American Journal of Transplantation 2013; 13: 189–200
Wiley Periodicals Inc.

© Copyright 2013 The American Society of Transplantation and the American Society of Transplant Surgeons

doi: 10.1111/ajt.12142

Special Article

Human Papillomavirus in Solid Organ Transplantation

P. V. Chin-Hong[a,*], E. J. Kwak[b] and the AST Infectious Diseases Community of Practice

[a] *Division of Infectious Diseases, University of California at San Francisco, San Francisco, CA*
[b] *Division of Infectious Diseases, University of Pittsburgh Medical Center, Pittsburgh, PA*
* *Corresponding author: Peter Chin-Hong, phong@php.ucsf.edu*

Key words: Anal cancer, anal intraepithelial neoplasia, cervical cancer, cervical intraepithelial neoplasia, human papillomavirus, immunocompromised host, papillomaviridae, transplantation, vaccination

Abbreviations: AIDS, acquired immunodeficiency syndrome; AIN, anal intraepithelial neoplasia; ASC-H, ASC suspicious for HSIL; ASC-US, atypical squamous cells of undetermined significance; CIN, cervical intraepithelial neoplasia; CMI, cell mediated immunity; CMT, combined-modality therapy; DNA, deoxyribonucleic acid; FDA, Food and Drug Administration; HRA, high resolution anoscopy; HPV, human papillomavirus; HSIL, high-grade SIL; LEEP, loop electrosurgical excision procedure; LSIL, low-grade squamous intraepithelial lesions; PCR, polymerase chain reaction; SCC, squamous cell carcinoma; VLP, virus-like particle.

Introduction

Human papillomavirus (HPV) infection is one of the most common sexually transmitted infections worldwide and causes cervical and anal cancer, as well as its associated precancer lesions of cervical intraepithelial neoplasia (CIN) and anal intraepithelial neoplasia (AIN). HPV also causes a proportion of vulvar, vaginal and penile squamous cell cancers (1). There is increasing evidence that HPV plays an important role in head and neck cancer. HPV also causes cutaneous and anogenital warts, which are of low malignant potential. Cell-mediated immunity is important for the control of HPV infection. Immunosuppression for solid organ transplantation decreases the capacity to eradicate new HPV infection, and enables increased HPV replication in latently infected cells. As a result, transplant recipients have a substantially increased risk of HPV-associated malignancies compared with the general population. Transplant patients also experience an increased occurrence of extensive and treatment-refractory cutaneous and anogenital warts.

Transmission and Host Response

HPV is a double-stranded DNA virus that infects the basal epithelial cells of keratinized skin, mucous membranes and the transformation zone of the cervix. Different HPV types have tissue tropism for cutaneous versus mucosal membranes in different body sites, with varying level of malignant potential (2,3). HPV types can be broadly classified into "high risk" and "low risk" types based on their propensity to cause cancer. In a large, global epidemiological study, Munoz and others found that at least 40 HPV types were associated with neoplasms. Of these, 18 were classified as "low risk" and associated with anogenital warts, mild cervical dysplasia and recurrent respiratory papillomatosis, and 12 were considered "high risk" including types 16 and 18 (4). More frequent HPV types associated with various clinical manifestations are listed in Table 1 (5).

The vast majority of HPV acquisition occurs via direct person-to-person transmission. Indeed, anogenital HPV is estimated to be the most common sexually transmitted infection in the United States (6). HPV can also be acquired by infants during the passage through the birth canal of HPV-infected mothers—this is likely the mode of viral transmission in children who later develop recurrent respiratory papillomatosis (7,8). Most persons infected with HPV are asymptomatic so transmission of the infection from individuals without visible lesions is common. In addition, anogential HPV can be seen concurrently with cutaneous warts or oral mucosal disease, suggesting that auto-infection can occur from one site to another (9,10). To date, there have been no reports of HPV acquired through organ transplantation.

Once HPV has infected epithelial cells, it evades the host immune response by various mechanisms. These include a prolonged infection cycle, a relative lack of inflammatory response during viral replication, and downregulation of the interferon response. In addition, HPV infection rarely causes viremia. Infection is localized to the mucosal and cutaneous surfaces and away from the vascular and lymphatic systems where adaptive immune responses are initiated (11,12). Nevertheless, at least 80–90% of genital

Table 1: HPV and tissue tropism

Disease	HPV types frequently associated
Plantar and common warts	1,2,4
Flat or plane warts	3,10
Butcher's wart	7,2
Bowen's disease	
Genital	16
Extragenital	2,3,4,16
Condylomata acuminta	6,11
Bowenoid papulosis	16,34,37,42
Intraepithelial neoplasia	
Low grade	6,11
High grade	16,18
Respiratory papillomatosis	6,11

Adapted from Table 1 in epidemiology of human papillomavirus infection (Ref. 5).

HPV infections clear spontaneously over time. Histologic analysis of regressing warts show a CD4+ T cell-dominated Th1 response. Resolution of the lesions depends on a successful cell-mediated immune response against early viral proteins (12,13). Failure to develop effective cell mediated immunity (CMI) results in an inability of the host to clear or control the HPV infection, leading to persistent infection, and resulting in an increased probability of cancer.

The importance of CMI was highlighted in a recent systematic review of population-based registry studies in HIV/AIDS and in transplant recipients. The investigators demonstrated a similar pattern of significantly increased incidence of all HPV-related cancers in both populations (14). This suggests that immune deficiency likely plays the most important role in the increased risk of HPV-associated neoplasia. Among HIV-infected patients, the risk of HPV-associated cancers is increased in those with higher HIV viral load and is inversely related to CD4+ count (15–17). Similarly, in a single-center review of renal transplant recipients over 40 years, T cell depleting induction with antithymocyte globulin was an independent risk factor for the development of anogenital cancer. This again suggests an association between the degree of immunosuppression and the probability of HPV-related malignancy (18). As a result of impaired cell-mediated immunity, transplant recipients experience an increased frequency of extensive, sometimes treatment-refractory cutaneous and anogenital warts (19,20) and are at a higher risk for neoplastic transformation in cervical and anogenital HPV infections (21,22).

Epidemiology and Clinical Presentation

HPV is associated with both benign and premalignant/malignant neoplasms in a variety of sites (Table 2).

Cutaneous and anogenital warts

Cutaneous warts are skin lesions of characteristic appearance and include common warts, deep plantar and flat warts. The prevalence of warts in transplant patients corresponds with the duration of immunosuppressive therapy, increasing to 50–92% in patients who are more than 4–5 years after transplantation (23). Ultraviolet light is also believed to be an important risk factor for the development of cutaneous warts in transplant recipients, as most lesions appear in sun-exposed areas (24).

Table 2: Clinical manifestations of HPV

Localization	Benign	Premalignant/ Malignant
Skin	Cutaneous warts	Potential role in squamous cell carcinoma of the skin
Anogenital	Anogenital warts	CIN, cervical cancer, AIN, anal cancer, vulvar and penile carcinoma
Respiratory tract	Respiratory papillomatosis	No clearly established link to malignant respiratory neoplasm
Head and neck	None established	Squamous cell carcinoma of head and neck

Anogenital warts, also known as condyloma acuminata, are one of the most common sexually transmitted diseases worldwide. They are caused by low-risk HPV types, most commonly types 6 and 11. However, at least 18 other HPV types have been associated with anogenital warts, including types 16 and 18, which are more commonly associated with malignant lesions (25,26). These exophytic, typically flesh- or gray-colored lesions are frequently multifocal, involving different parts of the anogenital tract simultaneously. In women, external anogenital warts are often associated with cervical lesions (27). Patients with anogenital warts, especially those who are immunosuppressed, are often also infected with high-risk HPV types. Therefore, immunosuppressed patients with anogenital warts will require monitoring and screening for HPV-mediated malignancies. A French study of organ transplant recipients reported a prevalence of anogenital warts of 1.8% (19).

Premalignant and malignant lesions of the cervix and anal canal

The oncogenic role of HPV infection has been most firmly established in the pathogenesis of CIN and cervical cancer. Persistent HPV infection, particularly with types 16 and 18, may lead to progressive deregulation of the replication of epithelial cells and potential malignant transformation (28). HPV infection also causes AIN and anal cancer with similar high risk HPV-types as those implicated in cervical neoplasia (3).

An increasing number of studies have investigated the epidemiology of cervical and AIN among transplant recipients.

In a Scottish study in the late 1980s, CIN and high-risk HPV types 16 and 18 were present more frequently in renal transplant recipients compared to age-matched controls (29). In a more recent study from Italy, 7% of 151 transplant recipients were found to have CIN (21). One of the largest reports to date is a retrospective Dutch single center study of 1023 women who underwent renal transplants between 1968 and 2008. Of these patients, a total of 16 anogential malignancies (1.6%) were noted, including six vulvar, five cervical and six anal carcinomas (18). Investigators found detectable HPV in 22/24 malignant and precancer lesions, and 54.5% of these were HPV type 16. Using cancer registry data from the general Dutch population, the authors estimated that these kidney transplant patients had increased risks of 5-fold for cervical, 41-fold for vulvar and 122-fold for anal carcinoma. Another review of 453 women who received renal transplants from 1990 to 2008 in South Korea revealed an incidence of 58.1 cervical carcinomas per 100 000 patient-years, which was 3.5-fold higher than the general population (29).

There is also a high burden of HPV-associated anal precancer lesions among transplant recipients. Ogunbiyi et al. showed a high proportion of AIN in renal transplant recipients who presented for elective lower gastrointestinal or genitourinary surgeries compared to matched controls (20% vs. 1%; Ref.30). Patel and others collected anal cytology and performed anal HPV polymerase chain reaction (PCR) in 108 renal transplant recipients (68 men and 40 women). They reported a 5.8% prevalence of AIN, with risk factors as follows: oncogenic HPV infection, duration of immunosuppression, a previous history of genital warts and receptive anal intercourse (31). Similar results were found in a systematic review of 32 000 transplant recipients from Danish, Finnish, Swedish, Canadian and Australian cohort studies. This study demonstrated a twofold increased risk of cervical cancer compared to the general population, and a nearly fivefold excess risk for anal cancer (14). Particularly striking was the 22-fold excess risk of vulvar and vaginal cancers. Compared to the general population, carcinomas of the anogenital region occurred at an earlier average age (41 years) in transplant recipients and were frequently multifocal. Over 40% of transplant recipients with anogenital carcinomas reported a prior history of anogenital warts (32).

Nonmelanoma cancer of the skin

SCC of the skin occur 65–250 times more frequently in transplant recipients than in the general population, and are often characterized by earlier age of onset, multiple lesions, a rapid course and more frequent node metastases than in the general population (33). Using degenerate PCR, a high prevalence (65–81%) of a variety of HPV DNA types has also been consistently demonstrated in premalignant skin lesions and in skin cancers of transplant recipients (34). Another study reported high-risk HPV in 46.2% of the SCC epithelium in renal transplant recipients compared to 23.5% in the immunocompetent control group (35). HPV was highly prevalent (>94%) in DNA analysis of eyebrow hairs in renal transplant patients, both with SCC and without SCC, although the presence of HPV DNA and the corresponding antibodies for the same HPV type was associated with increased risk of SCC (36). While the results of these studies are intriguing, it is not clear to what extent HPV contributes to the development of skin cancer among transplant recipients (37). Interestingly, sirolimus, an immunosuppressant with antineoplastic and antiviral properties, may have a protective effect against skin cancers compared to other immunosuppressive agents. A cohort of 1000 renal transplant recipients on sirolimus regimens had a similar incidence of skin cancers compared with the general population (38). However, HPV infection was not examined in this cohort, and the potential benefit of the antiviral effect of sirolimus in this setting remains speculative.

HPV and cancer of head and neck

There is increasing evidence that HPV is implicated in the pathogenesis of some head and neck cancers. This is especially seen in neoplasms arising from the base of the tongue and tonsillar region, and is not typically associated with smoking or alcohol consumption as seen in other head and neck cancers. D'Souza et al. (39) conducted a case-control study and showed that seropositivity for HPV-16 (odds ratio 32.2) and the presence of an HPV oral infection (odds ratio 14.6) had strong associations with oropharyngeal cancer. Of note, HPV-associated head and neck cancer appears to have a better prognosis compared to those not associated with HPV (40). HPV infection in the oral cavity is not rare. One large cross sectional study (41) showed a prevalence of oral HPV infection in the general population in the United States of 6.9%, with more men than women infected (10.1% vs. 3.6%). There are no published studies that explicitly investigate the association between oral HPV infection and head and neck cancer in transplant recipients. However, the prevalence of oral HPV infection is known to be higher in renal transplant recipients compared to immunocompetent patients (42). In one systematic review, transplant recipients were found to have a threefold excess risk of oropharyngeal cancer (14). It is likely that the increased rate of head and neck cancer is partly attributable to more persistent HPV infection in transplant recipients. Further studies are needed to clarify this relationship.

Respiratory papillomatosis and lung cancer

HPV can also cause a benign upper airway neoplasm called recurrent respiratory papillomatosis. The most frequently affected population is young children. Babies acquire HPV (typically HPV types 6 and 11) through contact with infected secretions in the birth canal. Lesions can also be adult-onset, occurring as a sequelae of HPV infection acquired sexually (43). It has been proposed that there is a relationship between HPV and SCC or adenocarcinomas of the lungs. However, studies are conflicting (44,45). Whether there is a more substantial role of HPV in the pathogenesis of pulmonary neoplasms among transplant recipients remains to be determined.

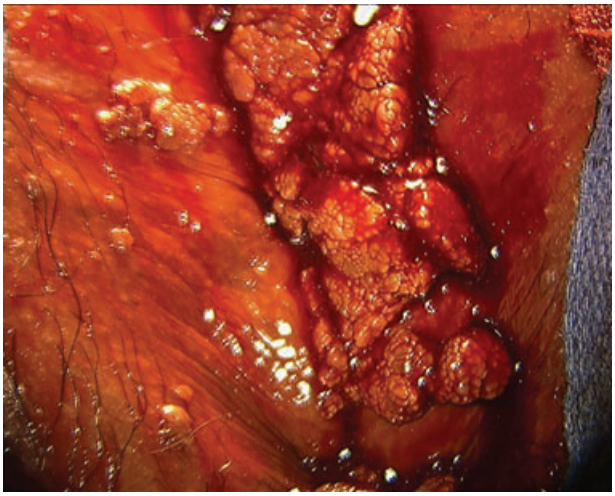

Figure 1: Extensive anal condylomata in a heterosexual male kidney transplant recipient.

Diagnosis

General principles

A thorough clinical inspection of the entire genital tract is sufficient to diagnose most external anogenital warts. Bright light and magnification with a hand lens or colposcope may assist in the diagnosis (Figure 1). All women with external anogenital warts must have a speculum examination for possible vaginal and cervical lesions. For men and women with recurrent perianal warts and/or a history of receptive anal intercourse, evaluation for intra-anal warts is recommended (46). If urinary symptoms are prominent, the distal urethra and meatus should be visually examined and a referral for urethroscopy should be considered.

Providers should have a low threshold to biopsy any genital warts that have an atypical appearance. This is because high-grade squamous epithelial neoplastic lesions are common and may be clinically indistinguishable from genital warts among immunocompromised patients (47). Using dilute (3–5%) acetic acid solutions (i.e. "acetowhite test") may be of help in delineating the extent of disease before biopsy; however, routine use of the test for screening individuals for HPV infection is not recommended due to poor sensitivity and specificity (32) in predicting active disease. Patients with anogenital warts and their sex partners should be screened for other sexually transmitted diseases including gonorrhea, chlamydia, syphilis, trichomonas, hepatitis B virus infection and HIV infection (48).

Cytology

The Papanicolau (Pap) smear is the backbone of the screening strategy for early diagnosis of HPV-related cervical atypia and cancer. The implementation of regular Pap tests has reduced the rate of invasive cervical cancer by approximately 70% since the 1950s.

Molecular-based methods

Molecular diagnostic methods to detect HPV have become more widely available in the last few years. These methods include *in situ* hybridization on cell smears or histological sections, DNA hybrid capture and PCR on clinical specimens. A high viral load of HPV 16 has been shown to be associated with development of carcinoma *in situ* (49,50). There are now multiple FDA-approved tests to detect high-risk HPV DNA. See Table 3 for recommendations for HPV co-testing in immunocompetent and the immuncompromised women. Detection and typing of HPV have no proven benefit in the diagnosis and management of anogenital warts and is therefore not recommended (50). When the diagnosis is in doubt, consider referral to a practitioner experienced in the diagnosis of anogenital warts. See below for the incorporation of molecular methods in screening.

Cervical cancer and CIN screening

A magnifying glass and a bright light source are used to examine the external genitalia. Given that genital warts may coexist with CIN, we recommend further evaluation such as colposcopy if genital warts are present on the external examination. Cervical cancer screening has been very successful where it has been established given that there is a long preinvasive state with CIN before the onset of cervical cancer, and that these precancer lesions can generally be successfully treated.

The American Cancer Society, the American Society for Colposcopy and Cervical Pathology, the American Society for Clinical Pathology, the American College of Obstetricians and Gynecologists and the U.S. Preventive Services Task Force have all issued cervical cancer screening guidelines. Many of these guidelines have been updated recently for the general population (51–54). Refer to Table 2 for a summary of the various guidelines including recommendations for immunocompromised individuals. In general, experts recommend initiating screening in women at age 21 and discontinuing screening at age 65. For women 21–29, screening should occur with cervical Pap tests only every 3 years. For women 30–65, screening can occur with cytology alone every 3 years, or by a combination of an HPV molecular test (testing for high-risk HPV types) and cytology every 5 years. However, these guidelines do not apply to immunocompromised women.

We recommend that transplant recipients be screened with the same periodicity as women who are HIV-infected (55). In solid organ transplant recipients (as in HIV-infected women), we recommend that a cervical Pap test be performed every 6 months for the first year after the transplant. If these tests are normal, then the screening interval can be increased to annual cervical Pap testing. There is little guidance from published studies, but it may be reasonable to reinstate cervical Pap tests every 6 months for 1 year after treatment for rejection, particularly if

Table 3: Guidelines for cervical cancer screening for different populations

	Immunocompetent women				
	American Cancer Society (52)	US Preventive Services Task Forces (53)	American College of Obstetricians and Gynecologists (54)	HIV positive women (55)	Solid organ transplant recipients
When to start	Age 21, recommend against screening women aged< 21	Age 21, recommend against screening women aged< 21	Age 21 regardless of the age of onset of sexual activity	Twice in the first year after the diagnosis of HIV[1]	Every 6 months in the first year posttransplant
Intervals					
Conventional or liquid based cytology	Every 3 years for women 21-65 years (Strong recommendation)	Every 3 years for women 21-65 years	Every 2 years (age 21-29); May move to 3 years for 30-65 of age after 3 negative tests	Annually if the first two tests after HIV diagnosis are normal	Annually if negative tests after every 6 month screening for a year
HPV co-test	Every 5 years for women aged 30-65 (Weak recommendation); not recommended for women < 30 years	HPV every 5 years an option for women (30–65) who want to extend the screening interval	Every 3 years if cytology normal and HPV test negative.	Insufficient evidence to use HPV to space out screening in HIV+	HPV test (if negative) as an adjunct to move on to annual screening
Primary HPV testing	For women 30-65 years, HPV test alone is not the recommended screening method in most clinical settings	Recommended against those < 30 years of age either alone or in combination with cytology	Not addressed	Not addressed	Not addressed
When to stop	Women ≥ 65 with adequate screening (Weak recommendation)	Women ≥ 65 years with negative tests, if they are at low risk for cervical cancer	Between age 65-70 if ≥ 3 negative consecutive results	Insufficient evidence; continue annually	Insufficient evidence; continue annually
Vaccinated against HPV 16/18	Continue screening per age-appropriate recommendation	Continue the same screening	Same regardless of vaccination	Same regardless of vaccination	Same as unvaccinated

[1] Routine colposcopy is recommended for HIV+ women with atypical squamous cells of undetermined significance.

antilymphocyte agents are used. There is less consensus about the incorporation of high-risk HPV testing in the algorithm in transplant recipients. However, some providers use high-risk HPV testing (if negative) for further reassurance that the Pap testing can increase from 6 months to 1 year. If high-risk HPV testing is positive, then screening can be continued every 6 months. Every visit should also be accompanied by a careful inspection of vulva, vagina and anus as well as the cervix. Women found to have abnormal cervical cytology on screening (atypical squamous cells of undetermined significance [ASC-US], ASC suspicious for HSIL [ASC-H], low-grade squamous intraepithelial lesions [LSIL] and high-grade SIL [HSIL]) should undergo colposcopy and biopsy of any suspicious-looking lesions.

Unfortunately, adherence to the minimum recommended annual cervical cancer screening appears to be very low in transplant recipients (56). Every effort should be made to encourage patients to adhere to regular screening schedule, and individuals with an abnormal screening test should be promptly referred to a qualified specialist.

Anal cancer and AIN screening

Cervical and anal cancers share many similarities. They both arise in the transformation zone, they are both caused by high-risk HPV types and they are preceded by precancer lesions (57). Cancers also have been noted to arise in the same location as antecedent precancer disease. Given the high prevalence of AIN and anal cancer in the HIV-infected population, and given the similarities between cervical and anal cancers, Chin-Hong and Palefsky have proposed an anal cancer screening algorithm (57,58). This incorporates many of the elements of cervical cancer screening above. Given the high prevalence of anal cancer in the transplant population, we recommend a similar approach for transplant recipients as in the HIV-infected population.

Like the protocol used for cervical cancer screening, the Pap test is the first step. To perform an anal Pap test, we recommend using a water-moistened polyester swab (Fisher Scientific, Pittsburgh, PA, USA). We recommend polyester swabs because cells cling to cotton and this may decrease the yield of the Pap test. The polyester swab

is inserted in the anal canal. As the swab is withdrawn, rotate the swab and maintain pressure against the anal canal. The goal is to obtain exfoliated cells from the areas most at risk for HPV-associated disease such as cells from the lower rectum, the squamocolumnar junction and the anal canal. Either a glass slide or liquid-based media can be used to collect and transport these cells for analysis.

Men and women who are found to have abnormal anal cytology (ASC-US, ASC-H, LSIH and HSIL) can be referred to the next step, which is high resolution anoscopy (HRA). HRA uses similar equipment as in cervical colposcopy (powerful light and binocular lens). As in colposcopy, we use HRA to locate and biopsy lesions that have contributed to the cytologic abnormalities seen. Lugol's (iodine) solution and 3% acetic acid are tools that we can use to increase the ability to identify abnormal lesions. We recommend this screening approach in transplant patients only if there is sufficient infrastructure to do so. This includes the availability of trained high resolution anoscopists and pathologists used to interpreting AIN.

Recommendations

(1) Perform a cervical Pap test every 6 months for the first year after the transplant. If these tests are normal, then the screening interval can be increased to annual cervical Pap testing (II-2).
(2) Women found to have abnormal cervical cytology on screening (atypical squamous cells of undetermined significance [ASC-US], ASC suspicious for HSIL [ASC-H], low-grade squamous intraepithelial lesions [LSIL] and high-grade SIL [HSIL]) should undergo colposcopy and biopsy of any suspicious-looking lesions (III).
(3) Perform an anal Pap test once yearly for transplant patients (III).
(4) Refer patients with abnormal anal cytology on screening (ASC-US, ASC-H, LSIL and HSIL) for high-resolution anoscopy for biopsy and treatment (III).

Treatment

General principles

There are several principles in the treatment of HPV-associated disease. Treatment options depend on the size, location and grade of the lesion (57,59). For cutaneous and external genital warts with very little malignant potential, goals of treatment may be for cosmesis or to relieve anxiety in general. However, in immunosuppressed patients such as transplant recipients, these low grade lesions may become quite large. In these cases, removal of warts may be needed to alleviate obstruction, itching and bleeding. CIN I and AIN I have a very low probability of progression to cancer in general. However, some providers may treat these lesions in immunocompromised patients given the observations in some clinical studies that there is progression from low-grade to high-grade cervical disease among HIV-infected individuals (60,61). CIN II, CIN III, AIN II and AIN III are treated when possible as they are considered direct precursors to cervical and anal cancers, respectively.

Although there is limited evidence, some providers will also try to reduce immunosuppression if this is possible. This is particularly if disease is refractory to treatment, or if recurrent. There is also a theoretical basis for switching from calcineurin inhibitors to mTOR inhibitors such as sirolimus, particularly if malignant transformation has already occurred (62). However, there are few published studies that specifically address the role of mTOR inhibition in HPV-associated malignancies, other than in non-melanoma skin cancer (63).

Treatment of cutaneous warts

Cure is maximized when presoaked dead skin is first pared down using a pumice stone, nail file, emery board or scalpel. Common treatment options then include products containing salicylic acid, cryotherapy and imiquimod 5% cream (64,65). A salicyclic acid preparation in combination with an occlusive dressing such as duct tape may increase the efficacy of the treatment modality. Cryotherapy can be performed using liquid nitrogen spray, a liquid nitrogen soaked swab, or a cryoprobe cooled with nitrous oxide. This can be repeated every three weeks. Imiquimod 5% cream (Aldara) is a topical immune response modifier that induces cytokines locally. We advise patients to apply the cream once daily before bedtime, three times a week for up to 16 weeks. In our experience, transplant and other immunocompromised patients may require repeat cycles of therapy, or may not respond completely. If lesions look atypical or are refractory to treatment, we recommend referral to a dermatologist to rule out nonmelanoma skin cancer and other malignancies given the high incidence in this population (Ref. 33; see Figures 3 and 4).

Treatment of CIN

Some providers may elect to treat CIN I given that the natural history may be unpredictable in transplant recipients as has been observed for HIV-infected women (66). In most immune competent patients, however, CIN I is generally not treated. CIN II and CIN III are treated in all women to prevent cancer.

A variety of excisional and ablative therapies can be used. Loop electrosurgical excision procedure (LEEP) is generally the treatment of choice for CIN II and CIN III. LEEP uses an adjustable wire loop to diathermically excise lesions of various dimensions. In general LEEP is widely used because it is easy to use and has a low complication rate. In addition, tissue is relatively well preserved and can be used to confirm the diagnosis histopathologically and to ensure that clear margins are obtained (67). Cryotherapy may also be employed with the direct application of a supercooled probe to the affected cervical area using multiple

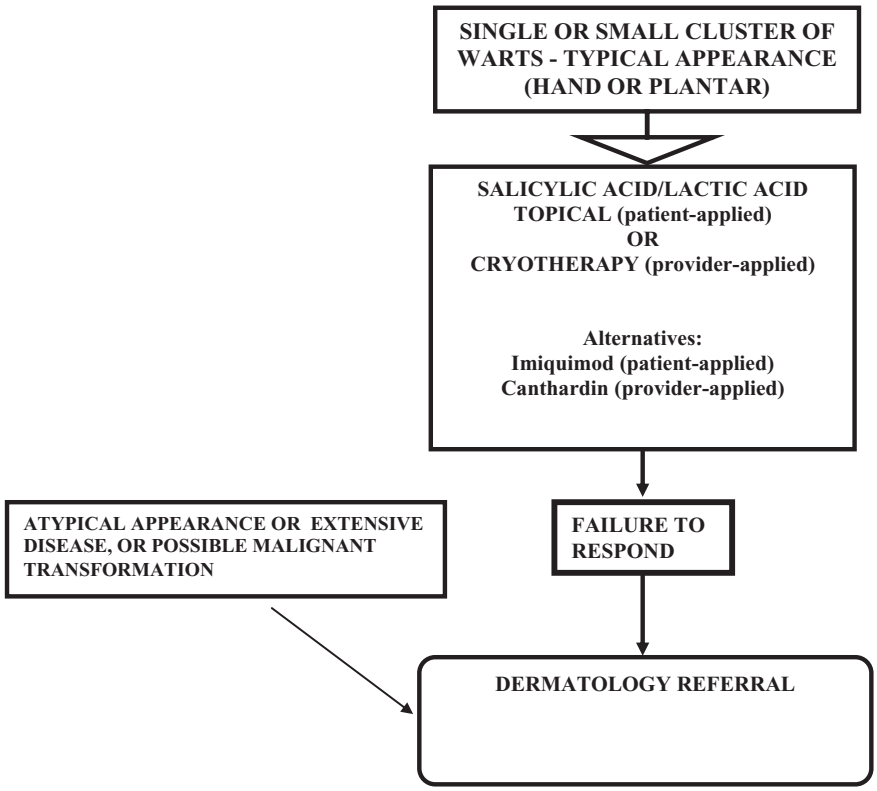

Figure 2: Management of cutaneous warts.

freeze-thaw cycles. Adverse effects are mild cramping and persistent vaginal discharge. The advantages are low cost, ease of use and the absence of major complications in general. The disadvantages are a higher failure rate compared to LEEP, and the inability to get tissue to assess whether treatment is adequate with clear margins (68). Other less used options include laser therapy (69) and cold-knife conization (70). Laser therapy uses carbon dioxide under colposcopy to precisely vaporize lesions to the adequate depth needed. Cold-knife conization utilizes a scalpel to excise a cone-shaped portion of the cervix including the entire transformation zone. General anesthesia must be used in these cases and there is a higher risk of complications (e.g. bleeding, infection and cervical incompetence) compared with the other office-based procedures.

Treatment of cervical cancer

Treatment options depend on the stage of cervical cancer diagnosed. For early stage microinvasive disease (<3 mm), conization may be offered to young women who want to maintain fertility (71). For disease up to stage IIa, a primary regimen of chemoradiation (primary radiotherapy with chemotherapy) is preferred (72). The role of surgery (radical hysterectomy with para-aortic and pelvic lymphectomy) for all cases is controversial, particularly if there is no residual disease burden (73). For patients with locally advanced disease, radiotherapy followed by chemotherapy is usually offered (74). Women with metastatic cervical cancer could have combined chemotherapy (75) or radiotherapy (if symptomatic) (76) to help alleviate symptoms.

Treatment of AIN

It may be more difficult to treat AIN compared with CIN given the anatomical challenges of the anal canal compared with the cervix (57). Treatment depends on the grade of the lesion. Patients with AIN I may elect to have lesions treated for symptomatic or psychological relief since these have low malignant potential. Some providers may elect to treat AIN I in transplant patients given the observation that there is a faster progression from AIN I to AIN II/III in HIV-infected patients when compared to HIV noninfected patients (77). We treat AIN II and AIN III to prevent anal cancer. Size and location are important considerations when deciding on the appropriate treatment strategy. Intraanal AIN I lesions <1 cm^2 at the base (including condyloma) can be treated with 80% trichloroacetic acid (59), topical 5-fluorouracil (78) or cryotherapy. Some providers may use imiquimod 5% cream for AIN given recent data to support this practice (79,80). For larger and higher grade lesions, infrared coagulation in the outpatient setting (81–83) or intraoperative fulguration (using intraoperative HRA to localize lesions) can be used (84). For very large lesions of any grade that are not causing patients symptoms, we may elect to follow patients closely rather than automatically remove disease, given the associated morbidity of these procedures (pain, anal stenosis and anal incontinence; Ref.57).

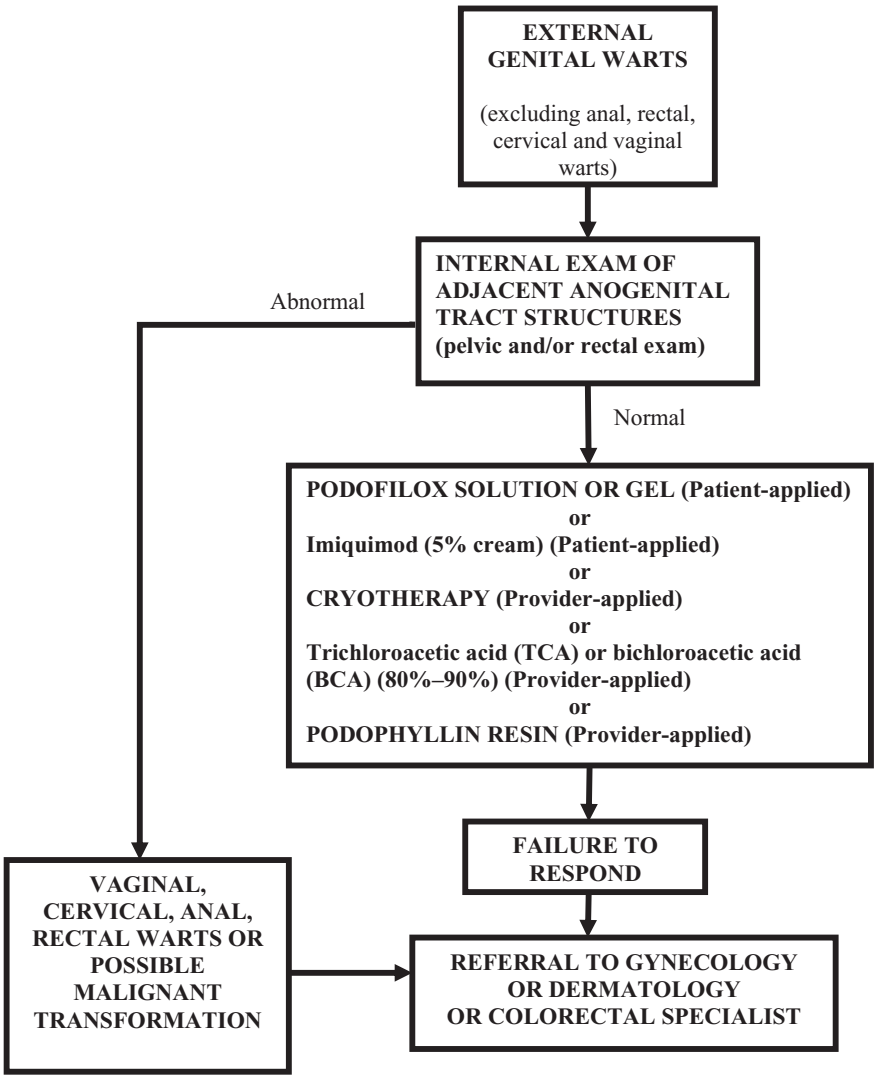

Figure 3: Management of anogenital warts.

Treatment of anal cancer

Invasive anal cancer is usually treated with a combination of radiotherapy and chemotherapy (5-fluorouracil and mitomycin; Ref.85). This combined-modality therapy (CMT) approach could avoid the morbidity of abdominoperineal resection with removal of the anorectum and creation of a permanent colostomy. Because immunosuppressed patients may experience CMT toxicity, sometimes lower doses of radiotherapy and alternative chemotherapy (e.g. cisplatin instead of mitomycin) can be offered (85).

Prevention

Trials of prophylactic HPV vaccines have been very effective in those unexposed to the HPV types included in the vaccine. The vaccines use components of the major HPV capsid proteins (L1 alone or in combination with L2) which self-assemble into virus-like particles (VLP). VLP induce neutralizing antibodies which protect the individual before exposure to HPV infection. There are two prophylactic HPV vaccines currently available. One is a quadrivalent vaccine (HPV types 6, 11, 16 and 18) (Gardasil, Merck, Whitehouse Station,NJ, USA) and the other is a bivalent (HPV types 16 and 18) vaccine (Cervarix, GlaxoSmithKline, Rixensart, Belgium). Both vaccines have demonstrated over 90% efficacy in preventing CIN II, CIN III, adenocarcinoma *in situ* and cervical cancer associated with the HPV types included in the vaccine provided that women had not been previously exposed to these types (86–88). Because the quadrivalent vaccine also includes HPV types 6 and 11 which are the major causes of genital warts, clinical trials have demonstrated over 90% efficacy in preventing warts caused by the four HPV types included in the vaccine in both women and men (86,87,89). In addition, trials of the quadrivalent vaccine have shown 78% efficacy in preventing incident AIN among men who have sex with men (90).

Given these findings, multiple expert panels have recommended HPV vaccination of girls and young women. Routine vaccination should be offered to all females 11–12 years old, and as young as 9 years old, with catch up vaccination from 13 to 26 years if not previously immunized (91). Routine HPV vaccination is also recommended for boys aged 11–12 years old, and as early as 9 years old, with catch-up vaccination between 13 and 21 years old, and permissive use for ages 22–26 (92). Only the quadrivalent vaccine has been widely studied in males, with only limited immunogenicity data for the efficacy of the bivalent vaccine in boys (93). The schedule of the quadrivalent vaccine is three doses at time 0, and at months 2 and 6. The corresponding schedule of the bivalent vaccine is three doses at time 0, and at 1 and 6 months of follow up.

There are limited safety and efficacy data specifically in the transplant population. However, given that the HPV vaccines do not contain live virus, we suggest vaccination of transplant patients using similar guidelines as above. There are also no data on whether vaccination would increase the likelihood of allograft rejection. There is some evidence in the HIV-infected population that the HPV vaccine is safe and immunogenic (94,95). Vaccination of eligible patients before transplantation would be preferred, given the higher likelihood of developing a robust neutralizing antibody response. Note that vaccination does not substitute for ongoing Pap screening in the transplant population. Not all oncogenic HPV types are included in the current generation of prophylactic vaccines.

Until the advent of HPV vaccines, there were few other options for primary prevention of HPV infection. HPV vaccines now form part of a menu of options that can be discussed with transplant candidates and patients (96,97). Limiting the number of sexual partners can help reduce the rate of HPV-related disease, as a high number of partners is associated with increased rate of HPV infection and cervical cancer. Sexual contact with anyone who has genital sores or unusual growths in the genital area or anus should be avoided. Condoms can reduce, but do not eliminate, the risk for HPV transmission to uninfected partners. Condoms should be used nonetheless, not only to reduce HPV transmission, but also to prevent other sexually transmitted diseases (97). Circumcision is also effective in decreasing the risk of HPV transmission (96). Limiting exposure to UV radiation is important to prevent skin carcinogenesis, which may be associated with HPV (98). In transplant recipients, avoidance of overimmunosuppression may reduce the probability of HPV-associated disease, although there is less evidence for this.

Recommendations

Immunize all male and female transplant patients (ideally before transplantation) ages 9–26 (target age 11–12) with the HPV quadrivalent vaccine. Females can also receive the HPV bivalent vaccine (I)

Infection Control

Some reports have indicated that intact HPV virus can be isolated from the laser generated plume used to treat human lesions (99,100). Given these observations, safety precautions are recommended during laser surgery such as gloves and gowns to cover exposed skin surfaces. Likewise use of eye protection, masks and smoke suction systems that have high flow volume and good filtration are recommended if carbon dioxide laser must be used as a treatment modality (101).

Future Research

Although there is increasing population-based data that transplant recipients have a substantial burden of HPV-associated malignancies, there have been few natural history cohorts that aim to describe the precise epidemiology of disease in this population. In contrast, there is a robust literature in the HIV-infected population that demonstrates a high proportion of HPV-associated precancer lesions and cancer, and its association with immunosuppression. We need to begin to examine knowledge and attitudes of patients and providers regarding these issues, and as knowledge becomes available, raise awareness of screening and treatment paradigms. Perhaps one of the most exciting developments in the field has been the success of the HPV prophylactic vaccines in the general population. We need targeted studies in our transplant populations to study immunogenicity and safety, as well as efficacy. Small studies are underway, but multicenter studies will provide more robust and generalizable data. As the new generation of 9-valent HPV prophylactic vaccines and HPV therapeutic vaccines continue to be developed and studied, we need to consider how they fit in to our armamentarium of cancer prevention options for transplant recipients.

Acknowledgment

This manuscript was modified from a previous guideline written by EJ Kwak and K Julian published in *American Journal of Transplantation* 2009; 9(Suppl 4): S151–S160 and endorsed by the American Society of Transplantation/Canadian Society of Transplantation.

Disclosure

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation.*

References

1. Monk BJ, Tewari KS. The spectrum and clinical sequelae of human papillomavirus infection. Gynecol Oncol 2007; 107: S6–13.
2. de Sanjose S, Quint WG, Alemany L, et al. Human papillomavirus genotype attribution in invasive cervical cancer: A retrospective cross-sectional worldwide study. Lancet Oncol 2010; 11: 1048–1056.

3. Tilston P. Anal human papillomavirus and anal cancer. J Clin Pathol 1997; 50: 625–634.
4. Munoz N, Bosch FX, de Sanjose S, et al. Epidemiologic classification of human papillomavirus types associated with cervical cancer. N Engl J Med 2003; 348: 518–527.
5. Palefsky JM. Epidemiology of human papillomavirus infections. UpToDate 2012.
6. Weinstock H, Berman S, Cates W, Jr. Sexually transmitted diseases among American youth: Incidence and prevalence estimates, 2000. Perspect Sex Reprod Health 2004; 36: 6–10.
7. Merckx M, Liesbeth WV, Arbyn M, et al. Transmission of carcinogenic human papillomavirus types from mother to child: A meta-analysis of published studies. Eur J Cancer Prev 2012.
8. Shah KV, Stern WF, Shah FK, Bishai D, Kashima HK. Risk factors for juvenile onset recurrent respiratory papillomatosis. Pediatr Infect Dis J 1998; 17: 372–376.
9. Eversole LR, Laipis PJ, Green TL. Human papillomavirus type 2 DNA in oral and labial verruca vulgaris. J Cutan Pathol 1987; 14: 319–325.
10. Hernandez BY, Shvetsov YB, Goodman MT, et al. Genital and extra-genital warts increase the risk of asymptomatic genital human papillomavirus infection in men. Sex Transm Infect 2011; 87: 391–395.
11. Stanley MA. Immune responses to human papilloma viruses. Indian J Med Res 2009; 130: 266–276.
12. Stanley MA. Epithelial cell responses to infection with human papillomavirus. Clin Microbiol Rev 2012; 25: 215–222.
13. de Jong A, van der Burg SH, Kwappenberg KM, et al. Frequent detection of human papillomavirus 16 E2-specific T-helper immunity in healthy subjects. Cancer Res 2002; 62: 472–479.
14. Grulich AE, van Leeuwen MT, Falster MO, Vajdic CM. Incidence of cancers in people with HIV/AIDS compared with immunosuppressed transplant recipients: A meta-analysis. Lancet 2007; 370: 59–67.
15. Ahdieh L, Munoz A, Vlahov D, Trimble CL, Timpson LA, Shah K. Cervical neoplasia and repeated positivity of human papillomavirus infection in human immunodeficiency virus-seropositive and -seronegative women. Am J Epidemiol 2000; 151: 1148–1157.
16. Palefsky JM, Minkoff H, Kalish LA, et al. Cervicovaginal human papillomavirus infection in human immunodeficiency virus-1 (HIV)-positive and high-risk HIV-negative women. J Natl Cancer Inst 1999; 91: 226–236.
17. Vernon SD, Holmes KK, Reeves WC. Human papillomavirus infection and associated disease in persons infected with human immunodeficiency virus. Clin Infect Dis 1995; 21: S121–124.
18. Meeuwis KA, Melchers WJ, Bouten H, et al. Anogenital malignancies in women after renal transplantation over 40 years in a single center. Transplantation 2012; 93: 914–922.
19. Euvrard S, Kanitakis J, Chardonnet Y,et al. External anogenital lesions in organ transplant recipients. A clinicopathologic and virologic assessment. Arch Dermatol 1997; 133: 175–178.
20. Euvrard S, Kanitakis J, Cochat P, Cambazard F, Claudy A. Skin diseases in children with organ transplants. J Am Acad Dermatol 2001; 44: 932–939.
21. Paternoster DM, Cester M, Resente C, et al. Human papilloma virus infection and cervical intraepithelial neoplasia in transplanted patients. Transplant Proc 2008; 40: 1877–1880.
22. Penn I. Cancers of the anogenital region in renal transplant recipients. Analysis of 65 cases. Cancer 1986; 58: 611–616.
23. Dyall-Smith D, Trowell H, Dyall-Smith ML. Benign human papillomavirus infection in renal transplant recipients. Int J Dermatol 1991; 30: 785–789.
24. Boyle J, MacKie RM, Briggs JD, Junor BJ, Aitchison TC. Cancer, warts, and sunshine in renal transplant patients. A case-control study. Lancet 1984; 1: 702–705.
25. Gormley RH, Kovarik CL. Human papillomavirus-related genital disease in the immunocompromised host: Part II. J Am Acad Dermatol 2012; 66: 883 e1–17; quiz 99–900.
26. Wiley DJ, Douglas J, Beutner K, et al. External genital warts: Diagnosis, treatment, and prevention. Clin Infect Dis 2002; 35: S210–224.
27. Moscicki AB, Hills N, Shiboski S, et al. Risks for incident human papillomavirus infection and low-grade squamous intraepithelial lesion development in young females. JAMA 2001; 285: 2995–3002.
28. Rodriguez AC, Schiffman M, Herrero R, et al. Rapid clearance of human papillomavirus and implications for clinical focus on persistent infections. J Natl Cancer Inst 2008; 100: 513–517.
29. Alloub MI, Barr BB, McLaren KM, Smith IW, Bunney MH, Smart GE. Human papillomavirus infection and cervical intraepithelial neoplasia in women with renal allografts. Br Med J 1989; 298: 153–156.
30. Ogunbiyi OA, Scholefield JH, Raftery AT, et al. Prevalence of anal human papillomavirus infection and intraepithelial neoplasia in renal allograft recipients. Br J Surg 1994; 81: 365–367.
31. Patel HS, Silver AR, Levine T, Williams G, Northover JM. Human papillomavirus infection and anal dysplasia in renal transplant recipients. Br J Surg 2010; 97: 1716–1721.
32. Penn I. Post-transplant malignancy: The role of immunosuppression. Drug Saf 2000; 23: 101–113.
33. Euvrard S, Kanitakis J, Claudy A. Skin cancers after organ transplantation. N Engl J Med 2003; 348: 1681–1691.
34. Harwood CA, Surentheran T, McGregor JM, et al. Human papillomavirus infection and non-melanoma skin cancer in immunosuppressed and immunocompetent individuals. J Med Virol 2000; 61: 289–297.
35. Reuschenbach M, Tran T, Faulstich F, et al. High-risk human papillomavirus in non-melanoma skin lesions from renal allograft recipients and immunocompetent patients. Br J Cancer 2011; 104: 1334–1341.
36. Proby CM, Harwood CA, Neale RE, et al. A case-control study of betapapillomavirus infection and cutaneous squamous cell carcinoma in organ transplant recipients. Am J Transplant 2011; 11: 1498–1508.
37. Ho WL, Murphy GM. Update on the pathogenesis of post-transplant skin cancer in renal transplant recipients. Br J Dermatol 2008; 158: 217–224.
38. Kahan BD, Knight R, Schoenberg L, et al. Ten years of sirolimus therapy for human renal transplantation: The University of Texas at Houston experience. Transplant Proc 2003; 35: 25S–34S.
39. D'Souza G, Kreimer AR, Viscidi R, et al. Case-control study of human papillomavirus and oropharyngeal cancer. N Engl J Med 2007; 356: 1944–1956.
40. Ang KK, Harris J, Wheeler R, et al. Human papillomavirus and survival of patients with oropharyngeal cancer. N Engl J Med 2010 ; 363: 24–35.
41. Gillison ML, Broutian T, Pickard RK, et al. Prevalence of oral HPV infection in the United States, 2009–2010. JAMA 2012; 307: 693–703.
42. Rose B, Wilkins D, Li W, et al. Human papillomavirus in the oral cavity of patients with and without renal transplantation. Transplantation 2006 ; 82: 570–573.
43. Tasca RA, Clarke RW. Recurrent respiratory papillomatosis. Arch Dis Child 2006; 91: 689–691.

44. Klein F, Amin Kotb WF, Petersen I. Incidence of human papilloma virus in lung cancer. Lung Cancer 2009; 65: 13–18.
45. Koshiol J, Rotunno M, Gillison ML, et al. Assessment of human papillomavirus in lung tumor tissue. J Natl Cancer Inst 2011; 103: 501–507.
46. von Krogh G, Lacey CJ, Gross G, Barrasso R, Schneider A. European guideline for the management of anogenital warts. Int J STD AIDS 2001; 12: 40–47.
47. Sillman FH, Sentovich S, Shaffer D. Ano-genital neoplasia in renal transplant patients. Ann Transplant 1997; 2: 59–66.
48. Workowski KA, Berman S. Sexually transmitted diseases treatment guidelines, 2010. MMWR Recomm Rep 2010; 59: 1–110.
49. Josefsson AM, Magnusson PK, Ylitalo N, et al. Viral load of human papilloma virus 16 as a determinant for development of cervical carcinoma in situ: A nested case-control study. Lancet 2000; 355: 2189–2193.
50. Ylitalo N, Sorensen P, Josefsson AM, et al. Consistent high viral load of human papillomavirus 16 and risk of cervical carcinoma in situ: A nested case-control study. Lancet 2000; 355: 2194–2198.
51. ACOG committee opinion No. 431: Routine pelvic examination and cervical cytology screening. Obstet Gynecol 2009; 113: 1190–1193.
52. Saslow D, Solomon D, Lawson HW, et al. American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology screening guidelines for the prevention and early detection of cervical cancer. CA Cancer J Clin 2012; 62: 147–172.
53. Moyer VA. Screening for cervical cancer: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med 2012; 156: 880–891, W312.
54. Screening for cervical cancer. Obstet Gynecol 2012; 120: 1222–1238.
55. Kaplan JE, Benson C, Holmes KH, Brooks JT, Pau A, Masur H. Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: Recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. MMWR Recomm Rep 2009; 58: 1–207; quiz CE1–4.
56. Courtney AE, Leonard N, O'Neill CJ, McNamee PT, Maxwell AP. The uptake of cervical cancer screening by renal transplant recipients. Nephrol Dial Transplant 2009; 24: 647–652.
57. 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: 1127–1134.
58. Chin-Hong PV, Palefsky JM. Human papillomavirus anogenital disease in HIV-infected individuals. Dermatol Ther 2005; 18: 67–76.
59. Singh JC, Kuohung V, Palefsky JM. Efficacy of trichloroacetic acid in the treatment of anal intraepithelial neoplasia in HIV-positive and HIV-negative men who have sex with men. J Acquir Immune Defic Syndr 2009; 52: 474–479.
60. Melnikow J, Nuovo J, Willan AR, Chan BK, Howell LP. Natural history of cervical squamous intraepithelial lesions: A meta-analysis. Obstet Gynecol 1998; 92: 727–735.
61. Robinson WR, Luck MB, Kendall MA, Darragh TM. The predictive value of cytologic testing in women with the human immunodeficiency virus who have low-grade squamous cervical lesions: A substudy of a randomized, phase III chemoprevention trial. Am J Obstet Gynecol 2003; 188: 896–900.
62. Guba M, Graeb C, Jauch KW, Geissler EK. Pro- and anti-cancer effects of immunosuppressive agents used in organ transplantation. Transplantation 2004; 77: 1777–1782.
63. Euvrard S, Morelon E, Rostaing L, et al. Sirolimus and secondary skin-cancer prevention in kidney transplantation. N Engl J Med 2012; 367: 329–339.
64. Gibbs S, Harvey I. Topical treatments for cutaneous warts. Cochrane Database Syst Rev 2006; 3: CD001781.
65. Kwok CS, Holland R, Gibbs S. Efficacy of topical treatments for cutaneous warts: A meta-analysis and pooled analysis of randomized controlled trials. Br J Dermatol 2011; 165: 233–246.
66. Holcomb K, Maiman M, Dimaio T, Gates J. Rapid progression to invasive cervix cancer in a woman infected with the human immunodeficiency virus. Obstet Gynecol 1998; 91: 848–850.
67. Bigrigg MA, Codling BW, Pearson P, Read MD, Swingler GR. Colposcopic diagnosis and treatment of cervical dysplasia at a single clinic visit. Experience of low-voltage diathermy loop in 1000 patients. Lancet 1990; 336: 229–231.
68. Hatch KD. Cryotherapy. Baillieres Clin Obstet Gynaecol 1995; 9: 133–143.
69. Ferenczy A. Comparison of cryo- and carbon dioxide laser therapy for cervical intraepithelial neoplasia. Obstet Gynecol 1985; 66: 793–798.
70. Duncan ID. Cold coagulation. Baillieres Clin Obstet Gynaecol 1995; 9: 145–55.
71. Bisseling KC, Bekkers RL, Rome RM, Quinn MA. Treatment of microinvasive adenocarcinoma of the uterine cervix: A retrospective study and review of the literature. Gynecol Oncol 2007; 107: 424–430.
72. Stehman FB, Ali S, Keys HM, et al. Radiation therapy with or without weekly cisplatin for bulky stage 1B cervical carcinoma: Follow-up of a Gynecologic Oncology Group trial. Am J Obstet Gynecol 2007; 197: 503 e1–6.
73. Morice P, Rouanet P, Rey A, et al. Results of the GYNECO 02 study, an FNCLCC phase III trial comparing hysterectomy with no hysterectomy in patients with a (clinical and radiological) complete response after chemoradiation therapy for stage IB2 or II cervical cancer. Oncologist 2012; 17: 64–71.
74. ACOG practice bulletin. Diagnosis and treatment of cervical carcinomas, number 35, May 2002. Obstet Gynecol 2002; 99: 855–867.
75. Moore DH, Tian C, Monk BJ, Long HJ, Omura GA, Bloss JD. Prognostic factors for response to cisplatin-based chemotherapy in advanced cervical carcinoma: A Gynecologic Oncology Group Study. Gynecol Oncol 2010; 116: 44–49.
76. van Lonkhuijzen L, Thomas G. Palliative radiotherapy for cervical carcinoma, a systematic review. Radiother Oncol 2011; 98: 287–291.
77. Palefsky JM, Holly EA, Ralston ML, Jay N, Berry JM, Darragh TM. High incidence of anal high-grade squamous intra-epithelial lesions among HIV-positive and HIV-negative homosexual and bisexual men. AIDS 1998; 12: 495–503.
78. Richel O, Wieland U, de Vries HJ, et al. Topical 5-fluorouracil treatment of anal intraepithelial neoplasia in human immunodeficiency virus-positive men. Br J Dermatol 2010; 163: 1301–1307.
79. Fox PA, Nathan M, Francis N, et al. A double-blind, randomized controlled trial of the use of imiquimod cream for the treatment of anal canal high-grade anal intraepithelial neoplasia in HIV-positive MSM on HAART, with long-term follow-up data including the use of open-label imiquimod. AIDS 2010; 24: 2331–2335.
80. Kreuter A, Potthoff A, Brockmeyer NH, et al. Imiquimod leads to a decrease of human papillomavirus DNA and to a sustained

clearance of anal intraepithelial neoplasia in HIV-infected men. J Invest Dermatol 2008; 128: 2078–2083.
81. Cranston RD, Hirschowitz SL, Cortina G, Moe AA. A retrospective clinical study of the treatment of high-grade anal dysplasia by infrared coagulation in a population of HIV-positive men who have sex with men. Int J STD AIDS 2008; 19: 118–120.
82. Goldstone SE, Kawalek AZ, Huyett JW. Infrared coagulator: A useful tool for treating anal squamous intraepithelial lesions. Dis Colon Rectum 2005; 48: 1042–1054.
83. Stier EA, Goldstone SE, Berry JM, et al. Infrared coagulator treatment of high-grade anal dysplasia in HIV-infected individuals: An AIDS malignancy consortium pilot study. J Acquir Immune Defic Syndr 2008; 47: 56–61.
84. Pineda CE, Berry JM, Jay N, Palefsky JM, Welton ML. High-resolution anoscopy targeted surgical destruction of anal high-grade squamous intraepithelial lesions: A ten-year experience. Dis Colon Rectum 2008; 51: 829–835; discussion 35–7.
85. National Comprehensive Cancer Network (NCCN) guidelines. Available at: www.nccn.org.
86. Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. N Engl J Med 2007; 356: 1915–1927.
87. Garland SM, Hernandez-Avila M, Wheeler CM, et al. Quadrivalent vaccine against human papillomavirus to prevent anogenital diseases. N Engl J Med 2007; 356: 1928–1943.
88. Paavonen J, Naud P, Salmeron J, et al. Efficacy of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine against cervical infection and precancer caused by oncogenic HPV types (PATRICIA): Final analysis of a double-blind, randomised study in young women. Lancet 2009; 374: 301–314.
89. Giuliano AR, Palefsky JM, Goldstone S, et al. Efficacy of quadrivalent HPV vaccine against HPV Infection and disease in males. N Engl J Med 2011; 364: 401–411.
90. Palefsky JM, Giuliano AR, Goldstone S, et al. HPV vaccine against anal HPV infection and anal intraepithelial neoplasia. N Engl J Med 2011; 365: 1576–1585.
91. FDA licensure of bivalent human papillomavirus vaccine (HPV2, Cervarix) for use in females and updated HPV vaccination recommendations from the Advisory Committee on Immunization Practices (ACIP). MMWR Morb Mortal Wkly Rep 2010; 59: 626–629.
92. Recommendations on the use of quadrivalent human papillomavirus vaccine in males–Advisory Committee on Immunization Practices (ACIP). MMWR Morb Mortal Wkly Rep 2011; 60: 1705–1708.
93. Petaja T, Keranen H, Karppa T, et al. Immunogenicity and safety of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine in healthy boys aged 10–18 years. J Adolesc Health 2009; 44(1): 33–40.
94. Levin MJ, Moscicki AB, Song LY, et al. Safety and immunogenicity of a quadrivalent human papillomavirus (types 6, 11, 16, and 18) vaccine in HIV-infected children 7 to 12 years old. J Acquir Immune Defic Syndr 2010; 55: 197–204.
95. Wilkin T, Lee JY, Lensing SY, et al. Safety and immunogenicity of the quadrivalent human papillomavirus vaccine in HIV-1-infected men. J Infect Dis 2010; 202: 1246–1253.
96. Chin-Hong PV. Cutting human papillomavirus infection in men. J Infect Dis 2008; 197: 781–783.
97. Diaz ML. Human papilloma virus: Prevention and treatment. Obstet Gynecol Clin North Am 2008; 35: 199–217.
98. Stockfleth E, Nindl I, Sterry W, Ulrich C, Schmook T, Meyer T. Human papillomaviruses in transplant-associated skin cancers. Dermatol Surg 2004; 30: 604–609.
99. Ferenczy A, Bergeron C, Richart RM. Human papillomavirus DNA in CO_2 laser-generated plume of smoke and its consequences to the surgeon. Obstet Gynecol 1990; 75: 114–118.
100. Kashima HK, Kessis T, Mounts P, Shah K. Polymerase chain reaction identification of human papillomavirus DNA in CO_2 laser plume from recurrent respiratory papillomatosis. Otolaryngol Head Neck Surg 1991; 104: 191–195.
101. AORN. 2012 Perioperative Standards and Recommended Practices: For Inpatient and Ambulatory Settings AORN, Inc.; 2012.