Cervical Cancer Screening in HIV

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Presentation prepared by:
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Outline

• Epidemiology of HPV and cervical cancer in HIV
• Review of cervical anatomy and HPV pathophysiology
• Current cervical cancer screening guidelines
  - When to start
  - When to stop
  - What to order and how often
  - What to do after hysterectomy
  - Role of HPV testing
  - Special populations
• Follow-up of abnormal cytology
• Future directions in cervical cancer screening
Epidemiology of HPV and Cervical Cancer in HIV
HPV Epidemiology

- 5th most common cancer in humans
- 2nd most common cancer in women
- 190,000 women die each year worldwide
  - 78% in resource poor settings, still the leading cause of death from cancer for women
- Up to 50% of sexually active women in the US HPV+ 36 months after coitarche
  - Prevalence of ~57% in sexually active adolescent women
  - Resolution of infection occurs in 90% of adolescents in 2y
- Women 50 years of age: 80% will have acquired genital HPV infection

Human Papilloma Virus (HPV)

- Most common sexually acquired infection in the world
- DNA tumor virus
- Intraepithelial infection

- > 100 types
  - 40 infect cervix
  - 13 oncogenic (16, 18, 31, 33…) \( \rightarrow \) cancer
  - 6, 11 \( \rightarrow \) genital warts

- Recurrent infections common

- Available prevention: HPV vaccine and CONDOMS!

HPV and HIV

- HPV is more persistent in HIV positive women
- Higher levels of HPV are detected in HIV positive women
- Multiple HPV infections are more common
- The incidence rate of cervical cancer is still up to 9 times more likely in women with HIV
- Cervical cancer → AIDS-defining condition
- Cervical dysplasia → “B” condition

Persistent HPV infection can lead to:

- Warts
  - Genital
  - Anal
  - Oral

- Cancer precursors
  - CIN
  - VIN
  - VAIN
  - AIN

- Cancer (squamous and adenocarcinoma)
  - Cervix
  - Vulva
  - Vagina
  - Oral cavity
  - Penis
  - Oropharynx
# HPV and Cancer, US Rates 2004-2008

<table>
<thead>
<tr>
<th>Site</th>
<th>Average #/yr</th>
<th>% HPV related</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervix</td>
<td>11967</td>
<td>96</td>
<td>95-97</td>
</tr>
<tr>
<td>Vulva</td>
<td>3136</td>
<td>51</td>
<td>37-65</td>
</tr>
<tr>
<td>Vagina</td>
<td>729</td>
<td>51</td>
<td>37-65</td>
</tr>
<tr>
<td>Anus-female</td>
<td>3089</td>
<td>93</td>
<td>86-97</td>
</tr>
<tr>
<td>Anus-male</td>
<td>1678</td>
<td>93</td>
<td>86-97</td>
</tr>
<tr>
<td>Oral-female</td>
<td>2370</td>
<td>63</td>
<td>50-75</td>
</tr>
<tr>
<td>Oral-male</td>
<td>9356</td>
<td>63</td>
<td>50-75</td>
</tr>
</tbody>
</table>

Gillison, Cancer 2008; 113: 3036-46
Review of Cervical Anatomy and HPV Pathophysiology
Definitions and Anatomy

- Pre-pubescent cervix covered with columnar epithelium
- Columnar cells gradually replaced by squamous epithelium (squamous metaplasia)
- Squamocolumnar junction: intersection between columnar and squamous epithelium
- Transformation Zone: the area of squamous metaplasia
  - Most common location of neoplastic change
  - Important landmark for colposcopy

Figure 3. Cervical Squamocolumnar Junction (SCJ) and Transformation Zone

Mid-later Reproductive Stage (30s age-range)

New SCJ
Original SCJ
Transformation Zone

http://www.prn.org/index.php/coinfections/article/anogenital_hpv_neoplasia_hiv_positive_502
Normal Cervix

http://screening.iarc.fr/colpo.php
The Three Steps of Cervical Carcinogenesis.

The steps can be conceptualized as infection with specific high-risk types of human papillomavirus (HPV), progression to a precancerous lesion, and invasion. HPV infections are usually transient and are often associated with mild cytologic abnormalities. Persistent infection with high-risk types of HPV is uncommon and is required for progression.
Current Cervical Cancer Screening Guidelines
Different Guidelines: Different Functions

- USPSTF/ACS/ASCCP/ASCP → age, interval and frequency of screening (updated March 2012)
- ASCCP Consensus Guidelines → interpretation and management of screening and colposcopy results (updated 2006, minor changes March 2012)
- IDSA/CDC/HHS OI Guidelines → both (updated 2009)

- Ultimate goal of all guidelines is cervical cancer prevention via:
  - Screening (cytology with or without HPV DNA testing)
  - Evaluation of screen positive women using colposcopy and biopsy
  - Treatment of women with biopsy-confirmed high-grade cancer precursors
Frequency of Screening in HIV

• Pap smear twice in the first year after diagnosis or entry into care
  - If both Pap smears are normal, then annual screening with Pap
  - If abnormal, follow-up will depend on the abnormality

• Refer to colposcopy if:
  - ASCUS (Atypical squamous cells of undetermined significance)
  - ASC-H (Atypical squamous cells – cannot exclude high grade)
  - AGC (Atypical glandular cells)
  - LSIL (Low grade squamous intraepithelial lesion)
  - HSIL (High grade squamous intraepithelial lesion)

Cervical Cancer Screening Guidelines

<table>
<thead>
<tr>
<th></th>
<th>USPSTF/ACS/ASCCP (WOMEN WITHOUT HIV)</th>
<th>WOMEN WITH HIV</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGE AT INITIATION</td>
<td>21 regardless of risk factors</td>
<td>Onset of sexual activity</td>
</tr>
<tr>
<td>FREQUENCY</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age 21-29</td>
<td>Pap every 3 years</td>
<td>Annually</td>
</tr>
<tr>
<td>Age ≥30</td>
<td>Pap every 3 years OR Pap + HPV every 5 years</td>
<td>Annually</td>
</tr>
<tr>
<td>DISCONTINUATION</td>
<td>Age 65</td>
<td>??????? Never ???????</td>
</tr>
<tr>
<td>s/p HYSTERECTOMY</td>
<td>D/C if for benign reasons and no history of CIN 2+ for 20 years, otherwise screen for 20 years after</td>
<td>??????? Same ???????</td>
</tr>
<tr>
<td>HPV VACCINATED</td>
<td>No change</td>
<td>No change</td>
</tr>
</tbody>
</table>


Screening of Adolescents with HIV

- Symposium sponsored by NIH/ACS/ASCCP in 2009 to address adolescents
- Less is more approach
  - Start screening at age 21 regardless of risk factors
  - Never use HPV testing in adolescents
  - Rarely intervene with colposcopy or LEEP/CONE except HSIL, CIN3
    - Rationale: increased risk of pre-term delivery and LBW infants, psycho-sexual dysfunction, high rates of regression even with CIN 2,3
- But in HIV, regression rates are lower, more CIN
  - Start screening right away at onset of sexual activity
  - Any abnormality, ASCUS+ → colposcopy
  - Reserve treatment for CIN3
  - No role for HPV testing
Oops, I ordered HPV and it’s Positive

Pap negative, HPV positive

Repeat both in 1 year

Pap negative, HPV negative

Annual Pap screening

Pap negative, HPV positive

Colposcopy

Pap ASCUS+, any HPV result

Manage per ASCCP
Role for HPV Testing

General Population
- Triage ASCUS result
- Co-test with Pap ≥ 30 y
- Post-menopausal women LSIL
- Follow-up after colpo or treatment procedure (LEEP/CONE) per guidelines

HIV Population
- Triage ASCUS result?
- Co-test with Pap ≥ 30 y
- Post-menopausal women LSIL
- Follow-up after colpo or treatment procedure (LEEP/CONE) per ASCCP guidelines?
- Per CDC OI Guidelines: NEVER!

Pap Smear Results

- Inadequate
  - Repeat

- Negative
  - Trichomonas
    - Treat
  - Other non-neoplastic
    - Atrophy
    - Glandular Cells
      - Intravaginal Estrogen and repeat in 3 months
      - Gynecologic Exam

2006 Consensus Guidelines www.asccp.org
Pap Smear Results

Squamous Cell Abnormalities

- ASCUS
  - See next slide

- ASC-H
  - Can not exclude HSIL
  - Colposcopy

- LSIL or HSIL
  - Colposcopy
Triage of ASCUS Results

• Conflicting guidelines
  - 2006 ASCCP Guidelines
  - CDC OI Guidelines

• ASCUS common in HIV, up to 78% in 4-5 year follow-up

• ASCCP: HIV infected women with ASCUS can be triaged as uninfected women
  - UNLESS severely immunocompromised?

• CDC: Never use HPV, data insufficient in this population
ASCCP Algorithm for ASCUS Management

Management of Women with Atypical Squamous Cells of Undetermined Significance (ASC-US)

Repeat Cytology @ 6 & 12 mos

- Both Tests Negative
  - Routine Screening
- ≥ ASC (on either result)

HPV DNA Testing*
Preferred if liquid-based cytology or co-collection available

HPV Positive*
(managed in same manner as women with LSIL)

HPV Negative
Repeat Cytology @ 12 mos

Colposcopy
Endocervical sampling preferred in women with no lesions, and those with unsatisfactory colposcopy

- NO CIN
  - HPV Unknown
    - Repeat Cytology @ 12 mos
  - HPV Positive*
    - Cytology @ 6 & 12 mos OR HPV DNA Testing @ 12 mos
      - ≥ ASC or HPV (+)
        - Repeat Colposcopy
      - Negative
        - Routine Screening

CIN

Manage per ASCCP Guideline

*Test only for high-risk (oncogenic) types of HPV

Management of the Pregnant Woman

- Want to avoid invasive intervention in pregnant women
- Only finding that would affect management, timing, route of delivery is invasive cancer
- Can defer colposcopy for ASCUS and LSIL until 6 weeks post-partum
- Immediate colposcopy for HSIL or AGC

www.asccp.org
Follow-up of Abnormal Screening
Goal of Colposcopy

- Localize the Transitional Zone (squamo-columnar junction)
- Evaluate the extent of the disease with application of acetic acid
- Locate the area most suspicious for biopsy
- Determine if invasive cancer is present

http://screening.iarc.fr/colpo.php
Vazquez E. General Principles of Colposcopy, Residents Academic Day 7/22/2010 #7
• Available at ASCCP website
  - [http://www.asccp.org/LinkClick.aspx?fileticket=FRKDC1RPF7A%3d&tabid=5965](http://www.asccp.org/LinkClick.aspx?fileticket=FRKDC1RPF7A%3d&tabid=5965)

• Not specifically for women with HIV, but very similar to the OI Guidelines with the exception of HPV testing
Strategies for Improving Screening Rates

- Patient education addressing rationale and importance of Pap smears for women living with HIV
  - Face-to-face
  - Public Health materials in multiple languages
- Ask about specific concerns and normalize fear and embarrassment
- Offer options for a female clinician if patient uncomfortable with male provider, if possible
- Reminder notices, systemic ticklers
- Coordination of care with GYN
Possible Future Directions

- Role for HPV testing in women with HIV?
  - Increase interval for testing
- HPV Vaccine efficacy data in women with HIV
- New HPV vaccines
  - 9 valent, predicted to cover 85% of HPV infections (current 70%)
- More specific HPV tests for infection (DNA methylation)
- Anal Pap guidelines
  - Women with HIV, CIN3 likely candidates for screening
- Better financial coverage for HPV co-testing
  - Again not currently recommended in HIV
Take-Home Points

- Abnormal cervical cytology is more common among HIV-infected women
- Early diagnosis and treatment can be achieved only by routine screening, ideally as part of primary care
- Complete pelvic exam needed to evaluate for uterine, vaginal, and vulvar abnormalities, as well as vaginitis, condyloma, HSV and other STDs
- At this time, annual Pap smears are the standard of care
- Role of HPV testing is limited in women with HIV
  - Triage of women with ASCUS?
  - Follow-up after colposcopy?
- Be aware of and address cultural/individual factors that may be interfering with screening
- Refer to colposcopy for results of ASCUS (+/- HPV?) or worse
Resources

• ACS/ASCCP/ASCP Screening Guidelines

• USPSTF Screening Guidelines

• Adult and Adolescent OI Guidelines, pages 68-75

• American Society for Colposcopy and Cervical Pathology (ASCCP) Guidelines
  - www.asccp.org

• HRSA A Guide to the Clinical Care of Women with HIV/AIDS
  - www.hab.hrsa.gov

• Adolescent Guidelines and Rationale
  - http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3058950/