HPV - all it can do…
Now, what we can do??

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Epidemiology of HPV

- 6.2 million infected annually
- 100 serotypes
- 40+ that affect/infect anogenital area
- Divided into high risk and low risk serotypes
- Most infections are asymptomatic or subclinical and **regress/clear over time**

**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 genital warts

*High risk; †Low risk.

Human Papillomavirus types
Over 140 genotypes infect human epithelium
Types are distinguished by the DNA sequence for the L1 protein

- Cutaneous
  - HPV-1, etc

- Mucosal (e.g. cervical, anal, oral)

- Low-risk/Non-Oncogenic
  - HPV-6, HPV-11

- High-risk/Oncogenic
  - HPV-16, 18, 31, 45, 33, 52, 58, 35

Genital warts
Dysplasia
Cancers

adapted from J. Kahn

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HPV and Cancer\(^1\)

<table>
<thead>
<tr>
<th>Cancer</th>
<th>% Associated With Certain HPV Types</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervical(^*)</td>
<td>≥95%</td>
</tr>
<tr>
<td>Vaginal(^*)</td>
<td>50%</td>
</tr>
<tr>
<td>Vulvar(^*)</td>
<td>&gt;50%</td>
</tr>
<tr>
<td>Penile</td>
<td>50%</td>
</tr>
<tr>
<td>Anal</td>
<td>&gt;70%</td>
</tr>
<tr>
<td>Oropharyngeal</td>
<td>20%</td>
</tr>
<tr>
<td>Nonmelanoma skin/cutaneous squamous cell</td>
<td>90%(^*)</td>
</tr>
</tbody>
</table>

*Includes cancer and intraepithelial neoplasia

\(^1\)Immune-compromised patients

Common HPV types

- **High Risk**
  - 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59

- **Low Risk**
  - 6, 11

Estimated Annual Incidence of HPV Cervical Infection/Dysplasia

<table>
<thead>
<tr>
<th>Cervical Infection/Dysplasia</th>
<th>United States</th>
<th>Worldwide</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPV infection without detectable cytologic abnormalities</td>
<td>10 million</td>
<td>300 million</td>
</tr>
<tr>
<td>Low-grade dysplasia</td>
<td>1 million</td>
<td>30 million</td>
</tr>
<tr>
<td>High-grade dysplasia</td>
<td>300,000</td>
<td>10 million</td>
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</table>

- Virtually all cases of cervical cancer come from high-grade dysplasias.

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Oncogenic HPV Types Are a Necessary Cause of Cervical Cancer

- Infection with oncogenic HPV types is the most significant risk factor in cervical cancer etiology.\(^1\)
- Analysis of 932 specimens from women in 22 countries indicated prevalence of HPV DNA in cervical cancers worldwide = 99.7\%.\(^1\)
- Specific oncogenic HPV types (16, 18, 31, 33, and 45) have been detected in 63\%–97\% of invasive cervical cancer cases worldwide.\(^2\)

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Invasive Cervical Cancer: 2001 US Incidence and Mortality\(^1\)

- In 2003, US cases of cervical cancer \(\sim\)12,200; deaths \(\sim\)4,100\(^2\)

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Mechanisms of HPV Transmission and Acquisition

- Sexual contact
  - Through sexual intercourse\(^1\)
  - Genital–genital, manual–genital, oral–genital\(^2\)
  - Genital HPV infection in virgins is rare, but may result from nonpenetrative sexual contact.\(^2\)
  - Condom use may help reduce the risk, but it is not fully protective.\(^2\)

- Nonsexual routes
  - Mother to newborn (vertical transmission; rare)\(^5\)
  - Fomites (e.g., undergarments, surgical gloves, biopsy forceps)\(^6\)\(^7\)
    - Hypothesized but not well documented


Risk Factors for HPV Infection

**Women**
- Young age (peak age group 20–24 years of age)\(^1\)
- Lifetime number of sex partners\(^2\)
- Early age of first sexual intercourse\(^3\)
- Male partner sexual behavior\(^4\)
- Smoking\(^4\)
- Oral contraceptive use\(^4\)
- Uncircumcised male partners\(^5\)

**Men**
- Young age (peak age group 25–29 years of age)
- Lifetime number of sex partners\(^6\)
- Being uncircumcised\(^6\)

Infection From Time of First Sexual Intercourse

![Graph showing cumulative incidence of HPV infection over months since first intercourse.](image)

Study of female college students (N=803)


HPV Clearance

- In women 15–25 years of age, ~80% of HPV infections are transient.
  - Gradual development of cell-mediated immune response presumed mechanism.
- In a study of 608 college women, 70% of new HPV infections cleared within 1 year and 91% within 2 years.
  - Median duration of infection = 8 months.
  - Certain HPV types are more likely to persist (eg, HPV 16 and HPV 18).

HPV Disease Progression

- In a study of women (N=899) 13–22 years of age positive for HPV DNA:
  - 260 (29%) were diagnosed with LSIL by cytology.
  - Probability of LSIL regression
    - 61% at 12 months’ follow-up
    - 91% at 36 months’ follow-up
  - Probability of progression to HSIL = 3%


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HPV Persistence

- Persistent infection: Detection of same HPV type two or more times over several months to 1 year

- Widely accepted that persistence of high-risk types of HPV is crucial for development of cervical precancer and cancer

- Other associated factors
  - Age (≥30 years)\(^2\)
  - Infection with multiple HPV types\(^3\)
  - Immune suppression\(^4\)

- Currently, there are no antivirals available to treat the underlying HPV infection.\(^5\)

*May be partially confounded by duration of infection
Cervical cancer screening

- Current ACOG guidelines support annual screening beginning at age 21, may decrease frequency to every 3 years if repeatedly normal

- HPV testing may be used in conjunction with cervical cytology in women 30 years and older to help guide frequency of screening
Cervical Cancer Prevention

- Cervical cancer screening (the Pap smear) has reduced cervical cancer deaths by 74% between 1955 and 1992
- In 2008,
  - 11,000 new diagnoses of cervical cancer in the U.S.
  - 3,900 deaths

Horner 2007, Ries 2007
http://www.papsociety.org/drpag.html

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Natural History of HPV Infection and Potential Progression to Cervical Cancer

Dysplasia

High risk and low risk HPV types can cause dysplasia, for example:

- Atypical squamous cells (ASC)
- Low grade squamous intraepithelial lesion (LSIL)
- High grade squamous intraepithelial lesion (HSIL)

Synergy between HIV and STIs

<table>
<thead>
<tr>
<th></th>
<th>Syphilis</th>
<th>GC/ CT/ Trich</th>
<th>HPV</th>
<th>HIV</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>↑↑↑↑↑↑↑↑</td>
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<td>↑↑↑</td>
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</table>
HIV and Pap Smears

- 30-60% of Pap smears from HIV positive women have cytological abnormalities (Larkin et al., 1999)
- 15-40% of these Pap smears exhibit dysplasia (Larkin et al., 1999)
- Women with HIV are more likely to have persistence of HPV and cervical dysplasia

Abnormal Pap Smears in HIV Positive Women
Genital Tract Neoplasia

### Pap Smear Screening - WIHS Cohort followed for 3.5 years

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Cumulative Risk</th>
</tr>
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<tbody>
<tr>
<td>HIV +</td>
<td>HIV -</td>
</tr>
<tr>
<td>Benign</td>
<td>33% 67%</td>
</tr>
<tr>
<td>Ascus</td>
<td>28% 23%</td>
</tr>
<tr>
<td>LGSIL</td>
<td>34% 8%</td>
</tr>
<tr>
<td>HGSIL</td>
<td>5% 3%</td>
</tr>
<tr>
<td>Cancer</td>
<td>0.4% 0%</td>
</tr>
</tbody>
</table>
Cervical Neoplasia

1. Cervical cancer is an AIDS defining illness
   1. In a study of 2,015 HIV-infected women and 577 seronegative controls, 58% of HIV-infected women had HPV as compared with the seronegative controls of 26%

2. In HIV positive women, dysplasia is associated with more extensive cervical involvement and is more likely to involve other sites in the lower genital tract

Anal and Cervical Cancer Incidence

- Cervical cancer prior to cervical cytology 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 70-??/100,000
What about the women?

Anal and cervical HPV infection in HIV-positive women

Figure 1. Four-year incidence of anal intraepithelial neoplasia (AIN) II and III in HIV-positive men who have sex with men (MSM), by CD4+ cell count (cells/μL), and in HIV-negative MSM.

Chin-Hong and Palefsky, Clin Inf Dis 2002; 35:1127–34
NOTE. Histological specimens are high-resolution anoscopy–guided biopsy specimens that were obtained during the same examination as the anal Papanicolaou (Pap) smear; if biopsy was not performed at this time, histological specimens represent surgical pathology findings, if they were recorded within 3 months of the anal Pap smear. AIN, anal intraepithelial neoplasia; ASCUS, atypical squamous cells of uncertain significance; HSIL, high-grade squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion; SCC, anal squamous cell carcinoma.

Panther CID 2004:38 (15 May)

### Table 1. Detailed histological grades for paired cytological specimens.

<table>
<thead>
<tr>
<th>Cytological category</th>
<th>No. of specimens</th>
<th>Histological grade, no. (%) of specimens</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Normal</td>
</tr>
<tr>
<td>Normal</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td></td>
<td>11 (59)</td>
<td>7 (37)</td>
</tr>
<tr>
<td>ASCUS</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td></td>
<td>11 (37)</td>
<td>7 (23)</td>
</tr>
<tr>
<td>LSIL</td>
<td>72</td>
<td></td>
</tr>
<tr>
<td></td>
<td>10 (14)</td>
<td>90 (50)</td>
</tr>
<tr>
<td>HSIL</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 (2)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Total</td>
<td>153</td>
<td>33</td>
</tr>
</tbody>
</table>

HPV clearance in HIV+ individuals

Pokomandy 2009
Genital warts

• Low risk for cancer but still problematic

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HPV and Anogenital Warts

- HPV 6 and 11 responsible for >90% of anogenital warts
- Peak prevalence
  - Women 20–24 years of age (6.2/1,000 person years)
  - Men 25–29 years of age (5.0/1,000 person years)
- Clinically apparent in ~1% of sexually active US adult population

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Treatment options

- Local TCA, podophyllin
- Imiquimod 5%
- Liquid nitrogen
- Infrared laser coagulation
- Surgery
What can be done??

VACCINATE!!
And do it soon
HPV vaccines

- Quadrivalent
  - Merck 6,11,16,18 *Gardasil*
  - FDA approved for men and women 9-26

- Bivalent
  - GSK 16,18 *Cervarix*
  - FDA approval for women 10-25

- Both are 3 series and highly immunogenic

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HPV vaccines
cont’d

- None offer therapeutic benefit once infected
- Not approved for use in men although studies ongoing
- Not protect against all high risk serotypes—
  - ⇒ Sero-replacement?
HPV Vaccine

- HPV vaccination prevents
  - HPV infection
  - Cervical cancer and its precursors
  - Genital warts

Rationale for Recommended Ages of Vaccination

- Vaccination should occur prior to HPV infection
- 6.2% of adolescents have sexual intercourse before 13 yo
HPV Vaccines Clinical Trials

• Clinical trials with
  – >50,000 young women
  – ~4,000 young men

• Randomized, controlled

Quadrivalent Vaccine Efficacy Against Abn. Histology

Future II, 2007
Bivalent Vaccine Efficacy Against Abnormal Histology

- HPV 16/18-related CIN2, CIN3, adenocarcinoma in women without high-risk HPV infection or abnormal cytology at the first dose
- 98% efficacy (96.1% confidence interval 90.4%-100%)
- Paavonen 2009

Quadrivalent Vaccine Efficacy Against Warts in Men

- HPV 6/11/16/18-related condyloma in men infected with HPV6/11/16/18 at the first dose
- 70.6% efficacy (95% confidence interval 59%-91%)

Safety Post-Licensing

• 23 million doses of the quadrivalent vaccine administered since 2006
• VAERS
  – Vaccine adverse event reporting system

Nonserious VAERS Reports

• 94% of VAERS reports are classified as nonserious
• The most common events were
  – Syncope
  – Pain at injection site
  – Dizziness
  – Nausea
  – Headaches
Serious Events Reported to VAERS

- 6% of VAERS reports classified as serious
  - Death (32 reported)
    - 26 confirmed deaths
    - No clustering
    - No association with vaccine
    - e.g., Diabetes, viral illness, illicit drug use, heart failure
    - 2 reports of unusual neurological illnesses
  - CDC/FDA review concluded that these events do not appear to be causally linked to the vaccine

Age of Vaccination in Females

- Bivalent (HPV2, Cervarix) and Quadrivalent (HPV4, Gardasil)
- Target population is 11 to 12 year olds
- 9 to 10 year olds can be vaccinated at provider discretion
- 13 to 26 year olds should be vaccinated
  - Follow recommended dosing intervals in 13-26 yo, not the minimum recommended intervals

HPV Vaccination in Males

- **Quadrivalent vaccine only (HPV4, Gardasil)**
- “may be given to males aged 9 through 26 years to reduce their likelihood of acquiring genital warts. Ideally, vaccine should be administered before potential exposure to HPV through sexual contact”

Precautions

- **Syncope**
  - Due to vasovagal reactions
  - Because of the risk of head injury from falling, sit or lie for 15 minutes after vaccination
Vaccine and Pregnancy

- HPV vaccines are not recommended in pregnancy
  - Ask about chance of pregnancy
  - Pregnancy test only required if indicated by patient’s history

- Neither vaccine has been shown to be causally associated with adverse outcomes in pregnant women or fetuses

Contraindications

- Immediate hypersensitivity to yeast

- Any vaccine component
HIV and HPV vaccination

- One completed study of safety and efficacy in HIV+ men.
- Safe
- Very immunogenic but less so than HIV-
- Unclear if clinically significant
- Currently enrolling HIV+ females for similar study

Still Give the Vaccine

- Regardless of abnormal Pap smears
- Regardless of genital warts
- Breast-feeding
- Immunocompromised
  - Vaccine not infectious
  - Immunocompromised patients may be at increased risk from HPV associated cancers
- Concomitantly with other vaccines
Even Though You’re Vaccinated

• Cervical cancer screening should continue regardless of vaccination status
  – Patients may already be infected with vaccine-HPV types before vaccination
  – Nonvaccine types can still cause dysplasia, precancersous lesions, and cancer

• Condoms are still needed to prevent other STIs

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