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Abstract
Squamous cell carcinoma (SCC) of the anus is a human papilloma virus (HPV) related malignancy that is preceded by anal intraepithelial neoplasia (AIN) making this cancer, at least theoretically, a preventable disease. In the past 10 years the diagnosis, management and nomenclature of AIN has dramatically changed. Increased life expectancy in human immunodeficiency virus (HIV) positive patients due to highly active antiretroviral therapy (HAART) has caused an increase in the incidence of SCC of the anus. While many experts recommend screening and treatment of anal high-grade squamous intraepithelial lesion (HSIL), there is no consensus on the optimal management these lesions. Therefore, there is a need to review the current evidence on diagnosis and treatment of AIN and formulate recommendations to guide management. Surgeons who are members of the Italian Society of Colorectal Surgery (SICCR) with a recognized interest in AIN were invited to contribute on various topics after a comprehensive literature search. Levels of evidence were classified using the Oxford Centre for Evidence-based Medicine of 2009 and the strength of recommendation was graded according to the United States (US) preventive services task force. These recommendations are among the few entirely dedicated only to the precursors of SCC of the anus and provide an evidence-based summary of the current knowledge about the management of AIN that will serve as a reference for clinicians involved in the treatment of patients at risk for anal cancer.

Keywords Guidelines · Anal intraepithelial neoplasia · HPV, human papillomavirus viruses · Squamous intraepithelial lesions

Introduction

Clinical practice guidelines are one of the most important instrument for any Scientific Society to provide therapeutic decision-making support, based on the best scientific evidence available at the time.
Guidelines are advisory and not prescriptive, susceptible to continual variations secondary to innovations and new scientifice vidence.
The Italian Society of Colorectal Surgery (Società Italiana di Chirurgia Colorettale; SICCR) recommendations are intended for the use of all colorectal surgeons, health care professionals, and patients who desire information and clinical guidance.
Anal intraepithelial neoplasia (AIN) is a known precursor of squamous cell carcinoma (SCC) of the anus. In many cases the natural history of AIN has been deduced from retrospective studies; thus prospective data for AIN are very limited. Considering the increasing incidence of this pathology SICCR decided to produce a clinical guide for all colorectal surgeons and physicians who approach anal HPV-related dysplasia.

Methodology

SICCR appointed various specialists who referred to Sexually Transmitted Infections (STI) and HPV centers to draft guidelines of AIN. This group includes colorectal surgeons, dermatologists, pathologists and infectious disease specialists all trained in HPV-related diseases. They were invited to contribute on various topics after a comprehensive literature search. Levels of evidence were classified using the Oxford Centre for Evidence-based Medicine of 2009 and the strength of recommendation was graded according to the United States (US) preventive services task force. A MedLine search of English language references canal carcinoma, anal margin carcinoma. The Cochrane library was further reviewed.
The levels of scientific evidence were adapted from those of the Oxford Centre for Evidence-based Medicine of 2009 [1] and the strength of recommendation was graded according to the US preventive services task force [2].

Epidemiology and risk factors

Anal neoplasms comprise a variety of different c ancers, including SCC, adenocarcinoma, melanoma and sarcoma. Among them, the most frequent are those originating from the mucosal and perianal keratinized epithelium. These cancersare preceded by cellular alterations mostly induced by a viral sexually transmitted infection. Therefore, it is important to focus on the epidemiology of human papilloma virus (HPV) infection, a large group of deoxyribonucleic acid (DNA) viruses that affect epithelial cells of the higher vertebrates.

More than 40 HPV types infect genital epithelia including the anal region [3, 4]: of them, up to 20 types are oncogenic, HPV16 and 18 being the most prevalent ones [5, 6].

HPV infection is one of the most widespread infections worldwide. According to WHO, more than 300 million new cases are annually recorded in women and, therefore, a huge number should be found in men [7]. However, only a few HPV infections by the oncogenic types are linked to persistence and eventually to transformation of infected cells towards cancer precursors. These altered cellular lines aredefi ned as AIN and are graded according severity of transformation from AIN I to AIN3. They are similar to the modification seen in female cervix (CIN 1–3) that can precede the development of cervical cancer [8].

In spite of the fact that epidemiology of cervical HPV infection among women is quite well known, similar large scale data on anal infection are not available for general populations and are often restricted to data from men who have sex with men (MSM). To date, the prevalence of anal HPV, recorded mainly among MSM, tends to be very high: from 12% up to 91% depending on country, gender, and sexual orientation [9]. HIV positive MSM have higher prevalence anal HPV rates in comparison to HIV negative ones, as well as HIV positive women and heterosexuals [9–13]. Data on the incidence of HPV are also worrisome. Incidence rates range from 4.5 to 12.4 per 100 person/years [9]. However, the natural history of HPV infection includes the possibility of infection clearance: HPV 16 disappeared at a variable rate between 12.2 and 18.7 per 1000 [14]. Once HPV infection is permanently established, the development of AIN follows in a variable timeframe, depending on the risk factors present. The prevalence of any grade of AIN is highly variable, ranging from 0% to 55.1% according to gender, sexual orientation and immunosuppression. As a general rule, people living with HIV, in particular MSM, tend to have higher prevalence [15–23].

Incidence of high grade AIN shows a rate of progression among persons without HIV infection of 3–6/100 years/ person compared to 7.4 up to 15.4 among people with HIV [24–26].

Many studies have evaluated the factors associated with risk of acquiring HPV infection through sexual intercourse. As a general rule, there is a consistent association between an increasing number of sexual partners, or a recent new partner and the detection of HPV DNA in genital specimens. Along with these factors, the previous habits of the new partners, smoking habits, hormonal and pregnancy status have also been linked to a higher incidence rate of HPV infection. In terms of likelihood of developing AIN, several studies have addressed their attention to risky conditions that promote the presence of abnormal anal cytology. In summary, the following factors have been identified: infection by HPV 16/18, coexisting multiple HPV types and HIV infection, especially among those with lower nadir CD4+ cell count [27]. According to gender, among women the presence of CIN 3 or vulvar dysplasia increases fourfold the likelihood of AIN along with practising receptive anal intercourse. Among MSM, the presence of anal condylomata was associated with abnormal anal canal cytology [28]. HIV infection and the relative degree of immunosuppression, as well as the use of antiretroviral therapy, have been evaluated but results are conflicting. However, as expected, the worst is immunosuppression; the highest is the rate of high-grade AIN. Other proven risk factors are immunosuppressive drugs in transplant recipients, immunosuppressive diseases [like systemic lupus erythematosus (SLE)], cigarette smoking and at-risk sexual behaviors (such as multiple partners, no condoms, the use of sex toys and sex parties).

Taking into account the previous data, it is not surprising that the prevalence and the incidence of SCC are increasing worldwide. In the USA, according to the American Cancer Society the estimated new cases of anal, anal canal and ano-rectal cancers between 2012 and 2017 rose from 3900 in women and more than 2200 in men to 5250 and 2950, respectively [29]. The incidence rate is calculated about 1 per 100,000 persons/year. The risk factors for developing SCC are again the presence of HPV infection, receptive anal intercourse, a diagnosis of cervical cancer, older age along with smoking habit [9, 30]. However, it must be remembered that people with end-stage renal disease also show an excess of SCC cases; therefore, this population also deserves attention in terms of screening or early diagnosis [31, 32]. HIV positive MSM remain the group at highest risk for anal cancer. Since 1994, when the first description of an increase in SCC incidence

was published [33], further studies confirmed the effect of the HIV epidemic on the increased risk of development of anal canal cancer, showing incidence rates of up to 131/100,000 compared to 2/100,000 among men not infected with HIV [9, 34].
To date very few data on AIN or SCC prevalence are available from Italy; therefore, a common effort is needed to cope with this growing problem [35, 36]. The data reported above could be the starting point for implementation of screening and treatment for AIN at least in high-risk populations, even if randomized controlled trials evaluating screening and treatment outcomes are still inconclusive [37].

Histology
Non-invasive human papillomavirus-related intraepithelial lesions of the anal canal include the following:
(i) AIN (Anal Intraepithelial Neoplasia), which could be subdivided in AIN1 (LSIL) e AIN2/3 (HSIL);
(ii) Verrucous carcinoma that includes also Buschke Lowenstein neoplasm; (iii) superficially invasive squamous carcinoma SISCCA. The College of American Pathologists and the American Society for Colposcopy and Cervical Pathology described non-invasive HPV anal lesions in a complete classification that permits a unique terminology worldwide: "The Lower Anogenital Squamous Terminology" (LAST) [8]. This classification might be used by all experts in this field to obtain a comparable international Literature.
The histological diagnostic algorithm is based on the following:
(a) Identification of diagnostic category related to the degree of dysplasia (points 1–3); (b) Assessment of the value of p16 with immunochemistry in selected cases as reported in point 4. Results of diagnostic categories could be as follows: 1. Negative for squamous intraepithelial lesions; 2. Low-grade squamous intraepithelial lesions (LSIL). Histological criteria are the following: epithelial changes are related to viral cytopathic effects and include abnormal nuclear features including increased nuclear size, irregular nuclear membranes and increased nuclear-tocytoplasmic ratios. A slight modification of the usual maturation process is observed in the lower third of the epithelium. 3. High-grade squamous intraepithelial lesions (HSIL). Modifications of maturation, like mitotic figures, can be found in the middle and/or superficial thirds of the epithelium that can be completely involved. HSIL include AIN 2 and 3. Immunohistochemical research of p16 expression could be helpful in the following:
1. p16 immunostaining improves the accuracy of singlepathologist interpretations of high-grade versus lowgrade disease. Il could be used in the differential diagnosis between HSIL and similar features such as immature squamous metaplasia and atrophy. It also useful in artifacts due to a tangential section of the specimen
2. The confirmation of an AIN2, that in the absence of p16 positivity must be considered a LSIL.
The use of p16 must be avoided in case of certain diagnosis (AIN 1 or AIN 3). P16 is considered positive if a strong nuclear or cytoplasmic staining is present at the lower epithelium level and extended up to one-third of its thickness at least [8, 38]. SISCCA is an invasive squamous carcinoma with a depth of invasion less or equal to 3 mm and a maximum lateral spread of 7 mm. This definition originally applied to invasive
lesions that are completely excised and are potentially amenable to conservative surgical therapy. However, the definition can be extended to incompletely excised lesions that may fit into the same size category. [8].

Diagnosis
Which are the best tests for the diagnosis of AIN? Clinical examination and high-resolution anoscopy (HRA) are the most important tests for an appropriate diagnosis of AIN. Every suspected lesion must be biopsied. The role of anal brushing needs to be further clarified. Grade of Recommendation: Weak recommendation based on moderate-quality evidence, 2B. Diagnosis of non-invasive-related intraepithelial lesions of perianal and anal canal lesions include Clinical examination After an accurate clinical history of the patient, including sexual habits and previous sexually transmitted infections, an exploration of perianal area and of the anal orifice, associated with a digital rectal examination (DARE) are mandatory [39–41]. These procedures could reveal lesions that must be immediately biopsied. Grade of Recommendation: Strong recommendation based on moderate-quality evidence, 1B. It is important to evaluate completely the perianal and genital area to exclude associated lesions of the penis, scrotum, vulva and vagina. When a HRA is indicated DARE must be performed after the HRA because the ointment usedfor the DARE could reduce the properties of acetic acid and
Lugol.

This recommendation is indicated also in case of a pap smear and brushing examinations. DARE must be performed accurately in order to value the entire anal canal and to value eventual fixity of anal canal lesions. This is an important issue when differentiating benign from infiltrative lesions.

Morphological valuation of these lesions is also important to identify lesions suspicious for malignancy [39–41]. Brushing and viral typing Anal pap smear is included in the screening of patients at risk for precancerous anal lesions [42–44]. It includes the cytological exam of the pap smear and the research of viral DNA with its typing. Another important evaluation in recent years is viral load. Moreover, published studies demonstrated that anal pap smear presents a higher rate of false negatives (FN) than HRA. In fact the result of anal cytology correlates poorly with the treatment of lesions. Results of anal pap smear could be negative, L-SIL, H-SIL, atypical squamous cells of undetermined significance (ASCUS), atypical squamous cells, not excluding HSIL ASC-H. This exam must be followed by HRA to complete the diagnosis more accurately. In a study on 300 patients who underwent anal cytology prior to surgery the sensitivity for detecting AIN was 56 and specificity was 77% [45]. Cuming reviewed the results of anal cytology reporting sensitivity between 54 and 89% with a specificity reported between 37 and 76% [46]. The combination of HPV testing and cytology in HIV negative patients improves sensitivity. The negative predictive value of combining the tests is 93% [46, 47]. However, the sensitivity is higher (87%) in HIV positive
patients [47] and MSM (83%) [48] and, therefore, even if not currently recommended, may have some benefits as a screening tool in high-risk populations. The high proportion of AIN grade 2 or worse, not detected by cytology, suggests insufficient sensitivity to be of value as a standalone screening test.
Grade of Recommendation on the use of cytology: Weak recommendations based on moderate-quality evidence, 2B. However, when anal cytology was compared to HRA and HPV typing in a decision analytical model, direct
HRA was found to be the most cost-effective screening strategy [49]. Genotyping of anal HPV could distinguish high-risk vs. low-risk virus, stratifying potential oncologic degeneration.
Grade of Recommendation on the use of HPV typization: Weak recommendations based on moderate-quality evidence, 2B. Considering that in case of positivity of cytology and HPV typing a guided HRA biopsy is mandatory, the cost of HPV typization is not justified. As suggested above the detection of p16 on anal biopsies could recognize the potential oncologic progression of precancerous lesions. Grade of Recommendation: Weak recommendations based on moderate-quality evidence, 2B.

Anoscopy
Traditional anoscopy has a marginal role in the screening and detection of precancerous lesions since the introduction into clinical practice of HRA. Otherwise, it has an important role in the detection of lesions larger than a few millimeters. The disadvantage is that traditional anoscopy does not have magnification so it is impossible to observe typical patterns of AIN lesions, even if they may be suspected in many cases.
However, DARE and traditional anoscopy are considered as the initial steps for any patient with a history of symptoms suggestive of anal cancer [41, 50]. Grade of Recommendation: Strong recommendation
based on moderate-quality evidence, 1B. High-resolution anoscopy (HRA) is actually considered the best diagnostic and screening tool for HPV-related intraepithelial lesions of the perianal area and anal canal. It permits magnification of images obtained with a traditional proctoscope.
Nowadays there are no specific requirements about the type of proctoscope, magnification, resolution of video and so on. Usually tools for colposcopy have been used even if in recent times specific digital tools to obtain a precise HRA have been proposed.
The technique consists in the topical application of acetic acid (3–5%) and finally with application of Lugol solution 2%. Anal canal condyloma and AIN lesions are not receptive to the Lugol coloration, so the absence of coloration after application of Lugol is indicative of anal canal localization of HPV and HPV induced dysplasia. Many centers do not use Lugol solution in the diagnosis of these lesions [41, 51]. However, both the clinical practice Guidelines of American Society of Colorectal Surgeons and SICCR report that the Grade of Recommendation is a weak recommendation based on moderate-quality evidence, 2B.
The availability of HRA is currently limited in the majority of health care environments and there are few physicians trained in its use [52, 53]. There are indeed some HRA competency standards that require a long learning curve and need attendance at HRA course or other relevant course and at least once every 3 years

thereafter; log book recording of first 50 HRA examinations under direct supervision by a trainer; further 100 HRA examination with indirect trainer supervision, logged by trainee; 20 biopsies from anal canal
and 20 from perianal skin, of which 50% under supervision; inadequate biopsy < 10%; 50 anal cytology samples with < 5% unsuitable samples; no more than 2% of missed lesions in the first 50 training cases; enrolment in a multidisciplinary team consisting of pathologists and cancer specialists and 80% attendance at regular multidisciplinary team (MDT) meetings. The growing demand for anal cancer screening will make it impossible to offer rapid specialized care to the entire at-risk population [54], and probably in many countries outside USA it will be impossible to obtain that grade of expertise

Biopsy
Suspicious lesions that must be biopsied are perfectly described by the paper of Marine Camus and colleagues [52]. A combination of irregular epithelial and vascular patterns, as well as acetic acid and Lugol staining results, correlated with the grade of AIN. None of the lesions that exhibited acetic acid-induced whitening only without an irregular epithelial pattern, vascular changes, or abnormal. Lugol staining was HSIL. These criteria should be considered the guidelines for HRA-targeted biopsy. Grade of Recommendation: Weak recommendation based on moderate-quality evidence, 2B.
In conclusion, there are no universal recommendations for the screening and management of HSIL, even if HRA is considered the best diagnostic tool in the detection of anal cancer precursors mainly in high-risk populations. When HRA is not performed, multiple random biopsies should be instituted to detect preneoplastic lesions.

Treatment of AIN
Many specialties are involved in the management of anal precancerosis: dermatologists, colorectal surgeons, venereologists, gastroenterologists, gynecologists, other physicians, nurse practitioners that perform anal cytology smears and HRA, but there are no uniformly accepted management guidelines worldwide [55]. The majority of data concerning the treatment of highgrade and low-grade dysplasia mostly reflect the results in high-risk patients (immunocompromised, HIV-positive/acquired immunodeficiency syndrome (AIDS) patients, especially MSM, and solid organ transplant recipients) and
there are limited studies on the general population. The different non-surgical treatment modalities may be divided into topical therapy, consisting of direct application of a medication to the whole anal canal by the patient, and local ablative therapy, consisting of targeted destructive therapy performed by the physician during examination. • *Topical methods* include imiquimod [56], 5-fluorouracil (5-FU) [57], cidofovir [58] and topical applications of trichloroacetic acid (TCA) [59]. • *Ablative methods* consist of electrocautery, radiofrequency ablation (RFA) [60], CO2 laser [61], infrared coagulation (IRC) [62], photodynamic therapy [63] and surgery.

There is no level 1 evidence and studies comparing different treatments as well as treatment with placebo are lacking. HSIL lesions should be treated since they can progress to invasive cancer.
Grade of Recommendation: Strong recommendation based on moderate-quality evidence, 1B. Although the rate of progression from dysplasia to anal SCC is still unknown, and robust natural history data are
lacking, there is evidence that malignant transformation occurs, especially in high-risk patients. Recently Arens et al reported that the cumulative incidence of SCC after AIN III diagnosis was 1.2% at 12 months; 2.6% at 24 months; 3.7% at 36 months, and 5.7% at 60 months [64]. With respect to analyzing the results from case series, it is important to benchmark these results against outcomes of untreated AIN. The condition is complicated by its multicenter and multifocal nature high rates of relapse and morbidity and no treatment modality, to date, has demonstrated consistent clearance of HPV in treated AIN disease.
Recurrence of AIN after treatment may depend on a number of factors such as duration of follow-up, age of the population studied, HIV status, size (surface area) of the disease, anatomical area (perianal or intra-anal), CD4 cell status, CD4 nadir and the duration of their HIV infection, when positive.
A large series of 138 HIV positive patients, followed for 15 years, showed that 72 (52%) developed SCC after an average interval of 5 years. The average interval between the diagnosis of HSIL and the development of anal cancer was approximately 5 years. Studies with shorter follow-up showed a lower rate of progression.

Devaraj et al. who followed 40 patients with anal squamous dysplasia (low or high grade) for a minimum of 12 months eventually found SCC in 3 (6.6%) patients [65]. In one of the largest published series, Watson et al. [66] described an observational study of 72 patients with untreated AIN: 8 (11%) progressed to SCC over an 8-year period. There was a progression to SCC in 2 out of 10 patients with AIN II (20%) and 6 of 45 patients with AIN III (13.3%). They also noted that the AIN grade of 25 of their 72 (35%) patients regressed. In a randomized study of imiquimod Fox et al. [67] found 2 SCC out of 25 (8%) patients treated with placebo and no cancer in the 28 patients of the treatment arm. The recurrence rates of AIN after treatment with electrocautery ablation are dependent on HIV serostatus, (0% recurrence in HIV negative compared to 79% in HIV positive patients) particularly with high-grade AIN; thus, post treatment surveillance is essential [68]. Screening by anal cytology is recommended for high-risk individuals every 1–3 years. Grade of Recommendation: Weak recommendations based on moderate-quality evidence, 2B.

A Markov model of anal cytology showed an incremental cost-effectiveness ratio compared to no screening of $16,600 per quality-adjusted life year (QALY) saved (similar to other accepted screening tests such as colon cancer screening) when HIV-positive men are screened every year and HIVnegative MSM are screened every 3 years [69, 70]. These two analyses were performed from a US perspective; while in a health care model with lower incidence of anal cancer such as in the UK screening high-risk MSM for anal cancer is not cost-effective [71, 72]. While the evidence for the different treatment options for AIN is weak, the consensus appears to be unanimous that some treatment is required to prevent progression from highgrade AIN to SCC.

Thus, watchful waiting is no longer considered to be a justifiable option and regular post-treatment follow-up visits are mandatory. Particular care and close follow-up should be undertaken in the highest risk groups such as those HIV positive patients with high grade AIN.

Topical treatments for AIN

Topical therapy appears to be generally well tolerated and has reasonable efficacy, although a substantial portion of patients will not respond and others will recur, but it is a good compromise between surgery and the watch and wait strategy. For these reasons, topical therapy should be considered either the first choice in therapeutics strategy or as an adjunct before or after local ablative therapy.

Traditional excisional surgery for AIN has been associated with very high rates of morbidity and recurrences and, therefore, there has been an increasing interest for less invasive treatment options. Although many pilot studies on ablative and topical AIN treatment are available, only one randomized placebo-controlled trial of AIN therapy with imiquimod vs. placebo was found in the most recent Cochrane review of randomized studies [73] and the 2 evidence-based review on treatment of AIN include highly heterogeneous studies: some studies are of external disease, whereas others are of anal canal disease, and study populations are made up of HIV-positive and HIV-negative individuals [74, 75].

Imiquimod

Topical imiquimod cream, 5%, is an immunomodulatory that activates both the cellular and humoral immune system to cause the regression of the visible lesion and to prevent recurrence.

It is administered 3 times per week for up to 16 weeks. The patient applies the cream to the perianal skin at night, and then washes it off the following morning. Although imiquimod is officially indicated for use only on the anal margin, some studies describe application within the anal canal with a finger or through suppositories [76, 77]. Side effects are irritation, burning, erosions and potential stenosis of anal canal due to local reaction and ulceration. Imiquimod therapy was the only treatment for AIN to be evaluated in a double-blind, randomized controlled trial of 53 HIV + MSM, with 28 patients on active drug therapy and 25 patients on placebo. Of the 28 individuals on active drug therapy, 43% experienced either resolution or downgrading of their lesion, and 61% of imiquimod responders achieved sustained response at 36 months. This trial failed to demonstrate any statistically significant efficacy of imiquimod in the management of AIN [73]. Imiquimod has been compared with 5-fluoruracil (5-FU) and electrocautery in an open-label randomized controlled trial of 156 HIV-positive men having sex with men (MSM).

Imiquimod showed to be the best treatment only when considering the perianal lesions but not the intra-anal ones while electrocautery was the first-line option for intra-anal highgrade AIN [78].

Grade of recommendation: Strong recommendation based on moderate-quality evidence, 1B.

The extended use of imiquimod in the anal canal leads to pain and irritation, side effects leading to treatment suspension that occurred in 4–27% of patients in these trials [66, 78].
This agent is emerging as a safe effective topical treatment, even in HIV-positive patients with their high propensity for recurrence. Due to its characteristics imiquimod might be considered as a non-aggressive first approach to AIN as an adjunct before or after more directed ablative therapies for external anal lesions.
Grade of Recommendation: Weak recommendation based on moderate-quality evidence, 2B.
5-fluorouracil (5FU) Topical 5-FU is a pyrimidine analogue which inhibits DNA synthesis through inhibition of the enzyme thymidylate synthase in neoplastic tissue. It is licensed for the treatment of actinic keratosis, Bowen disease and superficial basal cell carcinoma. It has long been described for treatment of cervical intraepithelial neoplasia (CIN), vaginal intraepithelial neoplasia (VAIN) and penile intraepithelial neoplasia (PeIN) [79–81].It has been used in HIV-positive MSM with AIN [1–3] in an open prospective pilot study: 5-FU 5% cream was selfadministered twice weekly for a total of 16 weeks showing a complete response in 39%, partial response in 17% and no response in 37%. Half of the patients with a complete response to the treatment had a reccurrence of the lesions after 6 moths of follow-up [57]. In the trial comparing Imiquimod, 5FU and electrocautery there was no statistically significant difference between 5-FU and imiquimod while 5-FU was inferior to electrocautery in clearing or downgrading AIN [78].
Its use, like that of imiquimod, is limited by the frequent occurrence of irritation, burning and bleeding.
Grade of Recommendation: Weak recommendation based on moderate-quality evidence, 2B.
Cidofovir
Cidofovir 1% is an acyclic nucleoside phosphonate with broad spectrum anti-viral activity. It has activity against vulvar, vaginal and perianal intraepithelial neoplasia [82]. In a three-arm open label randomized pilot study [83], a complete response was achieved in 76% of 26 patients by cidofovir, 93.1% of 29 patients by surgery alone and 100% of 19 patients treated by a combination of cidofovir and surgery ($p = 0.0033$). The rate of clearance of high-risk and low-risk genotypes was 0% and 57.14% in the surgery arm, 25% and 50% in the cidofovir arm and 100% and 71.42% in the combined arm ($p = 0.23$) leading to a significantly lower recurrence rate at 6 months after a complete response in patients using cidofovir (27–35%) compared to surgery alone (74%; $p = 0.018$).
Although these studies are of interest, the follow-up is very short and this precludes its routine use for widespread clinical application.
Grade of Recommendation: Weak recommendation based on moderate-quality evidence, 2B.
Photodynamic therapy (PDT)
PDT involves administration of a photo-sensitizer, either oral or intravenous. This is taken up by the tissues of the anal canal and administration of a specific wavelength of light causes activation of the sensitizer and destruction of the affected cells. A pilot study of 12 HIV-positive patients with high-grade dysplasia used the photosensitizer d-aminolevulinic acid followed by PDT [63]. Consistent downgrading of dysplasia was seen, and the treatment was well tolerated, although response was based on cytology and a complete response was seen in just 2 cases. Although more recent studies [84, 85] confirm the former results, large, prospective studies have not been performed yet and the longterm outcomes are uncertain.
PDT is a safe and feasible treatment option for AIN, associated with reasonable response rates and relatively little morbidity but it is painful and often requires multiple treatments.
Grade of Recommendation: Weak recommendation based on low- or very low-quality evidence, 2C.
Trichloroacetic acid (TCA)
Topical 85% TCA is one of the accepted cytotoxic therapies for anogenital warts and is recommended by the Center for Disease Control (CDC) as one of the first-line treatments for cervical, vaginal and intra-anal warts [85]. The treatment is provided by the physician who applies TCA to the lesions repeatedly until the lesion turns a dense white color during HRA. In all reports the treatment consisted of up to 4 applications of TCA at 1- to 6-month intervals. Three retrospective cohort studies have described the results of TCA in AIN.
Of 98 HSILs from 72 HIV+ patients, 77 (78.6%) resolved or downgraded to LSIL. At 6 months of the 53 patients with resolved lesions 41.5% had a recurrence at the index site, another site or both and 15.1% had recurrent HSILs at the index [86].

In another study on 28 patients with AIN 2/3 lesions, 32% resolved completely and 29% downgraded to AIN 1 with a complete resolution obtained in 65% of the 55 AIN 2/3 lesions [87]. At 6 months there was recurrence in 15 (72%) of 21 patients whose lesions had completely resolved.
Treatment was more effective in younger patients, among HIV-positive patients and in AIN 2/3 lesions.
Finally, in a recent retrospective propensity score matched comparison between TCA and electrocautery, complete and partial response were achieved in 33.5% and 28% of 182 patients treated with electrocautery and in 60.7% and 23.2% of 56 patients treated with TCA, respectively (p = 0.001 vs. ECA) [88]. This study showed a higher efficacy of TCA than ECA with similar rates of side effects. Considering the benefits of TCA, the authors recommended that it should be considered as a first-line therapy for most anal HSIL management, also considering the low cost, ease of use and safety profile.
Grade of Recommendation: Weak recommendation based on low or very low-quality evidence, 2C.

Ablative treatments of AIN

Ablative techniques include electrocautery, cryotherapy, laser ablation and infrared coagulation. Remarkably all these techniques do not provide histology. Irrespective of the technique initial response ranges between 30 and 70%. However, a high recurrence rate has been observed, in particular in immunocompromised patients; therefore, HRA should be repeated every 3 to 4 months and ablative procedures performed as new lesions are identified [68, 89]. Low morbidity has been described and serious adverse events are rarely reported. HRA is performed with a standard colposcope and thus can be performed in the primary care setting.
Targeted destruction based on high-resolution anoscopy could be effective in identifying and controlling HSIL. Grade of Recommendation: Weak recommendation based on moderate-quality evidence, 2B.

Electrocautery

The use of HRA to guide ablation of HSIL lesions was firstdescribed in 2002: lesions were ablated by cauterization in 29 HIV positive and 8 HIV negative patients; resolution was achieved in all the 8 HIV negative patients; however, 79% of the HIV positive patients recurred. Nevertheless, neither SCC nor major complications were observed.
Pineda et al. [90] retrospectively reviewed 246 patients of whom 197 (81%) had extensive lesions and 194 (79%) were immunocompromised. Persistent disease occurred in 46 patients (18.7%) and recurrence in 114 (57%) after 3–92 months; overall, 36 patients required surgery while all the other were retreated in-office. At their last visit 192 patients (78%) had no evidence of HSIL. Complications included: anal fissure (n = 4), anal stenosis (n = 2), bleeding requiring reoperation (n = 1), myocardial infarction (MI) (n = 1) and cellulitis at the local anesthetic injection site (n = 1).
Electrocautery effectiveness was evaluated in another study in 83 patients with HSIL. A complete response was observed in 32.5%, a partial response in 33.7% (regression from HSIL to LSIL) and persistence in 33.7%. The patients required a minimum of two sessions of treatment. Although no patient progressed to SCC, after a mean follow-up of 12.1 months, 25% of patients with a response developed recurrent HGAIN within a mean time of 29.9 months [91].
Another study on electrocautery examined 232 MSM, 132 HIV positive, with a median follow-up of 18 months. The success rate after the first session was 85% in the HIV-negative and 75% in the HIV positive population, respectively. Over follow-up, 53% of HIV-negative and 61% of HIV-positive patients recurred. It is noteworthy that the majority of recurrence was due to development of additional lesions at untreated sites [92]. The authors perform their procedures in office using the Hyfrecator (ConMed Corporation, Utica, NY, USA), a low wattage highly precise bipolar cautery system used by dermatologists.
However, treatment is preceded by injection of local anesthetics, and intravenous sedation is required in 50% of cases.
When compared to topical agents (imiquimod, 5-FU and cidofovir) in prospective randomized studies, electrocautery shows higher rate of complete response which is offset by a higher recurrence rate. HRA-targeted electrocautery destruction of lesions is performed under local anesthesia or sedation with minimal morbidity and with a set of equipment widely available so it is considered a first-line treatment for anal HSIL.
Grade of Recommendation: Weak recommendation based on moderate-quality evidence, 2B.

Laser

Due to the low penetration depth of carbon dioxide (CO2-laser), the ablation does not cause scarring and a combination with HRA leads to a more targeted destruction of suspicious areas. As suggested by some authors, CO2- laser ablation is a better treatment option than a wide surgical excision that causes extensive scarring.
In the study by Nathan et al. 141 patients received laser ablative treatment as an outpatient procedure for high-grade anal intraepithelial neoplasia (HGAIN) or low-grade anal intraepithelial neoplasia (LGAIN) with a cure rate of 63%.Morbidity was low and pain lasted between 7 and 14 days, with patients resuming activities after the first 48 h [93]. Grade of Recommendation: Weak recommendation based on moderate-quality evidence, 2B.
Infrared coagulation (IRC) IRC is a technique developed for treating early-stage hemorrhoids in the US and is not available in Europe. During HRA each HSIL lesion is infiltrated with lidocaine, treated and debrided repetitively until reaching the submucosal vessels.
To date, there have been three retrospective studies and one prospective study on IRC for AIN. Goldstone et al. employed IRC for ablation of the dysplastic lesions. They demonstrated a high, early recurrence rate; however, after 3 rounds of treatment, resolution occurred in 79% of 75 HIV negative patients and in 70% of 68 HIV positive patients [62, 94]. More recently an 87.5% (49/56 patients) resolution has been reported by Sirera et al. [95] at mean follow-up of 25 (range 12–60) months. After 12 months there was 12.5% recurrence.
A prospective cohort study examined 98 patients who received IRC treatment and 42 who refused treatment. In the first group 74% had no evidence of HSIL on their first post-treatment evaluation and none had progressed to SCC. On the contrary, 88% of untreated patients had HSIL and 2 (5%) had developed SCC after 9 and 28 months of observation [96].
Stier reported the results of 44 patients with the primary aim of evaluating the safety of the IRC. No procedure related severe adverse events were reported. Twelve patients reported mild or moderate anal/rectal pain or bleeding. Two patients reported mild anal incontinence which resolved spontaneously within a few days to several weeks after the procedure. Of the 16 patients who were followed for 1 year, 6 (37.5%) had recurrent or persistent disease [97].
While IRC appears well tolerated, its availability and operator dependency limit its applications.
Grade of Recommendation: Weak recommendation based on moderate-quality evidence, 2B.

Wide local excision
Wide local excision (WLE) is usually performed under frozen section guidance by means of multiple punch biopsies. 6 to 12 biopsies are performed at 4 quadrants, and 3 or 4 levels into the anal canal and perianal skin. The identified lesions should be excised with a 1-cm margin whenever possible. When large mucosal or skin defects are left they can be closed with the aid of local flaps. In 1997 the results of a survey of the members of The American Society of Colon and Rectal Surgeons were reported, showing that 96% of responders used wide local excision for small lesions and 87% for large lesions. However, after excision of extensive disease there is a high rate of scarring and wound complications, mainly stenosis and incontinence. When surgery is limited to patients with less extensive disease disturbances in anal function affecting quality of life are significantly reduced. Therefore, a reappraisal of alternative therapies is being undertaken in particular for patients with extensive or multifocal disease. Wide local surgical excision is effective in controlling HSIL, but carries a high risk of complications and good evidence studies are lacking. An early study on 26 patients with perianal Bowen's disease, from the Cleveland Clinic, showed that wide local excision led to a lower recurrence rate than minor local excision or laser therapy: 23% vs 53% and 80%, respectively, after a median follow-up of 10 months. Moreover, only in the group of patients with WLE was there no development of SCC [98].
The results in 34 patients who had local excision of all macroscopically evident disease of whom 19 had evidence of incomplete excision were reported by Brown et al. [99]. After a median follow-up of 41 months, 63% out of the 19 patients with incomplete excision had a recurrence. None developed SCC; however, 13% of the patients after complete excision developed a recurrence during follow-up.
Surgery was performed as follows: for lesions involving less than 50% of the anal canal or margin a local excision was performed, for lesions greater than 50% either a colostomywas performed, followed by

excision and split graft resurfacing, or excision of the disease and pull-trough of the rectal mucosa. Of the 10 patients with extensive excisions 5 (50%) had serious treatment complications: 3 developed fecal incontinence and 2 anal stenosis, with 2 requiring a permanent colostomy.
Scholefield et al. [100] proposed a conservative surgical approach offering surgical excision only to patients with less than 30% involvement of the anal circumference. They reported the results in 28 patients with HSIL followed for a median of 63 months with 14% recurrence but no progression to SCC and no anal function disturbance.
More recently, Watson et al. [66], in a group of 72 patients, 55 with HSIL, of whom 30% were immunosuppressed, reported progression to malignancy in 11% of cases despite aggressive surgical treatment, and 9 (13% of the ones who were excised) developed fecal incontinence, 4 of whom required a colostomy. In summary, WLE is not well tolerated, does not guarantee eradication of HSIL and should be considered only in case of isolated, well-demarcated lesions occupying less than a third of circumference. Grade of Recommendation: Weak recommendation based on moderate-quality evidence, 2B.

Who is in charge of diagnosing and treatingAIN?
Referral to expert centers with the capability of interpreting cytology and pathology, performing HRA, and treating AIN is essential. Within an institution or region clinicians dealing with AIN need to be identified and any training requirements met. For diagnosis of anal intraepithelial neoplasia primary care practitioners must maintain a high index of suspicion, particularly in patients with risk factors. Every primary care doctor can easily perform DARE. Biopsies are needed for a definitive diagnosis. These will normally be performed by a referral specialist center [101]. Providers, usually colorectal surgeons, with a large AIN practice require specific collaborations with HIV clinicians and anatomo-pathologists [102]. Providers should have appropriate training and learn HRA by attending a formal course and/or by apprenticing with an experienced colleague because it is a specialist technique which requires training and regular practice. Both anal cytology and histological analysis are highly specialized diagnostic fields for trained and experienced specialists. This reduces the risk of misdiagnosis of invasive disease [102]. The management of patients with AIN is best achieved in centers with a special interest in this disease, as part of a cancer network [102–105]. Patient management should be discussed in a multidisciplinary fashion [104, 105] that includes at least colorectal surgeons, dermatologists, pathologists, infectivologists, venereologists, and possibly also gynecologists, urologists and otolaryngologists, all trained in HPV related diseases.

Vaccination
Is there a role for HPV vaccination in the prevention of premalignant and malignant anal lesions?
Since 2006 two prophylactic vaccines have been available to prevent infections with HPV types 16 and 18: the bivalent vaccine Cervarix ™ (GlaxoSmithKline House, Middlesex,TW, UK) and the quadrivalent (qHPV) vaccine Gardasil ™ (Merck Corporate Headquarters, NJ, USA). The qHPV vaccine also targets HPV types 6 and 11 [106, 107]. Both of these vaccines are composed of DNA-free, virus-like particles (VLP), produced using recombinant technology by inserting the major structural L1 gene of the HPV types into a host (either yeast or baculovirus) [108–111]. These particles do not contain any live biological product or DNA, so they are neither infectious nor oncogenic [112, 113]. Both vaccines are indicated from 9 years of age and approved for administration in a 2-dose schedule up to 14 years of age or a 3-dose schedule for all other ages, ideally prior the onset of sexual activity [112]. In December 2014 the U.S. Food and Drug Administration and in June 2015 the European Medicines Agency approved a multivalent VLP vaccine active against nine HPV subtypes, Gardasil 9 (Merck & Co., Inc., Whitehouse Station, NJ, USA), providing protection against HPV-types 31/33/45/52/58 in addition to the types 16/18, responsible for 90–95% of HPV-related cancers [112, 114]. Efficacy of prevention against high-grade cervical lesions has been adequately proven for both bivalent and qHPV vaccines [110, 115, 116]. Infection with oncogenic HPV types is associated with development of cervical cancer as well as of anal cancer [117, 118] and cervical and anal cancers are characterized by biologic similarity. The anal canal has a junction zone, that is similar to the cervical transformation zone, where the rectal columnar epithelium changes into the

squamous cells of the anus, the site where HPV histological manifestations occur most commonly [40, 108, 119]. It is estimated that oncogenic HPV variants are responsible for 91% of anal cancers [120] and for 78% of HPV-related HGAIN(AIN 2/3) [118, 121]; in these cases, the HPV16 is the most frequent HPV type identified [118, 122]. In a large retrospective cross-sectional study conducted to estimate the HPV DNA prevalence and type distribution in both male and females, high prevalence of HPV DNA was observed in patients with AIN 2/3 and invasive anal cancers [123].
The significant role of HPV16 confirms the potential impact of HPV vaccination in the prevention of these lesions. The authors concluded that the use of currently licensed prophylactic vaccines could prevent 84.3% of the anal cancers and 75.4% of AIN2/3 lesions [123].
The qHPV was effective in preventing persistent anal infections with HPV type 6, 11, 16 and 18 and AIN2+ in young MSM [124] and shown to be immunogenic and safe in HIV-1 infected men [125]. Swedish et al. demonstrated qHPV efficacy in preventing recurrent AIN2+ in older HIV negative MSM in a retrospective non-concurrent cohort study [126]. In the Costa Rica vaccine trial Kreimer et al. evaluated the efficacy, of the bivalent vaccine against anal HPV16 and HPV 18 infections in women [127]. The Advisory Committee on Immunization Practices (ACIP) recommended routine vaccination for children of both genders at age 11 or 12 years and for men and women at risk [40, 128]. In Italy, vaccination against HPV is recommended by the 2017–2019 National Immunization Prevention Plan, issued by the Italian Ministry of Health, in male and female adolescents [129]. In summary, the routine use of bivalent, quadrivalent and 9-valent HPV vaccines in both girls and boys is an effective approach to the prevention of AIN, best started before the boys/girls are sexually active to get the full benefit of immunization. Clinicians should be well informed about the importance of HPV vaccination in AIN/anal cancer prevention and motivate their patients to be vaccinated, focusing on those prone to these lesions.
The HPV vaccination is useful in the prevention of premalignant anal lesions in males. Grade of recommendation: Strong recommendation based on moderate-quality evidence, 1B.

Is there a role for HPV vaccination in the prevention of recurrent premalignant anal lesions?

Although the VLP HPV prophylactic vaccines have been demonstrated to have no therapeutic effect on active dysplasia or HPV infection [130, 131], some data have suggested their potential role in HPV-exposed populations [130]. In particular, vaccination showed to be effective in preventing recurrent high-grade AIN in a small non-concurrent cohort study among HIV negative MSM with a previously treated HGAIN [126]. In this study, significantly lower recurrence rates of HGAIN over at least 2 years were reported in patients immunized with qHPV compared with unvaccinated patients.
The authors concluded that the vaccine could be effective posttreatment adjuvant therapy [126]. These findings have subsequently been endorsed by a Markov model-based analysis in both HIV-positive and HIV-negative MSM demonstrating that vaccination after treatment for HGAIN decreased the lifetime risk of anal cancer and could be a cost-saving strategy in this setting [132, 133].
Although these data highlight the potential value of vaccination in preventing recurrence of anal dysplasia, prospective large-scale randomized controlled trials are needed to confirm these results.
Grade of recommendation: Weak recommendation based on low-quality evidence, 3C.

Follow-up after treatment

Algorithms for follow-up evaluation after treatment of HGAIN have been proposed, but there is currently no consensus on how to best manage this high-risk population post-treatment. Anoscopy, DARE, high-resolution anoscopy, anal cytology and targeted biopsies can be used.
Assoumou et al. [134] with a Markov model showed that surveillance strategies that included HRA at the 6- and 12-month visits, with or without anal cytology testing, were more effective than using HRA only for confirmatory testing of abnormal anal cytology tests. The combined strategy (HRA and cytology at 6 and 12 months) extended life expectancy and quality-adjusted life expectancy while remaining below the commonly cited threshold of $100,000/QALY gained. [134] and can be recommended.
Grade of Recommendation: Weak recommendation based on moderate-quality evidence, 2B.

Otherwise, considering data reported in the literature, after treatment of HPV-associated high-grade dysplasia or anal cancer, patients still have to be considered as highrisk patients. Surveillance on a regular basis is mandatory. DARE, high-resolution anoscopy and brush cytology are recommended every 4 months in the first 3 years after treatment, and every 6 months in the following 2 years.
Thereafter, follow-up may be extended to yearly examinations. If no lesions reoccur, brush cytology should be performed every year with high-resolution anoscopy being performed every 2–3 years.
A biopsy of any unusual or suspect anal lesion should be performed, especially in high-risk patients (MSM, HIVpositive, women with cervical dysplasia). Also, histological investigation is recommended of every tissue sample that is removed in the anal region since HPV-associated lesions are mostly asymptomatic and inconspicuous. Grade of Recommendation: Weak recommendation
based on moderate-quality evidence, 2B.

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