Epidemiology of HIV-associated cancers: findings from the long-term follow-up of cohorts on HAART

Gary Clifford

Infections and Cancer Epidemiology Group (ICE)

International Agency for Research on Cancer
Lyon, France

Office of HIV and AIDS Malignancy
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HIV-related immunodeficiency and cancer risk

- KS and NHL were recognised as AIDS-defining conditions early in the HIV epidemic.
- However, the association between immunosuppression and other infection-related cancers has been more difficult to establish.
- This is undoubtedly because the association is weaker and the "dose-response" relationship different. Furthermore, excess risks can be attributed to high frequency of co-infection with carcinogenic viruses due to sexual and/or other lifestyle factors.
- Understanding the influence of CD4+ counts within HIV+ persons on cancer risk can help disentangle the effects of immunodeficiency and lifestyle factors.

Major Cancers in Persons with HIV/AIDS

Cancer	Cancer agent	Role of immune suppression
AIDS-defining cancers		
Kaposi sarcoma	Human herpesvirus 8	++++
Non-Hodgkin Lymph.	Epstein Barr virus	+++
Cervical cancer	Human papillomavirus	+
Non-AIDS-defining cancers		
Hodgkin lymphoma	Epstein Barr virus	++
Anal cancer	Human papillomavirus	+
Liver cancer	Hepatitis B and C viruses, alcohol	+
Lung cancer	Tobacco	?

Immunity and cancer in people with HIV/AIDS

- What is the pattern of risk associated with CD4 ?
- When is the CD4 important (how long before the cancer)?
- Until which moment is the cancer process reversible ?
- Is CD4 the only/right measure of immunity ?
- HAART (or calendar year) as a proxy for immune reconstitution.

Many of these questions are best answered in large cohorts of long duration with regularly collected CD4 counts.

AIDS-defining cancers

Kaposi Sarcoma (KS) and Non-Hodgkin Lymphoma (NHL)

Standardised incidence rates of KS and NHL in the Swiss HIV Cohort Study, by calendar period

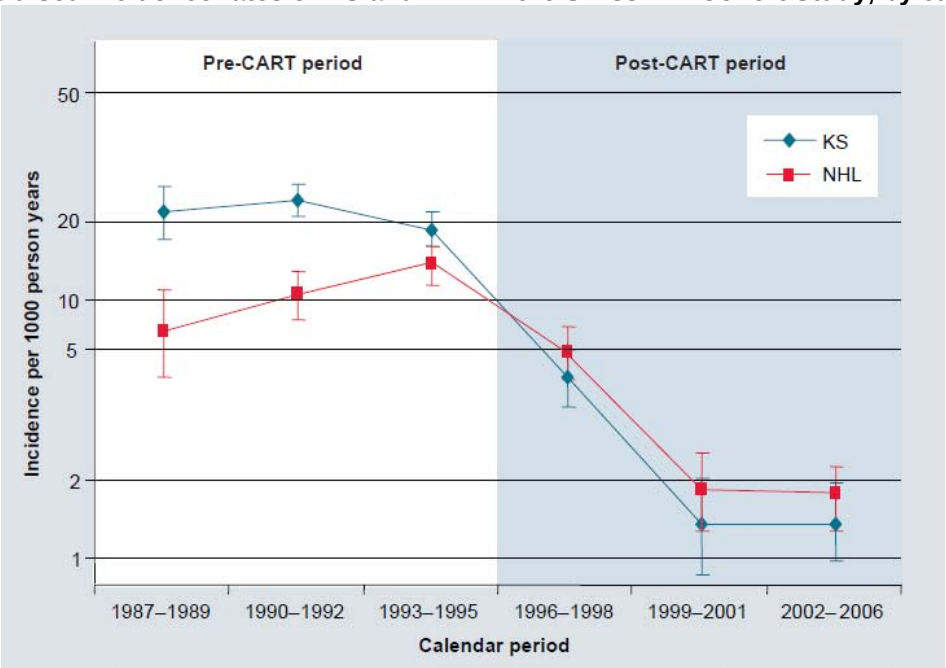
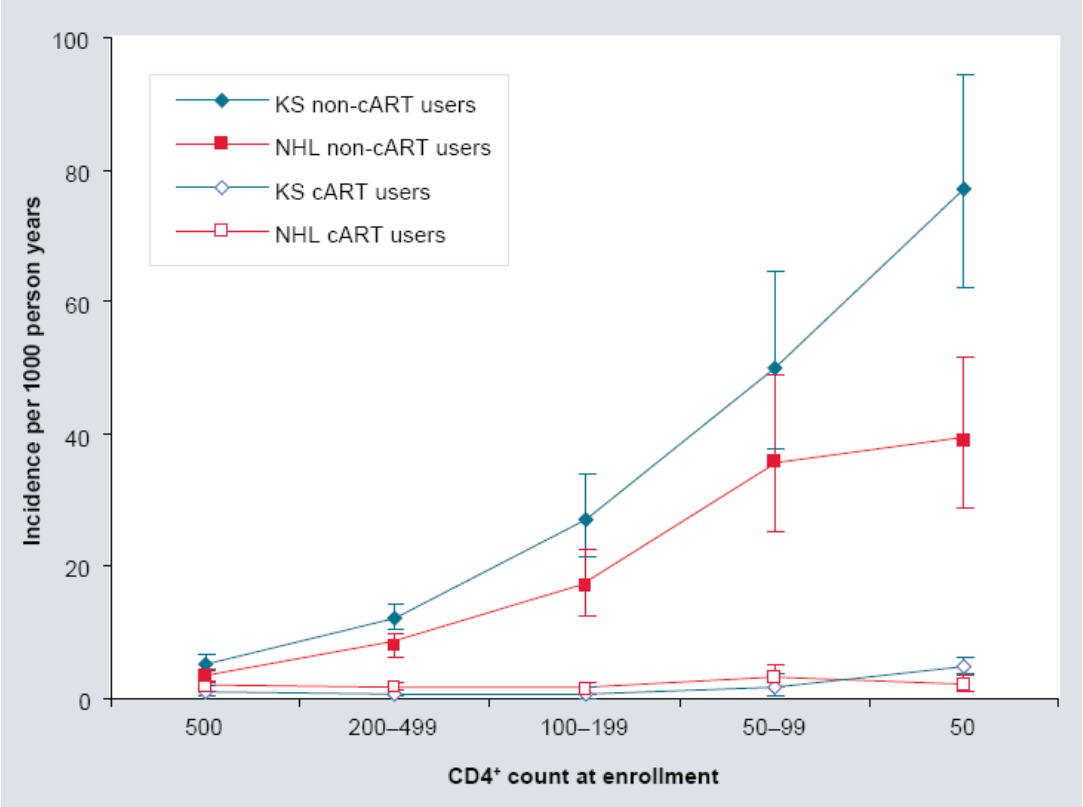


Figure 1. Standardized incidence rates of Kaposi sarcoma and Non-Hodgkin lymphoma by calendar period. (cART: Combined antiretroviral therapy; KS: Kaposi sarcoma; NHL: Non-Hodgkin lymphoma.
Adapted from data from [10,35].

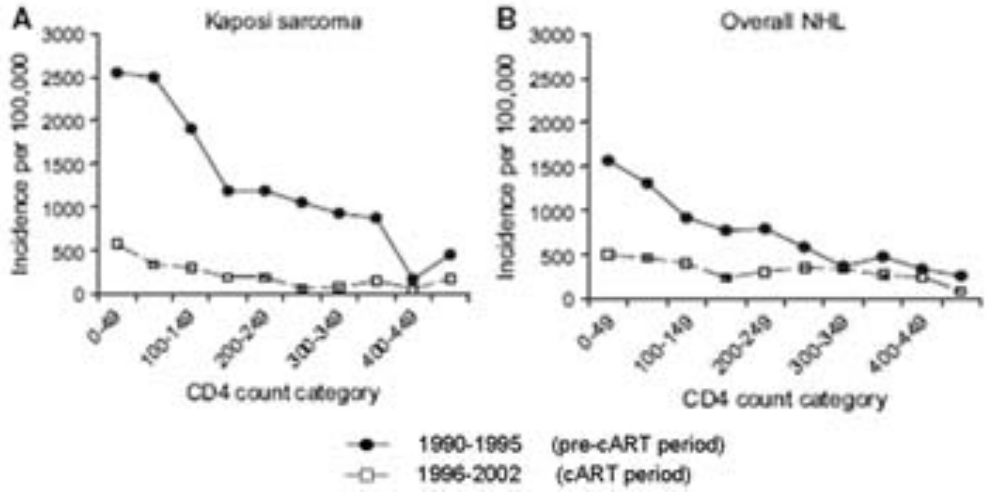
adapted from Polesel et al, AIDS 2008 and Franceschi et al, 2008, BJC

Standardised incidence rates of KS and NHL in the Swiss HIV Cohort Study, by cART use and CD4+ count



adapted from Polesel et al, AIDS 2008 and Franceschi et al, 2008, BJC

Incidence rates of KS and NHL in the U.S. AIDS Cancer Match Study, by calendar period and CD4+ count at AIDS



1990-1995 (pre-cART period) 1996-2002 (cART period)
Biggar et al, JNCI 2007

Cervical Cancer

HPV infection in HIV-positive women
Data from prospective screening studies

- HPV infections in HIV+ women are more likely to occur, to persist and to progress to high-grade precancerous lesions than in HIV-women. These increases are also related to CD4+ count.
- HAART use is associated with a significantly reduced burden of HPV infection and SILs [Minkoff et al, 2010]

Standardized incidence ratio's (SIR) for ICC in HIV/AIDS and cancer registry linkage studies

Source	Location(Period)	N women HIV/AIDS	SIR (95% CI)
Frisch et al., 2000	U.S. AIDS (1978 – 1996)	51,760	5.4 (3.9–7.2)
Dal Maso et al., 2009	Italy AIDS (1997 – 2004)	4,830	41.5 (28.0–59.3)
Allardice et al., 2003	Scotland HIV (1980 – 1996)	2,574	1.7 (0.04–9.26)
Clifford et al., 2005	Switzerland HIV (1985 – 2002)	2,045	8.0 (2.9–17.4)
Newnham et al., 2005	U.K. HIV (1985 – 2001)	7,110	1.0 (0.2–2.9)
Engels et al., 2006	U.S. AIDS (1996 – 2002)	27,282	5.3 (3.6–7.6)
Grulich et al., 2007	Meta-analysis of all the above		5.8 (3.0-11.3)
Engels et al., 2008	U.S. HIV (1991 – 2002)	19,785	2.9 (1.9–4.2)
Mbulaiteye et al., 2006	Uganda HIV (1989 – 2002)	8,423	2.7 (1.8–4.0)
Galceran et al., 2007	Spain AIDS (1981 – 1998)	355	41.8 (13.9–77.1)

Stein et al, 2008; Case:control study in South Africa, OR = 1.7 (1.4–2.0)

Non-AIDS-defining cancers

Anal Cancer

Standardized incidence ratio's (SIR) for anal cancer, by gender

		SIR (95% CI)	
Source	Location (Period)	Male	Female
Frisch et al., 2000	U.S. AIDS (1978 – 1996)	37.9 (33.0-43.4)	6.8 (2.7-14.0)
Dal Maso et al., 2003	Italy AIDS (1985 – 1998)	35.1 (11.1–82.5)	27.6 (0.0-158)
Clifford et al., 2005	Switzerland HIV (1985 – 2002)	48.1 (10.9–176)	18.5 (0.0-106)
Newnham et al., 2005	U.K. HIV (1985 – 2001)	25.1 (14.6–40.2)	9.7 (0.2–53.9)

Standardized incidence ratio's (SIR) for anal cancer, by HIV transmission category

		SIR (95% CI)	
Source	Location (Period)	MSM	IDU
Frisch et al., 2000	U.S. AIDS (1978 – 1996) Males	59.5 (51.5-68.4)	5.9 (2.7-11.2)
Dal Maso et al., 2003	Italy AIDS (1985 – 1998)	56.4 (10.6–167)	33.6 (3.2-124)
Clifford et al., 2005	Switzerland HIV (1985 – 2002)	68.0 (17.7–176)	27.4 (0-157)

Relative risks for abnormal anal cytology, CD4 cell count: Women Interagency Health Study

Colhead	N	Abnormal anal cytology (%)	RR (95% CI)
HIV-negative	61	8	1.0
HIV-positive			
CD4⁺ >500 cells/μl	71	13	1.6 (0.5–4.5)
CD4⁺ 200–500 cells/μl	103	24	3.0 (1.2–7.5)
CD4⁺ <200 cells/μl	60	45	5.5 (2.2–16)

Holly et al, JNCI, 2001

Immunodeficency and anal cancer risk.

Anal cancer incidence shown to be significantly associated with:

- Decreased nadir CD4+ count
  [Patel, Arch Intern Med,2008 ; Piketty C, AIDS, 2008]
- A history of AIDS
  [Piketty C, AIDS, 2008]
- Duration with CD4+ counts <200ul
  [Guiget et al, Lancet Oncol, 2010]

Hodgkin Lymphoma (HL)

Standardized incidence ratio's (SIR) for HL in HIV/AIDS and cancer registry linkage studies

Source	Location(Period)	N persons HIV/AIDS	SIR (95% CI)
Frisch et al., 2001	U.S. AIDS (1978 – 1996)	302,834	11.5 (10.6–12.5)
Engels et al., 2006	U.S. AIDS (1996 – 2002)	109,417	13.6 (10.6–17.1)
Dal Maso et al., 2003	Italy AIDS (1985 – 1998)	12,104	16.2 (11.8–21.7)
Allardice et al., 2003	Scotland HIV (1980 – 1996)	2,574	3.6 (0.4–13.1)
Clifford et al., 2005	Switzerland HIV (1985 – 2002)	7,304	17.3 (10.2–27.4)
Newnham et al., 2005	U.K. HIV (1985 – 2001)	33,190	5.6 (4.0–7.7)
Grulich et al., 2002	Australia HIV/AIDS (1985 - 1999)	13,067	7.9 (4.4-13.0)
Grulich et al., 2007	Meta-analysis of all above		11.0 (8.4-14.4)
Mbulaiteye et al., 2006	Uganda HIV (1989 – 2002)	12,607	5.7 (1.2–17.0)
Patel et al, 2008	U.S. HIV (1993-2003)	54,780	14.7 (11.6 - 18.2)
Galceran et al., 2007	Spain AIDS (1981-1999)	1,304 males	28.4 (10.2-62.3)

Standardized incidence ratio's (SIR) for HL, by HIV transmission category

Source	Location(Period)	SIR (95% CI)		
		MSM	IDU	Other
Frisch et al., 2000	U.S. AIDS (1978 – 1996)	12.5 (11.3-13.8)	10.0 (8.5-11.8)	8.4 (5.7-11.9)
Clifford et al., 2005	Switzerland HIV (1985 – 2002)	17.7 (6.4–38.8)	14.0 (5.0-30.6)	22.2 (8.0-48.6)
Herida et al., 2005	France HIV (1992 – 1995)	24.6 (16.6–35.1)	19.0 (10.6-31.3)	28.6 (13.7-52.6)
Herida et al., 2005	France HIV (1996 – 1999)	37.4 (28.4–48.4)	29.5 (18.7-44.3)	15.3 (7.0-29.0)

Standardized incidence ratio's (SIR) for HL, by gender

		SIR (95% CI)	
Source	Location (Period)	Male	Female
Frisch et al., 2000	U.S. AIDS (1978 – 1996)	12.0 (11.0-13.0)	8.3 (6.2-10.8)
Dal Maso et al., 2003	Italy AIDS (1985 – 1998)	16.7 (11.7–23.1)	14.6 (6.6-27.9)
Clifford et al., 2005	Switzerland HIV (1985 – 2002)	14.1 (7.0–25.3)	27.1 (10.7-52.6)
Newnham et al., 2005	U.K. HIV (1985 – 2001)	6.1 (4.3–8.5)	2.3 (0.3–8.3)

Apparent increases in excess risk for HL on HAART ?

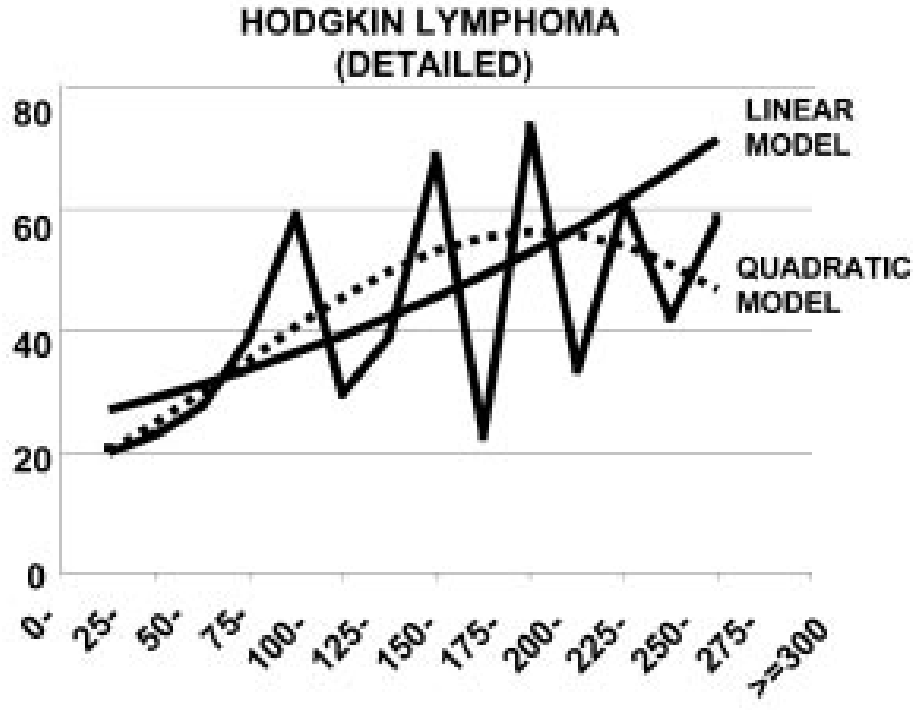
Source	Location (Period)	SIR (95% CI)	
		Non-HAART users	HAART users
Clifford et al., 2005	Switzerland HIV (1985 – 2002)	11.4 (5.2–21.7)	36.2 (16.4-68.9)
		<1996	>=1996
Herida et al., 2005	France HIV (1992 – 1999) Males	22.8 (17.3–29.4)	31.7 (25.8–38.5)
Herida et al., 2005	France HIV (1992 – 1999) Females	9.6 (3.1–22.4)	14.3 (6.8–26.3)
Engels et al., 2006	U.S. AIDS (1990 – 2002)	8.1 (6.4-10.1)	13.6 (10.6-17.1)
Engels et al., 2008	U.S. HIV (1991 – 2002)	2.8 (0.9-6.6)	6.7 (4.5-9.5)
Patel P et al, 2008	U.S. HIV (1993-1999)	11.7 (7.5 -18.2)	16.6 (11.5 – 24.0)

Adjusted incidence rate ratios for HL, by HAART

	Person years	Adjusted IRR
Swiss HIV Cohort Study (Clifford et al, Blood, 2009)		
Non-HAART users	39,560	ref
HAART users	45,051	1.0 (0.5 – 1.9)
French Hospital HIV Database (Fontas et al, JAIDS, 2009)		
5/1995 – 3/1996	15,797	ref
4/1996-8/1999	120,346	1.1 (0.8 – 1.5)
9/1999-12/2005	250,220	0.9 (0.5 -1.8)

Age-specific HL incidence :
inappropriateness of using SIRs to compare trends in HL in an

Immunodeficency and HL risk in the U.S. AIDS Cancer Match Study :
decreased risk at < 200 CD4 at AIDS



Biggar et al, Blood, 2007

Immunodeficency and HL risk in The French HIV Hospital Database:

increased risk at latest CD4 count <200

	Hodgkin's lymphoma (n=149)	
	RR (95% CI)	p value
CD4 count (cells per µL)		
≥500	1·0	<0·0001
350–499	1·2 (0·7–2·2)	..
200–349	2·2 (1·3–3·8)	..
100–199	4·8 (2·8–8·3)	..
50–99	7·7 (3·9–15·2)	..
0–49	5·4 (2·4–12·1)	..

Guiget et al, Lancet Oncol, 2009

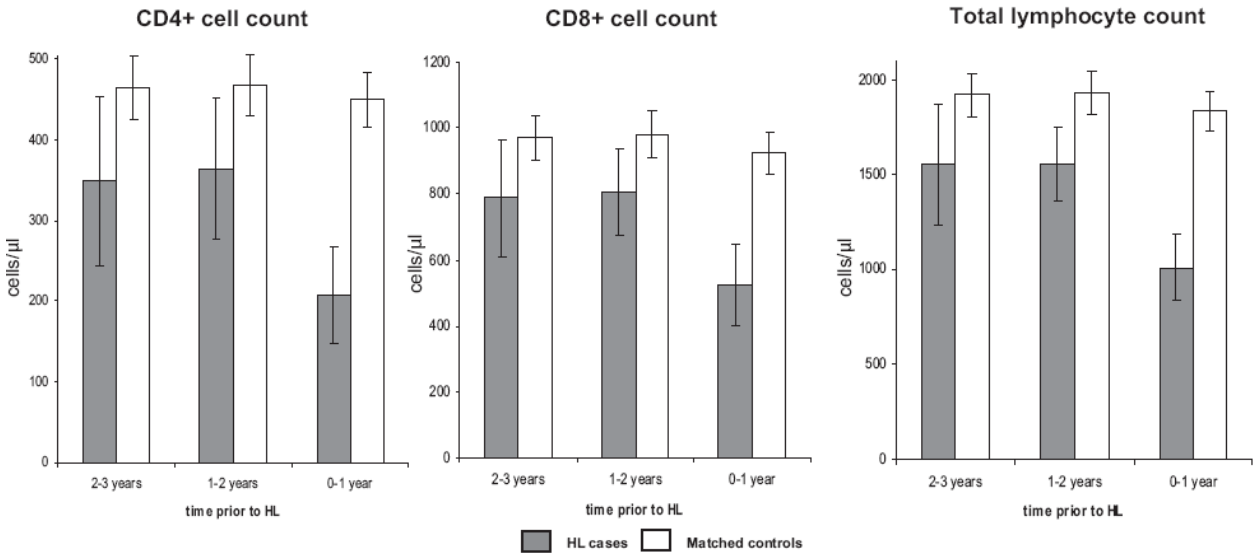
Immunodeficency and HL risk.
A nested case:control study in Swiss HIV Cohort Study

Nested case/control study: OR of HL, by markers of immunodeficiency at 2 different time periods before diagnosis

	1-2 years before HL					Within 1 year before HL				
	HL		Matched controls			HL		Matched controls		
	n	(%)	n	(%)	OR* (95% CI)	n	(%)	n	(%)	OR* (95% CI)
CD4+ cell count, cells/µL										
500 or more	13	(34.2)	126	(38.1)	1	3	(7.3)	136	(35.3)	1
200-499	17	(44.7)	151	(45.6)	1.10 (0.52-2.36)	14	(34.2)	177	(46.0)	3.65 (1.02-9.55)
50-199	8	(21.1)	47	(14.2)	1.24 (0.45-3.44)	18	(43.9)	50	(13.0)	18.0 (5.06-63.7)
0-49	0	(0.0)	7	(2.1)		6	(14.6)	22	(5.7)	
Unknown	9		113			6		59		
Per 100/µL decrease					1.08 (0.94-1.25)					1.65 (1.33-2.03)

Clifford et al, Blood, 2009a

Lymphocytopenia prior to HL onset
A case:control study nested in Swiss HIV Cohort Study



Clifford et al, Blood, 2009b

Difficulties with assessing the relationship between CD4 count and HL risk

- SIRs are inappropriate for assessing the period(HAART) effect.
- Lymphocytopenia preceding the diagnosis of the tumor complicates the assessment of the CD4 effect(latest time-updated CD4+ may be inappropriate).
- Most HL now occurs in patients with no history ofAIDS, so that CD4+ count at AIDS is also problematic.
- Might this also be an issue for other cancers ??

Hepatocellular Carcinoma (HCC)

Standardized incidence ratio's (SIR) for HCC in HIV/AIDS and cancer registry linkage studies

Source	Location (Period)	N HIV/AIDS	SIR (95% CI)
Engels et al., 2006	U.S. AIDS (1980 – 1989)	79,387	2.4 (0.5–7.1)
Engels et al., 2006	U.S. AIDS (1990 – 1995)	189,129	4.0 (2.6–5.8)
Engels et al., 2006	U.S. AIDS (1996 – 2002)	107,417	3.3 (2.0–5.1)
Dal Maso et al., 2003	Italy AIDS (1985 – 1998)	12,104	1.9 (0.4–5.6)
Grulich et al., 2002	Australia HIV/AIDS (1985 – 1999)	13,067	2.7 (0.6-7.9)
Clifford et al., 2005	Switzerland HIV (1985 – 2002)	7,304	7.0 (2.2–16.5)
Newnham et al., 2005	U.K. HIV (1985 – 2001)	33,190	5.9 (3.1–10.1)
Grulich et al., 2007	Meta-analysis of all the above		5.2 (3.3-8.2)
Mbulaiteye et., 2006	Uganda HIV (1988 - 2002)	12,607	2.1 (0.4-6.0)
Galceran et al., 2007	Spain AIDS (1981-1999)	1,304 males	13.1 (1.2-48.3)

Immunodeficency and hepatocellular carcinoma risk.
A case:control study nested in Swiss HIV Cohort Study

	HCC		Controls		
	N	(%)	N	(%)	OR (95% CI)
	26		251		
Latest CD4+ count [1]					
≥500	2	(16.7)	72	(30.9)	1
200-499	14	(33.3)	105	(45.1)	5.32 (1.15 – 24.5)
0-199	8	(50.0)	56	(24.0)	6.70 (1.24 – 36.1)
per 100cells/ul decrease					1.33 (1.06 – 1.68)
History of AIDS					
Never	14	(53.9)	186	(74.1)	1
Ever	12	(46.2)	65	(25.9)	2.40 (1.06 – 5.44)
History of HAART use					
No	8	(30.8)	64	(25.5)	1
Yes	18	(69.2)	187	(74.5)	0.59 (0.18 – 1.91)

[1] within 1 year prior to cancer diagnosis, or corresponding reference date among controls

NOTE: Association with CD4 concentrated in MSM/Hetero (or those HBsAg+).

Immunodeficency and HCC risk
The French HIV Hospital Database

	Liver cancer* (n=119)			
	Model 1		Model 2	
	RR (95% CI)	p value	RR (95% CI)	p value
CD4 count (cells per µL)				
≥500	1·0	<0·0001	1·0	<0·0001
350–499	2·0 (0·9–4·5)	..	1·6 (0·7–3·9)	..
200–349	4·1 (2·0–8·2)	..	4·1 (1·9–8·7)	..
100–199	7·3 (3·5–15·3)	..	5·9 (2·6–13·3)	..
50–99	6·6 (2·4–17·6)	..	5·0 (1·6–15·7)	..
0–49	7·6 (2·7–20·8)	..	4·3 (1·1–15·8)	..

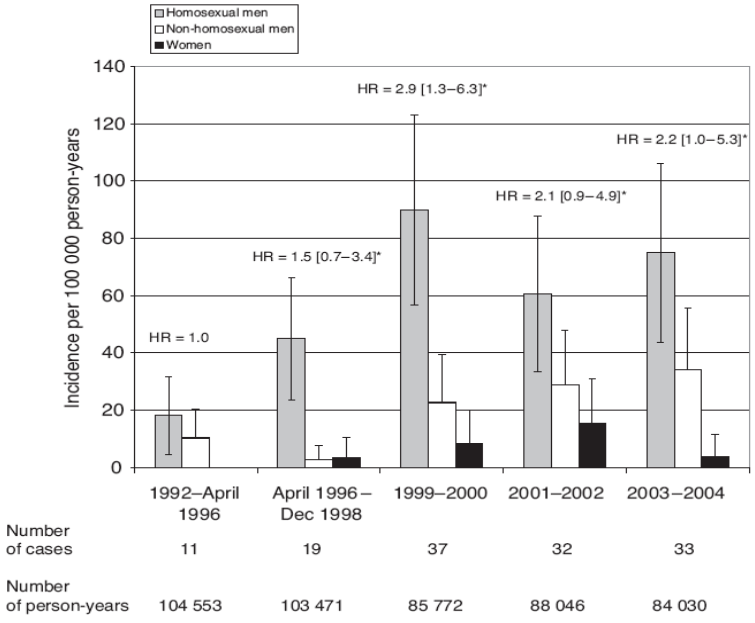
Guiget et al, Lancet Oncol, 2009

Trends in Non-AIDS defining cancer : effects of HAART and/or ageing

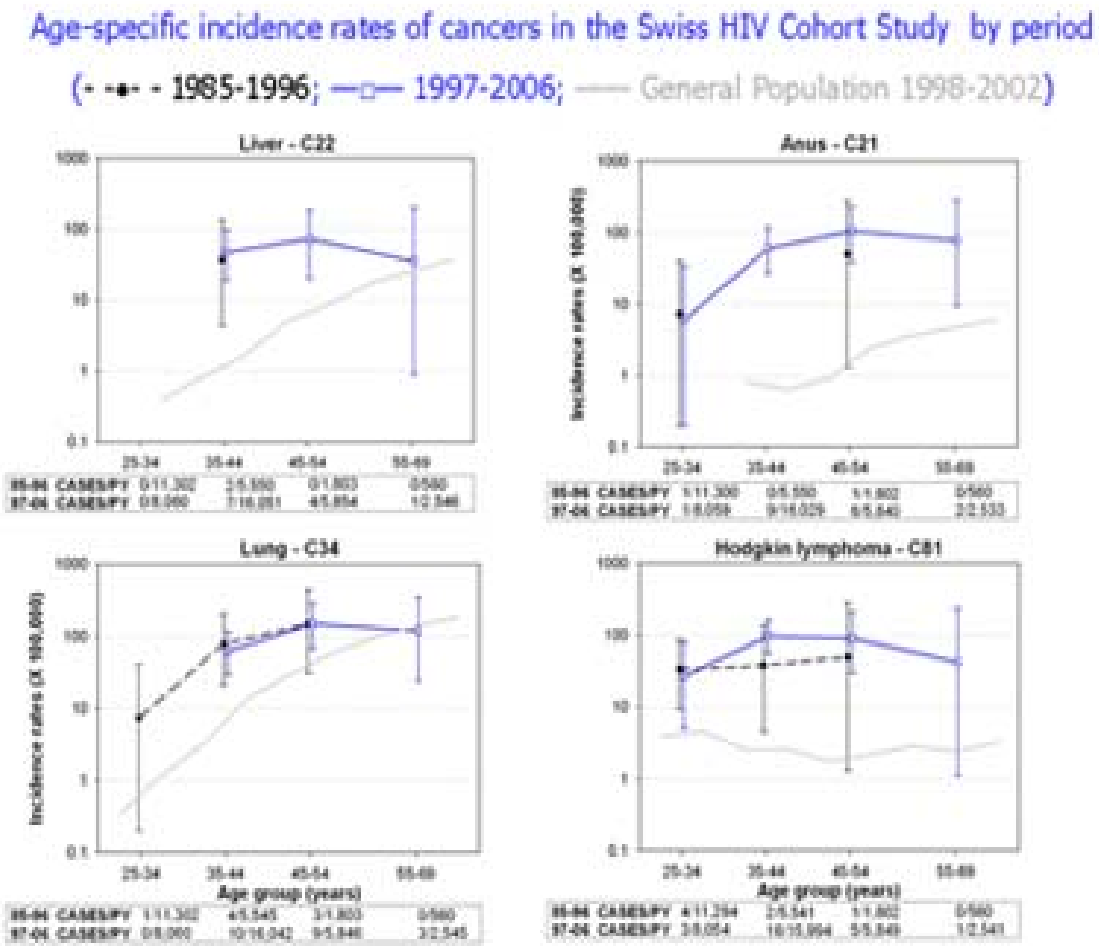
Age-standardised Incidence rates (per 100,000) of selected cancers, by period Swiss HIV Cohort Study, approx 54,000 person-years, submitted

Cancer site or type	Pre-HAART 1985-1996	Early-HAART 1997-2001	Late-HAART 2002-2006
	IR (95% CI)	IR (95% CI)	IR (95% CI)
Hodgkin lymphoma	**30.7** (12-64)	**42.9** (21-77)	**52.8** (20-102)
Anus	**8.3** (1-30)	**42.7** (22-75)	**25.3** (7-59)
Liver	**9.6** (1-35)	**25.9** (11-54)	**17.1** (5-41)
Lung	**38.1** (16-75)	**36.5** (17-67)	**33.9** (17-60)
All Non-AIDS-defining	**324** (244-421)	**405** (322-501)	**335** (260-424)

Incidence trends for anal cancer in persons infected with HIV. France (1992-2004)



* Adjusted for age, sex, HIV transmission group, CD4 nadir and AIDS (Piketty et al, AIDS, 2008)



Impossible to say whether the risk of some non-AIDS defining cancers have increased after HAART

Excess of cancer of the liver, anus, lung, and Hodgkin lymphoma have become more clear after HAART, but:

- Vast shift of HIV+ towards older age
- Comparison of Standardized Incidence Ratios (SIR) in pre-HAARTand HAART period can be distorted by extreme changes in age distribution
- Even age-standardized incidence rates can be potentiallymisleading because of problems with missing cells.
- Age-specific incidence rates among HIV+ do not show increases over time.