REVIEW
Human papillomavirus infection and disease in men: Impact of HIV

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There is growing evidence of a significant burden of human papillomavirus (HPV) infection and associated disease in men. High rates of HPV infection have been observed in men from sub-Saharan Africa where HIV prevalence is high. HIV infection increases HPV prevalence, incidence and persistence and is strongly associated with the development of anogenital warts and anal, penile and head and neck cancers in men. Despite increasing access to antiretroviral therapy, there appears to be little benefit in preventing the development of these cancers in HIV-positive men, making prevention of infection a priority. New prevention options that are being introduced in many African countries include male circumcision and HPV vaccination. However, more data are needed on the burden of HPV disease in men before boys are included in HPV vaccination programmes.

Human papillomavirus (HPV) is a common sexually transmitted infection (STI) affecting both men and women.[1] HPV infections can be classified as either low- (LR) or high-risk (HR).[2] HR-HPV infections have been associated with cancer of the anogenital and oropharyngeal tissues. While the majority of HPV infections are transient and clear spontaneously, persistent infection with HR-HPV is associated with the development of pre-neoplastic and neoplastic lesions in these areas (Fig. 1). While much is known about the natural history of HPV infection in cervical cancer in women, less is known about the development of HPV-associated disease in men. Emerging evidence points to a significant role for HIV infection in promoting HPV prevalence, incidence and persistence. This review provides an update on current evidence regarding the epidemiology of HPV infection and disease in men, the effects of HIV on HPV infection and disease in men in sub-Saharan Africa (SSA), and the prospects for prevention in this setting.

Global burden of HPV

HPV infection is ubiquitous in men. A systematic review of 62 studies using reliable methods of HPV DNA detection and conducted prior to 2009, representing 14 800 men in 23 countries, showed that anogenital HPV DNA prevalence is generally high in sexually active men. The review highlighted considerable variation in estimates by region, from 1% to 84% in LR men, to 2% to 93% in HR men.[3] Compared with studies in women, peak prevalence spanned a wide range of ages, suggesting that men have the potential for longer-term persistence of infection or higher rates of re-infection.[3] Type-specific HPV seroprevalence studies are better indicators of lifetime exposure to HPV infection, although they may underestimate cumulative HPV exposure, given that not all infections lead to seroconversion.[4] Recent population-based studies have estimated the prevalence of antibodies to vaccine-preventable HPV types 6, 11, 16 and 18. Among men aged 14 - 59 years in the USA, 12.2% of men were seropositive for any vaccine type, with a peak prevalence of 18% among men aged 50 - 59 years.[5] In a similar population-based study in Australia, peak prevalence of any vaccine type was 31.5% among men aged 40 - 49 years;[6] and a study from the Netherlands estimated that the seroprevalence of any HR-HPV in men aged ≥14 years was 20%.[7] There is some evidence that seroprevalence appears to be rising as a result of changes in sexual behaviour and earlier age of sexual debut. In a related study from the Netherlands comparing serosurveillance rates of HR-HPV in the periods 1995 - 1996 and 2006 - 2007, overall HR-HPV seroprevalence rates were significantly higher in the later survey, compared with the earlier survey across all age groups.[8]

Burden of infection in SSA

A recent global review of 117 studies worldwide suggests that the seroprevalence of HPV is even higher in SSA, although data on men in SSA are sparse.[4] In a small study of Tanzanian genital ulcer disease (GUD) patients, pregnant women and male blood donors, the prevalence of antibodies to HR-HPV ranged from 77% in male GUD patients to 15% in male blood donors. In this study, the prevalence of antibodies to HPV types 16, 18, 51 and 52 was considerably higher in HIV-positive patients with GUD.[9]

Although data on anogenital HPV DNA prevalence in men in SSA are also limited,[3] overall reported prevalences in men are high, ranging from 19% to 78%.[10-15] In most, but not all studies, the most prevalent type was HPV-16.[15] The observed heterogeneity in estimates can be attributed to differences in age distribution, sexual behaviour and HIV prevalence within the different populations. Emerging data
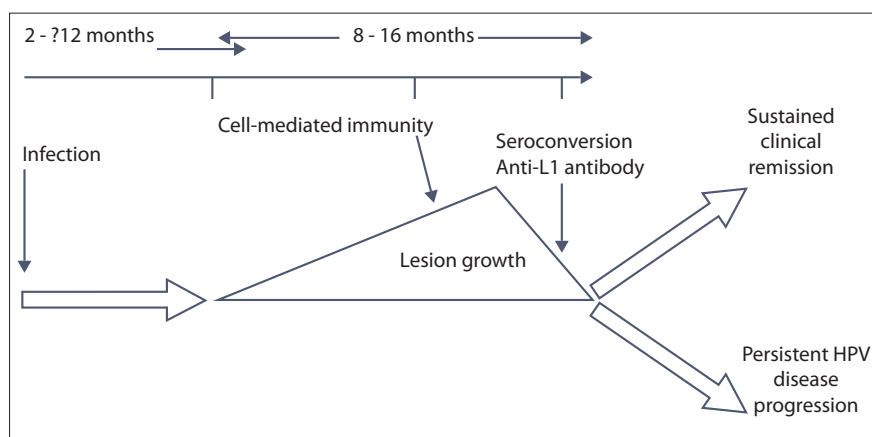
Fig. 1. Natural course of genital HR-HPV infection (source: Stanley[82]).

suggest that the incidence of HR anogenital HPV infection in men is also high, ranging from 35.7/100 person years in South African men to 40/100 person-years in East African men participating in male circumcision (MC) trials.[16-18] In both settings, the risk of HPV acquisition was doubled in HIV-positive men. These incidence rates are much higher than those previously observed elsewhere.[19,20]

Factors associated with HPV infection

HPV seroprevalence rates are consistently lower in men than in women,[6,21,22] with men also producing lower antibody titres than women.[23] There are several plausible biological explanations for differences in antibody responses between men and women. Men may experience a higher frequency of transient infections, a lower viral load, or produce less robust immunological responses than women.[24] It has been argued that the site of infection and/or type of epithelium influence antibody responses, with men experiencing a higher proportion of infections in more keratinised tissues (e.g. penile shaft) than women (e.g. anal canal or cervix). Thicker, more keratinised epithelium may present a barrier to infection, and if infected, may be less likely than mucosal surfaces to induce an immune response, given the relative distance from draining lymphatics and lymph nodes.[23,25] Recent data from a study comparing type-specific HPV antibody prevalence with the corresponding prevalence of HPV DNA detected in the external genitalia and anal canal in heterosexual men and men who have sex with men (MSM) support this notion. Higher HPV-6 and -16 seroprevalence rates were observed in men that had a same HPV-type infection in the anal canal, than in those with the same HPV-type infection in the external genitalia only. Higher seroprevalence rates were also observed in MSM compared with heterosexual men.[26]

The association between HPV infection and age is somewhat inconsistent, with fairly flat prevalence curves reported in populations where HIV prevalence is relatively low.[3,27] Data emerging from Africa, present a similarly mixed picture. A study among Kenyan fishermen showed a lower risk for HPV infection in older age groups,[10] while data from Kenyan men participating in an MC trial showed little variation in prevalence with age.[28] A more recent study in men from Tanzania demonstrated an association between increasing age and HPV prevalence, but that this association was driven by HIV-positive men.[15] Two recent incidence studies confirmed that increasing age is associated with a lower risk for HPV infection.[16,17] Combined, these data tend to suggest that the association between HPV infection and age in men in SSA is related to patterns of sexual activity, but confounded by HIV status, which may promote the persistence of HPV infection.

Sexual behaviour is an important risk factor for anogenital HPV infection. More recent publications have highlighted the importance of age of sexual debut,[8] marital status,[29] high number of lifetime sexual partners,[5,30,31] number of recent sexual partners,[30] longer history of sexual activity,[30] route of exposure,[26,30,32] and having sex with men[32-34] as risk factors for anogenital HPV infection. Similar observations about sexual risk behaviour and an association with HPV have been made in studies of men in SSA.[10,17,28] While the data on the protective effects of condoms are somewhat mixed,[35] evidence from African studies in men show a reduced risk of genital HPV infection associated with

condom use.[10,28,36,37] Evidence from randomised controlled trials (RCTs) of MC has conclusively demonstrated the protective benefits of MC in reducing the risk of HPV prevalence and incidence.[17,36,38,39] Related findings from the trial in Kenya have highlighted less frequent bathing as a risk factor for HPV infection, which may be associated with poor genital hygiene in uncircumcised men.[18,28]

STIs are independently associated with the risk of HPV infection, particularly chlamydia,[19,30] herpes simplex virus (HSV)-2,[34] and hepatitis B.[40] While they may share a common mode of transmission, STIs are thought to increase the risk of HPV infection by facilitating access to the basal epithelium through micro-abrasions in the skin.[35] Recent reports on male populations in Africa point to a higher risk of penile HPV in men co-infected with laboratory-diagnosed *Chlamydia trachomatis* or *Neisseria gonorrhoeae*, and those who are HSV-2-seropositive.[28] Interestingly, HR-HPV clearance was recently shown to shown to be higher in HIV-negative men co-infected with syphilis or HSV-2, suggesting that other genital tract infections may also create an inflammatory cytokine milieu that may facilitate the clearance of HPV.[17]

HIV is a strong risk factor for HPV infection in men. While studies of anal HPV infection in MSM from Europe and the Americas first identified an increased risk for infection in HIV-positive men,[24] there is now a growing body of evidence from studies of men in SSA that shows that prevalent and incident anogenital HPV infection is more common in HIV-positive men.[15,16,37] Multiple infections, particularly with HR-HPV, are more common in HIV-positive men.[13,41] Prevalence of infection increases with declining CD4+ count.[42] Partner HIV status has also been shown to increase the risk of HPV detection in men.[14,43]

Anogenital warts

Anogenital warts (AGWs) are the most common clinical manifestation of HPV infection.[44] Caused mainly by infection with HPV-6 and -11,[45] they are highly infectious. An estimated 65% of people whose sexual partner has genital warts will develop warts themselves.[46] The estimated incubation period from HPV infection to genital wart development is 2 weeks - 8 months.[47] While approximately 20 - 30% of genital warts will spontaneously regress,[48] recurrence is common, resulting in significant psychological morbidity and high medical costs for repeated treatment. These costs are not insignificant when compared

with costs for treatment of cervical cancer in women.[49] Two recent reviews estimated the prevalence and incidence of AGWs in the general adult population worldwide[45] and in SSA,[50] respectively. Worldwide, the overall prevalence of AGWs, based on genital examinations, ranged from 0.2% to 5.1%, with higher prevalence rates observed in males. Data suggest that prevalence has increased in recent decades, possibly as a result of changes in sexual behaviour.

Studies in male populations in SSA suggest much higher prevalence rates than in high-income countries, possibly as a result of higher HIV prevalence rates. Highest rates of 4.8 - 12.2% have been observed in HR men from Central and South Africa, a region of high HIV prevalence. Lack of circumcision and HIV infection have been identified as risk factors for AGWs in men.[12] Importantly, HIV-positive men with AGWs may also be at risk for infection with HR-HPV. In a small study in Johannesburg among HIV-positive men with penile warts, 85% were found to have HR-HPV as well. HPV-16 and -18 were most frequently detected.[41] These high rates of HR-HPV detection in men with HIV suggest that they are at significant risk for the future development of pre-neoplastic and neoplastic lesions, emphasising the importance of targeting screening programmes for HIV-positive men with AGWs.

Anal cancer

While relatively uncommon, the incidence of anal cancer in men appears to be rising.[51] A systematic review examined these trends, and found that age-adjusted incidence rates for anal cancer have increased in several high-income countries, with HPV infection identified as the most important associated aetiological factor.[52] Besides increasing age, smoking, receptive anal intercourse and HIV infection were the most important risk factors for anal cancer, with the highest incidence rates observed in HIV-positive MSM. While anal cancer incidence is highest in HIV-positive MSM, it should be noted that receptive anal intercourse is not a prerequisite for anal HPV infection, pre-cancer lesions or anal cancer. Piketty et al.[53] demonstrated high rates of anal infection and squamous intraepithelial lesions in HIV-positive men with no previous history of anal intercourse – an observation made subsequently in other studies.[54] In such instances, anal HPV infection is thought be transferred to the anal canal through transiently infected fingers or toys, as well as by shedding from other infected genital sites.

Anal cancer is considered to be biologically similar to cervical cancer. Like cervical cancer, it is thought to be preceded by a spectrum of intraepithelial changes and anal intraepithelial neoplasia (AIN), which can be graded similarly to cervical cancer. While there is strong supportive evidence that high-grade AIN is a precursor to invasive cancer, there is no consensus regarding the prevalence or significance of AIN, nor on the rate of AIN progression to cancer. Almost all of the natural history data come from studies in MSM, with few data on heterosexual, HIV-negative or African populations. A recent meta-analysis of anal HPV and associated lesions in MSM found that HIV-positive men were consistently more likely to be infected with HPV, to have associated lesions, and to have higher rates of anal cancer, although the excess in HIV-positive men was smallest for high-grade AIN, and was not statistically significant for that category. While there were no data on progression rates of AIN to cancer, estimates from this analysis suggest that rates of progression are significantly lower than those observed in cervical cancer.[55] Despite significant heterogeneity in the data, and a lack of prospective data, it remains plausible that high-grade AIN lesions regress more frequently than high-grade cervical lesions.[56] While the prevention of anal cancers in high-risk HIV-positive men is a priority, these findings raise doubts about the utility of anal cancer screening programmes at present. Until further evidence of benefit for screening in terms of reductions in anal cancer incidence and mortality become available, anal cancer screening programmes for men are likely to be controversial.

Despite immune reconstitution associated with highly active antiretroviral therapy (HAART), there appears to be little evidence that this therapy has a preventive effect on the development of anal cancer. The recent meta-analysis and other analyses of temporal trends in anal cancer incidence have highlighted the continuing high incidence of anal cancer, despite the widespread introduction of HAART.[55,57,58] These data suggest that prolonged survival afforded by HAART initiation may allow more time for AIN to progress to cancer, thus leading to higher anal cancer rates.

Penile cancer

Penile cancers are relatively rare. In 2008, of the estimated 22 000 new penile cancer cases, half were attributable to HPV, with much higher rates observed in regions with a low human development index.[59] Data from Zimbabwe suggest that southern Africa has higher incidence rates,[60] and a recently published report of HPV detection in cancerous and pre-cancerous penile lesions from men in South Africa demonstrated multiple HPV infections, with high rates of HPV-16.[61] Risk factors for penile cancer include: a lack of MC; phimosis and/or poor genital hygiene; AGWs; and HIV infection. HIV-positive men have an eight-fold increased risk of penile cancer, which may be associated with higher HPV infection rates.[62] Other risk factors for penile cancer that have been reported include current smoking, early age of first sexual intercourse, high lifetime number of female sexual partners, lack of condom use, chronic inflammatory conditions including balanitis and lichen sclerosus, and treatment with ultraviolet photochemotherapy for psoriasis.[63]

Head and neck squamous cell carcinomas

Head and neck cancer commonly refers to squamous cell carcinomas (SCCs) arising in the upper aerodigestive tract (oral cavity, nasopharynx, hypopharynx and larynx). Traditionally, most head and neck cancers were associated with tobacco and alcohol exposures and presented after the age of 60 years. More recently, a shift in the epidemiology of oropharyngeal SCC has been observed, with a rising incidence, particularly in the palatine tonsils and base of the tongue, occurring in younger age groups and in people who have never smoked.[64] Like the cervix and anus, there is an epithelial transition zone within the oropharynx which is prone to HPV infection, dysplasia and the development of SCCs. In a systematic review of studies involving histological specimens of head and neck SCCs, in 36% HPV DNA was detected, and HPV-16 was the most common HPV type associated with head and neck SCC.[65] HIV-infected individuals have a 1.5 - four-fold higher risk of oropharyngeal or tonsillar cancer than the general population. Although the proportion of oropharyngeal cancers is unknown, HIV-positive individuals appear to be at moderately increased risk of HPV-associated head and neck SCC compared with the general population.[66] D'Souza et al.[67] showed convincing evidence that oral cavity HPV DNA infection was related to sexual behaviour, including oral sex. There is

evidence that HIV-positive individuals have a higher prevalence of oral HR-HPV, even after controlling for sexual behaviour,[68] and that the risk for infection appears to be higher among those with a declining CD4+ count.[69] While there are limited data on the natural history of oral HPV infection, the majority of infections clear within two years,[70] although persistence appears to be associated with a CD4+ count <500 cells/μl.[71] There do not appear to be benefits for HAART on either the persistence of HPV infection or the clearance of oral lesions, but more evidence is needed in this regard.[66] Data on oral HPV and HPV-associated head and neck SCC in African populations is currently scarce, although one study from Senegal,[72] which included 117 invasive head and neck cancer histology specimens, mainly from men with a mean age of 52 years, found only four cases to be positive for HPV DNA. The authors remarked that larger studies are needed to confirm these findings and explore other potential risk factors specific to the region.[72]

Prevention of HPV-associated infection and disease in men

Evidence for the benefit of several strategies to prevent HPV infection and subsequent disease in men has emerged in recent years. Studies have shown a greater protective effect of condoms in the prevention of HPV acquisition in men. Analysis of data from a multi-national cohort study in men showed a two-fold lower risk of HPV acquisition in men with no steady partner and who always used condoms. In addition, the probability of clearing an oncogenic infection was 30% higher in men who consistently used condoms with non-steady partners.[73] Consistent condom use has also been associated with the regression of penile lesions in men.[74] Recent RCTs in Africa provide strong evidence that MC is protective against HPV infection. In these trials, MC has been associated with reductions in the incidence, prevalence and persistence of HPV infection in men. In HIV-negative men, MC has also been shown to reduce HR-HPV transmission to female partners.[75] Recent data suggests that decreased penile shedding of HR-HPV observed in HPV-infected circumcised men may help to explain the protective effects observed for female partners.[38] MC has also been associated with a lower prevalence of flat penile lesions in men.[39]

Vaccines are the ideal form of primary prevention for infectious diseases, and have been successful in the control of many other infectious diseases. Having been shown to be efficacious in women, HPV vaccine studies have now demonstrated evidence of benefit in men. An RCT involving 4 065 men from 18 countries aged 16 - 26 years showed that the quadrivalent vaccine was 90% effective in preventing infection with vaccine-specific types in the per protocol analysis, and 89% effective in preventing AGWs in the same population.[76] In 602 MSM aged 16 - 26 years, the quadrivalent vaccine was 77.5% effective in preventing HPV-6-, -11-, -16- and -18-associated AIN.[77] The bivalent vaccine is not currently registered for use in men. HPV vaccination has been shown to be safe and highly immunogenic in HIV-1 infected men.[78] Modelling studies predict benefits of vaccination for boys, when high levels of vaccine coverage are achieved in girls,[79] and data emerging from countries where national vaccination programmes have been introduced confirm this. Even though vaccination was restricted to girls, in Australia, there has been an 82% decline in AGWs in men aged <21 years since the introduction of the vaccine.[80] In Denmark, a 50% decline in AGWs in young men aged <19 years was observed only three years post vaccine introduction.[81] However, these benefits may not translate to all men, particularly MSM who may not benefit from herd immunity. Australia is the first country to extend vaccination to men. While several countries in Africa have recently introduced HPV vaccination programmes, these school-based programmes do not include boys. Further evidence is needed of the HPV-associated burden of disease in men, and the potential effects of HIV on HPV-associated disease in men before the vaccination of boys can be considered in lower-resource settings.

Conclusion

HPV infection and associated disease are common in men in SSA. While data on the burden of disease are limited, studies suggest that infection with HPV is common, particularly in the context of HIV. There is also growing evidence to suggest that HIV infection enhances HPV persistence – a precursor for the development of cancer. Given expanding access to HAART in Africa, there is now potential for significant morbidity and mortality from HPV-related cancers in men in the future. While MC and HPV vaccination programmes are being rolled out in many African countries where the burden of HIV is high, more data are needed on the natural history and burden of HPV-associated disease in men in Africa to inform the development of prevention programmes.

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