HPV and HIV: a terrible tango

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Outline

- Epidemiology of AIN and anal cancer
- Role of primary care provider in screening for anal dysplasia
- Management of anal dysplasia
- Prevention approaches

Disclosures

- Merck and Co- study investigator, research grant and travel support, advisory boards
- Aura Biosciences- advisory board
- Pharmajet- advisory board
- Hologic- research grant support

HPV infection and productive life cycle

Virus introduced through mucosal wound

Infects squamous cell

Gene products

HPV genome

L1, L2, 14, 15, 16, & 18

Early HPV protein

P1, P2, P3, P4, P5, & P7

HPV infection and productive life cycle

Spectrum of HPV disease

Morphologic Continuum

Low-grade disease
- Condyloma
- CIN/AIN grade 1
- Moderate dysplasia

High-grade disease
- CIN/AIN grade 2
- Severe dysplasia
- In situ carcinoma

Natural history of cervical and anal neoplasia

- Initial HPV infection
- Continuing infection
- CIN/AIN 1
- Median duration 1-2 years
- Potential cofactors for progression:
  - HPV-related type, variants, viral load
  - Parity, oral contraceptive use
  - Smoking
  - Chlamydia, HSV-2 coinfection
  - Diet (vitamins A, C, E, carotenoids, folic acid, etc.)
  - Immunogenetics (HLA type)
  - Chronic inflammation
  - Host factors: immune response

Invasive cervical/anal cancer

Cleared HPV infection


Rectal mucosa
- Columns of Morgagni
- Dentate (pectinate) line
- Skin
- Squamous mucosa
- Levator ani muscle
- Subcutaneous and deep muscles

Anal anatomy

Anal cancer in the U.S.-2012

Women: 3,980 new cases and 480 deaths
Men: 2,250 new cases and 300 deaths

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

<table>
<thead>
<tr>
<th>HPV-associated cancer</th>
<th>Relative risk (95% confidence interval) [vs. at observed cancer]</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>1.00 (0.85-1.17)</td>
</tr>
<tr>
<td>Lower genitourinary</td>
<td>1.10 (0.88-1.37)</td>
</tr>
<tr>
<td>Rectal cancer</td>
<td>1.00 (0.76-1.30)</td>
</tr>
<tr>
<td>Upper gastrointestinal</td>
<td>1.00 (0.81-1.22)</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>1.00 (0.82-1.21)</td>
</tr>
</tbody>
</table>

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

Recent reports of incidence in anal cancer since introduction of HAART

- 78/100,000 person-years among HIV+ MSM since 1999
- 78/100,000 person-years among HIV+ MSM since 2000
- 137/100,000 person-years among HIV+ MSM since 1996

Which of the following is true of the epidemiology of anal cancer?

1. Anal cancer is more common among men than women in the general population in the US.
2. The incidence of anal cancer is increasing among both men and women in the general population in the US.
3. Anal cancer is rarely associated with human papillomavirus infection.
4. Among HIV-seropositive men and women, anal cancer almost always develops in those with CD4 levels below 200/mm³ at the time of diagnosis.

Prevalence of anal HPV among MSM
Population-based data


Anal HPV infection by age group in sexually active HIV-negative MSM

Anal and cervical HPV infection in HIV-positive women and HIV-negative women at high risk of HIV infection


Which of the following is true of anal HPV infection?

1. It is found in fewer than half of sexually active HIV-seronegative men who have sex with men (MSM)
2. The prevalence of anal HPV infection declines substantially among HIV-seronegative MSM after the age of 30 years
3. Almost all women with anal HPV infection report a history of receptive anal intercourse
4. It is found more commonly than cervical HPV infection among HIV-seropositive women

Prevalence of AIN among MSM

Population-based data

Prevalence, %


AIN in HIV-positive and HIV-negative women in the Women’s Interagency HIV Study

AIN in women with CIN/VIN/VAIN

- Of 205 patients with CIN/VIN/VAIN, 12.2% (95% CI 8-17%) had AIN
- 8% with AIN 2 or 3


AIN 2/3 is the precursor to anal cancer

- Roozen RR et al. CA. 1977; 27:160-6

Progression of AIN 2/3 to invasive cancer

Superficially invasive anal cancer arising from AIN 2/3
Which of the following should prompt a high degree of suspicion for anal cancer?

1. Bleeding with hard bowel movement
2. A painless ulcer with smooth edges
3. Painful ulcers with adjacent vesicles
4. Painful ulcer with adjacent coarse punctation or atypical blood vessels
5. None of the above

Role of primary care provider in screening

- Anal cancer screening
  - Digital anorectal exam (DARE)

Anal cytology screening for AIN

- AIN screening if infrastructure present
  - Perform anal cytology
    - Moistened Dacron swab as far as it will go
    - Liquid cytology
  - Triage for HRA using severity of disease
    - HSIL/ASC-H>LSIL>ASCUS
Who should be screened?

- All HIV-positive men regardless of sexual orientation over the age of 30 years
- All HIV-negative MSM over the age of 40 years
- Women with high-grade cervical or vulvar lesions or cancer
- All HIV+ women
- All men and women with perianal condyloma
- Solid organ transplant recipients

Treatment of HGAIN

- Prevention of anal cancer
- Relief of symptoms

Which of the following is true about anal cytology?

1. It is graded differently from cervical cytology
2. A normal anal cytology usually means that no AIN will be found on high resolution anoscopy among HIV-seropositive MSM
3. A high-grade anal cytology usually indicates the presence of a true high-grade lesion on biopsy among HIV-seropositive MSM
4. Liquid-based cytology methods cannot be used for anal samples

In a population of HIV-seropositive MSM doing well on ART, which of the following is true?

1. All such men should have routine high resolution anoscopy
2. Anal HPV testing should be performed routinely among all HIV-seropositive MSM over the age of 30 to determine the risk of high-grade AIN
3. HPV serology may be useful to determine the risk of AIN
4. Patients undergoing anal cytology testing should be told that no special measure such as douching should be done prior to the sample collection
Anal Neoplasia Clinic

- First visit
  - HRA will be performed
  - Biopsies of visible lesions will be done
  - Treatment plan put together based on results
- Second visit
  - Treatment initiated

Anal Neoplasia Clinic

- Follow-up visits
  - Depend on number, volume and severity of any remaining disease
  - Goal is to have patient on annual or semi-annual cytology screening

Treatment of AIN 2/3

- Challenging due to multifocal nature, size of lesions
- Multiple procedures often needed
- High recurrence rate and incidence of new lesions
- No evidence yet that treatment of HGAIN reduces the incidence of anal cancer
- Therapy is ablative
  - infra-red coagulation
  - 85% trichloroacetic acid

Choice of treatment

- Location internal or external
- Size of the lesion or volume of disease
- Type of lesion: AIN 1 or AIN 2-3
- Patient preference and tolerance
85% trichloroacetic acid

- Greater clearance in younger age 41-48 vs >49 (OR 8.4, 95%CI: 1.1-94, P=0.04)
- Among HIV+, greater clearance if 2 or fewer lesions (OR 14.3, 95%CI: 1.5-662, P=0.01)
- 32% of patients with AIN 2-3 cleared to no lesions
- 73% of AIN 1 and 71% AIN 2-3 cleared to no lesions or AIN 1 respectively


Treatment with infrared coagulation

- Well tolerated with substantially less pain compared with surgical treatment, minor bleeding for a few days to weeks, very low incidence of significant problems

IRC 2/00™ Infrared Coagulator
Redfield Corporation
Rochelle Park, NJ

IRC and electrocautery ablation in HIV+ MSM

<table>
<thead>
<tr>
<th></th>
<th>Infra-red coagulation</th>
<th>Electrocautery</th>
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<tbody>
<tr>
<td>Number of patients</td>
<td>68</td>
<td>132</td>
</tr>
<tr>
<td>Number of lesions treated</td>
<td>165</td>
<td>375</td>
</tr>
<tr>
<td>% lesions gone after 1 treatment</td>
<td>72%</td>
<td>75%</td>
</tr>
<tr>
<td>% with metachronous lesions</td>
<td>59%</td>
<td>49%</td>
</tr>
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*No statistically significant differences

5-fluorouracil 5% cream

- To treat HGAIN
- To debulk disease
- Protect normal skin with zinc oxide
- Use for 4 cycles (2 months)
When we refer patients to the surgeon

- Complications of diagnosis or therapy that can’t be managed in the office
- Exam under anesthesia for lesions that cannot be adequately biopsied in the office to exclude cancer
- Lesions too large to be treated in the office

Primary prevention of anal HPV infection and anal cancer

HPV Vaccine against Anal HPV Infection and Anal Intraepithelial Neoplasia

HPV vaccination of boys and men

- Approved for routine use to prevent genital warts, AIN and anal cancer in boys and men aged 9-21 years
- Permissive use 22-26 years unless immunocompromised or HIV-positive (routine to 26 years)
- Prevention of AIN and anal cancer in women

Vaccination of HIV-positive men and women

- Safety-PACTG, ACTG, AMC studies
- Immunogenicity
- Effectiveness
Geometric mean titers among participants naïve to HPV 6, 11, 16, 18

<table>
<thead>
<tr>
<th></th>
<th>HPV 6</th>
<th>HPV 11</th>
<th>HPV 16</th>
<th>HPV 18</th>
</tr>
</thead>
<tbody>
<tr>
<td>Month 7</td>
<td>674</td>
<td>652</td>
<td>2822</td>
<td>439</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(447, 903)</td>
<td>(621, 884)</td>
<td>(2485, 2767)</td>
<td>(416, 464)</td>
</tr>
</tbody>
</table>

Percentage of participants sero- and HPV DNA-negative to HPV 6/11/16/18

<table>
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<tr>
<th></th>
<th>Merck 020</th>
<th>AMC 052</th>
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<tbody>
<tr>
<td>HIV-negative</td>
<td>HIV-positive</td>
<td></td>
</tr>
<tr>
<td>N=602</td>
<td>N=104</td>
<td></td>
</tr>
<tr>
<td>HPV 6</td>
<td>7.3</td>
<td>8.0</td>
</tr>
<tr>
<td>HPV 11</td>
<td>8.6</td>
<td>9.8</td>
</tr>
<tr>
<td>HPV 16</td>
<td>8.1</td>
<td>8.2</td>
</tr>
<tr>
<td>HPV 18</td>
<td>8.6</td>
<td>7.8</td>
</tr>
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Vaccination to prevent HPV infection:

1. Effective in preventing HPV infection with vaccine types in both the anus and external genital epithelium
2. Should be offered to all HIV-seropositive men and women regardless of age or sexual history
3. May be useful as an adjunctive therapy for AIN
4. Generates titers in HPV-positive men and women that are higher than those seen among similarly-aged HIV-negative men and women

Summary

- HGAIN can be sought and treated to reduce the risk of anal cancer
  - Treatment can be challenging
  - Efficacy in reduction of anal cancer not yet shown
- The quadrivalent vaccine is highly efficacious in prevention of AIN in men who have sex with men (MSM) naïve to those HPV types
- Important tool to prevent anal cancer
Resources

- International Anal Neoplasia Society
  - www.iansoc.org
- HRA courses given through the American Society for Cervical Colposcopy and Pathology (ASCCP)
  - Next one is April 19-21, 2013 in Atlanta
  - www.analcancerinfo.ucsf.edu