Anal Intraepithelial Neoplasia in Men Living with HIV in the Era of Highly Active Antiretroviral Therapy

Alberto Severini
National Microbiology Laboratory, Public Health Agency of Canada, and Department of Medical Microbiology and Infectious Diseases, University of Manitoba, Winnipeg, Manitoba, Canada

(See the article by Pokomandy et al, on pages 1174–1181.)

The introduction of highly active antiretroviral therapy (HAART) has achieved a sustained improvement in the immune status of patients with AIDS. HAART has reduced infectious complications to such a degree that infections have become a relatively uncommon cause of death among people living with the human immunodeficiency virus (HIV) and, thankfully, the life expectancy of such individuals has dramatically improved.

In the pre-HAART era, AIDS-defining malignancies (Kaposi sarcoma, non-Hodgkin lymphoma, and cervical cancer) afflicted HIV-positive individuals disproportionately, with incidences that were 50–200-fold higher than in the general population [1, 2]. Kaposi sarcoma, non-Hodgkin lymphomas, and cervical cancer are associated with infections due to human herpesvirus 8, Epstein-Barr virus, and human papillomavirus (HPV), respectively. Their progression becomes more probable when the immune system is compromised by AIDS. Indeed, a nadir CD4+ cell count is a risk factor for AIDS-defining malignancies, both in the pre- and post-HAART eras [2].

The introduction of HAART reduced the incidences of Kaposi sarcoma and non-Hodgkin lymphoma by 80%–85% [1–3], but the same cannot be said for malignancies caused by HPV. Cervical cancer incidence in HPV-positive women has not changed since the introduction of HAART; according to one study [1], the incidence remains at approximately 150 cases per 100,000 persons-year. Other studies have shown an increasing trend, although not a statistically significant one [2, 4]. Thus, women living with HIV infection continue to be affected disproportionately by cervical cancer, with an incidence that is 10-fold higher than in the general population.

Anal squamous cell carcinoma is not formally included among the AIDS-defining malignancies, but its incidence is also greatly increased in patients living with HIV infection. We now know that >90% of anal cancers are caused by HPV infection, with most cases being caused by HPV 16 [5]. Study after study has shown a definite increasing trend in the incidence of anal cancer in the HAART era. For example, in the study by Chaturvedi et al [4], the incidence was 10.5 cases per 100,000 person-years for the period from 1980 through 1989 and 42.3 cases per person-year for the period from 1996 through 2004. In HIV-infected men who have sex with men (MSM), the incidence of anal cancer now approaches the incidence of cervical cancer in HIV-positive women. The prevalence of other, rarer genital HPV-associated tumors and, especially, of oral and pharyngeal tumors has also been observed to increase in HIV-positive individuals in the HAART era [1–3].

Many cross-sectional studies have shown that HIV-positive individuals have a much higher prevalence of carcinogenic HPV infection, a much higher prevalence of infection due to multiple types, and a high prevalence of high-grade cervical or anal dysplasia. MSM-infected with HIV are also nearly all infected with 1 or more HPV types. Obviously, HAART does not have the power to clear HPV infections, and the increasing incidence of HPV-associated malignancies has been attributed to the longer survival of people with HIV infection, which provides a sufficient amount of time for the tumor progression to take place.

Although pap screening for cervical dysplasia and ablation of precancerous lesions (cervical intraepithelial neoplasia,
If anything, HAART has increased the need for monitoring anal HPV disease in individuals with HIV infection. In contrast with cervical disease, in which the detection of a cervical abnormality by regular screening is followed by effective treatment options that prevent invasive cancer, treatment of AIN is more difficult, prone to adverse effects, and plagued by a 60%–70% rate of recurrence [11]. Therefore, although a regular anal cytological screening program would seem to be reasonable, several reports have shown that this approach may be of little use without a definite cure for AIN [11, 12]. In the de Pokomandy et al [6] cohort, 39% of MSM with HIV infection developed AIN over a 3-year period, whereas only 0.12% will develop invasive cancer over the same period of time, if one extrapolates from the data presented by Bower et al [13]. Therefore, some AIN cases must not experience disease progression or may even experience disease regression. Testing for persistent infection due to HPV 16 and 18 may be a way to identify patients at increased risk of invasive cancer, but the very high prevalence of these HPV types (>40% prevalence in the de Pokomandy et al [7] cohort) will not help much in reducing the screened population.

It would be very useful in the future if cohorts like the one described in the article by de Pokomandy et al [6] could be used to study, over a longer period of time, the rate of progression of AIN to invasive cancer and, perhaps, the rate of regression, as was done with the same cohort for HPV infection [7]. Studies such as this may bring us closer to the identification of biological markers of AIN progression and provide a practical screening tool for anal HPV disease.

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References

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