



# 5

## HUMAN PAPILLOMAVIRUS INFECTIONS



# HUMAN PAPILLOMAVIRUS (HPV) INFECTIONS

## OBJECTIVES

1. Describe the epidemiology, pathogenesis and clinical manifestations of human papillomavirus infections (HPV) in men and women.
2. Define and discuss the methods available for the detection of clinical and subclinical infections, including indications and reliability of new methods.
3. Define the subtypes of HPV and their potential for inducing malignant transformation and sequelae.
4. Describe the different treatment strategies for each anatomical sites, identify advantages and disadvantages of each, identify their goal and discuss the management of asymptomatic HPV.
5. Name the conditions, anatomic variants and benign and malignant neoplasms to be considered in the differential diagnosis.
6. Identify conditions requiring biopsy/referral.
7. Discuss the evaluation, treatment strategies and follow-up for pregnant women.
8. Discuss the relationship between HIV and HPV, and discuss the diagnosis and management of HPV for HIV infected individuals.
9. Describe the management of sexual partners of persons infected with HPV.
10. State the current recommendations for cervical cancer screening and the management of abnormal Pap smears.

## 1.0 BIOLOGY

Human papillomavirus (HPV) is a small, double-stranded DNA non-enveloped virus of the papovaviridia family. HPV contains about 7,800 to 7,900 base pairs. No system for reliable *in vitro* cultivation exists.

Papillomaviruses are widely distributed throughout mammals and are highly species specific. Within each species, there are multiple subtypes (based on DNA homology) that are very specific for a particular area of the body. Thus, genital types have specific tropism for anogenital mucosa. More than 20 subtypes can infect genital skin, and are considered mucosotropic. In the human there are over 100 subtypes of human papillomavirus identified. In order to be classified as a new subtype, the HPV must have less than 50 percent similarity in the genome with other known HPV types. The entire genome must be cloned, and the nucleotide sequence of its genes E6, E7, and L1 open reading frame has to share less than 90 percent homology to other papillomaviruses. All the sequenced papillomaviral genomes are similar in their overall genomic organization. Five open reading frames that are early transcriptional units (E1, E2, E4, E6 and E7) and two that are late transcriptional units (L1 and L2) as well as a long non-coding region, have been identified on all papilloma virus genome studies. All are similar in terms of size and location within the genome.

## 1.1 PATHOGENESIS

### MECHANISM OF INFECTION

HPV infects stratified squamous epithelial cells and epithelial basal cells (skin and mucous membranes), and stimulates cellular proliferation. Infection with the virus causes changes in the cell (koilocytosis) including enlarged nuclei, irregular chromatin, perinuclear clearing and cytoplasmic vacuolization, a cytoplasmic border that varies from thick to thin (koilocytosis). Koilocytes are found to be positive for HPV viral particles in 40% of cases, HPV antigen in 50% to 60% of cases, and HPV DNA in 60% to 70% of cases. Infection can result in benign hyperplasia, dysplasia, or invasive carcinoma. The role of HPV in malignant transformation has become fairly well-established.

In the teenage and young adult group, the glandular endocervical lining is present on the exocervix (cervical ectropion). As the cervix matures over a woman's reproductive life, the cervical ectropion is replaced through a process of squamous metaplasia to stratified squamous epithelium. The stratified squamous epithelium is thought to be more protective in general against sexually transmitted diseases. There is also the possibility that hormonal changes have an influence in susceptibility to HPV infection.

#### NOTES:

HPV replicates in the nucleus of the cell. The life cycle of the virus can follow one of two pathways. The course of the viral infection is probably dependent on its subtype, associated co-factors such as smoking, nutritional status (folate deficiency?), immune status, hormonal influences (pregnancy, OCP use) and other co-existing sexually transmitted diseases. Pathway I involves replication of the human papillomavirus as a plasmid. Pathway II involves intercalation within the host genome. The second pathway is thought to lead to neoplastic change.

n

## NATURAL HISTORY OF INFECTION

The natural history of HPV infection follows three possible routes:

1. Complete clearance of HPV after acute infection.
2. A latent infection.
3. Active, progressive infection.

Data demonstrating the transient nature of HPV infection are illustrated by the following:

- HO et al in 1998 demonstrated that the median duration of incident infection was eight months and that only 30% and 9% of infected persons had detectable HPV by DNA techniques after one and two years, respectively.
- Tate et al, 1996, evaluated the cervical mucosa adjacent to cervical intraepithelial neoplastic lesions in 28 women. They determined that, while 89 percent of lesions contained HPV nucleic acids, none of the normal surrounding tissue contained HPV. This finding is consistent with the low recurrence rates following ablation of lesions, as well as low indices of HPV positivity in normal cervixes during follow up.
- Additionally, it has been widely noted that the prevalence of HPV decreases with age, indicating that genital HPV infections are age dependent, and that genital HPV infections at young age can be transient. Observations supporting the transient nature of some infections include the increase of host immunity (both cell mediated and mucosal IgA) with age, and the anatomical changes in the normal maturation of the cervix.

Mucosal immunity occurs through the common mucosal immune system with the production of IgA over time. This is a slow, delayed response that does not immediately occur with initial exposure to HPV.

Latent infection is thought to occur in 10% of patients with HPV infection. In this



setting, it is hypothesized that a reservoir of virus exists which can be reactivated by stresses or changes in the patient's immune function. Ferenczy, et al, 1985, demonstrated that, in patients where HPV could be documented in the normal tissue surrounding anogenital lesions, 67 percent recurred after treatment. In contrast, only 9 percent of patients whose margins were negative for the presence of papillomaviral sequences after treatment recurred. High risk HPV types, infection with multiple types, and older age are associated with persistent infection, which in turn is associated with a higher risk of CIN disease.

Risk markers for disease expression include diminished cellular immunity and immunosuppression (higher rates of HPV positivity and worse disease). Hormonal influences (oral contraceptives, pregnancy), smoking and nutritional factors (folate deficiency) are less well documented.

n

## ONCOGENIC POTENTIAL

Integration of the E6 and E7 genes of HPV into the cell genome is important for malignant transformation to occur. Both E6 and E7 genes code for proteins that suppress the actions of the tumor suppresser gene products P53 and retinoblastoma gene. The more malignant HPV subtypes have gene product E6, E7 that bind more efficiently to the tumor suppressor genes than the low oncogenic subtypes.

While 30 to 50% of sexually active people are infected with human papillomavirus, progression to cancer occurs in less than 1% of women. High risk type HPV infection alone is not sufficient for the development of cervical cancer: other co-factors, such as smoking, hormonal exposure (multiparity, prolonged OC use??), nutritional deficiency, HLA haplotypes, other genital tract infections, and immunodeficiency (especially HIV infection), may be involved.

An earlier study, (Nash et al, 1987) evaluating 45 patients who had HPV on Pap smears demonstrated that 33% progressed from normal cervix to cervical intraepithelial neoplasia over an average of 10 months. :

CLASSIFICATION OF HPV TYPES: Mucosa/genital subtypes can be classified by oncogenic potential: as low or high risk.

### KEY POINTS:

- Natural history varies among individuals depending on viral and host factors
- Many have asymptomatic infection
- Genital warts can regress spontaneously in **10% to 30%**
- **Reoccurrences** common after treatment (up to 60%).

## MUCOSAL AND GENITAL TYPES

Type	Associated Disease
<b>Low Risk</b>	
6,11	Cause papillomas of upper airways and external genital condyloma. Type 6 found in only 0% to 5% of cancers while type 11 is found in 0% to 10% of cancers
42, 43, 44	Closely related in their nucleotide to 6, 11
<b>High Risk</b>	
16	Present in 50% (range: 45% to 65%) of high grade squamous intraepithelial lesions of the cervix and invasive cancer. Present in 15% to 40% of low grade lesions of the cervix. Present in 85% of high grade lesions in other areas of the anogenital tract. Present in 40% of subclinical lesions of the vulva and 10% of recalcitrant condyloma acuminata.
18	Very rarely found in low grade lesions. Involved in faster transit time to invasive cancer in and glandular lesions. Closely linked to glandular dysplasia and adenocarcinoma of the cervix. Found in 15% to 25% of cancers.
squamous	
31,33,35,39,45,51,52	Associated with Dysplasia Types 31, 33, 35 found in 5-10% of cancers.

**KEY POINTS:**

- HPV type 6 and 11 are most common types to cause genital warts and are rarely associated with genital tract cancers.
- HPV subtype 16 and 18 are the types most commonly associated with genital tract cancers
- **More than 95% of cervical cancers are associated with oncogenic HPV types.**
- **The majority of women infected with HPV (16,18) do not develop cervical cancer.**

## 1.2 EPIDEMIOLOGY

### PREVALENCE IN THE USA

More accurate to speak in terms of prevalence than incidence. An accurate evaluation of prevalence of HPV infections is difficult: the infection is not generally reportable (except in MA and LA), most infections are subclinical and often go undiagnosed, sensitivity of detection varies with the method used, and progression and regression of infection occurs.

Based on serological studies, it is estimated that, among sexually active women, over 50% have been infected by one or more genital HPV types, with 15% having evidence of current infection, 50-75% of which is with high risk types, and 1% have genital warts. A recent study demonstrated that incident HPV infection over a 36 month period was 43%. Levels of current infection in men appear to be the same as for women, but positive serum positivity is less common. The accuracy of serology is being evaluated and this technique is currently only used for research purposes.

The prevalence of HPV infection in the USA (assessed by DNA techniques) is estimated to be 20 million, the majority of which are subclinical. Based on various studies, the annual incidence is estimated to be 5.5 million. Estimated prevalence of genital warts is 1.4 million. Most infections occur in young adults, peaking in the 20 to 24 age group. Currently HPV infections have reached epidemic proportions in young, sexually active populations.

Overall, 1% to 2% of Pap smears have evidence of HPV infection. Some studies have demonstrated higher prevalence. Mass screening studies using hybridization techniques on cells collected from cervical smears demonstrated that 10 to 30% of specimens had evidence of HPV infection. Cross sectional studies of certain populations of women with normal cytologies suggest that 20 to 50% of sexually active young women have detectable HPV infection, and that prevalence decreases with age.

HPV DNA has been found in over 95% of cervical condyloma accuminata, all pre-malignant cervical lesions, and invasive cancers. An estimated 400,000 to 500,000 cases of cervical cancers occur annually. Cervical cancer is the second leading cause of cancer death world wide. Therefore, understanding of the epidemiology and pathogenesis of human papillomaviral infections is crucial. The mean age for women who develop cervical dysplasia is 20 to 25, and carcinoma in situ and invasive cervical cancer is 30 and 50 respectively.

**KEY POINTS:**

- HPV is the most frequent viral STD, estimated to infect 20-40 million adults in the US
- Rates Highest in young, sexually active population, with peak prevalence in 20-24 year olds



## TRANSMISSION AND INCUBATION

HPV is predominantly transmitted by direct sexual contact which involves micro-trauma as part of sexual behavior. This leads to the introduction of viral particles in the basement membrane of the skin. Transmission occurs from male to female, female to male, male to male and female to female, and can occur from asymptomatic and subclinical patients. Over  $\frac{2}{3}$  of partners of persons infected with genital warts developed condylomata on average 2 to 3 months after exposure. The number of lifetime partners is associated with current and lifetime infection. More importantly, the number of more recent partners is associated with current infection. HPV type 6 and 11 can be transmitted vertically during childbirth. Juvenile laryngeal papillomatosis is a rare sequela of vaginal delivery. Condyloma in preadolescent children: often, but not always due to sexual abuse. Male partners of women with cervical cancer have a high incidence of HPV infection.

The incubation period is long, and can be difficult to accurately assess because of subclinical infections and the effect of host immunity. It is estimated to be anywhere from three weeks to 20 months or more.

Role of fomite transmission is unclear and is probably rare.

Co-factors for transmission, persistence and neoplastic change in HPV: tobacco use, oral contraceptives, and possibly concurrent sexually transmitted diseases such as herpes simplex, Chlamydia trachomatis, Cytomegalovirus and Epstein-Barr virus.

Prior HPV infection at other sites does not appear to offer protection.

## 1.3 CLINICAL MANIFESTATIONS

The majority of HPV lesions are asymptomatic. In addition to genital tract manifestations, oral lesions can occur in men and women, but are relatively uncommon.

### WOMEN

CLINICAL MANIFESTATIONS OF HPV INFECTION CAN BE DIVIDED INTO BENIGN LESIONS, PREMALIGNANT LESIONS AND INVASIVE CANCERS.

#### KEY POINTS:

- Transmission of HPV probably requires contact with viable HPV and microtrauma to the skin/mucous membranes.
- It can occur from asymptomatic and subclinical patients.
- Prior HPV infection at other sites does not appear to convey protection.
- Incubation period can be long, and subclinical infections predominate.



## BENIGN LESIONS

Lesions commonly occur in areas of coital friction: fourchette, labia minora, labia majora, perineum, vagina, cervix, anus.

### A. Vulvar condyloma: acuminata or flat

Can show a wide range of appearances. Classically, condyloma acuminata appear as exophytic flesh colored pink or hyperpigmented papules or plaques. Small, raised, crusted lesions can appear on the vulvar or perianal region. The lesions can be hyperkeratotic on dry skin. Bigger condyloma can appear confluent, rising above the skin level. In immunocompromised patients, the condyloma can extend up onto the mons and back onto the buttocks. Vulvar condyloma can be completely asymptomatic, or can be associated with dyspareunia, pruritis and burning discomfort. For lesions that are quite large there can be irritation from the wearing of underwear. Small papular changes on the skin can sometimes be attributed to HPV infection. These visual changes can either be completely asymptomatic or can be associated with vulvar pruritus and burning. Flat condyloma are minimally elevated flesh colored pink smooth surface, and are generally more often seen on internal structures such as the cervix.

### B. Vaginal condyloma

Exophytic condyloma (acuminata) can also occur in a multifocal pattern in the vagina, and are generally non-keratinized when present on mucosal surfaces. Flat lesions are common. Symptoms include discharge/bleeding, although they are most often asymptomatic. Rarely, obstruction of the birth canal may occur due to increased growth of lesions during pregnancy.

### C. Cervical condyloma

The majority of cervical condyloma are flat, although occasionally raised leukoplasic lesions can be seen.

### D. Anal condyloma

Do not necessarily imply anal intercourse: they may be secondary to autoinoculation. Usually asymptomatic, but may cause pain and bleeding on defecation.

## PREMALIGNANT LESIONS

Intraepithelial neoplasia of the lower genital tract can be categorized by site.

### NOTES:



All intraepithelial neoplasia can be divided into low grade or high grade lesions (high grade squamous intraepithelial lesion or HGSIL and low grade squamous intraepithelial lesions or LGSIL). Low grade lesions are usually histopathologically associated with cytopathic changes of human papillomaviral infection. High grade lesions include moderate to severely dysplastic changes.

A. Vulvar Intraepithelial Neoplasia (VIN)

Appears as a discrete pigment change on the vulvar skin. This pigment change can be white, gray, black or red. Most commonly it is gray to black. There is a sharp border to the lesion. The lesion may or may not be raised and is usually multifocal. These lesions can be completely asymptomatic, or can be associated with burning and itching.

B. Vaginal Intraepithelial Neoplasia (VAIN)

Is an asymptomatic mucosal change that can occur anywhere in the vagina. It is seen under colposcopic direction as discrete, sharp bordered regions of white epithelium that may or may not be associated with atypical vascular changes.

C. Cervical Intraepithelial Neoplasia (CIN)

Is also asymptomatic. This can appear as unifocal or multifocal white, discrete lesions seen by colposcopy, but usually not by the naked eye. These lesions can be associated with atypical blood vessels such as a mosaic (cobblestone) or punctate vascular pattern.

D. Bowenoid Papulosis

Bowenoid papulosis is a form of carcinoma-in-situ which presents with single or multiple flat-topped or rough papules which are 2-4 mm in diameter, flesh colored to red brown. The lesions are usually recalcitrant to normal wart therapies. They may be confused with genital warts, pigmented nevi or seborrheic keratoses, and generally follow an indolent course without invasion, except when located on the cervix or the anus.

#### MALIGNANT LESIONS

Invasive cancers of the lower genital tract have all been associated with human papillomavirus infections. These include anal, vulvar, vaginal and cervical invasive cancers.

**NOTES:**



#### A. Vulvar and Perianal Cancers

Can appear as a raised or ulcerated lesion on the surface of the skin. Very small cancers may be asymptomatic. However, with time these cancers become painful and can bleed. Invasive vulvar cancers have a bimodal age distribution. The younger age group, mean age 40 years, is highly associated with HPV. These lesions are usually multifocal and can be associated with immunosuppression. The second age group, mean age 70 years, have vulvar cancers that are not associated with HPV. These cancers are usually unifocal and may be related to chronic irritation of the vulvar skin. There is an average delay in diagnosis of one year for women with vulvar cancers. This is due to both patient and healthcare provider delay. Commonly women who complain of vulvar itching or discomfort are treated with creams before a diagnosis by biopsy is made. Additionally, women may delay presenting to their healthcare provider because of embarrassment. Perianal cancers are highly associated with immunosuppression.

#### B. Vaginal Cancers

Comprise 1% of all female genital malignancies. They are associated with HPV infections. The most common site of vaginal cancer is the posterior upper third of the vagina. Frequently these cancers are missed when they are small because they are hidden by the speculum blades. Early cancers are asymptomatic. However, more advanced cancers are associated with abnormal vaginal bleeding and pain. On physical examination, these cancers will appear as a discrete, raised or ulcerated lesion that are hard to palpation.

#### C. Cervical Cancer

Is highly associated with HPV infection. Asymptomatic cancers are picked up by Pap smear screening. On inspection, a cervical cancer can appear exophytic with a polypoid, raised growth on the exocervix, or endophytic with expansion of the cervix from a cancer arising in the endocervical canal. Early symptoms include post-coital spotting, abnormal vaginal bleeding, and an abnormal discharge. Late symptoms that are worrisome for metastatic spread include bladder outlet obstruction, constipation, back pain and leg swelling.

Risk factors for cervical cancer suggest sexual transmission: early age of sexual activity, multiple sex partners, partners with penile cancers or prior consorts with cervical cancers, history of STDs (syphilis, GC, CT, HIV, HPV).

n

**NOTES:**



## MEN

HPV infection is commonly subclinical in men. The pick up of subclinical infections in men is usually due to the development of active disease in their sexual partner. Manifestations of HVP infection include benign lesions, pre-invasive lesions, and invasive cancers. Manifestations can be multicentric.

### BENIGN LESIONS

#### A. Penile Condyloma Acuminata

Can be seen as exophytic genital warts that are most often present on the frenulum, coronal sulcus, inner prepuce and glans. These are areas where microtrauma during coitus is most likely. Lesions can also be present on the shaft or the scrotum. Penile flat condyloma can be seen as aceto-white macules and papules. Most are asymptomatic. Periurethral lesions can occur. The majority are in the terminal urethra (80 percent) but these can spread to the proximal urethra. Men will present with complaints of reduction in urinary stream or urethral discharge and bleeding.

#### B. Perianal Condyloma and Rectal Condyloma

Can be seen, and this is seen most often in men who engage in receptive anal intercourse. Subclinical lesions of the rectal mucosa can also be present.

### PREMALIGNANT LESIONS AND MALIGNANT LESIONS

Premalignant lesions of the penis (PIN) and malignant penile cancer is very rare. Anal carcinoma can have the same manifestations as in women.

## 1.4 DIAGNOSIS

The diagnosis of HPV infections and clinical manifestations can be made by clinical examination, HPV DNA detection methods, cytology, and colposcopy with biopsy.

n

### PHYSICAL EXAMINATION

Condyloma acuminata are visible at the time of the examination. Many patients will present because they have noticed them on the external genitalia. Careful examination

#### KEY POINTS:

The spectrum of clinical manifestations of HPV includes:

- Subclinical infection
- Benign Lesions (condyloma acuminata, dome-shaped papules, keratococ warts and flat warts)
- Premalignant lesions (Bowenoid papulosis, intraepithelial neoplasia)
- Malignant lesions (cancer - vulvar, cervical, anal, penile)



of the vulva, perineum, vagina, cervix, penis, scrotum and anus for the presence of lesions should be performed. Simple and easy, but will miss subclinical infections.

The use of 3 to 5% acetic acid can enhance detection of flat lesions of the anogenital area and the vagina because they turn white. Cells become dehydrated and lesions that are more nuclear dense appear white. Keratinized skin is slower to demonstrate acetowhitening than thinner mucous membranes. Low specificity: 50% to 60%, because often noted at sites of prior trauma/inflammation. Overall, it has limited value in routine clinical practice.

Counseling on STDs should be offered, and all patients should be offered a human immunodeficiency virus (HIV) test. Patients should also be screened for gonorrhea, syphilis and chlamydia.

n

## DNA DETECTION

HPV detection methods are specific for the detection of HPV. They usually report by types grouped as "low risk" or "high risk" HPV. These methods include: Southern Blot, Dot Blot, in situ hybridization, hybrid capture (including Vira-Pap and Vira-Type) and polymerase chain reaction (PCR). The Dot Blot technique is the cheapest and quickest evaluation, while the PCR is the most sensitive.

The Digene Hybrid Capture II is a commercially available highly sensitive HPV DNA amplification assay. It is comprised of a battery of RNA probes testing for any of the high risk HPV subtypes (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68). Its performance in the triage of ASCUS and ASGUS has recently been assessed and shows promising results: it is 90% sensitive in detecting CIN2/3 in ASCUS, with an acceptable specificity (40-65%). Performance was similar with ASGUS. Ongoing studies are evaluating its use as an adjunct to Pap smear screening (increasing the detection of CIN2/3, determining intervals for screening or cut-off age for older women, follow-up management of CIN 1) or sole method of cervical cancer screening (in countries where women are not reached by conventional Pap smear screening).

n

## CYTOLOGY

Cytology with the Pap smear or the ThinPrep liquid cytology system will provide indirect evidence of HPV based on koilocytosis changes in the vagina and cervix. Its main use is to detect preinvasive and invasive lesions. It is relatively non-invasive

### KEY POINTS:

- Visual inspection usually adequate for diagnosis of genital warts; biopsy recommended for atypical appearance (pigmented, fixed, indurated or ulcerated).
- Acetic acid staining not generally recommended.
- Cervical cytology, by standard or liquid-based methods, recommended annually for sexually-active women.
- HPV DNA testing and typing not generally recommended, but may be useful for triaging ASCUS



and inexpensive. It has a good specificity but a poor sensitivity for HPV. The ThinPrep system is more expensive, but is more sensitive and specific: fewer unsatisfactory Paps, fewer ASCUS (20-30% decrease), increased sensitivity for HGSIL (50-120%) and increased sensitivity for LGSIL (50-70%).

The role of anal Pap for cytologic screening is under investigation (see page 21).

## PAPSMEAR

It is important to use good technique for performing the smear cytology to improve accuracy:

- ä Ideally, nothing in the vagina for at least 48 hours
- ä Best in mid-cycle, avoid during menstruation
- ä Do not use lubricant
- ä Gently remove excess mucus with a large scopette
- ä Insert small end of spatula in the endocervix, and rotate 360° to sample the ectocervix
- ä Sample the endocervix by inserting and rotating cytobrush
- ä Apply each to slide in thin monolayer of cells; roll endocervical sample onto slide
- ä Quickly add fixative or spray, have everything ready to avoid air drying

## THINPREP SYSTEM

Approved by the FDA in 1996. As with the conventional Pap smear, requires collection of cells from the exocervix and the endocervix (broom or spatula and cytobrush). The collection tools are shaken vigorously in the vial containing the preservative solution and then removed. A fully automated system removes blood, mucus, debris and white blood cells from the specimen, which is then evenly distributed on a slide. This results in a smear that is more representative of the sample and with minimal obscuring material.

## COLPOSCOPY

Colposcopy is the use of a high powered light source and magnification to evaluate mucosal regions of the vagina, cervix or penis for preinvasive and early invasive lesions. All lesions that are seen need to be biopsied for direct histologic analysis before a diagnosis can be definitively made.

### NOTES:



The indication for colposcopy is based on cytologic findings. The presence of external warts is not an indication for colposcopy.

n

## HISTOLOGY



Used in conjunction with colposcopy to confirm cytologic findings as described above and to determine the grade of neoplasia when present. It is also used on external lesions when the diagnosis is uncertain, the lesions are atypical in appearance and refractory to standard therapy, or in immunosuppressed hosts (see below).

Histologic confirmation of the presence of HPV becomes less certain when one of the following is missing: basal cell hyperplasia, acanthosis, papillomatosis, koilocytosis, parakeratosis, mild nuclear atypia.

## 1.5 DIFFERENTIAL DIAGNOSIS

Please see the videotape for visualization and further description of these lesions. The differential diagnosis of HPV include:

- ä Condyloma lata: lesions of secondary syphilis (see Section 2). Tend to be smoother, moister, and more rounded than HPV lesions. They are DF positive for *T. pallidum*. Can be easily confused with HPV, therefore, always request RPR when evaluating condyloma acuminata.
- ä Molluscum contagiosum: papules with a central dimple, caused by pox virus. Rarely involves mucosal surfaces. Most often found on the mons pubis, lower abdomen, labia majora, inner thighs.
- ä Seborrheic keratosis: raised, whitish, scaled lesions that can found on the labia majora.
- ä Lichen planus: generally seen in older women. Appears as white lesions on the vulva.
- ä Pink pearly penile papules: multiple papules often surrounding the skin just below the glans. Often mistaken for HPV by inexperienced clinicians.
- ä Other lesions to be distinguished include vestibular papillae, sebaceous glands and





skin tags.

- a Perform a biopsy for atypical presentation of lesions (dark, ulcerated, pigmented, fixed, indurated, extensive), if lesions worsen during therapy or are unresponsive to standard therapy, and in immunocompromised hosts.

## 1.6 TREATMENT

The goal of treatment is to eradicate warts for cosmetic reasons or for reduction of symptoms, or treatment of preinvasive and invasive lesions. No treatment modality will eradicate the virus. It is important, therefore, to avoid causing excess scarring, which can lead to pain and mutilation of the external genitalia. Small and asymptomatic lesions that are not pre-invasive or invasive can be followed clinically without treatment if the patient is comfortable with this, has a normal immune function, and there is a mechanism for close follow up, since a large percentage of lesions will regress. There is no evidence that the treatment of visible warts influences the development of cervical cancer. The removal of warts may or may not decrease infectivity.

None of the currently available treatment modalities is superior to others, so none is ideal for all patients and all warts. Factors that may influence the choice of treatment include number, size, anatomic site, morphology, cost of treatment, convenience, adverse effects, patient preference, provider experience, and host immune status (pregnancy, HIV infection). In general, warts on moist surfaces and/or located in intertriginous areas respond better to topical treatments such as TCA, podophyllin, podofilox and imiquimod than do warts on drier surfaces.

Regardless of treatment, up to  $\frac{2}{3}$  of patients will experience recurrences of condyloma within 3 to 6 months of therapy. Many patients will experience multiple recurrences after clearance.

CONSULT THE CDC 1998 GUIDELINES FOR TREATMENT OF STDs FOR MORE COMPLETE INFORMATION

n

### TREATMENT OF EXTERNAL CONDYLOMA OF THE GENITAL TRACT

Treatment can be divided into medical and surgical therapy, and patient applied and provider administered therapies. Medical therapy involves placement of some sort of

**NOTES:**



locally destructive compound that causes exfoliation and sloughing of the skin or mucosal membrane.

#### PATIENT - APPLIED THERAPIES

##### ä Podofilox 0.5% solution (Condylox®)

Purified active ingredient of podophyllin. Can be used for self-treatment in patients who are able to perform visual inspection of the external genitalia. It needs to be applied twice daily for three days followed by four days without therapy. The solution can be applied with a cotton swab, and the gel with the fingers. The therapy should be repeated as necessary for a total of four cycles. Total wart area treated should not exceed 10 cm<sup>2</sup> and total volume used should not exceed 0.5 ml per day. Well tolerated with few side effects. Patients with chronic warts often appreciate the freedom from frequent visits. If possible, the health care provider should apply the first treatment to demonstrate proper application technique and identify which warts should be treated. Safety not established during pregnancy.

##### Imiquimod 5% cream (Aldara®)

New topical immuno-modulator that has been tried both for condyloma and in cancer patients as an interferon inducer. It can be applied by patients with a finger three times a week at bedtime for up to 16 weeks. It is recommended that the treatment be washed with mild soap and water 6 to 10 hours after application. Erythema is most frequent side effect, followed by excoriation and edema. Clearance rates are higher for women than for men. More effective for less keratinized warts. Maybe associated with lower recurrence rates (19% vs the 30-60% recurrence rates reported with other treatments), but data is limited. Most patients may be clear of warts by 8 to 10 weeks or sooner. Safety not established during pregnancy.

#### PROVIDER - APPLIED THERAPIES

##### ä Trichloroacetic acid (TCA) or Bichloroacetic acid (BCA) 80 to 90%

Causes chemical cauthery of the lesion. Caustic agents that destroy warts by chemical coagulation of the proteins. Often preferred because it is inexpensive and safe to use during pregnancy. Very caustic: a protecting agent such as Lubriderm or Vaseline jelly can be applied around the surrounding condyloma. Apply a small amount of TCA directly to the lesion by using a cotton tipped applicator. Avoid leakage. This immediately causes a whitish change and the patient will experience a burning sensation upon application. This burning will resolve within minutes.

#### KEY POINTS:

- Goal of treatment is removal of symptomatic warts; no treatment modality will eradicate the virus.
- Small lesions may regress on their own in immunocompetent patients.
- Treatment of warts may or may not lower infectivity, and does not influence the risk of developing cervical cancer.
- Cervical cytology screening is not recommended any more frequently in women with genital warts.
- Recurrence of genital warts after treatment is common



Bicarbonate solution or talcum powder can be applied to reduce burning and absorb excess acid. This treatment should be repeated weekly. If lesions persist after six applications, another therapy should be considered (after ruling out malignancy). Three weeks is usually enough. Allow to air-dry before the patient dresses to avoid spread of agent.

• Podophyllin 10% to 25% in tincture of Benzoin

Inhibits mitosis (cytotoxic). Less frequently used and less effective than other options. It is contraindicated during pregnancy. Do not use in the vagina because it can be systemically absorbed and cause toxicity. After application, some experts recommend that the podophyllin be rinsed off 1 to 4 hours later. If warts persist after six applications, other therapy must be considered (again, r/o malignancy). Do not use podophyllin on a surface of more than 10 cm<sup>2</sup>, or use more than 0.5 ml per session. Can be combined with cryotherapy. Allow to air-dry before patient dresses to avoid spread of agent.

• Cryotherapy

Destruction by freezing using either liquid nitrogen in a tank applied with a swab, or a probe, or a spray gun. It is safe to use during pregnancy. It can be used in the rectum, vagina or on the cervix. Use in the vagina\rectum must be very carefully done as it can cause perforation. The usual mode of application to external genital warts involves applying the liquid nitrogen to the wart for 20-30 seconds until a white ice halo forms 1-2 mm beyond the border of the lesion. Many practitioners will allow the lesion to thaw and immediately repeat the second freeze cycle. Multiple weekly applications may be necessary for larger lesions. It is good for localized small lesions. It is painful during application.

• Laser

Carbon dioxide laser is used routinely for treatment of massive external condyloma. It is also used on the penis, vulva, vagina and cervix for pre-invasive lesions. Laser is used to ablate only the skin and does not effect the subdermal tissues. Laser of the vulva is extremely painful in the postoperative period until new skin has grown into the areas of ablation. During this time period, sitz baths and the use of a sulfadene cream to protect from superinfection with bacteria should be used. Generally, excellent healing with good cosmetic results. In the vagina, all methods of treatment can cause narrowing, scarring and synechia. After treatment of the vagina, especially one that causes desquamation, Premarin® vaginal cream should be used to keep the vagina from closing in.

**NOTES:**



ä Surgical Excision

Usually reserved for pre-invasive lesions of the vulva, vagina and cervix or very large lesions.

ä Electrocautery or electrodesiccation

Local anesthesia is required. Patient discomfort is usually moderate. It is contraindicated for patients with cardiac pacemakers or for lesions proximal to the anal verge

n

## TREATMENT OF VAGINAL CONDYLOMA

Cryotherapy with liquid nitrogen (avoid probe as risk of vaginal perforation and fistula formation) or TCA/BCA. Podophyllin can also be used, but treatment should be for 2 cm<sup>2</sup> or less per session. Some experts caution against vaginal application of podophyllin because of concerns about potential systemic absorption. Podophyllin is contraindicated during pregnancy.

n

## TREATMENT OF URETHRAL MEATAL WARTS

Cryotherapy or podophyllin recommended.

## TREATMENT OF ANAL WARTS

Cryotherapy, TCA/BCA or surgical removal recommended.

n

## TREATMENT OF ORAL WARTS

Cryotherapy or surgical removal is recommended.

n

## TREATMENT OF CERVICAL LESIONS

Dysplasia/neoplasia must be ruled out before any treatment is initiated. Refer to expert for evaluation.

**NOTES:**



## MANAGEMENT OF ABNORMAL PAP SMEARS

Abnormal Pap smears are classified according to the 1988 Bethesda System for Reporting Cervical/Vaginal Cytologic Diagnoses and consists of 3 grades of abnormality:

- ä Atypical Squamous Cells of Unknown Significance (ASCUS): indicates mild cellular atypia which may be due to infection, HPV, estrogen deficiency or reaction to an irritant; may be further qualified by the cytopathologist (i.e. favoring benign or reactive process, or favoring neoplastic process)
- ä Low-grade squamous intraepithelial lesions (LSIL): encompasses cellular changes previously classified as mild dysplasia/cervical intraepithelial neoplasia 1 (CIN 1)
- ä High-grade SIL (HSIL): encompasses previous classification of moderate dysplasia/CIN 2, severe dysplasia/CIN 3, and carcinoma in situ/CIN 3.
- ä Mostly mildly abnormal pap smears (ASCUS or LSIL) will revert to normal without specific therapy in immunocompetent women, so conservative management with repeated pap smears is usually indicated. Some experts recommend HPV typing to assist in triaging ASCUS smears, and recommended more aggressive follow-up for those found to have high-risk HPV types.

## RECOMMENDED FOLLOW-UP OF ABNORMAL SMEARS

Management of ASCUS Pap smear results may vary by clinical settings. Some practices use HPV typing to triage the management of these Pap smear results. For more information about proposed algorithms see reference number ???) Patients who have 2 or more ASCUS or any high-risk patient with 1 ASCUS (HIV+, prior history of CIN) should be referred for coloscopy.

Per CDC Guidelines:

- ä ASCUS with severe inflammation: treat infection if present, repeat in 2-3 months, then repeat every 4-6 months for 2 years until the results of three consecutive pap smears are negative.
- ä ASCUS which is consistent with benign or reactive process: repeat pap smears every 4-6 months for 2 years until the results of three consecutive pap smears are negative.
- ä Low-grade SIL which is not qualified further or favors a reactive process: repeat pap smears every 4-6 months for 2 years until the results of three consecutive smears are negative (if patient is immunocompromised, has a history of ä abnormal pap smear in the past or has unreliable follow-up, consider colposcopy)

### NOTES:



immediately instead of conservative follow-up)

- ä Persistent ASCUS or low-grade SIL: colposcopy
- ä High-grade SIL: colposcopy

Recommendation of the management of ASCUS may vary by expert or professional organization.

## TREATMENT OF PRE-INVASIVE AND INVASIVE LESIONS

Pre-invasive lesions can be treated by destructive measures that completely remove the lesion. This is usually done by either laser or surgical excision. Invasive lesions should be referred to a gynecologic oncologist in the case of women, and a urologist in the case of men.

### 1.7 FOLLOW-UP

After diagnosis and successful treatment of benign HPV lesions, follow-up is not necessary. Patients should return if lesions recur. Annual cytologic screening is recommended for women with or without genital condyloma. The presence of external condyloma is not an indication for colposcopy.

After treatment of the cervix for a pre-invasive lesion, follow up with Pap smears every three months for the first year should be performed. If there has been no recurrence of the lesion within a year, yearly Pap smear screening is appropriate.

Aggressive smoking cessation program should be instituted.

### 1.8 MANAGEMENT DURING PREGNANCY

Disease may be more extensive during pregnancy. Treatment with cryotherapy or TCA is safe during pregnancy.

C-section is not routinely recommended to avoid neonatal transmission. However, may be necessary if lesions are so extensive that they will obstruct the birth canal or bleed excessively during delivery.

If the cytology is abnormal, rule out invasion with colposcopy and biopsy. If no invasion, follow with serial colposcopy. Cervical disease is not treated unless invasion is present. The majority of lesions will regress in the post partum period.

## 1.9 HPV AND HIV INFECTION

In HIV infected patients, HPV infection is detected more frequently, has more pronounced clinical manifestations, a higher recurrence rate, a lower response to conventional therapy, and appears to progress to intraepithelial neoplasia and invasive cancer more rapidly than in HIV-negative patients.

Since immunocompromised patients are more likely to have persistent infection with HPV and progression to neoplastic change, they need to be monitored more closely over time. For routine screening, the CDC recommends a pap smear at the initial visit after HIV is diagnosed, with a repeat at 6 months, and then annually thereafter if the initial two were normal. Some experts recommend baseline colposcopy for all HIV infected women with the presence of HPV infection, but cost-effectiveness of this practice has not been established. Colposcopy should be done on all abnormal pap smears, including atypia and low grade lesions, and all dysplasias should be treated aggressively and followed closely after treatment. Annual visual inspection of the external genitalia in women is also important to detect any new vulvar perineal lesions.

Men who have sex with men (MSMs) develop anal cancer at a rate approximately 80 times higher than the population in general. Cross sectional and prospective studies show high rates of prevalent and incident anal squamous intraepithelial lesions (SIL) in this population. Anal pap screening is a sensitive method for detecting anal SIL, and some experts have recommended annual anal pap screening among HIV + and HIV-MSMs. However, the natural history of anal SIL has not been determined, and the usefulness of screening programs has not been validated. Also, the lack of clinician training in the procedure and the paucity of protocols and referral networks for dealing with abnormal smears are significant barriers to wide implementation. As with women, however, annual visual inspection of the external genitalia and anoscopy (if indicated) should be performed to detect abnormal lesions.

## 1.10 MANAGEMENT OF SEXUAL PARTNERS AND PREVENTION

Role of re-infection is minimal in the recurrence of manifestations of HPV.

The discussion should be raised about the possibility of screening the sexual partner for sexually transmitted diseases (STDs). All partners with symptomatic lesions need to be evaluated by the appropriate healthcare provider. Condoms may reduce the transmission of HPV to new, uninfected partners and will protect against other STDs. For individuals who are engaged in a monogamous relationship, and who have had unprotected intercourse before detection of disease, the use of condoms will not affect the outcome.

HPV resources: American Social Health Association (ASHA), ASHA/HPV PO BOX 13827, Research Triangle Park, NC 27709.

## 1.11 REVIEW QUESTIONS

1. A 22 year old male presents to the clinic because his girlfriend was diagnosed with genital external condyloma. Upon examination, you detect the presence of condyloma in the urethral meatus, but find no other lesions visible to the naked eye. How would you manage and treat this patient?

---

---

---

---

---

---

---

---

---

---

2. A 25 year old woman presents for her first prenatal visit at 16 weeks of pregnancy. She noticed "big bumps" on her vulva. Upon examination, you find more than 15 condyloma acuminata, with some larger than 5 cm. How would you manage this patient?

---

---

---

---

---

---

---

---

---

---

3. A 21 year old presents to your office for her annual gynecologic examination. You find two very small condyloma acuminata at the fourchette. She has been with the same sexual partner for the past year. What follow-up would you recommend for her? For her partner?

---

---

---

---

---

---

---

---

## 1.12 REFERENCES

### Epidemiology

- 1 Carson HJ, Demay RM. The mode ages of women with cervical dysplasia. *Obstet Gynecol* 1993 82:432-4.
- 2 CDC. Prevention of genital HPV infection and sequelae: report of an external consultants' meeting. December 1999;DHHS,CDC Division of STD Prevention.
- 3 Daling JR, Sherman KJ, Weiss NS. Risk factors for condyloma acuminata in women. *Sex Trans Dis* 1986;13(1):16-18.
- 4 Dillner J, Lerner P, Lehtinen M, et al. A population based seroepidemiological study of cervical cancer. *Cancer Res* 1994 54:134-141.
- 5 Doll R, Franceschi S, Galloway J, et al. Genital warts and cervical neoplasia: an epidemiologic study. *Br J Cancer* 1983 48:621-628.
- 6 Feldman JG, Chirgwin K, Dehovitz JA, et al. The association of smoking and risk of condyloma accuminatum in women. *Obstet Gynecol* 1997 89:346-350.
- 7 Hildesheim A, et al. Persistence of type specific human papillomavirus infection among cytologically normal women. *J Infect Dis* 1994;169:235-240.
- 8 Ho G, et al. Natural History of cervicovaginal papillomavirus infection in young women. *NEJM* 1998;338:423-428.
- 9 Koutsky IA, Galloway DA, Holmes KK. Epidemiology of genital human papillomavirus infection. *Epidemiol Rev* 1988 10:122-163.
- 10 Munoz N, Kato I, Xavier Bosch F et al. Risk factors for HPV DNA detection in middle aged women. *Sex Transm Dis* 1996, 23:504-10.
- 11 Negrini BP, Schiffman MH, Kurman RJ, et al. Oral contraceptive use, human papilloma virus infection and risk of early cytologic abnormalities of the cervix. *Cancer Res* 1990 50:4670-4675.
- 12 Scarewiski A, Jarvis MJ, Sasieni P, et al. Effect of smoking cessation on cervical lesion size. *Lancet* 1996 347:941-3.
- 13 Schiffman MH, Bauer HM, Hoover RN, et al. Epidemiologic evidence showing that human papillomavirus infection causes most cervical intraepithelial neoplasia. *J Natl Cancer Inst* 1993 85:958-964.
- 14 Trevathan E, Layde P, Webster IA, et al. Cigarette smoking and dysplasia and carcinoma in situ of the uterine cervix. *JAMA* 1983 250:499-502.
- 15 Winkelstein W. Smoking and cancer of the uterine cervix: hypothesis. *Am J Epidemiol* 1977 106:257-259.
- 16 Xavierbosch F, Manos MM, Munoz N, et al. Prevalence of human papillomavirus in cervical cancer, a world wide prospective. *J Natl Cancer Inst* 1995 87:796-802.

### Biology and Oncogenic Potential

- 1 Burnett AF, Grendys EC, Willett GD, et al. Preservation of multiple oncogenic human papilloma virus types in recurrences of early stage cervical cancers. *J Obstet Gynecol* 1993 170:1230-33.
- 2 Fukushima M, Yamakawa Y, Shimano S, et al. The physical state of human papillomavirus 16 DNA in cervical carcinoma and cervical intraepithelial neoplasia. *Cancer* 1990 66:2155-2161
- 3 Higgins GD, Phillips GE, Smith IA, et al. High prevalence of human papillomavirus transcripts in all grades of cervical intraepithelial glandular neoplasia. *Cancer* 1992 70:136-146.
- 4 Kaufman RH, Adam E, Icenogle J, et al. Relavence of human papillomavirus screening in management of cervical intraepithelial neoplasia. *Am J Obstet Gynecol* 1997 176:87-92.
- 5 Lungu O, Wei Sun X, Felix J, et al. Relationship of human papillomavirus type to grade of cervical intraepithelial neoplasia. *JAMA* 1992 267:2493-2496.
- 6 MacNab JCM, Walkinshaw SA, Cordiner JW, et al. Human papillomavirus in clinically and histologically normal tissue of patients with genital cancer. *N Engl J Med* 1986 315:1052-1058.
- 7 Schneider A, Zahm DM, Greinke C, et al. Different detectability of high risk HPV in smears from incident and prevalent high grade squamous intraepithelial lesions of the cervix. *Gynecol Oncol* 1997 65:399-404.
- 8 Syrjanen K, Mantyjarvi R, Saarikoski S, et al. Factors associated with progression of cervical human papillomavirus infections into carcinoma in situ during a long term prospective follow up. *Br J Obstet Gynecol* 1988 95:1096-1102.

### Pathogenesis

- 1 Bollen LJM, Tjong-A-Hung SP, Van Der Velden J, et al. Human papillomavirus DNA after treatment of cervical dysplasia: low prevalence in normal cytologic smears. *Cancer* 1996 77:2538-2543.
- 2 Burke RD, Kelly P, Feldman J, et al. Declining prevalence of cervical vaginal human papillomavirus infection with age is independent of other risk factors. *Sex Trans Dis* 1996 23:333-341.
- 3 Chua KL, Hjerpe A. Persistence of human papillomavirus (HPV) infections preceding cervical cancer. *Cancer* 1996 77:121-127.
- 4 Der Villiers EM, Wagner D, Schneider A, et al. Human papillomavirus DNA in women without and with cytologic abnormalities: results of a five year follow up study. *Gynecol Oncol* 1992 44:33-39.
- 5 Ferenczy A, Mitao M, Nagai N, et al. Latent papillomavirus and recurring genital warts. *N Engl J Med* 1985 313:784-788.
- 6 Franco EL. Human papillomavirus and the natural history of cervical cancer. *Inf in Med*. 1993; Jan: 57-63

- 7 Kiviat N. Natural History of Cervical Neoplasia: overview and update. *Am J Obstet Gynecol* 1996 175:1099-1104.
- 8 Koutsky IA, Holmes KK, Critchlow CW, et al. A cohort study of the risk of cervical intraepithelial neoplasia grade II or III in relation to papillomavirus infection. *N Engl J Med* 1992 327:1272-1278.
- 9 Moscicki AB, Palefsky J, Smith G, et al. Variability of human papillomavirus DNA testing in a longitudinal cohort of young women. *Obstet Gynecol* 1993 82:578-585.
- 10 Nash JD, Burke TW, Hoskins WJ. Biologic course of cervical human papillomavirus infection. *Obstet Gynecol* 1987 69:160-162.
- 11 Ostor AG. Natural history of cervical intraepithelial neoplasia: a critical review. *Int J Gynecol Pathol* 1993 12:186-192.
- 12 Tate JE, Resnik M, Sheets EE, et al. Absence of papillomavirus DNA in normal tissue adjacent to most cervical intraepithelial neoplasms. *Obstet Gynecol* 1996 88:257-260.

#### Clinical Manifestations

- 1 Andersen WA, Franquemont DW, Williams J, et al. Vulvar squamous cell carcinoma and papillomavirus: two separate entities. *Am J Obstet and Gynecol* 1991 165:329-336.
- 2 Binder MA, Cates GW, Emson HE, et al. The changing concepts of condyloma. A retrospective study of colposcopically directed cervical biopsies. *Am J Obstet Gynecol* 1985 151:213-219.
- 3 Bornstein J, Kaufman RH, Adam E, et al. Human papillomavirus associated with vaginal intraepithelial neoplasia in women exposed to diethylstilbestrol in utero. *Obstet Gynecol* 1987 70(1):75-80.
- 4 Bucana J, Naghashfar Z, Sawada E, et al. The predominance of human papillomavirus type 16 in vulvar neoplasia. *Obstet Gynecol* 1988 71:601-606.
- 5 Campion MJ. Clinical manifestations and natural history of genital human papillomavirus infection. *Obstet Gynecol Clin N Amer* 1987;14(2):363-388.
- 6 Fisher G, Harlow SD, Schottenfeld D. *Gynecol Oncol* 1997 64:213-223.
- 7 Gardeil F, Barry-Walsh C, Prendiville W, et al. Persistent intraepithelial neoplasia after excision for cervical intraepithelial neoplasia grade III. *Obstet Gynecol* 1997 89:419-422.
- 8 Ikenberg H, Runge M, Goppinger E, et al. Human papillomavirus DNA and invasive ca' of the vagina. *Obstet Gynecol* 76:432-438.
- 9 Meisels A, Fortin R, Roy M. Condylomatous lesions of the cervix. 2. Cytologic colposcopic and histopathologic study. *Acta Cytol* 21:379-390.
- 10 Monsonego J, Zerat L, Catalan F, et al. Genital human papillomavirus infections: correlation of cytological, colposcopy and histologic features with viral types in women and their male partners. *Int J STD AIDS* 1993 4:13-20.
- 11 Nasiell K, Nasiell M, Vaclavinkova V. Behavior of moderate cervical dysplasia during long term follow up. *Obstet Gynecol* 1983 61:609-614.
- 12 Noffsinger A, Witte D, and Fenoglio-Preiser CM. The relationship of human papillomavirus to anorectal neoplasia. *Cancer* 1992 70:1276-1287
- 13 Planner RS, Hobbs JB. Human papillomavirus infection and associated intraepithelial neoplasia of the cervix, vaginal and vulva. *Aust N Z J Obstet Gynecol* 1987 21:132-135.
- 14 Richart RM, Barron BA. A follow up study of patients with cervical dysplasia. *Am J Obstet Gynecol* 1969 105:386-393.
- 15 Schneider A, Devilliers EM, Schneider V. Multifocal squamous neoplasia of the female genital tract: significance of human papillomavirus infection of the vagina after hysterectomy. *Obstet Gynecol* 1987 80:294-298.
- 16 Scinicariello F, Rady P, Saltzstein D, et al. Human papillomavirus 16 exhibits a similar integration pattern in primary squamous cell carcinoma of the penis and in its metastasis. *Cancer* 1992 70:2143-2148.

#### Diagnosis

- 1 Cuzick J, Scarewski A, Terry G, et al. Human papillomavirus testing in primary cervical screening. *Lancet* 1995 345:1533-1536.
- 2 Hatch KD, Schneider A, Abdel-Nour MW. Evaluation of human papillomavirus testing for intermediate and high risks types as triage before colposcopy. *Am J Obstet Gynecol* 1995 172:1150-1157.
- 3 Lungu O, Wright TC, Silverstein S. Typing of human papillomaviruses by preliminary chain reaction amplification with L1 consensus primers and RFLP analysis. *Mol Cell Probes* 1992 6:145-152.

- 4 Reid R, Herschman BR, Crum CP, et al. Genital warts and cervical cancer Part V: The tissue basis for colposcopic change. Am J Obstet Gynecol 1984 149:293-303.
- 5 Reid R, Scalzi P. Genital warts and cervical cancer Part VII: An improved colposcopic index for differentiating benign papillomaviral infections from high grade cervical intraepithelial neoplasia. Am J Obstet Gynecol 1985 153:611-618.
- 6 Hatch KD. Multisite clinical outcomes trial to evaluate performance of the thinprep pap test. Obstet Gynecol 2000;95(SS1):S51.
- 7 Lentricchia BB, et al. Comparability of the thinprep pap test and the LCX probe system chlamydia trachomatis assay. Obstet Gynecol 2000;95(SS4):S3-S4.
- 8 Manos M, et al. Identifying women with cervical neoplasia using human papillomavirus DNA testing for equivocal Pap results. JAMA 1999;281:1605-1610
- 9 Diaz-Rosario IA. Performance of a fluid-based thin-layer papanicolaou smear method in the clinical setting of an independent laboratory and an outpatient screening population in New England. Arch Pathol Lab Med 1999;123:817-21
10. Brown AD, et al. Cost-effectiveness of 3 methods to enhance the sensitivity of pap testing. JAMA 1999;281:347-53
11. Weintraub J, et al. Efficacy of a liquid-based thin layer method for cervical cancer screening in a population with a low incidence of cervical cancer. Diagn Cytopathol 2000;22:52-9

#### Treatment

- 1 Bornstein J, Ben-David Y, Atad J, et al. Treatment of cervical intraepithelial neoplasia in invasive squamous cell carcinoma by interferon. Obstet Gynecol Surv 1993 48:251-260.
- 2 Centers for Disease Control and Prevention, DHHS, PHS. 1998 CDC STD Treatment Guidelines.
- 3 Ferenczy A, Bergeron C, Richart RM. Carbon dioxide laser energy disperses human papillomavirus deoxyribonucleic acid onto treatment fields. Am J Obstet Gynecol 1990 163:1271-1274.
- 4 Fujisawa H, Shivji GM, Kondo S, et al. Effect of a novel topical immuno-modulator S-28463, on keratinocyte cytokine gene expression and production. J Interferon Cytokine Res 1996 16:555-559.
- 5 Greenberg MD, Rutledge IH, Reid R, et al. A double-blind, randomized trial of 0.5 percent Podofilox and placebo for the treatment of genital warts in women. Obstet Gynecol 1991 77:735-739.
- 6 Kraus SJ, Stone KM. Management of genital infection caused by human papillomavirus. Rev Inf Dis 1990;12(suppl 6):S620-632.
- 7 Krebs HB, Helmkamp BF. Chronic ulcerations following topical therapy with 5-Fluorouracil for vaginal human papillomavirus associated lesions. Obstet Gynecol 1991 78:205-208.
- 8 Petrilli ES, Townsend DE, Morrow CP et al. Vaginal intraepithelial neoplasia: biological aspects and treatment with topical 5-Fluorouracil and the carbon dioxide laser. Am J Obstet Gynecol 1980 138:321-328.
- 9 Sand-Petersen C, Bjerring P, Larsen J, et al. Systemic interferon alfa IIB increases the cure rate in laser treated patients with multiple persistent genital warts: A placebo controlled study. Genitourin Med 1991 67:99.
10. Reid R, Stanhope CR, Herschman BR et al. Genital warts and cervical cancer Part IV: A colposcopic index for differentiated subclinical papillomaviral infection from cervical intraepithelial neoplasia. Am J Obstet Gynecol 1984 149:815-823.
11. Beutner KR, et al. External genital warts: report of the AMA Consensus Conference. AMA Expert Panel on EGW. Clin Infect Dis 1998;27:796-806
12. Beutner KR, et al. Genital warts and their treatment. Clin Infect Dis 1999;28(SS1):S37-S46.
13. Edwards L, et al. Self-administered topical 5% imiquimod cream for external anogenital warts. Arch Dermatol 1998;134:25-30.

#### Immunosuppression

- 1 Euvrard S, Chardonnet Y, Pouteil-Noble C, et al. Association of skin malignancies with various and multiple carcinogenic and non-carcinogenic human papillomaviruses in renal transplant recipients. Cancer 1993 72:2198-2206.
- 2 Sillman F, Stanek A, Sedlis A, et al. The relationship between human papillomavirus and lower genital intraepithelial neoplasia in immunosuppressed women. Am J Obstet Gynecol 1984 150:300-308.
- 3 Naiman M, Tarricone N, Vieira J, et al. Colposcopic evaluation of human immunodeficiency virus - seropositive woman. Obstet Gynecol 1991 78: 84-88

