

Evaluation and Management of Anal Intraepithelial Neoplasia in HIV-Negative and HIV-Positive Men Who Have Sex with Men

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Abstract The incidence of human papillomavirus (HPV)–associated anal cancer in men who have sex with men (MSM) is striking and has not been mitigated by the use of highly active antiretroviral therapy. Detection and treatment of high-grade anal intraepithelial neoplasia (HGAIN) may reduce the incidence of anal cancer. Anal cytology is a useful tool to detect HGAIN; annual screening of HIV-positive MSM and biennial screening of HIV-negative MSM appears to be cost-effective. MSM with abnormal cytology should be referred for high-resolution anoscopy and biopsy. Individuals with HGAIN should receive treatment; treatment modalities for HGAIN demonstrate moderate efficacy and are usually well tolerated, but greater study is required to determine which treatment is optimal. Large prospective studies are needed to document the efficacy of screening and treatment of HGAIN on anal cancer incidence. The HPV vaccine holds promise for primary prevention of anal cancer in MSM, but significant implementation challenges remain.

Keywords Anal intraepithelial neoplasia · Anal cancer · Prevention · HIV · Human papillomavirus · Screening

Introduction

Anal cancer occurs at alarming rates in HIV-positive and HIV-negative men who have sex with men (MSM)

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compared with the general population. According to recent data from the United States and Europe, the incidence of anal cancer among HIV-positive individuals ranges from 42 to 137 cases per 100,000 person-years, a rate that is 30 to 100 times higher than that of the general population [1•, 2•, 3•, 4•, 5]. Even before the HIV epidemic, anal cancer incidence among MSM was estimated to be as high as about 35 cases per 100,000 person-years, which is comparable to the incidence of cervical cancer in the United States before the advent of routine cervical cytology screening [6]. Anal cancer pathogenesis is similar to that of cervical cancer, including a causative association with the human papillomavirus (HPV) [7•]. Persistence of oncogenic HPV infection is thought to be a necessary factor in the development of anal cancer and high-grade anal intraepithelial neoplasia (HGAIN), the putative anal cancer precursor.

Unlike cervical HPV infection, which peaks in the third decade in women, anal HPV infection is highly prevalent throughout adult life among MSM well into the sixth decade [8, 9]. Among HIV-positive MSM, the prevalence of anal HPV infection ranges between 72% and 90%, whereas among HIV-negative MSM, the prevalence ranges from 57% to 61% [10, 11•]. Consistent with the high prevalence of anal HPV infection, HGAIN is highly pervasive among HIV-positive MSM, with a prevalence of 43% to 52% and an incidence of 49% over 4 years [12, 13]. Though less widespread, HGAIN among HIV-negative MSM is still substantial, with a prevalence of 25% and incidence of 17% over 4 years [11•, 12].

If left untreated, HGAIN has demonstrated potential for malignant transformation [14, 15]. Even with surveillance and treatment of HGAIN, malignancy can develop, especially in immunosuppressed individuals with extensive disease [16]. In HIV-positive individuals, restoration of immune function such as that afforded by highly active antiretroviral therapy (HAART) has not demonstrated

substantial benefit in reducing incidence of HGAIN or regression of existing high-grade lesions [2••, 17]. Several studies have demonstrated a higher incidence of anal cancer since the introduction of HAART compared with the pre-HAART era [1••, 18]. This may be attributable to increased survival on HAART allowing HIV-positive individuals to live with oncogenic HPV infection long enough to develop HGAIN and anal cancer.

Screening

The goal of anal cancer screening is similar to that of cervical cancer screening, namely, to identify and treat HGAIN before the development of cancer. Cytology is the primary screening tool for detection of HPV-associated disease in the anus. The cytology technique is simple and can easily be performed in the context of an office visit. Although anal cytology is typically performed by clinicians, patient self-collected anal cytology has also been evaluated. Self-collected specimens offer the advantage of convenience and privacy, are acceptable to patients, and have been used for rectal specimens to screen for other sexually transmitted diseases [19]. Though specimen adequacy rates for cytology are slightly lower for self-collected samples, sensitivity for detection of anal intraepithelial neoplasia (AIN) is comparable [11••, 20]. Samples that are inadequate because of scant cellularity may also be repeated.

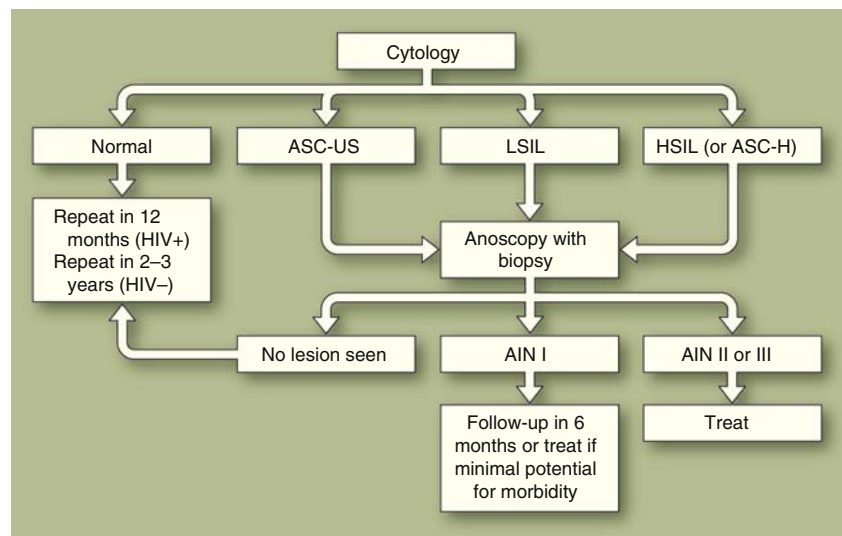
To perform cytology, a rayon or polyester swab is first moistened with tap water and then inserted blindly as far as possible, with gentle pressure and rotation until it reaches the entire rectum. Synthetic fiber swabs are preferred over cotton because cells cling to cotton, decreasing cellular

yield. The swab is then rotated 360 degrees while gentle pressure is applied to the walls of the anal canal as the swab is gradually withdrawn. The swab can then be placed in liquid cytology media or smeared on a glass slide (conventional cytology). Both liquid-based and conventional cytology are acceptable modalities with similar cellular yield and adequacy rates [21].

Anal cytology is categorized according to the Bethesda system for cervical cytology: normal, atypical squamous cells of undetermined significance—ASC-US, low-grade squamous intraepithelial lesion—LSIL, high-grade squamous intraepithelial lesion—HSIL, atypical squamous cells, cannot rule out HSIL—ASC-H [22]. Anal histology is graded according to severity; mild abnormalities are graded as AIN I, and moderate to severe abnormalities are graded as AIN II or AIN III (HGAIN). Although a cytologic diagnosis of HSIL is nearly always associated with HGAIN diagnosed on biopsy, HGAIN is also frequently associated with mildly abnormal cytologic diagnoses (ASC-US, LSIL) [23]. Therefore, we recommend that individuals with abnormal cytology findings of ASCUS or worse be referred for high-resolution anoscopy (HRA) with biopsy. Individuals with HGAIN on biopsy should subsequently be treated (Fig. 1).

If resources for HRA are limited, then cytology can be used for triage: patients with HSIL or ASC-H cytology should be prioritized for HRA, followed by patients with LSIL, and finally by those with ASC-US. Cytology can also be useful as a quality control measure for the anoscopist, because individuals with HSIL on cytology should have HGAIN on biopsy. If no AIN or only low-grade AIN is detected in an individual with HSIL cytology, we recommend repeat HRA to ensure the high-grade lesion was not missed.

Fig. 1 Protocol for screening of anal intraepithelial neoplasia (AIN). ASC-H—atypical squamous cells, cannot rule out HSIL; ASC-US—atypical squamous cells of undetermined significance; HSIL—high-grade squamous intraepithelial lesion; LSIL—low-grade squamous intraepithelial lesion



Multiple studies have examined the operating characteristics of anal cytology. The reported sensitivity to detect AIN on HRA among different high-risk populations (including HIV-positive MSM) is between 69% and 93%, with specificity ranging from 32% to 64% [24]. Among HIV-negative MSM, cytology is generally less sensitive but more specific than in HIV-positive MSM, with sensitivity reported as about 50% to 60% and specificity of 76% to 84% [11••, 25]. The predictive value of cytology can be improved through repeated testing; in a large, prospective, cohort study by Palefsky et al. [26], the positive predictive value of cytology improved from 38% to 78% and the negative predictive value improved from 46% to 79% after consecutive testing for 2 years.

Although cervical HPV testing is regularly used as an adjunct to triage women with mildly abnormal cervical cytology test results, the role of anal HPV testing as an adjunct to anal cytology is unclear. Based on limited data, it appears that in HIV-positive MSM, using HPV testing as an adjunct to cytology for detection of HGAIN is highly sensitive but has poor specificity and poor positive predictive value [27]. HPV testing may be more useful in HIV-negative MSM, because the presence of oncogenic HPV infection, especially HPV-16, is highly specific for HGAIN on biopsy [25•]. HPV testing may also be useful among populations with a lower prevalence of anal HPV infection than HIV-positive MSM (eg, HIV-negative MSM) for its negative predictive value.

Because of the high prevalence of AIN in certain populations, some researchers have advocated foregoing cytology and using HRA as a primary screening test. This consideration is reasonable, given that a single negative cytology result has a poor negative predictive value in populations with a high prevalence of disease (eg, HIV-positive MSM). However, given the insufficient availability of HRA, we believe that use of cytology to triage individuals to HRA and biopsy is the appropriate approach to AIN or anal cancer screening in most settings.

Currently, no national consensus exists on an optimal method and frequency for anal cancer screening. Guidelines from the Centers for Disease Control and Prevention acknowledge that cytology is used by many experts to screen for AIN in HIV-positive individuals [28••]. Screening HIV-positive MSM annually and screening HIV-negative MSM every 2 years appears to be cost-effective, with a cost of about \$16,000 per quality-adjusted life year (QALY) saved; this is comparable to other commonly used preventive health measures [29, 30]. However, modeling studies conducted under different assumptions in the United Kingdom demonstrate much higher costs per QALY for MSM, thus the issue of cost efficacy must be analyzed separately in health care systems where screening may be used [31].

An important caveat regarding our recommendation for anal cytology screening is that screening should only be instituted if treatment is available for individuals with HGAIN. If expertise is not available to perform HRA and treat HGAIN, then, at a minimum, high-risk patients should receive an annual digital rectal exam (DRE) to feel for masses in the anal canal. Although no data exist on the performance of DRE in detecting anal cancer, DRE is easy to perform and offers the potential benefit of detecting anal cancers at an early and treatable stage.

Diagnosis

HRA is typically performed in an outpatient setting using techniques similar to those of cervical colposcopy. After insertion of an anoscope and the application of 3% acetic acid with or without Lugol's iodine, the transformation zone between rectal columnar and anal squamous epithelium, up to and including the perianal epithelium, is visualized under magnification, and abnormal areas are biopsied. Local anesthesia is usually not required to perform biopsy unless the lesion is perianal or close to the anal verge.

Although HRA-guided biopsy is the gold standard for diagnosis of HGAIN, like cervical colposcopy, the performance of HRA as a diagnostic test is dependent on operator ability to visualize and properly perform biopsy of lesions. In our experience, a significant and lengthy learning curve exists for developing competence in HRA. No large studies have been conducted on the magnitude of interobserver variability associated with this technique.

Our institution is committed to addressing the current shortage of HRA providers by educating and training providers in HRA techniques. Courses in HRA are provided by clinician-investigators from our institution in collaboration with American Society of Colposcopy and Cervical Pathology. HRA can be performed by any clinician who cares for at-risk patients, including advance practice clinicians, primary care and specialist physicians (ie, dermatology, infectious disease, oncology), and surgeons. Clinicians may also receive advanced training and experience at the University of California San Francisco Anal Neoplasia Clinic.

Current Treatment Modalities

AIN treatment can be challenging because recurrence after treatment and development of metachronous lesions (concurrent separate lesions) is common. There are no randomized controlled trials of AIN treatments to inform treatment recommendations, thus selection of treatment modality is

directed not only by the extent and location of disease but also by available expertise and resources. Treatment of AIN generally falls into three categories: local treatment with clinician or patient-applied creams and liquids, clinician-applied ablative techniques such as electrocautery, carbon dioxide (CO₂) laser, infrared coagulation (IRC; Redfield Corporation, Rochelle Park, NJ), and surgery. The advantages and disadvantages of these approaches are listed in Table 1. Although complications are uncommon, patients should be counseled that ablative and surgical therapies may be associated with side effects such as painful defecation, abscess formation, anal stenosis, incontinence, and scarring/disfigurement.

We generally recommend treatment for HGAIN except in situations of extensive circumferential disease where morbidity from treatment may outweigh benefit. One treatment approach under study for diffuse disease includes use of 5-fluorouracil cream to reduce the extent of disease, which may then lend itself to focal therapy with IRC [32]. Extensive disease that includes both HGAIN and low-grade AIN (LGAIN) can be addressed by focusing treatment on areas of HGAIN. Extensive HGAIN is more common and more difficult to eradicate in HIV-positive MSM, but successful treatment is possible with use of surgery followed by IRC [33••]. Although the malignant potential of LGAIN (AIN I) is unknown, AIN I has the potential to

Table 1 Treatments for perianal and intra-anal intraepithelial neoplasia

Treatment modality	Efficacy data	Advantages	Disadvantages
<i>Topical treatments</i>			
85% trichloroacetic acid (TCA)	X	Inexpensive Office-based pain usually shortlived and relatively mild	May lead to scarring Multiple visits may be needed More effective for limited disease
Liquid nitrogen		Inexpensive Office-based pain usually shortlived and relatively mild	May lead to scarring Multiple visits may be needed More effective for limited disease
Imiquimod	X	Patient-applied	Pain/irritation Multiple visits may be needed Patients may miss small lesions May be less efficacious in HIV-positive individuals Approved only for perianal lesions Approved only for condyloma
<i>Ablative therapies</i>			
Infrared coagulation	X	Office-based Can treat extensive disease	Pain Bleeding Infection
Electrocautery		May be office-based Inexpensive	Pain Bleeding Infection
CO ₂ laser	X	May be office-based Can treat extensive disease	Pain Bleeding Infection Generates smoke “plume” that requires evacuation
Surgical excision		Used to treat extensive disease	Requires surgical setting Pain Bleeding Infection Relatively expensive compared with other therapies

X—Designates therapy shown to be potentially effective in retrospective studies or open-label trials.

progress to HGAIN [12]. Therefore, if treatment for HGAIN is undertaken, it is advisable to treat adjacent LGAIN as well if the lesions can be treated without excessive morbidity. In addition, it is appropriate to treat individuals with LGAIN who manifest symptoms such as pain or pruritus.

For small lesions (<1 cm²) located in the perianal or intra-anal region, there are several topical treatment options. Multiple treatment sessions are often necessary, but these therapies are generally well tolerated. Trichloroacetic acid was effective in treating intra-anal HGAIN in a small series of HIV-positive and HIV-negative MSM and appeared most effective in individuals with limited disease (fewer than two lesions) [34•]. Perianal and intra-anal disease can also be treated with liquid nitrogen. Imiquimod has also been used in small open-label studies in Europe and shows promise for treatment of intra-anal HGAIN [35]. In long-term follow-up (30 months) 14 of 19 (74%) treated patients remained clear of AIN at the originally treated site, whereas 4 of 19 developed recurrence of HGAIN at the original site and more than 50% developed HGAIN at a different site [36•]. Although encouraging, these results have not been successfully replicated by North American groups and further study is needed.

For larger lesions, ablative therapies including IRC, CO₂ laser, and electrocautery are usually warranted. IRC is an office-based procedure and offers an advantage over electrocautery because no smoke is created. Several retrospective studies and a phase 1 safety study indicate that IRC is well tolerated and is about 65% effective at treating an individual HGAIN lesion in HIV-positive MSM, with even better efficacy (81% for a single lesion) in HIV-negative MSM [37, 38•, 39]. One retrospective study conducted primarily in MSM used CO₂ laser alone or in combination with surgical excision and/or imiquimod and found that 65% of patients were completely disease free at 12 months [40]. Because of the use of multiple treatment modalities, it is difficult to infer the independent effect of CO₂ laser. No published studies have described the efficacy of electrocautery.

Surgical destruction is usually reserved for individuals with extensive disease who require an examination under anesthesia and multiple biopsies to rule out invasive cancer. In a large retrospective study of surgical treatment followed by repeated office-based procedures to treat recurrent disease, a high resolution rate at 36 months was achieved (86%) [33••].

Follow-up and Surveillance after Treatment

No consensus exists about optimal frequency of follow-up and surveillance after treatment of AIN with surgical or

ablative techniques. At our institution, individuals are seen for repeat anosopic evaluation as soon as they are able to tolerate examination, typically within 2 months post-treatment. If further small pockets of disease are found, they can often be treated topically as described above. If no further evidence of disease is found, the patient can then return for HRA in 6 to 12 months.

For individuals with untreated HGAIN (eg, patients with contraindications to treatment or disease too extensive to treat), we recommend close monitoring with repeat clinical evaluation and HRA every 3 to 4 months to search for any signs of progression to cancer (eg, pain, bleeding, ulceration). Frequent evaluation is imperative so that if anal cancer occurs, it is detected at an early and highly curable stage.

The Promise of Prevention

Given that at a large majority of anal cancers are attributable to HPV-16 (~72%), the implications are enormous for HPV vaccination as a primary prevention tool to prevent AIN and anal cancer [7•]. The quadrivalent vaccine against HPV types 6, 11, 16, and 18 was demonstrated to be safe and effective in preventing genital warts and persistent HPV infection in males as well as preventing cervical and genital cancer precursor lesions in females [41, 42]. Data regarding vaccine efficacy to prevent AIN are forthcoming. Currently, the vaccine is licensed for males between the ages of 9 and 26 years for the prevention of warts. Though the efficacy of the vaccine against persistent HPV infection implies that it would also be effective at preventing anal cancers attributable to HPV 16 and 18, the vaccine's efficacy against AIN and anal cancer will depend on the timing of vaccination and the levels of penetration achieved in the target population of MSM. If only low levels of vaccination are achieved or vaccination primarily occurs after the acquisition of anal HPV, then the vaccine may not have a great impact on anal cancer incidence in MSM.

Although the recent licensure of the quadrivalent HPV vaccine for boys heralds an era of opportunity for prevention of anal cancer in MSM, numerous challenges may prevent the vaccine from achieving high levels of penetration in the male population. First, the vaccine is costly, and cost-efficacy studies have suggested that vaccination of males to prevent cervical cancer in females would not be cost efficient if high levels of coverage were achieved in the female population [43]. As of 2008, vaccination coverage in the US female population ranging in age from 13 to 17 years (37% received ≥ one dose, 18% received all three doses) is much lower than that used in the above cost-efficacy model, so vaccination of males is likely more cost-effective than current estimates suggest [44]. Furthermore, these analyses did not take into account the

vaccine's potential impact on anal cancer among MSM, a factor that should be considered in deciding whether vaccination of males is warranted. Another issue is that the vaccine is most effective in HPV-naïve individuals, so that ideally males should be targeted for vaccination prior to sexual debut. Identifying young MSM at risk for anal cancer prior to sexual debut would be challenging, if not impossible. Therefore, if the HPV vaccine is to be effective in decreasing anal cancer in MSM, universal vaccination of preadolescent males would likely be necessary.

Conclusions

Of foremost interest for future study is whether detection and treatment of HGAIN ultimately reduces anal cancer incidence. A randomized, controlled trial would provide definitive evidence for the efficacy of anal cancer screening. Anal HPV infection may also have public health implications beyond anal cancer because recent data have demonstrated that infection with multiple HPV types is independently associated with acquisition of HIV infection among MSM [45]. A link between sexually transmitted infections and increased susceptibility to HIV infection has been established over the past decade; however, interventions to treat or prevent sexually transmitted infections to reduce HIV acquisition have generally been disappointing [46]. The possible role that anal HPV infection might play in HIV acquisition certainly warrants further investigation, especially given the availability of a highly efficacious vaccine against HPV infection.

Disclosure No potential conflict of interest relevant to this article was reported.

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