

Non-AIDS Complication: Malignancies Among HIV- Infected Patients

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Learning Objectives

At the conclusion of this presentation, participants should be able to:

1. Describe the change in causes of mortality in the Highly Active Anti-Retroviral Therapy era
2. Identify risk factors of selected cancers in HIV-infected patients in your practice.
3. Discuss the role of immunodeficiency in the incidence of non-AIDS-defining cancers.
4. Utilize the management and prognosis of selected non-AIDS-defining cancers to plan care for affected HIV-infected patients in their practice

Off-Label Disclosure

- This presentation will not discuss any non-FDA-approved or investigational uses of any products/devices.

Which statement is true?

1. The risk of non-AIDS-defining cancers has substantially decreased in the HAART era.
2. Among patients with HIV, mortality from non-AIDS-defining cancers increased in the HAART era.
3. The risk of Hodgkin's lymphoma is significantly higher among HIV-infected patients with a CD4+ count of less than 200.
4. Anal Papanicolaou testing can be used to screen for anal dysplasia and anal cancer. High-grade anal dysplasia, like cervical dysplasia, likely represents a precancerous lesion.

All the following are thought to be contributors for the higher incidence of non-AIDS-defining cancers among HIV-infected patients, except:

1. Increased survival and ageing resulting in decrease in fatal opportunistic infections
2. High prevalence of traditional cancer risk factors (such as smoking or excessive alcohol intake)
3. Higher prevalence of viral co-infections (such as HCV and HPV)
4. Low CD4 count
5. The Pre-HAART era

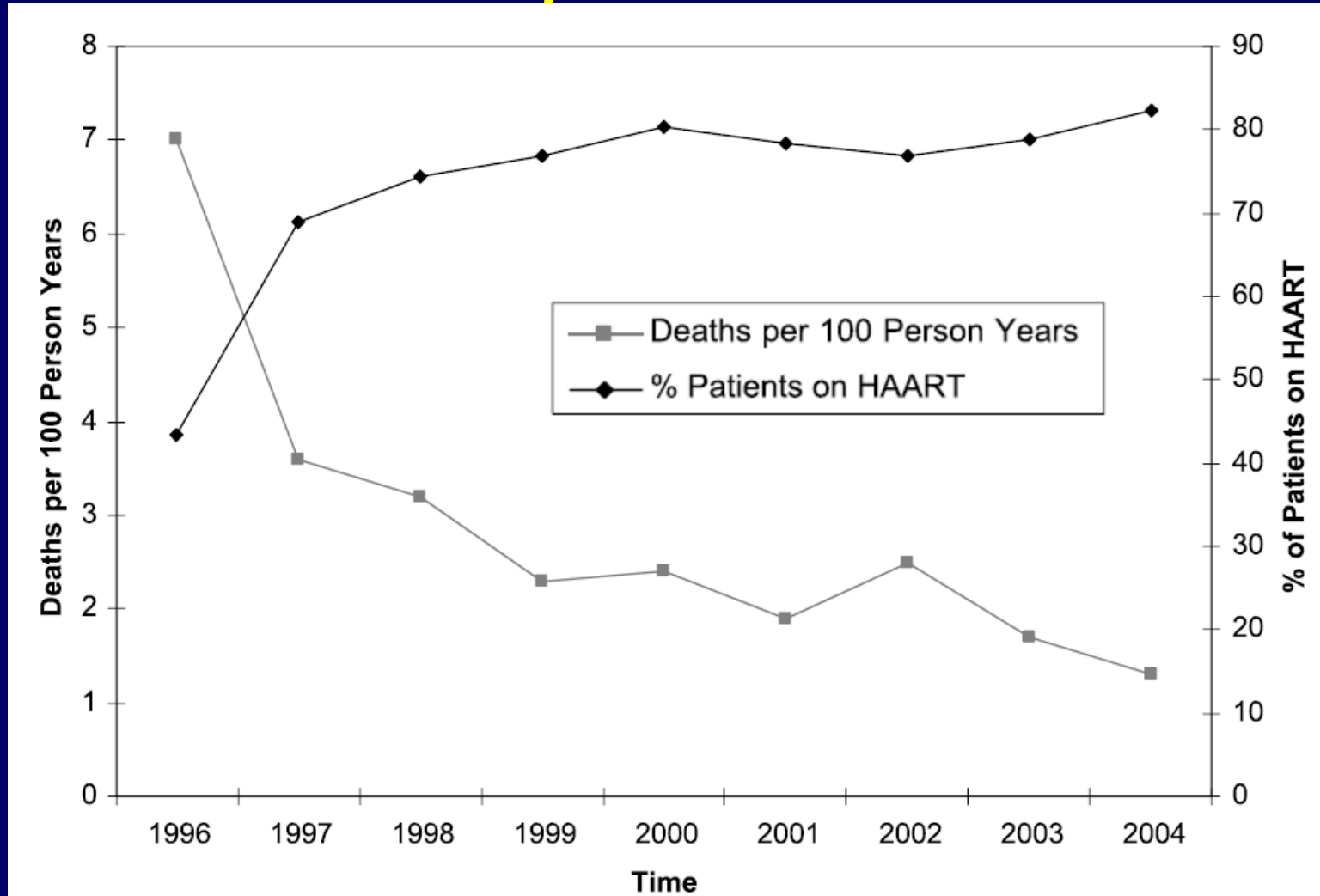
Outline

- Role of Malignancies in the Mortality of HIV-Infected Patients
- Changing Spectrum of Malignancies Among HIV-Infected Patients
 - Trends of AIDS-Defining vs. Non-AIDS-Defining Malignancies
 - Seven Key Facts in non-AIDS-Defining Malignancies
- Prevention, Management and Prognosis

Trends in Morbidity and Mortality: The Changing Face of HIV Disease

- Increased survival and aging of HIV-infected patients
- Trends in causes of death among persons with HIV/AIDS in the HAART era

Changing Face of HIV/AIDS Epidemic

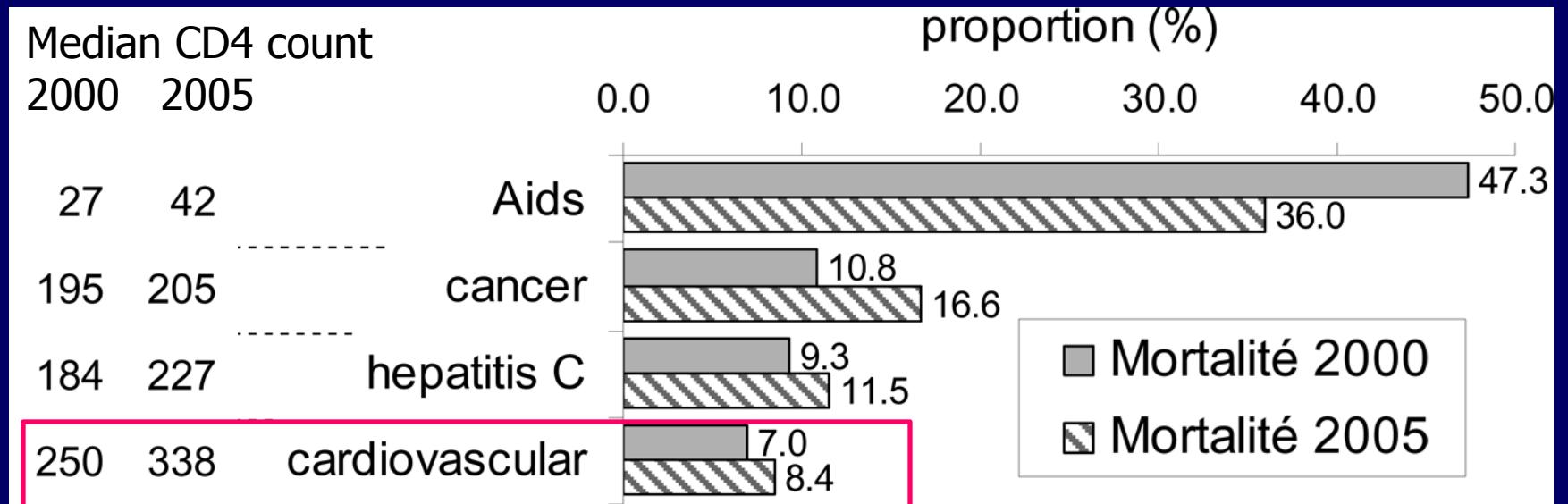


Age Distribution of HIV Infected Veterans In Care

Year	Number in Care	Age <30	Age 30-39	Age 40-49	Age 50-59	Age 60-69	Age 70-79	Age >79	Mean Age
2000	19,688	2.1%	18.1%	43.3%	28.1%	6.3%	2.1%		
2002	19,346	1.4%	14.4%	40.7%	33.9%	7.1%	2.6%		
2005	23,541	1.5%	10.1%	34.3%	39.8%	11.4%	2.6%	0.3%	50.5
2006	23,329	1.4%	9.0%	32.1%	41.1%	13.2%	2.9%	0.3%	51.2
2007	22,956	1.3%	8.0%	29.8%	41.3%	16.1%	3.2%	0.4%	52.0
2008	23,463	1.4%	7.3%	27.6%	40.8%	19.1%	3.3%	0.4%	52.6

Data from: National VA HIV Registry Reports; 2008 and Center for Quality Management Historic Reports 2000, 2002, 2005-2006; <http://vaww.hiv.va.gov/vahiv?page=prin-cqm-01#t-5>; accessed 02/22/10

Changing Face of HIV/AIDS Epidemic



Underlying cause of death in HIV-infected adults: Overall distribution in 2000 (n = 964) and 2005 (n = 1042), and most recent CD4 cell count by cause; Mortalite' 2000 and 2005 surveys, France.

No absolute increase in age-adjusted deaths from CVD shown

Cardiovascular Risk in HIV

- Is there a truly increased incidence of MI as a result of HIV infection?
 - Or is it just that HIV patients have more risk factors for cardiovascular disease (smoking, hypercholesterolemia, etc..)
- If HIV infection is implicated, what are the mechanisms?
 - HIV infection itself and/or immune dysfunction?
- How do potential ART-related toxicities influence the incidence of MI?

Rates of AMI by HIV Status and Age Group

Status	Age Group, y					
	30-39	40-49	50-59	60-69	70-79	80-89
Uninfected						
No. of participants	6783	21 866	19 805	4209	1120	148
No. of AMI events	10	164	218	66	36	14
AMI rates per 1000 person-years (95% CI)	0.3 (0.2-0.6)	1.5 (1.3-1.7)	2.2 (1.9-2.5)	3.3 (2.6-4.2)	6.7 (4.8-9.2)	21.5 (12.7-36.4)
HIV Infected						
No. of participants	3848	10 575	9342	2065	557	56
No. of AMI events	13	105	171	46	25	3
AMI rates per 1000 person-years (95% CI)	0.7 (0.4-1.2)	2.0 (1.6-2.4)	3.9 (3.3-4.5)	5.0 (3.8-6.7)	10.0 (6.7-14.7)	13.5 (4.3-42.0)
Incidence rate ratio (95% CI)	2.19 (0.89-5.58)	1.34 (1.04-1.72)	1.80 (1.47-1.21)	1.53 (1.03- 2.26)	1.50 (0.86-2.57)	0.63 (0.12-2.25)

US Veterans Study: 82 459 participants. Median f/u: 5.9 years. 871 AMI events.

After adjusting for Framingham risk factors, comorbidities, and substance use, HIV-positive veterans had an increased risk of incident AMI compared with uninfected veterans (hazard ratio, 1.48; 95% CI, 1.27-1.72).

Freiberg. *JAMA Intern Med.* 2013;173(8):614-622.

CVD RISK FACTORS

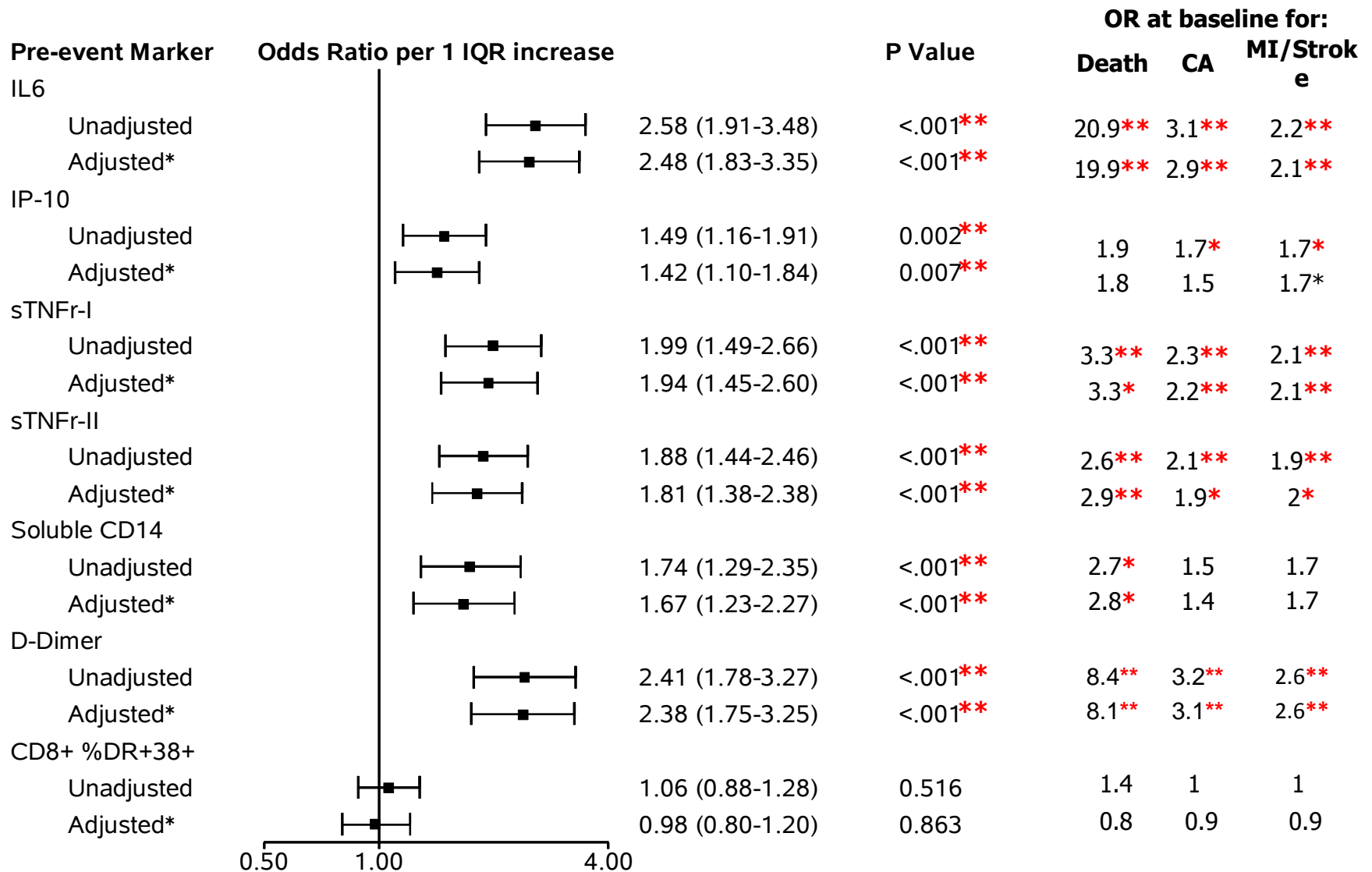
COMPARISON OF CVD RISK FACTOR PREVALENCE BETWEEN HIV-INFECTED MEN AND CONTROLS IN LARGE COHORT STUDIES

RISK FACTOR	APROCO VS. WHO MONICA ¹ (Data for men 34-44 yo)		WIHS/MACS COHORTS ² (Data for men only shown)	
	HIV-POS	HIV-NEG	HIV-POS	HIV-NEG
Smoking	56.6%	32.7%	35%	28%
HTN	5.2%	12.8%	33%	34%
Diabetes	2%	3%	16%	11%
Elevated TC	59.6%	60.8%	NR	NR
Elevated TG	32.3%	13.5%	10%	2%
Low HDL	44.9%	23.1%	43%	21%

Statistically significant differences in **bold**

1. Saves M, et al. *Clin Infect Dis.* 2003; 37:292.
2. Kaplan RC, et al. *Clin Infect Dis.* 2007; 45:1074.

Pre-Event Soluble Markers and Outcome



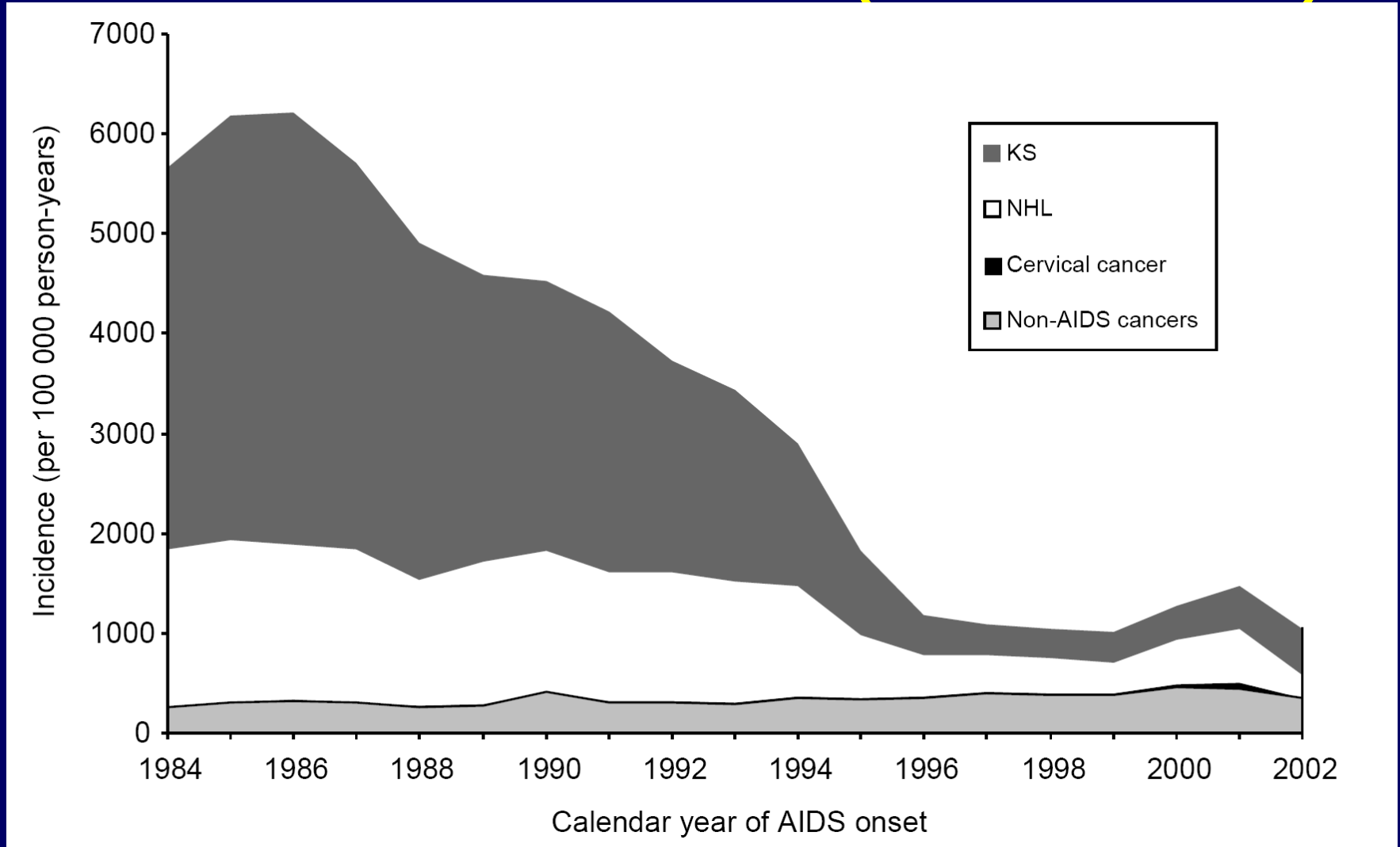
*Adjusted by CD4 count

Cause of death	No. of deaths per 1000 person-years (95% CI), according to calendar year of AIDS onset ^b			<i>P</i> ^c
	1980–1989	1990–1995	1996–2006	
Deaths reported to HIV/AIDS registry	302 (297–307)	140 (139–142)	29 (27–30)	<.01
Nonmissing cause of death	280 (275–285)	119 (117–120)	27 (25–28)	<.01
Cancer cause of death	5.16 (4.53–5.86)	3.48 (3.22–3.78)	1.49 (1.25–1.77)	<.01
AIDS-defining cancer				
All	2.95 (2.47–3.49)	1.66 (1.48–1.85)	0.65 (0.50–0.85)	<.01
KS	0.89 (0.64–1.21)	0.33 (0.25–0.42)	0.08 (0.03–0.17)	<.01
NHL	2.00 (1.61–2.45)	1.31 (1.15–1.48)	0.54 (0.40–0.72)	<.01
Cervical cancer ^d	0.49 (0.10–1.44)	0.12 (0.03–0.30)	0.14 (0.03–0.42)	.35
Non-AIDS-defining cancer				
All	2.21 (1.80–2.69)	1.83 (1.64–2.03)	0.84 (0.66–1.05)	<.05
Lung cancer	0.87 (0.62–1.18)	0.58 (0.48–0.70)	0.32 (0.21–0.46)	<.01
Liver cancer	0.13 (0.05–0.28)	0.10 (0.06–0.16)	0.06 (0.02–0.13)	<.01
Hodgkin lymphoma	0.15 (0.06–0.31)	0.08 (0.04–0.13)	0.01 (0.00–0.06)	<.01
Anal cancer ^e	0.04 (0.06–0.16)	0.07 (0.04–0.12)	0 (0–0.04)	.51
Other non-AIDS-defining cancers	1.02 (0.75–1.36)	0.99 (0.86–1.15)	0.45 (0.32–0.61)	.17
AIDS-related (excluding AIDS-defining cancer)	207 (203–212)	90 (89–92)	11 (10–12)	<.01
Other non-cancer, non-AIDS-related	67 (65–70)	25 (24–26)	14 (13–15)	<.01

Key Fact #1

While the risk of ADM has declined, the risk of non-ADM among HIV-infected patients is increasing in the HAART era.

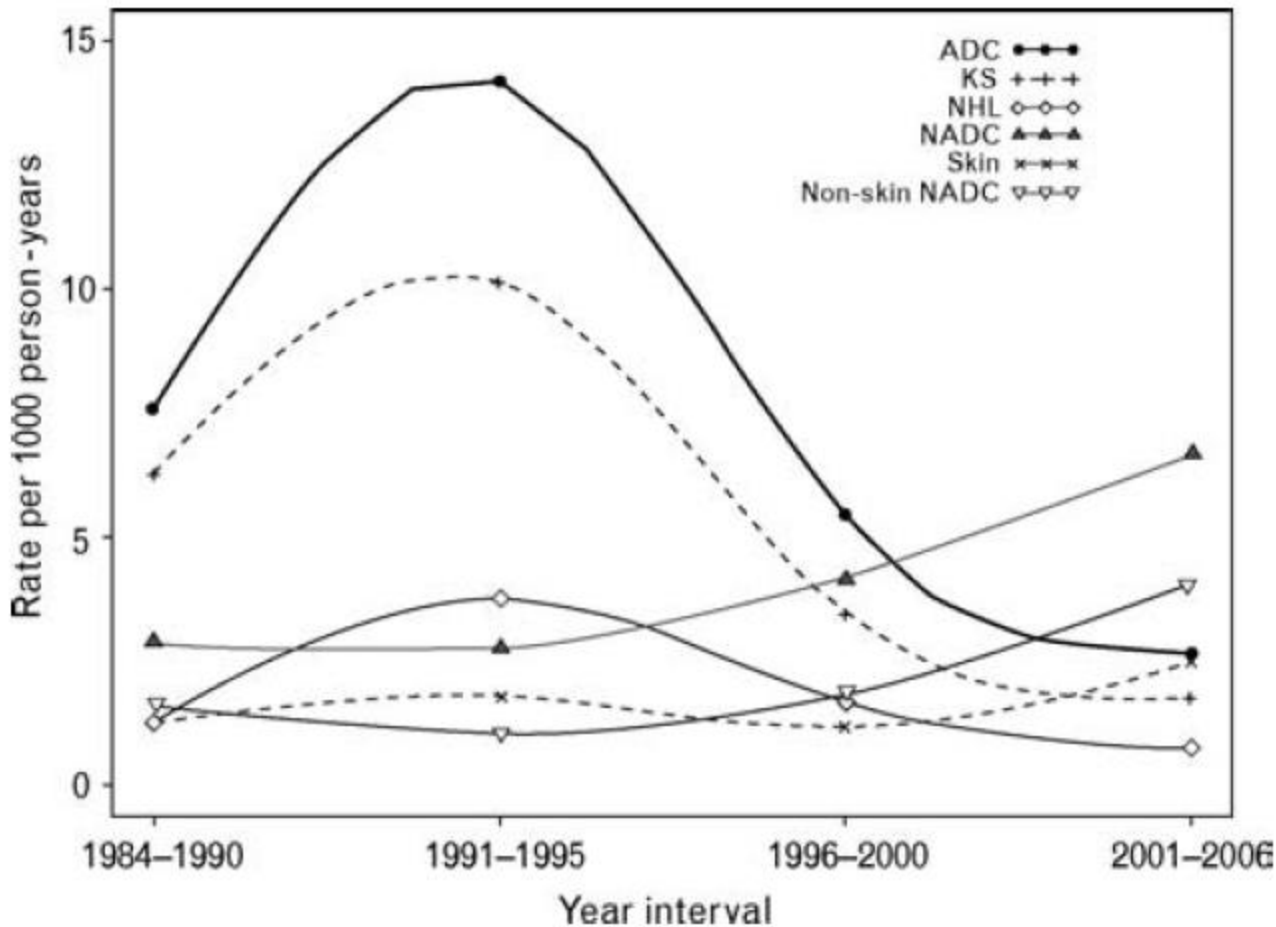
Cancer incidence among people with AIDS in the US (1984–2002)



Incidence and Types of Cancers in HIV Patients

Cancer	ASD and HOPSt (HIV-Infected Population)			
	Standardized Incidence Rate§ per 100 000 Person-Years			Linear Trend P Value
	1992–1995	1996–1999	2000–2003	
Kaposi sarcoma**	2628.5	848.8	356.3	<0.001
Non-Hodgkin lymphoma**	1011.8	494.1	212.2	<0.001
Cervical**	149.9	194.6	134.5	0.63
Anal	19.0	48.3	78.2	<0.001
Hodgkin lymphoma	34.3	54.7	64.4	0.03
Liver	19.9	35.9	35.4	0.35
Lung	91.9	93.8	84.9	0.29
Melanoma	15.6	24.8	37.5	<0.05
Oropharyngeal	29.0	31.0	36.9	0.22
Colorectal	39.9	39.7	66.2	0.03
Breast	56.0	69.9	96.0	0.09
Prostate	14.7	38.0	37.5	0.01

Incidence and Types of Cancers in HIV Patients



- Rates of NADCs have risen over the four periods (2.9, 2.8, 4.2, 6.7; $P=0.0004$).
- During the late HAART era, 71% of cancers were NADCs.
- NADCs were predicted by increasing age and white race (due to skin cancers).

Key Fact # 2

The risk of non-ADM among HIV-infected patients is much higher than that of HIV-uninfected population, even after adjusting for age, gender, and race.

Incidence and Types of Cancers in HIV Patients Compared to General Population

	1992–1995	1996–1999	2000–2003
Kaposi sarcoma ¶	197.0 (185.0–209.7)	174.7 (156.3–195.4)	112.1 (94.7–132.8)
Non-Hodgkin lymph	79.4 (72.4–87.1)	40.3 (35.6–45.6)	17.0 (14.3–20.3)
Cervical	11.8 (7.2–19.2)	13.3 (9.1–19.4)	10.1 (6.5–15.7)
Anal**	31.4 (16.2–60.8)	48.2 (32.4–71.6)	59.4 (44.0–80.3)
Hodgkin lymphoma	11.7 (7.5–18.2)	16.6 (11.5–24.0)	17.9 (12.6–25.5)
Liver	9.3 (4.8–18.0)	10.2 (6.5–16.1)	7.0 (4.6–10.7)
Lung	3.5 (2.5–4.9)	3.8 (2.8–5.0)	3.6 (2.8–4.6)
Melanoma	1.3 (0.6–2.8)	2.2 (1.3–3.9)	3.0 (2.0–4.7)
Oropharyngeal	2.5 (1.4–4.4)	2.5 (1.6–4.1)	3.0 (2.0–4.5)
Colorectal	2.5 (1.6–4.0)	2.0 (1.3–3.1)	2.4 (1.7–3.3)
Breast	0.7 (0.3–1.9)	0.8 (0.4–1.6)	1.1 (0.7–1.8)
Prostate	0.3 (0.1–0.9)	0.7 (0.4–1.3)	0.7 (0.4–1.0)

Non-AIDS-Defining Malignancies: VA Aging Cohort Study

- A total of 33,420 HIV+ and 66,840 HIV- veterans were followed for a median of 5.1 and 6.4 years respectively.
- Incidence rates of non-ADM per 100,000 person-years were 1260 and 841 among HIV+ and HIV- patients respectively.
- Compared to HIV-, the incidence rate ratio (IRR) of non-ADM in HIV+ was 1.6 (95% CI: 1.5-1.7).

Non-ADM Rates in HIV Patients Compared to Matched Controls

Cancer Type	Frequency		Incidence Rate ¹		HIV+ to HIV-
					IRR ³ (95% CI)
	HIV+	HIV-	HIV+	HIV-	
anal	195	29	111.2	7.4	14.9 (10.1-22.1)
lung	503	604	287.4	155.5	2.0 (1.7-2.2)
melanoma	96	124	54.7	31.9	1.7 (1.3-2.3)
prostate	443	1042	254.8	271.8	1.0 (0.9-1.2)
Hodgkin's	135	62	76.9	15.9	4.6 (3.6-6.6)
liver	172	144	97.8	36.9	2.8 (2.2-3.5)
All non-ADM²	2127	3139	1260.0	841.0	1.6 (1.5-1.7)

¹per 100,000 person-years

²includes all cancers except KS, lymphoma, cervical, skin, and ill-defined

³Incidence Rate Ratios (IRR) and 95% CI adjusted for age, race, and gender using Poisson models

Key Fact #3

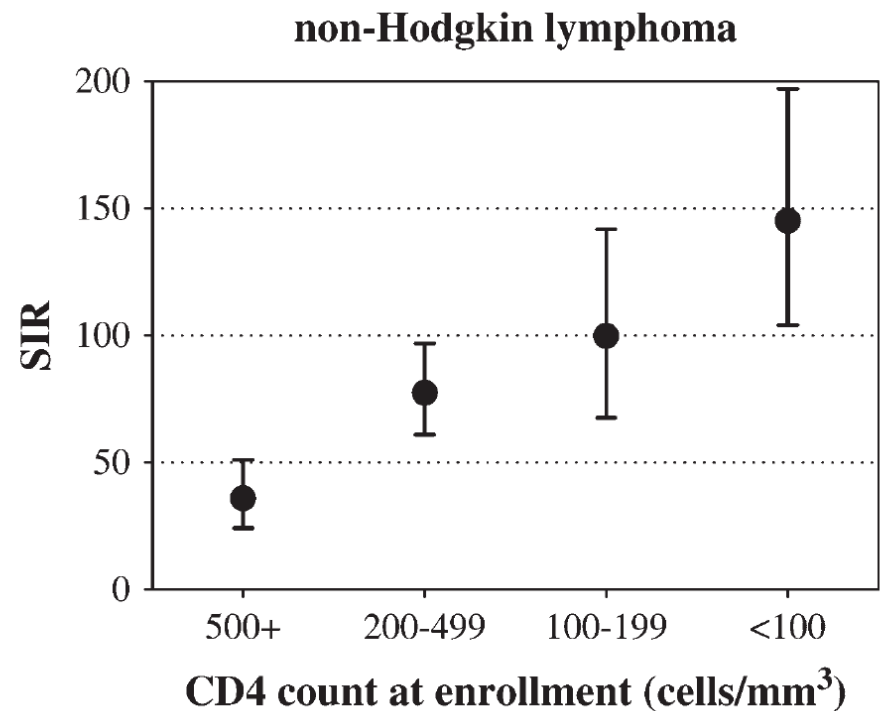
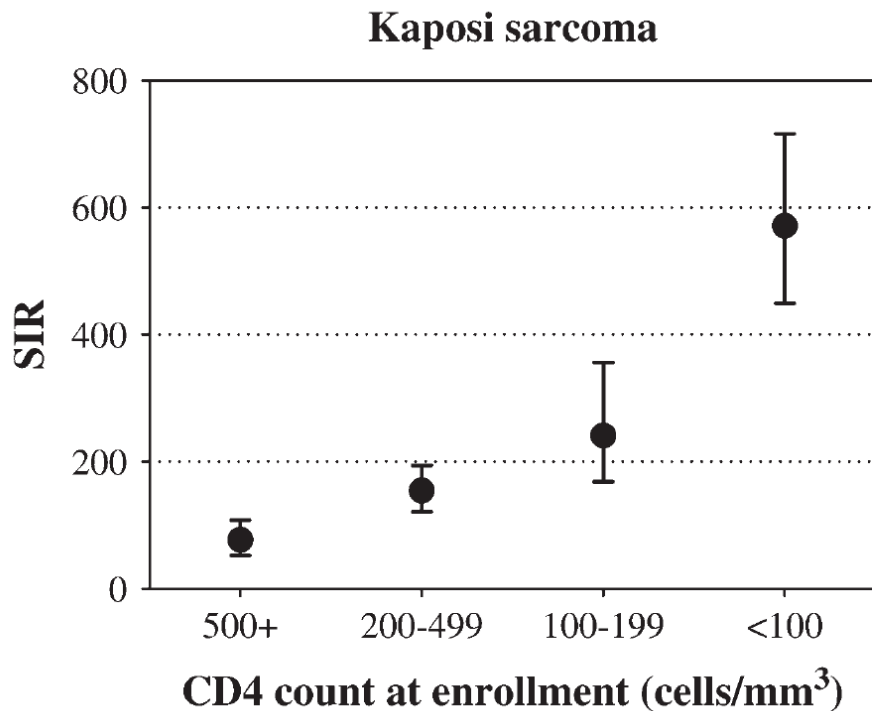
Many non-ADMs have not been found to be associated with low CD4 counts

AIDS-Defining Malignancies and Degree of Immunosuppression

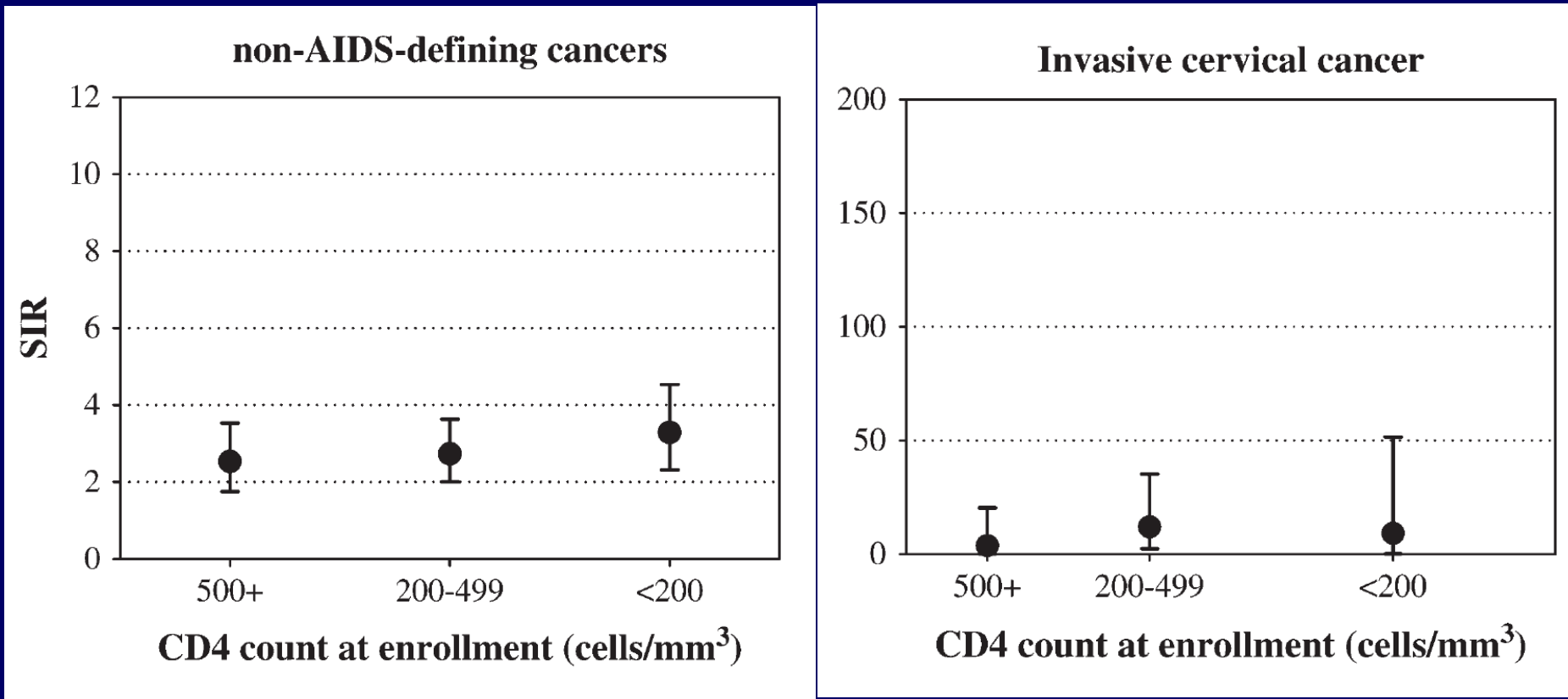
All data was pre-1996 (pre-HAART)

- Linked records from AIDS and cancer registries in 11 US regions (1990-1996)
- Standardized incidence ratios of Kaposi's sarcoma (258) and Non-Hodgkin's lymphoma (78) increased with level of immunosuppression
 - RR for each fall of 100 CD4 cells = 1.36 & 1.48 resp.
- Risk of other cancers, including cervical cancer were unrelated to CD4 counts

CD4 Count and Risk of AIDS-Defining Malignancies



CD4 Count and Risk of Non-AIDS-Defining Malignancies



Non-ADM Rates in HIV Patients: Impact of Immunosuppression

Cancer Type	Frequency		Incidence Rate ¹		HIV+ to HIV-	Median CD4 of HIV+		
					IRR ³ (95% CI)	Cancer		P-value
	HIV+	HIV-	HIV+	HIV-		Yes	No	
anal	195	29	111.2	7.4	14.9 (10.1-22.1)	154	270	<0.001
lung	503	604	287.4	155.5	2.0 (1.7-2.2)	246	269	0.2
melanoma	96	124	54.7	31.9	1.7 (1.3-2.3)	267	268	0.3
prostate	443	1042	254.8	271.8	1.0 (0.9-1.2)	310	267	<.001
Hodgkin's	135	62	76.9	15.9	4.6 (3.6-6.6)	217	269	0.03
liver	172	144	97.8	36.9	2.8 (2.2-3.5)	271	268	0.3
All non-ADM²	2127	3139	1260.0	841.0	1.6 (1.5-1.7)	249	270	.02

¹per 100,000 person-years

²includes all cancers except KS, lymphoma, cervical, skin, and ill-defined

³Incidence Rate Ratios (IRR) and 95% CI adjusted for age, race, and gender using Poisson models

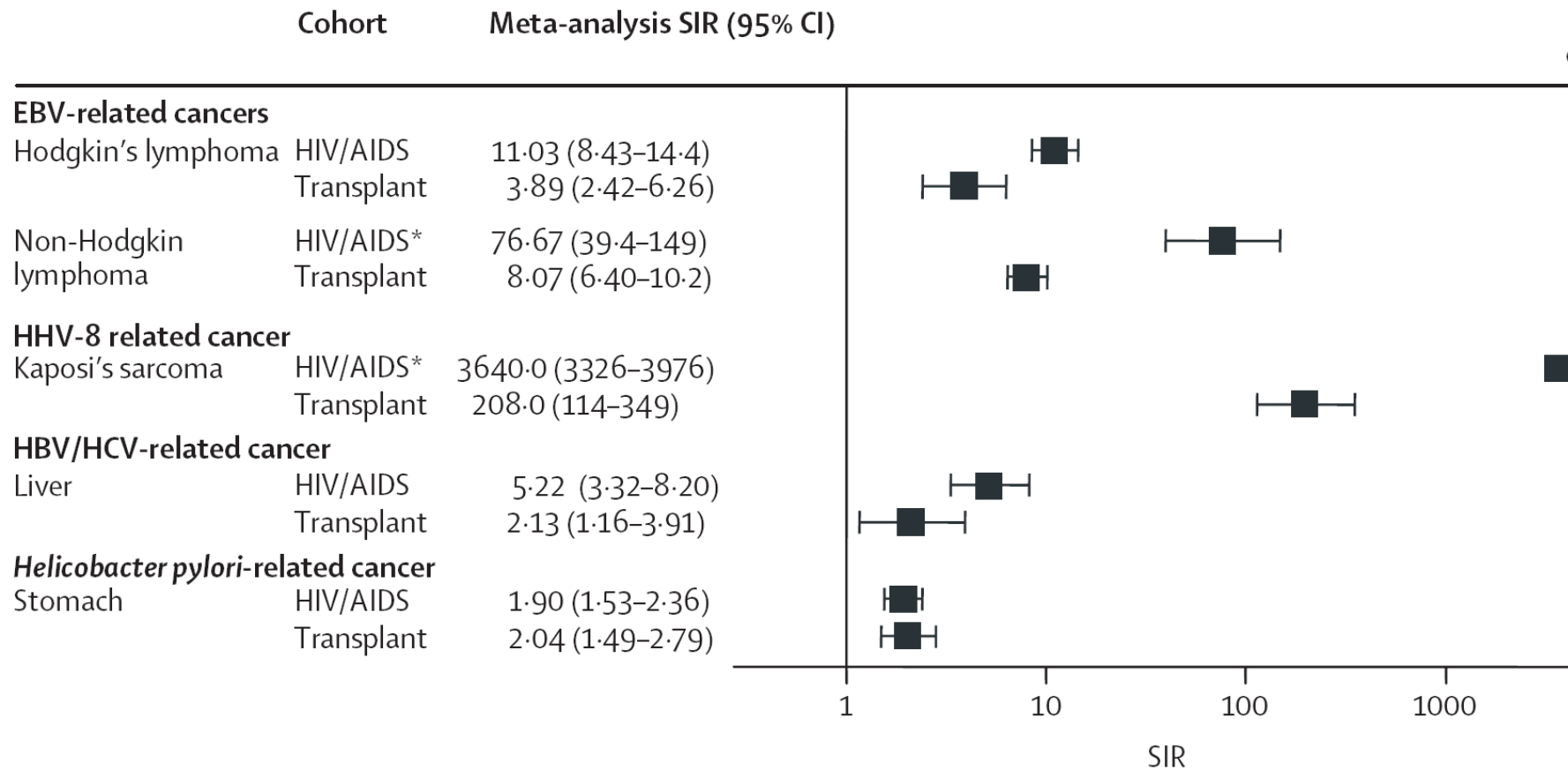
Non-AIDS-defining Cancers in HIV+ and HIV- Patients

- 18,890 adult HIV patients, matched with 189,804 HIV negative Kaiser members.
- Follow-up: 01/96 → cancer development or 12/06 (81,831 PY for HIV+ and 971,675 PY for HIV-).
- RR compared b/w HIV+ and HIV-; Changes in RRs over time were evaluated for the periods 1996-1999, 2000-2003, and 2004-2006
- Non-AIDS-defining cancers: HIV+: 482; HIV-: 3065
- Infection-related cancers: anal cancer, head and neck cancer (often linked to HPV, but also to non-infectious causes such as smoking), liver cancer (HBV & HCV), and Hodgkin's lymphoma (EBV).

Key Fact #4

The spectrum of non-ADM among HIV-infected patients is somewhat similar to the spectrum of malignancies among recipients of solid-organ transplantation

Cancers in HIV Patients vs. Transplant Patients



Immune Deficiency Linked to Non-AIDS-defining Cancers with Infectious Causes

- Infection-related non-AIDS cancers in HIV+: 220 (29.7 per 10,000 PY); HIV-: 398 (4.4 per 10,000 PY); RR: 6.8.
 - Anal cancer (RR 81.4; $P < 0.001$), Hodgkin's (RR 17.4; $P < 0.001$), and head and neck cancers (RR 2.1; $P < 0.001$).
- Infection-unrelated rates: HIV+: 36.4; HIV-: 30.6 ; RR 1.2 ($P = 0.002$).
 - 1.2 in 1996-1999 ($P = 0.26$), 1.2 in 2000-2003 ($P = 0.12$), and 1.3 in 2004-2006 ($P = 0.02$) (P for trend = 0.85).
 - kidney cancer (RR 1.8; $P = 0.045$), lung cancer (RR 1.7; $P = 0.004$), and melanoma skin cancer (RR 1.7; $P = 0.002$).
 - HIV positive patients had a lower rate of prostate cancer (RR 0.7; $P = 0.007$).

Key Fact #5

The increased risk of non-ADM is not entirely accounted for by higher prevalence of traditional malignancy risk factors among HIV-infected patients

Potential Causes of High Rates of Non-AIDS-Defining Malignancies

- Differences in lifestyle and rates of traditional cancer risk factors among HIV patients (eg. Smoking)
- HIV, Immune deficiency and Immune activation
 - Chronic B-cell stimulation, Cytokine dysregulation
 - CD4 count almost certainly doesn't explain all effects of HIV on immunological surveillance
- Oncogenic potential of viral co-infections or HAART?

Traditional Cancer Risk Factors in Individuals with HIV/AIDS

- Higher incidence of smoking among HIV patients
 - lung, head and neck, renal and colon cancers
 - Synergy with HPV for cervical cancer
- Higher prevalence of virus co-infections: HPV, HBV, HCV, HSV and EBV
 - Cervical, anal, head and neck, liver, Hodgkin's, nasopharyngeal carcinoma
- Direct and indirect adjustments for some of these risk factors show HIV independently associated with higher risk of non-AIDS-defining cancers

HIV infection is associated with an increased risk for lung cancer.

- After adjusting for age, sex, smoking status, and calendar period, HIV infection was associated with increased lung cancer risk (RR, 3.6; 95% CI, 1.6-7.9).
- Among HIV-infected persons, smoking remained the major risk factor;
- CD4 cell count and HIV load were not strongly associated with increased lung cancer risk, and trends for increased risk with use of highly active antiretroviral therapy were not significant.

Lung Cancer Increase Independent of Smoking

Table 3. Predictors of lung cancer mortality in the AIDS Link to Intravenous Experience Study cohort.

Variable	Univariate model	Multivariate model ^a
	Hazard ratio (95% CI)	Hazard ratio (95% CI)
Sex		
Male	1.0	1.0
Female	2.0 (0.88–4.7)	1.9 (0.82–4.4)
Mean no. of packs of cigarettes smoked		
Per 1 pack/day increase	1.8 (1.3–2.6)	1.8 (1.3–2.5)
HIV status		
Uninfected	1.0	1.0
Infected	3.4 (1.6–7.4)	3.6 (1.6–7.9)
Time period		
Pre-HAART era	1.0	1.0
HAART era	1.9 (0.69–5.1)	1.7 (0.62–4.6)

Impact of HAART on Non-AIDS-Defining Malignancies

- Comparing incidence in pre-HAART vs. HAART period
 - Incidence unchanged in most earlier studies
 - Higher incidence in the HAART era reported for Hodgkin's disease, skin, lung, anal and for all Non-ADMs combined
- Accounting for individual patients' HAART use
 - Trend towards higher incidence in users¹
 - Trend for an increased risk in the ART era, but a lower risk of NADMs for ART users²

¹Clifford et al., J Natl Cancer Inst. 2005 Mar 16;97(6):425-32

²Hessol et al., J Epidemiol 2007; 165:1143

Key Fact #6

The clinical presentation and prognosis of non-ADM among HIV-infected patients might be different from that of HIV-uninfected patients; some non-ADM show improved prognosis in the HAART era

Prognosis of non-ADM before and after HAART

- Historically, non-ADM have had poorer outcome in HIV patients (even after immune recovery on antiretrovirals) than in general population
- Non-ADM prognosis appears to have significantly improved in the HAART era. Best outcomes with HAART + Chemo
- Non-Small Cell Lung Cancer:
 - Prognosis was worse in HIV than non-HIV patients before HAART
 - Now, similar: Median survival: 4 months
- Hodgkin's disease:
 - HIV patients have more aggressive disease (mixed cellularity or lymphocytic depletion subtype); Also, more associated with EBV
 - Improved prognosis in HAART era, especially with concomitant use of HAART and chemotherapy.

Cervical Cancer in HIV Patients

- Most common HIV-associated cancer among women in some US centers
- Occurs at younger age; higher rate of recurrence and high mortality
 - Incidence of cervical intra-epithelial neoplasia 4-5 times higher than in non-HIV women with high-risk sexual behavior
- Degree of immunosuppression predicts occurrence and severity of disease in some series
 - HPV infection prevalence, HPV persistence & more oncogenic HPV types,

Anal Cancer in HIV Patients

- Incidence much higher in HIV-infected MSM than in heterosexual men or HIV-infected women;
- Much higher in African-Americans than in Whites (OR: 3.0; CI: 2.1 - 4.3; $P < .001$).
- Median age: 49 y vs. 63 y in HIV-negative in VA cohort ($P < .001$).
- In MSM, abnormal anal cytology highly predicative of any anal dysplasia on biopsy ($95.7 \pm 2.1\%$, and high-grade anal dysplasia was $55.9 \pm 5.1\%$).
- Survival was similar to HIV-negative patients (2-year survival: 77% vs. 75%)

Key Fact #7

There is as yet no solid evidence for HIV-specific cancer prevention guidelines for most non-ADMs.

Reducing the Cancer Risk in HIV Infection

- Diagnose and treat HIV infection before advanced stage (relationship between cancer risk and CD4 cell count)
- Customary prevention message re: smoking, alcohol
- Vaccinate appropriately (HBV, HPV)
- Screen as recommended, especially with lower CD4 cell count
- Early referral to oncologist knowledgeable regarding HIV infection

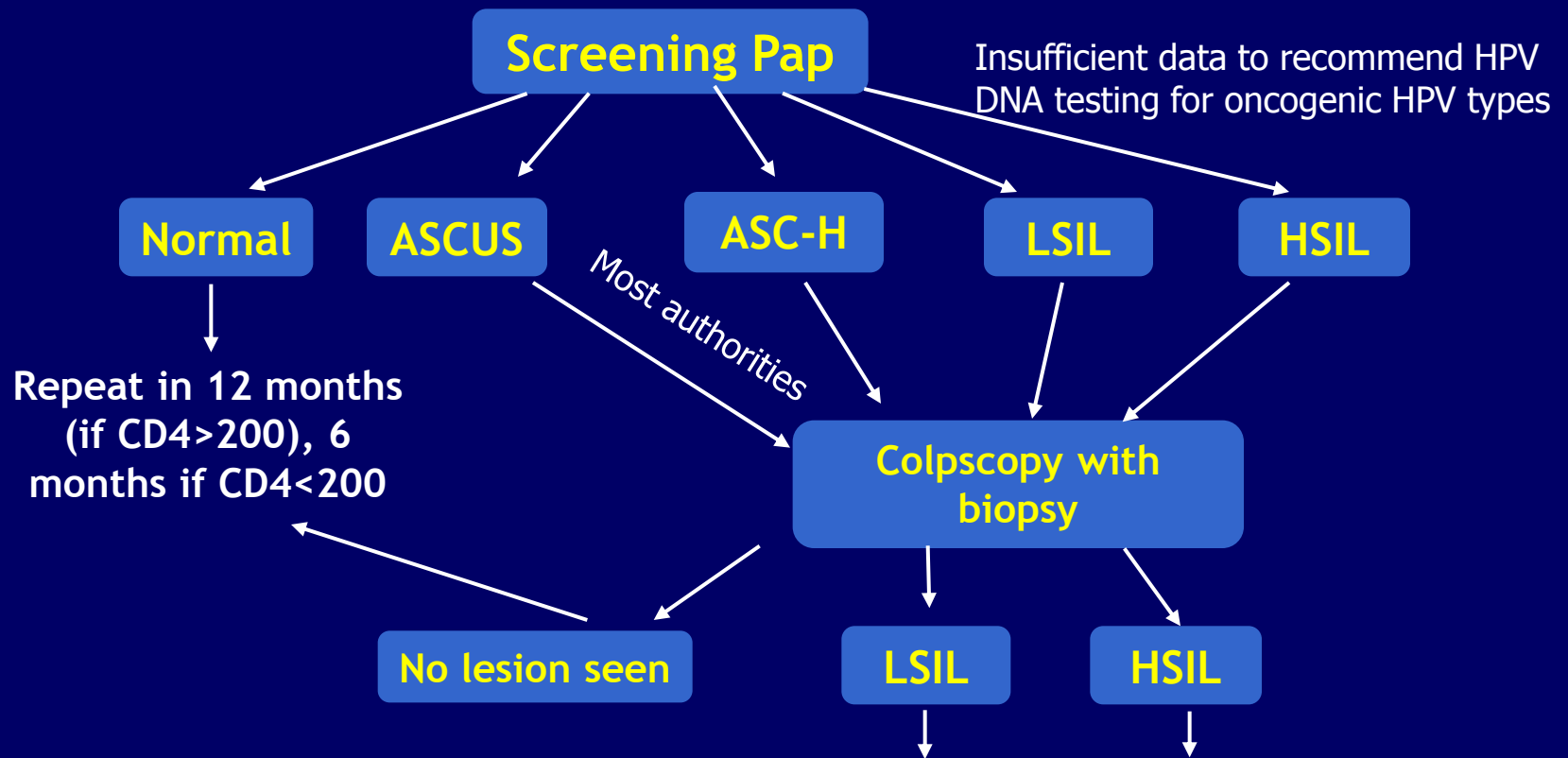
Cancer Screening: USPSFT Guidelines

Problem	Patients ¹	Procedure	Evidence of benefit	Screening interval	Additional comments
Breast cancer	Women ≥ 40 y	Mammography	↓ breast cancer mortality	1-2 years	High rate of false + b/w 40 & 50 y; Individualize if >70 y.
Cervical cancer	Sexually active women	Papanicolaou test	↓ cervical cancer mortality	@HIV diag. & q 6 mo.	If CD4>200 & normal cytology, q 1y. If Pap test abnormal, colposcopy
Anal cancer	Homosexual men, women	Digital rectal exam ± Papanicolaou test	Unknown - advocated by some experts	1-3 years	Benefit is marginal; High-res. anoscopy (HRA) if abnormal cytology
Colorectal cancer	Persons 50-75 yrs	FOBT, C-scope, Flex Sig, DCBE	↓ colorectal cancer mortality	FOBT q1 Flex q5, C-scope q10	Except if high risk group ² Pros: ↑ early diagnosis Cons: Overtreatment, no ↓ cancer-related mortality
Prostate cancer	Men >50 yrs	Digital rectal exam ± PSA	Controversial	1-3 years	No recomm. By USPSTF, but by AUA

¹If CD4<350, discuss screening in context of prognosis, preferences and health goals

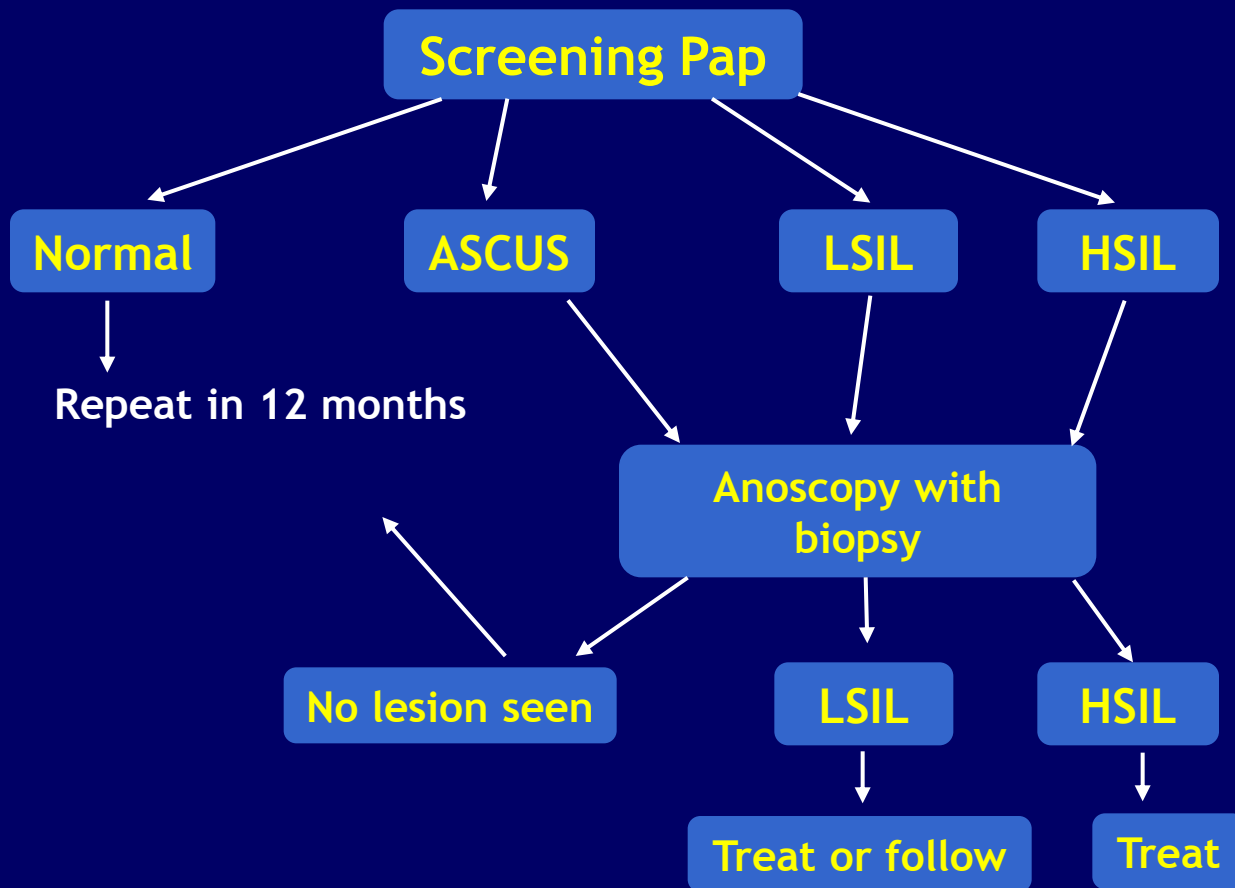
²High risk: 1st & 2nd degree relatives (earlier), IBD & Hx of colon Ca (earlier & more freq.)

Cervical Dysplasia and Management of Abnormal Pap Smear Results



Optimal ablative therapy, role of postablative treatment with topical agents, and timing and method of follow-up, are still largely unknown; American Society for Colposcopy and Cervical Pathology (ASCCP) recommends management similar to non-HIV patients. ; Wright et al., Am J Obstet Gynecol. 2007 Oct;197(4):346-55.

Anal Cytology Screening for AIN in HIV-Positives



Conclusions

1. Incidence of non-ADM increased in the HAART era
2. Incidence of non-ADM higher than in non-HIV pts
 - a. Much higher for “infection-related” non-ADM
3. Spectrum of non-ADM similar to transplant recipients
4. Risk of many non-ADM not associated with degree of immunosuppression
5. Increased risk of non-ADM among HIV patients not entirely explained by increased prevalence of risk factors
 - a. Unclear role of long survival, immune activation, HAART, HIV itself
6. Clinical presentation and prognosis of non-ADM different from those among HIV-negative patients
7. No HIV-specific prevention guidelines for most non-ADMs