The HIV TREATMENT CASCADE
Emilia Romagna post-ICAR 2018

The Evolving Features of HIV-related Cancers
Focus on Prevention and Surveillance Strategies

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HIV-related Cancers

TOPICS

Evolving epidemiology of HIV-cancers

Mortality and causes of death

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.

Despite this progress, HIV-infected individuals still have excess mortality risk compared to general population

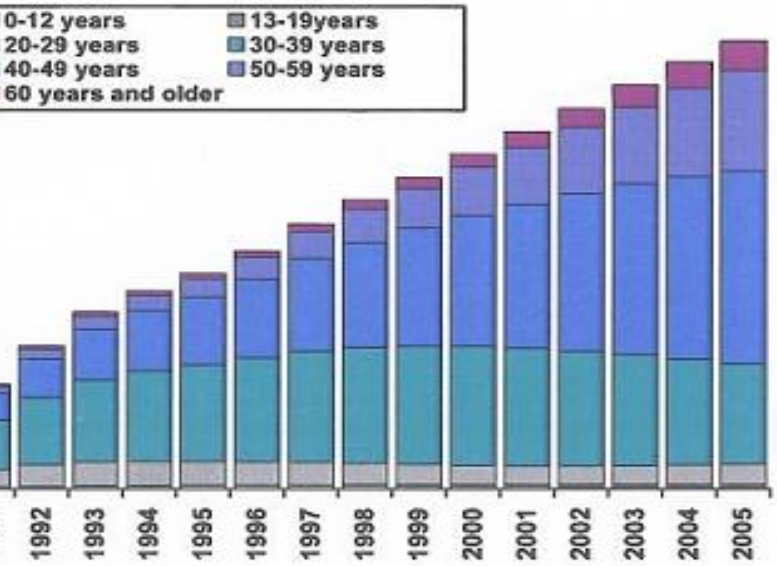
Non-AIDS Defining Cancers (NADCs) now represent a much larger fraction of the overall cancer burden.

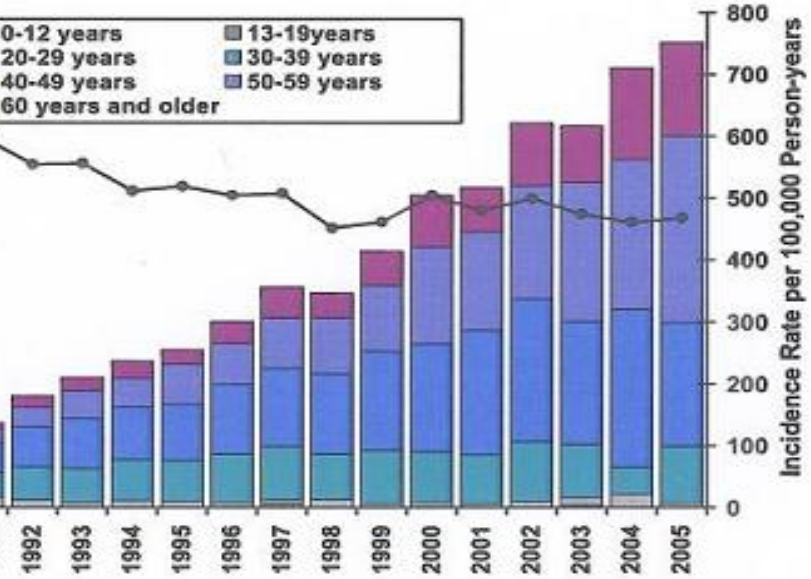
Evolving Epidemiology of HIV-associated Cancers

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

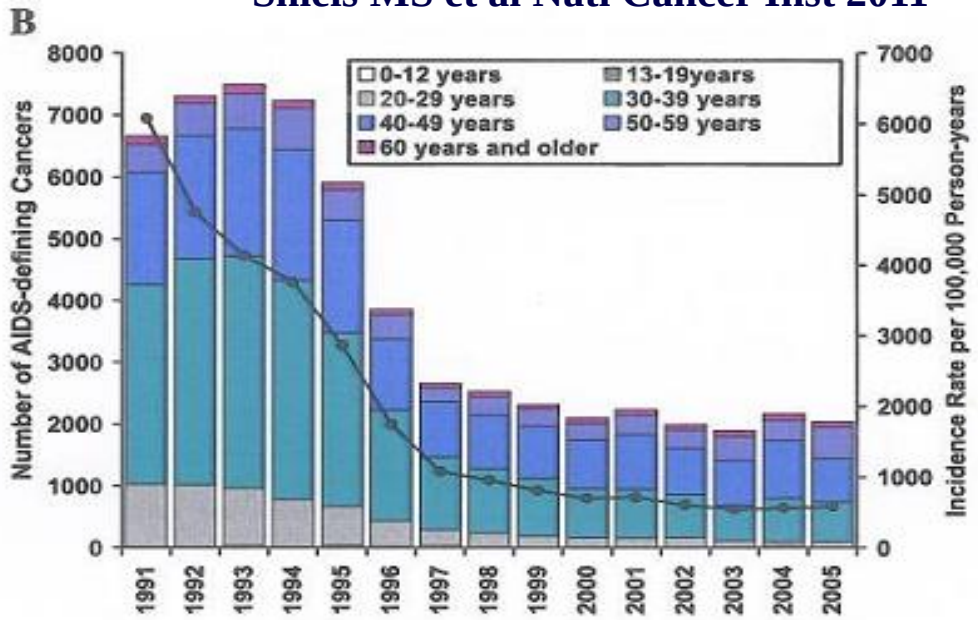
urden in HIV-Infected population in the USA

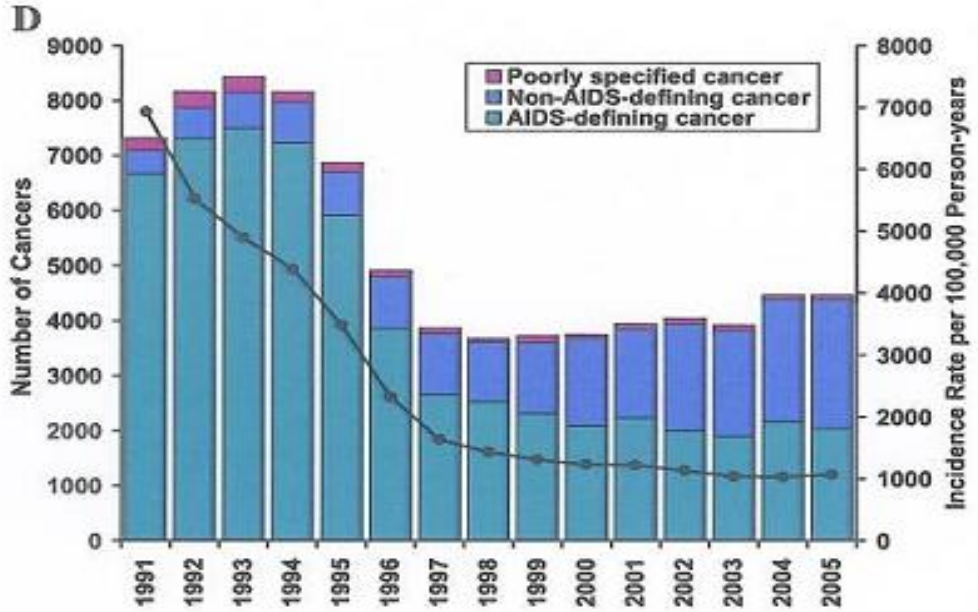
Shiels MS et al Natl Cancer Inst 2011





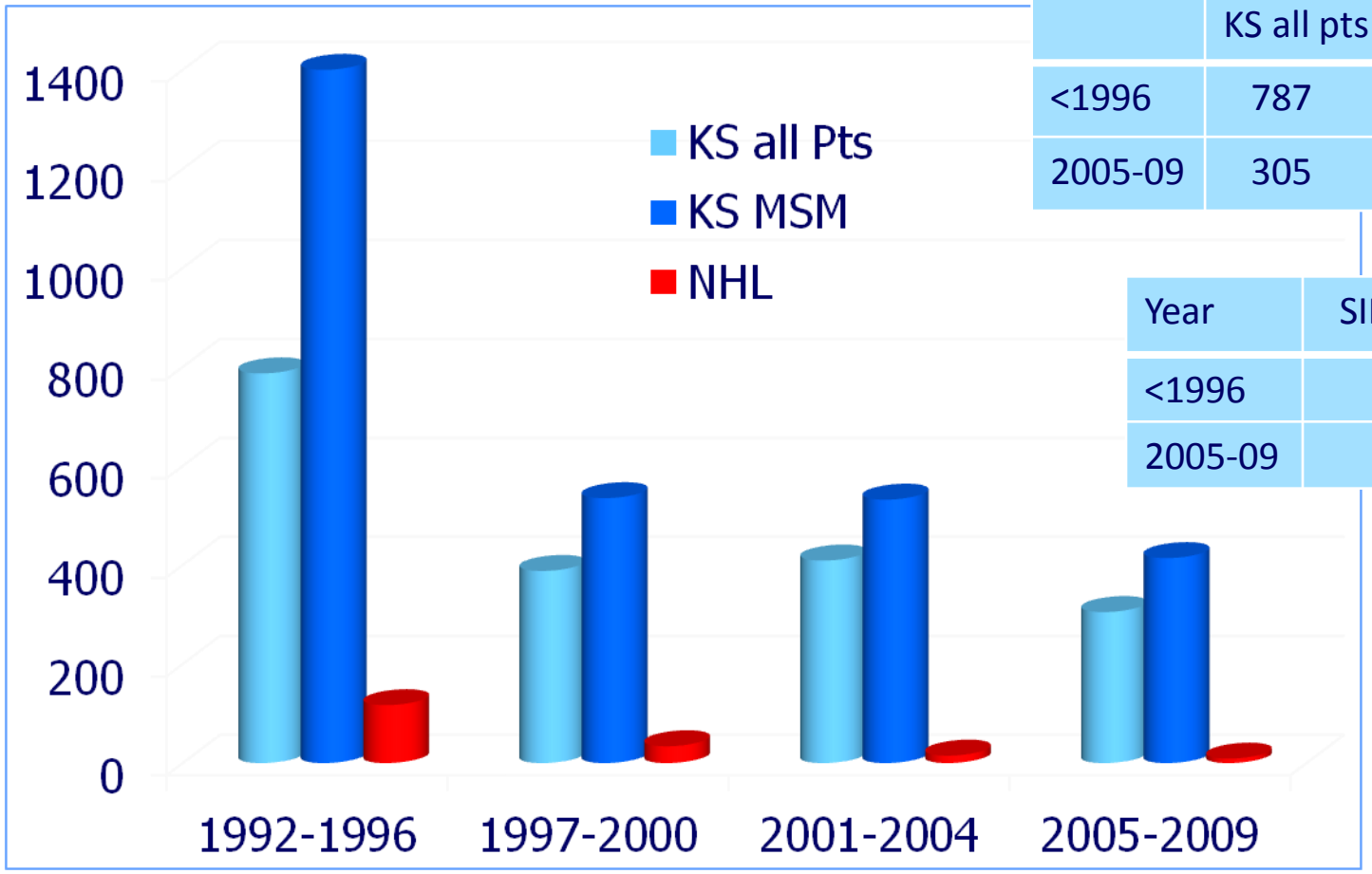
of people living with AIDS, AIDS-defining cancers, non-
ancers, and all cancers in the United States during





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

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)



Year	SIR KS all pts	KS MSM	NHL
<1996	787	1400	117
2005-09	305	414	9

Year	SIR Cervical ca
<1996	12
2005-09	5

Hleyhel M. et al. CID 2013

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

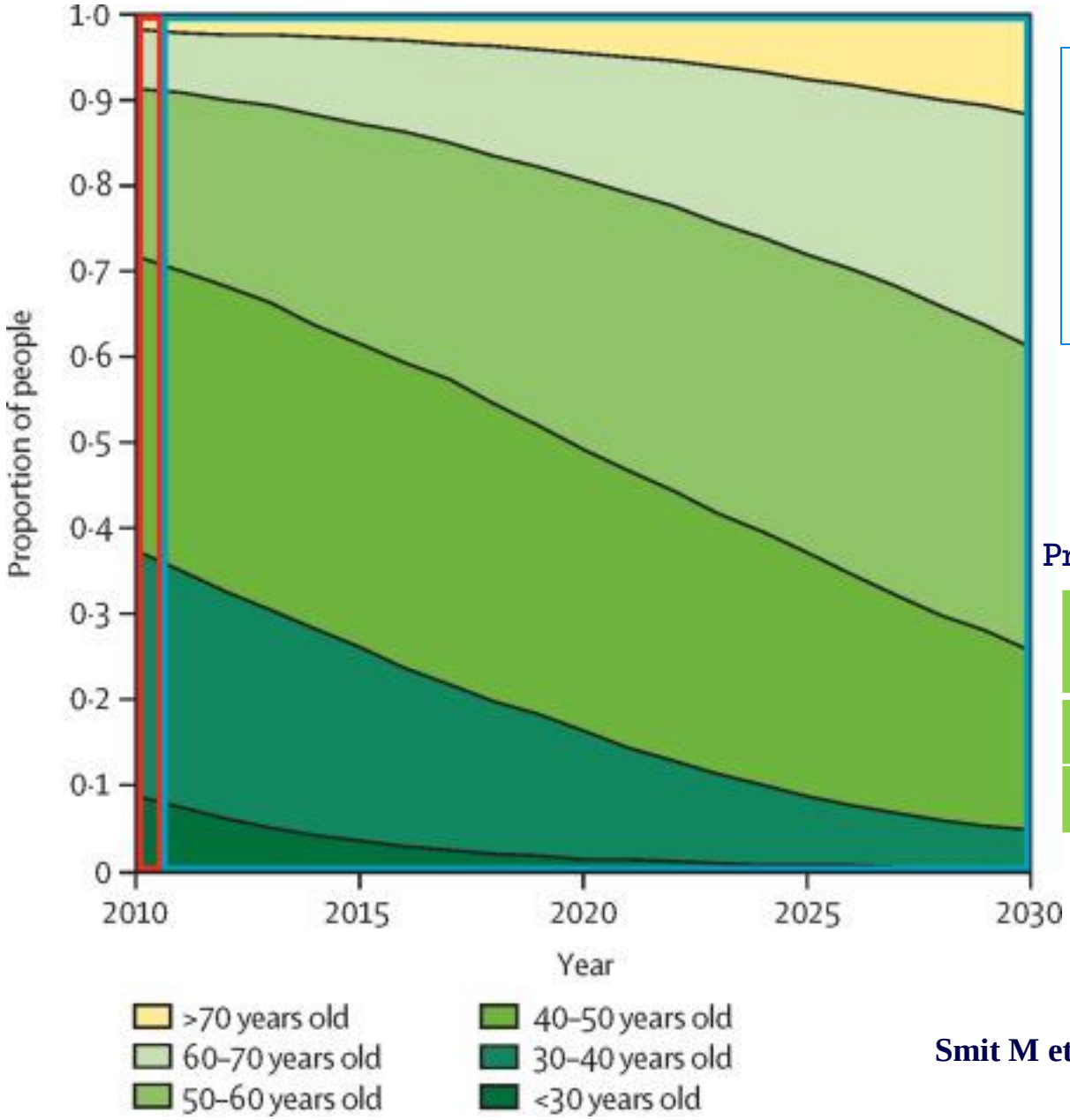
Cancer	Grulich (2007) SIR (95%CI	Engels (2008) SIR (95%CI)	Dal Maso (2009) SIR (95%CI	Franceschi (2010) SIR (95%CI
All NADCs		**1.9** (1.8-2.1)		**3.0** (2.6-3.6)
Hodgkin's lymphoma	**11.0** (8.4-14.4)	**6.7** (4.5-9.5)	**21** (15-28)	**28** (15-48)
Anal cancer	**29** (22-38)	**9.1** (5.1-15)	**44** (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)

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)

Lee JY. et al. J Cancer Epidemiol 2016

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

Smit M et al. www.thelancet.com/infection 2015

Cancer Risk among 183.542 HIV-infected Older (age ≥ 50 yrs) compared to general population in the USA (1996--2012:Total n°of Cancers: 10.371)

Mahale P et al CID 2018

Cancer	SIR (95%CI)
All Cancers	**1.16** (1.14-1.18)
AIDS-defining	
Kaposi Sarcoma	**103.34** (92.62-114.97)
NHL	**3.05** (2.88-3.22)
Diffuse Large B-Cell Lymphoma	**6.12** (5.67-6.61)
Burkitt Lymphoma	**13.8** (11.23-16.68)
NAS Lymphoma	**1.32** (1.18-1.46)
CNS Lymphoma	**47.39** (37.21-59.49)

Message: Cancer risk is elevated among older HIV-infected individuals

Cancer Risk among 183.542 HIV-infected Older (age ≥ 50 yrs) compared to general population in the USA (1996--2012:Total n°of Cancers: 10.371)

Mahale P et al CID 2018

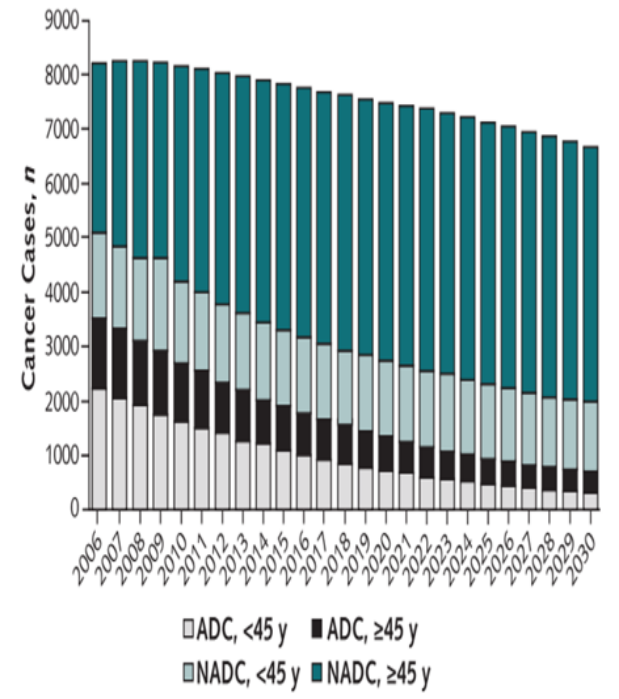
Non-AIDS Defining Cancers	SIR (95%CI)
Anus	**14.0** (12.82-15.25)
Liver	**2.91** (2.71-3.12)
Oral Cavity/Pharynx	**1.66** (1.51-1.81)
Lung	**1.71** (1.63-1.79)
Hodgkin Lymphoma	**7.61** (6.70-8.70)
Prostate	0.47 (0.45-0.50)
Colorectum	0.63 (0.57-0.70)
Breast	0.61 (0.54-0.68)

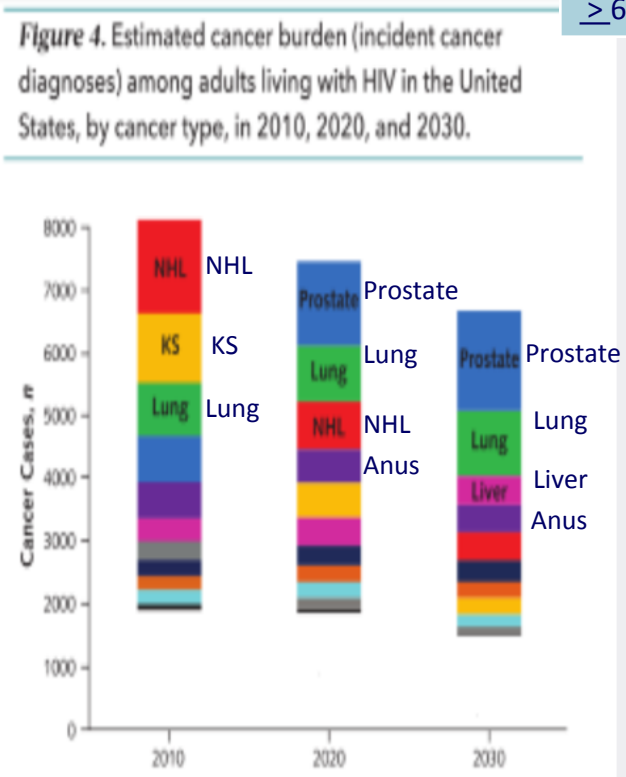
Cancer risk was significantly increased for anal cancer,HD, liver,lung and oropharynx cancers and was reduced for breast,prostate and colorectal cancers

Project Cancer Burden in HIV-infected Adults in USA through 2030

Age	2010	2030	%
45-64	39	48	
≥65	8.5	27	

Shiels M P et al Ann Int Med 2018





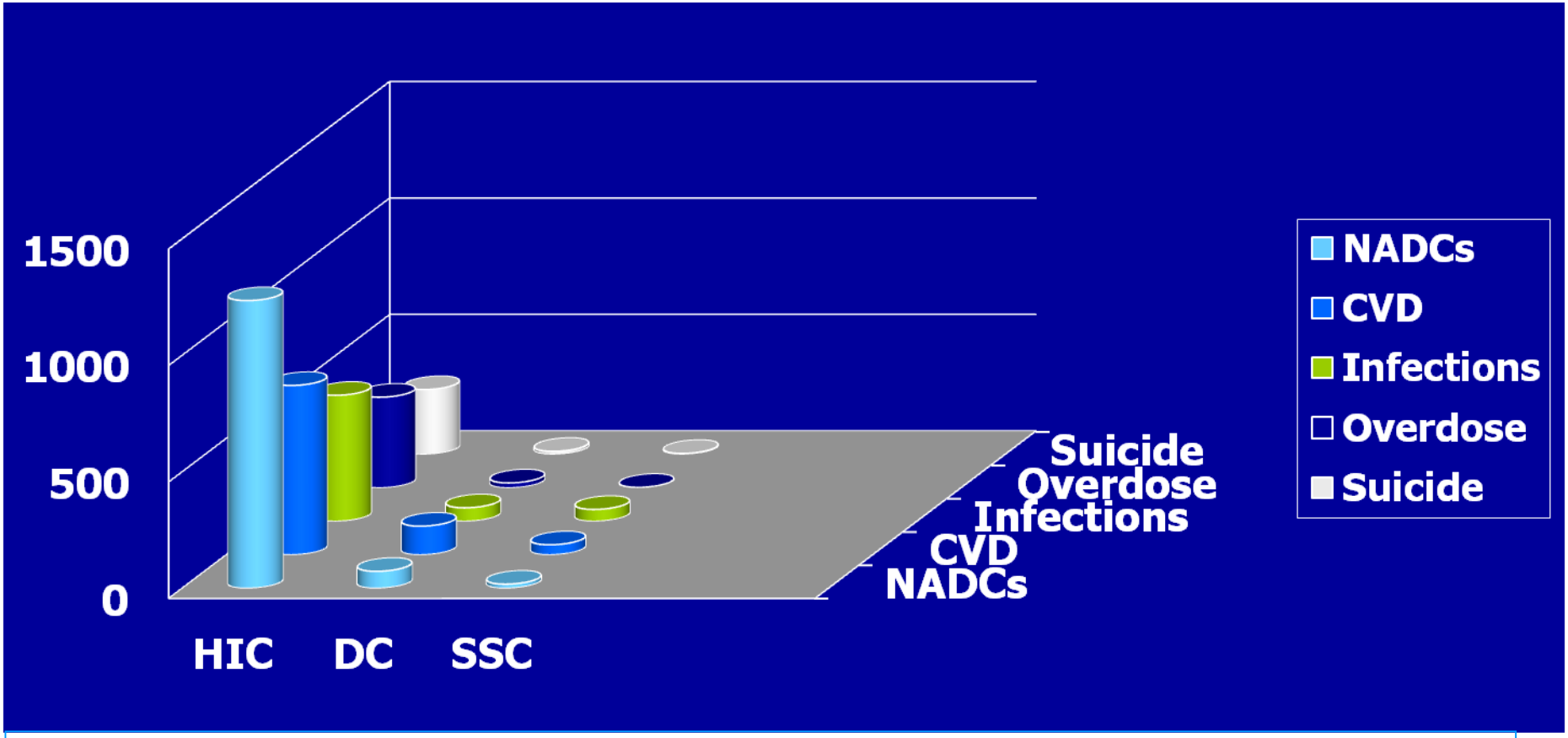
Dramatic shift in the cancer burden over time among HIV-infected people.

With declines in AIDS-cancers and the aging of the HIV-infected population,in 2030 the most common cancer will be prostate, lung and liver cancers

Cancer will remain an important comorbid condition. Expanded access to cART and cancer prevention, screening and treatment is needed

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

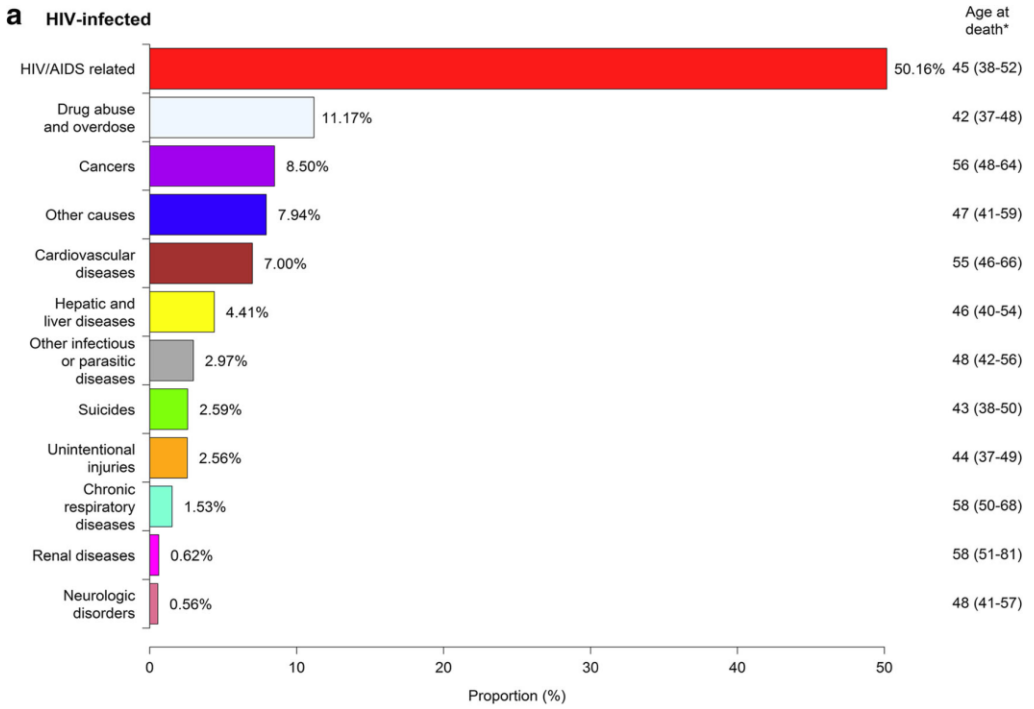
Farahani M. et al. Int J STD AIDS 2016

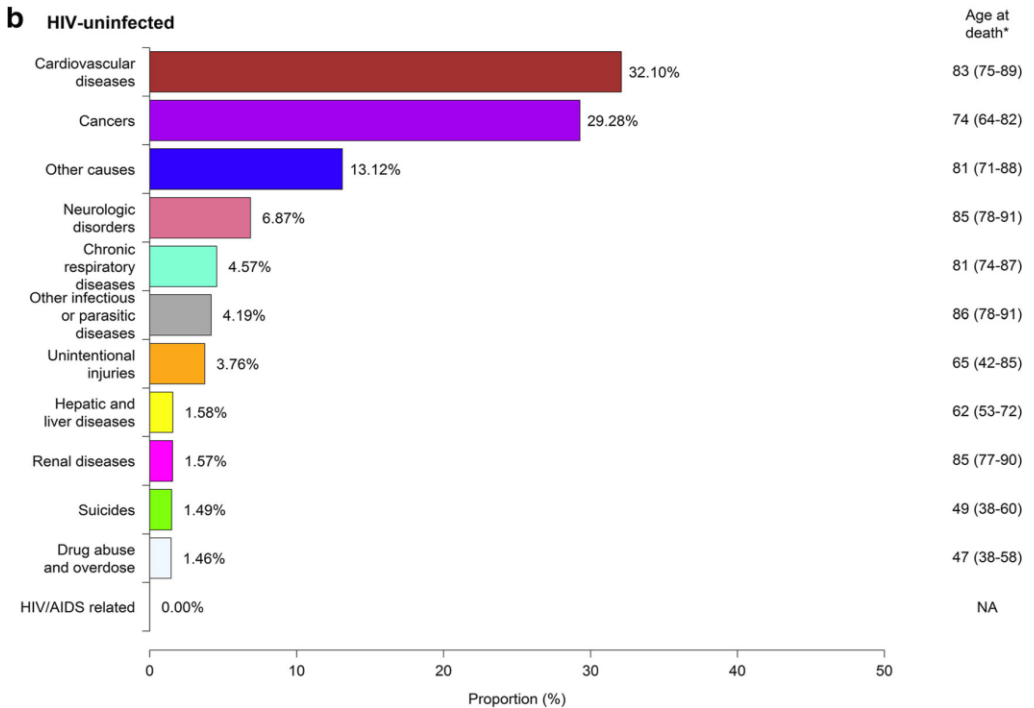


***Message*:**

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

Changes in mortality rates and cause of death in 13.729 HIV-infected and 510.313 uninfected individuals (Canada 1996-2012)





Eyawo O et al. J BMC Infectious Disease 2017

Changes in mortality rates and cause of death in 13.729 HIV-infected and 510.313 uninfected individuals (Canada 1996-2012)

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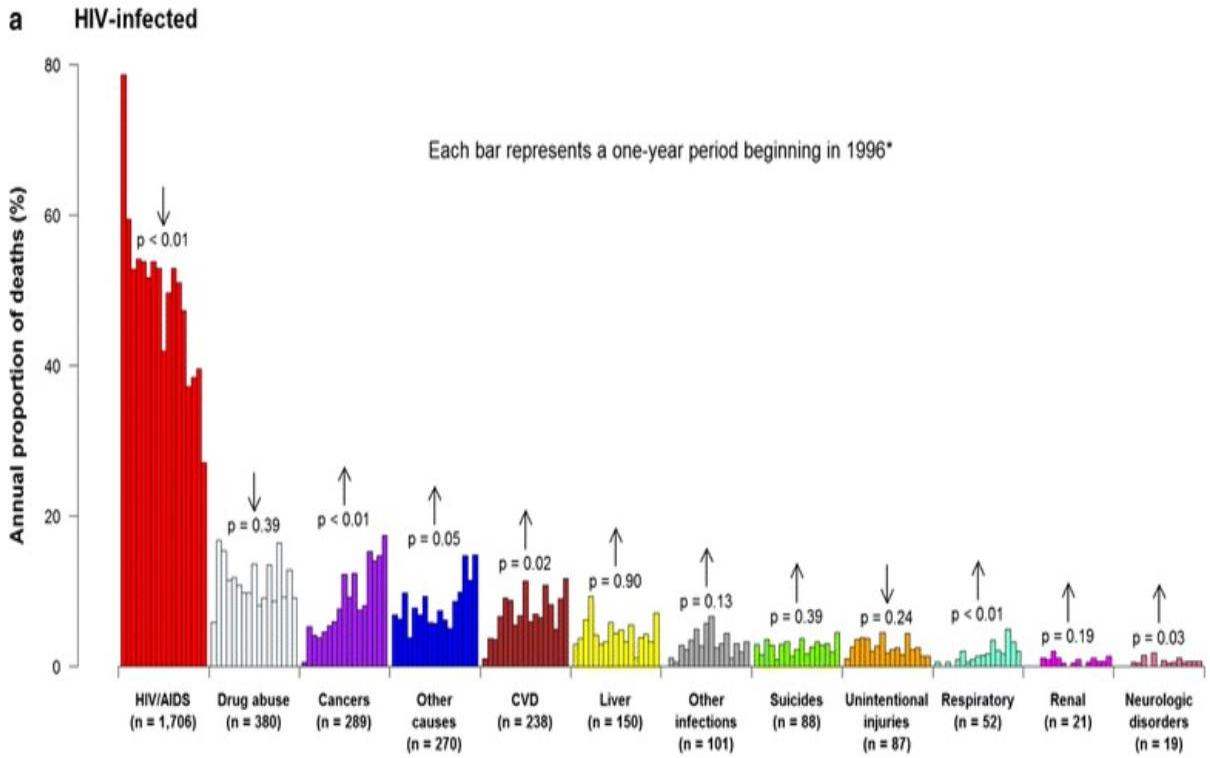

Mortality rate from AIDS-related causes, including AIDS-Defining Cancers.decreased by 94% in the cART era. NADCs are currently the leading non-AIDS related cause of death accounting for 17% of cases.

Cancer-Attributable Mortality among 46.956 HIV-infected Patients *on cART in North American HIV Cohorts (1995-2009)

* Mean follow-up 5.7 yrs

Engels AE. et al CID 2017

Cancer	Adjusted HR	Population Attributable Fractions (PAF) %	(95% CI)
Total Cancers	**5.54**	**9,8**	(9.1-10.5)
AIDS Defining	**4.11**	**2.6**	(2.2-2.9)
Kaposi Sarcoma	**2.06**	**0.5**	(0.3-0.8)
Non-Hodgkin L.	**7.23**	**2.0**	(1.7-2.3)
Cervix	**-**	**0**	-
Non-AIDS Defining	**5.91**	**7.1**	(6.5-7.7)
			(2.0-2.6)
Lung	**14.71**	**2.3**	
Anus	**2.73**	**0.4**	(0.3-0.6)
Liver	**31.26**	**0.9**	(0.7-11)
Other	**4.04**	**3.4**	(2.9-3.8)

Approximately 10% of deaths in HIV-infected pts prescribed cART were attributable to cancer. A large proportions of PAFs were associated with NHL, lung and liver cancer

Cancer-Attributable Mortality among 46.956 HIV-infected Patients *on cART in North American HIV Cohorts (1995-2009)

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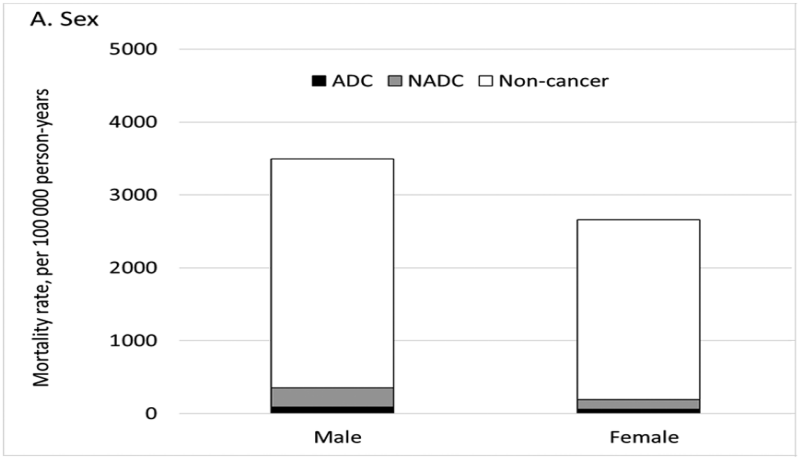
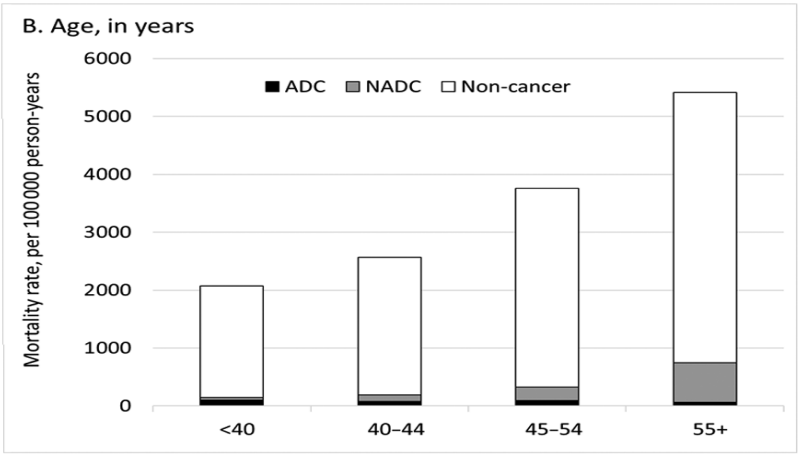
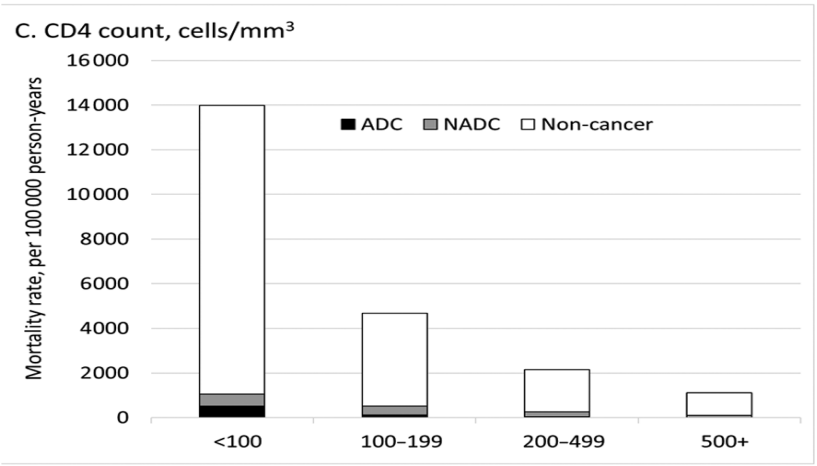
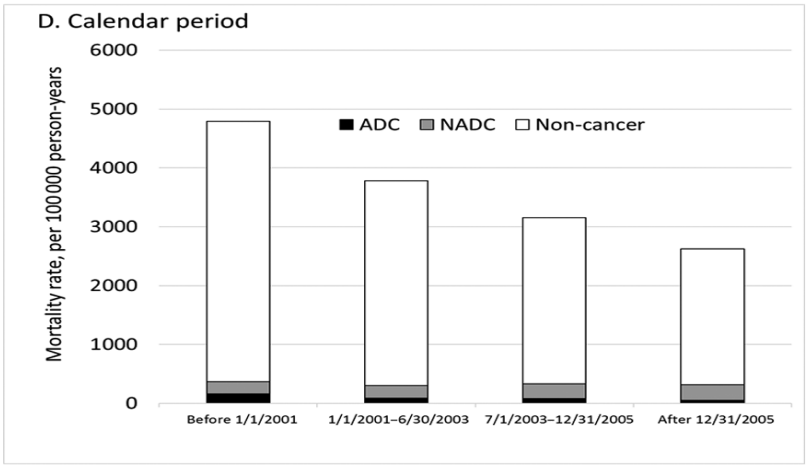
Engels AE. et al CID 2017





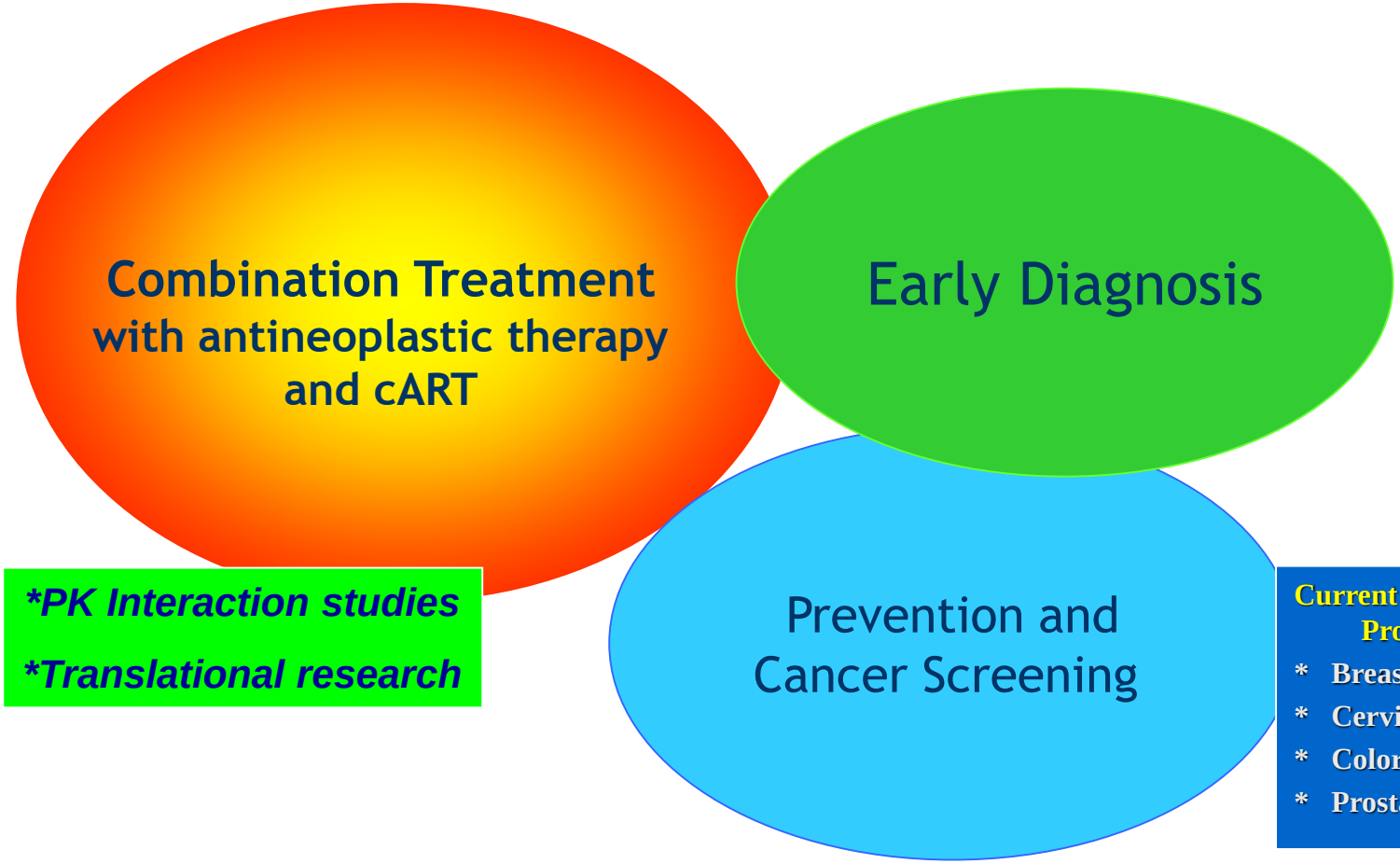




Cancer-attributable mortality for NADCs were higher in males and increased strongly with age (13% in pts aged 55+ yrs) and over time (10% in 2001-2005).

HIV and Cancer

Key Strategies



***PK Interaction studies**

***Translational research**

Current Screening Programs:

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

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Programmi di screening per la popolazione generale (1).

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	°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 ≥ 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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Screening Carcinoma Cervice Uterina in HIV
Linee Guida Italiane

Popolazione	Procedura Screening	Tempistica
Donne sessualmente attive. Lo screening deve iniziare entro un anno dall'inizio dell'attività sessuale o alla diagnosi di HIV.	PAP test convenzionale - - PAP test su base liquida -solo Pap test o 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://www.salute.gov.it/hiv/hiv.jsp.

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Screening Carcinoma Anale in HIV
Linee Guida Italiane

Popolazione	Procedura Screening	Tempistica
-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

http://www.salute.gov.it/hiv/hiv.jsp.

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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

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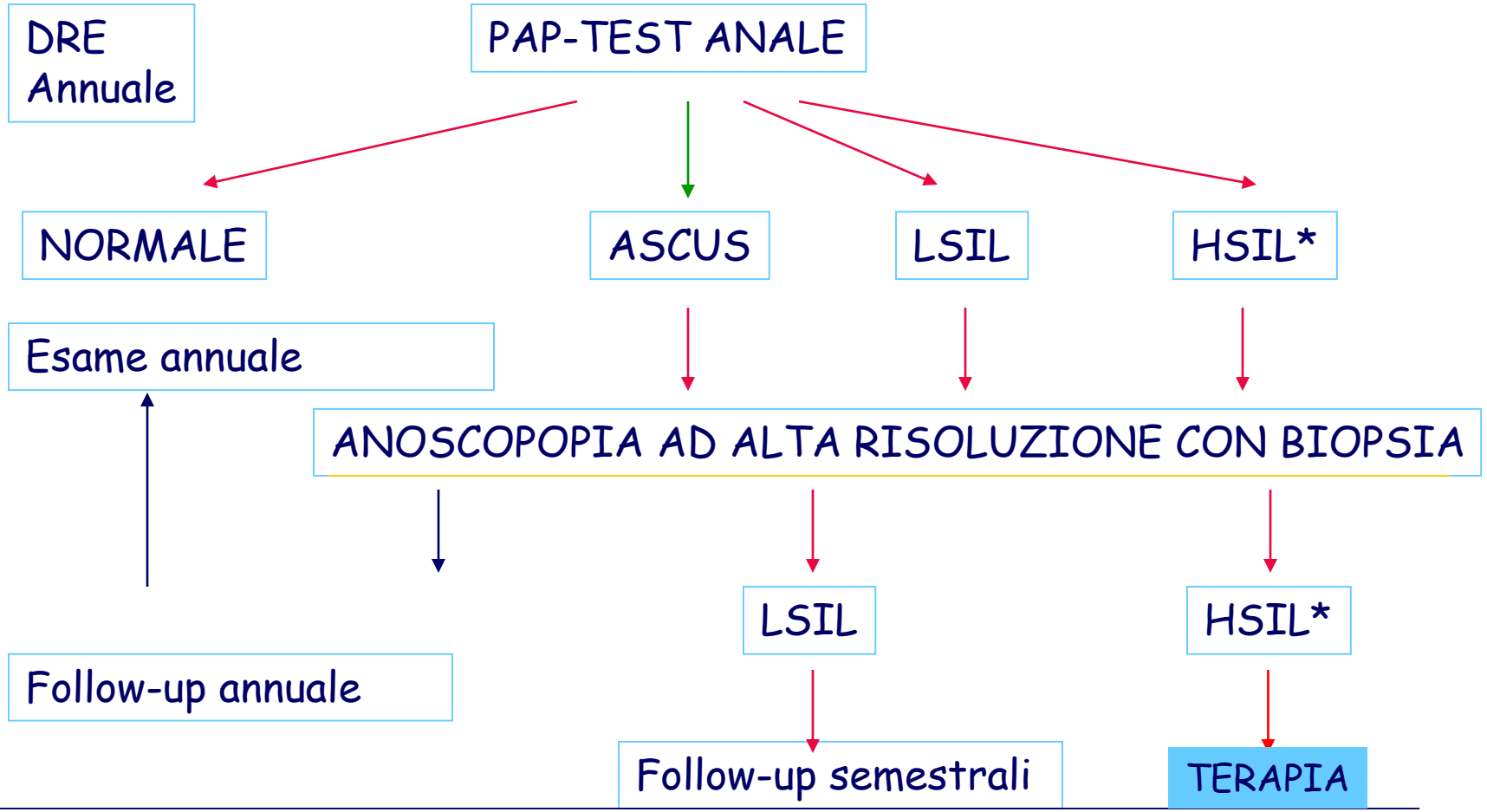
LINEE GUIDA PER DIAGNOSI E TERAPIA DELLE DISPLASIE ANALI INTRAEPITELIALI



Palefsky JM et al, Semin Oncol 2000

Altri Screening Specifici per HIV
Linee Guida Italiane

Tumore	Popolazione	Procedura Screening	Tempistica
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 pacchi di sigarette/anno; -se ex-fumatori entro 15 anni dalla cessazione - Età> 40 aa**	TAC spirale a basso dosaggio senza mdc	Annuale
Cute	- Pelle chiara; - Razza bianca non-ispanica	Esame della cute Dermatoscopia	Annuale

http://www.salute.gov.it/hiv/hiv.jsp.

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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 <30 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

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***

Cancer Burden Attributable to Smoking among 51.441 HIV-infected Patients in North American HIV Cohorts

Altekruse SF. et al AIDS 2018

* Mean follow-up 3.8 yrs

Cancer	Adjusted HR	Population Attributable Fractions (PAF) %	(95% CI)
All Cancers	**1.41**	**22**	(1.26-1.58)
Smoking -related	**2.65**	**54**	(2.07-3.39)
Lung cancer	**21.73**	**95**	(6.7-68.71)
Other	**1.77**	**35**	(1.37-2.28)
Not smoking-related	**1.16**	**10**	(1.02-1.32)

Enhanced smoking cessation efforts targeted to HIV-infected individuals are needed

Potential opportunities for Prevention of HIV-HPV Cancers: MajorVaccine Trials

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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.