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HPV Infection and Prevention of HPV Infection in Men Who Have Sex with Men (MSM)

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Abstract

The research landscape in relation to human papillomavirus (HPV) infection has evolved rapidly since the causal association between the virus and cervical cancer was made in the 1970s. Cervical screening programmes have resulted in a dramatic decrease in the incidence of cervical cancer. The first vaccine for HPV was licensed in 2006 with real-world data demonstrating high levels of vaccine efficacy.

In the setting of decreased rates of cervical cancer, the burden of HPV-associated disease in men (including genital warts, anal cancer, penile cancer and oropharyngeal cancer) has become more apparent. The incidence of anal cancer is increasing steadily. Men who have sex with men (MSM) in particular HIV-infected MSM are disproportionately affected. In contrast to the successes observed with cervical screening programmes, anal cancer screening tools have not demonstrated improvements in morbidity or mortality, and while many experts recommend screening high-risk groups for anal cancer, no consensus recommendations exist.

HPV vaccine has potential to decrease HPV-related malignancies including anal cancer. The majority of countries including Ireland offer HPV vaccine to females through national immunization programmes. However, only a minority of countries have extended the HPV vaccine recommendation to include males. The HPV vaccine is most effective prior to sexual debut; thus, immunisation programmes, including boys and girls, offer the greatest preventative opportunity. However, such programmes will not impact the high burden of HPV-associated disease currently observed in groups at high risk of HPV infection and HPV-associated disease such as men who have sex with men (MSM).

This chapter focuses on HPV infection and associated disease in MSM with particular focus on HIV-infected MSM. Host and viral factors influencing HPV infection and progression to disease are reviewed.

The potential for primary preventative strategies such as vaccination as well as secondary preventative strategies such as screening to impact on the burden of anal cancer in this cohort are reviewed.

Keywords: HPV, MSM, HIV, anal cancer, vaccine, screening

1. Introduction

Human papillomavirus (HPV) is the most common sexually transmitted infection (STI) worldwide. It is highly prevalent in the sexually active population and rapidly acquired after sexual debut [1]. The majority of HPV infections are subclinical and clear spontaneously; however, HPV can result in a wide variety of presentations ranging from benign genital dermatoses to disseminated invasive malignancy.

HPV is causally associated with genital warts, cervical cancer, vulvar cancer, anal cancer, penile cancer, and head and neck cancers [2]. HPV now accounts for approximately 5% of all cancers worldwide [3]. Over 150 types of HPV have been identified with over a dozen HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, and 82) classified as highly oncogenic [4].

The incidence of cervical cancer has decreased dramatically since the introduction of cervical screening programmes [5]. In the same time period, the incidence of extra-cervical HPV-associated cancers, particularly oropharyngeal and anal cancers, have increased steadily [6].

Anal cancer is a relatively rare occurrence in the general population (1–2 cases per 100,000) [7]; however, certain risk groups including MSM (up to 40 cases per 100,000) and in particular HIV-infected MSM are disproportionately affected (up to 135 cases per 100,000) [8, 9]. The incidence of anal cancer in MSM is now greater than the incidence of cervical cancer pre-introduction of cervical screening programs [5, 10]. To date, screening programs for anal cancer have failed to demonstrate improvements in morbidity or mortality relating to anal cancer. Some experts advocate screening of at risk populations such as MSM for anal cancer [11, 12]. However, the utility of screening for prevention of anal cancer remains very much debated and no consensus recommendations for anal cancer screening exist.

Three HPV vaccines have been licensed. The bivalent HPV vaccine (HPV-2v) (Cervarix™, GlaxoSmithKline) protects against oncogenic HPV types 16 and 18. The quadrivalent HPV vaccine (HPV-4v) (Gardasil™, Merck and Co., Inc.) offers additional protection against HPV types 6 and 11, commonly associated with genital warts. The recently licensed nonavalent HPV vaccine (HPV-9v) (Gardasil 9™, Merck and Co., Inc.) provides protection against five additional oncogenic HPV types (31, 33, 45, 52, and 58).

National immunization programs delivering HPV vaccine to females have been established in the majority of developed countries. In recent years, there has been a move by countries including the United States, Canada, and Australia to recommend HPV-4v for boys also, given the broader benefits of the vaccine. The majority of European countries do not recommend

HPV vaccine for boys due to lack of cost-effectiveness data in the setting of high vaccine coverage in girls. Where high levels of HPV vaccine coverage have been achieved in females, heterosexual men have been observed to benefit from herd immunity; however, no protective effect has been observed in MSM, the highest group for HPV infection and associated disease [13].

HPV vaccine has been shown to be most effective prior to exposure to HPV [14]. Gender neutral immunization programmes providing vaccine for boys and girls will offer the greatest preventative potential; however, such programmes will not address the increased risk of HPV-associated disease in high-risk groups such as MSM. In addition, universal immunisation programmes are unlikely to be implemented in the short term given cost implication.

HPV vaccine has been demonstrated to be cost effective in MSM up to the age of 26 years over a range of assumptions [15]. Emerging evidence suggests that the vaccine may offer additional protective benefits in older MSM and that the vaccine may be cost effective in this group [16, 17].

The overarching aim of this chapter is to examine the burden of HPV infection and HPV-associated disease in MSM and HIV-infected MSM and to review potential preventative strategies.

Specifically this chapter examine the following:

1. Epidemiology of HPV infection and HPV-associated disease in MSM
2. Anal cancer screening in MSM
3. HPV vaccine for prevention of HPV infection and associated disease in MSM
4. Acceptability and feasibility of implementing targeted HPV vaccine programmes in MSM

2. HPV infection in MSM and HIV-positive MSM

HPV is the most common sexually transmitted infection worldwide. Lifetime risk of infection is estimated at 80% [18]. The vast majority of HPV infections are sub-clinical resolving spontaneously; however, a broad spectrum of presentations exist ranging from benign genital dermatoses to invasive malignancy. A complex interplay between host factors and viral factors impact on transmission and clearance as well as the clinical manifestation of HPV.

HPV infection in females has been the primary focus of research until recently given the causal link between HPV and cervical cancer. As the burden of extra-cervical HPV-associated malignancies has increased, and with the emergence of particular high-risk groups such as MSM, the research focus shifted.

While the natural history of HPV in females is well described, less is known about HPV infection in men. Numerous large longitudinal cohort studies have been undertaken in recent years to address this issue; however, eliciting the natural history of HPV infection is difficult.

Distinguishing between reinfection, reactivation of latent infection, incident infection, and clearance of infection is challenging in the setting of a multitude of host, viral, behavioral as well as sampling and analysis factors.

3. Prevalence of HPV infection in MSM

Prevalence of ano-genital HPV infection in men in the general population has been reported 1–84% [19, 20]. The wide range in prevalence observed is likely multifactorial relating to differences in study populations, sampling methods (including the anatomical sites of sampling), and analysis methods used.

The prevalence of anal HPV infection in MSM is higher than that observed in heterosexual men (47.2% versus 12.2%) [21]. The prevalence of high-risk (hr) or oncogenic anal HPV infection is documented at 26–73% in HIV negative MSM [10, 22, 23]. Prevalence of hr HPV has been shown to be significantly higher in HIV-infected MSM compared to HIV negative MSM with prevalence reported at up to 93% [24–26]. Receptive anal intercourse, number of sexual partners in the preceding six months and HIV infection have been identified as independent predictors of anal HPV infection [27, 28].

Prevalence of oropharyngeal and genital HPV infection has also been reported at significant rates (up to 45%) in MSM and HIV-infected MSM [29, 30].

Studies examining point prevalence of HPV infection provide important epidemiological insights. However, it is persistence of hr HPV infection that is the critical factor associated with development of malignancy.

4. Clearance of HPV infection

Clearance rates of hr HPV 16 anal infection have been reported at 12.2–18.7 per 1000 person months [31, 32]. Decreased clearance rates of hr HPV have been observed in HIV-infected compared with HIV-negative MSM, after adjusting for sexual behavior [28].

HIV infection has been identified as an independent predictor of HPV infection. Neither CD4 count nor nadir CD4 count has not been shown to influence clearance of HPV infection [10, 28, 33, 34]. This may partly explain high incidence of anal cancer observed in HIV-infected individuals despite immune reconstitution in the setting of highly active antiretroviral therapy (HAART).

5. Persistence of anal HPV infection

Persistence of hr HPV infection is the most important factor associated with anal cancer. MSM are frequently found to have multiple concurrent HPV infections in the anal canal. The most

oncogenic hr HPV type 16 has been identified as the most likely HPV type to persist over time [35].

Given that prevalence of hr HPV is more common in HIV-infected MSM and rates of clearance are decreased, it is unsurprising that persistence of anal HPV in HIV-infected individuals is higher compared to HIV negative individuals [29, 36].

6. Incidence of HPV infection

Incidence of hr HPV type 16 in HIV-negative MSM ranged from 4.5 to 12.4 per 100 person-years. Incidence of hr HPV-16 in HIV-infected MSM is reported at 7.1 to 13.0 per 100 person years [28, 31, 32]. It remains unclear whether CD4 T cell count influences the incidence rate of anal hr HPV infection. One study reported increased hazards ratio in people with CD4 counts 200–499 cells/mm³, compared to those with CD4 >500 cells/mm³ [37]; however, this has not been a consistent finding [38].

7. Anal cancer

Anal squamous cell cancer (ASCC) accounts for 80% of all anal cancers. ASCC is a relatively rare occurrence in the general population with a reported incidence of 1–2 cases per 100,000 [8]; however, certain risk groups such as MSM and HIV-infected MSM are disproportionately affected. The incidence of anal cancer in MSM is reported at up to 40 cases per 100,000 [39] with up to 135 cases per 100,000 reported in HIV-infected MSM [8, 35].

The majority of AIDS defining malignancies have decreased since the advent of HAART; however, the incidence of anal cancer has increased dramatically [40]. The survival benefits associated with HAART have unmasked a cumulative risk of anal cancer which was not evident previously due to premature mortality relating to HIV infection.

HPV infection is causally associated with over 80% of anal cancers. HPV type 16 causes 66% of anal cancers while HPV type 18 is responsible for an additional 6% of cases [41]. Prevalence and persistence of the oncogenic HPV 16 are high in MSM and particularly HIV-positive MSM. So too is anal intraepithelial neoplasia (AIN), the precursor lesion for anal cancer. The natural history of progression from AIN to anal cancer differs from that of cervical intraepithelial neoplasia and remains poorly understood.

8. Similarities between anal cancer and cervical cancer

A number of similarities exist between ASCC and cervical cancer. Both cancers occur at the squamo-columnar junction epithelium. These transformation zones are characterised by high turnover epithelium that is thought to be particularly vulnerable to malignancy-inducing

genetic alterations [42]. Both cancers are HPV associated. HPV is thought to promulgate changes to cells' DNA [43]. Immunosuppression is an important risk factor for both cancers with increased incidence observed in immunosuppressed patients such as transplant recipients and HIV-infected individuals [28, 44]. Both types of cancer also have widely divergent outcomes for early *vs* late presenting disease [45].

Similar to cervical cytology, cytological examination of anal cells can detect dysplastic cells. In contrast to the successes observed with cervical screening programmes, no effective screening modality has been demonstrated to impact on the morbidity and mortality associated with anal cancer.

9. Anal cancer and screening for anal cancer

Anal cancer frequently presents late (39% stage 3A or higher at diagnosis) with a lump, bleeding, incontinence from sphincter infiltration, fissure or fistula, and pain but also with nonspecific symptoms such as pruritus, discomfort, pelvic mass sensation, or change in bowel habit [46, 47].

Progression from normal epithelial mucosa to anal cancer transits through several precancerous stages, named anal intra-epithelial neoplasia (AIN) 1 to 3. AIN1 is considered low grade AIN (LGAIN); AIN 2 and 3 are considered high-grade AIN (HGAIN). AIN of any grade is common in MSM with rates of up to 50% reported in the literature [35].

Nearly a quarter of HGAIN lesions regress spontaneously within one year, while a minority of HGAIN (~1% per year) progresses to anal cancer [48].

Screening for anal cancer is a topic of much international debate. Some experts advocate for screening of high-risk populations such as MSM [49, 50]. However, no screening tool has been shown to impact morbidity or mortality of anal cancer.

Anal cytology is a poor predictor of HGAIN [51]. High resolution anoscopy (HRA) and biopsy of suspect lesions is considered the gold standard for detection of AIN in high-risk groups, although there are several important challenges including high cost, intra and inter-observer variability, and varying acceptability rates for HRA in patients [52]. In addition, the optimal treatment for HGAIN is yet to be established. Rate of recurrence of HGAIN after treatment is relatively high [50].

10. Head and neck cancer

Persistent infection with human papillomavirus (HPV) type 16 is also a major risk factor for the development of head and neck squamous cell carcinoma (HNSCC) and particularly development of oropharyngeal squamous cell carcinoma (OPSCC) [53]. HNSCCs include cancers of the oropharynx, oral cavity, and larynx. The incidence of HNSCC is increasing [54] and HNSCCs are now one of the 10 most common cancer seen worldwide [55].

HPV positive OPSCC has a unique clinical, histological, and molecular profile compared to HPV-negative OPSCC. Prognosis for HPV positive versus HPV negative OPSCC is significantly better independent of stage at diagnosis [56, 57]. HPV-negative OPSCC is associated with exposure to traditional carcinogens, such as tobacco and alcohol.

HIV-infected individuals are at increased risk of HPV infection and persistence of HPV infection. Similar to findings with other HPV-associated malignancies, prevalence of HNSCC is higher in HIV-infected individuals compared to the general population [58, 59]. The incidence of HNSCC is reported at 2–3 folds higher in HIV-infected individuals [60].

11. Penile cancer

Invasive penile cancer is rare. Over a third of penile cancer is associated with HPV, most commonly HPV type 16 and 18 [61]. The risk of penile cancer is up to four fold greater in HIV infected individuals compared to the general population [59].

12. HPV vaccine

Three vaccines have been licensed for the prevention of persistent HPV infection. All are subunit vaccines which use a recombinant form of the L1 major capsid protein of HPV as an antigen. L1 proteins self-assemble into noninfectious, nononcogenic units called virus-like particles (VLP).

The bivalent HPV vaccine HPV-2v (Cervarix™, GlaxoSmithKline) was approved by the FDA in 2009. The vaccine is approved for females 9 through 25 years of age. HPV2 is not approved for males. It protects against oncogenic HPV types 16 and 18 [62].

The quadrivalent HPV vaccine (HPV-4v) (Gardasil™, Merck and Co., Inc.) was approved by the FDA in June 2006. The vaccine is approved for females and males, 9 through 26 years of age. It offers additional protection against HPV types 6 and 11 commonly associated with genital warts as well as oncogenic HPV types 16 and 18 [63].

The nonavalent HPV vaccine (HPV-9v) (Gardasil 9™, Merck and Co., Inc.) was approved by the FDA in December 2014 and provides protection against 5 additional oncogenic HPV types (31, 33, 45, 52, and 58) [64].

HPV vaccines are highly immunogenic. More than 99% of recipients develop an antibody response to HPV types included in the respective vaccines one month after completing the three-dose series with comparable levels of antibody response following two doses [65]. However, there is no known serologic correlate of immunity and no known minimal titer has been determined to be protective.

HPV-4v has been demonstrated to be highly efficacious in preventing infection with HPV vaccine types related to external genital lesions, and anal intraepithelial neoplasia (AIN) in men [66]. The HPV-9v has been demonstrated to be highly efficacious in preventing infection with HPV vaccine types and disease related to the additional 5 types HPV-31, 33, 45, 52, and 58 in a susceptible population. Antibody response generated to HPV-6, 11, 16, and 18 were non-inferior to that generated by the HPV-4v vaccine, and thus the same indication as HPV-4v was applied [67]. No HPV vaccine has demonstrated protection beyond type covered in the vaccine.

The majority of developed countries have introduced national HPV immunization programmes for girls. A minority of countries including the US, Canada, and Australia now recommend provision of HPV vaccine for boys and girls.

While gender neutral vaccination programmes offer the best preventive opportunities, such programmes are unlikely to be implemented where levels of female vaccination coverage is high due to lack of cost-effectiveness evidence [68]. HPV vaccination of boys and male adolescents is not yet recommended in Ireland or in the majority of European countries that provide HPV vaccination for girls through national immunisation programs due to lack of cost effectiveness data.

High levels of female vaccination coverage have been shown to decrease genital warts in both females and unvaccinated heterosexual males through herd immunity; however, no protection has been observed in MSM. [13] Targeted vaccination of MSM has been shown to be cost-effective up to and beyond the age of 26 years [15, 16].

Despite the substantial clinical benefit of HPV vaccine in males, mathematical models suggest that HPV vaccination of males would exceed a cost-effectiveness threshold when vaccination coverage in females is high [68].

As yet no therapeutic benefit of the HPV vaccine has been demonstrated for the treatment of active disease present at the time of vaccination although early data suggests possible benefit of HPV vaccine in the setting of previous disease. This finding may represent an important opportunity for intervention in older high-risk patient groups such as HIV-infected MSM [69].

A single study has indicated that if the HPV vaccine proved efficacious in the HIV-positive population against vaccine sub-types, the potential reduction in anal cancer rates could be up to 61% [25].

In addition, data from female studies suggests that HPV vaccine of seropositive individuals who have cleared infection will provide increased protection against future infection [26].

In November 2014, the Joint Committee on Immunisation and Vaccination in the United Kingdom HPV sub-committee recommended implementation of a targeted programme of HPV vaccination for MSM >18 years to 40 years of age in GUM and HIV clinics if it could be delivered cost effectively [27].

13. Targeted HPV vaccine programmes

For HPV immunization programmes to have the desired effect, high levels of vaccine uptake are required. When considering feasibility of targeted HPV immunization programmes for MSM, HPV vaccine acceptability and factors influencing vaccine acceptability must be examined.

HPV vaccine acceptability in MSM in Ireland is reported at 31–78%. Acceptability varied with stated vaccine cost and efficacy [70]. A meta-analysis of HPV vaccine acceptability in MSM including data from North America and Australia (where HPV vaccine is offered to boys and MSM up to the age of 26 years through national programmes) reported similar acceptability (47–74%) [71].

Factors identified as positively associated with HPV vaccine acceptability include knowledge of HPV infection and associated disease in MSM and no cost vaccine. Recommendation from a medical practitioner was also identified as being associated with HPV vaccine acceptability [72].

Evidence suggest that uptake of HPV vaccination in MSM would likely be high and would be expected to increase following implementation of health education programs outlining the risks of HPV-associated disease and efficacies of the HPV vaccine. Much of this education could be delivered synergistically using existing infrastructure alongside HIV prevention programmes.

14. Conclusion

The incidence of anal cancer is high in MSM, particularly HIV-infected MSM. Almost 80% of anal cancer is caused by persistent infection with hr HPV type 16 which is preventable through vaccination. While many experts advocate routine screening for anal cancer in high-risk groups such as MSM, it has not been demonstrated to impact on anal cancer related morbidity or mortality to date.

A growing body of evidence supports the potential of HPV vaccine to prevent development of HPV-associated disease in older MSM [69, 73]. Although no definite therapeutic benefit of HPV vaccine has been demonstrated for the treatment of active disease present at the time of vaccination, emerging data suggests a possible benefit of HPV vaccination in the setting of previous disease [16, 17].

Sexual health and HIV clinics would be well placed to facilitate targeted/catch-up HPV vaccination for the high-risk groups including HIV-infected and HIV negative MSM, particularly in the setting of similar effective models for hepatitis B vaccination[74, 75].

Further research is needed to assess potential for alternative screening modalities to impact the burden of anal cancer currently observed in MSM. Targeted HPV vaccine has potential to greatly reduce the burden of HPV-associated anal cancer in MSM and HIV-infected MSM in

the future. Given the potential individual and population health benefits conferred, the HPV vaccine should not be withheld.

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