Published in final edited form as:

Curr Opin Oncol. 2009 September ; 21(5): 433–438. doi:10.1097/CCO.0b013e32832f511a.

Anal cancer prevention in HIV-positive men and women

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Abstract

Purpose of review—The incidence of human papillomavirus (HPV)-associated anal cancer is unacceptably high among HIV-positive men who have sex with men (MSM) and possibly in HIV-positive women. Unlike most other malignancies occurring in the HIV-positive population, anal cancer is potentially preventable, using methods similar to those used to prevent cervical cancer in women. This review discusses the issues around screening to prevent anal cancer.

Recent findings—Recent reports show that the incidence of anal cancer has increased since the introduction of highly active antiretroviral therapy (HAART) in this population and now exceeds the highest incidence of cervical cancer among women reported anywhere in the world.

Summary—The high incidence of anal cancer among HIV-positive individuals must not be ignored, since it may be preventable. Given the current evidence and analogy with cervical cancer prevention model, many clinicians believe that identification and treatment of HGAIN to prevent anal cancer are warranted. Where the expertise to do so exists, this is a reasonable approach, particularly if coupled with efforts to optimize further screening and treatment approaches, as well as efforts to document the efficacy of HGAIN treatment to reduce the incidence of anal cancer.

Keywords

Anal cancer; human papillomavirus; anal intraepithelial neoplasia; cancer prevention; screening; HIV

1) Introduction

In the last few decades the incidence of cervical cancer has declined with the introduction of cervical cytology screening to identify women with the cervical cancer precursor lesion, high-grade cervical intraepithelial neoplasia (CIN), or CIN 2-3, particularly CIN 3. Ablation of high-grade CIN through a variety of modalities has substantially reduced the incidence of cervical cancer. Consequently, the highest incidence of cervical cancer occurs in countries where there is no routine cervical cytology screening and treatment of high-grade CIN.

Anal cancer is very similar to cervical cancer biologically, including an etiologic association with human papillomavirus (HPV) [1], and the equivalent to high-grade CIN, high-grade anal intraepithelial neoplasia (HGAIN) is known to progress to anal cancer [2]. The techniques to screen for HGAIN (anal cytology) and locate the lesion and confirm the grade

Conflict of interest: Dr. Palefsky receives grant support from Merck and Co.

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of the lesion (high resolution anoscopy (HRA)-directed biopsy) are modeled after techniques used to identify high-grade CIN [3]. Given the biological similarity between cervical and anal cancer, and CIN and AIN, it is likely, albeit unproven, that removal of HGAIN would reduce the risk of anal cancer.

HPV is the most common sexually transmitted agent, and individuals infected with the human immunodeficiency virus (HIV) have been consistently shown to have a higher prevalence of anogenital HPV infection than their healthy HIV-negative counterparts [4]. Consistent with this, the prevalence and incidence of HPV-associated CIN and AIN is higher among HIV-positive men and women, as is the incidence of anogenital cancers, including the cervix and anus.

One of the emerging questions concerning the care of HIV-positive MSM and women is whether or not they should be screened for HGAIN and treated if the lesion is identified. There is continued evidence for the lack of substantial beneficial effect of highly active antiretroviral therapy (HAART) to reduce the incidence of anogenital cancer precursor lesions, regression of existing high-grade lesions, and clearance of HPV infection itself [5]. Given the current absence of anal screening for most HIV-positive individuals, the longer survival time afforded by HAART creates the potential for the perfect storm: a high incidence and prevalence of oncogenic HPV infection and HGAIN among individuals who are living longer with increased time for potential to progress to cancer, and no routine AIN screening or treatment programs. We predicted that the incidence of anal cancer would increase among HIV-positive individuals, and three recent reports now confirm this [6-8]. Despite the potential to prevent anal cancer, with the exception of the State of New York, there are no guidelines recommending anal cytology screening in HIV-positive individuals. The primary reasons for this are the lack of evidence documenting that HGAIN treatment reduces the incidence of anal cancer, the large number of individuals who might need treatment, paucity of data on treatment modalities for HGAIN, and a limited number of clinicians with the necessary expertise. The purpose of this article is to review the issues on both sides of the anal screening debate and to describe a plan to address this increasingly important clinical issue.

2) High incidence of anal cancer among HIV-positive men who have sex with men

HAART was introduced for widespread use in 1996. Three recent reports have shown a high incidence of anal cancer among HIV-positive MSM since that time. Piketty et al showed an incidence of anal cancer from a registry in France of 75/100,000 person-years among HIV-positive MSM since 1999 [6]. D'Souza et al showed an incidence of 137/100,000 person-years among HIV-positive MSM since 1996 among men participating in the Multicenter AIDS Cohort Study [7]. Patel et al showed an incidence of 78/100,000 person-years among HIV-positive MSM from a Surveillance, Epidemiology, and End Results Program-HIV registry match in the United States since 2000 [8]. Notably, the incidence of anal cancer reported in these studies exceeds the highest reported incidence of cervical cancer anywhere in the world.

3) Screening and treatment of HGAIN to reduce the incidence of anal cancer

If HGAIN can be successfully identified and treated, and if treatment of HGAIN reduces the incidence of anal cancer, then screening and treatment of HGAIN is desirable, if not imperative among high-risk individuals such as HIV-positive MSM. Other at-risk groups that could potentially benefit include HIV-positive women, HIV-positive men regardless of

sexual history, HIV-negative MSM, HIV-negative women with vulvar or cervical cancer, and men and women immunosuppressed for reasons other than HIV such as organ transplant.

Although treatment of anal cancer, chemoradiation therapy, is often successful for early stage cancers, it is also associated with substantial morbidity, including chronic proctitis with pain and bleeding. Treatment of later stage anal cancer is less successful. Clearly, prevention of anal cancer is preferable to identifying and treating cancer after it has developed. More than 15 years ago, at the University of California, San Francisco (UCSF), we established the first clinic devoted specifically to diagnose and treat HGAIN to prevent anal cancer.

The primary arguments against anal screening include: absence of data showing that treatment of HGAIN reduces the incidence of anal cancer; paucity of cost-effectiveness data on anal screening approaches; and paucity of data on the effectiveness of treatments of HGAIN to resolve these lesions. Additionally a high proportion of HIV-positive individuals have HGAIN [4], and therefore a large number of HIV-positive MSM would need to be treated. The risk factors for progression to invasive cancer are not known, and some individuals with HGAIN may undergo unnecessary treatment. More information on biomarkers to predict progression to cancer is clearly needed.

There are potential adverse effects associated with HGAIN treatments, as well as costs associated with the procedures and the required office follow-up visits. There is an inadequate number of clinicians trained to provide these services. There is also a limited number of surgeons trained to diagnose and treat HGAIN for those patients who require surgical referral.

4) Current screening approaches for HGAIN

The primary screening tool for HPV-associated diseases is cytology, in which the cervical or anal epithelium is scraped and the cells are placed on a slide for cytopathologic examination. The cervical cytology grading system used in the United States is the Bethesda 2001 system [9] and the terminology for anal cytology and histology is based on that of cervical disease [10]. Treatment decisions are based on histology and not cytology grade. If screening is performed, individuals with an abnormal anal cytology should be referred for HRA and anal biopsy, with treatment decisions based on the grade of the lesion on histology.

Like the cervical cytology screening program, an anal cytology screening program should be focused on cancer prevention, not cancer detection. Anal cytology and HRA-guided biopsy are therefore primarily aimed at identifying HGAIN. Cancer detection is critical as well, and in addition to anal cytology, we strongly recommend an annual digital rectal exam (DRE) among HIV-positive individuals to feel for anal cancers with the goal of identify these cancers at a treatable stage. This is important since DRE may identify cancers missed on HRA.

It is well known that cervical cytology has variable sensitivity to detect high-grade CIN, and that the grade of cervical cytology does not necessarily accurately reflect the true grade of the lesion as determined by histology. Anal cytology is similar to cervical cytology in its performance characteristics [3]. Several studies have shown that it is more sensitive among HIV-positive individuals than HIV-negative individuals perhaps because lesions among the former are larger and/or more numerous. A high-grade anal cytology result has high predictive value of a high-grade lesion on biopsy, but HGAIN is often found in association with low-grade cytology, atypical squamous cells of undetermined significance (ASCUS) or normal cytology. For this reason, we have recommended that individuals with anal cytologic

abnormalities of any grade be referred for HRA and those with normal anal cytology be re-screened annually to reduce the risk of a false-negative result. A recent population-based study showed an 87% sensitivity of anal cytology to detect HGAIN among HIV-positive MSM and 55% among HIV-negative MSM [4]. Unlike cervical self-sampling which can be done for HPV infection but not cytology, anal self-sampling for cytology was non-inferior to clinician-collected samples. Although additional validation studies are needed, these data indicate that anal cytology self-sampling may be a viable alternative to clinician sampling, particularly in settings where access to clinicians to perform the sampling is limited.

5) High resolution anoscopy-guided biopsy

A separate but important set of challenges includes the paucity of clinicians trained to perform the next step in the evaluation, HRA with biopsy of visible lesions, the time required to achieve competence in HRA and the shortage of highly-skilled HRA practitioners available to train others. Development of HRA competency is at least as challenging as for cervical colposcopy and takes time, experience and commitment. Combined with the potentially very large pool of individuals who would need HRA if screened with cytology, access to HRA is therefore currently very limited in most areas, including those with a high concentration of HIV-positive MSM. This alone may constitute a valid reason not to screen, since in the opinion of the author it is unethical to screen an individual with anal cytology in the absence of a viable plan to perform a complete evaluation of an abnormal specimen. For such individuals, at a minimum, we strongly recommend an annual DRE to detect anal cancers.

A better approach to addressing the shortage of HRA-trained clinicians is to train more providers skilled in HRA. In collaboration with the American Society for Cervical Colposcopy and Pathology, the UCSF group and others teach a course on HRA, complemented by training at the UCSF Anal Neoplasia Clinic.

Given the very high prevalence of abnormal cytology among HIV-positive MSM, one might consider eliminating the cytology screening step and performing HRA on all such individuals. Although theoretically desirable, such an approach is not practical given the shortage of HRA resources. Instead, providers may consider prioritizing their HRA referrals according to the grade of cytology, with the highest priority accorded to those with high-grade disease, followed by those with low-grade disease or ASCUS. Those with normal cytology could be re-screened in a year.

Performance of anal biopsy is a key step in the evaluation since treatment is based on histologic grade. Adequate biopsying depends on the skill of the HRA clinician to identify HGAIN visually, including the use of 3% acetic acid and Lugol's iodine. Biopsy forceps and the size of the biopsy should be small to avoid complications such as hemorrhage and infection. Performed properly, anal biopsy is well tolerated by patients and safe with a low complication rate.

6) Current treatment approaches for HGAIN

Treatment of high-grade CIN in the developed world is primarily based on the loop electroexcision procedure (LEEP) in which a cone of cervical tissue containing the lesion is removed using an electric wire. In developing countries where LEEP is not as readily available, cryotherapy is often used. Although these techniques are highly effective to treat the lesions, treatment failure is observed more commonly among HIV-positive women than among healthy HIV-negative women.

Treatment of HGAIN has several challenges beyond those known for treatment of high-grade CIN. Ablation of cervical tissue may have several possible adverse effects, including pain, bleeding, cervical stenosis and cervical incompetence. Ablation of tissue in the anal canal and perianal area may have complications as well including pain on bowel movements, bleeding, abscess formation, anal stenosis, incontinence, and esthetic changes. Fortunately, each of the above is rare if performed properly. Opponents of anal screening point to two key areas of inadequate information: lack of data showing the efficacy of different HGAIN treatment techniques to successfully remove the lesion; and lack of data showing the successful removal of HGAIN reduces the risk of anal cancer.

Identification of HGAIN with the goal of preventing anal cancer is a relatively new practice. Data on various HGAIN treatments are indeed limited and there are no randomized controlled trials reported. However, the corpus of knowledge is growing. Treatment for HGAIN generally falls into 3 categories: 1) Local treatment with clinician- or patient-applied creams or liquids; 2) Clinician-applied ablative techniques such as electrocautery, laser or infra-red coagulation (IRC); and 3) surgery. Advantages and disadvantages of these approaches are listed in Table 1.

One of the first-line therapies used by some clinicians is 85% trichloroacetic acid (TCA). Recent data suggest that this approach is most effective for individuals with a limited amount of disease [11]. Perianal disease and some intra-anal lesions may also be treated with liquid nitrogen. Both of these approaches usually require multiple applications. Recent reports from Europe indicate that intra-anal imiquimod applied by the patient may be effective to treat intra-anal HGAIN [5, 12], but no randomized controlled studies have been reported.

Larger lesions usually require more aggressive approaches. IRC is growing in popularity because it can be performed in the office setting and does not create smoke. Large lesions that would in the past have required referral to surgery may be treated using this approach. Retrospective chart review studies and a multicenter Phase I safety study indicate that the efficacy of IRC to treat individual HGAIN lesions is about 65% within a year, with up to three treatments [13, 14]. The efficacy of laser or electrocautery has not been reported.

In clinical settings where IRC is available, surgery is reserved for treating those with the most extensive disease, those who require an examination under anesthesia to allow for biopsies large enough to definitely exclude invasive cancer, or rarely, treatment of complications of office procedures such as bleeding or infection. When performed in conjunction with HRA, surgery is effective to treat HGAIN in a retrospective chart review [15].

Taken together, while there are few data from randomized controlled trials, methods to treat HGAIN may be effective to treat individual HGAIN lesions in most patients. Problems include treatment failure in some patients as has been noted in HIV-positive women treated for CIN, and development of metachronous lesions, i.e., newly detected lesions in areas other than those under active treatment. The recurrence rate for treated lesions may also be high, and further information is needed as to whether recurrent disease has the same risk of progression to cancer as the original lesion.

Even more challenging is the issue of documenting the efficacy of HGAIN treatment to reduce the incidence of anal cancer. A randomized controlled trial (RCT) to document that treatment of CIN reduces the incidence of cervical cancer was never performed; the efficacy of cervical screening and treatment was only determined after decades of observing declining cervical cancer incidence in regions where screening had been implemented. However, we currently live in the era of evidence-based medicine and many policy-

makers believe that anal screening should not be routinely implemented until the highest levels of evidence of efficacy have been obtained. Such a study, while not impossible will be expensive and time-consuming. It will require the agreement of participants to be randomized to an observation-only study arm in which some may develop invasive cancer. In the opinion of the author, this study should be done if a successful outcome will lead to the adoption of routine screening for at-risk patients, and if follow-up in the observation arm is performed carefully enough to minimize the risk of serious risk of morbidity or mortality due to the development of cancer. To achieve equipoise in an RCT, participants in an observation-only arm will need to be at lower risk of morbidity and mortality than if they were receiving current standard of care, which typically does not include screening of any kind. Ethical issues will therefore need to be addressed and a high level of community support will be required.

7) Conclusion

Regardless of where one stands on the screening debate, it is clear that it is not an option to do nothing. In the opinion of the author, the lack of evidence that HGAIN reduces the incidence of anal cancer does not mean that clinicians should passively wait for their patients to present with invasive anal cancer. Although there are no studies on the performance of DRE to detect anal cancer, given the ease of performing this technique, at a minimum all at-risk individuals should have this procedure annually, followed by referral to a skilled clinician if there is suspicion of a tumor. In clinical settings where the entire range of skills needed to assess and treat patients for HGAIN is available- cytology, pathology, HRA, office-based treatment, and surgery-the likelihood that that screening and treatment of HGAIN will be beneficial is high enough that at-risk patients should be screened. Studies should be performed in these settings to optimize anal cytology screening procedures and RCTs of different treatment approaches should be performed.

The large RCT to demonstrate efficacy of HGAIN treatment to reduce anal cancer should be implemented as soon as possible. In addition to providing critical information on efficacy to reduce progression to cancer, a RCT to prevent anal cancer may provide a unique opportunity to identify biomarkers of progression to invasive cancer, hopefully reducing the need to treat a large number of individuals. Given the biological similarity of anal and cervical cancer, it is likely that data collected in this RCT will be informative for that disease as well. Since it is currently the standard of care to treat high-grade CIN to prevent cervical cancer, this may be our only remaining opportunity to collect data on biomarkers of progression of HPV-associated high-grade precursors to invasive cancer.

Finally, most anal cancers are associated with HPV 16. HPV vaccination has been shown to be highly effective to prevent HPV 16 infection and HPV16-associated CIN in women [16, 17]. Data are beginning to emerge on the efficacy of HPV vaccination to prevent HPV infection and associated lesions in males. If effective to reduce anal HPV infection and AIN in MSM, vaccination of males may greatly reduce the incidence of anal cancer in the future. The impact of preventing anal cancer among MSM must be considered by policy-makers when evaluating male HPV vaccination in general. In many individuals, HPV infection will be acquired before HIV infection, but given the high risk of anal cancer in HIV-positive individuals, studies among HIV-positive MSM should also be performed to assess vaccine safety and efficacy.

Acknowledgments

Supported by R01CA 88739, M01 RR00079 and the American Cancer Society.

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Table 1

Treatment of anal condyloma and anal intraepithelial neoplasia

Treatment modality	Indications				Advantages	Disadvantages
	Perianal condyloma	Perianal AIN 2-3	Intra-anal condyloma	Intra-anal AIN 2-3		
Topical treatments						
Liquid nitrogen	x	x	x		Inexpensive Office-based	Pain May lead to scarring Multiple office visits may be needed More effective for limited disease
85% trichloroacetic acid	x	x**	x	x**	Inexpensive Office-based	Pain May lead to scarring Multiple office visits may be needed More effective for limited disease
Podophyllotoxin	x*				Patient-applied	Pain/irritation Multiple office visits may be needed Patients may miss small lesions
Sinecatechins	x*				Patient-applied	Pain/irritation Multiple office visits may be needed Patients may miss small lesions
Imiquimod	x*	x**	x**	x**	Patient- applied	Pain/irritation Multiple office visits may be needed Patients may miss small lesions May be less effective in men than women May be less effective in HIV-positive individuals
Infra-red coagulation	x*	x**	x*	x**	Office-based May be used to treat extensive disease Relatively inexpensive	Pain Bleeding Infection
Electrocautery	x	x	x	x	May be office-based Inexpensive	Pain Bleeding Infection
Laser	x	x	x	x	May be performed in some office settings May be used to treat extensive disease	Pain Bleeding Infection
Cold scalpel excision	x	x	x	x	Used to treat extensive disease	Requires surgical setting Pain Bleeding Infection

* Food and Drug Administration-approved for this use

** Shown to be potentially effective in small open-label trials or retrospective chart reviews