Managing HPV for HIV-Positive Women

Nikole D. Gettings, CNM, MSN
Memphis Center for Reproductive Health

Presented on September 9, 2010 at MCRH’s Parallel Paths Lunch and Learn for HIV/AIDS Providers
Supported through a generous grant from the MAC AIDS Fund
Parallel Paths Project

• A series of training sessions on topics of reproductive health for HIV/AIDS social and medical service providers

• Find more and updated information at: http://mcrh-tn.org/outreach_parallel_paths.asp

• Funding for this project provided by the MAC AIDS Fund.
Expert Medical Advisory Committee

- Nancy R. Berman, MSN, APRN, BC
- Barbara Clark, MPAS, PA-C
- Don Downing, RPh
- Francisco Garcia, MD, MPH
- Sherri Sheinfeld Gorin, PhD
- Richard Guido, MD
- Julie Hibben, LMSW, CPSI

more…
Expert Medical Advisory Committee
(Continued)

- Mary M. Rubin, RNC, PhD, CRNP
- Marie Savard, MD
- Anafidelia Tavares, MD, MPH
- Maria Trent, MD, MPH
- Jeffrey Waldman, MD
- Thomas C. Wright, Jr, MD
Learning Objectives

• Discuss the epidemiology and natural history of HPV infection and cervical intraepithelial neoplasia
• Identify the most common genital HPV types in benign and malignant disease
Learning Objectives (Continued)

• Discuss the significance of persistent infection with high-risk HPV type
• Identify the most common mode of HPV transmission
• Identify additional impact of HPV for HIV positive individuals
## HPV Associated with Cancer and External Genital Warts

<table>
<thead>
<tr>
<th>Selected types</th>
<th>High-Risk Types</th>
<th>Low-Risk Types</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>16,18,31,33,35, 39,45,51,52,56, 58,59,68,82</td>
<td>6,11,40,42,43, 44,54,61,72,81</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Associated abnormalities</th>
<th>Low-grade cervical lesions</th>
<th>Low-grade cervical lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-grade cervical lesions</td>
<td></td>
<td>External genital warts</td>
</tr>
<tr>
<td>Anogenital cancers</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

HPV Necessary for Cervical Cancer

Transmission: genital skin to skin contact
Via basal epithelium cells

LATENT HPV infection

Cofactors:
- Oral contraceptive use, other hormonal influences
- Parity
- Other STIs
- Smoking
- Nutrition
- Host genetics: Polymorphisms in HLA and other genes
- Viral genetics: Genotype, molecular variants

Persistent infection with oncogenic HPV types

Low grade lesions: CIN 1/LSIL
(Episomal HPV, koilocytotic atypia, mild dysplasia, lesion extends to less than 1/3 of the epithelium, most lesions regress)

High grade lesions: CIN 2-3/HSIL
(HPV integrates into the genome, genomic instability, moderate or severe dysplasia, extension to full thickness of the epithelium, regression less frequent than for CIN 1)

Invasive cervical carcinoma
(Disease extends beyond basement membrane and invades connective tissue, metastatic spread to lymph nodes and distant sites)

HPV Transmission

- Virus primarily transmitted via genital contact
- Primarily through sexual intercourse, including receptive anal intercourse
- Can also be transmitted by:
  - Non-penetrating sexual activities
  - Oral-genital contact
- Fomite transmission has never been proven

Natural History of HPV & Cervical Cancer

Persistence

Normal Cervix → Infection → HPV Infection → Progression → Pre-cancer → Invasion → Cancer

Clearance ← Infection ← HPV Infection ← Progression ← Regression ← Pre-cancer ← Invasion ← Cancer

Courtesy of M. Schiffman, National Cancer Institute.
High Lifetime Risk of HPV Infection

- 6.2 million new infections
- NHANES 2003-2004 reports a prevalence rate of 26.8% in US females age 14 - 59
- Approximately 75% lifetime risk for sexually active individuals
- Additional research for HIV positive individuals, show similar prevalence of HPV

New HPV Infection is Common in Young Women

Study of 603 female college students
• About 20% were HPV positive at entry
• Almost 40% converted to positive within 24 months

HPV Cumulative Incidence: Ho Study

Three-year study
• 608 college students in NJ
  ▪ Mean age 20 years
• Cumulative 36-month incidence of high-risk HPV in women negative at baseline: 43%
• By 12 months after infection, 70% had cleared the infection
• By 24 months, over 90% had cleared the infection

Prevalence of HPV in Men

- HPV prevalence in men ranged from 1.3% to 72.9%.
- Most studies (56%) showed ≥ 20% prevalence

Prevalence of HPV in Men (Continued)

• Rates were influenced by:
  ▪ Study population
  ▪ Number of sites collected
  ▪ Number of samples collected
  ▪ Methods used to detect HPV DNA
• Multiple types were common (>50%) and HPV 16 was consistently among the most common anogenital types isolated.

HPV Cumulative Incidence: Brown Study

Two-year study
• 60 female adolescents 14-17 years old
• 80% had high-risk HPV at some point
• Only 3 had all specimens test negative
• All 3 denied any sexual exposure

Role of Persistent Infection

• Persistent infection with high-risk types of HPV is necessary for the progression of high grade lesions to invasive cancer

• Only persistent infection with high-risk types of HPV progresses to high-grade precancerous lesions and invasive cancer

Role of Persistent Infection (Continued)

• Average episode lasts 4-20 months
• <50% of women have same type 1 year later
• Type 16 has a greater risk of persistence

HPV-Associated Disease

Anogenital cancers
• Cervical
• Anal
• Vulvar and vaginal

Munoz N. *Vaccine*. 2006; Lacey CJN. *Vaccine*.2006.
HPV-Associated Disease (Continued)

- Other cancers
  - Oral cavity, pharynx, larynx
  - Skin
  - Conjunctiva
- External genital warts
- Laryngeal papillomatosis

Munoz N. *Vaccine*. 2006; Lacey CJN. *Vaccine*. 2006.
HPV and Cervical Cancer

• Virtually all cervical cancers are associated with persistent infection with high-risk HPV types

• Data from a variety of studies have confirmed that certain HPV types are associated with cervical cancer:
  - 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59

• Others are probably associated:
  - 26, 53, 66, 68, 73, 82

HPV Impact: Cervical Cancer

• In the US in 2007:
  ▪ 11,150 cases
  ▪ 3,670 deaths

• Worldwide (2005 estimate):
  ▪ 288,000 deaths per year
  ▪ 80% of deaths occur in developing countries

• Cervical cancer screening: costs $3.4 billion annually

HPV Types Associated with Cervical Cancer

HPV and Non-Cervical Cancers

• HPV 16 and 18
  ▪ Evidence of causal role in cancer of vagina, vulva, penis, anus

• HPV 16
  ▪ Evidence of carcinogenicity in oral cavity, oropharynx, periungual skin

HPV and Non-Cervical Cancers
(Continued)

• HPV 18
  ▪ Some evidence of carcinogenicity in oral cavity
• HPV 6, 11, 16, and 18
  ▪ Limited evidence for carcinogenicity in larynx

## HPV Associated Cancer - US

<table>
<thead>
<tr>
<th>Site</th>
<th>Total Cancers</th>
<th># Cases Attributable to HPV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervix</td>
<td>11,150</td>
<td>11,150 (100)</td>
</tr>
<tr>
<td>Penis</td>
<td>1,280</td>
<td>512 (40)</td>
</tr>
<tr>
<td>Vulva/Vagina</td>
<td>5,630</td>
<td>2,252 (40)</td>
</tr>
<tr>
<td>Anus</td>
<td>4,650</td>
<td>4,185 (90)</td>
</tr>
<tr>
<td>Airway</td>
<td>24,540</td>
<td>6,380 (26)</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>47,250</strong></td>
<td><strong>24,479 (12)</strong></td>
</tr>
</tbody>
</table>

## HPV 16 and Abnormal Pap Tests

<table>
<thead>
<tr>
<th>Category</th>
<th>Percentage</th>
<th>Total per Year</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Paps</td>
<td>16+</td>
</tr>
<tr>
<td>ASC</td>
<td>5.1%</td>
<td>13.3%</td>
</tr>
<tr>
<td>LSIL</td>
<td>2.6%</td>
<td>23.6%</td>
</tr>
<tr>
<td>HSIL</td>
<td>0.7%</td>
<td>60.7%</td>
</tr>
</tbody>
</table>

CDC. MMWR (RR-2). 2007
Impact: External Genital Warts

- 90% caused by HPV types 6 and 11
- Affects 1% of sexually active women age 18 to 45
- 500,000 to 1 million cases annually
- 240,000 initial office visits
- 1/3 of all STI dollars
- $167 million annually annually

Transformation Zones and HPV Infection

- Area where one type of epithelium contacts and gradually replaces another through process of metaplasia
- Present in cervix, anus, tonsils
- Areas of HPV-related carcinogenesis

Moscicki AB. *Vaccine*. 2006.
Cervical Transformation Zone

Source:
<table>
<thead>
<tr>
<th>Antigen</th>
<th>Humoral Immunity</th>
<th>Cellular Immunity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacteria, Parasite</td>
<td>Antibody Production</td>
<td>Viruses, Tumors</td>
</tr>
<tr>
<td>B Cells</td>
<td>T Cells</td>
<td></td>
</tr>
<tr>
<td>Result</td>
<td>Cytotoxic T cell activation</td>
<td></td>
</tr>
</tbody>
</table>
T Lymphocytes

- Recognize peptide antigen presented in HLA
- T Helper Cells secrete cytokines
- Cytotoxic T lymphocytes attack tumor and HPV presenting cells
Risk Factors for HPV Infection

- Sexual Activity
- Multiple Partners
- Younger age at sexual debut
- Lack of condom use

Risk Factors for *Persistent HPV Infection &/or Neoplastic Progression*

- Smoking
- HPV type
- Increasing age
- Lack of condom use
- Immunodeficiency (eg, HIV)
- Possibly OC use
- Possibly other STIs, such as chlamydia

### Risk of Progression

<table>
<thead>
<tr>
<th>Degree of dysplasia</th>
<th>Regression</th>
<th>Persistence</th>
<th>Progression to invasive cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIN 1</td>
<td>60%</td>
<td>30%</td>
<td>1%</td>
</tr>
<tr>
<td>CIN 2</td>
<td>40-50%</td>
<td>40%</td>
<td>5%</td>
</tr>
<tr>
<td>CIN 3</td>
<td>33%</td>
<td>55%</td>
<td>&gt;12%</td>
</tr>
</tbody>
</table>

Current Approach to Cervical Cancer Prevention

Requires 3 separate but linked components:

• Screening
  ▪ Cytology with or without HPV DNA testing

• Evaluation of screen positive women using colposcopy and cervical biopsy

• Treatment of women with biopsy-confirmed high-grade cervical cancer precursors

Guidelines: Cervical Cancer Screening Interval

ACS

• Annually with conventional Pap test
• Every 2 years with liquid-based test
• At age 30 if 3 normal consecutive Pap tests, change to every 2 to 3 years

Management of Abnormal Pap Results in HIV-infected Women

Cytology

- Normal: Repeat in 6 months. After two consecutive normal results, screen annually
- ASCUS: 3 options
- ASC-H: Refer for colposcopy
- LSIL or HSIL: Refer for colposcopy
- AGUS: Refer for Colposcopy
In Summary

• Most will get HPV at some time
• Most will clear high risk HPV, but some will not
• The time to clear HPV is variable
• Persistence of HIGH RISK HPV can lead to true pre-cancer
• LONG persistence of HPV and CIN 3 are necessary for the accumulations of random mutations that can lead to cancer