



CHAPTER 5

HPV infection and HPV-associated neoplasia in immunocompromised women

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KEYWORDS

Human papillomavirus;
Human
immunodeficiency virus;
Neoplasia

Abstract Human immunodeficiency virus (HIV)-positive women and women with transplant-associated immunocompromise are at increased risk for cervical intraepithelial neoplasia (CIN) and cervical cancer compared with healthy, immunocompetent women. HPV often manifests as a “field” effect in immunocompromised women who are also at increased risk for vaginal, vulval, and anal intraepithelial neoplasia. Immunocompromised women require careful follow-up with regular cytologic screening, and there should be a low threshold for performing colposcopic evaluation in these women. Once detected, CIN should be treated aggressively and the patient followed up closely for recurrence. Although treatment regimens are similar for immunocompromised and healthy women, the former may need multiple treatment modalities. Data on the ability of highly active antiretroviral therapy (HAART) to reduce the incidence of high-grade CIN and on the regression of existing CIN are mixed, some studies showing no benefit and others a modest benefit from HAART. However, the incidence of cervical cancer has not declined since the introduction of HAART, and the use of HAART among HIV-positive women has not changed the suggested approach to cervical cancer screening and treatment. Finally, prophylactic HPV vaccination offers the possibility of reducing the burden of disease among immunocompromised women, particularly if they are vaccinated before the onset of both sexual activity and immunocompromise. However, studies are needed to document safety and immunogenicity, and – given their high rate of prior HPV exposure – the effectiveness of the vaccine in these women.

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1. Introduction

There is abundant literature and long-standing clinical experience to document that immunocompromised women are at increased risk for anogenital HPV infection, anogenital precancerous intraepithelial neoplasia, and invasive anogenital cancer compared with healthy, immunocompetent women.

There is a long experience of HPV-related neoplasia in women with transplant-associated immunocompromise, but in the last few decades HIV infection has emerged as the most common cause of immunocompromise among women. Epidemiologic understanding of HPV infection and HPV-associated neoplasia in both these groups is in a state of flux. Active antiretroviral therapy (HAART) may con-

tinue to improve the overall immune status of HIV-positive women, possibly to the point of affecting the natural history of HPV-associated neoplasia; and women who undergo organ transplantation now benefit from immunosuppressive regimens that lead to less compromise of the immune system than previous regimens. The long-term effects of these changes on HPV-related neoplasia will not be known for many years. This chapter briefly summarizes current understanding of the prevalence and incidence of anogenital HPV infection and HPV-associated neoplasia in immunocompromised women and focuses on the diagnosis and management of HPV-associated neoplasia in these women. The implications of prophylactic HPV vaccines for immunocompromised women are discussed.

2. Anogenital HPV infection and anogenital neoplasia in HIV-positive women

2.1. Cervical HPV infection

Studies around the world have consistently documented a higher prevalence of cervical HPV infection in women who are HIV-positive. Cu-Uvin and coworkers [1], whose study was among the largest, examined the prevalence of cervical HPV infection in 851 HIV-positive and 434 HIV-negative women at high risk participating in the HIV Epidemiology Research (HER) study. They found that HPV infection was more prevalent among HIV-positive women (64% vs. 28%). Ahdieh and colleagues [2] performed a prospective study of HPV infection among the women in the HER study and reported that HPV persistence was nearly double in those with a CD4+ count less than 200 cells/ μ L than in those with a CD4+ count greater than 500 cells/ μ L.

Assessing the baseline prevalence of cervicovaginal HPV infection in 1778 HIV-positive and 500 HIV-negative women participating in the Women's Interagency HIV Study (WIHS), Palefsky and colleagues [3] found that 63% of the HIV-positive women and 30% of the HIV-negative risk-matched women had cervicovaginal HPV infection. In a prospective analysis of the same cohort, the highest risk of incident HPV was among women with a CD4+ count less than 200/ μ L or a HIV RNA level greater than 100,000 copies/mL [4]. Moreover, 22% of sexually inactive HIV-positive women with a CD4+ count less than 200/ μ L also had incident detection of at least 1 HPV type, suggesting that these women may have had reactivation of a pre-existing HPV infection.

2.2. Cervical intraepithelial neoplasia in HIV-positive women

Consistent with these HPV data, many studies worldwide have shown a higher prevalence of cervical intraepithelial neoplasia (CIN) among HIV-positive than among HIV-negative women. In the HER study, one of the larger studies of HIV-positive women, Duerr and associates [5] showed that CIN was present in 19% of HIV-positive women and 5% of the HIV-negative women. Similar findings have been reported from the WIHS [6] and from a large study of women in Abidjan, Ivory Coast [7].

Incident CIN is also more common among HIV-positive women. In a study conducted in New York the incidence of CIN among HIV-positive women was 8.3 per 100 person-years, compared with 1.8 per 100 person-years among HIV-negative women [8]. In the WIHS, at least 1 abnormal smear was found during follow-up for 73.0% of HIV-positive women and 42.3% of HIV-negative women, although the detection of new high-grade squamous intraepithelial lesions (HSILs) was low in both groups [9]. HIV positivity, HPV positivity, lower CD4+ count, and higher HIV RNA level were associated with the incidence of abnormal cytologic findings.

One of the themes that emerges from these studies is a central role for HPV infection and HPV persistence in the development of CIN among both HIV-positive and HIV-negative women. In a study of 627 women from Senegal, HIV-1 and HIV-2 infection were both associated with increased risk for HSIL. Although women with HIV-2 had a lower risk of developing HSIL than those with HIV-1 in univariate analyses, the main risk factor for developing HSIL in both groups was increased HPV persistence [10]. Consistent with this finding, in an analysis from the WIHS, the cumulative incidence of any SIL was low among HIV-negative and HIV-positive women with CD4+ counts greater than 500/ μ L who had normal cervical cytologic findings and tested negative for HPV [11].

Reports published to date on the impact of HAART on the natural history and treatment of CIN have been varied, probably owing to differences in study design, study outcome, patterns of HAART use, and study populations [12]. Still, the data suggest that HAART has a modest positive impact on the natural history of CIN. Women receiving HAART have been shown to have a lower incidence of cervical HSIL and a higher regression rate from HSIL to low-grade squamous intraepithelial lesion (LSIL) or lower [13]. However, as described later in this chapter, there has not been a HAART-associated reduction in the incidence of cervical cancer.

2.3. Anal HPV infection and anal intraepithelial neoplasia in HIV-positive women

As with cervical HPV infection and CIN, the prevalence of anal HPV infection and anal intraepithelial neoplasia (AIN) is higher among HIV-positive than among HIV-negative women. Palefsky and colleagues [15] studied anal HPV infection in HIV-positive and HIV-negative women participating at the San Francisco site of the WIHS. Among 200 women for whom there were concurrent anal and cervical HPV data, anal infection was more common than cervical infection in both HIV-positive (79% vs. 53%) and HIV-negative women (43% vs. 24%) [14]. Holly and coworkers examined the prevalence of anal lesions in the same population and reported abnormal anal cytologic finding in 26% of HIV-positive and 8% of HIV-negative women [15].

In a study of 925 HIV-positive and HIV-negative women from the New York area, vulvovaginal and perianal condylomata acuminata or intraepithelial neoplasia were found in 6% of HIV-positive and 1% of HIV-negative women at baseline. Among women without lesions at enrollment, vulvovaginal or perianal lesions developed in 9% of the HIV-positive and 1% of the HIV-negative women over a median follow-up of 3.2 years [16]. No studies have been reported yet on the effect of HAART on the natural history of AIN in women, but data in men suggest that HAART has little beneficial effect [17].

2.4. Anogenital cancer in HIV-positive women

Studies using data derived from cancer and AIDS registry matches from developed countries consistently show an increased incidence of cervical and anal cancer in HIV-positive individuals compared with the general population [18,19]. In the United States and Europe, women with a history of injection drug use appear to be at the highest risk for cervical cancer, which perhaps reflects their difficulty in accessing routine medical care, including cytologic screening. The incidence of vulvovaginal cancer among these women is also elevated compared with the general population [18]. In countries with no routine cervical cytologic testing, the increase in cervical cancer incidence among HIV-positive women is not as clear. There have been conflicting reports from Africa, as some studies found HIV to be associated with a modestly increased risk of cervical cancer while others have not shown an association [20–24].

The findings regarding the effect of HAART on cervical and anal cancer incidence are consistent with those discerning a modest benefit of HAART on the natural history of CIN but no benefit of HAART on AIN. To date, there is no evidence that the incidence

of anal or cervical cancer has declined since the introduction of HAART, unlike the incidence of other HIV-associated malignancies such as Kaposi sarcoma and non-Hodgkins lymphoma [25–28].

2.5. Anogenital HPV infection, intraepithelial neoplasia, and cancer in women with transplant-associated immunocompromise

It has long been established that individuals who undergo organ transplantation are at increased risk for HPV-associated anogenital cancers [29–32], and data from several studies also show an elevated prevalence of anogenital HPV infection and SIL among transplantation patients [33,34]. In one study, while cervical HPV infection was more common among transplant recipients than among age-matched controls, there were no differences after controlling for number of sexual partners [33]. Other studies have described a high prevalence of anal HPV infection among transplant recipients [35,36]. These studies suggest that the prevalence of HPV infection is high in transplant recipients prior to the transplantation, and that it further increases after iatrogenic immunosuppression is initiated to prevent graft rejection. In one study, the prevalence of anal HPV DNA was found to be high among men and women undergoing liver or renal transplantation before initiation of immunosuppressive therapy (23%) [35]. In another study, 23% of recent and 47% of established renal transplant recipients had anal HPV infection [36].

CIN is detected more frequently among women with a renal transplant, along with precancerous lesions at anogenital sites such as the vulva, vagina, and anus [30,33]. Similar findings have been reported in women following lung transplantation [37]. Moreover, the suspicion that individuals undergoing transplantation may be at increased risk of carrying anogenital HPV infection prior to the transplantation was raised for CIN. An elevated prevalence of positive cervical cytologic findings was noted in women prior to undergoing bone marrow transplantation, and CIN developed more frequently after transplantation in patients receiving allogeneic transplants than in those receiving autologous transplants – suggesting that conditioning therapy and immunosuppression further increase the risk of CIN [38].

3. Management of anogenital neoplasia in HIV-positive women

3.1. Cervical cytologic screening

Early studies suggested that the sensitivity of cervical cytologic screening to detect CIN was lower in HIV-positive than in HIV-negative women [39], but this was not corroborated in more recent, larger studies. There are only a few key differences in the guidelines for screening HIV-positive and HIV-negative women [40]. When presenting for their initial visit, all HIV-positive women should be screened with cervical cytology. If the results are normal, the cytologic evaluation should be repeated 6 months later. If the results of the second cytologic evaluation are normal, the patient can then undergo annual screening. There are no guidelines to indicate how long HIV-positive women should be screened annually. However, it seems reasonable to continue annual screening for a long time, if not indefinitely, because these women are at especially high risk for persistent HPV infection, acquisition of new HPV types, or reactivation of previously latent HPV types. This is true as well for women receiving HAART, since HAART has only a modest effect on the natural history of CIN and its treatment outcomes, and has not been shown to eradicate HPV infection. In general, there should be a low threshold for giving an HIV-positive woman a colposcopic examination.

American Society for Colposcopy and Cervical Pathology (ASCCP) guidelines suggest routine colposcopy referral for HIV-positive women found to have atypical squamous cells of undetermined significance (ASC-US) on cytologic evaluation [41]. Indeed, all HIV-positive women with atypical squamous cells – cannot exclude high-grade lesion (ASC-H), LSIL, or HSIL should be referred for colposcopy. When colposcopy is performed, the perineal and perianal regions must be examined as closely as the vagina and vulva for condylomas, intraepithelial neoplasia, and cancer because HIV-positive women often have multifocal disease. There is no evidence to date that supports performing systematic HPV DNA testing in HIV-positive women, although it has been shown to have value in the triage of HIV-negative women with equivocal cytology (e.g., ASC-US).

3.2. Treatment of CIN and cancer in HIV-positive women

Several studies suggest that treatment failure for CIN is more common among HIV-positive than among HIV-negative women [42–44]. This may reflect a lower immune competence and the possibility that

lesions may be larger and more numerous in HIV-positive women. For this reason, the careful monitoring of these women is necessary to assess therapeutic efficacy. Several therapeutic modalities may be needed to clear a lesion in a given patient.

Most of the studies on CIN treatment in HIV-positive women were performed before the advent of HAART. While treatment has been shown to be more effective in HIV-positive women receiving HAART, it is clear that HAART alone is not sufficient to treat CIN [44]. HAART should therefore not be initiated in HIV-positive women to treat CIN in the absence of established indications for HAART, such as those recommended by the International AIDS Society – USA. These indications are CD4+ cell count less than 350/ μ L, HIV viral load $>100,000$ i.u., and development of an AIDS-defining illness [45].

Data from the pre-HAART era suggest that HIV-positive women may present with cervical cancer at more advanced stages than HIV-negative women, possibly reflecting a more rapid progression [46]. At least in part because their disease is more advanced, treatment outcome is less favorable in HIV-positive women who therefore need to be monitored carefully for disease recurrence. There are few data on treatment outcome for cervical cancer among HIV-positive women in the HAART era; however, the data on the limited effect of HAART on CIN as well as the high incidence of cervical cancer in these women would suggest that the effect of HAART on cervical cancer treatment is also limited.

While treatment of cervical cancer is essentially the same for HIV-positive and HIV-negative women, as with CIN, there should be a relatively low threshold for initiating HAART. There are also few data on the interaction between HAART and various treatment modalities for cervical cancer. Pelvic radiation therapy has the potential to lower CD4+ cell levels through its effect on bone marrow. Theoretically, HAART might mitigate this adverse effect by minimizing the additional contribution of HIV to the lowering of CD4+ cell levels. Interactions between HAART and chemotherapy for cervical cancer have not been described.

3.3. Screening and treatment of AIN and anal cancer in HIV-positive women

Screening for and treating CIN prevent many cervical cancers from developing, and the same is most likely true for AIN and anal cancer. The main arguments to delay routine anal screening in HIV-positive women are that no formal cost-benefit analyses have been performed for this population, and that no studies have yet demonstrated that treatment for AIN reduces the incidence of anal cancer. Hence,

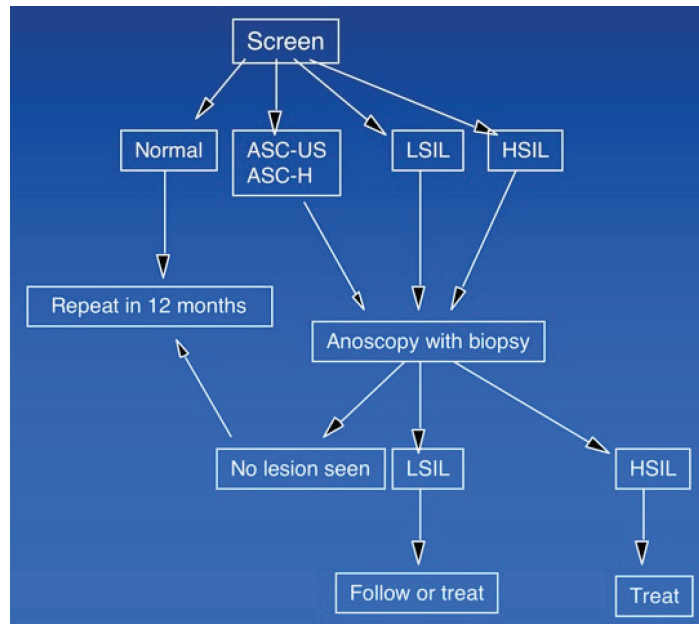


Figure 1 Algorithm for screening for anal squamous intraepithelial lesions in HIV-positive women. Women in whom cytologic abnormalities are found are referred for high-resolution anoscopy and biopsy. Treatment of anal high-grade squamous intraepithelial lesions (HSILs) is recommended whenever possible to prevent anal cancer. Treatment of low-grade squamous intraepithelial lesions (LSILs) is not necessary but should be considered if the lesions can be treated with relatively little morbidity, as LSILs may continue to increase in size and progress to HSIL over time.

Abbreviations: ASC-H, atypical squamous cells – cannot exclude high-grade lesion; ASC-US, atypical squamous cells of undetermined significance; HSIL, high-grade squamous intraepithelial lesion.

there are no formal guidelines at this time indicating that anal screening should be performed in HIV-positive women. While data are clearly needed to definitively demonstrate the utility of anal screening and treatment, the question is whether to delay these procedures until those data become available. In the opinion of the author, the prevalence data for AIN and the incidence of anal cancer in HIV-positive women are sufficiently compelling to initiate routine anal screening and treatment. Ideally, if and when anal screening should be initiated, this would be performed in a research setting that would also contribute to the collection of the data needed to establish the utility of screening.

Guidelines have been published for screening and treatment of AIN in HIV-positive men [46], and a similar approach may be taken for HIV-positive women (Figure 1). There are insufficient published data to perform a formal cost-benefit analysis to determine whether the same guidelines should be followed for women. However, if screening is initiated, women who should be particularly targeted include those with a history of CIN or cervical cancer and those with a history of receptive anal intercourse. Methods to obtain an adequate anal cytologic assessment have been described elsewhere [47]. Like cervical cytology, anal cytology is classified as ASC-US, ASC-H, LSIL, HSIL, or cancer. HIV-

positive women with any abnormal anal cytologic finding should be referred for the next step, i.e., high-resolution anoscopy (HRA) and biopsy of visible disease. Women with ASC-US are normally referred because an ASC-US finding has a high predictive value for AIN on biopsy [48].

In assessing HIV-positive women for AIN and cancer, the cytology specimen is obtained first. Thereafter a digital rectal examination (DRE) should be performed, using lubrication if required. The DRE is an important tool to screen for anal cancer, since masses that might not be detected on cytologic evaluation or visualized on HRA may be felt below the mucosal surface. But cytology and biopsy results may be falsely negative when invasive cancer is present, particularly if the tumor is below the mucosal surface. The goal of DRE should therefore be to feel for masses suggestive of cancer, whereas cytology and HRA-guided biopsy should primarily be considered to be screening tests for precancerous lesions.

Just as in cervical colposcopy, HRA permits the identification and biopsy of lesions that have caused the abnormal cytologic results. As with cervical colposcopy, acetic acid allows the visualization of abnormal tissue by a change known as acetowhitening. In the anal canal, a 3% solution of acetic acid is used. Abnormal vascular patterns can be seen fol-

lowing the application of acetic acid and magnification, and they are similar to those seen in CIN. Likewise, AIN has reduced uptake of Lugol's iodine. As in the cervix, the goal is to identify the most advanced lesion to guide treatment. Techniques to perform anal biopsies have been described elsewhere [46].

The choice of treatment for AIN depends on location (perianal vs. intra-anal) and on the size and number of lesions [47]. Perianal condylomas may be treated with podophyllotoxin or imiquimod. Perianal SIL often requires ablation using liquid nitrogen, trichloroacetic acid, infrared coagulation, or electrocautery, or cold scalpel excision. For limited intra-anal disease, it is often helpful to begin with trichloroacetic acid. Larger lesions or lesions that do not respond to trichloroacetic acid applications may be treated with electrocautery or infrared coagulation. Lesions too large or diffuse to be treated with infrared coagulation most often require surgical excision with anesthesia in an outpatient surgical setting. Other approaches to treatment of AIN have been described, including the use of imiquimod and photodynamic therapy, although not in randomized controlled studies [49–51].

As described previously, HAART appears to have an even less beneficial effect on AIN than on CIN, and HAART has not led to a reduction in the incidence of anal cancer. HIV-positive women receiving HAART are therefore at high risk for AIN, and HAART should not lead to a change in the screening and treatment approach.

The treatment of anal cancer is similar in HIV-positive and HIV-negative women. There are no published data on the effect of HAART on the treatment of anal cancer in women. Prior to the introduction of HAART there were concerns about whether HIV-positive patients would tolerate full-dose anal cancer therapy [52], but recent data suggest that HIV-positive men receiving HAART who are treated for anal cancer have fewer treatment-related complications and are better able to tolerate full therapy [53]. Treatment for anal cancer is typically 5-fluorouracil and mitomycin C combined with radiation therapy [54–56], but in recent years cisplatin has been increasingly used instead of mitomycin C. As with cervical cancer, the success of treatment for anal cancer correlates inversely with the stage at which the diagnosis is made. Abdominoperineal resection is usually required for local disease if lesions recur after chemoradiation therapy.

The major morbidity associated with treatment of anal cancer is proctitis secondary to the radiation therapy, a condition that can lead to severe pain and bleeding for months or years after completion of therapy. Therefore, although treatment

for anal cancer is often successful, especially if the disease is detected at its earliest stages, preventing the need to treat for cancer is a powerful incentive to detect and treat AIN prior to malignant progression.

4. Management of anogenital neoplasia in women with transplant-associated immunocompromise

There is little literature on the efficacy of CIN and cervical cancer treatment in women with transplant-associated immunocompromise. Given their increased risk of CIN and anogenital cancer, it is clear that these women require very close monitoring, similar to HIV-positive women. There are no official guidelines regarding the screening or treatment of women with transplant-associated immunocompromise, but it seems reasonable to use the guidelines published for HIV-positive women. Similar to HIV-positive women who will likely remain immunocompromised to some degree for the remainder of their lives, even when they receive HAART, women with transplant-associated immunocompromise remain immunocompromised as long as they continue to require iatrogenic immunosuppression to prevent graft rejection. Recent advances in immunosuppressive regimens may mitigate this situation but there are no data yet indicating that modern immunosuppressive regimens have led to reduced risk of anogenital SIL or cancer. As with HIV-positive women, there should be a low threshold for colposcopy referral and women with transplant-associated immunocompromise should be aggressively treated for CIN once it is detected. They should also be examined carefully for HPV-associated lesions elsewhere in the anogenital tract, and they should be considered for anal cytologic screening.

5. Prospects for prophylactic vaccination of HIV-positive women and women with transplant-associated immunocompromise

The HPV vaccines that will likely be approved for commercial use have been shown to be effective in reducing rates of initial infection with HPV-16 and HPV-18 [57–59] as well as HPV-6 and HPV-11 [59] in healthy young women. And because most women who are HIV positive or transplant recipients acquire HPV infection before they become immunocompromised, over time, routine HPV vaccination would likely have a major beneficial impact on anogenital HPV-related neoplasia in these 2 groups of women. If the duration of vaccine protection is sufficiently

long, it might be expected that women will test negative for the HPV types present in the vaccine at the time they become immunocompromised, and therefore should not be at risk for disease from these viral types. Major questions remain, however, including whether vaccine protection will last beyond the third and fourth decade of the women's lives, when they continue to be at risk for becoming immunocompromised.

It is also not known how vaccine efficacy is affected once a woman becomes immunocompromised. Theoretically, there should be relatively little impact on humoral immune responses in HIV-positive women and women with transplant-associated immunocompromise, but it is not known if these women will remain protected. The vaccines are expected to reduce the acquisition of HPV types that account for only 70% of cervical cancers. Thus, healthy, immunocompetent women as well as vaccinated women who later become immunocompromised will require periodic cervical and possibly anal cytologic screening.

A more immediate issue is whether women should receive HPV vaccination after they are known to be immunocompromised. Many HIV-positive women will already have acquired 1 or more of the HPV types in the vaccine by the time the vaccines become available. Further, although the prevalent infection rate with HPV-16 or HPV-18 may be low [3], a high proportion of women have already seroconverted, at least for HPV-16, when they become immunocompromised, indicating prior exposure [60,?].

But these considerations do not necessarily mean that HIV-positive women would not benefit from HPV vaccination. First, many women may derive benefit from being protected against HPV types that they have not yet acquired. Second, it is theoretically possible that HPV vaccination may reduce the risk of incident lesions in association with reactivation of previously acquired HPV infection. Safety studies should be performed in HIV-positive women, and if the vaccine is shown to be safe, as expected, then studies should be conducted to determine if this population of women benefit from HPV vaccination. Measurable outcomes should include incident detection of vaccine HPV types and incident SIL in the entire anogenital tract. Similar considerations apply to women who are immunocompromised because of organ transplant.

6. Conclusions

HIV-positive women and women with transplant-associated immunocompromise are clearly at increased risk for CIN and cervical cancer com-

pared with healthy, immunocompetent women. In addition, HPV often manifests as a "field" infection in immunocompromised women, who are also at increased risk for vaginal, vulvar, and anal disease. HIV-positive women and women with transplant-associated immunocompromise require careful follow-up with regular and more frequent cytologic screening than immunocompetent women – e.g., annual screening over a longer time. While screening intervals are typically increased in healthy women over time, annual screening of HIV-positive women and women with transplant-associated immunocompromise seems prudent for as long as they remain immunocompromised. There should be a low threshold to refer immunocompromised women for colposcopic evaluation; and once a lesion is detected, it needs to be treated aggressively and followed up closely for recurrence. Immunocompromised women should be considered for anal cytologic screening followed by a digital rectal examination and a HRA-guided anal biopsy. Although treatment regimens are similar for immunocompromised and healthy women, multiple treatment modalities are sometimes needed for the former, and immunocompromised women should be followed up closely after treatment to monitor for disease recurrence. The use of HAART among HIV-positive women has not changed the suggested approach to screening and treatment. Finally, HPV vaccination offers the possibility of reducing the burden of disease among immunocompromised women if they are vaccinated before they become immunocompromised. Vaccination may also benefit women who are immunocompromised at the time of HPV vaccination, but future studies will be needed to document these benefits.

References

- [1] Cu-Uvin S, Hogan JW, Warren D, Klein RS, Peipert J, Schuman P, et al; HIV Epidemiology Research Study Group. Prevalence of lower genital tract infections among human immunodeficiency virus (HIV)-seropositive and high-risk HIV-seronegative women. *Clin Infect Dis* 1999;29(5): 1145–50.
- [2] Ahdieh L, Klein RS, Burk R, Cu-Uvin S, Schuman P, Duerr A, et al. Prevalence, incidence, and type-specific persistence of human papillomavirus in human immunodeficiency virus (HIV)-positive and HIV-negative women. *J Infect Dis* 2001;184(6):682–90.
- [3] Palefsky JM, Minkoff H, Kalish LA, Levine A, Sacks HS, Garcia P, et al. Cervicovaginal human papillomavirus infection in human immunodeficiency virus-1 (HIV)-positive and high-risk HIV-negative women [see comments]. *J Natl Cancer Inst* 1999;91(3):226–36.
- [4] Strickler HD, Burk RD, Fazzari M, Anastos K, Minkoff H, Massad LS, et al. Natural history and possible reactivation of human papillomavirus in human immun-

- odeficiency virus-positive women. *J Natl Cancer Inst* 2005;97(8):577–86.
- [5] Duerr A, Kieke B, Warren D, Shah K, Burk R, Peipert JF, et al. Human papillomavirus-associated cervical cytologic abnormalities among women with or at risk of infection with human immunodeficiency virus. *Am J Obstet Gynecol* 2001;184(4):584–90.
- [6] Massad LS, Riestler KA, Anastos KM, Fruchter RG, Palefsky JM, Burk RD, et al; Women's Interagency HIV Study Group. Prevalence and predictors of squamous cell abnormalities in Papanicolaou smears from women infected with HIV-1. *J Acquir Immune Defic Syndr* 1999;21(1):33–41.
- [7] La Ruche G, Ramon R, Mensah-Ado I, Bergeron C, Diomande M, Sylla-Koko F, et al; Dyscer-CI Group. Squamous intraepithelial lesions of the cervix, invasive cervical carcinoma, and immunosuppression induced by human immunodeficiency virus in Africa. *Cancer* 1998;82(12):2401–8.
- [8] Ellerbrock TV, Chiasson MA, Bush TJ, Sun XW, Sawo D, Brudney K, et al. Incidence of cervical squamous intraepithelial lesions in HIV-infected women. *JAMA* 2000;283(8):1031–7.
- [9] Massad LS, Ahdieh L, Benning L, Minkoff H, Greenblatt RM, Watts H, et al. Evolution of cervical abnormalities among women with HIV-1: evidence from surveillance cytology in the women's interagency HIV study. *J Acquir Immune Defic Syndr* 2001;27(5):432–42.
- [10] Hawes SE, Critchlow CW, Sow PS, Toure P, N'Doye I, Diop A, et al. Incident high-grade squamous intraepithelial lesions in Senegalese women with and without human immunodeficiency virus type 1 (HIV-1) and HIV-2. *J Natl Cancer Inst* 2006;98(2):100–9.
- [11] Harris TG, Burk RD, Palefsky JM, Massad LS, Bang JY, Anastos K, et al. Incidence of cervical squamous intraepithelial lesions associated with HIV serostatus, CD4 cell counts, and human papillomavirus test results. *JAMA* 2005;293(12):1471–6.
- [12] Heard I, Palefsky JM, Kazatchkine MD. The impact of HIV antiviral therapy on human papillomavirus (HPV) infections and HPV-related diseases. *Antivir Ther* 2004;9(1):13–22.
- [13] Minkoff H, Ahdieh L, Massad LS, Anastos K, Watts DH, Melnick S, et al. The effect of highly active antiretroviral therapy on cervical cytologic changes associated with oncogenic HPV among HIV-infected women. *Aids* 2001;15(16):2157–64.
- [14] Palefsky JM, Holly EA, Ralston ML, Da Costa M, Greenblatt RM. Prevalence and risk factors for anal human papillomavirus infection in human immunodeficiency virus (HIV)-positive and high-risk HIV-negative women. *J Infect Dis* 2001;183(3):383–91.
- [15] Holly EA, Ralston ML, Darragh TM, Greenblatt RM, Jay N, Palefsky JM. Prevalence and risk factors for anal squamous intraepithelial lesions in women. *J Natl Cancer Inst* 2001;93(11):843–9.
- [16] Conley LJ, Ellerbrock TV, Bush TJ, Chiasson MA, Sawo D, Wright TC. HIV-1 infection and risk of vulvovaginal and perianal condylomata acuminata and intraepithelial neoplasia: a prospective cohort study. *Lancet* 2002;359(9301):108–13.
- [17] Palefsky JM, Holly EA, Efirde JT, Da Costa M, Jay N, Berry JM, et al. Anal intraepithelial neoplasia in the highly active antiretroviral therapy era among HIV-positive men who have sex with men. *Aids* 2005;19(13):1407–14.
- [18] Frisch M, Biggar RJ, Goedert JJ. Human papillomavirus-associated cancers in patients with human immunodeficiency virus infection and acquired immunodeficiency syndrome. *J Natl Cancer Inst* 2000;92(18):1500–10.
- [19] Frisch M, Biggar RJ, Engels EA, Goedert JJ. Association of cancer with AIDS-related immunosuppression in adults. *JAMA* 2001;285(13):1736–45.
- [20] Sitas F, Pacella-Norman R, Carrara H, Patel M, Ruff P, Sur R, et al. The spectrum of HIV-1 related cancers in South Africa. *Int J Cancer* 2000;88(3):489–92.
- [21] Newton R, Ziegler J, Beral V, Mbidde E, Carpenter L, Wabinga H, et al. A case-control study of human immunodeficiency virus infection and cancer in adults and children residing in Kampala, Uganda. *Int J Cancer* 2001;92(5):622–7.
- [22] Gichangi P, De Vuyst H, Estambale B, Rogo K, Bwayo J, Temmerman M. HIV and cervical cancer in Kenya. *Int J Gynaecol Obstet* 2002;76(1):55–63.
- [23] Mbulaiteye SM, Parkin DM, Rabkin CS. Epidemiology of AIDS-related malignancies an international perspective. *Hematol Oncol Clin North Am* 2003;17(3):673–96, v.
- [24] Mbulaiteye SM, Biggar RJ, Goedert JJ, Engels EA. Immune deficiency and risk for malignancy among persons with AIDS. *J Acquir Immune Defic Syndr* 2003;32(5):527–33.
- [25] Cress RD, Holly EA. Incidence of anal cancer in California: increased incidence among men in San Francisco, 1973–1999. *Prev Med* 2003;36(5):555–60.
- [26] Bower M, Powles T, Newsom-Davis T, Thirlwell C, Stebbing J, Mandalia S, et al. HIV-associated anal cancer: has highly active antiretroviral therapy reduced the incidence or improved the outcome? *J Acquir Immune Defic Syndr* 2004;37(5):1563–1565.
- [27] Chiao EY, Krown SE, Stier EA, Schrag D. A population-based analysis of temporal trends in the incidence of squamous anal canal cancer in relation to the HIV epidemic. *J Acquir Immune Defic Syndr* 2005;40(4):451–5.
- [28] Diamond C, Taylor TH, Aboumrad T, Bringman D, Anton-Culver H. Increased incidence of squamous cell anal cancer among men with AIDS in the era of highly active antiretroviral therapy. *Sex Transm Dis* 2005;32(5):314–20.
- [29] Penn I. The changing pattern of posttransplant malignancies. *Transplant Proc* 1991;23(1 Pt 2):1101–3.
- [30] Penn I. Cancer in the immunosuppressed organ recipient. *Transplant Proc* 1991;23(2):1771–2.
- [31] Bhatia S, Louie AD, Bhatia R, O'Donnell MR, Fung H, Kashyap A, et al. Solid cancers after bone marrow transplantation. *J Clin Oncol* 2001;19(2):464–71.
- [32] Adami J, Gabel H, Lindelof B, Ekstrom K, Rydh B, Glimelius B, et al. Cancer risk following organ transplantation: a nationwide cohort study in Sweden. *Br J Cancer* 2003;89(7):1221–7.
- [33] Fairley CK, Chen S, Tabrizi SN, McNeil J, Becker G, Walker R, et al. Prevalence of HPV DNA in cervical specimens in women with renal transplants: a comparison with dialysis-dependent patients and patients with renal impairment. *Nephrol Dial Transplant* 1994;9(4):416–20.
- [34] Brown MR, Noffsinger A, First MR, Penn I, Husseinzadeh N. HPV subtype analysis in lower genital tract neoplasms of female renal transplant recipients. *Gynecol Oncol* 2000;79(2):220–4.
- [35] Roka S, Rasoul-Rockenschaub S, Roka J, Kirnbauer R, Muhlbacher F, Salat A. Prevalence of anal HPV infection in solid-organ transplant patients prior to immunosuppression. *Transpl Int* 2004;17(7):366–9.
- [36] Patel HS, Silver AR, Northrope JM. Anal cancer in renal transplant patients. *Int J Colorectal Dis* 2005:1–5.
- [37] Malouf MA, Hopkins PM, Singleton L, Chhajed PN, Plit ML, Glanville AR. Sexual health issues after lung transplantation: importance of cervical screening. *J Heart Lung Transplant* 2004;23(7):894–7.
- [38] Sasadeusz J, Kelly H, Szer J, Schwarzer AP, Mitchell H, Grigg

- A. Abnormal cervical cytology in bone marrow transplant recipients. *Bone Marrow Transplant* 2001;28(4):393-7.
- [39] Maiman M, Tarricone N, Vieira J, Suarez J, Serur E, Boyce JG. Colposcopic evaluation of human immunodeficiency virus-seropositive women. *Obstet Gynecol* 1991;78(1):84-8.
- [40] Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines 2002. *MMWR Recomm Rep* 2002;51(RR-6): 41. Wright TC, Cox JT, Massad LS, Twigg LB, Wilkinson EJ, et al. 2001 Consensus guidelines for the management of women with cervical cytological abnormalities. *JAMA* 2002; 287:2120-29.
- [41] Maiman M, Fruchter RG, Serur E, Levine PA, Arrastia CD, Sedlis A. Recurrent cervical intraepithelial neoplasia in human immunodeficiency virus-seropositive women. *Obstet Gynecol* 1993;82(2):170-4.
- [42] Fruchter RG, Maiman M, Sedlis A, Bartley L, Camilien L, Arrastia CD. Multiple recurrences of cervical intraepithelial neoplasia in women with the human immunodeficiency virus. *Obstet Gynecol* 1996;87(3):338.
- [43] Heard I, Potard V, Foulot H, Chapron C, Costagliola D, Kazatchkine MD. High rate of recurrence of cervical intraepithelial neoplasia after surgery in HIV-positive women. *J Acquir Immune Defic Syndr* 2005;39(4):412-8.
- [44] Carpenter CC, Cooper DA, Fischl MA, Gatell JM, Gazzard BG, Hammer SM, et al. Antiretroviral therapy in adults: updated recommendations of the International AIDS Society-USA Panel. *JAMA* 2000;283(3):381-90.
- [45] Maiman M, Fruchter RG, Serur E, Remy JC, Feuer G, Boyce J. Human immunodeficiency virus infection and cervical neoplasia. *Gynecol Oncol* 1990;38(3):377-82.
- [46] Chin-Hong PV, Palefsky JM. Natural history and clinical management of anal human papillomavirus disease in men and women infected with human immunodeficiency virus. *Clin Infect Dis* 2002;35(9):1127-34.
- [47] Palefsky JM, Holly EA, Hogeboom CJ, Jay N, Berry M, Darragh TM. Anal cytology as a screening tool for anal squamous intraepithelial lesions. *J Acq Immun Defic Syndr* 1997;14:415-422.
- [48] Hamdan KA, Tait IS, Nadeau V, Padgett M, Carey F, Steele RJ. Treatment of grade III anal intraepithelial neoplasia with photodynamic therapy: report of a case. *Dis Colon Rectum* 2003;46(11):1555-9.
- [49] Scholefield JH. Treatment of grade III anal intraepithelial neoplasia with photodynamic therapy: report of a case. *Dis Colon Rectum*, 2003;46(11):1555-1559. *Tech Coloproctol* 2004;8(3):200.
- [50] Webber J, Fromm D. Photodynamic therapy for carcinoma in situ of the anus. *Arch Surg* 2004;139(3):259-61.
- [51] Peddada AV, Smith DE, Rao AR, Frost DB, Kagan AR. Chemotherapy and low-dose radiotherapy in the treatment of HIV-infected patients with carcinoma of the anal canal. *Int J Radiat Oncol Biol Phys* 1997;37(5):1101-5.
- [52] Blazy A, Hennequin C, Gornet JM, Furco A, Gerard L, Lemann M, et al. Anal carcinomas in HIV-positive patients: high-dose chemoradiotherapy is feasible in the era of highly active antiretroviral therapy. *Dis Colon Rectum* 2005;48(6):1176-81.
- [53] Flam M, John M, Pajak TF, Petrelli N, Myerson R, Doggett S, et al. Role of mitomycin in combination with fluorouracil and radiotherapy, and of salvage chemoradiation in the definitive nonsurgical treatment of epidermoid carcinoma of the anal canal: results of a phase III randomized intergroup study. *J Clin Oncol* 1996;14(9):2527-39.
- [54] UK Co-ordinating Committee on Cancer Research. Epidermoid anal cancer: results from the UKCCCR randomised trial of radiotherapy alone versus radiotherapy, 5-fluorouracil, and mitomycin: UKCCCR Anal Cancer Trial Working Party. *Lancet* 1996;348(9034):1049-54.
- [55] Bartelink H, Roelofsen F, Eschwege F, Rougier P, Bosset JF, Gonzalez DG, et al. Concomitant radiotherapy and chemotherapy is superior to radiotherapy alone in the treatment of locally advanced anal cancer: results of a phase III randomized trial of the European Organization for Research and Treatment of Cancer Radiotherapy and Gastrointestinal Cooperative Groups. *J Clin Oncol* 1997;15(5):2040-9.
- [56] Koutsky LA, Ault KA, Wheeler CM, Brown DR, Barr E, Alvarez FB, et al. A controlled trial of a human papillomavirus type 16 vaccine. *N Engl J Med* 2002;347(21):1645-51.
- [57] Harper DM, Franco EL, Wheeler C, Ferris DG, Jenkins D, Schuind A, et al. Efficacy of a bivalent L1 virus-like particle vaccine in prevention of infection with human papillomavirus types 16 and 18 in young women: a randomised controlled trial. *Lancet* 2004;364(9447):1757-65.
- [58] Villa LL, Costa RL, Petta CA, Andrade RP, Ault KA, Giuliano AR, et al. Prophylactic quadrivalent human papillomavirus (types 6, 11, 16, and 18) L1 virus-like particle vaccine in young women: a randomised double-blind placebo-controlled multicentre phase II efficacy trial. *Lancet Oncol* 2005;6(5):271-8.
- [59] Viscidi RP, Ahdieh-Grant L, Clayman B, Fox K, Massad LS, Cu-Uvin S, et al. Serum immunoglobulin G response to human papillomavirus type 16 virus-like particles in human immunodeficiency virus (HIV)-positive and risk-matched HIV-negative women. *J Infect Dis* 2003;187(2):194-205.
- [60] Viscidi RP, Ahdieh-Grant L, Schneider MF, Clayman B, Massad LS, Anastos KM, et al. Serum immunoglobulin A response to human papillomavirus type 16 virus-like particles in human immunodeficiency virus (HIV)-positive and high-risk HIV-negative women. *J Infect Dis* 2003;188(12):1834-44.