

# 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 potential applications for HPV testing.
4. Discuss the treatment options for genital warts.
5. Deliver appropriate patient counseling and partner management messages.

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## I. Epidemiology

### A. Incidence/prevalence of infection:

1. Difficult to define because:
  - a) Asymptomatic subclinical infections often go undiagnosed.
  - b) No case reporting of various manifestations of infection (HPV detection, genital warts, abnormal Pap smears,) except for data on HPV-associated cancers available through cancer registries.
  - c) Most studies estimating incidence and prevalence have been performed in women, with little data for men.
2. Prevalence of HPV infection is high; exact numbers unknown on population level, but estimated in U.S. at 1% for genital warts, and 14% for subclinical infection detectable by cytology, colposcopy, or DNA testing (approximately 20 million). Many clinic-based studies suggest genital HPV prevalence of 50% or more, highest in age group 20 to 24. It is estimated that 75% of sexually active adults are infected with genital HPV over their lifetime.
3. Incidence harder to determine. Genital warts incidence estimated to be approximately 0.3% per year overall. Annual incidence of all types of genital HPV infection estimated to be 5.5 million in U.S. and in young sexually active women approximately 10% per year.
4. Estimates for HPV-associated cancers: for cervical cancer, in U.S., an estimated 14,000 cases and 5,000 deaths, but worldwide, an estimated 450,000 cases and 200,000 deaths. Cancer rates at other anogenital sites (penis, vulva, vagina, anus) 8-10-fold lower.

### B. Transmission of genital HPV:

1. Predominantly sexual transmission.
2. Likely requires contact with viable HPV and microtrauma to skin/mucous membranes.
3. Can occur from asymptomatic and subclinical patients.
4. Prior HPV infection at other sites does not appear to offer protection, and there does not appear to be cross-protection between genital HPV types.
5. Role of fomite transmission unclear, probably rare.

6. Value of condoms in preventing transmission not well-studied: may be more effective for men than women and in preventing disease (genital warts and cervical cancer) than infection detectable by DNA tests. Lifetime mutual monogamy (or abstinence) are the likely the most effective options to prevent transmission.
7. Infectivity after treatment of warts or squamous intraepithelial lesions (SIL) unknown.
8. Vertical transmission may very rarely result 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 development of HPV-associated disease:

1. Diminished cellular immunity and immunosuppression associated with higher rates of HPV infection and faster progression of disease.
2. Hormonal influences (pregnancy, oral contraceptives), smoking, nutritional factors (folate deficiency), other STDs (e.g., *Chlamydia trachomatis*, HSV-2), and genetic predisposition associated with cervical cancer in some studies.

## II. Pathogenesis

A. Virology:

1. Key features of HPV:
  - a) Belongs to double-stranded DNA papovaviridae family, genus papillomavirus.
  - b) Virions small, non-enveloped.
  - c) Over 80 characterized types.
  - d) Genital types (over 30 identified) have specific tropism for genital skin and mucosa.
  - e) Very limited animal models and no widely available system for *in vitro* cultivation. Infection is generally indicated by the detection of HPV DNA.
2. HPV genotyping system:
  - a) Different diseases caused by different types, generally grouped as mucosal (including genital) or cutaneous types.

### Clinical Manifestations Associated With Different Types of HPV

Clinical manifestation	HPV types
<b>Skin Lesions</b>	
Plantar warts	1, 2, 4
Common warts	2, 4, 26, 27, 29, 57
Flat warts	3, 10, 28, 49
Butcher's warts	7
Epidermodysplasia verruciformis	2, 3, 5, 8, 9, 10, 12, 14, 15, 17, 19, 20-25, 36, 37, 46, 47, 50
<b>Genital</b>	
Condylomata acuminata	6, 11, 42-44, 54
Squamous intraepithelial lesions (SIL)	6, 11, 16, 18, 30, 31, 33, 34, 35, 39, 40, 42, 43, 51, 52, 55, 57-59, 61 62, 64, 67-70
Carcinoma	16, 18, 31, 33, 35, 39, 45, 51, 52, 54, 56, 66, 68
<b>Nongenital mucosal</b>	
Mouth (focal epithelial hyperplasia)	13, 32
Recurrent respiratory papillomatosis	6, 11, 30
Carcinoma (head/neck/lung)	2, 6, 11, 16, 18, 30

Modified from Koutsky LA, Kiviat NB. Genital human papillomavirus. Holmes KK, Mardh PA, Sparling PF, et al., eds. In: Sexually Transmitted Diseases. (3<sup>rd</sup> ed.). New York: McGraw-Hill; 1999:347-359.

- b) Types distinguished by different DNA sequences (>10% difference) at L1 capsid (surface) protein.
- c) Genital mucosal types are generally characterized as “high-risk” types (e.g., HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, etc.) which are associated with high-grade SIL (HSIL) and invasive cancer and “low-risk” types (e.g., HPV 6, 11, 42, 43, 44, etc.) which are primarily associated with genital warts and low-grade SIL (LSIL)
- d) Actual numbers of recognized HPV types are gradually increasing as more types are identified and genetically characterized.

**B. Pathology:**

1. Infect stratified squamous epithelium and stimulate cellular proliferation, resulting in latent and subclinical infection, condyloma, or dysplasia.
2. Affected cells display koilocytosis (cells with enlarged nuclei, irregular chromatin, perinuclear clearing, and a cytoplasmic border that varies from thick to thin).
3. Cervical lesions have been classified by several systems dependent on the proportion of the epithelium involved by the process. In the cervical intraepithelial neoplasia (CIN) system, lesions are considered to be CIN 1 (with undifferentiated cells in the lower one-third of the epithelium), CIN 2 (with undifferentiated cells in the lower one-third to two-thirds of the epithelium), and CIN 3/carcinoma in situ (with undifferentiated cells across the full thickness of the epithelium). The Bethesda System uses categories of LSIL (equivalent to CIN 1) and HSIL (HSIL, equivalent to CIN 2 and 3).

**Comparison of Bethesda System and Other Systems**

<b>Papanicolaou Class</b>	<b>Dysplasia</b>	<b>CIN</b>	<b>BETHESDA (NCI-ACOG)</b>
I	Negative	Negative	Within normal limits
II	Atypia HPV	Atypia HPV	ASCUS* Low grade SIL**
III	Mild dysplasia Moderate dysplasia	CIN 1 CIN 2	Low grade SIL High grade SIL
IV	Severe dysplasia CIS	CIN 3 CIN 3	High grade SIL High grade SIL
V	ICC***	ICC	ICC

\*ASCUS = Atypical squamous cells of undetermined significance.

\*\*SIL = Squamous intraepithelial lesion.

\*\*\*ICC = Invasive cervical cancer.

### C. HPV association with anogenital cancer:

1. Risk factors for cervical cancer suggest sexual transmission (early age of sexual activity, multiple sex partners, partners with penile cancer or whose prior partners had cervical cancer, and history of STDs). The link is now known to be genital HPV infection.
2. HPV infection is causally associated with cervical cancer and probably 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.
3. 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.
4. Estimated distribution of HPV types found in genital cancer: 16 (50%), 18 (14%), 45 (8%), 31 (5%), 33 (3%), other high-risk types (15-20%).

### D. Natural history of HPV:

1. Most genital HPV infections are transient and subclinical in immunocompetent individuals, with an average duration of infection as measured by detection of viral DNA of 6-12 months. 30% of infections persist >12 months and 10% >24 months. Persistence of infection confers the highest risk for development of subsequent HSIL and neoplasia; factors associated with persistent infection include older age, high-risk HPV types, and immunodeficiency. 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. Manifestations of infection include:
  - a) Transient infections and latent subclinical infections.
  - b) Genital warts.
  - c) SIL, carcinomas.
  - d) Respiratory papillomatosis.

3. Incubation period unclear: probably 3 weeks to several months for genital warts, and several months to years for cervical SIL.
4. Majority of women with "high-risk" HPV types (e.g. 16, 18) do not develop cervical cancer. Routine Pap smear screening ensures early detection (and treatment) of pre-cancerous lesions. In the absence of treatment, estimates for risk of progression to invasive cancer and spontaneous regression are estimated to be 1% and 60% for CIN 1, 5% and 40% for CIN 2, and 12 % and 32% for CIN 3.
5. 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) Progress to dysplasia and vulvar cancer rare but possible.
  - d) Recurrences after treatment (20-50% recurrence rate at 3-6 months) are common.

### III. Clinical Manifestations

#### A. Genital warts:

1. Appearance:
  - a) Condylomata acuminata:
    - 1) Cauliflower-shaped, flesh-colored, pink, or hyperpigmented.
    - 2) 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:
    - 1) Macular to slightly raised.
    - 2) Flesh-colored, with smooth surface.
    - 3) 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 genital warts can occasionally cause lesions on oral, upper respiratory, upper GI, and ocular locations.
3. Symptoms:
- a) The majority are probably 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: usually asymptomatic; occasional discharge, bleeding, obstruction of birth canal (secondary to increased wart growth during pregnancy).
  - g) Perianal warts (usually asymptomatic): pain, bleeding on defecation, itching.

#### B. Squamous intraepithelial lesions:

1. Appearance:
- a) Occurs in what is usually macroscopically normal epithelium and mucosal tissue.
  - b) Generally detected by cytology (for cervical SIL), and requires histology for confirmation and staging.
  - c) The most commonly recognized clinical manifestation of external genital SIL is bowenoid papulosis, dome-shaped or flat papules that are often hyperpigmented. These lesions can sometimes be flesh-colored and clinically indistinguishable from genital warts, but on biopsy demonstrate HSIL.
  - d) Detection is enhanced by application of acetic acid to mucosal membrane, producing acetowhitening, and by magnification with colposcopy.
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. 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, 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, and transmission of non-genital HPV types to genital surface, 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 warts 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 rectal warts; however, the clinical utility of diagnosing and treating these usually asymptomatic lesions has not been established.

3. Differential diagnosis of genital warts:
  - a) Infectious/acquired
    - 1) Condylomata lata: tend to be smoother, moist, more rounded, and darkfield-positive for *Treponema pallidum*, manifestation of secondary syphilis (RPR/VDRL is positive).
    - 2) Molluscum contagiosum: papules with central dimple, caused by a pox virus; rarely involves mucosal surfaces.
  - b) Acquired dermatologic
    - 1) Seborrheic keratosis.
    - 2) Lichen planus.
    - 3) Fibroepithelial polyp, adenoma.
    - 4) Melanocytic nevus.
    - 5) Neoplastic lesions.
  - c) Normal anatomic variants
    - 1) Pearly penile papules.
    - 2) Vestibular papillae (micropapillomatosis labialis).
    - 3) Skin tags (acrochordons).

## B. Diagnosis of SIL lesions

1. Diagnosis requires additional techniques as outlined above (e.g., cytology, colposcopy, and histopathology).
2. Cytology (Pap test):
  - a) Useful screening test to detect cervical dysplasia (not for HPV screening per se).
  - b) Pap screening should begin up to 3 years after onset of vaginal intercourse; no later than age 21. Exceptions include known or suspected history of sexual abuse, HIV infection, or immunocompromise.
  - c) Frequency of screening: annual testing until age 30 if using conventional Pap smear; every 2 years if using liquid based Pap test. At age 30, women with 3 consecutive satisfactory normal Paps can be screened every 2-3 years. Exceptions include DES exposure, HIV infection, or immunocompromise.
  - d) Pap screening may be discontinued at age 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.
  - e) Pap test provides indirect evidence of HPV on the basis of epithelial cell changes. Bethesda grading system replaces old nomenclature. Colposcopy referral is indicated for HSIL, LSIL in adults, and AGUS. Management strategies for ASCUS include repeat Pap testing at 4-6 month intervals, colposcopy, or HPV testing.

- f) Role of anal Pap for cytologic screening is under investigation, especially among HIV-infected persons.
  - g) No need for more frequent Pap tests if external genital warts.
  - h) 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 smear, which is the rationale for serial testing). New technologies using liquid collection media (Thinprep, Autocyte Prep) and computer-assisted reading may enhance sensitivity, but reduce specificity.
3. Colposcopy:
- a) Indication for colposcopy is guided by physical exam and/or Pap findings (sometimes assisted by HPV testing).
  - b) External genital warts are not an indication for cervical colposcopy.
4. Histology (biopsy): indications for cervical biopsy include visible exophytic lesions on the cervix, SIL on cytology, and other colposcopic abnormalities. Biopsy is also indicated for suspected bowenoid papulosis or other atypical lesions where diagnosis is uncertain.
5. HPV DNA Testing:
- a) The Hybrid Capture-II test (Digene) for HPV DNA is commercially available and is formatted to detect either “high-risk” (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, or 68) or “low-risk” type HPV DNA (6, 11, 42, 43, or 44). Results are reported as positive or negative.
  - b) Useful for triage of women with ASCUS on Pap smear. Women with high-risk HPV types benefit from colposcopy, while those who are negative can be followed with Pap smears. Not useful in triage of women with LSIL, because a large majority of those with LSIL have high-risk types which would suggest referral to colposcopy.
  - c) There is currently no clinical indication for use of the “low-risk” HPV test.
  - d) Test approved as adjunct to Pap test in women age 30 or older. Because of high negative predictive value, women whose test is negative for high-risk HPV types may be safely screened ever 2-3 years. Optimal management of women with normal Pap tests and positive high-risk HPV test results is unknown.
  - e) Other detection methods such as PCR are investigational.

## V. Treatment of Genital Warts

### A. General considerations:

1. Labor intensive: non-surgical, locally destructive techniques may require multiple treatments.
2. Effectiveness up to 2/3 of patients will experience recurrences of warts with 6-12 weeks of therapy; however, after 6 months, most patients have clearance.
3. If persistent after 3 months, or poor response to treatment, consider biopsy to exclude a premalignant or neoplastic condition, especially in an immunocompromised person.
4. Response affected by number, size, duration, location of warts and host immune status (pregnancy, HIV infection).
5. There is no evidence that any specific treatment is superior to any of the others. Considerations in the choice of therapy include patient preference, clinician experience, side effects, and cost.
6. General treatment considerations: if condylomata cover a small area, are asymptomatic, and the patient is not bothered by the knowledge that they are there, it is reasonable to follow clinically, since in a large percentage of cases, the lesions will regress. If warts are symptomatic or patient wants to be rid of them, there are several modalities available.
7. The benefit of treatment in reducing infectivity and preventing transmission is unknown.
8. Consideration should be given to screening persons with newly-diagnosed genital warts for other STD, (e.g., chlamydia, gonorrhea, HIV, syphilis).

### B. Recommended treatment regimens:

1. Patient-applied (provider should identify warts for treatment and teach how to apply substance):
  - a) Podofilox 0.5% solution or gel (Condylox): patients may apply podofilox solution with a cotton swab, or podofilox 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<sup>2</sup>, and a total volume of podofilox should not exceed 0.5mL per day. If possible, the healthcare provider should apply the initial treatment to demonstrate the proper application technique and identify which warts should be treated. Local irritation is common. *The safety and efficacy of podofilox has not been evaluated in pregnant women (category C).*

- b) Imiquimod 5% cream (Aldara): patients should apply imiquimod cream with a finger, at bedtime, 3 x per week every other day, 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. Local skin reactions are common. *The safety and efficacy of imiquimod has not been evaluated in pregnancy (Category B).*
2. Provider-administered:
- a) Cryotherapy with liquid nitrogen or cryoprobe: two freeze cycles using spray, cryoprobe, or cotton-tipped applicator, with a 1-minute thaw between freezings should be used. Repeat applications every 1 to 2 weeks. May be used on internal or external warts and 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<sup>2</sup> 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 the shelf life is uncertain. *The safety and efficacy of podophyllin resin has 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 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 treatments 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. 5FU is not currently recommended because of side effects.

D. Treatment of cervical warts: for women with exophytic cervical warts, treatment should be based on histopathologic lesion stage as determined by colposcopy and biopsy.

E. Treatment of vaginal warts:

*Treat only if symptomatic, since most treatments also affect normal tissue and could cause scarring and pain.*

1. Cryotherapy with liquid nitrogen: the use of a cryoprobe in the vagina is not recommended,
- or**
2. TCA or BCA 80-90%.

F. Treatment of distal urethral meatus warts:

1. Cryotherapy with liquid nitrogen,
- or**
2. Podophyllin 10-25%: must be dry before contact with normal mucosa,
- or**
3. Podofilox: limited data; may be useful for selected patients,
- or**
4. Imiquimod: limited data; may be useful for selected patients.

G. Treatment of anal warts:

1. Cryotherapy with liquid nitrogen,
- or**
2. TCA or BCA 80-90%,
- or**

3. Surgical removal.

H. Treatment of oral warts:

1. Cryotherapy with liquid nitrogen,
  2. Surgical removal.
- or**

I. 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.

J. 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 Squamous Intraepithelial Lesions**

Treatment of SIL at the cervix and other sites should be based on the results of colposcopy and histopathologic staging. 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; alternatively, to avoid the need for compliance with follow-up visits, some patients and providers prefer to treat CIN1 lesions. For CIN 2 and 3 lesions, ablative treatment is recommended with cryocautery, laser, or loop electrosurgical excision procedure (LEEP), each of

which appears to have similar rates of efficacy and complications.

## **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. Management:**

1. External anogenital warts: treatment unlikely to be effective due to high recurrence rate; treat only if symptomatic. 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.
2. Role of warts (or irritated treatment sites) in HIV transmission unknown.
3. Cervical Pap smear screening 6 monthly intervals x 2, then annually for all HIV+ women with or without genital warts.
4. Anal pap smears and anoscopy: value in absence of symptoms not established, but is under investigation.

## **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 smear screening.
4. Partners with exophytic warts may want treatment.
5. Partners may benefit from counseling.

B. Patient counseling and education:

1. Treatment options and considerations:
  - a) Goals of treatment (including whether to treat at all).
  - b) Patient vs. provider-applied options.
  - c) Potential for recurrence (and future therapy).
  - d) Cost/convenience.
  - e) Prior treatments.
  - f) Pregnancy.
  - g) Potential adverse effects of treatment options.
2. Nature of infection:
  - a) Chronic viral infection, usually self-limited, with 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 virtually never cause cancer.
  - d) Few (but rare) pregnancy issues.
3. Transmission issues:
  - a) Determining source of infection usually difficult; not evidence of infidelity.
  - b) Recurrences usually not re-infection.
  - c) Additional risk to current partner low (probably already infected).
  - 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. While the effect of condoms in preventing HPV infection is unknown, condom use has been associated with a lower rate of cervical cancer, an HPV-associated disease.
  - 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. HPV Vaccines:

1. Despite absence of in vitro system for cultivation and animal model for challenge studies, several potential approaches under investigation.
2. Most promising vaccines use of virus-like particles (VLPs), which preserve native conformations of viral proteins without presence of viral DNA.
3. Prophylactic immunization with VLPs containing capsid proteins has produced protective immunity in 3 animal models (rabbit, beagle, cow), although immunity appears to be PV-species-specific.
4. Human trials of HPV type 16 vaccine demonstrate high efficacy without significant adverse events. Experts anticipate that vaccines will be available by 2010.
5. Human trials are underway with multivalent and low-risk HPV type vaccines.

## **IX. HPV resources:**

American Social Health Association  
ASHA/HPV  
P.O. Box 13827  
Research Triangle Park, NC 27709  
[www.ashastd.org](http://www.ashastd.org)

American College of Obstetrics and Gynecology  
[www.acog.org](http://www.acog.org)

American Society of Colposcopy and Cervical Pathology (ASCCP)  
[www.asccp.org](http://www.asccp.org)

Centers for Disease Control and Prevention (1998 Guidelines for Treatment of Sexually Transmitted Diseases)  
[www.cdc.gov](http://www.cdc.gov)

National Cancer Institute (NCI)  
[www.nci.nih.gov](http://www.nci.nih.gov)

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