Anal cytology and anal cancer in HIV-infected men and women.

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Disclosures

- Merck and Co: Research grant support, advisory boards
Cervical Squamo-columnar Transformation Zone

- Active transformation zone
- External os
- Original squamo-columnar junction
- Active squamo-columnar junction
- Columnar epithelium
- Cervical cleft opening
From condyloma to cancer

<table>
<thead>
<tr>
<th>Bethesda Classification</th>
<th>Low-grade squamous intra-epithelial lesion*</th>
<th>High-grade squamous intra-epithelial lesion</th>
<th>Invasive cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervical Intraepithelial Neoplasia</td>
<td>Normal</td>
<td>Flat condyloma</td>
<td>CIN 1</td>
</tr>
<tr>
<td>Histology of the Squamous Cervical Epithelium</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Associated HPV Types (Relative Frequency)</td>
<td>negative or other HPV types</td>
<td>HPV 6, 11, 42, 43, 44</td>
<td>HPV 31, 33, 35, 52, 58</td>
</tr>
</tbody>
</table>

The incidence of HPV-related cancers is increasing.
Recent reports of incidence in anal cancer since introduction of ART

75/100,000 person-years among HIV+ MSM since 1999

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

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

11/100,000 person-years among HIV+ men and women since 1996
Progression of HGAIN to anal cancer
Percent with anal HPV infection

- HIV-: 60%
- HIV+: CD4 > 500: 80%, CD4 200-500: 60%, CD4 < 200: 40%
Anal HPV infection by age group in sexually active HIV-negative MSM
HPV infection
Low-grade CIN
High-grade CIN
Cervical cancer

Percent with abnormal anal cytology

- HIV-: CD4 > 500
- HIV+: CD4 200-500
- HIV+: CD4 < 200
Prevalence of anal cytologic abnormalities by age among sexually active HIV-negative MSM

![Graph showing prevalence of anal cytologic abnormalities by age among sexually active HIV-negative MSM.](image-url)
Population-based data

Chin-Hong et al Ann Int Med 2008; 149; 300-6
Anal and cervical HPV infection in HIV-positive women
Cervical vs anal HPV types

Distribution of Genotypes Among HIV-uninfected Women

Distribution of Genotypes Among HIV-infected Women
AIN in HIV+ and HIV- women (N= 655)

- AIN (16%) was more common among HIV-positive women than HIV- women (4%) p<.001

- CIN (16%) was more common than among HIV-positive women than HIV- women (5%) p=.003

The cervical cancer model

- Anal and cervical cancer are biologically similar
- The incidence of cervical cancer has declined largely due to screening and treatment of high-grade CIN
- HGAIN is a true anal cancer precursor
Progression of HGAIN to cancer

- Classic Bowen’s: 5-10% progression (Rickert RR et al. CA 1977; 27:160-6)
- 8 of 72 (11%) immunosuppressed patients progressed from HGAIN to cancer over 42 months (Watson et al, ANZ J Surg. Aug 2006;76(8):715-17)
- 22 patients with HGAIN progressed to cancer over an average of 52 months from time of first diagnosis (Berry et al, submitted)
Reasons for lack of routine screening

- Lack of data on the optimal screening strategy
- Paucity of clinicians trained in high resolution anoscopy, biopsy and treatment of AIN
- Paucity of data on efficacy of treatment for HGAIN
- Paucity of cost-effectiveness data
- No data yet that treatment of HGAIN reduces the incidence of anal cancer
Recommendations of the National Institutes of Health (NIH), the Centers for Disease Control and Prevention (CDC), and the HIV Medicine Association of the Infectious Diseases Society of America (HIVMA/IDSA)

“….anal cytology screening of HIV-seropositive MSM and of women may be useful preventive measures. However, studies of screening and treatment programs for AIN 2 or 3 need to be implemented before definitive recommendations for anal cytology screening can be made”.
Lack of data on the optimal screening strategy

- Anal cytology has similar performance characteristics to cervical cytology
### Anal cytology and histology correlation

<table>
<thead>
<tr>
<th>Anal cytology*</th>
<th>Normal</th>
<th>Atypical</th>
<th>AIN 1</th>
<th>AIN 2 or 3</th>
<th>Insufficient</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>4</td>
<td>1</td>
<td>10</td>
<td>18</td>
<td>0</td>
<td>33 (32%)</td>
</tr>
<tr>
<td>ASCUS</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>3 (3%)</td>
</tr>
<tr>
<td>LSIL</td>
<td>0</td>
<td>1</td>
<td>13</td>
<td>22</td>
<td>0</td>
<td>36 (35%)</td>
</tr>
<tr>
<td>HSIL</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>27</td>
<td>0</td>
<td>29 (28%)</td>
</tr>
<tr>
<td>Insufficient</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Total (%)</td>
<td>5 (5%)</td>
<td>2 (2%)</td>
<td>26 (26%)</td>
<td>69 (68%)</td>
<td>0 (0%)</td>
<td>102</td>
</tr>
</tbody>
</table>
Paucity of clinicians trained in high resolution anoscopy, biopsy and treatment of AIN

- ASCCP and other courses
- More and more clinicians being trained
  - U.S., Canada, Australia, U.K., France, Germany and others
Paucity of data on efficacy of treatment for HGAIN

- Early in natural history- increased ease of treating small lesions
  - 85% TCA  

- Mid-natural history- local vs. surgical removal
  - Infra-red coagulation
    - 65% free of disease after median of 413 days

- Late in natural history- monitoring to detect early development of cancer
Early detection of anal cancer: superficially invasive squamous cell carcinoma of the anus (SISCCA)

- 19 patients treated with local excision
  - No patients died of SCCA
  - 5 of 19 (26%) developed recurrent cancer
    - 2 required RAC
  - No patients required a colostomy
  - 17 of 19 (89%) developed recurrent HGD
    - Careful follow-up is essential

Berry, Jay and Palefsky, unpublished data
Paucity of cost-effectiveness data

Anal cytology screening ($/QALY):

<table>
<thead>
<tr>
<th></th>
<th>+HIV*</th>
<th>-HIV**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Every year</td>
<td>$16,600</td>
<td>$34,800</td>
</tr>
<tr>
<td>Every 2 years</td>
<td>$13,000</td>
<td>$15,100</td>
</tr>
</tbody>
</table>

Until this is sorted out….

- What to do in the meantime?
The anal cancer screening test

Digital rectal exam
Figure 1. Anal cytology screening in HIV-uninfected MSM and HIV-infected persons for prevention of anal cancer

Anal cytology

Negative

ASC-US
ASC-H

LSIL

High resolution anoscopy

No lesions seen or squamous atypia

Repeat HRA, if HSIL cytology
Repeat HRA 4 mos., if ASC-H
Repeat HRA 6 mos., if LSIL
Repeat HRA 6-12 mos., if ASCUS

Follow or treat if symptomatic

LGAIN AIN I

HGAIN AIN II or III

Treat

Cancer

If HIV+, consider baseline HRA, then repeat 6 months
If HIV-, consider baseline HRA if > 40, then repeat 12-36 months

Suspicious/suggestive of cancer

If Cancer, refer for CMT

If HRA non-diagnostic, then exam in OR
Who should be screened?

- All HIV+ MSM with good prognosis
- ? All HIV+ men regardless of sexual orientation
- All HIV- MSM over the age of 40
- ? Women with high-grade vulvar lesions or cancer
- ? All HIV+ women?
- ? All men and women with perianal condyloma
- ? Men and women with transplant-associated immunosuppression
Before setting up screening

- Ability to perform cytology
- Ability to perform HRA and anal biopsies
- Ability to read cytology and biopsies
- Ability to perform office-based treatment
Before setting up screening

- Surgeons who understand AIN to whom you can refer patients as needed
Until the definitive studies are done

- All of the evidence combined suggests that we should be treating HGAIN
  - Proven carcinogenic potential, rising rates of anal cancer, proven prevention in the cervix
- If feasible, screen and treat
- Monitor for progression to anal cancer among those who cannot be treated
- If screening not feasible, annual DRE
Protocol 020 objectives

**Primary**
- Safety
- Efficacy: Combined incidence of HPV 6/11/16/18-related external genital lesions:
  - **Main study**: HM + MSM
    - External genital warts
    - Penile/perianal/perineal intraepithelial neoplasia (PIN)
    - Penile, perianal, or perineal cancer
  - **Sub-study**: MSM
    - Anal intraepithelial neoplasia (AIN)
    - Anal Cancer
- Immunogenicity
  - Geometric mean titers, seroconversion

**Secondary**
- Efficacy:
  - Incidence of persistent HPV 6/11/16/18 infection*
## Efficacy against persistent anal infection in MSM

### Per-protocol population

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>GARDASIL™ (N=299)</th>
<th>Placebo (N=299)</th>
<th>Efficacy (%) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td># of Cases</td>
<td>PY At Risk</td>
<td>IR per 100 PY at Risk</td>
</tr>
<tr>
<td><strong>HPV 6/11/16/18</strong></td>
<td>193</td>
<td>2</td>
<td>385.6</td>
</tr>
<tr>
<td><strong>HPV 6</strong></td>
<td>140</td>
<td>1</td>
<td>277.9</td>
</tr>
<tr>
<td><strong>HPV 11</strong></td>
<td>140</td>
<td>0</td>
<td>279.4</td>
</tr>
<tr>
<td><strong>HPV 16</strong></td>
<td>166</td>
<td>1</td>
<td>331.5</td>
</tr>
<tr>
<td><strong>HPV 18</strong></td>
<td>172</td>
<td>0</td>
<td>346.3</td>
</tr>
</tbody>
</table>

**N = Number of subjects randomized to the respective vaccination group who received at least 1 injection.**

**n = Number of subjects who have at least one follow-up visit after Month 7.**
### Efficacy against HPV 6/11/16/18-related AIN and anal cancer in MSM

**Per protocol population**

<table>
<thead>
<tr>
<th></th>
<th>Quadrivalent HPV vaccine (N=299)</th>
<th>Placebo (N=299)</th>
<th>Efficacy (%)</th>
<th>Cl</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>Cases</td>
<td>Rate</td>
<td>n</td>
<td>Cases</td>
</tr>
<tr>
<td>HPV 6/11/16/18–related AIN and anal cancer</td>
<td>194</td>
<td>5</td>
<td>1.3</td>
<td>208</td>
</tr>
<tr>
<td>By lesion type</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AIN 1</td>
<td>194</td>
<td>4</td>
<td>1.0</td>
<td>208</td>
</tr>
<tr>
<td>Condyloma acuminata</td>
<td>194</td>
<td>0</td>
<td>0.0</td>
<td>208</td>
</tr>
<tr>
<td>Non-acuminate</td>
<td>194</td>
<td>4</td>
<td>1.0</td>
<td>208</td>
</tr>
<tr>
<td>AIN 2 or worse</td>
<td>194</td>
<td>3</td>
<td>0.8</td>
<td>208</td>
</tr>
<tr>
<td>AIN 2</td>
<td>194</td>
<td>2</td>
<td>0.5</td>
<td>208</td>
</tr>
<tr>
<td>AIN 3</td>
<td>194</td>
<td>2</td>
<td>0.5</td>
<td>208</td>
</tr>
<tr>
<td>Anal cancer</td>
<td>194</td>
<td>0</td>
<td>0.0</td>
<td>208</td>
</tr>
</tbody>
</table>

Summary

- HIV-positive men and women are at unacceptably high risk of anal cancer
- Screening and treatment of HGAIN should be considered in high-risk populations to reduce the risk of progression to cancer
- HPV vaccines may also reduce the incidence of anal cancer in the future