Unveiling the interplay of cervical erosion, leucorrhea, and HPV coinfection in the development of abnormal cervical lesion among HIV-positive women

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Abstract. Cervical cancer is a one of significant malignancy in women, especially in developing country. High-risk HPV (*hr*-HPV) infection is the leading cause of cervical cancer. This study provides novel insight by analyzing the combined effect of cervical erosion, leukorrhea, HPV infection (both low and high-risk), and their co-infection on the risk of developing atypical cervical epithelial lesions (ASCUS+) in HIV+ women. A population at heightened oncogenic risk due to immunosuppression. This study uniquely quantifies how these clinical and virological factors interact to influence abnormal cervical pathology in HIV+ population. A cross-sectional study of 130 HIV+ women from Bali VCT clinics included cytological cervical screening (Bethesda system), HPV genotyping, and clinical assessment for cervical errosion and leukorrhea. The results showed that 75.4% of samples had portio erosion, 30.8% had leukorrhea, 16.9% had low-risk HPV, 51.5% had *hr*-HPV, and 12.3% had both. Statistical study indicates significant relationship between portio erosion, *hr*-HPV infection, and ASCUS+ HPV coinfection ($p < 0.05$). The findings support integrated cervical screening with targeted HPV testing and clinical assessment of cervical erosion in HIV+ populations. Future studies should utilize multi-center designs and consider additional confounders to further clarify causal mechanisms and optimal screening strategies.

Keywords: Cervical_Cancer, Abnormal_Cervical_Lesions, HPV, Portio_Erosion, Leukorrhea

1. Background

Cervical cancer remains one of the major global health problems, particularly in developing countries, and is the fourth leading cause of cancer-related deaths among women worldwide [1]. Human papillomavirus (HPV), especially high-risk types such as HPV 16, 52, 58, 53, and 51, are the top five types most commonly implicated as the primary cause of cervical cancer [2, 3]. Persistent HPV infection can lead to the development of precancerous lesions and eventually cervical cancer [4]. This risk increases significantly in women with compromised immunity, such as those living with HIV/AIDS [4, 5]. Preliminary studies have shown that 50% of HIV-positive women undergoing cervical screening are diagnosed with precancerous lesions (ASCUS+), and 81% of these cases are associated with high-risk HPV infection[7].

HIV-positive women have a much higher prevalence of HPV infection compared to HIV-negative women and are at greater risk of acquiring multiple high-risk HPV infections and developing more severe cervical lesions [3, 7, 8]. Immunosuppression due to HIV leads to a reduction in the number and function of CD4 cells, impairing the body's ability to clear HPV infection [8, 9]. As a result, HPV infection tends to persist and accelerates progression to precancerous lesions and cervical cancer [6, 8, 9]. A meta-analysis has shown that HIV-positive women have a 2.6-fold higher risk of HPV infection and a fourfold higher risk of developing cervical cancer compared to HIV-negative women [5], [8]. Moreover, the lower the CD4 count, the higher the risk of HPV infection and progression of cervical lesions [3, 8].

Previous studies have also found that HIV and HPV co-infection increases the expression of HPV oncogenes (such as E6 and E7), accelerates the degradation of tumor suppressor proteins (p53 and pRB), and exacerbates epigenetic changes that promote tumor growth [9]. Additionally, HIV-positive women are more likely to develop multiple cervical lesions, with faster progression and greater severity compared to women with HPV infection alone[3, 8]. Other factors such as cervical erosion (ectropion) and leukorrhea (pathological vaginal discharge) are also commonly observed in HIV-positive women and are suspected to increase the risk of abnormal cervical epithelial lesions [10]. Cervical erosion may facilitate exposure of cervical tissue to infection, while leukorrhea often indicates the presence of reproductive tract infections that can worsen cervical conditions [11]. However, data on the association between these factors and abnormal cervical epithelial lesions in HIV-positive women remain limited and warrant further investigation.

In addition to single high-risk HPV infections, co-infection with both low-risk and high-risk HPV types is of particular concern in HIV-positive women[12, 13]. Recent studies have demonstrated that HIV-positive women have a much higher prevalence of multiple HPV co-infections, both low-risk and high-risk types, compared to HIV-negative women [12,13]. Such co-infections not only increase the viral load in cervical tissue but also prolong the duration of infection and heighten the risk of developing precancerous lesions and cervical cancer[14]. Meta-analyses confirm that HIV-positive women with multiple HPV co-infections, whether low-risk or high-risk, have a greater risk of developing high-grade cervical lesions (HSIL) compared to those with single HPV infections or HIV-negative women [13].

These co-infections are thought to exacerbate oncogenic processes through several mechanisms, including increased expression of HPV oncogenes (E6/E7), immune system impairment due to HIV, and changes in the cervical microenvironment that support HPV persistence and progression [14]. Furthermore, multiple HPV co-infections are associated with reduced effectiveness of local immune responses, thereby accelerating the progression of cervical lesions from early to more advanced stages [9]. Therefore, early detection and screening for co-infection with low-risk and high-risk HPV types are crucial in HIV-positive women to prevent progression to more aggressive cervical cancer.

The aim of this study was to analyze the association between these risk factors and the presence of abnormal cervical epithelial lesions among HIV-positive women. The findings of this study provide important evidence supporting the need for comprehensive screening programs, including testing for multiple HPV types, to enable early identification of co-infections and associated risk factors. Such targeted interventions have the potential to reduce the burden of cervical cancer in high-risk populations, particularly in resource-limited settings, and highlight the importance of improving access to HPV screening and vaccination as integral parts of cervical cancer prevention strategies in developing countries.

2. Methods

2.1 Study Design

This study employed a cross-sectional design conducted at the Biomolecular Laboratory of the Faculty of Medicine and Health Sciences, Warmadewa University, as well as at the VCT Clinics in Bali. The aim was to analyze the association between risk factors (cervical erosion, leukorrhea, low-risk and high-risk HPV infection, and co-infection) and abnormal cervical epithelial lesions among HIV-positive women.

2.2 Population and Sampling

The study population consisted of HIV-positive women who had undergone routine Pap smear screening. A total of 130 participants were included in this study, selected using total sampling method with the following inclusion criteria: women aged 20–50 years, confirmed HIV-positive status, and willingness to participate as indicated by informed consent.

2.3 Data Collection

Data were collected through structured interviews and review of medical records regarding HIV history and the presence of leukorrhea. A physical examination was conducted to assess cervical condition prior to Pap smear (PAPS) testing.

2.4 Pap Smear Examination

Pap smear samples were collected by trained medical personnel using a cytobrush to obtain cervical epithelial cells. The samples were smeared onto glass slides, fixed, and sent to an accredited anatomical pathology laboratory for cytological examination. Interpretation of Pap smear results referred to the Bethesda System, categorized as NILM (Negative for Intraepithelial Lesion or Malignancy) and ASCUS+ (Atypical Squamous Cells of Undetermined Significance or abnormal epithelial lesions).

2.5 HPV Genotyping

HPV genotyping was performed using the HPV XpressMatrix™ Genotyping Kit. Detection included 13 high-risk HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68) and 6 low-risk HPV types (6, 11, 40, 42, 43, 44). Samples were considered positive if DNA from any of the targeted HPV types was detected.

2.6 Data Analysis

Descriptive analysis was conducted to describe the characteristics of the study subjects and the distribution of variables. The chi-square test was used to analyze the association between risk factors and abnormal cervical epithelial lesions. Multivariate logistic regression analysis was performed to identify dominant risk factors for abnormal cervical lesions ($\alpha = 0.05$).

2.7 Ethics Statement

This study received ethical approval from the Ethics Committee of the Faculty of Medicine, Warmadewa University. All participants provided written informed consent, and data confidentiality was strictly maintained.

3. Results

The findings of this study demonstrate several important associations were observed between risk factors and the presence of abnormal cervical epithelial lesions (ASCUS+) among HIV-positive women (Table.1). Women with cervical erosion showed a significantly higher proportion of abnormal cervical lesions compared to those without erosion (41.8% vs 15.6%, $p = 0.007$), indicating that cervical erosion is significantly associated with an increased risk of abnormal epithelial changes. In contrast, the presence of leucorrhea was not associated with a higher risk of abnormal lesions, with similar proportions in both leucorrhea positive and negative groups (35.0% vs 35.6%, $p = 0.951$).

Furthermore, HPV genotyping revealed that women with low-risk HPV infection had a higher proportion of abnormal lesions compared to those without (50.0% vs 32.4%); however, this association was not statistically significant ($p = 0.116$). On the other hand, infection with high-risk HPV was strongly associated with the presence of abnormal cervical lesions, with 64.2% of high-risk HPV-positive women exhibiting ASCUS+ lesions compared to only 4.8% among those negative for high-risk HPV ($p = 0.000$). Notably, women with co-infection of both low-risk and high-risk HPV types had an even higher prevalence of abnormal lesions (68.8%), and this association was statistically significant ($p = 0.003$).

These findings indicate that cervical erosion, high-risk HPV infection, and co-infection with low- and high-risk HPV types are significantly associated with the occurrence of abnormal cervical epithelial lesions among HIV-positive women, whereas leucorrhea and low-risk HPV infection alone were not found to be significant risk factors in this population.

Table 1. Distribution and association of risk factors with the incidence of abnormal cervical epithelial lesions in HIV-positive women

Variable	Categori	ASCUS+ (n, %)	NILM (n, %)	Total (n)	p-value
Porsio Erosion	Yes	41 (41.8)	57 (58.2)	98	0.007
	No	5 (15.6)	27 (84.4)	32	
Leucorrhea	Positive	14 (35.0)	26 (65.0)	40	0.951
	Negative	32 (35.6)	58 (64.4)	90	
HPV Low Risk	Positive	11 (50.0)	11 (50.0)	22	0.116
	Negative	35 (32.4)	73 (67.6)	108	
HPV High Risk	Positive	43 (64.2)	24 (35.8)	67	0.000
	Negative	3 (4.8)	60 (95.2)	63	
Coinfection HPV Low & High Risk	Positive	11 (68.8)	5 (31.2)	16	0.003

4. Discussion

This study confirms that cervical erosion, high-risk HPV infection, and co-infection with both low-risk and high-risk HPV types are significant risk factors for the occurrence of abnormal cervical epithelial lesions in HIV-positive women. These findings are consistent with previous research indicating that women living with HIV have a higher prevalence of high-risk HPV infection and more severe precancerous cervical lesions compared to the general population[15]. Immunosuppression due to HIV exacerbates the persistence of HPV infection, especially oncogenic types, thereby accelerating the progression of cervical lesions toward malignancy[7]. HPV oncogenic proteins such as E5, E6, and E7 play a central role in malignant transformation[16]. Specifically, E6 degrades p53 and E7 inactivates pRb, resulting in uncontrolled cell proliferation and impaired apoptosis[17]. In the context of weakened immunity due to HIV, the activity of these proteins becomes more aggressive, leading to a significantly increased risk of precancerous and cancerous cervical lesions [7], [18].

The biomolecular interaction between HIV and HPV further strengthens the pathogenesis of cervical cancer[15]. HIV proteins Tat and gp120 can enhance the activity of the E6 and E7 promoters of HPV, increasing oncogene expression and accelerating cellular transformation[15]. Additionally, HIV leads to a reduction in the number and function of CD4+ T cells and disrupts the maturation of dendritic cells in the cervical tissue, making the immune response to HPV less effective and allowing persistent infection to occur more readily [18]. Recent studies have also shown that HIV and HPV together induce changes in the vaginal microbiome, increase chronic inflammation, and facilitate epithelial–mesenchymal transition (EMT), all of which support the invasion and metastasis of cancer cells [18]. HIV-positive women with high-risk HPV infection have a greater risk of developing HSIL, and uncontrolled immunosuppression worsens disease progression. Furthermore, increased expression of COX-2 and other inflammatory mediators in the cervical tissue of HIV/HPV-positive women is associated with a poorer prognosis and more rapid cancer progression [19].

In contrast, leukorrhea and low-risk HPV infection were not found to be significantly associated with abnormal cervical epithelial lesions in this study. This is consistent with the literature, which states that low-risk HPV types are more likely to cause genital warts and rarely play a role in cervical oncogenesis [20]. Recent studies also indicate that low-risk HPV infection does not significantly increase the risk of precancerous cervical lesions in either HIV-positive or HIV-negative women, as these types generally lack high cellular transformation potential [20]. Leukorrhea, although frequently observed in HIV-positive women, is more commonly associated with non-HPV reproductive tract infections or alterations in vaginal flora, and does not directly increase the risk of precancerous cervical lesions [21]. Epidemiological studies in the past five years have emphasized that pathological leukorrhea in HIV-positive women is more often caused by non HPV factors, but does not show a significant association with the incidence of precancerous cervical lesions [22].

Therefore, these findings underscore that the primary focus for the prevention and early detection of abnormal cervical epithelial lesions in HIV-positive women should be directed at significant risk factors such as high-risk HPV infection and unhealthy cervical conditions, while leukorrhea and low-risk HPV infection are more relevant as indicators of vaginal ecosystem disturbances or other infections not directly related to cervical oncogenesis. However, this study is limited by the use of cytology alone for lesion diagnosis, which may

result in misclassification due to its lower sensitivity compared to histological confirmation. Additionally, potential confounders such as sexual behavior, immunological status (including CD4+ T cell count), and other concurrent sexually transmitted infections were not comprehensively controlled, potentially influencing the observed associations. These limitations should be considered when interpreting the results, and further studies using more robust diagnostic methods and comprehensive confounder assessment are warranted to validate these findings.

5. Conclusion

Cervical erosion, high-risk HPV infection, and co-infection with both low-risk and high-risk HPV types are significant risk factors for the development of abnormal cervical epithelial lesions in HIV-positive women, whereas leukorrhea and low-risk HPV infection do not show a meaningful association. These findings highlight the importance of early detection, routine screening, and management of risk factors in HIV-positive women to prevent the progression of more severe cervical disease. Further research is needed to explore other risk factors and multifactorial interactions in cervical lesions within this vulnerable population.

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