Preventing Anal Cancer in HIV-infected Persons

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Plan

- Anal cancer epidemiology
- The anorectum
- Human papillomavirus infection
- Anal dysplasia
- Anal cancer clinical presentation
- Anal cytology screening
- High resolution anoscopy
- Treatment modalities
- Education and awareness

Epidemiology of HIV and Anal Cancer

- Anal Cancer Incidence Rates – General Population
  - 2003-2007: 1.6/100 000
  - Anal cancer incidence increasing
- Anal Cancer Incidence reported in HIV+ MSM ranges from 37.1 - 219/100 000
- Relative risk of anal cancer in HIV+ MSM compared to general population ranges from 8.2 - 352
- Anal cancer incidence in HIV-positive women approximately 6-8 times that of women in the general population

SEER database, Grulich 2002, Petruckevitch 1999, Biggar 2004, Diamond 2005

Kaiser Permanente cohort

- Popn Kaiser Permanente California
- Cohort 1996-2007, 10 HIV-pos: 1 HIV-neg (matched by age, sex, year, medical center)
- Analysis by:
  - Anal cancer, death, left plan, or 12-31-07
  - 6 monthly data points for HIV-pos
  - CD4/HIV RNA

Infection related non AIDS defining malignancy

	HIV-pos		HIV-neg		Adjusted hazard ratio (95% CI)##
	n	Rate#	n	Rate#	
Any	215	267	284	28	5.9 (4.7-7.5)
Anal	140	174	21	2	74.9 (46.8-120.0)
Hodgkin's	44	54	29	3	17.7 (10.6-29.7)
Oral cavity	35	43	162	16	1.7 (1.1-2.5)
Liver	21	26	94	9	0.6 (0.4-1.0)

HIV-pos ###	**CD4 < 200**	**CD4 201- 499**	**CD4 > 500**	**P-value**
Anal hazard ratio ##	164.2	83.1	34.2	< 0.001

Cases per 100,000 person years

Adjusted for age, sex, tobacco use, overweight/obese, alcohol/drug use, HBV/HCV

HIV-negative reference

Silverberg CROI 2010

Age and anal cancer

- From 2003-2007, the median age at diagnosis for cancer of the anus, anal canal, and anorectum was 60 years of age

Age	Anal cancer incidence (%)
< 20	0
20-34	1.1
35-44	9.7
45-54	24.1
55-64	24.3
65-74	18.5
75-84	15.8
>85	6.5

SEER database

HIV and aging

- CDC definition of ‘Elderly’ in the context of HIV is defined as persons ≥ 50 years
- 4 x increase in ‘elderly’ US AIDS cases in last 10 years
- 2000 - 10 and 15% of US AIDS cases were ‘elderly’
- 2015 - 50% of prevalent HIV cases will be >50 years

Anal cancer survival (general popn)

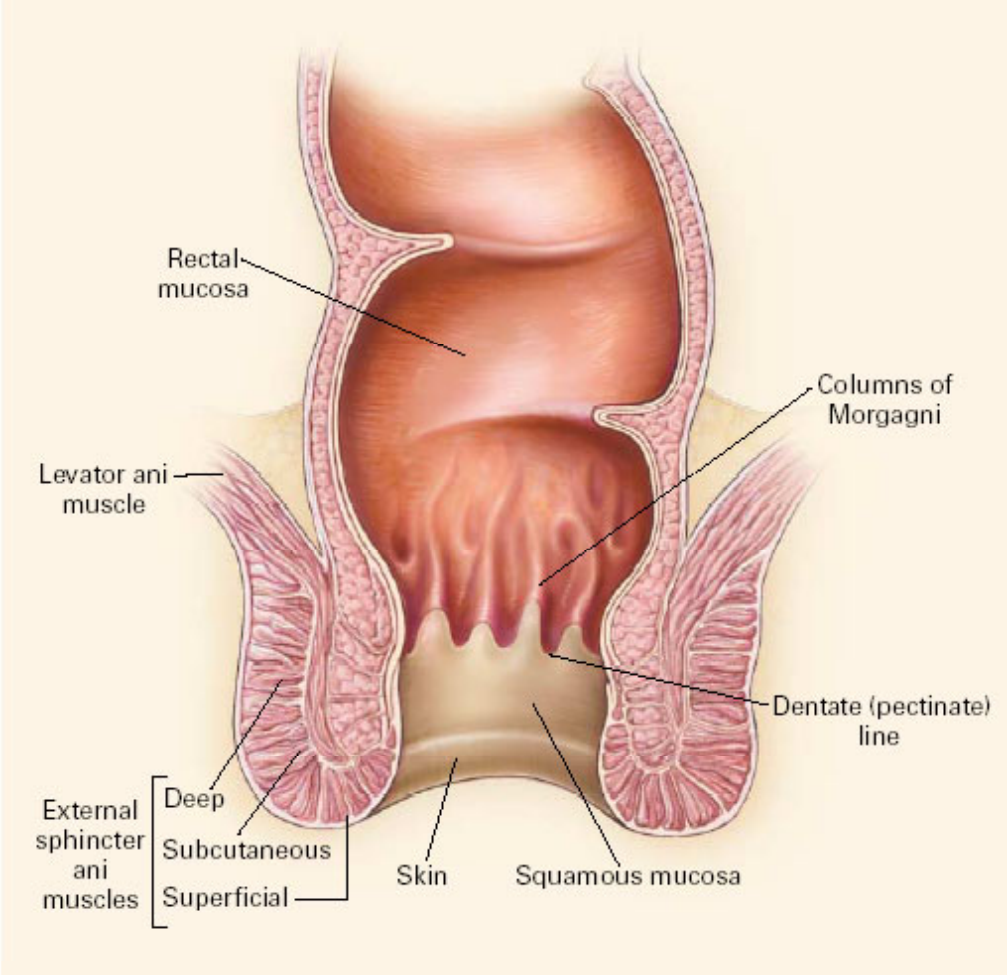
Stage distribution and 5-year relative survival by stage at diagnosis for 1999-2006, all races, both sexes

Stage at Diagnosis	Stage distribution (%)	5-year relative survival (%)
Localized (confined to primary site)	50	80.1
Regional (spread to regional lymph nodes)	29	59.8
Distant (cancer has metastasized)	12	30.5
Unknown (unstaged)	9	56.0

SEER database

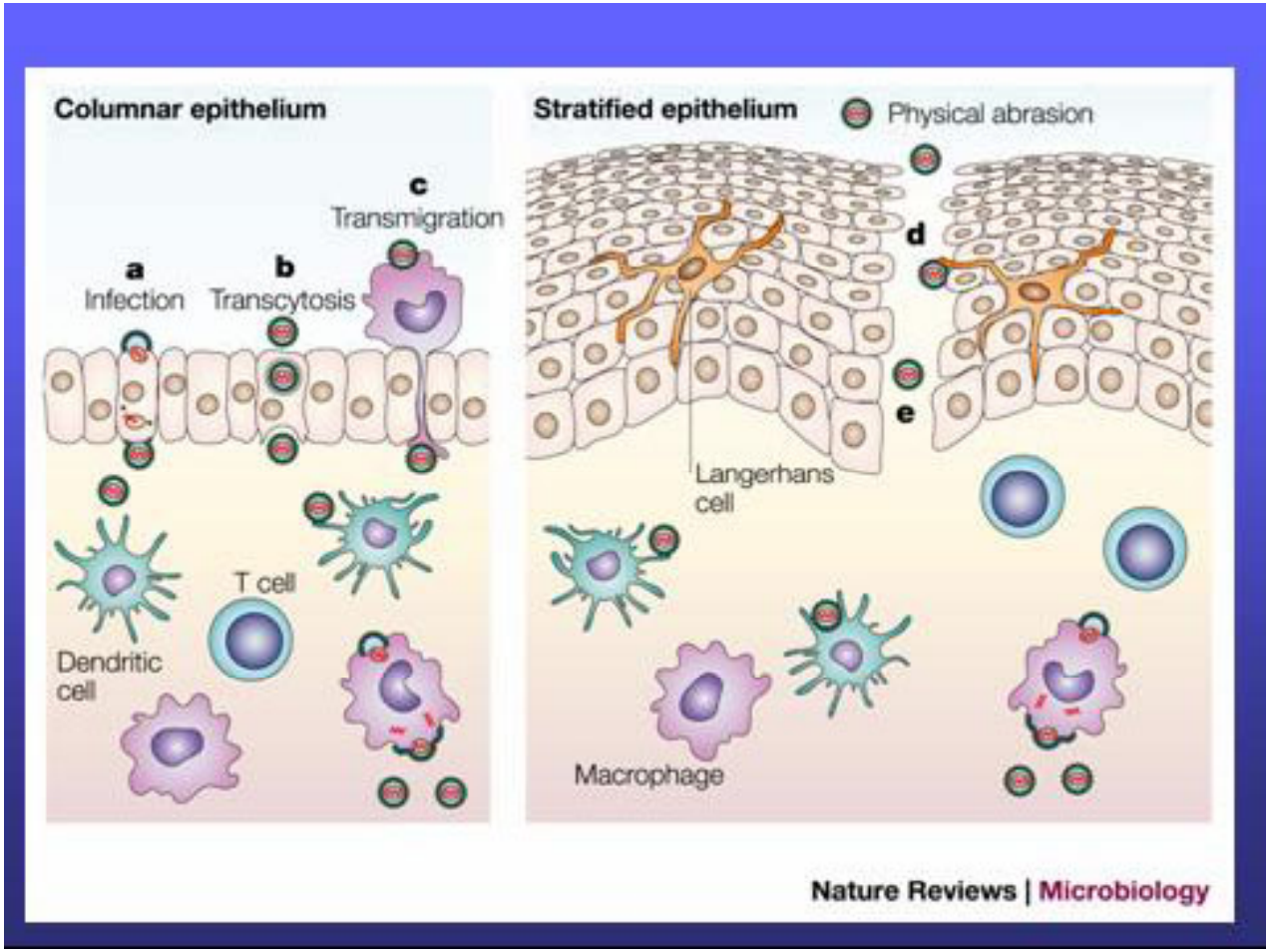
Anatomy and physiology

The anorectum



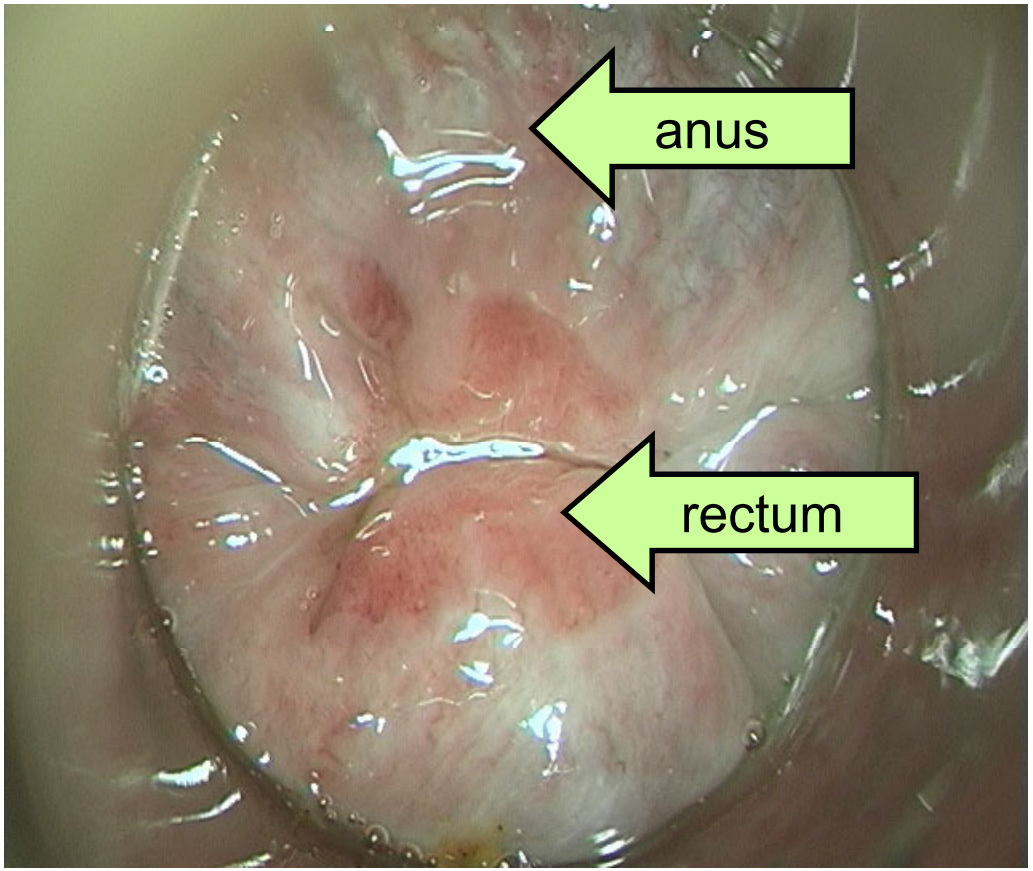
Ryan 2000

Rectal and anal epithelium

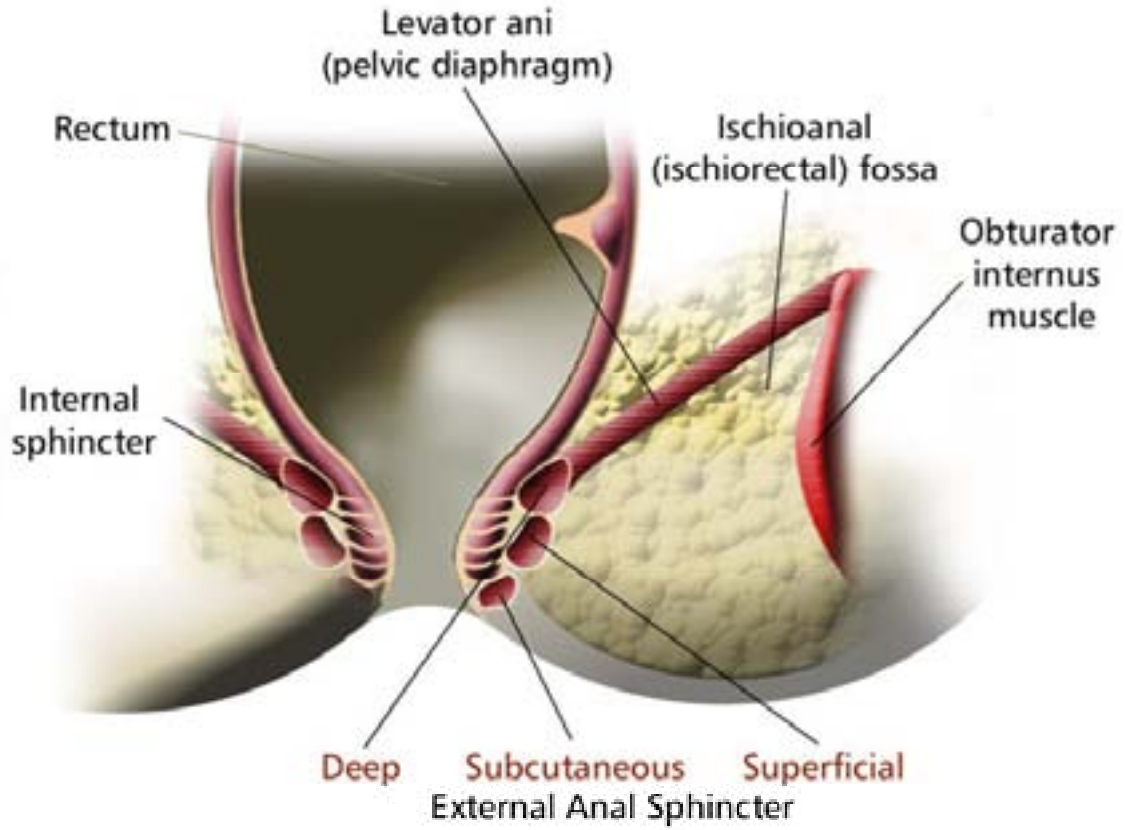


Shattock 2003

Anorectal transition zone



Anorectum


Levator ani
(pelvic diaphragm)
Rectum
Ischioanal
(ischiorectal) fossa
Obturator
internus
muscle
Internal
sphincter
Deep
Subcutaneous
Superficial
External Anal Sphincter

Manometry

Test site	Resting (mmHg)	Squeeze (mmHg)
Anal (male and female)	56	178
Anal no RAI male	91	152
Anal RAI male	71	177
Pelvic floor (nulliparous)	-	15-20

AGA Technical Review on Anorectal Testing Techniques 1998, Chun 1997, Fischer 1996

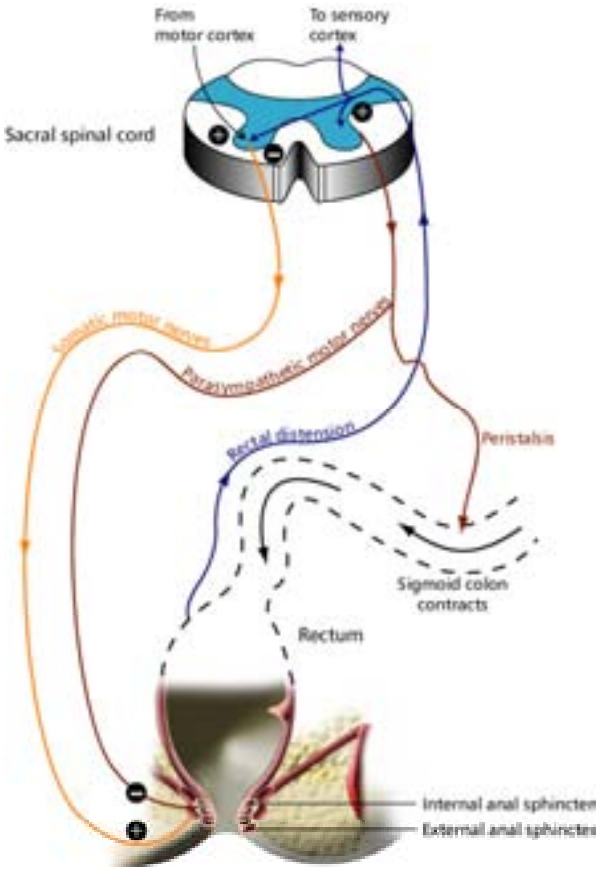
Anal and rectal sensation

- **Anal canal:**

  Somatic sensation (light touch, pin-prick, heat, cold, pain, distension)

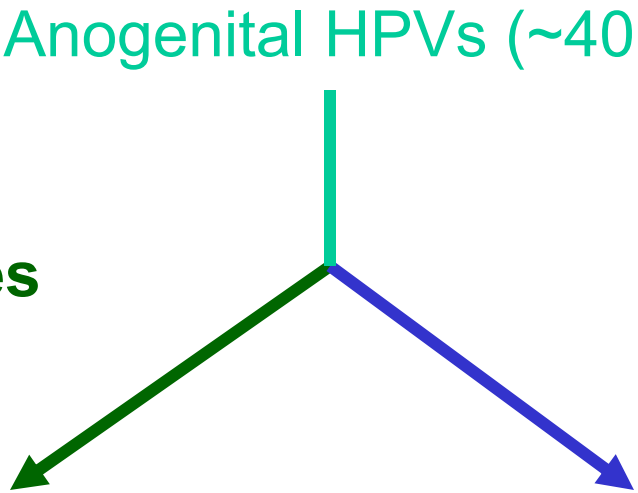
- **Rectum:**

  Visceral sensation (distension, pain)



Human papillomavirus

Anogenital HPV types



High-risk types (HPV 16,18)

- low-grade dysplasia
- high-grade dysplasia
- anogenital cancers

Low-risk types (HPV 6,11)

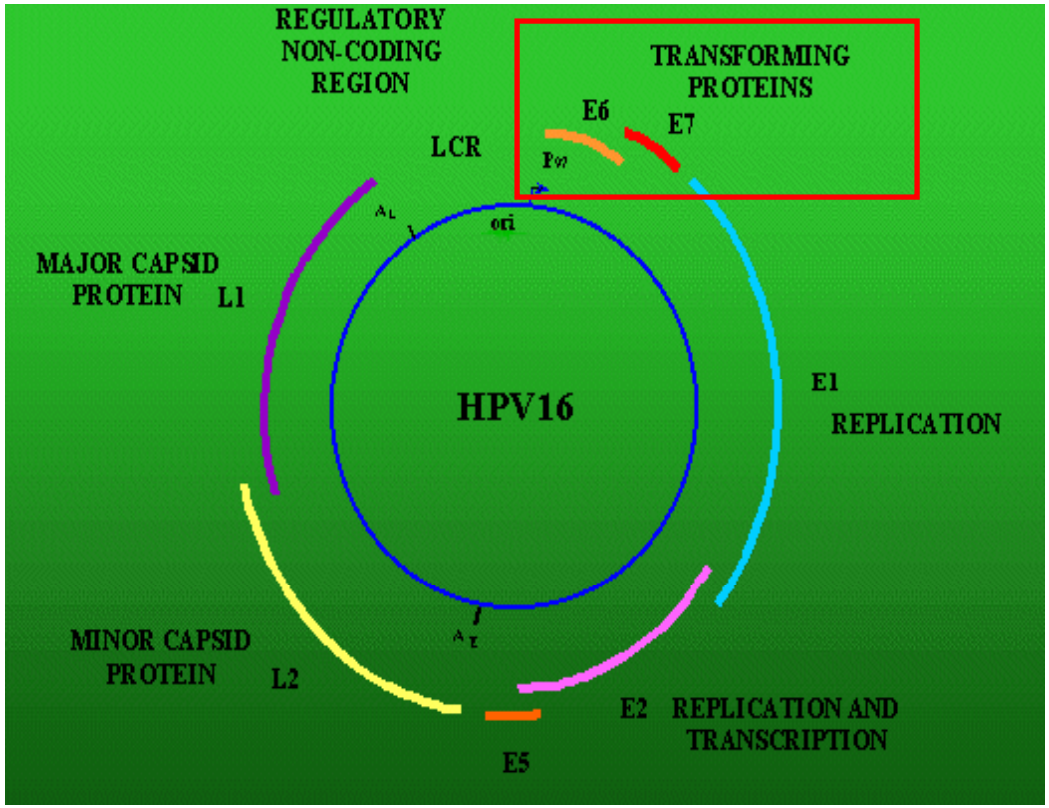
- low-grade dysplasia
- genital warts
- respiratory papillomatosis

Human Papillomavirus

- DNA tumor virus (8 KB)
- High-Risk Types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68
- Associated with dysplasia and cancer of the cervix, anus, penis, vulva, and vagina
- Required for the development of cervical cancer

HR-HPV pathogenesis

- Integration of episomal viral genome
- Expression of HPV E6 and E7 oncoproteins
- Disruption of cell cycle checkpoints (p53/pRB)
- Genomic instability leads to malignant progression



Anal HPV infection

- Risk factors
  - Receptive anal sex
  - History of anal warts
  - HIV infection
  - CD4<200 cell µL
  - Cervical HPV
  - Smoking history
  - Younger age
- Consequences
  - Nil
  - Condyloma accuminata
  - Anal dysplasia
  - Anal malignancy

Palefsky 1998, Holly 2001

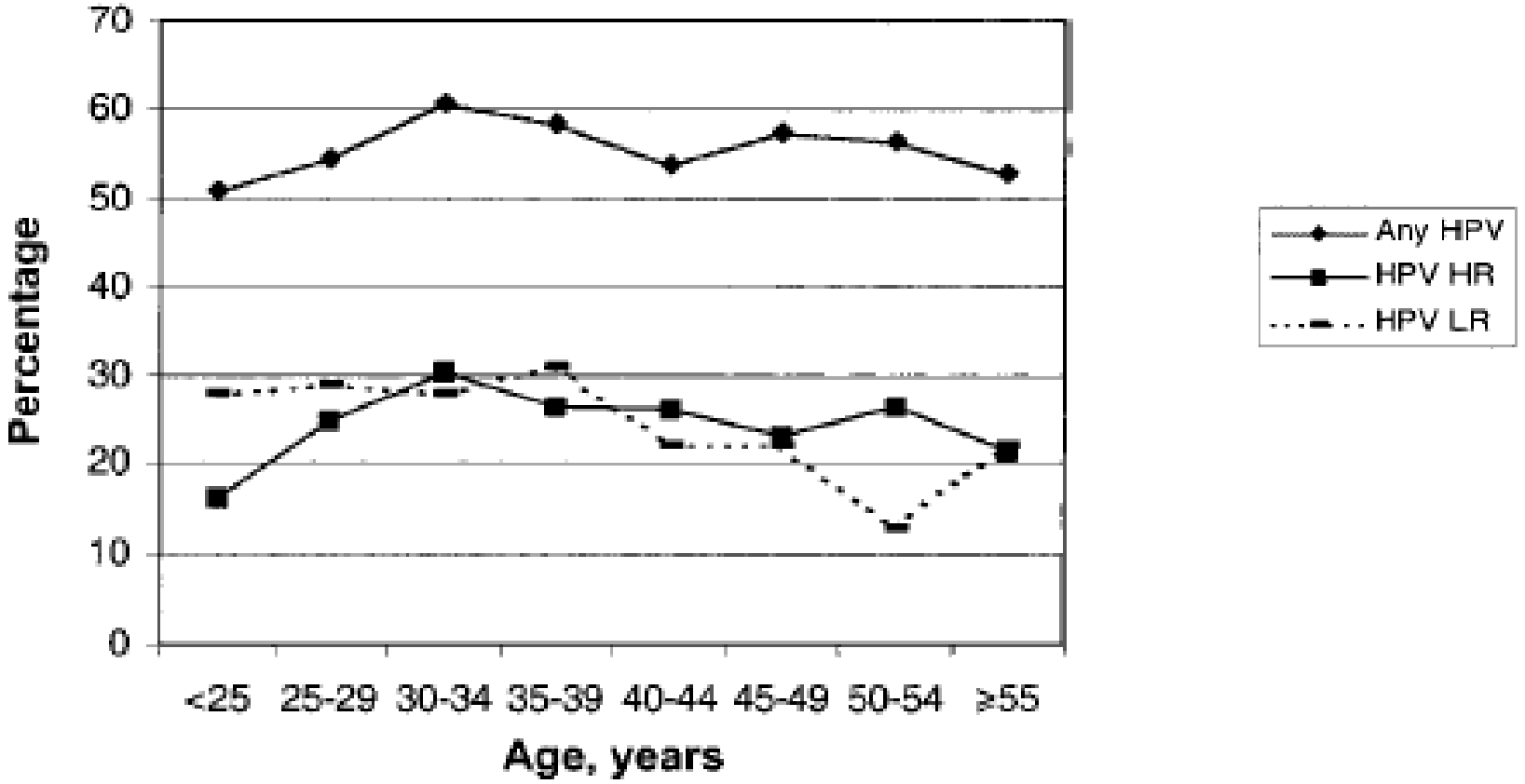
Anal HPV prevalence

- 50-70 % of the general population exposed to anogenital HPV (serology)

- Anal HPV by PCR
  - 42 % HIV-neg female
  - 61 % HIV-neg MSM
  - 76 % HIV-pos female
  - 93 % HIV-pos MSM

Koutsky 1999, Palefsky 2001, Palefsky 2001, Palefsky 1998

Anal HPV by age in HIV-neg MSM



Chin-Hong 2004

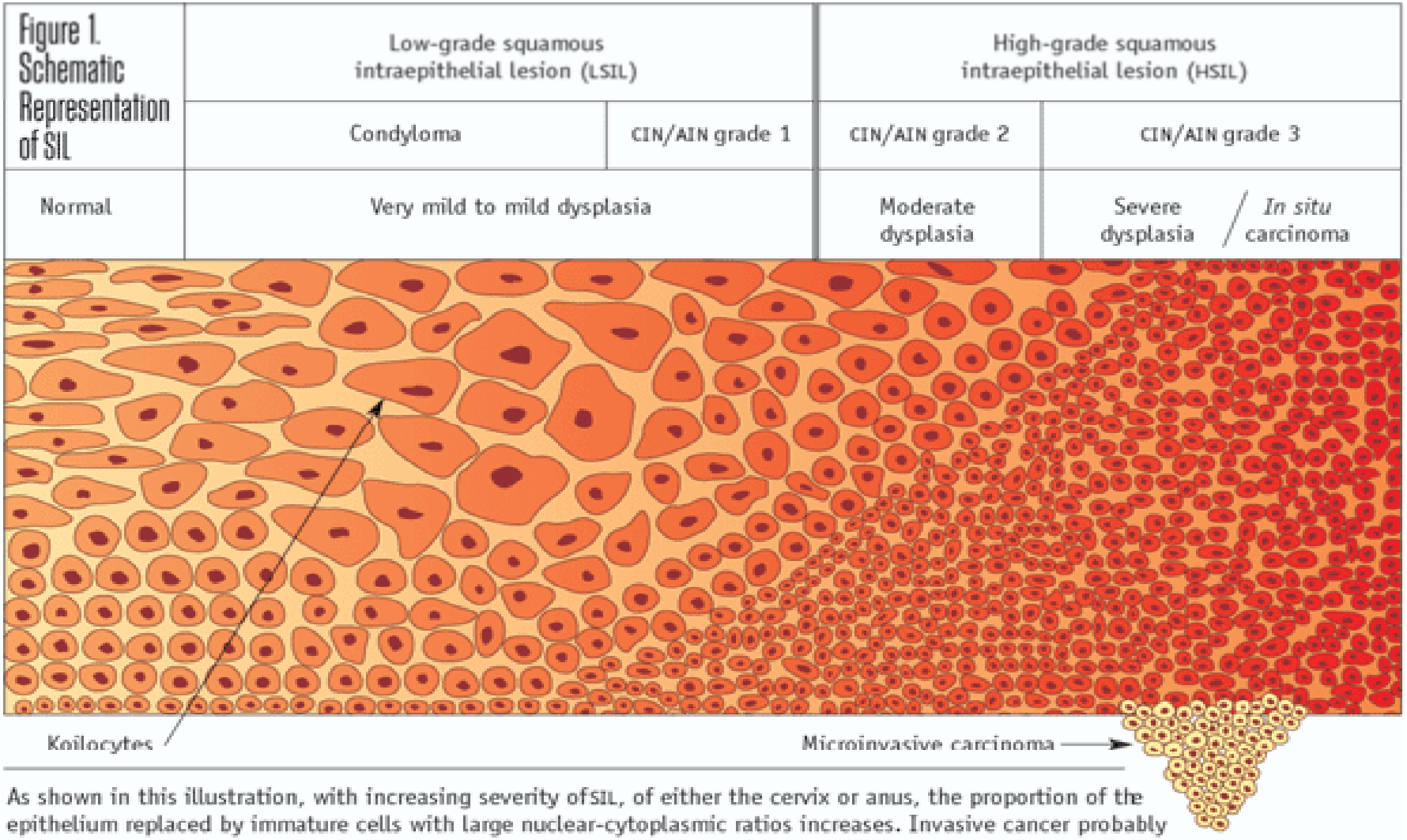
Anal HPV in HIV-pos MSW IDU

- Comparison of HIV-pos MSM with HIV-pos MSW infected by IDU with no history of RAI

	n	Anal HPV-pos
MSM	67	57 (85%)
MSW	50	23 (46%)

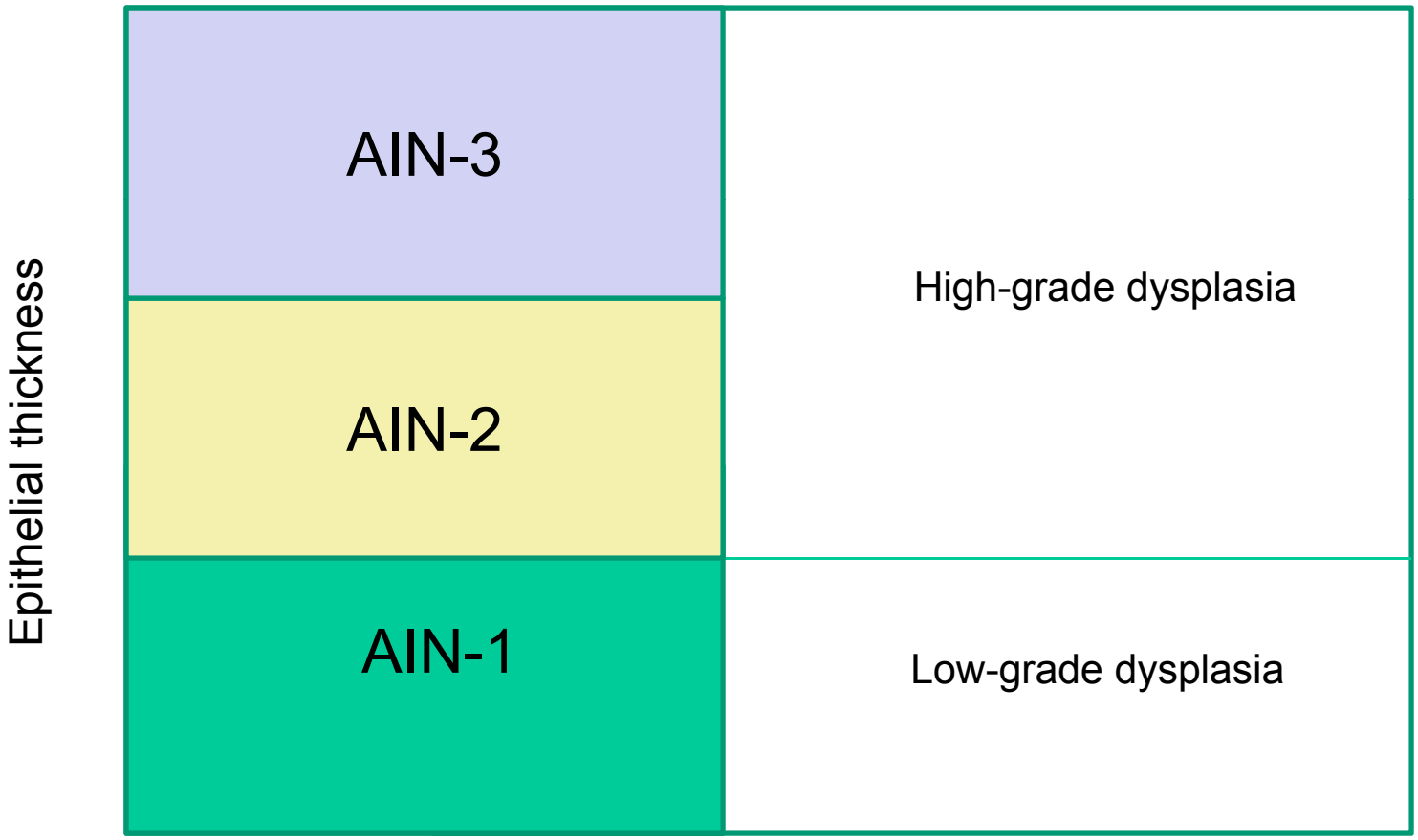
Piketty 2003

Anal dysplasia



Palefsky 2004

Schematic representation of anal dysplasia reporting



Risk factors for anal dysplasia

- HPV infection
- Receptive anal sex
- HIV infection
- CD4 <200 cells µL
- Genital wart diagnosis
- History of anal discharge
- Current cigarette smoking
- High-grade cervical/vulvar/vaginal dysplasia or cancer
- Iatrogenic immunosuppression (steroid/transplant)

Palefsky 1997, Palefsky 1998, Melbye 1996, Williams 1994, Moscicki 1999

Natural history of anal dysplasia

- San Francisco natural history cohort
  - 32% of HIV+ men and 9% HIV-neg men with no anal disease developed AIN-1 in 2 years
  - >50% HIV+ men with AIN-1 at baseline developed high grade dysplasia within 2 years
    - HIV infection
    - CD4 < 200
    - Multiple HPV types
    - High-level high-risk HPV infection
- Clinically - high grade dysplasia rarely regresses

Palefsky 1998, Hessol 2009

Prevalence of anal dysplasia

- San Francisco: 81% HIV-pos MSM
- Los Angeles: 69% HIV-pos MSM
- EXPLORE: 20% in HIV-neg MSM
- San Francisco 26% HIV-pos and 8% HIV-neg women
- Thailand: 33.9% HIV-pos and 12.5% HIV-neg MSM

Palefsky 2005, Cranston 2007, Chin-Hong 2005, Holly 2001, Phanuphak 2009

Anal HPV/dysplasia pre and post HAART

- MSM with anal swab and biopsy results compared 6/12 pre- and post-HAART
  - No change in anal HPV positive tests or level of HPV infection
  - Similar anal biopsy pathology results in both groups
- High Prevalence of anal dysplasia (70%) and HPV (80%) in patients after instituting HAART regardless of CD4 increase

Palefsky 2005 , Piketty 2004

Anal dysplasia as an anal cancer precursor

- Comparing anal dysplasia/cancer with cervical dysplasia/cancer:
  - Same HPV risk types
  - Similar pathology
  - Same chromosomal abnormalities
  - Frequently diagnosed simultaneously
  - (For anal: same risk groups)

Bosch 1995, Palefsky 2000, Frisch 1999

Progression of HGAIN to cancer

- 1994-2003, 35 HIV-negative patients diagnosed with HGAIN by anal biopsy
  - Surgical excision in 28
  - 6 immunosuppressed patients had multifocal perianal disease
  - 3 progressed to anal cancer during follow up (63 month median (14-120))
- 1997-2007 UCSF among 1700 HIV-positive MSM, 65 cancer were diagnosed
  - 21 ppts had previous biopsy of HGAIN at site of new cancer

Scholefield 2005, Berry CROI 2009

Table 6. Summary of studies evaluating prevalence of high-risk human papillomavirus (HPV) infection, cytologic dysplasia, and biopsy-proven anal intraepithelial neoplasia (AIN) in cohorts of HIV-positive individuals.

Study	Year	Sex	Location	No. of HIV-positive subjects	Subjects with high-risk HPV infection, %	Subjects with cytologic dysplasia, %		Subjects with AIN revealed by biopsy, %	
						Any	High grade	Any	High grade
Melbye et al. [62]	1996	Women	Denmark	81	...	14		...	...
Hillemanns et al. [59]	1996	Women	New York, New York	102		28	0	...	...
Palefsky et al. [51]	1998	Men[a]	San Francisco, California	346	80	46	2	23	3
Sayers et al. [63]	1998	Men[a]	United Kingdom	66	...	41	8	...	...
Friedman et al. [52]	1998	Men[a]	Multicenter AIDS cohort	135	56	41	2	...	...
Lacey et al. [53]	1999	Men[a]	United Kingdom	57	81	67	7	...	...
Goldstone et al. [64]	2001	Men[a]	New York, New York	200	...	97	57	96	68[b]
Palefsky et al. [60]	2001	Women	San Francisco, California	223	37	...	...	...	...
Holly et al. [61]	2001	Women	San Francisco, California	235	...	26	1	...	...
Alfonzo et al. [56]	2002	NR	NR	162	...	59	43	...	...
Fine et al. [57]	2002	NR	Rochester, New York	458	...	14	4	...	...
Norton et al. [58]	2003	NR	New York, New York	115	...	30	4	...	...
Durante et al. [10]	2003	Women	New England	164	44	14	0	...	...
Piketty et al. [50]	2003	Men[c]	France	117	59	44	18	...	...
Lee et al. [34]	2004	Men[a]	San Francisco, California	417	...	54	4	...	...
Wilkin et al. [49]	2004	Men[d]	New York, New York	92	61	47	6	40	9
Chin-Hong et al. [55]	2004	Men[e]	Brazil	33	...	68	27	...	...
Mathews et al. [33]	2004	Men and women	San Diego, California	1732	...	57	8	...	...
Kreuter et al. [54]	2005	Men[a]	Germany	103	53	...	...	20	6
Palefsky et al. [46]	2005	Men[a]	San Francisco, California	357	95	81[f]	25[f]	...	...

NOTE. MSM, men who have sex with men; NR, not reported.

[a] MSM, 100%.
[b] Cancer, 3%.
[c] MSM, 43%.
[d] MSM, 60%.
[e] MSM, 34%.
[f] Combined results of cytological and histological examination conducted at the same visit. The more-severe diagnosis is represented.

Anal cancer

Clinical presentation

- History:
  - Pain, bleeding, ulceration, mass, change in stools
  - Presentation may be non specific, confused with HSV, condyloma, medication side effects, fissure, or hemorrhoids
- Physical:
  - 56% of early anal cancer cases asymptomatic but with palpable mass

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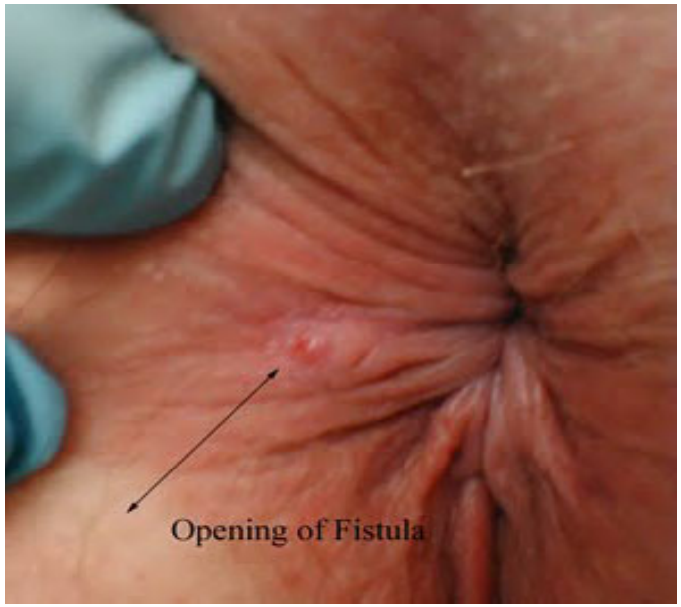

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Anal cancer risk: pre & post HAART

Table 2. Relative risk (RR) of anal cancer and anal cancer incidence among HIV-infected individuals.

Study	Location	Study population	Years of study	Total no. of patients in HIV/AIDS cohort	SIR (95% CI)	RR (95% CI)	Anal cancer incidence (95% CI) per 100,000 person-years		Statistically significant difference between HAART and pre-HAART incidences
							Pre-HAART era	HAART era	
Gallagher et al. [16]	New York State	AIDS Cancer Registry match	1981–1994	122,993	3.3 (2.86–3.75)[a]	...	NR	NR	NR
Petruckevitch et al. [21]	United Kingdom	Cohort study	1982–1995	2048	222 (27–803)[b]	...	NR	NR	NR
Frisch et al. [7]	United States	AIDS Cancer Registry match	1978–1996	366,034	...	Men, 37.9 (33.0–43.4); women, 6.9 (2.7–14)	Men, 18.2; women, 3.9	NR	NR
Biggar et al. [17]	United States	AIDS Cancer Registry match	1981–1996	8829	...	8.2 (3.0–17.8)	NR	NR	NR
Grulich et al. [20]	Australia	Cohort study	1980–1999	13,067	37.1 (17.8–68.3)[c]	...	NR	NR	NR
Diamond et al. [18]	San Diego County, California	AIDS Cancer Registry match	1988–2000	11,867	...	Pre HAART era, 98 (36–264); HAART era, 352 (186–669	49 (16–114)	144 (93–112)	No
Clifford et al. [19]	Switzerland	Swiss cohort study	1985–2002	7304	...	33.4 (10.5–78.6)[c]	NR	NR	No
Bower et al. [22]	United Kingdom	Cohort study	1984–2003	8640	...	115.4[b]	60 (40–89)	92 (52–149)	No

NOTE. NR, not reported; SIR, standardized incidence ratio.

[a] Includes rectal and anal cancer and may underestimate the SIR, because this study included cancer of the rectum in the incidence calculation. Data are standardized for age, sex, region and race.

[b] Data are standardized for age and sex.

[c] Data are standardized for age, sex, and time period.

Anal Cancer Screening

Anal cytology

- Dacron swab inserted into anal canal
- Cells fixed on slide or re-suspended in ThinPrep solution
- Read by pathologist according to Revised Bethesda classification scheme
- ASC-US, ASC-H, LSIL, HSIL
- Performed easily as part of routine clinic visit
- Patient vs. provider specimens

Assessing anal cytology

- Moderate to high sensitivity
- Poor specificity (32-59%)
- Anal histopathology mandatory
- 244 HIV+ MSM correlating cytolog
  - 67% men with abnormal cytolog
  - PPV for any anal cytological ab
    degree of anal dysplasia was 9

Palefsky 1997, Cranston 2007, Panther 2004

Anal cytology performance

Table 4. Summary of studies reporting sensitivity and specificity for anal Papanicolau (Pap) smear cytological examination, compared with histological examination.

Reference	Year	No. of subjects	Liquid cytological examination or convential histological examination	Sensitivity, %	Specificity, %
Palefsky et al. [32]	1997	407	Liquid (ThinPrep; Cytyc)	69	59
Lee et al. [34]	2004	192	Not stated	95	Not stated
Matthews et al. [33]	2004	154	Conventional	85	56
Panther et al. [35]	2004	153	Not stated	93	33
Fox et al. [36]	2005	99	Conventional	83	38
Salit et al. [37]	2005	246	Liquid (ThinPrep; Cytyc)	84	32
Arain et al. [30][a]	2005	200	Liquid (SurePath; Medical Solutions)	98	50
Papaconstantinou et al. [31][b]	2005	37[c]	Liquid (ThinPrep; Cytyc)	42	96

[a] Only patients with abnormal Pap smear results underwent high-resolution anoscopy and biopsy; therefore, sensitivity and specificity may be biased.
[b] Did not include atypical squamous cells of uncertain significance in definition of abnormal Pap smear.
[c] All patients had condyloma.

Anal 'Home Cytology'

- 102 MSM in UCSF Anal Neoplasia Study
- 82 HIV-pos, 20 HIV-neg, 87% Caucasian
- Matched anal cytology and concurrent anal biopsy
- Explanation given on technique and subjects requested to obtain 'home' sample in 1 month

N=102	clinician	subject	p value
Specimen adequacy (%)	101/102 (99)	93/102 (91)	0.02

Cranston 2004

Current guidelines

Anal Pap Smear *Optional for All Programs*

In addition to an anorectal exam, **all HIV+ MSM, females with an abnormal vaginal pap smear, and patients with a history of anogenital HPV infection** are evaluated on whether they have received an anal pap smear.

eHIVQUAL identifies MSM patients in the exposure category of the patient entry screen and identifies females with an abnormal vaginal pap smear within the gynecological exam indicator. eHIVQUAL will prompt, *"Does the patient have a documented history of anogenital HPV infection?"* If the patient is eligible, eHIVQUAL will prompt, *"Did the patient have an anal pap smear during the review period?"*

Yes: Anal pap smear was a performed within the 12-month review period (stop).
No: An anal pap smear was not performed (stop).

HIVQUAL Indicator Definitions
New York State Department of Health AIDS Institute
DHHS, HRSA
May 5 2010

ADC algorithm

Anal Cytology

Abnormal

Negative

Repeat annually

High-resolution anoscopy

ADC and follow-up

Anal cytology cost effectiveness

$13 000 per QALY (CD4 >500, biannual)

$16 600 per QALY (CD4 >500, annual)

$25 000 per QALY (CD4 <500, annual)

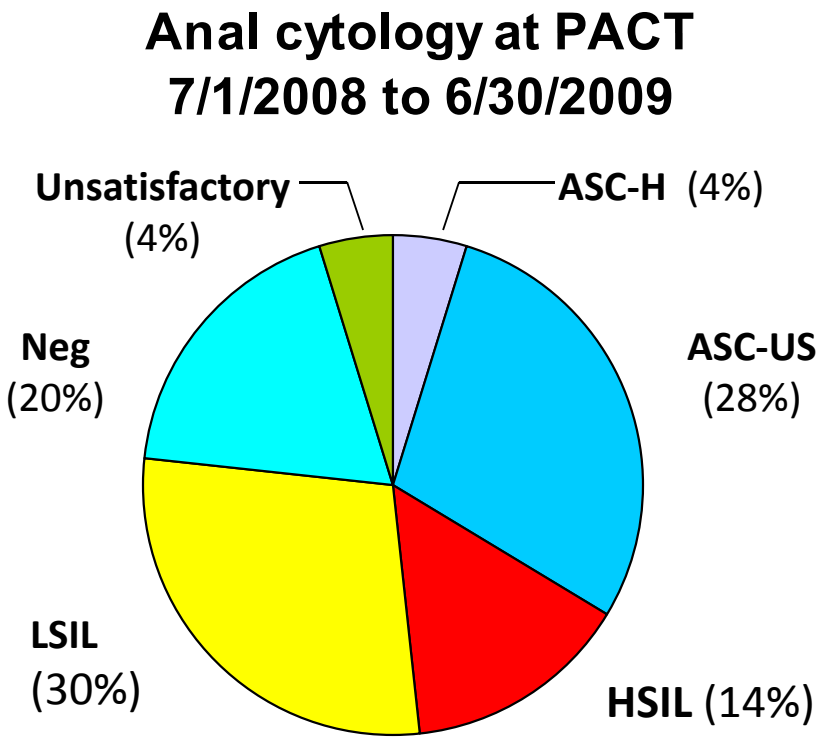
(Annual cervical cytology: $180 000 per QALY)

- Authors suggested yearly anal cytology screening in HIV-pos MSM

Goldie 1999

U Pitt ADC

- First satisfactory anal cytology in men seen between 7/1/08 and 6/30/2009
- ~ 75% first anal Paps abnormal
- Number of anal Paps performed – 280
- Percentage of MSM screened – 63%



Anal cytology alternatives

- Education
- Regular digital rectal examination
- No cytology without a referral route for high-resolution anoscopy with Rx capability

Biomarkers

Biomarker research

- Laboratory markers that predict progression of dysplasia
  - Low-grade ⟹ high grade
  - High-grade ⟹ cancer
- Objective assessments of risk

P-16

- pRB is inactivated by the E7 oncogene product.
- pRB inhibits transcription of the cyclin dependent kinase inhibitor gene $p16^{INK4a}$
- Increased viral oncogene expression may be expected to increase levels of $p16^{INK4a}$
  - Over expression seen in all cervical biopsy tissue
    - CIN-1 (40/47) except those associated with low-risk HPV (7)
    - CIN-2 (32/32)
    - CIN-3 (60/60)
    - SCC (58/60)
  - No over expression seen in
    - Normal epithelium (42/42)
    - Inflammatory lesions (48/48)
    - CIN-1 associated with low-risk HPV (7)

Klaes 2001

P16 and anal dysplasia

- Assessment of 8 potential biomarkers using immunohistochemical methods
- Minichromosomal maintenance proteins (MCM3, MCM4, MSM 6, MCM7), p21, Ki-67, p16 and proliferating cell nuclear antigen
- 392 biopsy slides were assessed.
- Using a cutoff of 25% and 50% lesional positivity for the MCMs, Ki-67 and p16 resulted in 100% sensitivity and 100% specificity to diagnose high-grade AIN

Kreuter 2010

High-resolution anoscopy

HRA and image capture

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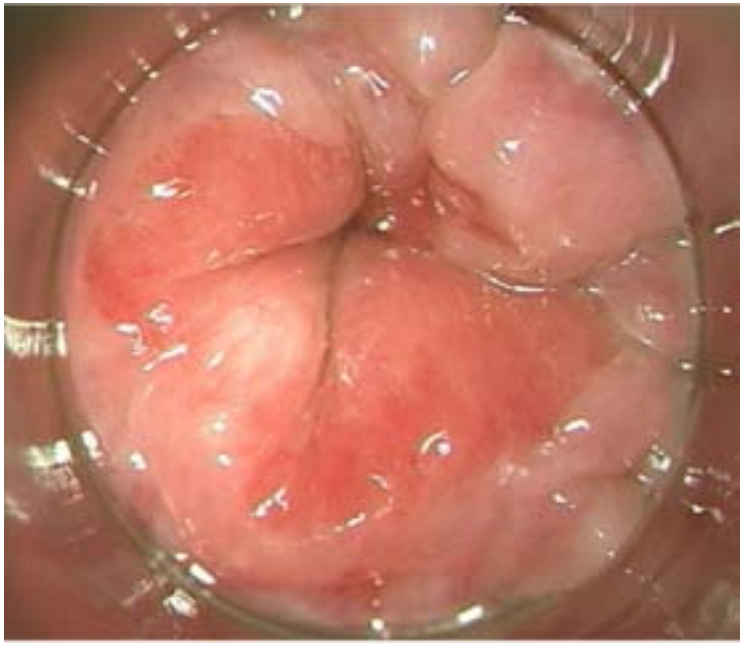

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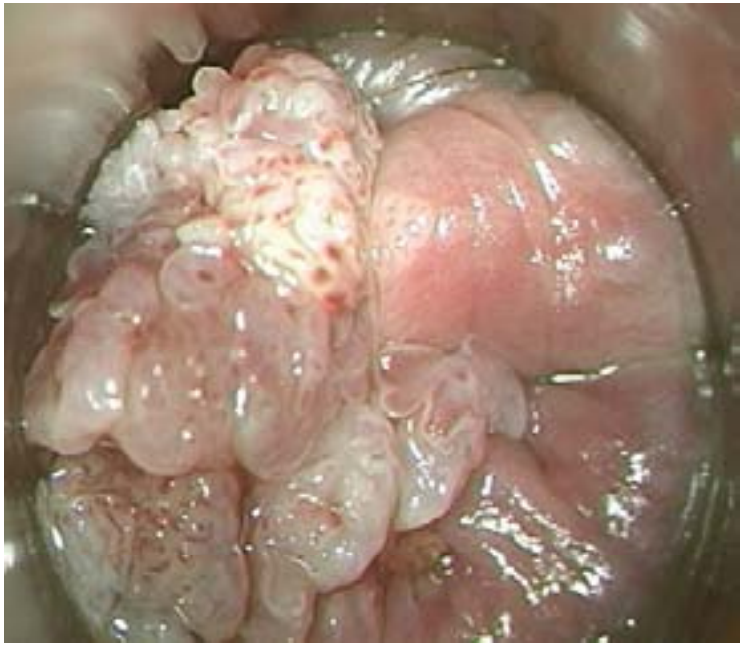

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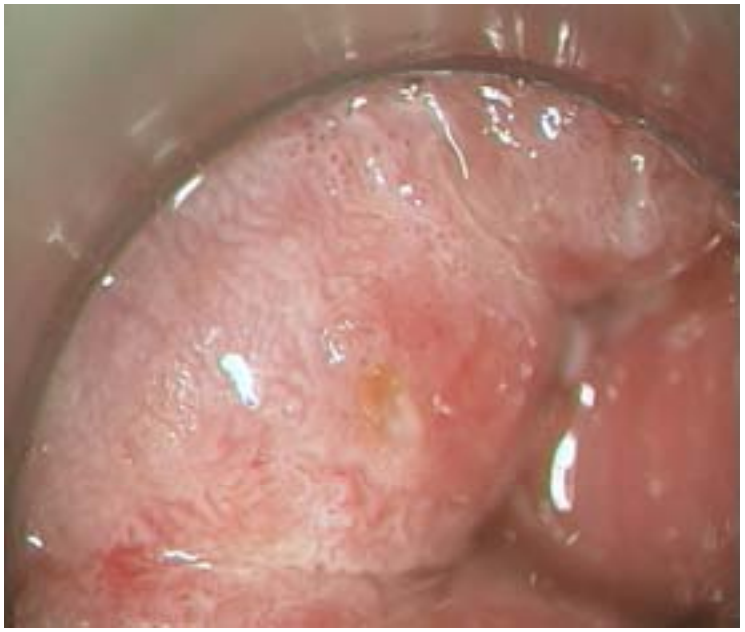

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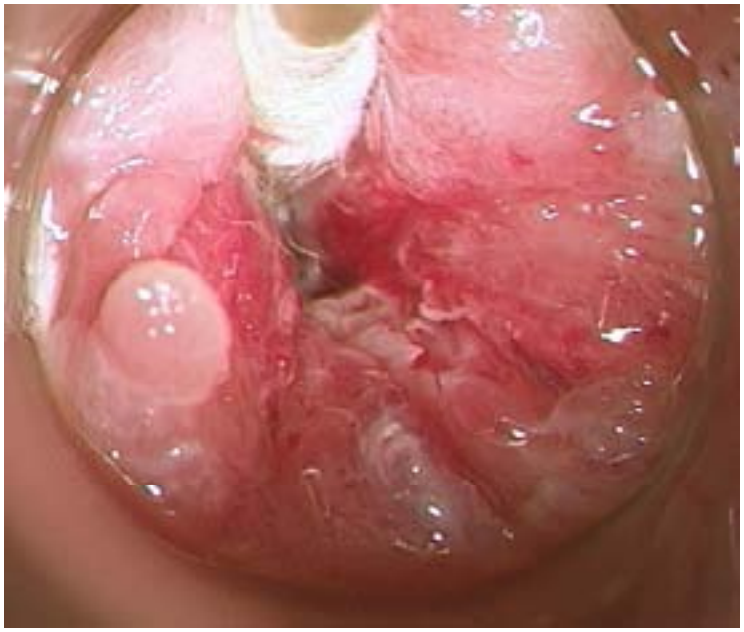


Clock face

3

12

6

9

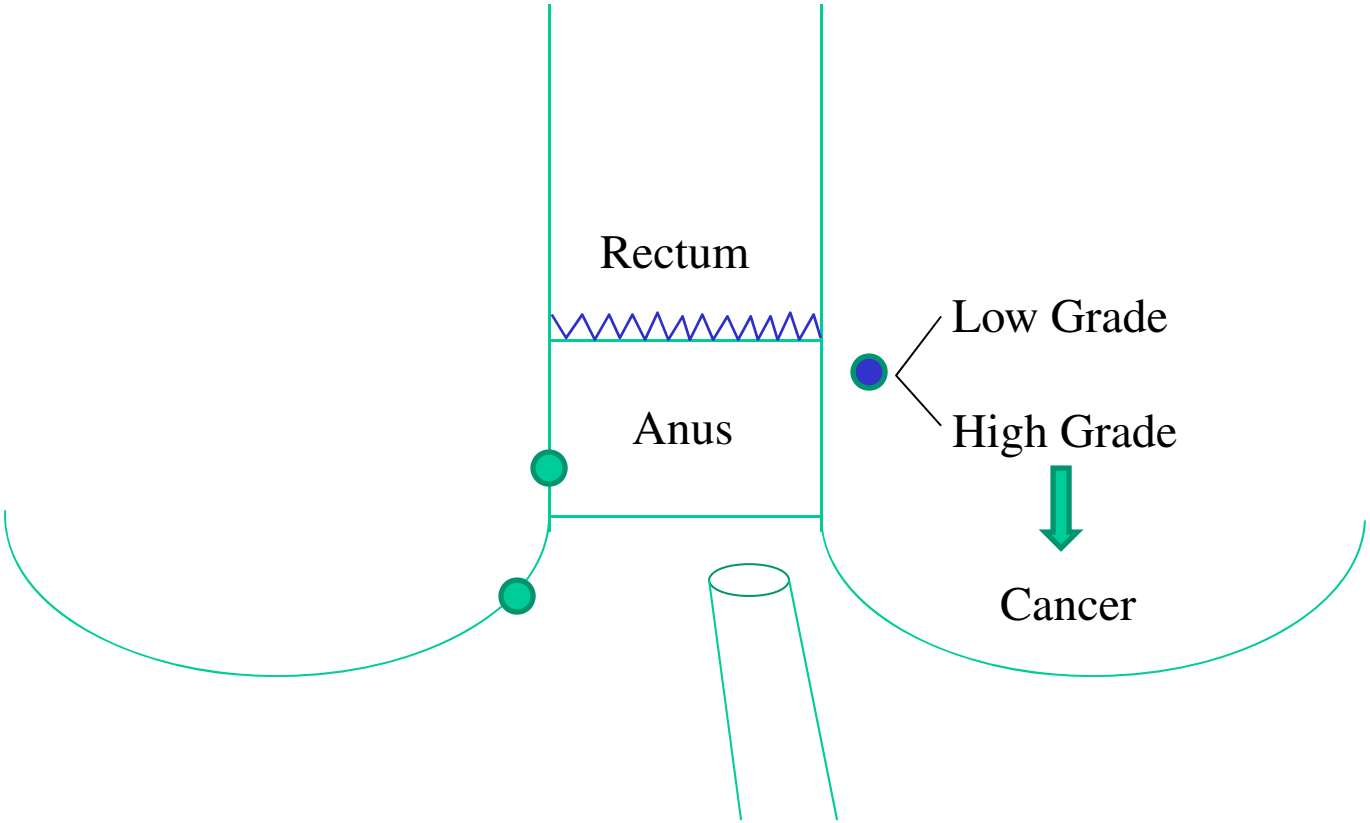
High-resolution anoscopy (HRA)

- Peri-anal inspection
- Digital examination
- Soak anal canal in 3% acetic acid
- Visualize transitional zone using a high-resolution anoscope (colposcope) with x 16 magnification

HRA – ADC Visit

- Discussion with patient
- External examination of the anus
- Digital Rectal Examination

Explaining anal dysplasia to patients



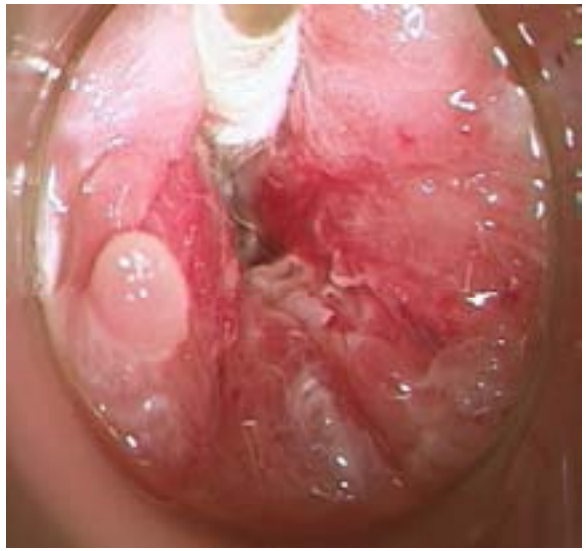
HRA

- Gold standard for diagnosis of high grade dysplasia
- Anoscopy with application of acetic acid
- Assessment for abnormal visual markers (acetowhite change, punctation, mosaicism, lugol's iodine negative)
- Biopsy if abnormal visual markers seen

HRA images

Normal

High Grade Dysplasia



Carcinoma

Anal high-grade dysplasia treatment

- Medical
  - Trichloroacetic acid
  - Imiquimod
  - Infra Red Coagulation
  - 5-Fluorouracil
  - Interferon
  - Liquid nitrogen
- Surgical
  - Electrofulguration
  - Cold scalpel excision
  - Laser ablation

Efficacy of surgical treatment

- Surgical (cold scalpel/electrofulguration)
- High-grade dysplasia recurrence or persistence:
  HIV- : 0/8 (32.3 +/- 20.6 months FU)
  HIV+: 23/29 (28.6 +/- 12.9 months FU)
- Mean time to recurrence in HIV+ group was 12 months

Chang 2002

IRC clinical experience

- HIV-positive MSM with high-grade anal dysplasia
  - HIV+ MSM – 72% cure (AIN 1 or normal epithelium) after 3 treatments with IRC
  - HIV+ MSM – 64% efficacy per treated lesion at 3 months

Goldstone 2007, Cranston 2008,

TCA

- TCA as primary Rx of AIN 2/3 at UCSF ADC between Jan 2000 and Dec 2004
- Clearance defines as absence of AIN by cytology/HRA after up to 4 treatments
- Population: 53 HIV-pos and 19 HIV-neg MSM
- Results:
  - 32% AIN 2/3 cleared to no lesions
  - Clearance improved with younger age, and if $\leq$ 2 lesions in HIV-pos men
  - Per lesion
    - 73% AIN cleared
    - 71% AIN 2/3 cleared to AIN 1 or less

Singh 2009

Imiquimod

- Cell activation by imiquimod via TLR-7 and secrete cytokines (IFN-α), (IL-6) and TNF-α
- FDA approved to treat actinic keratosis, superficial basal cell carcinoma, and external genital warts
- 61% efficacy when used in HIV-positive men to treat all grades of intra and perianal dysplasia

Kreuter 2008

Combination

- Treatment in one center of both low- and high-grade anal dysplasia
- Laser ablation initially, with surgical excision and Imiquimod used in follow up
- 65% disease free at 12 months
- Median time to cure was 31.5 months (significantly impacted by HIV status and volume of disease)

Nathan 2008

Vaccination

- Quadrivalent HPV VLP vaccine
  - Safe
  - Acceptable
  - Immunogenic
  - No efficacy data
- Therapeutic vaccination?

Acceptability

- Anal cytology
  - Age 18 to 59 years who self-identified as gay (n = 236) or bisexual (n = 70)
  - 83% willing to have a free test
  - 31% willing to pay
    - Perception of risk, worry, higher income
- Treatment of dysplasia
  - ?
- HPV vaccination
  - Gay/bisexual men: 74%
  - Heterosexual men: 34%

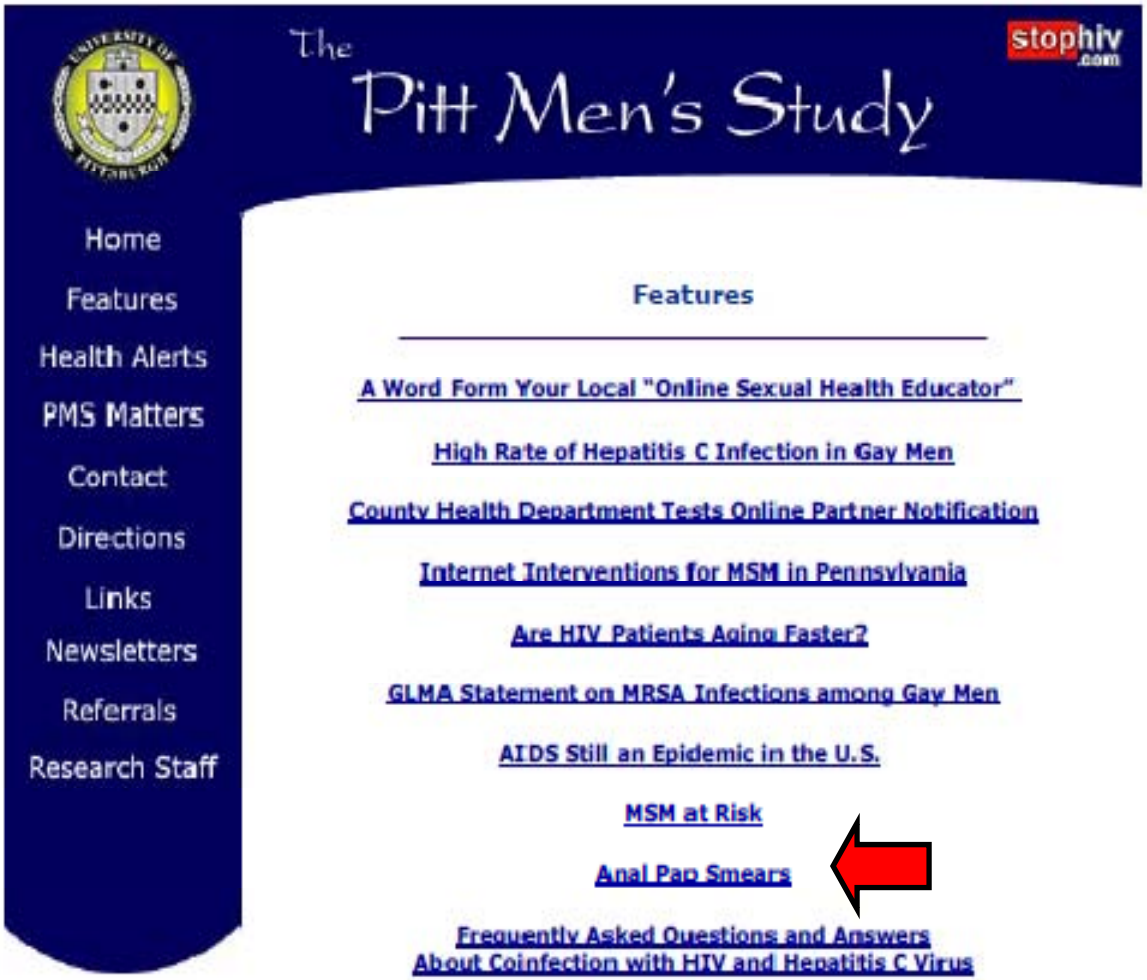
Reed 2010, Reiter 2010

Education

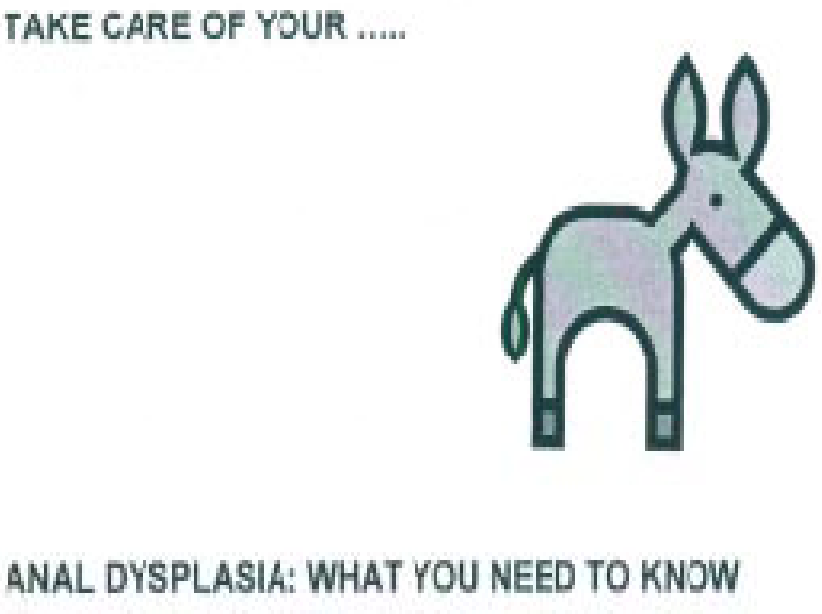
Anal dysplasia knowledge

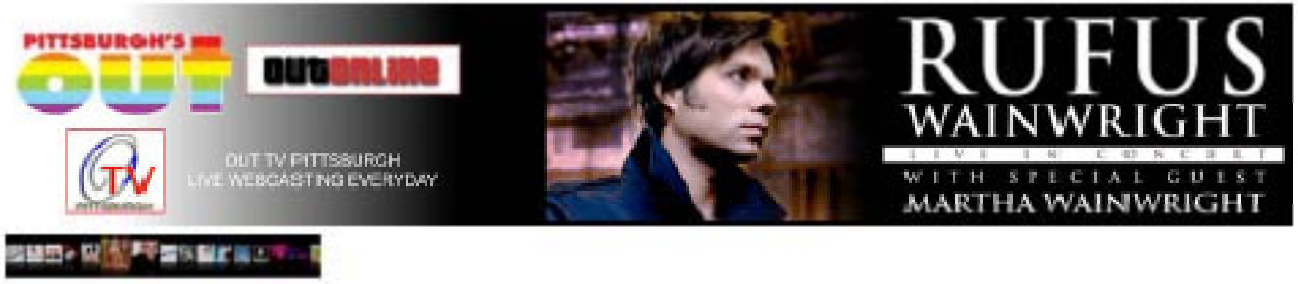
- Gay community event, Melbourne, Australia
- 92% gay identified, 6.4% HIV-positive, 3.5% unknown status
- On a 12 point knowledge scale, zero scores were found for
  - Anal cancer - 19%
  - HPV knowledge - 47%
  - anal Pap knowledge - 55%

Community


The
Pitt Men's Study
stophiv.com
Home
Features
Health Alerts
PMS Matters
Contact
Directions
Links
Newsletters
Referrals
Research Staff
Features
A Word Form Your Local "Online Sexual Health Educator"
High Rate of Hepatitis C Infection in Gay Men
County Health Department Tests Online Partner Notification
Internet Interventions for MSM in Pennsylvania
Are HIV Patients Aging Faster?
GLMA Statement on MRSA Infections among Gay Men
AIDS Still an Epidemic in the U.S.
MSM at Risk
Anal Pap Smears
Frequently Asked Questions and Answers About Coinfection with HIV and Hepatitis C Virus
Living with Lipodystrophy

Pittsburgh Pride 2009/10





AIDShilfe

Summary

- HIV-positive individuals are at increased risk of HPV associated anal cancer
- This may be addressed by
  - Education
  - Anal cytology and HRA where available
  - Regular digital rectal examinations

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