Human Papillomavirus: Overview of Epidemiology and Genital Warts

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Epidemiology of HPV
Viral versus Bacterial STDs

- Prolonged, often lifelong infection
- Incurable
- More widespread in the population; everyone (almost) is really at risk
- Lower ratio of serious outcomes to overall incidence and prevalence
- Traditional diagnostic methods are less sensitive
- Prevention is more dependent on behavioral measures or immunization
- Better prospects for effective vaccines
HPV and Neoplasia

HPV *causes* pre-cancerous neoplasia and squamous cell cancer of the cervix, anus, vulva, and penis.
HPV-Associated Anogenital Cancer

• Cervical
  – Pre-Pap incidence in the United States was 30-40/100,000 women, now 8.5/100,000 (-75%), primarily attributed to cytology screening
  – Still 30-40/100,000 in developing countries without screening and related services

• Other cancers
  – Penile, vulvar, etc approx 1/100,000
  – Anal cancer in MSM 30-40/100,000
  – Oropharyngeal
Genital HPV Infection

- >100 HPV types, of which 30-40 are primarily genital
- Low-risk types (HPV-6,11)
  - Genital warts
  - Low-grade Pap smear changes (ASCUS, LSIL)
- High-risk types (HPV 16, 18, 31, 33, 35, others)
  - LSIL, HSIL, squamous cell cancer
- Natural course
  - HPV 6/11: probably ≥80% develop visible warts
  - HPV 16, 18, etc: Primarily subclinical
  - Spontaneous resolution is the rule
    - HPV 6/11: 6-12 months
    - HPV 16/18: 12-24 months
Patterns of Cervical Lesions Associated with Low- and High-Risk Genital HPV Types

Bar chart showing the relative percentage of lesions associated with low-risk HPV and high-risk HPV for exophytic condylomata, low-grade SIL, high-grade SIL, and invasive cancer.
Transmission of Genital HPV

- Probably requires microtrauma; warts occur most frequently at sites of maximum sexual friction
  - Men: Glans penis, shaft
  - Women: Introitus, labia minor, anus
  - However, others sites common, often through autoinoculation (scrotum, groin, anus, etc)

- Direct genital-genital or anogenital contact
  - Genital to oral transmission occurs, but relatively inefficient
  - Hand-genital rare, but probably explains some cases
  - Fomite transmission not documented

- Circumcision is partially protective

- Perinatal transmission causes recurrent respiratory papillomatosis in infants and young children (rare)

- Source contact usually has unrecognized infection
Prevalence of HPV in Undergraduate University Women

Source: Koutsky et al.
Natural History of HPV in Young Women

- 608 university students, followed q 6 mo x 3 yr; PCR for 35 types of genital HPV on cervicovaginal lavage

- Baseline prevalence 26%

- Incidence in baseline HPV-negative women
  - 1 yr 20%
  - 2 yr 14%
  - 3 yr 9%
  - Cumulative 36%

- Risk factors: younger, minority, alcohol; >3 SP in past 6 mo; main SP known to have had other partners

Ho et al. NEJM 1998; 338:423-8
Natural History of HPV in Young Women

- Type-specific cumulative 24 mo incidence & median duration
  
<table>
<thead>
<tr>
<th>Type</th>
<th>Incidence</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPV 51</td>
<td>8%</td>
<td>7 mo</td>
</tr>
<tr>
<td>HPV 6</td>
<td>5%</td>
<td>6 mo</td>
</tr>
<tr>
<td>HPV 66</td>
<td>7%</td>
<td>6 mo</td>
</tr>
<tr>
<td>HPV 18</td>
<td>4%</td>
<td>12 mo</td>
</tr>
<tr>
<td>HPV 16</td>
<td>7%</td>
<td>11 mo</td>
</tr>
<tr>
<td>HPV 59</td>
<td>4%</td>
<td>6 mo</td>
</tr>
</tbody>
</table>

- Reinfection with same HPV type was not seen

- Persistent infection
  
  - Median duration of incident infection: 8 mo
  - 30% had infection that persisted ≥12 mo
  - 9% had infection that persisted ≥24 mo
  - Risk factors: older; infection with >1 type or HR type; previously persistent; non-smoker

Ho et al. NEJM 1998; 338:423-8
Prevalence of Genital HPV Infection in Women
Prevalence of HPV in Men
Dunne EF et al.  *J Infect Dis* 2006;194:1044-57

Circle size proportionate to N
HPV in Zimbabwe

- HPV types associated with cervical cancer are typical: HPV 16, 18 account for 60-70% (Chirenje et al, 2002)
- HPV prevalence and types in women without cancer (Baay et al, 2005)
  - N = 200, rural setting
  - Overall prevalence 25%
    - Age 15 – 24 35%
    - Age 45 – 49 12%
- Similar results more recently (Fukuchi et al, 2009)
  - N = 2,040 (Harare, Bulawayo)
  - Prevalence 25% overall, oncogenic types 16%
  - Incidence 23%/yr overall, onco types 11%
Condom Use and Risk of HPV in Young Women


- Initially virgin university students followed through first vaginal intercourse and thereafter;  N = 82
- Prospective on-line diaries of sexual events and condom use
- Mean follow-up time: 33.9 (±11.8) months
- By 1 year after their first intercourse, 37% of women tested positive for HPV
  - 126 incident type-specific HPV infections were detected in 40 women after first intercourse
- By 2 years after their first intercourse, 15% of women developed cervical SIL
## Condom Use and Risk of HPV in Young Women


<table>
<thead>
<tr>
<th>Condom use</th>
<th>Adjusted Hazard Ratio* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5%</td>
<td>1.0</td>
</tr>
<tr>
<td>5-54%</td>
<td>1.0 (0.5-1.8)</td>
</tr>
<tr>
<td>55-99%</td>
<td>0.5 (0.3-0.9)</td>
</tr>
<tr>
<td>100%</td>
<td>0.3 (0.1-0.6)</td>
</tr>
</tbody>
</table>

* Adjusted for number of new sex partners and perceived number of male partner’s previous sex partners
Effectiveness of Condoms in Preventing HPV

- Condoms provide a high degree of protection against genital HPV in women  \textit{Winer et al (NEJM 6/06)}
  - 123 F university students followed \textasciitilde 2 yr with real-time computer-reported diaries of sex and condom use
  - 24 mo. incidence of 47.5\% first-time HPV; 100\% condom use \textcolor{red}{\textit{\rightarrow adjusted HR 0.30 (0.10-0.88)}} (controlled for all conceivable confounders)
    * HR 0.13 when also controlled for non-insertive genital apposition

- Condoms protect against anal HPV in MSM; prospective cohort study, controlled for all the usual variables \textit{Chin-Hong et al}
Immunocompromised patients

- Detection of HPV, EGW, and HPV-associated SIL are more prevalent in HIV+ persons, especially with advancing immunodeficiency
- It is less clear whether cancer per se occurs with increased frequency, but it probably does
- Probably related to impaired immunity; perhaps also viral interaction (transactivation of HPV by HIV)
- Uncertain whether HPV enhances HIV transmission
Genital Warts
Weighted percentage of sexually active persons aged 18 to 59 years who reported ever having a diagnosis of genital warts by sex and age group, NHANES, 1999-2004.

Figure 3. Estimated cumulative incidence of self-reported clinically diagnosed genital warts, by country and birth cohort. The cumulative incidence of having had genital warts up to a certain age was estimated on the basis of information on age at first diagnosis of genital warts.
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Proportion Developing GW Due to HPV-6 and/or -11
Garland SM et al. *JID* 2009;199:805-14

Biopsy-confirmed GW
(n = 351)

Positive for HPV-6
(n = 261; 74.4%)

Positive for HPV-11
(n = 50; 14.2%)

Positive for both HPV-6 and HPV-11
(n = 13; 3.7%)

Negative for both HPV-6 and HPV-11
(n = 53; 15.1%)
Cumulative Incidence of Clinically Apparent GW Among Women with Incident HPV Infection

Winer RL et al. *JID* 2005;191:731-738

- **N = 603**
- In 45 women with incident HPV 6/11 infection, 64% (95%CI 51-77%) developed clinically apparent warts within 36 months
- Median ~6 months
- Anatomic site (N = 31)
  - Vulvar, perineal, perianal 28
  - Cervical 2
  - Vaginal 1
Cumulative Incidence of Clinically Apparent GW Among Women with Incident HPV Infection

Winer RL et al. *JID* 2005;191:731-738

N = 603 female university students, mean 39 mo. follow-up

HPV 6 or 11

Other HPV types
Time to Development of Genital Warts Caused by HPV-6/11

Garland SM et al. JID 2009;199:805-15

A Negative for HPV-6/11 at enrollment
- HPV-11 (n = 29)
- HPV-6 (n = 168)

B Positive for HPV-6/11 at enrollment or within 7 months
- HPV-11 (n = 7)
- HPV-6 (n = 71)
Clinical Presentation and Transmission of Genital Warts

- Incubation period 2-12+ mo (up to 36 mo)
- Symptoms ~60% (range ~50-70%)
  - “Bumps”, self-recognition of warts
  - ? Pruritus, “irritation”, “burning” [PROBABLY NOT]
- Transmission: Vaginal and anal intercourse; perhaps occasional orogenital or hand-genital transmission
- Predominantly at sites of maximum friction during sex
  - Introitus, labia minor
  - Penis
  - Anus
  - Less commonly: scrotum, labia major, pubic area
Clinical Manifestations of Genital Warts

- Condylomata acuminata: Moist surfaces; “cauliflower” morphology with capillaries in individual fronds
- Papular (smooth appearance)
- Keratotic (cauliflower shape, dry, horny)
- Flat warts
Psychosexual Impact of Genital Warts and Intraepithelial Lesions

Based on a systematic Medline search:

- Most frequent reported emotions
  - Depression
  - Anxiety
  - Anger

- Emotional morbidity increases with rising numbers of episodes and/or recurrences

- No clear evidence of association of GW with psychosexual morbidity per se (sexual dysfunction, vulvodynia, etc)
  - Research is needed
Immunocompromised patients

• Detection of HPV, EGW, and HPV-associated SIL are more prevalent in HIV+ persons, especially with advancing immunodeficiency
• It is less clear whether cancer per se occurs with increased frequency, but it probably does
• Probably related to impaired immunity; perhaps also viral interaction (transactivation of HPV by HIV)
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Available Treatment Modalities

- Podophyllin resin
- Tri- and bichloroacetic acid
- Imiquimod (Aldara®)
- Podofilox (Condylox®)
- Sinecatechins (Veregen®)
- Interferon (lesional, systemic)
- IntraleSIONal immunotherapy
- Cidofovir
- Isotretinoin
- Cryotherapy
- Electrocautery
- Surgical excision
- Laser cautery
- Photodynamic therapy
- Green tea extract (Polyphenon E®)

- All except excision have 60-80% short-term efficacy; all have high rates of recurrence
- Effect on transmission unknown: Reduced viral load? Transmissibility from adjacent, clinically normal areas?
Figure 1  Cumulative wart clearance rate, by treatment, intention-to-treat analysis

N = 409

Management of HIV-infected Patients with HPV

- Pap smear screening for women (twice in first year after HIV Dx, then annually)
- Role of anal cytology unclear
- Response to treatment of EGW is impaired, with more frequent recurrences; when/how to treat should be individualized