Chapter 16: HPV vaccines in immunocompromised women and men

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Abstract

HIV-positive as well as other immunocompromised women and men have increased risk of human papillomavirus (HPV)-associated anogenital and oral cancers. The effectiveness of a HPV vaccine to reduce the incidence of these tumors in immunocompromised individuals may depend on several factors, including the effects of immunocompromise on the response to vaccination, the extent of prior infection with the HPV types included in the vaccine, whether immunocompromised women and men have tumors that contain types of HPV not in the vaccines more often than the general population, and whether or not immunization occurs before immunocompromise is severe. Clinical studies are needed to determine HPV vaccine safety and effectiveness in different populations of immunocompromised women and men.

Keywords: HIV; HPV; Vaccines

1. Introduction

Control of HPV infection is thought to involve innate and adaptive immune responses that either prevent HPV infection or eliminate HPV-infected keratinocytes. Several immunocompromised populations are known to have increased risk of HPV-associated cancers. HIV-positive women and men are the largest immunocompromised population and the most important from a public health perspective. Other immunocompromised groups include those who are iatrogenically immunosuppressed to prevent graft rejection following organ transplant or to control autoimmune diseases, and those with chronic conditions such as renal failure requiring dialysis. Whether chronic infections that are common in certain developing countries (e.g., malaria) or malnutrition may also lead to increased risk of HPV-associated disease due to immunosuppression is unknown.

The HPV virus-like particle (VLP) vaccines that are likely to be approved for commercial use in the near future include a bivalent vaccine that contains HPV-16 and -18 VLPs\cite{1–4}, and a tetravalent vaccine that contains HPV-16, -18, -6, and -11 VLPs\cite{3}. These vaccines have been shown to have efficacy to reduce incident infection with these HPV types as well as the development of high-grade cervical intraepithelial neoplasia (CIN-2/3) that contain HPV-16 or -18. The clinical trials involved mainly healthy young women with no prior sexual history or a limited number of sexual partners.

Given the challenges associated with treating HPV-associated neoplasia and increased risk of HPV-associated cancer among immunocompromised women and men, HPV vaccination may be an important new approach to reduce the risk of HPV-associated cancers in these populations. However, there are few or no data on the effects of HPV vaccination in any immunocompromised populations.
This paper explores the rationale for vaccination in immunocompromised women and men. There is first an overview of HPV infection and neoplasia of the cervix, anus, and oral mucosa in immunocompromised populations, with emphasis on data that are most relevant to HPV vaccination. This is followed by a discussion of the major factors likely to determine whether HPV vaccines are safe and effective in immunocompromised individuals based, in part, on clinical experience with other vaccines. Finally, we suggest approaches to future clinical trials of HPV VLP vaccine that should be conducted.

2. Cervical HPV infection and cervical neoplasia in HIV-positive and other immunocompromised women

2.1. Cervical cancer in HIV-positive women

Cervical cancer occurs at significantly higher rates in HIV-positive women than in the general population and it is an AIDS-defining illness. In developing countries – against the backdrop of already high cervical cancer rates – smaller associations between HIV and cervical cancer have been observed than in the US and Europe but, combined with the high prevalence of HIV in certain developing countries, even small increases in risk have substantial public health implications. Furthermore, unlike two other virus-associated tumors, namely Kaposi’s sarcoma and non-Hodgkin’s lymphoma, whose incidence has markedly declined with the widespread use of highly active antiretroviral therapy (HAART), there is no evidence that the incidence of either cervical or anal cancer has declined in the HAART era, and there have been conflicting reports regarding the impact of HAART on HPV and CIN [5]. Moreover, unlike CIN and anal intraepithelial neoplasia (AIN), which are both associated with lower CD4+ levels, neither anal nor cervical cancer are associated with lower CD4+ levels. Based on the cumulative data, it is likely that HAART will have only a moderate effect, if any, on the incidence of cervical cancer. As women live longer on HAART with improved, but still diminished, immune status, they are also increasingly entering the older age-groups with higher cervical cancer rates. It thus remains unclear whether HAART will be associated with a decrease or an increase in the number of cervical cancer cases among HIV-positive women.

2.2. Cervical HPV infection and CIN in HIV-positive women

HPV positivity is associated with increased prevalence of cervical HPV infection, greater prevalence of CIN, and higher grade of CIN [6]. Moreover, the strength of these associations increases with diminished immune status [7]. Recent data suggest that there are strong interactions between the effects of plasma HIV-RNA and CD4+ T-cell count on both HPV infection and CIN [8]. Recent data also show that a substantial proportion of cervical HPV detected in HIV-positive women reflects reactivation of previously acquired infections rather than recent sexual transmission [8], although it remains unclear whether this represents true reactivation from a latent state or an increase in the viral load of a current infection to a level above the lower limit of detection of available assays. Furthermore, there may be HPV type-specific differences in the effects of host immune status on the risk of HPV infection. Most notably, HPV-16, the HPV type that by itself accounts for approximately half of all cervical cancers, was found to be the least affected of all HPV types by diminished immunity, as measured by CD4+ T-cell level [9]. This has been interpreted as evidence that HPV-16 may, in part, be the dominant cause of cervical cancer because of an innate ability to avoid immune surveillance. Consequently, HIV-associated immunosuppression may have less impact on HPV-16 than other HPV types. While the tumorigenicity of HPV-16 is not in any way reduced in HIV-positive women, these data imply that other oncogenic HPV types that are relatively uncommon causes of cancer in HIV-negative women may account for an increasing proportion of cervical cancers among HIV-positive women because they are disproportionately affected by their diminished immune status.

Studies of the serologic response to HPV in HIV-positive women have been revealing in several ways. A recent study found that HPV-16 seroprevalence was approximately 50% among HIV-positive women and was similar across CD4+ T-cell strata [10]. These data indicate that the cumulative exposure to a given HPV type such as HPV-16 is high in this population, and may be underestimated by DNA prevalence studies, since the prevalence of HPV-16 DNA was 5% [7]. The data also demonstrate that HIV-positive women can continue to generate HPV antibodies even with a low CD4+ T-cell count. Current HPV infection was associated with higher titers, thereby suggesting the continued ability of HIV-positive women to respond to new HPV antigen exposure.

2.3. Cervical HPV-associated neoplasia in other immunocompromised women

It is well established that organ transplant patients are at increased risk of HPV-associated anogenital cancers and CIN compared with the general population [11]. The prevalence of CIN is also increased in those with advanced systemic lupus erythematosus using immunosuppressive therapy and patients with chronic medical conditions, such as renal failure requiring dialysis. However, HPV-associated neoplasia has been much less studied in these patients than in HIV-positive women. Although cervical HPV prevalence rates are known to be high in many HIV-negative immunocompromised patient populations, the cumulative burden of HPV infection has not been prospectively studied in such women, the role of HPV reactivation is unclear, and it is unknown whether the distribution of HPV types in the cervix is similar to that of HIV-positive women.
3. Anal HPV infection and anal neoplasia in HIV-positive and other immunocompromised men and women

3.1. Anal cancer in HIV-positive men and women

Like cervical cancer, anal cancer is associated with HPV infection [12]. HPV-16 is even more common in anal than in cervical cancer, representing the majority of anal tumors; HPV-18 and other oncogenic HPV types are found in only a subset of anal tumors [13]. The incidence of anal cancer is greatly elevated in HIV-negative men who have sex with men (MSM) and to an even greater extent in HIV-positive MSM [14]. The incidence of anal cancer in these populations is consistent with the high prevalence of anal HPV infection and AIN-2–3 among HIV-positive and HIV-negative MSM described below. HIV-positive women are also at higher risk of developing anal cancer than women in the general population [14]. Further, consistent with the high prevalence of AIN among HIV-positive MSM on HAART, the incidence of anal cancer has not declined since 1996 when HAART was introduced for widespread use, and may even be increasing [15].

3.2. Anal HPV infection and AIN among HIV-positive men and women

A high proportion of HIV-positive MSM have anal HPV infection [16]. Consistent with these data, studies have reported a high prevalence and incidence of AIN, including AIN-2–3, including one in which incident AIN-2–3 developed in over 50% of HIV-positive men with a CD4+ T-cell count under 500/mm³ over a 4-year follow-up period [17]. As in the cervix, HAART appears to have had limited beneficial effect on reducing AIN; in a recent study, 52% of HIV-positive MSM, most of whom were on HAART, had AIN-2–3 [18].

As in men, anal HPV infection and AIN are surprisingly common in women, and even more common among HIV-positive than HIV-negative women [19]. Anal HPV was found in 43% and 79% of HIV-negative and HIV-positive women, respectively, with cervical HPV infection in 24% of HIV-negative and 53% of HIV-positive women. Consistent with these data, another recent study found abnormal anal cytology in 8% of HIV-negative and 26% of HIV-positive women [20].

3.3. Anal HPV infection and AIN in men and women with transplant-associated immunocompromise

A high prevalence of anal HPV infection has been demonstrated among transplant recipients [21,22]. In one study, anal HPV-DNA was detected in 23% of men and women undergoing liver or renal transplant before initiation of immunosuppressive therapy [21]. In another study, 23% of recent and 47% of established renal transplant recipients had anal HPV infection and 20% had AIN [22].

4. Oral HPV infection and oral cancer in HIV-positive and other immunocompromised men and women

4.1. Oral cancer and HPV

Squamous-cell carcinomas that arise from the mucosal epithelium of the upper aerodigestive tract are a major cause of morbidity and mortality worldwide, exceeding 300,000 cases worldwide each year [23]. While the majority of head and neck squamous-cell carcinomas (HNSCCs) are attributable to alcohol and tobacco exposure, oral HPV infection is thought to be a potential etiologic agent for only a subset of HNSCCs [23].

Case–control studies have associated sexual behavior, HPV exposure, and oral HPV infection with risk of oral cancers, including those of the oral cavity and oropharyngeal cancers. Analogous to cervical cancer, an elevated risk for oral cancer has been associated with age at first intercourse, oral–genital contact, a history of genital warts, and number of lifetime sexual partners [24]. Seropositivity to the HPV-16 capsid protein is also associated with elevated odds (odds ratio, OR ≈ 2–3) for oral cancer [25].

In a recent pooled analysis of 5,046 HNSCC specimens from 60 published studies, 25.9% of oral cavity, pharynx, and larynx cancers were positive for HPV genomic sequences, predominantly HPV-16, followed by HPV-18 [26]. Other oncogenic HPV types were uncommon. Oropharyngeal cancers (35.6%) were significantly more likely than oral cavity (23.5%) or laryngeal (24%) cancers to be HPV-DNA-positive.

However, HPV prevalence data are likely to overestimate the proportion of HNSCCs attributable to HPV-16 or HPV-18 infection since detection of the virus alone is insufficient evidence to establish a causal association [23]. To estimate the potential impact of a prophylactic HPV vaccine on the annual global incidence of HNSCCs, the proportion of these cancers that are attributable to HPV infection must be considered. A prophylactic vaccine for HPV would be expected to have an effect primarily on the annual incidence of oropharyngeal cancers, estimated as 52,100 incident cases worldwide each year. HPV-16 consistently accounts for 87–95% of HPV-positive oropharyngeal cancers, and HPV-18, -31, -33, and -35 account for the remainder [27]. Therefore, a bivalent vaccine including HPV-16 and -18, which is potentially capable of preventing 71% of cervical cancers, may be capable of preventing as many as 95% of HPV-associated oral cancers.

4.2. Oral HPV infection and oral cancer in HIV-positive men and women

Oropharyngeal cancer occurs at higher rates in HIV-positive men and women than in the general population [14,28]. In agreement with this increased risk for oropharyngeal cancers, HIV-infected individuals are at an increased risk of oral HPV infection [29]. The cross-sectional prevalence of...
oral HPV infection is estimated to be between 14% and 35% among HIV-infected individuals and, as with HPV-associated oral cancers, HPV-16 is the most prevalent oral HPV type detected [29]. Similar to cervical HPV infection, oral HPV infection has been associated with sexual behavior, in particular oral–genital contact, which provides further rationale for targeting vaccination to individuals before sexual debut. Furthermore, while the prevalence of several oral infectious complications has declined in the post-HAART era, those attributable to oral HPV infections may be increasing, thus underscoring the potential importance of HPV vaccination in HIV-positive men and women [30].

Because of the increased heterogeneity in HPV type-distribution in oral papillomas (e.g., 6, 7, 11, 13, 32, 16, and 18), the existing quadrivalent vaccine may be less effective in preventing papillomas in HIV-positive individuals than in immunocompetent individuals, in which the majority of papillomas are attributable to types 6 and 11. Whether the distribution of HPV types in oropharyngeal cancers is different for HIV-positive than for HIV-negative cases is not known, but has clear implications for the potential impact of the HPV VLP vaccines on the risk of HNSCCs among HIV-positive men and women. Although oropharyngeal cancers have been reported in solid organ transplant recipients, excess risk has not been consistently found in prospective studies in this patient population.

5. Safety and efficacy of HPV VLP vaccines in HIV-positive and other immunocompromised populations

Because of their high incidence of cancer, all practical methods should be employed to reduce its risk in HIV-positive and other immunocompromised individuals. A preventive HPV vaccine might be especially useful in developing nations, where the prevalence of HIV and cervical cancer are both very high. In developed countries, HIV-positive women are commonly from underprivileged subgroups, with limited access to cervical cytology screening and treatment programs, again making vaccination an attractive option. The major question is whether preventive HPV vaccines will be safe and effective in immunocompromised women and men.

The safety of the HPV VLP vaccines in immunocompromised populations has not been demonstrated. The fact that these are not live vaccines eliminates potential concern that vaccination could cause harm due to iatrogenic infection, but other sources of toxicity and complications must be assessed. The experience with other vaccines, however, is instructive, and somewhat reassuring. Several different bacterial and viral vaccines are recommended for use in solid organ transplant patients, including pneumococcal, influenza, hepatitis A virus (HAV), hepatitis B virus (HBV), diphtheria, and tetanus vaccines. These patients have diminished, but often effective, immune responses, with no increases in graft rejection or other major consequences [31]. Similarly, vaccination against a number of viral and bacterial pathogens is recommended in HIV-positive children and adults. The possibility of transient infection increases in HIV viremia has been reported primarily in the pre-HAART era, but the data regarding this are conflicting and the rate of HIV/AIDS progression appears unaffected [32,33]. Overall, the safety and effectiveness of HPV VLP vaccines must be directly studied in each of the different immunocompromised populations in which it might be used.

Several factors may play a role in determining the effectiveness of the HPV vaccines in these populations, and these are discussed below.

5.1. Effect of immune deficiency on response to vaccination

The immune response to vaccines is diminished among HIV-positive and other immunocompromised individuals [32,33], but this effect may vary among vaccines. For example, while the immune response to HAV vaccine is generally adequate among HIV-positive patients (even those with reduced CD4+ T-cell count), HBV vaccination often induces inadequate antibody titer of limited duration unless the CD4+ T-cell count is high [33].

There are reasons to expect that many immunocompromised women and men will have an adequate response to HPV vaccination, including (i) HPV VLPs are highly immunogenic and (ii) HIV-positive women can mount a humoral immune response to HPV antigens. However, the effect of CD4+ level and HIV viral load on vaccine effectiveness is not known and, given the interaction of CD4+ T-cell count and HIV RNA level on risk of HPV infection, it will be important that any clinical trial of HPV VLP vaccination in HIV-positive patients is of sufficient size to stratify patients by combined CD4+ T-cell/HIV RNA strata to avoid a null bias, such as a failure to detect the effectiveness of HPV VLP vaccination in patients with a high CD4+ T-cell count because the subset with high HIV RNA levels was unresponsive.

Furthermore, studies should consider the use of a prolonged HPV vaccine schedule (including additional vaccinations) and/or the use of higher antigen levels in each inoculation, as has been done with HBV vaccination [33]. In HIV-positive patients, the use of HAART to improve responses to HPV VLP vaccination should also be assessed.

5.2. Prior exposure to HPV

It is likely that many, if not most, HIV-positive men and women have already been exposed to the HPV types present in current HPV VLP vaccines. Vaccination may benefit those women and men not yet exposed to these types, although for individuals already exposed to these types, the vaccine may be of more limited value (the relevant clinical trial data have not yet been published). Consistent with this, antibodies produced in response to natural infection were found...
to be largely ineffective in preventing subsequent HPV re-infection/reactivation [34]. However, these are complex issues. Observational studies have shown that HIV-positive women can mount a humoral immune response to natural infection with HPV and it is reasonable to assume that vaccination (which leads to titers well above those of natural infection) would induce high HPV antibody titers in at least a subset of HIV-positive patients. HPV antibodies should bind to the virus regardless of whether it is a first or a subsequent exposure, and therefore high antibody titers may offer some protection against re-infection or reactivation. Lastly, HPV VLPs can stimulate innate immunity, including activation of plasmacytoid dendritic cells [35], and HPV-VLP antibodies might elicit antibody-dependent cellular cytotoxicity.

5.3. Timing of acquisition of HPV and HIV infection

The effectiveness of HPV vaccination might vary with the timing of vaccination relative to time of HIV acquisition (Fig. 1), or other sources of immune suppression. Among children infected with HIV at the time of birth or as neonates, vaccination prior to sexual debut may prevent initial HPV-16 or -18 infection and CIN due to these types. Adolescents who acquire HIV at, or subsequent to, sexual debut, may derive less benefit because of the higher likelihood of prior exposure to the HPV types in the vaccine. As discussed above, the benefit of vaccination in reducing reactivation of these HPV types or incident CIN or AIN is not known. Similar considerations apply to older HIV-positive men and women. In general, HPV vaccination is likely to be more effective if initiated at a time when the patient is less immunosuppressed, either: (a) prior to an advanced stage of HIV/AIDS, (b) after initiation of a successful HAART regimen, (c) at an early rather than an advanced stage of a chronic disease, (d) prior to the initiation of transplant and/or iatrogenic immune suppression, or (e) at times of reduced iatrogenic immunosuppression in transplant recipients.

5.4. HPV types not included in current vaccines

Although HPV-16 remains a common and undiminished major cause of CIN-2/3 in HIV-positive women (see above), other oncogenic HPV types may play a larger role in cervical cancer among HIV-positive than among HIV-negative women. However, the only oncogenic HPV types included in the vaccines most likely to become commercially available in the near future are HPV-16 and -18.

5.5. Efficacy of HPV vaccines in preventing anal and oral cancer

The rationale for vaccination to reduce anal HPV infection and anal cancer is similar to that for cervical HPV infection and cervical cancer. In addition to the considerations described above, there are several specific issues relevant to anal HPV infection and disease. Studies have not yet been reported on the efficacy of HPV vaccination in men in general, or on efficacy in preventing anal HPV infection or AIN in either men or women. Theoretically, if the HPV vaccine is effective in preventing cervical HPV infection it may well also prevent anal HPV infection. However, this has not yet been demonstrated. While the relationship between local cervical antibody levels and vaccine efficacy is not well understood, it is also not known if antibody titers reach the same level in the anal canal as in the cervix or if they are as effective in preventing HPV entry into epithelial cells in the anal microenvironment. Some MSM have higher numbers of receptive anal intercourse partners than do women with vaginal intercourse partners, particularly after the age of 30 years, and exposure levels to HPV may be higher among these men. Although it is presumed that if the vaccine prevents anal HPV infection, it will also prevent incident AIN, but it has not yet been shown that treatment of AIN reduces the incidence of anal cancer. Thus, it is not known if reduction in the incidence of AIN due to vaccination will lead to reduced incidence of anal cancer. Among women dually infected with HPV in the
cervix and anus, the relative efficacy of HPV vaccination at these two sites is not known.

Many of the same issues described for vaccination to prevent anal HPV infection in HIV-positive men and women apply to oral HPV infection. Low titers of HPV-16-specific IgG antibodies have been detected in oral mucosal fluid of HIV-positive subjects [36,37], and low-titer IgA has been induced by mucosal immunization with HPV-16 VLP in human subjects [38]. Salivary IgG is largely derived from serum via transudation across the oral mucosa. Therefore, high serum IgG antibody titers induced by the HPV VLP vaccine may result in sufficient transudation of serum IgG into oral mucosal fluid to be protective against oral HPV infection. Unfortunately, as with anal HPV infection, none of the randomized, controlled trials of the bivalent or quadrivalent vaccines currently in development have incorporated analysis of the effect of vaccination on oral HPV infection. Analysis of oral cancer incidence trends in vaccinated populations may be the only means by which vaccine effectiveness to prevent oral cancer can be studied.

6. Conclusions

Overall, given the high rates of HPV infection and HPV-associated cancer in immunocompromised populations, there is sufficient rationale to consider HPV vaccination in these groups. However, vaccination strategies need to be based on the outcomes of clinical trials in these populations. Ideally, vaccine trials in immunocompromised women and men should concurrently assess cervical, anal, and oral HPV infection and disease. Penile and vulvar infection should be assessed as well. The association of HPV-16 with anal and oropharyngeal cancer provides an additional rationale for exploring HPV vaccination of men, beyond the goal of reducing transmission of HPV-16 to women.

Studies to demonstrate the immunogenicity in immunocompromised patients will be needed but are not sufficient to provide adequate information for making clinical decisions by physicians or policy decisions by regulators. Additional questions that should be addressed in future studies include: (1) Will the vaccine be safe in these populations? (2) Will the vaccine be effective in populations that already have a high prevalence of exposure to the HPV types in the vaccine? (3) Will the vaccine be effective in immunocompromised men and women against HPV types to which they have not yet been exposed, and will the efficacy of vaccination differ according to the cause of immunosuppression? (4) When should immunocompromised individuals be vaccinated? (5) What antigen concentrations and frequency of immunization should be used? (6) Will revaccination need to be considered? (7) Will the vaccine be equally effective in preventing cancers at all potentially infectable mucosal sites such as the cervix, anus, and oral cavity? and (8) Will the vaccine be cost-effective in immunocompromised men and women?

In the future a universal HPV vaccination strategy may render several of these considerations moot since, eventually, most women and men who become immunocompromised will already have been vaccinated. In this setting, the major question will be whether new onset immunosuppression affects titers and duration of neutralizing antibody or other immunologic factors related to HPV vaccine effectiveness among previously vaccinated women and men. Until that time, however, there are many reasons to be hopeful that a preventive HPV VLP vaccine will be at least partially effective in reducing the risk of HPV-associated cervical, anal, and oral cancer in those who are immunocompromised at the time of vaccination. It is hoped that studies to address these issues will be initiated in the near future.

Disclosed potential conflicts of interest

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