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Human Papillomavirus Related Diseases in HIV-infected individuals

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Abstract

Purpose of review—To present recent publications in human papillomavirus (HPV)-associated diseases and their relationship to HIV-infected patients.

Recent findings—Studies assessing geographic variations in HPV types and prevalence in cervical dysplasia and cancer in HIV-infected women suggest that although HPV types 16 and 18 dominate, multiple other HPV types may play a role in carcinogenesis. Anal dysplasia and cancer incidence continues to rise in the highly active antiretroviral therapy (HAART) era; however, data on outcomes following therapy for anal dysplasia (infra-red coagulator, high resolution anoscopy guided ablation) and anal cancer (chemoradiation and possibly intensity modulated radiation therapy) have been encouraging. Oral HPV may be associated with lower genital tract HPV infection and may have implications in the development of oropharyngeal cancer.

Summary—As HIV-infected patients in the HAART era continue to have high rates of cervical and anal cancer, it is important to continue screening efforts and treatment of pre-invasive disease. Treatment options for anal dysplasia and anal cancer in HIV-infected individuals are expanding and may lead to decreased morbidity and mortality. Trials assessing safety and immunogenicity of the HPV quadrivalent vaccine in people with HIV have started enrollment, and if successful, may prevent many HPV-associated cancers.

Keywords

HPV; HIV; cervical and anal dysplasia

Introduction

The incidence of many HIV associated co-morbidities has decreased in the era of highly active antiretroviral therapy (HAART); however, the incidence of diseases related to human papillomavirus (HPV) infection has remained stable or continued to rise [1,2]. The HIV/AIDS Cancer Match Study found that cervical cancer incidence among HIV-infected women in the U.S. has been unchanged since the introduction of HAART at 64.2 cases per 100,000 person-years (1990-1995) compared to 86.5 cases per 100,000 person-years (1996-2002) (RR 1.41,

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Additional Resources:

**Arora A, Chiao E, Tyring SK. AIDS malignancies. *Cancer Treatment and Research* 2007; 133: 21-67.

A comprehensive review of HIV associated malignancies with a discussion of cervical and anal cancers and the role of HAART.

**Cameron JE, Hagensee ME. Human papillomavirus infection and disease in the HIV positive individual. *Cancer Treatment and Research*. 2007; 133: 185-213.

This is a very comprehensive review article on this subject.

Palefsky J. Human papillomavirus infection in HIV-infected persons. *Topics in HIV Medicine* 2007; 15(4): 130-3.

**Uronis HE, Bendell JC. Anal Cancer: An Overview. *The Oncologist* 2007; 12: 524-34.

This paper is a comprehensive review article discussing the epidemiology, diagnosis, and treatment of anal cancer.

95% C.I. 0.81 to 2.46) [3**]. Anal cancer rates, however, appear to be increasing with cohort studies finding that the anal cancer incidence in men with HIV has climbed from 35-49 cases per 100,000 person-years in the pre-HAART era to 92 to 144 cases per 100,000 person-years [4,5]. The cancer risk in HIV-infected individuals compared to the general population has been estimated to be as high as 29 times increased for anal cancer, 4 times for penile cancer, 6 times for vulvar and vaginal cancer as well as cervical cancer [6**]. As the increased incidence of these HPV-associated cancers in HIV-infected persons persists despite apparent immune reconstitution with HAART, the importance of optimizing screening, prevention and treatment of these diseases becomes even more important.

Cervical HPV

Cervical cancer is the second most common cancer among women worldwide; of the 274,000 deaths due to cervical cancer annually, 80% occur in developing countries [7]. In countries where cervical cancer screening with Papanicolaou (Pap) testing is routinely performed, the incidence and mortality of cervical cancer has decreased to one-third of pre-Pap screening levels [8]. It is likely that the treatment of premalignant lesions and diagnosis of earlier stage cervical cancers contributed to the decrease in incidence and mortality of cervical cancer.

Despite the apparent success of the Pap test, cases of cervical cancers still occur in areas where routine cervical screening is performed due to missed Pap tests, inadequate follow-up or inaccurate cytology results. As HPV has been detected in more than 99% of cases of squamous cell cervical cancer and a reliable HPV test, Digene's hybrid capture 2 (HC2), is available, several studies have compared cervical cytology with HPV testing for detection of HSIL for women over 30 years of age and found that HPV testing is more sensitive and less specific for identifying women with HSIL of the cervix [9,10].

Kitchener et al investigated the best method of cervical surveillance in HIV-infected women by comparing colposcopy, cervical cytology, and HPV testing with HC2 for the detection of high-grade cervical dysplasia in a cohort of 1534 European and South African women with HIV. The rates of baseline high- grade cytology were similar in the European and South African women, 10% and 13% respectively, despite the widespread use of HAART in Europe compared to South Africa. The overall abnormal cytology rate was higher in South Africa: 55% compared with 34% in Europe. Cytology and colposcopy had similar rates of diagnostic accuracy (sensitivity of 98-100%, specificity of 63-65%, and PPV of 22-23%) for the detection of cervical intraepithelial neoplasia (CIN) 2 or higher. HPV testing had similar sensitivity (91%) but significantly poorer specificity (48%) [11**].

Current U.S. guidelines recommend women diagnosed with HIV undergo screening for cervical cancer with cytology at 6 month intervals until two Pap tests have been documented negative, and then annually thereafter [12]. In addition, the recently released guidelines for the management of women with abnormal cervical cytology screening tests recommend that an HIV-infected patient with a Pap test showing atypical squamous cells of undetermined significance (ASCUS) does not need to be referred for a colposcopic evaluation if reflex HPV testing is negative. This is a change from prior recommendations where it was suggested that all HIV-infected women with ASCUS Pap test results be referred for colposcopic evaluation [13].

Massad et al reported on 170 HIV-positive women from the Women's Interagency HIV Study (WIHS) and the HIV Epidemiology Research Study (HERS) treated for cervical dysplasia with either ablation or excision and followed after treatment with cytologic and HPV testing. The overall rate of persistent dysplasia was 46% with a recurrence rate of 56% in the 101 patients apparently clear of dysplasia at 6 months. In both cases, the majority had low-grade lesions:

only one patient developed adenocarcinoma 4.2 years after treatment for CIN1 despite intervening normal cytology and endocervical sampling [14].

Many resource poor countries lack the infrastructure needed for a traditional cervical cancer screening program with cytology and/or HPV testing. Less expensive alternatives such as screening of 30-45 year old women with visual inspection with acetic acid (VIA) and/or rapid HPV testing with immediate treatment with cryotherapy may greatly decrease the incidence of cervical cancer worldwide [7].

In healthy young women, about 90% of HPV infections clear at 2 years, with an average duration of infection of 8 months [15]. Although HPV persistence greatly increases the risk of developing HSIL and cancer of the cervix, the majority of HPV-infected women will never develop these conditions. A combination of viral, environmental, and host factors interact in the development of high-grade squamous intraepithelial lesion (HSIL) and cancer [16]. A number of recent studies have attempted to assess molecular, immunologic, and genetic factors associated with persistence and progression of HPV infections to dysplasia in both immuno-competent and HIV-infected women with mixed results [16-22].

A recent meta-analysis shows that the rate of cervical HPV infection in HIV-infected women with normal cervical cytology varied from more than 55% in South and Central America and Africa to over 30% in Asia, North America, and Europe [23]. In comparison, the National Health and Nutrition Examination Survey (NHANES) has estimated the prevalence of cervical HPV infection at 26.8% in U.S. women aged 14 to 59 with a peak prevalence of 44.8% in women aged 20 to 24. The most commonly isolated high-risk HPV types in the general population of U.S. women was 53, followed by 52, 59, 66, 51, and 16 [24].

Among HIV-infected women with HSIL on cytology, HPV type 16 was present in 31.9% followed by type 18 in 12.9% compared with women with HSIL in the general population (45% and 7.1% prevalence respectively). In addition, HIV-infected women with HSIL are more likely to be infected with multiple HPV types compared to women with HIV in general (41.4% vs. 6.7%) [24]. In Sub-Saharan Africa, the HPV types associated with HSIL in HIV-infected women include HPV 52, 58, 53, 35 and 45, in addition to types 16 and 18 [25*,26*,27*].

Rowhani-Rahbar et al examined the impact of HIV infection on HPV clearance with a longitudinal study of cervical HPV infection and cytology in Senegal. Of the 614 women, 176 (29%) were infected with HIV-1 or 2 and 3% were infected with both. Women with CD4 counts under 200 cells per cubic milliliter had a 71% lower chance of clearance of HPV infection compared to the women with CD4 counts over 500 cells per cubic milliliter. However, independent of CD4 count, HPV was more likely to persist in HIV-infected patients [28*].

HPV 16 and 18 are the most common oncogenic HPV types in cervical cancers and are identified in about 67% of all squamous cervical cancers worldwide [29]. The data are limited regarding the prevalence of HPV types in invasive cervical cancer in women with HIV. In a study of 51 HIV-positive and 153 HIV-negative Kenyan women with invasive cervical cancer, the distribution of HPV types was similar in the two groups, although the women with HIV were more likely to have multiple HPV types present (37.2% versus 13.7). HPV types 16 and 18 were the most common in this study and detected in 65% of the invasive cervical cancers in the HIV-infected patients. Almost half of the type 16 or 18 associated cancers involved multiple HPV types [30]. A Zambian study found that of 28 HIV-infected patients with Pap tests consistent with invasive cervical cancer, HPV 52 was most prevalent (46.4%), followed by types 58 and 16 (36%). However, in this Zambian study, HPV testing was performed from cytology and not histology specimens and may not reflect the full spectrum of the HPV types present in the cancer [25*]. HPV types 16 and 18 may still be the dominant HPV types

associated with cervical cancers in HIV-infected women, but the role of infection with other HPV types including 52 and 58 is unclear.

Anal HPV

Anal cytology can be used to screen for anal dysplasia and cancer. Any abnormal anal Pap test should be referred for High Resolution Anoscopy (HRA); a procedure similar to colposcopy, where the anal canal is bathed in acetic acid and visually inspected with a colposcope for evidence of abnormal lesions, which can then be biopsied to assess for dysplastic changes. The sensitivity and specificity of anal cytology to detect high grade anal dysplasia or anal cancer is similar to that of cervical cytology, however, the likelihood of finding high grade anal dysplasia during HRA after minimally abnormal anal cytology is significantly higher. Cranston et al found that of 93 HIV-infected men who have sex with men (MSM) referred for HRA because of minimally abnormal anal cytology, 52% of the subjects had biopsies consistent with high-grade dysplasia [31*].

The prevalence of anal dysplasia in HIV-infected populations in the HAART era remains high. Abramowitz et al evaluated 473 consecutive HIV-infected patients presenting for routine care between 2003 and 2004 with gross visual inspection and biopsy of suspicious lesions [32**]. They found lesions in 36.5%, 14.6%, and 11.3% of MSM, heterosexual men, and women, respectively. Of the 108 participants with apparent lesions, almost half of the lesions were condyloma and 56% showed dysplasia (all anal intraepithelial [AIN]1-2 except for two AIN3 lesions and one invasive cancer). As these were macroscopic lesions, it is likely that the prevalence would be increased if HRA had been utilized.

High grade anal dysplasia, like cervical dysplasia, likely represents a precursor to cancer and therefore we advocate treatment to decrease the risk of carcinogenesis. Although the absolute risk of carcinogenesis is not known, Devaraj et al showed that 3 of 31 HIV-infected patients (9.7%) with moderate to severe anal dysplasia at initial examination developed invasive squamous cell carcinoma (SCC) at 10 to 84 months during follow-up with expectant management [33].

There is no standard of care for treatment of anal dysplasia. Unlike the cervix, where high-grade dysplasia is typically treated with excision of the transformation zone, anal treatment typically involve a focal ablative therapy as treatment of the entire anus would result in significant morbidity and diminishment of quality of life.

Pineda et al recently published the largest series to date showing their 10 year experience with HRA targeted surgical destruction of high grade AIN in 246 subjects, 74% of whom had HIV [34**]. Eighty-one percent of the patients had widespread HSIL of the anal canal. Of the 188 patients with intraoperative biopsy at time of first surgery, 9 (5%) had superficially invasive SCC (defined as invasion of less than 3mm depth) and 5 (3%) had invasive SCC. Of the 154 immunocompromised patients who had a single planned procedure, 57% developed recurrence of HSIL at an average of 19 months. The most significant risk factor for recurrence was the extent of initial HSIL disease, regardless of immune status. Two patients progressed to cancer despite therapy. Significant complications occurred in less than 4% of patients and included bleeding, anal stenosis, and anal fissures, as well as one myocardial infarction. Although over half of the patients had recurrences, the majority were focal and treated as an office procedure. Most reassuring was that the progression to cancer in these patients following HRA directed ablation with baseline extensive high grade dysplasia was only 1.2% [34**].

A variety of therapeutic modalities utilizing office procedures or medical treatment for anal dysplasia are being assessed. A pilot study to examine the role of infrared coagulation (used for treatment of hemorrhoids) in the treatment of focal high-grade dysplastic lesions in HIV-

infected individuals showed a complete response to treatment in 10 of 16 subjects followed for 1 year (62.5%). There were no significant adverse events due to the procedure [35**]. A larger study to better assess efficacy is in development. Imiquimod, a topical, immune-modulating agent appears to show benefit in decreasing HPV viral load and clearing perianal warts and mild dysplasia in HIV-infected men [36-8]. Larger studies with long-term follow-up and analysis will be necessary to assess the durability of these novel treatment approaches in anal HPV-related disease.

Standard treatment for invasive anal cancer includes combined therapy with fluorouracil, mitomycin or cisplatin, plus radiation therapy for all stages of anal cancer and yields a 5 year overall survival of 50-78% and a colostomy free survival of 61-76%. However, treatment associated morbidity is significant with serious hematologic toxicity in 18-49%, dermatologic toxicity in 49-76%, and GI toxicity in 33-45% [39**].

Prior to the introduction of HAART, several observational studies had reported significantly poorer outcomes in HIV-infected patients treated for invasive anal cancer. Recently published studies, however, have found more favorable results. A retrospective cohort study by Chiao et al utilized the VA administrative database to compare outcomes for SCC in HIV-negative and positive patients [40**]. Fifteen percent (175 of 1184) of patients with invasive SCC of the anus were HIV-infected. The HIV-infected patients were younger (49 vs. 63 ($p<.001$)), 8 times more likely to be male ($p=.01$), and 3 times more likely to be African American ($p<.001$). Two-year survival was similar between the 2 groups (about 75%) and survival was not dependent on HIV status, but rather age, sex, metastases at diagnosis and comorbidity score. This study, however, did not address any difference in treatment-associated morbidity. Wexler et al. report on 32 HIV-infected subjects with invasive SCC of the anus treated with chemoradiation in the HAART era and found similar outcomes but significantly greater hematologic toxicity compared with HIV-negative patients [41**].

Intensity Modulated Radiation Therapy (IMRT) has become the standard way to deliver radiation therapy in the treatment of head-and-neck and prostate cancers. In anal cancer, IMRT has the potential to reduce radiation dose to proximal structures such as small and large bowel, bladder, external genitalia, femoral head, bone marrow and skin, thereby reducing toxicity. A recently published study by Salama et al. reports the largest series to date of 53 patients (8 HIV-positive) with invasive anal cancer treated with concurrent IMRT and chemotherapy and found markedly decreased GI toxicity (15%) and dermatologic toxicity (38%), as well as similar serious hematologic toxicities (40%) compared with historical outcomes from standard radiation therapy. Eighteen month outcomes are comparable to standard therapies and all 8 HIV-infected patients had a complete response and similar toxicities compared to the HIV-negative group [39**].

Oral HPV

One area of growing evidence is the association between HPV infection and oropharyngeal cancer. A large case-control study by D'Souza et al. compared subjects with recently diagnosed oropharyngeal cancer with clinic-based controls. The oral cancer patients were 14.6 times (95% C.I. 6.3 to 36.6) more likely to have an oral HPV-16 infection and 32.2 times (95% C.I. 14.6 to 71.3) more likely to be seropositive for HPV 16 compared to the controls. Subjects with oropharyngeal cancer were significantly more likely to report higher numbers of sexual partners, history of casual-sex partners, and rare or no condom use compared to the control group [42**]. A meta-analysis of cancer incidence in people with HIV showed that HIV-positive individuals are 2.32 times as likely to develop oral cavity or pharyngeal cancers compared to HIV-negative individuals (95% C.I. 1.65 to 3.25) [6**].

Two recent studies have assessed oral and cervical HPV infection in HIV-positive and negative women from the WIHS cohort. A cross-sectional study involving 172 HIV-positive and 86 negative women found a higher prevalence of cervical HPV infections compared to oral HPV infections in both groups. The HIV-infected women had 77% prevalence of cervical HPV infections and 26% prevalence oral infections ($p<0.001$), compared to a 45% prevalence of cervical and 9% prevalence of oral HPV infections in the HIV-negative women. The study further suggested a relationship between HPV infections at different anatomic sites; with 25.5% of women with cervical HPV infections also showing evidence of oral HPV infection, compared with only 7.9% prevalence of oral HPV in the women without cervical HPV infection ($p=0.002$) [43**].

The second WIHS study involved 136 HIV-infected women and 63 high-risk HIV-negative women who were assessed for oral and cervical HPV infections at two time-points over a 6 month period. Baseline HPV infection rates of the cervix and oropharynx were similar to those reported in the prior study. Cervical and oral HPV infections were equally likely to persist at six months in women in both groups with 63% of oral HPV infections and 55% of cervical HPV infections persisting in HIV-positive women ($p=0.27$) compared with 60% of cervical and 51% of oral HPV infections persisting in women without HIV ($p=0.70$) [44**].

Larger studies are underway to further explore the natural history of oral HPV infections, their association with genital HPV infections and whether persistent oral infections are associated with the development of oral dysplasias and cancers.

Prophylactic Vaccination

As treatment options for HPV associated diseases in the HIV-infected patient remain limited, there are important opportunities for disease prevention with vaccination. The HPV quadrivalent vaccine which provides protection against persistent infection and disease associated with HPV types 6, 11, 16 and 18 for women ages 15-26 with no evidence of prior HPV infection was FDA approved in 2006. The outcomes at 3 years of follow-up from two large phase 3 randomized controlled trials were published in 2007. In these studies, HPV vaccination prevented the development of HPV types 16 and 18 infections and associated CIN 2 or 3, adenocarcinoma in situ, or invasive cervical cancer with 98% efficacy in young women without prior HPV 16 or 18 infection [45]. In addition, there was 100% efficacy in preventing the development of genital warts and vulvar, vaginal, and perianal HPV related disease associated with the vaccine HPV types in women without prior infection with these HPV types [46].

With the high prevalence of HPV infection at multiple anatomic sites, as well as issues regarding immunosuppression, the role for HPV vaccination in HIV-infected individuals is unclear. Clinical trials through the AIDS Clinical Trials Group (ACTG) and AIDS Malignancy Consortium (AMC) have begun enrollment to assess the safety and immunogenicity of HPV vaccination in both HIV-infected men and women [47,48]. If the HPV vaccine is safe and effective, then vaccination with the quadrivalent vaccine may prove crucial for preventing a significant number of HPV associated cancers in individuals with HIV worldwide.

Conclusion

While the burden of HPV related disease in HIV-infected people remains high, the literature regarding the prevalence of HPV infection continues to grow. As the evidence on the optimal screening for cervical dysplasia increases, routine screening and treatment remains prohibitively expensive for much of the world population most at risk. Although data regarding screening and treatment for anal dysplasia in HIV-infected individuals continues to accumulate, there are not yet consensus guidelines in this area. Evidence for the relationship

between HPV infection and other malignancies, such as squamous cell carcinoma of the conjunctiva is slowly accumulating [49*]. With many difficulties for screening and treatment of HPV related diseases, the HPV quadrivalent vaccine holds much future potential to decrease the impact of HPV in people living with HIV.

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