Screening for Anal Cancer and Precursors in HIV Patients

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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
Learning Objectives

• Review current HPV vaccination guidelines for HIV-infected adults
• Review guidelines related to screening for anal cancer and its precursors in HIV-infected patients
• Review the evidence base to support screening
• Describe screening options and procedures as related to screening goals and screening procedure expertise
Polling question 1

• Which groups of HIV-infected patients should be routinely offered HPV vaccination? (select the one best answer)
  – All HIV-infected adults who have not yet been vaccinated
  – All HIV-infected males and females ≤ 21 years of age
  – All HIV-infected males and females ≤ 26 years of age
  – The HPV vaccines are unlikely to be immunogenic and shouldn’t be given to HIV-infected patients
  – The HPV vaccines are live attenuated vaccines and shouldn’t be administered to HIV-infected patients
Polling question 2

According to 2016 CDC guidelines, how many HPV vaccinations are recommended to complete the series for HIV-infected patients?

- 1
- 2
- 3
HPV VACCINATION UPDATE
HPV Vaccination Recommendations: 2016 update

HPV Vaccination Recommendations for HIV-infected Persons

Preventing First Episode of HPV Infection

Indications for HPV Vaccination:
• HIV-infected; aged 9–26 years (BIII)

Note: Please refer to Pediatric OI guidelines for vaccination of boys and girls younger than age 13.

Vaccination Schedules

For Women:
• HPV recombinant vaccine 9 valent (Types 6, 11, 16, 18, 31, 33, 45, 52, 58) 0.5 mL IM at 0, 1–2, and 6 months (BIII), or
• HPV recombinant vaccine quadrivalent (Types 6, 11, 16, 18) 0.5 mL IM at 0, 1–2, and 6 months (BIII), or
• HPV recombinant vaccine bivalent (Types 16, 18) 0.5 mL IM at 0, 1–2, and 6 months (BIII)

For Men:
• HPV recombinant vaccine 9 valent (Types 6, 11, 16, 18, 31, 33, 45, 52, 58) 0.5 mL IM at 0, 1–2, and 6 months (BIII), or
• HPV recombinant vaccine quadrivalent (Types 6, 11, 16, 18) 0.5 mL IM at 0, 1–2, and 6 months (BIII)

ANAL CANCER SCREENING GUIDELINES
Polling question 3

- Which of the following categories of HIV-infected patients do you routinely screen with anal cytology (Pap) smears? (select all that apply)
  - MSM
  - Non-MSM males
  - Women with cervical dysplasia
  - Women without cervical dysplasia
  - All patients with history of genital warts
  - I don’t currently screen anyone
Polling question 4

• Which of the following procedures are recommended by experts as components of initial screening for anal cancer and its precursors in HIV-infected patients? (select all that apply)
  – Digital anorectal examination
  – Anal cytology
  – Anal HPV typing
  – High resolution anoscopy
HIVMA/IDSA HIV Primary Care Guidelines (2014)

• Screening for Anal Human Papillomavirus

• Recommendation

• 42. HIV-infected men and women with human papillomavirus (HPV) infection are at increased risk for anal dysplasia and cancer.
  – MSM
  – women with a history of receptive anal intercourse or abnormal cervical Pap test results, and
  – all HIV-infected persons with genital warts should have anal Pap tests
    • (weak recommendation, moderate quality evidence).

USPHS Recommendations on Anal Cancer Screening in HIV-infected Persons (2016)

• At this time, no national recommendations exist for routine screening for anal cancer.
• However, some specialists recommend anal cytologic screening or high resolution anoscopy for HIV-seropositive men and women (CIII).
• An annual digital anal examination may be useful to detect masses on palpation that could be anal cancer (BIII).
• Screening for anal cancer with anal cytology should not be done without the availability of referral for high resolution anoscopy.
• If anal cytology is performed and indicates ASC-US, ASC cannot rule out ASC-H, LSIL, or high-grade squamous intraepithelial lesion (HSIL), then it should be followed by high-resolution anoscopy (BIII).

EVIDENCE TO SUPPORT SCREENING
Evidence-based screening: What kind of evidence is needed?

- How important is the health condition to be sought in terms of frequency, morbidity, and mortality?
- How good is the screening test in terms of accuracy, safety, simplicity, acceptability (to patients and providers), labeling effects, and financial costs?
- 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)

Incidence of anal cancer according to sex, HIV transmission group, and calendar period.

Piketty C et al. JCO 2012;30:4360-4366

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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 ⇒ Cervical CA
  - Anal HSIL suspected ⇒ Anal CA

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 (1)
  – Present in 78% of invasive anal CA (2)

(1) Bosch et al, JNCI, 1995
Table 3: Estimated average annual percentage and estimated number of cancer attributable to HPV, by anatomic site and sex--United States, 2008-2012

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Average annual no.</th>
<th>Attributable to any HPV type</th>
<th>Attributable to HPV 16/18</th>
<th>Attributable to HPV 16/18/31/33/45/52/58</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. (%)</td>
<td>No. (%)</td>
<td>No. (%)</td>
<td>No. (%)</td>
</tr>
<tr>
<td>Cervical cancer</td>
<td>11,771</td>
<td>10,700 (90.6)</td>
<td>7,800 (66.2)</td>
<td>9,500 (80.9)</td>
</tr>
<tr>
<td>All anal cancers</td>
<td>5,010</td>
<td>4,600 (91.1)</td>
<td>4,000 (79.4)</td>
<td>4,400 (87.6)</td>
</tr>
<tr>
<td>Female</td>
<td>3,260</td>
<td>3,000 (92.5)</td>
<td>2,600 (79.5)</td>
<td>2,900 (90.3)</td>
</tr>
<tr>
<td>Male</td>
<td>1,750</td>
<td>1,600 (88.7)</td>
<td>1,400 (79.1)</td>
<td>1,500 (82.9)</td>
</tr>
</tbody>
</table>

High Risk HPV in HIV-infected Women

Anal and Cervical HR-HPV infection

<table>
<thead>
<tr>
<th>Anal HR-HPV</th>
<th>Cervical HR-HPV</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>-</td>
<td>-</td>
<td>132</td>
<td>42.4</td>
</tr>
<tr>
<td>+</td>
<td>-</td>
<td>97</td>
<td>31.2</td>
</tr>
<tr>
<td>-</td>
<td>+</td>
<td>31</td>
<td>10.0</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>51</td>
<td>16.4</td>
</tr>
</tbody>
</table>

Heard et al, IANS Scientific Meeting, San Francisco, 2016
High Rates of Anal High-Grade Squamous Intraepithelial Lesions in HIV-Infected Women Who Do Not Meet Screening Guidelines.

Table 5. Proportion of High-Grade Squamous Intraepithelial Lesion Diagnoses Meeting Screening Guidelines

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Met Screening Guidelines</th>
<th>Did Not Meet Screening Guidelines</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NYSDOH(^a)</td>
<td>44 (24)</td>
<td>5 (21)</td>
<td>.7</td>
</tr>
<tr>
<td>IDSA(^b)</td>
<td>48 (24)</td>
<td>1 (10)</td>
<td>.3</td>
</tr>
</tbody>
</table>

Abbreviations: HSIL, high-grade squamous intraepithelial lesion; IDSA, Infectious Diseases Society of America; NYSDOH, New York State Department of Health.

\(^a\)One hundred eighty-four subjects met New York State AIDS Institute screening guidelines, 24 did not.

\(^b\)One hundred ninety-eight subjects met Infectious Diseases Society of America screening guidelines, 10 did not.

SCREENING OPTIONS AND PROCEDURES
Bethesda Staging System (2014) & LAST Project Terminology

• 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
## Figure 1. Schematic Representation of SIL

<table>
<thead>
<tr>
<th></th>
<th>Low-grade squamous intraepithelial lesion (LSIL)</th>
<th>High-grade squamous intraepithelial lesion (HSIL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Condyloma</td>
<td>CIN/AIN grade 2</td>
</tr>
<tr>
<td>Normal</td>
<td>Very mild to mild dysplasia</td>
<td>Moderate dysplasia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Severe dysplasia / In situ carcinoma</td>
</tr>
</tbody>
</table>

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, FACP
How accurate is anal cytology compared to cervical cytology?

<table>
<thead>
<tr>
<th>Cytology Cut-Point</th>
<th>Sensitivity (SE)</th>
<th>Specificity (SP)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Anal</td>
<td>Cervical</td>
</tr>
<tr>
<td></td>
<td>SE (95% CI)</td>
<td>SE (95% CI)</td>
</tr>
<tr>
<td>(HSIL or ASC-H) vs. (LSIL, ASCUS, Normal)¹</td>
<td>0.30 (0.19-0.44)</td>
<td>0.63 (0.56-0.69)</td>
</tr>
<tr>
<td>(HSIL or ASC-H, LSIL) vs. (ASCUS, Normal)²</td>
<td>0.73 (0.62-0.82)</td>
<td>0.80 (0.75-0.85)</td>
</tr>
<tr>
<td>(HSIL or ASC-H, LSIL, ASCUS) vs. (Normal)³</td>
<td>0.90 (0.76-0.96)</td>
<td>0.91 (0.88-0.94)</td>
</tr>
</tbody>
</table>

Is there a role for anal HPV testing in HIV-infected MSM?

<table>
<thead>
<tr>
<th>Assay for any carcinogenic HPV type</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Roche Linear Array</td>
<td>98.4</td>
<td>28.9</td>
<td>23.9</td>
<td>98.8</td>
</tr>
<tr>
<td>Cobas Assay</td>
<td>100.0</td>
<td>26.0</td>
<td>24.1</td>
<td>100.0</td>
</tr>
</tbody>
</table>

Adapted from: Wentzensen et al. J Clin Microbiology 2014 52(8):2892-2897
Estimates of HSIL→IAC Progression from a Baseline Cytology Inception Cohort (n=23 IAC cases dx >180d after baseline cytology)

<table>
<thead>
<tr>
<th>Time in years</th>
<th>Nº patients</th>
<th>Percent developing IAC from baseline at risk [percentage, (95% Confidence interval)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; HSIL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>2182</td>
<td>0.09 (0.02 - 0.36)</td>
</tr>
<tr>
<td>2</td>
<td>1827</td>
<td>0.14 (0.05 - 0.45)</td>
</tr>
<tr>
<td>3</td>
<td>1516</td>
<td>0.33 (0.15 - 0.73)</td>
</tr>
<tr>
<td>4</td>
<td>1223</td>
<td>0.47 (0.23 - 0.95)</td>
</tr>
<tr>
<td>5</td>
<td>983</td>
<td>0.47 (0.23 - 0.95)</td>
</tr>
<tr>
<td>HSIL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>320</td>
<td>0.30 (0.04 - 2.13)</td>
</tr>
<tr>
<td>2</td>
<td>266</td>
<td>0.65 (0.16 - 2.60)</td>
</tr>
<tr>
<td>3</td>
<td>217</td>
<td>1.03 (0.33 - 3.17)</td>
</tr>
<tr>
<td>4</td>
<td>176</td>
<td>1.03 (0.33 - 3.17)</td>
</tr>
<tr>
<td>5</td>
<td>141</td>
<td>1.65 (0.59 - 4.52)</td>
</tr>
</tbody>
</table>

Sensitivity analysis including 10 cases diagnosed d30-d180: HSIL 5-yr incidence 3.24% (95% CI: 1.70 – 6.12)

Does treatment of HSIL favorably alter the natural history of AIN?

- ANCHOR study in progress:
  - Anal Cancer HSIL Outcomes Research
    - https://anchorstudy.org/

- Observational studies:
  - SPANC study: Study of the Prevention of Anal Cancer
    - http://www.nchecrsurveys.unsw.edu.au/spanc/
  - UCSD Owen Clinic AIN Cohort studies
3-State Model of Progression to IAC: Unadjusted Summary Estimates at 2 years

Estimates are 2-year transition unadjusted probabilities from multistate transition models
Range of estimates are based on assumptions regarding sensitivity and specificity of anal cytology
### Estimated Unadjusted Hazard Ratios (95% CI) of Time-Updated Covariate Effects on State Transitions

<table>
<thead>
<tr>
<th>Covariate</th>
<th>IAC exclusion window</th>
<th>Cytology SE/SP</th>
<th>&lt;HSIL to HSIL</th>
<th>HSIL to &lt;HSIL</th>
<th>HSIL to IAC</th>
</tr>
</thead>
<tbody>
<tr>
<td>IRC [reference: no IRC]</td>
<td>&lt;180 days</td>
<td>0.6/0.90</td>
<td>2.2 (0.6–7.9)</td>
<td>4.2 (2.0–8.5)</td>
<td>2.7 (0.6–11.7)</td>
</tr>
<tr>
<td>ART [reference: no ART]</td>
<td>&lt;180 days</td>
<td>0.6/0.90</td>
<td><strong>0.4 (0.2–0.6)</strong></td>
<td>0.9 (0.4–2.1)</td>
<td>2.2 (0.5–9.4)</td>
</tr>
<tr>
<td>HIV Viral load [reference: &lt;400 copies/mm3]</td>
<td>&lt;180 days</td>
<td>0.6/0.90</td>
<td><strong>0.3 (0.2–0.5)</strong></td>
<td>1.3 (0.7–2.3)</td>
<td>1.6 (0.7–3.9)</td>
</tr>
<tr>
<td>CD4 Category [reference: &lt;350/mm3]</td>
<td>&lt;180 days</td>
<td>0.6/0.90</td>
<td><strong>0.3 (0.2–0.5)</strong></td>
<td>0.8 (0.5–1.3)</td>
<td>1.4 (0.6–3.3)</td>
</tr>
</tbody>
</table>

Polling question 5

- Who should be referred for high resolution anoscopy (if available)? (select the one best answer)
  - Only those with HSIL anal cytology or palpable abnormalities
  - All those with any anal cytological (≥ ASCUS) or palpable abnormalities
  - All those with anal LSIL, HSIL, ASC-H or palpable abnormalities
  - Because cytology is so unreliable, all HIV-infected patients should be referred for HRA
Anal Cancer Screening

Anal Cytology + DARE if clinically suspicious

- Negative
  - Repeat in 12 months in HIV+
  - Repeat in 2-3 years in HIV-

- ASC-US or ASC-H

- LSIL
  - HRA with biopsy

- HSIL
  - EUA with biopsy

- Carcinoma
  - either/or

- Benign or no lesion seen
  - Repeat HRA for HSIL
  - Repeat HRA in ~6 months for ASC or LSIL on Pap

- Low-grade AIN
  - Follow or treat if symptomatic

- High-grade AIN
  - Treat

- Carcinoma
  - CMT

Darragh et al. The Anal Canal and Perianus: HPV-Related Disease
Anatomy of the Anal Canal

Darragh et al. The Anal Canal and Perianus: HPV-Related Disease
Obtaining Anal Cytology

Nothing inserted p.r. for at least 24 h

Obtain cytology before digital anorectal exam (DARE)

Dacron swab moistened in tap water

Insert until tip hits rectal wall (about 5-7 cm)

Slowly twirl swab 360° as you gradually withdraw it

Sample time: 10 – 20 seconds

Process swab using slide fixation or liquid media

Then perform DARE

FIGURE 17.19. Anal cytology collection.
New Category I CPT Codes for HRA (2015)

- **SURVEY CODES**
- **466X1** Anoscopy; *diagnostic*, with high-resolution magnification (HRA) (eg, colposcope, operating microscope) and chemical agent enhancement including collection of specimen(s) by brushing or washing, when performed
- **466X7** Anoscopy; with high-resolution magnification (HRA) (eg, colposcope, operating microscope) and chemical agent enhancement, *with biopsy*, single or multiple
Conclusion & Recommendations for Screening Strategies

• **Goal: Early Diagnosis** IAC in HIV infected patients
  – Annual digital anorectal exam (DARE) ± anal cytology to identify higher risk patients (minimalist approach)
  – Annual DARE + anal cytology + HRA directed biopsy to identify microinvasive disease (maximalist)

• **Goal: Prevention of IAC** in HIV infected patients
  – Annual DARE + anal cytology + HRA directed biopsy + Rx of HGAIN (uncertain efficacy)
Useful Online Resources

4. MCWCRS. Self Anal Pap. 2011; 2:46 minutes. Available at: https://www.youtube.com/watch?v=ytOTNi8yVOC.