SUPPLEMENT ARTICLE

Human Papillomavirus and Genital Warts: A Review of the Evidence for the 2015 Centers for Disease Control and Prevention Sexually Transmitted Diseases Treatment Guidelines

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To provide updates for the 2015 Centers for Disease Control and Prevention sexually transmitted diseases treatment guidelines on human papillomavirus (HPV) and anogenital warts (AGWs), a review of the literature was conducted in key topic areas: (1) epidemiology and burden of disease; (2) transmission and natural history; (3) diagnosis and management of AGWs; (4) occupational exposure of healthcare workers; (5) anal cancer screening among men who have sex with men (MSM); and (6) HPV vaccine recommendations. Most sexually active persons will have detectable HPV at least once in their lifetime; 14 million persons are infected annually, and 79 million persons have prevalent infection. HPV is transmitted frequently between partners; more frequent transmission has been reported from females to males than from males to females. A new formulation of imiquimod (3.75% cream) is recommended for AGW treatment. Appropriate infection control, including performing laser or electrocautery in ventilated rooms using standard precautions, is recommended to prevent possible transmission to healthcare workers who treat anogenital warts, oral warts, and anogenital intraepithelial neoplasias (eg, cervical intraepithelial neoplasia). Data are insufficient to recommend routine anal cancer screening with anal cytology in persons living with human immunodeficiency virus (HIV)/AIDS or HIV-negative MSM. An annual digital anorectal examination may be useful for early detection of anal cancer in these populations. HPV vaccine is recommended routinely for 11- or 12-year-olds, as well as for young men through age 21 years and young women through age 26 years who have not previously been vaccinated. HPV vaccine is also recommended for MSM, people living with HIV/AIDS, and immunocompromised persons through age 26 years.

Keywords. HPV; genital warts; treatment; HPV vaccine.

In April 2013, sexually transmitted disease (STD) experts convened and proposed updates to the 2010 Centers for Disease Control and Prevention (CDC) STD treatment guidelines related to: (1) burden of human papillomavirus (HPV) infection and related disease; (2) HPV transmission and natural history; (3) diagnosis and management of anogenital warts (AGWs), including indications for biopsy; (4) occupational exposure of healthcare workers to HPV; (5) anal cancer screening among men who have sex with men (MSM); and (6) HPV vaccine recommendations.

Prior to the consultation, key questions in each arena were identified, a systematic review of the literature was conducted, and an expert panel critiqued the evidence supporting the responses to the key questions. This article highlights updates for the 2015 CDC STD treatment guidelines for HPV and AGWs.

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METHODS

A review panel of 11 HPV content experts was assembled. Key questions on HPV and genital warts were generated in consultation with these experts. Subsequently, a systematic review of the literature related to each key question was conducted. We searched the English-language literature for human studies using the PubMed electronic database of the US National Library of Medicine from the date of the last review (January 2008) to February 2013. We also included review of conference abstracts from the International Papillomavirus Society and IDWeek conferences from 2011 and 2012. We restricted our search to the English-language literature for topic areas addressed in prior guidelines to keep consistent the methodology across different versions of the guidelines over time. However, the key question related to risk of HPV transmission and occupational exposure was a new topic area for the 2015 guidelines; therefore, we expanded our search to include both human and animal studies and non-English-language publications, and searched PubMed from its inception until February 2013. Because of the need to review older data in the context of newer, more efficacious treatments, PubMed was also searched from its inception to February 2013 for studies on podophyllin and genital wart treatment using 5-fluorouracil. We also asked the expert review panel for relevant publications or publications in press at the time of the review.

We used the following search and Medical Subject Heading (MeSH) terms: "HPV"; "warts"; "condylomata acuminata" (MeSH); "condyloma"; "condyloma" and "HIV" or "pregnancy" (MeSH); "HPV" and "transmission," "pathogenicity," "infectivity," "HIV," or "pregnancy" (MeSH); "warts" and "transmission"; "cancer burden" and "HPV"; "genital warts burden"; "men who have sex with men" and "anal cancer"; "HIV" and "anal cancer." For wart treatment: "genital warts"; "anogenital warts"; "perianal warts"; "condylomata acuminata" (MeSH); "condylomata acuminatum"; "imiquimod" (MeSH) or "Aldara"; "sinecatechins" or "Veregen" or "polyphenon E" (MeSH); "genital warts" or "condyloma" and "podofilox," "cryotherapy" (MeSH), "trichloroacetic acid" (MeSH), "bichloroacetic acid," "surgery" (MeSH), "intralesional interferon," "lasers" (MeSH), "cidofovir" (MeSH), "ammonium trichlorotellurate," "resiquimod" (MeSH), "5-fluorouracil," "podophyllum" (MeSH), "podophyllin" (MeSH), or "pregnancy" (MeSH); "pregnancy" (MeSH) and "genital wart treatment." For anal cancer screening: "anus" and "HPV"; "anus neoplasms (MeSH)"; "anal cancer"; "mass screening (MeSH)"; "early detection of cancer (MeSH)"; "anal" and "intraepithelial neoplasia" or "carcinoma in situ" (MeSH). For occupational exposure to HPV: "condylomata acuminata" (MeSH) and "lasers" (MeSH); "papillomaviridae" (MeSH), "surgical procedures, operative" (MeSH) and "smoke" (MeSH); "HPV" and "contamination"; "papillomaviridae" (MeSH) and "occupational exposure" (MeSH). For HPV vaccine: "HPV vaccine efficacy"; "HPV vaccine" and "HIV," "HPV vaccine," and "STD clinics." A systematic review was not conducted for HPV vaccine recommendations; rather, we referred to the existing Advisory Committee on Immunization Practices (ACIP) recommendations and background.

RESULTS

Highlights of HPV-related information determined to be most important for providers in the arena of STD care and treatment are summarized in this manuscript.

Burden of HPV Infection and Associated Diseases

Most sexually active persons will have detectable HPV at least once in their lifetime [1]. The estimated incidence of HPV infection is high, with 14 million persons infected annually and 79 million persons with prevalent infection [2]. HPV-associated diseases include anogenital and other mucocutaneous warts as well as cervical, anal, vaginal, vulvar, penile, and oropharyngeal cancers. Based on data from the Surveillance Epidemiology and End Results and National Program of Cancer Registries, it is estimated that 34 788 new HPV-associated cancers occurred in the United States in 2009 [3]. Overall annual direct medical costs for HPV-associated diseases in the United States are an estimated $8 billion US dollars, including $6.6 billion (82.3%) for routine cervical cancer screening and follow-up, $1.0 billion (12.0%) for cancer treatment, $300 million (3.6%) for AGW treatment, and $200 million (2.1%) for recurrent respiratory papillomatosis treatment [4].

Based on a systematic review, global incidence of AGWs ranged from 160 to 289 cases per 100 000 person-years (PY) [5]. Estimating incidence in the United States is challenging as AGWs are not a reportable condition. Based on estimates from a US health claims database, AGW incidence was 1.2 cases per 1000 PY among women and 1.1 per 1000 PY among men; rates were highest among women aged 20–24 years and men aged 25–29 years [6].

HPV Natural History

Median time to clearance of cervical HPV in women was 9.4 months [7] and of genital HPV in men was 7.5 months (including oncogenic and nononcogenic types) [8]. Between heterosexual partners, 3 studies demonstrated higher rates of HPV transmission from females to males vs from males to females [9–11], and one study found that transmission occurred at similar rates between males to females and females to males [12].

Median time to wart development after incident infection with HPV 6 or 11 was 6–10 months (range up to 18 months) [13–15]. This is longer than the median time period of 2.9 months previously reported for women with HPV type 6 or 11 [16]. Regression of warts among both women living with human

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immunodeficiency virus (HIV)/AIDS and HIV-negative women was common even in the absence of treatment: 60% of women living with HIV/AIDS and 80% of HIV-negative women demonstrated regression of warts in the first year after diagnosis [17].

Diagnosis and Treatment of Anogenital Warts

Diagnosis and Indications for Biopsy

AGWs are most often diagnosed based on their clinical appearance, and tests for the presence of HPV are not recommended for diagnosis of AGWs. Histologic examination of biopsy specimens can be performed to rule out intraepithelial or invasive squamous cell carcinomas (SCCs), which can coexist with or appear similar to AGWs. A Danish study of nearly 50 000 people with AGWs found an elevated risk of HPV-associated cancers in people with AGWs compared with the general population. Standardized incidence ratios (SIRs) were increased for anogenital cancers (SIR, 1.5–14.8) and head and neck cancers (SIR, 2.8), and the highest SIRs were found for anal cancer among men (SIR, 21.5) [18]. A retrospective series of MSM with AGWs requiring surgical removal found high-grade intraepithelial neoplasms or SCCs in the excised AGW tissue of 47% (75/159) of MSM living with HIV/AIDS and 26% (42/160) of HIV-negative MSM [19]. Another study of immunosuppressed women with both vaginal intraepithelial neoplasia (VIN) and AGWs reported that in all 11 subjects, VIN occurred admixed with or directly adjacent to the site of AGWs [20].

Healthcare providers should have a higher suspicion for HPV-associated cancers in immunocompromised patients with AGWs. The dx of anogenital warts can be confirmed by biopsy, which is indicated if lesions are atypical (eg, pigmented, indurated, affixed to underlying tissue, bleeding, or ulcerated lesions). Biopsy might also be indicated in the following circumstances, particularly if the patient is immunocompromised (including those infected with HIV): 1) the diagnosis is uncertain; 2) the lesions do not respond to standard therapy; or 3) the disease worsens during therapy.

Treatment

Since the publication of the 2010 STD treatment guidelines, one new formulation of a previously recommended medication, imiquimod 3.75% cream, has been approved by the Food and Drug Administration (FDA) for the treatment of external AGWs in patients aged 12 years and older. Instructions for use are similar to imiquimod 5.0% cream, with the exception that imiquimod 3.75% cream is applied once daily instead of 3 times per week (Table 1). Safety and efficacy have not been evaluated in pregnant, breastfeeding, or immunosuppressed patients, or in patients with intravaginal, cervical, rectal, or intra-anal warts [21]. FDA approval was based on 2 randomized, double-blinded, placebo-controlled trials involving 601 adult patients with external genital warts treated with vehicle or imiquimod 3.75% cream daily for up to 8 weeks. Sixteen weeks after the start of the study period, treated patients had a clearance rate of 27%–29%, while patients receiving the vehicle had a clearance rate of 9%–10% [21]. Treatment-related adverse effects that occurred in >1% of those treated with imiquimod 3.75% cream included application site pain, pruritus, irritation, erythema, bleeding, and discharge [22].

Review of the safety literature for podophyllin resin included reviews and case reports of severe toxicity, including some reports of death and fetal loss after podophyllin was applied longer than recommended or applied to broken/friable skin [23–30]. Given potentially severe consequences with misuse and the availability of a myriad of safe and effective therapies, podophyllin resin 10%–25% should be considered as an alternative therapy with strict adherence to application guidelines (Tables 1 and 2). Podophyllin should be applied to each wart and allowed to dry before the treated area comes into contact with clothing; overapplication or failure to dry can result in local irritation caused by spread of the compound to adjacent areas. Treatment can be repeated weekly, if necessary. To avoid the possibility of systemic absorption and toxicity: (1) application should be limited to <0.5 mL of podophyllin or an area

Table 1. Recommended and Alternative Regimens for Treatment of External Anogenital Warts

Recommended Patient-Applied Regimen	Dosing
Imiquimod 5% cream	Topically every night at bedtime for 3 times/wk up to 16 wk
Imiquimod 3.75% cream	Topically every night at bedtime up to 16 wk
Podofilox 0.5% solution or gel	Topically twice daily × 3 d followed by 4 d off for up to 4 cycles
Sinecatechins 15% ointment	Topically 3 times daily, for up to 16 wk
Bichloracetic acid 80%–90%	Applied once every 1–2 wk
Cryotherapy	Applied once every 1–2 wk
Surgical removal	
Trichloroacetic acid 80%–90%	Applied once every 1–2 wk

Source: CDC, MMWR Recomm Rep 2015; 64(No. RR-3):1–137.

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Table 2. Recommended and Alternative Regimens for Treatment of Mucosal Warts (Intra-anal, Urethral Meatus, Intravaginal)

Recommended Provider-Administered Regimen	Dosing/Route
Bichloracetic acid 80%–90%	Applied once every 1–2 wk (anal, vaginal)
Cryotherapy	Applied once every 1–2 wk (anal, urethral meatus, vaginal)
Surgical removal	
Trichloroacetic acid 80%–90%	Applied once every 1–2 wk (anal, vaginal)

Source: CDC, MMWR Recomm Rep 2015; 64(No. RR-3):1–137.

of <10 cm^2 of warts per session; (2) podophyllin should not be applied to open lesions, wounds, or friable tissue; and (3) the preparation should be thoroughly washed off 1–4 hours after application.

HPV Occupational Exposure

Genital warts are commonly treated by a wide variety of practitioners in both hospital and outpatient settings with electrosurgical and laser procedures. However, there are scant data about whether healthcare workers who treat genital warts with electrosurgery are at risk for occupational exposure to HPV, and whether this exposure could put healthcare workers at risk of disease.

Multiple studies have documented the presence of intact HPV DNA in laser smoke plumes after treatment of genital and common warts with electrosurgical modalities [31–36]. In studies of bovine papillomavirus, collection of smoke plume after carbon dioxide laser treatment (at settings used for treatment of AGWs in humans) and reinoculation into the skin of calves caused papillomas [32].

Two studies examining healthcare workers for HPV DNA contamination did not find evidence of facial/oral contamination after electrosurgical treatment of genital warts. Personal protective equipment (PPE) used in the studies included goggles and masks (either laser plume masks or standard surgical masks), and smoke evacuators were used or procedures were performed in the operating room with exhaust ventilation [33, 35]. However, a separate study of 19 surgeons did demonstrate detection of nostril HPV in 3 of 19 (16%) and new nasolabial HPV in 4 of 19 (21%) after electrosurgical ablation of warts was performed. PPE used in this study included goggles, standard surgical masks, and a smoke evacuator [37].

Two case reports of laryngeal papillomas have been reported in healthcare workers who treated anogenital warts. The first report was a 44-year-old surgeon who regularly performed treatment of anogenital warts with a yittrium-argon-garnet laser, and had treated 5 patients with anogenital warts in a 2.5-year period. The hospital did not have a laser smoke evacuator system but described use of an "ordinary" smoke evacuator; the surgeon wore a conventional mask, gloves, and eye protection. Biopsies from the surgeon's papillomas were positive for HPV 6/11 by in situ hybridization [38]. The second case report was a 28-year-old gynecologic surgical nurse who assisted repeatedly in electrosurgical and laser ablations/excisions of anogenital condyloma. Inspection revealed that the treatment room was improperly ventilated, and the laryngeal papillomas were thought to be likely due to occupational exposure. Use of PPE, the time course between exposure and manifestation of laryngeal papillomas, and HPV typing of the papillomas were not reported in this case [39].

Appropriate infection control is recommended to prevent possible transmission to healthcare workers who treat anogenital warts, oral warts, and anogenital intraepithelial neoplasias (eg, cervical intraepithetial neoplasia) with laser or electrosurgical procedures. The National Institute of Occupational Safety and Health and the American Society for Laser Medicine recommend use of local exhaust ventilation such as smoke evacuators when performing laser or electrosurgical procedures on patients with anogenital warts and anogenital intraepithelial neoplasias (http://www.cdc.gov/niosh/docs/hazardcontrol/hc11.html).

Anal Cancer Screening and Treatment of Anal Intraepithelial Neoplasia

Epidemiology

Though anal cancer is rare in the general population (1–2 cases/100 000 PY), anal cancer burden is much higher among certain populations, including MSM. Anal cancer incidence among HIV-negative MSM is estimated at 5 cases/100 000 PY; for MSM living with HIV/AIDS, this estimate is 45.9 cases/100 000 PY overall and 77.8 cases/100 000 PY in the post–highly active antiretroviral therapy era [40]. Anal HPV infection is nearly ubiquitous in MSM living with HIV/AIDS (93% prevalence), with high-risk HPV prevalence estimated to be 73.5% for MSM living with HIV/AIDS and 37.2% for HIV-negative MSM. A systematic review concluded that more than half of MSM living with HIV/AIDS have abnormal cytology (57%), and 29% have high-grade anal intraepithelial neoplasia (HGAIN) [40]. The incidence of HGAIN among MSM living with HIV/AIDS has been estimated by 2 studies [41, 42] and ranges from 8.5% to 15.4% per year.

Test Performance of Screening Methods

Since the last review, there have been no published studies describing or comparing efficacy of various available screening methods for prevention and/or early detection of anal cancer. Anal cytology demonstrates moderate sensitivity but poor specificity for detection of HGAIN, a precursor of anal cancer. Using atypical squamous cells of undetermined significance as the cutoff for abnormal, the sensitivity and specificity of anal cytology among

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MSM living with HIV/AIDS range from 81% to 87% and 39% to 41%, respectively [43–46]. HPV testing has poor specificity for HGAIN and is not recommended for screening due to the high prevalence of high-risk HPV infection among MSM [47].

Cost Analyses

There were no published US cost analyses since the last review. Two United Kingdom cost analyses found that not screening for anal cancer would result in a lower cost per quality-adjusted life-year gained than screening at any interval using anal cytology for MSM living with HIV/AIDS or HIV-negative MSM [48, 49]. A Canadian study found that using high resolution anoscopy (HRA) alone for screening was the least costly compared to a combination of HRA, cytology, and/or HPV testing at US$809 per case of HGAIN diagnosed [50].

Psychologic Impact and Programmatic Issues

Anal cancer screening did not have an adverse impact on measures of anxiety and depression or quality of life based on 2 studies [51, 52]. Low reimbursement for HRA was reported by a single study, at $60 for Medicare patients and $150 for private payers (in 2009 US dollars) [53].

Prevention and Treatment of HGAIN

Quadrivalent HPV vaccine has been demonstrated to prevent incident AIN and HGAIN among MSM [54]. Treatment for HGAIN was evaluated in a Cochrane review [55], which included only a single study of intra-anal imiquimod vs placebo [56]. The study did not have sufficient power to detect a significant difference in clearance of HGAIN or downgrading of HGAIN to low-grade AIN, although a statistically significant benefit was found when the outcomes were combined. A small, open-label study of 5- fluorouracil found that 26 of 46 patients (56.5%) had complete or partial response, but 25% recurred at 6 months [57]. A prospective pilot study of infrared coagulation (IRC) found that IRC was well tolerated, and 10 of 16 (62.5%) patients were disease free after 1 year, with the remainder (37.5%) having a recurrence [58]. The remaining studies of AIN treatment were retrospective and included surgery, infrared coagulation, electrocautery, trichloroacetic acid, and intra-anal 5-fluorouracil [59–66]. No serious adverse events were reported; per lesion cure ranges from 63%–85% but recurrence ranged from 25% to 75% at 6 months–1 year in MSM living with HIV/AIDS, and was slightly lower in HIV-negative MSM [57, 59, 60, 65]. Since the last review, there have been no prospective data available on progression or regression rates of HGAIN, or on treatment of HGAIN for prevention of anal cancer or cancer-related morbidity and mortality.

Data are insufficient to recommend anal cancer screening with anal cytology in people living with HIV, MSM without HIV infection, and the general population based on the available evidence. More evidence is needed concerning the natural history of AIN, the best screening methods and target populations, potential harms of screening, safety of, and response to treatments, and other programmatic considerations before screening can be routinely recommended. There is currently an ongoing trial of anal cancer screening (NCT02135419), which may address many of these outstanding issues.

HPV Vaccine Recommendations

The ACIP recommends routine HPV vaccination at age 11–12 years; the vaccination series can be started beginning at age 9 years [67] (Table 3). Vaccination is also recommended for females aged 13–26 years and for males aged 13–21 years who have not been vaccinated previously or who have not completed the 3-dose series [67]. Men aged 22–26 years may be vaccinated. Vaccination of females is recommended with bivalent HPV vaccine, Cervarix (2vHPV), quadrivalent HPV vaccine, Gardasil (4vHPV) (as long as this formulation is available), or nonavalent HPV vaccine, Gardasil9 (9vHPV). Vaccination of males is recommended with 4vHPV (as long as this formulation is available) or 9vHPV [68].

The 2vHPV, 4vHPV, and 9vHPV vaccines all protect against HPV 16 and 18, types that cause about 66% of cervical cancers and the majority of other HPV-attributable cancers in the United States; 9vHPV targets 5 additional cancer-causing types, which account for about 15% of cervical cancers. 4vHPV and 9vHPV also protect against HPV 6 and 11, types that cause anogenital warts [68]. MSM, people living with HIV, and immunocompromised persons should be vaccinated through age 26 years [68].

Table 3. Human Papillomavirus Vaccine Recommendations From the Advisory Committee on Immunization Practices

Population PLHA	Age Group, y	Recommendation
Females	11-12 (may start at 9)	Routine vaccination with either 2vHPV, 4vHPV, or 9vHPV
	13–26	Routine vaccination with either 2vHPV, 4vHPV, or 9vHPV[a]
Males	11–12 (may start at 9)	Routine vaccination: 4vHPV or 9vHPV
	13–21	Routine vaccination: 4vHPV or 9vHPV
	22–26	4vHPV or 9vHPV may be administered
MSM and HIV^+	22–26	Routine vaccination: 4vHPV or 9vHPV

Sources: CDC, Morb Mortal Wkly Rep 2010; 59:626–32. CDC, Morb Mortal Wkly Rep 2011; 60:1705–8. CDC, Morb Mortal Wkly Rep 2015; 64:300–4.

Abbreviations: 2vHPV, bivalent HPV vaccine; 4vHPV, quadrivalent HPV vaccine; 9vHPV, nonavalent HPV vaccine; HIV, human immunodeficiency virus; HPV, human papillomavirus; MSM, men who have sex with men; PLHA, people living with HIV/AIDS.

[a] Vaccination should be given respective of history of abnormal Pap, HPV, genital warts.

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Notes

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