

Anal Cancer Increasing among People Living with HIV

By Timothy Wilkin, MD, MPH

Why Screen for Anal Cancer in HIV-Positive Patients?

Anal cancer is emerging as a common non-AIDS defining cancer in HIV-positive people. Anal cancer, like cervical cancer, is caused by infection with high-risk types of human papillomavirus (HPV)—low risk types of the virus can cause genital and anal warts. The rate of anal cancer appears to be increasing in the era of antiretroviral therapy.¹⁻⁵ A recent analysis from Kaiser-Permanente in California estimated the rate of anal cancer among the HIV-positive population to be 174/100,000 person-years—and even higher among individuals with lower CD4+ counts—compared to 2/100,000 person-years among the HIV-negative population.⁶ This rate is significantly higher than the rate of cervical cancer before Papanicolaou (PAP) screenings became routinely performed on women (35/100,000).

Anal Cancer: Who to Screen

HIV-positive men with a history of sex with other men appear to be at highest risk for anal cancer. A study conducted by the North American AIDS Cohort Collaboration on Research and Design (NA-AACCORD) combined data from 19 cohorts of HIV positive participants and estimated the cumulative incidence of anal cancer by age 60 years to be 2.8%.⁷ Less is known about the rate of anal cancer in HIV-positive women or in men without a history of sex with other men. However, anal HPV infections are more common than cervical HPV infections among HIV-positive women.⁸ About 10% of HIV-positive women have pre-cancer of the anus.⁹ The rate of anal cancer is seven times higher for HIV-positive women compared with HIV-negative women.¹⁰ Organizations setting the standard for healthcare maintenance of HIV-infected patients have not yet adopted recommendations for routine anal cancer screening. However, the New York State AIDS Institute recommends anal cancer screening for HIV-positive men with a history of sex with other men, HIV-positive women with a history of pre-cancer of the cervix or vulva, and anyone with a history of anal or genital warts.

Anal Cancer: How to Screen

The screening protocol to prevent anal cancer is based on that for cervical cancer.¹¹ The goal of screening is to prevent invasive anal cancer by identifying and removing pre-cancerous areas of the anal skin, called high-grade anal intraepithelial neoplasia (HGAIN), before they progress to invasive cancer. The initial screening test is a PAP smear of the anus. The skin around the anus should also be examined for warts or dark patches. Patients with an abnormal PAP smear or an abnormal exam should be referred for anoscopy.

Anoscopy

High resolution anoscopy is done to identify HGAIN or warts. A lubricated plastic anoscope is inserted into the anus. A cotton swab wrapped in gauze and soaked in diluted vinegar is then inserted through the anoscope, and the anoscope is removed, leaving the gauze in place. The acetic acid reacts with the skin, making HGAIN appear white. After two minutes, the gauze is removed and the anoscope re-inserted. A colposcope (a machine used to look at the skin under magnification) is used to view the walls of the anus under magnification to look for areas of whitening consistent with HGAIN. Areas suspicious for pre-cancer are biopsied. If HGAIN is found on these biopsies, then the patient is seen for treatment of these areas.

Treatments of HGAIN

The Food and Drug Administration (FDA) has approved the infrared coagulator (IRC), a medical device that delivers controlled pulses of visible and infrared light through an applicator that is applied directly to the skin, for treatment of HGAIN. The light results in thermal coagulation to a controlled depth. Infrared coagulation of HGAIN can lead to mild to moderate post-procedural pain and bleeding for up to two weeks. Complete healing usually occurs by two to four weeks. Rare complications (occurring <1% of the time) include infection of the treated area and severe bleeding resulting in emergency room evaluation or hospital admission. Severe bleeding can occur one to two weeks after the procedure. There are no randomized clinical trial data to support the efficacy of IRC. The existing data are from retrospective reviews and one prospective single-arm clinical trial. One retrospective review of IRC in 68 HIV-positive men who have sex with men found that 72% of HGAIN lesions were

successfully treated with a single IRC treatment.¹² However, HGAIN lesions were commonly found in followup at other untreated sites resulting in approximately 60% having HGAIN after receiving one IRC treatment. Recurrent lesions were relatively common and had a similar response to a second treatment. A second study found a per-lesion cure rate of 64%.¹³ A study of 18 HIV-positive participants found that 64% of these participants were cured of HGAIN lesions at one year.¹⁴ Ten of 18 participants had post-procedural pain described as mild to moderate. Eleven participants had post-procedural bleeding: 10 described the bleeding as mild and one participant described the bleeding as moderate. Clinicians may also use cryotherapy (or freezing), trichloroacetic acid, or electrocautery to treat HGAIN. Several topical treatments, such as gels and creams, are under investigation, including 5-fluorouracil (a chemotherapy cream), imiquimod (a cream used to treat warts), and cidofovir (a drug used to treat cytomegalovirus infections).

Should HGAIN progress to anal cancer, the standard treatment is a combination of chemotherapy and radiation therapy, which is associated with significant morbidity. Many clinicians believe that anal cancer is a reasonable target for a cancer prevention strategy.

Options for preventing HGAIN

The HPV vaccination is a promising prevention tool that prevents against the 4 types of HPV that cause the majority of genital warts and cervical cancer. The Merck quadrivalent HPV vaccine was studied in a large clinical trial of young HIV-positive men and showed that the vaccine prevented genital warts in participants.¹⁵ The trial also included a substudy of young men who have sex with men and was shown to prevent anal infection of HPV in these participants.¹⁶ The AIDS Malignancy Consortium presented data on the safety and immunogenicity of the quadrivalent vaccine in HIV-positive men.¹⁷ They found that the vaccine was safe and elicited a strong antibody response to each of the four HPV types. The Merck quadrivalent HPV vaccine is FDA approved for prevention of cervical cancer in females age 9–26. The vaccine protects against two low-risk HPV types that cause 90% of warts and two high-risk HPV types that cause 70% of cervical cancers. Similarly, the FDA has approved this vaccine for males age 9–26 to prevent genital warts. The studies discussed above suggest that HPV vaccination in HIV-positive men and women will prevent anal HPV infections and associated anal cancer. However, most HIV-positive patients are older than 26 and have current or past HPV infections. It is not clear how much benefit the vaccine will yield in this population. HPV vaccination does not remove the need for cancer screening as anal cancer can be caused by HPV types not prevented by the vaccine. Another prevention option to be considered is consistent use of condoms. Although condoms are not 100% effective in preventing new HPV infections, they have been shown to be partially effective. A randomized clinical trial of monogamous heterosexual couples with HPV infection found that couples that used condoms consistently had faster clearance of HPV infection and HPV-related lesions.^{18,19}

Major Challenges in Implementing Anal Cancer Screening

Accessing anoscopy and treatment for HGAIN.

Over half of HIV-positive men who have sex with men and 20% to 30% of HIV-positive women will have abnormal anal cytology and require referral for anoscopy. It is preferable to perform anoscopy at a clinic that is prepared for a large number of clinical referrals. Unfortunately, these specialized clinics are not available in many places or the available clinics cannot accommodate the clinical need. Thus, many clinics and medical practices are developing the infrastructure to offer anoscopy within their clinics. This procedure does not naturally fall under a single medical specialty. High-resolution anoscopy has been performed by general internists, infectious disease physicians, nurse practitioners, and physician assistants. Gynecologists, general or colorectal surgeons, gastroenterologists, and dermatologists also perform these procedures. Training usually begins with a course in cervical colposcopy by the American Society of Colposcopy and Cervical Pathology (ASCCP). The ASCCP also offers training in high-resolution anoscopy. It is helpful for medical practitioners to observe the procedure in clinical practice, and then perform the procedure with in-clinic supervision.

Lack of awareness regarding HPV and anal cancer. Many patients have little or no knowledge about HPV and anal cancer. It is important to help the patient understand the rationale for screening, existing gaps in knowledge, and the possible need for invasive procedures. Patients should make informed decisions before being screened for anal cancer. Timothy Wilkin, MD, MPH, is an Associate Professor of Medicine at Weill Cornell Medical College. *Portions of this article were previously featured in Medscape Today, on April 22, 2010. For a full list of references, please visit: gmhc.org/research/