

## **Male HPV Infection - A Challenge For Diagnosis & Treatment**

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### **Outline**

Overview of HPV

Differential diagnosis

Special cases

HPV screening in males

Treatment and follow up for HPV in males

Prevention of HPV in males

Conclusions

### **HPV Facts**

- Until recently, HPV prevalence was the least known STD among college students
- HPV research has focused on women and cervical cancer
- By comparison, few efforts have been made in male HPV research
- Little concrete data is available on the natural history of HPV infection in males
- Data on male HPV prevalence varies among studies

### **HPV Facts**

Reasons for the lack of knowledge regarding HPV infection in males:

- HPV infection has fewer serious consequences for men than for women
- Adequate screening methods have been established for women
- No practical or universally accepted method has been developed for men

### **HPV Facts**

- Cutaneous HPV types account for two-thirds of all infection: common & plantar warts
- Mucosal HPV types account for the remaining one-third in the form of condyloma (anogenital warts) and/or neoplasia
- Low-Risk HPV: **6, 11**, 42, 43, 44, 54, 61, 70, 72 & 81 (84 also under study)
- High-Risk HPV: **16, 18**, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73 & 82

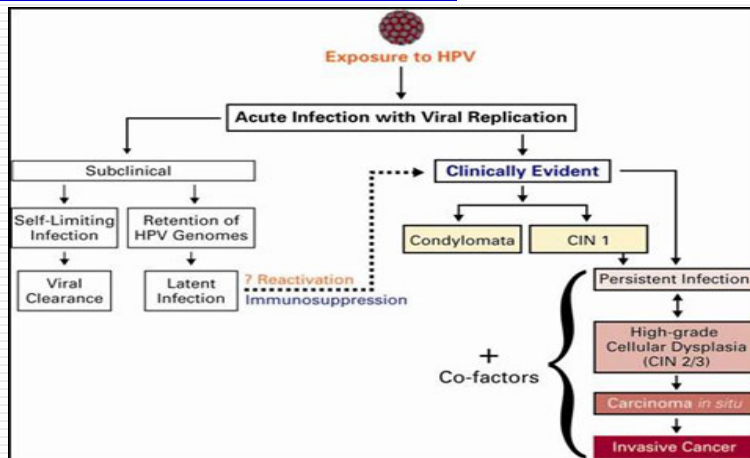
### **HPV Facts**

- **Low-Risk HPV Types:**
  - Non-oncogenic (rarely isolated from neoplastic lesions)
  - Types 6 & 11 account for > 90% of all condyloma
- **High-Risk HPV Types:**
  - Oncogenic - responsible for 99.7% of all cervical cancer (16 & 18 account for 70% of cervical neoplasms)
  - Oncogenic possibilities exist for males in the form of penile, anal, urethral and bladder cancer

### **HPV Transmission**

- Direct Contact with Infected Skin Surfaces
- Fomite Transmission has not been ruled out (Stevens-Simon, et al, 2000)
- Vertical Transmission rate has been determined at < 1% (Smith, et al, 2004)
  - ~2,000 of 4,000,000 infants neonates are infected with **Respiratory Papillomatosis** via vertical transmission

## Natural History of HPV



MerckMedicus: HPV Disease – July, 2006

Male HPV Infection

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Transmission: starting point

Latent Period/Incubation: -Lasts several weeks to several years (average 1 – 12 months)

-Subclinical phase

-Many HPV infections are self-limiting and resolve without symptoms

Host Cell-Mediated Immune Response:

-begins ~ 3 months post infection

-most HPV infections clear without symptoms

-HPV infection that is not contained can enter a latent phase and reappear as condyloma or intraepithelial neoplasia at a later date

HPV Clearance vs. Persistent Infection:

Clearance:

-Eradication

-Levels too low to be detectable

Persistence:

-Clinical evidence of infection

Condyloma (genital warts)

Squamous Intraepithelial Lesions (abnormal proliferation of cells)

Cause = Low or High Risk HPV

Clearance vs. Persistent HPV Infection:

-even with active gene expression, as many as 90% of HPV infections will either clear or become latent

-10% - 20% of HPV infections will persist due to host, viral or environmental factors:

-immune compromise

-smoking

-infection with high-risk types

-infection with > one type of HPV

	Male HPV	Female HPV
Research	Beginning in 21st Century	Studies since 1920
Literature	Few specifically male	Most target females
Screening Method	No approved method	Pap Test since 1943
Testing Method	No approved method	Hybrid Capture, PCR
Visible Symptoms	Not easily detected	Often self detected
Health Ed. Efforts	Males overlooked	Favor females
Treatment	Only with symptoms	Symptoms & Pap F/U
Prevention	Condoms	Approved Vaccine
	<b>Male</b>	<b>Female</b>
Role in Transmission	Viewed as a <i>vector</i> for female infection	Viewed as a <i>victim</i> of HPV infection
Morbidity	Condyloma and neoplasms ( <b>Anus, Penis, Urethra &amp; Bladder</b> )	Condyloma and neoplasms of the cervix
Mortality	Anal, Penile and Bladder carcinomas	Predominantly Cervical Carcinoma

**HPV Facts:**  
Male vs. Female

#### Prevalence

- Anogenital HPV infections are highest among college-age men & women (estimates from 50% to 80% among the 18 - 25 year age group)
- Overall prevalence rate of HPV in women is 22% to 35%
- HPV prevalence in men is 2% to 35%
- HPV prevalence in men relates to sexual practices and the ability to diagnose infection (Gearhart, Peter A., MD, ACOG, Jan., 2007)

Incidence rates for male HPV infection are difficult to assess due to:

- tendency for infection to be asymptomatic
- lack of approved screening methods

Studies in male HPV infection yield widely ranging prevalence estimates (5.5 – 76%) depending on the population, site tested, sampling method and procedure used. (Weaver et al, Journal of Infectious Disease, 2004:189, February 15)

#### **Factors in Statistical Variations:**

Population: HPV prevalence is greater in certain locations, e.g., Mexico

Site Tested: HPV detection varies by male genital or anal site

Sampling Method: wet vs. dry, swab vs. cytobrush, with/without abrasion, dermis vs. urine vs. blood

Procedure: serology, HPV DNA detection (hybrid capture or PCR), cytology

Estimated prevalence of genital HPV infection among men & women 15-49 years of age in the US (1994) adapted from Soutshy et al. Am J Med:10295a, 1997

Visible Genital Warts:	1%
Subclinical Papillomavirus Infection, Colposcopy or Cytology:	4%
Subclinical Papillomavirus Infection, DNA or RNA Probes:	10%
Prior Infection:	60%
No Prior or Current Infection:	25%

HPV Prevalence in Healthy Men vs. Men with Urethritis

- 75 “healthy” volunteers (18-35yrs) & 130 men with urethritis (17-49yrs)
- Specimen collection via moist cotton swab → Hybrid Capture II
- Sites = glans, coronal sulcus & inner surface of the prepuce

**RESULTS:**

	<u>“healthy” men</u>	<u>men w/ urethritis</u>
	74 (98.7%) HPV-	106 (81.5%) HPV-
	1 (1.3%) HPV+	24 (18.5%) HPV+
	low-risk: 0	low-risk: 4 (16.7%)
	high-risk: 1 (100%)	high-risk: 12 (50%)
	both types: 0	both types: 8 (33.3%)

Variables:

- men with urethritis had coitus more frequently and had more partners
- samples among those w/ urethritis were collected by physicians – samples among the “healthy” men were self-collected

**CONCLUSION:** frequency of sexual activity and number of sexual partners increase the probability of HPV infection - collection process may influence outcome (Takahashi, S. et al. DOI:10; August, 2003)

**Prevalence of HPV Infection Among Men: A Systematic Review of the Literature** (Dunne, E. et al. JID:2004;194:1044-1057:October 15)

- “HPV prevalence varied on the basis of sampling, processing methods, anatomic sites or specimens...”
  - “Serologic testing for IgG antibodies may be a better measurement of cumulative exposure...but likely underestimates the cumulative incidence of HPV....”
  - “..using a saline-wetted sterile Dacron swab after ..rubbing the sample site with..emery paper was superior for specimen adequacy...”
  - “...best anatomic sites for....detection of HPV DNA appear to be the glans, corona, prepuce and shaft of the penis”
  - “The prepuce is possibly the best single site for HPV DNA detection” however, sampling multiple sites increases adequacy
  - “overall viral loads were much lower in penile-scrape specimens than in cervical scrape specimens”
  - “..semen, urine and urethral swabs”....are less useful as specimens
- Male HPV prevalence proved “as high as 72.9% and usually >20%”
  - “Eight of 9 studies that compared seroprevalence in men & women reported a higher seroprevalence in women than in men”
  - “High-risk and low-risk types were less likely to be detected in circumcised men”
  - “..76% of male partners of women with HPV were HPV DNA positive”
  - “HPV types detected in men...were similar to types commonly detected in women...type 16 was consistently most common...” with 6,11 & 18

(Dunne et al, JOI, October, 2006)

<b>ACHA/NCHA HPV Data (2003 – 2006)</b>	Total: Not all ID'd gender	Female n	Female %	Male n	Male %
2003	302	228	75%	60	20%
2004	845	649	77%	152	18%
2005	1155	885	77%	234	20%
2006	2060	1594	77%	421	20%

**Comparison of Physician & Self-Collected Genital Specimens for Detection of HPV in Men: (Hernandez et al, JOCB, Feb. 2006)**

- Study included 136 males 18yrs – 63yrs – mean 28.5
- 5.2% (7/136) had visible condyloma – 3.7% (5/136) had “lesions”
- Findings:
  - Asymptomatic HPV is common in men
  - Male HPV appears to be multifocal
  - Male HPV prevalence varies between studies (41 – 43%)
  - Predominant oncogenic types: HPV-16, HPV-51 & HPV-59
  - Predominant nononcogenic type in all genital sites: HPV-84
  - HPV-84 was one of the most prominent on hand swabs suggesting the possibility of hand-to-genital transmission
  - HPV genotype distribution is inconsistent between men & women suggesting selective transmission
  - An ideal & consistent sampling method would facilitate repeated measurements of HPV in men over time

**Male-Specific HPV Issues (presenting at College Health Services):**

- My girlfriend was diagnosed with genital warts....
- My ex-girlfriend received an abnormal Pap result....
- I’ve seen the Ad on TV and want to be tested for HPV.....
- I have had this bump all my life – is it a genital wart??
- I have a male partner and receive anal penetration – what tests should I have?

**Differential diagnosis for popular urogenital lesions in males\***

Genital warts  
Pearly penile papules  
Molluscum contagiosum  
Milia  
Sebaceous cyst  
Herpes  
Other

**Genital warts (Condyloma accuminata)**

Usually soft, moist, pink polyp  
Usually cluster  
May become pendunculated  
Classic “cauliflower” appearance  
Can appear on lower abdomen and other areas not typically covered by a condom  
Often not classic-appearing

**Pearly penile papules**

The classic misdiagnosis  
Relatively common benign tumors  
Histology: angiofibroma  
Seen as regular projections for the edge of the glans at the coronal margin  
Do not contain HPV DNA by polymerase chain reaction  
Should not be “treated” – consider as a variation of normal

**Molluscum contagiosum**

Benign viral infection  
Most cases resolve within 6-9 months  
Sometimes lesions are large, pustule-appearing

Potential for autoinoculation  
Common for lesions to become inflamed (erythematous border)

Treatment:

- Benign neglect
- Cryotherapy
- Lesional trauma
- Others

### **Milia**

Ectopic sebaceous glands  
Known by some as “Fordyce’s spots”  
Uniform appearance and distribution  
Commonly seen on the faces of adults or in areas of trauma or inflammation  
In adults, milia may persist indefinitely

### **Other**

Sebaceous cysts  
Herpes  
Misdiagnosis = missed opportunity for appropriate counseling and treatment  
Scabies (usually nodular scabies)  
Lichen planus  
Condyloma lata  
Secondary syphilis  
Usually more flat-topped than condyloma acuminata  
If ANY doubt, test for syphilis  
Folliculitis

### **Hints for diagnosis**

Urogenital HPV lesions  
Generally are not associated with inguinal lymphadenopathy  
Might itch but do not hurt (unless inflamed)  
Do not wax and wane over a course of days/weeks

### **Oropharyngeal HPV infection**

Independent risk factor for oropharyngeal squamous-cell carcinoma  
HPV 16 associated with 15-fold increase in risk  
Seropositivity for HPV 16 associated with 32-fold increase in risk  
Tobacco and alcohol provided no additional risk  
Believed to be transmitted by oral sex

### **Anal warts**

Consider skin tags and fissures in the differential diagnosis

### **Anal cancer**

In the US, anal cancer in MSM is more common than cervical cancer in women  
Clear association with HPV infection  
Study of 1218 HIV-negative MSM age 18-89:  
Correlated with history of:  
receptive anal intercourse during the preceding 6 months  
and with >5 sex partners during the preceding 6 months  
did not correlate with subject age  
Rare in general population  
70-80 per 100,000 HIV-positive MSM  
Incidence has gone up in era of HAART

## Anal Pap testing

Evolving protocols

Consult with reference laboratory for protocol

Evolving standard of care

Males and females who practice receptive anal intercourse

Concept: Dysplasia testing vs. HPV testing

Most studies involve HIV-positive MSM

Anal cytology UNDERestimates the degree of anal dysplasia

ANY abnormality (ASCUS and >) should be referred for high-resolution anoscopy and biopsy

## **Squamous cell carcinoma of the penis**

HPV infection associated with 15-71% of penile SCC

Subtypes 16 and 18

But also 6, 11, and 30

Risk factors

Smegma retention

Chronic balanitis

Ultraviolet light exposure

Chemical carcinogen exposure

Cigarette smoking

HIV infection

Immunosuppression

**\*For visual examples, please refer to the links indicated in the reference portion at the end of the handout**

## **HPV screening**

Visual diagnosis

Many cases asymptomatic

Visible lesions

Clinical skill

Acetowhitening likely adds little to visual screening

Acetowhitening + peniscopy

An evolving standard of care?

Primary care?

College health?

Follow-up?

HPV DNA detection

Multiple studies using penis "scraping" techniques to screen for HPV DNA

None approved

Laboratory processing similar to HPV DNA testing of liquid-based Pap samples

## **Male HPV Treatment:**

- Goal: eradication or reduction in symptoms
- Treatment may not eliminate HPV
- Selection of modality depends on
  - size of lesion
  - number of lesions

- anatomic site
- patient preference
- provider experience

ABLATION (by Provider):

- Bi-Chloroacetic/Tri-Chloroacetic Acid (BCA/TCA): causes chemical destruction of the condyloma epithelium; applied weekly until resolved
- Cryo-Surgery: freezes intracellular fluid; Liquid N2 directly applied to each lesion weekly until resolved; applied with a cotton swab or cyroprobe
- Podophyllin: blocks cell growth by blocking cell division; applied weekly until resolved; patient must completely wash the treated area in one to four hours

ABLATION (ordered by provider & self-administered)

- Podofilox: causes tissue necrosis; applied bid x 3 days followed by no treatment for 4 days; may be repeated for a maximum of four cycles
- Aldara 5% Cream (Imiquimod): modifies the immune response; applied qod x 3 of 7 days & removed with soap & water in 6 – 10 hrs; can be repeated weekly up to 16 weeks

Treatments Requiring a Referral:

Surgical Intervention

- Electro-cautery: high-frequency current to cut & coagulate condyloma
- Laser Surgery: precisely controlled method targeting a specific area; CO2 Laser useful in persistent HPV infection; used in treatment of urethral and periurethral condyloma
- Surgical Excision: removal of condyloma with a scapel, scissors or curette; allows pathologic analysis

Medical Intervention

- 5-Fluorouracil (5-FU): antimetabolite causing tissue destruction by interfering with DNA/RNA synthesis; self-applied 1 to 3 x weekly; absorbed systemically
- Interferon: both immunomodulatory & antiviral activities; given intralesionally at the base of each condyloma 3 x week x 3 weeks

REFER:

- **Persistent Condyloma**
- **Urethral Condyloma**
- **Distal Anal Condyloma**

Non-Prescription HPV Treatments:

OTC's (not recommended for genital warts):

- Salicylic Acid** (Compound W)
- Liquid Nitrogen**

Homeopathic Remedies:

- PHP HPV Super Kit**: series of herbal meds that “teach” the immune system the suppress the virus ([www.biogetica.com](http://www.biogetica.com))



-**Naturasil:** plant extract, topical solution, anti-viral activity, absorbed cutaneously & systemically ([www.naturasil.com](http://www.naturasil.com))

-**Oxi-MED:** anti-viral/o2 infusion cream ([www.wartcream.com](http://www.wartcream.com))

#### Home Remedies Males May Try:

-OTC Tagamet – 2 tabs qd until clear

-Raw red potatoes – rub warts with cut end for 5 minutes at hs – wash off in am

-Castor Oil – apply bid until clear

-Banana peel – cut a piece to cover wart with inside surface and secure with a Band-Aid overnight

-Windex – spray warts qd x 10 days

-Cigarette Ashes – rub on warts for 1 – 2 weeks

-Clear Nailpolish – apply to warts am and hs until clear

#### Male HPV Prevention:

A direct correlation exists between anogenital HPV infection and measures of sexual activity including:

- Age at first coitus
- Life-time number of sexual partners
- Frequency of sexual activity
- Type of sexual activity
- Males tend to become sexually active earlier than females

#### Education targeting males:

- Value of abstinence: and ultimately a single monogamous relationship with an equally abstinent partner
- Delay sexual debut: HPV infection tends to follow the first sexual encounter (ASCCP: June, 2006)
- Limit number of lifetime sexual partners: a direct correlation between multiple sexual partners and HPV infection has been demonstrated in numerous studies (Gearhart: January, 2007)
- Consistent Condom use: can decrease but not completely eliminate HPV transmission. One study of 82 female college students demonstrated that those 100% compliant with condom use were 70% less apt to contract HPV infection (Winer, et al: NEJM, 2006)

#### Circumcision:

-Baldwin, et al. *Condom Use & Other Factors Affecting Penile HPV Detection in Men....STD's*, 2004, 31(10).

-”HPV detection was significantly less common among.. participants who were circumcised..(20% vs. 40%)”

-”In multivariate analyses.....only circumcision remained ..linked to reduced odds of oncogenic & nononcogenic HPV detection”

-Castellsague et al. *Male Circumcision, Penile HPV & Cervical Cancer in Female Partners*. NEJM, April 11, 2002.

-”Male circumcision is associated with a reduced risk of penile HPV infection...”

#### Circumcision:

Adami et al. *Cervical Cancer & the Elusive Male Factor*. NEJM. 2002, 346(15).

-”Circumcised men are less likely than uncircumcised men to have penile HPV”

-”Female partners of men who engage in risky sexual behavior have a reduced

likelihood of having cervical cancer if the man is circumcised”  
 -”...the effect of circumcision status on the prevalence of cervical cancer suggested that circumcision may reduce the likelihood...in current partners..however, this result was not statistically significant’

**HPV Vaccine Use in Males:**

- *Cervarix* (Glaxo, FDA approval pending)
  - Covers HPV Types 16 & 18
  - Clinical Trials on Females ONLY
  - No Anal cancer component
  - Marketing will address only females

**HPV Vaccine Use in Males:**

HPV Vaccine Use in Males:

- **Gardasil** (Merck; June, 2006 FDA Approval)
  - Effective for HPV Types 6 & 11, 16 & 18
  - Ongoing trials in males 9 – 15yrs (include an anal cancer component)
  - Trials → substantial immune response in men, but difficult to measure protection
  - Current government study targets the use of Gardasil in HIV-infected preteen boys & girls (CHAMP: June, 2006)

**January, 2007 SHS listserv query: “Is your Health Service making Gardasil available to males?”**

**Results: n=33**

<b>No</b>	<b>31</b>
<b>Yes</b>	<b>0</b>
<b>No?*</b>	<b>2</b>

**\*Did not offer a specific yes or no answer**

**HPV Vaccine use in Males – The Facts:**

- Safe use of *Gardasil* in males has been established
- *Gardasil* is being administered to males in Australia, New Zealand and the European Union
- HPV 16 & 18 cause at least 70% of anal cancer and 70% of precancerous penile lesions
- The incidence of anal cancer in MSM has more than doubled in the last 30 years
- HPV 6 & 11 cause >90% of condyloma in men & women
- *Gardasil* is nearly 100% effective in preventing cervical cancer  
 JNCI: 2005 97(9)

**HPV Vaccine Use in Males – The Facts:**

- **90%** conditions caused by HPV Types 6 & 11 and 16 & 18 could be eliminated if boys and girls were vaccinated before the age of 12
- Girls only vaccination = 75% reduction
- The only debates surrounding male HPV vaccination relate to:

-Religious Beliefs  
-Cost/Benefit Ratio  
-Political Pressure

JCNI 2005 97(9)

“When you want to reduce disease in a population, you to immunize as many people as you can. If you can immunize a large percentage of men and prevent them from infecting women you can reduce the disease in women.”

Darron Brown, M.D.  
Indiana University  
School of Medicine

Male HPV Infection – A Challenge to Diagnosis & Treatment  
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