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HIV e neoplasie: vecchie e nuove

Dott. Rodolfo Punzi

U.O.C. Malattie Infettive

Direttore: Dott. M. Mazzeo

Causes of Death in HIV-1–Infected Patients Treated with Antiretroviral Therapy, 1996–2006: Collaborative Analysis of 13 HIV Cohort Studies

The Antiretroviral Therapy Cohort Collaboration[a]

Table 3. Frequencies of Specific Causes of Death in the 1597 Patients Who Died, with Crude Incidence Rates per 1000 Person-Years of Follow-up

Cause of death	No (%) of patients[a] (n = 1597)	Incidence rate (95% CI) per 1000 years
AIDS		
All	792 (49.6)	5.12 (4.78–5.49)
Nonspecified AIDS	190 (11.9)	1.23 (1.07–1.42)
AIDS infection	366 (22.9)	2.37 (2.14–2.62)
AIDS malignancy	236 (14.8)	1.52 (1.34–1.73)
Non-AIDS malignancy	189 (11.8)	1.22 (1.06–1.41)
Non-AIDS infection	131 (8.2)	0.85 (0.71–1.01)
CVD[b]		
All	126 (7.9)	0.81 (0.68–0.97)
MI/IHD	51 (3.2)	0.33 (0.25–0.43)
Stroke	23 (1.4)	0.15 (0.10–0.22)
Other heart disease	52 (3.3)	0.34 (0.26–0.44)
Violence[c]		
All	124 (7.8)	0.80 (0.67–0.96)
Suicide	48 (3.0)	0.31 (0.23–0.41)
Substance abuse	42 (2.6)	0.41 (0.32–0.52)
Other violent death	34 (2.1)	0.22 (0.16–0.31)
Liver related		
All	113 (7.1)	0.73 (0.61–0.88)
Hepatitis related	63 (3.9)	0.41 (0.32–0.52)
Other liver related	50 (3.1)	0.32 (0.25–0.43)
Respiratory disease	25 (1.6)	0.16 (0.11–0.24)
Renal failure	24 (1.5)	0.16 (0.10–0.23)
Other causes with $n < 20$	73 (4.6)	0.47 (0.38–0.59)

NOTE. CI, confidence interval; CVD, cardiovascular disease; MI/IHD, myocardial infarction/ischemic heart disease.

[a] 39,272 patients with 154,667 years of follow-up.
[b] CVD includes MI/IHD, stroke, heart failure/unspecified, and other heart disease.
[c] Violence includes homicide, accident, suicide, and substance abuse, as well as ill-defined violent deaths.

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Excess Mortality for Non–AIDS-Defining Cancers among People with AIDS

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During the period 1999–2006, non–AIDS-defining cancers accounted for 7.4% of deaths among Italian people with AIDS. The risk of death was 6.6-fold higher than in the general population, being particularly elevated for virus-related cancers. The study findings highlighted the importance of monitoring the cancer burden on mortality for people with AIDS.

Clinical Infectious Diseases 2010; 51(9):1099–1101

Table 1. Observed and Expected Numbers of Deaths and Corresponding Standardized Mortality Ratios (SMRs) for Non–AIDS-Defining Cancers (NADCs) among 10,392 People with AIDS (35,224 Person-Years), Italy, 1999–2006

Cause of death: cancer type or site (ICD-10)	Median time from AIDS diagnosis to death (months)	Median age at death (years)	No. (%) of deaths		SMR (95% CI)
			Observed	Expected	
Lung (C34)	9.0	48.0	58 (24.6)	9.92	5.85 (4.44–7.57)
Liver (C22)	11.0	45.0	28 (11.9)	2.51	11.14 (7.39–16.12)
Hodgkin lymphoma (C81)	4.0	41.0	28 (11.9)	0.16	174 (115–251)
Head and neck (C00–C14, C30–C32)	17.5	49.5	18 (7.6)	2.20	8.17 (4.83–12.93)
Brain and central nervous system (C70–C72)	4.0	41.5	14 (5.9)	1.40	9.99 (5.44–16.80)
Myeloma and leukemia (C90, C91–C95)	7.5	46.0	10 (4.2)	1.70	5.89 (2.80–10.87)
Anus (C21)	24.0	45.0	9 (3.8)	0.03	270 (122–514)
Stomach (C16)	20.5	58.5	8 (3.4)	2.54	3.14 (1.34–6.23)
Pancreas (C25)	8.0	36.0	5 (2.1)	1.99	2.51 (0.79–5.91)
Other defined sites[a]	10.0	50.0	32 (13.6)	10.57	3.03 (2.07–4.28)
Unknown and ill-defined primary site[b]	12.0	46.0	26 (11.0)	2.16	12.06 (7.87–17.69)
All NADCs	9.0	46.0	236 (100)	35.83	6.59 (5.77–7.48)

ADC

- KS
- NHL
- Cervical cancer
- Primary central nervous system lymphoma (PCNSL)
- Primary effusion lymphoma (PEL)
- Plasmablastic lymphoma

NADC

Virus related

- Anal cancer
- HL
- Hepatocellular carcinoma
- Multicenter Castleman

Non virus related

- Non small lung carcinoma
- Testicular germ cell cancer
- Skin cancer
- Colorectal cancer
- Merkell cell carcinoma
- Penis precancer e cancer

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British HIV Association guidelines for HIV-associated malignancies 2014

12 Non-AIDS-defining malignancies

12.1 Introduction

This section aims to address the evidence-based guidelines for non-AIDS-defining cancers in people with HIV infection. It will exclude Hodgkin disease and anal cancer, which have been covered already. The cancers it will specifically address are:

- Testicular germ cell tumours
- Non-small cell lung cancer (NSCLC)
- Hepatocellular cancer (HCC)

There is very limited data available on:

- Colon cancer
- Head and neck cancer
- Melanoma
- Other urological cancers
- Haematological cancers
- Breast cancer

NADC

- Tumori anogenitali
- Linfoma di Hodgkin
- Cancro del polmone
- Epatocarcinoma
- Tumori del testicolo a cellule germinali
- Carcinomi cutanei non melanoma

Cancer Burden in the HIV-Infected Population in the United States

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Background Effective antiretroviral therapy has reduced the risk of AIDS and dramatically prolonged the survival of HIV-infected people in the United States. Consequently, an increasing number of HIV-infected people are at risk of non-AIDS-defining cancers that typically occur at older ages. We estimated the annual number of cancers in the HIV-infected population, both with and without AIDS, in the United States.

Methods Incidence rates for individual cancer types were obtained from the HIV/AIDS Cancer Match Study by linking 15 HIV and cancer registries in the United States. Estimated counts of the US HIV-infected and AIDS populations were obtained from Centers for Disease Control and Prevention surveillance data. We obtained estimated counts of AIDS-defining (ie, Kaposi sarcoma, non-Hodgkin lymphoma, and cervical cancer) and non-AIDS-defining cancers in the US AIDS population during 1991–2005 by multiplying cancer incidence rates and AIDS population counts, stratified by year, age, sex, race and ethnicity, transmission category, and AIDS-relative time. We tested trends in counts and standardized incidence rates using linear regression models. We multiplied overall cancer rates and HIV-only (HIV infected, without AIDS) population counts, available from 34 US states during 2004–2007, to estimate cancers in the HIV-only population. All statistical tests were two-sided.

Results The US AIDS population expanded fourfold from 1991 to 2005 (96 179 to 413 080) largely because of an increase in the number of people aged 40 years or older. During 1991–2005, an estimated 79 656 cancers occurred in the AIDS population. From 1991–1995 to 2001–2005, the estimated number of AIDS-defining cancers decreased by greater than threefold (34 587 to 10 325 cancers; $P_{trend} < .001$), whereas non-AIDS-defining cancers increased by approximately threefold (3193 to 10 059 cancers; $P_{trend} < .001$). From 1991–1995 to 2001–2005, estimated counts increased for anal (206 to 1564 cancers), liver (116 to 583 cancers), prostate (87 to 759 cancers), and lung cancers (875 to 1882 cancers), and Hodgkin lymphoma (426 to 897 cancers). In the HIV-only population in 34 US states, an estimated 2191 non-AIDS-defining cancers occurred during 2004–2007, including 454 lung, 166 breast, and 154 anal cancers.

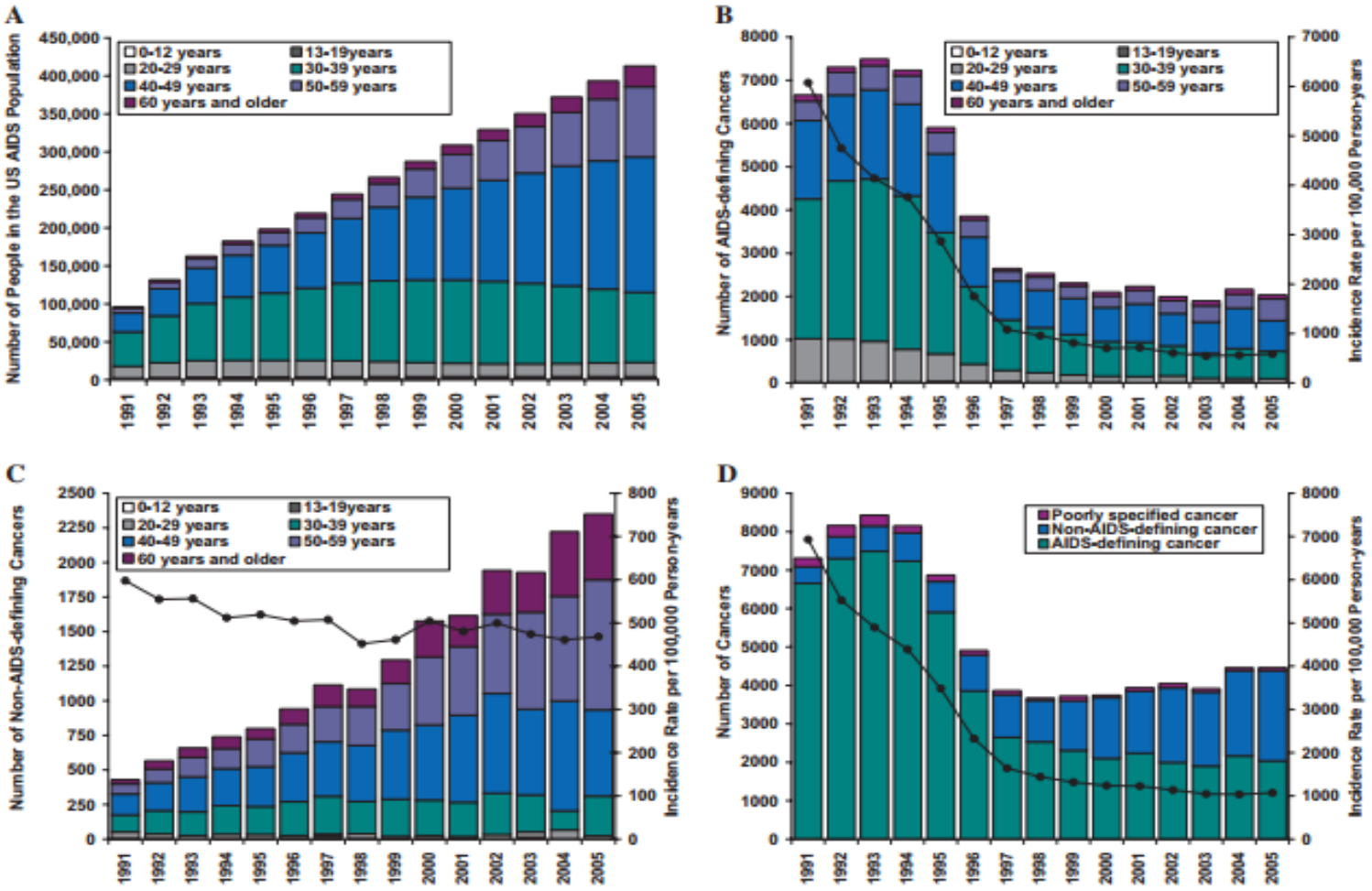
Conclusions Over a 15-year period (1991–2005), increases in non-AIDS-defining cancers were mainly driven by growth and aging of the AIDS population. This growing burden requires targeted cancer prevention and treatment strategies.

J Natl Cancer Inst 2011;103:753–762

- Il numero delle persone con AIDS è passato da 96179 del 1991 a 413.080 nel 2005 (CDC di Atlanta)
- 1991-1995 8,2% NADC
- 2001-2005 49,6% NADC, 48,3% ADC
- Rispetto alla popolazione generale i pazienti con infezione da HIV hanno un aumentato rischio di ammalarsi di patologie neoplastiche:
  - ✓ 3460 volte in più per il SK
  - ✓ 77 volte in più per il NHL
  - ✓ 29 volte in più il cancro ano-genitale
  - ✓ 11 volte in più il HL
  - ✓ 6 volte in più per il cancro della cervice uterina
  - ✓ 5 volte in più l'epatocarcinoma
  - ✓ 3 volte in più per il cancro del polmone

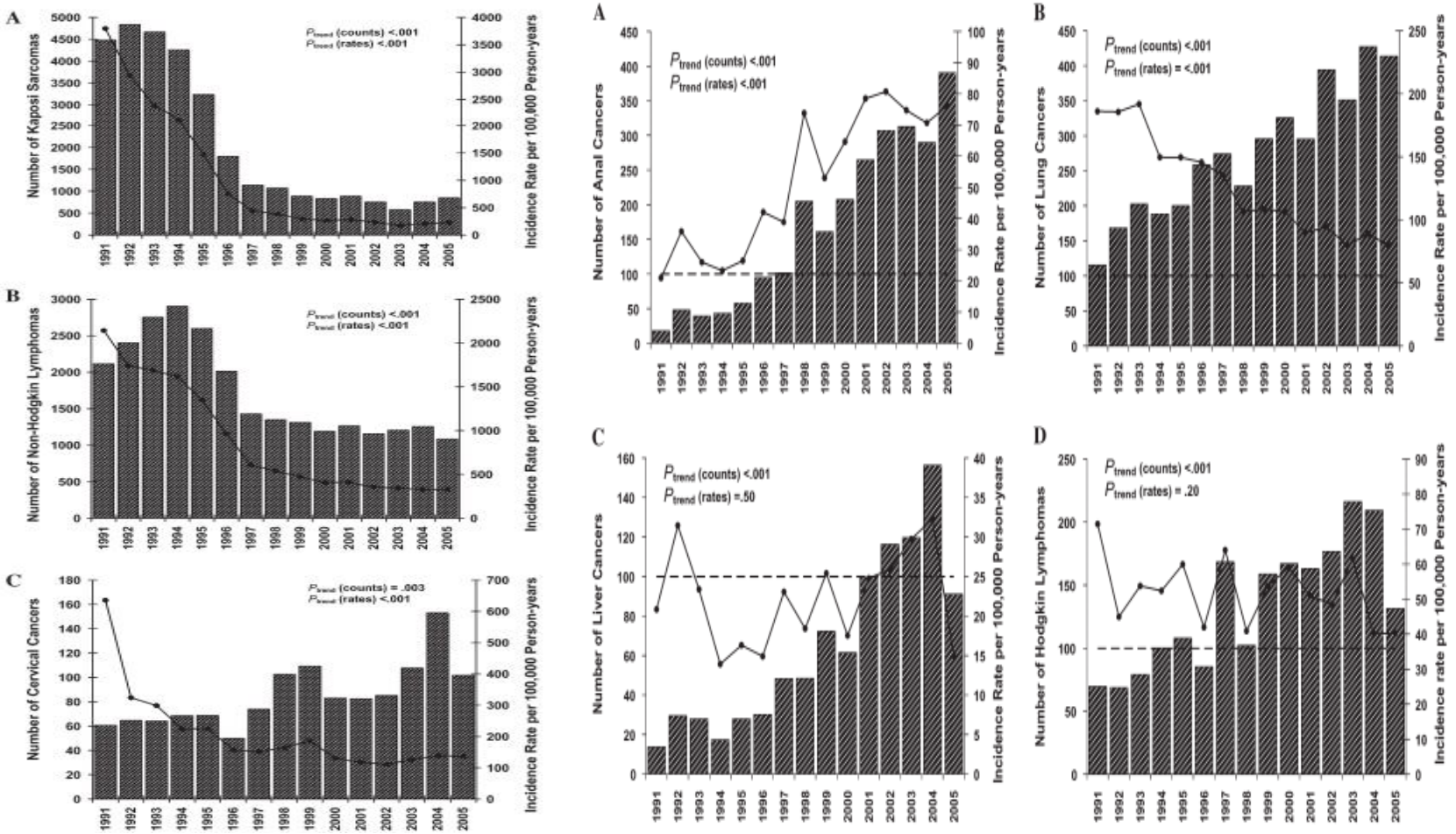
J Natl Cancer Inst 2011;103:753–762

Cancer Burden in the HIV-Infected Population in the United States



J Natl Cancer Inst 2011;103:753–762

Cancer Burden in the HIV-Infected Population in the United States



J Natl Cancer Inst 2011;103:753–76

Cancer Burden in the HIV-Infected Population in the United States

Table 2. Cancer burden in the HIV-infected population in the United States*

Cancer	Estimated number of cancers in people living with AIDS in 50 US states and DC				Estimated number of cancers in people in 34 US states living with AIDS or HIV-only	
	1991–1995	1996–2000	2001–2005	P_{trend}†	AIDS 2004–2007	HIV-only 2004–2007
AIDS-defining cancers						
Kaposi sarcoma	21 483	5727	3827	<.001	2941	—
Non-Hodgkin lymphoma	12 778	7292	5968	<.001	4584	—
Cervix	327	419	530	.003	383	—
All AIDS-defining cancers	34 587	13 439	10 325	<.001	7869	—
Non-AIDS-defining cancers						
Oral cavity and pharynx	181	341	503	<.001	297	103
Esophagus	41	62	254	.002	86	25
Stomach	50	78	118	.06	67	41
Small intestine	13	25	24	.48	12	13
Colorectum	108	230	438	<.001	237	135
Anus	206	770	1,564	<.001	751	154
Liver	116	261	583	<.001	269	91
Pancreas	25	62	188	<.001	76	63
Larynx	70	192	317	<.001	161	50
Lung	875	1383	1882	<.001	1143	454
Bone	5	9	2	.15	2	9
Soft tissue including heart	33	43	112	.06	40	6
Melanoma	76	154	264	.001	120	25
Female breast	36	198	337	<.001	203	166
Uterine corpus	7	15	47	.04	19	20
Ovary	10	21	28	.10	31	20
Vagina	0	0	9	.10	4	0
Vulva	10	23	74	.01	39	17
Prostate	87	322	759	<.001	271	147
Testis	88	73	81	.95	38	22
Penis	13	35	64	.06	23	4
Bladder	31	62	70	.07	50	19
Kidney	66	97	208	<.001	104	75
Brain	44	53	61	.48	45	9
Thyroid	20	51	84	.02	47	34
Hodgkin lymphoma	426	682	897	<.001	546	150
Myeloma	63	93	159	.02	71	41
Lymphocytic leukemia	36	44	36	.88	29	13
Myeloid and monocytic leukemia	47	101	118	.06	67	25
Mesothelioma	12	9	14	.80	6	0
Miscellaneous	396	511	760	<.001	431	160
All non-AIDS-defining cancers	3193	6011	10 059	<.001	5372	2191
Poorly specified malignancy	1142	464	438	<.001	340	113
Total cancers	38 922	19 913	20 821	<.001	13 581	2303

J Natl Cancer Inst 2011;103:753–76

Worm et al. BMC Infectious Diseases 2013, 13:471
http://www.biomedcentral.com/1471-2334/13/471

BMC Infectious Diseases

RESEARCH ARTICLE Open Access

Non-AIDS defining cancers in the D:A:D Study - time trends and predictors of survival: a cohort study

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Abstract

Background: Non-AIDS defining cancers (NADC) are an important cause of morbidity and mortality in HIV-positive individuals. Using data from a large international cohort of HIV-positive individuals, we described the incidence of NADC from 2004–2010, and described subsequent mortality and predictors of these.

Methods: Individuals were followed from 1st January 2004/enrolment in study, until the earliest of a new NADC, 1st February 2010, death or six months after the patient's last visit. Incidence rates were estimated for each year of follow-up, overall and stratified by gender, age and mode of HIV acquisition. Cumulative risk of mortality following NADC diagnosis was summarised using Kaplan-Meier methods, with follow-up for these analyses from the date of NADC diagnosis until the patient's death, 1st February 2010 or 6 months after the patient's last visit. Factors associated with mortality following NADC diagnosis were identified using multivariable Cox proportional hazards regression.

Results: Over 176,775 person-years (PY), 880 (2.1%) patients developed a new NADC (incidence: 4.98/1000PY [95% confidence interval 4.65, 5.31]). Over a third of these patients (327, 37.2%) had died by 1st February 2010. Time trends for lung cancer, anal cancer and Hodgkin's lymphoma were broadly consistent. Kaplan-Meier cumulative mortality estimates at 1, 3 and 5 years after NADC diagnosis were 28.2% [95% CI 25.1-31.2], 42.0% [38.2-45.8] and 47.3% [42.4-52.2], respectively. Significant predictors of poorer survival after diagnosis of NADC were lung cancer (compared to other cancer types), male gender, non-white ethnicity, and smoking status. Later year of diagnosis and higher CD4 count at NADC diagnosis were associated with improved survival. The incidence of NADC remained stable over the period 2004–2010 in this large observational cohort.

Conclusions: The prognosis after diagnosis of NADC, in particular lung cancer and disseminated cancer, is poor but has improved somewhat over time. Modifiable risk factors, such as smoking and low CD4 counts, were associated with mortality following a diagnosis of NADC.

Keywords: HIV, Non-AIDS defining cancers, Incidence, Trends, Prognosis

BMC Infectious Disease 2013 13:471

- Studio prospettico: 41.746 pazienti HIV positivi
- Coorte DAD: 1 gennaio 2004 / 1 febbraio 2010
- 880 pazienti (2,1%) si ammalarono di NADC
- 612 pazienti (1,4%) si ammalarono di ADC
- La prognosi dei pazienti HIV+ è senz'altro per i NADC peggiore che per per i pazienti HIV negativi: mortalità ad 1 anno 28%, a 3 anni 42%, a 5 anni 47%
- Fattori prognostici negativi sono: cancro del polmone, sesso maschile, etnia non caucasica, fumo

Table 2 Summary of NADC and ADC reported in the D:A:D study from 2004-2010

	n (% of total events)
Number of NADC events	*880 (100.0)*
Lung cancer	140 (15.9)
Hodgkin's lymphoma	112 (12.7)
Anal cancer	79 (9.0)
Head and neck cancers	71 (8.1)
Liver cancer	59 (6.7)
Prostate	57 (6.5)
Breast cancer	43 (4.9)
Malignant melanoma	31 (3.5)
Colon cancer	26 (3.0)
Bladder cancer	21 (2.4)
Rectal	20 (2.3)
Gynecological cancers*	14 (1.6)
Stomach	13 (1.5)
Penile cancer	12 (1.4)
Kidney cancers	12 (1.4)
Acute myeloid leukemia	11 (1.3)
Metastasis of adenocarcinoma	9 (1.0)
Testicular	9 (1.0)
Lip cancer	6 (0.7)
Uterus	5 (0.6)
Brain cancer	5 (0.6)
Multiple myeloma	5 (0.6)
Metastasis of other cancer type	5 (0.6)
Metastasis of squamous cell carcinoma	5 (0.6)
Metastasis unspecified	4 (0.5)
Chronic lymphatic leukemia	2 (0.2)
Chronic myeloid leukemia	2 (0.2)
Connective tissue cancer	2 (0.2)
Bone cancer	1 (0.1)
Acute lymphatic leukemia	1 (0.1)
Leukemia unspecified	1 (0.1)
Type unknown	8 (0.9)
Unknown primary cancer	7 (0.8)
Other**	82 (9.3)
Number of ADC events	*621 (100.0)*
Kaposi's sarcoma	331 (53.3)
Non-Hodgkin's lymphoma	251 (40.4)
Cervical carcinoma	46 (7.4)

HIV/AIDS BRIEF REPORT

Incidence of Malignancies in HIV-Infected Patients and Prognostic Role of Current CD4 Cell Count: Evidence from a Large Italian Cohort Study

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Clinical Infectious Diseases 2010; 509(9): 1316-1321

- Studio prospettico, 6695 pazienti
- Arruolamento 1997-2002
- Durata mediana di follow up: 58 mesi

- 252 (3,76%) neoplasie

169 (67%) ADM

- 94 SK
- 61 LNH
- 14 Cervical cancer

83(33%) NADM

- 22 LH
- 16 urogenital
- 14 liver cancer
- 9 lung cancer

- Il rischio di ammalarsi di ADM o NADM era più alto per conte di CD4+ più basse
- A più basse conte di CD4+ maggior rischio di ADM
- Il rischio di ADM e NADM era uguale a più alte conte di CD4+

Clinical Infectious Diseases 2010; 50(9):1316–1321

HIV Med. 2013 Sep;14(8):481-90. doi: 10.1111/hiv.12034. Epub 2013 Apr 7.

Incidence of AIDS-defining cancers and virus-related and non-virus-related non-AIDS-defining cancers among HIV-infected patients compared with the general population in a large health district of Northern Italy, 1999-2009.

Calabresi A[1], Ferraresi A, Festa A, Scarcella C, Donato F, Vassallo F, Limina R, Castelli F, Quiros-Roldan E; Brescia HIV Cancer Study Group.

⊕ Collaborators (8)

⊕ Author information

Abstract

OBJECTIVES: The aim of the study was to investigate the incidence of AIDS-defining cancers (ADCs) and virus-related and non-virus-related non-AIDS-defining cancers (NADCs) in HIV-infected patients compared with the general population, and to assess the risk factors associated with these malignancies.

METHODS: We performed a retrospective cohort study for the period from 1999 to 2009 of HIV-infected patients residing in the Local Health Authority of Brescia (northern Italy). Observed cancers in patients with HIV infection were compared with expected cancers in the population living in the same area using standardized incidence ratios (SIRs). Risk factors were assessed using Poisson regression analysis.

RESULTS: A total of 5090 HIV-infected patients were included in the study, with 32 390 person-years of follow-up. We recorded 416 tumours in 390 HIV-infected patients. Two hundred of these (48.1%) were ADCs, 138 (33.2%) were non-virus-related NADCs and 78 (18.7%) were virus-related NADCs. An increased risk (SIR = 4.2) of cancers overall was found in HIV-infected patients. A large excess of ADCs (SIR = 31.0) and virus-related NADCs (SIR = 12.3) was observed in HIV-infected patients, while the excess risk for non-virus-related NADCs was small (SIR = 1.6). The highest SIRs were observed for Kaposi sarcoma among ADCs and for Hodgkin lymphoma among virus-related NADCs. Conversely, among non-virus-related NADCs, SIRs for a broad range of malignancies were close to unity. In multivariate analysis, increasing age and CD4 cell count < 50 cells/μL were the only factors independently associated with all cancers.

CONCLUSIONS: Among HIV-infected people there was an excess of ADCs and also of NADCs, particularly those related to viral infections. Ageing and severe immunodeficiency were the strongest predictors.

Coorte Brescia HIV Cancer Study, studio retrospettivo: 1999/ 2009

- 5090 pazienti
- 416 tumori in 390 pazienti
  - 200 (48,1%): ADC
  - 138 (33,2%): NADC virus correlati
  - 78 (18,7%): NADC non virus correlati

- SIR 4,2 HIV+ HIV-
  - SIR 31 ADC
  - SIR 12,3 NADC virus correlati
  - SIR 1,6 NADC non virus correlati

Table 1 | **HIV-associated malignancies**

Tumour type	Relative risk*	Viral co-factors (prevalence of viral DNA in tumours)	Reported effects of HAART‡ on incidence	Reported effects of HAART‡ on outcome
AIDS-defining§				
KS	258	HHV8 (100%)	Decreased	Regression/remission
NHL	78.1	EBV, HHV8	Decreased	Improved survival/ regression
Burkitt's (classic form)	103	EBV (30%)	Unchanged/decreased	Improved survival
DLCL, centroblastic	NA	EBV (40%)	Unchanged/decreased	Improved survival
DLCL, immunoblastic	134	EBV LMP1 (90%)	Decreased	Improved survival
PCNS	175	EBV LMP1 (100%)	Decreased	Regression (anecdotal evidence)
PEL	NA	HHV8 (100%), EBV (80%)	NA	Regression (anecdotal evidence)
Uterine cervix (invasive)	8.8	HPV (100%)	Unchanged	Regression (anecdotal evidence)
Non-AIDS-defining§				
HD	11	EBV LMP1 (80–100%)	Unchanged/increased	Improved survival
Lung	2.8	?	Increased	Prolonged time from HIV infection to tumour development
Liver	5.1‖	HBV; HCV	Unchanged	Worsening
Skin (non-KS)	20.9‖	HPV (non-melanomatous)	?	?
Anal	49.9	HPV	?	Regression (anecdotal)
Uterine cervix (pre-invasive)	9.3	HPV	?	No effect/regression; longer time to relapse
Testis	1.4	?	?	Unchanged survival

*Calculated as standardized incidence ratio (SIR) in the United States population before the widespread use of highly active antiretroviral therapy (HAART). SIRs are from REF. 26 for AIDS-defining tumours, Hodgkin's disease (HD), lung cancer, anal cancer, pre-invasive cervical cancer and testicular cancer; and from REF. 189 for liver and skin cancer. ‡For references relative to AIDS-defining tumours as well as to HD, pre-invasive cervical cancer and anal cancer, see main text; for other non-AIDS-defining tumours, see REFS 8,190,192,193. §AIDS-defining tumours, like opportunistic infections, are considered to mark AIDS onset in HIV-infected individuals. ‖SIRs were calculated for men. DLCL, diffuse large-cell lymphoma; EBV, Epstein–Barr virus; HBV, hepatitis B virus; HCV, hepatitis C virus; HHV8, human herpesvirus type 8; HPV, human papillomavirus; KS, Kaposi's sarcoma; LMP1, latency membrane protein 1; NA, not available; NHL, non-Hodgkin's lymphoma; PCNS, primary-nervous-system lymphoma; PEL, primary effusion lymphoma.

- **Il rischio di ammalarsi di Cancro del polmone è tre volte più alto nel paziente con infezione da HIV**

- **L'infezione da HIV non sembra avere un ruolo diretto nella patogenesi del tumore polmonare, ma è stato ipotizzato che *l'inflammation* HIV indotta nei polmoni possa predisporre il danno del fumo.**

- **Inoltre certamente la storia di patologie polmonari AIDS correlate (PCP e tubercolosi) pregresse è associata con una maggiore probabilità di ammalarsi di Cancro del polmone**


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Non-AIDS-defining cancers among HIV-infected people

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National Cancer Institute

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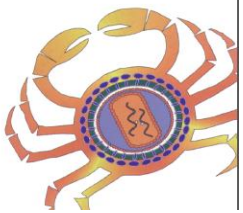

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

P9. Chronic Inflammation and Lung Cancer

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Lung cancer is the most common cause of cancer-related mortality in the U.S. general population. Tobacco smoking is the predominant risk factor for lung cancer, accounting for approximately 90% of all lung cancers. Additionally, chronic pulmonary inflammation is increasingly recognized as an important co-factor in lung carcinogenesis. Studies show that several indicators of inflammation, including chronic pulmonary infections (*Mycobacterium tuberculosis* and *Chlamydia pneumoniae*), pulmonary inflammatory conditions (asthma and chronic obstructive pulmonary disease), and polymorphisms in key inflammation genes (NFkappa B) are associated with increased risk of lung cancer. More recently, prospective epidemiologic studies have shown that circulating levels of several classes of inflammation markers, including acute-phase proteins (CRP and SAA), pro-and anti-inflammatory cytokines (IL-6, IL-8, sTNFRII and IL-1RA), chemokines (CXCL5/ENA78, CXCL13/BCA-1, CCL17/TARC, and CCL22/MDC), and growth and angiogenesis factors (TGF-A and CXCL9/MIG) are associated with a 2-3 fold increased risk of lung cancer, even after carefully accounting for the confounding effects of cigarette smoking. These epidemiologic studies, coupled with molecular and experimental studies, underscore an etiologic role for chronic inflammation in lung carcinogenesis.

Chronic inflammation could be particularly relevant in lung carcinogenesis among HIV-infected individuals, a group with a 2-4 fold higher incidence of lung cancer when compared to the general population. Several studies show that this elevated lung cancer incidence among HIV-infected individuals is not entirely explained by patterns of cigarette smoking. Consequently, HIV-related changes in pulmonary immunity, repeated pulmonary infections, HIV-related systemic inflammation and immune activation, and accelerated pulmonary damage from tobacco smoke have all been suggested as risk factors for increased lung cancer risk among HIV-infected individuals.

- Il rischio di ammalarsi di HCC è sei volte più alto nel paziente con infezione da HIV
- L'immunosoppressione può accellerare la fibrosi epatica e quindi aumentare il rischio
- Più alta morbidità e mortalità per HCC nei pazienti con infezione da HIV


European Review for Medical and Pharmacological Sciences 2012; 16: 1377-1388

Non-AIDS-defining cancers among HIV-infected people

M.R. PINZONE, F. FIORICA[1], M. DI ROSA, G. MALAGUARNERA[2], L. MALAGUARNERA[2], B. CACOPARDO, G. ZANGHÌ[3], G. NUNNARI

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- Il rischio di ammalarsi di LH è 15 volte più alto nel paziente con infezione da HIV
- Il rischio di LH sembra significativamente aumentato dall'avvento della terapia HAART
- Terapia HAART (NNRTI?) e conta CD4+< 200 aumentano il rischio di LH


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- Il rischio di ammalarsi di carcinoma ano-genitale è 30 volte più alto nel paziente con infezione da HIV
- HPV-16 causa più del 80% dei casi di carcinoma dell'ano
- Rischio particolarmente alto nei MSM

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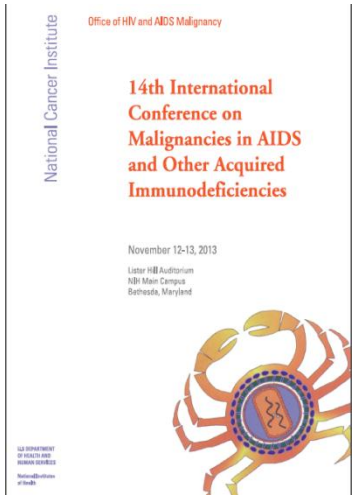
Epatite B	• Tutti (se suscettibili all'infezione). • Modalità di trasmissione condivisa con l'HIV; accelerazione della malattia epatica; maggior tendenza alla cronicizzazione.	A: schema a tre o a quatto dosi (schema accelerato). B: rivaccinare i "non responders" (HBsAb < 10 IU/L), preferibilmente, una volta che la conta dei T CD4+ sia > 500 cellule/*µL*, anche impiegando dosaggi aumentati.	Considerare vaccino combinato per HBV e HAV (tre dosi). Molti pazienti unicamente HBcAb+ non sono immuni e dovrebbero essere vaccinati.	[6, 20-31, 61, 68, 72]
RACCOMANDAZIONE (FORZA/EVIDENZA)	*La vaccinazione anti-HBV è raccomandata in tutti i soggetti HIV positivi suscettibili all'infezione da questo agente virale* **[AI]**, *impiegando la schedula somministrativa standard. In caso di risposta anticorpale insoddisfacente è possibile rivaccinare impiegando dosaggi vaccinali aumentate* **[BII]**. *È da considerare l'uso del vaccino combinato anti-HBV e anti-HAV per ragioni di praticità, costo e migliorata risposta immunitaria* **[CIII].**			
Papilloma virus umano (HPV)	• Tutti (a partire da 9 anni) con estensione fino a 26 anni e/o secondo aggiornamenti di scheda tecnica, pur con diverso livello di evidenza. • Rischio condiviso con l'HIV di contrarre l'infezione e più alta percentuale, in presenza di HIV, dei relativi tumori.	A: tre dosi. B: al momento, non previsti.	Utilizzare vaccino 4-valente nel maschio.	[6, 45-57, 61, 68]
RACCOMANDAZIONE (FORZA/EVIDENZA)	*La vaccinazione anti-HPV nei pazienti HIV-positivi ha un eccellente profilo di sicurezza* **[AI]** *ed è in grado di indurre una risposta anticorpale simile a quella ottenuta nei pazienti HIV-negativi* **[AI]**. *Non sono ancora disponibili studi clinici sull'efficacia di questa vaccinazione nel prevenire le neoplasie HPV associate in soggetti con HIV/AIDS, tuttavia la vaccinazione quadrivalente risulta attrattiva e da valutarsi visto il profilo, gli studi e le implicazioni epidemiologiche precedentemente prospettate* **[BIII]**.			



P2. HPV Vaccination in HIV-Infected Men and Women

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HIV-infected men and women are at increased risk of anogenital and oral HPV infection and HPV-associated cancers at these anatomic sites. Vaccination of HIV-infected men and women has the potential to reduce the risk of these cancers if the vaccine is administered prior to initial exposure to the HPV types in the vaccine. HIV-infected men and women may benefit from vaccination but several issues need to be considered, including safety, immunogenicity and efficacy to prevent disease. The target population for HPV vaccination is 11-12 years, but it is recommended for routine use as early as 9 years and up to age 26 years. Many HIV-infected men and women are older than 26 years.

Safety has now been evaluated in several HIV-infected cohorts in the U.S., including children (IMPAACT P1047), adult women over the age of 26 years (ACTG 5240) and adult men who have sex with men over the age of 26 years (AMC 052). Safety has also been evaluated in adult HIV-infected Indian women in Tamil Nadu (AMC 054). The safety profile of the vaccine appears to be similar to that reported in HIV-uninfected populations, and there do not appear to be any HIV-specific adverse events, such as vaccine-associated increase in HIV viral load or reduction in CD4+ level.

Another key consideration is the immunogenicity of the vaccine in HIV-infected men and women. Results differ from population to population but overall the percentage who seroconvert after vaccination is very high. Titers to individual HPV types have been lower for some HPV types than seen in healthy young men and women, but most have been well above what are likely to be protective levels. The impact of having lower peak titers on duration of protection is not yet known.

Few studies have evaluated efficacy of HPV vaccination in HIV-infected men and women to prevent HPV-related cancer. Many HIV-infected men and women will have had prior exposure to vaccine HPV types when they present for possible vaccination, and thus would be expected to have limited efficacy. Surprisingly, however, more than half of HIV-infected MSM, with a mean age of 44 years, were "naïve" to HPV 6, 11, 16 or 18 as defined by being DNA-negative n the anal canal and sero-negative to these types. Since it is possible, if not probable, that many of these sero-negative individuals were previously sero-positive and sero-reverted over time, it remains unclear as to whether HPV vaccination offers clinical benefit to these individuals.

Taken together, HPV vaccination should be a high priority for HIV-infected men and women age 26 or younger, and should ideally be administered prior to the onset of sexual activity. HPV vaccination is safe and immunogenic in HIV-infected individuals. Given the high proportion of "naïve" individuals over 40 years of age and the lower titers seen in HIV-infected males and females, future studies should examine the duration and kinetics of vaccine-induced antibody responses in HIV-infected men and women.

Cancer: Screening Methods[i]

Problem	Persons	Procedure	Evidence of benefit	Screening interval	Additional comments
Anal cancer	MSM	Digital rectal exam ± PAP test	Unknown; advocated by some experts	1-3 years	If PAP test abnormal, anoscopy
Breast cancer	Women 50-70 years	Mammography	↓ Breast cancer mortality	1-3 years	
Cervical cancer	Sexually active women	PAP test	↓ Cervical cancer mortality	1-3 years	Target age group should include the 30 to 59-year age range at least. Longer screening interval if prior screening tests repeatedly negative
Colorectal cancer	Persons 50-75 years	Faecal occult blood test	↓ Colorectal cancer mortality	1-3 years	Benefit is marginal
Hepatocellular carcinoma	Persons with cirrhosis & Persons with HBV irrespective of fibrosis stage	Ultrasound and alpha-foetoprotein	Earlier diagnosis allowing for improved ability for surgical eradication	Every 6 months	
Prostate cancer	Men > 50 years	Digital rectal exam ± prostate specific antigen (PSA)	Use of PSA is controversial	1-3 years	Pros: ↑ early diagnosis Cons: Overtreatment, no ↓ cancer-related mortality

i Screening recommendations derived from the general population.

These screenings should preferably be done as part of national general population-screening programmes. Although non-Hodgkin's lymphoma has a higher incidence in HIV-positive persons than in the general population, it is currently unknown whether it can be screened.
Careful examination of skin should be performed regularly to detect cancers such as Kaposi's sarcoma, basal cell carcinoma and malignant melanoma.

Tabella 1 - Norme generali di prevenzione oncologica.

STRATEGIA DI PREVENZIONE	RACCOMANDAZIONE (FORZA/EVIDENZA)	RIFERIMENTI BIBLIOGRAFICI
Inizio precoce della terapia antiretrovirale*, le modificazioni dello stile di vita (interruzione del fumo ed astinenza da alcolici) e la terapia delle infezioni da HBV/HCV rappresentano i più importanti strumenti di prevenzione oncologica.	[AI]	[15-20]
*I pazienti coinfetti con HPV e con nadir di T CD4+ < 200 cellule/µL e/o viremia HIV persistentemente elevata (>100.000 cp/mL), rimangono ad alto rischio di neoplasie anogenitali invasive da HPV, anche dopo il recupero viroimmunologico [18,20].		

Tabella 2- Programmi di screening oncologico per la popolazione generale.

TUMORE	POPOLAZIONE	PROCEDURE SCREENING	TEMPISTICHE SCREENING	RACCOMANDAZIONE (FORZA/EVIDENZA)	RIFERIMENTI BIBLIOGRAFICI
Mammella	Donne 50-70 aa(E) Donne>40 aa (A)	Mammografia	1-2 aa (E) Annuale (A)	[AI]	[39,40]
Prostata	Uomini≥50 aa	Esame rettale + PSA test	Annuale	[AI]	[39,40]
Colon-retto	Tutti, 50-75 aa (E) ≥ 50 aa (A)	° Ricerca sangue occulto feci °°rettosigmoidoscopia § rettocolonscopia	° annuale °° ogni 5 aa § ogni 10 aa	[AI]	[39,40]
E: Linee guida Europee; A: Linee guida Americane					

Tabella 3- Programmi di Screening oncologici adattati/specifici per la popolazione HIV-positiva.

TUMORE	POPOLAZIONE	PROCEDURE SCREENING	TEMPISTICA SCREENING	RACCOMANDAZIONE (FORZA/EVIDENZA)	RIFERIMENTI BIBLIOGRAFICI
Cervice uterina	Donne sessualmente attive ≥20 aa (E) ≥ 18 aa (A)	-PAP test convenzionale - PAP test su base liquida - Colposcopia	Annuale se 2 esami consecu-tivi neg Se Pap test patologico	[AI]	[39-42]
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	*Annuale, se 2 esami consecutivi neg Se Pap test patologico	[AIII [AII]	[41-46] [45,46]
Fegato	-HCV coinfetti con cirrosi; -Tutti HBV/HCV resistenti agli antivirali	Ecografia addome +/- α-fetoproteina	Ogni 6-12 mesi	[AI]	[41,42,47-51]
Polmone	-Fumatori ≥ 30 pacchetti s./anno; -se ex-fumatori entro 15 anni dalla cessazione	TAC spirale a basso dosaggio	Annuale	[AI]	[41,42,52,53]
	-Età≥ 40 aa**				
Cute	-Pelle chiara; - Razza bianca non-ispanica	Esame della cute	Annuale	[AIII]	[41,42,54]

E: Linee guida Europee; A: Linee guida Americane; MSM: Men who have Sex with Men; MSM*: l'impiego diretto dell'anoscopia ad alta risoluzione è costo-efficace nei MSM; Età≥ 40 aa**: questo limite di età si base sull'opinione degli esperti.

DOI: 10.1111/hiv.12136
HIV Medicine (2014), **15** (Suppl. 2), 1–92

British HIV Association guidelines for HIV-associated malignancies 2014

Cervical intraepithelial neoplasia (CIN) and cervical cancer

8.6 Key recommendations

- We recommend that all women newly diagnosed with HIV should have cervical surveillance performed by, or in conjunction with, the medical team managing their HIV infection (level of evidence 1B). An initial colposcopy and annual cytology should be performed if resources permit (level of evidence 2C).
- We recommend that subsequent colposcopy for cytological abnormality should follow UK national guidelines, and the age range screened should be the same as for HIV-negative women (level of evidence 1B).

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British HIV Association guidelines for HIV-associated malignancies 2014

Anal cancer

All major HIV units should develop clinical guidelines for the management of suspected anal cancer and pre- cancer.All major HIV units should develop either local clinical expertise or referral pathways for suspected anal cancer and pre-cancer.The role of annual anal cytology and anoscopy is not yet proven; however, patients should be encouraged to check and report any lumps noticed in the anal canal.

STRATEGIA TERAPEUTICA	POPOLAZIONE/PATOLOGIA	RACCOMANDAZIONE (FORZA/EVIDENZA)	RIFERIMENTI BIBLIOGRAFICI
Strategia Generale			
L'inizio/continuazione della terapia antiretrovirale è fortemente raccomandato indipendentemente dai parametri viro-immunologici.	- Tumori AIDS e non-AIDS definenti - Spettanza di vita >1 mese	[AI] [AIII]	[15-29,32-38,55-57] [21]
La terapia antiretrovirale è raccomandata in concomitanza con la terapia antitumorale.	- Linfomi - Sarcoma di Kaposi - Tumori solidi	[AI] [AI] [AII]	[21-29,32-38] [21,58-69] [15-20,49,50,55-57]
La terapia antiretrovirale concomitante alla terapia antitumorale è sconsigliata in particolari sottogruppi di pazienti.	- Ridotta spettanza di vita - Ridotta riserva funzionale d'organo - Multiresistenza alla terapia antiretrovirale	[AIII] [BIII] [AIII]	[21] [21,30] [21]
Strategia durante il Trattamento Concomitante			
Monitoraggio intensivo della tossicità.	- Pz trattati con terapia antiretrovirale in associazione ad antiblastici e/o radioterapia	[AI]	[21,24,30]
Le potenziali interazioni farmacologiche fra antiretrovirali e antiblastici guidano la scelta del regime cART. Evitare l'uso dell'AZT.	- Tutti i pz con tumore	[AII]	[70-74]
Uso di regimi cART a base di RAL/DTG (per minori interazioni PK).	- In associazione a terapie mielotossiche	[AII]	[21,24,30,75]
-Evitare antiretrovirali neurotossici (ddI, d4T) o inibitori delle proteasi boostati con RTV.	- Uso di antiblastici metabolizzati dal citocromo P-450*; - Assenza di studi clinici/PK	[AII] [AIII]	[70-74] [70-73]
-Evitare l'uso di MVC°, in assenza di studi di farmacocinetica.	-In associazione con alcaloidi della vinca	[AII]	[70-73]
-Non usare la bilirubina per ridurre la dose degli antiblastici a metabolizzazione epatica**.	-Uso di chemioterapici, inibitori della Tirosin Kinasi	[AII]	[70-73]
-Intensificare monitoraggio tossicità renale da TDF.	- In associazione con IDV, ATV	[AI]	[70-73]
	- In associazione con metotrexate, platino-derivati	[BII]	[70-73]

*: tassani, alchilanti, epipodofilotossine, alcaloidi vinca, inibitori della Tirosina Kinasi; °: potenziale riduzione della concentrazione di MCV;
** :adriamicina, etoposide, tassani, irinotecan, vincristina, gemcitabina, sorafenib, imatinib.

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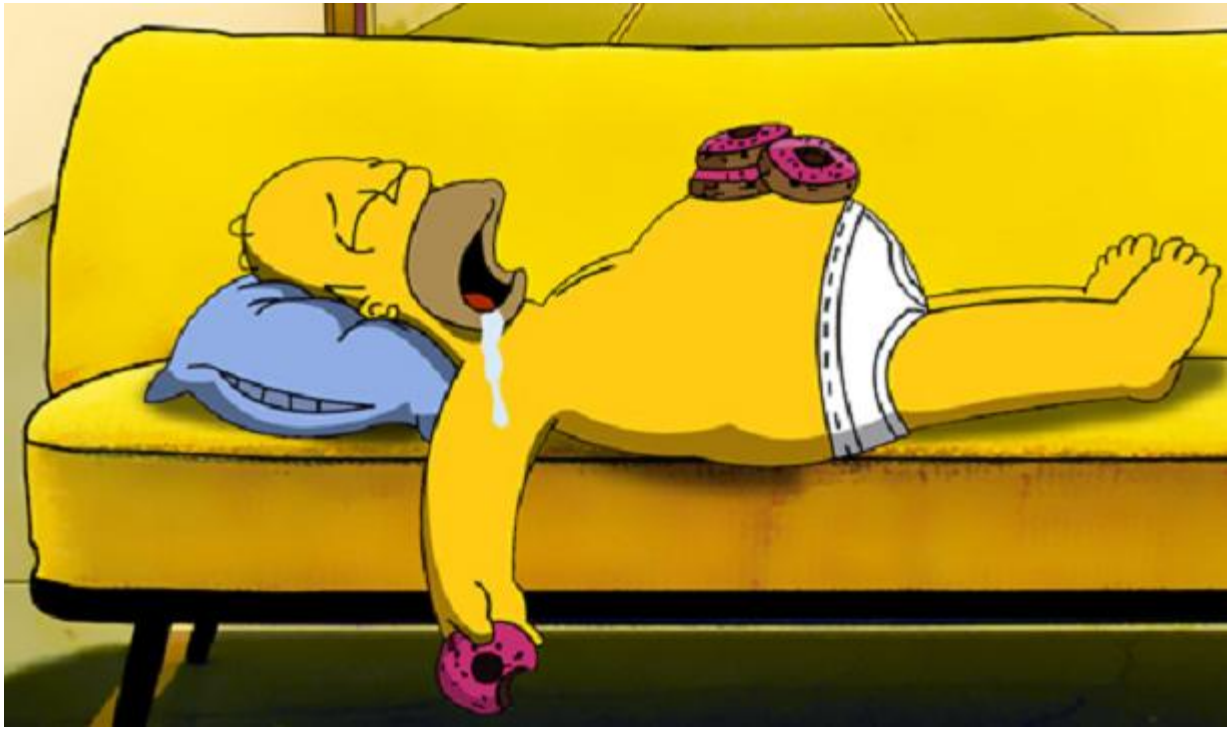
- We recommend that all patients with AIDS-defining malignancies should start HAART (level of evidence 1B).
- We suggest that all patients with non-AIDS-defining malignancies who are due to start chemotherapy or radiotherapy should be started on HAART unless contraindicated (level of evidence 2C).
- We recommend that prophylaxis against *Pneumocystis jirovecii* pneumonia (PCP) should be started for those who have a CD4 cell count less than 200 cells/μL (level of evidence 1A) and should be considered at higher levels in all patients starting chemotherapy or radiotherapy (GPP).
- We recommend prophylaxis against MAC for individuals with a CD4 cell count less than 50 cells/μL (level of evidence 1B) and in those whose treatment puts their CD4 count at risk of falling below this level.
- We recommend that systemic azole antifungal prophylaxis should be used in all patients receiving chemotherapy or radiotherapy for HIV-associated malignancy (level of evidence 1D).
- We do not recommend routine fluoroquinolone prophylaxis in low-risk patients and the use of cotrimoxazole to prevent PCP may provide some protection against bacterial infection for patients living with HIV (level of evidence 1C).
- We recommend HSV prophylaxis in people living with HIV with a history of HSV infection who are starting chemotherapy to reduce the incidence and severity of reactivations (level of evidence 1D).
- We recommend annual influenza vaccination (level of evidence 1B).
- We recommend vaccination against pneumococcus and hepatitis B virus (level of evidence 1D).
- We recommend that patients with antibodies against hepatitis B core antigen (HBcAb) should be treated with prophylactic antivirals in line with BHIVA hepatitis guidelines (level of evidence 1B).

Conclusioni

I tumori, sia diagnostici (ADC) che non diagnostici per AIDS (NADCs), rappresentano oggi una delle principali cause di morte per il soggetto con infezione da HIV. L'aumento della sopravvivenza, il loro progressivo invecchiamento, il frequente abuso di noti carcinogeni ambientali (fumo di tabacco e/o abuso di alcol) e l'elevata associazione di HIV con altri virus oncogeni hanno ampliato lo spettro neoplastico. Il linfoma di Hodgkin, i tumori ano-genitali associati ad HPV (carcinoma dell'ano), l'epatocarcinoma, il carcinoma del polmone e i carcinomi cutanei non-melanoma, sono NADCs più frequenti nella popolazione HIV in corso di cART. L'immunodepressione influenza negativamente la storia naturale di tutti i tumori, compresi i NADCs, con un aumento del loro rischio, della loro aggressività biologica e della mortalità, che correla con l'entità del deficit immunitario stesso.



Grazie