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Spectrum of Human Papillomavirus–Related Dysplasia and Carcinoma of the Anus in HIV-infected Patients

Lori A. Panther, MD, MPH; Hans P. Schlecht, MD; Bruce J. Dezube, MD

The incidence of human papillomavirus (HPV)-related anal squamous cell carcinoma is increasing. It is likely that long-standing HIV-related immunosuppression plays a significant role in the pathogenesis of anal carcinoma; however, a direct HIV-HPV interaction has also been implicated. Using cervical cancer prevention as a paradigm, anal Pap smear screening as part of routine HIV preventive care has been proposed to detect and treat precancerous anal lesions in the hope of decreasing anal cancer rates. All HIV-positive patients with invasive cancer of the anal canal, particularly those with CD4⁺ cell counts greater than 200/μL and those receiving HAART, should be managed in the same manner as their HIV-negative counterparts. [AIDS Reader. 2005;15:79-91]

Key words: HIV/AIDS • Human papillomavirus • Papanicolaou smear • Dysplasia • Anal carcinoma

DUAL INFECTION AND ONCOGENESIS

Anogenital acquisition of human papillomavirus (HPV) begins shortly after the onset of sexual activity. The highest rates of anogenital HPV shedding occur in sexually active men and women less than 30 years old. Acquisition of more than 1 HPV type is associated with an increased number of lifetime sexual partners, high frequency of sexual activity, and a history of sexual partners with genital warts.

HIV infection further increases the risk of anogenital HPV infection, possibly because of a high cumulative number of sexual partners in some HIV risk groups.¹ Among HIV-infected patients, men who have sex with men (MSM) have a high prevalence of detectable anal HPV DNA by polymerase chain reaction (PCR) testing, from roughly 54% in earlier studies to 80% to 93% in more recent series.²⁻⁸ Moreover, HIV-positive MSM have a

higher rate of harboring multiple types of HPV than do their HIV-negative counterparts.^{3,6,7} Fewer data exist on HIV-positive women; however, roughly 75% have positive anal HPV PCR test results; HIV-positive women also display a higher rate of infection with multiple HPV types than do HIV-negative women.^{9,10} Even without a history of receptive anal intercourse, HIV-positive heterosexuals have been found to have a 46% prevalence of anal HPV infection by PCR.¹¹

More than 100 HPV types have been documented, and approximately 30 are known to infect the human genital tract. These have been further classified into low-risk types (mainly types 6 and 11), which are associated with condylomata and low-grade dysplasia, and high-risk types (mainly types 16, 18, and 31), which are associated with high-grade dysplasia and invasive carcinoma.

The hallmark of high-risk HPV types is their ability to integrate into

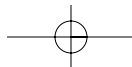
This is the fourth of a 4-part review series on cancers in persons with HIV/AIDS. The previous 3 articles appeared in 2004.

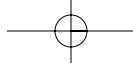
the host cell genome. Following direct exposure to squamous cell epithelium, the HPV virion infects the immortalized basal lamina cells of the epidermis. As the basal cells ascend the strata of the epidermis, both integrated and unintegrated HPV possess the capacity to express the oncoproteins E6 and E7, which inhibit cellular p53 and retinoblastoma tumor suppressor proteins, thereby transforming normal cell proliferation into cells with malignant potential.¹²

En route to anal squamous cell carcinoma is a spectrum of anal dysplasias similar to that of cervical dysplasias and histologically categorized as anal intraepithelial neoplasia (AIN) 1, AIN 2, or AIN 3, based mainly on nuclear characteristics as well as proportion of the epithelial layer replaced by dysplastic cells. Identification of AIN 1 on histology corresponds to the diagnosis of low-grade squamous intraepithelial lesion (LSIL) on cytology; likewise, AIN 2 and AIN 3 correspond to high-grade squamous intraepithelial lesion (HSIL). Analogous to HPV-related cervical carcinoma, AIN 2 and AIN 3 are thought to be precursors of anal squamous cell carcinoma.¹³

The natural history of HPV-related squamous cell dysplasia in HIV-infected persons is accelerated compared with that in the HIV-negative population. HIV-positive women are 3 times more likely than their HIV-negative counterparts to have an anal squamous intraepithelial lesion during 2 years of follow-up.¹⁴

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Prevalence and incidence of anal dysplasia are also higher in HIV-infected MSM than in HIV-negative MSM, and the risk of anal dysplasia for both men and women increases as CD4⁺ cell count declines.¹⁴⁻¹⁶ Compared with the general population, HPV-related anogenital disease—including condylomata; high-grade squamous dysplasia; Bowen disease of perineum, perianal area and vulva; and invasive squamous cell carcinoma—tends to be more prevalent

in HIV-infected persons, more advanced at diagnosis, and more recalcitrant to standard therapies.

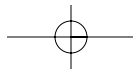
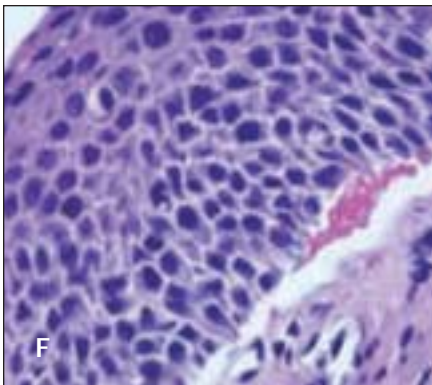
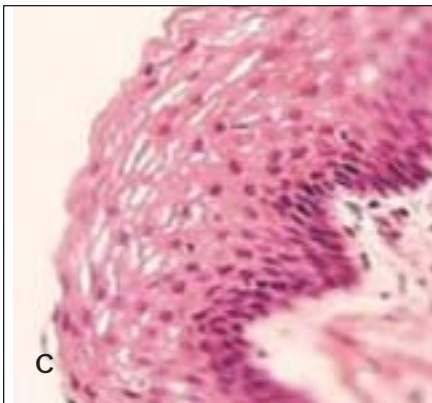
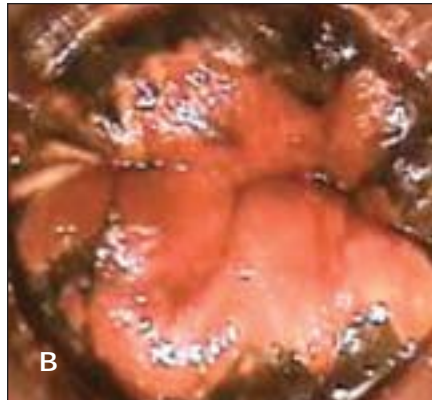
Duration and severity of immunosuppression are major factors in the acceleration of HPV oncogenesis in HIV-infected persons, analogous to the epidemiology of cervical cancer in transplant recipients. In addition, *in vitro* studies have suggested a direct role for HIV in the acceleration of HPV-induced oncogenesis, though this direct HIV-HPV interac-

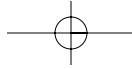
tion is a subject of some controversy. Proposed mechanisms of this interaction include upregulation of HPV-16 oncoprotein expression by the HIV-1 regulatory protein Tat and expression of HIV regulatory proteins contributing to cell cycle disruption.¹⁷

EPIDEMIOLOGY OF ANAL CARCINOMA

As a result of the benefits of HAART, there are now more people in the United States living with HIV infection than ever before.¹⁸ Our expanded expertise in treating HIV infection and its complications has shifted the spectrum of diseases in HIV-infected persons.¹⁹

In the 1960s and 1970s, the annual incidence of anal cancer in the United States was 0.5/100,000 and was primarily found among older persons in a 1:2 male-female ratio. In the late 1980s, the incidence of anal cancer among men with a history of receptive anal intercourse was re-





ported to be 35/100,000—strikingly similar to the incidence of cervical carcinoma before the initiation of cervical Pap smear screening.²⁰

A recent analysis of more than 3000 MSM found a similar relative risk of 37 for anal carcinoma compared with that of the general population.²¹ Among MSM, the estimated rate of anal cancer in the HIV-positive is twice that in the HIV-negative population, or roughly 70 cases per 100,000.²² HIV-infected persons with anal carcinoma are younger at initial diagnosis than the general population: a report of more than 200 cases of invasive anal carcinoma from an AIDS cancer registry demonstrated a mean age of 40.9 years at diagnosis, in contrast to the general population, in which most cases present in persons aged over 60 years.²³

CLINICAL FEATURES

As with cervical carcinoma, the precancerous stages of anal HPV infec-

tion remain largely asymptomatic until there is invasion beyond the epithelial basement membrane, concurrent with tumor enlargement. Occasionally, patients may report anal itching, bleeding, pain with defecation, or receptive anal dyspareunia. Carcinoma in situ (Bowen disease) of the external genital area is often diagnosed incidentally on pathologic examination of surgically excised hemorrhoids or warts; however, patients presenting de novo tend to complain of thickening and irritation of perianal skin, itching, and bleeding.

Of concern are numerous cases of high-grade AIN, microinvasive or invasive squamous cell carcinoma incidentally diagnosed on pathologic examination of excised anal warts in HIV-infected persons.²⁴ Though squamous cell cancer within giant condyloma accuminatum is well described in the literature, the relative risk of concurrent malignancy in genital warts of HIV-infected versus

non-HIV-infected persons remains unknown.²⁵

Patients presenting with invasive squamous cell carcinoma of the anal canal most often complain of anal pain, bleeding, constipation, rapidly growing anal mass, or discomfort with defecation or with receptive intercourse (Figure 1). These patients may present de novo to their provider or alternatively may be seen in the context of follow-up and treatment visits for previously diagnosed HPV disease, including condylomata and dysplasia.

Diagnostic biopsy is often accomplished in the operating room. Pelvic CAT scan is helpful in evaluating lymph nodes. Tumors originating above the dentate line drain to the perirectal and paravertebral nodes; those below the dentate line drain to the inguinal and femoral nodes. Many HIV-positive patients with invasive anal cancer have lesions that are too large to remove without dam-

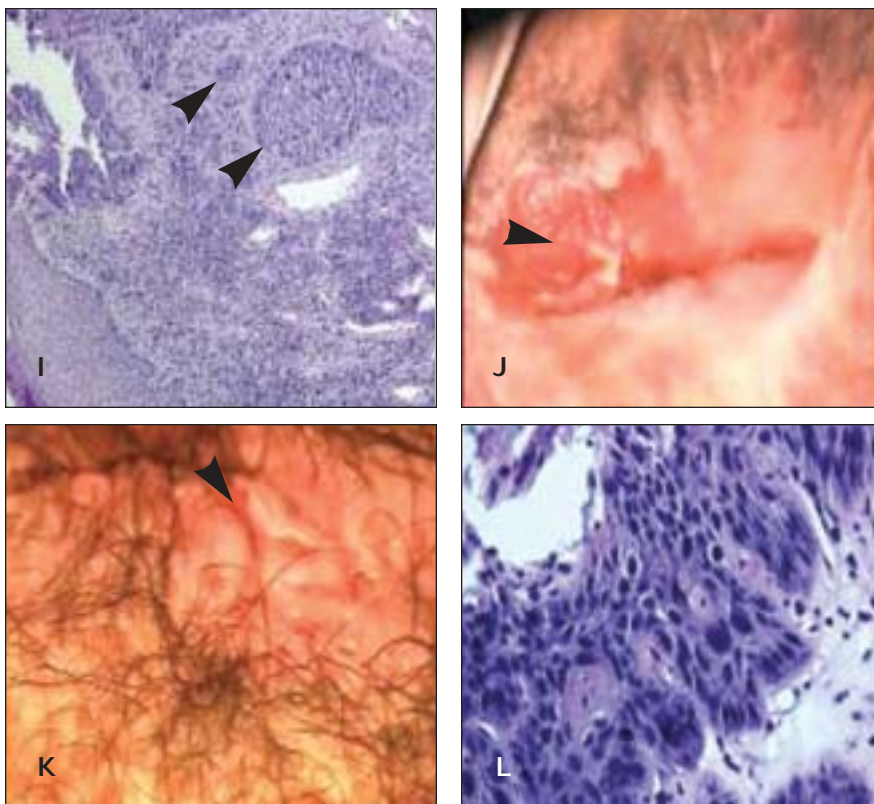
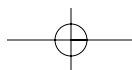
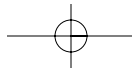


Figure 1. Normal anal transformation zone epithelium: A, opalescent appearance after application of 3% acetic acid; B, avid uptake of Lugol iodine solution; C, nonkeratinized stratified squamous epithelium typical of normal transformation zone. In D, the anal transformation zone reveals an acetowhite area that remains free of significant Lugol solution uptake (E). Biopsy of the area shows cells with large nuclei and little cytoplasm ascending to the top of the epidermal strata, consistent with anal intraepithelial neoplasia (AIN) 2 and AIN 3 (F). A friable area that is firm on digital examination, with irregular vessels at the surface (G) and that is Lugol-negative (H), reveals nests of invasive squamous cell carcinoma on biopsy of the lesion (I). Superficial ulceration within an area of leukoplakia (J) and subtle area of perianal leukoplakia (K) both revealed external AIN 3 or Bowen disease (L).





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aging the internal sphincter. Such patients should be referred for concurrent radiotherapy and chemotherapy (combined modality therapy).

TREATMENT OF ANAL CANCER

From an anatomic standpoint, the anus can be divided into the mucosa-lined anal canal and the more distal epidermis-covered anal margin. Cancers arising in the anal margin are considered skin cancers and are treated typically with local excision. Carcinoma of the anal canal is treated according to a very different paradigm.

Combined modality therapy is currently the standard of care for invasive squamous carcinoma of the anal canal. In the 1970s, investigators at Wayne State treating anal cancer patients with infusional 5-fluorouracil (5-FU), bolus mitomycin, and intermediate-dose radiation therapy demonstrated that combined modality therapy, which takes advantage of the ability of 5-FU to potentiate radiotherapy, is able to lead to pathologic complete responses and preservation of the anal sphincter.²⁶ Follow-up series confirmed that combined modality therapy obviated the need for abdominoperitoneal resection and permanent colostomy.²⁷⁻²⁹

Although the details of these studies are beyond the scope of this article, several important principles were established. Patients treated with concomitant chemotherapy and radiation therapy fare better than those treated with radiation alone, with higher 5-year locoregional control rates, higher colostomy-free rates, and longer progression-free survival.²⁸ Combination chemotherapy with mitomycin and 5-FU is better than 5-FU alone. The addition of mitomycin led to marked improvements in 4-year colostomy-free survival (71% vs 59%) and disease-free survival (73% vs 51%).²⁹ Ongoing studies are investigating the optimal dose of radiation and whether mitomycin can be replaced by cisplatin.

With the understanding that concomitant radiation therapy and chemotherapy (5-FU and mitomycin) is the current standard of care for HIV-negative patients with invasive anal cancer, such an approach has been investigated and used successfully in HIV-positive patients, particularly those with CD4⁺ cell counts of greater than 200/ μ L. HIV-positive patients with low CD4⁺ cell counts, particularly those with counts of less than 200 cells/ μ L, have a higher incidence of late toxicity, longer breaks in therapy because of toxicity, and a greater likelihood of chemotherapy dose reduction, all of which compromise optimal therapy.³⁰ Most of the published series of HIV-positive anal cancer patients predate the wide availability of HAART—a point that needs to be kept in mind when evaluating response rates and toxicities in the literature.

In one series, 60 HIV-negative and 13 HIV-positive patients were treated for invasive anal cancer between 1985 and 1998. As expected, HIV-positive patients tended to have less benefit and increased toxicity compared with their HIV-negative counterparts. Complete clinical response was achieved by 62% of the HIV-positive patients, compared with 85% of the HIV-negative group.³¹ Moreover, 80% of HIV-positive patients had severe or life-threatening acute toxicity, compared with 30% of the HIV-negative patients. Skin breakdown, diarrhea, and myelosuppression are particularly problematic in the setting of HIV infection, but HIV-positive patients who were receiving HAART fared better than those who were not.³² It is important that the HAART regimen in this setting not include zidovudine, because of the myelosuppression associated with this antiretroviral agent.

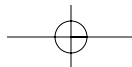
HIV-positive patients who are being treated with combined modality therapy need to be followed closely and carefully, with great at-

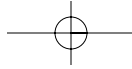
tention to skin care, supportive care, pain control, irregularities of bowel habit, and serial blood counts. The goal is to minimize treatment interruptions to approximate the treatment schedules of their HIV-negative counterparts. The best way to treat invasive anal cancer, however, is to prevent it in the first place.

PREVENTION OF ANAL CANCER Screening for Anal Dysplasia

In HIV-positive MSM, an anal Pap smear has sensitivity and specificity comparable to cervical Pap smear screening.³³ To obtain an anal Pap smear, a water-moistened Dacron swab is inserted 1 to 1.5 inches into the anal canal, and the circumference of the canal surface is “scraped” with the swab. The sample is acquired blindly, without visualization of the transformation zone. The swab is then processed exactly as with a cervical Pap smear, using the standard slide method or liquid media processing. Samples are less prone to drying artifact when the liquid medium is used, but initial studies reveal that the traditional smear technique yields similar results.³⁴

The recently revised Bethesda System of cervical cytologic classification is also the accepted means of classifying anal cytology. Consequently, anal cytology may be described as normal, atypical squamous cells of uncertain significance (ASCUS), LSIL, or HSIL.^{35,36} While LSIL is the cytologic counterpart of AIN 1 and HSIL of AIN 2 or 3 or carcinoma in situ, ASCUS refers to a mixture of both low-grade and high-grade features on cytologic examination, which thereby limits diagnostic accuracy. Anal Pap smears, especially those that are read as ASCUS or LSIL, do not correlate well with biopsy findings in paired specimens: more than one third of anal Pap smears classified as low-grade cytology have high-grade histologic findings on biopsy.³⁷





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Unlike with cervical ASCUS, HPV typing has not been shown to aid in predicting which patients with anal ASCUS are at risk for high-grade AIN.³⁸ Thus, existing anal cancer screening and treatment programs generally follow the practice of proceeding directly to high-resolution anoscopy (HRA) if the anal Pap smear is read as anything but normal. Anal Pap smears showing HSIL almost always portend high-grade internal anal dysplasia (AIN 2 or AIN 3) on biopsy; thus, patients with persistent HSIL on Pap smears without biopsy-proven high-grade internal anal dysplasia on HRA should be referred for examination under anesthesia in the operating room.³³

HRA is performed by inserting a clear plastic anoscope approximately

2 inches into the anal canal. Then, a standard gynecologic colposcope is used to locate the transformation zone with the aid of 3% acetic acid solution applied to the anal canal surface.³⁹ In areas of dysplasia, an opaque white ("acetowhite") plaque may be seen within the transformation zone. If high-grade dysplasia exists within the plaque, hallmark surface vessel changes consistent with neovascularization may be visible under high-power (20×) magnification.

Application of Lugol iodine solution also aids clinical detection of lesions. Cells with high nucleus-cytoplasm ratios that compose a dysplastic plaque do not absorb Lugol solution and appear bright yellow, whereas cells of normal epithelium

with relatively more cytoplasm readily take up the iodine solution and appear dark brown.

Last, anoscopic examination of the perianal area is performed. Application of 3% acetic acid does not work as well on perianal tissue but may aid in detecting subtle condylomatous changes, plaques, and vascular abnormalities that may indicate the presence of HPV-related disease of the perianal skin.

An anal Pap smear screening program is projected to be a cost-effective modality for anal cancer prevention. A cost-benefit analysis of instituting a screening anal Pap smear every 2 years in HIV-positive MSM increased life expectancy by approximately 4 months, with a quality-adjusted life-year cost of \$16,600—

Management of PAP smear results

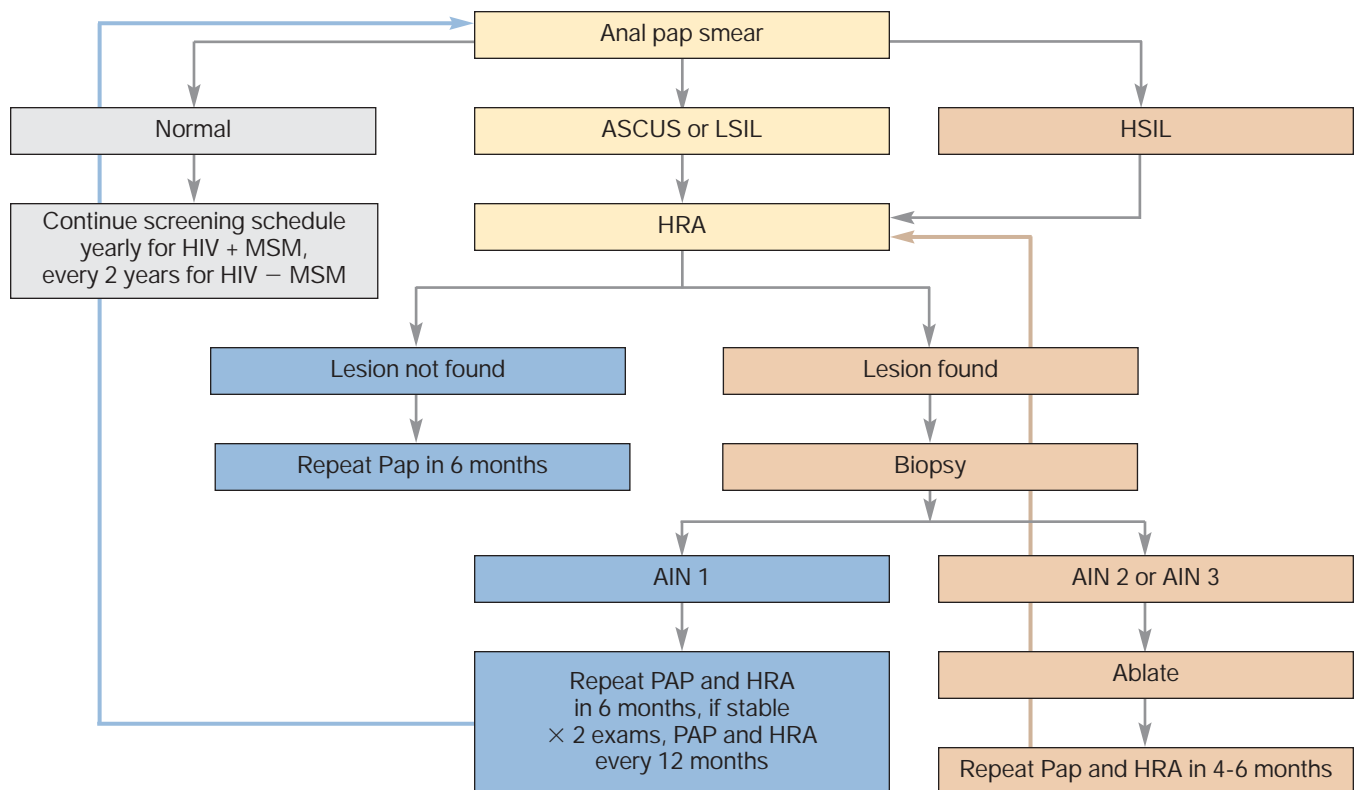
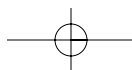
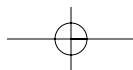


Figure 2. Algorithm for the management of high-grade internal anal dysplasia based on Pap smear results. (ASCUS, atypical squamous cells of uncertain significance; LSIL, low-grade squamous intraepithelial lesion; HSIL, high-grade squamous intraepithelial lesion; AIN, anal intraepithelial neoplasia; HRA, high-resolution anoscopy.)





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equivalent to the cost-effectiveness of instituting *Pneumocystis pneumonia* prophylaxis in HIV-infected patients with CD4⁺ cell counts of less than 200/μL.^{40,41}

Currently there are no formal guidelines for anal Pap smear screening of MSM; the most recent recommendations from the CDC state that “[A]nal cytology screening of HIV-infected men who have sex with men . . . might become useful preventive measures. However, studies of screening and treatment programs for anal HSILs need to be implemented before recommendations for anal cytology screening can be made.”⁴²

Nevertheless, some state agencies are beginning to include screening for anal Pap smears in their guidelines for HIV preventive medicine.⁴³ Periodic anal Pap smear screening should be considered for any MSM or HIV-positive woman with a history of anal condylomata or anal dysplasia, HIV-positive persons with CD4⁺ cell counts of less than 200/μL, HIV-positive women with a history of dysplasia or cancer of the cervix or vulva, and HIV-positive persons who are recipients of solid organ transplants. However, published comprehensive primary care guidelines for HIV management fall short of recommending anal Pap smears as part of routine preventive care.^{44,45} All patients, regardless of their access to the multidisciplinary team needed to screen, treat, and follow patients at risk for anal cancer, should have a yearly digital examination and should be referred to a skilled surgeon if this examination is abnormal or if anogenital symptoms occur.

Treatment of Anal Dysplasia

Much of the management of anal dysplasia springs from the model of cervical dysplasia. Analogous to cervical cancer prevention, there has been no consensus to ablate low-

grade anal intraepithelial lesions. Nevertheless, patients with anal symptoms referable to a low-grade lesion should be treated. However, using the historical epidemiology of cervical cancer as a model, treatment of high-grade anal dysplasia should reduce the chances of progression to invasive squamous cell carcinoma; thus, therapy is recommended for patients with anal HSIL regardless of symptoms. There have been no randomized, placebo-controlled trials investigating whether treatment of high-grade cervical dysplasia prevents the development of invasive cervical carcinoma; it is possible that there may never be such a trial in patients with anal HSIL because of the number of subjects required to achieve adequate power and the length of follow-up involved.

Although there are no sanctioned guidelines for the treatment of high-grade internal anal dysplasia, several academic centers have begun to institute treatment protocols (Figure 2). In addition to a practitioner skilled in anal HRA and office ablation techniques, a clinic would require a collaborative group of interested and committed providers from several medical subspecialties: skilled anorectal surgeons, oncologists experienced in the management of invasive anal carcinoma, and infectious diseases specialists (given that the population at highest risk for high-grade internal anal dysplasia is HIV infected).

Techniques for ablation of high-grade internal anal dysplasia are similar to those for treatment of high-grade cervical lesions and include local application of 80% to 90% trichloroacetic acid, liquid nitrogen, or infrared beam therapy. There have been no controlled studies of the relative effectiveness of the ablation modalities described above. Choice of ablation modality currently depends on the availability and ease of use of a particular modality for each

practitioner. Other modalities that have shown promise in the treatment of anogenital condylomata are now being tested in the treatment of anal dysplasia; these include local application of imiquimod,⁴⁶ cidofovir,⁴⁷ or interferon.⁴⁸

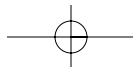
A patient should be referred to a skilled anorectal surgeon for examination and treatment under anesthesia in cases of widespread dysplasia:

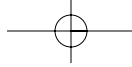
- When the burden of disease is more than 40% of the circumference of the transformation zone.
- When there is suspicion of an anal fistula.
- When the patient presents with rapidly progressive anogenital signs or symptoms such as a palpable mass, rectal bleeding, or anogenital pain.
- When adequate exposure of the lesions is difficult in the office.

Options for ablation in the operating room include laser excision, electrocautery, or cold-knife excision. As with cervical dysplasia, recurrence of high-grade anal dysplasia after ablation is increased in the HIV-positive compared with the HIV-negative population such that multiple treatments are often needed and closer follow-up is required.⁴⁹

Reconstitution of the Immune System With HAART

With the advent of HAART, it was postulated that reconstitution of the immune system would lead to regression of high-grade anal intraepithelial lesions. Unfortunately, this does not appear to be the case. Longitudinal follow-up of antiretroviral-naive HIV-positive patients with high-grade internal anal dysplasia at baseline demonstrated no significant regression of high-grade lesions, decrease in progression of low-grade lesions, or decrease in anal HPV shedding at 6 months after the institution of HAART.⁵⁰ Furthermore, in a cohort of 8640 HIV-positive persons, the incidence of anal cancer did





Editorial Comment: Screening and Treatment of AIN to Prevent Anal Cancer—Where Do We Stand?

Panther and colleagues¹ nicely describe the spectrum of human papillomavirus (HPV)-associated dysplasia and cancer of the anus in HIV-seropositive patients. Existing data summarized in part by the authors demonstrate that anal HPV infection and anal intraepithelial neoplasia (AIN) are more common among HIV-seropositive men and women than HIV-seronegative men and women; that the incidence of high-grade AIN is higher and progression to high-grade AIN is accelerated among HIV-seropositive persons; and that anal cancer is more common in this population.

The mechanisms for the increased risk of anal HPV infection and AIN in part reflect the higher cumulative number of sexual partners in some HIV risk groups, increasing the risk of acquisition of HPV. But there is almost certainly more to this: it is also possible that HIV-related immunosuppression indirectly increases the risk of reactivation of previously acquired HPV infection through attenuation of immune response and loss of control of viral replication. And as Panther and colleagues¹ point out, it is possible that HIV plays a direct role in the pathogenesis of HPV-associated lesions—an attractive hypothesis from *in vitro* data, but an interaction that has never been confirmed *in vivo*.

The authors also make the important point that the problem of AIN and anal cancer is not going to disappear with the use of HAART. Although there is evidence that HAART may beneficially affect the natural history of cervical intraepithelial neoplasia (CIN), its effect on CIN is modest at best, and its effect on AIN appears to be even less impressive. In the absence of routine screening for and treatment of high-grade AIN, it is possible that persons living longer thanks to HAART and with untreated high-grade AIN may have a high risk of their lesions progressing to anal cancer given sufficient time. The data are just beginning to come in on this issue; unlike other HIV-related malignancies, it is clear that the incidence of neither cervical nor anal cancer has dropped since the introduction of HAART. Some data are showing an increase in anal cancer.

So what to do about the problem of AIN? Panther and colleagues¹ outline an algorithm for screening for AIN. It is critical to remember that anal cytology screening is designed to detect AIN, not anal cancer. The optimal screening test for *anal cancer* currently is a digital rectal examination (DRE), which allows the clinician to feel for masses that he or she might miss on cytology, or even direct visualization during high-resolution anoscopy (HRA).

On the other hand, anal cytology screening should identify persons at risk for high-grade AIN, allowing the lesion to be treated before it progresses to cancer. All HIV-seropositive men and women should have a DRE annually by their primary care provider, but the DRE can also be done by the clinician performing the anal cytology and/or HRA. If so, clini-

cians must obtain the cytology first, because cytology should be collected before lubrication is introduced into the anal canal.

These authors list some of the groups that might benefit from anal cytology screening. On the list is HIV-seropositive persons with CD4⁺ cell counts below 200/μL. This seems reasonable given the high risk of AIN in this group, but the data show that men and women with CD4⁺ cell counts above 200/μL are also at high risk. In fact, the prevalence of anal HPV infection and AIN is high at all CD4⁺ cell counts, and some experts believe that *all* HIV-positive men and women should be considered for screening, regardless of the CD4⁺ cell count.

There are now data indicating that we, as clinicians, have the tools to diagnose high-grade AIN. But do we know how to treat it, and will successful treatment prevent anal cancer? These are perhaps the most important questions of the moment. The quick answer is that we do not yet have the information. That said, it is critical that the medical community understand that this does *not* mean that treatment of AIN does not prevent anal cancer; it merely means that the data have not yet been collected.

The analogy between CIN and AIN suggests that treatment of AIN ought to successfully prevent anal cancer. On the other hand, there are additional challenges to the treatment of AIN that do not exist for CIN, namely, the multifocality of the lesions, the difficulty in removing large areas of anal tissue without causing excessive morbidity, and the risk of recurrence of AIN even after successful treatment. Despite these challenges, it is possible that even temporarily successful treatment of AIN sets the molecular clock back and reduces, perhaps completely, the risk of cancer.

The “bottom” line: the definitive study needs to be done, and the data need to be collected. Obtaining the answers will take many years, though, assuming that the study can be done. In the meantime, some experts consider it reasonable to follow the screening and treatment algorithms outlined by Panther and colleagues¹ or variations of these guidelines published by others. Highly trained teams of clinicians skilled in diagnosis and treatment of AIN in the office as well as the operative suite are needed, but the incidence of anal cancer among HIV-seropositive persons, especially men who have sex with men, is simply too large to ignore while we wait for the answers.

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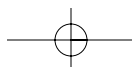
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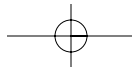
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not change after the introduction of HAART.⁵¹

Immunomodulation via HPV Vaccination

The utility of boosting the immune response to HPV in adult MSM and HIV-positive populations lies in its effectiveness at controlling rather than preventing infection. HPV vaccination has demonstrated its most promising effect as a prophylactic vaccine against cervical HPV infection, as reported in a placebo-controlled trial of over 2000 young women receiving 3 doses of an HPV-16 L1 particle-like vaccine. This trial demonstrated a very favorable anti-HPV-16 antibody response compared with the placebo group, prevention of HPV acquisition and persistent infection, and no cases of cervical intraepithelial neoplasia in the vaccine group.⁵²

Results of candidate HPV vaccines as immunomodulators to prevent anal dysplasia and carcinoma are few and less clear. A phase 1 trial of a plasmid DNA expressing a portion of the HPV-16 E7 protein showed safety, 83% immunogenicity, and partial regression of high-grade AIN to a lower grade in 25% of HIV-negative subjects with biopsy-proven high-grade AIN at baseline.⁵³

Data from a phase 2 study of a vaccine comprising *Mycobacterium bovis* heat shock protein 65 (HSP-65) fused to HPV-16 E7 protein was recently reported. This trial of 3 monthly 500- μ g subcutaneous injections eventually showed a relatively durable regression from high-grade dysplasia to normal in approximately half of the 80 participants studied.⁵⁴

The available data suggest that the HPV vaccines under study are safe. Larger trials are planned to assess their efficacy as prophylactic and therapeutic vaccines as well as to determine whether their efficacy varies among risk groups. With those data, the target population of

persons infected with HPV or at risk for HPV infection may be more accurately defined to bring the most benefit to the largest groups. Conversely, more substantial data from studies of current vaccine preparations will allow refinements that will further increase their efficacy and with it the possibility of preventing a major cause of morbidity and mortality worldwide.

SUMMARY

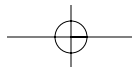
HPV coinfection in HIV disease is common. As HIV-infected patients are surviving longer in the era of HAART, the morbidity and mortality caused by anogenital HPV infection is increasing. Moreover, it is suspected that anogenital condylomata harboring high-grade dysplasia and invasive squamous cell carcinoma may be more prevalent in HIV-infected persons. Similarly, perianal Bowen disease may be underdetected in this population.

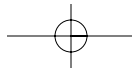
Given the increased incidence of anal carcinoma in the HIV-positive population, eradication of high-grade dysplasia has been recommended as a method of anal cancer prevention, analogous to the management of high-grade cervical dysplasia. Studies of HPV vaccines for prevention and treatment of HPV-related anogenital disease have been encouraging and are ongoing. HIV-positive patients with invasive cancer of the anal canal, particularly those with CD4⁺ cell counts greater than 200/ μ L and those receiving HAART, should be treated in a manner similar to that of their HIV-negative counterparts. In health care settings where appropriate treatment and follow-up of patients with abnormal anal Pap smears is not possible, the next best prevention tool is referral to a skilled surgeon for any signs and symptoms referable to the anogenital tract, with consistent performance and documentation of a yearly digital rectal examination. □

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