Human Papillomavirus (HPV): Screening in At-Risk Groups

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Life cycle of HPV

- HPV infects basal cells
- Parabasal cells and HPV replicate together
  - E1, E2, E6, E7 expressed
  - E6 inhibits p53: cell immortalization
  - E7 inhibits RBP: accelerates cell cycle progression
- Suprabasal cells terminally differentiate; HPV replicates
  - L1, L2 expressed
- Surface cells die and lyse
  - millions of infectious HPV/cell released

HPV Transmission

- HPV is released from infected desquamating cells
- Transmission mainly via direct contact with infected cells
- Transmission of genital HPV typically occurs through sexual contact

Practically everyone gets infected at some point during their lives
HPV Clearance and Persistence

- ~80% of HPV infections are transient
  - 70% of new HPV infections clear within 1 year and 91% within 2 years.
  - Median duration of infection = 8 months
- Persistence of high-risk HPV is crucial for development of disease
  - Other associated factors:
    - Age at acquisition (≥30 years)
    - Immunosuppression
    - Infection with oncogenic HPV types (more likely to persist)

Anal HPV Infection

- Cross sectional studies of any HPV detected in anal canal:
  - HIV neg MSM 40-60%
  - HIV pos MSM 60-90+%
  - HIV neg women 40%
  - HIV pos women 75%

- Factors:
  - Age
  - CD4 count

Chin-Hong J Infect Dis. 2004 Dec 15;190(12):2070-6
Anal vs. Cervical HPV Infection in Women

Palefsky et al.
HPV Causes Two Diseases

1. CANCER
   -- due to high risk (oncogenic) HPV types: 16, 18, 31, 33, 35, 39, 45, 51, 52, 58

2. WARTS
   -- due to low risk (non-oncogenic) HPV types: 6, 11, 40, 42, 43, 44, 54

Natural History of HPV Infection


HIV INFECTION COMPRESSES THE NATURAL HISTORY OF HPV INFECTION
HPV Infection Statistics: United States

- At least 80% of us will have an HPV infection by the time we reach 50.
- 3/4 of first-time HPV infections occur at <25 y.o.
- About 20 million new infections annually
  - Half of these are 15-24 years of age
  - 5-30% of these infected with multiple HPV types

HPV-Associated Cancers: General Population

- **In 2013:**
  - About 7,000 cases
    - 65% in women
    - 35% in men
  - About 900 deaths

Estimated Cancer Cases, 2013
## HPV-Associated Cancers: HIV+ Patients

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Relative Risk [95% CI]</th>
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<tbody>
<tr>
<td>Cervix</td>
<td>5.4 [3.9-7.2]</td>
</tr>
<tr>
<td>Vulva/Vagina</td>
<td>5.8 [3.0-10.2]</td>
</tr>
<tr>
<td>Penis</td>
<td>3.7 [2.0-6.2]</td>
</tr>
<tr>
<td>Anus (female)</td>
<td>6.8 [2.7-14.0]</td>
</tr>
<tr>
<td>Anus (male)</td>
<td>37.9 [33.0-43.4]</td>
</tr>
<tr>
<td>Tonsillar cancer (men)</td>
<td>2.6 [1.8-3.8]</td>
</tr>
<tr>
<td>Oropharynx</td>
<td>6.0 [3.5-9.7]</td>
</tr>
</tbody>
</table>

Frisch et. al.
Warts

- HPV 6 and 11 responsible for >90% of anogenital warts
- Peak prevalence
  - Women 20-24 years
  - Men 25-29 years
Genital Warts: Statistics

New cases per year in the United States:
1 million

Sexually active adults with visible genital warts:
1 in 100 (1 in 20 HIV+ patients)

People who will develop genital warts in their lifetime:
1 in 10

Invasive Anal Squamous Cell Carcinoma

- **Incidence rate:**
  - 60-80 cases/100,000 HIV+ MSM
  - Twice that of HIV- MSM rates

- **Typical HIV+ patient:**
  - MSM 42 years old
  - CD4 count 200/mm$^3$ or less
  - Low nadir CD4 count

- **Mortality rate at 5 years:** 50-80%
Perianal Squamous Carcinoma-in-situ (Bowen’s Disease)

- Symptoms: pruritis, mass, bleeding, pain
- Increased incidence in HIV+ patients, and not predictably associated with internal lesions
- Perianal Bowen’s has higher incidence of invasion (10-14%) compared to SCCIS of other sites (3-4%)
- High rate of recurrence: 1/3 of cases recurred in 5 years

Sarmiento et al., Dis Colon Rectum 40(8); 1997
Chin-Hong et al., Clin Inf Dis 35(9); 2002
A Brief History of the Pap Smear

- 1915: initially noted cyclic changes in vaginal cytology of the guinea pig
- 1923: abnormal vaginal cytology in women with uterine cancer
- 1943: published “Diagnosis of Uterine Cancer by the Vaginal Smear”
- 1960s: noted decrease in cervical cancer from 1st to 3rd most common cancer in women

George Nicholas Papanicolaou, 1883-1962
Transformation Zones of ♀ and ♂ Have Identical Embryologic Origins
How to Collect Anal Cytology

1. Wet dacron or rayon (NOT cotton) swab ~1½” into canal
   No prior douching, enemas or K-Y
2. Gentle outward pressure swabbing circumference
3. Process using dry slide or liquid media
Anal Cytology Screening: Current Approach

- All MSM, regardless of HIV status
  - HIV+: annually
  - HIV-: every 2-3 years
- Women with high-grade cervical or vulvar disease
- HIV-positive men and women, regardless of route of transmission
- Transplant recipients (immunocompromised)

Cervical and Anal Cytology Screening in HIV

Abnormal *Cervical* Pap, Prevalence

Abnormal *Anal* Pap in MSM, Relative Risk

<table>
<thead>
<tr>
<th>CD4 count, cells/ml</th>
<th>Percent</th>
<th>RR</th>
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<tbody>
<tr>
<td>&gt;500</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>200-499</td>
<td>10</td>
<td>2</td>
</tr>
<tr>
<td>&lt;200</td>
<td>70</td>
<td>5</td>
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Abnormal Cytology: What Next?

- Abnormal cervical Pap:
  - Current approach varies - many advocate colposcopy for all abnormal cervical Paps in HIV+ women

- Abnormal anal Pap:
  - External examination: biopsy if lesion seen, and if AIN2-3 refer for surgical management
  - Internal examination: high resolution anoscopy (HRA) with biopsy and ablation of AIN2-3
Algorithm for the Management of Anal Pap Smear Results

ASCUS, atypical squamous cells of uncertain significance; LSIL, low-grade squamous intraepithelial lesion; HSIL, high-grade squamous intraepithelial lesion; AIN, anal intraepithelial neoplasia; HRA, high resolution anoscopy.
High Resolution Examination of Transformation Zones

3% Acetic Acid

Lugol’s

Anus

Cervix
HPV Vaccine

- Quadrivalent 6/11/16/18 (Gardasil)
- Bivalent 16/18 (Cervarix)
- Both are virus-like particle (VLP) vaccines
Prevention: HPV Vaccine

- ACIP approved for 9-26 y.o.
- FDA approved for prevention of:
  - cervical dysplasia
  - cervical, vulvar, vaginal cancers
  - genital warts in females and males
  - anal dysplasia and cancer in females and males
- Guidelines for vaccination same for HIV-positive as for HIV-negative patients
- Vaccine schedule: IM, 0.5 ml, at 0, 2 and 6 months
Keep in mind...

- Vaccination *does not substitute* for routine cervical cancer screening
- Vaccination *does not offer protection* from infection with non-vaccine HPV types
- Vaccination is *preventive*, not therapeutic
SUMMARY

- HPV causes two diseases
- Persistent HPV infection underlies most genital epithelial cancers
- HIV+ persons are at higher risk for the development and recurrence of HPV-associated disease
- Cytology screening may be of use in detecting HPV-associated anal disease
- Vaccination against HPV may substantially change HPV-associated cancer epidemiology in coming decades