Screening and Management of Anal Dysplasia and Anal Cancer in HIV-Infected Patients: A Guide for Practice

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People living with HIV infection have a significantly higher rate of anal cancer as compared with that of uninfected people. It is believed that high-grade anal dysplasia secondary to human papillomavirus infection is a precursor to anal cancer. Considering this, screening and treatment of high-grade anal dysplasia is a possible means of preventing the development of anal cancer. No national or international guidelines exist to guide practice for screening and management of anal dysplasia. On the basis of a review of research and expert recommendations, a guide to practice for screening and management of anal dysplasia and anal cancer is made for clinicians.

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Key words: *anal cancer, anal dysplasia, anal intraepithelial neoplasia, anal pap, anoscopy*

As the most common sexually transmitted infection, human papillomavirus (HPV) infects the skin and mucous membranes of the genital areas and anus (Dunne et al., 2007; Weinstock, Berman, & Cates, 2004). The virus can affect the lining of the vagina, cervix, and anus, resulting in cellular dysplasia. Over the past 10 years, an increasing body of research has focused on HPV and anal dysplasia. Impetus for this research has been the increased incidence of anal cancer in the general population, as well as in specific populations (Johnson, Madeleine, Newcomer, Schwartz, & Daling, 2004). This article reviews research and expert recommendations related to the screening and management of anal dysplasia in people living with HIV (PLWH) infection as a guide to practice and nursing care.

Background

Between 1973 and 1979, the incidence of anal cancer in the general population was 1.06 per 100,000 for men and 1.39 per 100,000 for females; between 1994 and 2000, the incidence of anal cancer nearly doubled, to 2.04 per 100,000 for men and 2.06 per 100,000 for women (Johnson et al., 2004). Specific populations in which an increase in anal cancer occurred included men who have sex with men (MSM) and HIV-infected individuals (Bower

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et al., 2004; Daling et al., 1987; Frisch, Biggar, & Goedert, 2000). The incidence of anal cancer in MSM before HIV was 35 per 100,000, which approximates the rate of cervical cancer before cervical cytology screening (Daling et al., 1987). Bower et al. (2004) reported the incidence of anal cancer in HIV-infected MSM to be 60 per 100,000 patient-years, showing that the incidence of anal cancer increased in this population after the advent of HIV. Increased rates of malignancies, including anal cancer, have been reported to be significantly higher in PLWH than among uninfected individuals (Patel et al., 2008). Frisch et al. (2000) reported an approximately seven-fold increased risk for anal cancer in HIV-infected women and an approximately 6-fold increased risk in HIV-infected heterosexual men who used intravenous drug. As such, the data reflect a significant risk for anal cancer in PLWH.

There are histopathological and epidemiological similarities between cervical cancer and anal cancer that allow cervical cancer screening to serve as a model for anal cancer screening (Daling et al., 2004; Daling & Sherman, 1992; Palefsky, Holly, Gonzales, Berline, Ahn, & Greenspan, 1991). Within this paradigm, HPV can lead to increasing cellular atypia, known as squamous intraepithelial lesions, and may result in high-grade squamous intraepithelial lesions (HSIL), which are considered to be precursors to cervical carcinoma. Cytological screening based on the Papanicolaou (Pap) smear has been used to identify cervical squamous intraepithelial lesions as a means to prevent the development of cervical cancer. The decreased incidence of cervical cancer over the past few decades has been attributed to consistent use of cervical cytology screening (Qualters, Lee, Smith, & Aubert, 1992).

Cytology results for squamous intraepithelial lesions are classified as low-grade squamous intraepithelial lesions (LSIL) or HSIL by the Bethesda system. Terminology and grading of dysplasia is described by the Bethesda system and is presented in Table 1. Anal intraepithelial neoplasia (AIN) is not a classification term in the Bethesda system, but it has been commonly used to denote either LSIL or HSIL. The grading of AIN with regard to AIN 1, AIN 2, and AIN 3 is based on histopathological results from biopsy of a dysplastic lesion.

Table 1. Bethesda System and Histopathologic Correlates for Grading Dysplasia

Term	Definition	Histopathology
ASCUS	Atypical squamous cells of undetermined significance	
ASC-H	Atypical squamous cells of undetermined significance, cannot rule out high-grade	
LSIL	Low-grade squamous intraepithelial lesions	AIN 1
HSIL	High-grade squamous intraepithelial lesions	AIN 2 AIN 3

NOTE: AIN = anal intraepithelial neoplasia; AIN is not a classification term in the Bethesda system. AIN 1, 2, or 3 reflect the degree of histologic abnormality as determined by biopsy.

Research by Palefsky et al. (1991) and Daling et al. (2004) implicated HPV as a necessary factor for the development of anal cancer. As such, HPV infection in the anal canal can lead to cellular dysplasia and HSIL. Recent research by Berry et al. (2009) reported that HSIL has the potential to progress to anal squamous cell carcinoma (SCC), suggesting that HSIL is the precursor to anal SCC. Clinicians have used the anal Pap smear to screen for anal squamous intraepithelial lesions (ASIL) in high-risk populations (Friedlander, Stier, & Lin, 2004; Palefsky et al., 1997), analogous to cervical Pap tests for cervical cancer screening. Abnormal anal cytology is then evaluated by high-resolution anoscopy (HRA; the anal equivalent of colposcopy) with possible biopsy to determine whether HSIL is present (Goldstone, Winkler, Ufford, Alt, & Palefsky, 2001; Chin-Hong & Palefsky, 2002). The identified HSIL can be ablated or excised as treatment (Goldstone et al., 2001). It is believed that such an approach to screening and treatment of anal HSIL may lower the incidence of anal cancer (Berry, Palefsky, & Welton, 2004).

Palefsky et al. (1998) reported an increased incidence of HSIL in HIV-infected MSM, and Abramowitz et al. (2007) reported an increased incidence of HPV-related lesions in PLWH. Considering the increased incidence of HSIL and HPV-related lesions in HIV-infected MSM and HIV-infected individuals, respectively, anal cytology screening and

treatment of HSIL has merit in preventing anal cancer within the HIV-infected population. Because data support the need to screen PLWH for anal dysplasia and anal cancer, nurses and nurse practitioners need to be informed and be knowledgeable about this care concern. Currently, no national or international guidelines exist to guide practice in the management of this disease entity.

Review of Literature

Six significant research studies that address the screening and management of anal dysplasia were identified. Currently, expert recommendations reflect a consensus on how anal dysplasia screening should be approached. The authors make no new implications for practice here. More importantly, expert recommendations based on the research are presented and summarized as a guide to practice.

Studies by Palefsky and Colleagues

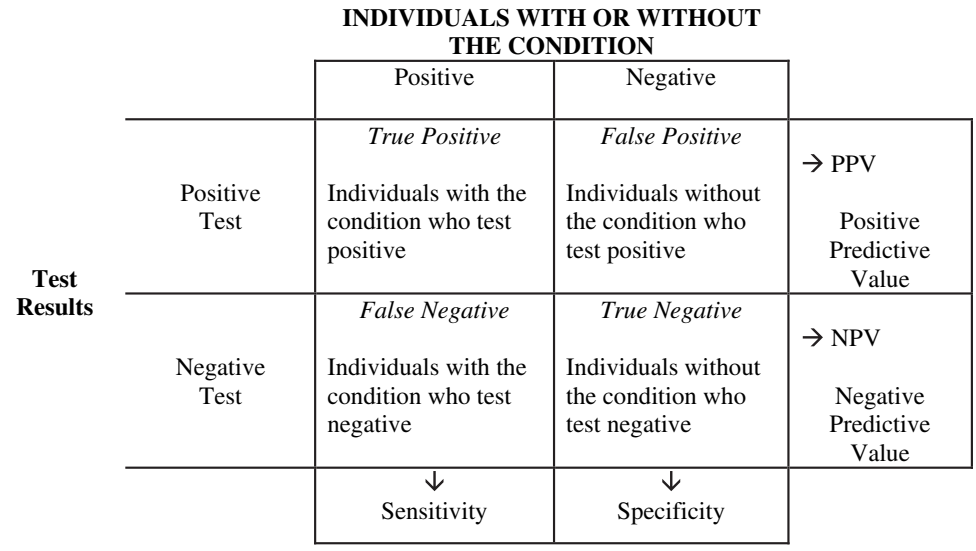
Palefsky et al. (1997) conducted a prospective cohort study of HIV-infected and uninfected MSM to determine the sensitivity, specificity, and positive predictive value (PPV) of anal cytology with regard to screening for ASIL. The study included 658 subjects, of which 407 were HIV-infected and 257 were uninfected. An anal cytology specimen (anal Pap) was obtained from subjects, and then HRA was performed. Subjects underwent biopsy if ASIL were visualized on colposcopy. As the gold standard, biopsy was performed to determine whether the lesions were LSIL or HSIL. Anal cytology results were compared to biopsy results and the sensitivity, specificity, PPV, and negative predictive value (NPV) were calculated. The definitions of sensitivity, specificity, PPV, and NPV are presented in Figure 1.

Overall results for HIV-infected men indicated a PPV of 70% when atypical squamous cells of undetermined significance (ASCUS) were categorized as abnormal, and 78% when categorized as normal. For uninfected men, the PPV was 43% with ASCUS categorized as abnormal, and 50% when ASCUS was excluded. The NPV for HIV-infected men was 79% and 70% with ASCUS included or excluded, respectively. For uninfected men, the NPV was 92% and 90%, respectively. Correlation between anal cytology results and biopsy results was poor. Among 147 biopsy-proven cases of HSIL in HIV-infected men, only 39 (27%) indicated HSIL on cytology. Among uninfected men, 22 cases of biopsy-proven HSIL were identified and only 4 (18%) were detected by cytology. Among 397 patient visits where LSIL were detected by cytology, 81 cases (20%) had biopsy-proven HSIL.

On the basis of these results, Palefsky et al. (1997) concluded that the sensitivity of anal cytology to detect biopsy-proven anal disease in HIV-infected men was similar to cervical cytology to detect cervical disease. Sensitivity among uninfected men was lower. It was also found that anal cytology had a high PPV of ASIL for populations where a high prevalence of anal disease existed. The researchers concluded that determination of the grade of disease needed to be based on histology secondary to biopsy because correlation between cytology and biopsy results was poor.

Palefsky et al. (1998) conducted a prospective cohort study of HIV-infected ($n = 346$) and uninfected ($n = 262$) homosexual and bisexual men to assess the incidence of, and associated risk factors for, HSIL. Baseline anal cytology specimens were collected and followed by HRA with biopsy of visible lesions. Study subjects were followed up every 3 to 12 months to determine whether HSIL developed. Analysis of the data was based on a 4-year period of follow-up.

Palefsky et al. (1998) reported that 38% of HIV-infected and 15% of uninfected subjects developed HSIL during the study. Among HIV-infected subjects, 52% with LSIL progressed to HSIL, whereas 41% of uninfected subjects progressed from LSIL to HSIL during the follow-up period. This study reported that the 4-year incidence of HSIL among HIV-infected and uninfected men was 49% and 17%, respectively. Earlier development of HSIL was associated with lower baseline CD4+ T-cell counts in the HIV-infected men. The authors concluded that the 4-year incidence of anal HSIL was high among both HIV-infected and uninfected men, and that HIV-infected men with abnormal anal cytology were more likely to progress to HSIL than uninfected men, although both



Terms Defined	
Sensitivity	Of all individuals **with the condition**, the percent who actually show positive by the test
Specificity	Of all individuals **without the condition**, the percent who actually show negative by the test
PPV	Of all individuals **who are tested and show positive**, the percent who actually have the condition
NPV	Of all individuals **who are tested and show negative**, the percent who actually do not have the condition

Figure 1. Terms and definitions relating to the validity of diagnostic and screening tests.

groups were at increased risk of progression to HSIL.

Study by Goldstone and Colleagues

Goldstone et al. (2001) studied the prevalence of HSIL and anal cancer in a descriptive study of MSM ($N = 200$) who presented to a surgical practice for anorectal disease. Anal cytology samples were obtained for all subjects, and HRA was performed with abnormal areas being biopsied to determine whether HSIL was present. Cytology for benign disease was reported in 3% of the HIV-infected subjects and 14% of the uninfected subjects. HSIL was detected by cytology in 57% of the HIV-infected subjects and 46% of the uninfected subjects. Overall, ASIL (composed of LSIL and HSIL) was detected in 89% of the HIV-infected subjects and 68% of the uninfected subjects.

Histological results from biopsy were reported as benign disease in 2% of HIV-infected subjects and 12% in uninfected subjects. On biopsy, HSIL was found to be present in 68% of HIV-infected subjects and 60% of uninfected subjects. ASIL or anal SCC was present in 96% of HIV-infected subjects and 72% of uninfected subjects. Although no patient was referred for suspected anal SCC, 5 men (3%)

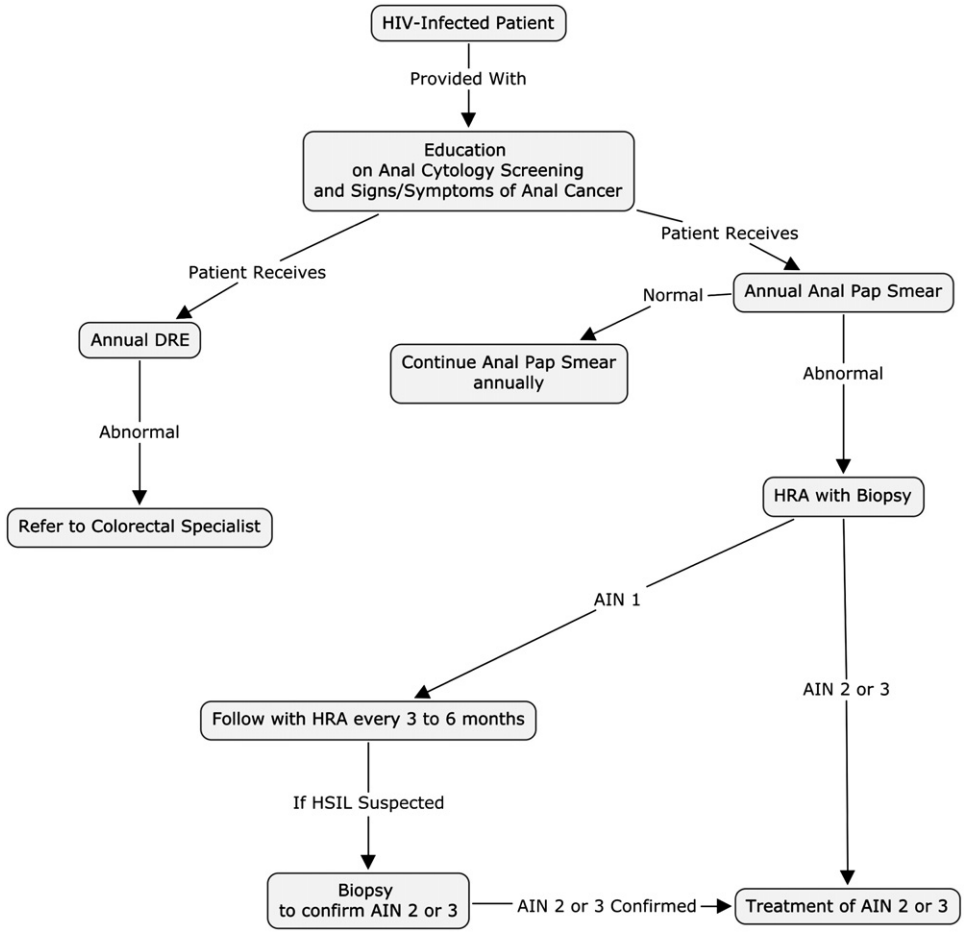


Figure 2. Graphical algorithm for screening and management of anal dysplasia and anal cancer in HIV-infected individuals. Adapted from "High prevalence of anal squamous intraepithelial lesions and squamous cell carcinoma in men who have sex with men as seen in a surgical practice," by S. E. Goldstone, B. Winkler, L. J. Ufford, E. Alt,and J. M. Palefsky, 2001, *Diseases of the Colon and Rectum, 44*(5), 690-698. AIN = anal intraepithelial neoplasia; DRE = digital rectal examination; HRA = high-resolution anoscopy.

had anal SCC found on biopsy. Goldstone et al. (2001) reported that the high prevalence of HSIL and anal SCC was an unexpected finding of the study. The results were important because HSIL was not expected to be present to such a high degree and the majority of the subjects were referred for treatment of condyloma.

On the basis of the study, Goldstone et al. (2001) recommended that MSM referred for condylomatous or noncondylomatous anal disease undergo HRA with biopsy of suspected lesions to evaluate the anal canal adequately. The researchers also argued that anal cytology underestimated the degree of HSIL and recommended that all MSM should have anal Pap smear screening: HIV-infected men with benign cytology should have annual Pap smears, and uninfected men with benign cytology should have Pap smears every 2 to 3 years. Further findings indicated that MSM with any degree of abnormal cytology should be evaluated with HRA, that lesions identified on HRA should be biopsied, and that identified HSIL should be ablated or excised. MSM with LSIL on biopsy should be closely monitored to rule out progression to HSIL: MSM with biopsy-proven LSIL should have repeat Pap smears in 3 to 6 months. MSM with repeat Pap smears in the presence of

ASCUS or LSIL should have yearly HRA to identify HSIL.

Study by Friedlander and Colleagues

In a descriptive correlational study, Friedlander et al. (2004) evaluated anorectal cytology as a screening tool and correlated cytology results with anoscopic and histologic findings. The study retrospectively looked at collected cytological and anorectal specimens from 51 patients. Cytologic and anoscopic findings were correlated with histologic findings. The authors reported that eight cases of HSIL were undercalled as LSIL or ASCUS. On the basis of the study data, the sensitivity of cytology to distinguish benign from dysplastic or malignant disease was found to be 92% and specificity was 50%. Friedlander et al. (2004) concluded that anal cytology could be useful in evaluation of anal dysplasia, that HRA was important to confirm the presence of a dysplastic lesion, and that only biopsy could accurately determine the grade of a lesion.

Study by Abramowitz and Colleagues

In a cross-sectional study of PLWH, Abramowitz et al. (2007) assessed the prevalence of and risk factors associated with ASIL and condyloma in 473 subjects. Study subjects included MSM ($n = 200$), heterosexual men ($n = 123$), and women ($n = 150$). All subjects received HRA and biopsy of abnormal areas.

Results indicated HPV-related lesions (condyloma or dysplasia) were present in 36.5% of the MSM, 14.6% of heterosexual men, and 11.3% of women. Dysplasia was seen among 21% of MSM, 7.3% of heterosexual men, and 6.7% of women. High-risk oncogenic HPV was identified in 90% of the patients with dysplasia. A history of HPV-related lesions and receptive anal intercourse were reported as independent factors associated with anal dysplasia. Abramowitz et al. (2007) concluded that HPV-related lesions or high-risk HPV anal infection was common in this group of PLWH, and that systematic screening was merited.

Study by Cranston and Colleagues

Cranston et al. (2007) examined the prevalence of abnormal anal cytology and the PPV of anal cytology to predict any degree of dysplasia and HSIL in a population of HIV-infected MSM ($n = 244$). Anal cytology specimens were collected, and those with abnormal cytology results received HRA and biopsy of abnormal areas. Anal cytology results indicated that 29% of subjects had normal cytology, 67% had abnormal cytology, and 4% had unsatisfactory samples. Within the abnormal cytology group, 48% had ASCUS, 46% had LSIL, and 3% had HSIL. With regard to anal cytology, 92% of the abnormal cytology was ASCUS or LSIL. However, biopsy indicated HSIL in 52% of the specimens. On the basis of the data, Cranston et al. (2007) reported that the PPV of any cytological abnormality for any grade of dysplasia was 95.7%. The PPV of any grade of dysplasia for HSIL on biopsy was 55.9%.

Cranston et al. (2007) concluded that the study corroborated the poor correlation between the grade of dysplasia by cytology and the grade of dysplasia by biopsy. Additionally, the high PPV of abnormal cytology to detect any grade of anal dysplasia provided confidence that an abnormal cytology result likely indicated the presence of some grade of dysplasia. The authors found that anal cytology was useful to predict the presence of anal dysplasia and that any abnormality on anal cytology testing should be followed with HRA and biopsy to determine the grade of dysplasia.

Discussion

Evidenced-based research has revealed that the prevalence of anal dysplasia in PLWH has increased in MSM, heterosexual men, and women. Research further indicated a faster rate of progression to HSIL in PLWH. High prevalence and increased risks for progression to HSIL support the need for annual dysplasia screening. The high rate of progression to HSIL also makes it clear that patients with LSIL should have more frequent monitoring for HSIL. According to Palefsky et al. (1997), the anal Pap smear was an appropriate screening tool to use for dysplasia screening in PLWH. However, research findings clearly showed that abnormal anal Pap results did not reliably measure the grade of dysplasia. In other words, all abnormal Pap results need follow-up with HRA and biopsy to determine the specific grade of dysplasia.

Table 2. Signs and Symptoms of Anal Cancer

- Anal pain
- Anal bleeding
- Anal lumps
- Anal discharge
- Anal itching

Biopsy-proven HSIL should be treated. Current treatment has focused on the use of infrared coagulation (IRC) to treat discrete HSIL (Cranston et al., 2007; Goldstone, Kawalek, & Huyett, 2005). Although IRC is currently the most popular treatment for discrete lesions, other treatment strategies may be chosen in practice. Trichloroacetic acid has been used in the treatment of lesions, and a recent study reported that trichloroacetic treatment was safe and effective for PLWH with two or fewer lesions (Singh, Kuohung, & Palefsky, 2009). Extensive HSIL in the anal canal has been approached by surgical excision or ablation.

Screening and treatment of high-grade anal dysplasia are steps to prevent development of anal cancer. With regard to screening for anal cancer, the digital rectal examination (DRE) is the principal screening test (Palefsky, 2008). Palefsky (2008) recommended that all individuals at risk for anal cancer have an annual DRE. Because PLWH are at increased risk for anal cancer, an annual DRE is of paramount importance.

Various clinicians have incorporated research findings into treatment algorithms (Chin-Hong & Palefsky, 2002; Goldstone et al., 2001). Of particular relevance to current practice, an algorithm has been adapted to incorporate anal cancer screening (Goldstone et al., 2001). Within the algorithm (Figure 2), the primary care nurse practitioner performs annual DRE and anal Pap smear for PLWH. The procedure for an anal Pap smear is simple; it involves inserting a Dacron swab approximately 1 to 1.5 inches into the anal canal and then rotating the swab while withdrawing it from the canal to obtain a cytology specimen. The swab is then used with a liquid-based Pap kit and sent to a laboratory for analysis.

For patients with an abnormal Pap smear, the clinician should refer the patient for HRA and biopsy to determine the grade of dysplasia and to treat HSIL if present. Because of the high rate of progression from LSIL to HSIL, patients with AIN 1 should be carefully followed up to ensure early detection and treatment. The time needed for AIN 1 to progress to AIN 2 or 3 is not known, and the length of time needed for AIN 2 or 3 to progress to SCC is also not known. Considering this, the optimal time for follow-up of AIN 1 is not clear. However, experts in anal dysplasia recommend that patients with biopsy-proven AIN 1 receive follow-up in 3 to 6 months (Goldstone et al., 2001; Chin-Hong & Palefsky, 2002).

However, the number of trained clinicians who can provide HRA and treatment of HSIL is limited. This care does, however, fall within the scope of nurse practitioner practice after additional training in HRA, biopsy procedures, and treatment of discrete HSIL with IRC or other modalities. Patients with extensive HSIL or SCC will need to be referred to an appropriate physician specialist or colorectal surgeon for evaluation and treatment but initial assessments and care can be ably performed by nurse practitioners with additional training. Nurse practitioners can specialize in these practices and provide needed care to PLWH.

Implications for nursing include the need to provide patient education regarding the need for and the rationale behind anal cytology screening for PLWH. Additionally, nursing should educate at-risk patients about the signs and symptoms of anal cancer. Table 2 lists common signs and symptoms of anal cancer. For nurse practitioners with HIV-infected patients, it is important to provide annual anal Pap smears, annual DREs, and to refer patients with abnormal anal cytology for HRA and biopsy.

Conclusions

The increased incidence of HSIL among PLWH and its association with anal cancer merits the time and expense of screening for HSIL. Anal cytology is an acceptable method for anal dysplasia screening. However, abnormal cytology results require HRA and biopsy to determine the grade of dysplasia. Nurses should provide education on the need for annual anal Pap examinations and the signs and symptoms of anal cancer. Primary care nurse practitioners with HIV-infected patients should provide annual screening for anal cancer and anal dysplasia. Nurse practitioners can also learn to provide HRA,

biopsy, treatment of anal dysplasia, and referral to physician specialists when extensive HSIL is found in the anal canal.

Clinical Considerations

For Nurses

- HIV-infected patients need to be educated about the signs and symptoms of anal cancer.
- HIV-infected patients need to be educated about the need for and rationale behind anal Pap smears.

For Nurse Practitioners

- HIV-infected patients should have an annual DRE to screen for anal cancer.
- HIV-infected patients should have an annual anal Pap smear to screen for anal dysplasia.
- Patients with abnormal Pap smears should be evaluated with high-resolution anoscopy and biopsy to determine the grade of dysplasia.
- Patients with biopsy-proven AIN 2 or 3 should be referred to a specialist for further evaluation and treatment of HSIL.
- Patients with biopsy-proven AIN 1 should be closely followed up with HRA to detect if HSIL develops.

Disclosures

The authors report no real or perceived vested interests that relate to this article (including relationships with pharmaceutical companies, biomedical device manufacturers, grantors, or other entities whose products or services are related to topics covered in this manuscript) that could be construed as a conflict of interest.

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