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UROLOGY - REVIEW

HPV infection in urology practice

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Abstract
Human papillomavirus (HPV) is the most common pathogen of sexually transmitted disease worldwide. While HPV is responsible for low-grade benign lesions in the anogenital area such as condyloma acuminatum, it is also strongly associated with cervical, anal, vulvar/vaginal, and penile carcinomas. In addition to being an oncogenic virus, HPV causes a substantial socioeconomic burden due to the recurrence of benign lesions, the lack of a definitive treatment option that provides a complete cure, and the high cost of treatment. The global incidence of HPV infection is rising, especially among young and sexually active individuals; as a result, in recent years these infections have also become increasingly conspicuous in urology practice, both as incidental findings and primary complaints. The aim of this review is to evaluate the pathogenesis, diagnosis, and treatment modalities of HPV infections in light of the current literature from the urologist's perspective.

Keywords HPV · Human papillomavirus · Condyloma acuminatum · Wart · Urology

Abbreviations

CA	Condyloma acuminatum
CDC	Centers for disease control and prevention
DNA	Deoxyribonucleic acid
FDA	Food and drug administration
HPV	Human papilomavirus
PCR	Polymerase chain reaction
RB	Retinoblastoma

Introduction

Human papillomavirus (HPV) is a double-helix DNA virus and the most common sexually transmitted infection today. Epidemiological studies have determined the global prevalence of HPV to be 11.7% [1]. HPV has become a major public health concern and imposes a substantial socioeconomic burden mainly due to its oncogenic potential. HPV, together with Epstein–Barr virus, causes the most common virus-associated cancers and is responsible for 7–8% of all malignancies worldwide [2]. To date, more than 200 types of HPV have been identified, approximately 40 of which cause

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anogenital infections. Unlike most other viruses, HPVs are classified based on their genomic sequence rather than their antigenic structures; therefore, their numbers represent genotypes instead of serotypes and are assigned based on the order of discovery [3]. The most important high-risk HPV types based on their oncogenic potential are 16, 18, 26, 31, 35, 39, 45, 48, 51, 52, 53, 56, 58, 59, 66, 68, 73, and 82, whereas the low-risk HPV types 6, 11, 40, 42, 43, 44, 54, 61, 70, 72, and 81 are responsible for low-grade benign lesions such as anogenital warts [4]. The high prevalence of HPV infection in society and the proximity of the lesions to the urinary tract have made HPV an increasingly important topic in the field of urology in recent years.

HPV and the immune response

Unlike many other viruses, the immune response to HPV is delayed. Antibodies against HPV develop as late as 8–18 months after HPV-DNA detection and even then are present at low levels [5]. This is mainly due to HPV immune evasion, which is explained by two mechanisms. The first is that HPV infection is non-lytic and thus has no viremic phase. Consequently, a sufficient immune response cannot develop naturally. The second of these mechanisms is ineffective antigen presentation by keratinocytes [6]. Despite this insufficient immune response, the virus is eliminated by the immune system within 2 years in 90% [7] of infected women and 80% [8] of infected men. Viral clearance is directly associated with HPV type. Eradication may take a long time, especially for high-risk HPV types [9]. Persistent infection occurs in 10% of patients and the development of invasive cancer in these cases spans a period of 15–20 years [10].

Cellular immunity plays a key role in the regression of lesions caused by HPV. This explains the higher incidence of HPV-associated lesions in patients with suppressed cellular immunity due to HIV infection or history of transplantation. In recent study, HIV + women and HIV + Men sex with men (MSM) were at 4.67 and 6.46 times higher risk for HPV infection than their HIV counterparts, respectively [11].

Clinical manifestations of HPV infection

HPV shows epithelial tropism. The main mode of transmission is through sexual contact. HPV that enters the body through abrasions or injuries in the squamous or mucosal epithelium during sexual activity first infects cells in the stratum germinativum near the basal lamina. In addition, direct or indirect transmission can occur from contaminated surfaces, cutaneous lesions, or the birth canal. HPV is highly contagious. Approximately, 60–66% of the spouses of individuals with genital HPV infection also develop genital HPV lesions after a period of about 3 months [12]. Another study determined that number of sexual partners was highly significant risk factor, with the probability of HPV infection increasing by sixfold in those with 1–2 partners and by 10.8 fold in those with > 15 partners compared to those who had never had sexual intercourse [13].

The clinical course of genital HPV infection is divided into the latent, subclinical, and clinical periods (Fig. 1) [14]. In the latent period, the disease has no cytological or morphological signs and can only be diagnosed with molecular tests such as Polymerase chain reaction (PCR) [15].

In the subclinical period, cytological/microscopic changes or lesions associated with HPV can be visualized with magnification methods such as colposcopy. Intraepithelial neoplasia usually develops during this period. The clinical period features visible lesions and symptoms such as condyloma acuminatum (CA) or invasive cancer. However, most HPV infections do not cause clinical symptoms. Latent and subclinical infections are more common. In addition to the latent and subclinical periods, it should be kept in mind that spontaneous regression of benign lesions can also occur in the clinical period. Ninety percent of infections remain latent. However, 10% of these cases progress to develop intraepithelial lesions or condylomatous lesions, 1% of which may transform into invasive cancer [16].

The clinical presentation of active HPV infection is variable and depends on the virus type, location of the lesion, immune status of the patient, and character of the infected epithelium.

Diagnosis of HPV

Conventional diagnostic methods for viral diseases such as sero-immunological methods, cell culture, and electron microscopy are not applicable in the diagnosis of HPV due to its structure and the course of infection. Serological

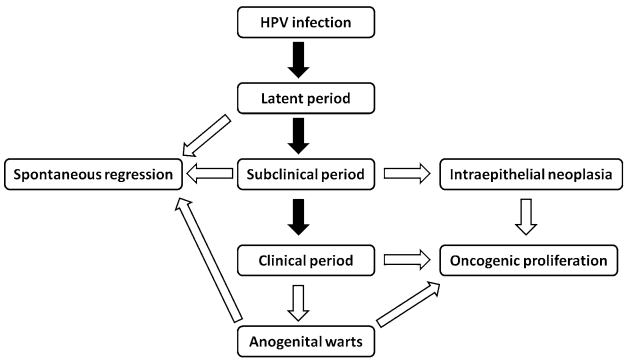

Fig. 1 Stages of HPV infection

tests are not suitable for distinguishing between acute and prior infections due to the weak immune response discussed above. HPV diagnosis can be made histopathologically by demonstrating koilocytosis under the microscope. Koilocytes are dead or dying stratum cells that do not exhibit malignant transformation [6]. This method, also known as the Pap smear, is cost effective and is, therefore, commonly used today as a cervicovaginal screening method. However, its main disadvantages are low sensitivity with the rate of 55.4% and inability to perform HPV typing [17].

As there is no reliable serological test for the differential diagnosis of past or current HPV infection and the virus cannot be isolated, definitive diagnosis is based on the detection of HPV-DNA with molecular tests. PCR analysis is the gold standard molecular diagnostic test for detecting HPV-DNA [18]. Both tissue and smear samples can be analyzed for HPV-DNA. It has also been demonstrated in recent years that PCR analysis of urine samples is also effective in the detection of HPV-DNA. A study performed by Tanzi et al. on patients with cervical carcinoma showed that HPV-DNA detection from urine had 98.6% sensitivity and 97.4% specificity when compared with cervical samples. Regarding urinary tract involvement, Cai et al. investigated the presence of HPV-DNA in tumor tissue and urine samples from patients with urothelial carcinoma using simultaneous PCR and reported no difference in HPV detection rates [19]. Results from studies on both tissue and cervical smear samples demonstrate that PCR assay for HPV-DNA in the initial urine sample is an appropriate and effective tool to achieve more comprehensive screenings in the future. In addition, urine collection has the obvious advantages of being noninvasive and easier than smear and tissue sampling.

Condyloma acuminatum

CA, also known as anogenital warts, are solitary or multiple benign lesions with hyperkeratotic, exophytic papillary structure that are sessile or have a short, broad pedicle and preferentially involve the mucocutaneous junction.

CA is the most common sexually transmitted disease seen in the sexually active population worldwide [20]. Anogenital warts are estimated to affect approximately 1% of the global population [21]. Therefore, they are commonly encountered in urology practice. After dermatologists, CA in the anogenital region of men are most commonly diagnosed by urologists [22]. The incidence of CA is highest among individuals aged 20–24 years, and approximately 90% are caused by low-risk HPV types 6 and 11 [23]. In men, they are most commonly seen on the penile shaft (Fig. 2a) and prepuce. They can also be found on the glans of the penis, in the infrapubic region (Fig. 2b), on the scrotum, and in the perianal region (Fig. 3a). In females, they are usually found in the vulvovaginal area (Fig. 3b).

They occasionally occur in the anterior urethra (Fig. 4a) and in very rare cases are seen in the proximal urethra behind the anterior urethra, the bladder (Fig. 4b), and upper urinary tract. These presentations have been documented in the literature as case reports and are always associated with an underlying immunosuppression-related cause [24]. The incubation period for CA can vary from 2 weeks to 6–18 months. CA typically appear 3–4 months after sexual intercourse [25].

CA that become very large and exhibit destructive local invasion without metastasizing are called Buschke–Löwenstein tumors, also known as verrucous carcinoma or giant condylomas.

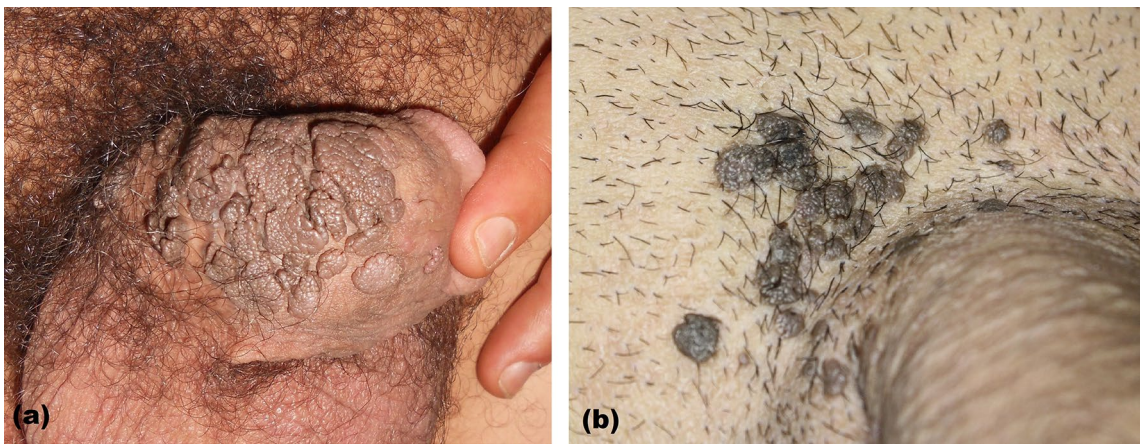

Fig. 2 **a** Penile shaft and **b** infrapubic condyloma acuminatum

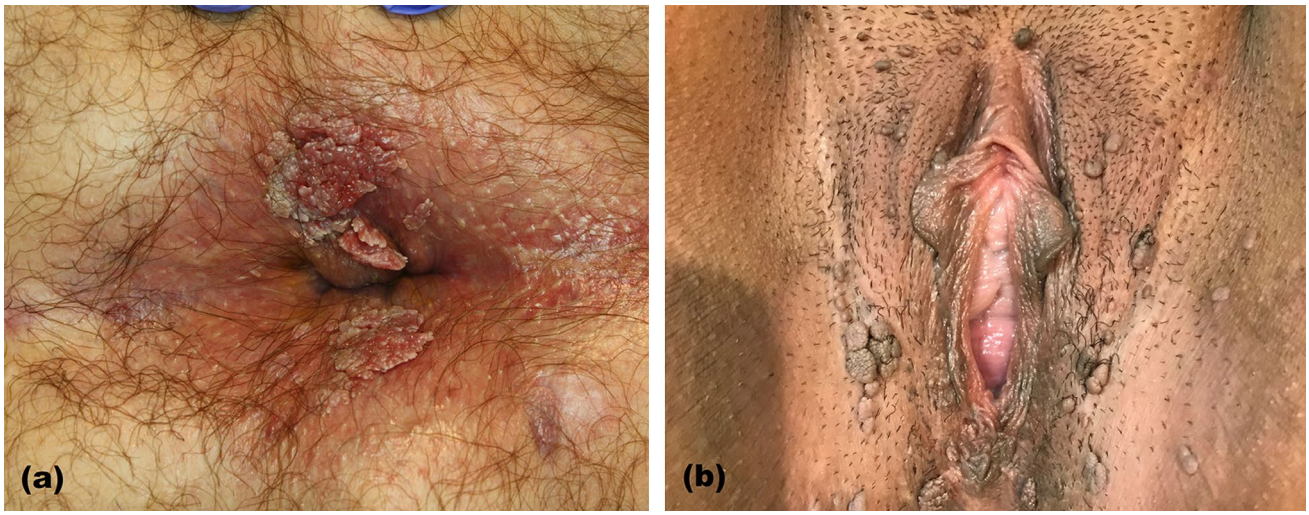

Fig. 3 **a** Perianal and **b** vulvar condyloma acuminatum

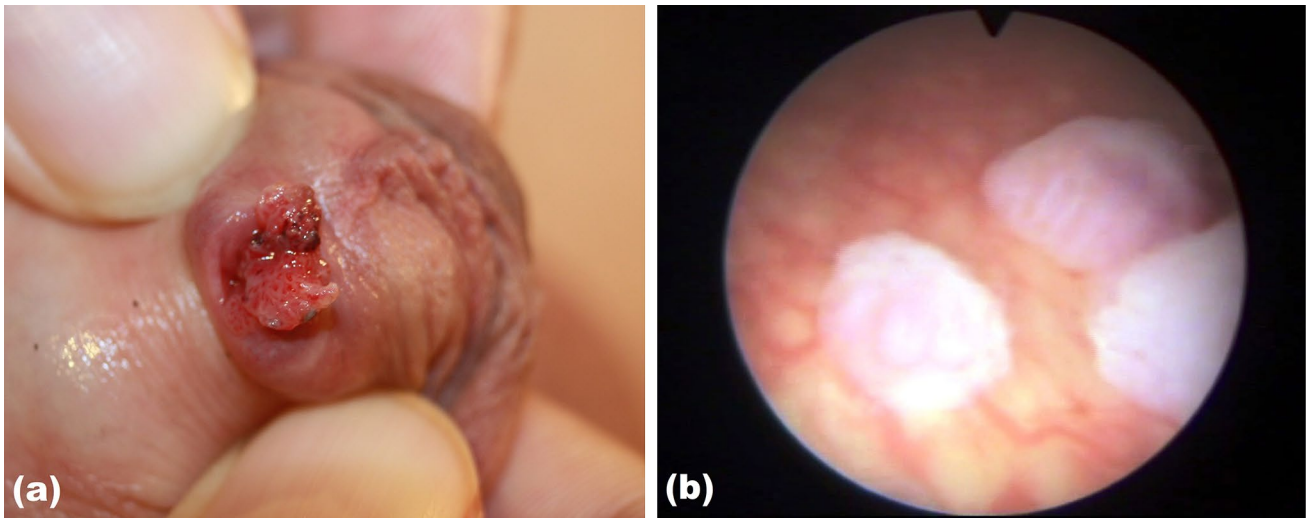

Fig. 4 **a** Anterior urethral and **b** bladder condyloma acuminatum

HPV-induced oncogenesis

HPV is known to be an oncogenic virus. Due to HPV tropism for squamous epithelium, squamous cell carcinoma is the most common histological type among HPV-associated cancers. The link between HPV and squamous cell carcinomas of the anogenital region in particular has been clearly demonstrated. Association with HPV is reported in 96% of cervical cancers, 36% of penile cancers, and 64% of anal cancers [26]. HPV-16 is most commonly responsible for HPV-associated malignancies [27]. In males, HPV also leads to the development of dysplastic, precancerous lesions in the anogenital region, including verrucous carcinoma of the penis and penile squamous intraepithelial neoplasia. Penile intraepithelial neoplasias are the main precursor lesions of penile cancers and are associated with HPV-DNA at rates of 70–100% [28].

High-risk HPV types exhibit their oncogenic properties via the E6 and E7 oncoproteins. E6 inhibits the function of tumor suppressor protein p53. This in turn inhibits apoptosis and disrupts the cell's ability to maintain genetic stability, thus increasing the risk of malignant transformation. E7 inactivates retinoblastoma (Rb), another tumor suppressor protein. This results in unregulated synthesis of the proteins necessary to continue the cell cycle, and the cells proliferate continuously [29]. The E6 and E7 proteins of the low-risk HPV types cannot inactivate p53 or Rb [30].

Despite its anatomical proximity, the relationship between HPV and urinary tract cancers has long been debated. Unlike

penile cancers, previous studies revealed no significant correlation between HPV and prostate, testicular, or renal cancers [3]. Currently, only its association with bladder cancer is still controversial. Studies have reported rates of association between bladder cancer and HPV ranging from 0 to 80% [31]. As stated in a meta-analysis on the topic, these discrepancies can be attributed to deficiencies related to methodological differences between the studies. These deficiencies can be summarized as small patient series, not sampling fresh tissue, and a lack of case–control studies [32, 33]. In light of this information, a recent case–control study by Sarier et al. [4] using fresh samples demonstrated a strong correlation between the urothelial carcinoma of the bladder and HPV infection (odds ratio 4.24, 95% confidence interval 1.63–12.34), and it was emphasized that this correlation was independent of tumor grade.

Another issue is the effect of HPV on the prognosis of associated carcinomas. The presence of HPV is considered a favorable prognostic factor in cervical and anal cancers [34]. However, its prognostic implications in bladder carcinoma have not been determined. Future follow-up studies will elucidate this matter.

Treatment of CA

The treatment of anogenital warts and intraepithelial neoplasias associated with HPV has become a substantial socioeconomic burden. Being precancerous lesions, surgical excision is the main approach for intraepithelial neoplasia to enable a complete and thorough pathological evaluation, while there are numerous alternatives for the treatment of more common benign lesions such as CA. However, a standard and ideal treatment with perfect efficiency has not been found for anogenital warts. As none of the treatment options are completely effective on their own, different methods can be used in combination and/or sequentially. None of the available treatment methods provide complete eradication or totally prevent recurrence, which is seen at varying rates. However, it is known that despite the resolution of visible lesions with treatment, the virus can be detected for months in apparently normal epithelium. There is also insufficient evidence that the treatment of genital warts completely eliminates infectivity. Therefore, the main goal of treatment is to eliminate symptomatic warts [35, 36].

Recurrence of HPV infection after treatment, the risk of malignancy, and tendency to spread due to autoinoculation adversely affect patients psychologically, while the risk of transmission to partners leads to shame, guilt, and sexual problems. Thus, treating the disease as early as possible will also prevent the potential psychological problems and sexual dysfunction that can result [37].

Factors to consider when choosing a treatment method for genital warts include their anatomic location, extent and size of the lesions, effectiveness of previous treatments, accompanying conditions (pregnancy, immunosuppression), the patient's preferences, treatment adherence, and expectations, and treatment cost. Treatment must be individualized for each patient [37, 38].

The treatment of anogenital warts is classified into three categories: topical cytotoxic, immunotherapeutic, and destructive therapies. However, for practical purposes, anogenital wart treatments are also classified as patient-administered therapies and clinician-administered therapies. Patient-administered therapies include topical podophyllotoxin, imiquimod, and sinecatechins, while clinician-administered therapies include trichloroacetic acid, podophyllin, cryotherapy, electrocauterization, surgical excision, laser therapy, and intralesional drug injections. Although all these methods have certain advantages and disadvantages, none is clearly superior and varying rates of recurrence have been reported with all treatment options [39, 40].

Patient-administered therapies

Podophyllotoxin

Podophyllotoxin is an antimitotic agent obtained from the plant *Podophylium hexandrum*, which arrests cell division at the metaphase stage and causes local tissue necrosis, thereby eliminating warts. Podophyllotoxin is available in 0.5% solution, cream, and gel forms. It is applied morning and night for three consecutive days followed by 4 days of no treatment, for a period of 4 weeks. The area to be treated should not exceed 10 cm^2 and the total amount of podophyllotoxin should be limited to 0.5 ml. It is contraindicated in pregnant patients [39].

Imiquimod

Imiquimod is a heterocyclic imidazoquinoline amide derivative with immunomodulatory activity, which it exerts by inducing cytokines including interferon alpha, tumor necrosis factor, granulocyte monocyte stimulating factor, and interleukins. Imiquimod 5% cream is applied to the affected area every other day (3 times a week) for 16 weeks, and is washed away with soap and water 6–10 h after application. It is only indicated in cutaneous anogenital warts; its use in mucosal tissues is contraindicated [41].

Sinecatechins

Sinecatechins are green tea extracts that reduce the expression of E6 and E7, which trigger HPV-induced cell growth and neoplasia. It is reported to have antioxidant, antiviral,

antiproliferative, and antitumor activity. A 15% ointment form is applied three times a day for 4 months or until the lesions completely regress [35].

Clinician-administered therapies

Podophyllin

Podophyllin as a 10–25% solution is a good alternative for the treatment of small cutaneous lesions. It is applied once a week to the dry lesion and the area is washed 1–4 h after application. Use on mucosal surfaces is not recommended as it may cause toxicity [35].

Trichloroacetic acid

Trichloroacetic acid, available as 80–90% solution, acts via chemical destruction and surface erosion. A thin layer is applied once a week by the clinician using a cotton-tipped applicator. It is especially suitable for small mucosal CA. As there is no systemic absorption, it can be used by pregnant women [36].

Cryotherapy

Cryotherapy is widely used in the treatment of genital warts because it is easy to implement, does not require anesthesia, is inexpensive, has a lower risk of scarring compared to cauterization, and can be safely used on pregnant women. Liquid nitrogen at a temperature of − 196 °C causes necrotic destruction and local inflammation that triggers cellular immune response in HPV-infected keratinocytes [38].

Electrocauterization and surgical excision

This is one of the most effective treatment methods for genital warts and is used successfully in the treatment of both mucosal and cutaneous CA. The main objective in cauterization is to plan the treatment to avoid causing dermal damage and deep burn. Otherwise, the risk of scarring is high. Surgical excision is especially preferable for solitary and giant genital verrucous lesions as it enables both treatment and diagnostic pathological evaluation for precancerous changes [39, 42]. In urology practice, surgical excision can be performed successfully in cases of anterior urethral CA in particular [43]. In addition, transurethral resection should be kept in mind as a reliable and effective method in the treatment of rare cases of bladder CA [24].

Laser therapy

This method uses focused infrared energy to vaporize tissue affected by warts. Of the various lasers available, carbon dioxide laser is used most frequently, especially for intraurethral and common extragenital verrucas. However, it is used relatively less often compared to other treatment methods because it requires special equipment and experience and is more costly [38].

Intralesional therapy

Although intralesional interferon therapy can be effective in the treatment of genital warts, it is not widely used due to the cost, potential adverse effects, and lack of significant superiority over other treatments. Cidofovir and 5-fluorouracil are the broad-spectrum antiviral agents administered intralesionally for the treatment of genital warts. In addition to intralesional therapy, they can be used topically either alone or in combination with other treatment methods [42].

HPV vaccination

HPV vaccines are currently used for prophylactic purposes. The goal of prophylactic vaccination is to prevent potential infection and reinfection by eliciting an effective humoral immune response against HPV. This is achieved by stimulating the production of antibodies against HPV L1 capsid protein present in the vaccine. The HPV vaccine causes a stronger immune response than the infection itself, primarily because the HPV infection is limited to the epithelium without causing viremia while the vaccine elicits a systemic immune response. Prophylactic vaccines have no therapeutic value. Therapeutic vaccines that act via cellular immunity are still in the clinical stage of development [44].

Currently available HPV vaccines include a bivalent vaccine (Cervarix®; target types 16 and 18) and a quadrivalent vaccine (Gardasil®; target types 6, 11, 16 and 18). However, the most recent 9-valent vaccine (Gardasil 9®) expands the targeted types to 6, 11, 16, 18, 31, 33, 45, 52, and 58, illustrating the need for vaccines with broader coverage of high-risk HPV types due to the growing genotypic diversity of HPV-associated malignancies.

Men play an important role in transmitting the virus to women. Male immunization helps to prevent HPV transmission, thereby reducing the HPV load and incidence of HPV-associated disease in women as well as helping to reduce the incidence of anogenital disease in men. The latest HPV vaccine to gain FDA approval was Gardasil 9 in 2014. Therefore, all vaccines in the market are FDA-approved. National vaccine programs have been implemented in a total of 87 countries, with female-only vaccination in 68 countries and both male and female vaccination in 19 countries [45]. The Centers for Disease Control and Prevention (CDC) recommended vaccination between the ages of 9 and 26 years for both males and females, with routine vaccination at age

11–12. The recommended vaccination schedule is two doses given 6–12 months apart for individuals aged 9–14 years and three doses at 0, 1–2, and 6 months for those aged 15 and older [46]. The rationale for starting vaccination at an early age is to provide protection before first sexual contact, thereby gaining maximum benefit from the prophylactic effect of the vaccine.

Conclusion

HPV infection is common worldwide and creates a substantial socioeconomic burden. It is clear that both anogenital carcinomas and anogenital warts will continue to be encountered frequently in urology practice. Urologists must also improve their knowledge of and experience with this virus to provide the best patient care.

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Compliance with ethical standards

Conflict of interest All authors declare no conflict of interest.

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