

Anal Dysplasia and Anal Cancer Prevention

Advances in Cytology and Small Biopsies
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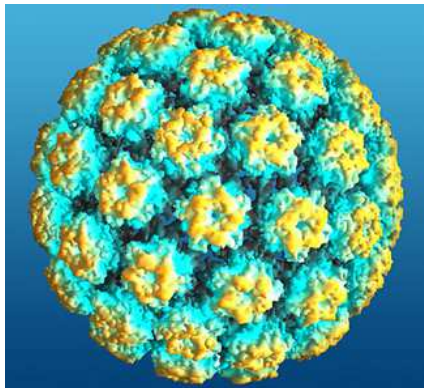
Learning Objectives

1. Understand the current state of the art for detection and treatment of anal dysplasia to prevent anal cancer.

Summary

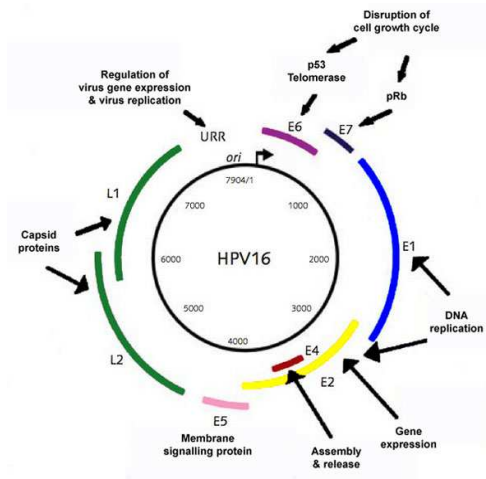
- HPV Biology
- Epidemiology of HPV, Dyplasia, and Cancer
- Screening
- Treatment
- Prevention

Human Papilloma Virus

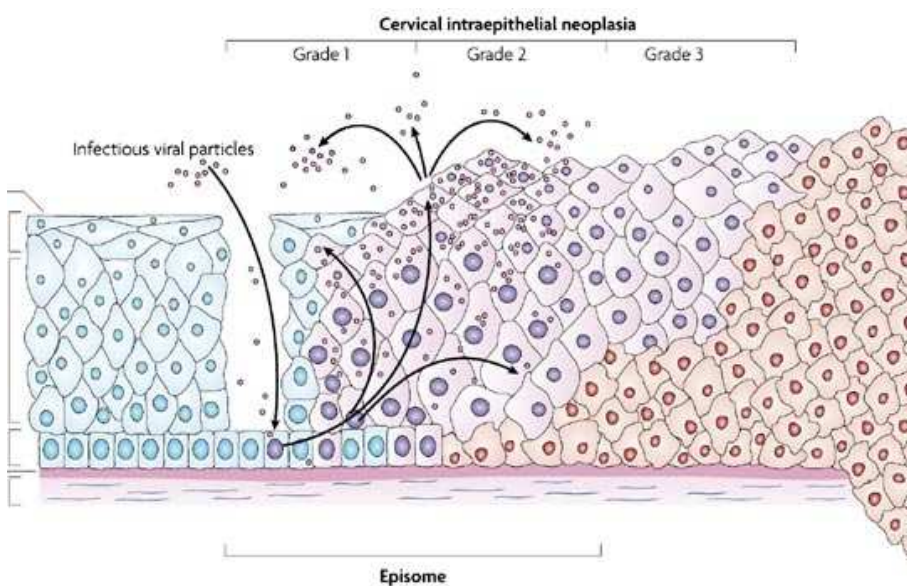


- Non-enveloped
- Double-stranded DNA
- >100 types identified
- 30-40 anogenital
- Oncogenic
16, 18, 31, 33, 35, 39, 45, 51, 52, 58
- Non-oncogenic
6, 11, 40, 42, 43, 44, 54

Human Papilloma Virus



- Early HPV protein
E1, E2, E4, E5, **E6, E7**
- **E6** and p53
DNA integrity
- **E7** and Rb
Cell replication
- Late HPV protein
L1, L2



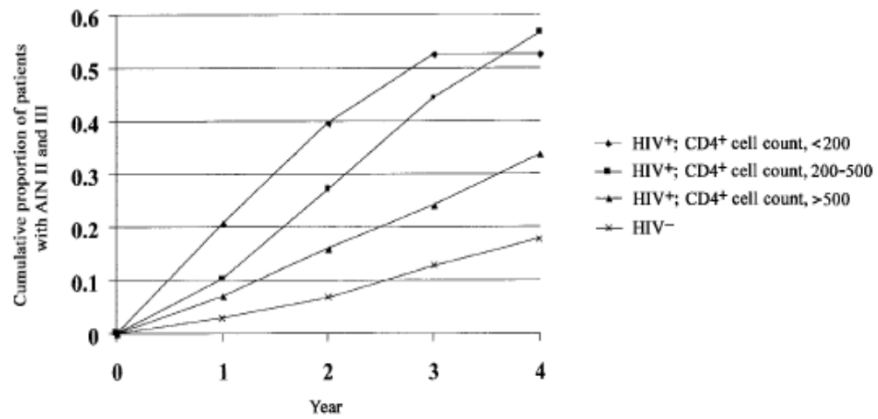
Nature Reviews Cancer 7, 11-22 (January 2007)

Risk Factors for HPV Persistence

- HIV or other immunosuppression
 - Infection with multiple subtypes
 - Infection with subtypes 16,18 (high risk)
 - Age >30
 - Smoking
-
- 80% of HPV infections are successfully cleared.
Mean duration 8 months

NEJM (1998) 338:423-8.



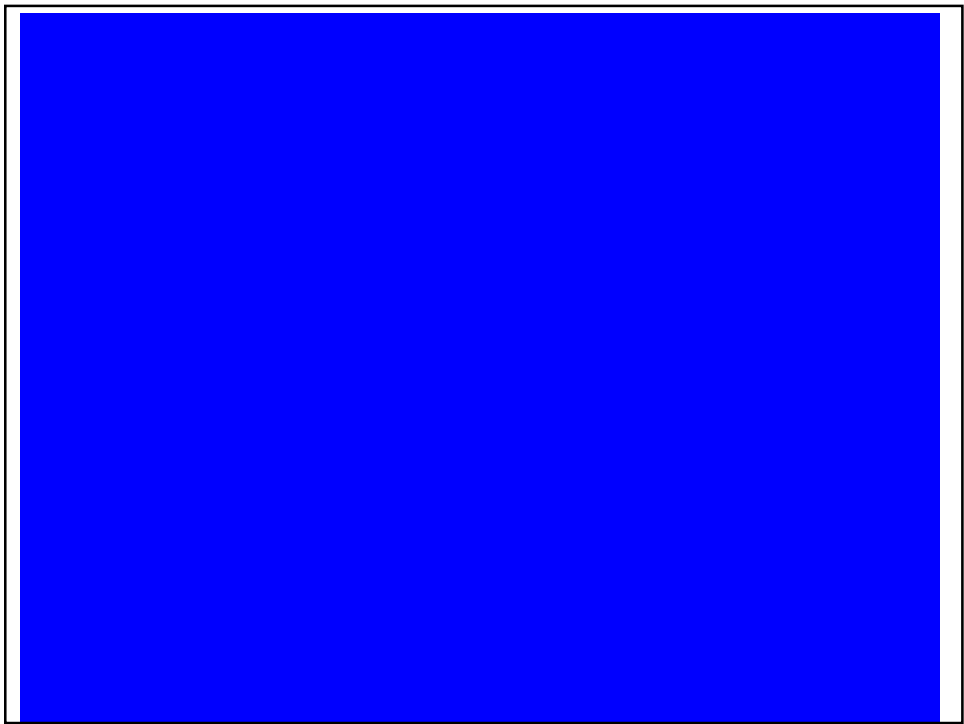
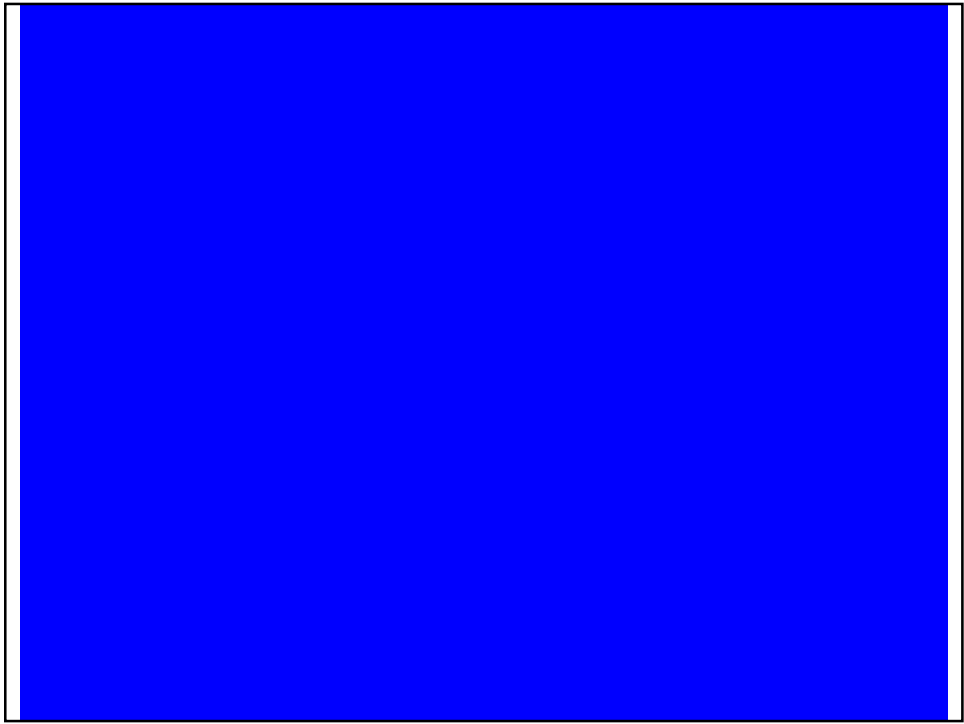


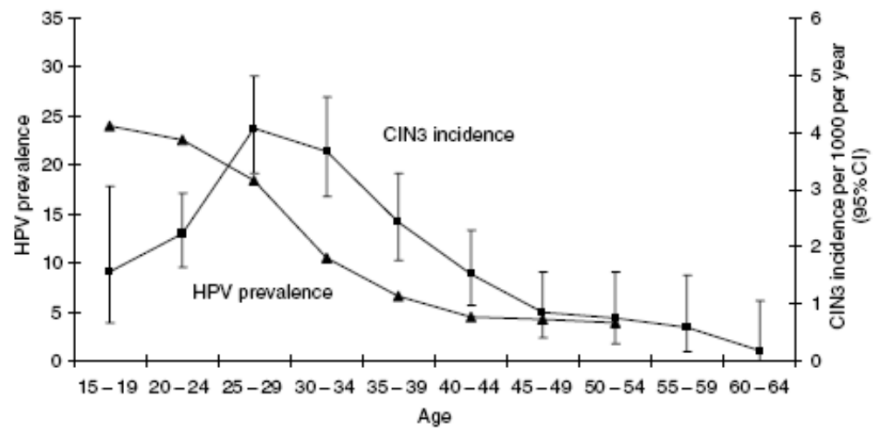
Incidence of AIN 2,3 in HIV (+) MSM

CID (2002) 35:1127-1134

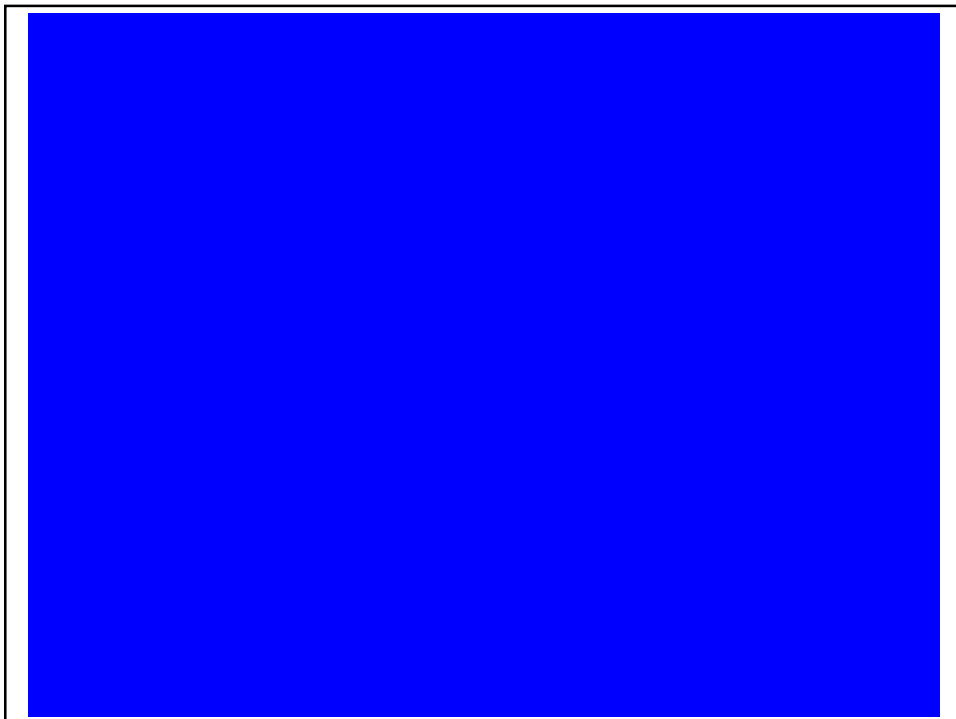








Br J Cancer (2004)91(5):942-953.



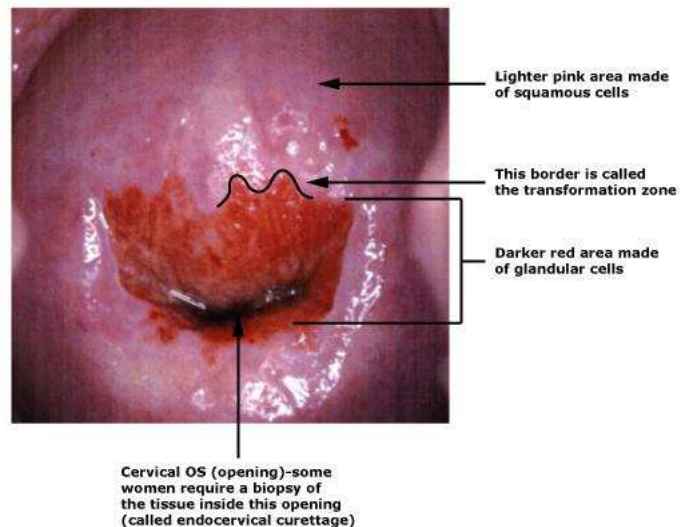
Incidences of Anal and Cervical Cancer

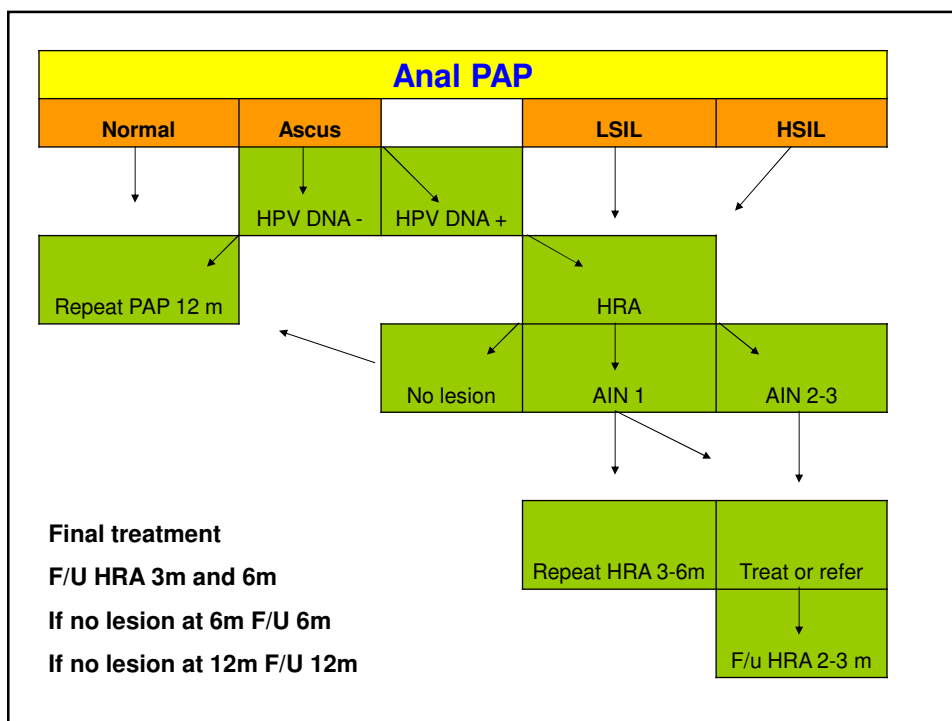
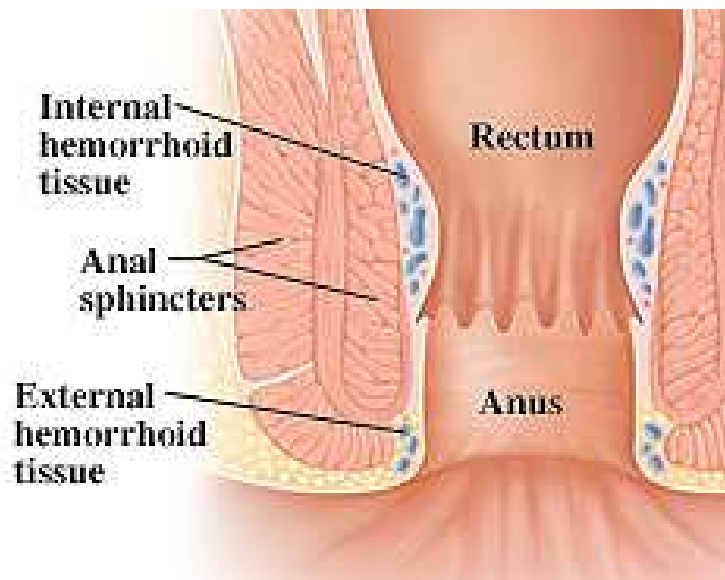
- Cervical Cancer prior to PAP smears
50/100,000
- Cervical Cancer, now
8/100,000
- Anal Cancer in the general population
0.8/100,000
- Anal Cancer among HIV (-) MSM
5-35/100,000
- Anal Cancer among HIV (+) Women
30/100,000
- Anal Cancer among HIV (+) MSM (HAART era)
131/100,000



Cervical PAP screening

- Baseline GYN exam with PAP smear for all HIV positive women.
- Repeat PAP in 6 months, and every 12 months thereafter if normal.
- If PAP is abnormal, repeat every 6 months until two sequential PAP smears are normal.
- PAP every six months if CD4 <200.
- Refer ASCUS and all higher grade cytology to GYN for colposcopy.
- After colposcopy:
 - CIN1: PAP every 4-6 months
 - CIN2-3: Refer to GYN for Ablation (LEEP, conization)
Then PAP q3-4m for 1yr.





HIVMA Primary Care Guidelines

Aberg, JA, et al. *Clin Infect Dis*, 2014;**58** e1-53.

Anal cytology for:

- HIV infected MSM.
- HIV-infected women with a history of receptive anal sex or abnormal cervical PAP smear.
- HIV-infected persons with ano-genital warts.
- Abnormal results should prompt HRA.

Weak recommendation, Moderate quality evidence.

ANCHOR Study Top Line Results

- Randomized trial to establish efficacy of destruction of HGAIN to prevent anal cancer
- 4446 patients enrolled in >10 sites in US and Puerto Rico. HIV pos men and women with biopsy-proven HGAIN. Broad gender and ethnic/racial diversity
- Randomized to treatment (93% had HYF although other treatments were permitted) vs observation
- Treatment associated with 57% reduced risk of anal cancer. P 0.029

Notable details

- 52% of patients had HGAIN at screening visit. This is high.
- Protocol initially did not permit prior treatment for HGAIN, but this was modified to increase enrollment.
- Thus, the study population was not only HIV pos and HGAIN, but also enriched for patients who had failed prior treatment for HGAIN.
- Cancer rates were much higher than historical controls:
 - Treatment 173/100,000 vs Observation 442/100,000
 - Compare this with cancer incident rate of 120/100,000 in HIV pos MSM
 - 4x excess cancer risk.
- Treatment effect was 57% risk reduction. Compare this with 10-fold risk reduction for cervical cancer in average risk women .

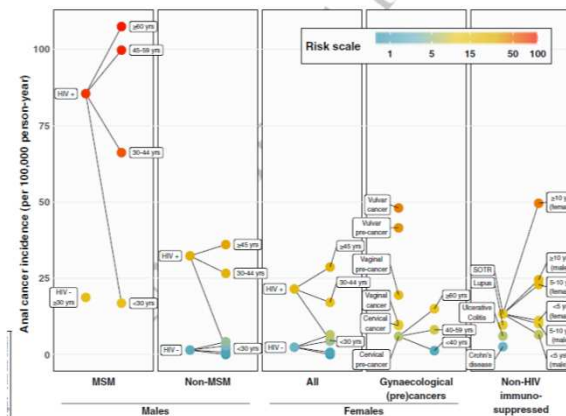


FIGURE 5 Anal cancer risk scale. 95% CIs around the point estimates can be found in the relevant Figures 1-4 and Tables S1 and S2. Estimates for HIV-negative men and men are shown, without labels, for age-groups <30, 30 to 44, 45 to 59, and ≥ 60 years (see Section 3). CI, confidence interval; MSM, men who have sex with men; MSW, men who have sex with women; yrs, years old; yst, years since transplant

Who should be screened with Anal Cytology?

- All HIV (+) MSM, annually.
- All HIV (+) patients with anogenital condylomata.
- All HIV (+) women with abnormal cervical or vulvar cytology.
- ? All HIV (+) women
- ? All HIV (-) MSM, if neg repeat every 2-3 years.
- ? All men and women with transplant associated immunosuppression

Cervical HPV and HSIL predicts anal HPV in HIV neg and HIV pos women

• Anal HPV-16 prevalence HIV NEG	41% 2%	Cervical HPV-16 + Cervical HPV-16 -
• Anal HPV-16 prevalence HIV POS	46% 11%	Cervical HPV-16 + Cervical HPV-16 -
• Anal HSIL HIV NEG	24% 2%	Cervical HPV-16 + Cervical HPV-16 -
• Anal HSIL HIV POS	17% 8%	Cervical HPV-16 + Cervical HPV-16 -
• Anal HPV-16 prevalence HIV NEG	44%	Cervical CA

Lancet ID 2019; 19:880-91

13,427 women with paired anal and cervical HPV DNA and cytology

Anal Cytology



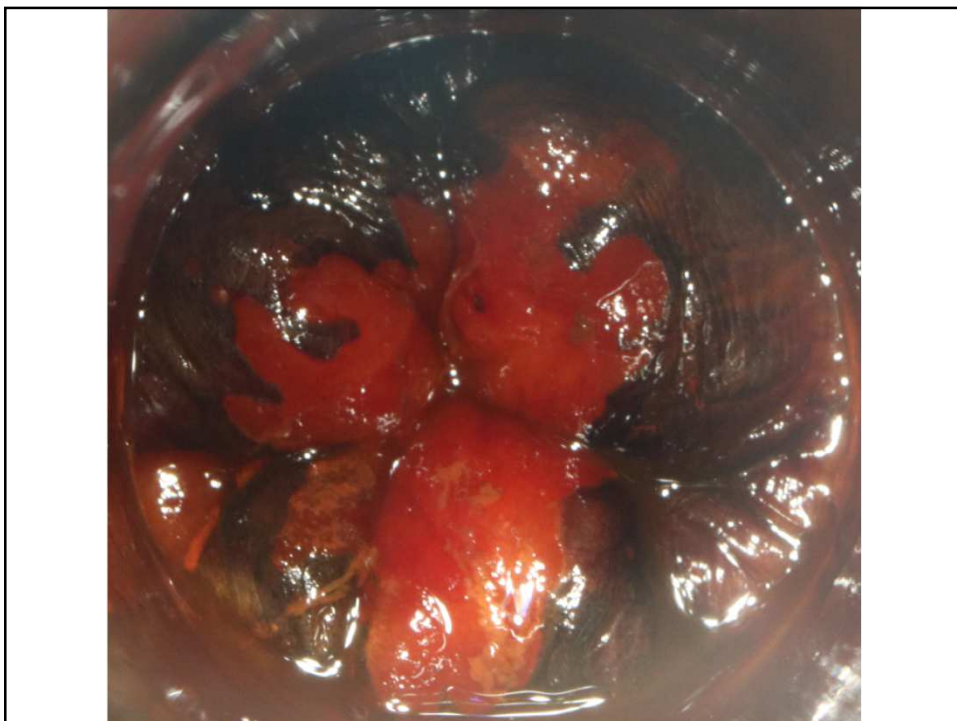
- Dacron swab moistened with tap water.
- Insert into anal canal until resistance is not met (2 cm).
- Rotate and apply pressure to walls of anal canal while slowly withdrawing.
- Liquid-based cytology or direct smear.

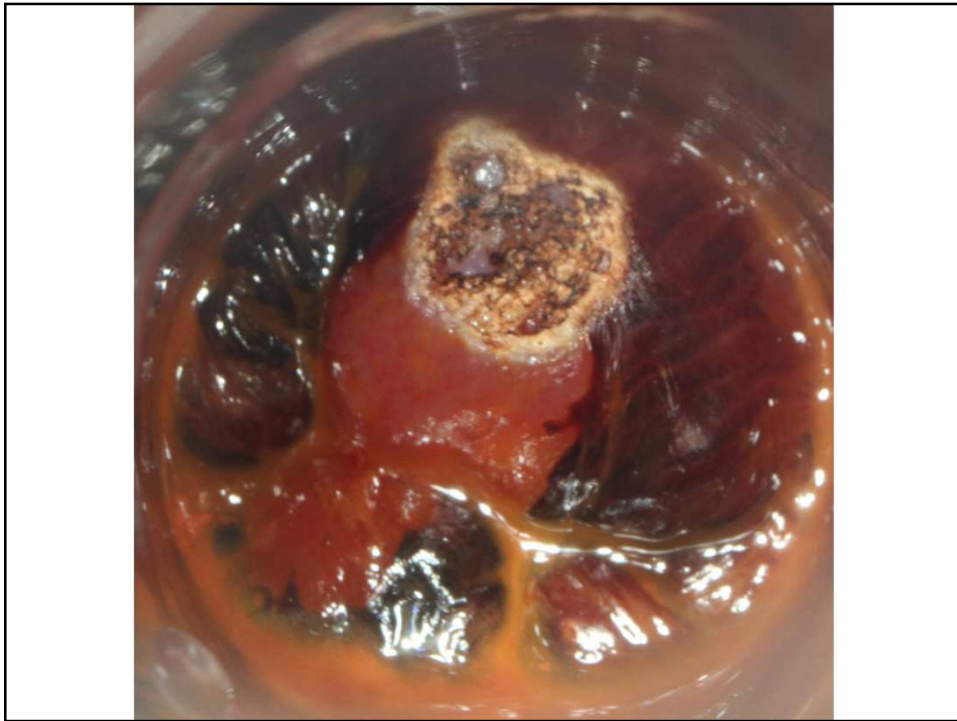
High Resolution Anoscopy

- Analogous to cervical colposcopy
- Application of 5% acetic acid turns dysplastic mucosa white
- Biopsy establishes degree of dysplasia
- Low-grade lesions (AIN1) may be ablated or followed.
- High-grade lesions (AIN2-3) may be ablated or referred for surgical excision.



01/09/2007 16:02 Fenway Community Health





Your patient complains of several weeks of anal pain and bleeding and has this on exam

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A reasonable next step would be:

1. Anal PAP smear
2. Liquid nitrogen cryotherapy every two weeks until resolution
3. Topical Imiquimod 3 times a week
4. Metameucil for prolapsed hemorrhoid
5. Referral for biopsy
6. CT scan of the abdomen and pelvis

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Warning Signs for Anal Cancer

- Pain
- Bleeding
- Abnormal DRE: thickening, induration, or mass
- Extensive lesions
- Ulceration
- Friability

Risk Factors for Anal Cancer

- Low CD4 nadir
- AIDS-defining event
- Tobacco use
- History of GC
- Age >50

Risk Factors for Anal Cancer

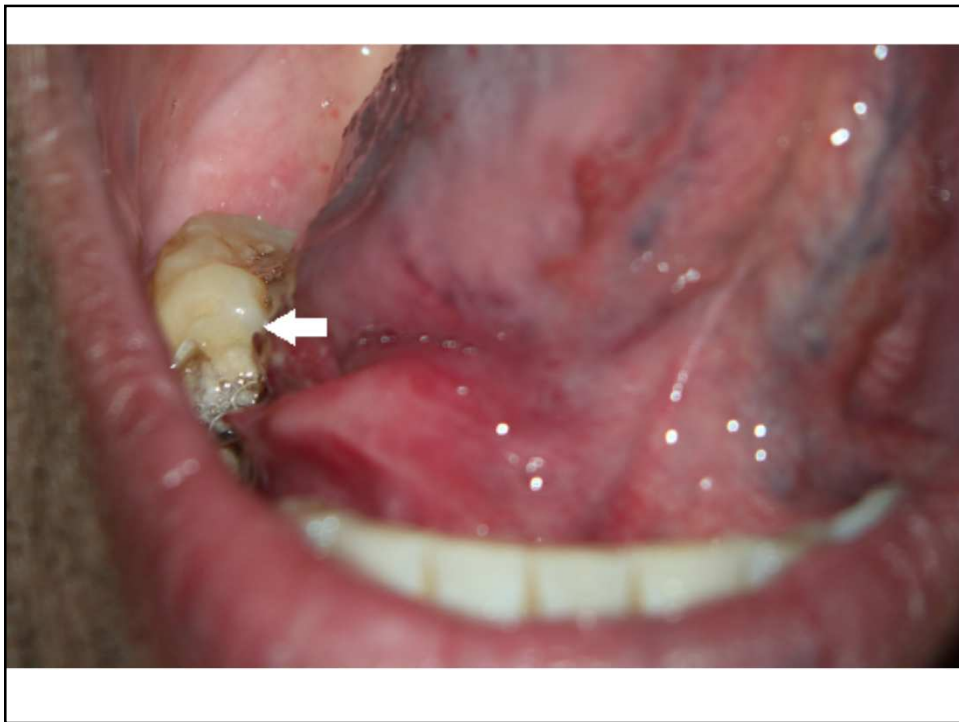
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Not Associated with Anal Cancer

- Current CD4 count
- HAART





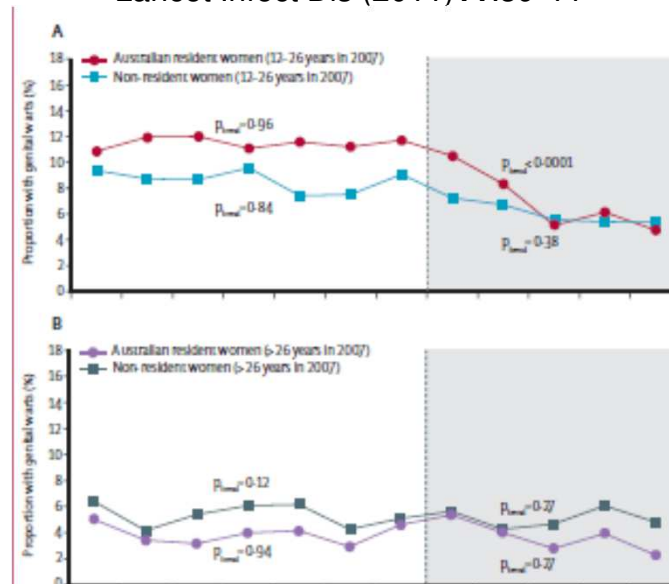


HPV Vaccine

- HPV L1 Protein
- Bivalent vaccine 16,18
- Quadrivalent vaccine (Gardasil) 6,11,16,18
- Gardasil-9, includes 31, 33, 45, 52, 58 (20% of cervical cancers)
- No observable protection against non-vaccine HPV types (still need PAP).
- No observable protection against strains acquired before vaccination
- Uncertain protection against oral or penile disease.
- Well tolerated with no SAE's yet reported.

HPV Vaccine Efficacy in Australia

Lancet Infect Dis (2011)11:39-44



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Lancet Infect Dis (2011)11:39-44

