Genital Human Papillomavirus Infection

Learning Objectives

Upon completion of this module, the learner will be able to:

1. Discuss the current epidemiology and risk factors for genital HPV.
2. Describe the pathogenesis and clinical manifestations of genital HPV.
3. Explain the current diagnostic methods for genital warts and cervical disease and the applications for HPV testing.
4. Discuss the treatment options for genital warts.
5. Deliver appropriate patient counseling and partner management messages.
6. Describe indications and recommendations for the HPV vaccines

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I. Epidemiology

A. Incidence and prevalence of infection and disease:

1. Exact incidence difficult to determine given that asymptomatic infections often go undiagnosed, and lack of case reporting for various manifestations of HPV infection (HPV test positivity, genital warts, cervical intraepithelial neoplasia).

2. The Centers for Disease Control and Prevention estimates that annual incidence of all types of genital HPV infection estimated to be 6.2 million cases in U.S. It is estimated that 80% of sexually active adults will have been infected with genital HPV by age 50.

3. Prevalence of HPV infection is high in both women and men.
   Women: Prevalence of cervical infection estimated at 10-12%; highest in younger women (<30 years). Recent population-based estimates from the National Health and Nutrition Examination Survey, demonstrated 26.8% of women ages 14-59 had HPV DNA detectable on self-collected vaginal swabs.

   Heterosexual Men: Based on systematic review of studies of both high/low risk populations, prevalence any anogenital site estimated to be 26-65%.

   Men who have sex with men: Prevalence of anal HPV infection in HIV-positive MSM estimated to be greater than 90% and in HIV-negative MSM to be 57-66%.

4. For genital warts, prevalence based on analysis of private health plan data was as high as 0.5-0.6% for men/women between ages 20-24. Genital warts incidence estimated to be approximately 1.1 cases per 1000 annually.

5. Estimates for HPV-associated cancers in the US from the American Cancer Society for 2011
   a) Cervical Cancer: 12170 cases and 4290 deaths
   b) Anal Cancer: 5820 cases and 770 deaths
   c) Vulvar cancer: 4340 cases and 940 deaths

B. Transmission of genital HPV:

1. Predominantly sexual transmission (penetrative genital or anal contact): Other types of sexual contact (oral-genital, manual-genital, genital-genital) can also lead to HPV infection.

2. Risk factors for HPV acquisition in women include: age <25 years, early age at first intercourse (16 years or younger), multiple sexual partners, having a male partner who has had multiple sex partners.

3. Can occur in patients with asymptomatic and subclinical infections

4. Prior HPV infection at other sites does not appear to offer protection, and there does not appear to be significant cross-protection between genital HPV types.

5. HPV can be detected on fomites, but transmission of genital types by this route not known to occur

6. Recent evidence demonstrates that condoms prevent subclinical HPV infection and may be effective in preventing actual disease manifestations (genital warts, cervical dysplasia and cancer).

7. Infectivity after treatment of warts or squamous intraepithelial lesions (SIL) unknown

8. Vertical transmission rarely results in recurrent respiratory papillomatosis due to HPV 6/11 in infants and young children. Caesarean section has not been shown to effectively reduce transmission.

C. Risk factors for progression of HPV infection to neoplasia:

1. Never or rarely having been screened for cervical cancer: Half of US women diagnosed with cervical cancer had not received screening in the 5 years prior to diagnosis.

2. Diminished cellular immunity and immunosuppression from any cause (including HIV) associated with higher rates of HPV persistence and increased risk of HPV-related cancer

3. Hormonal influences (pregnancy, oral contraceptives), smoking, nutritional factors (folate deficiency), other STDs (e.g., *Chlamydia trachomatis*, HSV-2, Trichomonas), and genetic predisposition associated with cervical cancer in some studies

II. Pathogenesis

A. Virology:

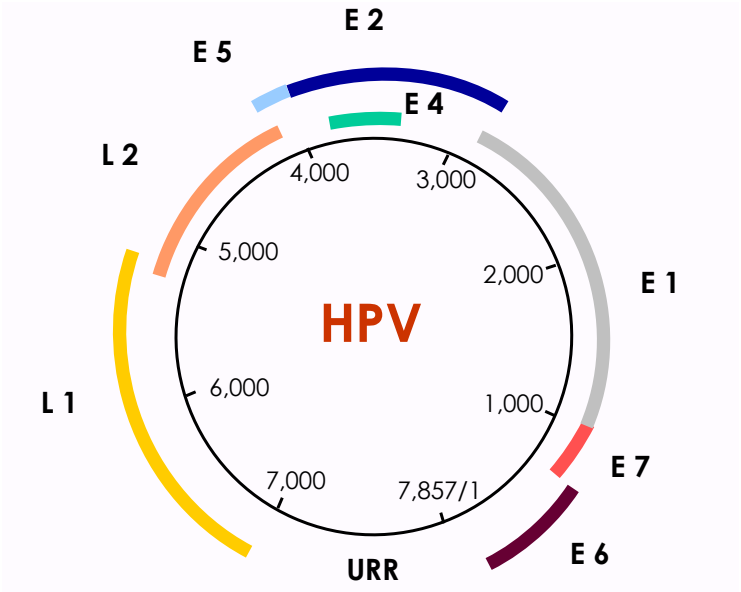
1. Key features of HPV:

a) Double-stranded DNA virus: family-Papovaviridae, genus-Papillomavirus

b) Virions: small, non-enveloped

c) Very limited animal models and no widely available system for *in vitro* cultivation. Infection is generally indicated by the detection of HPV DNA.

d) Genome of <8000 bases codes for early proteins (E1-E7) and late proteins (L1-L2). L1 and L2 are capsid (surface) proteins.



L1 and L2: capsid genes; URR: Upstream regulatory region
Reprinted from Macmillan Publishers Ltd: Nature Reviews Immunology 2004; 4(1) 46-54.

2. HPV genotyping system:

a) Over 100 characterized types

b) Different diseases are caused by different types, generally grouped as

either anogenital/oral or cutaneous types. Genital types (over 40 identified) have specific tropism for genital skin and mucosa.

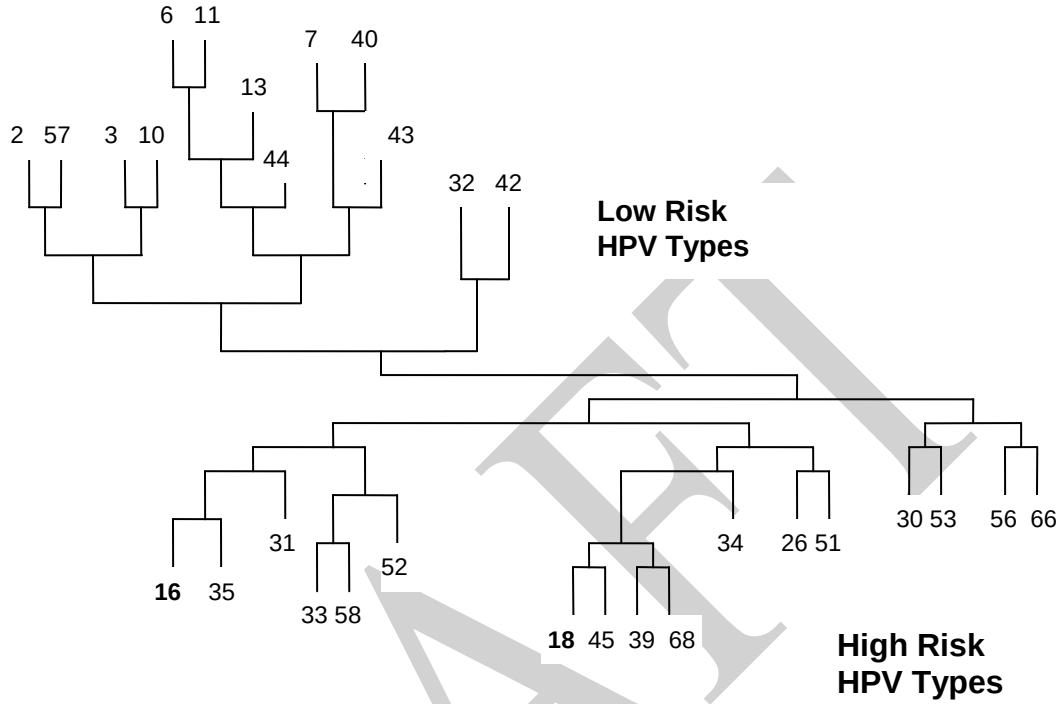
c) Types distinguished by different DNA sequences (>10% difference) at L1 capsid (surface) protein

d) Anogenital HPV types are generally characterized as either “high-risk” types (e.g., HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, etc.) which cause high-grade squamous intraepithelial lesions (HSIL) and invasive cancer. HPV 16, 18 are the most oncogenic or highest risk of these types. “Low-risk” types (e.g., HPV 6, 11, 42, 43, 44, etc.) cause genital warts and low-grade SIL (LSIL).

e) Actual numbers of recognized HPV types are gradually increasing as more types are identified and genetically characterized.

f) Phylogenetic tree demonstrates genetic similarities among low- and high-risk HPV types

Phylogenetic Tree of Anogenital HPV Types



Adapted from: Chan, SY, et al. J Virol 1995;69(5) 3074-83.

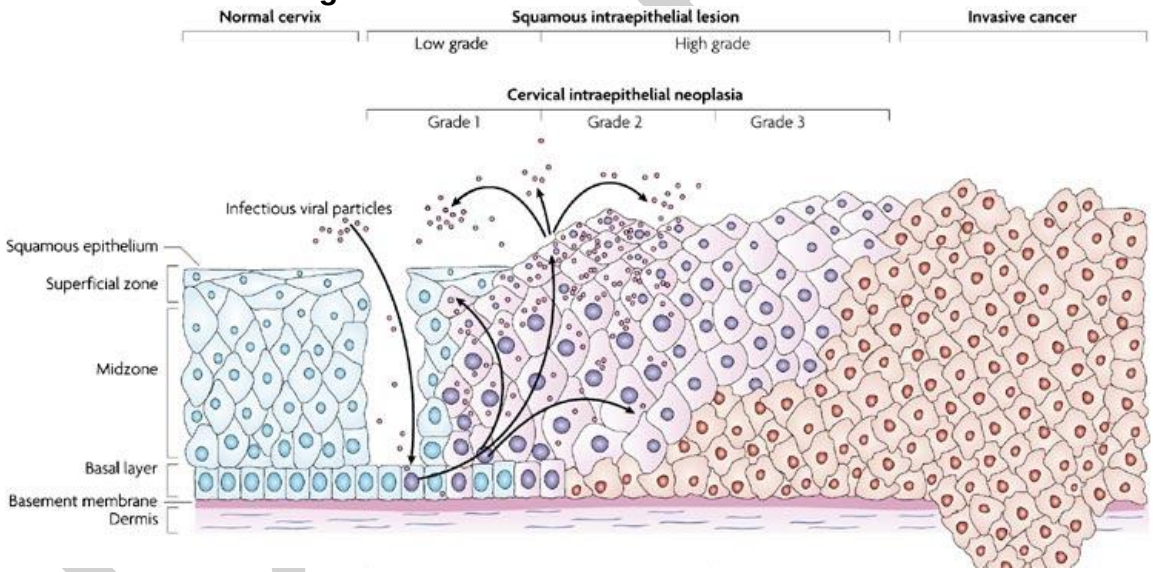
B. Pathophysiology:

1. Virus is introduced into the basal layer of the stratified squamous epithelium through microabrasions. Stimulates cellular proliferation, resulting in latent and subclinical infection, condyloma, or dysplasia. Glandular cells can also be infected.

2. Infected cells display koilocytosis (cells with enlarged nuclei, irregular chromatin, perinuclear clearing, and a cytoplasmic border that varies from thick to thin).

3. Viral proliferation, genomic integration, and oncogenic transformation play a role in the progression to severe dysplasia and invasive carcinoma.

Schematic of the Progression from HPV Infection to Invasive Cancer



Source: Woodman, CB, Collins, SI, Young, LS. Nature Reviews Cancer 2007;7:11-22.

C. HPV association with anogenital cancer:

1. HPV infection with high-risk types is causally associated with cervical cancer and has been consistently associated with other anogenital squamous cell cancers (e.g. anal, penile, vulvar, vaginal). Over 99% of cervical cancers have HPV DNA detected within the tumor. HPV infection is necessary but not sufficient to cause cervical cancer. Persistent HPV infection (e.g., infection which is not cleared by the immune system and which is

characterized by persistently detectable HPV DNA) and possibly other co-factors seem to be required for development of cancer.

2. High-risk types of HPV infection contain genomic sequences with oncogenic activity (E6 and E7) that are consistently retained and expressed in cancers. HPV is integrated into cellular DNA in the majority of cancers, an event which disrupts a transcription regulation gene (E2) and which can lead to increased expression of the E6 and E7 proteins. These proteins affect cell growth by binding with cellular tumor suppressor proteins causing their inactivation and disrupting normal cell cycle control.

3. Estimated distribution of common high risk HPV types found in cervical cancer: 16 (61%), 18 (10%), 45 (6%), 31 (4%), 33 (4%), 35 (2%)

4. Estimated distribution of common high risk HPV types in anal cancer: 16 (66%), 18 (5%), 6 (5%), 31(2%), 45 (1%)

D. Natural history of HPV:

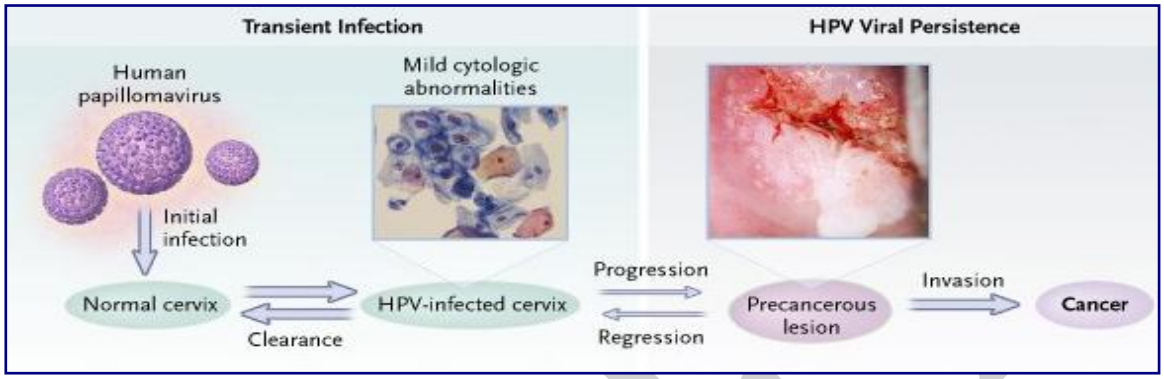
1. Most anogenital HPV infections are transient and subclinical in immune competent individuals. Among young women, the median duration of infection as measured by detection of viral DNA is 6-8 months; 30% of infections persist >12 months and 10% >24 months. It is unclear whether HPV infection which becomes non-detectable at mucosal surfaces has completely cleared or remains latent in basal cells with potential for later reactivation.

2. Persistence of infection with a high-risk type confers the highest risk for development of subsequent HSIL and neoplasia; factors associated with persistent infection include older age, infection with type 16 or 18, smoking, and immunodeficiency. Genetic, hormonal and chronic infections with other STDs may also play a role.

3. Manifestations of infection include:
   a) Transient infections and latent subclinical infections (all genital types)
   b) Genital warts, oral warts, respiratory papillomatosis (low-risk types)
   c) SIL, carcinomas (high-risk types)

4. Incubation period unclear: probably 3 weeks to several months for genital warts, and several months to years for cervical SIL. Although cytologic abnormalities can be detected shortly after infection, most resolve without treatment.

5. Once cervical cells are infected, abnormalities can progress (or regress) along a spectrum of disease.



Source: Wright, TC, Schiffman, M. NEJM 2003; 348(6):489-490.

6. Majority of women with high-risk HPV types do not develop cervical cancer. However, the likelihood of spontaneous regression and progression to cancer varies according to grade of dysplasia. The following likelihood estimates are based on studies with differing follow-up intervals (range: 3 weeks-20 years) and should be interpreted with caution.

Grade of Dysplasia	Spontaneous Regression	Progression to Cancer
Cervical Intraepithelial Neoplasia-1	60%	1%
Cervical Intraepithelial Neoplasia 2	40%	5%
Cervical Intraepithelial Neoplasia 3	33%	12%

Adapted from: Ostor, AG. Int J Gynecol Pathol 1993; 12 (2): 186-192 and Castle PE et al. Obstetrics and Gynecology 2009; 113 (1) 18-25.

7. Natural history of genital warts:
   a) Regress spontaneously (occurs, but frequency unclear; a few studies indicate 10-30% regression rate within 3 months)
   b) Remain the same (persistence of infection occurs, but frequency and duration is unknown)
   c) Recurrences after treatment (20-50% recurrence rate at 3-6 months) are common

III. Clinical Manifestations

A. Genital warts:

1. Appearance:
   a) Condylomata acuminata:
      i) Cauliflower-shaped, flesh-colored, pink, or hyperpigmented.
      ii) May be keratotic on skin; generally non-keratinized when present on mucosal surfaces
   b) Smooth papules: usually dome-shaped and skin-colored
   c) Keratotic warts: with thick horny layer which can resemble common warts or seborrheic keratosis
   d) Flat papules:
      i) Macular to slightly raised
      ii) Flesh-colored, with smooth surface.
      iii) More commonly found on internal structures (i.e., cervix), but also occur on external genitalia

2. Sites:
   a) Commonly occur in areas of coital friction
   b) Men: shaft, frenulum, corona, glans, prepuce, meatus, anus, scrotum
   c) Women: posterior introitus, labia minora, labia majora, perineum, vagina, cervix, anus
   d) Perianal warts do not necessarily indicate anal intercourse, but may be secondary to autoinoculation or sexual activity other than intercourse
   e) Cervical and vaginal condylomata are less common than external warts
   f) HPV types causing anogenital warts can occasionally cause lesions on oral, upper respiratory, upper GI, and ocular locations

3. Symptoms:
   a) The majority are asymptomatic.
   b) Most common symptom is cosmetic appearance of the wart, without other physical symptoms.
   c) Vulvar warts: dyspareunia, pruritis, burning discomfort
   d) Penile warts: occasional itching
   e) Urethral meatal warts: occasional hematuria or impairment of urinary stream
   f) Vaginal warts: occasional discharge, bleeding, obstruction of birth canal (secondary to increased wart growth during pregnancy)
   g) Perianal warts: pain, bleeding on defecation, itching

B. Squamous and glandular intraepithelial lesions:

1. Appearance:
   a) Cervical, vaginal or anal lesions: occur in what is usually macroscopically normal epithelium and mucosal tissue.

   b) Vulvar lesions: can present as verrucous, white lesions, though color may vary greatly. Vulvar lesions also commonly present as bowenoid papulosis, dome-shaped or flat papules that are often hyperpigmented. Lesions can also be flesh-colored and clinically indistinguishable from genital warts, but on biopsy demonstrate high grade dysplasia.

2 Sites:
   a) Women: cervix; less commonly vulva, vagina, anus
   b) Men: penis, anus
   c) Anal lesions more common among men who have receptive anal sex, particularly HIV-positive, as well as HIV-positive women

3. Detection:
   a) Cervical, vaginal, or anal dysplasia (SIL): generally detected by cytology, requires histology for confirmation and staging
   b) Vulvar dysplasia: generally detected by clinical exam, requires histology for confirmation and staging
   c) Detection of anogenital lesions is enhanced by application of acetic acid to mucosal membrane or epithelial surface producing acetowhitening, and by magnification with colposcopy.

4. Symptoms:
   a) The majority are asymptomatic.
   b) Cervical lesions may cause irregular or post-coital bleeding.

C. HPV infections in infants and children:

1. Laryngeal papillomatosis, also known as juvenile onset recurrent respiratory papillomatosis (JORRP). Vertical transmission, rare condition. Caused by HPV 6 and 11

2. Genital warts in preadolescent children may be due to sexual abuse and should prompt an evaluation for such, but may also result from vertical transmission, transmission of non-genital HPV types to genital surfaces, and

possibly fomite transmission.

IV. Diagnosis

A. Diagnosis of genital warts

1. Physical exam:
   a) Visual inspection with bright light is generally sufficient for diagnosis of genital warts.

   b) Acetic acid evaluation of external genitalia is of limited value in routine clinical practice. Acetowhitening (whitened area of skin or mucosa after application of 3-5% solution of acetic acid solution) has low specificity, as low as 50-60% (many false positives); often noted at sites of prior trauma/inflammation and not recommended for evaluation of external genitalia.

2. Indications for additional techniques:
   a) Indications for biopsy for histology of external genital lesions include induration, fixation of lesion to underlying tissue, persistent ulceration or bleeding, non-response to or worsening with standard treatment, pigmentation, or in situations where diagnosis is in doubt.

   b) There are no data to support the use of HPV testing in the routine diagnosis of genital warts.

   c) In persons who have practiced receptive anal intercourse who have perianal warts, anoscopy can help detect intra-anal warts; however, the value of diagnosing and treating asymptomatic intra-anal warts has not been established.

3. Differential diagnosis of genital warts:
   a) Infectious/acquired
      i) Condylomata lata: tend to be smoother, moist, rounded, and darkfield-positive for *Treponema pallidum*, manifestation of secondary syphilis (RPR/VDRL is positive).

      ii) Molluscum contagiosum: papules with central dimple, caused by a pox virus; rarely involves mucosal surfaces, resolves spontaneously

   b) Acquired dermatologic

i) Seborrheic keratosis
ii) Lichen planus
iii) Fibroepithelial polyp, adenoma
iv) Melanocytic nevus
v) Neoplastic lesions

c) Normal anatomic variants
i) Pearly penile papules
ii) Vestibular papillae (micropapillomatosis labialis)
iii) Skin tags (acrochordons)

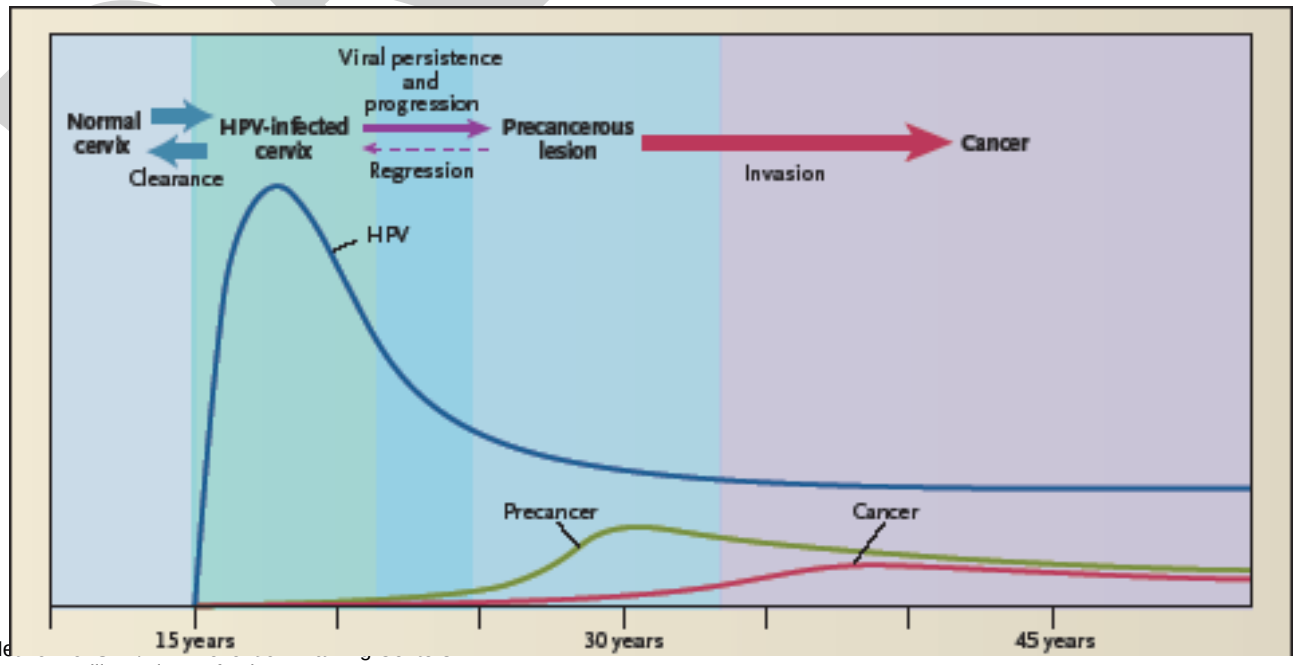
B. Diagnosis of HPV-associated cervical lesions

1. Diagnosis requires cytology, colposcopy, and histopathology.

2. Cytology (Pap test):
a) Useful screening test to detect cervical dysplasia. Not for HPV screening per se; however, Pap test provides indirect evidence of HPV on the basis of epithelial cell changes.

b) Because of the long length of time between infection and high-grade disease and the slow progression of cervical cancer, Pap screening and early treatment of precancerous lesions effectively prevents the development of cervical cancer.

Relative Frequency of HPV-Associated Cervical Disease by Age



Source: Schiffman, M, Castle, PE, NEJM 2005; 353(20):2101-2104.

c) Pap screening recommendations from American College of Obstetrics and Gynecology (2009)

i) Pap screening should begin at age 21. Exceptions include known or suspected history of sexual abuse, HIV infection, or immune compromise.

ii) Frequency of screening: every 2 years until age 30. Women age 30 or older (with 3 consecutive satisfactory normal Paps) may be screened every 3 years. Another option is a combination of Pap screening with a test for high-risk HPV. Those with negative combined tests should be screened with combined tests no more frequently than every 3 years. Exceptions to these guidelines include DES exposure, HIV infection, or immune compromise.

iii) Pap screening may be discontinued in the following women: those with total hysterectomy for benign disease and no history of CIN 2 or 3; age 65-70 with 3 or more consecutive satisfactory normal Paps and no abnormal Paps within the past 10 years. Exceptions include any history of cervical cancer, DES exposure, or HIV infection.

iv) The Bethesda System for cervical cytology uses categories of low-grade squamous intraepithelial lesions (LSIL) and high-grade SIL (HSIL). Atypical squamous cells of undetermined significance (ASC-US) and atypical squamous cells/cannot rule out high grade lesion (ASC-H) are less specific, but potentially important indicators of disease. Atypical glandular cells (AGC) may also be observed on cytology.

d) No increase in frequency of Pap tests for women with genital warts

e) Limitations of Pap tests include unsatisfactory results (requiring a repeat visit and specimen) up to 20% of the time and variable sensitivity (50-70% for a single Pap test, which is the rationale for serial testing).

f) Liquid media-based tests (e.g., Thinprep®, SurePath®) and computer-assisted reading may enhance sensitivity, but reduce specificity.

3. Colposcopy:

a) Indication for colposcopy is guided by physical exam, Pap findings, and sometimes by HPV testing.

b) Immediate colposcopy is indicated for HSIL, LSIL in adults (age ≥ 21 years), AGC and ASC-H. Recommendations for managing ASCUS in adults include repeat Pap testing at 6-month intervals, immediate colposcopy, or reflex high-risk HPV testing.

c) External genital warts are not an indication for cervical colposcopy.

d) The procedure involves the application of acetic acid and visualization of the cervix using magnifying scope

4. Histology (biopsy):

a) Indications for cervical biopsy include visible exophytic lesions on the cervix, certain abnormalities on cytology, and other colposcopic abnormalities.

b) Cervical lesions are graded according to the proportion of the epithelium involved by disease. In categorizing cervical intraepithelial neoplasia (CIN), lesions are considered to be CIN 1 (undifferentiated cells in the lower 1/3 of the epithelium), CIN 2 (undifferentiated cells in the lower 1/3 to 2/3 of the epithelium), or CIN 3/carcinoma in situ (with undifferentiated cells across the full thickness of the epithelium).

5. HPV DNA testing:

a) Hybrid Capture-II® (HC2) (Qiagen/Digene) test for HPV DNA detects 13 high-risk HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, or 68). The HC2 test for low-risk HPV detects 5 low-risk HPV types (6, 11, 42, 43, or 44). Results are reported as positive or negative; does not identify individual HPV types.

b) Cervista HPV HR (Hologic) detects 14 HPV types (all of above, plus HPV 66); the Cervista HPV 16/18 test detects presence of HPV 16 and/or 18.

c) Cobas HPV (Roche), detects 14 HPV types (same as above) and gives specific genotype results for HPV 16 and HPV 18.

d) FDA Approved Indications for HPV DNA Testing:

i) Triage of women with ASCUS on Pap test; adult women (age ≥ 21 years) with high-risk HPV types should be referred to colposcopy, while those who are negative can be followed with a Pap test in 12 months.
ii) Routine adjunctive screening to Pap test in women >30 years old. Because of high negative predictive value, women whose Pap and HPV tests are negative for high-risk HPV types may be safely screened every 3 years. Women with a normal Pap test and positive high-risk HPV test results should receive repeat HPV and Pap testing at 12 months. If results of either of these are abnormal, colposcopy should be performed.

e) Evidence-based use (not FDA-cleared) of HPV test for management of:
i) 12-month follow-up after a negative colposcopy/biopsy performed for ASC-H, LSIL, or ASC-US with a positive HPV test
ii) 12-month follow up of CIN 1
iii) 6- and 12-month follow-up of the initial work-up for AGC or the subsequent work-up of AGC with a negative colposcopy/biopsy
iv) 6- and 12-month follow-up post treatment CIN 2/3

f) HPV DNA testing NOT recommended:
i) Triage of adult women with LSIL. Large majority of these have high-risk types and should be referred to colposcopy.
ii) Triage of adolescent women (age ≤ 20 years) with ASCUS or LSIL. Most will resolve spontaneously, and should receive repeat cytology in 12 months.
iii) HPV testing in the following populations or scenarios: men, patients with genital warts or STIs, partners of patients with warts or STIs, partners of women with cervical cancer.
iv) Low Risk HPV DNA testing—not clinically indicated for any condition

C. Diagnosis of other anogenital lesions

1. Vulvar, vaginal, anal, and penile lesions require biopsy and histopathologic diagnosis.

2. Anal Pap (cytology) screening, followed by high resolution anoscopy (application of acetic acid and magnification with colposcope) and biopsy to detect anal intraepithelial lesions

3. Biopsy also indicated for suspected bowenoid papulosis or other atypical lesions where diagnosis is uncertain.

4. No role for HPV testing for diagnosis of penile, vulvar/vaginal or anal lesions

V. Treatment of Genital Warts

A. General considerations:

1. Several modalities available; with similar effectiveness. Considerations in the choice of therapy include patient preference, clinician experience, side effects, and cost.

2. Labor intensive: non-surgical, locally destructive techniques may require multiple treatments.

3. Effectiveness: 20-50% of patients will experience recurrences of warts after therapy within 3-6 months; however, after 6 months, most patients have clearance. There is no evidence that any specific treatment is superior to any of the others.

4. Response affected by number, size, duration, location of warts and host immune status (pregnancy, HIV infection)

5. If condylomata cover a small area, are asymptomatic, and the patient is not bothered by them, it is reasonable to follow clinically, since in 10-30% percent of cases, the lesions will regress without treatment.

6. The benefit of treatment in reducing infectivity and preventing transmission is unknown.

7. If persistent after 3 months, or poor response to treatment, consider biopsy to exclude a premalignant or neoplastic condition, especially in an immunocompromised person. Consider HIV testing.

8. Consideration should be given to screening persons with newly-diagnosed genital warts for other STDs, (e.g., chlamydia, gonorrhea, HIV, syphilis).

B. Recommended treatment regimens:

1. Patient-applied: provider should teach patient how to apply substance to wart; patient should be counseled to expect local irritation and skin reactions. None of the patient-applied therapies have not been evaluated in pregnancy (Category C).

   a) Podofilox 0.5% solution or gel (Condylox®): antimitotic drug that destroys

warts. Patient may apply solution with cotton swab, or gel with a finger to visible genital warts twice daily for 3 days, followed by 4 days of no therapy. This cycle may be repeated as necessary for a total of 4 cycles. Total wart area treated should not exceed 10cm^2, and a total volume of podofilox should not exceed 0.5mL per day.

b) Imiquimod 5% cream (Aldara®): topically active immune enhancer that stimulates cytokine and interferon production. Patient should apply imiquimod cream to warts with a finger at bedtime, 3 x per week, for up to 16 weeks. It is recommended that 6-10 hours following the application, the treatment area be washed with mild soap and water. Many patients may be clear of warts by 8-10 weeks or sooner. Response rates are lower in men with keratotic warts, and podofilox may be a more effective patient-applied treatment for these patients.

c) Sinecatechins 15% ointment (Veregen®): green tea extract, mechanism of action unknown. Patient should apply to warts 3 times daily up to 16 weeks. The medication should not be washed off after use. Not recommended in HIV-infected or other immunocompromised persons.

2. Provider-administered:

a) Cryotherapy with liquid nitrogen or cryoprobe: two freeze-thaw cycles per treatment. Treatment should be applied using spray, cryoprobe, or cotton-tipped applicator, until lesion and 1-2 mm surrounding area exhibit whitened ice ball. Repeat treatment every 1 to 2 weeks. Cryoprobe should not be used for vaginal warts due to risk of fistula formation. May be used in pregnancy.

b) Podophyllin resin 10-25% in compound tincture of benzoin: a small amount should be applied to each external wart and allowed to air dry. To avoid the possibility of problems with systemic absorption and toxicity, some experts recommend that application be limited to 0.5mL of podophyllin or 10cm^2 of warts per session. Some experts suggest that it should be thoroughly washed off 1 to 4 hours after application to reduce local irritation. Repeat weekly if necessary. Local irritation is common. Potency, components, and contaminants in podophyllin are not standardized**,** and shelf life is uncertain. Safety and efficacy have not been evaluated in pregnant women (Category C).

c) Trichloroacetic acid (TCA) or bichloroacetic acid (BCA) 80-90%: apply a small amount only to warts and allow to dry, at which time a white

"frosting" develops; powder with talc or sodium bicarbonate (baking soda) to remove unreacted acid if an excess amount is applied. Repeat weekly for 4-6 weeks if necessary. Can be painful after application and may be caustic to unprotected skin around the warts (which can be protected by the application of Vaseline). Can be used on vaginal and anal warts as well as external warts and in pregnancy.

d) Surgical removal: tangential scissor excision, tangential shave excision, curettage, or electrosurgery. Can be used on accessible internal warts and in pregnancy.

C. Alternative treatment regimens:

1. Laser surgery: costly but effective for very large and otherwise difficult-to-treat warts.

2. Interferon: systemic interferon is not effective. Intralesional interferon has efficacy because of antiviral and/or immunostimulating effects. However, interferon therapy is not recommended for routine use because of inconvenient routes of administration, frequent visits, and its association with a high frequency of systemic adverse effects.

3. 5-Fluorouracil (5FU) is not currently recommended because of side effects.

D. Treatment recommendations vary by anatomic site of warts

ANATOMIC SITE	TREATMENT RECOMMENDATION
Cervical warts	Treatment should be based on histopathologic lesion stage as determined by colposcopy and biopsy.
Vaginal warts	Treat only if symptomatic, since most treatments also affect normal tissue and could cause scarring and pain. a) Cryotherapy with liquid nitrogen: the use of a cryoprobe in the vagina is not recommended, **or** b) TCA or BCA 80-90%.
Distal urethral meatus warts	a) Cryotherapy with liquid nitrogen, **or** b) Podophyllin 10-25%: must be dry before contact with normal mucosa, **or** c) Podofilox: limited data; may be useful, **or**

	d) Imiquimod: limited data; may be useful.
Anal warts	a) Cryotherapy with liquid nitrogen, **or** b) TCA or BCA 80-90%, **or** c) Surgical removal.
Oral warts	a) Cryotherapy with liquid nitrogen, **or** b) Surgical removal.

E. Follow-up:

1. After warts have responded to therapy, follow-up is not necessary.
2. Routine cytologic screening is recommended for women with or without genital warts.
3. The presence of genital warts is not an indication for cervical colposcopy.

F. Management of genital warts in pregnancy:

1. Genital warts can increase in size and become more friable during pregnancy.
2. Cytotoxic agents (podophyllin, podofilox) should be avoided. Imiquimod should be avoided.
3. Cryotherapy, TCA, BCA, and surgical removal are acceptable in pregnant patients.
4. Prophylactic C-section is not recommended to avoid transmission to neonate.
5. In rare instances, C-section may be necessary if extensive warts obstruct the birth canal or the risk of extensive bleeding during vaginal delivery is thought to be high.

VI. Treatment of HPV-Associated Precancerous and Cancerous Lesions

A. Cervical pre-cancer:

1. Treatment of SIL is based on the results of colposcopy and histopathologic grade. Since most CIN 1 lesions regress spontaneously, conservative management with close observational follow-up and treatment only for those that persist is a reasonable option. For CIN 2 and 3 lesions, ablative or excisional treatment is recommended with cryocautery, laser, or loop electrosurgical excision procedure (LEEP), each of which appears to have

similar rates of efficacy and complications.

2. There is limited evidence that consistent condom use may promote the regression of CIN lesions and clearance of HPV infection in women and regression of penile lesions in men.

B. Anogenital pre-cancerous lesions are treated with ablative or excisional procedures.

C. Cancer is treated according the stage.

VII. HPV Infection in HIV-Positive Patients and other Patients with Deficiency of Cell-mediated Immunity

A. General considerations:

1. Occurs more frequently
2. More resistant to conventional therapy
3. Recurrence of lesions after treatment is more common
4. More pronounced clinical manifestations and occurrence of atypical lesions such as oral warts
5. Appears to accelerate intraepithelial neoplasia and invasive cancer

B. Screening

1. Cervical Pap screening at 6-month intervals x 2, then annually for all HIV+ women with or without genital warts
2. Anal Pap tests and high-resolution anoscopy is recommended by some experts for HIV-infected men who have sex with men; optimal frequency of screening yet to be determined
3. Guidelines for managing cytologic and histologic abnormalities vary by HIV status

C. Management considerations

External anogenital warts: treatment less likely to be effective due to high recurrence rate; treat only if symptomatic or bothersome to the patient. Because HSIL and invasive cancer can occur in wart-like lesions, especially in the perianal area, lesions that are hyperpigmented or that persist despite treatment should be evaluated by biopsy. The role of warts (or irritated treatment sites) in HIV transmission is unknown.

VIII. Prevention

A. Partner management:

1. Sex partner evaluation of no proven benefit in preventing transmission/reinfection or complications (the classic rationale for partner evaluation of a patient with STD).
2. Majority of partners are already subclinically infected.
3. Evaluation may provide an opportunity to perform STD and Pap screening.
4. Partners with exophytic warts may want treatment.
5. Partners may benefit from counseling.

B. Patient counseling and education:

1. Treatment considerations:
   a) Goals of treatment (warts or CIN 1 may not need to be treated at all)
   b) Patient vs. provider-applied options (warts)
   c) Potential for recurrence (warts recur frequently, cervical dysplasia may recur less often)
   d) Cost/convenience
   e) Prior treatments
   f) Pregnancy
   g) Potential adverse effects of treatment options

2. Nature of infection:
   a) Viral infection, usually self-limited and cleared spontaneously. Persistent infection over years can lead to cervical cancer. High recurrence rate after treatment of genital wart lesions.
   b) Usually sexually transmitted, but incubation period not well defined.
   c) HPV types causing external genital warts do not cause cancer.
   d) Few (but rare) pregnancy issues.

3. Transmission issues:
   a) Determining source of infection usually difficult; not evidence of infidelity.

   b) Recurrences may indicate reactivation of latent infection or infection with a different type.

   c) In an ongoing sexual relationship, both partners are usually infected at the time one person is diagnosed with HPV.

d) Risk to future partners unclear (probably decreases over time). HPV infections can occur in both male and female genital areas that are covered or protected by a latex condom, as well as in areas that are not covered. Condom use has been shown to reduce incident infection, is associated with a lower rate of cervical cancer, and has been associated with regression of HPV-related cervical and penile lesions.

e) Lack of consensus on need for full disclosure to future partners, although candid discussions about past STD should be encouraged and attempted whenever possible.

C. Vaccination

1. Gardasil® (Merck) is a prophylactic quadrivalent vaccine (HPV types 6, 11, 16, 18) that was licensed in June 2006 and indicated in females 9-26 years old for the prevention of cervical, vulvar, and vaginal cancers and their precursors. It is also indicated for males and females 9-26 years old for the prevention of anal cancer and its precursors, as well as genital warts.

2. Cervarix® (Glaxo Smith Kline) is a prophylactic bivalent vaccine (HPV types 16, 18) that was licensed in October 2009 and is indicated for the prevention of cervical cancer and its precursors in females 10-25 years old.

3. Immunogenicity/Efficacy
   a) Duration of immunity unknown, but appears to be effective for at least 5 years.

   b) In phase III trials, among HPV-naïve women, both vaccines appeared to be highly efficacious (nearly 100% efficacy) in preventing cervical precancers. Gardasil was also highly efficacious in preventing genital warts, vulvar, and vaginal precancers in women and both gential warts and anal precancers in men.

   c) Efficacy of the vaccine is substantially reduced in women who have been infected with HPV (types 6, 11, 16, 18) in the past. Therefore, vaccination should ideally be undertaken prior to initiation of sexual activity.

4. Safety
   a) During clinical trials, vaccine-related serious adverse events were rare (less than <0.1% of participants)

   b) Common side effects include injection-site pain, swelling, erythema, and

pruritis.

c) Adverse reactions should be reported to the Vaccine Adverse Event Reporting System (VAERS) www.vaers.hhs.gov or 800-822-7967.

d) Administration in pregnancy should be reported to the Merck Pregnancy registry: 1-800-986-8999 (www.merckpregnancyregistries.com/gardasil.html) or the GSK Pregnancy registry at: 1-888-452-9622 http://pregnancyregistry.gsk.com/cervarix.html

5. Recommendations/Dosing:
   a) Girls/Women: Advisory Committee on Immunization Practices (ACIP) and the American Cancer Society (ACS) recommend routine administration of either HPV vaccine for girls between 11-12 years old; may be given as young as 9 years of age. Catch-up vaccination for girls 13-18 years of age is recommended. Can by given despite history of abnormal Pap, HPV, warts.

   b) 19-26 year-old women: ACIP recommends catch-up vaccination. ACS recommends providers discuss an individual woman's likelihood of previous HPV exposure and potential for benefit prior to vaccination.

   c) Vaccine most effective in women prior to initiation of sexual activity and has not been tested in women with > 5 sexual partners.

   d) Males between 9-26 years old: ACIP gives permissive recommendation for vaccination.

   d) Recommended dosing schedule is 0, 2, and 6 months.

   e) If above schedule is not feasible, there should be a minimum of 4 weeks between the first and second doses and a minimum of 12 weeks between the second and third doses. No need to restart series for missed doses.

6. Special populations:
   a) Contraindications: allergy to yeast or other vaccine component, severe illness
   b) Not recommended for use in pregnancy; may be used in lactating women.
   c) May be used in immunocompromised individuals, but immunogenicity and efficacy may be decreased.

7. Cervical cancer screening in vaccinated females: regular screening should

continue according to current guidelines.

IX. HPV resources:

American College of Obstetrics and Gynecology- www.acog.org

American Society of Colposcopy and Cervical Pathology -www.asccp.org

American Social Health Association (ASHA)-www.ashastd.org

Centers for Disease Control and Prevention-www.cdc.gov/std

American Cancer Society- www.cancer.org

X. References

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