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HPV-associated anal and cervical cancers in HIV-infected individuals: Incidence and prevention in the antiretroviral therapy era

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Abstract

Purpose of review—The incidence of human papillomavirus (HPV)-related cancers has increased (anal cancer) or not declined (cervical cancer) since the introduction of antiretroviral therapy (ART). This article reviews recent data on incidence and prevention efforts for HPV-related cancers in the ART era.

Recent findings—ART may confer some benefit with respect to reducing the risk of anal HSIL and cancer, but the degree of that benefit appears to be limited. The prevalence of anal HPV infection, anal HSIL and anal cancer remain high among individuals on effective ART. The incidence of cervical cancer is high among HIV-infected women, particularly in countries where there are no organized cervical cancer prevention programs. Efforts are in progress to define optimal screen-and-treat cervical cancer prevention programs in different clinical settings and to define the efficacy of secondary prevention programs for prevention of anal cancer.

Summary—HPV-related cancers are likely to remain an important problem in HIV-infected men and women for the foreseeable future, even among those on effective ART.

Keywords

Anal cancer; cervical cancer; human immunodeficiency virus; human papillomavirus; high-grade squamous intraepithelial lesion

Introduction

The incidence of some of the most common AIDS-defining cancers such as Kaposi sarcoma and nonHodgkin lymphoma has declined substantially since the introduction of effective ART. Understanding changes in the incidence of human papillomavirus (HPV)-related cancers including cervical cancer and anal cancer since the introduction of ART is particularly important because a unique feature of these cancers is that they are potentially preventable. Interpreting changes in incidence is also more challenging, since these changes may reflect both the benefits of improved HIV control though ART and the results of prevention efforts. Primary prevention through HPV vaccination is not likely playing an important role in determining the incidence of HPV-related cancers in HIV-infected men and

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women because these vaccines only work to prevent initial HPV infection, and most HIV-infected individuals were not vaccinated against HPV in time to prevent initial anogenital HPV infection. Moreover, given the time usually required for HPV infection to progress to HSIL and ultimately cancer, any vaccination-related reduction in cancer would likely not be manifest for several decades from now.

Secondary prevention efforts for HPV-related cancers are likelier to be affecting the incidence of HPV-related cancers in HIV-infected men and women in the ART era. Identification and treatment of the cervical cancer precursor lesion, cervical high-grade squamous intraepithelial lesion (HSIL), before it progresses to cancer is well known to reduce the incidence of cervical cancer. In areas of the world where there are well-organized secondary prevention programs for both HIV-infected women and HIV-uninfected women, the incidence of cervical cancer in HIV-infected women is not substantially higher among than among HIV-uninfected women. Conversely the incidence of cervical cancer is higher among HIV-infected women than HIV-uninfected women in areas where organized programs do not exist for either of these groups of women, as is the case in several low and middle income countries (LMIC).

Compared with cervical cancer, the impact of ART on the incidence of anal cancer may be more directly measurable since secondary prevention programs to prevent anal cancer are available to only a small fraction of at-risk HIV-infected individuals. Moreover, the efficacy of these programs, in which anal HSIL is treated to prevent anal cancer, is not yet established and is currently under investigation in the ANal Cancer/HSIL Outcomes Research (ANCHOR) Study, (www.ANCHORstudy.org).

The purpose of this article is to 1) present the most recent information on the incidence of anal cancer and HSIL in the ART era; and 2) describe recent data on screen-and-treat programs for prevention of cervical cancer in HIV-infected women in LMIC.

ART and the incidence of anal cancer

In a earlier report from the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) cohort, the incidence of anal cancer among HIV-infected MSM was shown to be very high at 131/100,00 and clearly higher than that observed before the introduction of ART. Those of other HIV-infected men and HIV-infected women were also very higher at 46/100,000 and 30/100,000, respectively (1). In a recent publication from NA-ACCORD, the cumulative incidence of anal cancer among HIV-infected adults was reported to be 1.5% by age 75 years, compared with 0.5% among HIV-uninfected adults (2). However the authors did not report the cumulative incidence by HIV risk group, and it is likely that the cumulative incidence is substantially higher among HIV-infected MSM than other HIV-infected men or HIV-infected women.

A study of HIV-infected male US veterans looked specifically at use of protease inhibitors (PIs) and their relationship to incidence of anal cancer. In multivariate analysis, increasing percent time on PIs was associated with an increased risk of anal cancer (3). Poor immunologic recovery and virologic control, a history of condylomata acuminata, and case

registry enrolment in the late combined ART era were also associated with increased anal cancer risk.

In a retrospective cohort analysis, anal cancer was diagnosed in 23 of 2804 HIV-infected San Diego patients being followed for a median of 4 years (4). Those who had HSIL on anal cytology had an estimated 5-year probability of progression to cancer of 1.7%, and an estimated annual progression risk of 1 in 263. None of the examined covariates, including use of ART, was significantly associated with anal cancer incidence when examined in separate unadjusted Cox models. This estimate was higher than reported earlier in a meta-analysis of 1 in 377 per year among HIV-infected men with HSIL (5). One of the limitations of this study is that the baseline disease classification was based on cytology, which has been shown to have relatively low sensitivity for anal HSIL and underestimate the severity of anal disease (6). Progression from anal HSIL to cancer was also reported to be high in another study. 7of 38 patients (18%) followed in Toronto Canada with perianal HSIL developed anal cancer, with a progression rate of 6.9 cases of anal cancer per 100 person-years of follow-up (7).

Other data suggest that ART provides some protection against anal cancer. The same group reported previously that HIV control as measured by the percent of time with undetectable HIV viral load decreased, rather than increased the risk of anal cancer (8). An analysis of anal cancer in Canada suggested that early use of ART might be an important factor in protection against anal cancer (9). A cohort of British Columbia HIV-infected MSM receiving ART was followed between 1988 and 2008. Time from first CD4 cell count or HIV RNA viral load test to anal cancer diagnosis was analysed using Cox regression and Kaplan-Meier curves. The results showed that HIV-infected MSM in the ART era had a longer time to the development of anal cancer than those treated pre-ART. A lower CD4 nadir and longer duration of having CD4 levels below 100/mm^3 were associated with increased risk of anal cancer, suggesting that early use of ART might reduce the risk or delay progression to anal cancer. Lower CD4 nadir was also associated with increased risk of anal cancer in a population of Dutch HIV-infected MSM, as were alcohol use and smoking. In that population the incidence of anal cancer remained high at 100/100,00 men late in the post-ART era, between 2011 and 2012, but the increase seen compared with the early-ART era appears to have levelled off (10).

If ART is in fact reducing the incidence of anal cancer, it is not clear it is reducing the incidence of the cancer precursor lesion, HSIL, reducing progression from HSIL to cancer, or both. Most studies of the prevalence or incidence of anal HSIL in the post-ART era continue to show a high prevalence of this cancer precursor lesion in HIV-infected men and women (6). These cross-sectional studies suggest that ART has a limited effect on reducing HSIL incidence or inducing HSIL regression. However, in a recently reported cross-sectional study of HIV-infected MSM, being on ART for 2 years or longer was associated with a lower prevalence of anal HSIL (11).

Similar questions have been addressed for cervical HSIL and cervical cancer (12). In the Swiss Cohort Study, after adjustment for nadir CD4+, a protective effect of using ART for more than 2 years was seen for HSIL. Although a protective effect was also seen for cervical

cancer, the effect was not statistically significant. Few prospective studies have been able to examine the relationship between anal or cervical HSIL and ART rigorously given that use of ART is now standard of care in most if not all HIV-infected individuals.

With longer survival due to ART, the issue of aging and HIV is becoming increasingly important. In a case-cohort study including a 5% sample of U.S. Medicare enrollees and all cancer cases aged at least 65 years in linked cancer registries, absolute cancer risk among HIV-infected men and women was calculated accounting for the competing risk of death. HIV was strongly associated with incidence anal cancer in this population (adjusted hazard ratio=34.2, s5%CI=23.9–49.0) (13).

Overall the relationship use of ART and how it affects the incidence of anal cancer remains somewhat unclear. It is also possible that those who began ART earlier in the course of HIV disease may have lower cumulative risk but this may be counterbalanced by longer survival and the increased risk of anal cancer seen with increasing age in the general population (14). Thus the future incidence of anal cancer among HIV-infected men and women will need to be studied carefully over time. Factors that may influence the incidence of anal cancer in the future are summarized in Table 1.

Strategies for prevention of cervical cancer in HIV-infected women in low and middle income countries

Programs for prevention of cervical cancer present enormous challenges in low and middle income (LMIC) countries. However the high incidence of cervical cancer in many of these countries demands that this issue be addressed. Several different approaches have been proposed and have undergone testing in different settings, including “screen and treat” in which clinicians, mostly nurses apply 5% acetic acid to the cervix under direct visualization (visual inspection with acetic acid, or VIA), and if a lesion is suspected, then the cervix is treated on the spot, typically with cryotherapy. Women whose lesions extend into the endocervical canal where they cannot be easily visually assessed or biopsied, or those with lesions suspicious for cancer typically undergo colposcopically-directed biopsy, cone biopsy or loop electroexcision procedure.

Another version of visual inspection uses Lugol’s iodine instead of acetic acid. This procedure is known as visual inspection with Lugol’s iodine (VILI). A randomized clinical trial to compare the diagnostic accuracy of VIA and VILI among HIV-infected women was reported (15). There was no significant difference in the diagnostic performance of VIA and VILI for the detection of cervical HSIL among HIV-infected women.

Other methods of identifying HIV-infected women at risk for cervical HSIL to reduce the number of colposcopies needed have been studied in a variety of LMIC settings. A study in Burkina Faso and South Africa compared the careHPV test to the INNO-LIPA test (16). The careHPV assay is a test for high-risk (HR) human papillomaviruses (HPV) detection designed to be affordable in resource-poor settings. The INNO-LiPA HPV Genotyping Extra assay (INNO-LiPA) is an PCR amplification-based assay that was not specifically designed to be used in this setting. All women had cytology testing, VIA or VILI, and colposcopy. The sensitivity and specificity of careHPV for the diagnosis of cervical HSIL was 93% and

specificity was 58%. Overall careHPV had a similar clinical sensitivity but higher specificity than the INNO-LiPA assay for detection of cervical HSIL.

A cost effectiveness analysis comparing cervical cytology, VIA and HPV DNA testing for detecting cases of cervical HSIL among HIV-infected women in Johannesburg, South Africa showed that VIA was most cost-effective (17). However, there are still few data on long-term outcomes of VIA, cryotherapy, or LEEP among HIV-infected women in LMIC.

Recurrent cervical HSIL has been reported to be an important issue among HIV-infected women treated in the U.S. with LEEP (18). In a meta-analysis of the performance of VIA, recurrence after treatment was higher among HIV-infected compared with HIV-uninfected women but morbidity from treatment was similar (19). Among Nigerian HIV-infected women participating in a see-and-treat program and treated for cervical disease with thermal coagulation, there was no statistically significant difference in recurrence between HIV-infected and HIV-uninfected women (20). However among HIV-infected women the risk of recurrence was highest among those with lower CD4 levels.

Other technologies are showing promise for identifying women at risk for cervical HSIL in LMIC settings. A test that has shown some promise is OncoE6, which looks for the HPV E6 protein as a marker of HPV infection and potentially disease activity (21,22). Studies reported from rural China of presumably HIV-uninfected women showed that the sensitivity of OncoE6 as a screening test was lower than that of HPV DNA testing, but was more specific and had a higher positive predictive value for HSIL.

In a cross-sectional validation study conducted in Lusaka, Zambia, the investigators compared the clinical performance of VIA, digital cervicography (DC), HPV DNA detection using the Xpert HPV test, and OncoE6 for cervical cancer screening in an HIV-infected population (23). VIA and DC displayed moderate sensitivity and high specificity. Xpert HPV performed equivalently to currently approved HPV DNA tests, with high sensitivity and moderate specificity. OncoE6 displayed excellent specificity but low sensitivity. Overall the results confirm a potentially important role for these newer technologies but none is sufficient by itself, and different combinations will be needed in a staged screening process to provide optimal sensitivity, specificity and predictive value.

In a study from Kenyan HIV-infected women, exfoliated cervical cells were used to measure methylation levels of the CADM1, MAL, and MIR124-2 genes using quantitative methylation-specific polymerase chain reaction (24). When markers were combined into a single test, the test showed promising sensitivity for HSIL when compared with cytology, VIA and HPV16/18 genotyping. These results indicate that technologies that extend beyond those that measure HPV DNA or its gene products may be of value in this setting and will need further assessment.

Recently the World Health Organization produced guidelines for screen-and-treat strategies to prevent cervical cancer in LMIC as well as guidelines for treatment of cervical SIL (25). The guidelines may be downloaded from the WHO website http://apps.who.int/iris/bitstream/10665/94830/1/9789241548694_eng.pdf?ua=1, accessed September 15, 2016. They include recommendations specifically for HIV-infected women and for women of

unknown HIV status in areas with high rates of endemic HIV infection. These guidelines were based on the available data but as acknowledged by the authors, high quality evidence was largely lacking. Clearly further research in this area is needed, but the high burden of cervical cancer in these countries, particularly among HIV-infected women mandates that action be taken as soon as possible, even with imperfect data.

Conclusion

The best approach to cervical and anal cancer prevention in the long term is HPV vaccination, but most HIV-infected individuals are over the age of HPV vaccination. Vaccination of HIV-infected men and women under the age of 27 years should be a high priority but given the high incidence of anal and cervical cancer in HIV-infected individuals, great effort must also be made to implement secondary prevention measures. For cervical cancer these should include routine cytology screening with HPV testing as indicated, followed by colposcopically-directed biopsy and treatment of cervical HSIL. Screen-and-treat programs are an alternative in LMIC where implementation of organized cervical screening programs are difficult. For anal cancer, there are no definitive guidelines, but studies are in progress to determine if treatment of anal HSIL reduces the risk of anal cancer. Until the evidence is in, many experts are choosing to screen and treat individuals at risk for anal cancer, and doing so requires extensive training in HRA. All of these efforts are of great important to HIV-infected men and women, as HPV-related cancers are now among the most common cancers in this population. While ART may confer some reduced risk of developing these cancers, it is clear that this benefit is incomplete and HIV-infected men and women will remain at risk for many year to come.

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Conflicts of interest

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Abbreviations

HPV	Human papillomavirus
LSIL	low-grade squamous intraepithelial lesion
HSIL	high-grade squamous intraepithelial lesion
ASIL	anal squamous intraepithelial lesion
CSIL	cervical squamous intraepithelial lesion

ASC-H	atypical cells-cannot rule out high grade squamous intraepithelial lesion
ASC-US	atypical squamous cells of undetermined significance
MSM	men who have sex with men
ART	antiretroviral therapy
HRA	high resolution anoscopy

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Papers of particular interest, published within the annual period of review, (18 months/2015–2016) have been highlighted as:

• of special interest

•• of outstanding interest

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strategies for cervical HSIL. They include strategies specific to HIV-infected women. [PubMed: 26868062]

Key points

(3–5 key points/sentences that summarize your article)

- The incidence of HPV-related cancers has increased in the ART era among men and women in the absence of primary or secondary prevention efforts for those cancers.
- ART may confer some benefit with respect to reducing the risk of cancer, but that benefit is limited.
- Studies are in progress to determine the efficacy of treating anal HSIL to reduce the incidence of anal cancer
- Guidelines for screen and treat programs for prevention of cervical cancer in low and middle income countries, as well as treatment of cervical HSIL were recently released by the World Health Organization
- HPV vaccination of HIV-infected men and women under the age of 27 years should be standard of care.

Table 1

Factors that may affect the incidence of anal cancer among HIV-infected men and women

Risk factor	Increased incidence of anal cancer	Decreased incidence of anal cancer
Lower nadir CD4 level	Likely	
Lower current CD4 level	Possibly	
Time on effective ART		Possibly
Earlier initiation of ART		Possibly
Increasing age	Possibly	
HPV vaccination prior to initiation of sexual activity		Likely
Screening for and removal of anal HSIL		Possibly