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Human papillomavirus-related disease in people with HIV

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Abstract

Purpose of the review—The incidence of human papillomavirus (HPV)-related cancers is increased among people with HIV infection compared with the general population. This review will describe recent findings in HPV-associated cancer incidence since the introduction of antiretroviral therapy (ART), HPV/disease prevalence at sites other than cervix and anus, and recent data on screening and treatment of anal intraepithelial neoplasia (AIN).

Recent findings—Consistent with high prevalence of anogenital HPV infection, cervical intraepithelial neoplasia (CIN) and AIN in HIV-positive men and women, new data show that the incidence of cervical cancer has not declined since the introduction of ART and that the incidence of anal cancer is rising. Several studies also highlight high rates of HPV infection and HPV-associated disease at sites other than the cervix and anus, including the penis and mouth. Treatment methods for AIN have been described and show reasonable efficacy.

Summary—New data imply that the problem of HPV-related cancers will not decline among HIV-positive men and women in the ART era, highlighting the need to perform studies to determine if screening and treatment of AIN will prevent development of anal cancer. Recent data show progress in both of these areas.

Keywords

Human papillomavirus; anal cancer; cervical cancer; anal intraepithelial neoplasia; cervical intraepithelial neoplasia

Introduction

Many studies have consistently shown a high prevalence and incidence of anal and cervical HPV infection in HIV-positive men and women, along with known or potential cancer precursor lesions such as CIN and AIN. Early post-ART studies indicated that the prevalence of anogenital HPV infection and CIN/AIN were not declining substantially, nor was the incidence of anal or cervical cancer. This report describes further data on the incidence of anal and cervical cancer post-ART. With evidence of increasing incidence of anal cancer, there is increasing urgency to consider screening and treatment of high-grade AIN to prevent progression to cancer in at-risk populations. Recent considerations on AIN screening are discussed, as are new reports on different treatment methods for AIN.

Effect of ART on HPV-associated cancer

The incidence of HPV-associated cervical and anal cancers was previously shown to be elevated in HIV-positive men and women compared with the general population particularly

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among HIV-positive men who have sex with men (MSM) [1]. Data from several papers over the last few years suggested that the incidence of these cancers may not decline with the introduction in 1996 of antiretroviral therapy (ART). The first hint that this might occur was the observation that development of cervical and anal cancer were not clearly linked to development of AIDS, unlike other HIV-associated malignancies such as Kaposi's sarcoma and nonHodgkins lymphoma [2]. This suggested that reversal of HIV-related immunosuppression due to ART may not lead to a decline in the incidence of anal cancer or cervical cancer. Instead, it was predicted by some investigators that anal cancer might paradoxically increase if individuals were living longer due to ART but those with the putative anal cancer precursor, high-grade anal intraepithelial neoplasia (HGAIN) were not being treated to prevent progression to cancer [3]. Consistent with this prediction studies in San Francisco and London showed not only that there was no decline in the incidence of anal cancer among HIV-positive MSM since the introduction of ART but that the incidence was continuing to increase [4-6].

Several groups recently reported additional information on the incidence of anal cancer among HIV-positive individuals in the ART era [7]. An increasing incidence of anal cancer since the introduction of ART was also recently reported from France using the national French Hospital Database on HIV [8]. These data showed that the largest increase was seen in HIV-positive MSM compared with HIV-positive heterosexual men and HIV-positive women. The Multicenter AIDS Cohort Study (MACS) reported an overall incidence rate of anal cancer of 69 per 100,000 person-years in HIV-positive MSM, and the incidence did not decrease since the introduction of ART. Another study of cancer registries in 3 states in the U.S. showed combined data for HIV-positive men and women and the data for HIV-positive MSM, the highest risk group, were not reported. The authors demonstrated an increase of 1.7 in the relative risk of developing anal cancer in 1999-2002 period among HIV-positive men and women compared with 1991-1995, although that increased risk was not statistically significant [9]. In another recent analysis anal cancer was the only cancer found to be increasing in incidence among HIV-positive individuals in the United States [10]. In that analysis, the incidence of anal cancer increased from 19.0/100,000 person-years in the pre-ART era (1992-1995) to 48.3 person-years in the immediate post-ART era (1996-1999), to 78.2/100,000 person-years more recently (2000-2003), p for trend <0.001. These data included both men and women, and since the incidence of anal cancer is higher among HIV-positive men than HIV-positive women, the incidence of anal cancer among HIV-positive MSM is likely higher than 78.2/100,000 person-years.

In this analysis some differences between cervical and anal cancer emerged. The incidence of cervical cancer in HIV-positive women was even higher than that of anal cancer (149.9, 194.6 and 134.5/100,000 person-years in the 1992-1995,1996-1999, 2000-2003 time periods, respectively) but did not show a continued increase. Use of ART was independently associated with decreased risk for cervical cancer (relative risk 0.48; p=0.019) but not for anal cancer. The reason for this difference is not clear but may reflect active screening for CIN but not AIN. Also of note was the increased standardized rate ratio (2.6) for oropharyngeal cancer in the HIV-positive population compared with the HIV-negative population. This is of interest given recent data showing a clear association between a subset of oropharyngeal cancer and HPV [11,12].

Overall, the data clearly indicate a growing risk of anal cancer among HIV-positive individuals since the introduction of ART, particularly among HIV-positive MSM. The incidence of cervical cancer remains elevated among HIV-positive women, and while its incidence does not appear to be growing since the introduction of ART, there is also no evidence that its incidence is declining due to ART. There are fewer data on other HPV-related cancers such as oropharyngeal cancers, penile, vulvovaginal cancers; the incidence of these cancers is likely

increased in HIV-positive individuals but their fate since the introduction of ART is not yet known [1]. Given the high and potentially increasing incidence of HPV-associated cancers, it is important to understand the prevalence and incidence of their precursors, such as CIN and AIN. It is also important to consider the development of screening and treatment programs for AIN to prevent cancer similar to those currently in place for CIN.

HPV infection, CIN and AIN

Several papers have previously described the high prevalence and incidence of HGAIN among HIV-positive MSM and heterosexual men [13,14]. A high proportion of HIV-positive men were confirmed to have abnormal anal cytology in a recent paper from a French group [15], as were HIV-positive men in a study from New Haven [16] and Perth, Australia [17]. In the Australian study, a high proportion of the men referred for treatment of genital warts were found to have HGAIN in the lesions. However, these studies like previously published studies, were performed in convenience cohorts in different clinical settings. Population-based studies have not been reported until now but Chin-Hong et al recently reported the prevalence of anal HPV infection and AIN in a population-based sample of HIV-positive MSM in the San Francisco Bay area [18]. The data indicate that the prevalence of AIN of any grade in HIV-positive MSM was 57% with 43% having HGAIN. The prevalence of anal HPV infection was 88%, with 72% having at least one oncogenic HPV type. These data were highly consistent with data obtained from the convenience cohorts in San Francisco [13] and confirm the very high prevalence of oncogenic HPV and HGAIN in urban HIV-positive MSM.

HIV-positive men with AIN are also at risk of other HPV-related lesions. Kreuter et al showed that a high proportion of their study population had AIN (59%) [19]. A smaller proportion had penile intraepithelial neoplasia (PIN) (4%) but the proportion with PIN increased with the grade of AIN. Among men with HGAIN, 8.5% had PIN, mostly PIN 2 or PIN 3. No cases of penile cancer were observed, but HIV-positive patients with PIN 2/3 are likely to be at increased risk of penile cancer compared with the general population. HIV-positive MSM particularly those with AIN may therefore benefit from routine penile examination. Likewise, HIV-positive individuals with HPV-related lesions at non-anal sites are at risk for anal HPV infection. In a study of HIV-positive Brazilian women, Veo et al showed that HIV-positive women with CIN 3 (35%) were more likely to have anal HPV infection than those without CIN 3 (10%) [20]. Together these data are consistent with the concept of HPV as a field infection in which the entire anogenital tract may be affected, particularly in HIV-positive individuals.

Further extending the concept of HPV as a field infection, studies have examined the relationship between oral and cervical HPV infection, an emerging area of research interest given a potentially increased risk of HPV-associated oropharyngeal cancers in HIV-positive individuals. In a study of 30 women HIV-positive women from South Africa with a CD4 level less than 300 and naïve to ART, oral HPV DNA was detected in 20% of the women, compared with cervical HPV in 97% of the women [21]. Limited correlation between oral HPV types and those identified in the cervical mucosa was found. In a larger study of women with more experience on ART from the U.S. Women's Interagency HIV Study, HIV-positive women were more likely than HIV-negative women to have an oral (33 vs. 15%, $p = 0.016$) infection detected [22]. However, the six-month cumulative prevalence of oral HPV infection was significantly less than for cervical infection ($p < 0.0001$). These data suggest that while oral HPV infection is more common among HIV-positive women compared with HIV-negative women, the incidence and natural history of HPV infection at these two mucosal sites are not highly correlated. A similar relationship had been noted in the past between cervical HPV infection and anal HPV infection in HIV-positive women [23]; although anal infection was more common than cervical infection, the HPV types detected at the two sites were different in most of the women.

Screening and treatment of AIN to prevent anal cancer

The high prevalence and incidence of AIN in HIV-positive individuals, along with the increasing incidence of anal cancer suggest that screening for HGAIN and treatment of the lesion to prevent progression to cancer should be considered. This approach is analogous to the currently accepted cervical cytology screening approach to prevention of cervical cancer. Descriptions of such a proposed screening and treatment system have been published [12] and for the first time, an official government body, the State of New York has included anal cytology screening as a standard of care for HIV-positive individuals (HIV Clinical Resource. Primary Care Approach to the HIV-Infected Patient. Preventative Medicine. http://www.hivguidelines.org/GuideLine.aspx?pageID=257&guideLineID=13#VI.%20PREVENTIVE%20MEDICINE. Published March 2007).

Currently there is not universal acceptance of anal cytology screening to prevent anal cancer [24]. The primary reason is that studies to demonstrate that this approach leads to a reduction in the incidence of anal cancer have not yet been done. In the absence of this critical evidence, most professional societies have been reluctant to recommend routine screening. Additional reasons include a paucity of data on the optimal screening approach, as well as efficacy of methods to treat HGAIN.

Several studies have shown that cytology has limited sensitivity to detect HGAIN, similar to the sensitivity of cervical cytology [25,26]. Moreover, the high prevalence of HGAIN in HIV-positive men and women poses challenges to cytology screening, raising questions about whether cytology screening is worthwhile, or whether all at-risk individuals should forego cytology screening altogether and go directly to high resolution anoscopy [24]. While the latter would be ideal, there is currently an insufficient number of trained anoscopists, nor are there sufficient resources to adequately assess, treat and follow the lesions that would be detected. Given this limitation, anal cytology could be used as a screening tool as originally envisioned, with priority for referred to HRA given to those with high-grade squamous intraepithelial lesion (HSIL) on cytology, followed respectively by those with low-grade squamous intraepithelial lesion (LSIL), atypical squamous cells cannot rule out HSIL (ASC-H), atypical squamous cells of undetermined significance (ASC-US) or normal cytology.

Methods to perform anal cytology screening are still under development. Several groups have shown that self-screening is feasible, bypassing the requirement for a healthcare professional to be involved in the process [25,26]. Chin-Hong et al published an analysis of self-collected cytology versus clinician-collected cytology in a population-based study of HIV-positive and HIV-negative MSM in San Francisco who had no prior experience with anal cytology screening [18]. The sensitivity of cytology to detect AIN in HIV-positive men was 75% when self-collected and 90% when clinician-collected ($p=0.02$ for non-inferiority). The sensitivity of cytology to detect AIN in HIV-negative men was 48% when self-collected and 62% when clinician-collected ($p>0.10$ for non-inferiority). The data indicate that self-collection may be a useful approach, however, the limited sensitivity of any one individual test indicates that repeated testing at pre-defined intervals will be needed, as is currently the case for cervical cytology screening.

Several different methods of treatment of AIN have been described. One of the more promising methods, known as infra-red coagulation (IRC) uses heat energy to ablate lesions. Goldstone et al showed that 67% of HIV-negative patients were free of HGAIN after up to three IRC procedures [27], with the results being better than with HIV-positive patients [28]. A retrospective analysis of IRC in 68 HIV-positive MSM also showed similar results to the HIV-negative patients, with 64% efficacy per treated lesion [29]. These data were largely replicated in a small multicenter study showing that IRC was safe and well tolerated [30].

Imiquimod is approved for the treatment of external genital warts. It has also been tested as a topical treatment for peri-anal and intra-anal AIN. In a German study, 4 of 4 patients with AIN 2, and 7 of 10 patients with AIN 3 showed complete clinical and histologic clearance of AIN at the end of imiquimod therapy [31]. In a later study from the same group, 7 of 11 patients with HGAIN showed clearance at the end of the follow-up period [32]. However, as has been seen with IRC development of new lesions in untreated areas was quite common. In a separate analysis, decrease in HPV viral load after the use of imiquimod was noted along with reduction in expression of p16ink4a, Ki67, minichromosome maintenance protein and proliferating cell nuclear antigen, biomarkers of high-grade lesions [33]. It is notable that apart from a report of HPV DNA clearance in some patients after IRC treatment [30], few reports show clearance of HPV DNA after treatment with any of the therapeutic modalities discussed above or after institution of ART, consistent with the high recurrence rate and incidence of new lesions. Although the results with imiqiumod appear promising, controlled trials are needed to more definitively establish its efficacy.

In a study of patients treated with laser ablative treatment, 88 patients with HGAIN from the United Kingdom were followed [34]. Defined as a disease-free state at 12 months after treatment, 63% (114/181) showed no evidence of AIN. The median time to cure for the cohort was 31.5 months, with median time to cure being longer in the HIV-positive patients compared with the HIV-negative patients. Treatment outcome was not specifically reported by HIV status or disease severity but the authors reported that the outcome did not differ by disease state.

Finally, surgery remains an important part of the treatment armamentarium for patients with HGAIN. Recognizing that only the patients with the most extensive disease were being treated surgically, the early experience using surgery to treat HIV-positive patients with extensive HGAIN was disappointing, with extensive morbidity and a high recurrence rate [35]. More recently, however, surgery combined with careful post-operative monitoring and IRC ablation of persistent lesions was shown to have good results with 78% of patients showing no signs of HGAIN at the end of treatment. These data suggest that most if not all patients with HGAIN regardless of the extent of their disease, may potentially be successfully treated [36].

Conclusion

It is clear that the incidence of HPV-related cancers is not declining in the post-ART era, and at least in the case of anal cancer, may be increasing. It is also increasingly clear that a program to screen for and treat HGAIN to prevent development of anal cancer must be considered. However, before such a program can be adopted as standard of care, studies to demonstrate that treatment of HGAIN reduces the incidence of anal cancer must be done. Moreover, for such studies to be implemented, adequate screening and treatment methods must be available. Although there are limitations in each of the methods described in this report, perhaps the most important result of work performed in the last year or so is that there has been progress in screening and treatment of HGAIN has been made, and these should facilitate the implementation of anal screening and treatment studies needed to support the eventual implementation of anal screening as standard of care.

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