Screening HIV-Infected Men for Anal Dysplasia and Cancer: Are Practice Guidelines Needed?

LACEY L. SIEKAS, DNP, ARNP

From Virginia Mason Medical Center, Seattle, Washington

Author's disclosures of potential conflicts of interest are found at the end of this article.

Correspondence to: Lacey L. Siekas, DNP, ARNP, Anal Dysplasia Clinic, Virginia Mason Medical Center, 1100 Ninth Avenue, PO Box 900, C3-GAS, Seattle, WA 98111.
E-mail: laceysiekas@mac.com

Abstract

Human immunodeficiency virus (HIV)-infected men who have sex with men (MSM) have an increased risk of developing squamous cell carcinoma of the anus (SCCA) and precancerous anal dysplasia. Anal cancer precursor lesions may develop due to infection with high-risk strains of human papillomavirus (HPV) combined with the near-normal lifespan afforded by advancements in HIV care. No clinical practice guidelines currently exist for anal dysplasia or cancer screening in this high-risk population. The objective of this study was to determine if current knowledge and evidence support the creation of clinical practice guidelines for screening HIV-infected MSM for SCCA and anal dysplasia. A literature review of evidence for screening combined with a retrospective chart review of the first 212 HIV-infected males evaluated within a Seattle-based anal dysplasia clinic was undertaken. The purpose was to review incidence of SCCA and precursor lesions identified using digital rectal examination and anal cytology in combination with high-resolution anoscopy (HRA) within the author's clinic. Patient characteristics were examined to see if factors correlated with these diagnoses. Although results from the anal dysplasia clinic are compelling for early diagnosis of SCCA and anal dysplasia in HIV-infected MSM, additional research investigating the clinical efficacy and cost-effectiveness of anal cytology combined with HRA and targeted biopsy is needed. A review of the literature did not contain recommendations for screening guidelines for the HIV-infected MSM population.

J Adv Pract Oncol 2011;2:308–313

Anal dysplasia is the presence of premalignant changes in cells of the anal canal extending from the transitional zone of the squamocolumnar junction between the rectum and the anus as well as perianal tissue. Dysplastic cellular changes are triggered by persistent infection with high-risk strains of human papillomavirus (HPV), which are known to be responsible for nearly all cases of cervical cancer and squamous cell carcinoma of the anus (SCCA; Cranston et al., 2007; Hoots, Palefsky, Pimenta, & Smith, 2009). Anal cancer disproportionally affects HIV-infected men who have sex with men (MSM) at a rate of 70–137:100,000, compared to rates of 1:100,000 in HIV-seronegative persons (Chiao, Giordano, Palefsky,

Tyring, & El Serag, 2006; D'Souza et al., 2008; Blackwell, 2008). Diagnosis of anal dysplasia and SCCA can be made with digital rectal examination (DRE) and evaluation with anogenital colposcopy or high-resolution anoscopy (HRA) with clinician-directed biopsies of colposcopically identified abnormal tissue. Patients who receive a diagnosis of local disease have improved 5-year survival predictions compared to those diagnosed with regional disease, hence the recommendation for screening and possibly treatment of anal dysplasia to prevent anal cancer in this high-risk population (Chiao et al., 2006).

Persons with HIV are living near-normal life spans with the advent of antiretroviral therapy (ART). This in turn causes prolonged exposure to HPV, the dysplastic effects of which are predicted to increase rates of SCCA (Fagan et al., 2005; D'Souza et al., 2008). The use of ART and subsequent reconstitution of the immune system has not been shown to regress these precancerous anal lesions or prevent their progression to SCCA (Piketty et al., 2004; 2008). Given rising numbers of HIV-infected individuals, the need for appropriate and effective screening will be increasing. There are currently no formal recommendations or clinical practice guidelines regarding screening for anal dysplasia and SCCA in HIV-infected individuals. Compounding this problem is the fact that there are few national centers and specially trained providers capable of providing access for anal dysplasia screening and treatment. The purpose of this article is to determine whether current literature and evidence support the creation of clinical practice guidelines for screening HIV-infected MSM for SCCA and anal dysplasia.

Literature Review

A review of the literature pertaining to anal cancer and anal dysplasia screening was performed using evidence-based databases on Ovid, including the Cochrane reviews. The search was limited to works in the English language using the following terms: *anal dysplasia*, *anal intraepithelial neoplasia*, *HIV*, and *anal cancer screening*. Using the search term *anal cancer* in the Ovid combined evidence-based database yielded 27 reviews. The abstracts and full text (when available) were extensively reviewed, but were deemed inappropriate as they did not consider high-risk individuals such as the HIV-infected population and were aimed at reviewing treatment recommendations for invasive SCCA rather than anal dysplasia. Surprisingly, none of these reviews made any mention or endorsement of screening techniques or diagnostic evaluation with anal cytology or HRA. Within these reviews there were no recommendations for SCCA screening, including digital rectal exam.

Abstracts and full-text articles were reviewed to confirm whether they specifically addressed both HIV-infected individuals and the issue of screening. These search terms yielded two relevant results. One source was a systematic review of screening for anal cancer precursor lesions or anal dysplasia in HIV-infected men (Chiao et al., 2006). This review identified 63 original articles evaluating anal cytology screening. It was disappointing to note that there was no discussion regarding methods for the evaluation of an abnormal anal cytology, such as HRA or surgical biopsy. The author did not identify any randomized or cohort studies determining if there were any favorable survival or outcome data pertaining to SCCA, screening with anal cytology, or anal dysplasia treatment. Increased risk of SCCA-related morbidity and mortality was noted to be substantial in the HIV-infected individuals discussed in this review.

The Chiao et al. systematic review article's relevance to anal dysplasia screening guidelines is limited. The authors reviewed 63 original articles detailing original data on HIV-infected individuals (men and women), using anal cytology for screening for anal dysplasia with the intent to determine if this technique should be considered a recommendation for screening. The primary limitation of the article is that it assessed anal cytology only and not HRA, after other studies have demonstrated the inaccuracy of cytology compared to HRA (D'Souza et al., 2008; Panther et al., 2004). Chiao et al. confirm the existing knowledge and practice that anal cytology is limited in its ability to identify anal cancer in high-risk populations. Admittedly, the authors contend that additional research in the form of prospective randomized clinical trials is needed before consensus regarding anal cytology can be obtained.

The remaining source evaluated the efficacy and cost-effectiveness of screening HIV-infected men for anal dysplasia using only anal cytology based on the successful paradigm of cervical can-

cer and cervical Pap cytology (Goldie et al., 1999). The utility of both the Chiao et al. and Goldie et al. articles is limited, however, as there have been several subsequent research articles indicating that while anal cytology maybe cost-effective, it is less accurate for screening for anal dysplasia and SCCA compared to histologic findings on HRA (Panther et al., 2004; Cranston et al., 2007). Additionally, the Chiao et al. review notes low rates of compliance and follow-up with anal cytology (2006).

Using PubMED to perform a search with the terms *anal dysplasia*, *HIV*, and *screening*—and limiting to English language articles and those published within the last 5 years—yielded 111 results. Reviewing these nearly exclusively original articles identified that the majority described the incidence of anal dysplasia and SCCA as well as the link between coinfection with HIV and specific HPV strains (Abramowitz et al., 2008). Additionally, these articles reported colposcopic findings on HRA and outcomes of treatment of high-grade anal intraepithelial neoplasia (HGAIN) with an infrared coagulator (Goldstone, Kawalek, & Huyett, 2005), and discussed the sensitivity and specificity of anal cytology in screening for these conditions (Cranston et al., 2007). There were no articles specifically recommending a strategy for anal dysplasia or anal cancer screening in HIV-infected individuals. Most of the data came from well-established anal dysplasia centers in Boston, New York City, and San Francisco.

With consideration to the broad evidence search pertaining to anal dysplasia, the evidence stems nearly exclusively from primary or original research publications of clinical case reports describing the phenomena of increasing diagnosis and incidence of anal cancer, investigation of interventions for treatment, and review of anal dysplasia clinic experiences since the early 1990s. To date there are no randomized controlled clinical trials for diagnosis or screening with either anal cytology or HRA. However, it appears that HIV-infected populations are fairly homogeneous, as reported incidence of anal dysplasia and SCCA is stable in various anal dysplasia clinics across the United States, including the clinic administered by the author (Siekas & Aboulafia, 2009). Additionally, there are several descriptive epidemiologic studies identifying the association and implications of HIV and HPV coinfection and the lack of impact of ART on this disease process (Piketty et al., 2004; D'Souza et al., 2008).

In summary, the literature-based evidence for anal dysplasia is extensive and overall of high quality. This literature is strong in terms of defining the incidence of anal dysplasia and SCCA in HIV-infected individuals, the utility and limitations of anal cytology, the link between anal dysplasia and HPV infection, and the unfortunate evidence that suggests ART therapy does not impact the incidence or progression of anal dysplasia. Evaluation of the literature pertaining to invasive SCCA in the non–HIV-infected population was not helpful for screening purposes in the HIV-infected population, but the literature is sufficiently in depth for treatment considerations. Unfortunately, significant gaps in the literature for recommending screening and treatment of anal dysplasia in HIV-infected individuals remain (Nathan, Hicky, Mayuranathan, Vowler, & Singh, 2008). Whether this gap can be closed with further intensive evaluation of the existing literature or creation of new knowledge is the focus of this paper.

Methods

A retrospective chart review approved by the institutional review boards of both Virginia Mason Medical Center (VMMC) and Vanderbilt University evaluated all HIV-infected males screened within the author's anal dysplasia clinic at VMMC in Seattle from November 2007 until December 2009. A total of 212 HIV-infected male individuals aged 18 or older were included. Demographics including age, gender, ethnicity, and sexual orientation were noted. Information as to visit intervals for compliance, whether or not an individual was taking ART at the time of screening, most recent CD4+ count, HIV viral levels, results of anal cytology, and any biopsies taken during HRA were recorded into a deidentified data set. Compliance was determined by whether or not the patient returned to the anal dysplasia clinic within 1 month of the author's recommended screening interval.

Results

For the 212 HIV-infected men screened, the median age was 47 years (range, 24–83 years). Of these men, 173 (82%) were Caucasian, 14 (8%) were African-American, 15 (7%) were Hispanic,

4 (2%) were Asian, and 1 each was Native American and Middle Eastern. The vast majority (84%) indicated that they predominantly had sex with men or with both men and women, 12% did not identify their sexual preference, and only 4% identified themselves as strictly heterosexual. The median patient HIV RNA viral load was < 75 copies/mL (range, < 75–500,000 copies/mL), and the median patient CD4+ count was 509 cells/μL (range, 7–1,663 cells/μL). More than 95% of patients were receiving HAART at the time of the initial anal dysplasia screening. All individuals underwent anal dysplasia screening performed by the author to include anal cytology, DRE, and HRA with targeted biopsies of any suspicious anal lesions. All anal cytology and pathology results were reviewed by one of the two staff pathologists at VMMC.

With regard to anal cytology at the initial screening visit available for 211 of patients, 45 (21.2%) patients had a normal anal cytology, 7 (3.3%) specimens were inadequate, 39 (18.4%) had atypical cells of undetermined significance (ASCUS), 2 (1.6%) had ASCUS–cannot rule out high-grade dysplasia, 89 (42%) patients had LGAIN, and 29 (13.7%) had HGAIN suggested on their anal cytology. Concordance was strong between anal cytology and anal biopsy results for those patients identified with HGAIN findings on anal cytology assessment, accurately predicting HGAIN 92% of the time. Among the 182 patients who underwent anal biopsies during HRA, 74 (35%) patients had HGAIN and 61 (29%) had LGAIN, with the remaining biopsies being normal.

To date, 25 (11.8%) of individuals screened have progressed from either normal findings or LGAIN to HGAIN. Average time to progression from either normal findings or LGAIN to HGAIN or SCCA was 370 days (range, 99–656 days). Four individuals screened were identified to have microinvasive SCCA upon HRA or subsequent operative anal biopsy—2 of these 4 cancers developed in individuals who were being followed in the anal dysplasia clinic. The average number of visits per patient in the anal dysplasia clinic was 2.2 (range, 1–9) and the average number of biopsies per HRA was 1.4 (range, 0–6). There were no significant post-HRA biopsy complications (i.e., bleeding, pain, or infection) reported by patients to the anal dysplasia practitioner or referring medical provider. Compliance with screening intervals has been good, with an average of less than 25% of patients failing to show up for follow-up examinations during the study evaluation period.

An association was found between lower CD4+ counts and incidence of biopsy-proven HGAIN. An independent-measures one-tailed t-test was performed looking at the initial screening CD4+ counts of individuals with biopsy-proven LGAIN and biopsy-proven HGAIN. The average CD4+ count for individuals with LGAIN was 584.4 (standard deviation [SD], 333.6), and for HGAIN 438 (SD, 212.5). An alpha level of 0.01 was chosen to minimize risk of chance influencing the effect, and infinity degrees of freedom were selected for analysis. The t-statistic was statistically significant at 2.51, with Cohen's d of 0.53, suggesting at least a medium effect of CD4+ counts on dysplasia, with an effect size of 12.3%. This suggests that at least in this cohort, a lower CD4+ count is associated with higher rates of HGAIN. Unfortunately, association with SCCA cannot be determined due to small numbers of individuals within this cohort who have developed or presented with SCCA.

Only within the past 6 months has the anal dysplasia clinic been vigorously offering and screening individuals for sexually transmitted infections (STIs), specifically gonorrhea, chlamydia, herpes, and syphilis; hence the data collected thus far are incomplete. The author found that because a number of patients had been presenting to a local STI clinic for diagnosis and care, diagnostic information was not present in the chart review. Sexually transmitted infections will be monitored as the author continues in her clinic, for improved reliability and completeness of the data. This could be important information for this cohort, as a previous study suggested a link between anal dysplasia and concurrent anal coinfections (Sobhani et al., 2004).

Discussion and Recommenations

The limitations of this study include the fact that this analysis was performed retrospectively on a relatively small cohort of HIV-infected men in a single geographic area with access to an anal dysplasia clinic. However, the findings in terms of incidence of SCCA and anal dysplasia in this cohort are comparable to results in other major long-standing anal dysplasia clinics, making the findings relatively generalizable (Siekas & Abou-

lafia, 2009). Additionally, utilizing only one anal dysplasia provider and practice as well as limiting the number of pathologists reviewing both anal cytology and biopsies improved reliability.

From the results of this cohort and the lack of screening guidelines noted in the literature review, the first thing the author proposes is education of both health-care providers caring for HIV-infected individuals, as well as the individuals in this high-risk population, with regard to the risk of developing these entities as an essential prior to initiating screening HIV-infected MSM for SCCA and anal dysplasia. Advanced practitioners should discuss using safe sex practices to minimize exposure to other anal coinfections, as well as screening for and treating these coinfections when they are detected or when an individual suspects possible exposure (Sobhani et al., 2004). Additionally, instructing at-risk individuals in the signs and symptoms of anal cancer is important. This may help patients feel empowered in their own health care, leading to individuals seeking care rapidly and appropriately if symptoms arise.

Based on the author's anal dysplasia practice and cohort experience, the suggested guidelines for screening HIV-infected MSM are as follows: Anal cancer screening should be recommended to all HIV-infected MSM as part of routine HIV care. Acknowledging that access to high-volume anal dysplasia centers is severely regionally limited is necessary. In light of that limitation, providers should offer SCCA screening to all patients, review contributing factors (unprotected sexual activity, high number of sexual partners, tobacco abuse, noncompliance with HIV medication therapy), and discuss signs and symptoms of SCCA to include anal bleeding, anal pain, and presence of an anal mass/lump. The advanced practitioner is in a key position to have these discussions with patients.

At a minimum, anal cancer screening should include DRE circumferentially annually or more frequently if symptoms arise (Palefsky, 2009). The importance of DRE cannot be overstated. In addition to serving as an assessment for prostate cancer, it is a free, painless rapid exam, with no contraindications, that may yield findings warranting further investigation. Findings of indurations, masses, or new lesions warrant referral to an anal dysplasia provider or a capable surgeon or gastroenterologist for further evaluation and possible biopsy.

Anal cytology should be strongly considered for all HIV-seropositive MSM and is available wherever cervical cytology can be performed. Any HGAIN cytology result should be referred to an anal dysplasia clinic for further assessment with HRA for targeted biopsies to exclude SCCA or HGAIN given the strong positive predictive value of HGAIN anal cytology in predicting HGAIN at biopsy as found in the Seattle cohort. However, findings besides HGAIN cannot be considered adequate for exclusion of HGAIN or SCCA, as cytology has been shown to be a poor predictor for anal dysplasia in other studies (Panther et al., 2004). Patients should be counseled regarding these findings and reminded to notify the provider of any anal symptoms. Additionally, screening for STIs should be offered at each opportunity or if the patient has had an at-risk sexual encounter between interval visits.

For HIV-infected MSM who are near an anal dysplasia screening clinic, direct referral for concurrent anal cytology, DRE, and HRA should be considered given the poor correlation of anal cytology (if less than HGAIN) to findings on HRA. Alternatively, if an individual prefers, anal cytology initially, with triage of results meaning referral to an anal dysplasia clinic if anal cytology is abnormal, may be considered. Once an individual has been screened within an anal dysplasia clinic, follow-up intervals with repeat anal cytology and HRA can be performed as follows: for normal findings from anal cytology and/or HRA pathology, follow-up is recommended in 1 year; for ASCUS or LGAIN findings, follow-up is recommended in 6 months; and for ASCUS-H or HGAIN findings, follow-up is recommended in 3 to 4 months if the patient opts not to pursue treatment. These intervals appear to be safe and effective given the average progression interval time seen within the author's cohort. Patients are instructed to return to the anal dysplasia clinic sooner if any anal symptoms arise before their next interval screening. Lastly, symptomatic patients should be seen in the anal dysplasia clinic immediately in order to rule out or treat SCCA promptly, regardless of last screening results and interval.

Summary

In conclusion, the need for additional devoted anal dysplasia clinics capable of expert screening will continue to rise in order to serve this

high-risk population that continues to grow in size as HIV infection incidence climbs. Currently, access to anal dysplasia screening is severely regionally limited. The creation of treatment guidelines could promote clarity in screening recommendations and encourage screening in high-risk populations in order to identify this premalignant disease and allow early intervention, which has been shown to improve morbidity and mortality. Ongoing research investigating the Gardasil HPV vaccine may be incorporated into screening guidelines if HPV vaccination is shown to have benefit for HIV-infected men (Garland et al., 2007). Anal cancer and dysplasia screening guidelines based on high-quality evidence are necessary to help facilitate awareness in both HIV-infected MSM and providers caring for this population, leading to aggressive identification and treatment of invasive SCCA. Further research into the treatment of anal dysplasia to prevent SCCA progression, cost-effectiveness, clinical efficacy, and the impact of screening on patients' perceived health status is needed.

DISCLOSURES

The author has no conflicts of interest to disclose.

REFERENCES

Abramowitz, L., Bennabderrahmane, D., Ravaud, P., Walker, F., Rious, C., Jestin, C., Bouvet, E., Soule, J. C., Leport, C., & Duval, X. (2008). Anal squamous intraepithelial lesions and condyloma in HIV-infected heterosexual, homosexual men and women: Prevalence and associated factors. *AIDS, 21*, 1457–1465. doi:10.1097/QAD.0b013e3281c61201

Blackwell, C. (2008). Anorectal carcinoma screening in gay men: Implications for nurse practitioners. *American Journal for Nurse Practitioners, 12*, 60–63.

Chiao, E. Y., Giordano, T., Palefsky, J., Tyring, S., & El Serag, H. (2006). Screening HIV-infected individuals for anal cancer precursor lesions: A systematic review. *Clinical Infectious Diseases*, *43*, 223–233. doi:10.1086/505219

Cranston, R., Hart, S., Gornbein, J., Hirshowitz, S., Cortina, G., & Moe, A. (2007). The prevalence, and predictive value, of abnormal cytology to diagnose anal dysplasia in a population of HIV-positive men who have sex with men. *International Journal of STD & AIDS*, *18*, 77–80.

D'Souza, G., Wiley, D., Xiuhong, L., Chmiel, J., Margolick, J., Cranston, R., & Jacobson, L. (2008). Incidence and epidemiology of anal cancer in the multicenter AIDS cohort study. *Journal of Acquired Immune Deficiency Syndromes*, *48*(4), 491–499. doi:10.1097/QAI.0b013e31817aebfe

Fagan, S., Bellows, C., Albo, D., Rodriquez-Barradas, M., Feanny, M., Awad, S. S., Berger, D. H. (2005). Length of human immunodeficiency virus disease and not immune status is a risk factor for development of anal carcinoma. *The American Journal of Surgery*, *190*(5), 732–735. doi:10.1016/j.amjsurg.2005.07.011

Garland, S. M., Hernandez-Avila, M., Wheeler, C., Perez, G., Harper, D., Leodolter, S.,...Koutsky, L. A. (2007). Quadrivalent vaccine against human papillomavirus to prevent anogenital diseases. *New England Journal of Medicine, 356*, 1928–1943.

Goldie, S., Kuntz, K., Weinsein, M., Freedberg, K., Welton, M., & Palefsky, J. (1999). The clinical effectiveness and cost-effectiveness of screening for anal squamous intraepithelial lesions in homosexual and bisexual HIV-positive men. *Journal of the American Medical Association*, *281*(19), 1822–1829.

Goldstone, S., Kawalek, A., & Huyett, J. (2007). InfraRed Coagulator: A useful tool for treating anal squamous intraepithelial lesions. (2005). *Diseases of the Colon & Rectum*, *48*, 1042–1054. doi:10.1007/s10350-004-0889-0

Hoots, B., Palefsky, J., Pimenta, J., & Smith, J. (2009). Human papillomavirus type distribution in anal cancer and anal intraepithelial lesions. *International Journal of Cancer,* 124, 2375–2383. doi:10.1002/ijc.24215

Nathan, M., Hickey, N., Mayuranathan, L., Vowler, S., & Singh, N. (2008). Treatment of anal human papillomavirus-associated disease: A long term outcome study. *International Journal of STD & AIDS, 19*, 445–449.

Palefsky, J. (2009). Anal cancer prevention in HIV-positive men and women. *Current Opinion in Oncology, 21*, 433–438. doi:10.1097/CCO.0b013e32832f511a

Panther, L., Wagner, K., Proper, J., Fugelso, D., Chatis, P., Weeded, W., Nasser, I., Doweiko, J., & Dezube, B. (2004). High resolution anoscopy findings for men who have sex with men: Inaccuracy of anal cytology as a predictor of histologic high-grade anal intraepithelial neoplasia and the impact of HIV serostatus. *Clinical Infectious Diseases*, *38*(10), 1490–1492. doi:10.1086/383574

Piketty, C., Darragh, T., Heard, I., Da Costa, M., Bruneval, P., Kazatchkine, & Palefsky, J. (2004). High prevalence of anal squamous intraepithelial lesions in HIV-positive men despite the use of highly active antiretroviral therapy. *Sexually Transmitted Diseases*, *31*(2), 96–99. doi:10.1097/01.OLQ.0000109515.75864.2B

Piketty, C., Selinger-Leneman, H., Grabar, S., Duvivier, C., Bonmarchand, M., Abramowitz, L., Costaglionia, D., & Mary-Krause, M. (2008). Marked increase in the incidence of invasive anal cancer among HIV-infected patients despite treatment with combination antiretroviral therapy. *AIDS, 22*, 1203–1211. doi:10.1097/QAD.0b013e3283023f78

Siekas, L., & Aboulafia, D. (2009). Establishing an anal dysplasia clinic for HIV-infected men: Initial experience. *AIDS Reader, 19*(5), 178–186.

Sobhani, I., Walker, F., Roudot-Thoraval, F., Abramowitz, L., Johanet, H., Henin, D., Delcier, J., & Soule, J. (2004). Anal carcinoma: Incidence and effect of cumulative infections. *AIDS*, *18*(11), 1561–1569. doi:10.1097/01.aids.0000131335.15301.dd