HIV-associated anal cancer
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F1000 Medicine Reports 2010, 2:85 (doi:10.3410/M2-85)
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Abstract
HIV-associated anal carcinoma, a non-AIDS-defining cancer, is a human papillomavirus-associated malignancy with a spectrum of preinvasive changes. The standardized incidence ratio for anal cancer in patients with HIV/AIDS is 20-50. Algorithms for anal cancer screening include anal cytology followed by high-resolution anoscopy for those with abnormal findings. Outpatient topical treatments for anal intraepithelial neoplasia include infrared coagulation therapy, trichloroacetic acid, and imiquimod. The development of cost-effective national screening programs for HIV-associated anal cancer remains a challenge.

Introduction and context
Within 5 years of the beginning of the human immuno-deficiency virus (HIV)-1 pandemic in 1981, Kaposi’s sarcoma and non-Hodgkin’s lymphoma had been classified as AIDS-defining illnesses, and invasive cervical cancer was added to this list in 1993. The introduction of highly active antiretroviral therapy (HAART) in the late 1990s transformed the care of patients with HIV and led to an overall fall in the incidence of AIDS-defining cancers [1,2]. It is now recognized that there is a higher incidence of a number of other malignancies, including anal carcinoma, in HIV-infected patients. Anal cancer has many parallels with cervical carcinoma in that human papillomavirus (HPV) infection is the causative factor in nearly all cases, and there is a spectrum of anal precancerous changes, referred to as anal intraepithelial neoplasia (AIN). However, the typically late clinical presentation of anal cancer, morbidity of treatments for invasive disease, and high relapse rates indicate that effective early detection and treatment of preinvasive disease are of considerable importance.

Incidence and risk of anal cancer
Prior to the HIV epidemic, it was known that anal carcinoma was more common in men who have sex with men (MSM) than in the general population [3]; however, anal carcinoma is currently at least twice as common in HIV-positive MSM as in HIV-negative MSM [4]. The standardized incidence ratio (SIR) of anal carcinoma in people with HIV/AIDS is between 19 and 50 [5]. In the Chelsea and Westminster Hospital cohort of 6127 HIV patients, the incidence of anal squamous carcinoma was 141 per 10^6 patients per annum [6], and the prevalence is rising as a consequence of increased longevity [6,7].

Unlike in AIDS-defining cancer, there has been no decline in SIR in the post-HAART era [6]. The risk of anal cancer was initially reported to be unrelated to CD4 cell count [8], although more recently others have identified an increased incidence at lower CD4 levels [7,9]. In a recent meta-analysis, patients immunosuppressed following organ transplant had an SIR for anal cancer of 4.85 whereas the SIR for those with HIV/AIDS was 28.75, reflecting the higher exposure to oncogenic HPV in the latter group [5].

People with a longer duration of HIV infection (>15 years) have a 12-fold higher rate of anal cancer than those that have been infected for less than 5 years [10]. Because the life expectancy of the HIV-positive population continues to increase and because HAART does not appear to be protective, preventative strategies against anal cancer are needed.
Natural history of anal cancer
HPV is a common sexually transmitted infection, with prevalence rates of 50-60% for anal HPV infection in HIV-negative MSM across all age groups [11]. Anal cancer probably arises because of HPV infection of metaplastic reserve cells within the transformation zone, the junction of the anal squamous and rectal columnar epithelia. Anal dysplasia can be classified according to the Richart grading scale (AIN) [12] or the Bethesda system (low-grade squamous intraepithelial lesion/high-grade squamous intraepithelial lesion, or LSIL/HSIL) [13] (Figure 1).

The natural history of anal cancer is not fully understood. Studies of HIV-negative MSM found the rates of prevalence of LSIL and HSIL to be 15% and 5%, respectively [14]. There is a very high prevalence (25-50%) of high-grade AIN in HIV-positive MSM [15-17]. The exact frequency of progression from AIN III to anal cancer is not known, although a figure of between 1% and 8% is estimated [18-21]. Treatment of HSIL appears to be associated with a lower rate of progression to invasive disease [20].

Protocols for screening for anal cancer
Given that AIN II/III is the likely precursor of anal cancer and given the parallels in natural history with cervical cancer, a screening program has been suggested (Figure 2) [22,23]. High-resolution anoscopy (HRA) is a technique to directly identify and treat anal dysplasia. The technique is analogous to colposcopy and is used because AIN severity can be established only after histopathologic assessment via biopsy.

The effectiveness of cytological screening has been studied by comparing the results of cytology smears and histology from HRA-directed biopsies. A sensitivity of 69-93% and a specificity of 32-59% were reported in one review [24], and a Chelsea and Westminster Hospital cohort of 99 patients found a sensitivity of 83% and a specificity of 38% [25].

Recent advances
Infrared coagulation therapy
Infrared (IR) coagulation therapy has been used successfully to treat a variety of lesions, including condylomas and benign cervical disease. It is employed in the outpatient setting and only local anesthesia is required. More recently, IR coagulation has been used in the treatment of high-grade anal dysplasia [26-28]. With follow-up between 6 and 14 months, response rates ranged from 35% to 63%. The procedure was well tolerated, only mild/moderate anal pain was reported, and bleeding was the most common side effect.

Imiquimod
Imiquimod was originally licensed for the treatment of external genital condyloma and is an immunomodulator that signals through Toll-like receptor 7 to induce inflammation through activation of the innate and adaptive immune response. Although imiquimod is not licensed for use in or around the anus, three recent studies have shown it to be effective and well tolerated [29-31]. And although the duration of follow-up was no more
than 9 months in two of the reports, response rates were reasonable, ranging from 46% to 74%. Sanclemente et al. [31] described a 29% recurrence rate; however, in the only other study to report recurrence rates (58%), all of these were found in previously untreated sites [30].

**Trichloroacetic acid**

Trichloroacetic acid (TCA) is widely used in the treatment of superficial skin lesions. In a nonrandomized comparison of TCA with IR coagulation therapy to treat HSIL in HIV-positive MSM, there was an 87% clearance rate with TCA at 13-month follow-up compared with 68% with IR coagulation [32]. More recently, Singh and colleagues [33] found that in HIV-positive men with one lesion, 48% showed clearance following TCA treatment in comparison with just 18% with four or more lesions. Topical 85% TCA was found to be both safe and well tolerated.

**Other treatments**

The quadrivalent prophylactic HPV vaccine, Gardasil (Merck & Co., Inc., Whitehouse Station, NJ, USA), is licensed for the prevention of HPV-associated cancers in women and for the prevention of genital warts in males and females. In a cohort of more than 4000 healthy men from 16 to 26 years of age, quadrivalent HPV vaccination resulted in an 85.6% efficacy against HPV 6/11/16/18-related persistent infection and DNA detection, with a favorable safety profile [34].

**Implications for clinical practice**

**Screening programs for anal cancer**

Advances in the accurate diagnosis and treatment of AIN raise the possibility of the introduction of national screening programs. In the American health-care system, screening HIV-positive MSM every 2 years with anal cytology would offer quality-adjusted life expectancy benefits at a cost per quality-adjusted life year (QALY) of $13,000, which is comparable to other established screening programs [35]. In contrast, anal screening appears to be much less cost-effective in the UK National Health Service model, in which increased low-grade AIN regression rates were found to result in a minimum incremental cost per QALY of £39,405 (approximately $61,555) [36].

**National guidelines**

Although recommendations exist for anal cancer screening, the paucity of clinicians with expertise in HRA has limited the introduction of screening guidelines for at-risk patient populations. Important questions that need to be answered prior to widespread screening include the impact of treatment on the natural progression of HSIL of the anus to invasive disease and whether biomarkers can be found to identify which patients with HSIL will go on to develop invasive cancer.

The degree of uncertainty regarding the benefits and cost-effectiveness of anal screening is reflected in the various professional recommendations. Guidelines produced jointly between the British HIV Association, the British Association for Sexual Health and HIV, and the Faculty of Family Planning and Reproductive Healthcare (2007) [37] state “the role of annual anal cytology and HRA is not yet proven; however, patients should be encouraged to check to report any lumps noticed in the anal canal (evidence level IV”).

In contrast, the New York State Department of Health AIDS Institute (2007) [38] suggests “screening for cellular dysplasia is prudent and recommended, particularly in persons at high risk for infection with papilloma virus” (HIV-positive MSM and those with anal warts). It is estimated that this would apply to 52% of the male HIV-positive population, of which less than 30% would require HRA.

The European Aids Clinical Society guidelines (2009) [39] recommend screening every 1-3 years with digital rectal examination with or without anal cytology, with HRA reserved for those with abnormal cytology. It is acknowledged that the evidence for benefit of screening is unknown but that screening is advocated by some experts. The Centre for Disease Control and Infection guidelines (2009) [40] acknowledge the potential benefits of cytology screening but state that “studies of screening and treatment programs for AIN 2 or 3 should be implemented before definitive recommendations for anal cytology screening can be made”. However, it is suggested that if anal cytology has indicated LSIL or HSIL, HRA should follow.

**Conclusion**

Anal cancer is an increasing problem in the management of patients with HIV. Through better understanding of the natural history of the disease, improvements in management of AIN, and judicious use of screening programs, the prognosis for this disease should continue to improve. History supports this ideal: in the 1980s, the 2-year survival for anal cancer was just 32%, by the mid-1990s it had risen to 54%, and by the end of the millennium it was 76%, which is comparable to that in the HIV-negative population [41].

**Abbreviations**

AIN, anal intraepithelial neoplasia; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency
virus; HPV, human papillomavirus; HRA, high-resolution anoscopy; HSIL, high-grade squamous intraepithelial lesion; IR, infrared; LSIL, low-grade squamous intraepithelial lesion; MSM, men who have sex with men; QALY, quality-adjusted life year; SIR, standardized incidence ratio; TCA, trichloroacetic acid.

Competing interests
The authors declare that they have no competing interests.

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