Preventing Anal Cancer in HIV-infected Persons

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Plan

- Anal cancer epidemiology
- The anorectum
- Human papillomavirus infection
- Anal dysplasia
- Anal cancer clinical presentation
- Anal cytology screening
- High resolution anoscopy
- Treatment modalities
- Education and awareness
Epidemiology of HIV and Anal Cancer

- Anal Cancer Incidence Rates – General Population
  - 2003-2007: 1.6/100 000
  - Anal cancer incidence increasing

- Anal Cancer Incidence reported in HIV+ MSM ranges from 37.1 - 219/100 000

- Relative risk of anal cancer in HIV+ MSM compared to general population ranges from 8.2 - 352

- Anal cancer incidence in HIV-positive women approximately 6-8 times that of women in the general population

Kaiser Permanente cohort

- Popn Kaiser Permanente California
- Cohort 1996-2007, 10 HIV-pos: 1 HIV-neg (matched by age, sex, year, medical center)
- Analysis by:
  - Anal cancer, death, left plan, or 12-31-07
  - 6 monthly data points for HIV-pos
  - CD4/HIV RNA
Infection related non AIDS defining malignancy

<table>
<thead>
<tr>
<th>HIV-pos</th>
<th>HIV-neg</th>
<th>Adjusted hazard ratio (95% CI)##</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Rate#</td>
</tr>
<tr>
<td>Any</td>
<td>215</td>
<td>267</td>
</tr>
<tr>
<td>Anal</td>
<td>140</td>
<td>174</td>
</tr>
<tr>
<td>Hodgkin’s</td>
<td>44</td>
<td>54</td>
</tr>
<tr>
<td>Oral cavity</td>
<td>35</td>
<td>43</td>
</tr>
<tr>
<td>Liver</td>
<td>21</td>
<td>26</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HIV-pos ###</th>
<th>CD4 &lt; 200</th>
<th>CD4 201- 499</th>
<th>CD4 &gt; 500</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anal hazard ratio ##</td>
<td>164.2</td>
<td>83.1</td>
<td>34.2</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

# Cases per 100,000 person years

## Adjusted for age, sex, tobacco use, overweight/obese, alcohol/drug use, HBV/HCV

### HIV-negative reference

Silverberg CROI 2010
Age and anal cancer

- From 2003-2007, the median age at diagnosis for cancer of the anus, anal canal, and anorectum was 60 years of age

<table>
<thead>
<tr>
<th>Age</th>
<th>Anal cancer incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 20</td>
<td>0</td>
</tr>
<tr>
<td>20-34</td>
<td>1.1</td>
</tr>
<tr>
<td>35-44</td>
<td>9.7</td>
</tr>
<tr>
<td>45-54</td>
<td>24.1</td>
</tr>
<tr>
<td>55-64</td>
<td>24.3</td>
</tr>
<tr>
<td>65-74</td>
<td>18.5</td>
</tr>
<tr>
<td>75-84</td>
<td>15.8</td>
</tr>
<tr>
<td>&gt;85</td>
<td>6.5</td>
</tr>
</tbody>
</table>

SEER database
HIV and aging

- CDC definition of ‘Elderly’ in the context of HIV is defined as persons ≥ 50 years
- 4 x increase in ‘elderly’ US AIDS cases in last 10 years
- 2000 - 10 and 15% of US AIDS cases were ‘elderly’
- 2015 - 50% of prevalent HIV cases will be >50 years
Anal cancer survival (general popn)

Stage distribution and 5-year relative survival by stage at diagnosis for 1999-2006, all races, both sexes

<table>
<thead>
<tr>
<th>Stage at Diagnosis</th>
<th>Stage distribution (%)</th>
<th>5-year relative survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Localized (confined to primary site)</td>
<td>50</td>
<td>80.1</td>
</tr>
<tr>
<td>Regional (spread to regional lymph nodes)</td>
<td>29</td>
<td>59.8</td>
</tr>
<tr>
<td>Distant (cancer has metastasized)</td>
<td>12</td>
<td>30.5</td>
</tr>
<tr>
<td>Unknown (unstaged)</td>
<td>9</td>
<td>56.0</td>
</tr>
</tbody>
</table>

SEER database
Anatomy and physiology
The anorectum

Ryan 2000
Rectal and anal epithelium

Shatock 2003
Anorectal transition zone
Anorectum

- Rectum
- Levator ani (pelvic diaphragm)
- Ischioanal (ischiorectal) fossa
- Obturator internus muscle
- Internal sphincter
- Deep, Subcutaneous, Superficial External Anal Sphincter
## Manometry

<table>
<thead>
<tr>
<th>Test site</th>
<th>Resting (mmHg)</th>
<th>Squeeze (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anal (male and female)</td>
<td>56</td>
<td>178</td>
</tr>
<tr>
<td>Anal no RAI male</td>
<td>91</td>
<td>152</td>
</tr>
<tr>
<td>Anal RAI male</td>
<td>71</td>
<td>177</td>
</tr>
<tr>
<td>Pelvic floor (nulliparous)</td>
<td>-</td>
<td>15-20</td>
</tr>
</tbody>
</table>

Anal and rectal sensation

- **Anal canal:**
  Somatic sensation (light touch, pin-prick, heat, cold, pain, distension)

- **Rectum:**
  Visceral sensation (distension, pain)
Human papillomavirus
Anogenital HPV types

Anogenital HPVs (~40)

High-risk types (HPV 16,18)
- low-grade dysplasia
- high-grade dysplasia
- anogenital cancers

Low-risk types (HPV 6,11)
- low-grade dysplasia
- genital warts
- respiratory papillomatosis
Human Papillomavirus

- DNA tumor virus (8 KB)
- High-Risk Types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68
- Associated with dysplasia and cancer of the cervix, anus, penis, vulva, and vagina
- Required for the development of cervical cancer
HR-HPV pathogenesis

- Integration of episomal viral genome
- Expression of HPV E6 and E7 oncoproteins
- Disruption of cell cycle checkpoints (p53/pRB)
- Genomic instability leads to malignant progression
Anal HPV infection

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

- **Consequences**
  - Nil
  - Condyloma accuminata
  - Anal dysplasia
  - Anal malignancy

Palefsky 1998, Holly 2001
Anal HPV prevalence

- 50-70 % of the general population exposed to anogenital HPV (serology)

- Anal HPV by PCR
  - 42 % HIV-neg female
  - 61 % HIV-neg MSM
  - 76 % HIV-pos female
  - 93 % HIV-pos MSM

Anal HPV by age in HIV-neg MSM

Chin-Hong 2004
Anal HPV in HIV-pos MSW IDU

- Comparison of HIV-pos MSM with HIV-pos MSW infected by IDU with no history of RAI

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Anal HPV-pos</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSM</td>
<td>67</td>
<td>57 (85%)</td>
</tr>
<tr>
<td>MSW</td>
<td>50</td>
<td>23 (46%)</td>
</tr>
</tbody>
</table>

Piketty 2003
Anal dysplasia
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, FRCP(C)

Palefsky 2004
Schematic representation of anal dysplasia reporting

Epithelial thickness

- AIN-1: Low-grade dysplasia
- AIN-2
- AIN-3: High-grade dysplasia

Epithelial basement membrane
Risk factors for anal dysplasia

- HPV infection
- Receptive anal sex
- HIV infection
- CD4 <200 cells µL
- Genital wart diagnosis
- History of anal discharge
- Current cigarette smoking
- High-grade cervical/vulvar/vaginal dysplasia or cancer
- Iatrogenic immunosuppression (steroid/transplant)

Natural history of anal dysplasia

- San Francisco natural history cohort
  - 32% of HIV+ men and 9% HIV-neg men with no anal disease developed AIN-1 in 2 years
  - >50% HIV+ men with AIN-1 at baseline developed high grade dysplasia within 2 years
    - HIV infection
    - CD4 < 200
    - Multiple HPV types
    - High-level high-risk HPV infection
  - Clinically - high grade dysplasia rarely regresses

Palefsky 1998, Hessol 2009
Prevalence of anal dysplasia

- San Francisco: 81% HIV-pos MSM
- Los Angeles: 69% HIV-pos MSM
- EXPLORE: 20% in HIV-neg MSM
- San Francisco 26% HIV-pos and 8% HIV-neg women
- Thailand: 33.9% HIV-pos and 12.5% HIV-neg MSM

Anal HPV/dysplasia pre and post HAART

- MSM with anal swab and biopsy results compared 6/12 pre- and post-HAART
  - No change in anal HPV positive tests or level of HPV infection
  - Similar anal biopsy pathology results in both groups

- High Prevalence of anal dysplasia (70%) and HPV (80%) in patients after instituting HAART regardless of CD4 increase

Palefsky 2005, Piketty 2004
Anal dysplasia as an anal cancer precursor

- Comparing anal dysplasia/cancer with cervical dysplasia/cancer:
  - Same HPV risk types
  - Similar pathology
  - Same chromosomal abnormalities
  - Frequently diagnosed simultaneously
  - (For anal: same risk groups)

Bosch 1995, Palefsky 2000, Frisch 1999
Progression of HGAIN to cancer

- 1994-2003, 35 HIV-negative patients diagnosed with HGAIN by anal biopsy
  - Surgical excision in 28
  - 6 immunosuppressed patients had multifocal perianal disease
  - 3 progressed to anal cancer during follow up (63 month median (14-120))

- 1997-2007 UCSF among 1700 HIV-positive MSM, 65 cancer were diagnosed
  - 21 ppts had previous biopsy of HGAIN at site of new cancer

Scholefield 2005, Berry CROI 2009
Table 6. Summary of studies evaluating prevalence of high-risk human papillomavirus (HPV) infection, cytologic dysplasia, and biopsy-proven anal intraepithelial neoplasia (AIN) in cohorts of HIV-positive individuals.

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Sex</th>
<th>Location</th>
<th>No. of HIV-positive subjects</th>
<th>Subjects with high-risk HPV infection, %</th>
<th>Subjects with cytologic dysplasia, %</th>
<th>Subjects with AIN revealed by biopsy, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melbye et al.</td>
<td>1996</td>
<td>Women</td>
<td>Denmark</td>
<td>81</td>
<td>14</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>Hillemanns et al.</td>
<td>1996</td>
<td>Women</td>
<td>New York, New York</td>
<td>102</td>
<td>28</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Palefsky et al.</td>
<td>1998</td>
<td>Men</td>
<td>San Francisco, California</td>
<td>346</td>
<td>46</td>
<td>2</td>
<td>23</td>
</tr>
<tr>
<td>Sayers et al.</td>
<td>1998</td>
<td>Men</td>
<td>United Kingdom</td>
<td>66</td>
<td>41</td>
<td>8</td>
<td>41</td>
</tr>
<tr>
<td>Friedman et al.</td>
<td>1998</td>
<td>Men</td>
<td>Multicenter AIDS cohort</td>
<td>135</td>
<td>41</td>
<td>2</td>
<td>41</td>
</tr>
<tr>
<td>Lacey et al.</td>
<td>1999</td>
<td>Men</td>
<td>United Kingdom</td>
<td>57</td>
<td>67</td>
<td>7</td>
<td>67</td>
</tr>
<tr>
<td>Goldstone et al.</td>
<td>2001</td>
<td>Men</td>
<td>New York, New York</td>
<td>200</td>
<td>97</td>
<td>57</td>
<td>96</td>
</tr>
<tr>
<td>Palefsky et al.</td>
<td>2001</td>
<td>Women</td>
<td>San Francisco, California</td>
<td>223</td>
<td>37</td>
<td>37</td>
<td>37</td>
</tr>
<tr>
<td>Holly et al.</td>
<td>2001</td>
<td>Women</td>
<td>San Francisco, California</td>
<td>235</td>
<td>26</td>
<td>1</td>
<td>26</td>
</tr>
<tr>
<td>Alfonzo et al.</td>
<td>2002</td>
<td>NR</td>
<td>NR</td>
<td>162</td>
<td>59</td>
<td>43</td>
<td>59</td>
</tr>
<tr>
<td>Fine et al.</td>
<td>2002</td>
<td>NR</td>
<td>Rochester, New York</td>
<td>458</td>
<td>14</td>
<td>4</td>
<td>14</td>
</tr>
<tr>
<td>Norton et al.</td>
<td>2003</td>
<td>NR</td>
<td>New York, New York</td>
<td>115</td>
<td>30</td>
<td>4</td>
<td>30</td>
</tr>
<tr>
<td>Durante et al.</td>
<td>2003</td>
<td>Women</td>
<td>New England</td>
<td>164</td>
<td>14</td>
<td>0</td>
<td>14</td>
</tr>
<tr>
<td>Piketty et al.</td>
<td>2003</td>
<td>Men</td>
<td>France</td>
<td>117</td>
<td>59</td>
<td>44</td>
<td>59</td>
</tr>
<tr>
<td>Lee et al.</td>
<td>2004</td>
<td>Men</td>
<td>San Francisco, California</td>
<td>417</td>
<td>54</td>
<td>4</td>
<td>54</td>
</tr>
<tr>
<td>Wilkin et al.</td>
<td>2004</td>
<td>Men</td>
<td>New York, New York</td>
<td>92</td>
<td>47</td>
<td>6</td>
<td>47</td>
</tr>
<tr>
<td>Chin-Hong et al.</td>
<td>2004</td>
<td>Men</td>
<td>Brazil</td>
<td>33</td>
<td>68</td>
<td>27</td>
<td>68</td>
</tr>
<tr>
<td>Mathews et al.</td>
<td>2004</td>
<td>Men and women</td>
<td>San Diego, California</td>
<td>1732</td>
<td>57</td>
<td>8</td>
<td>57</td>
</tr>
<tr>
<td>Kreuter et al.</td>
<td>2005</td>
<td>Men</td>
<td>Germany</td>
<td>103</td>
<td>53</td>
<td>20</td>
<td>53</td>
</tr>
<tr>
<td>Palefsky et al.</td>
<td>2005</td>
<td>Men</td>
<td>San Francisco, California</td>
<td>357</td>
<td>95</td>
<td>25f</td>
<td>25f</td>
</tr>
</tbody>
</table>

**NOTE.** MSM, men who have sex with men; NR, not reported.

- **a** MSM, 100%.
- **b** Cancer, 3%.
- **c** MSM, 43%.
- **d** MSM, 60%.
- **e** MSM, 34%.
- **f** Combined results of cytological and histological examination conducted at the same visit. The more-severe diagnosis is represented.
Anal cancer
Clinical presentation

- **History:**
  - Pain, bleeding, ulceration, mass, change in stools
  - Presentation may be non specific, confused with HSV, condyloma, medication side effects, fissure, or hemorrhoids

- **Physical:**
  - 56% of early anal cancer cases asymptomatic but with palpable mass
## Table 2: Relative risk (RR) of anal cancer and anal cancer incidence among HIV-infected individuals.

<table>
<thead>
<tr>
<th>Study</th>
<th>Location</th>
<th>Study population</th>
<th>Years of study</th>
<th>Total no. of patients in HIV/AIDS cohort</th>
<th>SIR (95% CI)</th>
<th>RR (95% CI)</th>
<th>Anal cancer incidence (95% CI) per 100,000 person-years</th>
<th>Statistically significant difference between HAART and pre-HAART incidences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gallagher et al. [16]</td>
<td>New York State</td>
<td>AIDS Cancer Registry match</td>
<td>1981–1994</td>
<td>122,993</td>
<td>3.3 (2.86–3.75)</td>
<td>...</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Petruccione A et al. [21]</td>
<td>United Kingdom</td>
<td>Cohort study</td>
<td>1982–1995</td>
<td>2048</td>
<td>222 (27–803)</td>
<td>...</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Frisch et al. [7]</td>
<td>United States</td>
<td>AIDS Cancer Registry match</td>
<td>1978–1996</td>
<td>366,034</td>
<td>...</td>
<td>Men, 37.9 (33.0–43.4); women, 6.9 (2.7–14)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Biggar et al. [17]</td>
<td>United States</td>
<td>AIDS Cancer Registry match</td>
<td>1981–1996</td>
<td>8829</td>
<td>8.2 (3.0–17.8)</td>
<td>...</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Grulich et al. [20]</td>
<td>Australia</td>
<td>Cohort study</td>
<td>1980–1999</td>
<td>13,067</td>
<td>37.1 (17.8–68.3)</td>
<td>...</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Diamond et al. [18]</td>
<td>San Diego County, California</td>
<td>AIDS Cancer Registry match</td>
<td>1988–2000</td>
<td>11,867</td>
<td>...</td>
<td>Pre HAART era, 98 (36–264); HAART era, 352 (186–666)</td>
<td>49 (16–114)</td>
<td>144 (93–112)</td>
</tr>
<tr>
<td>Clifford et al. [19]</td>
<td>Switzerland</td>
<td>Swiss cohort study</td>
<td>1985–2002</td>
<td>7304</td>
<td>33.4 (10.5–78.6)</td>
<td>...</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Bower et al. [22]</td>
<td>United Kingdom</td>
<td>Cohort study</td>
<td>1984–2003</td>
<td>8640</td>
<td>115.4b</td>
<td>...</td>
<td>60 (40–89)</td>
<td>92 (52–149)</td>
</tr>
</tbody>
</table>

**NOTE.** NR, not reported; SIR, standardized incidence ratio.

* Includes rectal and anal cancer and may underestimate the SIR, because this study included cancer of the rectum in the incidence calculation. Data are standardized for age, sex, region and race.

* Data are standardized for age and sex.

* Data are standardized for age, sex, and time period.
Anal Cancer Screening
Anal cytology

- Dacron swab inserted into anal canal
- Cells fixed on slide or re-suspended in ThinPrep solution
- Read by pathologist according to Revised Bethesda classification scheme
- ASC-US, ASC-H, LSIL, HSIL
- Performed easily as part of routine clinic visit
- Patient vs. provider specimens
Assessing anal cytology

- Moderate to high sensitivity
- Poor specificity (32-59%)
- Anal histopathology mandatory
- 244 HIV+ MSM correlating cytology:
  - 67% men with abnormal cytology
  - PPV for any anal cytological abnormality to predict any degree of anal dysplasia was 95%

Palefsky 1997, Cranston 2007, Panther 2004
## Anal cytology performance

Table 4. Summary of studies reporting sensitivity and specificity for anal Papanicolaou (Pap) smear cytological examination, compared with histological examination.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year</th>
<th>No. of subjects</th>
<th>Liquid cytological examination or conventional histological examination</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palefsky et al. [32]</td>
<td>1997</td>
<td>407</td>
<td>Liquid (ThinPrep; Cytyc)</td>
<td>69</td>
<td>59</td>
</tr>
<tr>
<td>Lee et al. [34]</td>
<td>2004</td>
<td>192</td>
<td>Not stated</td>
<td>95</td>
<td>Not stated</td>
</tr>
<tr>
<td>Matthews et al. [33]</td>
<td>2004</td>
<td>154</td>
<td>Conventional</td>
<td>85</td>
<td>56</td>
</tr>
<tr>
<td>Panther et al. [35]</td>
<td>2004</td>
<td>153</td>
<td>Not stated</td>
<td>93</td>
<td>33</td>
</tr>
<tr>
<td>Fox et al. [36]</td>
<td>2005</td>
<td>99</td>
<td>Conventional</td>
<td>83</td>
<td>38</td>
</tr>
<tr>
<td>Salit et al. [37]</td>
<td>2005</td>
<td>246</td>
<td>Liquid (ThinPrep; Cytyc)</td>
<td>84</td>
<td>32</td>
</tr>
<tr>
<td>Arain et al. [30]</td>
<td>2005</td>
<td>200</td>
<td>Liquid (SurePath; Medical Solutions)</td>
<td>98</td>
<td>50</td>
</tr>
<tr>
<td>Papaconstantinou et al. [31]</td>
<td>2005</td>
<td>37</td>
<td>Liquid (ThinPrep; Cytyc)</td>
<td>42</td>
<td>96</td>
</tr>
</tbody>
</table>

*a* Only patients with abnormal Pap smear results underwent high-resolution anoscopy and biopsy; therefore, sensitivity and specificity may be biased.

*b* Did not include atypical squamous cells of uncertain significance in definition of abnormal Pap smear.

*c* All patients had condyloma.
Anal ‘Home Cytology’

- 102 MSM in UCSF Anal Neoplasia Study
- 82 HIV-pos, 20 HIV-neg, 87% Caucasian
- Matched anal cytology and concurrent anal biopsy
- Explanation given on technique and subjects requested to obtain ‘home’ sample in 1 month

<table>
<thead>
<tr>
<th>Specimen adequacy (%)</th>
<th>N=102</th>
<th>clinician</th>
<th>subject</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>101/102 (99)</td>
<td>93/102 (91)</td>
<td>0.02</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Current guidelines

Anal Pap Smear

In addition to an anorectal exam, all HIV+ MSM, females with an abnormal vaginal pap smear, and patients with a history of anogenital HPV infection are evaluated on whether they have received an anal pap smear.

eHIVQUAL identifies MSM patients in the exposure category of the patient entry screen and identifies females with an abnormal vaginal pap smear within the gynecological exam indicator. eHIVQUAL will prompt, “Does the patient have a documented history of anogenital HPV infection?” If the patient is eligible, eHIVQUAL will prompt, “Did the patient have an anal pap smear during the review period?”

Yes: Anal pap smear was a performed within the 12-month review period (stop).
No: An anal pap smear was not performed (stop).
ADC algorithm

Anal Cytology

High-resolution anoscopy

Abnormal

Negative

Repeat annually

ADC and follow-up
Anal cytology cost effectiveness

$13 000 per QALY (CD4 >500, biannual)
$16 600 per QALY (CD4 >500, annual)
$25 000 per QALY (CD4 <500, annual)

(Annual cervical cytology: $180 000 per QALY)

- Authors suggested yearly anal cytology screening in HIV-pos MSM

Goldie 1999
First satisfactory anal cytology in men seen between 7/1/08 and 6/30/2009
~ 75% first anal Paps abnormal
Number of anal Paps performed – 280
Percentage of MSM screened – 63%
Anal cytology alternatives

- Education
- Regular digital rectal examination
- No cytology without a referral route for high-resolution anoscopy with Rx capability
Biomarkers
Biomarker research

- Laboratory markers that predict progression of dysplasia
  - Low-grade → high grade
  - High-grade → cancer

- Objective assessments of risk
P-16

- pRB is inactivated by the E7 oncogene product.
- pRB inhibits transcription of the cyclin dependent kinase inhibitor gene p16\(^{\text{INK4a}}\)
- Increased viral oncogene expression may be expected to increase levels of p16\(^{\text{INK4a}}\)
  - Over expression seen in all cervical biopsy tissue
    - CIN-1 (40/47) except those associated with low-risk HPV (7)
    - CIN-2 (32/32)
    - CIN-3 (60/60)
    - SCC (58/60)
  - No over expression seen in
    - Normal epithelium (42/42)
    - Inflammatory lesions (48/48)
    - CIN-1 associated with low-risk HPV (7)

Klaes 2001
P16 and anal dysplasia

- Assessment of 8 potential biomarkers using immunohistochemical methods
- Minichromosomal maintenance proteins (MCM3, MCM4, MSM 6, MCM7), p21, Ki-67, p16 and proliferating cell nuclear antigen
- 392 biopsy slides were assessed.
- Using a cutoff of 25% and 50% lesional positivity for the MCMs, Ki-67 and p16 resulted in 100% sensitivity and 100% specificity to diagnose high-grade AIN
High-resolution anoscopy
HRA and image capture
Clock face
High-resolution anoscopy (HRA)

- Peri-anal inspection
- Digital examination
- Soak anal canal in 3% acetic acid
- Visualize transitional zone using a high-resolution anoscope (colposcope) with x 16 magnification
HRA – ADC Visit

- Discussion with patient
- External examination of the anus
- Digital Rectal Examination
Explaining anal dysplasia to patients

Rectum

Anus

High Grade

Low Grade

Cancer
HRA

- Gold standard for diagnosis of high grade dysplasia
- Anoscopy with application of acetic acid
- Assessment for abnormal visual markers (acetowhite change, punctation, mosaicism, lugol’s iodine negative)
- Biopsy if abnormal visual markers seen
HRA images

Normal  High Grade Dysplasia  Carcinoma
Anal high-grade dysplasia treatment

- **Medical**
  - Trichloroacetic acid
  - Imiquimod
  - Infra Red Coagulation
  - 5-Fluorouracil
  - Interferon
  - Liquid nitrogen

- **Surgical**
  - Electrofulguration
  - Cold scalpel excision
  - Laser ablation
Efficacy of surgical treatment

- Surgical (cold scalpel/electrofulguration)

- High-grade dysplasia recurrence or persistence:
  HIV-: 0/8 (32.3 +/- 20.6 months FU)
  HIV+: 23/29 (28.6 +/- 12.9 months FU)

- Mean time to recurrence in HIV+ group was 12 months

Chang 2002
IRC clinical experience

- HIV-positive MSM with high-grade anal dysplasia
  - HIV+ MSM – 72% cure (AIN 1 or normal epithelium) after 3 treatments with IRC
  - HIV+ MSM – 64% efficacy per treated lesion at 3 months

Goldstone 2007, Cranston 2008,
TCA

- TCA as primary Rx of AIN 2/3 at UCSF ADC between Jan 2000 and Dec 2004
- Clearance defines as absence of AIN by cytology/HRA after up to 4 treatments
- Population: 53 HIV-pos and 19 HIV-neg MSM
- Results:
  - 32% AIN 2/3 cleared to no lesions
  - Clearance improved with younger age, and if ≤ 2 lesions in HIV-pos men
  - Per lesion
    - 73% AIN cleared
    - 71% AIN 2/3 cleared to AIN 1 or less

Singh 2009
Imiquimod

- Cell activation by imiquimod via TLR-7 and secrete cytokines (IFN-α), (IL-6) and TNF-α
- FDA approved to treat actinic keratosis, superficial basal cell carcinoma, and external genital warts
- 61% efficacy when used in HIV-positive men to treat all grades of intra and perianal dysplasia

Kreuter 2008
Combination

- Treatment in one center of both low- and high-grade anal dysplasia
- Laser ablation initially, with surgical excision and Imiquimod used in follow up
- 65% disease free at 12 months
- Median time to cure was 31.5 months (significantly impacted by HIV status and volume of disease)

Nathan 2008
Vaccination

- Quadrivalent HPV VLP vaccine
  - Safe
  - Acceptable
  - Immunogenic
  - No efficacy data
- Therapeutic vaccination?
Acceptability

- Anal cytology
  - Age 18 to 59 years who self-identified as gay (n = 236) or bisexual (n = 70)
  - 83% willing to have a free test
  - 31% willing to pay
    - Perception of risk, worry, higher income

- Treatment of dysplasia
  - ?

- HPV vaccination
  - Gay/bisexual men: 74%
  - Heterosexual men: 34%

Reed 2010, Reiter 2010
Education
Anal dysplasia knowledge

- Gay community event, Melbourne, Australia
- 92% gay identified, 6.4% HIV-positive, 3.5% unknown status
- On a 12 point knowledge scale, zero scores were found for
  - Anal cancer - 19%
  - HPV knowledge - 47%
  - anal Pap knowledge - 55%

Pitts STD 2007
Community

The Pitt Men's Study

Features

A Word From Your Local "Online Sexual Health Educator"

High Rate of Hepatitis C Infection in Gay Men

County Health Department Tests Online Partner Notification

Internet Interventions for MSM in Pennsylvania

Are HIV Patients Aging Faster?

GLMA Statement on MRSA Infections among Gay Men

AIDS Still an Epidemic in the U.S.

MSM at Risk

Anal Pap Smears

Frequently Asked Questions and Answers About Coinfection with HIV and Hepatitis C Virus

Living with Lipodystrophy
Pittsburgh Pride 2009/10

TAKE CARE OF YOUR ..... 

ANAL DYSPLASIA: WHAT YOU NEED TO KNOW
YOUR ASS IS AT STAKE – PROTECT IT!

AIDShilfe
Summary

- HIV-positive individuals are at increased risk of HPV associated anal cancer
- This may be addressed by
  - Education
  - Anal cytology and HRA where available
  - Regular digital rectal examinations
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