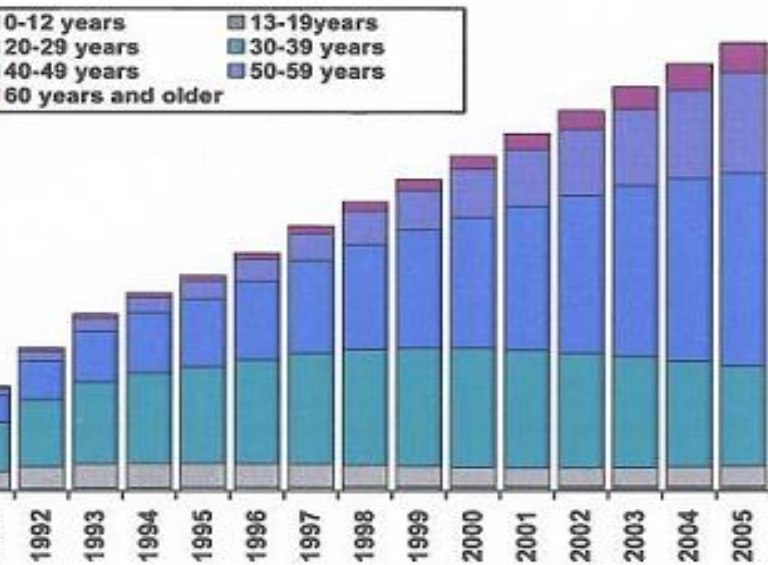
Non-AIDS Defining Cancers (NADCs) now represent a much larger fraction of the overall cancer burden.

The biology of cancers that arise despite effective cART likely differ from those that develop in patients with uncontrolled HIV viremia and severe immunodeficiency.

Evolving Epidemiology of HIV-associated Cancers

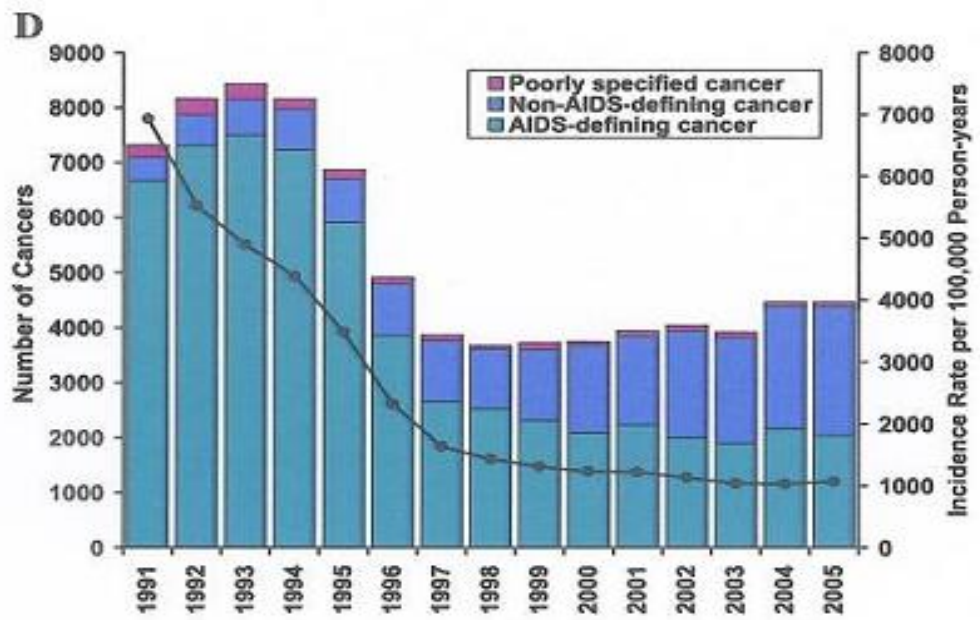
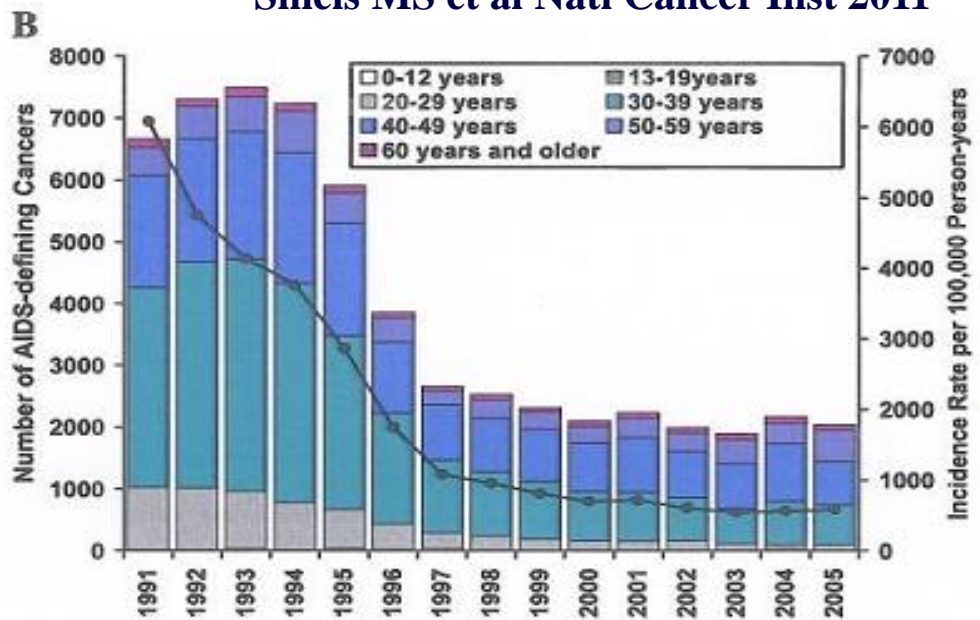
There is a growing need to address the changing epidemiology of cancers as the HIV population ages

Burden in HIV-Infected population in the USA



of people living with AIDS, AIDS-defining cancers, non-cancers, and all cancers in the United States during

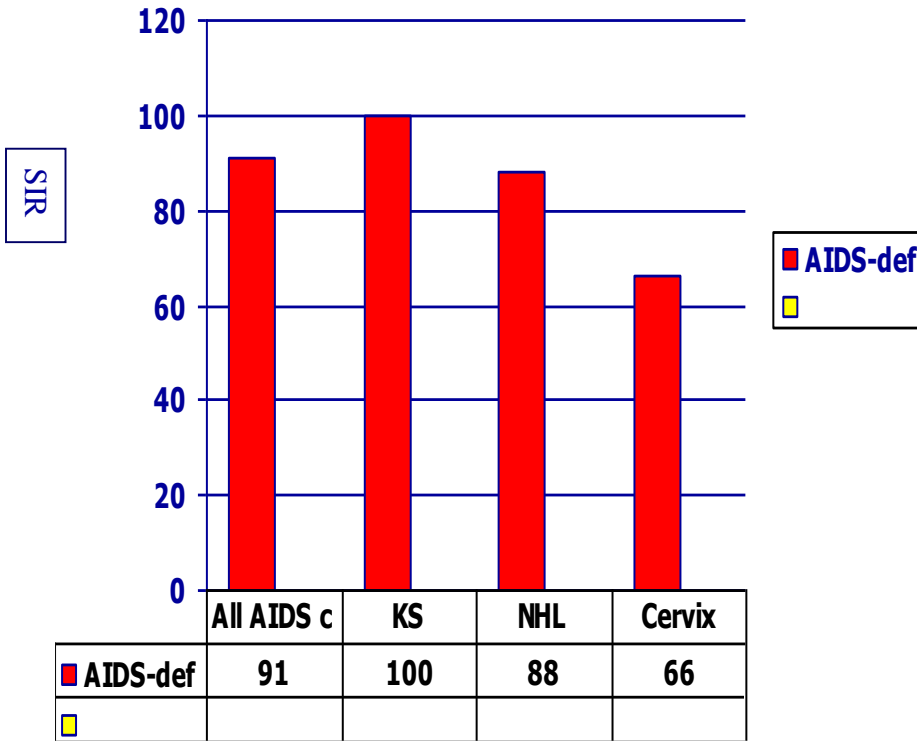
Shiels MS et al Natl Cancer Inst 2011



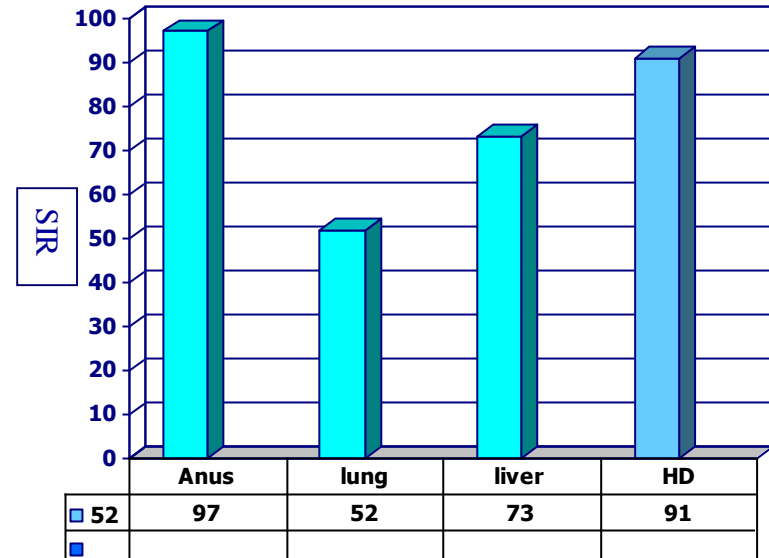
panels (B) and (C) are difficult to see because of small numbers of cancers in this age group during 1991–2005 (122 AIDS-defining cancers and

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

Excess of AIDS-Defining Cancers (%)



Excess of Non-AIDS-Defining Cancers %

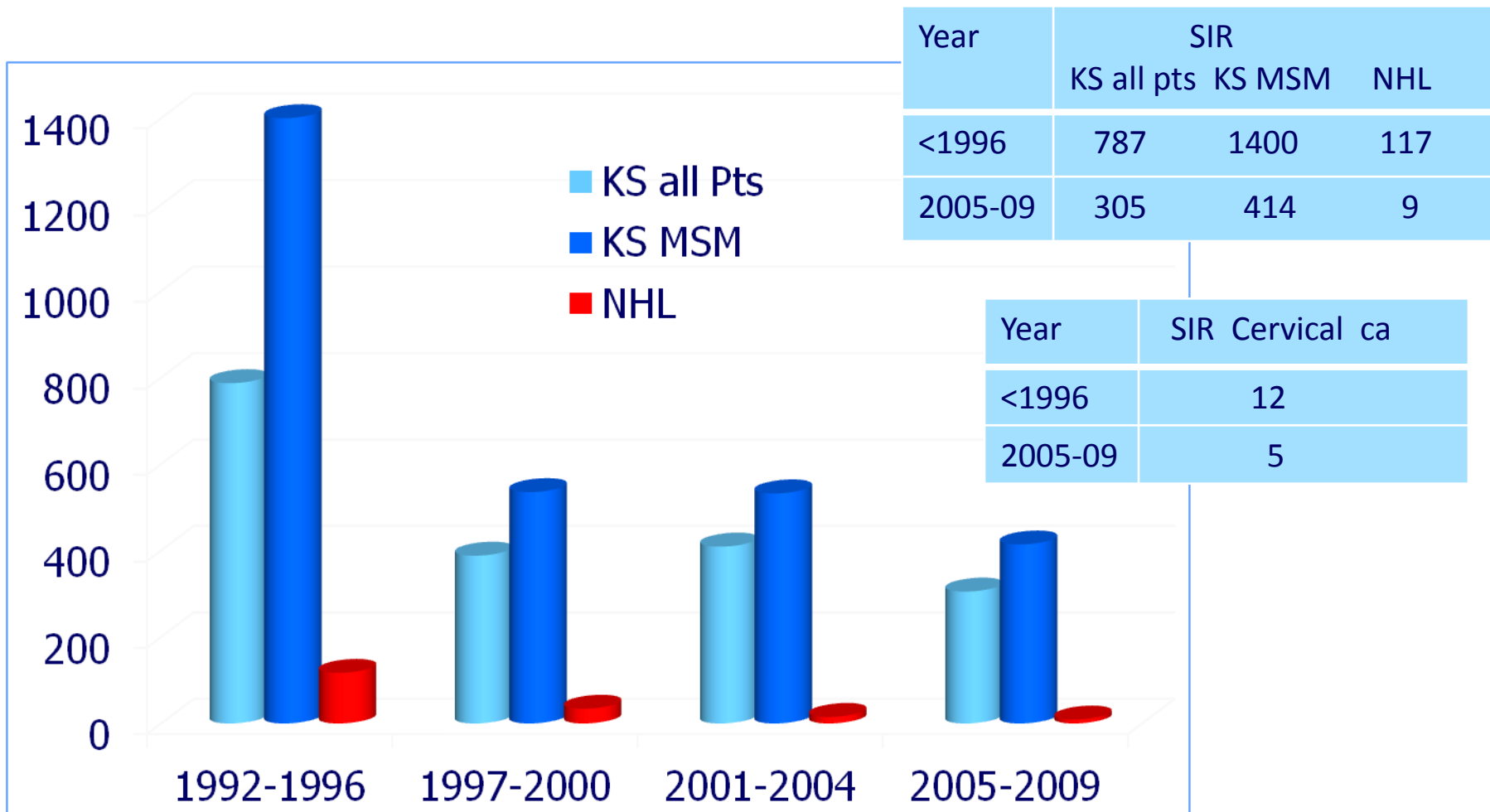


Cancer Incidence rates were evaluated by Poisson models applied to linked HIV and cancer registry data.

Excess count evaluated by subtracting the expected from total cancers

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

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)

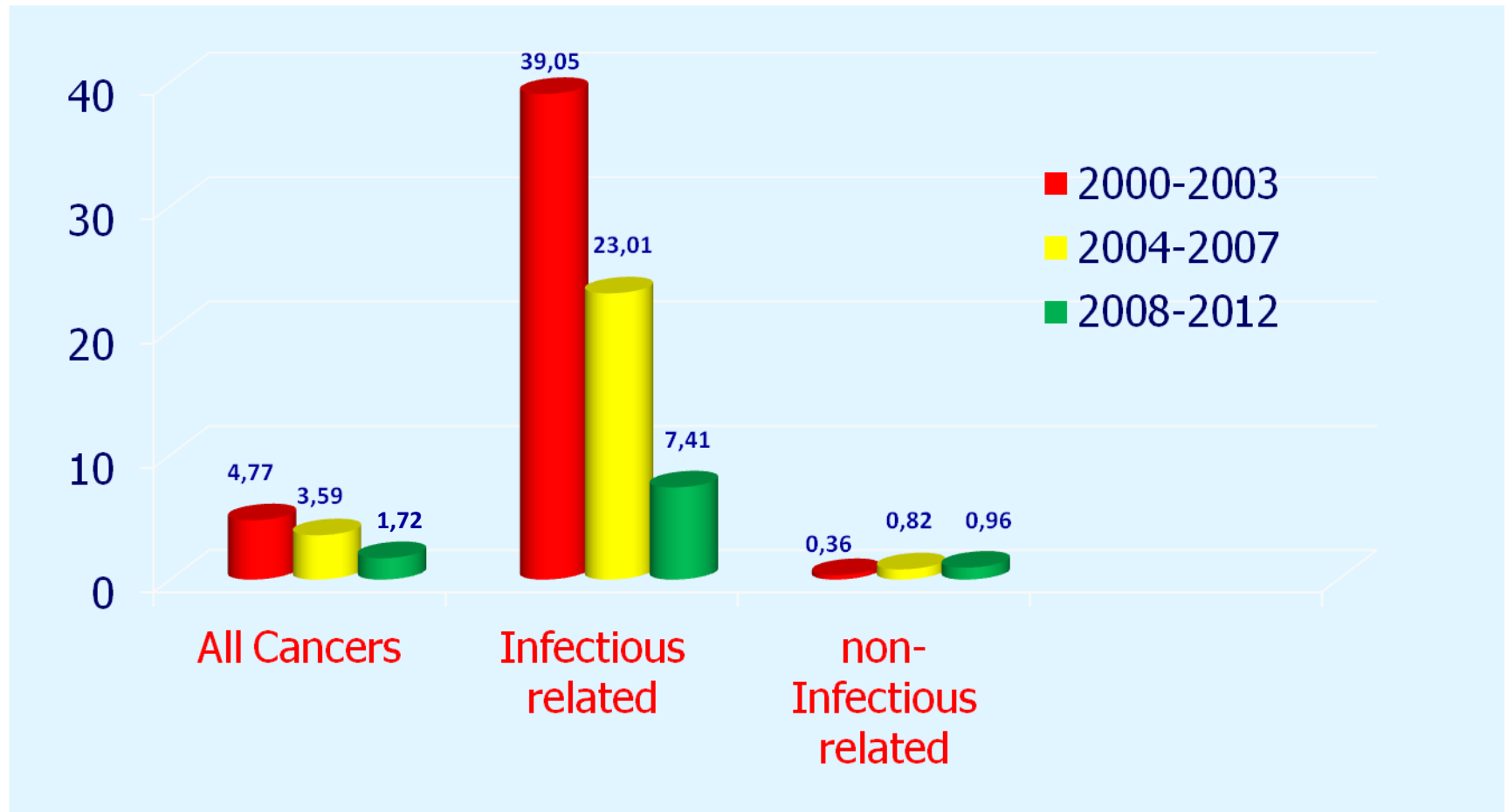


Standardized Incidence Ratio (SIR) of NADCs in people with HIV/AIDS from registry-linkage studies in the cART era

Cancer	Grulich (2007) SIR (95%CI)	Engels (2008) SIR (95%CI)	Dal Maso (2009) SIR (95%CI)	Franceschi (2010) SIR (95%CI)
All NADCs		1.9 (1.8-2.1)		3.0 (2.6-3.6)
Hodgkin's lymphoma	11.0 (8.4-14.4)	6.7 (4.5-9.5)	21 (15-28)	28 (15-48)
Anal cancer	29 (22-38)	9.1 (5.1-15)	44 (22-79)	50 (18-109)
Liver cancer	5.2 (3.3-8.2)	3.1 (1.7-5.2)	6.4 (3.7-10.5)	6.1 (1.9-14.3)
Lung cancer	2.7 (1.9-3.9)	2.6 (2.1-3.2)	4.1 (2.9-5.5)	2.6 (1.3-4.6)

Age-adjusted Incidence Rate Ratio (aIRR) of cancers among 4320 HIV-infected pts on modern cART by calendar yr (and 480.127 HIV-negative pts) (Canada 2000-2012)

Burchell AN. et al. Abs 161 CROI 2017



* adjusted for registry, age, race/ethnicity, sex, HIV risk group, HIV/AIDS relative time; ° per 1000 PY

Cancer Trends among HIV and General Population (USA 1996-2010)

Population-based registry linkage study including 279,975 HIV-infected pts

Robbins H.A et al. AIDS 2015

AIDS-defining Cancer	Adjusted*-HIV Trend Annual changes % (95%CI) 1996-2000	Adjusted*-HIV Trend Annual changes % (95%CI) 2001-2010
Kaposi Sarcoma	- 25.6 (-29.5,-21.6)	- 5.7 (-7.7,-3.7)
NHL	-15.4 (-17.1,-13.6)	- 5.2 (-7.6,-2.7)
Invasive Cervical cancer	NA	- 11.6 (-15,-8.1)

* adjusted for registry, age, race/ethnicity, sex, HIV risk group, HIV/AIDS relative time

Cancer Trends among HIV and General Population (USA 1996-2010)

Age groups >50 yrs : **13%** (1996-2000) vs **27%** (2001-2010)

Robbins H.A et al. AIDS 2015

Non-AIDS-defining Cancer	Adjusted*-HIV Trend Annual changes % (95%CI)	General Population Trend Annual changes % (95%CI)
Anus	+ 3.4 (0.8,to 5.9)	+ 3.3 (1.4 -5.2)
Liver	+ 6.6 (2.7-10.7)	+ 5.6 (4.6 - 6.6)
Prostate	+ 2.9 (-0.3-6.3)	+ 0.1 (-0.2-0.3)
Hodgkin's Lymphoma	- 3.4 (-6.0,-0.7)	- 0.1 (-1.2-1.1)
Lung cancer	- 6.8 (-8.5- 5.0)	- 3.2 (-3.5-2.8)
Female Breast	- 1.6 (-5.6-2.6)	- 0.8 (-1.2,-0.5)
Colorectum	- 0.9 (-4.2-2,5)	- 0.7 (-1.1,-0.3)

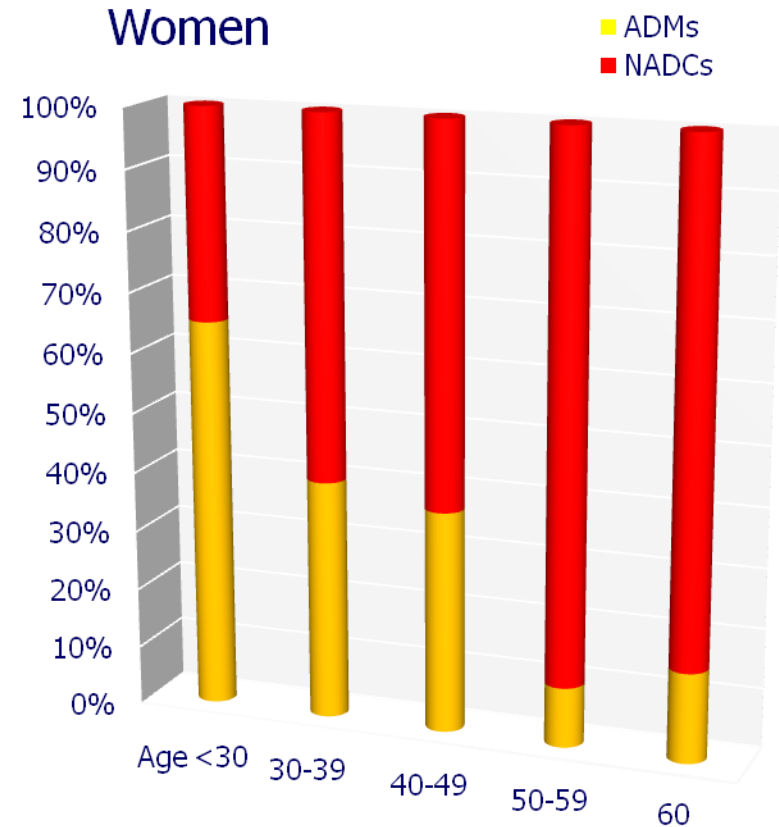
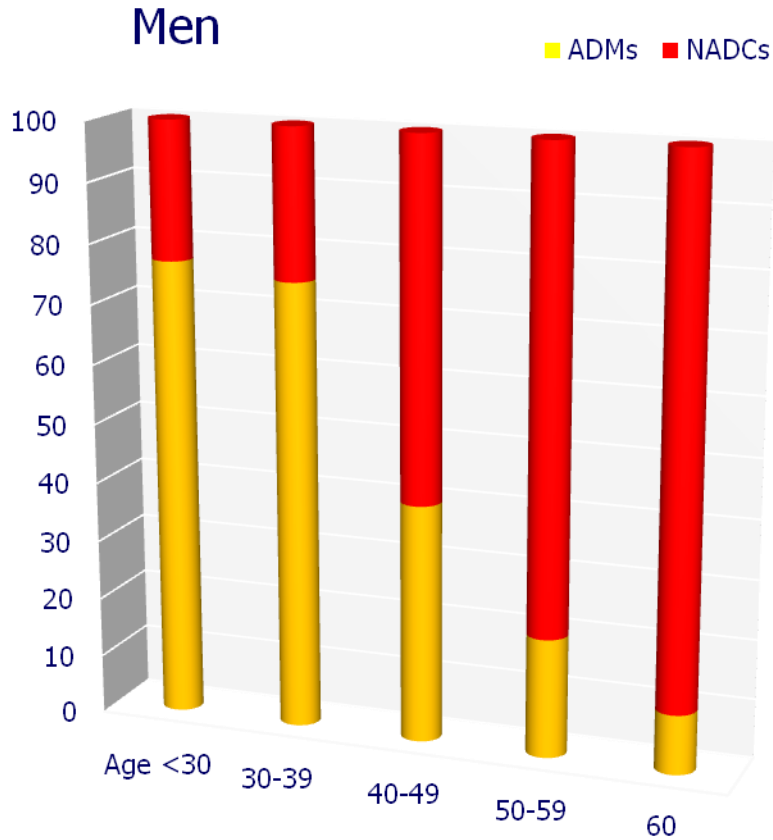
* adjusted for registry, age, race/ethnicity, sex, HIV risk group, HIV/AIDS relative time

Incidence Rate (IR) and Standardized Incidence Ratio (SIR) for cancer among 1130 commercially insured HIV-infected adults on cART- (USA 2006-2012)

Cancer	IR per 100.000 PY (95%CI)	SIR (95%CI)
KS	86.1 (72.9-101.6)	46.09 (38.74-48.94)
Male	103.5 (67.5-122.6)	45.25 (37.94-48.10)
Female	12.9 (4.8-34.3)	122.23 (32.89-194.04)
NHL	112.7 (97.5-130.3)	4.22 (3.63-4.45)
Anus	84.2 (71.2-99.6)	30.54 (25.62-32.46)
Hodgkin's L.	35.3 (27.2-45.8)	9.83 (7.45-10.84)
Lung	39.0 (30.5-49.9)	0.70 (0.54—0.77)
Prostate	91.3 (76.3-109.2)	0.54 (0.45—0.58)

Distribution of cancers among 1130 commercially insured HIV-infected adults on cART- (USA 2006-2012)

Lee JY. et al. J Cancer Epidemiol 2016

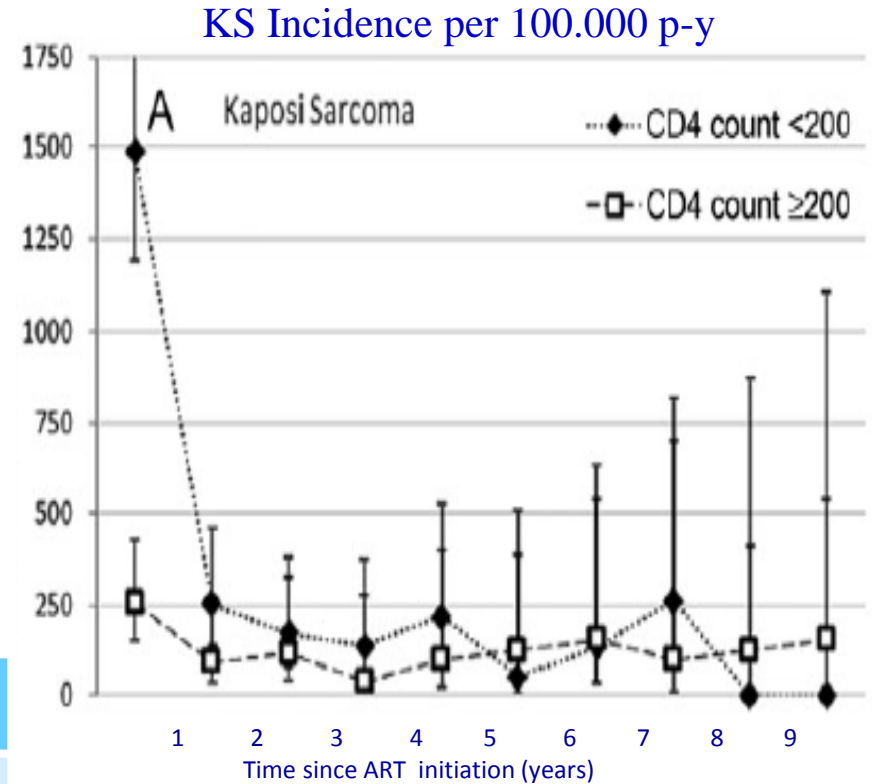


The proportion of AIDS-defining cancers decreases with age for both men ($p < 0.001$) and women ($p < 0.001$)

Risk of Kaposi Sarcoma during the first months on cART: Immune Reconstitution Inflammatory Syndrome (IRIS)-KS

(Lacombe JM et al AIDS 2013, Yanik EL AIDS 2013, HIV-Casual Coll.Group AIDS 2014, COHERE study CID 2016)

Duration of cART	French Cohort(2013) Adjusted RR (95% CI) (N° pts: 1181 KS / 66.369 tot)	HIV-Causal Coll.(2014) Adjusted RR (95% CI) (N° pts: 748 KS / 96562 tot)	
no cART, year \geq 1996	1	1	
\leq 3 mos	3.33 (2.74-4.05)	1.18 (0.87-1.55)	
4-6 mos	1.50 (1.15-1.96)	0.14 (0.10-0.21) 3 months	
> 6 mos	0.25 (0.21-0.29)		
COHERE study	at 1-3 mos	at > 3- 6 mos	at 1-2 yrs
Incidence Ratio/100.000PY	1472	582	120



Message : *In the late cART era, the epidemiology of KS is changing, with a rising incidence in the context of Immune Reconstitution Inflammatory Syndrome (IRIS-KS). Notably, this pattern was seen in pts initiating cART with a CD4 count <200 / μ L*

KS with high CD4 count and undetectable HIV-RNA (Cluster KS) in the late cART era

(Maurer Tet al NEJM 2007, Crum-Cianflone NF et al AIDS 2010, Unemori P et al AIDS 2013, COHERE study CID 2016)

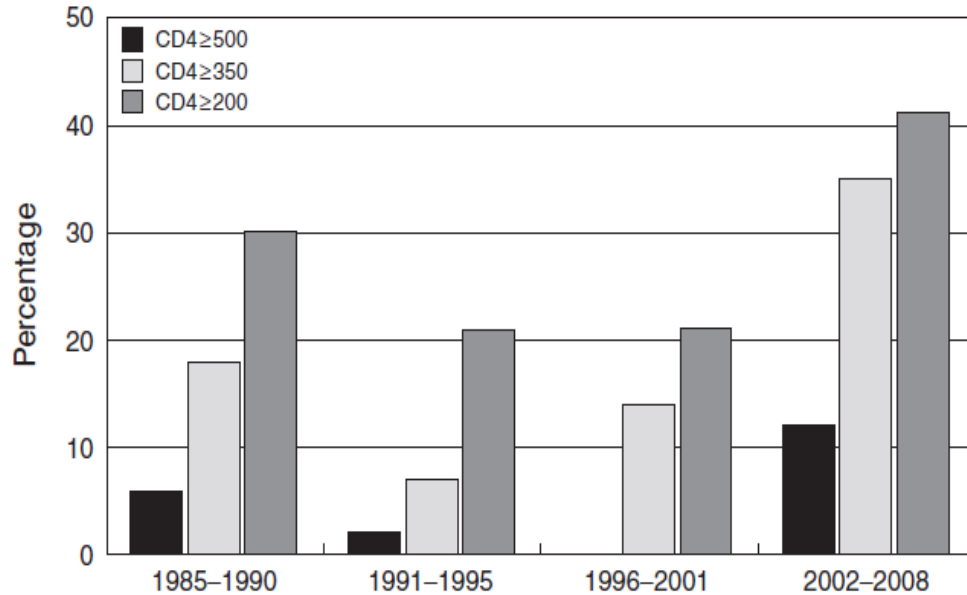
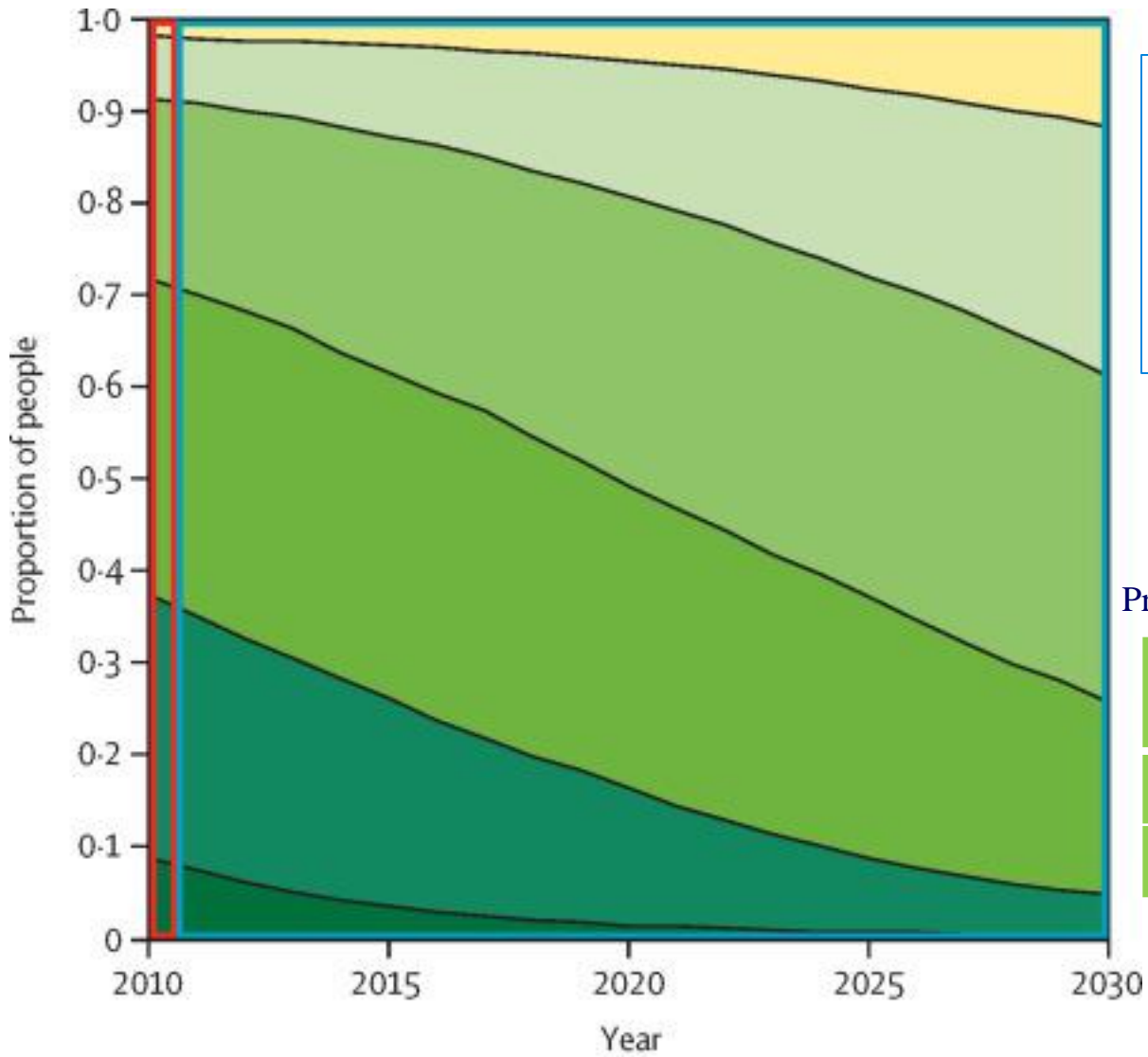


Fig. 1. CD4 cell count at diagnosis of Kaposi's sarcoma during the course of the HIV epidemic (1985–2008).

CD4 cells	Cluster KS % (n°19)	HIV+ Controls % (n°47)	P value Age-adjusted
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

Message : *The proportion of KS cases occurring of high CD4 count is rising in the cART era. Increased frequency of T cells with Immunosenescence phenotype and lower naive T cells* are associated with Kaposi's Sarcoma occurring in most pts with high CD4 count and undetectable HIV viral load*

Project Age Distribution of HIV-infected Persons: a Modelling Study by use the data of 10.278 HIV-infected Persons from the ATHENA Cohort (Netherlands 1996-2010)



The red box shows the age distribution of patients on antiretroviral therapy in clinical care in the Netherlands in 2010, which matches the data exactly, and the blue box shows model output from 2011–30.

Proportion of Patients older than 50 yrs

Year	Age Groups, yrs (%)		
	> 50	>60	> 70
2010	28	8	8
2030	73	39	12

- >70 years old
- 40-50 years old
- 60-70 years old
- 30-40 years old
- 50-60 years old
- <30 years old

Infection-related Malignancies (IRM) and Unrelated Malignancies (URM), HIV and the Aging Population- EuroSIDA Study (15.648 pts)- 2001-2012

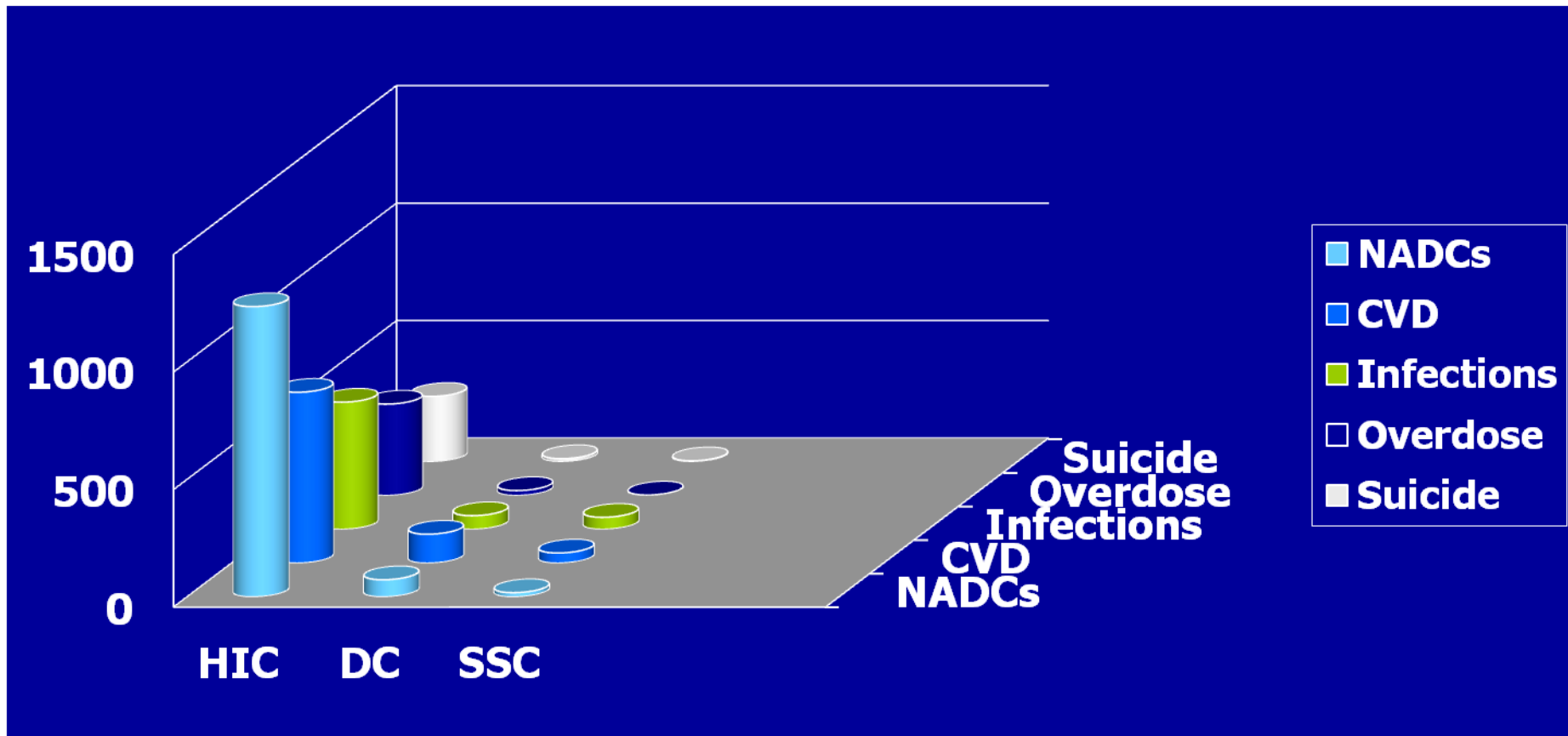
Shepherd L. et al HIV Medicine 2016

Variable	Infection RMs aRR (95%CI)	Population attributable %	URMs aRR (95%CI)	Population attributable %
Age, yrs				
36-40	Ref		Ref	
41-50	1.34 (0.97-1.85)	12	2.37 (1.31-4.27)*	17
≥ 51	1.62 (1.14-2.30)*		7.33 (4.07-13.21)*	56
HIV-RNA >400 cp/mL	1.84 (1.39-2.43)*		19	0.91 (0.62-1.35)
CD4 /μL				
< 200	3.77 (2.59-5.51)*	21	1.99 (1.26-3.17)*	6
≥ 500	Ref			
Prior AIDS	1.41 (1.02-1.06) ^o	3	0.92 (0.57-1.49)	
Smoking Status				
Never	Ref		Ref	
Current	1.15 (0.91-1.46)		1.56 (1.17-2.08)*	16

aRR: adjusted Rate Ratios; IRM:Infection-related Malignancies;IURM: IURM:Infection-unrelated Malignancies; *p<0.01 ^op< 0.05

Prevalence and distribution of major non-AIDS causes of death among HIV-infected individuals receiving antiretroviral therapy: a systematic review and meta-analysis

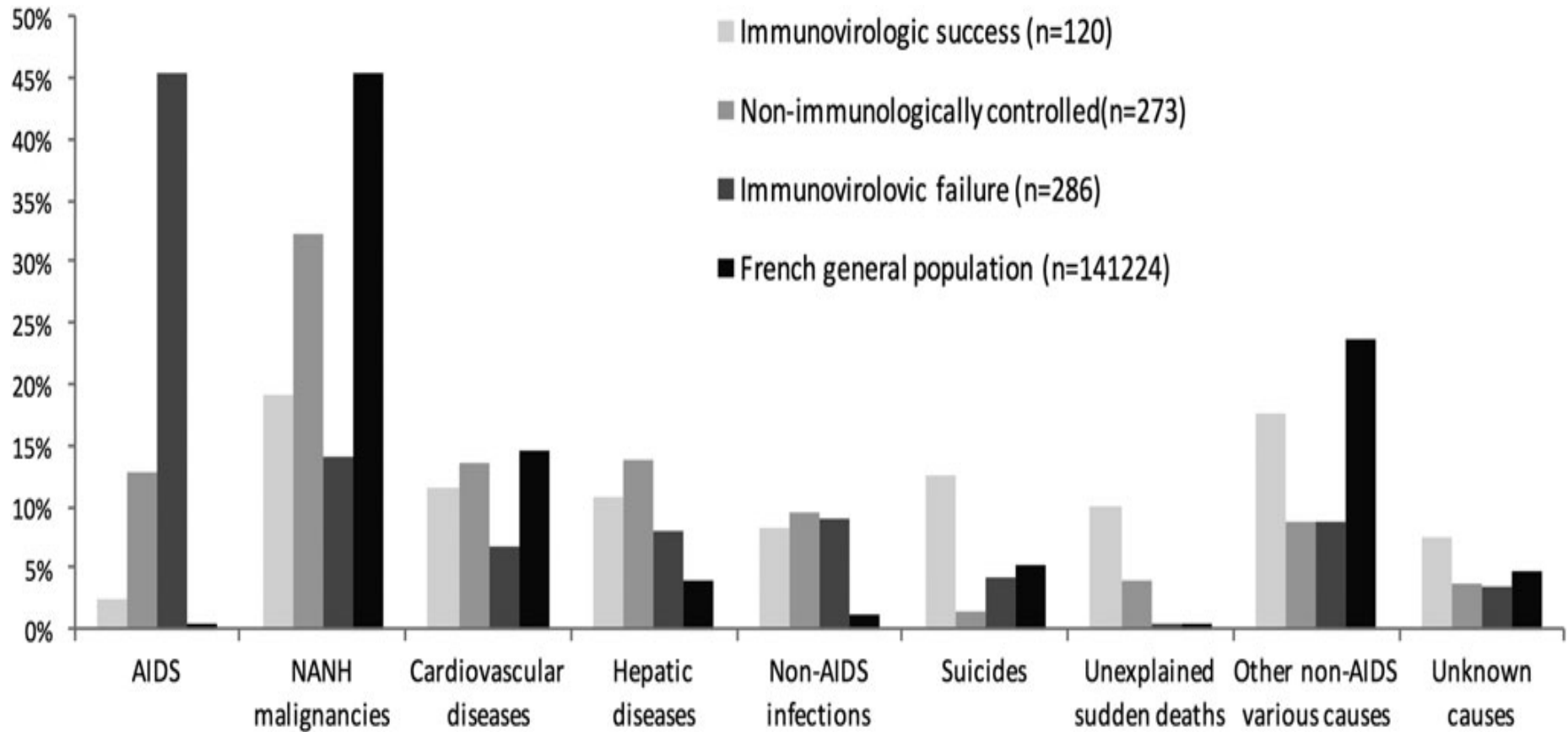
Farahani M. et al. Int J STD AIDS 2016



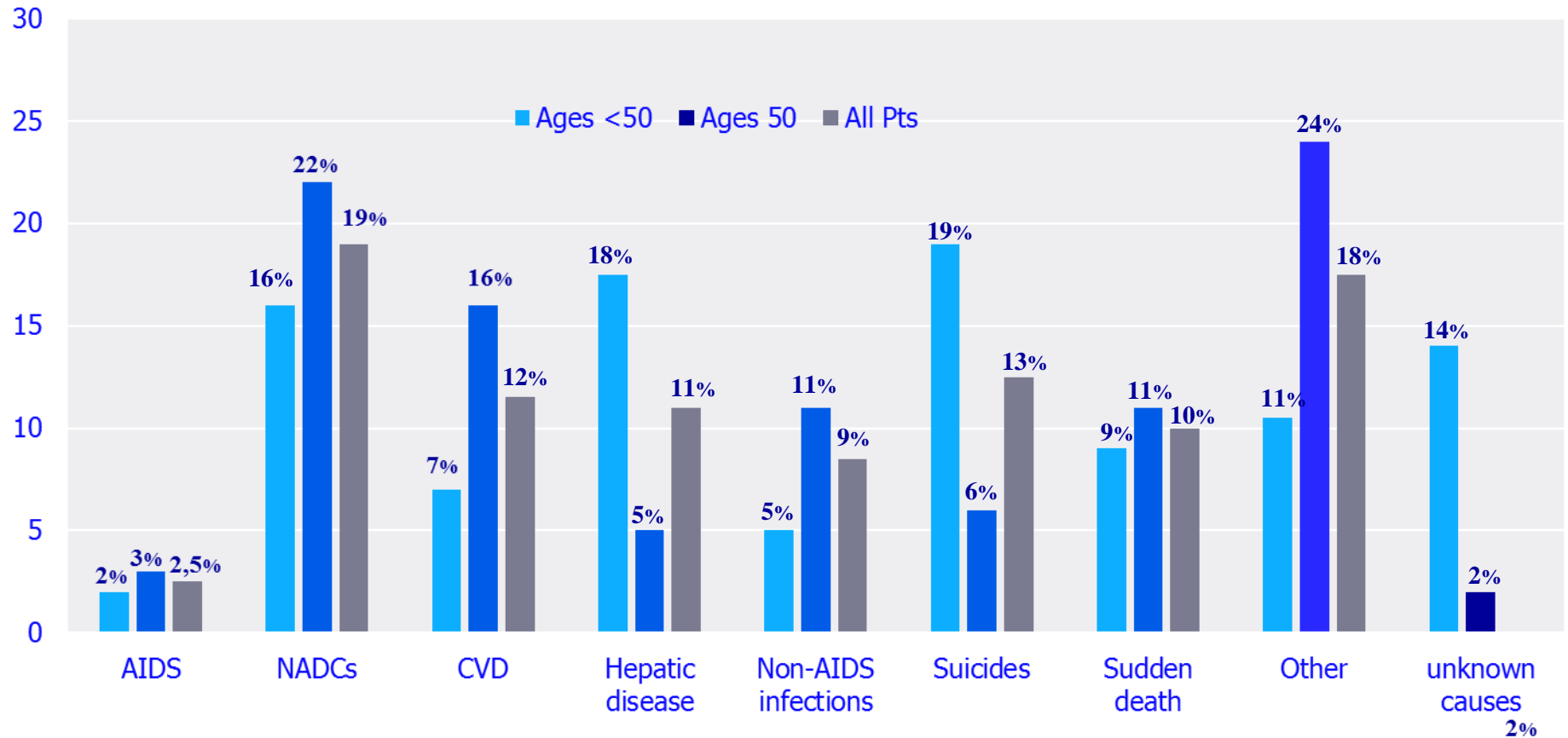
Message:

Pooled Non-AIDS causes of death prevalence in High-Income Countries (HIC) were 53%, in Developing Countries (DC) 34% and in sub-Saharan Countries (SSC) 19%

Comparison of Underlying Causes of Death among 728 French HIV- Infected Patients in 2010



Prevalence and distribution of Causes of Death among 120 HIV-Infected Individuals receiving cART with Immunovirologic Response (France 2010)



Survival of major HIV-Cancer

What is the natural history of cancers in HIV-infected patients on cART?

AIDS-Defining Tumors

Major Characteristics in the pre-cART era

Kaposi Sarcoma, NHL, Invasive Cervical Cancer

- Advanced stage at diagnosis
- Aggressive clinical course complicated by opportunistic infections and/or other cancer
- Poor Prognosis
- Detrimental impact of “standard” treatment commonly used for the general population

Major Prognostic Features

- CD4 cell count
 - <100/ μ L
 - \geq 100/ μ L
- * Poor Performance Status
- * Prior AIDS Diagnosis

Prognostic impact of HIV-related but no of cancer-related features

Overall Survival (OS) in the pre- and post-cART era of the most common HIV-related cancers (Prospective studies)

	OS pre-cART	OS post-cART
Kaposi Sarcoma	13 mos (median)	57- 100 % (3-yr)
NHL DLCL	6-8 mos (median)	60-80 % (5-yr)
Hodgkin Disease	45% (2-yr)	76-81 % (5 yr)
ANAL Cancer	20-34 % (5-yr)	64-71 % (5-yr)
HCC	6-8 mos (median)	35 mos (median)

Message: Safer and better tolerated cART regimens, reduced infectious morbidity, improved supportive care strategies and incremental refinements in cancer treatment have all contributed to improvement in overall survival

Mortality Rate (MR) and 2-yr Survival of 650 incident cancers among 20.677 HIV-infected pts treated with cART. (USA 1996-2009)

Achenbach CJ AIDS 2011

CANCER	<u>Mortality rate</u> (95% CI) per 100 person-years	<u>2-yr Survival rate</u> (%)
Anal cancer	8.7 (5.2-14.4)	77
Liver cancer	84.3 (53.8-132.2)	12
Lung cancer	68.1 (51.3-90.4)	24
Hodgkin’s L.	6.3 (2.8-14)	NA

Message. The highest mortality rate among pts with liver and Lung cancer. Appropriate cancer therapies including HAART need to be urgently performed.

HCC: which strategy ?

Factors associated with survival in 585 pts with HCC (104 HIV+)

	HR	95 % CI	P value	
BCLC stage A-B vs C-D	2.51	2.13-2.95	<0.001	Early diagnosis
Tumor \leq 3 cm	1.56	1.14-2.55	0.02	
Proven Effective Therapy	1.78	1.38-2.25	0.001	Aggressive treatment
Retreatment at Recurrence	1.65	1.21-2.86	0.04	Treat recurrence
Diagnosis under Screening	1.32	1.18-2.65	0.02	Screening of pts at risk
cART	1.25	1.00-3.11	0.03	Treat HIV

Predictors of mortality after cancer diagnosis among 650 HIV-infected patients with NADCs

	Hazard Ratio*	(95 % CI)
AGE, per decades	1.44	(1.25-1.66) [°]
STAGE IV	2.3	(1.69-3.13) [°]
CD4 cells /100/ μ L	0.90	(0.83-0.98) ^{°°}
HIV-RNA suppression to \leq 400/mL	0.32	(0.23-0.42) [°]
Cancer Treatment	0.55	(0.39-0.79) [°]

* adjusted; [°]p>0.01, ^{°°}p=0.05

Achenbach CJ AIDS 2011

Message: *Poor immune status, failure to suppress HIV-RNA on cART, cancer stage, lack of cancer treatment and aging are predictors of death.*

Cancer-specific Mortality among 6.459 HIV-infected Patients in the USA (1996-2010)

Coghill AE et al JCO 2015

Cancer	HR (95%CI (1996-2010))	HR (95%CI (2001-2010))
Colorectum	1.49 (1.21-1.84)	2.01 (1.49-2.71)
Pancreas	1.71 (1.35-2.18)	1.71 (1.35-2.18)
Larynx	1.62 (1.06-1.47)	1.58 (0.35-3.34)
Lung	1.28 (1.17-1.39)	1.38 (1.21-1.56)
Melanoma	1.72 (1.09-2.70)	1.55 (0.77-3.10)
Breast	2.61 (2.06-3.31)	3.43 (2.35-5.01)
Cervix	1.27 (0.95-1.70)	1.39 (0.9-2.11)
Prostate	1.57 (1.02-2.41)	1.21 (0.54-2.69)

Message. HIV was not associated with increased cancer-specific mortality for Anal cancer, Hodgkin Lymphoma, Diffuse Large cell Lymphoma.

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 in all HIV-infected Patients independently of CD4 cell count and/or HIV-RNA load

cART should be administered concurrently to antineoplastic treatment including chemotherapy.

However

cART has to be adjusted to avoid drug interactions



Prognostic and Treatment Factors in AIDS-Related Lymphomas –

“A Pooled Analysis of 1,546 Patients” **and**

“A New Prognostic Index for the Rituximab-era”

Blood 2013

Stefan K Barta, MD¹, Xiaonan Xue¹, Dan Wang¹, Roni Tamari², Jeannette Y Lee³, Nicolas Mounier⁴, Lawrence D Kaplan⁵, Josep-Maria Ribera⁶, Michele Spina⁷, Umberto Tirelli⁷, Rudolf Weiss⁸, Lionel Galicier⁹, Francois Boue¹⁰, Wyndham Wilson¹¹, Christoph Wyen¹², Albert Oriol⁶, José-Tomás Navarro⁶, Kieron Dunleavy¹¹, Richard F. Little¹¹, Lee Ratner¹³, Olga Garcia⁶, Mireia Morgades⁶, Eric Oksenhendler⁹, Scot C Remick¹⁴, and Joseph A Sparano¹

TREATMENT FACTORS & OUTCOMES: MULTIVARIATE ANALYSIS		Odds Ratio* (95% CI; p-value)	Hazard Ratio** (95% CI; p-value)	
		CR	PFS	OS
RITUXIMAB	Yes=542; No=1,004	2.89 (1.64-5.08; <0.001)	0.50 (0.34-0.72; <0.001)	0.51 (0.38-0.71; <0.0001)
CHEMO-REGIMEN	CHOP (n=632)***	1.0	1.0	1.0
	Intensive (n=155)	1.65 (0.57-4.77; p=0.36)	0.32 (0.18-0.54; p<0.0001)	0.54 (0.36-0.82; p=0.004)
	Ld-CHOP (n=165)	0.33 (0.19-0.58; p<0.001)	2.11 (1.53-2.89; p<0.0001)	1.91 (1.44-2.52; p<0.0001)
	EPOCH (n=166)	0.97 (0.42-2.24; p=0.95)	1.11 (0.56-2.05; p=0.75)	0.67 (0.33-1.22; p=0.22)
	VS (n=41)	0.04 (0.01-0.33; p=0.002)	3.34 (2.06-5.23; p<0.0001)	2.41 (1.58-3.60; p<0.0001)
	ACVBP (n=158)	1.70 (1.04-2.79; p=0.036)	0.72 (0.52-0.99; p=0.049)	0.88 (0.67-1.16; p=0.38)
	CDE (n=191)	0.87 (0.54-1.40; p=0.55)	0.93 (0.67-1.27; p=0.64)	0.73 (0.55-0.96; p=0.03)
	Remick (n=38)	0.77 (0.21-2.90; p=0.70)	N/A	0.86 (0.46-1.51; p=0.62)
CONCURRENT cART	Yes=779; No=724	1.89 (1.21-2.93; p=0.005)	0.89 (0.66-1.21; p=0.45)	0.78 (0.60-1.02; p=0.07)

All estimates in the multivariate analysis were adjusted for rituximab use, treatment, concurrent use of cART, age, sex, histological subtype, age-adjusted international prognostic index, CD4 count at baseline, prior history of AIDS, and enrollment period.

* Odds Ratios >1 indicate a favorable outcome (higher odds for achieving a complete response)

** Hazard Ratios <1 indicate a favorable outcome (less hazard of progression or death respectively)

*** CHOP was used as reference regimen

HIV and Cancer

Key Strategies

Combination Treatment
with antineoplastic therapy
and cART

Early Diagnosis

Prevention and
Cancer Screening

**PK Interaction studies*
**Translational research*

**Current Screening
Programs:**

- * Breast cancer
- * Cervical cancer
- * Colorectal cancer
- * Prostate cancer

Programmi di screening per la popolazione generale (1).

Tumore	Popolazione	Procedure di screening	Tempistiche dello screening	commenti
Mammella	Donne 50-70 aa (E) Donne \geq 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) \geq 50 aa (A)	°Ricerca sangue occulto feci °Rettosigmoidoscopia §Rettocolonscopia	°annuale °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 \geq 50 aa	Esame rettale + PSA test	Annuale	- Beneficio ancora controverso - Candidati se aspettanza di vita \geq 10 aa

E: linee guida europee; A: linee guida americane

Potenziali opportunità di Prevenzione, Screening e Diagnosi precoce dei Principali Tumori Solidi in HIV (1)

TUMORE	POPOLAZIONE	PROCEDURE SCREENING	TEMPISTICA SCREENING	Aspetti Controversi
Cervice uterina	Donne sessualmente attive ≥20 aa (E) ≥ 18 aa (A)	-PAP test convenzionale - PAP test su base liquida - Colposcopia	Annuale se 2 esami consecutivi neg Se Pap test patologico	Donne con CD4>500 ed HPV test negativo: screening ogni 3 aa?
Ano	-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	Assenza di metodiche standardizzate Assenza di una terapia efficace per neoplasie preinvasive
Fegato	-HCV coinfezzi/RSV con cirrosi; -Tutti HBV/HCV resistenti agli antivirali	Ecografia addome +/- α-fetoproteina	Ogni 6-12 mesi	Screening annuale nei pts con RSV?
Polmone	-Fumatori con storia di ≥ 30 pacchi sigarette./anno; -se ex-fumatori entro 15 anni dalla cessazione -Età ≥ 40 aa**	TAC spirale a basso dosaggio	Annuale	Sovradiagnosi Scarsa compliance
Cute	-Pelle chiara; - Razza bianca non-ispanica	Esame della cute	Annuale	Patologia sottostimata

Anal Screening Programs: Controversial Issues

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

*for HGAIN in MSM

HRA: limited expertise and equipment availability

- Lack of evidence documenting that HGAIN treatment reduces the incidence of Anal Cancer
 - *Paucity of data on performance of anal cancer screening
 - Limited n° of clinicians with necessary expertise
 - Scarcity of longitudinal data
 - Paucity of cost-effectiveness data on anal screening approaches
- Uncertainty regarding anal HPV natural history (i.e. rate of progression /regression of AIN3)

There are no formalized anal screening programs

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 <30 yrs)

Estimated Hazard Ratio for serious Events in Immediate-Initiation vs Deferred-Initiation 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

Borges AM et al CID 2016

Message: *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*

Potential opportunities for Prevention of HIV-HPV Cancers: Major Vaccine Trials

Study Vaccine	Major Results
PACTG 1047 Quadrivalent	Safe and highly immunogenic in 126 HIV children
AMC052 Quadrivalent	Safe and highly immunogenic in 109 HIV adult men. Lower Antibody titers in MSM
NCT00586339 Bivalent 120 HIV+Female (18-25 yrs) and 0 3HIV-neg. F	Safe and highly immunogenic in 120 HIV-pos. Females (18-25 yrs). Compared to 30 HIV-neg. Females lower antibody titers
Quadrivalent 310 females, ages 32-45 (Money DM et al, Vaccine 2016)	Safe and highly immunogenic vaccine. Pts with suppressed HIV-RNA had a 1.74-3.05 fold higher antibody response compared with viremic pts. Older pts can still benefit from HPV vaccination.

HIV- Cancers and cART

Conclusions

Cancers represent a leading cause of morbidity and mortality among HIV-infected people in resource-rich settings.

Many uncertainties remain about the underlying pathogenesis of cancer, as well as optimal prevention and treatment strategies in HIV-infected population.