



Invited Commentary

Invited Commentary: Biological and Clinical Insights From Epidemiologic Research Into HIV, HPV, and Anal Cancer

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Anal cancer is common among people infected with human immunodeficiency virus (HIV). This cancer is caused by human papillomavirus, and immunosuppression likely contributes to its development. In this issue of the *Journal*, Bertisch et al. (*Am J Epidemiol.* 2013;178(6):877–884) present the results of a case-control study of anal cancer among HIV-infected people in Switzerland. They demonstrate that anal cancer risk is increased in association with a low CD4+ cell count (a clinical measurement of immune status). In particular, HIV-induced immunosuppression was most severe among cases approximately 6–7 years prior to the diagnosis of anal cancer. A plausible biological interpretation is that immunosuppression is important at an early stage of the development of anal cancer, but that the neoplastic process becomes irreversible over time with persistent human papillomavirus infection and genetic damage. With current efforts to provide earlier combination antiretroviral therapy to HIV-infected people, anal cancer incidence may start to decline. Bertisch et al. also demonstrate a strong association between serum antibodies against the human papillomavirus type 16 protein E6 and anal cancer risk, highlighting the role of this viral oncoprotein in carcinogenesis. Additional biomarkers could help refine clinical approaches to anal cancer screening and prevention for the HIV-infected population.

acquired immunodeficiency syndrome; anal cancer; combination antiretroviral therapy; human immunodeficiency virus; human papillomavirus; immunosuppression; screening

Abbreviations: AIDS, acquired immunodeficiency syndrome; AIN, anal intraepithelial neoplasia; cART, combination antiretroviral therapy; HIV, human immunodeficiency virus; HPV, human papillomavirus.

Anal cancer is an important source of morbidity for people living with human immunodeficiency virus (HIV) infection in Western countries. Anal cancer is one of the most common malignancies in this population, and risk is elevated 30-fold compared with the general population (1). Furthermore, the large number of cases of anal cancer among HIV-infected people measurably contributes to the overall burden in the general population. For example, in the US general population during 2001–2005, approximately 28% of anal cancers in males and 1% in females occurred in association with HIV infection (2).

Anal cancer is caused by chronic infection with human papillomavirus (HPV), primarily HPV type 16 (3). Similar to other HPV-related cancers, anal cancer develops over a period of years in a series of stepwise lesions, termed anal

intraepithelial neoplasia (AIN). One plausible reason for the high risk for anal cancer among HIV-infected people in the United States is that homosexual and bisexual men (i.e., men who have sex with men) represent a major subgroup of the HIV population. Receptive anal intercourse, a major risk factor for HIV infection, also leads to a high prevalence of anal HPV16 coinfection and HPV-related AIN (4). Although this risk factor explains the very high burden of anal cancer among HIV-infected men who have sex with men, it is noteworthy that anal cancer risk is also substantially increased in other HIV-infected men and in HIV-infected women (5).

In addition, HIV-induced immunosuppression likely contributes to the high incidence of anal cancer. This hypothesis is aligned with a model in which immunosuppression increases the risk for virus-related cancers by impairing the host's ability

to clear or control chronic viral infections. Several lines of evidence support this conclusion for anal cancer. First, anal cancer incidence is elevated in men and women who are immunosuppressed because of an organ transplant, as well as in those with HIV (1). Second, anal cancer risk arises more frequently in HIV-infected people with advanced disease (i.e., acquired immunodeficiency syndrome (AIDS)) than among HIV-infected people who do not have AIDS (5). Third, the incidence of anal cancer increases with prolonged time spent with a CD4+ cell count below 200 cells/ μ L (a level of immunosuppression consistent with AIDS) (6).

The paper by Bertisch et al. (7) published in this issue of the *Journal* provides several pieces of important information that help fill out this picture. In a case-control study nested in a large Swiss cohort of HIV-infected people, they assessed the association of anal cancer with CD4+ cell counts measured within different time intervals prior to selection. The results (presented graphically in their Figure 1) suggest that HIV-induced immunosuppression is most severe approximately 6–7 years prior to the diagnosis of anal cancer. Furthermore, a CD4+ cell count of <200 cells/ μ L, compared with a CD4+ cell count of \geq 500 cells/ μ L was associated with a 14-fold increased risk of anal cancer over a subsequent latency period of 6–7 years. In contrast, when a much shorter latency period of 1 year was considered, the same level of immunosuppression was associated with only a 4.6-fold increased risk. A limitation of the results is that there is overlap in the confidence limits for these odds ratios, and it is unclear whether CD4+ cell counts measured during the 6- to 7-year window provide significantly more information than CD4+ cell counts measured closer to anal cancer diagnosis. Nonetheless, the odds ratios appear materially different, and therefore the results seem compelling.

A plausible biological interpretation of these findings is that immunosuppression is important at an early stage of the development of anal cancer. People with an intact immune system may be able to clear early AIN lesions. However, in the setting of immune suppression and presumably persistent HPV infection, genetic damage accumulates and AIN lesions become more highly dysplastic. The timeline presented in Figure 1 of the paper suggests that immunity is less relevant once the lesion has gone through this low point of immune suppression, and that progression would occur even with the subsequent administration of combination antiretroviral therapy (cART) and reconstitution of T-cell immunity.

This model helps explain a noteworthy and worrisome observation about trends in anal cancer among HIV-infected people. Since 1996, the availability of effective cART has reduced the incidence of AIDS and led to prolonged survival for HIV-infected people. In concert with the introduction of cART, there have been dramatic declines in Kaposi sarcoma and non-Hodgkin lymphoma (both of which, like anal cancer, are caused by viruses) (8, 9). However, the incidence of anal cancer has not declined and may actually have risen (5, 9, 10). The work by Bertisch et al. (7) provides an attractive explanation for this trend; that is, until now, cART has been given to HIV-infected people too late to stop the development of anal cancer. Indeed, until recently, many HIV-infected people would have survived for a prolonged period without the use of cART and under substantial immunosuppression, because

recommendations called for deferring cART until CD4+ cell counts dropped below 350 or 500 cells/ μ L (11). For these individuals, subsequent use of cART has prolonged their lives, but if they had a persistent anal infection with an oncogenic HPV that they were not able to clear, cART may not have halted the progression to anal cancer over a period of several years.

An additional interesting set of findings in the paper by Bertisch et al. (7) is the association of anal cancer with the presence of serum antibodies against HPV16. The authors found an increased risk of anal cancer associated with antibodies to the HPV16 L1 capsid protein, consistent with findings for anal cancer in the general population (12). An even stronger association was noted by Bertisch et al. for antibodies against the HPV16 E6 protein; these antibodies were observed in 22% of anal cancer cases but in none of the control subjects. The HPV16 E6 protein targets the cellular tumor suppressor protein p53, thereby facilitating progression to cancer. Bertisch et al. assessed the presence of E6 antibodies close in time to cancer diagnosis, and the presence of such antibodies in cases is consistent with the expression of E6 protein in late AIN lesions or in preclinical cancers. E6 antibodies are also found in patients with cervical and oropharyngeal cancers (2 other cancers caused by HPV) (13, 14).

These findings have at least 2 potential clinical and public health implications. The first concerns whether and how cART may decrease the risk of anal cancer. Importantly, Bertisch et al. (7) could not provide direct evidence that cART reduces the risk of anal cancer. Their measure of cART was somewhat crude (i.e., any cART use prior to anal cancer diagnosis or control selection), and they were not able to fully control for the fact that cART may have been prescribed to sicker HIV-infected patients. Thus, one should not interpret the borderline adverse association observed with cART to indicate that cART increases the risk of anal cancer.

Instead, as Bertisch et al. suggest (7), and we concur, it is likely that the initiation of cART at an earlier time point in HIV disease will reduce anal cancer risk, because early cART prevents declines in CD4+ cell counts. In turn, preservation of immunity will help patients to better control anal HPV infection and thereby slow or prevent the progression of early AIN or clear these lesions. Of note, with the recognition that early use of cART carries substantial clinical benefits in general, current HIV disease management guidelines now call for the early use of cART for most patients (15). Thus, we might hope that as these clinical guidelines are adopted and more HIV-infected patients receive cART earlier, we will observe population-wide declines in anal cancer incidence. The next few years of cancer surveillance of HIV-infected populations will be telling regarding this point.

The second potential implication concerns screening for anal cancer. Given the high risk of anal cancer, especially among HIV-infected men who have sex with men, some have proposed cytological screening for anal cancer (analogous to Papanicolaou smear screening for cervical cancer) in high-risk populations (16). One unresolved issue is the degree to which the treatment of precancerous AIN lesions prevents the development of cancer, and there has been concern regarding the morbidity associated with such treatments (17). Notably, the prevalence of precancerous AIN lesions is very high,

and it is not clear how to identify the small subset of people who will go on to develop anal cancer (4).

The finding that HPV16 E6 antibodies are present only among anal cancer cases might suggest that this marker could be used in screening, for example, to triage people with AIN detected on cytological screening. However, given the small proportion (22%) of anal cancer cases who manifest E6 antibodies, such an approach would lack sensitivity. Because E6 antibodies would miss 78% of people who go on to develop anal cancer in a short time, one could not recommend this test for clinical use. Nonetheless, it is likely that with further work, additional biomarkers (applied to anal specimens or blood) could help refine clinical approaches to anal cancer prevention in the HIV-infected population. Future work might also explore whether E6 antibodies are associated with anal cancer tumor stage or whether they provide prognostic information, as is seen for antibodies to the Merkel cell polyomavirus large T antigen in patients with Merkel cell carcinoma (18).

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