# Influence of HIV/AIDS on Cervical Cancer: A Retrospective Study From Tanzania

Ramadhani S. Chambuso

Stephen Shadrack

Salum J. Lidenge

Ntoli Mwakibete

Rui M. Medeiros

**Purpose** Cervical cancer is the leading cause of cancer-related morbidity and mortality in women in Tanzania. Any impact of the HIV/AIDS epidemic on cervical precancerous lesions and invasive cervical cancer has a significant implication, as for any public health concern, especially in an area such as the Morogoro region in Tanzania, which has one of the highest rates of cervical cancer in the world.

**Methods** A comparative retrospective study was performed of 536 women screened for cervical cancer by visual inspection methods at the Morogoro Regional Referral Hospital over a period of 3 years; the women were grouped according to their HIV status. The odds ratios (OR) with 95% CIs were estimated using $\chi^2$ test and multivariate analysis. The test statistics were evaluated with a significance level of $P < .05$.

**Results** The prevalence of precancerous lesions was 71.8% in HIV-positive women and 27.3% in HIV-seronegative women. Furthermore, the prevalence of extensive or large precancerous lesions was 40.5% in HIV-positive women and 13.5% in HIV-seronegative women. The prevalence of invasive cervical cancer was 8% in HIV-seronegative women and 11% in HIV-positive women. The risk factors for the cervical lesions were HIV-positive status (OR, 6.8; 95% CI, 4.2 to 11.2; $P < .001$) and being older than 30 years of age (OR, 11.99; 95% CI, 6.86 to 21.21; $P < .001$).

**Conclusion** HIV/AIDS has a highly statistically significant association with ($P < .001$) and a great influence on the development of cervical precancerous lesions in HIV-positive women; however, its direct involvement in the progression to invasive cervical cancer, especially in this era of highly active anti-retroviral therapy, is questionable.

**Ramadhani S. Chambuso** and **Ntoli Mwakibete**, Morogoro Regional Referral Hospital, Morogoro; **Stephen Shadrack** and **Salum J. Lidenge**, Ocean Road Cancer Institute, Dar Es Salaam, Tanzania; **Ramadhani S. Chambuso** and **Rui M. Medeiros**, Institute of Biomedical Sciences Abel Salazar of the University of Porto; and **Rui M. Medeiros**, Institute of Portuguese Oncology Francisco Gentil, Porto, Portugal.

Corresponding author: Ramadhani S. Chambuso, MPH, MSc, Morogoro Regional Referral Hospital, PO Box 110, Morogoro, Tanzania; e-mail: rchambuso@outlook.com.

## INTRODUCTION

Each year, more than 530,000 women worldwide are diagnosed with cervical cancer, and approximately 275,000 die as a result of the disease, with 88% of deaths occurring in developing countries, especially in sub-Saharan Africa.[1] Furthermore, women with HIV infection are more likely to have a concurrent human papillomavirus (HPV) infection, which is a causative agent of cervical cancer.[2] Some studies suggest that HIV infection is associated with the rapid progression of HPV-induced cervical premalignant lesions to invasive cervical cancer.[3] In addition, the HIV/AIDS epidemic in sub-Saharan Africa, which affects Tanzania with its high HIV prevalence rate (6.8% in 2007) in women 15 to 49 years of age, has significant implications for any public health concern attempting to address the impact of the disease on invasive cervical cancer.[4] Currently, however, there are no published data on the burden of the disease in the Morogoro region.[5] Moreover, the impact of HIV/AIDS on cervical cancer has not been determined, regardless of the increase in the number of invasive cervical cancer cases in young women in the eastern zone of Tanzania, specifically in the Morogoro region, a region with a high HIV/AIDS prevalence.[4]

Although numerous studies have documented the association between HIV infection and the presence of cervical intra-epithelial neoplasia (CIN), few have shown a direct involvement of HIV infection, apart from immunosuppression, in invasive cervical cancer. The unknown prevalence of HPV, CIN, and invasive cervical cancer in a high-risk population such as that of the Morogoro region is a matter of great concern, especially with the current HIV/AIDS epidemic in the country. This emphasizes the need to conduct a study on the impact of HIV/AIDS and the risk factors for and predictors of CIN and invasive cervical cancer. Previous studies have recommended the need for cervical cancer screening in HIV-infected women because of the increased incidence and prevalence of CIN and invasive cervical cancer among people living with HIV/AIDS. However, many of these studies have suggested that a visual screening test be used for the detection of

premalignant cervical lesions, especially in low-resource settings.[4]

This study's objective was to determine the impact of HIV/AIDS on the prevalence of and risk factors for cervical precancerous lesions and invasive cervical cancer among HIV-infected women in the Morogoro region. We hope the findings will lead to the implementation of a continuous cervical cancer screening program in all HIV/AIDS clinics and hence to a gradual decrease in the overall high cervical cancer mortality in this country.

## METHODS

A comparative retrospective study of 536 patients who were screened for 3 years for cervical cancer by visual inspection using acetic acid (VIA) or Lugol's iodine (VILI) at Morogoro Regional Referral Hospital was performed at the obstetrics and gynecology department; the patients were then grouped according to their HIV status, and those who were referred to a tertiary hospital were followed up for additional pathologic diagnosis. Extraction of information from the original patients' files and other logbooks contained in the hospital medical records was performed. Some women went to the hospital directly as a result of the cervical cancer awareness campaigns in the region, whereas others were observed at the care and treatment center for HIV/AIDS at the hospital.

The following information was extracted from the files: sociodemographic characteristics, age at screening, cervical appearance at screening, treatment, referral status and outcomes, HIV status, highly active antiretroviral therapy (HAART) usage and CD4 T-cell count if the case was previously identified as HIV/AIDS, method of screening used, age at menarche, age at sexual debut and first delivery, marital status, education level, occupation, contraceptive history, and parity.[4] Ethical clearance was requested, and permission was sought from the management of the hospital. To maintain the confidentiality of the screened women, the information obtained will be used for approved research purposes only.

The Tanzania HIV rapid test algorithm for detection of HIV antibodies was used as a standard operating procedure.[6] VIA or VILI involved naked-eye inspection of the cervix under bright light conditions at least 1 minute after the application of the solutions. The screening tests were performed by gynecologists or trained physicians, nurses, and midwives.[7] A positive result was based on the appearance of well-defined, acetowhite areas in the transformation zone.[7,8] For the inspection with VILI solution, it was applied to the cervix and it stained glycogen stored in cervical epithelial cells.[8,9] Neoplastic and immature squamous metaplastic epithelium did not turn mahogany brown. Instead, they appeared as mustard yellow changes, as easily recognizable as the acetowhite changes associated with VIA.[7,9]

Small loop biopsies were performed, mainly for pre-invasive lesions but occasionally for early invasive carcinomas if highly suggestive.[10] Wedge biopsies are usually performed for the confirmation and typing of tumors,[11] but they were not performed in this study because of the lack of a colposcopy device. Fixation in eosin-tinted formalin to facilitate their preservation and identification was performed, and all the biopsy fragments were processed equally to ensure there were no fragments lost.[12]

The request forms incorporated a macroscopic description of the specimens and identification of the areas of the cervix from which the biopsy specimen had originated (ie, ectocervix, endocervix, or transformation zone).[13] When a biopsy failed to reveal the source of the abnormal cells, it was clearly stated in the request form for the pathologist to note this and to differentiate between a biopsy that was technically adequate but failed to identify a lesion and a biopsy that was technically inadequate.[12] If invasive disease was suspected on the basis of the gynecologic examination,[14] a gynecologist was advised to examine the patient and referral was considered. Clinical information required on the specimen request form included full patient details, the date the biopsy was performed, cervical screening history (if available), clinical appearance of the cervix, site of the biopsy, and results of previous biopsies if any.

Precancerous lesions were treated either by using the ablative method, the most common being cryotherapy, or by using excisional methods, such as cone biopsy or loop electrosurgical excision procedure (LEEP).[4] Unlike LEEP, cryotherapy did not result in a biopsy sample, and thus it was not possible to know if the whole lesion had been destroyed.[9] Operational definitions were as follows: exclusion criteria: patients who were out of the study time frame and those with unknown HIV status; small precancerous lesions: the entire lesion was visible, the squamocolumnar junction was visible, and the lesion did not cover > 75% of the ectocervix[15]; extensive/large lesions: the lesion extended beyond the cryoprobe used or extended

> 2 mm into the cervical canal or into the vaginal wall.[4,15,16]

All women who were suggestive of cervical cancer were referred to a tertiary hospital for additional pathologic evaluations.[4] The record audits were performed from the data logbook with follow-up details of all patients' information, and other details were noted from the original files, coded, and then entered into the SPSS computer program (version 20; SPSS, Chicago, IL) to create a database. Further analysis of the coded database and categorical comparisons were performed with the $\chi^2$ test and Fisher's exact test on different occasions. Test statistics were evaluated with a significance level of $P < .05$.

## RESULTS

A total of 536 women were screened for cervical cancer using the VIA or the VILI methods. The baseline characteristics of these women according to their sociodemographic status are summarized in Table 1.

The prevalence of cervical precancerous lesions in HIV-positive women was 71.8%, which was higher than the 27.3% found in HIV-negative women (Fig 1).

In multivariate analysis, an association was found between HIV-positive status and VIA/VILI–positive results ($P < .001$; odds ratio [OR], 6.8; 95% CI, 4.2 to 11.2). In addition, women older than 30 years of age had a higher risk of being VIA/VILI positive during screening ($P < .001$; OR, 11.99; 95% CI, 6.86 to 21.21; Table 2).

## DISCUSSION

To our knowledge, this study provides the first comparative retrospective analysis of the influence of HIV/AIDS on precancerous lesions and invasive cervical cancer. A comparison between HIV-positive and HIV-seronegative women in the Morogoro region in Tanzania was performed. The prevalence of cervical precancerous lesions was 71.8% in the HIV-positive women and only 27.3% in the HIV-seronegative women. This indicates that HIV-positive women develop more cervical precancerous lesions compared with HIV-seronegative women ($P < .001$; OR, 6.8; 95% CI, 4.2 to 11.2).

These findings reinforce previous evidence and add data from a different study population to the current existing similar findings. Our results show a greater prevalence of precancerous lesions than do the previous studies performed to date in Tanzania. In studies performed in HIV-positive women

**Table 1 –** Sociodemographic Characteristics of Study Subjects (N = 536)

| Parameter/Characteristic | n | % |
|---|---|---|
| Age group, years | | |
| 21-45 | 385 | 71.8 |
| 46-70 | 145 | 27.1 |
| ⩾ 71 | 6 | 1.1 |
| Marital status | | |
| Married | 298 | 55.6 |
| Widowed/single | 170 | 31.7 |
| Divorced/separated | 68 | 12.7 |
| Occupation | | |
| Business | 171 | 31.9 |
| Peasant | 129 | 24.1 |
| Employed | 123 | 22.9 |
| Farmer | 65 | 12.1 |
| Student | 17 | 3.2 |
| Other | 31 | 5.8 |
| Education level | | |
| Nonformal | 197 | 36.8 |
| College | 115 | 21.5 |
| University | 102 | 19 |
| Secondary | 70 | 13.1 |
| Primary | 52 | 9.7 |
| Parity | | |
| 0-3 | 360 | 67.2 |
| 4-7 | 145 | 27.1 |
| ⩾ 8 | 31 | 5.2 |
| Age of sexual debut, years | | |
| 13-16 | 248 | 46.3 |
| 17-20 | 225 | 42 |
| ⩾ 21 | 63 | 11.7 |

in 2013 in Tanzania, Kafuruki et al[17] found the prevalence of precancerous lesions to be 26%, Mwakigonja et al[18] found the prevalence of precancerous lesions to be 38.3% in HIV-positive women and 34% in HIV-negative women, and Balandya et al[19] found a prevalence of precancerous lesions of 42.2% in HIV-positive women. Together, these results show that the incidence of cervical precancerous lesions has been increasing in HIV-positive women in different study populations over time. However, these findings should be challenged by the current use of HAART by women living with HIV/AIDS. In fact, HAART contributes to the immune reconstitution to fight opportunistic infections including HPV-induced precancerous lesions.

**Fig 1 –**
All screened women distributed according to their HIV status, VIA/VILI results, and methods of treatment used. (Nineteen women with unknown HIV status were removed.) LEEP, loop electrosurgical excision procedure; VIA, visual inspection using acetic acid; VILI, visual inspection using Lugol's iodine.
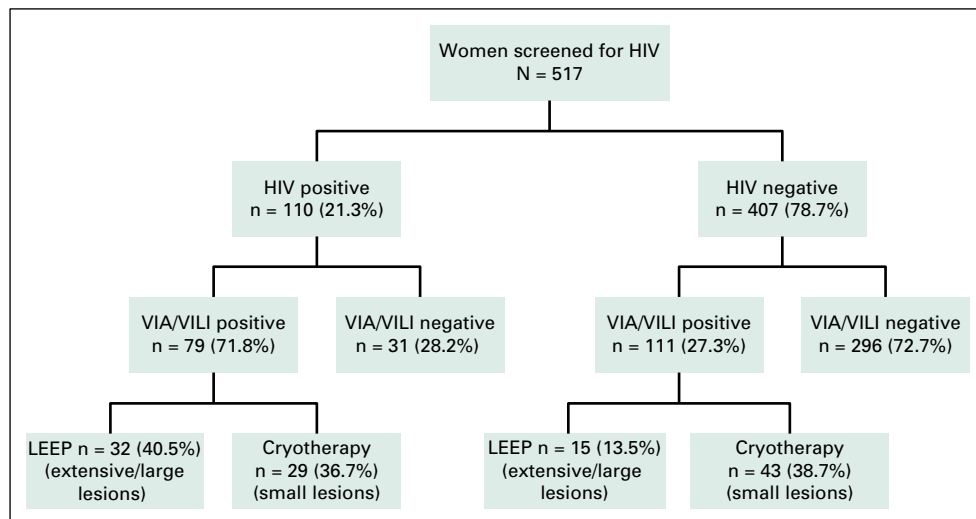
The high prevalence of cervical precancerous lesions found in this study may also be explained by the fact that our study used a lower CD4 count, up to 200 cells/mm$^3$, compared with other studies that used a CD4 count of 351 cells/mm$^3$[18,19] or 450 cells/mm$^3$.[17] The lower CD4 cell count and advanced stage of HIV could be responsible for the higher prevalence of cervical precancerous lesions seen in our study.[19,20] Kafuruki et al,[17] however, found that the prevalence of cervical precancerous lesions decreased from 26.8% to 16% when further investigated by cytology. This might be a result of high sensitivity and overdiagnosis, and hence,

overuse of VIA/VILI screening in the detection of cervical precancerous lesions.[16,21,22] The same effect was also seen in a study performed by Raguenaud et al[23] in Cambodia in HIV-positive women screened initially by VIA and later by cytology.

In our study, the prevalence of extensive/large cervical precancerous lesions was three times greater in HIV-positive women (40.5%) compared with HIV-negative women (13.5%).[18,24] In Africa, a high prevalence of CIN of 76% among HIV-infected women has been observed in Lusaka, Zambia.[25,26] An explanation could be that HIV induced immune suppression because the CD4 count was as low as

**Table 2 –** Summary of the VIA/VILI Results, HIV Status, and Cervical Cancer Diagnosis With *P*-Values, CIs, and Odds Ratios.

| Exposure | Disease | | *P* | CI | OR |
|---|---|---|---|---|---|
| | No Cancer (n = 472) | Cancer (n = 45) | | | |
| HIV negative | 374 | 33 | Ref. | | |
| HIV positive | 98 | 12 | .3551 | 0.72 to 2.52 | 1.39 |
| | VIA/VILI | VIA/VILI | | | |
| | Negative (n = 327) | Positive (n = 190) | | | |
| HIV negative | 296 | 111 | Ref. | | |
| HIV positive | 31 | 79 | <.0001 | 4.2 to 11.2 | 6.8 |
| Age in years | | | | | |
| 20-29 | 182 | 18 | Ref. | | |
| 30-39 | 80 | 68 | <.0001 | 4.64 to 16.8 | 8.59 |
| 40-49 | 34 | 54 | <.0001 | 8.04 to 32.43 | 16.06 |
| ⩾ 50 | 31 | 50 | <.0001 | 8.04 to 33.44 | 16.31 |
| Above 30 | 145 | 172 | <.0001 | 6.86 to 21.21 | 11.99 |

Abbreviations: LEEP, loop electrosurgical excision procedure; OR, odds ratio; Ref, reference; VIA, visual inspection using acetic acid; VILI, visual inspection using Lugol's iodine.

165 cells/mm$^3$; in our study, the lowest baseline CD4 count was 200 cells/mm$^3$.

However, in our study, the prevalence of invasive cervical cancer was slightly lower in HIV-seronegative women than in HIV-positive women (8% and 11%, respectively). This was probably because of the long duration of disease development; it takes 10 to 15 years for a precancerous lesion to develop into invasive cervical cancer. For instance, an HIV clinic–based case-control study conducted by Mwakigonja et al[18] found that the prevalence of invasive cervical cancer was higher (5.8%) in HIV-positive women and lower (2%) in HIV-seronegative women, although the *P* value was not statistically significant (*P* = .6). Furthermore, they used patients in HIV clinics, and many of the HIV-positive patients had been receiving HAART at the clinics for > 25 years, compared with the control subjects, who were simply HIV-seronegative from the general population in a cervical cancer screening program similar to ours.

Conversely, the incidence of HPV-induced diseases has increased rather than decreased since the introduction of HAART[27,28]; HAART restores the immune response to AIDS-defining opportunistic infections such as cytomegalovirus and Kaposi's sarcoma–associated virus; 25% of the HIV-infected CIN1 subjects receiving HAART still progressed to CIN2+, and HIV-infected patients with CIN2+ often do not show regression when treated with HAART.[27,29,30] Moreover, there are no data currently available to shed light on the effect of HAART on the incidence of invasive cervical cancer in HIV-positive women.[27,31]

Regression of CIN1 and CIN2+ depends on the type of HPV (oncogenic or not) rather than on immunocompetence.[32] The longer survival of HIV-infected patients related to HAART may have a proportionally greater impact on the risk of HPV-related cancers than the partial reversal of immunosuppression that occurs with HAART.[23,30,33] The strength of our investigation was that we performed a large, comparative, retrospective study in Tanzania. The weakness was that we had to rely on information documented by others, such as the biopsy diagnosis in the case of referred patients. In addition, there was no history of behavioral risk factors (eg, lifetime sex partners) and limited availability of post-treatment information because of loss to follow-up. However, all these minor shortcomings have little or no confounding effects on our results. Additional studies are needed to determine the crucial relationship between HIV and HPV and the development of invasive cervical cancer; however, to date, many studies report a continuing debate regarding the inclusion of cervical cancer as an AIDS-defining illness.

In conclusion, our findings may provide an important incentive for all HIV-infected women to be engaged in a gynecologic care program. To our knowledge, the prevalence of precancerous lesions in our study is one of the highest reported in any population worldwide. Therefore, HIV/AIDS has a highly statistically significant association (*P* < .001) with, and a great influence on, the development of cervical precancerous lesions in HIV-positive women. However, its direct involvement in the progression to invasive cervical cancer is questionable, especially in the era of HAART.

## REFERENCES

1. WHO: WHO World Cancer Report. Lyon, France, International Agency for Research on Cancer/World Health Organization, 2012

2. Gichangi P, De Vuyst H, Estambale B, et al: HIV and cervical cancer in Kenya. Int J Gynaecol Obstet 76:55-63, 2002

3. Louie KS, de Sanjose S, Mayaud P: Epidemiology and prevention of human papillomavirus and cervical cancer in sub-Saharan Africa: A comprehensive review. Trop Med Int Health 14:1287-1302, 2009

4. Tanzania Ministry of Health and Social Welfare: Service Delivery Guidelines for Cervical Cancer Prevention and Control in Tanzania 2011. Dar el Salaam, Tanzania, Ministry of Health and Social Welfare, 2011

5. Tanzania Ministry of Health and Social Welfare: National Cervical Cancer Prevention and Control Strategic Plan 2011-2015. Dar es Salaam, Tanzania, Reproductive and Child Health Section, Tanzania Ministry of Health and Social Welfare, 2011

6. Tanzania Ministry of Health and Social Welfare: Tanzania HIV Rapid Test Algorithm, 2007. http://ihi.eprints.org/823/1/MoHSW.pdf_%2853%29.pdf

7. Nowak RG, Gravitt PE, Morrison CS, et al: Increases in human papillomavirus detection during early HIV infection among women in Zimbabwe. J Infect Dis 203:1182-1191, 2011

8. Belinson JL, Pretorius RG, Zhang WH, et al: Cervical cancer screening by simple visual inspection after acetic acid. Obstet Gynecol 98:441-444, 2001

9. Urasa M, Darj E: Knowledge of cervical cancer and screening practices of nurses at a regional hospital in Tanzania. Afr Health Sci 11:48-57, 2011

10. Pecorelli S, Zigliani L, Odicino F: Revised FIGO staging for carcinoma of the cervix. Int J Gynaecol Obstet 105:107-108, 2009

11. Scurry J, Patel K, Wells M: ACP Broadsheet No 138: May 1993. Gross examination of uterine specimens. J Clin Pathol 46:388-393, 1993

12. Heatley M: Distribution of cervical intraepithelial neoplasia: Are hysterectomy specimens sampled appropriately? J Clin Pathol 48:323-324, 1995

13. Heatley MK: A comparison of three methods of orienting cervical punch biopsies. J Clin Pathol 52:149-150, 1999

14. McCluggage WG, Hirschowitz L, Ganesan R, et al: Which staging system to use for gynaecological cancers: A survey with recommendations for practice in the UK. J Clin Pathol 63:768-770, 2010

15. Chinchai T, Chansaenroj J, Swangvaree S, et al: Prevalence of human papillomavirus genotypes in cervical cancer. Int J Gynecol Cancer 22:1063-1068, 2012

16. Rustagi AS, Kamineni A, Weinmann S, et al: Cervical screening and cervical cancer death among older women: A population-based, case-control study. Am J Epidemiol 179:1107-1114, 2014

17. Kafuruki L, Rambau PF, Massinde A, et al: Prevalence and predictors of cervical intraepithelial neoplasia among HIV infected women at Bugando Medical Centre, Mwanza-Tanzania. Infect Agent Cancer 8:45, 2013

18. Mwakigonja AR, Torres LM, Mwakyoma HA, et al: Cervical cytological changes in HIV-infected patients attending care and treatment clinic at Muhimbili National Hospital, Dar es Salaam, Tanzania. Infect Agent Cancer 7:3, 2012

19. Balandya BS, Pembe AB, Mwakyoma HA: Cervical pre-malignant lesions in HIV infected women attending Care and Treatment Centre in a tertiary hospital, Dar es Salaam, Tanzania. East Afr J Public Health 8:185-189, 2011

20. van Bogaert LJ: Age at diagnosis of preinvasive and invasive cervical neoplasia in South Africa: HIV-positive versus HIV-negative women. Int J Gynecol Cancer 21:363-366, 2011

21. Ghaemmaghami F, Behtash N, Modares Gilani M, et al: Visual inspection with acetic acid as a feasible screening test for cervical neoplasia in Iran. Int J Gynecol Cancer 14:465-469, 2004

22. Rustagi AS, Kamineni A, Weiss NS: Point: Cervical cancer screening guidelines should consider observational data on screening efficacy in older women. Am J Epidemiol 178:1020-1022, 2013

23. Raguenaud ME, Isaakidis P, Ping C, et al: Screening and treating cervical cancer in HIV-positive women in Cambodia. J Acquir Immune Defic Syndr 51:644-646, 2009

24. Horo A, Jaquet A, Ekouevi DK, et al: Cervical cancer screening by visual inspection in Côte d'Ivoire, operational and clinical aspects according to HIV status. BMC Public Health 12:237, 2012

25. Parham GP, Sahasrabuddhe VV, Mwanahamuntu MH, et al: Prevalence and predictors of squamous intraepithelial lesions of the cervix in HIV-infected women in Lusaka, Zambia. Gynecol Oncol 103:1017-1022, 2006

26. Abdus-Salam A, Ogunnorin O, Abdus-Salam R: hiv seroprevalence in patients with carcinoma of the cervix in Ibadan, Nigeria. Ghana Med J 42:141-143, 2008

27. Chirenje ZM: HIV and cancer of the cervix. Best Pract Res Clin Obstet Gynaecol 19:269-276, 2005

28. Denslow SA, Rositch AF, Firnhaber C, et al: Incidence and progression of cervical lesions in women with HIV: A systematic global review. Int J STD AIDS 25:163-177, 2014

29. Stier EA, Baranoski AS: Human papillomavirus-related diseases in HIV-infected individuals. Curr Opin Oncol 20: 541-546, 2008

30. Boccalon M, Tirelli U, Sopracordevole F, et al: Intra-epithelial and invasive cervical neoplasia during HIV infection. Eur J Cancer 32A:2212-2217, 1996

31. Womack SD, Chirenje ZM, Gaffikin L, et al: HPV-based cervical cancer screening in a population at high risk for HIV infection. Int J Cancer 85:206-210, 2000

32. van der Burg SH, Melief CJ: Therapeutic vaccination against human papilloma virus induced malignancies. Curr Opin Immunol 23:252-257, 2011

33. Strickler HD: Does HIV/AIDS have a biological impact on the risk of human papillomavirus-related cancers? J Natl Cancer Inst 101:1103-1105, 2009