

The quarterly newsletter of
Asia Oceania research
organization on
Genital Infections and
Neoplasia - India



Office Bearers

Founder President

- Dr Neerja Bhatla

Past president

- Dr Shalini Rajaram

President

- Dr Abraham Peedicayil

Vice President

- Dr Rupinder Sekhon

Secretary

Dr Srabani Mittal

Joint Secretary

- Dr Alok Bharti
- Dr Latha Balasubramani

Treasurer

- Dr Sabhyata Gupta

Executive Committee

- Dr Anitha Thomas
- Dr Anupama Shyam
- Dr Bhagyalakshmi Nayak
- Dr Bindiya Gupta
- Dr Dipanwita Banerjee
- Dr Nisha Singh
- Dr Sandeep Mathur
- Dr Sarita Bhalerao

Editor

- Dr Seema Singhal

President ISCCP

- Dr Gauri Gandhi

From the editor's desk



Dear Readers,
The Science for today is the
technology for tomorrow....

We are here with yet another issue of AOGIN India newsletter. This edition features some latest updates about cervical cancer prevention. A major health care goal currently is to develop an approach to eliminate cervical cancer. HPV vaccination and universal screening for everyone remains our most effective tools for eliminating cervical cancer. Immunocompromised women are at high risk of developing cervical neoplasia. In this issue Dr. Sumita Mehta has given a well-constructed and educational expert review on Screening in HIV positive women. In Clinical Pearls two interesting case scenarios are explored by Dr. Latha Balasubramani. Journal Scan contributed by Dr Swasti highlights additional advantage of HPV vaccination in preventing vulvo-vaginal intra epithelial neoplasia.

I extend my warmest thanks to all the authors for their contribution. The entire AOGIN India team and I request you to submit novel and enlightening manuscripts to educate and support the growing field of preventive gynae oncology. I will be looking forward to your valuable feedback and suggestions.

Happy reading !!!

Dr Seema Singhal
AIIMS, Delhi



What's inside

| | |
|--|----|
| Message from the president | 2 |
| Expert Opinion: Cervical Cancer Screening in HIV Positive Women | 3 |
| Journal Scan | 8 |
| Clinical Pearls | 10 |
| Forthcoming Events | 11 |
| The Lighter Facet | 11 |
| Share your activity | 12 |

Message From the President

Dr Abraham peedicayil, Professor and Head Department of Gynae Oncology, CMC Vellore



Dear members of AOGIN-India,

Cervical cancer is one of the most preventable cancers with the availability of prophylactic vaccines as well as several screening tests. However, in India as well as other parts of Asia, Africa and Latin America there is still a lot of work to be done to achieve the “elimination of cervical” cancer goal of the WHO.

The WHO has set three targets to achieve the elimination of cervical cancer: increase coverage of vaccination, increase coverage of screening and optimal treatment of cervical cancer. The strategies adopted by developed nations may not be appropriate for low and middle income countries.

It is heartening to learn that one dose of the HPV vaccine may suffice to prevent cervical precancer and cancer. Again, to boost herd immunity, we may have to move away from vaccinating only the school girls. Coverage is the key as at least 70 % of the population have to be vaccinated to make the HPV vaccination programme cost-effective. Vaccinating boys as well as older women would increase herd immunity if vaccinating most girls would be difficult. The vaccination strategy would not pay dividends for 30 to 40 years during which time the burden of cervical cancer would continue to increase.

Hence, cervical cancer screening would have to continue along with vaccination. We have to move away from opportunistic screening to population based screening and this can be done on by a very committed state and national programme. Low cost HPV testing of women between 35 to 45 years and treatment of positives with thermocoagulation would seem to be the best way forward. Again coverage of over 70 % would be needed. If we are to achieve the WHO targets in a timely manner an accelerated approach with intensive vaccination and screening programmes would be necessary. Hopefully the national health policy makers would give sufficient priority to primary health care and preventive public health. As AOGIN India members we should interact with our colleagues in paediatrics and community health as well as try and influence policy makers in our states to heed the WHO call for action to eliminate cervical cancer.

Best wishes,

Abraham Peedicayil

Cervical Cancer Screening in HIV Positive Women

Dr Sumita Mehta*, Dr Anshul Grover**, *Specialist & In-Charge, ** Specialist
Dept of Obstetrics & Gynecology, BJRM Hospital, Delhi

Invasive cervical cancer (ICC) is a significant cause of morbidity and mortality worldwide. The fourth most common cancer accounts for 2,70,000 deaths every year (1,2). Human Papilloma virus (HPV) infection is now a well documented causative factor for development of cervical cancer (3,4). Majority of the HPV infection in adolescents and in the reproductive age group resolve within a year or two due to the inherent cell immunity. The persistence of oncogenic HPV infection especially in immunocompromised individuals is the key factor for development of cervical oncogenesis (5,6). A significantly higher rate of cervical cancer over the general population is noted in women with HIV / AIDS in Sub Saharan Africa, Western Europe and United States (3,4). A strong association between low CD4 count, HPV infection and precancerous cervical cancer lesions has been demonstrated in various studies. HIV-infected individuals are at higher risk of HPV infection and persistence and are infected by a broader range of HPV types. Women living with HIV have been found to be eight times more likely to develop invasive cervical cancers than women who were not HIV infected, and cervical cancer is an AIDS-defining illness (7).

PRIMARY PREVENTION BY HPV VACCINATION

The burden of HPV infections and HPV associated diseases is definitely higher in HIV infected women compared with HIV uninfected women. This is despite the immunologic reconstitution associated with the use of antiretroviral therapy. The quadrivalent HPV vaccine has been proven to be both safe and immunogenic in HIV infected women. A study conducted by the AIDS Clinical Trials Group (ACTG) found seroconversion rates for all HPV types to be more than 75% for the qHPV vaccine. This trial stratified women according to their CD4 cell counts and seroconversion proportions were high among women with baseline CD4 cell counts of >200 cells/mm³. (8)

Study by Giacomet et al which included both male and female HIV infected adolescents, found similar immunogenic efficacy in the study group with CD4 counts of over 350 cells/mm³ compared to healthy controls matched for gender and age (9).

In another study undertaken by IMPAACT (International Maternal Pediatric Adolescent AIDS Clinical Trials) found seroconversion after q-HPV vaccine to be 90-100%. This response was similar to the one reported in HIV uninfected adolescents (10).

Dosage: Three doses of quadri-valent vaccine is to be

administered to women with HIV infection. This is irrespective of their CD4 cell counts or whether they are on antiretroviral therapy.

The main barrier to uptake of vaccination in HIV infected population is that majority of such women are older than the population targeted for the vaccination. The vaccine is approved for use among women up to 26 years of age. There is lack of data on HPV vaccination rates among younger HIV perinatally infected girls. Among newly diagnosed HIV infected women, 78% are 25 years of age and older (11). Most women living with HIV infection would therefore not be offered the vaccine.

NEED FOR SCREENING PROGRAM IN HIV POSITIVE WOMEN

With the advent of antiretroviral agents, the life expectancy of HIV infected women has increased and now these women are at an increased risk of developing and dying from invasive cervical cancer. Also low CD4 cell counts in HIV infected women make them more vulnerable to development of cervical precancerous lesions. The HER study, by Duerr A et al found CIN was present in 19% of HIV-positive women as compared to only in 5% of the HIV-negative women (12). The Women's Interagency HIV Study Group (WIHS) conducted a large study of women in Abidjan, Ivory Coast and found similar results (13). A study conducted in 2325 HIV-positive women in South Africa between 2003 and 2009 showed a high incidence and prevalence of pre-cancerous cervical lesions. The study showed that women with lower CD4 counts were more likely to have abnormal Pap smears. 38% of women had pre-cancerous lesions at the initial screen with cytology. Their median CD4 cell count was 254 cells/mm³, which was significantly lower than the median of 351 cells/mm³ observed in women with normal cervical cytology ($p < 0.0001$). Each 100 cell/mm³ increase in CD4 cell count reduced the risk of low-grade lesions by 13%, and high-grade lesions by 18% (14). Similar results were seen in a study of HIV-positive women in Thailand which found the prevalence of cervical squamous cell abnormalities at initial Pap smear screenings to be 15.4%. The multivariate correlation analysis showed that women with a CD4 count <350 cells/mm³ had a significant correlation with ASCUS or worse cytology ($p = 0.043$) (15). In a study by Brogly et al, it was documented that 30% of female adolescents who acquire HIV had ASCUS or greater abnormalities at the initial PAPs test and a 12% increased incidence of genital warts (16). A study of Rwandan women who were both HIV and HPV-infected showed that risk factors for stage 3 invasive cervical cancer (ICC) included having been pregnant more than seven times (as against

women who had been pregnant once or twice), malarial infection in the previous six months and ≥ 7 lifetime sexual partners as compared to the risk in women with 0-2 lifetime sexual partners (17). Lack of both opportunistic and organized systematic population based screening programs amongst HIV seropositive women has complicated the matter further. Offering HPV vaccination, as primary cervical cancer prevention to HIV positive women will help in reducing cervical cancer incidence in them. The safety and immunogenicity of HPV vaccine are almost comparable in HIV-positive and HIV-negative women. But the role of secondary prevention with screening is immensely important. ICC rates have declined by 50% or more in many high-income countries, with the introduction of good quality, high-coverage cervical cytology based screening programs with paps smear. Timely follow-up of screen positives, treatment of women with pre-cancer lesions and management of cancers have been the key to reducing ICC related mortality (18). Now, almost 90% of ICC and ICC-related deaths occur in low/middle-income countries (LMICs) due to a lack of resources and healthcare infrastructure needed to provide preventive services. ICC and ICC-related mortality rates are particularly high in sub-Saharan Africa, which also has the highest rates of HIV infection in the world (19).

MODALITIES FOR CERVICAL CANCER SCREENING AMONGST HIV POSITIVE WOMEN

There are no standard screening tests for cervical screening amongst HIV seropositive women and the method needs to be tailored according to the resources and healthcare system of the country as priorities, resources and implementation of guidelines are different for every country. Since all the cervical cancer screening methods being used for HIV-positive women are the same for HIV-negative women, careful analysis of each method's risks and benefits is required to help decisions on which method to use in the meantime as further research is conducted to find the 'best' screening method.

Visual Inspection with acetic acid: A number of studies have quoted the sensitivity of VIA as 55-80% and specificity between 65-83% in detecting CIN2+ lesions in HIV positive women (20-22). A study from Zambia reported the specificity to be 92% which is higher than most studies. As a diagnostic test, VIA has a positive predictive value of approximately 40% and negative predictive value of 79% (23). Using the CIN 2+ threshold, VILI has a slightly better sensitivity and specificity when compared to VIA with sensitivity ranging from 68-96% and specificity of 71-91% (20). Using a combination of VIA and VILI in detecting CIN 2+ in HIV positive women resulted in increased clinical performance with a sensitivity of 81% and specificity of 93.2% (24).

Digital cervicography (DC): Two studies in Zambia reported different efficacy of DC in screening for high grade cervical

lesions in HIV positive women. Chibwesa et al reported sensitivity of DC to be 59%, specificity of 88%, PPV of 49% and NPV of 92% as against Bateman et al who found sensitivity of DC to be as high as 84%, specificity to be low (58%), PPV of 33% and NPV of 93% (23,25).

Cytology: Cytology is the most commonly used screening method in industrialised countries. Reasons for the poor performance of cytology in many LMIC include poor sample collection, poor slide preparation and poor quality screening. In addition, there is lack of human resource in the form of trained cytotechnicians to interpret the slides (19, 26). Owing to their limited health care resources, developing countries cannot afford the models of frequently repeated screening of women over a wide age range that are used in developed countries. Sensitivity and specificity of Pap smear in detecting CIN2+ in HIV positive women has been shown to be between 45-76% and 58-98% respectively (27, 24). Sequential use of VIA and pap smear significantly improves specificity of testing to 97 to 99.5% (24).

High risk HPV Testing: American Society for Clinical Oncology resource-stratified guidelines for secondary cervical cancer prevention suggest hr HPV testing should be preferred choice for screening over VIA especially in HIV positive individuals, with VIA only being used until hr HPV testing becomes available (28,29). Keller et al and Castle PE et al in a recent study conducted in the United States suggested that hr HPV testing may have clinical utility similar to that in HIV-negative women. The studies also concluded that an extended screening interval is safe in HIV-positive women who test hr HPV and Pap negative as it is for HIV-negative women (30-31). In a study of women enrolled in Women's Interagency Health Study in 2002, HIV-positive and HIV-negative women who tested hr HPV and Pap negative were at a similar low risk of CIN2 or more severe (CIN2+) histology over a 5-year follow-up (9). No cases of histologically confirmed CIN2+ were diagnosed in the follow-up of hr HPV-negative and Pap-negative HIV-positive women aged 30-64 years who underwent routine 3-year hr HPV and cytology co-testing at Kaiser Permanente Northern California. Both studies found high negative predictive values (NPV) >99% in HIV-positive women who are hr HPV negative. In a study by Joshi et al who screened for cervical neoplasia in HIV infected Indian women concluded that sequential testing with VIA and VILI is the most feasible screening approach for cervical cancer screening in HIV positive women in low resource countries till the time when HPV testing becomes affordable and feasible when HPV testing followed by VIA/VILI may be considered (24). In 2013 WHO released cervical cancer screening and treatment guidelines based on the model of Zambia which recommended two evidence-based approaches to cervical cancer screening: (1) hr HPV testing or visual inspection after acetic acid (VIA), as alternative initial screening tests instead of Pap, and (2) Screen-and-treat (S&T) approach -

immediately treat those who screen positive using the screening test, instead of subjecting them to colposcopy and biopsy. This approach is found to be more amenable to LMIC settings (32).

"See and Treat" Model

Groesbeck Parham and colleagues identified challenges for implementation of a cervical cancer screening program for women with HIV in Zambia. They developed a screening methodology which did not use HPV DNA testing due to cost, the need for patient recall and the low specificity of the test. Cytology was also not selected for screening because Zambia had only one trained cytotechnologist at the time. The programme was integrated into public health clinics and was not confined to women with HIV, in order to avoid stigmatisation, even through this population was the primary target. An eight-week nurse training in performing VIA and extensive community sensitization was done prior to the initiation of the program. In cases where an acetowhite lesion with well-defined borders was identified women received cryotherapy immediately and scheduled for return visits after 1, 6 and 12 months. Digital cervicography was used to magnify the image of the cervix on a lap-top screen, and to explain the findings to the patient. If the result was indeterminate it was sent to the on-call specialist for advice on what to do. More complex cases such as large-volume lesions, or those suspected of being extensive or invasive, were referred to the University of Zambia Teaching Hospital for biopsy or LEEP. The scheme screened 25,000 women in three years and is now being replicated in Cameroon, South Africa and Botswana. The investigators say that their combination of low tech (VIA), high tech (digital imaging) and high touch (peer education) has the potential to get round some of the major barriers to cervical cancer screening and treatment in resource-limited settings (33). Kuhn et al used screen- and -treat method with HPV DNA testing and cryotherapy in HIV infected women. They found a significant reduction in incidence of CIN2+ in these women, with a relative risk of 0.20. Screen -and -treat using high risk DNA testing and cryotherapy had better positive outcomes when compared to screen and treat using VIA and cryotherapy(34). Mutyaba et al in their study in HIV positive women in Uganda found high false positive rates leading to overtreatment if VIA and cryotherapy were used for screen - and -treat method but if colposcopy was also included then it reduced overtreatment by 72%(35).

SCREENING PROTOCOLS IN HIV INFECTED WOMEN

The following are the recommendations from the Centers for Disease Control and Prevention, National Institute of Health, and the HIV Medicine Association of the Infectious Diseases Society of America (36,37):

Women with HIV infection aged <30 years:

- If younger than 21 years, known to have HIV infection or newly diagnosed HIV infection, and sexually active, screen within 1 year of onset of sexual activity regardless of mode of HIV infection.
- Women with HIV infection aged 21 to 29 years should have a Pap test following initial diagnosis of HIV.
- Pap test should be done at baseline and every 12 months
- Some experts recommend a Pap test at 6 months after the baseline test
- If results of 3 consecutive Pap tests are normal, follow-up Pap tests can be performed every 3 years
- Co-testing (Pap test and HPV test) is not recommended for women younger than 30 years.

Rationale: These recommendations reflect evidence that women with HIV infection <21 years of age and sexually active may have a high rate of progression of abnormal cytology. No similar prospective data are available for adolescents who acquired HIV during the perinatal period. Because of the relatively high HPV prevalence before age 30 years, HPV co-testing is not recommended for women in this age group who do not have HIV infection.

Women with HIV infection aged ≥30 years

Cytology only:

- Pap test should be done at baseline and every 12 months.
- Some experts recommend a Pap test at 6 months after the baseline test.
- If results of 3 consecutive Pap tests are normal, follow-up Pap tests can be performed every 3 years.

Cytology and HPV co-testing:

- Pap test and HPV co-testing should be done at baseline.
- If result of the Pap test is normal and HPV co-testing is negative, follow up Pap test and HPV co-testing can be performed every 3 years.
- If the result of the Pap test is normal but HPV co-testing is positive:

Either

Follow-up test with Pap test and HPV co-testing should be performed in 1 year.

If the 1-year follow-up Pap test is abnormal or HPV co-testing is positive, referral to colposcopy is recommended.

Or

Perform HPV genotyping

- If positive for HPV-16 or HPV-18, colposcopy is recommended
- If negative for HPV-16 and HPV-18, repeat co-test in 1 year is recommended. If the follow-up HPV test is positive or Pap test is abnormal, colposcopy is recommended.

Pap Test and HPV 16 or HPV 16/18 Specified in Co-Testing:

- Pap test and HPV 16 or 16/18 co-testing should be done at baseline
- If result of the Pap test is normal, and HPV 16 or 16/18 co-

testing is negative, follow-up Pap test and HPV co-testing can be performed every 3 years

- If initial test or follow-up test is positive for HPV 16 or 16/18, referral to colposcopy is recommended

Rationale: Current guidelines from both the American Cancer Society and the U.S. Preventive Services Task Force allow for use of HPV co-testing with cytology. A negative HPV test predicts prolonged low risk of cancer. Cytology/ HPV co-testing can allow for a prolonged cervical cancer screening interval in women with HIV infection who are older than 29 years and have normal cervical cytology with concurrent negative HPV testing. For women older than 65 years, it is recommended to continue cervical cancer screening as women with HIV infection are at higher risk for cervical cancer. However, clinicians should consider other factors

such as the life expectancy of the patient and the risk for developing cervical cancer at this age.

CONCLUSION

HPV infection and associated diseases remain prevalent among HIV infected women despite effective antiretroviral therapy. This in turn leads to higher rates of cervical dysplasia and invasive cancers in these subset of women. Primary prevention with quadrivalent HPV vaccine has been found to be immunogenic and safe in HIV positive women and it's uptake in this group of women needs to be encouraged. Early diagnosis of cervical cancer requires universal screening which is lacking in almost all developing countries. There is a need to offer coordinated screening programs which should be integrated into already existing HIV services to promote early identification of cervical precancerous lesions.

REFERENCES

1. American Cancer Society. Global Cancer Facts & Figures 3rd Edition. Atlanta: American Cancer Society; 2015.
2. World Health Organization International Agency for Research on Cancer. Volume 90: Human Papillomaviruses. 2007. In: IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Lyon, France.
3. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer*. 2010;127(12):2893-2917.
4. Schiffman M, Castle PE, Jeronimo J, Rodriguez AC, Wacholder S. Human papillomavirus and cervical cancer. *Lancet*. 2007;370(9590):890-907.
5. Rodriguez AC, Schiffman M, Herrero R, et al. Longitudinal study of human papillomavirus persistence and cervical intraepithelial neoplasia grade 2/3: critical role of duration of infection. *J Natl Cancer Inst*. 2010;102(5):315-324.
6. Schiffman M, Clifford G, Buonaguro FM. Classification of weakly carcinogenic human papillomavirus types: addressing the limits of epidemiology at the borderline. *Infect Agent Cancer*. 2009; 4:8.
7. Clifford GM, Polesel J and Rickenbach M. Cancer risk in the Swiss HIV Cohort Study: associations with immunodeficiency, smoking, and highly active antiretroviral therapy. *Journal of the National Cancer Institute* 2005; 97 (6):425-32.
8. Kojic EM, Kang M, Cespedes MS, et al. Immunogenicity and safety of the quadrivalent human papillomavirus vaccine in HIV-1-infected women. *Clin Infect Dis*. 2014 Jul 1; 59(1):127-35.
9. Giacomet V, Penagini F, Trabattoni D, et al. Safety and immunogenicity of a quadrivalent human papillomavirus vaccine in HIV-infected and HIV-negative adolescents and young adults. *Vaccine*. 2014;32(43):5657-5661.
10. Levin MJ, Moscicki AB, Song LY, et al. Safety and immunogenicity of a quadrivalent human papillomavirus (types 6, 11, 16, and 18) vaccine in HIV-infected children 7 to 12 years old. *J Acquir Immune Defic Syndr*. 2010;55(2):197-204.
11. Women and HIV/AIDS in the United States [<http://kff.org/hivaids/fact-sheet/women-and-hivaids-in-the-united-states/>]
12. Duerr A, Kieke B, Warren D, et al. Human papillomavirus-associated cervical cytologic abnormalities among women with or at risk of infection with human immunodeficiency virus. *Am J Obstet Gynecol* 184(4):584-90, 2001.
13. La Ruche G, Ramon R, Mensah-Ado I, et al. Squamous intraepithelial lesions of the cervix, invasive cervical carcinoma, and immunosuppression induced by human immunodeficiency virus in Africa. *Cancer* 82(12):2401-8, 1998.
14. Omar T et al. Progression and regression of premalignant cervical lesions in HIV-infected women from Soweto: a prospective cohort. *AIDS*, online edition: DOI: 10.1097/QAD.0b013e328340fd99, 2010.
15. Chalermchokcharoenkit A et al. Prevalence and cumulative incidence of abnormal cervical cytology among HIV-infected Thai women: a 5.5-year retrospective cohort study. *BMC Infectious Diseases* 2011, 11:8
16. Brogly SB, Watts DH, Ylitalo N, et al. Reproductive health of adolescent girls perinatally infected with HIV. *Am J Public Health*. 2007;97(6):1047-1052.
17. Anastos K Risk factors for cervical precancer and cancer in HIV-infected, HPV-positive Rwandan women. *PLoS One*. 2010 Oct 20;5(10):e13525.
18. Lonnberg S, Hansen BT, Haldorsen T, et al. Cervical cancer prevented by screening: Long-term incidence trends by morphology in Norway. *Int J Cancer* 2015; 137:1758-64. doi: 10.1002/ijc.29541
19. Sankaranarayanan R, Budukh AM, Rajkuma R Effective Screening programmes for cervical cancer in low- and middle-income countries. *Bulletin of the World Health Organization*, 2001, 79 (10).

20. Huchko MJ, Sneden J, Leslie HH, et al. Bull World Health Organ. 2014; 92(3):195-203.
21. Bansil P, Lim J, Byamugisha J, Kumakech E, Nakisige C, Jeronimo JA. Performance of Cervical Cancer Screening Techniques in HIV-Infected Women in Uganda. Low Genit Tract Dis. 2015; 19(3):215-9.
22. Mabeya H, Khozaim K, Liu T, Orango O, Chumba D, Pisharodi L, Carter J, Cu-Uvin S
23. Comparison of conventional cervical cytology versus visual inspection with acetic acid among human immunodeficiency virus-infected women in Western Kenya. J Low Genit Tract Dis. 2012; 16(2):92-7.
24. Chibwesa CJ, Frett B, Katundu K, Bateman AC, Shibemba A et al. Clinical Performance Validation of 4 Point-of-Care Cervical Cancer Screening Tests in HIV-Infected Women in Zambia. J Low Genit Tract Dis. 2016 Jul; 20(3):218-23.
25. Joshi S, Sankaranarayanan R, Muwonge R, Kulkarni V, Somanathan T, Divate U. Screening of cervical neoplasia in HIV-infected women in India. AIDS. 2013 Feb 20; 27(4):607-15.
26. Bateman AC, Parham GP, Sahasrabudhe VV, Mwanahamuntu MH, Kapambwe S, et al. Clinical performance of digital cervicography and cytology for cervical cancer screening in HIV -infected women in Lusaka, Zambia. J Acquir Immune Defic Syndr. 2014 Oct 1; 67(2):212-5.
27. Sasieni P Has cytology become obsolete as a primary screening tool for cervical cancer? J Med Screen 2010;17:2-3.
28. Chung MH, McKenzie KP, De Vuyst H, Richardson BA, Rana F et al. Comparing Papanicolaou smear, visual inspection with acetic acid and human papillomavirus cervical cancer screening methods among HIV-positive women by immune status and antiretroviral therapy. AIDS. 2013 Nov 28; 27(18):2909-19.
29. Jeronimo J , Castle PE , Temin S , et al . Secondary prevention of cervical cancer: american society of clinical oncology resource-stratified clinical practice guideline summary. J Oncol Pract 2017;13.
30. Castle PE , Jeronimo J , Temin S , et al .Screening to prevent invasive cervical cancer: ASCO resource-stratified clinical practice guideline. J Clin Oncol 2017;35:1250–2.
31. Keller MJ , Burk RD , Xie X , et al . Risk of cervical precancer and cancer among HIV-infected women with normal cervical cytology and no evidence of Oncogenic HPV Infection. JAMA 2012;308:362–9.
32. Castle PE , Fetterman B , Poitras N , et al . Safety against cervical precancer and cancer following negative human papillomavirus and papanicolaou test results in human immunodeficiency virus–infected women. Arch Intern Med 2012;172:1041–3.
33. World Health Organization. New guidelines on screening and treatment for cervical cancer. South Africa: World Health Organization, 2013.
34. Parham GP et al. Building a cervical cancer prevention program into the HIV care and treatment infrastructure in Zambia. In: From the ground up: Building comprehensive HIV/AIDS care programs in resource-limited settings. Establishing a framework for success. Elizabeth Glaser Pediatric AIDS Foundation.
35. Kuhn L, Wang C, Tsai WY, wright TC, Denny L. Efficacy of human papilloma virus based screen –and-treat for cervical cancer prevention among HIV infected women. AIDS. 2010;24(16):2553–2561.
36. Mutyaba T, Mirembe F, Sandin S et al. Evaluation of see and treat strategy and role of HIV on cervical cancer prevention in Uganda. Reprod Health 2010;7:4.
37. Guidelines for the prevention and treatment of opportunistic infections in HIV- infected Adults and Adolescents. <http://aidsinfo.nih.gov/guidelines>



Changes in Cervical Human Papillomavirus (HPV) Prevalence at a Youth Clinic in Stockholm, Sweden, a Decade After the Introduction of the HPV Vaccine

Ährlund-Richter A, Cheng L, Hu YOO, Svensson M, Pennhag AAL, Ursu RG, Haeggbloom L, Grün N, Ramqvist T, Engstrand L, Dalianis T and Du J. *Frontiers*

Aim: The impact of human papillomavirus (HPV) catch-up and vaccination on the very high cervical HPV-prevalence in women at a youth clinic in central Stockholm during the period 2008–2018 is followed in this study.

Background: Between 2008–2010, the cervical HPV-prevalence (69.5%) and HPV16 prevalence (34.7%) were high in non-vaccinated women at a youth clinic in Stockholm. 2013–2015, after the introduction of the quadrivalent-Gardasil® HPV-vaccine, HPV16 and HPV6 prevalence had decreased. Here, cervical HPV-prevalence was investigated 10 years after primary sampling.

Material and Methods: 2017–2018, 178 cervical swabs, from women aged 15–23 years old, were tested for 27 HPV types by a bead-based multiplex method. HPV-prevalence data were then related to vaccination status and age and compared to HPV-prevalence in 615 samples from 2008 to 2010 and 338 samples from 2013 to 2015 from the same clinic, and to HPV types in 143 cervical cancer cases during 2003–2008 in Stockholm.

Results: The proportion of vaccinated women increased from 10.7% (2008–2010) to 82.1% (2017–2018). The prevalence of

all 27 HPVs, all high-risk HPVs (HR-HPVs) and the combined presence of the quadrivalent-Gardasil® types HPV16, 18, 6, and 11, was lower in vaccinated compared to unvaccinated women (67.4 vs. 93.3%, $p = 0.0031$, 60.1 vs. 86.7%, $p = 0.0057$ and 5.8 vs. 26.7%, $p = 0.002$, respectively). Furthermore, HPV16 prevalence in non-vaccinated women 2017–2018 was lower than that in 2008–2010 (16.7 and 34.7%, respectively, $p = 0.0471$) and similar trends were observed for HPV18 and 11. In both vaccinated and non-vaccinated women, the most common non-quadrivalent-Gardasil® vaccine HR-HPV types were HPV39, 51, 52, 56, and 59. Together they accounted for around 9.8% of cervical cancer cases in Stockholm during 2003–2008, and their prevalence tended to have increased during 2017–2018 compared to 2008–2010.

Conclusion: Quadrivalent-Gardasil R vaccination has significantly decreased the vaccine specific HPV-types HPV16, 18, 6, and 11, but five non-vaccine specific HRHPV types HPV 39, 51, 52, 56, and 59 still remain high in potentially high-risk women at a youth clinic in Stockholm. Of these five HR-HPV types, only HPV52 is included in Gardasil R 9. It is therefore important to follow up HPV infections in the future and possibly consider the most prevalent HPV types in this study for the next generation of HPV-vaccines

HPV vaccine in the treatment of usual type vulval and vaginal intraepithelial neoplasia: a systematic review

Stacey Bryan, Cynthia Barbara, Jane Thomas and Adeola Olaitan.
BMC Women's Health 2019;19:3.

Background: HPV DNA is found in almost 80% of VIN/VaIN. A variable period exists between the development of Vulval/Vaginal Intraepithelial Neoplasia (VIN/VaIN) and invasive cancer. HPV vaccines have an established role in the primary prevention of HPV infection generally in younger populations. The role of the HPV vaccine in secondary prevention and treatment has not yet been fully established. This article is a review of literature regarding the role of HPV vaccination for secondary prevention, in the treatment of women with HPV-related VIN and VaIN.

Methods: A systematic literature search for systematic reviews, and randomized controlled trials was conducted. In case of non-availability of these studies, controlled non-random studies and uncontrolled studies were included. Database searches included Ovid Medline, Embase, Web of Science, The Cochrane Library and clinicaltrials.gov. Search terms included HPV vaccine or Human Papilloma Virus vaccine or Papilloma virus vaccines or HPV Vaccin* and therapeutic vaccine* and vin or vain or Vulval intraepithelial neoplasia OR Vaginal intraepithelial neoplasia, published in English with no defined date limit. The use of any form of HPV vaccine in the treatment of women with a histologically confirmed diagnosis of HPV related VIN and/or vain, versus control/standard treatment was conducted. The search also included vaccines as adjuvant to usual care. Studies of other lower genital tract disease (pre-invasive or invasive), vulval/vaginal carcinoma, those concerning prophylactic use of vaccines were excluded. Studies whose participants were pregnant, immunocompromised, or had a history of allergy to vaccine products were excluded. In the included studies,

patients with VIN or VaIN were given any form of HPV vaccination. The outcome measures were lesion response to vaccination, symptom improvement, immune response and HPV clearance.

Results: 93 articles were identified. 7 studies met the inclusion criteria; these were uncontrolled case series. There were no RCTs or systematic reviews identified. Reduction in lesion size was reported by all 7 studies, symptom relief by 5, HPV clearance by 6, histological regression by 5, and immune response by 6.

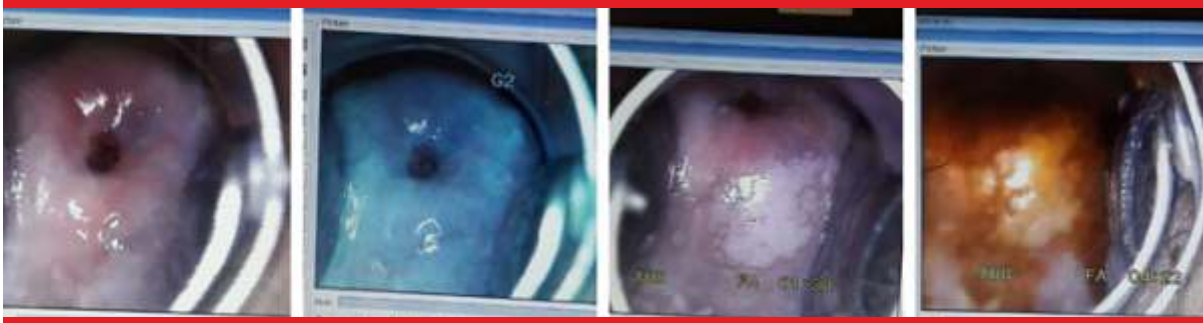
Discussion: This study is the first systematic review of the use of any HPV vaccination in the treatment of HPV related vulval and vaginal disorders. No high-quality studies using commercially available vaccines have addressed this research question. The available vaccines are designed for prevention. Studies that have been carried out are small, case series without control groups, rather than randomized controlled trials using experimental therapeutic vaccines. These study designs have a high risk of bias. Systematic reviews of randomized control trials indicate that available HPV vaccines are safe and effective for prevention. Effectiveness seems to decrease with age and exposure to HPV.

Conclusions: The role of these vaccines as adjuvant to treatment has not been studied. There is limited and low-quality evidence to answer the clinical questions of the role of HPV vaccination in the treatment of VIN/VAIN. Further longitudinal studies are needed to assess its use in prevention of progression to cancer.

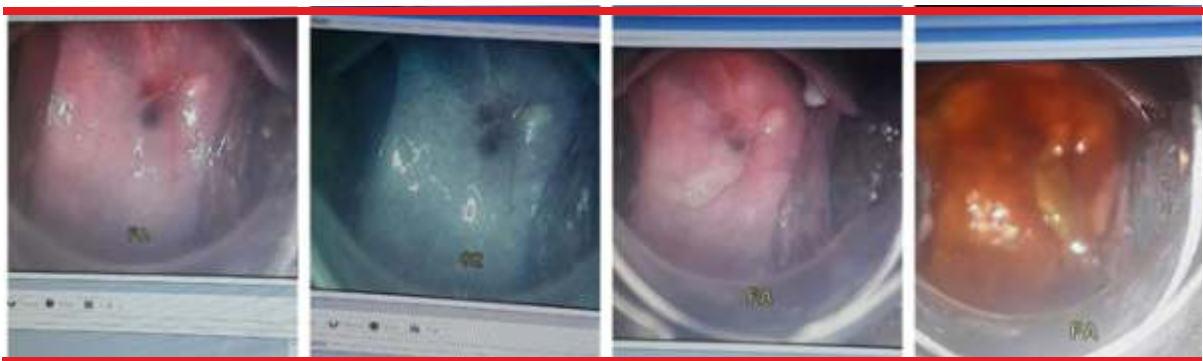
Clinical Pearls

Dr. Latha balasubramani, Dr Divikka Priya

- Q1** A 35 year old was seen at the community screening camp and was found to be VIA/VILI positive. She was referred for colposcopy and her images are seen below.



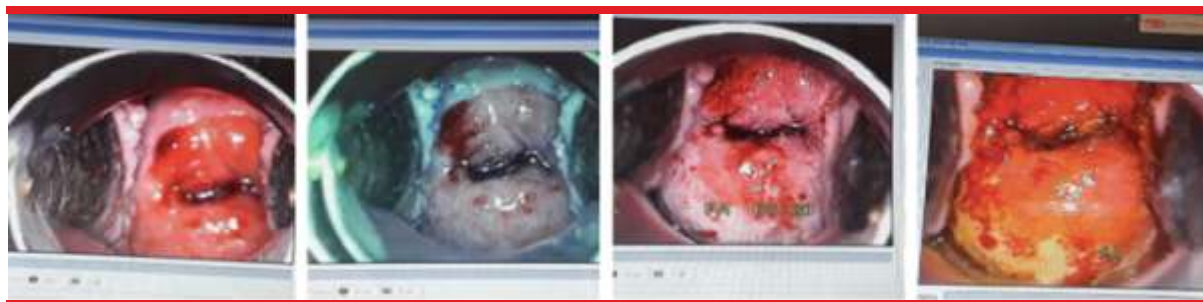
1. Based on these images would you treat her and what modality would you prefer?
2. What are the criteria that needs to be fulfilled to offer cryocautery.



The acetowhite seen on her previous colposcopy has regressed quite well following cryocautery.

- Q2** A 45 year seen in clinic with a pap smear of ASCUS-H. Her colposcopy images are seen below.

1. What is the colposcopic impression and what are the components of the Swede's score?
2. How would you interpret the Swede's score?



Forthcoming Events

- 9th Annual Conference of AOGIN India will be held on 13-15th December 2019 at Amrita Institute of Medical sciences, Kochi, Kerala.
 - 17th World Congress for Cervical Pathology and Colposcopy IFCCP India 2020 will be held on 1-4th October 2020 at Hyderabad India.
 - 33rd International Papillomavirus Conference IPVC 2020 will be held in March 23-27 2020 in Barcelona, Spain. (Abstract submission open)
-

The Lighter Facet



"There are no limits to what you can accomplish, Except the limits you place on your own thinking "

-Brian Tracy



Answers

Answer:1

1. A punch biopsy was taken prior to offering her cryocautery. Cryocautery was done in the community screening camp with the double freeze technique. The punch biopsy report later showed CIN1.
2. The squamo-columnar junction has to be seen completely. The lesion should not occupy all quadrants of the cervix and invasion should be ruled out.

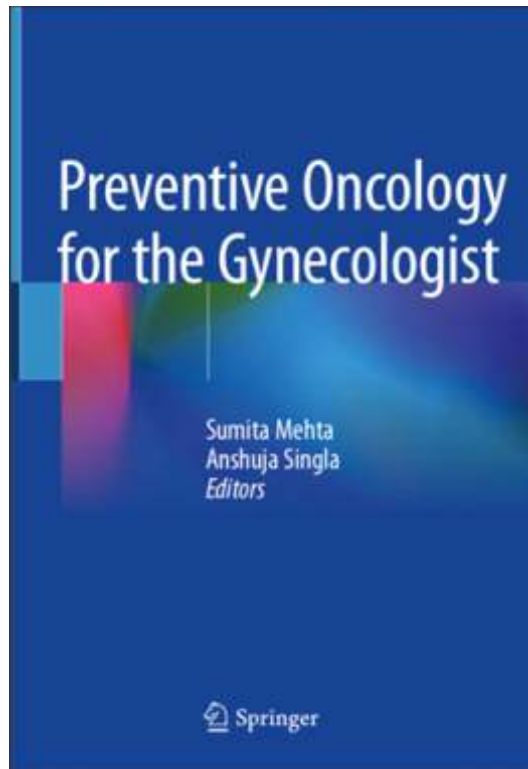
Follow up plan: Co-testing after 3 year.

Answer 2

1. The colposcopic impression was high grade CIN. The cervical biopsy report showed CIN II-III. The components of the Swede's score include Aceto-white uptake, margins, vessels, lesion size and iodine staining. Each parameter is marked 0,1,2 to a maximum of 10.
2. Overall Swede score of 0-4 is normal/low grade, 5-6 denotes high grade disease and 7-10 indicates high grade CIN/invasive cancer.

Preventive Oncology for the Gynecologist

Sumita Mehta & Anshuja Singla



“An ounce of prevention is worth a pound of cure”

This quote by Benjamin Franklin describes the essence of our recently published book “PREVENTIVE ONCOLOGY FOR THE GYNECOLOGIST” by Springer Nature Singapore Pte Ltd.

Cancer is the most dreadful of all diseases and is likely to be a global pandemic by 2050. We need to realize that curing cancers starts with preventing cancer in the first place. There are many books on oncology in the market but they only have a chapter dedicated to the preventive aspect. This book covers the concept of cancer prevention of female genital tract & breast holistically & completely.

The book has 34 chapters divided into six sections for the reader’s convenience; each section has chapters dealing with epidemiology, screening methods, guidelines, diagnosis and treatment of pre-invasive lesions of the endometrium, cervix, ovary, vagina, vulva and breast respectively.

The chapters have been contributed by national & international authors who are experts in their respective fields. All chapters are comprehensive, educative and supported by latest evidence.

The book will be useful for the gynecologists both working in private and teaching institutes.

It will be especially useful for the postgraduates who will find preventive methods & recommended guidelines for screening of various cancers in one book.

The book will also be beneficial to general practitioners as they are the ones who can do opportunistic screening on the women attending their clinic.

Not only the doctors but also the paramedics can gain from the book as many methods to detect premalignant lesions in women can be done at primary level.

This book serves as a “One–stop” book wherein all aspects of preventive oncology of the female genital tract have been discussed and we hope that it finds a place on the shelves of all those who care & work for the preventive aspect of women’s health.

The book is available at [amazon.com](https://www.amazon.com)
Preview of the book is available at: