Review

Human papillomavirus infections in HIV: A review

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The interaction between human papilloma virus (HPV) and human immunodeficiency virus (HIV), both sexually transmitted infections appears to be related to the alteration in cell-mediated immunity in HIV infected persons. Linkage studies of HIV/AIDs and cancer registries have indicated a 2 to 22 fold increase in cervical cancer in HIV positive women compared to HIV negative women. Data on the prevalence of HPV types in invasive cervical carcinoma (ICC) suggest that the proportion of infection with types HPV16/18 (responsible for over 70% of all cervical cancers) is similar in HIV negative and HIV positive women. The biological interaction between HIV and HPV needs further elucidation, although there is some evidence that the presence of HPV infection may be associated with increased HIV transmission. Adolescents perinatally infected by HIV are known to have higher rates of HPV infection and also have been shown to seroconvert in response to HPV vaccination with the quadrivalent vaccine, albeit to lower titers than HIV negative individuals. Anal cancer incidence is greatly increased in HIV positive individuals, particularly in HIV positive men who have sex with men. Screening for anal cancer precursors is feasible and effective; however, the impact on reduction of anal cancer remains to be demonstrated. There are ongoing studies on the safety, immunogenicity, and efficacy of current HPV vaccines in HIV positive individuals and mature data are awaited.

Key words: human immunodeficiency virus (HIV), human papilloma virus (HPV), cervicovaginal cancer.

INTRODUCTION

Human papilloma virus (HPV) infection has been linked to both cervical and anal cancer and genital warts. HIV infected individuals have been noted to have high frequencies of both these malignancies, as well as increased frequency of genital warts. HIV infected women are more likely than non HIV infected women to have detectable levels of HPV DNA in cervicovaginal specimens (Sun et al., 1995; Vermund et al., 1991; Hillemanns et al., 1996; Laga et al., 1992; Chaisson et al., 1997), squamous intraepithelial lesions (SIL), vulvovaginal condylomata acuminata, or anal intraepithelial neoplasia (Kreiss et al., 1992; Wright et al., 1994; Williams et al., 1994; Korn and Landers, 1995). The prevalence of SIL among HIV infected women has

been reported to range between approximately 12 and 40% (Sha et al., 1995; Massad et al., 1999) and adolescent HIV infected women have particularly high prevalence rates of HPV infection (77.4%) (Moscicki et al., 2000) and SIL (55%) (Fuller et al., 1996). Among HIV infected women, HPV disease, as manifested by findings of SIL or CIN (cervical intra-epithelial neoplasia) on cervical studies, is influenced by HIV induced immune suppression. SIL and clinically evident HPV infections have been associated with a declining CD4+ count (Delmas et al., 2000; Maiman et al., 1991). In addition, women with high plasma HIV RNA levels are at increased risk for cervical HPV infection with high risk types and cervical cytological abnormalities (Luque et al., 1999; Massad et al., 1999). However, cervical cancer has not shown such a dramatic relationship to lower CD4 cell counts. Although most HIV infected women with SIL present with low-grade lesions, SIL has been reported to be more severe and extensive in HIV infected women compared with non HIV infected women and can present as multifocal extensive cervical and lower genital tract lesions (Centers for Disease Control, 1990).

The increased incidence of HPV related disease among HIV infected women may be due to the high rate of persistent HPV infections, particularly among women with advanced immune suppression, with the oncogenic HPV types associated with the development of high grade lesions and cervical cancer (Sun et al., 1997; Ahdieh et al., 2001; Belafsky et al., 1996; Biggers and La Guardia, 1996). Only 20.6% of HIV infected women with low-grade cervical dysplasia experienced progression to high grade SIL in a randomized, observation-controlled clinical trial evaluating treatment with is otretinoin (median follow-up was 65 weeks for subjects on oral isotretinoin and 49 weeks for subjects on observation = 102); the difference between the two arms was not significant (Olaitan et al., 1997; Six et al., 1998; Robinson et al., 2002). In observational studies, progression of low grade SIL has been associated with lower CD4+ counts and presence of HPV types (Six et al., 1998; Massad et al., 2001; Nappi et al., 2005).

RESULTS AND DISCUSSION

The results from one clinical trial and few observational studies suggest that observation without excision therapy may be appropriate for HIV infected women with low-grade SIL or type 1 CIN who are not prone to loss to follow up. If treatment is recommended, loop electrosurgical excision procedure (LEEP) is a preferred treatment of CIN. HIV-infected women tolerate this pro-

cedure well with a low frequency of complications (Kietpeerakool et al., 2006). The relative low rate of HPV cervical infection that leads to pathological changes has prompted investigation into other risk factors for developing cervical dysplasia in HIV infected women. Invasive cervical carcinoma became an AIDS defining diagnosis in 1993. The incidence is low among HIV infected women, although the prevalence of SIL and CIN is high. In a large prospective study, the incidence of cervical cancer was not significantly higher among HIV infected women compared to HIV negative women (rate ratio 1:32, p = 0.80) (Massad et al., 2009). However, invasive cervical carcinoma is an important AIDS defining illness and may be the most common AIDS-related malignancy among HIV-infected women in areas with a high prevalence of HPV infection (Maiman et al., 1997). Compared with non HIV infected women, HIV infected women with invasive cervical carcinoma were likely to present with advanced clinical disease, have persistent or recurrent disease at follow-up, have a short time to recurrence, have a short survival after diagnosis, and die of cervical cancer (Maiman et al., 1990).

In the pre-HAART era, the median CD4+ count was relatively higher (153/mm^3 versus 50/mm^3) among women with invasive cervical carcinoma compared with women diagnosed with other opportunistic illnesses[32], but women with low CD4+ counts have a particularly poor prognosis (Maiman et al., 1993; Phelps et al., 2001). Several studies have also shown that anal cancer is increasing in HIV infected individuals with the advent of HAART, probably because of the prolonged life span due to therapy.

Guidelines from the CDC and NIH state "Although formal guidelines recommending anal Pap smear screening have not been adopted, certain specialists recommend anal cytological screening for HIV infected men and women. High resolution endoscopy should be considered if the anal Pap smear indicates ASCUS or ASC-H and should be performed if a person has LSIL or HSIL on anal Pap smear. Visible lesions should be biopsied to determine the level of histological changes and to rule out invasive cancer." Clinicians should also inquire about symptoms such as anal itching, bleeding, diarrhoea, or pain, and perform a visual inspection of the anal region and a digital rectal as a part of the physical examination. In many cases, the HIV infected woman is very sexually experienced, making the available HPV prophylactic vaccine potentially less effective. Several issues need to be clarified regarding use of the vaccine in HIV infected persons. The question of vaccinating men has also been raised to prevent penile infection and subsequent transmission to their partners. Five studies are currently ongoing in HIV infected adolescent girls and young

women, to evaluate the safety, tolerability, and immunogenicity of HPV vaccines. The quadrivalent vaccine is being evaluated in three studies and the bivalent in one study, whereas one study will compare safety and immunogenicity of the bivalent and the quadrivalent vaccine. Only one study will have clinical endpoints: prevalence and incidence of CIN in patients and description of the spectrum of cervical HPV types at baseline, 9 months, and 1 year after vaccination. Safety and immunogenicity of the bivalent vaccine have been evaluated in a Phase II interventional study in South Africa (Clinical trials registration: NCT00586339). Preliminary results were presented at AORTIC 7th International Conference, November 2011, Cairo Egypt. The study showed that regardless of baseline HPV status, all HIV positive and HIV negative subjects had seroconvert to HPV16/18 at Month 2 and 7. Nevertheless, as observed in HIV infected infants, geometric mean titers appeared to be significantly lower in the HIV positive women compare with HIV negative women. Whereas all these trials will provide much needed data on the safety, immunogenicity, and, to lesser extent, efficacy of HPV vaccines in HIV infected women, their findings will only apply to individuals similar to the trial population. Larke et al., (2011) published a systematic review and meta-analysis on male circumcision and HPV infection in men. They identified 23 papers about the association between circumcision and HPV DNA. Circumcised men were less likely to have prevalent genital HPV infection than uncircumcised men (summary odds ratio 0.57, 95% CI: 0.45 to 0.71).

The effect of circumcision was stronger at the glens/corona compared to sites more distant from the foreskin. There was, however, weak evidence that circumcision was associated with changes in HPV incidence and clearance and no evidence of a favourable effect on genital warts. Larke et al. (2011) concluded that male circumcision reduces HPV .

CONCLUSION AND RECOMMENDATIONS

In this review, we have discussed the strong inter-relationship between two sexually transmitted viruses: HIV and HPV. HPV infection is more common and more likely to persist in HIV positive versus HIV negative women. The burden of disease associated with infection with HPV, particularly high-risk types, is considerable and there is a strong association between HIV infection and genital cancers and their precursors. HPV is believed to be more dangerous among HIV positive individuals due to the impact of HIV on cell mediated immunity, a critical component required for clearance of HPV infection.

Linkage studies with HIV/AIDS and cancer registries have shown a 2 to 22 fold increase in invasive cancer in HIV positive women compared to the general female population, depending upon screening and competing mortality. HIV positive women with cervical cancer are more likely to have multiple HPV infections, but HPV16 and/or 18 prevalence in cervical cancer was similar in HIV positive and negative women, suggesting that the current HPV vaccines may prevent a similar proportion of cervical cancers regardless of HIV status. It is not clear whether HPV infection increases the risk of HIV acquisition although data are accruing that the inflammatory response evoked by HPV may solicit cells that are vulnerable to HIV infection. This is an important area for future research, as it would make the prevention of HPV infection even more urgent.

Conflicts of interest

Authors have none to interest.

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