Netherlands
The Journal of Medicine

REVIEW

HPV-related anogenital disease and HIV infection: not always 'ordinary' condylomata acuminata

T. Mudrikova*, C. Jaspers, P. Ellerbroek, A. Hoepelman

Department of Internal Medicine and Infectious Diseases, University Medical Centre Utrecht, Heidelberglaan 100 Utrecht 3584 CX, the Netherlands, *corresponding author

ABSTRACT

Human papillomavirus (HPV) is responsible for various diseases in the anogenital region which range from benign condylomata acuminata to anal carcinoma. Buschke-Loewenstein tumour is a clinically 'intermediate' condition which is histologically benign but due to extensive destruction of the local tissues can show malignant behaviour. Its early recognition as a different clinical entity to 'ordinary' condylomata acuminata is important for its adequate management. Immunocompromised persons, such as those with HIV infection, have a higher incidence of HPV-related anogenital disease. Different aspects of the HPV-related anogenital disease in HIV-positive individuals are discussed.

KEYWORDS

Buschke-Loewenstein tumour, HIV, human papillomavirus

INTRODUCTION

Human papillomavirus (HPV) is a common sexually transmitted pathogen. Different HPV genotypes are associated with a whole spectrum of the specific clinical conditions. Anogenital disease can range from the benign condylomata acuminata to anal carcinoma.

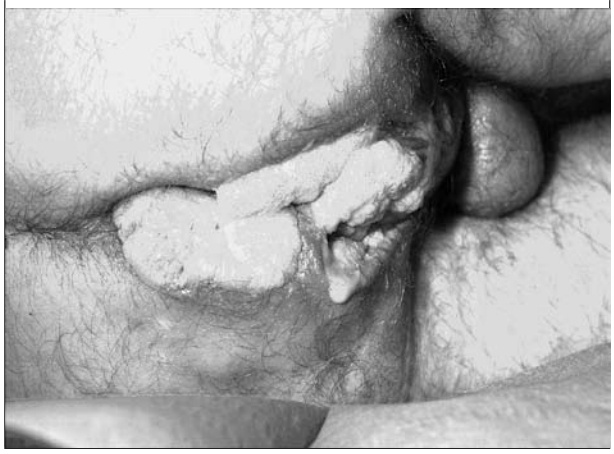
Condylomata acuminata (CA) is the commonest viral sexually transmitted disease in the world with a very low potential for malignant transformation.[1] However, under some (not yet completely understood) circumstances HPV can cause giant CA, also known as Buschke-Loewenstein tumour (BLT). BLT is typically histologically benign and does not metastasise, but it may manifest as a clinically malignant disease due to its expansive and invasive growth. Malignant transformation in the course of the disease occurs in up to 50% of the cases.[2] Although a number of cases of Buschke-Loewenstein tumour have been described in the literature, and a few reviews have summarised the information about this disease, many clinicians do not recognise this process as a different clinical entity with a different course and prognosis than CA.

We present a case of BLT in an HIV-positive patient and summarise the current information on BLT and its relation to the other HPV-related anogenital disorders with special attention to its occurrence and course in HIV-positive individuals.

A 44-year-old heterosexual Moroccan male with a history of type I diabetes mellitus and Hodgkin's lymphoma in complete remission was admitted because of extensive perianal abscesses, fever, chills, and weight loss. He had been known to be HIV positive for four years (CD4 count 491/mm^3, HIV-RNA 150,000 c/ml, no symptoms at presentation). No antiretroviral therapy was started. The patient attended his appointments regularly and reported being well. His laboratory results were stable, the CD4 count never dropped below 350/mm^3.

At admission, he appeared cachectic (BMI 18.2 kg/m^2), with multiple exophytic masses with fistulae and purulent secretion in the perineal and perianal area (*figure 1*). He admitted he had felt too embarrassed to discuss this problem earlier with his treating physician. The CT scan showed an extensive lobulated soft tissue mass between the rectum and corpora cavernosa, with multiple abscesses, and enlarged regional lymph nodes. Microscopically, a verrucous tissue covered with dysplastic epidermis, with hyper- and para-keratosis typical of condyloma acuminatum

Figure 1. *Buschke-Loewenstein tumour in the anogenital area*



was seen; the basal membrane was locally disrupted with invasive growth of dysplastic epithelium into the dermis. PCR was positive for HPV genotype 6. The diagnosis of BLT was made. The patient refused any radical surgery of his perineal disease. Radiotherapy or chemotherapy were not an option because of active infection and his poor general condition. He was treated with broad-spectrum antibiotics and incision of the abscesses. Highly active antiretroviral therapy (HAART) was started (zidovudine, lamivudine, lopinavir). Colostomy was performed which led to discernable relief of the symptoms.

Four months later he was admitted again because of severe sepsis due to major abscess formation in the condylomatous tissue. Because of his deteriorating haemodynamic and respiratory condition not responding to antibiotics and fluid resuscitation the patient eventually consented to (partial) surgical debulking of BLT. The surgical procedure was complicated by massive bleeding of the extensive wound bed. New biopsies showed an invasively growing well-differentiated spinocellular carcinoma which originated from the dysplastic epithelium of the pre-existent condylomata. Because no surgical options remained for radical removal of the tumour, treatment with a subcutaneous pegylated interferon and locally applied cidofovir cream was started, with no improvement. In the next few months the patient was reoperated several times and the newly formed abscesses were incised. The patient's condition slowly deteriorated, he suffered from progressive catabolism and relative adrenal insufficiency. Eight months after the initial admission, after the family of the patient had been consulted, all treatment was stopped and the patient died.

More than 80 different HPV genotypes have been characterised.[3] Anogenital HPV has been classified into low-risk genotypes (6 and 11) associated with 'ordinary' anogenital CA, BLT and mild intraepithelial dysplasia, and high-risk genotypes (16, 18, 31, and 45) which are found in high-grade intraepithelial neoplasia that may progress to anogenital cancer, such as cervical and anal carcinoma.[4,5] The competence of the immune system plays an important role in HPV infection as CA recurs significantly more often and within a shorter period of time after treatment in immunocompromised patients, including those with HIV infection, when compared with patients with a competent immune system.[6,7]

CHARACTERISTICS AND HISTOLOGY OF BLT

Under some (unknown) circumstances HPV 6 and 11 infection cannot be contained and leads to the development of a disfigurating cauliflower-like mass known as Buschke-Loewenstein tumour. It is described mainly in patients with an immunodeficiency (HIV infection, post-transplantation, malignancy, diabetes), during pregnancy, in persons with alcohol abuse, etc. Some local conditions (*Herpes simplex* infection, inadequate hygiene) can also be of importance.[8] It is not clear whether it is the immunological condition at the time of virus acquisition which is important for the development of an extensive disease, or whether the pre-existent HPV infection worsens during the immunosuppression.

BLT is a locally aggressive and extremely morbid condition[9] characterised by a malignant clinical course even when its histological features are benign.[10] It has a high recurrence rate varying between 18 to 67% in different case series[2,11] with an overall mortality of 21%.[2] A review by Trombetta *et al.*,[9] who studied 51 cases published in the English literature between 1958 and 2000, showed that this disease occurs more often in males than in females (ratio 2.7:1) with a mean age of patients of 43.9 years. Microscopically BLT shows thickened squamous epithelium, prominent papillomatosis, fistulous tracts, intact basement membrane, lack of anaplasia or invasion[12] and is distinguished from simple CA by the clear tendency to infiltrate the deeper tissue layers[13] and a 'pushing' rather than infiltrating effect.[9] Symptoms associated with BLT are due to the destruction of the local tissues (pain, bleeding, itching, fistulae) or due to the mechanical obstruction (ileus or problems with defecation which may lead to minimising of food intake and cachexia). Fistulas colonised with bacteria cause the formation of abscesses which can lead to sepsis. Distinction should probably be made between BLT cases presenting in the perianal area and those originating in the rectum as the latter often present only with fistula formation without an apparent exophytic tumour[9] and more often tend to exhibit malignant behaviour.[1]

BLT has much higher potency for malignant transformation than 'ordinary' CA (1.82 *vs* 30 to 56%).[1,2,9,14]

The average time to malignant transformation is five years (range 15 to 100 months).[2] This does not, however, necessarily mean a worse prognosis; in a review by Chu *et al*. patients with malignant transformation of BLT had a better prognosis than those without (33 *vs* 13 %).[2] The local tissue destruction can have fatal consequences before malignant transformation is apparent.

TREATMENT OF BLT

Treatment is often delayed because of the patient's embarrassment about visiting a doctor and fear of the consequences of the therapy. At the time of the first presentation most patients already have extensive disease. To our knowledge only one case of spontaneous regression of BLT has been reported after childbirth in a woman who was diagnosed with BLT during pregnancy.[15] Contrary to CA, conservative treatment alone usually fails. The therapeutic modalities generally used - alone or in combination - are surgery, chemotherapy and radiotherapy. No therapeutic guidelines exist as the number of reported cases is small, and various treatment modalities have been used.

A curative effect has been produced by surgical excision alone[9,10] or in combination with CO_2 surgery,[16,17] neoadjuvant chemotherapy,[14] postoperative radiation,[8,18,] combined chemoradiation [19] and local pelvis perfusion with chemotherapeutics.[2] The use of radiotherapy is still controversial because there is some evidence of anaplastic transformation and a reappearance of condylomas[19-21] as well as a lack of long-term results.[22] A combination of excision with postoperative treatment with interferon (subcutaneously[23] or intralaesionally[24]) or with a locally applied imiquimod crème[25] has also shown to be successful in some patients. Although the antiviral drug cidofovir has been used successfully for the topical treatment of genital warts in combination with surgery in HIV-positive patients,[26] no data in Buschke-Loewenstein tumour have been published.

It has become clear that the treatment of BLT must be early and aggressive to prevent local spread, extensive tissue destruction and eventually malignant transformation as potentially lethal complications. The best results are achieved with surgical therapy. The recommended techniques are either radical local excision or abdominoperineal resection.[22] There are three main problems regarding the surgical treatment: high recurrence rate (probably because of spillage of residual tumour during the operation),[2] difficult wound healing with secondary infection (due to faecal contamination) and high morbidity due to large soft tissue defects.[8,22] Most important for the appropriate management of this highly mutilating condition is the proper recognition of this clinical entity to institute the adequate therapeutic and follow-up measures as soon as possible.

HPV-RELATED DISEASE IN PATIENTS WITH HIV INFECTION

Anal disease is common in patients with HIV infection, especially in men who have sex with men (MSM). Both anal HPV infection and anal intraepithelial neoplasia (AIN) are more common in HIV-positive than in HIV-negative MSM (RR 3.7 for high-grade AIN).[27] Recurrence of anal condylomata has been more strongly associated with HIV positivity and CD4- lymphocytopenia than with persistence of HPV suggesting that HIV-negative individuals can clear the virus more easily.[28]

There seems to be a complex interaction between HIV, HPV and local mucosal immune mechanisms. HIV enhances the HPV transcription[29] and upregulates HPV E7 which influences the cellular differentiation[30] leading to the higher amounts of HPV DNA in the tissue. Furthermore, HPV causes a decrease in the number of the local macrophages, Langerhans and CD4 cells[29,31] and the impairment of the local cytokine production[32,33] resulting in impaired local immune control of HPV infection.

Because HIV seems to enhance replication of HPV one would expect that the initiation of HAART with subsequent suppression of HIV RNA should lead to the decrease in the amount of HPV in the affected mucosa followed by clinical improvement. The *sine qua non* is the good penetration of the antiretroviral drugs in the target tissues (genital of anal mucosa). The effect of HAART on the clinical course of BLT has never been studied systematically. A case describing even paradoxical worsening of BLT as a consequence of immune reconstitution syndrome after the start of HAART in a patient with low CD4 count at presentation (50/mm^3) has been reported.[34] A study in HIV-positive women showed that HAART can reduce the incidence of genital warts and vulvar intraepithelial neoplasia and this effect was mediated through the increase in CD4 cells and reduction of HIV RNA. [35]

BLT AND HIV INFECTION

Only a few cases of BLT have been published in patients with HIV infection, most of them reporting about the effect of the applied therapeutic modalities[36,37] or the co-existence of both conditions.[38-40]

ANAL CANCER AND HIV INFECTION

Anal cancer and its precursor, anal intraepithelial neoplasia (AIN), have a high prevalence in the HIV-positive population.[41] The relative risk for developing anal cancer among HIV-positive MSM is 37-times higher than for the general population.[42]

AIN can be distinguished into mild dysplasia (AIN I), moderate dysplasia (AIN II) and severe dysplasia (formerly known as carcinoma *in situ*, AIN III), [43] which can progress to anal cancer.[44] Anal cancer and high-grade AIN are associated with oncogenic or 'high-risk' HPV genotypes (16 and 18). The natural progression from AIN to anal cancer is unknown.[45] It seems that anal cancer arising from high-grade intraepithelial neoplasia is a result of a different aetiopathogenetic process than anal cancer which develops as a malignant transformation of BLT; they are associated with different HPV subtypes, the former originates typically as a flat intraepithelial lesion while the latter shows an exophytic growth very early.

It has been speculated that the higher incidence of HPV-associated cancers in HIV-positive patients could be due to the increased sexual HPV exposure. High-grade AIN can, however, also be detected in the absence of sexual risk factors in the HIV-positive individuals. When the groups of HIV-positive MSM and intravenous drug users (IVDU) without a history of anal intercourse were compared, more MSM than IVDU showed AIN of any grade (72 *vs* 36%, p<0.001) but the prevalence of high-risk AIN was similar (18 *vs* 18%).[46] The mean nadir CD4 count was significantly lower in IVDU who exhibited high-risk AIN than in those without (16 *vs* 140, p=0.03). Immunosuppression thus plays an important role in the high-risk AIN in HIV-positive persons even in the absence of anal intercourse. Similar data are reported in renal allograft recipients in the absence of receptive anal intercourse.[47] Another explanation for the higher incidence of anal cancer in HIV-positive individuals could be a higher HPV load in the affected tissues. This was shown to be significantly higher in the cervical lesions in HIV-positive than in HIV-negative women, and correlated significantly with severe immunosuppression (CD4 <200/mm^3).[48]

Immunosuppression is known to play an important role in a variety of cutaneous neoplasias.[49] Development of anal cancer in HIV-positive patients was, however, not shown to be related to lower CD4 counts.[50] Immune suppression probably plays a role in the earlier stages of HPV-associated disease but not in the established infection.[41] This might explain why no regression of high-grade AIN was observed after introduction of HAART.[50-52] It can be expected that AIN and anal cancer will probably be seen even more often in the HIV-positive population as a result of improved survival.[3]

The incidence of anal cancer in HIV-positive MSM is comparable with that of cervical cancer before the introduction of screening programmes[53] and the question raises whether such a screening would also be an effective strategy to decrease the incidence of anal malignancy. According to cost-benefit modelling, anal cytological screening in HIV-positive MSM should be cost-effective for preventing anal cancer.[54] Studies are needed to show an effect of dysplasia screening on the incidence of anal malignancy survival in HIV-positive individuals.[45]

Lowering of the prevalence of HPV infection is expected to lower the prevalence of the HPV-associated anogenital disease. One of the ways to prevent the infection with at least some of the HPV genotypes is the vaccination. The positive effect of the quadruple HPV vaccine in young women has recently been shown, with the reduction in the incidence of an HPV-associated anogenital disease and cervical cancer.[55,56] Whether the same effect could be expected in the HIV-positive population is still not known. Moreover, the effect of HPV vaccine has not yet been studied in males.

In conclusion, infection with HPV can cause various anogenital diseases with different prognosis and therapy. The proper and early recognition is essential for their adequate management to avoid unnecessary morbidity and mortality. This is of even more importance in HIV-infected individuals because the disease is more prevalent and more extensive in this population.

REFERENCES

1. Prasad, ML, Abcarian, H. Malignant potential of perianal condyloma acuminatum. Dis Colon Rectum 1980;23:191-7.
2. Chu, QD, Vezeridis MP, Libbey NP, Wanebo HJ. Giant condyloma acuminatum (Buschke-Loewenstein tumor) of the anorectal and perianal regions. Analysis of 42 cases. Dis Colon Rectum 1994;37:950-7.
3. Zbar AP, Fenger C, Efron J, Beer-Gabel M, Wexner S. The pathology and molecular biology of anal intraepithelial neoplasia: comparisons with cervical and vulvar intraepithelial carcinoma. Int J Colorectal Dis 2002;17:203-15.
4. Dunne EF, Nielson CM, Stone KM, Markowitz LE, Giuliano AR. Prevalence of HPV infection among men: a systematic review of the literature. J Infect Dis 2006;194:1044-57.
5. Gissmann L, DeVilliers EM, zur Hausen H. Analysis of human genital warts (condylomata acuminata) and other genital tumours for human papillomavirus type 6 DNA. Int J Cancer 1982;29:143-6.
6. De la Fuente SG, Ludwig KA, Mantyh ChR. Preoperative immune status determines anal condyloma recurrence after surgical excision. Dis Colon Rectum 2003;46:367-72.
7. De Panfilis G, Melzani G, Mori G, Ghidini A, Graifemberghi S. Relapses after treatment of external genital warts are more frequent in HIV-positive patients than in HIV-negative controls. Sex Transm Dis 2002;29:121-5.
8. Dolanc R, Kocher T, Langer I, Marti WR, Pierer G, Harder F. Maligne entarterer perianaler Buschke-Löwenstein-Tumor. Chirurg 2002;73:370-4.
9. Trombetta LJ, Place RJ. Giant condyloma acuminatum of the anorectum: trends in epidemiology and management. Report of a case and review of the literature. Dis Colon Rectum 2001;44:1878-86.
10. Creasman C, Haas PA, Fox TA, Balazs M. Malignant transformation of anorectal giant condyloma acuminatum (Buschke-Loewenstein tumor). Dis Colon Rectum 1989;32:481-7.
11. Reichenbach I, Koebele A, Foliguet B. A Buschke and Löwenstein tumour in a female patient. J Gynecol Obstet Biol Reprod 1995;24:491-5.
12. Hull MT, Eble JN, Priest JB, Mulcahy JJ. Ultrastructure of Buschke-Loewenstein tumour. J Urol 1981;126:485-9.
13. Steffen Ch. The men behind the eponym – Abraham Buschke and Ludwig Lowenstein: Giant Condyloma (Buschke-Loewenstein). Am J Dermatopathol 2006;28:526-36.

14. Hyacinthe M, Karl R, Coppola D, et al. Squamous-cell carcinoma of the pelvis in a giant condyloma acuminatum: use of neoadjuvant chemoradiation and surgical resection. Dis Colon Rectum 1998;41:1450-3.

15. Picaud A, Faye A, Ogowet-Igumu N, Ozouaki F, Nlom-Nze AR. Buschke-Loewenstein tumor during pregnancy. Apropos of 2 cases. Rev Fr Gynaecol Obstetr 1990;85:375-8.

16. Garozzo G, Nuciforo G, Rocchi CM, et al. B schke-Lowenstein tumour in pregnancy. Eur J Obstetr Gynaecol Reprod Biol 2003;111:88-90.

17. Perisic Z, Lazic JP, Terzic B, Perisic S, Rasic R. Condylomata gigantean in anal and perianal region: surgical and CO2 laser treatment. Arch Gynaecol Obstet 2003;267:263-5.

18. Sobrado CW, Mester M, Nadalin W, Nahas SC, Bocchini SF, Habr-Gama A. Radiation-induced total regression of a highly recurrent giant perianal condyloma. Report of a case. Dis Colon Rectum 2000;43:257-60.

19. Butler TW, Gefer J, Kleto D, Schuck EH III, Ruffner BW. Squamous cell carcinoma of the anus in condyloma acuminatum: successful treatment with preoperative chemotherapy and radiation. Dis Colon Rectum 1987;30:293-5.

20. Edstron S, Johansson S, Lindstron J. Verrucous squamous cell carcinoma of the larynx: evidence for increased metastatic potential after irradiation. Otolaryngol Head Neck Surg 1987;97:381-4.

21. Schawde JG, Wara WM, Dedo H, Philip TL. Radiotherapy for verrucous carcinoma. Radiology 1976;120:677-9.

22. De Toma G, Cavallaro G, Bitonti A, Polistena A, Onesti MG, Scuderi N. Surgical management of perianal giant condyloma acuminatum (Buschke-Löwenstein tumour). Eur Surg Res 2006;38:418-22.

23. Fierlbeck G, Rassner G. Condylomata acuminata gigantean with detection of HPV-6-DNA. A case report with adjuvant systemic IFN-gamma therapy. Hautartz 1989;40:767-70.

24. Geusau A, Heinz-Peer G, Volc-Platzer B, Stingl G, Kirnbauer R. Regression of deeply infiltrating giant condyloma (Buschke-Löwenstein tumuor) following long-term intralesional interferon alfa therapy. Arch Dermatol 2000;136:707-10.

25. Holbe HC, Lange-Ionescu S, Frosch PJ, Herbst RA. Condylomata acuminata gigantea. Surgical and combined immunomodulatory therapy. Hautartz 2004;55:1064-6.

26. Orlando G, Fasolo MM, Beretta R, Merli S, Cargnel A. Combined surgery and cidofovir is an effective treatment for genital warts in HIV-infected patients. AIDS 2002;16:447-50.

27. 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.

28. Sobhani I, Vaugnat A, Walker F, et al. Prevalence of high-grade dysplasia and cancer in the anal canal in human papillomatosis-infected individuals. Gastroenterology 2001;120:857-66.

29. Arany I, Evans T, Tyring SK. Tissue specific HPV expression and downregulation of local immune responses in condylomas from HIV seropositive individuals. Sex Transm Inf 1998;74:349-53.

30. Stoler MH, Wolinsky SM, Whitbeck A. Differentiation-linked human papillomavirus types 6 and 11 transcription in genital condylomata revealed by in situ hybridization with message-specific RNA probes. Virology 1989;172:331-40.

31. Spinillo A, Tenti P, Zappatore R. Langerhans cell counts and cervical intraepithelial neoplasia in women with human immunodeficiency virus infection. Gynaecol Oncol 1993;48:210-3.

32. Woodworth CD, Simpson S. Comparative lymphokine secretion by cultured normal human keratinocytes, papillomavirus-immortalized, and carcinoma cell lines. Am J Pathol 1993;142:1544-55.

33. Arany I, Rady P, Tyring SK. Alterations in cytokine/antioncogene expression in skin lesions caused by 'low risk' types of human papillomaviruses. Viral Immunol 1993;6:255-65.

34. Moussa R, Stephenson I, Fisk P, Dhar J, Nicholson KG, Wiselka MJ. Buschke-Loewenstein lesion: another possible manifestation of immune restoration inflammatory syndrome? AIDS 2004;18:1221-3.

35. Massad LS, Silverberg MJ, Springer G, et al. Effect of antiretroviral therapy on the incidence of genital warts and vulvar neoplasia among women with the human immunodeficiency virus. Am J Obstr Gyn 2004;190:1241-8.

36. Uribe N, Millan M, Flores J, Asencio F, Diaz F, Ruiz Del Castillo J. Excision and V-Y- plasty reconstruction for giant condyloma acuminatum. Tech Coloprotcol 2004;8:99-101.

37. Sepou A, Zoguereh DD. Giant anovulvar condylomata acuminata revealing hiv-1 seropositivity in a Centrafrican patient. Med Trop 1998;58:378-80.

38. Gonzalvo Perez V, Eres Saez FJ, Ramada Benlloch FJ, et al. Association of giant condyloma acuminatum of the penis with intraurethral simple condylomata. Apropos of a case. Arch Esp Urol 1991;44:1103-5.

39. Granados E, Palou J, Rios G, Vicente J. Urologic pathology in patients positive for anti-HIV antibodies. Actas Urol Esp 1989;13:378-80.

40. Yedomon HG, Hodonou R, Do Ango-Padonou F, Akpo C, Goudote E, Bourlond A. Buschke-Loewenstein tumor. Apropos of 2 cases in Cotonou, Benin. Bull Soc Pathol Exot 1997;90:184-5.

41. Palefsky J. Biology of HPV in HIV infection. Adv Dent Res 2006;19:99-105.

42. Frisch M, Bigger 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.

43. 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 Infectious Dis 2002;35:1127-34.

44. Holowaty P, Miller AB, Rohan, T, To T. Natural history of dysplasia of the uterine cervix. J Natl Cancer Inst 1999;91:252-8.

45. Chiao EY, Giordano TP, Palefsky JM, Tyring S, El Serag H. Screening HIV-infected individuals for anal cancer precursor lesions: A systematic review. Clin Infectious Dis 2006;43:223-33.

46. Piketty C, Darragh TM, Da Costa M, et al. High prevalence of anal human papillomavirus infection and anal cancer precursors among HIV-infected persons in the absence of anal intercourse. Ann Intern Med 2003,183:453-9.

47. Ogunbiyi OA, Scholefield JH, Raftery AT, Smith JH, Duffy S, Sharp F. Prevalence of anal human papillomavirus infection and intraepithelial neoplasia in renal allograft recipients. Br J Surg 1994;81:365-7.

48. Weissenborn SJ, Funke AM, Hellmich M, et al. Oncogenic human papillomavirus DNA loads in human immunodeficiency virus-positive women with high-grade cervical lesions are strongly elevated. J Clin Microbiol 2003;41:2763-7.

49. Kreuter A, Brockmeyer NH, Hochdorfer B, et al. for the Competence Network HIV/AIDS Clinical spectrum and virologic characteristics of anal intraepithelial neoplasia in HIV infection. J Am Acad Dermatol 2005;52:603-8.

50. Palefsky JM, Holly EA, Efirdc JT, et al. Anal intraepithelial neoplasia in the highly active antiretroviral therapy era among HIV-positive men who have sex with men. AIDS 2005;19:1407-14.

51. Fox P, Stebbing J, Portsmouth S, et al. Lack of response of anal intra-epithelial neoplasia to highly active antiretroviral therapy. AIDS 2003;17:279-80.

52. Piketty C, Darragh TM, Heard I, et al. High prevalence of anal squamous intraepithelial lesions in HIV-positive men despite the use of highly active antiretroviral therapy. Sex Transm Dis 2004;31:96-9.

53. Palefsky JM, Minkoff H, Kalish LA. Cervicovaginal human papillomavirus infection in human immunodeficiency virus-1 (HIV-) positive and high-risk HIV-negative women. J Natl Cancer Inst 1999;91:226-36.

54. Goldie SJ, Kuntz KM, Weinstein MC, Freedberg KA, Welson MI, Palefsky JM. The clinical effectiveness and cost-effectiveness of screening of anal squamous intraepithelial lesions in homosexual and bisexual HIV-positive men. JAMA 1999;281:1822-9.

55. Garland SM, Hernandez-Avila M, Wheeler CM, et al. for the Females United to Unilaterally Reduce Endo/Ectocervical Disease (FUTURE) I Investigators. Quadrivalent vaccine against human papillomavirus to prevent anogenital diseases. N Engl J Med 2007;356:1928-43.

56. Adams M, Jasani B, Fiander A. Human papilloma virus (HPV) prophylactic vaccination: Challenges for public health and implications for screening. Vaccine 2007,25:3007-13.