



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

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ON MALIGNANCIES IN AIDS AND  
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Disclosures

Clifford Gary, PhD

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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
<b><u>AIDS-defining cancers</u></b>		
Kaposi sarcoma	Human herpesvirus 8	++++
Non-Hodgkin Lymph.	Epstein Barr virus	+++
Cervical cancer	Human papillomavirus	+
<b><u>Non-AIDS-defining cancers</u></b>		
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.**

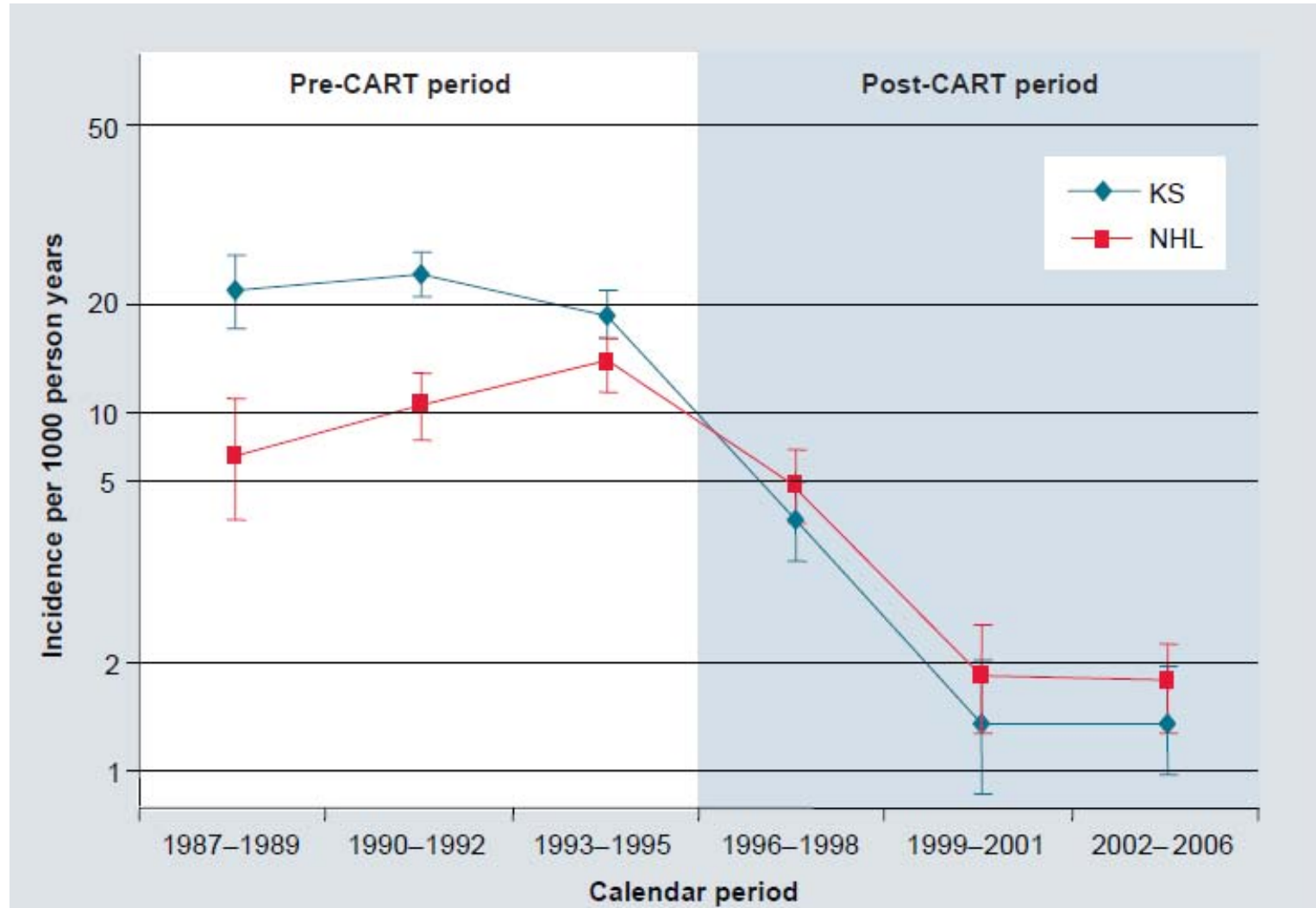
# AIDS-defining cancers

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

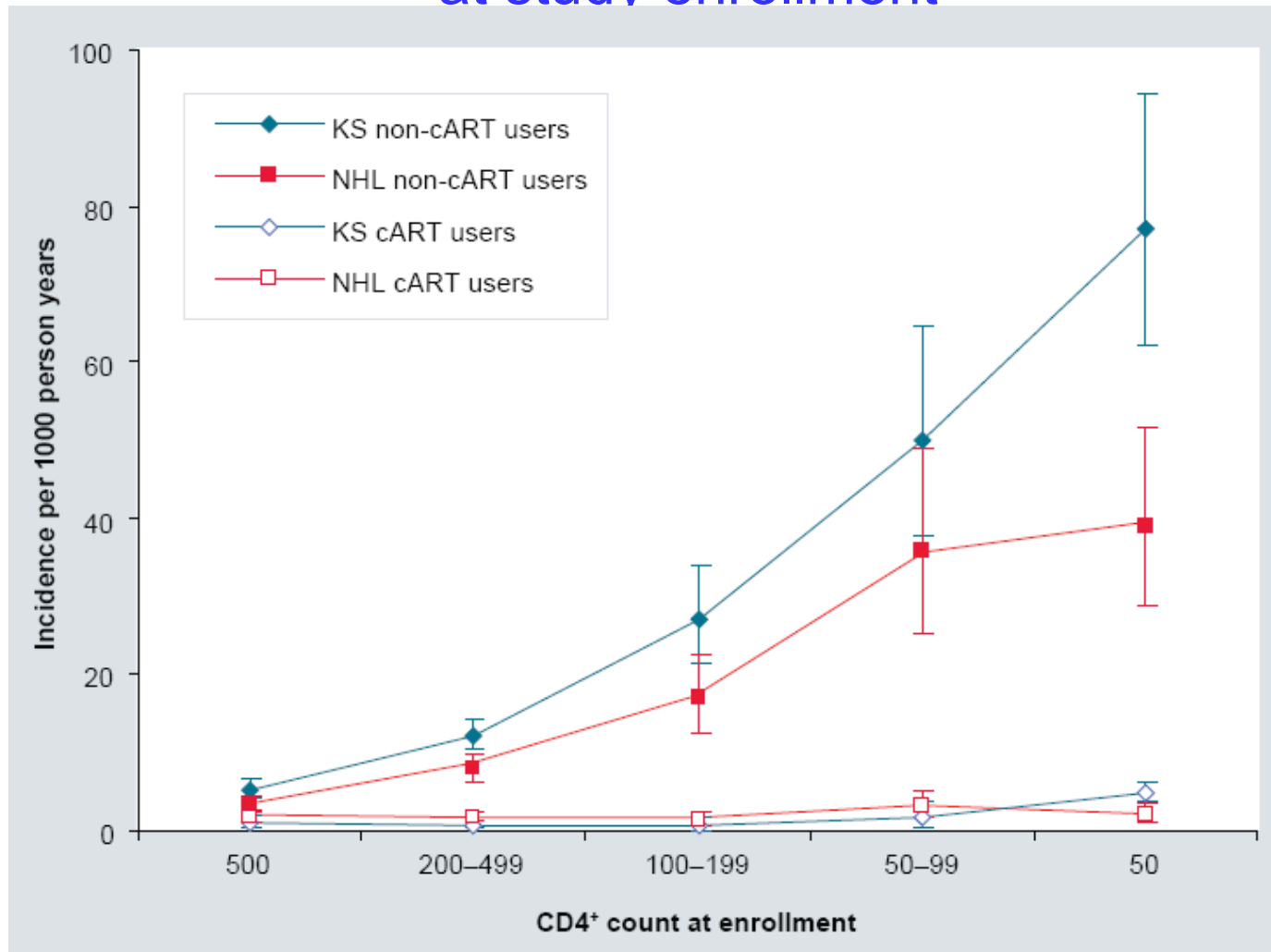
# Standardised incidence rates of KS and NHL in the Swiss HIV Cohort Study, by calendar period



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

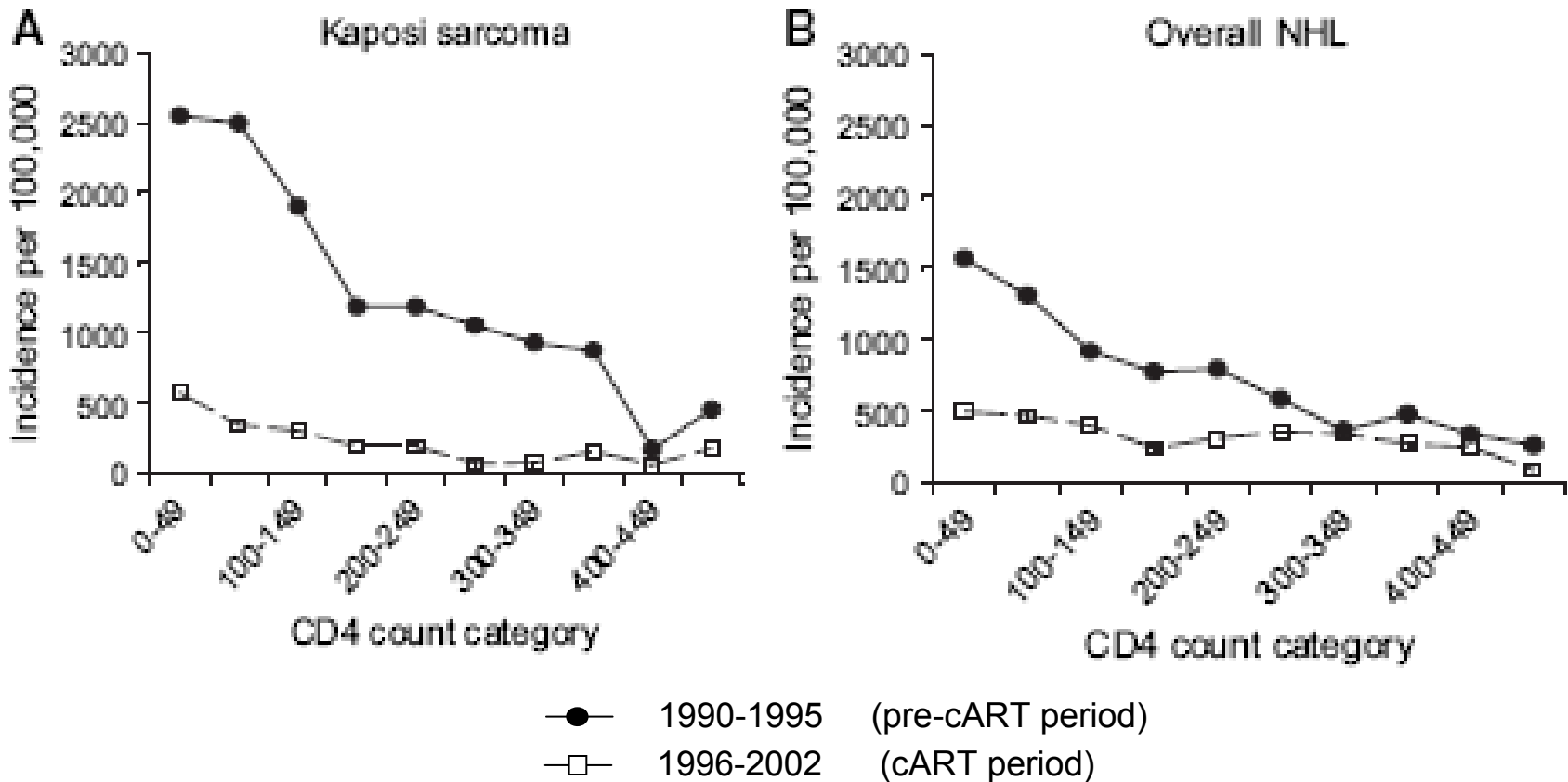


# Standardised incidence rates of KS and NHL in the Swiss HIV Cohort Study, by cART use and CD4+ count at study enrollment



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



# Cervical Cancer

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# 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	<b>5.4</b> (3.9–7.2)
Dal Maso et al., 2009	Italy AIDS (1997 – 2004)	4,830	<b>41.5</b> (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	<b>8.0</b> (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	<b>5.3</b> (3.6–7.6)
<i>Grulich et al., 2007</i>	<i>Meta-analysis of all the above</i>		<b>5.8</b> (3.0-11.3)
Engels et al., 2008	U.S. HIV (1991 – 2002)	19,785	<b>2.9</b> (1.9–4.2)
Mbulaiteye et al., 2006	Uganda HIV (1989 – 2002)	8,423	<b>2.7</b> (1.8–4.0)
Galceran et al., 2007	Spain AIDS (1981 – 1998)	355	<b>41.8</b> (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

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# Anal Cancer

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

SIR (95% CI)

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



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

Source	Location (Period)	SIR (95% CI)	
		MSM	IDU
Frisch et al., 2000	U.S. AIDS (1978 – 1996) Males	<b>59.5</b> (51.5-68.4)	<b>5.9</b> (2.7-11.2)
Dal Maso et al., 2003	Italy AIDS (1985 – 1998)	<b>56.4</b> (10.6–167)	<b>33.6</b> (3.2-124)
Clifford et al., 2005	Switzerland HIV (1985 – 2002)	<b>68.0</b> (17.7–176)	<b>27.4</b> (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
<b>HIV-positive</b>			
CD4+ >500 cells/ $\mu$ l	71	13	1.6 (0.5–4.5)
CD4+ 200–500 cells/ $\mu$ l	103	24	3.0 (1.2–7.5)
CD4+ <200 cells/ $\mu$ l	60	45	5.5 (2.2–16)

Holly et al, JNCI, 2001

# Immunodeficiency 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	<b>11.5</b> (10.6–12.5)
Engels et al., 2006	U.S. AIDS (1996 – 2002)	109,417	<b>13.6</b> (10.6–17.1)
Dal Maso et al., 2003	Italy AIDS (1985 – 1998)	12,104	<b>16.2</b> (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	<b>17.3</b> (10.2–27.4)
Newnham et al., 2005	U.K. HIV (1985 – 2001)	33,190	<b>5.6</b> (4.0–7.7)
Grulich et al., 2002	Australia HIV/AIDS (1985 - 1999)	13,067	<b>7.9</b> (4.4-13.0)
<i>Grulich et al., 2007</i>	<i>Meta-analysis of all above</i>		<b>11.0</b> (8.4-14.4)
Mbulaiteye et al., 2006	Uganda HIV (1989 – 2002)	12,607	<b>5.7</b> (1.2–17.0)
Patel et al, 2008	U.S. HIV (1993-2003)	54,780	<b>14.7</b> (11.6 - 18.2)
Galceran et al., 2007	Spain AIDS (1981-1999)	1,304 males	<b>28.4</b> (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)	<b>12.5</b> (11.3-13.8)	<b>10.0</b> (8.5-11.8)	<b>8.4</b> (5.7-11.9)
Clifford et al., 2005	Switzerland HIV (1985 – 2002)	<b>17.7</b> (6.4–38.8)	<b>14.0</b> (5.0-30.6)	<b>22.2</b> (8.0-48.6)
Herida et al., 2005	France HIV (1992 – 1995)	<b>24.6</b> (16.6–35.1)	<b>19.0</b> (10.6-31.3)	<b>28.6</b> (13.7-52.6)
Herida et al., 2005	France HIV (1996 – 1999)	<b>37.4</b> (28.4–48.4)	<b>29.5</b> (18.7-44.3)	<b>15.3</b> (7.0-29.0)

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

SIR (95% CI)

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

# Apparent increases in excess risk for HL on HAART ?

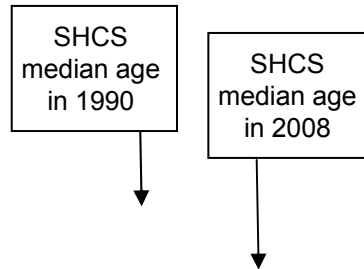
Source	Location (Period)	SIR (95% CI)	
		<u>Non- HAART users</u>	<u>HAART users</u>
Clifford et al., 2005	Switzerland HIV (1985 – 2002)	<b>11.4</b> (5.2–21.7)	<b>36.2</b> (16.4-68.9)
		<u>&lt;1996</u>	<u>&gt;=1996</u>
Herida et al., 2005	France HIV (1992 – 1999) Males	<b>22.8</b> (17.3–29.4)	<b>31.7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



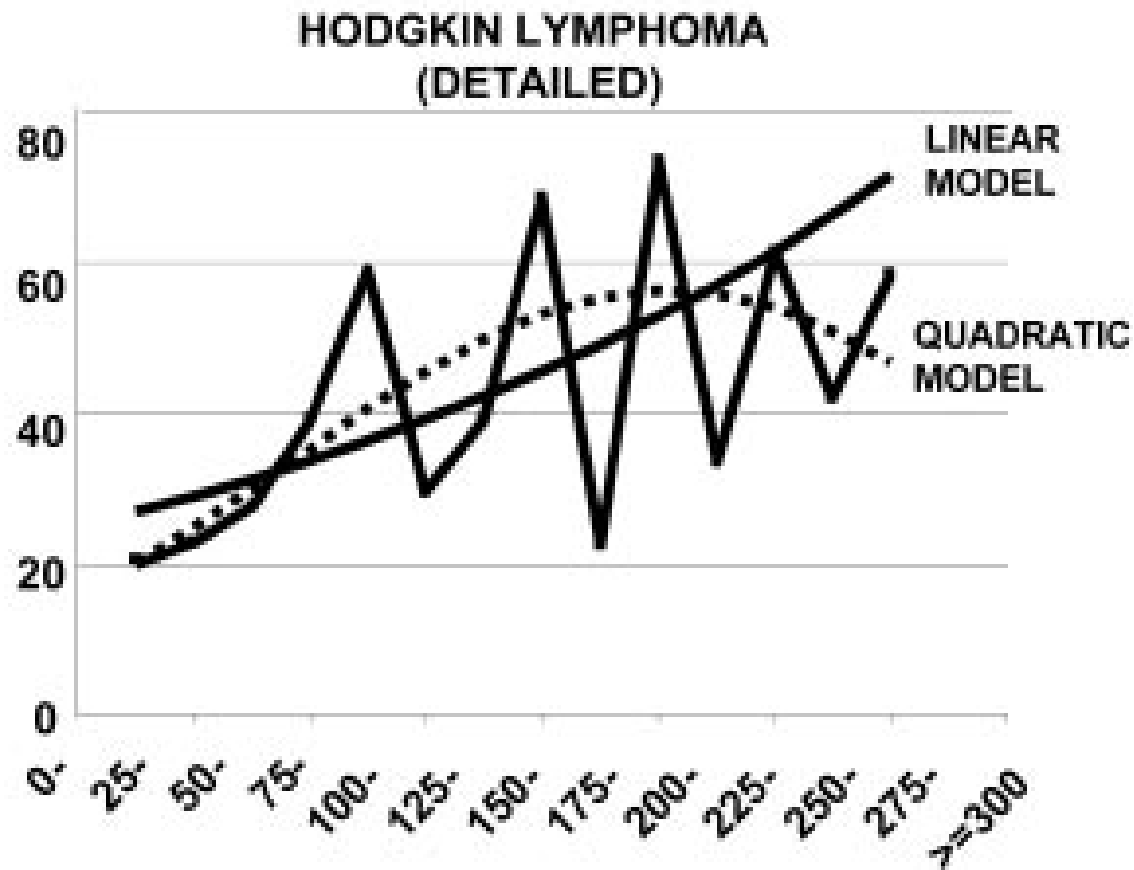
# Adjusted incidence rate ratios for HL, by HAART

	Person years	Adjusted IRR
<b>Swiss HIV Cohort Study (Clifford et al, Blood, 2009)</b>		
Non-HAART users	39,560	ref
HAART users	45,051	1.0 (0.5 – 1.9)
<b>French Hospital HIV Database (Fontas et al, JAIDS, 2009)</b>		
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 aging HIV population



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



# Immunodeficiency 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 $\mu$ L)		
≥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)	..

# Immunodeficiency and HL risk.

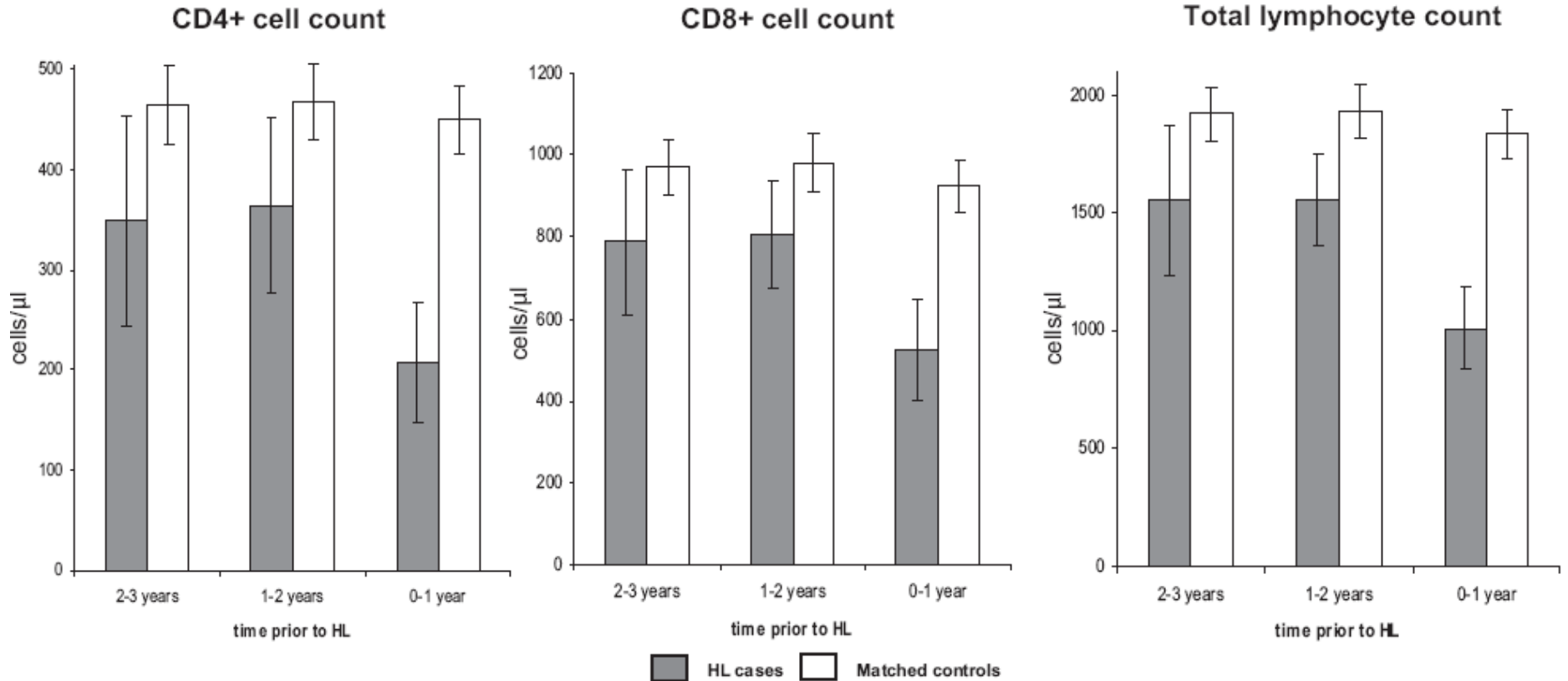
## A nested case:control study in Swiss HIV Cohort Study

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		OR* (95% CI)	HL		Matched controls		OR* (95% CI)
	n	(%)	n	(%)		n	(%)	n	(%)	
<b>CD4<sup>+</sup> cell count, cells/<math>\mu</math>L</b>										
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/ $\mu$ L decrease					1.08 (0.94-1.25)					1.65 (1.33-2.03)

# Lymphocytopenia prior to HL onset

A case:control study nested in Swiss HIV Cohort Study



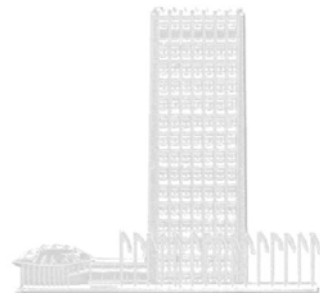
# Difficulties with assessing the relationship between CD4 count and HL risk

- 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 of AIDS, so that CD4+ count at AIDS is also problematic.
- Might this also be an issue for other cancers ??

# Hepatocellular Carcinoma (HCC)



International Agency for Research on Cancer  
Centre International de Recherche sur le Cancer





# 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	<b>4.0</b> (2.6–5.8)
Engels et al., 2006	U.S. AIDS (1996 – 2002)	107,417	<b>3.3</b> (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	<b>7.0</b> (2.2–16.5)
Newnham et al., 2005	U.K. HIV (1985 – 2001)	33,190	<b>5.9</b> (3.1–10.1)
<i>Grulich et al., 2007</i>	<i>Meta-analysis of all the above</i>		<b>5.2</b> (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	<b>13.1</b> (1.2-48.3)

# Immunodeficiency and hepatocellular carcinoma risk.

## A case:control study nested in Swiss HIV Cohort Study

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

# Immunodeficiency 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 $\mu$ L)				
$\geq 500$	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)	..

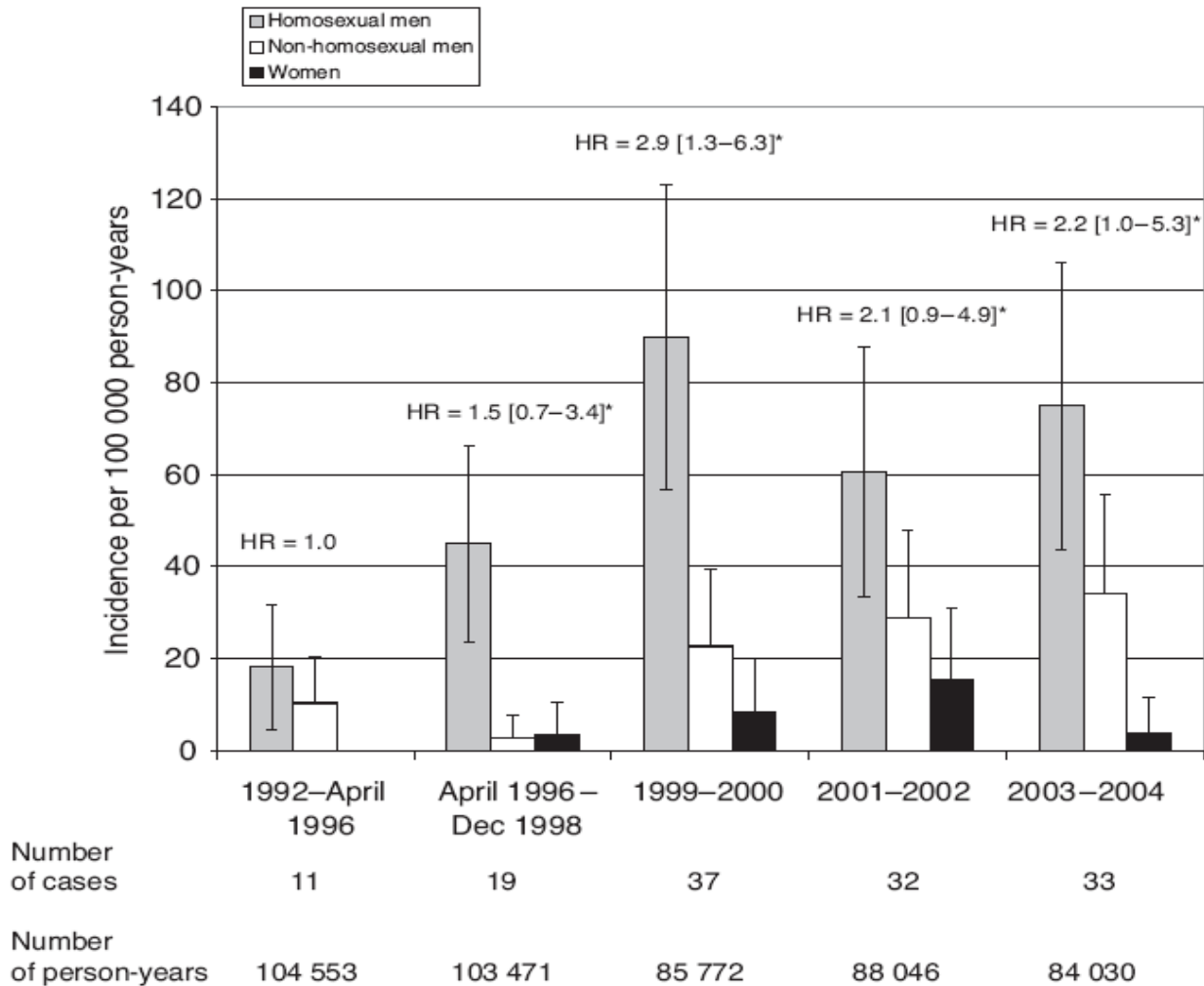
# Trends in Non-AIDS defining cancer : effects of HAART and/or ageing

## Age-standardised Incidence rates (per 100,000) of selected cancers, by period

**Swiss HIV Cohort Study, approx 54,000 person-years, submitted**

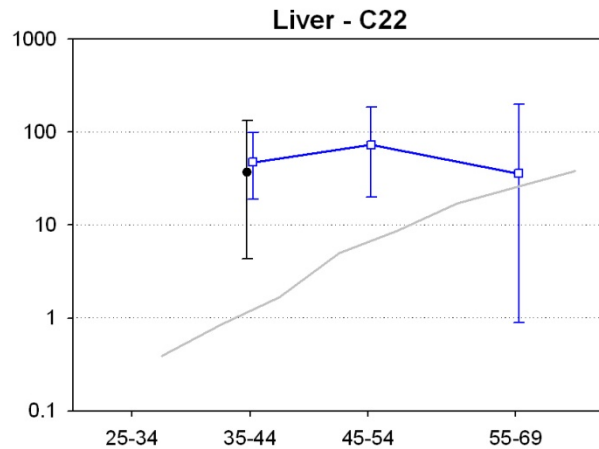
Cancer site or type	Pre-HAART 1985-1996	Early-HAART 1997-2001	Late-HAART 2002-2006
	IR (95% CI)	IR (95% CI)	IR (95% CI)
Hodgkin lymphoma	30.7 (12-64)	42.9 (21-77)	52.8 (20-102)
Anus	8.3 (1-30)	42.7 (22-75)	25.3 (7-59)
Liver	9.6 (1-35)	25.9 (11-54)	17.1 (5-41)
Lung	38.1 (16-75)	36.5 (17-67)	33.9 (17-60)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

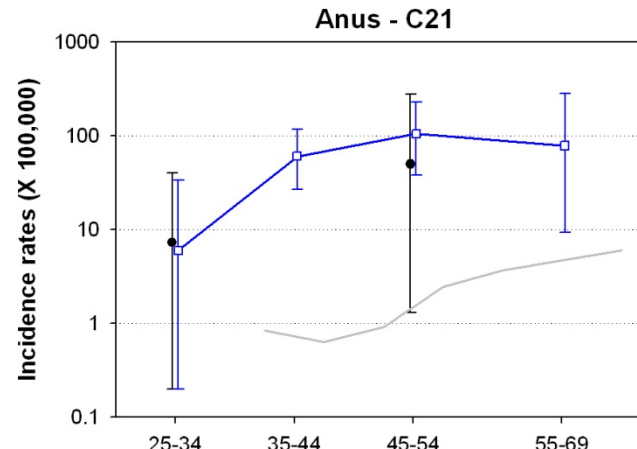


# Age-specific incidence rates of cancers in the Swiss HIV Cohort Study by period

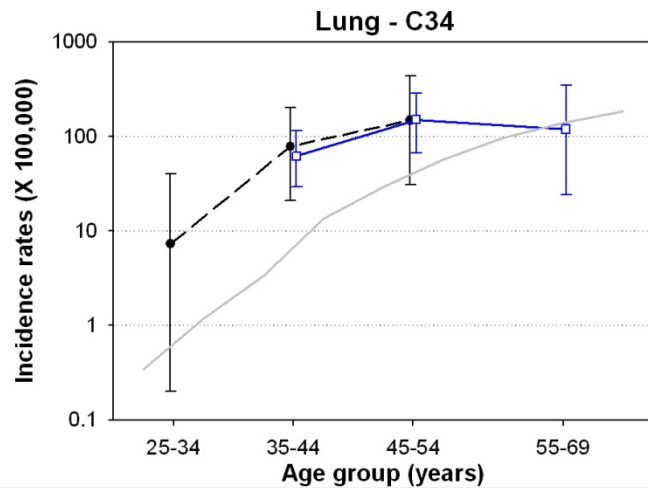
(- -●- - 1985-1996; —□— 1997-2006; — General Population 1998-2002)



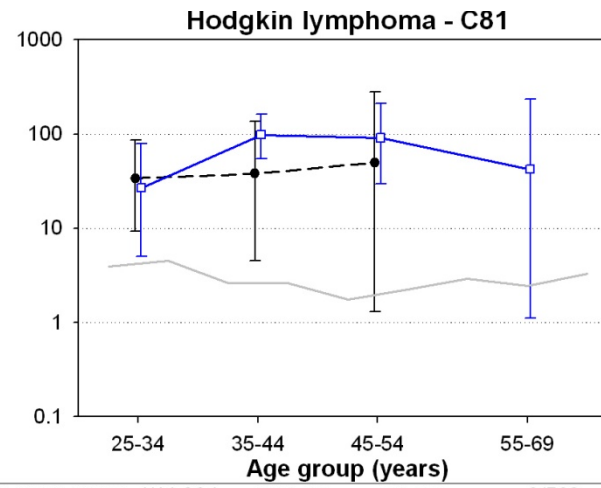
85-96 CASES/PY	0/11,302	2/5,550	0/1,803	0/560
97-06 CASES/PY	0/8,060	7/16,051	4/5,854	1/2,546



85-96 CASES/PY	1/11,300	0/5,550	1/1,802	0/560
97-06 CASES/PY	1/8,059	9/16,029	6/5,840	2/2,533



85-96 CASES/PY	1/11,302	4/5,545	3/1,803	0/560
97-06 CASES/PY	0/8,060	10/16,042	9/5,846	3/2,545



85-96 CASES/PY	4/11,294	2/5,541	1/1,802	0/560
97-06 CASES/PY	3/8,054	16/15,994	5/5,849	1/2,541

# 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-HAART and HAART period can be distorted by extreme changes in age distribution
- Even age-standardized incidence rates can be potentially misleading because of problems with missing cells.
- Age-specific incidence rates among HIV+ do not show increases over time.