CLINICAL PRACTICE GUIDELINES: SCREENING FOR SQUAMOUS CELL CARCINOMA OF THE ANUS IN HIV-INFECTED MEN WHO HAVE SEX WITH MEN.

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Introduction:

Prolonged exposure to high-risk strains of human papillomavirus (HPV) and the dysplastic effects that HPV exerts on cells of the squamocolumnar transitional junction of the anal canal leads to anal dysplasia, which is a precursor to squamous cell carcinoma of the anus (SCCA).[1] Anal HPV infection is present in 93% of HIV seropositive men who have anoreceptive intercourse.[2] Anal dysplasia has been reported in 56% of HIV-infected men who participate in anoreceptive intercourse, with high-grade lesions diagnosed in 4% of men and 6% of women, respectively.[3,4] HIV infection increases the risk for high-grade anal dysplasia; 38% to 60% of HIV-infected and 17% of HIV-seronegative men with normal or low-grade dysplasia at baseline, have been reported to develop high-grade dysplasia over 4 years. [5,6] Additional risk factors for anal dysplasia include low CD4+ cell counts, increased HIV RNA viral load, high HPV DNA levels, receptive anal intercourse, and in women concurrent abnormal cervical cytology.[3,4]

SCCA is also over represented in those with HIV infection, with rates in the range of 70-80 per 100,000, which is in contrast to 1 per 100,000 in the non-HIV-infected population.[7] In the era of highly active antiretroviral therapy (HAART), the median survival of HIV-infected individuals continues to improve, and for those with non-detectable HIV RNA viral loads, their longevity now rivals that of the general population.[8] Unfortunately, there is no compelling evidence that HAART-induced restoration of immunity promotes resolution or regression of high-grade anal intraepithelial neoplasia (AIN).[9,10] These patients will likely remain at a high risk for development of SCCA. One current estimate suggests that as many as 5% of HIV-infected men with high-grade AIN are destined to progress to SCCA.[11]

A cost effectiveness analysis has shown that screening and treatment for high-grade anal dysplasia could provide benefits and compare favorably to the approaches used to prevent other malignancies, most notably cervical cancer.[12] Although large-scale clinical trials to prove effectiveness have yet to be done, increasing awareness of the problem and projected potential effectiveness of screening recently led the New York Health Department to recommend that HIV-infected men and women undergo anal dysplasia screening.[13] With a strategy that is analogous to that which is employed in cervical cancer screening clinicians anticipate frequent detailed anal evaluations will ultimately lead to earlier detection of disconcerting lesions and a change in the natural history of HPV-induced anal malignancy.

Unfortunately, there are few well-established high-volume anal dysplasia screening clinics and specialty trained providers in the United States. Consequently, expertise in counseling, screening and treating at-risk HIV-infected individuals for HPV-associated anal dysplasia is limited. Further complicating attempts at screening this high risk group is the lack of formal clinical practice guidelines for screening for SCCA in HIV infected individuals.

Methods:

A combined literature review and retrospective chart review was performed. All patients seen in the anal dysplasia screening clinic at Virginia Mason Medical Center (VMMC) during a 25-month period between November 2007 and December 2009 were referred by HIV primary and specialty providers within the Pacific Northwest. After receiving approval from both the VMMC and Vanderbilt University Institutional Review Boards, a retrospective chart review of the first 212 consecutive HIV-infected male individuals who underwent anal dysplasia screening by the author. Demographic information including age, sex, and race were recorded, along with the patient's most recent CD4+ T-lymphocyte cell count and HIV RNA viral load at time of initial assessment. All patients underwent a digital rectal examination, anal cytology assessment and high resolution anoscopy. Disconcerting lesions identified on high-resolution anoscopy were biopsied. At time of chart review, additional historical information was collected regarding patient sexual practices and collated anal cytology and biopsy results.

Anal cytology collection and interpretation

All patients were examined while in the left lateral position. Anal Pap smear for cytology was performed in standard fashion with a Dacron sterile plastic Q-tip swabs.[14]

Anal cytology samples were read by one of two Virginia Mason cytopathologists experienced in anal cytology interpretation and reported as normal, atypical squamous cells of undetermined significance (ASCUS), ASCUS-cannot rule out high-grade (ASCUS-H), low-grade squamous intraepithelial lesions (LSIL) or high-grade squamous intraepithelial lesions (HSIL) using Bethesda 2001 terminology.[15]

High-resolution anoscopy:

A digital rectal examination was performed circumferentially with documentation of any abnormalities. A clear plastic disposable anoscope is inserted into the anal canal with lubrication with K-Y jelly, through which was placed a gauze-wrapped wooden Q-tip which was soaked in 3% acetic acid. The squamocolumnar junction of the anal canal, verge, and perianal skin was then visualized with a Zeiss 150 FC colposcope set at 16-25x magnification.[16] All suspicious areas were photographed using a beam splitter attached to the colposcope **(Figure 1, A-F)**. Abnormal epithelium was biopsied using baby Tischler forceps or Wilson Cook jumbo bite endoscopy forceps with samples preserved in 10% formalin. Perianal biopsies were obtained after injection of local anesthesia. Hemostasis, if needed, was achieved with pressure by the anoscope and/or direct application of either silver nitrate or Monsel's solution prior to the end of the procedure.

Figure 1:

A: High Resolution Anoscopy photo-documentation of an area of Low-Grade Anal Dysplasia. Notice the area of acetowhitening of the squamous epithelium to the left lateral internal anal canal.

B: High Resolution Anoscopy photo-documentation of High-Grade Anal Dysplasia to internal left lateral anal canal with dense acetowhite changes after acetic acid 3% application. This lesion was biopsy proven HGAIN.

C: High Resolution Anoscopy photo-documentation of external/perianal High-Grade Anal Dysplasia. External anterior perianal mass after application of acetic acid 3%. This lesion was biopsy confirmed HGAIN.

D: High Resolution Anoscopy photodocumentation of Lugol's iodine application. Mustard discoloration as noted to right posterolateral anal canal, is known as partial or negative Lugol's uptake may indicate dysplasia. The biopsy of this area returned low grade dysplasia.

E: High Resolution Anoscopy photo-documentation of internal anal canal left lateral HGAIN area with concern for invasion.

F: High Resolution Anoscopy photo-documentation of internal anal canal left lateral HGAIN lesion with concern for invasion.

Results of Literature Review:

•There were no clinical practice guidelines found for anal dysplasia or anal cancer screening. However there were numerous articles substantiating the increased risk of SCCA in HIV infected individuals.[15,16,17] Several articles suggest increasing incidence of SCCA is to be expected due to prolonged life span afforded by anti-viral therapy for HIV.[16,18].

• Literature suggests improved mortality and morbidity with early diagnosis of SCCA.[16]

•Systematic reviews identifies anal cytology as cost-effective compared to other routine screening.[20]

Anal cytology has been demonstrated to be poorly sensitive and specific compared to findings at HRA.[21]

•No cost effectiveness data yet for HRA.

•Evaluation of efficacy of treatment of anal dysplasia is needed.

•Sexually transmitted infections are associated with inability to clear anal dysplasia.[22]

Results of Retrospective Chart Review:

The median patient age was 47 years (range, 24-83 years), and all 212 were men. One hundred and seventy-three (82%) patients were Caucasian, 14 (8%) were African-American, 4 (2%) were Asian, 15 (7%) were Hispanic, two (1%) were other (Native American, and Middle Eastern). Only 4% of patients described themselves as strictly heterosexual. The vast majority (84%) indicated that they had sex predominantly with men or with both men and women. 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/microliter (range, 7-1663 cells/microliter). Greater than 95% of patients were receiving HAART at the time of initial anal dysplasia screening.

Forty-five patients (21%) had normal anal cytology, 89 (42%) had low grade anal cytology and 29 (14%) had high grade cytology **(Table 1)**. Thirty (14%) patients had a normal high resolution anoscopic exam and no biopsy was indicated. Forty-three (20%) patients had a colposcopically abnormal exam but a normal biopsy. Among the 182 patients who underwent anal biopsies, 61 (29%) patients had low-grade AIN, 74 (35%) had high-grade AIN, and 4 (1.8%) had SCCA **(Table 2)**.

AIN was identified more frequently by directed biopsy than by anal cytology assessment **(Table 1)**. Concordance was strong between anal cytology and anal biopsy results for those patients identified with high-grade findings on initial anal cytology assessment. Of patients with high-grade anal cytology findings who underwent anal biopsy, high-grade findings were confirmed in 92%. A biopsy was deferred in one patient with a high-grade anal cytology result due to thrombocytopenia.

Lower CD4+ counts were found in this cohort to be statistically significant for biopsy proven high grade dysplasia when compared to biopsy proven low grade dysplasia using an independent measures one tailed t test (α level 0.01, t-statistic=2.51) with moderate 12% effect size (Cohen's d=0.53).

Twenty-five (12%) of patients progressed from normal or low grade dysplasia to high grade dysplasia during this two year period. Average time of progression was 370 days (range: 99-656 days). Compliance was good with less than 25% being non-adherent to recommended follow up intervals.

There were no significant high resolution anoscopy procedural complications (i.e., bleeding, pain or infection) reported by patients to the anal dysplasia practitioner or referring medical provider. We have continued to monitor patients with low-grade AIN every 6 months and monitor patients with high-grade AIN every 3-4 months.

Table 1: Anal Cytology Diagnosis in HIV+ Men

Anal Cytology Diagnosis

N=211	Unsatisfactory	Normal	ASCUS	ASCUS-H	LGAIN	HGAIN
% (n)	3.3(7)	21.2(45)	18.4(39)	1.6(2)	42(89)	13.7(29)

ASCUS-atypical cells of undetermined significance, ASCUS-H-atypical cells of undetermined significance cannot rule out high grade anal dysplasia, LGAIN-low grade anal intraepithelial neoplasia, HGAIN-high grade anal intraepithelial neoplasia.

Table 2: Anal Biopsy Results

Anal Biopsy Diagnosis

n=182	Unsatisfactory	Abnormal exam/Normal biopsy	LGAIN	HGAIN	SCC
% (n)	0(0)	20(43)	29(61)	35(74)	1.8(4)

LGAIN-low grade anal intraepithelial neoplasia, HGAIN-high grade anal intraepithelial neoplasia, SCC-squamous cell carcinoma.

Recommendations:

•Education of HIV + men and providers of risk of anal cancer.
•Discuss with patients risk, methods of risk reduction and offer screening for anal cancer and sexually transmitted infections.
•Perform circumferential digital rectal exam annually or whenever patient is symptomatic.
•Anal cytology should be available wherever cervical cytology is available, refer any abnormal results to anal dysplasia center or gastroenterologist for further assessment.
•Direct referral to HRA with biopsy of suspect lesions, of all screened individuals if high-volume anal dysplasia center is available.

Recommended screening intervals with anal cytology and high resolution anoscopy:

- •Normal findings, repeat screening in one year
- •Low grade findings, repeat in six months
- •High grade findings, repeat in 3 months (offer treatment).
- •Cancer, referral to surgery for confirming biopsy followed by referral to oncology/radiation oncology.

Discussion:

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. Creation of guidelines could promote clarity in screening recommendations and promote and improve awareness to encourage screening in high-risk populations to identify this pre-malignant disease and allow early intervention, which has been shown to improve morbidity and mortality. Ongoing research investigating the Gardisil™ HPV vaccine may be incorporated into screening guidelines if HPV vaccination is shown to have benefit for HIV-infected men. Anal cancer and dysplasia screening guidelines based on high-quality evidence are necessary to help facilitate awareness in this population and providers caring for HIV-infected individuals to aggressively identify and treat invasive SCCA. Further research in treatment of anal dysplasia to prevent SCCA progression, cost effectiveness, clinical efficacy, and impact of screening on patient's perceived health status is needed.

Additional study into the risks of SCCA risks of other groups including women with and without HIV infection, HIV-seronegative men who have sex with other men, solid organ transplant recipients, and patients who have been treated for anal cancer are needed before assuming that the clinical guidelines for HIV infected individuals would be applicable.

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