**IMPACT OF CERVICITIS ON PERFORMANCE OF CERVICAL CANCER SCREENING USING HRHPV TESTING AND VISUAL EVALUATION IN WOMEN LIVING WITH HIV IN BOTSWANA.**

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**Key Words:**

Cervical Cancer

Screening

HPV

Visual inspection

Cervicitis

**Synopsis:**

Cervicitis may affect the accuracy of cervical cancer screening in women living with HIV, even when the high-risk human papilloma virus testing is used.

**Word Count:** 398

**Type of Article:** Brief Communication

**Brief Report Main Text:**

HIV co-infection and poor access to primary and secondary prevention mean cervical cancer mortality is highest in low- and middle-income countries (LMIC) [1]. In 2018, The World Health Organisation (WHO) made a call to action for the elimination of cervical cancer. Achievement of this relies on scale-up of effective screening for pre-invasive disease[1]. The WHO recommends screening algorithms using primary high-risk human papilloma virus (hrHPV) testing followed by visual assessment by visual inspection with acetic acid (VIA) or colposcopy[1]. There is concern that the accuracy of visual assessment may be affected by cervicitis [2,3].

This report describes a sub-analysis of a prospective cohort study evaluating performance of two-stage screening algorithms for cervical cancer in women living with HIV [4]. We evaluated the effect of cervicitis on the accuracy of screening algorithms using primary hrHPV testing followed by visual assessment. Participants were recruited from an HIV clinic in Gaborone for hrHPV testing. Participants with positive hrHPV results underwent VIA, colposcopy, and biopsy performed by trained clinicians according to national protocols. Histopathology was the reference standard for determination of cervicitis, pre-invasive cervical disease, and cervical cancer. Both screening algorithms underwent statistical analysis and diagnostic accuracy was compared between participants with and without cervicitis. Appropriate ethics and consent procedures were followed.

Among 300 women living with HIV screened, median age was 46 years (interquartile range 42-52) and median CD4 count was 649 cells/μL (interquartile range 484-842). 29% (n=88) tested positive for hrHPV and 81 participants underwent visual assessment and histopathological diagnosis. 22 of the 81 women (27%) had cervicitis and 28 of the 81 women (35%) had high grade cervical intraepithelial neoplasia (CIN), defined as CIN2 or higher (CIN2+). For VIA, diagnostic accuracy was 36% (95% confidence interval (CI): 17-51%) for women with cervicitis compared to 58% (CI:44-70%) for women without cervicitis (p=0.09). For colposcopy, diagnostic accuracy was 32% (CI:14-55) for participants with cervicitis compared to 71% (CI:58-82), for women without cervicitis (p=0.001) (table 1).

These data support the hypothesis that cervicitis may reduce the accuracy of visual assessment for predicting pre-invasive cervical disease, even after primary hrHPV testing. Further research is needed to understand the potential impact of cervicitis for screening programmes in LMIC where sexually transmitted infections and HIV/HPV coinfection are common. As new technologies such as automated visual evaluation of the cervix are introduced, the impact of cervicitis on accuracy of these methods must be considered.

**Author contributions:**

Helena Painter: Designed research question, performed data analysis, drafted and finalised manuscript

Adrienne Erlinger: Performed data analysis. Participated in manuscript drafting; approved final manuscript

Boikhutso Simon: Participated in planning and implementation of study. Participated in manuscript drafting; approved final manuscript

Chelsea Morroni: Co-principal investigator of study, guided data analysis. Participated in manuscript drafting; approved final manuscript

Doreen Masire-Ramogola: Co-principal investigator of study. Participated in manuscript drafting; approved final manuscript

Rebecca Luckett: Principal investigator of study, designed research question, guided data analysis. Participated in manuscript drafting; approved final manuscript

**Acknowledgements:**

This work was conducted with support from Harvard University Center for AIDS Research (NIH/NIAID 5P30AI060354-14 grant), Harvard Catalyst | The Harvard Clinical and Translational Science Center (National Center for Advancing Translational Sciences, National Institutes of Health Award UL 1TR002541) and financial contributions from Harvard University and its affiliated academic healthcare centers. The funders had no role in the conduct of the study, data analysis or manuscript preparation.

**Conflicts of interests:**

The authors have no competing interests or conflicts of interest to disclose.

**References:**

[1] World Health Organisation. *Comprehensive cervical cancer control: A Guide to Essential Practice, Second Edition.* Geneva: World Health Organisation; 2014

[2] Vedantham H, Silver H, Kalpana B et al. Determinants of VIA (Visual Inspection of the Cervix After Acetic Acid Application) positivity in cervical cancer screening of women in a peri-urban area in Andhra Pradesh, India. *Cancer Epidemiology and Prevention Biomarkers.* 2010;19:1373-80.

[3] Davis-Dao CA, Cremer M, Felix J, Cortessis VK. Effect of cervicitis on visual inspection with acetic acid. *Journal of lower genital tract disease.* 2008;12:282-6.

[4] Luckett R, Mogowa N, Li HJ, Erlinger AL, Hacker M, Esselen K, Feldman S, Shapiro R, Morroni C, Ramogola-Masire D. Performance of two-stage cervical cancer screening strategies utilizing primary hrHPV testing for women living with HIV. *Obstetric Gynecology.* 2019;134(4):840-849.

**Tables:**

Table 1. Performance of visual evaluation methods of cervical cancer screening following hrHPV testing according to presence of cervicitis in a cohort of women living with HIV in Gaborone, Botswana

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | **N =** | **Sensitivity%**  **(CI)** | **Specificity % (CI)** | **Positive Predictive Value % (CI)** | **Negative Predictive Value % (CI)** | **Diagnostic accuracya % (CI)** | **p valueb** |
| **hrHPV positive + VIA** | | | | | | | |
| All participants | 81 | 59  (39-77) | 48  (34-62) | 39  (24-55) | 68  (50-82) | 52  (41-63) |  |
| No cervicitis | 59 | 63  (42-81) | 53  (35-71) | 53  (35-71) | 63  (42-81) | 58  (44-70) | 0.09 |
| Cervicitis | 22 | 0c | 40  (19-64) | 0c | 80  (44-98) | 36  (17-59) |
| **hrHPV positive + Colposcopy** | | | | | | | |
| All participants | 81 | 823  (64-94) | 48  (34-62) | 47  (33-62) | 83  (65-94) | 61  (49-71) |  |
| No cervicitis | 59 | 89  (71-98) | 56  (38-74) | 63  (46-78) | 86  (64-97) | 71  (58-82) | 0.001 |
| Cervicitis | 22 | 0c | 35  (15-59) | 0c | 78  (40-97) | 32  (14-55) |
| a Diagnostic accuracy = True Positive + True Negative / True Positive + False Positive + True Negative + False Negative  b Chi-square calculated in SAS software to compare diagnostic accuracy proportions for participants with and without cervicitis for each algorithm. Significance p = <0.05  c Not calculated as true positive = 0 | | | | | | | |