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## Human Papillomavirus-Related Disease in Men: Not Just a Women's Issue

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### Abstract

The most common cause of mortality related to human papillomavirus (HPV) infection is cervical cancer. However, male HPV infection is also an important concern, both for the disease burden in men and for the risk of transmission to women. HPV is associated with a variety of cancers in men, including anal cancer and a subset of penile and oral cancers. The incidence of anal and oral cancers related to HPV is increasing in the general population and is growing even faster among individuals who are immunocompromised due to HIV infection. Penile HPV infection is very common among heterosexual men and remains high throughout a wide range of ages. Likewise, anal HPV infection and anal intraepithelial neoplasia are very common throughout a wide range of ages in both HIV-negative and HIV-positive men who have sex with men. Other HPV-related diseases of clinical importance in men include *condylomata acuminata* (genital warts) and recurrent respiratory papillomatosis. The quadrivalent HPV vaccine has been shown to be highly efficacious in the prevention of genital warts in women and precancerous lesions of the cervix, vulva, and vagina. In addition, recent interim data have shown that the quadrivalent HPV vaccine is highly effective in reducing external genital lesions in young men. Although the protective efficacy of HPV vaccination in males has not yet been fully established—pending the outcome of public policy discussions and cost-efficacy studies—there may be a strong rationale for vaccinating boys, similar to girls, at an early age when they have had limited or no prior sexual activity.

### Keywords

human papillomavirus; anal cancer; penile cancer; vaccination

### Introduction

Human papillomavirus (HPV) is one of the most common sexually transmitted infections. The most important clinical consequence of HPV infection is cervical cancer. Cervical cancer, with the death of approximately 250,000 women each year worldwide, remains one of the leading causes of cancer-related mortality in women [1]. The advent of screening to identify and treat cervical cancer precursor lesions, cervical intraepithelial neoplasia (CIN), has led to a substantial reduction in the incidence of cervical cancer in those countries where routine

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screening is in place. Conversely, most cervical cancer-related mortality occurs in countries where there is no routine cervical screening.

In countries with limited screening, mortality from cervical cancer far exceeds that of HPV-related disease in men. However, in the developed world, the number of HPV-related cancers in men, including penile, oral, and anal cancer, is similar to that of cervical cancer in women [2–5]. Additional morbidity due to HPV in men results from development of condylomata acuminata (genital warts) [6–10], and since HPV is sexually transmitted, HPV infection in men leads to substantial morbidity and mortality in women. Finally, recent data suggest that HPV infection in men may increase the risk of acquiring human immunodeficiency virus (HIV) infection [11]. Taken together, it is clear that HPV infection in men is a serious clinical issue. Compared with cervical HPV infection, relatively little is known about the epidemiology of HPV infection in men. With the advent of highly efficacious vaccines to prevent the most common HPV types in cervical cancer—HPV 16 and HPV 18 [12–15]—and the possibility that the vaccines may also be useful in preventing HPV infection in men, an understanding of HPV infection and associated disease in men has assumed increasing importance. This review summarizes some of the current knowledge about HPV infection and its consequences in men.

### Penile Disease

Penile cancer is a heterogeneous disease with respect to HPV infection, with the association with penile infection dependent on the histology [16,17]. Squamous cell cancers of the penis have a low association with HPV, whereas warty/basaloid cancers are strongly associated with HPV. Depending on the proportion of samples that are squamous vs warty/basaloid in any one report, the proportion of penile cancers associated with HPV is variable.

The incidence of penile cancer is low relative to cervical cancer, and is particularly low in developed countries [2,18]. In part this may reflect different rates of circumcision, which is known to be a protective factor for penile cancer [19–23]. In populations with low rates of circumcision, phimosis (tightness of the foreskin that prevents the retraction of the foreskin over the glans), and sexual behaviors leading to increased risk for HPV are the primary risk factors [5,22,24,25].

Until the last few years relatively little was known about the epidemiology of penile HPV infection, in part due to the lack of standardization of penile cell sampling techniques for HPV DNA detection. Several techniques have now been published and have been used to better define the prevalence, incidence, and clearance of penile HPV infection [26,27].

Notably, most of these studies do not describe HPV-associated disease of the penis using the most sensitive techniques, namely visualization with acetic acid and magnification, followed by biopsy confirmation. Thus, the epidemiology of penile disease, its relationship to HPV infection, and the role of penile disease in transmission of HPV to sexual partners remains poorly understood [28].

In one recent study conducted in Brazil, Mexico, and the United States, the prevalence of anogenital HPV infection, defined as on the penis, scrotum, and perianal and intra-anal areas, was remarkably constant as a function of age [29]; however, this finding stands in contrast to the prevalence of cervical HPV infection in women, which typically declines substantially after the age of 30 years, and in some parts of the world shows a small increase again after the age of 50 years. The prevalence of anogenital HPV infection in these men was high at approximately 60%, a prevalence that is also remarkably similar to earlier reports of the age-related prevalence of intra-anal HPV infection in men who have sex with men (MSM) [30] (Figure 1). The most common site of HPV infection was the penile shaft, followed by the corona and scrotum [3]. Despite that the likelihood that few of the men reported having had

sex with men, approximately 20% of the men had anal HPV infection. Other studies of penile HPV infection from outside the United States have shown a lower prevalence of infection. This may reflect demographic and behavioral differences among these populations, as well as differences in sampling techniques and HPV testing methodology [32–36].

In a study of penile HPV infection in the United States, the incidence rate of HPV infection was 29% within 12 months, while the median time to clearance was 5.9 months [37]. Thus, the incidence and clearance of penile HPV infection was similar to reported incidence and clearance of cervical HPV infection in women. Risk factors for acquisition of penile HPV have been shown to include a higher number of sex partners [32], lack of circumcision [20,21,38], having a sexual partner with CIN [39], a history of other sexually transmitted infections [38], and a history of smoking [40].

### Oral Disease

Penile cancer and oral cancer are similarly heterogeneous with respect to their association with HPV [41,42]. Most oral cancers are associated with alcohol and tobacco use; however, a subset of oral cancers is associated with HPV and the sexual behaviors associated with HPV acquisition. HPV-associated cancers typically occur in the oropharynx, particularly in the tonsils. Their incidence is increasing in the general population in contrast to oral cancers associated with tobacco and alcohol use, which are declining. Fortunately, the prognosis for HPV-associated cancers has been shown to be better in comparison with HPV-negative cancers [43].

Like penile disease, the natural history of putative oral cancer precursors is poorly understood; more is understood about oral HPV infection itself. Studies show that oral HPV infection is much less common in adults than anogenital HPV infection [44], but that risk factors associated with sexual behavior are associated with oral HPV detection [45].

Another serious consequence of oral HPV infection is recurrent respiratory papillomatosis (RRP) [16,46,47], which is a rare disease with substantial morbidity that occurs in a bimodal pattern. The first peak occurs in young children who acquire HPV 6 or 11 primarily through perinatal transmission. Male and female children are affected with equal frequency. HPV infection occurs in the larynx and elsewhere in the upper respiratory tract and the resulting warts lead to morbidity through obstruction of the narrow-diameter respiratory passages. Multiple surgeries are often required to relieve the obstruction. A second peak of RRP occurs in young adulthood, and HPV acquisition in this population is associated with sexual behaviors, particularly oral sex. In rare instances, laryngeal HPV infection may lead to laryngeal cancer [16].

### Anal Disease

Compared with cervical cancer, anal cancer is a rare disease in the general population. However, its incidence is increasing in the general population among both men and women at a rate of approximately 2% per year [48,49]. Unlike cervical cancer, in which HPV 16 accounts for approximately 50% of cases, HPV 16 may lead to more than 70% of anal cancer cases [50,51]. More common in women than in men within the general population, the annual incidence of anal cancer is approximately 1 per 100,000 [16,48,49]. While anal cancer is relatively uncommon in the general population, it is strikingly common in particular at-risk groups, notably MSM with a history of receptive anal intercourse and immunocompromised individuals, particularly those with HIV [52–55]. Among MSM the incidence of anal cancer was estimated to be as high as 37 per 100,000 prior to the onset of the HIV epidemic [56]. This incidence is not much different from that of cervical cancer in the general population of women in the United States prior to the introduction of routine cervical cytology screening [57]. Men

and women with a history of solid-organ transplantation have also been shown to be at increased risk of anal cancer compared with the general population [58], and it is therefore not surprising that those with HIV-associated immunosuppression were shown to be at increased risk.

Consistent with the high incidence of anal cancer among MSM, many studies have demonstrated that anal HPV infection is very common among both HIV-negative and HIV-positive MSM [59,60]. One study examining the age-related prevalence of anal HPV infection among sexually active HIV-negative MSM showed a consistent HPV prevalence of approximately 60% across all age groups, which is similar to the penile HPV infection data previously described [30] (Figure 2). HIV-positive MSM are at even higher risk of anal HPV infection, with nearly all having HPV, often with multiple HPV types [61,62]. This was true across the entire CD4+ spectrum [61].

Anal HPV infection and anal intraepithelial neoplasia (AIN) are both very common among MSM [63–65]. Low-grade AIN (LGAIN), including genital warts and AIN 1, is not considered to be a cancer precursor in contrast to high-grade AIN (HGAIN), comprised of AIN 2 and AIN 3, which has been demonstrated to progress to anal cancer [66]. The prevalence of AIN among sexually active HIV-negative MSM in both convenience cohorts and population-based studies was shown to be high, with a range between 18% to 23% across various age groups [60]. The prevalence of both LGAIN and HGAIN was even higher among HIV-positive MSM [62]. Unlike anal HPV infection, prior to the advent of highly active antiretroviral therapy (HAART), there was a clear association between a lower CD4+ level and increased prevalence and incidence of HGAIN [60,61]. Among HIV-positive MSM, approximately half developed HGAIN over a 4-year follow-up period [67,68].

Although the incidence of anal cancer was high among HIV-positive MSM prior to HAART, the exceptionally high prevalence of oncogenic HPV infection and HGAIN begged the question as to why the incidence of anal cancer wasn't even higher. The best explanation is competing mortality: HGAIN likely takes many years—perhaps even decades—to progress to anal cancer and HIV-positive individuals were dying of other HIV-related causes, prior to progression to anal cancer.

With the availability of HAART, it was hoped that the resulting immune reconstitution and increase in CD4+ level would lead to a reduced incidence of HGAIN and anal cancer. Conversely, it was recognized that the improved survival associated with HAART might also pose a challenge for AIN. If anal HPV infection and AIN do not resolve with HAART, then it was predicted that in the setting where HGAIN is not routinely sought and treated as is currently the case, then the improved survival may allow for more time for HGAIN to progress to cancer, leading to an increased incidence of anal cancer rather than a decreased incidence.

HAART was introduced for widespread use in 1996. Studies performed since the introduction of HAART show that the prevalence and incidence of HGAIN is even higher among HIV-positive MSM than reported in earlier studies, with both convenience cohorts and population-based studies showing a prevalence of 43% to 52% [62,65,68]. Although some of this may reflect ascertainment bias due to improved diagnostic techniques, it is clear that HAART is not having a substantial beneficial effect on anal HPV infection and AIN [69].

Consistent with these findings, 3 recent studies have shown that the incidence of anal cancer among HIV-positive MSM has continued to increase since the introduction of HAART. D'Souza et al showed an incidence of 137 per 100,000 person-years among HIV-positive MSM since 1996 among men participating in the Multicenter AIDS Cohort Study [53]. Piketty et al showed an incidence of anal cancer from a registry in France of 75 per 100,000 person-years among HIV-positive MSM from 1999 to 2004 [52]. Similarly, Patel et al showed an incidence of 78 per 100,000 person-years among HIV-positive MSM from a Surveillance, Epidemiology,

and End Results Program-HIV registry match in the United States since from 2000 to 2003 [54]. Notably, the incidence of anal cancer reported in these studies exceeds the highest reported incidence of cervical cancer anywhere in the world.

Anal HPV infection and HGAIN are not only problematic in men. The prevalence of anal HPV infection in HIV-positive women has been demonstrated to be even higher than that of cervical HPV infection [70]. HIV-negative women, including those at both low-and high-risk for HIV infection, in several studies were shown to have as much or more anal HPV infection than cervical HPV infection [71–73] (Figure 3). Consistent with these results, one recent study demonstrated that AIN was as common as CIN in these women [74]. Prior to the advent of HAART, the incidence of anal cancer was 6.8-fold higher among HIV-positive women than the general population of women [55]; no data have been published yet on the incidence of anal cancer in HIV-positive women since the introduction of HAART.

Taken together, these data indicate that certain populations are at an increased risk of anal cancer compared with the general population. These include MSM, HIV-positive men whether or not they report having had sex with men, men with immunosuppression due to organ transplantation, and HIV-positive women. HPV infection also appears to be common in the general population of healthy women, but clearly the incidence of cancer on a per-infection basis in this group is lower in the anal canal than it is in the cervix.

Another important source of HPV-associated disease burden in men is condylomata acuminata, most commonly found on the penis or the anus [6,75]. These lesions are usually due to HPV 6 or HPV 11, which are rarely carcinogenic. However, genital warts are associated with psychosocial stigma, depression, and lower quality of life [7,9]. Treatment of genital warts often requires multiple treatments as well as multiple visits to a health care provider. Treatment may be costly and warts may recur. The incidence of genital warts is high in the general population, with approximately 1 million new cases annually; the incidence of warts is increasing every year and, consequently, the economic burden is high.

Anal condyloma has also been shown to be associated with anal cancer [76]. Although genital warts are usually caused by non-oncogenic HPV 6 or HPV 11, the increased risk of cancer is therefore likely to be a marker for behaviors leading to exposure to the oncogenic HPV types associated with anal cancer. Therefore, men with perianal condyloma may be at increased risk of anal cancer, notwithstanding their association with any of the other above-named risk groups.

### **Transmission of HPV to Women**

In addition to the disease burden associated with HPV infection in men—anogenital cancer, oral cancer, RRP, and genital warts—another major clinical consequence of male HPV infection is the potential to infect women, where it may lead to substantial morbidity and mortality. Sexual transmission of HPV is a well-known fact, and there are now several studies showing the influence of male HPV infection on HPV infection and disease in women [20, 21,77,78]. Penile lesions are frequently found in sexual partners of women with CIN [35,39]. Regression of penile lesions is significantly slower in men whose partners are infected with the same HPV type [79]. There is also evidence supporting the role of men in cervical cancer. Studies from various countries have demonstrated that husbands of women with cervical cancer or cervical carcinoma in situ have a higher prevalence of HPV than husbands of control women [80]. The risk of cervical cancer was shown to be increased due to several behaviors engaged in by male partners, including multiple sex partners [81–83] and contact with prostitutes [82].

## The Case for Male HPV Vaccination

In 2006 the US Food and Drug Administration (FDA) approved the quadrivalent HPV vaccine to prevent initial infection against HPV 6, 11, 16, and 18 in women [12,13]. The quadrivalent vaccine has been approved in several other countries as well. The bivalent vaccine to prevent initial infection with HPV 16 and 18 has been approved in several countries, including the United States as of October 2009 [15]. Both vaccines have been shown to be highly efficacious in preventing HPV 16 and 18, which together are responsible for approximately 70% of cervical cancers, [84] and the quadrivalent vaccine has been shown to be efficacious in preventing HPV 6 and 11, which causes approximately 90% of genital warts [6]. Both vaccines have also been shown to be highly efficacious in preventing AIN and condylomata acuminata due to these types, and it is expected that they will ultimately reduce the incidence of cervical and vulvovaginal cancers due to these HPV types in women.

A Phase III study has recently been completed to examine the safety and efficacy of the quadrivalent vaccine containing HPV 6, 11, 16, and 18 in the prevention of external genital infection and disease associated with these types in heterosexual boys and men aged 16 to 23 years and MSM aged 16 to 26 years [85,86]. Previous bridging studies have demonstrated that boys mount high antibody titers in response to both the quadrivalent and bivalent vaccines [87,88], and preliminary data from the Phase III study show that the quadrivalent vaccine is safe and effective in preventing infection with all 4 vaccine types, as well as external genital lesions associated with these types among men naive to those types at baseline [85,86]. The preliminary data show an 86% reduction in persistent infection in the external genital area in heterosexual boys and men and MSM combined. The reduction in persistent infection is fairly consistent across all HPV types. The study shows a 90% efficacy to reduce the incidence of external genital lesions, again with a fairly consistent efficacy across various HPV types [85, 86]. This is the first study to examine the efficacy of the quadrivalent vaccine in boys and these encouraging results suggest that the vaccine may work as well or nearly as well in boys as in girls. Almost all of the external genital lesions found in the study population were demonstrated histologically to be warts and there were few cases of intraepithelial neoplasia in either the vaccine or the placebo group. With indications for the vaccine based on disease prevention rather than prevention of HPV infection per se, in October 2009, the FDA approved the use of quadrivalent vaccine in boys aged 9 to 26 years for the prevention of genital warts. Subsequently the Advisory Committee on Immunization Practices supported the permissive use of the quadrivalent vaccine for this indication and recommended that funding be provided for this purpose through the Vaccines For Children program. Additional data are expected to be forthcoming on the efficacy of quadrivalent vaccine to prevent AIN in the study subpopulation of men who have sex with men.

Because these vaccines are so effective in preventing infection with the vaccine HPV types in women naive to those types, and are probably effective in boys as well, what are the additional benefits of vaccinating boys and men? These benefits may be divided into 2 categories: reduction of HPV-associated disease burden in boys and men, and prevention of HPV transmission to women.

The information presented in this article highlights the ubiquitous nature of anogenital HPV infection in boys and men, and the high disease burden associated with genital warts. Among MSM and immunosuppressed men and women, anal HPV infection leads to a high disease burden of warts, AIN, and anal cancer. Male vaccination against HPV has the potential to lead to a substantial reduction in the burden of these diseases. In addition, there is also the possibility, as yet unproven, that both the quadrivalent and bivalent vaccines may protect against development of HPV 16- or HPV 18-associated oral cancers, and that the quadrivalent vaccine may protect against other HPV 6- or 11-associated diseases such as RRP.

If all susceptible girls and women were vaccinated, then this might provide protection to their male sexual partners in the form of herd immunity. There are, however, 3 problems with relying on female vaccination to protect men from the burden of HPV-associated disease. First, while reduction of HPV transmission by vaccinated individuals to their sexual partners is a strong possibility, it has never been directly demonstrated. Second, not all susceptible women in the United States are being vaccinated against HPV and the degree of herd immunity and protection in men will likely vary inversely with the proportion of vaccinated women. Third, even if there was nearly universal vaccination of women, this would have only a limited impact on sexual transmission among MSM. Consequently, particularly in settings where only a fraction of eligible women are being vaccinated, the optimal way to protect men would be to vaccinate them directly.

In addition to protecting men against HPV-associated disease, male vaccination has the potential to protect women through herd immunity for the same reason that female vaccination may protect men. As with HPV transmission from women to men, it has not yet been proven that male vaccination would reduce transmission of HPV from men to women. The degree to which male vaccination would be useful in this context and the cost-effectiveness of male vaccination will vary inversely with the proportion of vaccinated women, as well as the proportion of men who are vaccinated [89,90,91]. A recent study by Kim et al indicated that vaccinating 12-year-old boys with the quadrivalent vaccine would not be cost-effective. However this study assumed that 75% of eligible women would be vaccinated, a figure that is substantially higher than current rates of vaccine coverage in the U.S. Undoubtedly future studies will more accurately estimate the cost effectiveness of male vaccination as new, real-world data become available to refine the various models [91].

Ultimately, whether or not there will be routine male HPV vaccination will depend on a number of factors, including an evaluation of the final safety and efficacy data in men; insurance program coverage; implementation of a vaccine schedule that is conducive to the vaccination of boys; and the outcomes of cost-effectiveness analyses. These cost-effectiveness analyses should include prevention of HPV-associated diseases in men for which there is already proof of efficacy as well as for diseases for which there may well be protection, but for which there is no current evidence. The models should also include an assessment of herd immunity, assuming a range of reduction of sexual transmission between sexual partners that accounts for vaccinations of varying proportions of eligible girls and boys.

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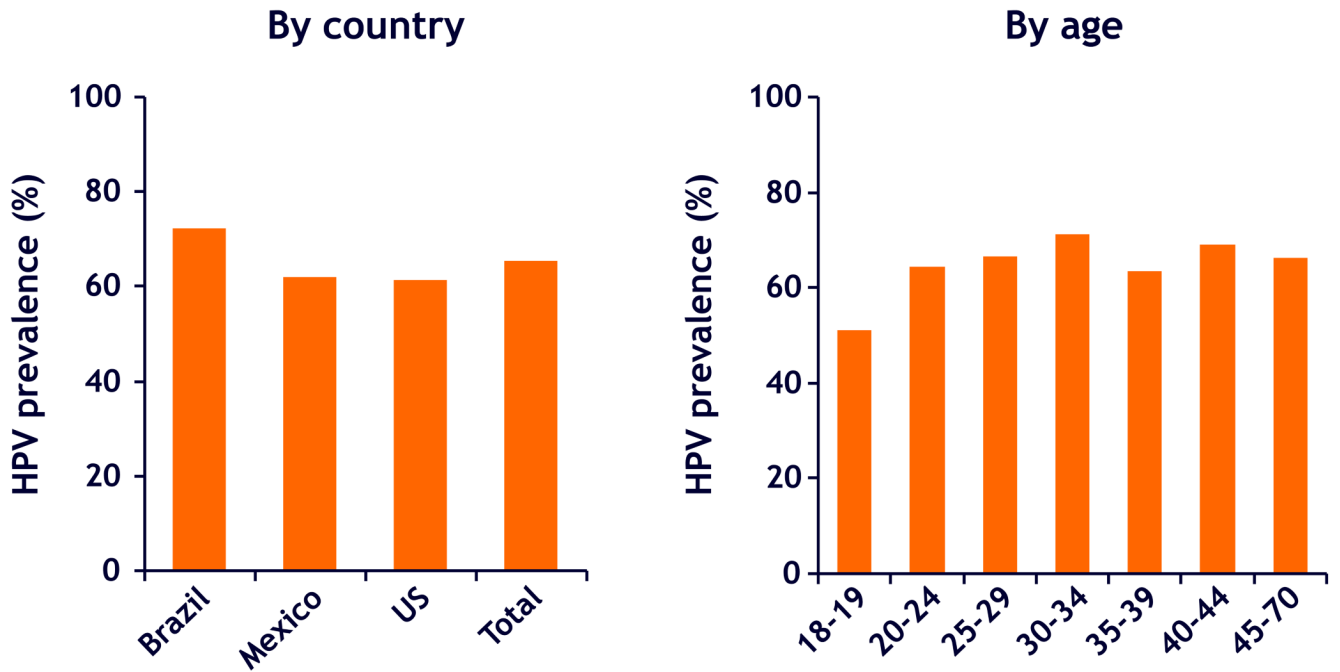


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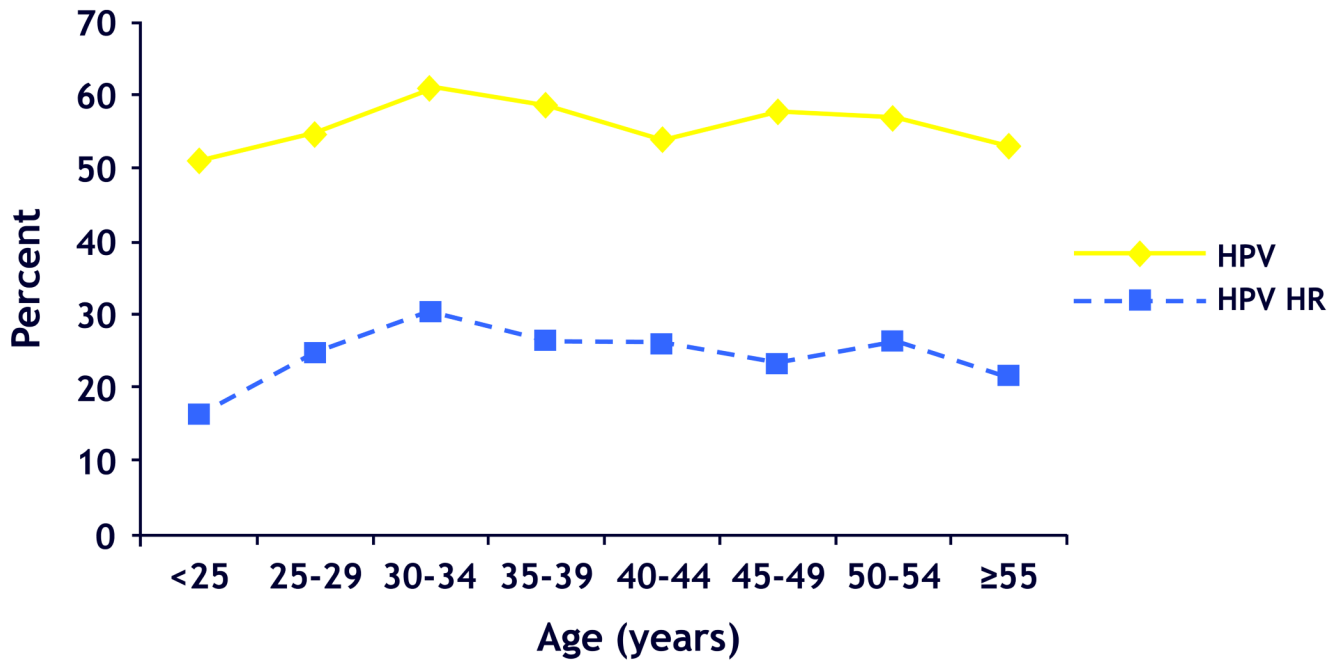
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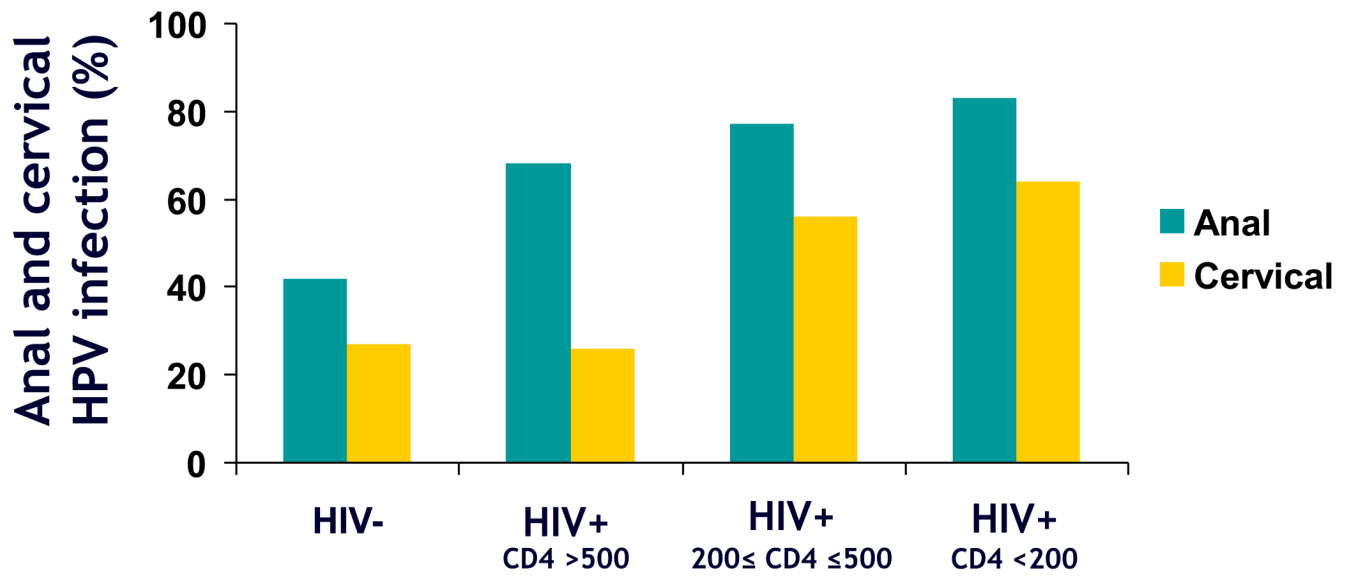


**Figure 1.**  
 Prevalence of Genital HPV Infection in Males  
 Giuliano AR et al. *Cancer Epidemiol Biomarkers Prev.* 2008;17:2036–2043.



HPV HR=HPV high-risk.

**Figure 2.**  
 Anal HPV Infection by Age Group in Sexually Active HIV-Negative MSM  
 Chin-Hong PV et al. *J Infect Dis.* 2004;190:2070–2076.



**Figure 3.**  
Anal and Cervical HPV Infections Are Common in HIV-Positive and HIV-Negative Women  
Palefsky JM et al. *J Infect Dis.* 2001;183:383–391.