HPV in HIV

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Objectives

• Discuss the epidemiology of HPV infection and disease.

• Outline the pathogenesis of cervical cancer.

• Review current guidelines for cervical cancer screening in HIV-infected women.
Human Papillomavirus (HPV)

- More than 200 types identified
- 40 types can infected the cervix
- 12 carcinogenic HPV types
  - HPV 16 (50-55%) and HPV 18 (10-15%) account for majority of invasive cervical cancer worldwide

Non-enveloped, double-stranded Circular DNA virus (8000bp)

Bosch FX et al Vaccine 2008
Schiffman M et al; JNCI 2011
HPV Infections in the US

• There are more than 14 million new HPV infections annually.

• It is estimated that 50% of sexually active men and women will get HPV at some point in their lives.

• Almost 50% of new infections occur in women ages 15-24.
HPV-Associated Cancers

![Bar chart showing annual number of cases worldwide by location.](chart)

- **Cervix**: Highest number of HPV-induced cases.
- **Anus**, **Vagina/Vulva**, **Penis**, and **Throat** have lower numbers compared to Cervix.
- **Mouth** shows the highest total number of cases, including both HPV-induced and total cases.
Natural History of HPV Infection

- **Initial HPV Infection**
  - Within 1 Year
  - 1-5 Years
  - Up to decades

- **Persisting Infection**
  - 1-5 Years
  - Up to decades

- **CIN 1**
- **CIN 2/3**
- **Cervical Cancer**

CDC *Epidemiology and Prevention of Vaccine-Preventable Diseases*
HPV Infection and Cancer

- HPV is related to almost **100%** of cervical cancer cases, with two strains (16 and 18) related to approximately 70% of cervical cancer cases.
HPV Infection and Cervical Cancer

- Persistent infection with oncogenic HPV types can lead to cervical dysplasia and precancerous lesions.

- Cervical cancer is the third most common cancer in women worldwide. Virtually all cervical cancers are attributable to HPV.

- Cervical cancer mortality is an avoidable cause of death and marker of health disparities.
Cervical Cancer in the General Population

• Cervical cancer represents 0.8% of all new cancer cases in the U.S.

• Cervical cancer is most frequently diagnosed among women aged 35-44.
New Cervical Cancer Cases and Deaths per 100,000 in the U.S.

Cervical Cancer
Incidence Rates* by Race and Ethnicity, † United States, 1999–2013\textsuperscript{\textregistered6}

Sources: National Program of Cancer Registries and NCI’s Surveillance, Epidemiology and End Results Program (SEER) \textsuperscript{8}Data are from the National Vital Statistics System (NVSS).
Source: Division of Cancer Prevention and Control, Centers for Disease Control and Prevention § Data are from the National Vital Statistics System (NVSS).
# Cervical Cancer 2016 U.S. Estimates

<p>| | |</p>
<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td><strong>Estimated New Cases in 2016</strong></td>
<td>12,990</td>
</tr>
<tr>
<td><strong>% of All New Cancer Cases</strong></td>
<td>0.8%</td>
</tr>
<tr>
<td><strong>Estimated Deaths in 2016</strong></td>
<td>4,120</td>
</tr>
<tr>
<td><strong>% of All Cancer Deaths</strong></td>
<td>0.7%</td>
</tr>
</tbody>
</table>

Cervical Cancer Incidence Rates/100,000 by State, 2013

Cervical Cancer in HIV-infected Women

• Cervical cancer was declared an AIDS defining malignancy in 1993¹.

• Cervical cancer incidence is decreasing in the US except in women with HIV $26 \times 100,000$ vs $6 \times 100,000$ in HIV uninfected².

¹MMWR December 18, 1992 / 41(RR-17) 1993 Revised Classification System for HIV Infection and Expanded Surveillance Case Definition for AIDS Among Adolescents and Adults
²Abraham AG. JAIDS 2013;62:405-413
Cumulative incidence of cervical cancer (ICC) per 100,000 person-years, by time-updated age, in HIV-infected vs HIV-uninfected Women

Crude Incidence rate: ICC= 26 X100,000 pys

Abraham AG. JAIDS 2013;62:405-413
Cervical Cancer Risk Increases with Immunosuppression in HIV-infected Women

Source: Abraham AG JAIDS 2013;62:405-413
Guiguet M Lancet Oncology 2009;10:1152-1159
Cumulative incidence of ICC per 100,000 person-years by time-updated age, by baseline HIV status and HIV viral load

Source: Abraham AG JAIDS 2013;62:405-413
Guiguet M Lancet Oncology 2009;10:1152-1159
HPV-Associated Cervical and Anal Diseases in HIV-Infected Women

• HIV-infected women
  • High risk of cervical (RR= 5.4; 95% CI:3.9-7.2) and anal cancer (RR= 6.8; 95% CI: 2.7-14)

• Potential for increase in disease burden
  • Living longer on ARVT
  • Potentially longer duration of HPV persistence
  • Increasingly entering the age groups in which cervical cancer rates reach their peak
HPV Progression

- Infection
- Clearaance
- Progression
- Transformation
- Genetic/Epigenetic Changes
HPV in HIV Infection

• Both HIV and HPV are sexually transmitted.

• Both Viruses can induce shift in T-helper cell profile leading to HPV Persistence.

• Clinically:
  • HIV-infected patients have higher HPV local viral loads
  • Less clearance
  • More re-infections
  • More persistent infections
Effect of HIV on HPV

• Association of persistent HPV comparing HIV-infected and HIV-uninfected women
  • Any HPV type: 2 to 6
  • HPV types: 16 & 18: 6

• Greater diversity of HPV types
• Greater prevalence of multiple HPV types

Sun, XW et al: NEJM 1997
Effect of HIV on HPV

• HIV-infected women have:

  • Greater preponderance of oncogenic types other than HPV 16 and 18.

  • Higher prevalence rates of LSIL and HSIL.

  • More rapid progression rates

  • Higher persistence/recurrence rates following treatment
Abnormal Pap Rates in HIV-infected Women

Cumulative risk of any abnormal cytology after >10y was 77% among HIV+s and 50% among HIV-s

Cumulative risk of HSIL among HIV+s was 4% among HIV-s 1%

Massad LS 2008 Am Obs Gyn
Association of HPV infection and HIV Viral load in HIV-Infected Women

Luque, AE et al. JID 1999;179

N=93 (34% HR HPV+)
HPV genotype occurrences in 480 cervico-vaginal lavage specimens from 202 HIV-infected women 1996-2003

Luque, AE at al. JID 2006; 194:428–34
### Prevalence of HPV genotypes in HIV-infected Women in Seattle and Nairobi

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Number of CVL samples</th>
<th>HPV infections</th>
<th>HPV types at initial visit (number of occurrences)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seattle (n = 37)</td>
<td>35</td>
<td>Triple: 1</td>
<td>56 (2), 66 (2), MM8 (2), 81 (2), 70 (1), 6 (1), 16 (1), 33 (1), MM7 (1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dual: 2</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Single: 6</td>
<td></td>
</tr>
<tr>
<td>Nairobi (n = 50)</td>
<td>49</td>
<td>Triple: 1</td>
<td>53 (3), 33 (2), 58 (2), 16 (1), 18 (1), 62 (1), MM8 (1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dual: 1</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Single: 9</td>
<td></td>
</tr>
</tbody>
</table>

HPV, human papillomavirus; CVL, cervicovaginal lavage.

Numbers in bold type denote high-risk HPV types.
Effect of HAART use on HPV

• HAART Initiation in adherent HIV-infected women
  • Reduced prevalence of oncogenic HPV by 40%
  • Reduced incidence of oncogenic HPV by 50%
  • Increased clearance of HR-HPV SIL by 235%

• Benefits are less among non-adherent women

• HAART use may reduce cervical cancer risk

Source: Minkoff H. JID 2010;201:680-690
Effect of HAART on Progression of Cervical Dysplasia

- 245 women receiving care at the UR from 1991 to 2011
- 52% had reduced risk of progression to SIL compared to women not on HAART or earlier ARVT (p=0.0001)
- A greater increase of CD4 cell count was associated with a greater reduction on the risk of progression to SIL
- Menopausal women had a 70% higher risk of progression to SIL than premenopausal women (p< 0.0001), after adjusting for HIV medications, CD4 cell count, duration of HIV infection, prior IVDU, and smoking.

Kim SC et al Infect Dis Obstet Gynecol 2013
Effect of HAART and Menopause on the Risk of Progression of Cervical Dysplasia in HIV-infected Women

- Women receiving HAART had a 52% reduced risk in the progression to SILs compared to women receiving any other antiretroviral regimen or no regimen (CI: 0.33–0.70, P = 0.0001).

- A greater increase of CD4+ cell counts was associated with a greater reduction on the risk of progression to SILs.

- Menopausal women had a 70% higher risk of progression to SILs than premenopausal women (CI: 1.11–2.62, P < 0.0001), adjusting for HIV medications, CD4+ count, duration of HIV infection, moderation effect of menopause by age, prior IV drug use, and smoking.

Effect of HAART and Menopause on the Risk of Progression of Cervical Dysplasia in HIV-infected Women

- HAART reduces the risk of progression to SILs in HIV-infected women.

- Menopause is a risk factor to the progression to SILs. HIV-infected women who reach menopause early have higher risk of progression to SILs.

Impact of Serial Negative Pap tests in HIV-infected Women

• Among 942 HIV-infected women with negative Pap, high grade CIN developed in:
  • 1% within 15 months, 4% within 39 months

• After 3 negative Pap tests, pre-cancer developed in:
  • 0% after 15 months, 2% after 39 months
  • No cancers

• Consider 3-yr screening intervals if persistently Pap negative

Masad, LS et al Obstet Gynecol 2012;120:791-797
HPV Reflex TestingPotentially Useful inTriage of ASCUS in HIV + Women

- HPV testing in women with ASCUS followed semi-annually for 8 years
- High Sensitivity and Moderate Specificity indicate that few cases of CIN-1 will be missed and colposcopies will be avoided in ~2/3 with ASCUS who do not have CIN-2

<table>
<thead>
<tr>
<th>Colpo &amp; Histology Results</th>
<th>Oncogenic HPV DNA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>YES</td>
</tr>
<tr>
<td>&lt; CIN-2 (n+116 controls)</td>
<td>35</td>
</tr>
<tr>
<td>CIN-2 + (n=24)</td>
<td>16</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>94%</td>
</tr>
<tr>
<td>Specificity</td>
<td></td>
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</table>

D’Souza G et al AIDS 2014;28:1696-1698
Based on this model, a woman with a normal Pap smear and no oncogenic HPV should have low risk of cervical pre-cancer/cancer for several years———Regardless of HIV Status
<table>
<thead>
<tr>
<th>Age at initiation</th>
<th>USPSTF/ASCCP Women without HIV</th>
<th>CDC/HHS/IDSA Women with HIV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>21 regardless of risk factors</strong></td>
<td>21 regardless of risk factors</td>
<td>Onset of sexual activity, regardless of mode of HIV transmission and no later than 21 years old</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Frequency</th>
<th><strong>Age 21-29</strong></th>
<th><strong>Age &gt;30</strong></th>
</tr>
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<tbody>
<tr>
<td>Pap every 3 years</td>
<td>Pap every 3 years or Pap + HPV &quot;co-testing&quot; every 5 years</td>
<td>Pap at time of HIV diagnosis and if normal repeat in 6 m to 1 year. If results of 3 consecutive Pap tests are normal, retest in 3 years. <strong>No co-testing</strong></td>
</tr>
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<table>
<thead>
<tr>
<th>Pap</th>
<th>HPV</th>
<th>Repeat/Next step</th>
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<tbody>
<tr>
<td>-</td>
<td>+</td>
<td>1 year unless 16/18</td>
</tr>
<tr>
<td>ASCUS</td>
<td>+</td>
<td>Colposcopy</td>
</tr>
<tr>
<td>&gt;ASCUS</td>
<td></td>
<td>Colposcopy</td>
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**Discontinuation**

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<tr>
<th><strong>Age 65</strong></th>
<th><strong>Never</strong></th>
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Considerations in Pregnant Women

- Avoid invasive intervention

- The only finding that would affect management, timing, route of delivery is invasive cancer.

- Pap recommended at initial prenatal visit unless normal in the past year.

- Can defer colposcopy for ASCUS and SIL until 6 weeks post-partum
Considerations in Pregnant Women

- Immediate colposcopy for HSIL or AGC

- Treatment for CIN not recommended unless invasive disease is suspected.

- HPV vaccination not recommended during pregnancy
Prevention of Cervical Cancer

You may reduce your risk of cervical cancer if you:

- Use a condom every time you have sex to reduce your risk of contracting HPV.
- Delay first intercourse
- Have fewer sexual partners
- Avoid smoking
- Get vaccinated against HPV
- Get regular Pap tests screenings
Cervical Cancer Care Delivery Gaps

- About 55% to 60% of cervical cancers occur in women who have never been screened.

- Lower income women, women in fee-for-service plans are more likely to be diagnosed in later stages.
Barriers to Cervical Cancer Screening in HIV

- Psychological
  - Self-esteem
  - Fear of the test/Fear of the results
- Enabling Resources:
  - Conflicting Needs/Lack of social support
  - Inadequate information
- External Resources
  - Transportation,
  - Inadequate insurance
Thank You