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Use of Human Papillomavirus Vaccine in HIV-infected Men for the Prevention of Anal Dysplasia and Cancer

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Abstract

There are two commercially available vaccines licensed worldwide for the prevention of cervical cancer and other human papillomavirus-associated cancers such as anal cancer. However, only two countries have implemented healthcare programs that include human papillomavirus vaccination for boys and men. Although most of the human papillomavirus-related cancers in the world are attributable to cervical cancer, in developed countries anal cancer accounts for a larger proportion of human papillomavirus-related cancers. Most cases of anal cancer occur in HIV-infected men who have sex with men. In this review, we discuss the burden of human papillomavirus-related cancers in men, the most plausible immune mechanism associated with the high efficacy of the human papillomavirus vaccine, and address key issues of vaccination for HIV-infected men. Finally, we review cost-effectiveness considerations for the use of the vaccine in boys and recent guidelines for vaccination in boys, with attention to HIV-infected men. **(AIDS Rev. 2014;16:90-100)**

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Key words

Human papillomavirus. HPV vaccine. HIV. Men who have sex with men. MSM. Anal cancer. Prevention.

A 43-year-old man infected with HIV was referred to our clinic to discuss whether the human papillomavirus (HPV) vaccine could be indicated for him. His HIV is well controlled (current CD4 cell count 1,004 cells/mm^3 and HIV viral load undetectable), but he was diagnosed with high-grade anal intraepithelial neoplasia (HGAIN) while living in New York in 2009. The patient was treated with infrared coagulation twice for his HGAIN prior to relocating to San Diego in 2012. He is now retired from the Navy and has settled in San Diego where he got married last year to an HIV-uninfected man. The patient acknowledges that they are in a monogamous relationship, but seldom practice protected sex. Upon establishing care with his new HIV provider, a repeated anal cytology recently showed recurrent high-grade squamous intraepithelial lesions. The patient would like to know if there is a role for the HPV vaccine to decrease his chances of progression to anal cancer.

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Introduction

The described case highlights one of the common clinical dilemmas we encounter in clinical practice regarding the use of HPV vaccine in HIV-infected men. HIV-infected individuals with persistent HPV infection are at increased risk for development of anal dysplasia and cancer[1]. In fact, the primary care guidelines for the management of persons infected with HIV from the HIV Medicine Association of the Infectious Disease Society of America recommend performing anal cytology screening in all HIV-infected persons with genital warts, women with a history of cervical dysplasia and/or anal receptive intercourse, and men who have sex with men (MSM)[2].

Human papillomavirus is a non-enveloped DNA, obligated intranuclear virus with a virion size of ~55 nm in diameter that primarily infects stratified squamous epithelium of the body[3]. From the hundreds of HPV types in the anal canal, most produce asymptomatic self-limited infections[1]. Others produce benign hyper-proliferative

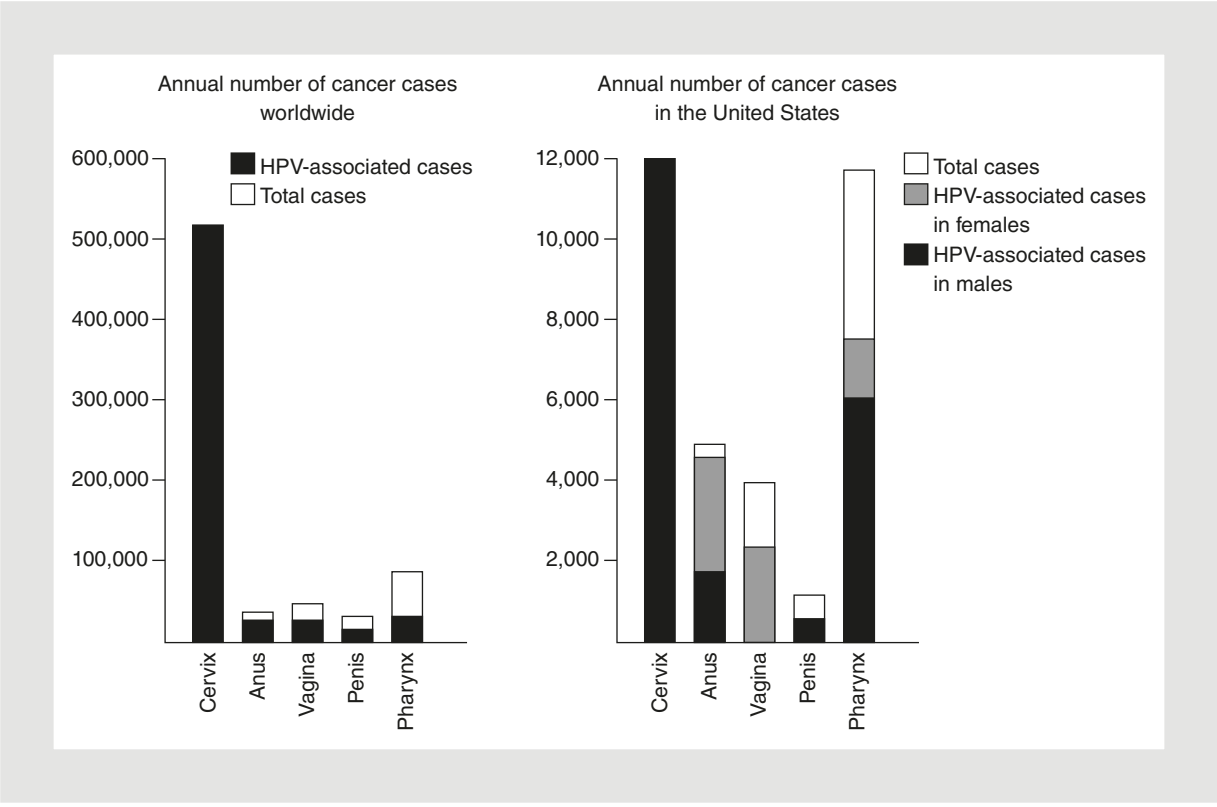

Figure 1. *Prevalence of human papillomavirus-associated cancers according to body sites worldwide and in the USA (adapted from Schiller, et al. Understanding and learning from the success of prophylactic human papillomavirus vaccines[19], data use to generate original figure came from references 7 & 9).*

condylomatous lesions. At least 88% of anogenital warts are caused by HPV types 6 and 11. Persistent HPV infection with high-risk HPV types 16 and 18 are associated with the majority of anal cancers[4]. Since 2006, there have been two commercially available vaccines licensed worldwide for the prevention of cervical cancer and other HPV-associated cancers such as anal cancer: the HPV 16/18 bivalent (Cervarix®) and HPV 6/11/16/18 quadrivalent (Gardasil®) vaccines. There are recent reports of the success of prophylactic HPV vaccine in HIV-uninfected women for the prevention of cervical cancer in real-world settings[5,6]. However, little is known at the population level of the HPV vaccine effectiveness in preventing anal dysplasia and cancer. Furthermore, the greatest burden of anal cancer is among HIV-infected MSM[1]. Given the known relative immunosuppression induced by HIV, are there specific considerations for the HPV vaccine in HIV-infected men to prevent anal cancer? In this review, we will briefly discuss the burden of HPV-related cancers in men, the historical landmarks that led to development of the current HPV vaccines, discuss the most plausible immune mechanism associated with the high efficacy of the HPV vaccines, and address key issues of HPV vaccination for HIV-infected men. Finally, we briefly discuss cost-effectiveness considerations for the use of HPV vaccines in HIV-infected boys and recent guidelines for HPV vaccination in boys and young men, with attention to HIV-infected MSM.

Burden of human papillomavirus-related cancers and heterogeneity of the problem in the world

Human papillomavirus accounts for approximately 5% of total cancers in the general population worldwide[7]. Most of the HPV-related cancers in the world are attributable to cervical cancer, and 85% of cervical cancers occur in developing countries[8]. However, in developed countries, anal cancer accounts for a larger proportion of HPV-related cancers (Fig. 1), largely due to widespread implementation of programs for screening and treatment for precursors of cervical cancer[1]. In the USA between 2004-2008, approximately 33,369 HPV-associated cancers were diagnosed annually (10.8 per 100,000). Multiplying the counts for HPV-associated

cancers by percentages attributable to HPV, The Centers for Disease Control (CDC) estimates that 26,000 can be attributed to HPV every year: 18,000 among females and 8,000 among males[9]. In Europe, it is estimated than 30% (17,000 cases per year) of all HPV-related cancers occur in males, of which close to 16,000 are attributed to HPV 16[10]. Most cases among males occur in HIV-infected MSM, who have a three-fold increased risk of HPV infection in comparison to HIV-negative MSM. HIV infection not only increases HPV persistence, but also increases the risk of acquisition of new HPV infections and/or reactivation of latent infections[11,12]. Moreover, rates of invasive anal cancer continue to increase in the HAART era[13], with incidence rates as high as 131 per 100,000 person-years reported in HIV-infected MSM[14]. In contrast, the rates of invasive anal cancer in the general population are considerably lower, at 2/100,000 person-years[1]. The most important public health strategy for anal cancer prevention is primary prevention through HPV vaccination of susceptible populations at risk.

Landmarks in the development of human papillomavirus vaccine

In 1977 Dr. Zur Hausen postulated his hypothesis that HPV plays a critical role in the cause of cervical cancer, assuming that the tumor cells, if they contained an oncogenic virus, would harbor viral DNA integrated into their genomes[15]. It was not until 1983 that he found novel HPV DNA in cervical cancer biopsies, discovering the oncogenic HPV 16[16]. Dr. Zur Hausen's work led to characterization of the natural history of HPV infection and the understanding of the mechanisms of HPV-induced carcinogenesis. The characterization of the HPV genome in 1986 presented the opportunity to develop vaccines against HPV infections[17]. Initial attempts using HPV denaturalized peptides failed[18]. The next breakthrough in the HPV vaccine development came in 1991, when it was discovered that the insertion of L1 gene into heterologous vectors (e.g. yeasts) generated noninfectious virus-like particles (VLP) that resemble HPV virions[18]. Virus-like particles are noninfectious assemblages of viral structural proteins, consisting of an ordered array of approximately 72 pentamers of L1, the major viral HPV capsid protein. The vast majority of the neutralizing antibodies that are induced by natural virions are directed against L1. Thus, the HPV vaccines mimic the outer shell of HPV virions to successfully elicit strong neutralizing antibodies that are protective against HPV infection. The VLP discovery constituted the basis for developing the currently available HPV vaccines that target HPV 6, 11, 16, and 18.

Factors implicated in mechanisms of protection induced by human papillomavirus vaccine

Human papillomavirus infection occurs at the basement membrane of the stratified epithelia where it remains attached for a prolonged time prior to cellular entry. In contrast to other sexually transmitted viruses like HIV, HPV requires a mechanical disruption of genital stratified mucosa exposing the basal membrane to initiate the HPV infectious process[1,19]. The HPV L1 surface protein attaches to exposed heparan sulphate proteoglycans on the basement membrane[19]. The HPV remains attached for hours to the basement membrane, facilitating cleavage by cellular furin, which triggers conformational changes of HPV L1 that expose the minor capsid protein L2[19]. Without this conformational change, the part of HPV required for its attachment to basal cells is not exposed (keratinocyte-binding determinant, presumably located on L1) and infection cannot progress. In HIV-infected patients, the anchoring and paracellular internalization of HPV to basal cells appears to be facilitated by HIV itself[20].

The strong immunogenicity of HPV vaccine appears to be crucial for its effectiveness. The HPV L1 vaccine induces high titers of neutralizing serum immunoglobulin G (IgG) that reach genital mucosa through transudation and exudation mechanisms[21]. The transudation is likely mediated by interactions with neonatal Fc receptor[22]. The exudation involves direct exposure of antibodies to the basal membrane of disrupted epithelia. The prolonged time that HPV spends in contact with the basal membrane makes HPV exceptionally susceptible to the antibody-mediated inhibition. The HPV L1 IgG neutralizing antibodies either prevent the attachment of HPV L1 protein to the basal cells of stratified genital mucosa and/or facilitate removal of basement membrane-bound capsid antibody complexes by local cellular scavengers (e.g. neutrophils)[19].

Additional factors that may contribute to the effectiveness of current HPV vaccines include: (i) small size (~55 nm) and shape (spherical) of the VLPs that facilitate transit and efficient presentation by dendritic cells in the lymph nodes[23]; (ii) VLPs facilitate adaptive immunity through their capacity to bind directly to different immunological cells such as dendritic cells, macrophages, and monocytes[24]; and (iii) VLPs may

Table 1. Comparison of main features of commercially available vaccines against human papillomavirus

Characteristics	Quadrivalent vaccine	Bivalent vaccine
Pharmaceutical	Merck & Co, Inc	GlaxoSmithKline
Commercial name	Gardasil	Cervarix
Vaccine composition (Protein L1)	20 mg HPV6 40 mg HPV 11 40 mg HPV 16 20 mg HPV 18	20 mg HPV 16 20 mg HPV 18
Heterologous system	*Saccharomyces cerevisiae* expressing L1	*Trichoplusia ni* (high 5) cell line infected with L1 recombinant baculovirus
Adjuvant	AAHS: 225 mg aluminum hydroxyphosphate sulphate	AS04: 500 mg aluminum hydroxide, 50 mg A 3-O-desacyl-4' monophosphoryl lipid A
Preservatives	None	None
Other contents	Sodium chloride, L-histidine, polysorbate-80, sodium borate, and water for the injection.	Sodium chloride, sodium dihydrogen phosphate dehydrate and water for the injection.
Storage temperature	2-8 ºC (do not freeze)	2-8 ºC (do not freeze)
Volume per dose	0.5 ml	0.5 ml
Administration	IM	IM
Interval	3 doses: 0, 1, 6 months	3 doses: 0, 2, 6 months

HPV: human papillomavirus.

facilitate B-cell responses, since VLPs effectively induce major histocompatibility complex class II-restricted responses[19].

Contributing to the long-term effectiveness of the VLP HPV vaccines at the population level are the slow HPV mutation rate[25] and the fact that VLP-neutralizing IgG antibodies recognize a diverse range of epitopes[26], making it unlikely that vaccine escape variants will emerge.

Comparison of two currently available human papillomavirus vaccines

Table 1 compares the main characteristics of the two licensed HPV vaccines. Both protect against HPV types 16 and 18 (which cause most anal cancers), but the quadrivalent vaccine offers additional protection against disease related to HPV types 6 and 11 (which cause most anogenital warts). Of note, the concentration of L1 particle HPV 16 in the quadrivalent vaccine is twice that in the bivalent vaccine (40 vs. 20 mg). The clinical significance of this difference in HIV-infected patients remains unclear. Both vaccines contain aluminum salt adjuvants that precipitate the VLPs and in this way ensure a slow release of the VLPs. The slow release of VLPs after injection effectively activates immune cells (e.g. monocytes) and B-cell responses. However, the bivalent vaccine adjuvant also contains monophosphoryl lipid A, a detoxified form of lipopolysaccharide also called AS04. The AS04 activates the innate immune response through toll-like receptor 4, leading to increased antibody responses to the VLPs[27]. Recently in Europe, a two-dose vaccination schedule for HPV 16/18 AS04 adjuvant vaccine has been approved for the prevention of premalignant cervical lesions in girls aged 9-14 years; there is no data on this approach in HIV-infected individuals[28]. Both vaccines are administered by intramuscular injection in three doses over six months, with slight variations in the timing of the second dose.

Safety of human papillomavirus vaccines in HIV-infected individuals

A number of studies have evaluated the safety and immunogenicity of HPV vaccines in HIV-infected men and women. Both vaccines are well tolerated and the few reported adverse events in HIV-infected patients were mild and temporary. These adverse events include

systemic reactions like mild nausea (~2%), headache (~3%), and influenza-like symptoms such as low-grade fever, chills, arthralgia, and fatigue (~9%)[29-32]. In one study of HIV-infected patients, injection site reactions including pain, swelling, and erythema were more common in the bivalent than in the quadrivalent HPV vaccine (91.1 vs. 69.6%; p = 0.02), but there were no gender differences in injection site reactions[33]. Syncope can occur among adolescents who receive vaccines, including quadrivalent HPV vaccine. To decrease the risk for falls and other injuries that might follow syncope, the Advisory Committee on Immunization Practices recommends that clinicians consider observing patients for 15 minutes after vaccination[34].

In earlier studies of HPV vaccines in healthy adolescent girls in Europe there were concerns that the vaccine was associated with coincidental autoimmune, neurological, and venous thromboembolic events[35,36]. On further assessment, these associations were judged weak and not temporally related to vaccine exposure[37]. Furthermore, in the USA, seven years of post-licensure vaccine safety monitoring provide further evidence of the safety of the HPV vaccine[38]. It could be argued that some side effects could be more apparent in HIV-infected patients, for example thromboembolic disorders, given a procoagulability state in the HIV population[39]. However, there were no serious adverse events related to HPV vaccines in any conducted studies that assess safety in HIV-infected patients (Table 2)[29-32]. The HPV vaccine has no effect on the CD4 cell count or HIV viral load of HIV-infected recipients[31].

Immunogenicity of human papillomavirus vaccines in HIV-infected individuals

Immunogenicity of current HPV vaccines is measured by a combination of the percentage of individuals who become seropositive for antibodies against the relevant vaccine HPV type, and the Geometric Mean Titer (GMT) achieved following completion of vaccination schedule[40]. Table 2 presents the main studies that have evaluated the immunogenicity of HPV vaccines in HIV-infected patients of different ages, ethnicities, and geographic location. Overall, more than 94% of HIV-infected patients achieved protective anti-HPV IgG antibodies four weeks after the third dose of HPV vaccine. This protection was not affected by CD4 cell count, percentage, or HIV viral load level, although most studied patients had relatively high CD4 cell counts[29-31,33]. However, a study suggested that HIV infection may influence the GMT of HPV-neutralizing antibodies. This study found that HIV-infected patients have median GMT lower for HPV 18 and 16 than historical age-matched controls[31]. The potential clinical importance of this observation is that the level of IgG-neutralizing antibody protection in mucosal secretions correlates directly with serum GMT of HPV antibodies four weeks after receiving the third HPV vaccine dose[21].

All these studies suggest that the robustness of HPV antibody response matters, but the clinical significance of specific differences of GMT of reported studies is unclear for the following reasons: (i) the minimum serum anti-HPV titer that confers protective efficacy has not been determined; (ii) there is no standardization of assays used to measure IgG responses to HPV vaccine; (iii) the assays that measure neutralizing antibodies against HPV are based on specific epitopes for each HPV type and thus are type-restricted and cannot be compared across types[41].

Another important consideration is the durability of HPV vaccine-induced antibody protection in HIV-infected patients. Among healthy individuals, following injection of the HPV vaccine, a rapid surge in the serum concentration of the HPV neutralizing antibodies occurs that is followed by a plateau state 1.5 years later, with preserved protecting antibodies for as long patients have been followed in studies (approximately 8.4 years)[42]. The continued expression of constant antibody levels over many years is probably due to long-lived plasma cells residing in the bone marrow[43]. In HIV-infected individuals, the antibody decay appears to be similar, but only a few studies have reported long-term follow-up. One study showed that 72 weeks after the last HPV vaccination, most of HIV-infected children remained seropositive for HPV 6, 11, and 16, but only 76% remained positive for HPV 18[21]. It is unknown, in HIV-infected patients, whether a subgroup of them with more immunosuppression may have an inadequate conversion of plasma blasts into memory B-cells, with downstream costs to durability of protection. Certainly, CD4 cell count and percentage at the time of HPV vaccination did not influence initial HPV antibody response; however, CD4 cell count correlated inversely with persistence of HPV antibodies up to 96 weeks from initial HPV vaccination[21].

Others have argued that persistence of detectable neutralizing antibodies is less important because of amnestic antibody response[19]. Healthy immunocompetent women vaccinated with the quadrivalent vaccine maintained protection against HPV-related cervical neoplasia even after the anti-HPV IgG titers fell below level of detection[44]. Whether this observation is attributable to

Table 2. Main clinical trials published assessing safety and immunogenicity of human papillomavirus vaccine in HIV-infected individuals

Author	Nº	Location	Study design	Study stratification	HPV Vaccine	Outcomes
Levin, et al. 2010[31] *†	126	USA	Randomized, double-blind, controlled	CD4 % nadir < 15 & CD4 % ≥ 15 CD4 % nadir ≥ 15 & CD4 % < 25 CD4 % nadir ≥ 25 & CD4 % ≥ 25	Quadrivalent	Safety similar to placebo. Immunogenicity: > 96% seroconversion in recipients.
Wilkin, et al. 2010[29] †	112	USA	Single-arm, open-label	If on ART; CD4 > 200 and VL < 200 copies/ml If not on ART CD4 >350	Quadrivalent	No grade 3 or greater adverse events. Seroconversion rates were > 95%: type 6 (98%), type 11 (99%), type 16 (100%), and type 18 (95%).
Kahn, et al. 2013[30] † ‡	99	USA & Puerto Rico	Open-label, multicenter	HAART vs. no HAART	Quadrivalent	One severe adverse event (fatigue) was noted. Among participants on HAART, seroconversion rate was 100% for all HPV types contained in vaccine. Among participants not taking HAART seroconversion rates were: type 6 (100%), type 11 (97.1%), type 16 (96.4%) and type 18 (92.3%).
Toft, et al. 2014[33] §	92	Denmark	Randomized, double blinded, controlled	Based on HAART and sex	Quadrivalent vs. bivalent	No serious adverse events reported. No difference in proportion of seroconversion between HPV vaccines to any HPV types. Anti-HPV 18 antibody titers were higher in the bivalent vaccine group compared with the quadrivalent vaccine, particularly in women. In the quadrivalent vaccine group there were no sex-specific differences in anti-HPV titers.
Palefsky, et al. 2014[32] †	150	India	Open-label, single-arm	Group 1: CD4 nadir ≤ 350 on HAART Group 2: CD4 nadir > 350, current CD4 350-500, not on HAART Group 3: CD4 nadir > 350, current CD4 > 500, not on HAART	Quadrivalent	No serious adverse events reported. Seroconversion rates were: anti-HPV 6 (96%), anti-HPV 11 (97%), anti-HPV 16 (99%), anti-HPV 18 (78%). There were no significant differences among the 3 enrollment groups in terms of the proportion of seroconverters.

*The only study performed in HIV-infected children ages 7 to 12 tears-old.
†The methods used to measure HPV neutralizing antibodies was Competitive Luminescence Immunoassay.
‡The study included only women 16 to 23 years-old.
§The methods used to measure HPV neutralizing antibodies was pseudovirion-based neutralization assay.
HPV: human papillomavirus; ART: antiretroviral therapy; VL: viral load.

variation in the assays used to measure HPV antibodies or reflects lack of characterization of mucosal compartment cellular immunity in reaction to HPV vaccine remains less clear. There is evidence that cytotoxic T lymphocytes (CTL) play a crucial role in the clearance of established HPV genital infection; at least one study in HIV-infected patients demonstrated that 60% of vaccinees developed CTLs for HPV 16 after vaccination[21].

Similar to what has been observed in healthy individuals, in HIV-infected patients there is some cross-type protective effect of HPV vaccines to other HPV types that are not included in the vaccines but are genetically related to the HPV vaccine types. The HPV neutralizing antibodies induced by VLP vaccines recognize multiple L1 epitopes that are closely related[26]. In a study of HIV-infected children aged 7-12, four weeks after the third dose of the quadrivalent vaccine, 67% of vaccinated children developed IgG protective antibodies against HPV 31, an HPV 16-related genotype that differs from the target sequence by a small number of amino acids[21].

Only one study has compared the safety and immunogenicity of the bivalent and quadrivalent vaccines using a randomized, double-blind method[33]. In this study, 92 HIV-infected individuals were enrolled and a different method of measuring HPV neutralizing antibodies was used (pseudovirion-based neutralization assay instead of the commonly used luminescence immunoassay). Both vaccines were immunogenic and well tolerated. Compared with quadrivalent HPV vaccine, the bivalent vaccine induced superior vaccine HPV 18 but not HPV 16 responses among HIV-infected women, whereas in HIV-infected men the immunogenicity was comparable.

Taken together, clinical trials have shown that the HPV vaccine is safe and induces a robust response of HPV neutralizing antibodies among HIV-infected patients. Furthermore, there are no differences between bivalent and quadrivalent HPV vaccines in safety and immunogenicity in HIV-infected men. Long-term studies of HPV vaccines in HIV-infected men are needed to ascertain the clinical impact of HPV neutralizing antibody decay and other protective vaccine cell-mediated effects in the mucosal compartment.

Efficacy of human papillomavirus vaccines to prevent anogenital warts and anal dysplasia in HIV-infected patients

Clinical trials conducted in more than 4,000 healthy HIV-uninfected men have documented the efficacy of the HPV quadrivalent vaccine in preventing external genital lesions (penis, scrotum, perineal, and perianal regions)[45,46]. In per-protocol (PP) population analyses, results are presented only in subjects who received three timely vaccine doses and had no evidence of prior HPV infection by negative baseline serum antibody, and undetectable anal HPV DNA polymerase chain reaction (PCR). In the intention-to-treat (ITT) population analyses, results are presented in subjects who received at least one dose of vaccine or placebo and returned for follow-up; however, these subjects may have been HPV-seropositive at enrollment or may had positive results for HPV DNA PCR that are contained in the quadrivalent HPV vaccine. The ITT group likely represents the general population of unvaccinated young men we find in clinical practice.

In comparison to placebo, the HPV quadrivalent vaccine significantly reduced the incidence of external genital lesions[46]. The observed ITT efficacy was 60.2% (95% CI: 40.8-73.8) for any HPV-related lesion, but increased to 65.5% (95% CI: 45.8-78.6) for lesions related to HPV 6, 11, 16, or 18. In the PP population, the efficacy in reducing external genital lesions related to HPV 6, 11, 16, or 18 was 90.4% (95% CI: 69.2-98.1). The efficacy with respect to persistent infection with HPV 6, 11, 16, or 18 was 47.8% (95% CI: 36.0-57.6) and 85.6% (95% CI: 73.4-92.9) in the ITT and PP populations, respectively. Similarly, the efficacy of the quadrivalent vaccine to prevent HPV DNA detection at any time of the vaccine-related HPV types was 27.1% (95% CI: 16.6-36.3) and 44.7% (95% CI: 31.5-55.6), respectively[46].

In a study of 602 HIV-uninfected MSM, 16-26 years of age, the use of the quadrivalent HPV vaccine reduced the rates of anal intraepithelial neoplasia (AIN), including grade 2 or 3, the direct precursors of anal cancer[45]. In comparison to the placebo group, rates of AIN per 100 person-years were lower in patients who received quadrivalent vaccine (13 vs. 17.5 and 4 vs. 8.9 for ITT and PP populations, respectively). The quadrivalent HPV vaccine prevented new HPV 6, 11, 16 or 18 associated AIN in 50.3% of patients (95% CI: 25.7-67.2) in the ITT population and in 77.5% (95% CI: 39.6-93.3) in the PP population. The corresponding efficacies against AIN associated with HPV of any type were 25.7% (95% CI: −1.1-45.6) and 54.9% (95% CI: 8.4-79.1), respectively. Furthermore, the rate of AIN-2 or -3 related to infection with HPV 6, 11, 16, or 18 was reduced by 54.2% (95% CI: 18.0-75.3) in the ITT population, and by 74.9% (95% CI: 8.8-95.4) in the PP efficacy population. Persistent anal infection defined

by the composite of detectable HPV DNA in a rectal swab or in anal histology samples with HPV 6, 11, 16, or 18 was also reduced by 59.4% (95% CI: 43.0-71.4) and 94.9% (95% CI: 80.4-99.4) in the ITT and PP populations, respectively[45].

There are no published studies for the prevention AIN in HIV-infected men yet, but many clinical trials are ongoing. For example, the AIDS Malignancy Consortium and the United States National Institute of Cancer are conducting the AMC 072 protocol, "Protective Effect of Quadrivalent Vaccine in Young HIV-positive MSM"[47]. The primary objectives of AMC 072 are to determine the protective effect of the quadrivalent HPV vaccine in preventing external genital condyloma, AIN, and persistent anogenital infection in HIV-positive MSM aged 13-26 years by comparing the incidence of these lesions among those naive to the relevant HPV type(s) at baseline to those who are not naive at baseline. Similarly, the AIDS Clinical Trials Group (ACTG) is conducting the ACTG 5298 study[48]. ACTG 5298 is a multicenter, randomized, double-blinded, placebo-controlled, phase III trial of the quadrivalent HPV vaccine (qHPV) in HIV-1-infected men to prevent anal HPV infection. The primary objective is to show that HPV vaccination prevents persistent anal infection with HPV types contained in the vaccine. Importantly, ACTG 5298 is enrolling a broader population of HIV-infected MSM, aged 27 years or older with no history of anal, penile, or oropharyngeal cancer; treatments for HGAIN and condyloma can be performed as clinically indicated by the local treating provider. The ACTG 5298 study results will be stratified according to the presence of HGAIN by histology at study screening (present vs. not present). Results of these studies are eagerly awaited.

Do virus-like particle human papillomavirus vaccines have a role in secondary prevention?

There is no categorical evidence that the currently licensed HPV vaccines act therapeutically to induce clearance of existing HPV infections or prevent their progression to high-grade dysplasia. A randomized clinical trial assigned more than 2,000 healthy HIV-uninfected women to receive either the HPV bivalent vaccine or control hepatitis A vaccine. Among those with cervical HPV DNA positive at baseline, there was no evidence of increased HPV viral clearance at 12 months in the group who received HPV vaccine compared with the control group. The HPV 16 or 18 clearance rates at 12 months were 48.8% (86/177) in the HPV vaccine group and 49.8% (110/220) in the control group, for a calculated vaccine efficacy for HPV viral clearance of –2.0% (95% CI: –24.3-16.3%)[49].

However, there is emerging data the VLP HPV vaccines may reduce the risk of recurrences following treatment of anogenital lesions. In a retrospective analysis of the FUTURE I and 2 Gardisil® trials, Joura, et al. examined 2,054 out of 17,622 women receiving excisional cervical treatments while participating in the clinical studies of the quadrivalent HPV vaccine[50]. Of those who underwent cervical surgery, 587 received vaccine and 763 placebo. These women were at high risk for having persistent or recurrent cervical disease. Within an average of only 1.4 years post-therapy follow-up (maximum 3.8 years), the incidence of any subsequent HPV-related disease was 6.6 and 12.2 in vaccine and placebo recipients, respectively (46.2% reduction [95% CI: 22.5-63.2] with vaccination). The HPV vaccination was associated with a significant reduction in risk of any subsequent high-grade disease of the cervix by 64.9% (20.1-86.3%)[50]. A non-concurrent cohort study included 202 MSM with a history of previously treated HGAIN[51]. One-third was infected with HIV. Eighty-eight patients were vaccinated and 114 were unvaccinated. During 340.4 person-years follow-up, 12 (13.6%) vaccinated patients and 35 (30.7%) unvaccinated patients developed recurrent HGAIN. Testing positive for oncogenic HPV genotypes within eight months before study entry was associated with increased risk of recurrent HGAIN at two years after study entry (HR: 4.06; 95% CI: 1.58-10.40). The quadrivalent HPV vaccine was associated with decreased risk of recurrent HGAIN (HR: 0.50; 95% CI: 0.26-0.98). Among patients infected with oncogenic HPV, qHPV was associated with decreased risk of recurrent HGAIN at two years after study entry (HR: 0.47; 95% CI: 0.22-1.00)[51].

Some possible mechanisms of secondary preventive effect of the VLP HPV vaccines have been speculated: (i) IgG anti-HPV neutralizing antibody levels are higher after vaccination than natural infection, preventing viral binding to the basement membrane and entry into basal cells; (ii) mutated epithelial cells with integrated virus in the primary disease site were removed at treatment, but cells with free nuclear HPV were left behind. Quadrivalent HPV antibodies may prevent host reinfection; and (iii) reinfection would increase the risk of integration and neoplasia, but antibody response stops the cascade, reducing the risk of recurrent high-grade cervical and anal neoplasia[51].

These data suggest that clinical trials are needed to address the question of whether HPV vaccination may improve outcomes to treatment of dysplasia.

Is human papillomavirus vaccination for men cost-effective?

In the general population there is an increasing economic burden attributable to HPV-related disease in males. In the USA, the estimated direct cost of genital warts for males was 119 million dollars in 2004[52]. This likely underestimates the impact on quality of life and indirect costs associated with genital warts. In Europe, the total cost of anogenital cancers to the hospital sector at the end of 2007 was estimated to be 7.6 million Euros per year, of which over 4 million Euros was associated with anal cancer[53]. In this European study, the total cost per year attributable to HPV 16 and 18 was 3.1 million Euros.

Earlier studies suggested that only HPV vaccination of girls was cost-effective, but adding boys to vaccination programs would exceed traditional cost-effectiveness thresholds[54]. In addition, HPV vaccination of girls would only introduce a "herd immunity effect" and reduce the HPV prevalence in men[54,55]. This has been proven to be true for heterosexual men, where a considerable decline in anogenital warts was observed after the introduction of quadrivalent vaccine in girls[56]. However, MSM did not benefit from this strategy. Most recent studies have agreed that HPV vaccination programs that include boys and girls are likely to further reduce the incidence of HPV 16 or 18[57,58]. Relative to a girls-only program, vaccination of girls and boys led to a reduction in female and male HPV-related carcinomas of 40 and 65%, respectively, and a reduction in the incidence of HPV 6 or 11-related genital warts of 58% for females and 71% for males versus girls-only vaccination[10].

One of the main challenges of HPV vaccination in HIV-infected men is that these men often carry multiple HPV types. A recent meta-analysis using anal HPV DNA PCR found that the pooled prevalence among HIV-infected MSM was 35.4 (95% CI: 32.9-37.9) and 18.6 (95% CI: 12.8-24.4) for HPV 16 and 18, respectively[59]. However, the median age of the patients included in this meta-analysis was beyond the age range recommended for vaccination in men in the USA. The true prevalence of high-risk HPV types in HIV male populations aged 26 or younger is uncertain because most studies do not comprehensively capture this group[60-62]. Nevertheless, targeted HPV vaccination in MSM is still considered cost-effective. The costs of HPV vaccination at age 12 in MSM without previous exposure is estimated at 15,290 USD per quality-adjusted life-year (QALY) gained, whereas for MSM 26 years, when previous exposure to all vaccine-targeted types was assumed to be 50%, the estimated cost is around 37,830 USD per QALY for vaccination – below the 50,000 USD cost-effectiveness threshold[63].

Age group vaccine considerations in men and current recommendations for the use of human papillomavirus vaccine in HIV-infected individuals

Human papillomavirus vaccination in boys needs to commence at an age before sexual debut for maximal prevention of HPV, especially among MSM. Early and high frequency per partner transmission of HPV occurs between men soon after their first sexual experiences. In an Australian study of MSM aged 16 to 20 years, the proportion of men with anal HPV of any type increased from 10.0% in men reporting no prior receptive anal sex to 47.3% in men reporting ≥ 4 receptive anal sex partners ($p < 0.001$). The proportion of men with penile HPV increased from 3.7% in men reporting no prior insertive anal sex to 14.8% in men reporting ≥ 4 insertive anal sex partners ($p = 0.014$). Overall, 39.0% (95% CI: 32.2-46.1) of men had at least one HPV type of whom 23.0% (95% CI: 17.4-29.5) had a vaccine-preventable type (6, 11, 16 or 18)[64].

Currently, only the USA and Australia have healthcare policies that include HPV vaccination for men. In the USA, the CDC recommends quadrivalent HPV vaccine for all boys aged 11 or 12 years, and for males aged 13 through 21 years, who did not get any or all of the three recommended doses when they were younger[65]. All men may receive the vaccine through age 26 after speaking with their doctor. In February 2013, Australia extended its national school-based vaccination program to include the HPV vaccine among males aged 12-13 years-old, with a catch-up program of 14-15 years-old.

Although there are no results of HPV vaccine efficacy in HIV-infected individuals yet, the CDC Advisory Committee on Immunization Practices has recommended that HPV vaccination be given to all HIV-infected males in a three-dose series at 11 or 12 years of age, and for those 13-26 years of age if not previously vaccinated[64]. The recently published guidelines by the HIV Medicine Association of the Infectious Disease Society of America also endorsed these recommendations[2].

Summary

The currently licensed HPV vaccines are safe and highly immunogenic in HIV-infected individuals. The HPV vaccine is also cost-effective in HIV-infected MSM. In the USA there is consensus that HPV vaccines should also be given to males, including those HIV-infected, ideally before age 26 years. Modeling using conservative analyses suggests that HPV vaccination in HIV-infected men is cost-effective. There is insufficient evidence to recommend the HPV vaccine as secondary prevention of HPV infection; clinical trials addressing this question are urgently needed.

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Conflict of interest

The authors have no conflict of interest.

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