YALE JOURNAL OF BIOLOGY AND MEDICINE 87 (2014), pp.537-547.


REVIEW

# Anorectal Human Papillomavirus: Current Concepts

Roland Assi, MD; Vikram Reddy, MD, PhD; Hulda Einarsdottir, MD; Walter E. Longo, MD*

*Department of Surgery, Yale School of Medicine, New Haven, Connecticut*

Increased anorectal human papillomavirus (HPV†) infection is related to the recent trends in sexual behavior in both homosexual and heterosexual groups and prevalence of infection with human immunodeficiency virus (HIV). Clinical presentation and natural history depend on the serotype involved. HPV 6 and 11 are found in the benign wart. Local control can be achieved with a wide selection of surgical and topical techniques. HPV 16, 18, and 31 are found in dysplastic lesions and have the potential to progress to invasive anal squamous cell carcinoma. Recognition and early management of dysplastic lesions is crucial to prevent the morbidity and mortality associated with anal cancer. While low-grade lesions can be closely observed, high-grade lesions should be eradicated. Different strategies can be used to eradicate the disease while preserving anorectal function. Studies on the efficacy of vaccination on anorectal HPV showed promising results in select population groups and led to the recent expansion of current vaccination recommendations.

*To whom all correspondence should be addressed: Walter E. Longo, 333 Cedar Street, LH 118, New Haven, CT 06510; Tele: 203-785-2616; Fax: 203-785-2615; Email: walter.longo@yale.edu.

†Abbreviations: STD(s), sexually transmitted disease(s); HPV, human papillomavirus; MSM, men who have sex with men, DNA, deoxyribonucleic acid; RAS, rat sarcoma gene; AIN, anal intraepithelial neoplasia, SCC, squamous cell carcinoma; LSIL, low-grade squamous intraepithelial lesion; HSIL, high-grade squamous intraepithelial lesion; HIV, human immunodeficiency virus; HAART, highly active anti-retroviral therapy; 5-FU, 5-FluoroUracil; FDA, Food and Drug Administration.

Keywords: sexually transmitted diseases, human papillomavirus, anorectal infections, anal intraepithelial neoplasia, anal squamous cell carcinoma, sexual behavior, perianal disease, human papillomavirus vaccine, anal cytology

Author contributions: Assi R: Study conception and design, drafting of manuscript, final approval. Reddy V: Study conception and design, critical revision, final approval. Einarsdottir H: Study conception and design, critical revision, final approval. Longo WE: Study conception and design, critical revision, final approval.

## INTRODUCTION

Sexually transmitted diseases (STDs) constitute a significant disease burden. Every year, 15 million new cases are reported in the United States [1]. Due to the recent increase in the practice of anal receptive intercourse among both homosexual and heterosexual groups, the incidence of STDs of the anus and rectum has increased; some cases, however, are the result of contiguous spread from the genital area [2,3].

Human papillomavirus (HPV) is the most common STD in the United States with an estimated 5.5 million new cases each year [1]. It has been on a steady increase over the last 50 years and is currently the most common STD seen by colorectal surgeons, with a million new cases seen every year [4]. Patients with HPV infection and anal lesions are frequently referred to the colorectal surgeon. The aim of this text is to review HPV infection of the anus and rectum that is commonly evaluated by the colorectal surgeon.

## EPIDEMIOLOGY

The majority of sexually active adults will acquire anogenital HPV at some point in their lives [5]. About one-third of sexually active young women have a detectable HPV infection on anal smear, with a higher prevalence among those who reported anal intercourse [6]. The presence of cervical HPV remains a major risk factor for anal HPV, even in the absence of anal intercourse [6-8].

In men, the reported prevalence of any site HPV infection ranges between 1.3 percent and 72.9 percent [9]. Men who have sex with men (MSM) have the highest prevalence of anal HPV, up to 57 percent, with HPV-16 being the most common type [10]. Lifetime number of sexual partners is the most important modifiable risk factor for anogenital HPV infection in MSM [11]. In heterosexual men, the prevalence of genital HPV is 53 percent, and the prevalence of anal HPV is 12 percent [12,13]. Risk factors for anal HPV in heterosexual men include a lifetime number of ≥ 10 female sex partners, a primary sexual relationship <1 year in duration, and a prior hepatitis B diagnosis [12].

## PATHOGENESIS

HPV are small non-enveloped deoxyribonucleic acid (DNA) viruses that induce proliferative lesions of the cutaneous and mucosal epithelium [14]. More than 100 serotypes have been identified, and pathology associated with HPV infection depends on the incriminated serotype. HPV can be classified into low risk found in condyloma acuminatum (benign wart) and high risk found in dysplasia and malignancies [15,16]. The most common low-risk serotypes are HPV 6 and 11, and the most common high-risk serotypes are HPV 16, 18, and 31, with serotype 16 found in approximately half of all cervical cancers [17,18]. Following transmission, the incubation period is usually 3 to 4 months but can extend up to 2 years [19,20]. HPV DNA is then incorporated into the host nucleus, either in free episomal form for low-risk serotypes or incorporated into the host genome for high-risk serotypes [21]. In low-risk lesions, viral replication results in excessive proliferation of all layers except the basal layer. This process produces several cytological changes, most characteristically koilocytosis, describing the appearance of large polygonal cell with a shrunken nucleus lodged inside a large cytoplasmic vacuole [22]. In high-risk lesions, the key pathophysiologic effect of HPV is the blockage of cellular differentiation by preventing cells from exiting the cell cycle. On the molecular level, the oncogenic potential of HPV can be related to the products of two viral genes, E6 and E7, that interact with a variety of proto-oncogenes and tumor suppressor genes, resulting in inhibition of apoptosis [14,21,23,24]. However, HPV infection by itself is not sufficient for carcinogenesis, and additional cofactors are implicated. This explains why only a small number of women infected with high-risk HPV develop cancer. Genetic factors include cotransfection with a mutated rat sarcoma gene (RAS) [21]. Environmental factors strongly involved in

progression to cervical cancer include cigarette smoking, multiparity, and long-term use of contraceptives. The mechanisms of action of these HPV cofactors remain poorly understood [25].

## CLINICAL PRESENTATION

Anal HPV disease is strongly related to the immunosuppression secondary to HIV infection and associated with a history of anal-receptive intercourse; however, autoinoculation of vulvar warts to the perianal skin can occur [26]. Some evidence exists regarding the protective effect of male circumcision on genital HPV, with decreased HPV incidence and increased HPV clearance in circumcised compared to uncircumcised males [27,28]. Condoms can decrease the transmission of anogenital HPV, but they are not completely effective because HPV can infect skin beyond the area covered by a condom [29]. Clinically, HPV infection of the anorectum can present as benign warts (condyloma acuminata), dysplastic lesions (anal intraepithelial neoplasia), or a combination of both.

### *Condyloma acuminatum*

Warts can be pedunculated or grow in radial rows around the anus. They can extend into the anal canal as far as 2 cm above the dentate line, which can be seen during anoscopy. Symptoms associated with anal warts include the presence of a raised lesion, pruritis ani, bleeding, discharge, pain, and difficulty with hygiene. Buschke-Lewenstein disease, although associated with HPV 6 and 11, refers to a malignant form of the disease with presence of a giant condyloma that tends to invade locally with formation of abscesses and fistulas and progression into carcinoma [30].

### *Anal Intraepithelial Neoplasia*

Anal intraepithelial neoplasia (AIN), a precursor of anal squamous cell carcinoma (SCC), has been associated with HPV strains 16, 18, and 31. The grading of AIN is classified following the Bethesda system into low-grade squamous intraepithelial lesion (LSIL), which reflects a transient, self-limited infection, and high-grade squamous intraepithelial lesion (HSIL), which is associated with chronic and long-standing infection [31]. AIN is often asymptomatic, while anal SCC can be associated with rectal bleeding and sensation of a mass. The current understanding, although limited, is that the pathophysiology is similar to the neoplastic progression described in cervical cancer associated with HPV. Contrary to previous belief, AIN has a high prevalence among HIV-positive males when CD4+ cell count falls below 500 cells/mm$^3$, even in the absence of a history of anal receptive intercourse [32]. It is notable that immune restoration with the use of highly active antiretroviral therapy (HAART) does not reduce the risk of AIN [33]. Non-HIV related immunosuppression following organ transplantation has been similarly associated with an increased risk of AIN and anal cancer; this excess risk might be of a lesser degree when newer, more selective anti-rejection medications are used [34,35].

## DIAGNOSIS

Physical examination is diagnostic of warts and shows the characteristic gray or pink fleshy cauliflower-like growths of variable size in the perianal region [26,36]. Similarly, dysplastic lesions are readily diagnosed on physical examination. Acetic acid application to the perianal area can help better visualize flat, dysplastic, and neoplastic lesions. High resolution anoscopy may be performed to exclude intra-anal disease [4]. When in doubt, diagnosis is confirmed histologically on a biopsy specimen. A higher index of suspicion for malignancy should be maintained in the immunocompromised patient, presence of large, atypical lesions, lesions that are refractory to treatment, pigmented lesions, and patients older than 40 years [15]. Anal cytology has been recommended but with limited evidence. Anal cytology screening for AIN lesions every 2 or 3 years in HIV-negative MSM men and yearly in HIV-positive MSM has been shown to provide cost-effective life-expectancy benefits [37,38].

## MANAGEMENT

### *Condyloma acuminatum*

All treatment modalities are associated with a significant risk of failure, recurrence, and side effects and require close long-term follow-up. There is no strong evidence to favor any specific treatment; the choice of treatment depends on the clinical presentation, host factors, patient preference, and surgeon's experience.

#### Medical approach

Although surgical eradication is considered the mainstay of treatment, a variety of topical agents is available for application to the perianal area and offers a convenient alternative to surgery.

Podophyllotoxin is available as a patient-applied 0.5 percent solution, cream, or gel. It acts on the cellular level to disrupt microtubules leading to cell death [39]. Complete resolution can be expected in 45 to 83 percent for genital warts and in 42 percent for perianal warts with recurrence rates of 12 to 60 percent [40-42]. Following wart clearance, podophyllotoxin can be used as a prophylactic treatment [41]. Side effects are common and include inflammation, erosion, pain, burning, and itching. Podophyllotoxin is not currently approved for use for anal canal lesions [41]. In addition, patient-application poses numerous difficulties related to the ease of application and associated pain with implications for treatment compliance [43].

Imiquimod, available as 5 percent cream, is an immune response modifier that increases local production of interferon and other cytokines leading to increased antiviral immunity [36,44-46]. In clinical trials, clearance rates for anogenital warts varied between 50 percent and 75 percent and recurrence rates between 13 percent and 23 percent [47-50]. In up to 67 percent of patients, the most common side effects are local irritation and erythema, which are usually mild to moderate in severity and rarely result in interruption of treatment [49,51]. Recent data suggest that it might be safe for use for anal canal lesions [52,53]. Imiquimod might be most beneficial when used as adjunct to fulguration therapy to treat remaining disease or prevent recurrence [36].

Trichloroacetic acid induces tissue necrosis resulting in destruction of small lesions [54]. Clearance rates for genital lesions varied between 70 percent and 81 percent, but more than a third recurred [42]. Side effects include discomfort, irritation, and scarring [55]. Because it has virtually no systemic absorption, trichloroacetic acid is the only topical agent that can be safely used in pregnant patients; it can also be used for anal canal lesions [56].

5-fluorouracil (5-FU) and interferons have been investigated with mixed results. They can be administered as topical gels and intralesional or intramuscular injections. They are rarely used for primary treatment of anogenital warts due to clearance rates similar to other topical agents and the potential for serious adverse effects. 5-FU is teratogenic and associated with severe local irritation, while interferons frequently result in a systemic flu-like syndrome [4,36,42,57-60].

Characteristics of each topical agent are summarized in Table 1.

#### Surgical approach

Several surgical modalities exist to achieve the goal of condyloma removal or destruction. The advantages of surgical treatment are that it allows for tissue diagnosis and usually requires fewer office visits than medical treatment. Surgical treatments are also safe in pregnant patients. Small lesions may be treated in the office under local anesthesia. Larger lesions and anal canal involvement often require general anesthesia or sedation in an operating room setting. Common techniques include tangential excision with surgical scissors or blade, fulguration with electrocautery, and cryotherapy.

Surgical excision has excellent clearance rates (71 to 100 percent) and low recurrence rates (8 to 9 percent) [61,62]. Fulguration consists of applying a high frequency electrical current to a lesion using a metallic blade or needle until the lesion is destroyed. It is equally effective with clearance rates up to 94 percent and variable re-

**Table 1. Summary of most commonly used topical agents for treatment of condyloma accuminata.**

| Agent | Mechanism of Action | Clearance Rate | Recurrence Rate | Side effects | Comments |
|---|---|---|---|---|---|
| Podophyllotoxin (0.5% solution) | Microtubules disruption leading to cell death | 42-83% | 12-60% | Inflammation, erosion, pain, burning, and itching | May be used prophylactically to prevent recurrence<br>Not for anal canal lesions<br>Difficult patient application |
| Imiquimod 5% cream | Immune response modifier, increases local production of interferons and cytokines | 50-75% | 13-23% | Local irritation and erythema, usually well tolerated | Might be safe for anal canal application<br>Most beneficial in conjunction with fulguration therapy |
| Trichloroacetic acid | Induces tissue necrosis resulting in destruction of small lesions | 70-81% | 35% | Discomfort, irritation and scarring | May be used in pregnancy<br>May be used for anal canal lesions |
| 5-Fluorouracil (topical or intralesional combined with epinephrine) | Antimetabolite leading to DNA and RNA synthesis arrest and immunomodulation | 44-73% | 7-50% | Severe local reaction | Teratogenic, contraindicated in pregnancy |
| Interferons (topical or intralesional) | Induces antiviral immunity | Variable | Variable | Common systemic flu-like syndrome and local inflammation | Not recommended as first line therapy |

currence rates [63]. Many times the lesion is sharply excised with scissors and the base is cauterized for the purpose of hemostasis and destruction of residual lesions. Also, topical agents might be used in combination with surgical techniques, especially when the area of skin involved is large. As with any surgical approach, side effects are infection, bleeding, and scarring. With fulguration, surgical masks should be used because HPV can be dispersed in the surrounding air [64].

Cryotherapy is another modality that aims at destroying lesions by cell lysis using nitrous oxide or, more commonly, liquid nitrogen. Multiple treatment sessions might be required to achieve clearance. It has accept-

able clearance rates but might be inferior to surgical excision or fulguration [63].

Wide local excision is reserved for the treatment of giant condyloma accuminata to obtain negative margins with or without fecal diversion. If the anal sphincter is involved, abdominal-perineal resection could be considered. Patients with extensive local disease might be treated with fecal diversion and chemoradiation followed by abdominal-perineal resection [65].

Many of the patients we encounter have failed topical treatment, either because of frequent recurrence or intolerance due to side effects. These patients are offered a surgical intervention. Our preferred modality is fulguration with electrocautery for small lesions and cold excision with fulguration of the base for larger lesions. For extensive disease that covers large skin area, larger or suspicious lesions are preferentially excised, while less prominent ones are left for a trial of topical treatment. Our preferred topical agent is imiquimod because it is associated with high clearance rates when combined with surgical therapy. Once the surgical area has healed, the patient is offered a subsequent surgical intervention until eradication of all remaining disease.

### *Anal Intraepithelial Neoplasia*

Timely diagnosis and treatment of AIN is important to prevent progression into invasive anal SCC. This could be challenging because AIN is often asymptomatic, the timeline of disease progression is variable, and the optimal management remains controversial. Over a follow-up period of 2 years, one-third of HIV-negative patients with LSIL progressed to HSIL compared to two-thirds of HIV-positive patients [66]. Once HSIL is present, progression to invasive cancer has been reported in half of immunosuppressed patients [67]. Therefore, expectant management might be appropriate only for HIV-negative patients with LSIL who are willing to undergo close follow-up every 4 to 6 months [68].

#### Medical approach

Topical imiquimod 5 percent is an effective treatment of AIN. Complete response can be expected in more than half of patients, but repeat treatment courses may be necessary [68,69]. Imiquimod may be most beneficial as monotherapy for LSIL or as an adjunct to targeted destruction for HSIL [70]. A similar response can be achieved with topical 5-fluorouracil (5-FU) [71]. When the disease pattern is extensive and only partial response is obtained, the remaining lesions are often amenable to surgical excision [71,72]. Topical treatments with imiquimod or 5-FU are appropriate therapies for both LSIL and HSIL when combined with close long-term follow-up, but compliance may be limited by frequent local side effects [68]. Topical trichloroacetic acid treatment is also effective for treatment of AIN and is most beneficial in patients with LSIL and limited extent of disease. Reported clearance rates with trichloroacetic acid for LSIL and HSIL were 73 percent and 32 percent, respectively [73].

Photodynamic therapy is a new modality that may be used for AIN. It involves administration of a photosensitizer agent that localizes to dysplastic anal canal cells, leading to their destruction after activation with a specific light wavelength. Current evidence is weak to support its widespread adoption [31,74].

#### Surgical approach

Surgical therapy includes wide local excision and targeted destruction. Wide local excision can eradicate the disease when negative microscopic margins are obtained. When only negative macroscopic margins are obtained, local recurrence is high but can be effectively treated with repeat local excision [75]. Due to the significant morbidity associated with wide local excision (incontinence, anal stenosis, need for fecal diversion, need for skin grafting or flap reconstruction), some authors have recommended two-staged operation after punch biopsy and permanent histology [31].

Targeted destruction using electrocautery may be used with limited morbidity, but recurrence rates remain high, especially in HIV-positive patients; however, treatment may be repeated until eradication of all le-

sions. In retrospective studies, more than 75 percent of patients achieved complete response after multiple treatment sessions [68,76,77]. Following treatment, it is recommended that patients are followed closely every 3 to 6 months as long as dysplasia is present. This is especially important in patients with a higher risk for progression to anal SCC, including HIV-positive patients, those with a history of other HPV-related genital malignancies, solid organ transplant recipients, and MSM [68].

Our management priorities are to prevent the development of invasive anal cancer and minimize any symptoms if they exist. Low-risk compliant patients with LSIL who do not wish to undergo surgical intervention are managed with close observation every 6 months. This group of patients, however, constitutes a minority. For all other patients, our preferred modality is surgical excision because it allows for eradication of disease and examination of the specimen. Topical therapy with imiquimod might be used as adjunct to surgical therapy with good local control but the recurrence rate can reach 40 percent. Even when disease is eradicated, we recommend that all patients remain under close surveillance due to the significant risk of recurrence. As AIN represents a complex disease process, often in a diverse patient population, treatment should be individualized on a case by case basis based on patient's disease burden, histology, pre-existing conditions and patient's wishes.

## VACCINATION

Over the last decade, HPV vaccination emerged as a promising preventive strategy. Two vaccines are available: the bivalent vaccine targets HPV 16 and 18 (Cervarix), and the quadrivalent vaccine targets HPV 6, 11, 16, and 18 (Gardasil). Vaccines are given as intra-muscular injections in 3 doses at 0, 2, and 6 months. Vaccination is effective when given to HPV-naïve patients (adolescents aged 9 to 15 years), with a seroconversion rate of >90 percent in males and females [78,79]. When HPV infection is present prior to immunization, there is no evidence that vaccination alters the course of the infection, so the purpose of vaccination remains preventive, not therapeutic [80-82].

Initial large clinical trials aimed at investigating the efficacy of prevention of genital and cervical lesions in HPV-naïve young females. The quadrivalent vaccine showed a 98 percent efficacy in preventing cervical intraepithelial neoplasia 2 or 3, adenocarcinoma *in situ*, or cervical cancer related to HPV 16 or 18 [80]. In addition, it showed a 100 percent efficacy of preventing anogenital warts, vulvar or vaginal intraepithelial neoplasia grades 1 to 3, or cancer associated with HPV 6, 11, 16, or 18 [81]. In 2006, the Food and Drug Administration (FDA) approved the quadrivalent vaccine (Gardasil) for use in females 9 to 26 years of age. The bivalent vaccine showed a 93 percent efficacy of preventing cervical intraepithelial neoplasia 2 or 3, adenocarcinoma *in situ*, or cervical cancer [83]. In 2009, the bivalent vaccine (Cervarix) was FDA-approved for use in females 9 to 26 years of age.

Following the demonstration of the efficacy of HPV vaccination in females, a large international clinical trial evaluated the efficacy of the quadrivalent vaccine in 4,065 boys and men from 18 countries. The appearance of penile, scrotal, and peri-anal lesions related to HPV-6, 11, 16, or 18 were prevented in 90.4 percent of the cases, and persistent infection was prevented in 85.6 percent [84]. In a substudy that included MSM, the quadrivalent vaccine reduced the incidence of AIN related to HPV 16 or 18 by 78.6 percent [85]. In 2009, the quadrivalent vaccine (Gardasil) was FDA-approved for use in males 9 to 26 years of age.

Since HPV vaccination is most clinically effective in HPV-naïve individuals and does not alter the course of an existent infection, the rationale is to initiate vaccination before infection or more practically before the individual is sexually active. The current consensus it to recommend the routine use of quadrivalent vaccine in males 11 or 12 years of age [86]. For MSM and for males who are immunocompromised (in-

cluding HIV infection), vaccination is recommended through age 26 for those not previously vaccinated. Vaccination is also recommended for males 13 to 21 years of age who have not been vaccinated previously or have not completed the three dose series. Males of 22 through 26 years of age may also be vaccinated using the quadrivalent vaccine [87].

## CONCLUSION

Contrary to earlier belief, sexually transmitted diseases of the anorectum, including HPV, are not limited to homosexual men, and it is important for both the primary care physician and the colorectal surgeon to recognize recent trends in sexual behavior. Early recognition is essential to initiate appropriate prevention and management strategies. HPV infection of the anorectum is associated with two clinical entities, the condyloma acuminata or benign warts and a spectrum of dysplastic lesions ranging from anal intraepithelial neoplasia to anal cancer. Benign warts are treated with a combination of topical agents and surgical techniques based on the extent of disease and patient tolerance and compliance. A variety of topical therapies offer a reasonable rate of clearance, but recurrence is common. Surgical therapies are associated with good clearance and low recurrence rates and remain the preferred approach when topical treatments have failed. Anal intraepithelial neoplasia is best managed with a combination of topical and surgical modalities, with the goal of disease eradication and the conservation of the anorectal function. Following treatment, close long-term surveillance is crucial to treat recurrence and prevent progression to anal cancer. Although routine screening remains controversial, screening with anal cytology is cost-effective for selected high-risk populations. Finally, vaccination has recently emerged as an effective modality for prevention. The quadrivalent HPV vaccine is effective in preventing anogenital warts in young males and anal intraepithelial neoplasia in men who have sex with men.

## REFERENCES

1. Cates W, Jr. Estimates of the incidence and prevalence of sexually transmitted diseases in the United States. American Social Health Association Panel. Sex Transm Dis. 1999;26(4 Suppl):S2-7.
2. Wexner SD. Sexually transmitted diseases of the colon, rectum, and anus. The challenge of the nineties. Dis Colon Rectum. 1990;33(12):1048-62.
3. Halperin DT. Heterosexual anal intercourse: prevalence, cultural factors, and HIV infection and other health risks, Part I. AIDS Patient Care STDS. 1999;13(12):717-30.
4. Townsend CM, Jr. Anus: Neoplastic Disorders. Sabiston textbook of surgery: the biological basis of modern surgical practice. 19th edition. Philadelphia: Elsevier Saunders; 2012.
5. Workowski KA, Berman SM. Sexually transmitted diseases treatment guidelines, 2006. MMWR Recomm Rep. 2006;55(RR-11):1-94.
6. Castro FA, Quint W, Gonzalez P, Katki HA, Herrero R, van Doorn LJ, et al. Prevalence of and risk factors for anal human papillomavirus infection among young healthy women in Costa Rica. J Infect Dis. 2012;206(7):1103-10.
7. Goodman MT, Shvetsov YB, McDuffie K, Wilkens LR, Zhu X, Ning L, et al. Acquisition of anal human papillomavirus (HPV) infection in women: the Hawaii HPV Cohort study. J Infect Dis. 2008;197(7):957-66.
8. Goodman MT, Shvetsov YB, McDuffie K, Wilkens LR, Zhu X, Thompson PJ, et al. Sequential acquisition of human papillomavirus (HPV) infection of the anus and cervix: the Hawaii HPV Cohort Study. J Infect Dis. 2010;201(9):1331-9.
9. Dunne EF, Nielson CM, Stone KM, Markowitz LE, Giuliano AR. Prevalence of HPV infection among men: A systematic review of the literature. J Infect Dis. 2006;194(8):1044-57.
10. Chin-Hong PV, Vittinghoff E, Cranston RD, Buchbinder S, Cohen D, Colfax G, et al. Age-Specific prevalence of anal human papillomavirus infection in HIV-negative sexually active men who have sex with men: the EXPLORE study. J Infect Dis. 2004;190(12):2070-6.
11. Goldstone S, Palefsky JM, Giuliano AR, Moreira ED, Jr., Aranda C, Jessen H, et al. Prevalence of and risk factors for human papillomavirus (HPV) infection among HIV-seronegative men who have sex with men. J Infect Dis. 2011;203(1):66-74.
12. Nyitray AG, Carvalho da Silva RJ, Baggio ML, Lu B, Smith D, Abrahamsen M, et al. Age-specific prevalence of and risk factors for anal human papillomavirus (HPV) among men who have sex with women and men who have sex with men: the HPV in men (HIM) study. J Infect Dis. 2011;203(1):49-57.

13. Nyitray AG, da Silva RJ, Baggio ML, Lu B, Smith D, Abrahamsen M, et al. The prevalence of genital HPV and factors associated with oncogenic HPV among men having sex with men and men having sex with women and men: the HIM study. Sex Transm Dis. 2011;38(10):932-40.
14. Hebner CM, Laimins LA. Human papillomaviruses: basic mechanisms of pathogenesis and oncogenicity. Rev Med Virol. 2006;16(2):83-97.
15. Gunter J. Genital and perianal warts: new treatment opportunities for human papillomavirus infection. Am J Obstet Gynecol. 2003;189(3 Suppl):S3-11.
16. Lorincz AT, Temple GF, Kurman RJ, Jenson AB, Lancaster WD. Oncogenic association of specific human papillomavirus types with cervical neoplasia. J Natl Cancer Inst. 1987;79(4):671-7.
17. de Sanjose S, Quint WG, Alemany L, Geraets DT, Klaustermeier JE, Lloveras B, et al. Human papillomavirus genotype attribution in invasive cervical cancer: a retrospective cross-sectional worldwide study. Lancet Oncol. 2010;11(11):1048-56.
18. Munoz N, Bosch FX, de Sanjose S, Herrero R, Castellsague X, Shah KV, et al. Epidemiologic classification of human papillomavirus types associated with cervical cancer. N Engl J Med. 2003;348(6):518-27.
19. Goldschmidt H, Kligman AM. Experimental inoculation of humans with ectodermotropic viruses. J Invest Dermatol. 1958;31(3):175-82.
20. Barrett TJ, Silbar JD, McGinley GP. Genital warts-a venereal disease. J Am Med Assoc. 1954;154(4):333-4.
21. Kumar V, Abbas AK, Fausto N, Aster JC. Robbins and Cotran pathologic basis of disease, professional edition: Expert Consult - Online and Print. Elsevier Health Sciences; 2009.
22. Mandell GL, Bennett JE, Dolin R. Mandell, Douglas and Bennett's principles and practice of infectious diseases. Churchill Livingstone Elsevier; 2010.
23. zur Hausen H. Papillomaviruses causing cancer: evasion from host-cell control in early events in carcinogenesis. J Natl Cancer Inst. 2000;92(9):690-8.
24. Stubenrauch F, Laimins LA. Human papillomavirus life cycle: active and latent phases. Semin Cancer Biol. 1999;9(6):379-86.
25. Schiffman M, Castle PE, Jeronimo J, Rodriguez AC, Wacholder S. Human papillomavirus and cervical cancer. Lancet. 2007;370(9590):890-907.
26. El-Attar SM, Evans DV. Anal warts, sexually transmitted diseases, and anorectal conditions associated with human immunodeficiency virus. Prim Care. 1999;26(1):81-100.
27. Larke N, Thomas SL, Dos Santos Silva I, Weiss HA. Male circumcision and human papillomavirus infection in men: a systematic review and meta-analysis. J Infect Dis. 2011;204(9):1375-90.
28. Hernandez BY, Shvetsov YB, Goodman MT, Wilkens LR, Thompson P, Zhu X, et al. Reduced clearance of penile human papillomavirus infection in uncircumcised men. J Infect Dis. 2010;201(9):1340-3.
29. Baldwin SB, Wallace DR, Papenfuss MR, Abrahamsen M, Vaught LC, Giuliano AR. Condom use and other factors affecting penile human papillomavirus detection in men attending a sexually transmitted disease clinic. Sex Transm Dis. 2004;31(10):601-7.
30. Buschke A, Lowenstein L. Uber carcinomahnliche condylomata accuminata. Klin Wochenschr. 1925;4:1726.
31. Bejarano PA, Boutros M, Berho M. Anal squamous intraepithelial neoplasia. Gastroenterol Clin North Am. 2013;42(4):893-912.
32. Piketty C, Darragh TM, Da Costa M, Bruneval P, Heard I, Kazatchkine MD, et al. High prevalence of anal human papillomavirus infection and anal cancer precursors among HIV-infected persons in the absence of anal intercourse. Ann Intern Med. 2003;138(6):453-9.
33. Piketty C, Darragh TM, Heard I, Da Costa M, Bruneval P, Kazatchkine MD, et al. High prevalence of anal squamous intraepithelial lesions in HIV-positive men despite the use of highly active antiretroviral therapy. Sex Transm Dis. 2004;31(2):96-9.
34. 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.
35. Mathew T, Kreis H, Friend P. Two-year incidence of malignancy in sirolimus-treated renal transplant recipients: results from five multicenter studies. Clin Transplant. 2004;18(4):446-9.
36. Beck DE. Sexually Transmitted Diseases. The ASCRS textbook of colon and rectal surgery. 2nd edition. New York: Springer; 2011. p. 295-307.
37. Goldie SJ, Kuntz KM, Weinstein MC, Freedberg KA, Palefsky JM. Cost-effectiveness of screening for anal squamous intraepithelial lesions and anal cancer in human immunodeficiency virus-negative homosexual and bisexual men. Am J Med. 2000;108(8):634-41.
38. Goldie SJ, Kuntz KM, Weinstein MC, Freedberg KA, Welton ML, Palefsky JM. The clinical effectiveness and cost-effectiveness of screening for anal squamous intraepithelial lesions in homosexual and bisexual HIV-positive men. JAMA. 1999;281(19):1822-9.
39. Ma Y, Fang S, Li H, Han C, Lu Y, Zhao Y, et al. Biological evaluation and molecular modelling study of podophyllotoxin derivatives as potent inhibitors of tubulin polymerization. Chem Biol Drug Des. 2013;82(1):12-21.
40. Tyring S, Edwards L, Cherry LK, Ramsdell WM, Kotner S, Greenberg MD, et al. Safety

and efficacy of 0.5% podofilox gel in the treatment of anogenital warts. Arch Dermatol. 1998;134(1):33-8.
41. Bonnez W, Elswick RK, Jr, Bailey-Farchione A, Hallahan D, Bell R, Isenberg R, et al. Efficacy and safety of 0.5% podofilox solution in the treatment and suppression of anogenital warts. Am J Med. 1994;96(5):420-5.
42. Ting PT, Dytoc MT. Therapy of external anogenital warts and molluscum contagiosum: a literature review. Dermatol Ther. 2004;17(1):68-101.
43. Hammarlund K, Nystrom M, Jomeen J. Young women's experiences of managing self-treatment for anogenital warts. Sex Reprod Healthc. 2012;3(3):117-21.
44. Tyring S. Immune response modification: imiquimod. Australas J Dermatol. 1998;39 Suppl 1:S11-3.
45. Pearson G, Langley R. Topical imiquimod. J Dermatolog Treat. 2001;12(1):37-40.
46. Tyring SK, Arany I, Stanley MA, Tomai MA, Miller RL, Smith MH, et al. A randomized, controlled, molecular study of condylomata acuminata clearance during treatment with imiquimod. J Infect Dis. 1998;178(2):551-5.
47. Buck HW, Fortier M, Knudsen J, Paavonen J. Imiquimod 5% cream in the treatment of anogenital warts in female patients. Int J Gynaecol Obstet. 2002;77(3):231-8.
48. Edwards L. Imiquimod in clinical practice. Australas J Dermatol. 1998;39 Suppl 1:S14-6.
49. Garland SM, Sellors JW, Wikstrom A, Petersen CS, Aranda C, Aractingi S, et al. Imiquimod 5% cream is a safe and effective self-applied treatment for anogenital warts--results of an open-label, multicentre Phase IIIB trial. Int J STD AIDS. 2001;12(11):722-9.
50. Gollnick H, Barasso R, Jappe U, Ward K, Eul A, Carey-Yard M, et al. Safety and efficacy of imiquimod 5% cream in the treatment of penile genital warts in uncircumcised men when applied three times weekly or once per day. Int J STD AIDS. 2001;12(1):22-8.
51. Syed TA, Ahmadpour OA, Ahmad SA, Ahmad SH. Management of female genital warts with an analog of imiquimod 2% in cream: a randomized, double-blind, placebo-controlled study. J Dermatol. 1998;25(7):429-33.
52. Dianzani C, Pierangeli A, Avola A, Borzomati D, Persichetti P, Degener AM. Intra-anal condyloma: surgical or topical treatment? Dermatol Online J. 2008;14(12):8.
53. Kaspari M, Gutzmer R, Kaspari T, Kapp A, Brodersen JP. Application of imiquimod by suppositories (anal tampons) efficiently prevents recurrences after ablation of anal canal condyloma. Br J Dermatol. 2002;147(4):757-9.
54. Brodland DG, Cullimore KC, Roenigk RK, Gibson LE. Depths of chemexfoliation induced by various concentrations and application techniques of trichloroacetic acid in a porcine model. J Dermatol Surg Oncol. 1989;15(9):967-71.
55. Beutner KR, Ferenczy A. Therapeutic approaches to genital warts. Am J Med. 1997;102(5a):28-37.
56. Schwartz DB, Greenberg MD, Daoud Y, Reid R. Genital condylomas in pregnancy: use of trichloroacetic acid and laser therapy. Am J Obstet Gynecol. 1988;158(6 Pt 1):1407-16.
57. Reichman RC, Micha JP, Weck PK, Bonnez W, Wold D, Whisnant JK, et al. Interferon alpha-n1 (Wellferon) for refractory genital warts: efficacy and tolerance of low dose systemic therapy. Antiviral Res. 1988;10(1-3):41-57.
58. Cardamakis E, Kotoulas IG, Metalinos K, Mantouvalos H, Relakis K, Scarpari M, et al. Treatment of urethral condylomata acuminata or flat condylomata with interferon-alpha 2a. J Urol. 1994;152(6 Pt 1):2011-3.
59. Swinehart JM, Skinner RB, McCarty JM, Miller BH, Tyring SK, Korey A, et al. Development of intralesional therapy with fluorouracil/adrenaline injectable gel for management of condylomata acuminata: two phase II clinical studies. Genitourin Med. 1997;73(6):481-7.
60. Ferenczy A. Comparison of 5-fluorouracil and CO2 laser for treatment of vaginal condylomata. Obstet Gynecol. 1984;64(6):773-8.
61. Gollock JM, Slatford K, Hunter JM. Scissor excision of anogenital warts. Br J Vener Dis. 1982;58(6):400-1.
62. McMillan A, Scott GR. Outpatient treatment of perianal warts by scissor excision. Genitourin Med. 1987;63(2):114-5.
63. Stone KM, Becker TM, Hadgu A, Kraus SJ. Treatment of external genital warts: a randomised clinical trial comparing podophyllin, cryotherapy, and electrodesiccation. Genitourin Med. 1990;66(1):16-9.
64. Ferenczy A, Bergeron C, Richart RM. Carbon dioxide laser energy disperses human papillomavirus deoxyribonucleic acid onto treatment fields. Am J Obstet Gynecol. 1990;163(4 Pt 1):1271-4.
65. Trombetta LJ, Place RJ. Giant condyloma acuminatum of the anorectum: trends in epidemiology and management: report of a case and review of the literature. Dis Colon Rectum. 2001;44(12):1878-86.
66. Palefsky JM, Holly EA, Hogeboom CJ, Ralston ML, DaCosta MM, Botts R, et al. Virologic, immunologic, and clinical parameters in the incidence and progression of anal squamous intraepithelial lesions in HIV-positive and HIV-negative homosexual men. J Acquir Immune Defic Syndr Hum Retrovirol. 1998;17(4):314-9.
67. Scholefield JH, Castle MT, Watson NFS. Malignant transformation of high-grade anal intraepithelial neoplasia. Br J Surg. 2005;92(9):1133-6.

68. Steele SR, Varma MG, Melton GB, Ross HM, Rafferty JF, Buie WD. Practice parameters for anal squamous neoplasms. Dis Colon Rectum. 2012;55(7):735-49.
69. Mahto M, Nathan M, O'Mahony C. More than a decade on: review of the use of imiquimod in lower anogenital intraepithelial neoplasia. Int J STD AIDS. 2010;21(1):8-16.
70. Pineda CE, Welton ML. Controversies in the management of anal high-grade squamous intraepithelial lesions. Minerva Chir. 2008;63(5):389-99.
71. Richel O, Wieland U, de Vries HJ, Brockmeyer NH, van Noesel C, Potthoff A, et al. Topical 5-fluorouracil treatment of anal intraepithelial neoplasia in human immunodeficiency virus-positive men. Br J Dermatol. 2010;163(6):1301-7.
72. Graham BD, Jetmore AB, Foote JE, Arnold KL. Topical 5-fluorouracil in the management of extensive anal Bowen's disease: a preferred approach. Dis Colon Rectum. 2005;48(3):444-50.
73. 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(4):474-9.
74. Abbasakoor F, Boulos PB. Anal intraepithelial neoplasia. Br J Surg. 2005;92(3):277-90.
75. Marchesa P, Fazio VW, Oliart S, Goldblum JR, Lavery IC. Perianal Bowen's disease: a clinicopathologic study of 47 patients. Dis Colon Rectum. 1997;40(11):1286-93.
76. 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(6):829-35; discussion 35-7.
77. Marks DK, Goldstone SE. Electrocautery ablation of high-grade anal squamous intraepithelial lesions in HIV-negative and HIV-positive men who have sex with men. J Acquir Immune Defic Syndr. 2012;59(3):259-65.
78. Petaja T, Keranen H, Karppa T, Kawa A, Lantela S, Siitari-Mattila M, 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.
79. Reisinger KS, Block SL, Lazcano-Ponce E, Samakoses R, Esser MT, Erick J, et al. Safety and persistent immunogenicity of a quadrivalent human papillomavirus types 6, 11, 16, 18 L1 virus-like particle vaccine in preadolescents and adolescents: a randomized controlled trial. Pediatr Infect Dis J. 2007;26(3):201-9.
80. The Future II Study Group. Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. N Engl J Med. 2007;356(19):1915-27.
81. Garland SM, Hernandez-Avila M, Wheeler CM, Perez G, Harper DM, Leodolter S, et al. Quadrivalent vaccine against human papillomavirus to prevent anogenital diseases. N Engl J Med. 2007;356(19):1928-43.
82. Hildesheim A, Herrero R, Wacholder S, Rodriguez AC, Solomon D, Bratti MC, et al. Effect of human papillomavirus 16/18 L1 viruslike particle vaccine among young women with preexisting infection: a randomized trial. JAMA. 2007;298(7):743-53.
83. Paavonen J, Naud P, Salmeron J, Wheeler CM, Chow SN, Apter D, 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(9686):301-14.
84. Giuliano AR, Palefsky JM, Goldstone S, Moreira ED Jr, Penny ME, Aranda C, et al. Efficacy of quadrivalent HPV vaccine against HPV Infection and disease in males. N Engl J Med. 2011;364(5):401-11.
85. Palefsky JM, Giuliano AR, Goldstone S, Moreira ED Jr, Aranda C, Jessen H, et al. HPV vaccine against anal HPV infection and anal intraepithelial neoplasia. N Engl J Med. 2011;365(17):1576-85.
86. Recommendations on the use of quadrivalent human papillomavirus vaccine in males--Advisory Committee on Immunization Practices (ACIP), 2011. MMWR Morb Mortal Wkly Rep. 2011;60(50):1705-8.
87. Advisory Committee on Immunization Practices (ACIP) recommended immunization schedules for persons aged 0 through 18 years and adults aged 19 years and older--United States, 2013. MMWR Surveill Summ. 2013;62 Suppl 1:1.