Anal neoplasia in HIV+ men and women

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Estimated Annual Burden of HPV-Related Diagnoses in the United States

- 9,710 new cases of cervical cancer
- 1.4 million new cases of low-grade cervical dysplasia (CIN 1)
- 330,000 new cases of high-grade cervical dysplasia (CIN 2/3)
- 1 million new cases of genital warts


3,700 deaths estimated in 2006
**HPV**

Nonenveloped double-stranded DNA virus

- >100 types identified
- 30–40 anogenital,
  - 15–20 oncogenic types, including 16, 18, 31, 33, 35, 39, 45, 51, 52, 58
  - HPV 16 (54%) and HPV 18 (13%) account for the majority of worldwide cervical cancers.
  - Nononcogenic types include 6, 11, 40, 42, 43, 44, 54
    - HPV 6 and 11 are most often associated with external anogenital warts.


**HPV Infection and Productive Life Cycle**

- Virus introduced through microabrasion
- Infectious virions shed
- Late HPV protein production
  - L1 & L2
- Early HPV protein production
  - E1, E2, E4, E5, E6, & E7

E6 leads to degradation of p53
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

The prevalence of high-risk oncogenic HPVs increases with the severity of the lesion

* LSIL also includes ASCUS (atypical squamous cells of unknown significance)

Natural history of cervical neoplasia

0-1 Year 0-5 Years 1-20 Years

Initial HPV Infection → Continuing Infection → CIN 2/3 → Invasive Cervical Cancer

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)
- Host factors: immune response

Median duration 1-2 years

Cleared HPV Infection

Features of cervical HPV infection unique to HIV+ women

- Persistence of infection past the age of 30
- Infection with multiple HPV types
- Reactivation of previously acquired HPV infection
Clinical challenges in HIV+ women

- Poor response to standard therapy
- Need for multiple treatments with different therapeutic modalities
- Faster progression of invasive cancer with poorer therapeutic response
Guidelines for assessment of CIN in HIV+ women

- Pap smear at initial evaluation
- Repeat Pap smear 6 months later
- If both negative, can do annual Pap
- Low threshold for colposcopy
- Frequent, careful follow-up

Anal and cervical cancer incidence

- Cervical cancer prior to cervical cytology screening: 40-50/100,000
- Cervical cancer currently: 8/100,000
- Anal cancer among HIV- MSM: 13-35/100,000
- Anal cancer twice as high among HIV+ MSM than HIV-MSM
Relative risk of anal cancer in U.S. AIDS-cancer registry match study*

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>HIV+ women</th>
<th>HIV+ men</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;30</td>
<td>134</td>
<td>163</td>
</tr>
<tr>
<td>30-39</td>
<td>12.2</td>
<td>40</td>
</tr>
<tr>
<td>≥40</td>
<td>2.6</td>
<td>32</td>
</tr>
<tr>
<td>All ages</td>
<td>6.8</td>
<td>37</td>
</tr>
</tbody>
</table>

* Frisch et al, JNCI, May, 2000
Intra-anal SISCCA

Diagnosis of AIN/anal cancer

- Digital rectal exam = cancer screening test
- Cytology = AIN screening test, followed by HRA and biopsy
Anal and cervical HPV infection in HIV-positive women

Graph shows the prevalence of anal and cervical HPV infections in different CD4 counts among HIV-positive women. The bars indicate a higher prevalence of HPV infections in HIV-positive women compared to HIV-negative women.

Development of anogenital cancer

Diagram illustrates the progression of anogenital disease from HIV infection to anogenital cancer. Key steps include:
- Initial HIV infection
- HPV infection
- Progressive immune suppression (adaptive and innate)
- Genetic changes
- Development of LSIL and HSIL
- Death

Anogenital disease includes various stages such as HSIL, LSIL, and cancer, highlighting the progression through immune suppression and genetic changes.
Effect of HAART on development of anogenital cancer

Decreased Incidence of Anogenital Cancer

Increased Incidence of Anogenital Cancer

Effect of HAART on development of anogenital cancer

Decreased Incidence of Anogenital Cancer

Increased Incidence of Anogenital Cancer
**Anal cancer since introduction of HAART**

- **Chiao et al, JAIDS 2005 40:451-5**
  - Pre-HIV: 1973-1981 0.6/100,000
  - HIV: 1982-1995 0.8/100,000
  - HAART: 1996-2001 1.0/100,000
  - Female to male ratio 1.6:1 → 1.2:1

- **Bowers et al, JAIDS 21:06:38 2004**
  - 8640 HIV+ MSM in London
    - Pre-HAART incidence- 35/100,000 patient-years (95% CI 15-72)
    - Post-HAART incidence-92/100,000 patient-years (95% CI 52-149)

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**San Francisco AIDS Surveillance Registry-California Cancer Registry match**

- 14,210 adults with AIDS diagnosed in 1990-2000
- risk of anal cancer increased after 1995 (RH=2.9)

Who should be screened?

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

Anal cytology screening for AIN in MSM

The big question:

- Will anal screening and treatment of AIN lower the incidence of anal cancer?

U.S. anal screening guidelines

“Although formal guidelines recommending anal Pap smear screening have not been adopted, certain specialists recommend anal cytologic screening for HIV-1-infected men and women. High-resolution anoscopy (HRA) should be considered if the anal Pap smear indicates ASCUS or ASC-H and should be performed if a person has LSIL or HSIL on anal Pap smear. Visible lesions should be biopsied to determine the level of histologic changes and to rule out invasive cancer.”

Treating Opportunistic Infections among HIV-Infected Adults and Adolescents: Recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association/Infectious Diseases Society of America, 2005
Guidelines: Primary Care Approach To The HIV-Infected Patient

“Like cervical cancer, invasive squamous cell cancers of the anal canal are associated with certain types of human papillomavirus (HPV) infection, most notably, HPV-16 and HPV-18. Although this is a new practice that may not be routinely available, screening for cellular dysplasia is prudent and recommended, particularly in persons at high risk for infection with papilloma viruses”

Treatment of AIN

- No HPV-specific therapy
- Removal of lesional tissue
- Treatment approach is based on size of lesion
  - Limited- local therapy (< 1 cm²) 85% TCA/LN₂
  - Moderate- infra-red coagulation
    - 65% free of disease after median of 413 days
  - Large- surgery with cold scalpel excision, electrocautery, laser
  - Diffuse (circumferential)-5-FU cream, “watch and wait”
  - Perianal- imiquimod?
Benefits of anal screening

- Early in natural history - increased ease of treating small lesions
  - TCA/LN₂
- Mid-natural history - local vs. surgical removal
  - Infra-red coagulation
- Late in natural history - monitoring to detect early development of 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
    - 3 were re-excised and remain cancer-free, 2 required RAC
  - No patients required a colostomy
  - 17 of 19 (89%) developed recurrent HGD
    - Careful follow-up is essential

Berry, Jay and Palefsky, 2006
HPV prophylactic vaccines

- Highly effective to prevent INITIAL infection with HPV 6, 11, 16 and 18 and their associated lesions
- Have little effect on other HPV types
- Have no effect on existing disease
- Can they be used to prevent anal HPV infection?
- Can they/should they be used in HIV+ men and women?

HPV L1 Protein Self-Assembles Into VLPs$^{1-3}$

Neutralizing anti-HPV antibodies bind to type-specific neutralizing epitopes on the surface of HPV virus antigens.1

Immune Response to HPV Vaccines

Neutralizing anti-HPV antibodies prevent HPV infection of the host epithelial cell.\(^1,4\)


Quadrivalent HPV vaccine

Analysis of Efficacy Against HPV 16/18 Related CIN 2/3 or Worse (Protocols 005, 007, 013, 015)

<table>
<thead>
<tr>
<th>Population</th>
<th>HPV L1 VLP Vaccine N=10268</th>
<th>Placebo N=10273</th>
<th>Efficacy (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Cases</td>
<td>Incidence</td>
<td>No. of Cases</td>
</tr>
<tr>
<td>PPE</td>
<td>6487</td>
<td>0</td>
<td>8460</td>
</tr>
<tr>
<td>MITT-3</td>
<td>9431</td>
<td>122</td>
<td>9896</td>
</tr>
</tbody>
</table>

Source: Table 2.7.3-cervixcancer: 29, p. 127-8
**Quadrivalent Vaccine**

Approved by FDA in June 2006

Indicated in girls and females 9-26 years of age for the prevention of following diseases caused by HPV 6, 11, 16, 18:

- Cervical cancer
- Genital warts
- Cervical AIS
- CIN 2,3
- CIN 1
- VIN 2,3
- VaIN 2,3

http://www.fda.gov/cber/label/hpvmreq060806LB.pdf

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**Phase II Bivalent Vaccine**

Efficacy at two time periods:

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Received Vaccine</th>
<th>Placebo</th>
<th>Vaccine Efficacy</th>
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</thead>
<tbody>
<tr>
<td>Persistent infection*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>extended period</td>
<td>0</td>
<td>7</td>
<td>100%</td>
</tr>
<tr>
<td>combined period</td>
<td>1</td>
<td>23</td>
<td>96%</td>
</tr>
<tr>
<td>CIN 2,3 lesions*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>extended period</td>
<td>0</td>
<td>5</td>
<td>100%</td>
</tr>
</tbody>
</table>

*According to protocol population HPV 16 or 18 (6 mo definition)

Harper et al. (2006) Lancet
Issues to consider with HPV vaccination of HIV+ men and women

- Does the vaccine prevent HPV infection in boys?
- Does the vaccine prevent anal HPV infection?
- Can HIV+ mount and maintain titers?
- Is there sufficient lack of exposure to HPV to make vaccination worth it?
- Is the vaccine safe?