Anal Cancer Prevention in HIV-Infected Men and Women

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Weill-Cornell Medical College
Case #1

- Bob is a 42 year-old HIV-infected man
  - Diagnosed 3 years ago with a CD4 of 250
  - On efavirenz/tenofovir/emtricitabine
  - Current CD4 455 cells/mm³
  - HIV-RNA <40 copies/mL
  - Sex with men only, 3 receptive anal sex partners in the past 6 months, uses condoms with HIV-uninfected partners

- History of perianal warts 10 years ago treated with cryotherapy

- No history of anal cancer screening
Case #1 Question #1

What proportion of your HIV-infected patients have been screened for anal cancer?

1. Do not offer anal cancer screening
2. <10%
3. 10-25%
4. 26-50%
5. >50%
Although US cervical cancer incidence and mortality rates have declined, there were still an estimated 3710 deaths in 2005. 

Anal Cancer, United States

Cancer Incidence 2008

Thousands

- Breast: 184.45
- Lung: 215.02
- Colon: 108.07
- Melanoma: 62.48
- Cervical: 11.07
- Anal: 5.07

60% of U.S. anal cancer cases are in women

Source: American Cancer Society
Anal Cancer in MSM

Anal Cancer Incidence

Per 100,000 patient-years

HIV-neg
HIV-pos pre-HAART
HIV-pos post-HAART

NA-ACCORD estimates 3% of HIV-infected adults will have anal cancer by age 60

1Silverberg M, Abstract 758 CROI 2010
Anal Cancer in MSM

Anal Cancer Incidence

<table>
<thead>
<tr>
<th>Group</th>
<th>Per 100,000 patient-years</th>
</tr>
</thead>
<tbody>
<tr>
<td>US Gen Pop</td>
<td>1.4</td>
</tr>
<tr>
<td>US MSM 1982</td>
<td>35</td>
</tr>
<tr>
<td>London HIV+ MSM</td>
<td>35</td>
</tr>
<tr>
<td>US MACS Cohort</td>
<td>14</td>
</tr>
<tr>
<td>US Cohort</td>
<td>78.2</td>
</tr>
<tr>
<td>French Cohort</td>
<td>144</td>
</tr>
<tr>
<td>San Diego Cohort</td>
<td>49</td>
</tr>
<tr>
<td>US MSMS</td>
<td>40</td>
</tr>
<tr>
<td>HIV-neg</td>
<td></td>
</tr>
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<td>HIV-pos post-HAART</td>
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</table>

cervical cancer rate prior to PAP

current cervical cancer rate
Case #1 - continued

- Bob elects to be screened for anal cancer
- His provider uses a rayon (or Dacron) swab to collect anal cells
- ASCUS
Case #1 – Question #2

What is the next step?

1. Repeat anal cytology in 6 months
2. Send HPV testing
3. Anoscopy
4. High resolution anoscopy
5. Referral to colorectal surgery for exam under anesthesia and biopsies
HRA
## Anal Dysplasia Schematic

### Figure 1: Schematic Representation of SIL

<table>
<thead>
<tr>
<th>Condition</th>
<th>Low-grade squamous intraepithelial lesion (LSIL)</th>
<th>High-grade squamous intraepithelial lesion (HSIL)</th>
</tr>
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<tbody>
<tr>
<td>Normal</td>
<td>Very mild to mild dysplasia</td>
<td>In situ carcinoma</td>
</tr>
<tr>
<td>Condyoma</td>
<td>CIN/AIN grade 1</td>
<td>CIN/AIN grade 3</td>
</tr>
<tr>
<td>CIN/AIN grade 2</td>
<td>Moderate dysplasia</td>
<td>Severe dysplasia</td>
</tr>
<tr>
<td>CIN/AIN grade 3</td>
<td></td>
<td>In situ carcinoma</td>
</tr>
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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.

Sources: Joel Palefsky, MD, FACP(S)

Palefsky 2004
**Treat high-grade AIN**

### Figure 1: Schematic Representation of SIL

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*Sources: Joel Palefsky, MD, FACP(C)*

Palefsky 2004
Anal Intraepithelial Neoplasia (AIN)

- Similar to cervical intraepithelial neoplasia
- Both have high risk HPV as cofactor (e.g. 16, 18)
- Occur in the transformation zone with the same embryonic origin
- Graded with same pathologic classifications
- Screening techniques (PAP smears, HPV test, \(^1\) colposcopy) are the same
- Cytology has a 70-80% sensitivity for high-grade AIN (HGAIN)
- Invasive anal cancer preceded by HGAIN\(^2,3\)

\(^1\) Digene HC2 not FDA-approved for anal testing
\(^2\) Sobhani I, *AIDS* 2004
Natural History of HPV Infection and Potential Progression to Anal Cancer

0–1 Year
- Initial HPV Infection
- Higher HPV exposure

0–5 Years
- Continuing Infection
- AIN 1

1–20 Years
- AIN 2/3
- Invasive Anal Cancer

Cleared HPV Infection

### HGAIN in MSM

#### Prevalence of HGAIN by biopsy in MSM across various measurements

<table>
<thead>
<tr>
<th>Study Description</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>UCSF population-based sample (2009)</td>
<td>44%</td>
</tr>
<tr>
<td>UCSF anal neoplasia clinic new patients (2006-08)</td>
<td>57%</td>
</tr>
<tr>
<td>UCLA patients with abnormal cytology (2007)</td>
<td>52%</td>
</tr>
<tr>
<td>NYC surgical practice (2001)</td>
<td>68%</td>
</tr>
<tr>
<td>UCSF baseline prevalence study in HIV+ (2005)</td>
<td>52%</td>
</tr>
<tr>
<td>UCSF baseline prevalence study in HIV- (2005)</td>
<td>16%</td>
</tr>
</tbody>
</table>

UCSF = University of California San Francisco

Population-based sample refers to a sample that includes all members of a defined population.

Anal neoplasia clinic new patients refers to patients who visited the clinic for the first time.

UCLA patients with abnormal cytology refers to patients with abnormal cytology results.

NYC surgical practice refers to patients who were treated in a surgical practice.

UCSF baseline prevalence study in HIV+ refers to patients who were HIV-positive at the baseline.

UCSF baseline prevalence study in HIV- refers to patients who were HIV-negative at the baseline.
Case #1- Question #3

Bob is concerned that he will develop anal cancer
In the absence of treatment, what is his risk of developing cancer over 5-10 years?

1. <1%
2. 1-5%
3. 6-20%
4. 20-50%
5. >50%
Progression of HGAIN to cancer

- Anal cancer developed in 5/32 (16%) HIV-infected patients with HGAIN at a mean of 6 years of follow up.\(^1\) *Condyloma tx only*
- Anal cancer developed in 5/36 (14%) HIV-infected patients with perianal HGAIN after a mean of 2.2 years of follow-up.\(^2\) *Imiquimod tx and some surgery*
- 8/55 (15%) with AIN 2/3 developed cancer with a median follow-up of 5 years.\(^3\) *No treatment*
- In UCSF cohort of extensive HGAIN, 2/184 (1%) developed anal cancer.\(^4\) *Treated with aggressive surgery and office-based treatment.*

\(^1\) Sobhani, AIDS 2004; 18:1561
\(^2\) Salit, 25th Intl HPV Conf 2009; P-05.06
\(^3\) Watson AJ, ANZ J of Surg 2006
\(^4\) Pineda Diseases of the Colon and Rectum 2008; 6:829
Case #1- Question #4

Bob’s provider offers treatment of high grade AIN vs. observation. Bob chooses treatment. Which of the following is the best treatment option for high grade AIN?

1. Wide surgical excision
2. Ablative therapy (infrared coagulation or electrocautery)
3. Change to protease inhibitor-based therapy
4. Combined radiation and chemotherapy
Infrared Coagulator
Procedure

HGAIN
Char dessicating
Char débrided bluntly
Bulging submucosal veins
Thrombosed submucosal veins

Images used with permission by Stephen Goldstone, MD
Treatment of High Grade AIN

• Ablative treatments are preferred
  – Infrared Coagulation or electrocautery

• AMC data on IRC found that 10 of 18 were free of HGAIN after the first IRC\(^1\)
  – Randomized clinical trial AMC076 [NCT01164722] is underway

• Largest series of HIV+ patients undergoing IRC treatment for HGAIN (n=68) suggests that it is safe, well-tolerated.\(^2\)
  – 70% of individual lesions cured, but HGAIN commonly found at other sites
  – Multiple treatments are usually necessary to eliminate HGAIN

\(^1\)Stier, JAIDS 2008  \(^2\)Goldstone S, Dis Colon Rectum 2005
Necessary components of screening program

- **Goal of anal cancer screening:**
  - Identify HGAIN that can be treated to reduce the probability of developing anal carcinoma
- **Anal cytology** performed by primary care provider
  - Easy to perform
  - Interpretation is the same as cervical cytology
- **High resolution anoscopy**
  - Can use as initial screen in high prevalence populations
  - Training in cervical colposcopy and HRA through the ASCCP
  - Supervised HRA is recommended
- **Office-based treatment for high grade AIN and condyloma**
  - IRC treatment can be performed by internists and mid-level practitioners
  - Electrocautery also used commonly
  - Can consider topical therapies, but data are limited
Case #2

- Jill is a 53 year old HIV-infected woman. She was diagnosed in 1992 during pregnancy.
  - Nadir CD4 35, history of pneumocystis pneumonia
  - Current CD4 235, HIV-1 RNA <40 copies/mL
  - Darunavir/ritonavir, raltegravir, etravirine, tenofovir/emtricitabine
- History of microinvasive cervical cancer treated with hysterectomy
- Currently has vulvar intraepithelial neoplasia being treated with imiquimod
HGAIN in Women

Prevalence of HGAIN by biopsy in women across various measurements

HIV-infected women at 6 fold higher risk of anal cancer

1Frisch et al, JNCI 2000
Anal HPV Infection

• Risk factors
  – Receptive anal sex
  – History of anal warts
  – HIV infection
  – CD4<200 cell µL
  – Cervical HPV
  – History of CIN
  – Smoking history
  – Younger age

• Prevalence
  – 42 % HIV-neg female
  – 61 % HIV-neg MSM
  – **76 % HIV-pos female**
  – 93 % HIV-pos MSM

Case #2 - continued

- During anal cytology, she is noted to have perianal lesions
Topical therapy for AIN

- **Imiquimod**
  - Randomized clinical trial supports use in vulvar intraepithelial neoplasia\(^1\)
  - Randomized clinical trial supports intraanal use.\(^2\)
- **Cidofovir**
  - Randomized clinical trial supports use for condyloma\(^3\)
  - AMC046: trial for perianal intraepithelial neoplasia showed 21/33 (59\%) had complete or partial response\(^4\)
- **Topical 5-fluorouracil\(^5\)-\(^6\)**
  - Retrospective series of 41 patients treated with 1 application twice daily for 5 days, followed by 9 days off. Treated for a mean of 6 cycles. Patients had >75\% circumferential disease.
  - 23 completed at least 3 cycles: 1 had no response, 3 had complete response and 19 had partial response allowing treatment with IRC or surgery
  - A second study using a lower dose showed 69\% had a complete or partial response

\(^1\)von Seters M, NEJM 2008
\(^2\)Fox PA, AIDS 2010
\(^3\)Snoeck R, CID 2001
\(^4\)Stier EA, 26\(^{th}\) Intl HPV Conference 2010; P-402
\(^5\)Jay 25\(^{th}\) Intl HPV Conference 2009; P-19:16.
\(^6\)Richel, Abstract 768, CROI 2010
Perianal diffuse HGAIN with acetic acid.

Pre-5FU  Post-5FU

Courtesy of Naomi Jay
Case #3

• Steve is a 25 year old newly diagnosed with HIV.
  – At diagnosis, CD4 520, HIV-1 RNA 12,000 copies/mL.
  – Recently started ART (raltegravir, tenofovir/emtricitabine)
  – Current HIV-1 RNA <40 copies/mL
  – Anal cytology obtained (low grade SIL), small perianal condyloma noted
Case #3 - continued

- HRA reveals condyloma only
Case #3 – Question #1

He asks about HPV vaccination. His sister received the vaccine a few years ago.

Which would you choose?

1. Do not prescribe HPV vaccine because there are no efficacy data in HIV-infected people
2. Do not prescribe HPV vaccine because he already has warts and the vaccine is preventive
3. Prescribe HPV vaccine as it may prevent new infections
4. Prescribe HPV vaccine as it helps treat ongoing condyloma and HPV infection
Note to reviewers: this is controversial so I will outline the pros/cons, and not be absolute

Tim W, 23/08/2011
HPV vaccine in HIV-uninfected MSM

• Merck 020 randomized 598 HIV-uninfected MSM to the quadrivalent HPV vaccine (qHPV) or placebo
• qHPV vaccine reduced AIN related to vaccine types by 78% (5 cases vs. 24 cases; 95% CI 40-93)
• Among HIV- young MSM, vaccine reduced persistent anal infection with vaccine-types by 95% (2 case vs. 39 cases, 95% CI 80%-99%)

1Giuliano A, 25th Intl HPV Conference 2009; O-01.07
2Palefsky J, 25th Intl HPV Conference 2009; O-27.01
Bivalent HPV vaccine in women

- Randomized clinical trial of bivalent HPV vaccine in HIV-uninfected women in Guanacaste, Costa Rica
- Collect anal swabs for HPV typing at a single timepoint 4 years post randomization

Kreimer A, Lancet Oncology, 2011
HPV Vaccine in HIV-infected Men, Women, and Children

• Highly immunogenic in HIV-infected children
  – 99.5% rate of seroconversion
  – Safe with no effects on CD4 counts
  – Supports routine vaccination of all HIV-infected children

• ACTG 5240 found that HPV vaccination is safe and immunogenic in HIV-infected women

• AMC052
  – Single-arm, open-label trial of qHPV vaccine in HIV-1 infected adult men without HGAIN
  – 109 men received at least one dose of vaccine
  – Safe with no grade 3 or 4 events related to vaccine
  – No effects noted on CD4 and HIV RNA

¹Levin MJ, JAIDS 2010
²Wilkin T, JID, 2010
### AMC052 Immunogenicity

<table>
<thead>
<tr>
<th>HPV type</th>
<th>6</th>
<th>11</th>
<th>16</th>
<th>18</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seropositive at Week 28</td>
<td>57/58, 98%</td>
<td>67/68, 99%</td>
<td>60/60, 100%</td>
<td>73/77, 95%</td>
</tr>
<tr>
<td>Seropositive at Week 76</td>
<td>52/53, 98%</td>
<td>58/60, 97%</td>
<td>49/52, 94%</td>
<td>39/67, 58%</td>
</tr>
<tr>
<td>GMT at Week 28</td>
<td>336</td>
<td>525</td>
<td>1125</td>
<td>181</td>
</tr>
<tr>
<td>GMT at Week 76</td>
<td>148</td>
<td>190</td>
<td>304</td>
<td>38</td>
</tr>
</tbody>
</table>
Conclusions

• HPV-associated anal cancer continues to be a significant issue for HIV-infected patients.
• Anal HPV infection and AIN are highly prevalent in HIV-infected men and women.
• Screening programs for AIN should be strongly considered.
• Recommend routine vaccination of HIV-infected people age 9-26.
• Further research is needed to expand our treatment and prevention options.
Acknowledgements

• Weill-Cornell Med. Coll.
  – Roy Gulick
  – Marshall Glesby
  – CCTU Staff
  – CTSC

• AIDS Malignancy Consortium
  – Joel Palefsky
  – Elizabeth Stier
  – Ron Mitsuyasu

• Other Colleagues
  – Stephen Goldstone
  – J. Michael Berry
  – Naomi Jay
  – Gal Mayer

• Research Funding
  – NIAID K23
  – DAIDS
  – NCI

Special thanks to the patient volunteers!!