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S2k guideline: HPV-associated lesions of the external genital region and the anus – anogenital warts and precancerous lesions of the vulva, the penis, and the peri- and intra-anal skin (short version)

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1 Introduction

Clinical practice guidelines are systematically developed tools meant to serve as counseling and decision-making aids for various clinical situations. When developing guidelines, only a limited selection of standardized clinical situations can be taken into consideration. Recommendations provided in guidelines are not of a legally binding character; certain situations may necessitate a deviation from the recommendations contained therein [1]. Implementing guideline recommendations in specific clinical situations always requires that all individual patient-related circumstances be taken into account [2].

The present publication is a short version of the guideline on HPV-associated lesions of the external genital areas and anus. The long version (online supplement, AWMF registry of guidelines) additionally contains the following information:

- Composition of the expert panel
- Presentation and handling of conflicts of interest
- Detailed information on the methodology used
- Scope, target audience, and objectives of the guidelines
- Detailed clinical introduction and glossary
- Specific requirements for diagnostic workup and treatment in children
- Recommendations on patient education, partner management, and sexual behavior
- References.

The present guideline is consensus-based (S2k), which means it was developed with a structured consensus process and a representative panel of experts. Table 1 shows

Table 1 Strengths of recommendations – wording, symbols, and interpretation (modified from Kaminski-Hartenthaler et al. 2014 [11]).

Strength of recommendation	Wording	Symbol	Interpretation
Strong recommendation *for* a course of action	"We recommend..."	↑↑	We believe that all, or virtually all, informed people would make this decision. Clinicians will require less time for the decision-making process with the patient. In most clinical situations, the recommendation can be adopted as the standard course of action.
Weak recommendation *for* a course of action	"We suggest..."	↑	We believe that most informed people would make this decision, but a substantial number would not. Clinicians and other health care providers will need to spend more time ensuring that the course of action, including potentially associated consequences, reflects the values and preferences of each individual patient. Policy makers will have to involve many stakeholders, and policy making will require substantial debate.
No recommendation for or against a course of action	"... can be considered ..."	o	We are currently unable to make a recommendation for or against the course of action due to various reasons (for example, no evidence available, unclear or unfavorable risk/benefit ratio).
Weak recommendation *against* a course of action	"We suggest against..."	↓	We believe that most informed people would make this decision, but a substantial number would not.
Strong recommendation *against* a course of action	"We recommend against..."	↓↓	We believe that all, or virtually all, informed people would make this decision.

the strength of the recommendations and the implication of a given strength of recommendation.

Anogenital human papillomavirus (HPV) infections rank among the most common sexually transmitted infections, giving rise to anogenital warts, intraepithelial neoplasia, and cancer. Clinically manifest disease caused by HPV is associated with considerable impairment of the quality of life [12–17] and high recurrences rates following treatment. Treatment of HPV-associated anogenital lesions has considerable economic impact on the entire health care system [18–22]. Finally, given the contagiousness of the disease, it is imperative that efficient approaches to treating HPV-associated anogenital lesions be identified and implemented in patient management.

2 Diagnostic workup of anogenital HPV-associated lesions

2.1 Basic diagnostic workup of all anogenital HPV-associated lesions

Recommendation	Strength	Agreement
In case of suspected HPV-associated lesions, we *recommend* performing a visual inspection and palpation of the entire external genital and perianal region; this includes spreading the meatus to inspect the navicular fossa.	↑↑	Strong consensus (100 %)
We *recommend* that women with HPV-associated anogenital lesions undergo a gynecologic examination, including colposcopy and cervical cytology.	↑↑	Strong consensus (100 %)
In case of perianal HPV-associated lesions, we *recommend* performing digital rectal examination as well as proctoscopy/anoscopy or high-resolution anoscopy (HRA) to assess the anal canal.	↑↑	Strong consensus (100 %)
In case of HPV-associated lesions of the urethral meatus/navicular fossa, we *recommend* endourologic procedures to determine the extent to which the lesions have spread into the urethra, but only during surgical removal, with external lesions treated first. The success of treatment of intraurethral condylomata can be improved by using fluorescence-based methods.	↑↑	Strong consensus (100 %)
Following the diagnosis of HPV-associated anogenital lesions, we *recommend* ruling out other sexually transmitted infections (gonorrhea, chlamydia, syphilis, HIV, hepatitis B/C) based on past exposure and individual risk factors.	↑↑	Strong consensus (100 %)
In case of repeated recurrences of anogenital HPV-associated lesions, we *suggest* that further diagnostic workup and treatment be performed by experts experienced in the diagnosis and treatment of such lesions.	↑	Strong consensus (100 %)

Anogenital HPV-associated lesions, anogenital warts (AGW) in particular, frequently occur at multiple sites. Furthermore, patients with AGW are at increased risk of other HPV-associated disorders such as cervical, vulvar, vaginal, anal, and penile intraepithelial neoplasia, which may constitute cancer precursors (high-grade CIN, VIN, VAIN, AIN, PIN), or of corresponding carcinomas [49, 76, 77]. Thus, clinical examination of the entire anogenital region is recommended following the occurrence of anogenital HPV-associated lesions [78–81]. Apart from inspection of the perianal region and a gynecologic exam in female patients (including colposcopy and cervical cytology; for cervix carcinoma screening, refer to the consultation version of the current S3 guidelines [82]), it is recommended that the meatus be spread to allow for inspection of the navicular fossa.

Depending on the location of HPV-associated lesions, additional diagnostic studies are recommended: patients with perianal lesions frequently also exhibit HPV-associated intra-anal findings [81, 83]. Thus, in case of perianal HPV-associated lesions, digital rectal examination and inspection of the anal canal using proctoscopy/anoscopy or high-resolution anoscopy (HRA) is recommended. The participants in the consensus conference were not able to reach an agreement as to the optimal sequence in which diagnostic studies of the anal canal should be done in the presence of perianal HPV-associated lesions. On the one hand, one group of participants in the consensus conference favored not carrying out intra-anal studies prior to complete removal of perianal lesions in order to reduce the risk of iatrogenic inoculation of the anal canal with HPV. The other group of participants in the consensus conference, on the other hand, expressed preference for performing intra-anal studies as soon as perianal lesions have been diagnosed in order to allow for a definitive treatment plan that takes into account the full extent of

the disease and to avoid any undue delay in diagnosis and treatment. There is evidence from the literature indicating that – besides sexual practices – autoinoculation of the anal canal (e.g. cleaning of the anus after defecation, insertion of suppositories, or application of an ointment) may be responsible for intra-anal HPV infections [84–88]. For this reason, too, it is impossible to accurately quantify the risk of iatrogenic HPV transmission as a result of diagnostic measures. To date, there have been no published case reports on iatrogenic transmission of HPV into the anal canal due to diagnostic measures (digital rectal examination, anoscopy, proctoscopy, rectoscopy, colonoscopy). Given the lack of scientific studies aimed at resolving this problem of conflicting risk assessment, it is up to each individual physician to determine the sequence of diagnostic procedures.

Only 10–20 % of all low-risk HPV-associated condylomata affect the urethra [89]; high-risk HPV-induced intraepithelial or invasive neoplasia of the urethra been described only in individual case reports and case series [90]. In case of lesions of the urethral meatus, proximal involvement of the urethra cannot be sufficiently assessed from the outside, even when spreading the meatus [91, 92]. However, approximately 20 % of meatal condylomata are associated with proximal urethral condylomata that can only be diagnosed endoscopically. For this reason, it is recommended that – in case of HPV-associated lesions around the meatus and in the navicular fossa – the urethra be examined, but only in the context of a therapeutic urethroscopy aimed at removing all lesions, with external lesions treated first in order to avoid inoculation of the urethra with HPV. Fluorescence-based methods may be useful in the detection of urethral condylomata [93] and penile carcinomas [94] and may have positive effects on post-treatment recurrence rates.

Patients with HPV-associated anogenital lesions are at increased risk of sexually transmitted infections (STIs) such as syphilis, gonorrhea, *Chlamydia trachomatis*, HBV, HCV, and HIV [78, 79, 95–97]. These should therefore be ruled out based on past exposure and any previous test results, if available. HIV-positive patients with HPV-associated lesions in particular very frequently have other asymptomatic STIs [95].

2.2 Special diagnostic workup of anogenital warts

Recommendation	Strength	Agreement
In immunocompetent patients with clinically typical AGW, histopathological examination *can be considered.*	0	Strong consensus (100 %)
We *recommend* performing a histopathological examination of AGW in the following situations: ▸ Diagnostic uncertainty ▸ Atypical lesions (e.g. pigmented, multicolored, indurated, ulcerated, hemorrhagic, fused with the surrounding tissue) ▸ Large lesions (> 1 cm) ▸ Suspected giant condyloma (Buschke-Lowenstein tumor) ▸ Recalcitrant and rapidly recurring lesions	↑↑	Strong consensus (100 %)
We *suggest against* performing molecular methods for detecting HPV or HPV typing in case of AGW.	↓	Consensus (91 %)
In case of giant condyloma (Buschke-Lowenstein), we *suggest* using molecular methods for the detection of HPV or HPV typing.	↑	
Acetic acid testing (acetic acid 3–5 % m/V) *can be considered* in case of unclear clinical findings and perianal AGW in order to be able to better determine the extent of the lesions and suspicious areas.	0	Strong consensus (100 %)

Clinically typical AGW in immunocompetent patients generally require no histopathological examination. The indication for a histopathological examination of AGW arises in the case of diagnostic uncertainty and the presence of atypical lesions (e.g. pigmented, multicolored, indurated, ulcerated, hemorrhagic, fused with the surrounding tissue) and those with a diameter of more than 1 cm [98]. In case of giant condylomata, it is imperative to rule out a verrucous carcinoma [76]. Recalcitrant and rapidly recurring AGW should likewise be examined histopathologically [98].

Anogenital warts – in particular intra-anal lesions – in immunocompetent and HIV-negative patients may also harbor high-grade dysplasia or carcinomas [28, 99]. The transition zone from the anoderm (non-cornified squamous epithelium) to the columnar epithelium of the rectum is characterized by an increased risk of developing carcinomas [100, 101]. Thus, before treating intra-anal condylomata in particular, lesions that are conspicuous based on the aforementioned criteria should be biopsied and

histopathologically examined to rule out anal intraepithelial neoplasia (AIN) and anal carcinoma.

Molecular methods for HPV typing of AGW are not suggested as they do not provide any additional treatment-relevant information. More than 90 % of AGW contain the low-risk HPV types 6 and 11 [45]. At the same time, there have also been reports of HIV-positive patients with higher-grade dysplasia in which only HPV types 6 or 11 were detected [29]. Frequently, infection with multiple different HPV types can be found at various anogenital sites without any clinical relevance. This applies to both immunocompetent and HIV-positive patients [40, 62].

Intra-anal cytology may be used as a screening tool for the detection of intra-anal IEN (AIN); however, compared to biopsying proctoscopically conspicuous lesions, it shows a sensitivity of only 47 % in HIV-negative individuals [102].

Given its low specificity, various authors do not recommend acetic acid testing [78, 81, 103]. In the case of AGW, such a test can be considered in order to be able to better determine the extent of the lesions and suspicious areas.

2.3 Specific diagnostic workup of anogenital intraepithelial neoplasia

Recommendation	Strength	Agreement
In case of suspected anogenital intraepithelial neoplasia (IEN), we recommend a histopathological examination to assess the degree of dysplasia and rule out invasive lesions. (Depending on the extent of the lesions, this may include a simple biopsy, mapping biopsies, or possibly therapeutic excision.)	↑↑	Strong consensus (100 %)
Molecular methods for detecting HPV or HPV typing *can be considered* in case of anogenital IEN.	0	Strong consensus (100 %)
We *suggest* acetic acid testing (acetic acid 3–5 % m/V) so that the extent of the lesions and suspicious areas can be better determined.	↑	Strong consensus (100 %)
In addition to acetic acid testing, the use of Lugol's iodine solution (iodine test) *can be considered* in order to improve identification and visualization of intra-anal IEN.	0	Strong consensus (100 %)
With respect to the diagnostic workup of suspected vulvar IEN, the reader is referred to the existing guidelines for "Diagnosis, Treatment, and Follow-up of Vulvar Cancer and its Precursors" [4].		

Given the vast number of differential diagnoses, great clinical variability, and in order to rule out invasive carcinoma, it is recommended that histopathological confirmation of the diagnosis always be obtained before treatment initiation in patients with anogenital IEN [98, 104–106]. Only histopathological examination allows for definitive determination as to the degree of dysplasia and for unequivocal distinction between intraepithelial and invasive lesions. In this context, small lesions should be therapeutically resected, whereas extensive lesions should be biopsied at multiple sites (mapping biopsy). It must be borne in mind, though, that any biopsy only provides information about the region biopsied but not about the lesion in its entirety. In case of inconspicuous histological and persistent clinical findings, the lesion should be completely excised.

For anogenital IEN, too, molecular methods for the purpose of HPV typing provide no additional treatment-relevant information compared to histopathology. However, molecular HPV detection may be useful in differentiating HPV-associated IEN from IEN associated with lichenoid and chronic inflammatory disorders [57]. HPV-positive penile tumors are thought to be associated with a more favorable prognosis.

Given its low specificity, various authors do not recommend acetic acid testing [78, 81, 103]. However, acetic acid tests do help improve visualization of suspicious areas, which can then be biopsied or excised in a targeted manner. In addition to acetic acid testing, the use of Lugol's iodine solution may be considered for visualizing intra-anal IEN.

2.4 Specific situations: diagnostic workup in immunodeficient/HIV-positive patients

Recommendation	Strength	Agreement
We *suggest* referring immunodeficient women with anogenital HPV-associated lesions to a DKG/AG-CPC-certified gynecologic dysplasia clinic (DKG – German Cancer Society, AG-CPC –Working Group on Cervical Pathology and Colposcopy).	↑	Consensus (86 %)
We *recommend* to perform digital rectal examination (DRE) and inspection of the anal canal using proctoscopy or high-resolution anoscopy (HRA) in case of anogenital HPV-associated lesions of any primary site.	↑↑	Consensus (93 %)

In immunodeficient patients with perianal and intra-anal AGW and/or IEN, cytological examination of the anal canal *can be considered*.	o	Strong consensus (100 %)
We *recommend* that immunodeficient patients with HPV-lesions of the urethra also be examined for potential bladder involvement using urethrocystoscopy.	↑↑	Strong consensus (100 %)
In immunodeficient patients with anogenital HPV-associated lesions, we *recommend* performing a histopathological examination (in case of multiple or extensive lesions, possibly mapping biopsies).	↑↑	Strong consensus (100 %)
With respect to the diagnostic workup of perianal and intra-anal IEN in HIV-positive patients, the reader is referred to the existing guidelines for "HIV-associated Anal Dysplasia and Anal Carcinoma: Prevention, Diagnosis, and Treatment [5].		

Explanatory notes and background information on these recommendations can be found in the long version of the guideline.

2.5 Specific situations: diagnostic workup in pregnant women

Recommendation	Strength	Agreement
We *recommend* referring pregnant women with anogenital IEN to a DKG/AG-CPC-certified gynecologic dysplasia clinic for further diagnosis and treatment.	↑↑	Strong consensus (100 %)
In pregnant women with reactivation of latent HPV infections, inconspicuous prenatal care (including chlamydia/HIV/hepatitis/syphilis workup) and without a history of exposure, we *suggest against* re-testing for other sexually transmitted infections.	↓	Consensus (86 %)

Explanatory notes and background information on these recommendations can be found in the long version of the guideline.

3 Treatment of HIV-associated anogenital lesions

3.1 Principles of treatment of HPV-associated anogenital lesions

Recommendation	Strength	Agreement
We *recommend* always offering treatment to patients with anogenital HPV-associated lesions.	↑↑	Strong consensus (100 %)
We recommend informing patients about contagiousness, measures to reduce the risk of transmission, the expected disease course (including spontaneous remission and the risk of progression in case of IEN), and treatment options.	↑↑	Strong consensus (100 %)
During surgical treatment of HPV-associated lesions, specifically when using fume-generating ablative treatment methods (lasers, electrosurgery), we recommend complying with laser safety regulations and hygiene guidelines in order to protect patients and surgical staff from exposure to infectious particles.	↑↑	Strong consensus (100 %)

In light of the contagiousness of HPV-associated anogenital lesions, treatment is generally recommended despite the possibility of spontaneous remission. Objectives of the treatment of AGW include complete remission of the lesions without recurrence, improvement of the disease-related impairment in quality of life [13, 14, 17, 130–132] and prevention of further transmission [30, 31, 34, 35]. With respect to HPV-associated anogenital IEN, it is also crucial to prevent disease progression to invasive lesions (carcinoma). Relief from symptoms – such as burning sensation, pruritus, and discharge – is another important objective of treatment.

It is recommended that patients be informed about contagiousness, measures to reduce the risk of transmission [35], the expected disease course (including the possibility of spontaneous remission and the risk of progression in case of IEN), and treatment options. This may include the provision of easy-read written information.

When using laser systems that vaporize tissue (CO_2 lasers in particular) or electrosurgical procedures associated with fumes, surgical masks (e.g. FFP2/FFP3 masks) and fume extraction are generally recommended [136].

3.2 Treatment of external anogenital warts

Recommendation	Strength	Agreement
We *recommend* that the choice of treatment be reached by physician and patient through joint, informed decision making.	↑↑	Strong consensus (100 %)
We *recommend* limiting treatment of AGW to clinically manifest and surrounding subclinical lesions.	↑↑	Strong consensus (100 %)
We *recommend* considering the following factors when choosing a treatment: • Size, number, and location of lesions • Patient preference and expected adherence to treatment • Expertise of and equipment available to the treating physician • Nature and success of previous treatments • Underlying conditions and comorbidities	↑↑	Consensus (86 %)
Depending on the aforementioned factors, we *recommend* using one of the following options as primary treatment of external AGW: • Topical treatment: – Podophyllotoxin 0.5 % solution – Imiquimod 5 % cream – Sinecatechins 10 % ointment • Surgical/ablative treatment options: – Curettage, scissor excision – Electrocautery and modified coagulation methods – Laser systems with adequate wavelengths and biological tissue effects – Cryotherapy – Trichloroacetic acid 80–90 % (m/V)	↑↑	Strong consensus (100 %)
Treatment using one of the following options *can be considered*: • Podophyllotoxin 0.15 % cream • Imiquimod 3.75 % cream (off-label use) • 5-Fluorouracil 5 % cream (off-label use) • Interferon alpha (topical, intralesional) (off-label use).	0	Strong consensus (100 %)
We *recommend against* treatment using either of the following options: • Podophyllin solution • Cidofovir 1 % cream/gel (off-label use)	↓↓	Strong consensus (100 %)
In case external AGW recur repeatedly while patients are on the aforementioned (strongly recommended) treatment regimens, we *suggest* treatment with surgical/ablative measures followed, after wound healing, by topical treatment with imiquimod 5 % cream or sinecatechins 10 % ointment to prevent recurrence.	↑	Majority agreement (73 %)
In case of AGW that are very voluminous, extensive, disseminated or suspected of being malignant, we *recommend* that further assessment and treatment be carried out by specialists experienced in the treatment of such lesions.	↑↑	Strong consensus (100 %)

For the treatment of external anogenital warts (AGW, condylomata acuminata), there is a broad range of options, which can be roughly divided into topical (non-surgical) treatments applied by patients and administered, ablative (destructive)/surgical treatments undertaken by physicians. There is no antiviral treatment specifically targeting HPV. Even in cases where treatment is initially successful, HPV DNA can persist in the (perilesional) tissue and lead to new, manifest lesions. Multifocal HPV infection, which is typical for the anogenital region, or incomplete removal of wart tissue, can also lead to recurrences. Reinfection from an infected partner is also possible.

Treatment of anogenital warts consists primarily of eliminating obvious, clinically manifest lesions and the directly surrounding perimeter of subclinical lesions. There is no

indication for treating subclinical HPV infections that can be diagnosed only by acetic acid testing or HPV DNA/RNA detection.

In the simplest case, treatment can be carried out by patients themselves. Methods suitable for self-treatment include the application of podophyllotoxin 0.5 % solution or 0.15 % cream, imiquimod 5 % or 3.75 % (off-label use) cream, and green tea extracts (sinecatechins [polyphenon E] 10 % ointment). A recent systematic review with meta-analysis on the effectiveness and adverse effects of topical treatments in immunocompetent patients with AGW [137] revealed all topical therapeutic options investigated in the context of randomized controlled trials (RCTs) to be statistically significantly superior to placebo in terms of short-term and/or medium-term complete remission (imiquimod 3.75 % and 5 % cream, podophyllotoxin 0.5 % solution, sinecatechins 10 % ointment). No placebo-controlled RCTs were available for podophyllotoxin 0.15 % cream; in a direct comparison, however, it was statistically significantly inferior to podophyllotoxin 0.5 % solution with regard to short-term complete remission. Direct comparison of podophyllotoxin 0.5 % solution and imiquimod 5 % cream showed no significant differences in terms of effectiveness or adverse drug reactions (ADRs) [137].

In clinical studies, recurrence rates following complete remission in patients on topical treatment ranged from 6–100 % for podophyllotoxin [138–144]; 6–26 % for imiquimod 5 % cream [145–148]; and 7–11 % for sinecatechins [149–151]. From a methodological perspective, however, direct comparison of such data, which is exceedingly relevant with respect to patient management, is problematic for various reasons. The most significant limitation arises from the insufficient comparability of the study populations, as exemplified by the great differences in spontaneous remission rates in the placebo groups: In the sinecatechins studies [149–151], remission rates ranged from 33–38 %; by contrast, placebo-controlled studies on other interventions [138, 140, 144–147, 152] have shown remission rates between 0 % and 15 %. Other limitations related to direct comparisons of remission and recurrence rates are caused by differences in the length of follow-up and in the methodological quality of the studies concerned.

Surgical or ablative methods undertaken by physicians include cryotherapy, trichloroacetic acid 80–90 % (m/V) solution, excision (scissor excision, curettage, conventional scalpel surgery), laser procedures (such as CO_2, Nd:YAG, diode, erbium lasers) and electrocoagulation including modified coagulation methods ("wet field" technique according to Wienert, soft coagulation, argon plasma coagulation). For cryotherapy, clinical studies showed cure rates of 44–75 % [153–155] and relapse rates of 21–42 % one to three months after clearance [153, 155–157]. Cure rates for electrosurgery and scissor excision observed in clinical studies ranged from 94–100 % and 89–100 %, respectively [155, 158–161]. Recurrence rates after electrosurgical removal and scissor excision were between 19 % and 29 % in the aforementioned studies [155, 158–161]. Similar to the above-mentioned clinical study data on topical treatment methods, direct comparison of clearance and recurrence rates between various treatment groups is – from a methodological perspective – conclusive to only a limited extent.

Direct comparisons of treatment options in clinical studies yielded the following results: one RCT showed that topical treatment with imiquimod 5 % cream was superior to ablative methods in terms of complete remission after six months (93.7 % vs. 73.6 %) [148]. In another RCT, electrodesiccation proved to be superior to cryotherapy (complete remission after three months: 71 % vs. 55 %, *per protocol population*) [155]. No significant differences were demonstrated in one study comparing cryotherapy and physician-applied trichloroacetic acid [153]; by contrast, another controlled study revealed higher cure rates and a lower risk of genital ulcerations for cryotherapy (complete remission after treatment cessation: 86 % vs. 70 %) [156]. One factor to be observed when employing ablative methods (in particular electrocautery, CO_2 and Nd:YAG lasers) is the possibility of fumes being generated that potentially contain viral particles, thus requiring an extraction system and individual protective gear. Modified techniques (e.g. "wet field" electrocoagulation technique according to Wienert, soft coagulation, layer-by-layer argon plasma coagulation [162]) allow for virtually fume-free and less invasive thermal destruction of AGW.

The guideline panel considers the application of podophyllin solution to be outdated. Clinical studies have revealed it to be less effective than podophyllotoxin 0.5 % solution [141, 163], cryotherapy, electrodesiccation [155] and surgical excision [158, 159]. What is more, two of the components of podophyllin – quercetin and kaempferol – are believed to have mutagenic properties [164]. Severe systemic toxicity reactions including death, intrauterine death, teratogenicity and various neurological complications have been observed [165].

Described as an effective treatment option in case reports and case series, topical application of ingenol mebutate potentially represents a novel therapeutic approach for the treatment of AGW (off-label use) [166, 167]. There are, however, no controlled studies available and the experience gathered thus far is insufficient.

While case reports [168, 169] and small controlled studies [170] have shown topical cidofovir (off-label use) to be likewise effective, here, too, the experience accumulated to date is insufficient. At the same time, severe adverse events (including nephrotoxicity) have been observed in patients on topical cidofovir [171]. It is therefore recommended not to use cidofovir in the treatment of AGW.

With respect to the efficacy of local interferon treatment, controlled studies have – overall – yielded heterogeneous results. This applies both to topical [172–174] and intralesional [175–178] treatment. The interferon most commonly investigated in the aforementioned studies was interferon alpha.

Considering the aforementioned study data on potential treatment options, it is recommended that the choice of treatment be jointly made by physician and patient and be based on informed decision making. Various factors included in the above-listed recommendation should be considered in the decision to be taken by physician and patient. Particularly relevant factors include the patient preference and expected adherence to treatment. Compared to topical treatment options, surgical interventions are beneficial in that they result in immediate reduction in the amount of affected and infectious tissue. The strong recommendation for choosing topical and ablative treatment methods (see box) is based on scientific evidence and/or long-term experience. Table 2 provides an overview of various recommended interventions with their respective pros and cons.

3.3 Treatment of external anogenital intraepithelial neoplasia

Recommendation	Strength	Agreement
We *recommend* an approach to treatment of anogenital IEN that, as far as possible, preserves organs and functioning and avoids mutilation.	↑↑	Strong consensus (100 %)
We *recommend* that treatment of IEN include clinically manifest and/or histopathologically conspicuous lesions, as well as surrounding subclinical lesions.	↑↑	Strong consensus (100 %)
We *recommend* considering the following factors when choosing treatment: • Size, number, and location of lesions • Patient preference and expected adherence to treatment • Expertise of and equipment available to the treating physician • Nature and success of previous treatments • Underlying conditions and comorbidities	↑↑	Strong consensus (100 %)
Depending on the aforementioned factors, we *recommend* using one of the following surgical/ablative methods as primary treatment of external anogenital IEN: • Curettage, excision • Electrocautery and modified coagulation methods • Laser systems with adequate wavelengths and biological tissue effects • Cryotherapy.	↑↑	Strong consensus (100 %)
As an alternative to surgical/ablative methods, especially in case of penile IEN (PIN), we *suggest* treatment using one of the following topical agents: • 5-Fluorouracil 5 % cream (off-label use) • Imiquimod 5 % cream (off-label use)	↑	Strong consensus (100 %)
Treatment using one of the following options *can be considered*: • Trichloroacetic acid 80–90 % (m/V) (no label) • Imiquimod 3.75 % cream (off-label use)	0	Strong consensus (100 %)
We *recommend against* using any of the following treatment options: • Podophyllotoxin 0.5 % solution (off-label use) • Podophyllotoxin 0.15 % cream (off-label use) • Cidofovir 1 % cream/gel (off-label use)	↓↓	Strong consensus (100 %)
In case external IEN recur repeatedly in patients on the aforementioned (recommended or suggested) regimens, treatment with surgical/ablative measures followed, after wound healing, by topical treatment with imiquimod 5 % cream (off-label use) *can be considered* to prevent recurrence.	0	Strong consensus (100 %)

Table 2 Treatment method, advantages and disadvantages of strongly recommended interventions for external anogenital warts.

Treatment method	Recommended mode and duration of treatment	Treatable area*	Advantages*	Disadvantages	Especially suitable for...*
Podophyllotoxin 0.5 % solution	Topical application BID on three consecutive days with a subsequent interval of four days; treatment may be repeated, with up to four cycles.	No more than 10 genital warts of a size of 1–10 mm and a total area of approximately 150 mm² (1.5 cm²).	– Self-treatment	▸ Not approved for individuals under 18 years of age ▸ Inflammatory reaction ▸ Erosions / ulcerations ▸ Burning sensation	Untreated, solitary, localized AGW in areas easily accessible and visible to the patient
Imiquimod 5 % cream	Topical application overnight (6–10 hours) three times weekly; up to 16 weeks	One sachet is sufficient to treat 20 cm².	– Self-treatment – Can be combined with ablative methods	▸ Not recommended for use in children and adolescents (summary of product characteristics) ▸ Duration of treatment ▸ Inflammatory reaction ▸ Edema, erosions / ulcerations ▸ Hypopigmentation ▸ Flu-like symptoms possible ▸ Phimosis / stricture rarely described following application on the foreskin	Untreated AGW of the genital and perianal skin
Sinecatechins 10 % ointment	Topical application TID; up to 16 weeks	A total of no more than 250 mg (roughly 0.5 cm) of ointment	– Self-treatment – Very good safety profile with moderate local reactions and lack of systemic adverse reactions	▸ Not approved for individuals under 18 years of age ▸ Duration of treatment ▸ Application TID ▸ Inflammatory reaction ▸ Phimosis / stricture rarely described following application on the foreskin	Untreated AGW of the genital and perianal skin
Ablative/surgical procedures: Curettage, scissor excision, electrocautery and modified coagulation methods, laser therapy (CO_2, erbium, Nd:YAG, diode lasers)	Depending on the extent of the lesions, the procedure is performed under local or general anesthesia; single or multiple sessions, superficial ablation down to the basement membrane	–	– Very good cosmetic results if carefully performed – Single session, quick treatment	▸ Postoperative pain ▸ Generation of fumes in some cases	Multifocal, extensive (in patches), recurrent AGW (exception: curettage/scissor excision recommended for solitary AGW in particular)
Cryotherapy	Exposure time approximately 10–20 sec, maximum of 2 more applications at roughly 30-second intervals (freeze-thaw-freeze technique), repeat treatment at weekly intervals	–	– Can be used during pregnancy – Simple technique, inexpensive – No local anesthesia required	▸ Burning sensation and pain ▸ Pigment changes ▸ Potential superficial scarring	Multifocal AGW; pregnant women
Trichloroacetic acid 80–90 % (m/V)	Applied by physician with cotton swabs or wooden sticks; repeat treatment at weekly intervals. Protection of the surrounding skin, for example with soft zinc paste.	–	– Can be applied during pregnancy – Simple technique, inexpensive	▸ Immediate burning sensation and pain ▸ Ulceration and fistulation possible ▸ Excessive use requires neutralization with sodium bicarbonate	Multifocal, small, localized AGWs; mucosal lesions in particular; pregnant women

*This table is not intended to be an exhaustive and comprehensive presentation of indications, adverse reactions and contraindications. Users are encouraged to review the information contained herein against the product information provided by the manufacturers.
Abbr.: AGW, anogenital warts; m/V, mass concentration (mass/volume).

In case of IEN that are very extensive, disseminated or suspected of being invasive, we *recommend* further assessment and treatment be carried out by specialists experienced in the treatment of such lesions.	↑↑	Strong consensus (100 %)

With respect to the treatment of vulvar IEN, the reader is referred to the existing guidelines for "Diagnosis, Treatment, and Follow-up of Vulvar Cancer and its Precursors" [4].

It is recommended that external anogenital intraepithelial neoplasia (IEN) – as superficial, non-invasive epithelial lesions – be treated in a way that preserves organs and functioning, and avoids mutilation as far as possible. Only histopathology allows for definitive determination of the degree of dysplasia and unequivocal distinction between intraepithelial and invasive lesions. In case of suspected anogenital IEN, histopathological examination is therefore recommended; small lesions should be completely resected, whereas large lesions should be biopsied at multiple sites (mapping biopsies). Given the limited study data available for any of the treatment methods for anogenital IEN, recommendations are based primarily on retrospective data analysis and expert consensus. In principle, surgical or ablative methods are the preferred mode of treatment for external anogenital IEN (curettage, excision [179–183]; electrocautery [184] and modified coagulation methods, e.g. infrared coagulation [184–186]; laser therapy [e.g. CO_2, erbium, ND:YAG, diode lasers] [184]; cryotherapy) [187, 188]. For lesions located in areas with hair follicles and glandular structures (e.g. perianal skin), excision should be given preference as epithelial changes may extend deep into skin appendages [189]. In addition, excision offers the advantage of complete histopathological assessment of a specimen, thus allowing for re-excision if margins are not tumor-free. Depending on the individual location and extent of the lesions, specific surgical techniques may be required; in case of penile involvement, for example, circumcision or de-epithelialization of the glans with subsequent skin graft. Extensive perianal lesions require sufficiently wide skin bridges to be left in place in order to avoid stenosis; while flaps are a possible option for reconstructing defects, they are usually not required.

Depending on the site involved, topical methods are also employed as first-line treatment. Data is available from predominantly retrospective studies: In such a retrospective review, 57 % of individuals with PIN showed complete remission on either 5-fluorouracil 5 % cream or imiquimod 5 % cream [190]. In a small prospective study, 5-fluorouracil 5 % cream also proved to be a potential treatment option for the treatment of anal and perianal IEN (n = 8) [191]. The application of trichloroacetic acid 85 % has likewise been successfully used for the ablation of anal IEN [192]. In addition, topical cidofovir 1 % has been shown to be beneficial in HIV-positive patients (n = 33) [193]; however, the aforementioned limitations with regard to drug safety (potential severe adverse reactions) also apply in this context [171].

No published data is available on the use of sinecatechins or ingenol mebutate in the treatment of anogenital IEN.

In principle, anogenital IEN – just like AGW – is associated with a high risk of recurrence, even after initially successful treatment.

3.4 Treatment of HPV-associated intra-anal lesions

Recommendation	Strength	Agreement
Depending on the extent of disease, we *recommend* using one of the following superficial ablative options as primary treatment of intra-anal AGW or IEN: • Electrocautery and modified coagulation methods • Laser systems with suitable wavelengths and biological tissue effects • Curettage, excision	↑↑	Consensus (91 %)
Primary treatment of intra-anal AGW and IEN using one of the following therapeutic options *can be considered*: • Trichloroacetic acid 80–90 % (m/V) • Imiquimod 5 % cream/suppositories (off-label use) • Cryotherapy.	o	
We *suggest against* performing deep excisions unless doing so involves an excisional biopsy in case of suspected carcinoma of the anal canal.	↓	
We *recommend* administering, stool softeners and adequate pain management postoperatively; extensive lesions are an indication for inpatient treatment.	↑↑	Strong consensus (100 %)
In case of recurrent intra-anal AGW and IEN, adjuvant treatment with imiquimod 5 % cream (as anal tampons) *can be considered* once the wound has healed (off-label use).	o	Strong consensus (100 %)

With respect to the treatment of intra-anal IEN in *HIV-positive patients*, the reader is referred to the existing guidelines for "HIV-associated Anal Dysplasia and Anal Carcinoma: Prevention, Diagnosis, and Treatment" [5].

In general, treatment of intra-anal AGW and IEN follows the same principles as described for similar perianal lesions. It includes surgical procedures, non-surgical methods or a combination thereof. Unlike the treatment of external AGW, however, study data is scarce. All treatment options are associated with a high risk of recurrence. Treatment limitations arise from the more difficult access, anatomic peculiarities, and the lack of approved topical agents for mucosal application.

With respect to surgical/ablative treatment, which is generally carried out under general or local anesthesia, it should be borne in mind that "radical" excision/ablation down to the subanodermal/submucosal layer is not required and associated with the risk of scar contractures or anal stenosis. For circular lesions of the anal canal, a sufficient number of "epithelial islands" are to be left in place; alternatively, a two-stage segmental approach is to be chosen. Tissue destruction in the area around the excretory ducts of the proctodeal glands should be avoided. Superficial ablative procedures (electrocautery, lasers) are most commonly used. In this context, modified electrocoagulation methods ("wet field" technique according to Wienert, soft coagulation, layer-by-layer argon plasma coagulation [162]) do not generate any fumes if used correctly. Other options include cryotherapy, a method that is difficult to control with regard to depth of penetration. Targeted ablative treatment with trichloroacetic acid 80–90 % (m/V) is another option commonly used. Important postoperative measures include stool softeners and adequate pain management; extensive lesions are an indication for inpatient treatment.

Topical agents are given off label as they have not been approved for intra-anal mucosal application. What is more, topical self-treatment using the various agents available (creams, ointments, solutions) is difficult to implement. Imiquimod 5 % may be given in the form of suppositories (anal tampons) (off-label use). In an uncontrolled study, adjuvant treatment using imiquimod 5 % suppositories (anal tampons) after ablation of intra-anal AGW resulted in low recurrence rates [194].

A comparison of various treatment methods for AIN in HIV-positive men who have sex with men carried out in the context of a randomized trial revealed the following complete remission rates four weeks after completion of one treatment cycle: 24 % for imiquimod; 17 % for topically applied 5-fluorouracil; and 39 % for electrocautery; more than two-thirds of patients who had been treated successfully had recurrence within 72 weeks [195].

3.5 Treatment of HPV-associated meatal and intraurethral lesions

Recommendation	Strength	Agreement
We *recommend* treating meatal AGW and IEN with surgical/ablative methods, such as forceps resection, electroresection/electrocoagulation, or laser therapy (e.g. Nd:YAG, diode, holmium:YAG, thulium, or CO_2 lasers).	↑↑	Strong consensus (100 %)
In general, we *recommend* using endourologic procedures as primary treatment of intraurethral AGW and IEN. (Open surgery on the urethra remains the last resort.)	↑↑	Strong consensus (100 %)
We *recommend* treating intraurethral AGW and IEN using surgical/ablative methods such as forceps resection, electroresection/electrocoagulation or laser therapy (e.g. Nd:YAG, diode, holmium:YAG, or thulium lasers).	↑↑	Strong consensus (100 %)
We *suggest* leaving treatment of extensive meatal and intraurethral AGW and IEN, which is frequently associated with complications, to surgically experienced and technically well-equipped urologists.	↑	Strong consensus (100 %)
We *recommend* that drugs and active ingredients not approved for intra-urethral use only be employed in the context of studies and/or with the patient's express consent.	↑↑	Strong consensus (100 %)

Explanatory notes and background information on these recommendations can be found in the long version of the guideline.

3.6 Adjuvant systemic interventions to boost the immune response

Recommendation	Strength	Agreement
We *suggest against* the systemic administration of interferon aimed at increasing the efficacy of the recommended topical treatments for AGW and IEN.	↓	Strong consensus (100 %)

We *suggest against* simultaneous or adjuvant "therapeutic" vaccination with HPV vaccines aimed at increasing the efficacy of the recommended topical treatments for AGW and IEN.	↓	Strong consensus (100 %)
HPV vaccination *can be considered* following successful treatment of AGW or IEN with the objective of reducing recurrence or reinfection rates (off-label use).	o	

Explanatory notes and background information on these recommendations can be found in the long version of the guidelines.

3.7 Specific situation: treatment of immunodeficient/HIV-positive patients

Recommendation	Strength	Agreement
In general, we *recommend* treating immunosuppressed and HIV-positive patients who have external AGW or IEN using the same methods as with immunocompetent individuals, giving preference to methods that spare tissue.	↑↑	Consensus (93 %)
With respect to the treatment of perianal and intra-anal IEN in *HIV-positive patients*, the reader is referred to the existing guideline for "HIV-associated Anal Dysplasia and Anal Carcinoma: Prevention, Diagnosis, and Treatment" [5].		

Explanatory notes and background information on these recommendations can be found in the long version of the guideline.

3.8 Specific situations: treatment during pregnancy

Recommendation	Strength	Agreement
In pregnant women with external AGW, we *recommend* establishing the indication for treatment with caution until the 34th week of gestation.	↑↑	Strong consensus (100 %)
In pregnant women with external AGW or IEN in whom treatment is indicated, we *recommend* giving preference to cryotherapy, trichloroacetic acid 80–90 % (m/V), or surgical/ablative procedures, taking into account individual circumstances.	↑↑	Strong consensus (100 %)
With respect to the treatment of vulvar IEN, the reader is referred to the existing guideline for "Diagnosis, Treatment, and Follow-up of Vulvar Cancer and its Precursors" [4].		

Explanatory notes and background information on these recommendations can be found in the long version of the guideline.

4 Follow-up of patients with HPV-associated anogenital lesions

4.1 Follow-up after treatment of anogenital warts

Recommendation	Strength	Agreement
In case of first-time infection with external AGW and no recurrence detected during the follow-up exam 4–8 weeks post treatment, we *recommend* performing a final follow-up exam after another 3–6 months.	↑↑	Strong consensus (100 %)
In case of first-time infection with intra-anal or intraurethral AGW and no recurrence detected during the follow-up exam 4–8 weeks post treatment, we *recommend* performing further follow-up exams at 3–6-month intervals for a recurrence-free period of at least 12 months.	↑↑	Strong consensus (100 %)
In case of recurrent AGW, we *recommend* performing follow-up exams at 3–6-month intervals for a recurrence-free period of at least 12 months.	↑↑	Strong consensus (100 %)
In immunodeficient and HIV-positive patients with AGW, we *recommend* performing life-long follow-up exams at 3–12 month intervals (depending on individual findings) due to the increased risk of recurrence and HPV-associated carcinomas.	↑↑	Strong consensus (100 %)

Explanatory notes and background information on these recommendations can be found in the long version of the guideline.

4.2 Follow-up after treatment of anogenital intraepithelial neoplasia

Recommendation	Strength	Agreement
In case of low-grade anogenital IEN (AIN1, PIN1, PaIN1), we *recommend* following up patients according to the same recommendations as those made above for the follow-up after treatment of anogenital warts (observing the specific recommendations on recurrent lesions, sites affected, and immune status).	↑↑	Strong consensus (100 %)
In immunocompetent patients with high-grade anogenital IEN (AIN2/3, PIN2/3, PaIN2/3), we *recommend* performing follow-up exams at 6-month intervals for a recurrence-free period of five years and, subsequently, annually.	↑↑	Strong consensus (100 %)
In immunodeficient and HIV-positive patients with high-grade anogenital IEN (AIN2/3, PIN2/3, PaIN2/3), we *recommend* performing life-long follow-up exams at 3–12 month intervals (depending on individual findings).	↑↑	Strong consensus (100 %)
With regard to follow-up treatment of perianal and intra-anal intraepithelial neoplasia in HIV-positive patients and follow-up of vulvar intraepithelial neoplasia, the reader is referred to existing guidelines [4, 5].		

Explanatory notes and background information on these recommendations can be found in the long version of the guideline.

Conflict of interest

A full disclosure of the conflicts of interest and how they were managed during guideline development can be found in the long version of the guideline (available as an online supplement and on the AWMF's website).

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References

The list of references can be found in the long version of these guidelines (long version available as online supplement and on the AWMF's website).