F1000Reports MEDICINE

Published: 08 December 2010

HIV-associated anal cancer

Thomas Newsom-Davis and Mark Bower*

Address: Department of Oncology, Chelsea and Westminster Hospital NHS Foundation Trust, 369 Fulham Road, London SW10 9NH, UK

* Corresponding author: Mark Bower (m.bower@imperial.ac.uk)

F1000 Medicine Reports 2010, **2**:85 (doi:10.3410/M2-85)

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 immunodeficiency 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.

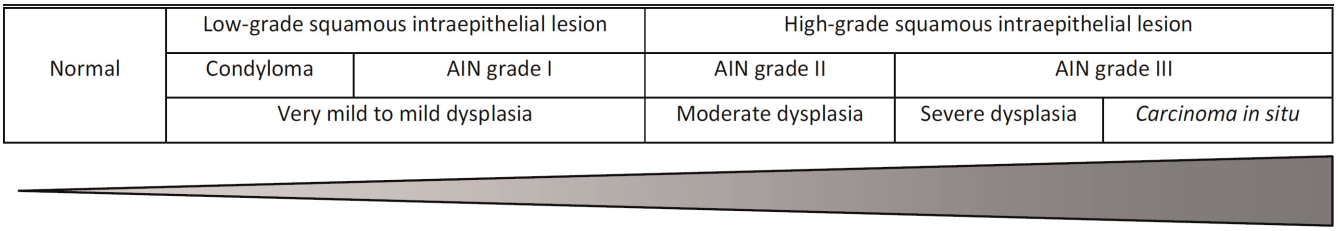
Incidence and risk of anal cancer

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.

Figure 1. The Richart and Bethesda classification of anal dysplastic changes



AIN, anal intraepithelial neoplasia.

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).

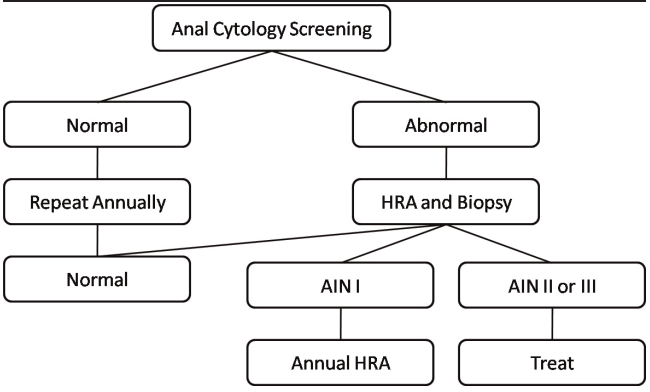
The natural history of anal cancer is not fully understood. Studies of HIV-negative MSM found the rates of prevalence of LSIL and HSIL to be 15% and 5%, respectively [14]. There is a very high prevalence (25-50%) of high-grade AIN in HIV-positive MSM [15-17]. The exact frequency of progression from AIN 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].

Figure 2. Suggested screening algorithm for anal cancer



AIN, anal intraepithelial neoplasia; HRA, high-resolution anoscopy. Adapted from [23].

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.

References

1. International Collaboration on HIV and Cancer: **Highly active antiretroviral therapy and incidence of cancer in human immunodeficiency virus-infected adults.** *J Natl Cancer Inst* 2000, **92:**1823-30.
2. Minkoff H, Ahdieh L, Massad LS, Anastos K, Watts DH, Melnick S, Muderspach L, Burk R, Palefsky J: **The effect of highly active antiretroviral therapy on cervical cytologic changes associated with oncogenic HPV among HIV-infected women.** *AIDS* 2001, **15:**2157-64.
3. Daling JR, Weiss NS, Klopfenstein LL, Cochran LE, Chow WH, Daifuku R: **Correlates of homosexual behavior and the incidence of anal cancer.** *JAMA* 1982, **247:**1988-90.
4. Palefsky JM, Holly EA, Ralston ML, Jay N, Berry JM, Darragh TM: **High incidence of anal high-grade squamous intra-epithelial lesions among HIV-positive and HIV-negative homosexual and bisexual men.** *AIDS* 1998, **12:**495-503.
5. Grulich AE, van Leeuwen MT, Falster MO, Vajdic CM: **Incidence of cancers in people with HIV/AIDS compared with immunosuppressed transplant recipients: a meta-analysis.** *Lancet* 2007, **370:**59-67.

   F1000 Factor 9
   Evaluated by Kiyoshi Nishioka 21 Aug 2007, John Zaia 16 Jan 2008
6. Powles T, Robinson D, Stebbing J, Shamash J, Nelson M, Gazzard B, Mandelia S, Moller H, Bower M: **Highly active antiretroviral therapy and the incidence of non-AIDS-defining cancers in people with HIV infection.** *J Clin Oncol* 2009, **27:**884-90.

   F1000 Factor 8
   Evaluated by James Goedert 16 Jan 2009
7. Chaturvedi AK, Madeleine MM, Biggar RJ, Engels EA: **Risk of human papillomavirus-associated cancers among persons with AIDS.** *J Natl Cancer Inst* 2009, **101:**1120-30.
8. Frisch M, Biggar RJ, Goedert JJ: **Human papillomavirus-associated cancers in patients with human immunodeficiency virus infection and acquired immunodeficiency syndrome.** *J Natl Cancer Inst* 2000, **92:**1500-10.
9. Silverberg M, Xu L, Chao C, Leyden W, Horberg M, Klein D, Towner W, Quesenberry C, Neugebauer R, Abrams D: **Immunodeficiency, HIV RNA Levels, and Risk of Non-AIDS-defining Cancers.** Presented at 17th Conference on Retroviruses and Opportunistic Infection; 16-19 February 2010; San Francisco, CA, USA.
10. Crum-Cianflone NF, Hullsiek KH, Marconi VC, Ganesan A, Weintrob A, Barthel RV, Agan BK: **Anal cancers among HIV-infected persons: HAART is not slowing rising incidence.** *AIDS* 2010, **24:**535-43.
11. Chin-Hong PV, Vittinghoff E, Cranston RD, Buchbinder S, Cohen D, Colfax G, Da Costa M, Darragh T, Hess E, Judson F, Koblin B, Madison M, Palefsky JM: **Age-specific prevalence of anal human papillomavirus infection in HIV-negative sexually active men who have sex with men: the EXPLORE study.** *J Infect Dis* 2004, **190:**2070-6.
12. Fenger C, Nielsen VT: **Intraepithelial neoplasia in the anal canal. The appearance and relation to genital neoplasia.** *Acta Pathol Microbiol Immunol Scand A* 1986, **94:**343-9.
13. Broder S: **Rapid Communication–The Bethesda System for Reporting Cervical/Vaginal Cytologic Diagnoses–Report of the 1991 Bethesda Workshop.** *JAMA* 1992, **267:**1892.
14. Chin-Hong PV, Vittinghoff E, Cranston RD, Browne L, Buchbinder S, Colfax G, Da Costa M, Darragh T, Benet DJ, Judson F, Koblin B, Mayer KH, Palefsky JM: **Age-related prevalence of anal cancer precursors in homosexual men: the EXPLORE study.** *J Natl Cancer Inst* 2005, **97:**896-905.
15. Salit IE, Lytwyn A, Raboud J, Sano M, Chong S, Diong C, Chapman W, Mahony JB, Tinmouth J: **The role of cytology (Pap tests) and human papillomavirus testing in anal cancer screening.** *AIDS* 2010, **24:**1307-13.
16. Palefsky JM, Holly EA, Efirdc JT, Da Costa M, Jay N, Berry JM, Darragh TM: **Anal intraepithelial neoplasia in the highly active antiretroviral therapy era among HIV-positive men who have sex with men.** *AIDS* 2005, **19:**1407-14.
17. Kreuter A, Potthoff A, Brockmeyer NH, Gambichler T, Swoboda J, Stucker M, Schmitt M, Pfister H, Wieland U: **Anal carcinoma in human immunodeficiency virus-positive men: results of a prospective study from Germany.** *Br J Dermatol* 2010, [Epub ahead of print].
18. Marfing TE, Abel ME, Gallagher DM: **Perianal Bowen's disease and associated malignancies. Results of a survey.** *Dis Colon Rectum* 1987, **30:**782-5.
19. Sobhani I, Walker F, Roudot-Thoraval F, Abramowitz L, Johanet H, Henin D, Delchier JC, Soule JC: **Anal carcinoma: incidence and effect of cumulative infections.** *AIDS* 2004, **18:**1561-9.
20. Pineda CE, Berry JM, Jay N, Palefsky JM, Welton ML: **High-resolution anoscopy targeted surgical destruction of anal high-grade squamous intraepithelial lesions: a ten-year experience.** *Dis Colon Rectum* 2008, **51:**829-35.
21. Devaraj B, Cosman BC: **Expectant management of anal squamous dysplasia in patients with HIV.** *Dis Colon Rectum* 2006, **49:**36-40.
22. Palefsky JM, Holly EA, Hogeboom CJ, Berry JM, Jay N, Darragh TM: **Anal cytology as a screening tool for anal squamous intraepithelial lesions.** *J Acquir Immune Defic Syndr Hum Retrovirol* 1997, **14:**415-22.
23. Chin-Hong PV, Palefsky JM: **Natural history and clinical management of anal human papillomavirus disease in men and women infected with human immunodeficiency virus.** *Clin Infect Dis* 2002, **35:**1127-34.
24. Chiao EY, Giordano TP, Palefsky JM, Tyring S, El Serag H: **Screening HIV-infected individuals for anal cancer precursor lesions: a systematic review.** *Clin Infect Dis* 2006, **43:**223-33.
25. Fox PA, Seet JE, Stebbing J, Francis N, Barton SE, Strauss S, Allen-Mersh TG, Gazzard BG, Bower M: **The value of anal cytology and human papillomavirus typing in the detection of anal intraepithelial neoplasia: a review of cases from an anoscopy clinic.** *Sex Transm Infect* 2005, **81:**142-6.
26. Goldstone SE, Kawalek AZ, Huyett JW: **Infrared coagulator: a useful tool for treating anal squamous intraepithelial lesions.** *Dis Colon Rectum* 2005, **48:**1042-54.
27. Stier EA, Goldstone SE, Berry JM, Panther LA, Jay N, Krown SE, Lee J, Palefsky JM: **Infrared coagulator treatment of high-grade anal dysplasia in HIV-infected individuals: an AIDS malignancy consortium pilot study.** *J Acquir Immune Defic Syndr* 2008, **47:**56-61.
28. Cranston RD, Hirschowitz SL, Cortina G, Moe AA: **A retrospective clinical study of the treatment of high-grade anal dysplasia by infrared coagulation in a population of HIV-positive men who have sex with men.** *Int J STD AIDS* 2008, **19:**118-20.
29. Wieland U, Brockmeyer NH, Weissenborn SJ, Hochdorfer B, Stucker M, Swoboda J, Altmeyer P, Pfister H, Kreuter A: **Imiquimod**

treatment of anal intraepithelial neoplasia in HIV-positive men. *Arch Dermatol* 2006, **142:**1438-44.

F1000 Factor 6
Evaluated by Kieron Leslie 09 Feb 2007

30. Kreuter A, Potthoff A, Brockmeyer NH, Gambichler T, Stucker M, Altmeyer P, Swoboda J, Pfister H, Wieland U: **Imiquimod leads to a decrease of human papillomavirus DNA and to a sustained clearance of anal intraepithelial neoplasia in HIV-infected men.** *J Invest Dermatol* 2008, **128:**2078-83.

31. Sanclemente G, Herrera S, Tyring SK, Rady PL, Zuleta JJ, Correa LA, He Q, Wolff JC: **Human papillomavirus (HPV) viral load and HPV type in the clinical outcome of HIV-positive patients treated with imiquimod for anogenital warts and anal intraepithelial neoplasia.** *J Eur Acad Dermatol Venereol* 2007, **21:**1054-60.

32. Salit IE, Tinmouth J, Raboud J, Lytwyn A, Chapman W, Sano M, Diong C: **Anal Dysplasia (the TRACE Study): Comparative Effectiveness of Ablative Therapies.** Presented at 24th International Papillomavirus Conference; 2-10 November 2007: Beijing, China.

33. Singh JC, Kuohung V, Palefsky JM: **Efficacy of trichloroacetic acid in the treatment of anal intraepithelial neoplasia in HIV-positive and HIV-negative men who have sex with men.** *J Acquir Immune Defic Syndr* 2009, **52:**474-9.

34. Jessen H, Giuliano A, Palefsky J, Goldstone S, Moreira E, Penny M, Aranda C, Vardas E, Moi H, Hillman R, Chang Y-H, Ferris D, Rouleau D, Bryan J, Marshall JB, Vuocolo S, Barr E, Radley D, Haupt R, Guris D: **Quadrivalent HPV vaccine efficacy against HPV 6/11/16/18 infection and disease in men.** Presented at 18th International AIDS Conference; 18-23 July 2010: Vienna, Austria.

35. Goldie SJ, Kuntz KM, Weinstein MC, Freedberg KA, Palefsky JM: **Cost-effectiveness of screening for anal squamous intraepithelial lesions and anal cancer in human immunodeficiency virus-negative homosexual and bisexual men.** *Am J Med* 2000, **108:**634-41.

36. Karnon J, Jones R, Czoski-Murray C, Smith KJ: **Cost-utility analysis of screening high-risk groups for anal cancer.** *J Public Health (Oxf)* 2008, **30:**293-304.

37. Fakoya A, Lamba H, Mackie N, Nandwani R, Brown A, Bernard EJ, Gilling-Smith C, Lacey C, Sherr L, Claydon P, Wallage S, Gazzard B; British HIV Association; British Association for Sexual Health and HIV; Faculty of Family Planning and Reproductive Healthcare: *2007 UK guidelines for the management of sexual and reproductive health (SRH) of people living with HIV infection.* [http://www.bashh.org/documents/91/91.pdf]

38. New York State Department of Health AIDS Institute. *Primary Care Approach To The HIV-Infected Patient.* New York; 2007. [http://www.hivguidelines.org/wp-content/uploads/a-primary-care-posted-05-24-2010.pdf]

39. European AIDS Clinical Society (EACS): *Clinical management and treatment of HIV infected adults in Europe.* Paris, France; 2009. [http://www.europeanaidsclinicalsociety.org/guidelinespdf/EACS-EuroGuidelines2009FullVersion.pdf]

40. Kaplan JE, Benson C, Holmes KK, Brooks JT, Pau A, Masur H; Centers for Disease Control and Prevention (CDC); National Institutes of Health; HIV Medicine Association of the Infectious Diseases Society of America: **Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America.** *MMWR Recomm Rep* 2009; **58:**1-207.

41. Biggar RJ, Engels EA, Ly S, Kahn A, Schymura MJ, Sackoff J, Virgo P, Pfeiffer RM: **Survival after cancer diagnosis in persons with AIDS.** *J Acquir Immune Defic Syndr* 2005, **39:**293-9.