

Recommendations for the Diagnosis and Treatment of HPV Lesions of the Female Genital Tract

E. R. Weissenbacher
A. Schneider
L. Gissmann
G. Gross
J. Heinrich
P. Hillemanns
M. Link
K. U. Petry
P. Schneede
H. Spitzbart

from

Arbeitsgemeinschaft für Infektionen und Infektionsimmunologie in der Gynäkologie und Geburtshilfe der Deutschen Gesellschaft für Gynäkologie und Geburtshilfe (AGII der DGGG)

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I. Introduction

Human papillomavirus (HPV) is a double-stranded DNA virus with a tropism for epithelial cells. There are more than 100 different HPV types, 40 of which have been identified in the human anogenital tract. Some of the human HPV viruses are potentially oncogenic and a necessary factor for development of cervical cancer. These HPV viruses, predominately types 16, 18, 31 and 45, are, therefore, classified as “high risk” HPV. The other human HPV types, predominately types 6 and 11, always cause only benign lesions and are known as “low risk” HPV.

HPV is acquired chiefly through sexual intercourse and is the most common sexually transmitted microorganism. Sexually active teenagers and women in their 20’s frequently test positive for HPV, although in the vast majority of cases no clinical signs or symptoms of infection are evident. Utilization of a condom has been shown to be ineffective in HPV sexual transmission. Immunity to HPV is type specific and, therefore, exposure to one HPV type does not prevent subsequent infection by other HPV types. Concomitant infections with more than one HPV type are common.

In most women, cervical infections with HPV remain asymptomatic and are transient, becoming undetectable even by the most sensitive gene amplification assays in 1-2 years. This is also true for high risk HPV types, leading to the conclusion that most high risk HPV infections are, in reality, not a high risk for development of cervical cancer. The prevalence of HPV infection in women decreases markedly at about the age of 30. It is the persistence of high risk HPV types in some women, i.e., an inability of the immune system to spontaneously clear these viruses, that is strongly associated with development of precancerous cervical lesions.

The Food and Drug Administration (FDA) in the United States has approved the HPV Hybrid Capture Assay as a primary screening tool for HPV cervical infections in women 30 years of age and older. The assay determines whether HPV is present and if so whether they are high risk and/or low risk types. Since the presence of high risk HPV types is a necessary precondition for the subsequent development of a cervical malignancy the absence of HPV suggests that the woman tested is at minimal risk. Similarly, in women whose cervical cytological screening results a diagnosis of atypical squamous cells of undetermined significance (ASCUS), a subsequent objective HPV assay can provide critical information as to the subsequent management and treatment.

Cervical cancer is an uncommon consequence of acquisition of a high risk HPV type cervical infection. The challenge facing society is to determine the optimal combination of cytological screening and HPV testing that will provide the most sensitive criteria for identifying those women at risk for cervical cancer and at the same time reduce costs by lengthening the interval between analyses.

II. Natural history

The incidence of detectable HPV infections peaks at an age between 20 and 25 years. The cumulative incidence determined by HPV DNA tests in young women who were observed for a period of several years after their first sexual experience constitutes up to 50% depending on sexual behaviour. Of the HR HPV-positive women, 5-10% develop abnormal cytological findings. The prevalence of detectable HPV infections declines with increasing age. HPV is no longer detectable by molecular biology techniques in 80% of HPV-infected patients after a period of about 12 months. Persistence or progression is observed in only 20%. If an HPV infection in the lower genital tract persists for several years, a precancerous stage (dysplasia, intraepithelial neoplasia) can develop. Nevertheless, less than 1% of persisting HR HPV infections lead to cancer after an interval of an average of 15 years. Because only a few of infected patients develop uterine cancer, other cofactors in addition to HPV are important. In addition to immunosuppression, HIV, infection, smoking, and chlamydia infections, genetic factors that do not allow the immune system to suppress or eliminate (15) the HPV infection appear to have considerable importance. The circumcision of male was identified as prophylaxis factor for HPV infection (2). There is indirect evidence that a genital HPV infection can persist throughout life and that a latent infection is reactivated in immune weakness (e.g., in HIV infection).

III. Clinical Manifestation

We find the following clinical pictures in the field of obstetrics and gynecology:

- Condylomata acuminata in vulvar, vaginal, and vaginal cervix regions, and extragenitally in the anal region; rarely the urethra is affected (1-3%).
- Precancerous stages of the uterine cervix (dysplasia, CIN 1-3) up to cervical cancer.
- Vulvar intraepithelial neoplasia (VIN, bowenoid papulosis, Bowen's disease) up to vulvar carcinoma and verrucous carcinoma (Buschke-Löwenstein).
- Perianal (PAIN) and anal intraepithelial neoplasias (AIN) up to invasive carcinoma.
- Laryngeal papilloma in the newborn and infants.

Condylomata acuminata (CA)

Because of the frequently long incubation period (3 weeks to 8 months), it is generally impossible to determine the exact time of infection. Macroscopically visible condylomata are found in less than 1% of all women.

Condylomata acuminata are detected by examination (vulva, vagina, and cervix) and by palpation (rectum, anus). A speculum examination is always necessary to rule out the presence of vaginal or cervical condylomata. A proctoscopy is indicated for the diagnosis of intra-anal and rectal CA. The use of the colposcope with the topical application of 3-5% acetic acid is an essential adjunct to inspection techniques. Syphilis or HIV infection is to be ruled serologically. Examination of the sexual partner is recommended. Condylomata lata (Syphilis), VIN and anal skin tags should be ruled out by examination, if necessary histologically. This also applies to anal papillae and rectal polyps in case of intra anal-findings.

Condylomata acuminata during pregnancy are associated in very rare cases with the late occurrence of laryngeal papillomas in the child. There is a certain risk for the transmission of HPV to the newborn in primiparas under the age of 20. A compelling indication for a primary caesarean section exists only if the birth canal is blocked by extensive condylomata. The

treatment of condylomata during pregnancy is achieved best by TCA, laser vaporization, or cryotherapy. The optimal time is not known; it seems appropriate to perform the treatment outside of the premature birth period: superinfection of the wound surfaces could lead to an ascending infection with subsequent premature labor or rupture of the amniotic membrane.

Intraepithelial Neoplasias

Intraepithelial neoplasias of the vulva (VIN) are generally slightly raised and multicentric. Similar changes in the vagina (VAIN) are rare, but can be easily missed (3, 5% Acetic acid, Schiller's iodine test).

Intraepithelial neoplasias of the vagina and of the cervix can be localized precisely only by a colposcopic examination.

Documentation:

Drawings, photographs, videos, computer presentations
(also see the guidelines of the AG-CPC of the DGGG)

IV. Diagnostic Procedures

Cytology

Cytology is not a suitable method for detecting HPV. Koilocytes and dyskeratocytes are specific markers only for a florid infection, whereas the majority of HPV infections cannot be detected by this technique. The accuracy of cytology in HPV infection alone is given today as only 15%.

Colposcopy

Native, green filter, acetic acid, iodine
(also see the guidelines of the AG-CPC of the DGGG)

HPV Detection in the Laboratory

The techniques for HPV detection differ in their sensitivity. The laboratory's experience is very critical for reliable results (particularly with PCR techniques).

The traditional methods of viral diagnosis such as electron microscopy, cell culture and certain immunological methods are not suitable for HPV detection. HPV cannot be cultured in cell cultures. The established routine method for viral detection is the hybridisation of viral nucleic acids by:

- Hybrid Capture® HPV DNA Test 2 (hc2). HC2 in conjunction with the Pap test is now approved by the FDA (12).
- Polymerase Chain Reaction (PCR)

Since the FDA-approved Hybrid Capture 2 test (Digene, USA) can detect as little as 1 pg of HPV DNA/ml, its sensitivity and specificity are almost comparable with PCR-based detection methods. The advantages of the Hybrid Capture 2 test are the relatively simple handling and good reproducibility of results, which make this test the best standardized HPV detection method. While the exact HPV type cannot be identified, "low-risk" (6, 11, 42, 43, 44) and "high-risk" (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68) HPV genotype groups (HR HPV and LR HPV) are detected.

The first step in PCR is amplification of the viral DNA. While a level of sensitivity exceeding that of the Hybrid Capture 2 test can be achieved in appropriately specialised laboratories, the variations in findings between the various laboratories can occasionally be considerable. HPV DNA detection by PCR at a facility specializing in this technique is the method of choice for numerous scientific studies.

Indications for HPV detection

The clinical use of the HPV test has been evaluated to date for the following indications unless other national decisions are made (9, 11):

1. Women 35 years and older as one of the cervical cancer screens in addition to cytology
2. Patients with inconclusive cytology results (for example ASCUS, AGUS, IIR or III)
3. Patients with mild and moderate precancerous stages to predict regression, persistence, or progression
4. Patients who have received treatment for precancerous lesions and cervical carcinomas

Re 1:

The HR HPV test is more sensitive but less specific than the cytological examination for detecting high-grade dysplasia and cervical cancers. A negative finding for HR HPV indicates that the presence of a serious precancerous stage or a carcinoma is extremely unlikely (6, 17). A study has shown that a combination of cytology and HPV testing at 2-yearly intervals can prove cost effective for the American healthcare system (12).

Adequate counselling of the woman by informed doctors and the existence of colposcopy facilities to clarify inconclusive findings are essential if HPV diagnosis is to prove effective in primary screening programmes.

Re 2:

The question most frequently examined in connection with the HPV test is the triage of women with minor or doubtful cytological changes (Pap class IIR, III*, ASCUS, AGUS and CIN I). Although the histological investigation of most women with these cytological diagnoses shows normal findings or lesions with a high regression potential (CIN I), CIN II or CIN III can be detected histologically in 5-20% of all women with these cytological diagnoses. In all the studies conducted to date, the value of the HPV test for the triage of women with Pap class IIR or III for CIN II/III appears to be superior to repetition of the cytological examination (18, 19). For this indication also, initial cost-benefit analyses confirm the efficiency of thin-layer cytology techniques that enable an HPV test to be performed subsequently on the residue (reflex testing) (7, 17).

* for the German nomenclature only

Re 3:

The cytological suspicion of the presence of mild or moderate dysplasia corresponding to Pap class IIID does not rule out with sufficient reliability the presence of severe dysplasia, Ca in situ (CIN III) or invasive carcinoma. In the event of recurrent Pap IIID findings, underlying CIN III must be expected in 30% of cases and invasive cancers in one percent. Since 90% of these findings are associated with HR HPV, the HPV test is not helpful in terms of diagnosis. Consequently, recurrent Pap IIID findings must always be clarified by a colposcopy or

histological investigation. By contrast, HR HPV is detected in just 50% of Pap IIIID smears that are recorded for the first time. In these cases, the HPV test is superior to control cytology in discriminating between lesions that need to be clarified in the short term by colposcopy or histology and findings that can simply be monitored. (14)

Up to 70% of cases of mild dysplasia (CIN I) and up to 50% of all moderate dysplasias (CIN II) regress over a period of 5 years. A negative HR HPV result with colposcopically and histologically confirmed CIN I/II rules out progression with 99% certainty (1).

Re 4:

About 10-15% of all women experience persistence or recurrence after removal of CIN. The annual incidence of invasive cervical cancer in women who have previously undergone conisation for CIN III is 1 per 1000. All studies conducted to date agree that the High-Risk HPV DNA test is superior to cytological examination in persistent or recurrent CIN (13).

Indications for colposcopy

Any woman with confirmed HPV infection (e.g. condylomata acuminata) should undergo colposcopy regardless of the detection method and site, abnormal cytology smear and/or diagnosis of intraepithelial neoplasia of the lower genital tract.

Colposcopy is also recommended for the targeted removal of tissue.

Since false-negative cytological smears are predominantly attributable to an incorrect smear technique, colposcopy with targeted biopsies taken from the most pronounced area of atypical epithelium is recommended. In cases of suspicious cytology findings, a cytology smear under colposcopic control is a quality requirement (cf. Munich Nomenclature II, note the special features of the Austrian terminology described in the appendix).

The best results are obtained in dedicated dysplasia clinics (an objective is certification according to the requirements of the European Federation for Colposcopy (EFC)).

Indications for Further Diagnostic Procedures

The partner of a woman with genital warts should be examined clinically and treated appropriately if visible warts or HPV-associated lesions are found (e.g., clarification of PAIN). In recurrent CIN, VIN, VAIN, or PIN, examination of the partner is also recommended.

Further diagnostic procedures are strongly advised to rule out other sexually transmitted infections.

(also see the guidelines of the DGSTD (3) and of the DDG (10))

V. Treatment

Current Guidelines for VIN

- VIN 1 and VIN 2
- Surface destruction (laser vaporization) under colposcopic control after prior
 - histological clarification

- VIN 3
- Surgical excision in healthy tissue,
 - Extensive areas: laser vaporization after histological exclusion of an invasive lesion,
 - skinning vulvectomy, simple vulvectomy

Current Guidelines for CIN

1. Surface Destruction:

- Method: CO₂ laser, guided colposcopically with micromanipulator
- Indications:
- benign findings (e.g., papilloma), CIN 1 or CIN 2 with ectocervical location,
 - completely visible, after prior biopsy, cooperative patient
 - CIN 2-3 (HGSIL) individually performed by experts only with multiple biopsies

2. Treatment by Resection:

HF surgery loop conisation (loop excision, large-loop-excision of the transformation zone, LLETZ)

- Indication:
- persistent CIN 2-3 (HGSIL)
 - Conisation (therapeutic conisation is based on the histology of the biopsy material)

Method: - loop or laser conisation, scalpel

- Indications:
- CIN 2 (endocervical), CIN 3, adenocarcinoma in situ
 - Persistent CIN 1 and CIN 2 with endocervical extension

(also see the guidelines of the AG-CPC of the DGGG) (4)

Treatment of the Partner

A specific positive effect on the risk of infection or reinfection by condom use has not been proven in HPV-associated diseases. Until other STIs are ruled out or treated, the use of condoms should be recommended.

Evidence-based, Recommended Treatment Procedures (for anogenital warts)

Evidence-based stages (I to IV) and value of the recommendations (A to C) correspond internationally to the quality assurance in conventional literature evaluations (also see Appendix)

Medically prescribed self-treatment	Medically preformed treatment
<ul style="list-style-type: none"> - Podophyllotoxin (0.15% cream, 0.5% solution); (Ib, A) - Imiquimod cream (5% cream); (Ib, A) - (Interferon beta gel (0.1 million IU/g) adjuvant) 	<ul style="list-style-type: none"> - Trichloroacetic acid - Cryotherapy - Electrosurgery (Ib, A) / laser (IIb, B) - Scissors excision / curettage

Medically Prescribed Self-treatment

Podophyllotoxin 0.5% solution, Podophyllotoxin 0.15% cream

Podophyllotoxin 0.5% solution is applied to the genital warts by the patient using a cotton swab, and podophyllotoxin 0.15% cream with the finger twice daily for 3 days. This is followed by a 4-day pause. The treatment is repeated for a maximum of four cycles. Maximum treatable wart surface area: 10 cm², maximum daily dose: 0.5 ml.

Podophyllotoxin 0.15% cream has been approved for the treatment of external genital warts in men and women. Podophyllotoxin 0.5% solution has been approved for men only.

Imiquimod % Cream (Aldara®)

Imiquimod is the first "topical" immunostimulant on the market. Topical therapy of genital warts three times a week at night up to a maximum of 16 weeks. It is recommended that the treated area be washed off with water 6 to 10 hours later. If the primary response to treatment in studies was successful, imiquimod revealed very low recurrence rates (16%) over the subsequent course of the disease.

Topical Adjuvant Interferon beta Gel Therapy After Removal of Anogenital Warts

Topical therapy after removal of external anogenital warts with electrocautery or laser consists of five applications of Interferon beta gel (0.1 million IU/g of gel) per day for the period of 4 weeks. Maximum treatable wart area ≤ 10 cm².

The self-treatment with the indicated medications is generally to be recommended in new lesions with limited keratosis. Treatment failure in the case of keratotic lesions and, because of insufficient penetration depth of the substances, local recurrences are to be expected more frequently. The substances have been approved thus far only for the external genitalia.

Podophyllotoxin, imiquimod, and interferon beta are contraindicated during pregnancy and are not approved for the mucous membranes or for patients with immunosuppression.

Medically Performed Treatments

Trichloroacetic acid (up to 85%)

The application of trichloroacetic acid leads to cell necrosis. Trichloroacetic acid is applied to the warts by the physician with an applicator. Very good results are achieved in small, non-keratotic condylomata acuminata in areas of mucous membranes. Treatment is repeated at weekly intervals.

Disadvantage: burning and pain

Advantage: healing with no scar formation. Safe to use during pregnancy. Used only in very small amounts. Neutralization with sodium bicarbonate is necessary in the case of overdosage. The surrounding epithelium can be covered with a fatty ointment if necessary.

Cryotherapy

Use of cold with liquid nitrogen in an open procedure (spraying or cotton swab) or as contact cryotherapy (closed procedure - cryoprobe with CO₂, N₂O, N₂). Treatment is repeated weekly or every 2 weeks.

Advantage: low cost, simple procedure, hardly any long-term complications

Disadvantage: initial local complications, recurrences are frequent (up to 75%)

Surgical Methods

Removal by means of scissors excision or sharp spoon, curettage, electrocautery, or CO₂ Laser / Nd-YAG laser. Surgical methods can be used as the primary treatment. Local anesthesia is always necessary. Treatment with electrocautery or laser is indicated in extensive and recurrent, primarily patchy warts.

Advantage: immediate treatment effect

Disadvantage: Smoke formation by the CO₂ laser and electrocautery treatment. This could be a safety problem because of possible infectious viral particles in the smoke (detection of viral DNA). Special face masks and protective glasses must be worn, and smoke removed by suction.

Recommended Treatments for Genital Warts with a Special Localization

Anal canal

Cryotherapy with liquid nitrogen, trichloroacetic acid (only with small condylomata acuminata), or surgical methods (CO₂-/Nd-YAG laser or electrocautery).

Vagina

Cryotherapy (liquid nitrogen only, cryoprobe is contraindicated), trichloroacetic acid, or surgical procedure (CO₂ laser or electrocautery).

Uterine cervix

CO₂ laser

(in regard to the Urethra see guidelines of the DGU) (16)

VI. Vaccination

Both the important role of human pathogenic papillomaviruses in the etiology of cancer and the infection-associated morbidity in women patients indicate that the search for suitable prophylactic and therapeutic vaccines is appropriate. DNA-free virus particles (VLP), which have already been tested successfully in phase III studies, have been developed for immunoprophylaxis and preventing infection (8). Because VLPs have a highly specific activity, various HPV types must be included in an effective prophylaxis. Vaccines that stimulate the immune system to reject HPV-positive cells can be used for the treatment of existing lesions. Because this reaction is probably type-specific as well, an HPV diagnostic procedure in the lesion to be treated is necessary (by a PCR-based method). At present, various vaccines are in preclinical or clinical development; it will take several years for the first HPV vaccine to reach the market, however.

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Appendix

Evidence Evaluation (stages I-IV) and Grading (A-C) of Treatment Recommendations of Relevance to the Guidelines:

Literature sources with evidence degree A and evidence evaluation stage Ib were used for the guidelines, i.e., evidence based on controlled, randomized studies. Meta-analysis-controlled, randomized studies (degree A, stage Ia) were not available. The evaluation of laser therapy was possible only based on studies of evidence stage IIa (degree B), i.e., expertly designed scientific studies with no randomization. Expertly designed quasi-experimental studies (IIb, B), nonexperimental descriptive studies (comparison studies, correlation studies, and case studies) (degree B, stage III), and expert opinions (degree C, stage IV) were basically not considered.

Abbreviations

AG-CPC	Arbeitsgemeinschaft Zervixpathologie und Zytologie der DGGG [Study Group on Cervical Pathology and Cytology of the DGGG]
AGII	Arbeitsgemeinschaft Infektiologie und Infektionsimmunologie der DGGG [Study Group on Infectology and Infectious Immunology of the DGGG]
AIN	Anal intraepithelial neoplasia
AGUS	Atypical glandular cells of undetermined significance
ASCUS	Atypical squamous cells of undetermined significance
CIN	Cervical intraepithelial neoplasia
DGGG	Deutsche Gesellschaft für Gynäkologie und Geburtshilfe [German Society for Obstetrics and Gynecology]
DNA	Desoxyribonucleic acid
HC II	Hybrid capture II
HPV	Human papillomavirus
HR HPV	High-risk HPV
HGSIL	High-grade squamous intraepithelial lesion
LLETZ	Large-loop-excision of the transformation zone
LR HPV	Low-risk HPV
LGSIL	Low-grade squamous intraepithelial lesion
PCR	Polymerase chain reaction
PIN	Penile intraepithelial neoplasia
TCA	Trichloroacetic acid
VAIN	Vaginal intraepithelial neoplasia
VIN	Vulvar intraepithelial neoplasia
VLP	Virus-like particles