The role of Human Papilloma Virus (HPV) vaccination in the prevention of anal cancer in individuals with Human Immunodeficiency Virus-1 (HIV-1) infection

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Abstract: The incidence of anal cancer is increasing in the general population and especially in high-risk groups. A total of 90% of anal cancers are caused by human papilloma virus (HPV) infection of the anal canal. Similar to cervical cancer, anal cancer progresses through a predictable series of premalignant stages before resulting in invasive cancer; this process begins with persistent HPV infection. The HPV vaccine represents a promising strategy to combat the increasing incidence of anal cancer.

Human Immunodeficiency Virus (HIV) predisposes people to persistent HPV infection, dysplasia, and subsequent anal cancer. Patients infected with HIV should be targeted for vaccination against HPV. There are difficulties in targeting this population, the most notable being that the optimal age for vaccination is prior to identification with any high-risk groups. Universal vaccination against HPV represents the best strategy to achieve maximum protection against anal cancer in high-risk groups.

Keywords: Human Papilloma Virus (HPV), HPV vaccine, HPV vaccination, anal dysplasia, Human Immunodeficiency Virus (HIV), anal Paps, anal cancer

Introduction

The last few decades have seen a much greater appreciation for the role of Human Papilloma Virus (HPV) in the oncogenesis of various cancers. Initially the virus was discovered as a necessary causal agent for cervical cancers, where it causes over 95% of all invasive squamous cell carcinomas (SCCs) [Walboomers *et al.* 1999]. It has also been implicated for its role in SCC of the penis. HPV DNA can be found in up to 80% of SCCs of the oropharynx, although the virus only plays a causative role in about 25% of oral SCCs when viral oncogene expression occurs [Marur *et al.* 2010; Wong and Munger, 2000]. The virus is also a major contributor to SCCs of the anal canal, causing about 90% of cancers in this region [Parkin, 2006; Forman *et al.* 2012].

Anal cancer remains relatively rare in the general population, although the incidence is increasing by about 2% per year [Johnson *et al.* 2004]. In the pre-Human Immunodeficiency Virus (HIV) and early HIV era the incidence rate was 0.8 per 100,000

person years [Chiao *et al.* 2005], although more recent data show that the incidence rate has risen to 2 per 100,000 person years [Johnson *et al.* 2004]. There are risk groups for which the incidence is much higher, such as men who have sex with men (MSM) who are HIV negative, patients who are HIV positive as a whole group, and MSM who are HIV positive, for which the incidence peaks at around 75–137 per 100,000 person years [D’Souza *et al.* 2008; Patel *et al.* 2008; Silverberg *et al.* 2012]. HIV has greatly impacted anal cancer rates, probably through its effect on the natural history of HPV [Johnson *et al.* 2004; Denny *et al.* 2012].

While the HIV-positive population is living longer and staying healthier, there are an increasing number of non-acquired immune deficiency syndrome (AIDS) defining illnesses that are becoming more problematic; malignancy (particularly anal cancer) is a major driver of this trend [Frisch *et al.* 2000]. Paradoxically, highly active antiretroviral treatment (HAART) does not ameliorate this

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effect in anal cancer and may be indirectly contributing to the rising incidence by increasing the longevity of the HIV-positive population [Chiao *et al.* 2005; D'Souza *et al.* 2008; Crum-Cianflone *et al.* 2010; van Leeuwen *et al.* 2009; Bower *et al.* 2004; Piketty *et al.* 2008]. Strategies to curtail this increasing risk include screening and HPV vaccination. This review focuses on HPV vaccination and its role in preventing anal cancer, particularly in the HIV-positive population.

The burden of anal HPV infection

HPV is the most common sexually transmitted disease, highly prevalent in the sexually active population and rapidly acquired after sexual debut [Winer *et al.* 2003; Dunne *et al.* 2007; Weinstock *et al.* 2004]. Exact prevalence estimates depend upon the demographic group and the site tested for HPV infection; anal HPV prevalence is high across sexually active populations but varies tremendously across demographic groups. HPV infection of the mucosa of the anal canal occurs through direct inoculation through anal intercourse, or through a 'field effect' of autoinoculation from other sites in the perineum [Castro *et al.* 2012; Goodman *et al.* 2010]. Anal penetration with fingers is another possible route of infection [Winer *et al.* 2010]. There is good evidence that autoinoculation can occur from cervical to anal HPV transfer and vice versa [Goodman *et al.* 2010]. Anal HPV prevalence in a cohort of healthy women was 27% and closely correlated with cervical HPV prevalence [Hernandez *et al.* 2005]. Anal HPV prevalence in MSM without HIV infection has been shown to be as high as 74% [Ostor, 1993]. Another study of MSM who were HIV negative showed a prevalence of 57%, and unlike cervical infection, the rate remained stable across age groups [Chin-Hong *et al.* 2004]. Even with no risk factors for anal infection, anal HPV is not uncommon, such as in one cohort of healthy men who have sex with women (MSW) with anal HPV prevalence of 10% [Nielson *et al.* 2009].

HIV-positive populations generally have a higher prevalence of HPV [Damay *et al.* 2010; Dona *et al.* 2012; Palefsky, 2009; Adler 2010]. Anal HPV infections are exceedingly common in MSM who are HIV positive, with studies showing a prevalence from 84% to upwards of 90% [Stebbing *et al.* 2003; Palefsky *et al.* 1998c; Videla *et al.* 2013; Palefsky, 2007; Chin-Hong *et al.* 2008]. In this population coinfections with multiple HPV types are common, and high-risk serotypes are the most common [Palefsky *et al.* 1998c; Videla *et al.* 2013;

Palefsky, 2007]. Even in the absence of anal intercourse, anal HPV prevalence has been shown to be up 46% in patients who are HIV positive [Piketty *et al.* 2003]. One cohort of high-risk women who were HIV positive had anal HPV prevalence of 76% [Palefsky *et al.* 2001].

Mirroring these HPV prevalence data, anal dysplasia rates are high among high-risk groups. A recent cross-sectional study in a random cohort of MSM who were HIV positive found dysplasia in 57% with high-grade disease [anal intraepithelial neoplasia (AIN) 2 or 3] in 43%. In MSM who were HIV negative in the same cohort, 35% had dysplasia and 25% had high-grade disease [Chin-Hong *et al.* 2008]. Convenience cohorts of MSM who were HIV positive yielded similar prevalence results [Palefsky *et al.* 1998b, 2005; Kreuter *et al.* 2008]. Other high-risk groups include non-MSM who are HIV positive and women who are HIV positive. Even without any history of anal receptive intercourse, anal dysplasia rates are not negligible. For example, a study of non-MSM who were HIV positive showed a rate of 36%, 18% of which was high-grade disease [Piketty *et al.* 2003]. One study in women who were HIV positive showed AIN rates up to 26% by cytology, with up to 6% high-grade disease [Holly *et al.* 2001].

In contrast to cervical disease, for which there are ample data on the natural history of dysplasia in normal hosts, the natural history of anal disease remains poorly characterized. What is known regarding the natural history of anal dysplasia comes largely from the study of high-risk populations such as individuals who are HIV positive. Available data suggest that high-grade AIN (HGAIN) persists in the majority of cases, especially in the HIV-positive population. One study found that low-grade anal dysplasia (AIN 1) was followed by subsequent high-grade dysplasia in 62% of MSM who were HIV positive over a 2-year period [Palefsky *et al.* 1998a]. A separate cohort of MSM who were HIV positive with normal or low-grade AIN at baseline showed a similar rate of later discovery of high-grade dysplasia (70% over 17 months) [Lacey *et al.* 1999].

The exact rate of progression to anal cancer remains largely unknown. One large meta-analysis of anal dysplasia studies compared with anal cancer incidence attempted to estimate the risk of progression of HGAIN [Machalek *et al.* 2012]. This study estimated an HGAIN (AIN 2 or 3) progression rate to invasive anal cancer of 1 per

377 patients per year in the HAART era compared with an estimated cervical intraepithelial neoplasia (CIN3) progression rate of 1 per 80 patients per year. These data suggest somewhat different natural histories for anal dysplasia compared with cervical dysplasia, although the authors note that the estimates were severely hindered by a lack of good natural history studies of anal dysplasia, particularly in low-risk populations. At this point it is clear that anal dysplasia is common, especially in high-risk groups, but that the rate of progression to invasive cancer likely depends on associated risk factors and is generally unknown at this time.

The advent of the 'cervical cancer vaccine'

A landmark trial, published in 2007, showed that the quadrivalent virus-like particle (VLP) L1 HPV vaccine (quadrivalent HPV vaccine, trade name Gardasil, Merck Corporate Headquarters, NJ, USA) was effective at preventing high-grade cervical dysplasia compared with placebo [FUTURE II Study Group, 2007]. This was subsequently also demonstrated for the bivalent VLP HPV L1 vaccine (bivalent HPV vaccine, trade name Cervarix, GSK House, Middlesex, TW, UK) [Paavonen *et al.* 2009].

These studies demonstrate that several important factors guide the HPV vaccination paradigm and have persisted through multiple studies. For example, in the quadrivalent HPV vaccine 2007 study, analysis of the results showed that although the vaccine was effective against high-grade cervical dysplasia caused by HPV 16 or 18 in the modified intent-to-treat (ITT) population, efficacy was strongly dependent on prevalent disease at the time of vaccination. The efficacy in the ITT population was shown to be 44%; this efficacy was lower than the per-protocol population as the ITT population included some women who had cervical dysplasia and infection with HPV 16 or 18 at the time of enrollment. When the women with HPV 16/18 infection or dysplasia were excluded, the efficacy increased dramatically to 98%.

These results clearly demonstrate what has been the essence of the vaccination strategy against HPV-associated diseases; namely that vaccination provides exceptional coverage against vaccine strains so long as the patient is naïve to those particular strains. L1 VLP vaccines have been repeatedly shown to have no therapeutic effect on dysplasia or HPV infection

that is present at the time of vaccination [Stanley *et al.* 2012]. This drives the rationale behind HPV vaccination recommendations, that the vaccine should be targeted toward a preadolescent population to maximize vaccine efficacy [Centers for Disease Control and Prevention, 2011]. Vaccination prior to sexual debut would prevent prior HPV exposure, while delaying vaccination until early adolescence (as opposed to birth) would prevent waning immunity associated with a delay of over a decade between vaccination and first HPV exposure.

Anal cancer pathophysiology

There are several parallels between cervical histology and anal histology that result in similarities between cervical and anal SCC. Both organs possess a proximal columnar epithelium (endocervix/rectum) that transitions into a stratified squamous epithelium (ectocervix/anal canal); both possess a squamo-columnar junction (SCJ) [Stanley, 2010]. The SCJ is particularly prone to HPV infections, and is often the site of the original dysplasia. High-risk HPV serotypes that establish persistent infections can result in high-grade dysplasia (CIN2/3, AIN2/3). These dysplastic lesions can develop over time into invasive cancer. There are compelling data that anal SCC arises from these areas of pre-existing high-grade dysplasia [Berry *et al.* 2009], and that nearly 90% of anal cancers are due to HPV infection [Parkin, 2006; Forman *et al.* 2012]. While high-grade dysplasia is far more prevalent than invasive carcinoma [D'Souza *et al.* 2008; Charua-Guindic *et al.* 2009], it is poorly understood which high-grade lesions progress and which persist, therefore treatment is recommended for all high-grade lesions. Cervical dysplasia is typically treated with loop electrosurgical excision procedure, which allows for the removal of the entire transition zone. Unfortunately such an aggressive treatment is not feasible in the anal canal as complication rates, particularly anal stenosis, would be unacceptably high [Katdare and Ricciardi, 2010]. Anal dysplasia treatment requires either topical intra-anal therapy, or focused ablation with electrocautery or infrared coagulation; the optimal treatment regimen is still an area of active research [Stier *et al.* 2008; Graham *et al.* 2005; Fox *et al.* 2010].

HPV and HIV synergy

HIV contributes to HPV oncogenesis through immunosuppression of the host, which allows persistence of HPV and subsequent genetic changes in the epithelium promoting dysplasia and eventual

cancer [D'Souza *et al.* 2008; Charua-Guindic *et al.* 2009]. This results in higher prevalence of high-grade dysplasia, and decreased likelihood of spontaneous dysplasia regression [Critchlow *et al.* 1998]. Furthermore, the HIV-positive population often engages in other high-risk activity for the acquisition of multiple HPV strains (such as multiple sexual partners and anal receptive intercourse) [Ordonez and Marconi, 2012; Koblin *et al.* 2006], and has a higher prevalence of tobacco abuse which promotes development of HPV-associated dysplasia [Silverberg *et al.* 2009]. These combined factors result in a very high prevalence for anal dysplasia and anal cancer in the HIV-positive population, particularly MSM who are HIV positive [Patel *et al.* 2008; Silverberg *et al.* 2012; Chin-Hong *et al.* 2008]. Strategies to decrease the incidence of anal cancer in this population include anal dysplasia screening and ablation, as well as HPV vaccination. Both of these strategies have strengths and weaknesses as noted below.

HPV vaccine in anal cancer prevention

The pathophysiology of anal SCC theoretically makes it amenable to prevention with HPV vaccination. This was recently demonstrated in a randomized, controlled trial [Palefsky *et al.* 2011]. Similar to the cervical cancer/HPV vaccination trial, the primary endpoint was a reduction in HPV 16/18 associated premalignant lesions (AIN2/3). The population studied was healthy MSM who were 16–26 years of age, which is a high-risk population for anal HPV infection and anal dysplasia.

Analogous results were found compared with the cervical dysplasia prevention study. The vaccine's efficacy at preventing anal dysplasia associated with vaccine types was higher in the per-protocol population (77.5%) than the ITT population (50.3%). This is due to the fact that the former population was HPV and dysplasia free at the time of vaccination, whereas the latter included patients who had active dysplasia or HPV infection, or had incident disease prior to completing the series. This association also held for dysplasia associated with any HPV type, for which the efficacy in the per-protocol population was 54.9%, and the ITT population was 25.7%, as well as protection from persistent HPV infection with vaccine types (94.9% *versus* 59.4% respectively). Both populations displayed efficacy compared with placebo.

Of note, one inclusion criterion was five or fewer lifetime sexual partners; this was chosen to

minimize active disease at the time of study entry. The study population was also HIV free at the time of enrolment. Thus, while the study demonstrates that the quadrivalent HPV vaccine has tremendous potential for preventing anal dysplasia in an HPV-naïve population, it also highlights the limitations of this vaccine in the HIV-positive population. Typically the HIV-positive population has history of high-risk sexual behavior as well as a high number of sexual partners, particularly among MSM who are HIV positive [Koblin *et al.* 2003, 2006]; and as previously noted the prevalence of HPV is high in the adult HIV-positive population.

HPV vaccination in HPV-experienced populations

This high HPV prevalence represents a unique challenge for HPV-associated disease prevention through vaccination. Although HPV vaccination has no therapeutic benefit for the treatment of active disease present at the time of vaccination, there are some data suggesting a possible benefit of HPV vaccination in the setting of previous disease. The mechanism likely stems from the difference between immune clearance of natural infection *versus* the immunity induced through vaccination. Immune clearance of HPV infection relies on different mechanisms and is influenced by the duration of infection. Very early clearance likely takes place through innate immune mechanisms [Daud *et al.* 2011], with limited establishment of immune memory. Later clearance relies more on cell-mediated immunity (CMI) [Stanley *et al.* 2012]. Although natural infection generates antibodies, the titers are not high compared with the titers induced by vaccination [Villa *et al.* 2006; Schwarz and Leo, 2008]. Since natural infection results in a different response compared with vaccination, this opens the possibility that even when HPV is cleared, that protection against reinfection is not absolute; this role could potentially be filled through HPV vaccination.

There are some data suggesting that this is the case, that is, that HPV vaccination may play a role in preventing reinfection if the vaccine strains have been previously encountered and cleared. Retrospective analysis of subgroups of HPV vaccine trial participants suggests this effect. In one study of pooled data from three HPV vaccine trials, subjects who were DNA negative but seropositive to vaccine HPV types (indicating prior cleared infection) were analyzed. There were no cases of dysplasia or external genital disease in the

vaccinated subgroup, but among placebo patients seven developed cervical dysplasia and eight developed external anogenital lesions related to a vaccine subtype that they had previously encountered [Olsson *et al.* 2009]. In another study of HPV vaccine trial participants who developed dysplasia and underwent treatment with cervical surgery, recurrence of dysplasia was reduced by 46% in vaccine recipients compared with placebo [Joura *et al.* 2012].

However, the serospecific attack rate in HPV DNA-negative, seropositive subjects is two-five-fold lower than HPV-DNA-negative, seronegative subjects [Schiller *et al.* 2012]; so while the vaccine appears to offer some protection in the HPV-DNA-negative, seropositive subgroup its relative efficacy is decreased. There is evidence from one study that in the subset of patients with high antibody titers induced by natural infection, that subsequent HPV DNA detection (i.e. reinfection or reactivation) from the same HPV type is relatively rare [Safaeian *et al.* 2010]. HPV serologic data are complicated in that the literature is varied as to how much protection cleared natural infection truly offers; this is likely dependent on host factors as well as antibody titers which may in themselves be a surrogate for CMI [Moscicki *et al.* 2012; Farhat *et al.* 2009].

Of particular relevance is a recent nonrandomized study among MSM who were HIV negative with a diagnosis of HGAIN. In this study the group that electively received quadrivalent HPV vaccination had a significantly lower recurrence rate of HGAIN over at least 2 years [Swedish *et al.* 2012]. The mean age in the study was over 40, and the population was taken from a high-risk group for HPV active disease, prior disease, and reinfection. While these results are intriguing and highly relevant to the prevention of anal cancer, they remain to be verified with a large-scale randomized trial. Verification would likely result in an expansion of the US Food and Drug Administration (FDA) approved indications for the HPV vaccine, as well as providing a much-needed tool in the fight against anal dysplasia recurrence.

While these data point to a potential use of the HPV vaccine in older populations with previous HPV exposure, at this time vaccine efficacy has only been directly demonstrated in trials that focused on relatively low-risk populations of men and women with relatively limited past exposure to HPV [Palefsky *et al.* 2011; Kjaer *et al.* 2009;

Lehtinen *et al.* 2012]. Further prospective, randomized trials that focus on patients who are HIV positive and high-risk older patients would be especially relevant for the prevention of anal cancer through vaccination in patients who are HIV positive.

HPV vaccine trials in the HIV-positive population

Application of these data to the HIV-positive population remains challenging, since most HPV vaccination data come from HIV-negative low-risk cohorts. There are data for HPV vaccination in the HIV-positive population as well as ongoing trials. Most of these focus on immunogenicity and safety of HPV vaccines in the HIV-positive population. Two completed studies show that L1 VLP HPV vaccines are immunogenic and well tolerated in the HIV-positive population, although antibody titers produced are lower than HIV-negative controls [Centers for Disease Control and Prevention, 2011; Levin *et al.* 2010]. Assuming that the vaccine proved efficacious in the HIV-positive population against vaccine subtypes, the potential reduction in anal cancer rates could be up to 61%, depending on the attributable proportion of HGAIN to vaccine-specific HPV types [Sahasrabudde *et al.* 2013].

As of early 2013 there are six ongoing studies evaluating HPV vaccines in the HIV positive population [ClinicalTrials.gov identifier: NCT01209325, NCT01031069, NCT00941889, NCT01386164, NCT01461096, NCT01512784]. Four of these are primarily evaluating the safety and immunogenicity of the vaccine. Three of these studies have clinical endpoints, such as prevalence and incidence of CIN, AIN, and HPV types after vaccination. Two studies evaluate the immunogenicity of quadrivalent HPV and bivalent HPV vaccines head to head in the HIV-positive population [ClinicalTrials.gov identifier: NCT01031069, NCT01386164]. Only one study evaluates adults over 26 years of age; the rest focus on young adults and adolescents. An especially relevant open-label phase II study focuses on MSM aged 13–26 who are HIV positive and primary endpoints include incidence of anal dysplasia [ClinicalTrials.gov identifier: NCT01209325]; however without a placebo arm the resulting data will likely be compelling but not definitive. A study evaluating anal condyloma recurrence rates in patients who are HIV positive will also yield some anal dysplasia data from excised warts as a secondary endpoint [ClinicalTrials.gov identifier:

NCT00941889]. A phase III study is underway focusing on quadrivalent HPV vaccine in MSM with HIV infection and women over age 27, with clinical endpoints of time to HPV infection and diagnosis of HGAIN [ClinicalTrials.gov identifier: NCT01461096]. This study in particular addresses the problem of vaccinating adults who are HIV positive who have likely had past HPV exposure and are high risk for future disease. These studies will provide much needed data regarding the HIV-positive population and the HPV vaccination, particularly the studies with clinical endpoints. There is an efficacy trial of the bivalent HPV vaccine in women over 26 years of age that will provide some data in older populations, but the patients are HIV negative [ClinicalTrials.gov identifier: NCT00196937]. For the immediate future clinicians will have to make patient-specific decisions regarding HPV vaccination in adults who are HIV positive with imperfect information regarding efficacy against anal dysplasia, although specific relevant data will be available after completion of these trials.

The HIV population and the HPV vaccine

Despite these limitations there are strong reasons to consider HPV vaccination in subsets of the HIV-positive population. Currently the American Committee on Immunization Practices (ACIP) recommends HPV vaccination for boys aged 11–12 years of age, as well as ‘catch-up’ vaccination for unvaccinated men from 13 to 21 years of age. The recommendation is weaker for men aged 22–26 years, for whom the ACIP recommends that they ‘may be vaccinated’ [Centers for Disease Control and Prevention, 2011]. From age 27 on, no recommendation is made regarding HPV vaccination. Furthermore the ACIP makes no distinction regarding higher risk groups (such as MSM who are HIV positive) and suggests that the same age criterion be applied to these groups.

These upper-age cutoffs come in part from an HPV vaccine study in women aged 24–45, for whom the vaccine did not achieve significance in the endpoint of prevention of high-grade CIN [Castellsague *et al.* 2011]. However, in the population subset that was naïve to the vaccination HPV subtypes, the vaccine efficacy remained high. Therefore the lack of efficacy in the overall population was likely due to prevalent HPV disease at the time of vaccination or prior exposure. Exposure to HPV in this age group would statistically be high, given the data that HPV infection

typically occurs rapidly after sexual debut [Winer *et al.* 2003] and new infections are common with new sexual partners [Nyitray *et al.* 2012]. In older populations there is the further complication that HPV infection may have become latent, that is, it is not detectable by biopsy or polymerase chain reaction, then reactivate at a later date. Incident HPV disease in older populations could therefore represent new infection or reactivation of latent disease, but likely represents some combination of both [Moscicki *et al.* 2012]. Although this concept remains somewhat controversial, current data suggest that the HPV vaccine does not prevent reactivation of latent infection [Roberts *et al.* 2008], which would be particularly important in older adults.

Since in clinical practice it is very difficult to determine if exposure to HPV vaccination subtypes has occurred, and exposure is quite likely after age 26, the FDA did not approve the quadrivalent HPV vaccine for the indication of cervical cancer prevention past this age. But understanding the rationale for this decision is important and may allow the clinician to use the vaccine off label in certain exceptional circumstances, such as an older patient who has not yet become sexually active and plans to do so in the future. It should be noted, however, that these exceptions are rare and should not become standard practice.

Certain nuances bear mentioning. Like any population, the earlier the vaccine is administered, the less likely exposure to HPV vaccine subtypes has occurred. This makes the vaccine more cost effective in younger age groups [Westra *et al.* 2011], so patients who are HIV positive should be vaccinated as early as possible, preferably before age 21. Younger patients with an extremely high number of past sexual partners are very likely to have had HPV exposure and prevalent disease, but there are some modeling data suggesting that the vaccine may remain cost effective in high-risk populations as exposure to all four vaccine subtypes may not yet have occurred [Kim, 2010]. The vaccine should be offered, although cost efficacy in these patients is likely somewhat compromised. Finally, in patients aged 27 years and older, the data suggest that the vaccine is not cost effective, so vaccination of this group cannot be routinely recommended at this time [Castellsague *et al.* 2011; Westra *et al.* 2011; Kim *et al.* 2009]. However, most cost-efficacy data come from modeling based on data in women who are HIV negative and relatively low-risk populations. Cost

efficacy can only be extrapolated for high-risk HIV-positive populations given that efficacy data are limited in this group. As discussed, there are potential benefits in certain circumstances, such as the potential for decreased recurrence of anal dysplasia. These benefits should be discussed with certain patients who may wish to pursue off-label HPV vaccination. As the vaccine is low risk [Slade *et al.* 2009], the detriment to widespread application of off-label use primarily is cost, which can be upwards of \$200 per injection in a three-part series.

Cost efficacy of HPV vaccination

The most efficacious use of the HPV vaccine requires administration prior to sexual debut, which per the guidelines involves targeting girls and boys for vaccination between the ages of 11 and 12. As all women are at risk for cervical cancer, the vaccine clearly benefits girls. As previously discussed anal cancer is only a significant risk in certain subgroups of the population. Unfortunately these particular subgroups (MSM, HIV positive, etc.) are often impossible to identify at the appropriate age to intervene with vaccination. From a practical standpoint the only way to reach these at-risk groups at the ideal time is to universally vaccinate all boys at an early age.

Universal vaccination of boys for HPV has been criticized from a cost-efficacy standpoint [Kim and Goldie, 2009]. Anal cancer, while problematic in certain minority subgroups, is not yet a significant problem in the general population. While the vaccine should have a significant impact on the endpoint of anal cancer, the low incidence in the general population predicts that the vaccine, when used for this purpose alone, will not be cost effective.

Fortunately there are several other benefits to universal HPV vaccination of boys that positively influence the cost effectiveness of this strategy. These include a sharp decrease in the incidence of anogenital warts [Giuliano *et al.* 2011], a decrease in the incidence of cervical disease due to herd immunity [Elbasha and Dasbach, 2010], and theoretical decrease in penile and oral SCCs, although these latter two benefits have not yet been definitively proven. Mathematical models show that the overall cost effectiveness of universal HPV vaccination of boys is highly sensitive to mild fluctuations in variables, such as the duration of immunity, the circulating prevalence of

vaccine serotypes, and the percentage of girls who are vaccinated. In particular, some models show that cost efficacy for male vaccination is compromised once female vaccination rates approach or exceed 75% [Kim and Goldie, 2009].

Despite these data, focusing solely on female vaccination is problematic for two reasons. In practice the vaccination rate in the USA is significantly below 75% [Jemal *et al.* 2013]. Even if the impractical goal of 100% vaccination of girls could be achieved, the herd immunity that resulted would have little to no benefit for the MSM population, which already bears a high burden of HPV-associated diseases [D'Souza *et al.* 2008; Palefsky, 2007; Chin-Hong *et al.* 2008]. The most practical and cost-efficient way to reduce the burden of HPV-associated diseases, including anal cancer, remains universal vaccination of boys and girls at the ages of 11–12 as per ACIP guidelines.

This recommendation does little to help the clinician who focuses on adults who are HIV positive, for whom the practical question remains: Who among my HIV-positive patients should I vaccinate against HPV? Based on currently available evidence and ACIP guidelines, the vaccine should be administered as early as possible in all patients under the age of 27 in the absence of contraindications. In older patients with the insight to understand risk/benefit discussions, the vaccine could be offered off label, as long as the cost is not prohibitive. Excessive cost could be particularly detrimental if it detracts from other resources in HIV care, but this may not be particularly problematic for patients who are willing and able to pay for off-label vaccination.

Conclusion

HPV-associated diseases are distributed throughout the general population and are heavily concentrated in high-risk groups. This is especially true for anal SCC. The incidence of this disease is increasing in the general population and the HIV-positive population. The HPV vaccine is very effective when used prophylactically to prevent infection and subsequent dysplasia, but it has no therapeutic effect on active infection or dysplasia. Some retrospective data suggest that vaccination plays a role in preventing reinfection if natural clearance of HPV has taken place, but randomized prospective studies are needed. Due to the rapid acquisition of HPV after sexual debut, the most effective use of the vaccine involves targeting

sexually naïve populations at 11–12 years of age. As the high-risk male subpopulations (MSM, HIV positive, etc.) are essentially impossible to identify at this age, universal HPV vaccination of boys and girls is the most effective method to prevent future HPV-associated disease. HIV-positive patients should still be offered the vaccine if they are under 27 years of age, but will hopefully be vaccinated at earlier ages. Older patients who are HIV positive may be offered the vaccine, but they should be prepared to absorb significant costs. The HPV vaccine represents a promising advance to stem the increase in future HPV-associated cancers.

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