

Screening for Anal Cancer and its Precursors

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Clinical Case

- 50 year old asymptomatic physician with HIV infection presented for routine care in May 1999
- CD4=350, HIV viral load 35,000
- Physical exam normal except for 3 cm irregular hard anal mass
- Biopsy: invasive squamous cell carcinoma

Clinical Case -2

- Resection had positive margins
- He was treated with radiotherapy and mitomycin C + 5FU
- Severe disabling radiation proctitis
- Biopsy at end of treatment showed residual tumor
- Abdominal perineal resection in 11/99
- Small bowel obstruction → ileocolic anastomosis (3/00)
- Bilateral hydronephrosis and renal failure
- Declined intervention
- Viral load <50 prior to withdrawal of therapy

Evidence-based screening: What kind of evidence is needed?

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- How strong is the evidence that the outcome will improve if treatment is given after screening rather than at the time the patient presents with symptoms?

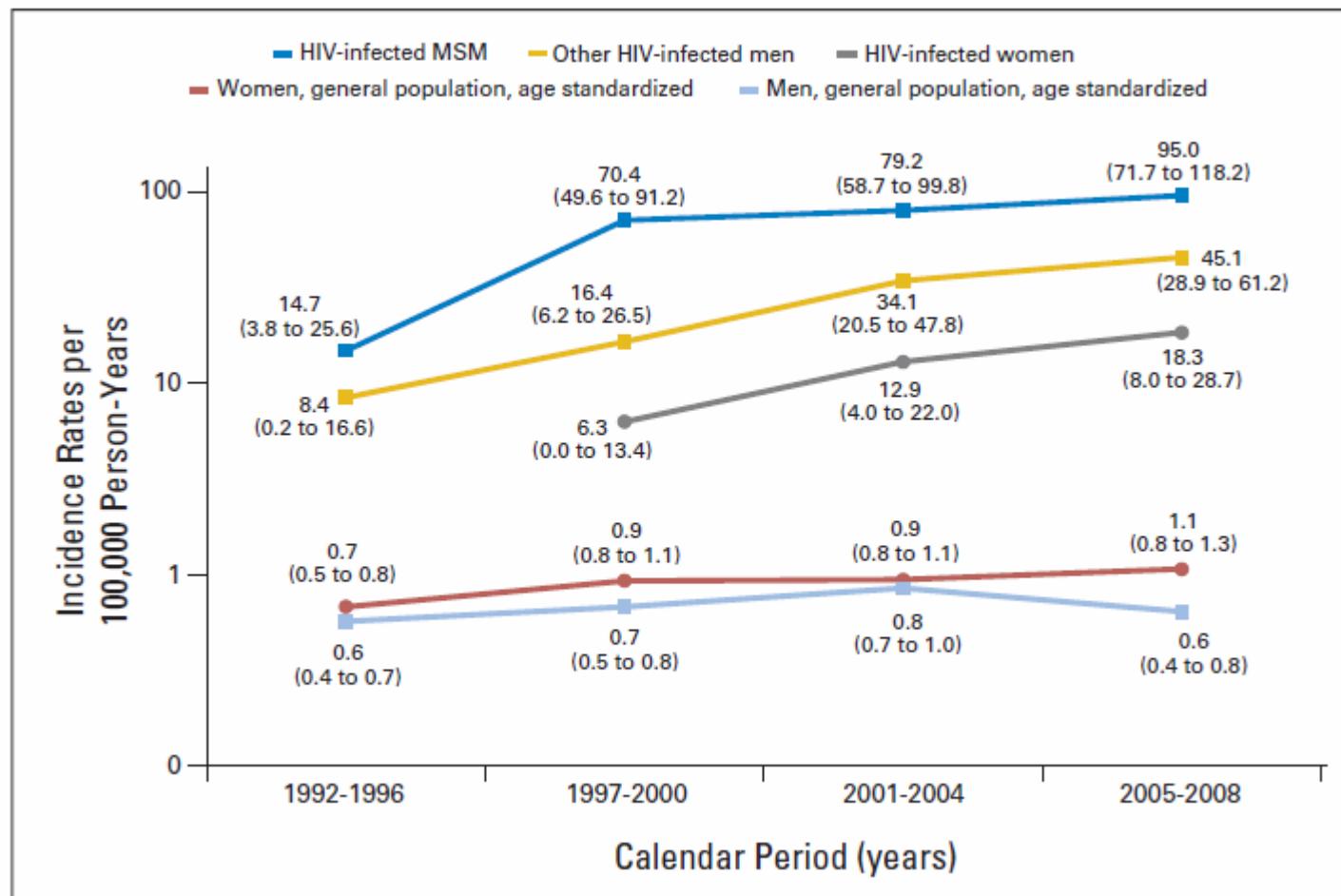
(Fletcher, S. ACP Journal Club. 1998; 128:A12)

Epidemiology

- US Incidence of cervical cancer: 8 / 100,000 ⁽¹⁾
- Incidence of anal carcinoma in men with history of anal receptive intercourse: 35 / 100,000 ⁽²⁾
- Current incidence of anal carcinoma similar to that of cervical CA prior to routine PAP screening
- Anal CA among HIV + MSM about twice the incidence among HIV – MSM ⁽³⁾

(1) Qaulters et al, 1992. (2) Daling et al, 1987. (3)Goedert et al, 1998

IAC incidence on long-term cART



Piketty et al. *J Clin Oncol* 30:4360-4366 (2012) French Hospital Database

Invasive Anal Cancer Incidence: NA-ACCORD

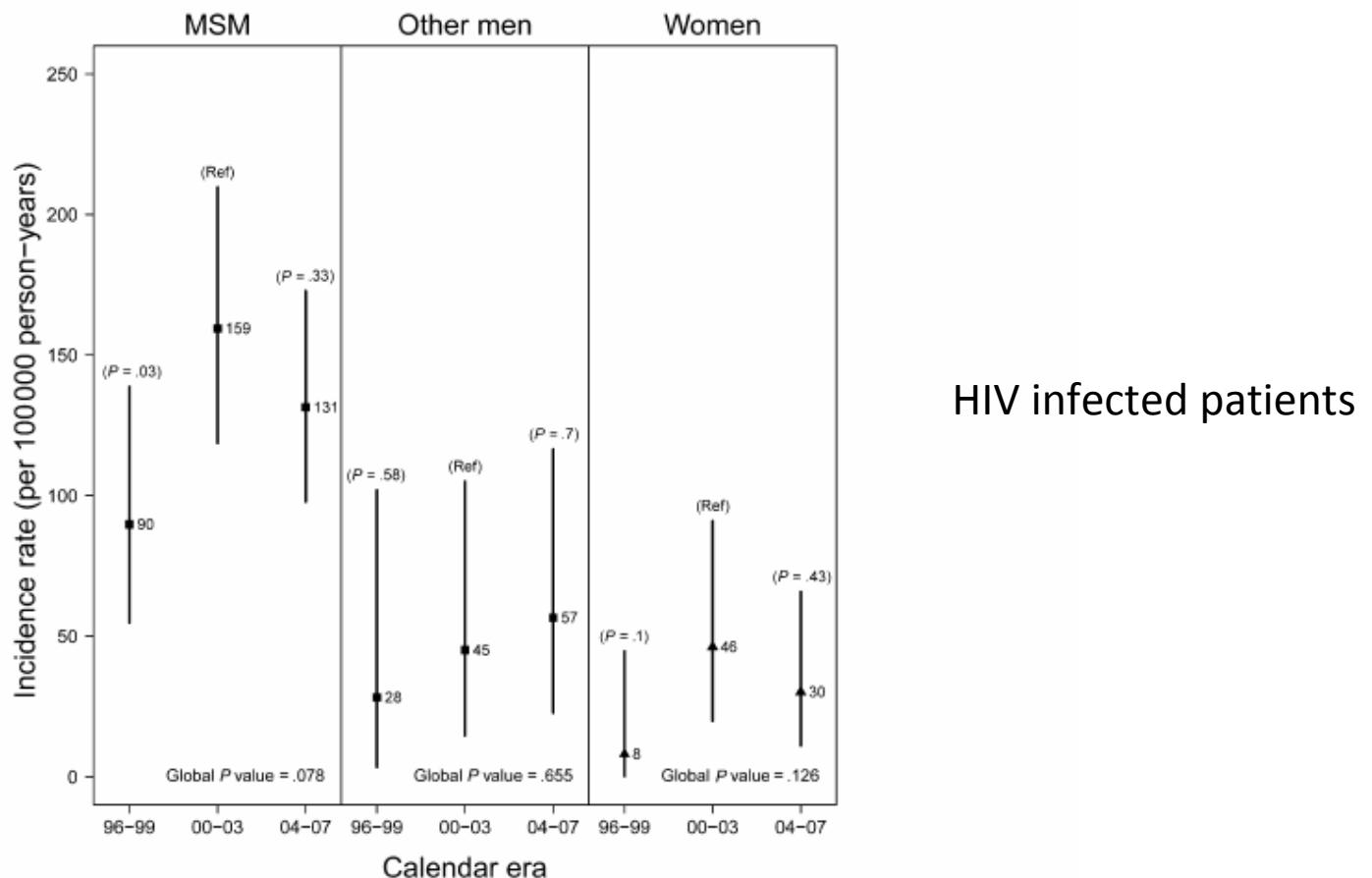


Figure 2. Anal cancer incidence rates by calendar era for human immunodeficiency virus infected men who have sex with men (MSM), other men, and women, North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD), years 1996–2007. Vertical lines are 95% confidence intervals. *P* values from the Poisson regression model compare rates by calendar era with 2000–2003 as reference. The global *P* value for comparison of rates across eras is based on the likelihood ratio statistic.

Invasive Anal Cancer (IAC) Outcomes

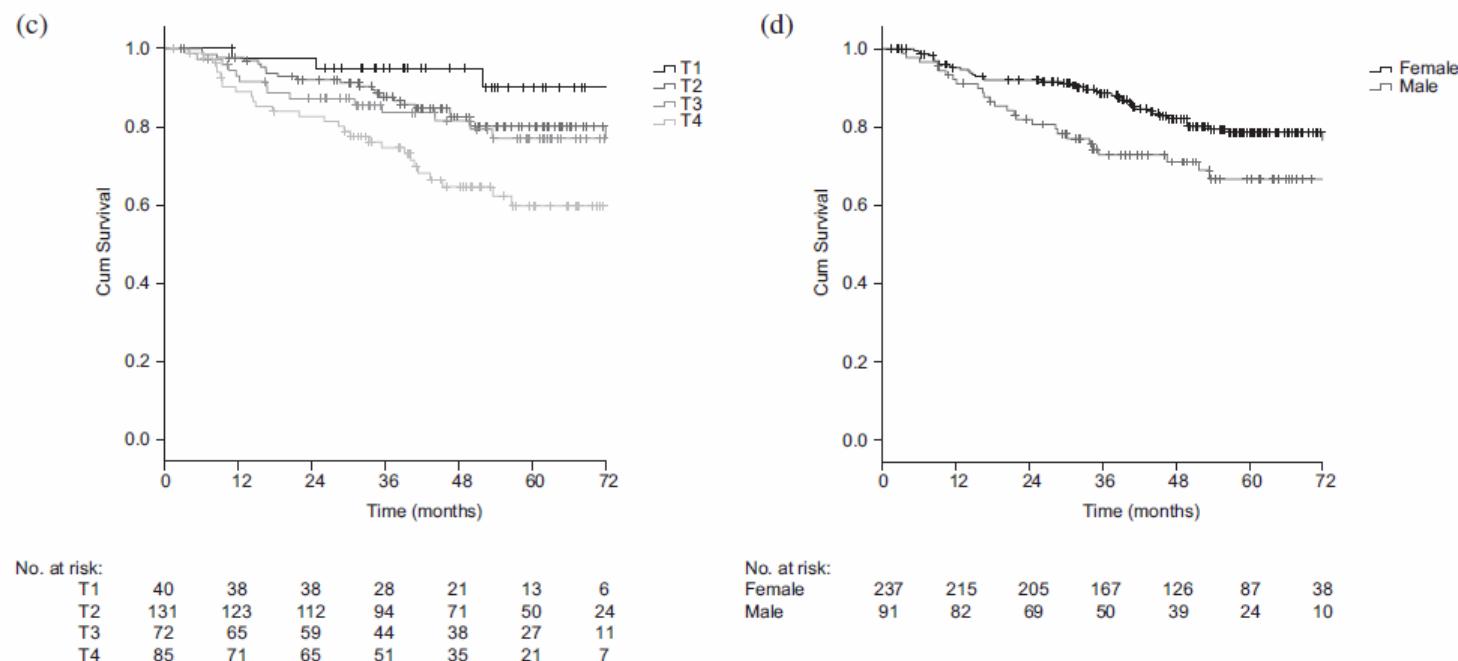


Fig. 1. Recurrence-free survival according to T-stage (a) and gender (b). Cancer-specific survival according to T-stage (c) and gender (d). Kaplan-Meier.

Bentzen et al. Int J Radiation Oncol Biol Phys, Vol. 83, No. 2, pp. e173ee180, 2012

Invasive Anal Cancer (IAC) Outcomes

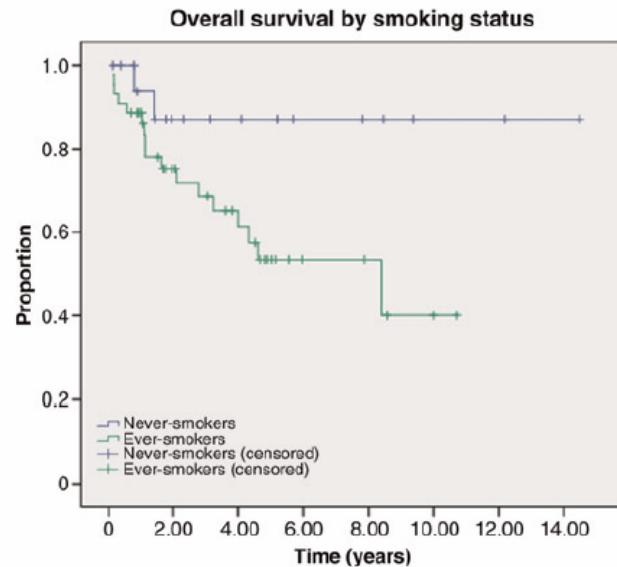


Figure 2 Proportion surviving (overall survival) by smoking history ($P < 0.05$, log-rank test). The hash marks represent conventional Kaplan-Meier patient 'censoring,' at which time-point a patient was alive but after which point no further follow-up data were available. The 'censored' patient is removed from the analysis at the next event (in this case, a patient death)

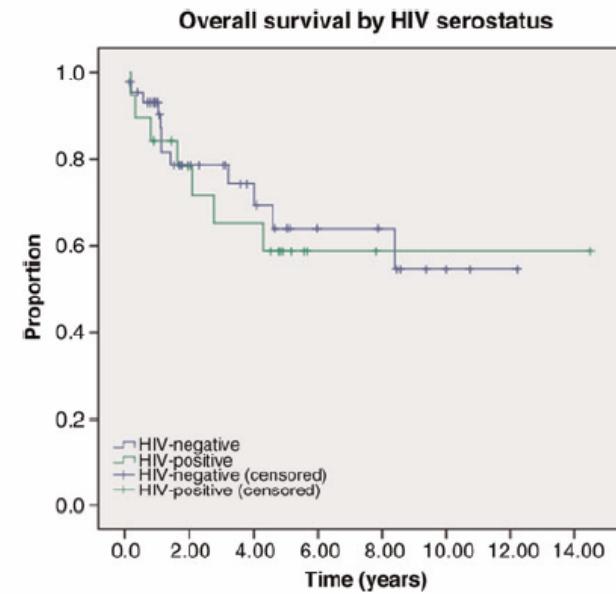


Figure 4 Proportion surviving (overall survival) by HIV status ($P = \text{NS}$, log-rank test)

Linam et al. International Journal of STD & AIDS 2012; 23: 77–82

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(Fletcher, S. ACP Journal Club. 1998; 128:A12)

Screening Issues

- Screening for early IAC vs. Screening for AIN
- Potential screening components
 - Cytology
 - Oncogenic HPV testing
 - HRA visual impression
 - HRA directed biopsy
 - Digital rectal examination
- Is HRA-directed biopsy a true “gold standard”?
- AIN progression and regression rates

Cervical CA as Model for Anal CA

- Similar histology
- Frequently arise in transformation zone ⁽⁴⁾
- Both strongly associated with oncogenic strains of HPV ⁽⁵⁾
- Both associated with squamous intraepithelial lesions (SIL)
 - Cervical HSIL \Rightarrow Cervical CA
 - Anal HSIL suspected \Rightarrow Anal CA

(4) Palefsky, AIDS, 1994. (5) Frisch et al, NEJM, 1997

HPV Types and Anal Dysplasia

- HPV is double stranded DNA virus (>100 subtypes)
- Low risk types (**6, 11**) associated with condyloma and LSIL
- Intermediate risk types (31, 33, 35, 45, 51, 52, 56)
- High risk types (**16, 18**)
 - Present in 64% of invasive cervical CA ₍₆₎

(6) Bosch et al, JNCI, 1995

Bethesda Staging System(2001): CIN/AIN

- Atypical squamous cells
 - Of undetermined significance (ASCUS-US)
 - Cannot exclude HSIL (ASC-H)
- Squamous intraepithelial lesion (SIL)
 - Low grade SIL (LSIL)
 - Mild dysplasia/CIN 1 (HPV cellular changes)
 - High grade SIL (HSIL)
 - Moderate dysplasia/CIN2
 - Severe dysplasia/ CIS / CIN 3
- Squamous cell carcinoma

(Wright et al. JAMA 2002;287:2120-2129)

Natural history of CIN: summary

	Regress	Persist	Progress to CIS	Progress to invasion
CIN 1	57%	32%	11%	1%
CIN 2	43%	35%	22%	5%
CIN 3	32%	< 56%	--	>12%

64 studies, 274 carcinomas, 15,473 CIN cases

Followup <1-12 years

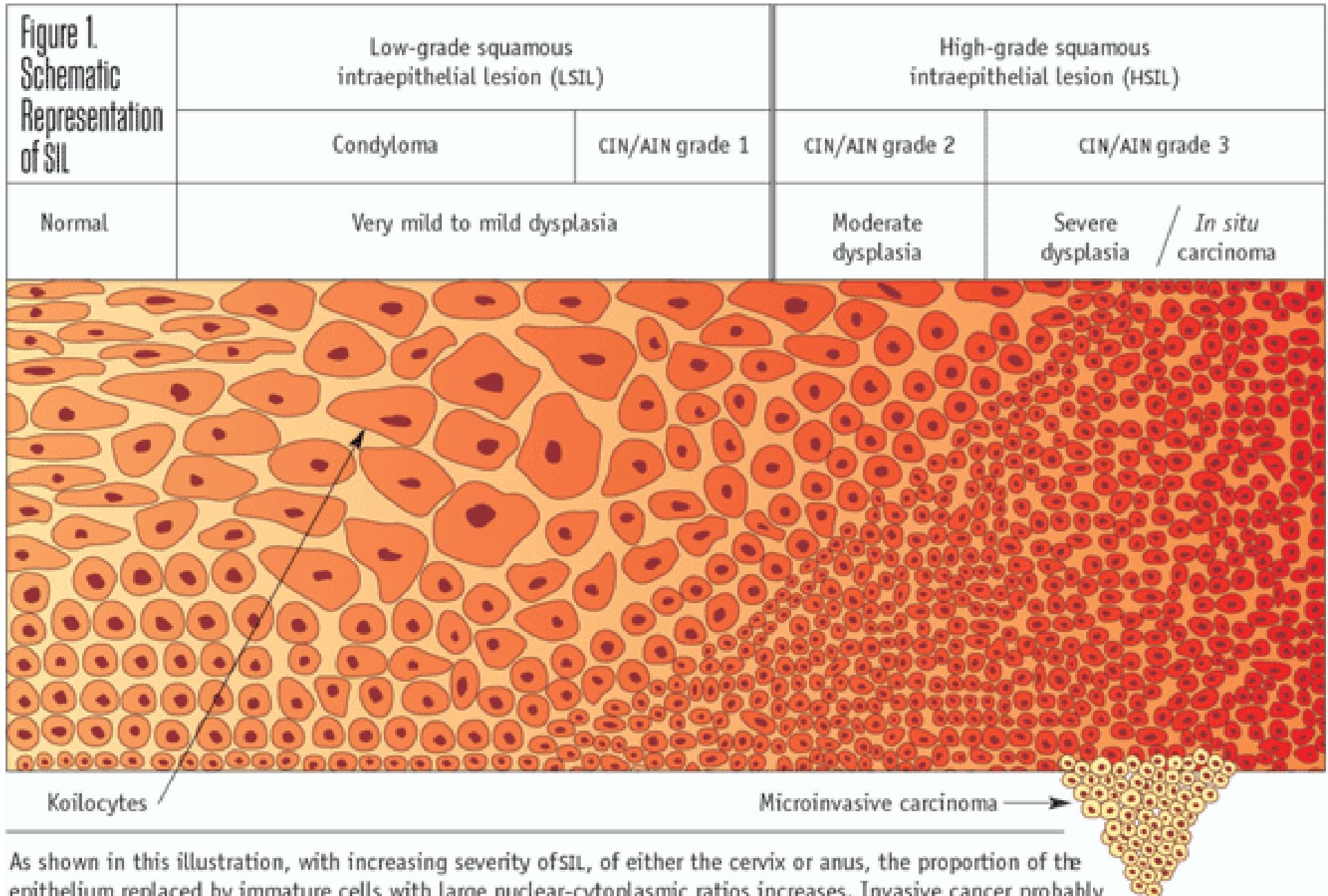
Natural History of AIN

- Modeling of cross sectional data suggests that progression rates from AIN 2-3 to invasive anal cancer may be lower than from CIN 2-3 to invasive cervical cancer
 - Machalek et al estimated HGAIN progression rates of
 - HIV + men: 1/377 per year (265/100,000)
 - HIV – men: 1/4196 per year (24/100,000)
 - McCredie et al estimated crude CIN 2-3 progression rate of
 - 823/100,000

Machalek et al. *Lancet Oncol* 2012; 13: 487–500

McCredie et al. *Lancet Oncol* 2008; 9: 425–34

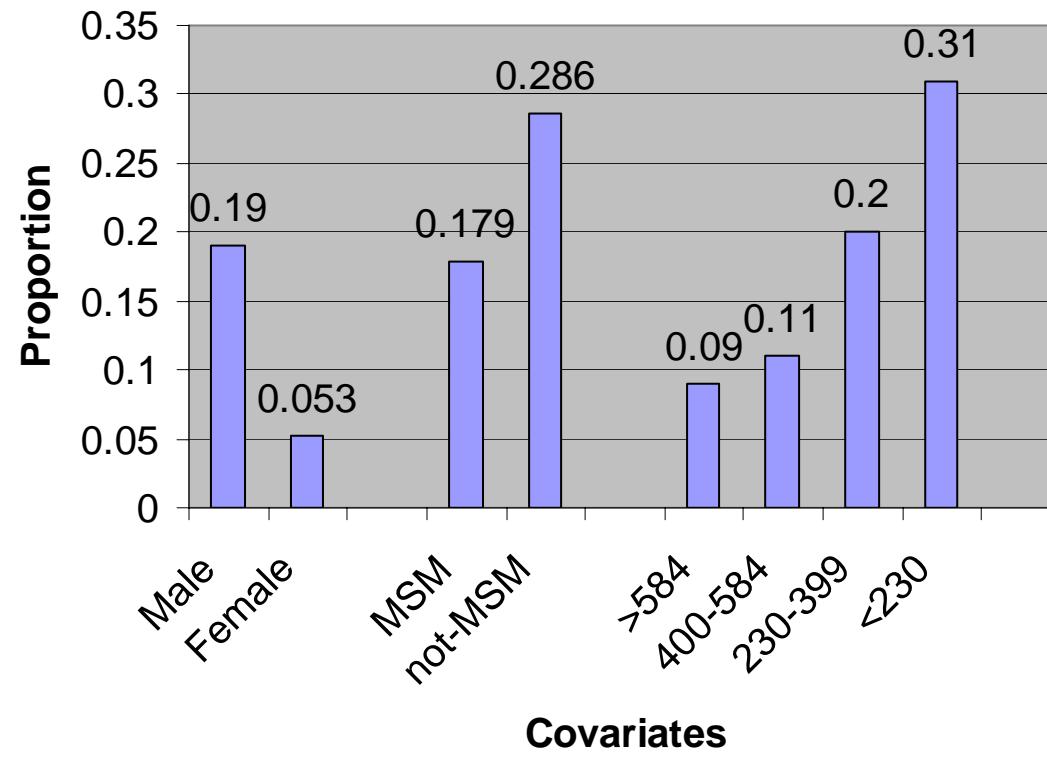
Figure 1.
Schematic
Representation
of SIL



As shown in this illustration, with increasing severity of SIL, of either the cervix or anus, the proportion of the epithelium replaced by immature cells with large nuclear-cytoplasmic ratios increases. Invasive cancer probably arises from one or more foci of high-grade SIL (HSIL), as depicted in the drawing by epithelial cells crossing the basement membrane below the region of HSIL.

Source: Joel Palefsky, MD, MACP(C)

**Figure 1:Prevalence of LSIL or HSIL:
by Sex₁, HIV Risk₂(males only), and
CD4 Stratum₃**



1. 1. p-value for Sex= 0.036
2. 2. p-value for MSM= 0.088
3. p-value for CD4 Stratum <0.0001

Anal cytology and Anal HPV Test results by participant category for the 621 HIV-infected participants in the SUN study, 2004 -2006

Diagnosis	All participants	MSM	Women	MSW
Anal cytology				
Negative	336 (54)	165 (44)	97 (65)	74 (80)
ASC-US	79 (13)	52 (14)	20 (13)	7 (8)
ASC-H	17 (3)	12 (3)	3 (2)	2 (2)
LSIL	149 (24)	116 (31)	25 (17)	8 (9)
HSIL	40 (6)	34 (9)	5 (3)	1 (1)
Median Nº of HPV genotypes (IQR)	5 (3-8)	6 (4-8)	5 (2-7)	2 (1-4)
Median Nº of high risk HPV genotypes (IQR)	3 (2-5)	4 (2-6)	3 (1-4)	1.5 (1-2)
Median Nº of low risk HPV genotypes (IQR)	2 (1-3)	2 (1-3)	2 (1-3)	1 (0-2)



Impact of HAART on ASIL

- 2 possible scenarios
 - Immune reconstitution includes HPV specific immune response and regression of high grade lesions → ↓ Risk Anal CA
 - If immune reconstitution has no effect on HPV pathogenesis but patients live longer → ↑ Risk Anal CA
- Which scenario will predominate is unknown

Effect of HAART on AIN unclear

Summary of studies of the effect of HAART on human papillomavirus (HPV)-related disease

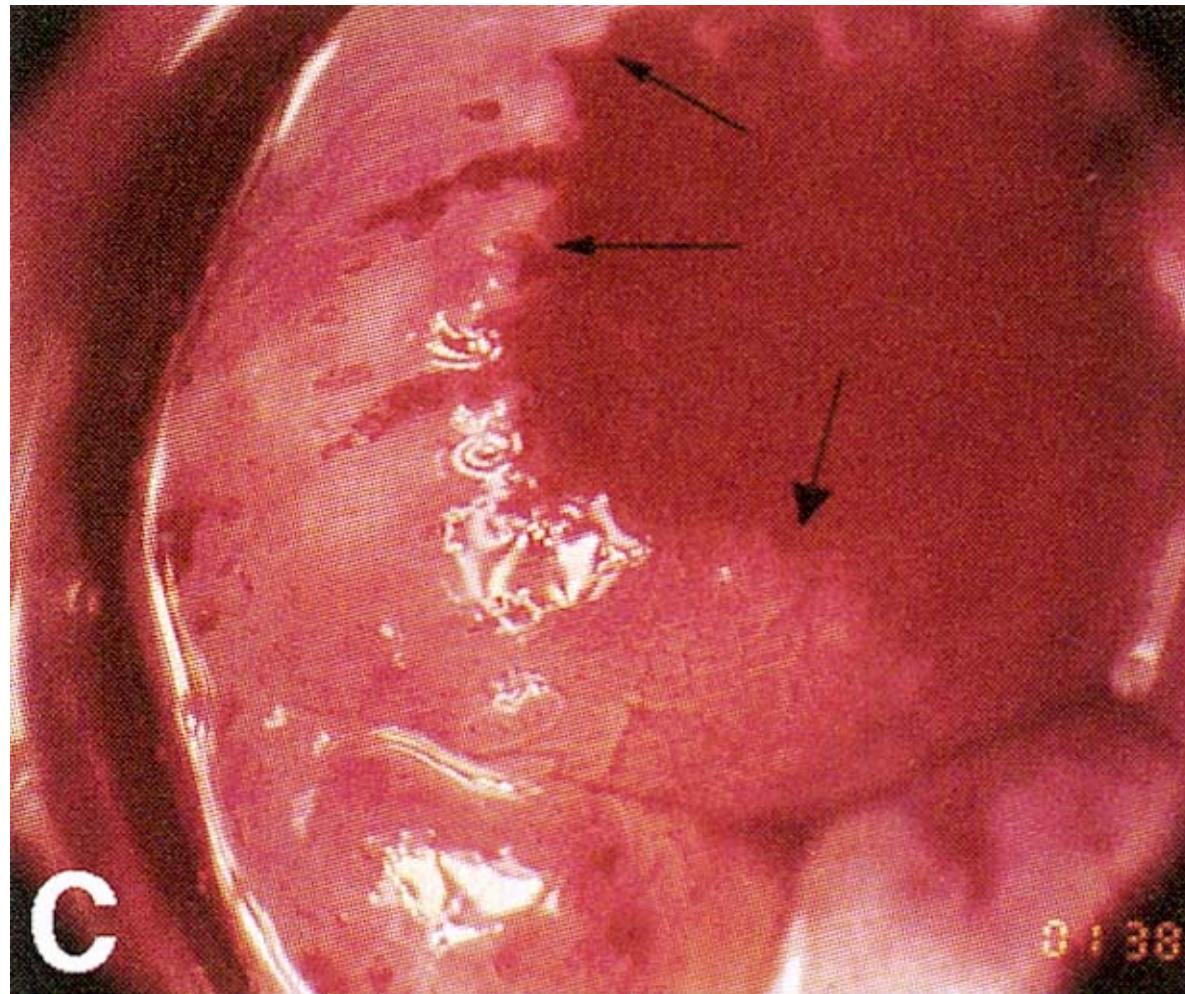
Reference	Date	Nº of subjects	Location	Study design	Outcome	Positive attributed to HAART
Palefsky et al	2001	98	San Francisco, California	Cohort	Rates of progression and regression of Anal dysplasia	No, but there was a correlation between CD4+ and regression of HPV related disease
Kiviat et al	2002	102	Seattle, Washington	Cohort	Prevalence of HPV and low grade dysplasia	Yes
Piketty et al.	2003	45	Paris, France	Cross sectional	Prevalence of anal HPV infection and dysplasia	No
Wilkin et al.	2004	92	New York	Cross sectional	Prevalence of anal HPV infection and dysplasia	Yes
Palefsky et al	2005	357	San Francisco, California	Cross sectional	Prevalence of anal HPV infection and dysplasia	No
Conley et al	2010	621	Denver, Minneapolis, Providence & St Louis	Cohort	Prevalence of anal HPV infection and dysplasia	No
De Pokomandy et al.	2011	247	Quebec, Canada	Cohort	Prevalence of anal HPV infection and high grade dysplasia	Yes
Van der Snoek et al 2/24/2013	2012	250	Rotterdam, Netherlands	Cross sectional	Prevalence of anal HPV infection and dysplasia	Yes

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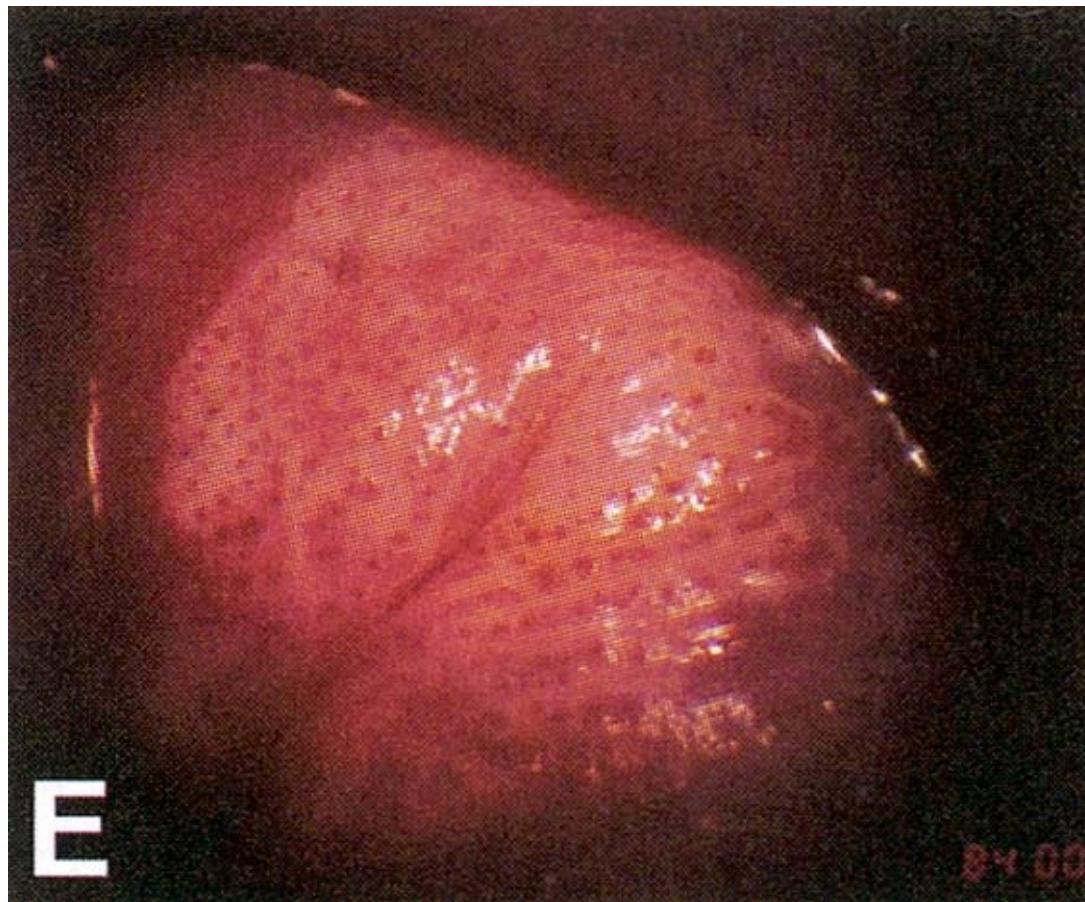
(Fletcher, S. ACP Journal Club. 1998; 128:A12)

Anal Transition Zone after Acetic Acid (x40)



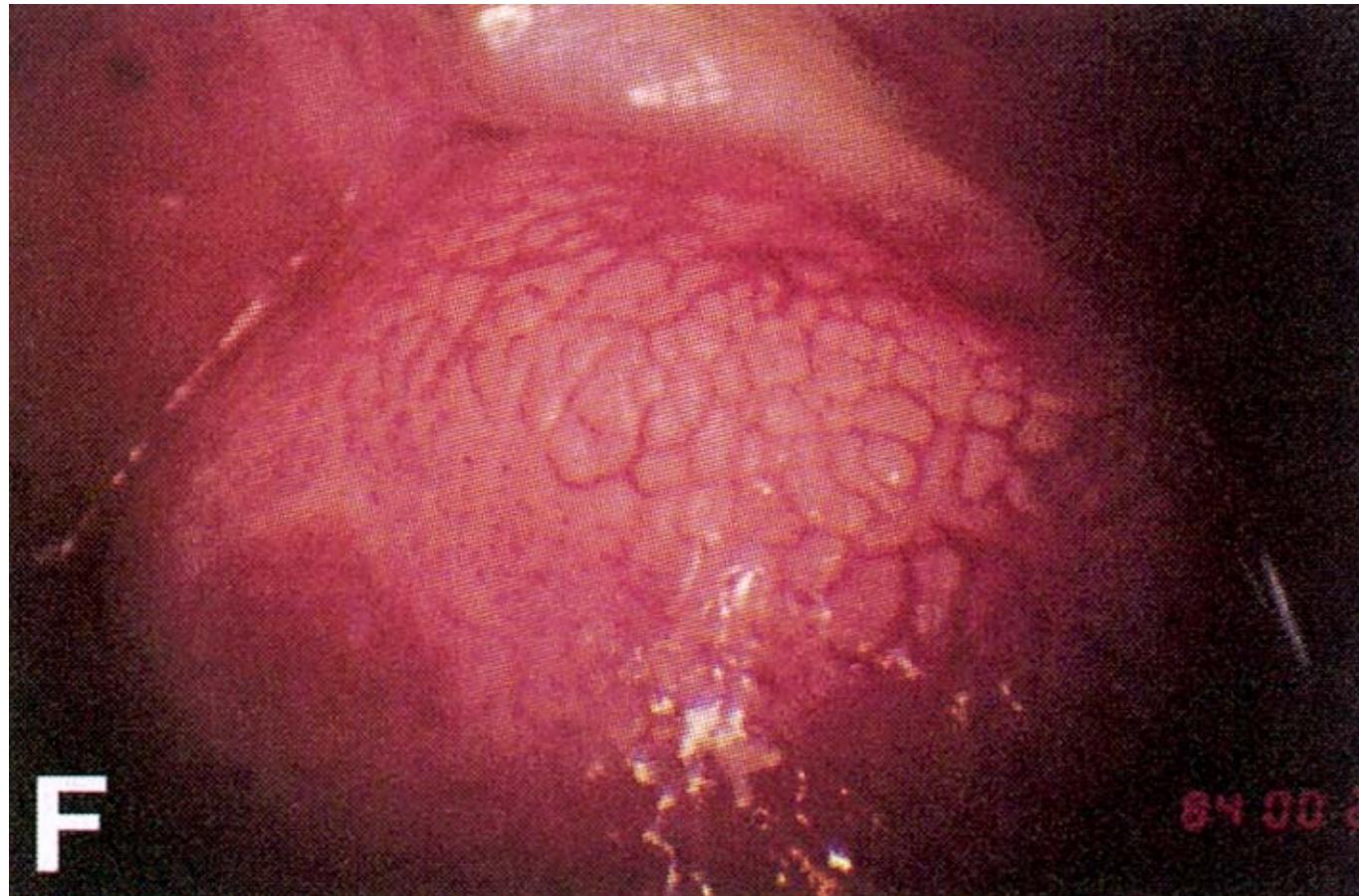
(Jay N et al. Dis Colon Rectum 1997;40:923)

HGSIL with Punctuation (X40)



(Jay N et al. Dis Colon Rectum 1997;40:923)

Coarse Mosaicism & Punctuation (x40)



(Jay N et al. Dis Colon Rectum 1997;40:923)

Cytology performance depends on extent of disease

Performance of anal cytology compared with area of disease by high-resolution anoscopy

		Number of quadrants involved				
		$\geq 1 +$ positive HPV effect	≥ 1	≥ 2	≥ 3	4
Sensitivity 95% CI		68% (255/376) 63-73	69% (218/315) 64-74	86% (136/158) 80-91	86% (48/56) 74-94	100% (16/16) 79-100
Specificity 95% CI		71% (147/206) 65-77	64% (171/267) 58-70	58% (246/424) 53-63	49% (260/526) 45-54	47% (268/566) 43-52
PPV 95% CI		81% (255/314) 76-85	69% (218/314) 64-74	43% (136/314) 38-49	15% (48/314) 11-20	5% (16/314) 3-8
NPV 95% CI		55% (147/268) 49-61	64% (171/268) 58-70	92% (246/268) 88-95	97% (260/268) 94-99	100% (268/268) 99-100

Nathan et al. AIDS 2010, 24:373–379

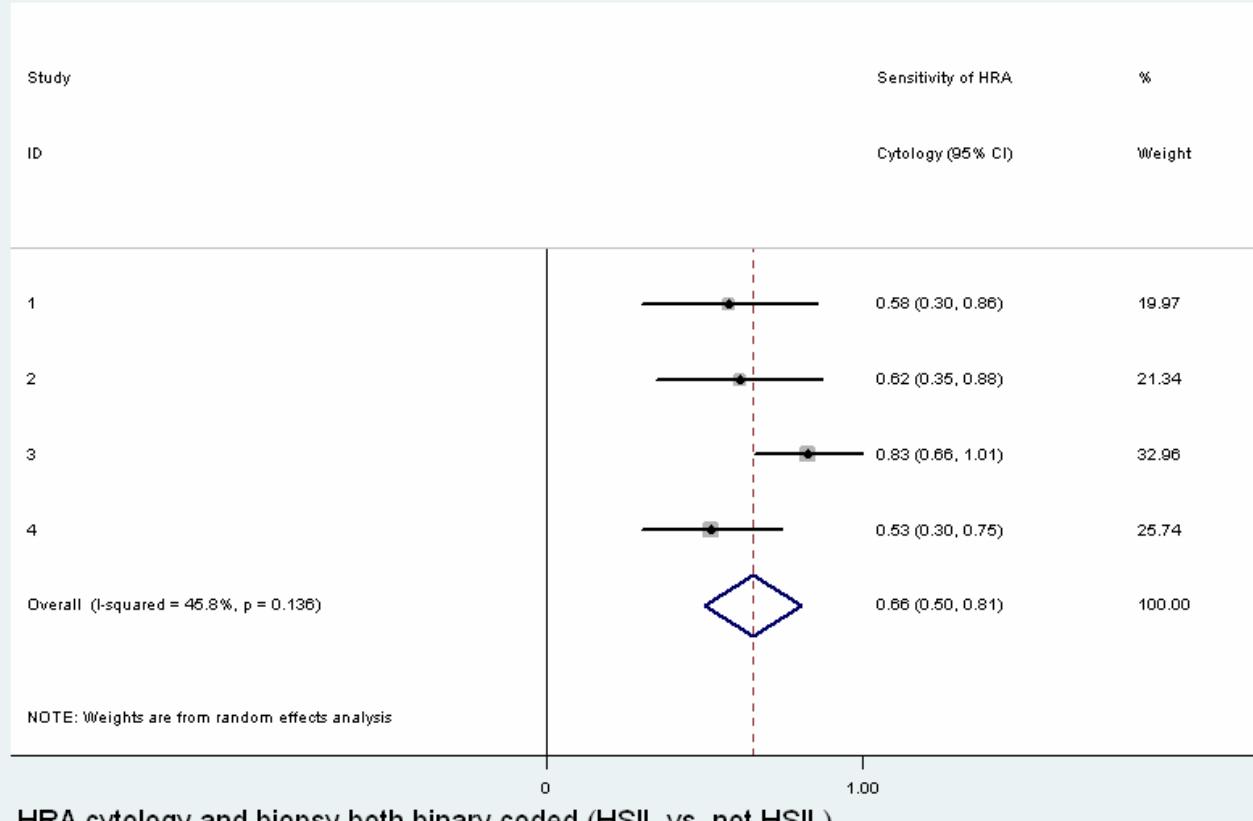
Overall Reproducibility of Cytologic Diagnosis (n = 642 Patients)

		Time 2			
		Normal	ASCUS	LSIL	HSIL
Time 1	Normal	102	91	27	14
	ASCUS	44	97	51	31
	LSIL	6	31	50	23
	HSIL	2	17	17	39
		154	236	145	107
					642
Weighted Agreement		Expected Agreement		Kappa	SE
75.8%		62.4%		0.36	0.03

[Mathews et al, J Acquir Immune Defic Syndr. 2004;37:1610-5](#)

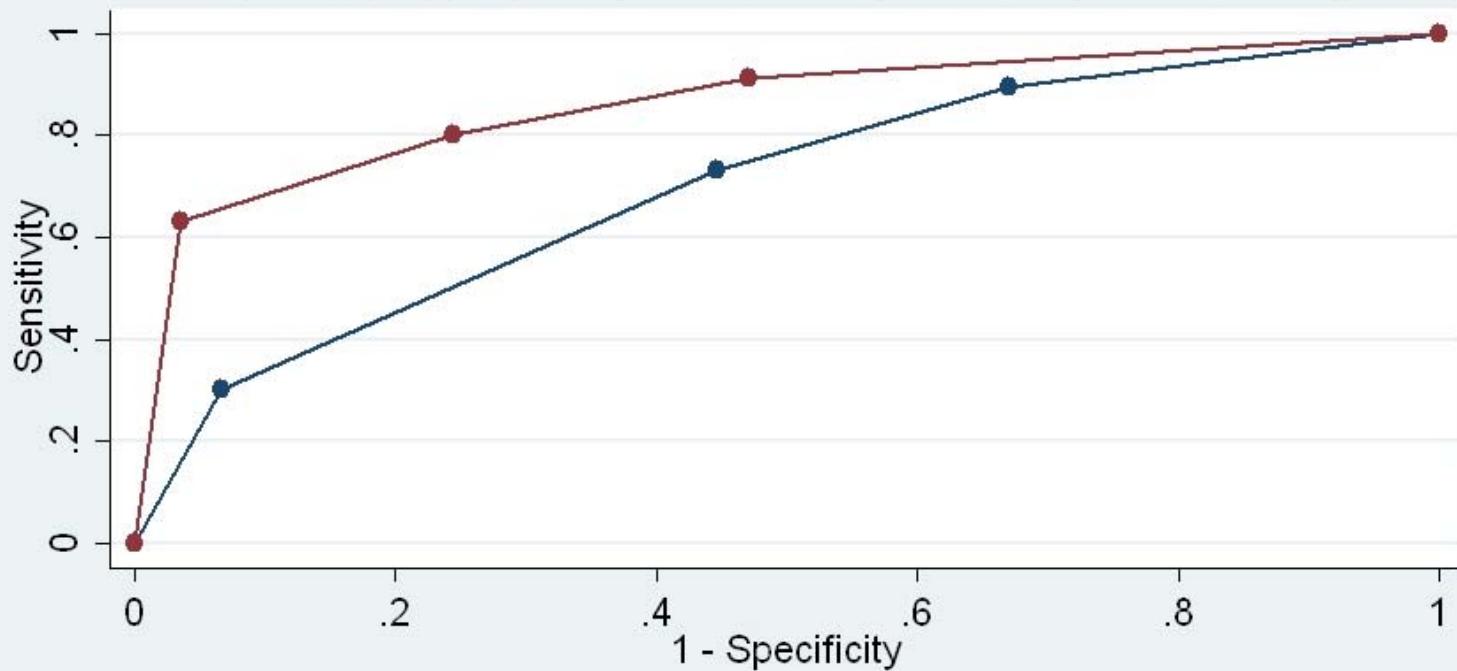
Operator Dependence of Screening Performance

Sensitivity of HRA Cytology for HSIL on Biopsy (n=261 exams)
by Anoscopist and Pooled Overall



Mathews et al. UCSD Owen Clinic data
2/24/2013

Cytology Receiver Operating Characteristic (ROC) Curves by Study Type (Anal [n=11 studies], Cervical [n=33 studies])



ROC area calculated from cut point specific meta-analytic estimates of sensitivity and specificity

	Sensitivity (SE)				Specificity (SP)			
	Cytology Cut-Point		Anal		Cervical		Anal	
	SE	(95% CI)	SE	(95% CI)	SP	(95% CI)	SP	(95% CI)
(HSIL or ASC-H) vs. (LSIL, ASCUS, Normal)¹	0.30	(0.19-0.44)	0.63	(0.56-0.69)	0.93	(0.90-0.95)	0.96	(0.95-0.98)
(HSIL or ASC-H, LSIL) vs. (ASCUS, Normal)²	0.73	(0.62-0.82)	0.80	(0.75-0.85)	0.55	(0.45-0.65)	0.76	(0.66-0.83)
(HSIL or ASC-H, LSIL, ASCUS) vs. (Normal)³	0.90	(0.76-0.96)	0.91	(0.88-0.94)	0.33	(0.20-0.49)	0.53	(0.40-0.66)

Cachay et al, PLoS One. 2012;7(7):e38956

Cost-Effectiveness of ASIL & CSIL Screening (Goldie, 1999 & 2000)

Preventive Intervention	Months Gained	\$ / Year of Life Saved
<u>Cervical cytology screening</u>		
HIV- (q 3 yrs)	3.1	~180,000
HIV+ (annual)	2.9	~13,100
<u>Anal cytology screening</u>		
HIV+ men (annual)	2.4	~11,000
HIV- men (q 3y)		~7,800

UCSF Algorithm

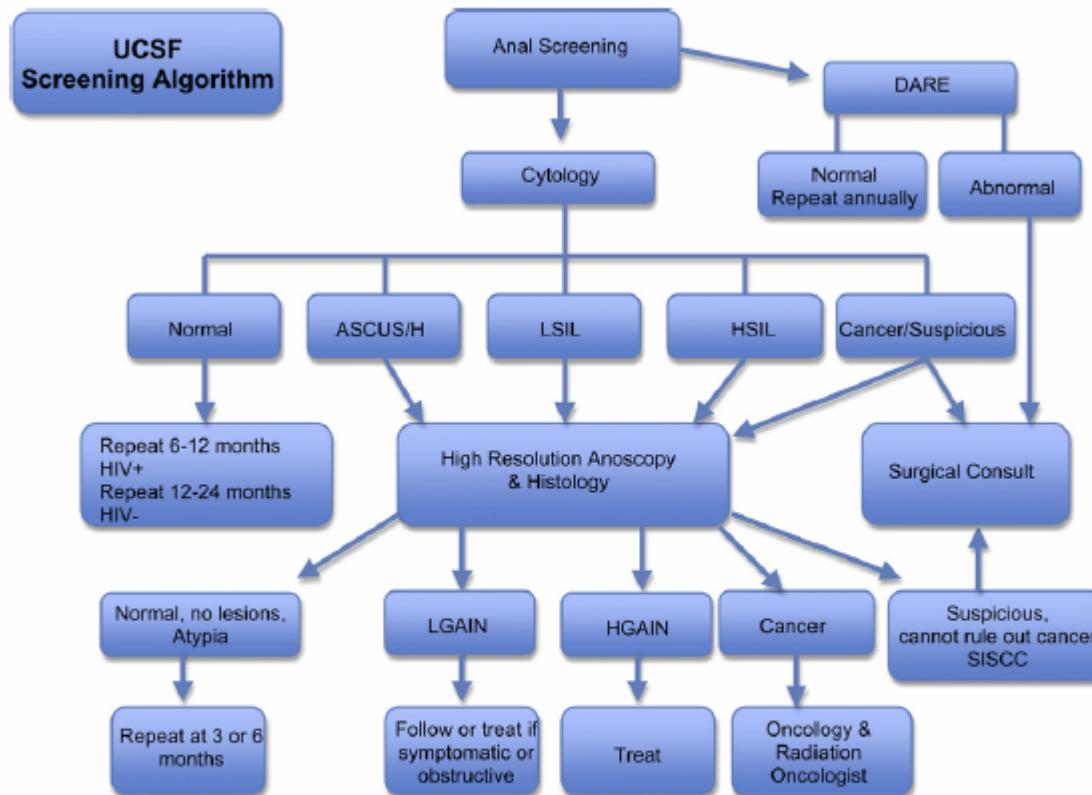


Figure 2. University of California San Francisco (UCSF) anal screening algorithm. NOTE: DARE = digital anorectal examination; ASCUS/H = atypical squamous cells of undetermined significance/atypical squamous cells suggestive of high-grade squamous intraepithelial lesions; HGAIN = high-grade anal intraepithelial neoplasia; LGAIN = low-grade anal intraepithelial neoplasia.

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(Fletcher, S. ACP Journal Club. 1998; 128:A12)

Management of Anal Cancer Precursors

- Expectant management
 - Devaraj & Cosman (2006)
- Ablative treatments
 - 85% TCA
 - Cryotherapy
 - IRC
 - CO₂ laser
 - Photodynamic therapy
- Topical non-ablative treatments
 - Imiquimod
 - 5-fluorouracil
 - Cidofovir gel 1%
- Immunotherapy
 - HPV therapeutic vaccines
 - Hsp E7 HPV immunogen
 - Palefsky et al AIDS 2006
 - Anderson et al JAIDS 2009

Cochrane Review of Treatment for AIN

DATA AND ANALYSES

Comparison 1. Topical imiquimod versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 AIN eradication	1	53	Risk Ratio (M-H, Random, 95% CI)	3.57 [0.43, 29.87]
2 Development of invasive anal cancer	1	53	Risk Ratio (M-H, Fixed, 95% CI)	0.30 [0.01, 7.02]
3 Dowgrading from AIN-III or II to two AIN-I	1	53	Risk Ratio (M-H, Fixed, 95% CI)	15.24 [0.92, 251.29]
4 Recurrence	1	5	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Macaya et al. *Cochrane Database of Systematic Reviews* 2012, Issue 12. Art. No.: CD009244.

HPV Preventive Vaccination in HIV-infected Patients

- PACTG 1047
 - Quadrivalent HPV vaccine in 126 HIV infected children (ages 7-12)
 - 96% seroconversion to all 4 serotypes
- AMC 052
 - Quadrivalent HPV vaccine in 109 HIV-infected men without HGAIN at baseline
 - 95% seroconversion to all 4 serotypes
- (Merck 020 substudy – HIV *uninfected* MSM)
 - qHPV vaccine reduced vaccine strain related AIN 2/3 by 54.2%

Firnhaber & Wilkin. Curr HIV/AIDS Rep (2012) 9:278–286

2/24/2013 Palefsky et al. N Engl J Med 2011;365:1576-85

Conclusion & Recommendations

- Goal: Early Diagnosis IAC in HIV infected patients
 - Annual digital rectal exam (DRE) ± anal cytology to identify higher risk patients (minimalist approach)
 - Annual DRE + anal cytology + HRA directed biopsy to identify microinvasive disease (maximalist)
- Goal: Prevention of IAC in HIV infected patients
 - Annual DRE + anal cytology + HRA directly biopsy + Rx of HGAIN (unproven efficacy)