

HPV screening and anal cancers in HIV-infected patients

Joel Palefsky, M.D.

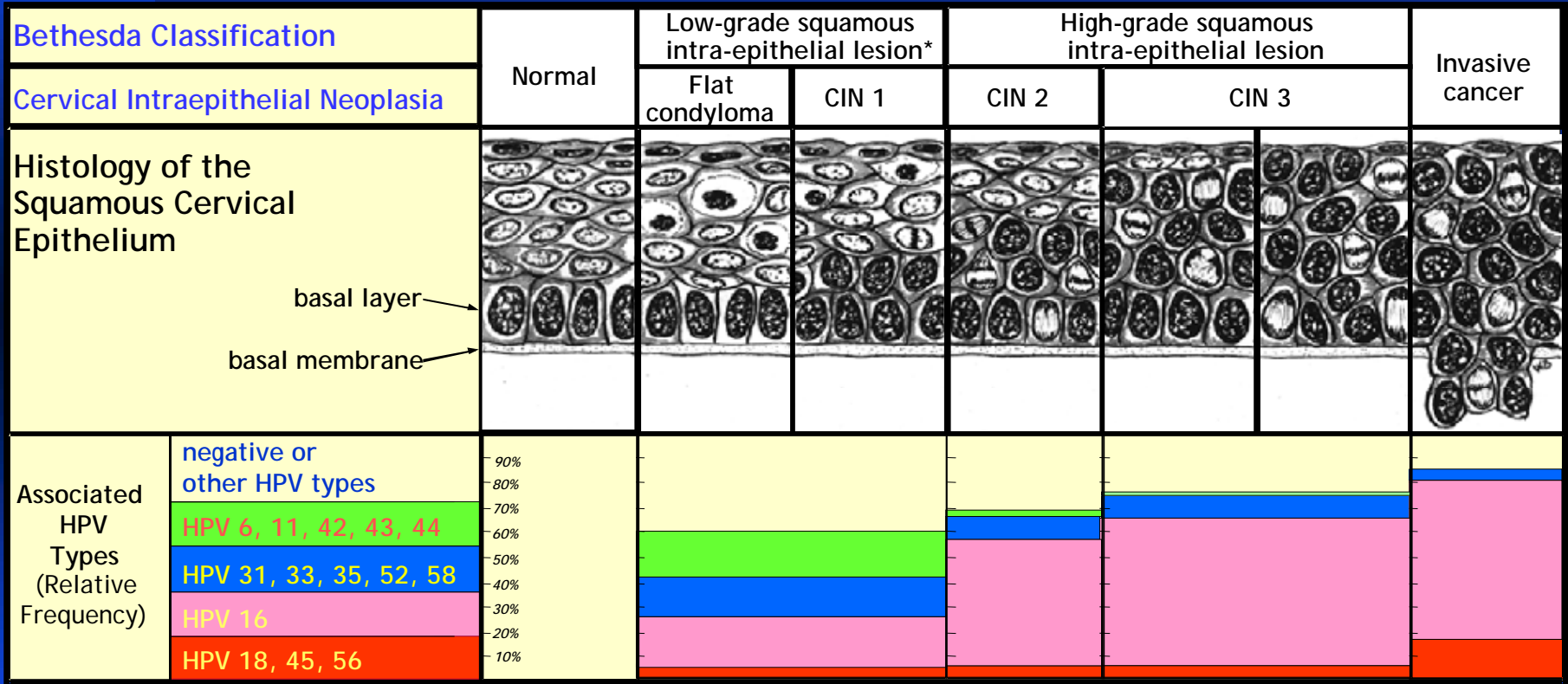
University of California, San Francisco

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Outline

- Rationale for screening for anal cancer
- Rationale for screening for AIN
- Understanding the available screening tools
 - DRE, cytology, HRA, HPV testing, HPV serology
- Tailoring a screening program according to risk
- Management algorithms for AIN and anal cancer

From Condyloma to Cancer

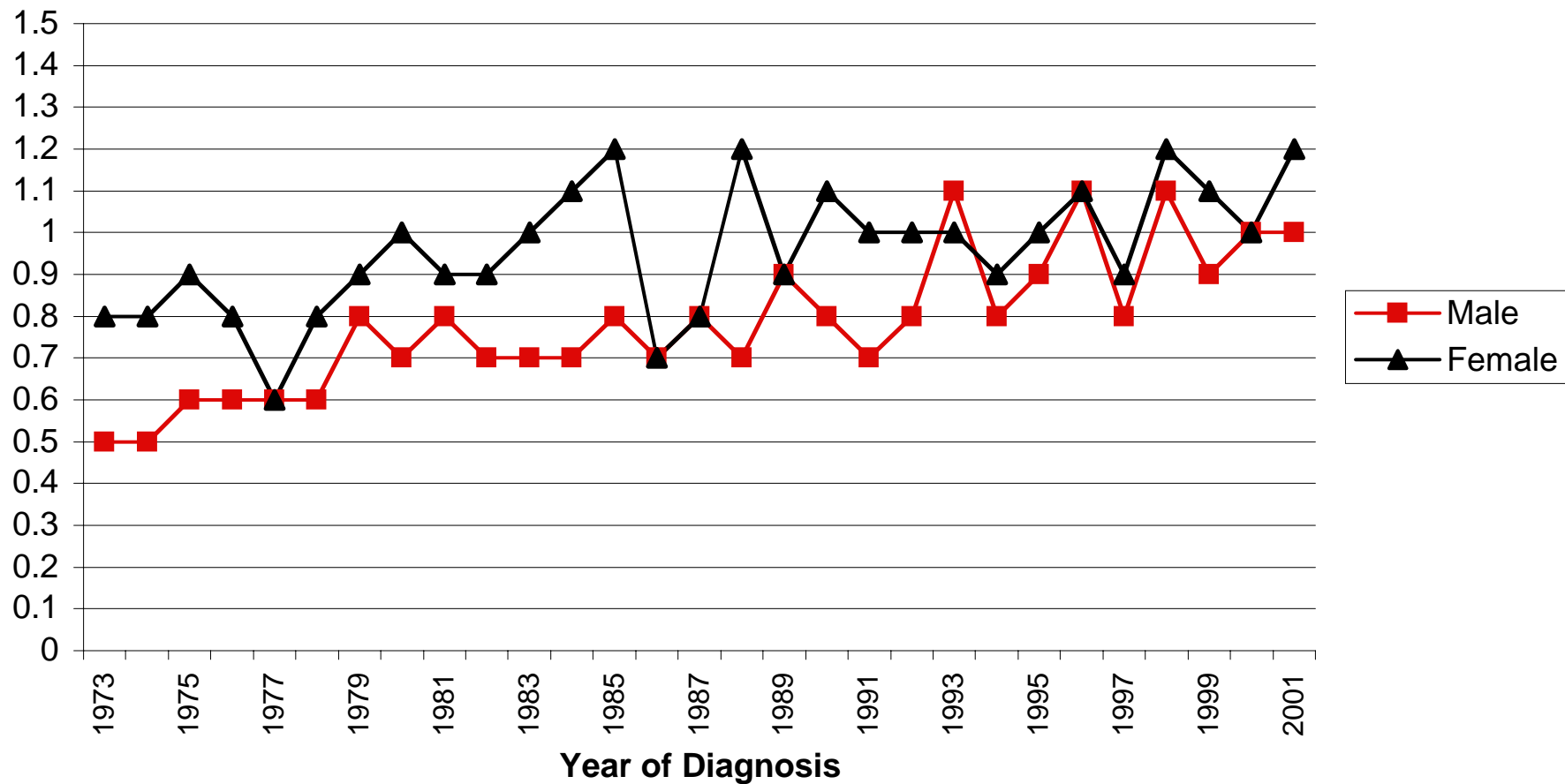


The prevalence of high-risk oncogenic HPVs increases with the severity of the lesion

* LSIL also includes ASCUS (atypical squamous cells of unknown significance)

Modified from Bonnez W. Papillomavirus. In: Richman RD et al eds. *Clinical Virology*. 2nd ed. Washington, DC: American Society for Microbiology; 2002:557-596.

Age-adjusted Incidence Rate of Primary Anal cancer by Gender and Year of Diagnosis



Anal and cervical cancer incidence

- Cervical cancer prior to cervical cytology screening: 40-50/100,000
- Cervical cancer currently: 8/100,000
- Anal cancer among HIV- MSM: up to 35/100,000
- Anal cancer twice as high among HIV+ MSM than HIV-MSM

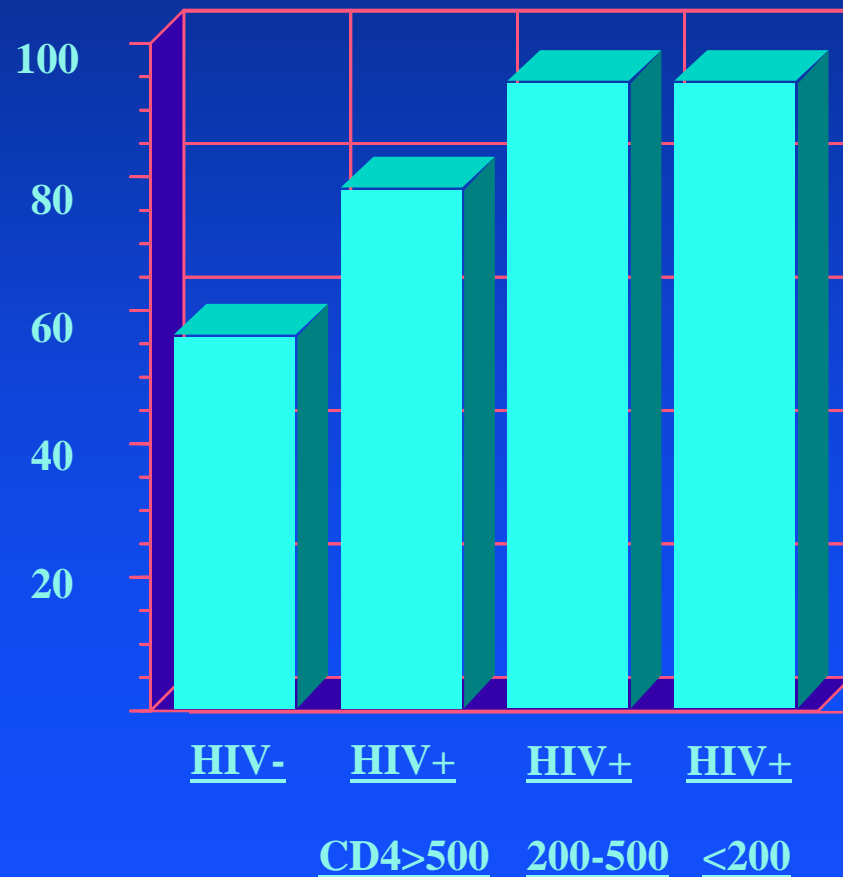
Incidence of HPV-associated cancers in HIV-cancer registry match

Table 6. Relative risks* (by human immunodeficiency virus [HIV] exposure group) of human papillomavirus-associated anogenital cancers among 309 365 patients with acquired immunodeficiency syndrome (AIDS) (AIDS–Cancer Match Registry, United States, 1978–1996)

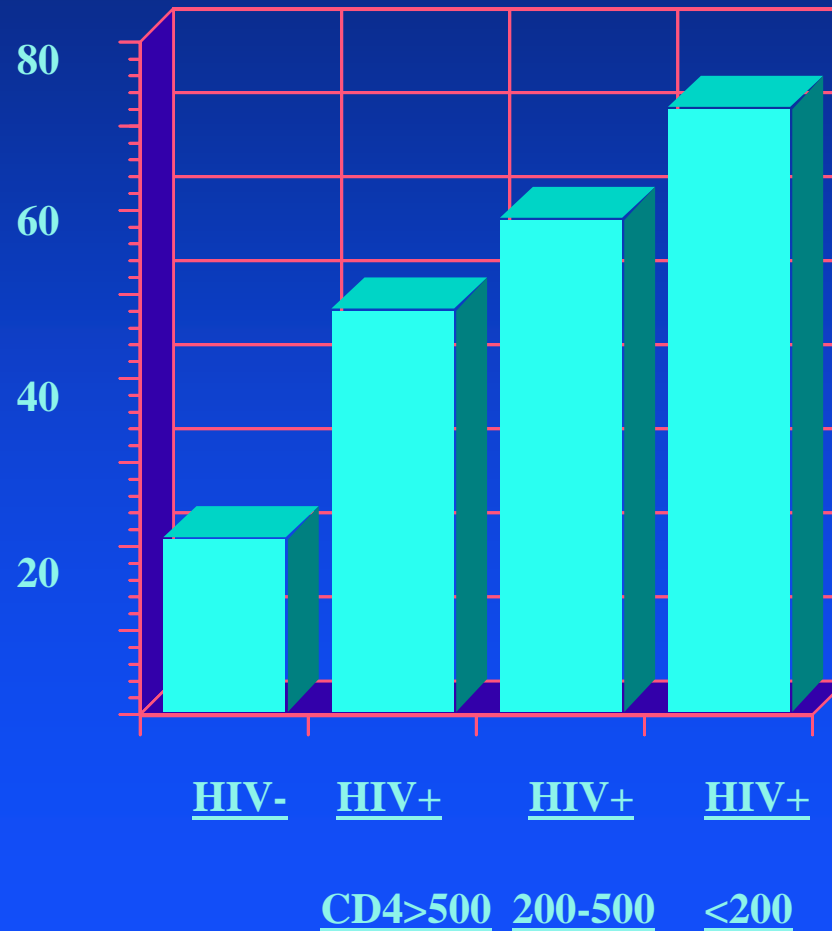
HIV exposure category	Relative risk (95% confidence interval) [No. of observed cancers]									
	Cervix		Vulva/vagina		Anus (women)		Anus (men)		Penis	
<i>Invasive cancers</i>										
Homosexual contact†	NA‡		NA‡		NA‡		59.5 (51.5–68.4)	[197]	2.8 (1.0–6.1) [6]	
Heterosexual contact	4.9 (2.7–8.2)	[14]	7.1 (2.3–16.4)	[5]	8.0 (1.7–23.4)	[3]	—	[0]	— [0]	
Intravenous drug use§	7.0 (4.7–10.0)	[29]	5.5 (1.8–12.8)	[5]	7.3 (1.5–21.4)	[3]	5.9 (2.7–11.2)	[9]	7.1 (2.8–14.6) [7]	
Hemophilia/transfusion	— [0]		— [0]		— [0]		— [0]		— [0]	
Other/unknown¶	1.1 (0.0–6.2)	[1]	7.0 (0.9–25.3)	[2]	6.4 (0.2–35.9)	[1]	17.1 (7.4–33.7)	[8]	2.7 (0.1–15.1) [1]	
All	5.4 (3.9–7.2)	[44]	5.8 (3.0–10.2)	[12]	6.8 (2.7–14.0)	[7]	57.9 (33.0–43.4)	[214]	3.7 (2.0–6.2) [14]	
<i>In situ cancers</i>										
Homosexual contact†	NA‡		NA‡		NA‡		99.8 (81.4–121.2)	[102]	6.1 (3.0–10.9) [11]	
Heterosexual contact	4.5 (4.0–5.1)	[251]	5.1 (1.7–12.0)	[5]	—	[0]	—	[0]	9.5 (0.2–52.8) [1]	
Intravenous drug use§	4.6 (4.2–5.1)	[371]	2.2 (0.5–6.3)	[3]	17.2 (0.4–96.0)	[1]	5.6 (1.2–16.5)	[3]	7.2 (2.3–16.8) [5]	
Hemophilia/transfusion	3.9 (2.1–6.5) [14]		— [0]		— [0]		— [0]		15.8 (0.4–87.9) [1]	
Other/unknown¶	5.0 (4.0–6.2)	[86]	9.0 (1.9–26.3)	[3]	—	[0]	7.9 (0.2–43.7)	[1]	9.0 (1.1–32.4) [2]	
All	4.6 (4.3–5.0)	[722]	3.9 (2.0–7.0)	[11]	7.8 (0.2–43.6)	[1]	60.1 (49.2–72.7)	[106]	6.9 (4.2–10.6) [20]	

Frisch et al; JNCI 2000; 92: 1500-10

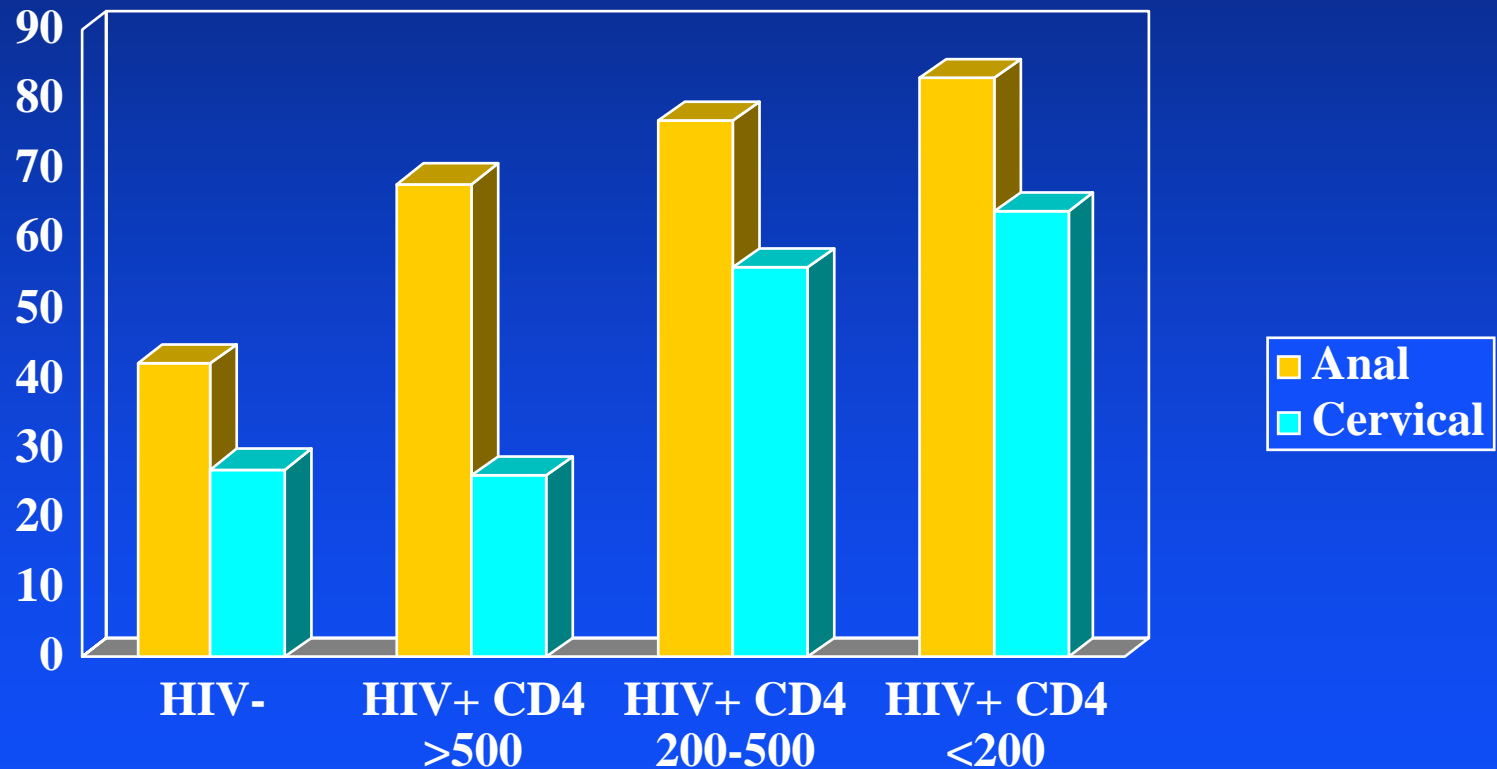
Percent with anal HPV infection



Percent with abnormal anal cytology

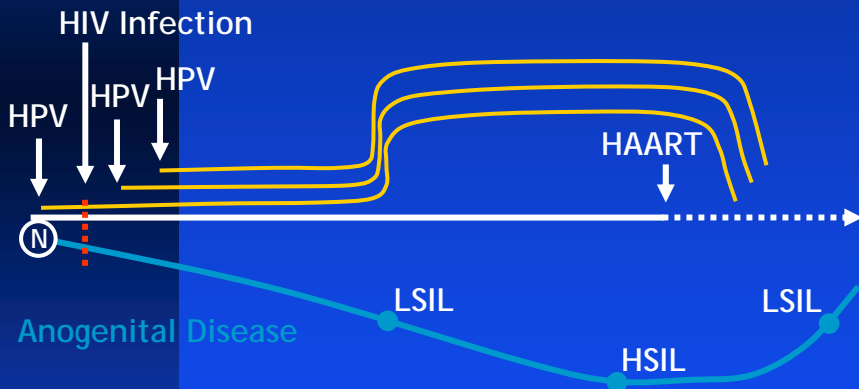


Anal and cervical HPV infection in HIV-positive women

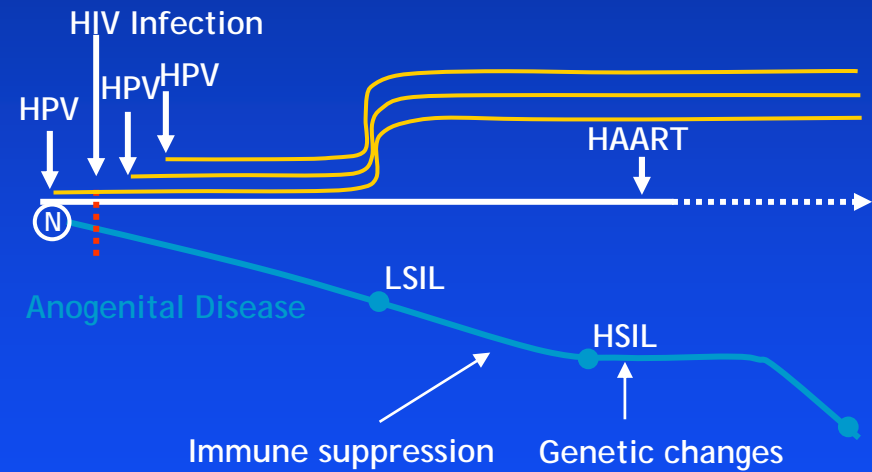


HPV Infection (cont'd)

Decreased Incidence of Anogenital Cancer



Increased Incidence of Anogenital Cancer



AIN prevalence at baseline among HIV+ MSM since the introduction of HAART

	n (%)
No lesions/normal	35 (10)
Lesions/no biopsy	10 (3)
ASCUS	24 (7)
AIN 1 or condyloma	102 (29)
AIN 2	139 (39)
AIN 3	47 (13)
Total	357

AIN in HIV+ and HIV- women (N= 657)

- AIN was more common among HIV-infected women (21%) than among HIV-uninfected women (6%), $p < 0.001$
- CIN was also more common among HIV-infected women (13%) than among HIV-uninfected women (4%), $p = 0.003$

J. Palefsky, unpublished data

Anal cancer since introduction of HAART

- Chiao et al, JAIDS 2005 40:451-5
 - Pre-HIV: 1973-1981 0.6/100,000
 - HIV: 1982-1995 0.8/100,000
 - HAART: 1996-2001 1.0/100,000
 - Female to male ratio 1.6:1 → 1.2:1
- Bowers et al, JAIDS 21:06:38 2004
 - 8640 HIV+ MSM in London
 - Pre-HAART incidence- 35/100,000 patient-years (95% CI 15-72)
 - Post-HAART incidence-92/100,00 patient-years (95% CI 52-149)

San Francisco AIDS Surveillance Registry- California Cancer Registry match

- 14,210 adults with AIDS diagnosed in 1990-2000
- risk of anal cancer increased after 1995 (RH=2.9)
- Hessol NA et al. [Am J Epidemiol](#), 2007;165:1143-53

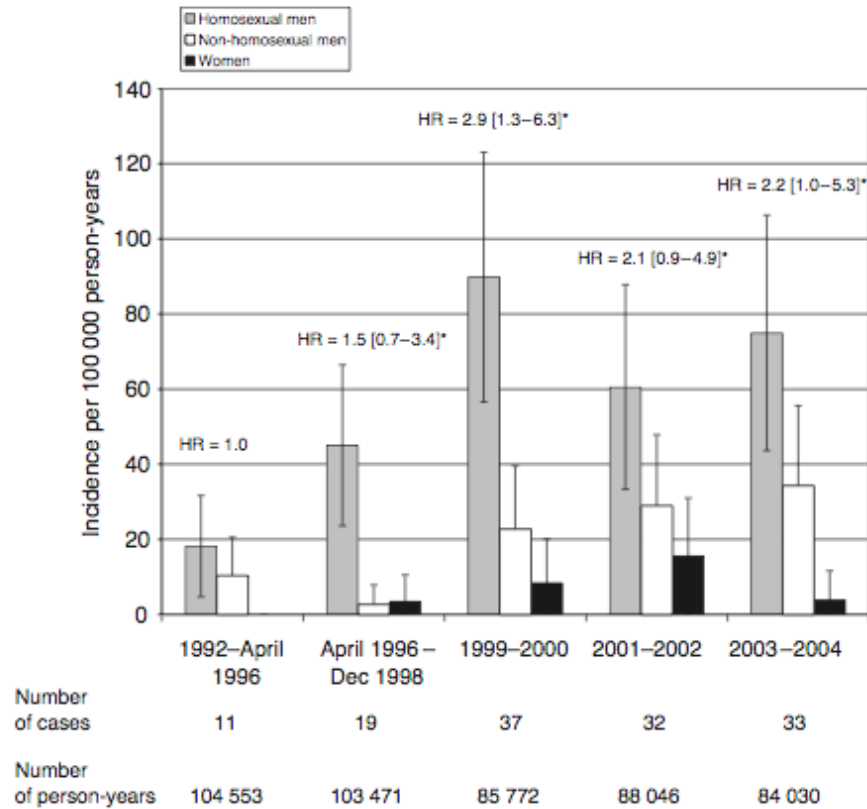
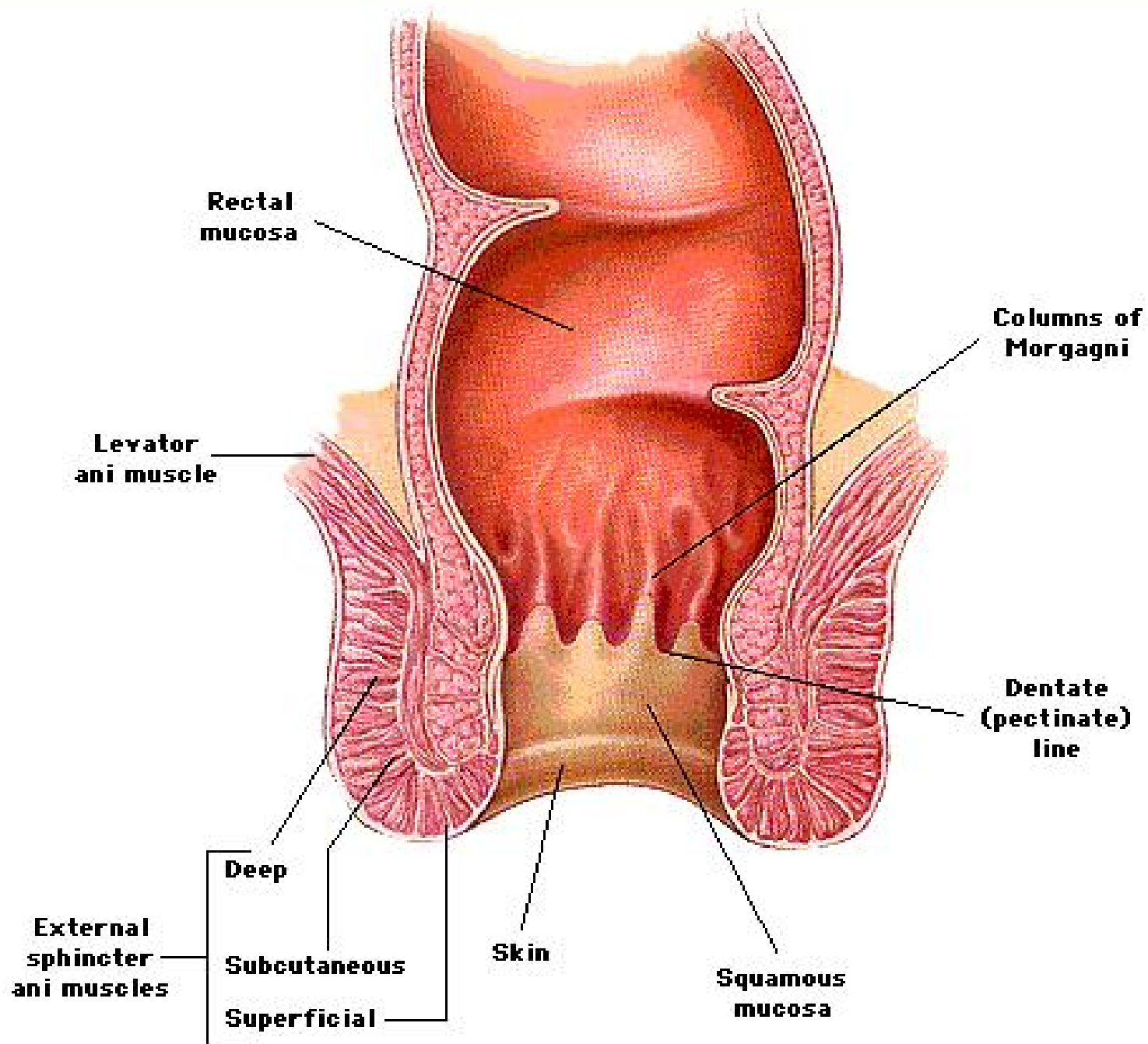
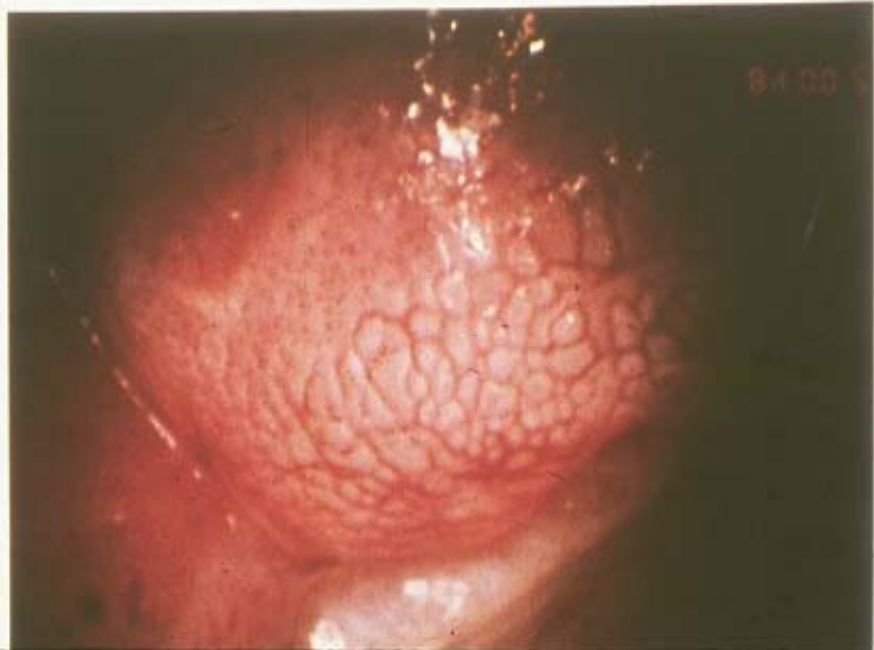
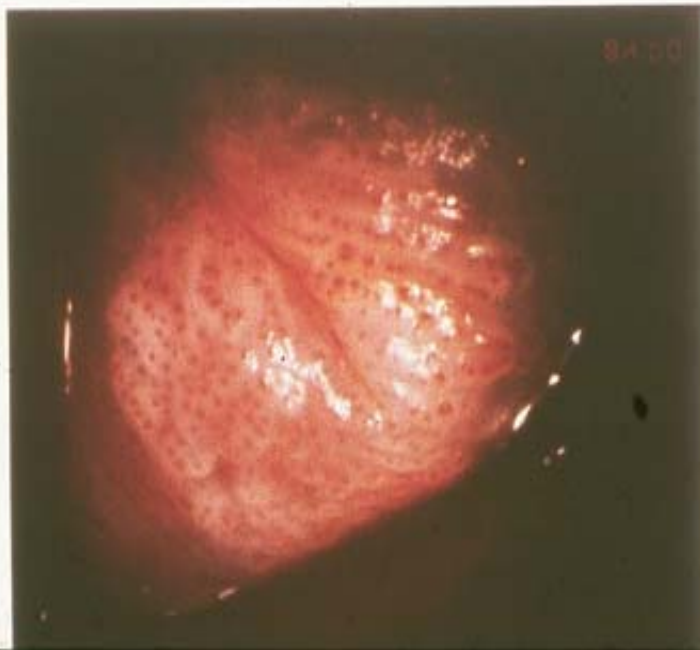
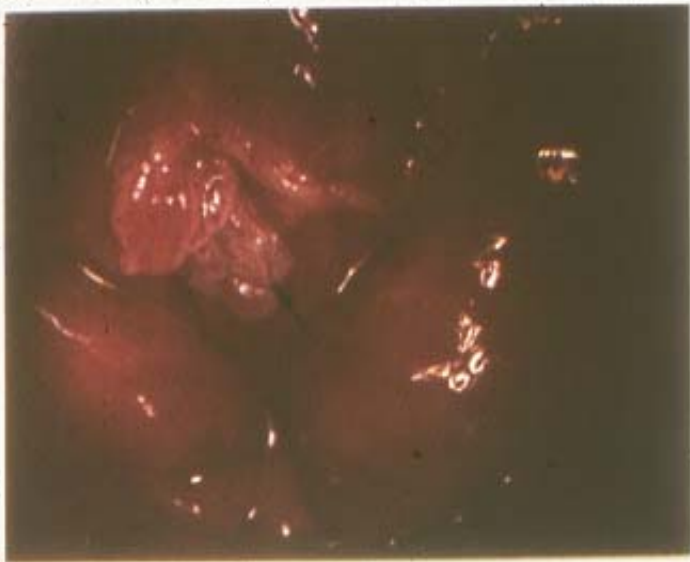


Fig. 3. Change in the incidence of anal cancer according to gender, HIV transmission group and calendar period. HR, hazard ratio. Adjusted for age, sex, HIV transmission group, CD4 nadir, and AIDS.









Anal screening options

Digital rectal exam!



Screening tools: DRE

- Feeling for hard and/or immobile masses
- Sensitivity, specificity, PPV and NPV unknown
- Can also test for prostate disease, occult blood

Screening tools: cytology

- Used for primary screening
- Used as quality control measure for HRA and biopsy, post-treatment

Anal cytology and histology correlation

Anal cytology*	Anal histopathology					Total (%)
	Normal	Atypical	AIN 1	AIN 2 or 3	Insufficient	
Normal	4	1	10	18	0	33 (32%)
ASCUS	1	0	0	2	0	3 (3%)
LSIL	0	1	13	22	0	36 (35%)
HSIL	0	0	2	27	0	29 (28%)
Insufficient	0	0	1	0	0	1 (1%)
Total (%)	5 (5%)	2 (2%)	26 (26%)	69 (68%)	0 (0%)	102

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Uses for cytology

- As screening tool: beware limited sensitivity for AIN overall and for HGAIN
- High PPV for HGAIN if cytology is HSIL
- Might be useful to confirm treatment outcome

Screening tools: HRA and anal biopsy

- These are the most specific tests and are still the gold standard
- HRA may have high inter-observer variability
- Interpretation of anal biopsies may have high inter-observer variability

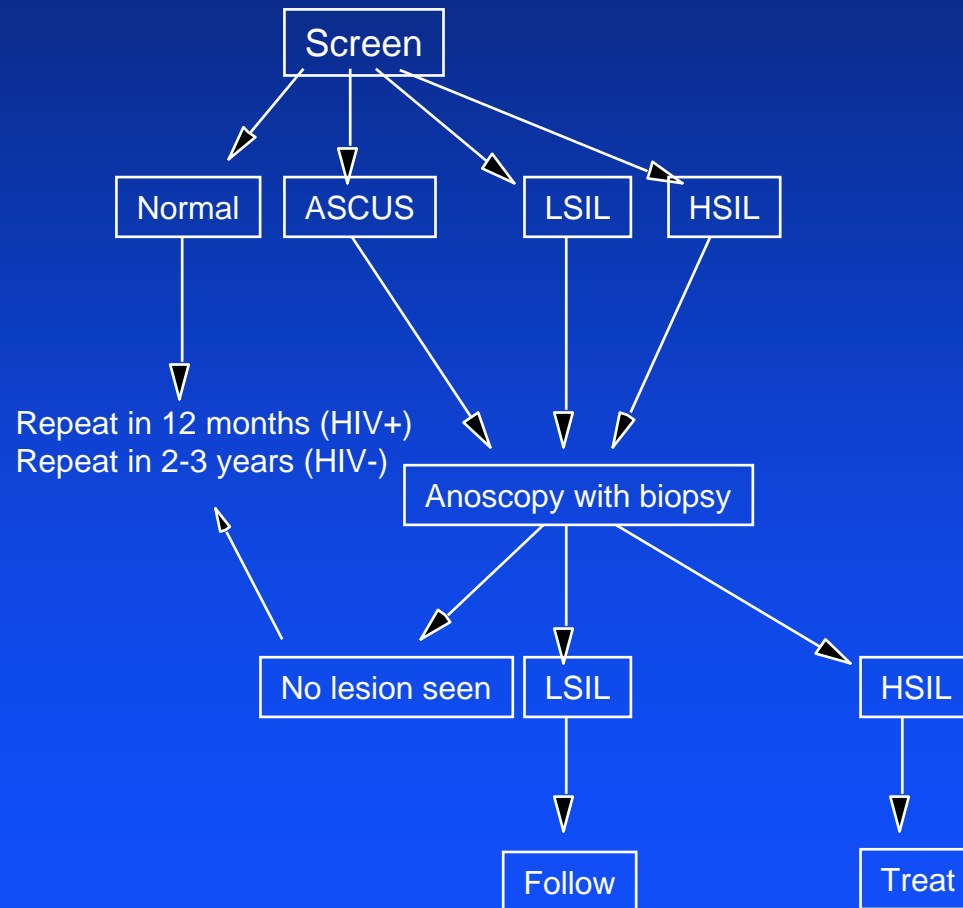
Screening tools: HPV testing

- Positive predictive value (PPV) in HIV+ men and women will be low
- PPV and negative predictive value may be higher in HIV-negative men and women
- ? Value of HPV 16 testing specifically?

Screening tools: HPV serology

- Even lower value than HPV DNA testing
 - Seropositivity does not correlate well with disease
 - Not used to screen people prior to HPV vaccination

Anal cytology screening for AIN



Anal cytology screening: Cost effectiveness (\$/QALY)

Anal cytology screening	+HIV*	-HIV**
Every year	\$16,600	\$34,800
Every 2 years	\$13,000	\$15,100

*Goldie et al. *JAMA*. 1999; 281:1822-1829.

**Goldie et al. *Am J Med*. 2000; 108:634-41.

Who should be screened?

- All HIV+ MSM with good prognosis
- ? All HIV+ men regardless of sexual orientation
- ? All HIV+ women?
- ? Women with vulvar disease
- ? All men and women with transplant-associated immunosuppression

New York State Department of Public Health AIDS Institute

Guidelines: Primary Care Approach To The HIV-Infected Patient

“Like cervical cancer, invasive squamous cell cancers of the anal canal are associated with certain types of human papillomavirus (HPV) infection, most notably, HPV-16 and HPV-18. **Although this is a new practice that may not be routinely available, screening for cellular dysplasia is prudent and recommended,** particularly in persons at high risk for infection with papilloma viruses”

Before setting up screening

- Ability to perform cytology
- Ability to perform HRA and anal biopsies
- Ability to read cytology and biopsies
- Ability to perform office-based treatment
- Surgeons who understand AIN to whom you can refer patients as needed

Benefits of anal screening

- Early in natural history- increased ease of treating small lesions
- Mid-natural history- local vs. surgical removal
 - Infra-red coagulation
 - 65% free of disease after median of 413 days*
- Late in natural history- monitoring to detect early development of cancer

* Goldstone SE et al, Dis Colon Rectum. 2006; 49:1648-9

Superficially invasive squamous cell carcinoma of the anus (SISCCA)

- 19 patients treated with local excision
 - No patients died of SCCA
 - 5 of 19 (26%) developed recurrent cancer
 - 2 required RAC
 - No patients required a colostomy
 - 17 of 19 (89%) developed recurrent HGD
 - Careful follow-up is essential

Berry, Jay and Palefsky, unpublished data

Screening options: low risk populations

- Cytology as screening test
- Refer patients with all grades of abnormal cytology for HRA, etc.

Screening options: high risk, HIV-negative populations

- Limited HRA resources
 - Cytology as screening test
 - Refer patients with all grades of abnormal cytology for HRA, etc.
- Unlimited HRA resources
 - HRA and biopsy as screening test
 -

Screening options:

high risk HIV-positive populations

- Limited HRA resources
 - Cytology as screening test
 - Refer patients with HSIL, then ASC-H, then LSIL, then ASCUS on cytology for HRA, etc.
- Unlimited HRA resources
 - HRA and biopsy as screening test

Why are we not screening routinely?

- Further data are clearly needed before widespread screening should be adopted
 - Is effective treatment of AIN possible?
 - Does treatment of AIN reduce the incidence of anal cancer?

Until a screening program is in place

- Be aware of the warning signs of anal cancer:
 - unexplained pain
 - bleeding
 - inguinal lymphadenopathy
- Digital rectal exam!

Summary

- Anal cancer is a growing problem that is likely preventable
- The screening test for **anal cancer** is DRE
- The screening tests for **AIN** are cytology and HRA
- There may be benefits for screening AIN at all stages of disease

Management algorithms for AIN

- Intra-anal, limited in size and number
 - TCA for small, flat lesions
 - Apply every 2 weeks if possible up to 4 times
- Intra-anal, larger in size and number
 - IRC up to 50% in circumference (practice varies)
 - Laser
 - Re-examine in 2 months
 - Can be repeated up to 3 times
- Efudex
- Imiquimod?
- Surgery

Management algorithms for AIN

- Perianal, limited in size and number
 - Liquid nitrogen, TCA, Efudex, podophyllotoxin, imiquimod
- Intra-anal, larger in size and number
 - Hyfurcation, laser
- Surgery

For further information

- <http://www.analcancerinfo.ucsf.edu>