

Clinical Study

Correlating Pap Smear Results and Colposcopy-Directed Large Loop Excision of the Transformation Zone Histopathology in HIV-Infected and HIV-Uninfected Women: A Case-Control Study in South Africa

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Background. In low-resource settings (LRS) with high HIV/AIDS and cervical cancer rates, new screening strategies face many logistic hurdles. Since cytology is there to stay, at least in the median-term future, it is important to assess to what extent HIV-HPV coinfection impacts the accuracy of screening methods and strategies. **Methods.** We audited the correlation between cytological diagnosis of minimal abnormality (\leq CIN1), CIN2+, or cancer and the histological diagnosis of colposcopy-directed large loop excision of the transformation zone of 399 HIV-uninfected controls and 389 HIV-infected cases. **Results.** The average age at diagnosis of CIN2+ of the cases was 4.2 years younger than controls ($P < 0.0001$). The endpoint used to assess the accuracy of cytology was minimal cytological abnormality (\leq CIN1/LGSIL). The sensitivity, specificity, and negative and positive predictive values were 92.7, 18.5, 45.1, and 77.9%, respectively. The overall ratio of discordance/concordance between cytology and histology was similar in both groups. **Conclusion.** In LRS, where rapid-HPV testing is not yet part of screening algorithms, a cytological diagnosis of minimal abnormality requires visual inspection and treatment of visualized lesions especially in HIV-infected women aged ≤ 30 years. The cytological endpoint of accuracy should be set low to avoid false negative smears.

1. Introduction

It is often stated that more stringent follow-up by means of Pap smears is warranted in HIV-infected than uninfected women [1–3]. The rationale is based on the assumption that cervical cancer is an AIDS-defining illness [4]. However, this assumption is debatable since there is no convincing evidence indicating that the incidence of cervical cancer increased with the spread of HIV/AIDS, be it in the developing or the developed world [5–8]. This being said, the question remains whether preventative strategies should be tailor-made for HIV-infected women.

The prevention of cervical cancer encompasses primary (HPV vaccination and life style) and secondary (screening) measures. In low-resource settings (LRS), HPV vaccination is not yet practiced because of a wide array of logistical hurdles,

and cytological screening is mostly either absent or limited to opportunistic testing [9, 10].

Cervical cytology has been the mainstay of prevention for many decades. Because of its wide range of sensitivity and specificity and the availability of low-cost/low-technology HPV-DNA test kits, there is a slowly growing paradigm shift favoring alternatives based on cytology, rapid-HPV testing, visual inspection, destruction or excision, single or combined. Up to a dozen screening methods are under investigation with the aim of being validated as the best available evidence in this regard [11–14]. In LRS, “see and treat” policies seem to be acceptable [14]. However, there are different ways of seeing (naked eye, visual inspection with acetic acid or Lugol’s iodine, cervicospoty, and colposcopy) and treating (destruction or excision) [15]. Cytology’s primacy is debated but not yet discarded. Combined cytology and HPV testing is

becoming one of the preferred and recommended screening methods [16, 17].

There is evidence that HIV-infected women tend to have an increased risk of carrying one or more high-risk (HR) HPV [18]. On the other hand, HPVs are elusive; they come, go, or persist unpredictably. Therefore, the regression, persistence, or progression of HPV-induced lesions is as elusive as the virus that causes them. If cytology is to stay, it remains to be seen whether the sensitivity and specificity of cytology are affected by the HIV-HPV coinfection. This is particularly relevant in LRS where HIV/AIDS and cervical cancer are endemic as it might need reconsideration or adaptation of existing screening strategies.

2. Methods

The study was carried out at the histopathology department of the National Health Laboratory Service, Polokwane, Limpopo province. The population is in excess of 5 M; the majority receives health care from the public health facilities. Over a period of 5 years (2008–2012), 5500 cervical biopsy specimens were received; an average of 50000 Pap smears are handled annually.

The entry criterion for this study was a previous cytological diagnosis of minimally abnormal Pap test of atypical squamous cells of undetermined significance (ASCUS) or low-grade squamous intraepithelial lesion (LGSIL), or of high-grade squamous intraepithelial lesion (HGSIL) or worse. This had to be followed by a colposcopy-directed large loop excision of the transformation zone (LLETZ) histopathological diagnosis. Naked eye or colposcopy-directed punch biopsies were not eligible since they may not be fully representative. Among the 5500 cases, there were 389 HIV-infected cases fulfilling the entry criteria. The 399 HIV-uninfected controls were collected from the 2000 first consecutive cases of the 5500 biopsies.

The average length of the LLETZ specimens was $1.8 \text{ cm} \pm 0.8$ (median 1.5) (range 0.8–2.0). The average thickness was $0.6 \text{ cm} \pm 0.2$ (0.5). The average number of sections per case was 9.6 ± 3.5 (9.0) (4–19). The average width of the lesion was $5.3 \text{ mm} \pm 3.9$ (4.5). Four μ -thin sections were stained with hematoxylin-eosin. The histopathological diagnosis was based on the two-tier or dichotomous classification latest recommendations for the lower anogenital squamous terminology (LAST) of preinvasive lesions (CIN ≤ 1 /LGSIL, and CIN ≥ 2 /HGSIL) or invasive cervical carcinoma (ICC) [19]. The cytological accuracy was evaluated by the correlation with the colposcopy-directed biopsy diagnosis on LLETZ specimens. CIN ≤ 1 was used as an endpoint.

Statistical analysis was carried out using column statistics, interquartile ranges (IQR), contingency table analysis, and 95% confidence intervals (CI) of proportions. The level of statistical significance was set at $P < 0.05$.

3. Results

The average age at diagnosis of CIN2+ was $38.1 \text{ years} \pm 7.3$ (37.0) (IQR 33.0–44.0) for HIV-infected cases and 42.3 ± 10.8 (41.0) (IQR 35.0–48.0) for the controls ($t = 4.4$;

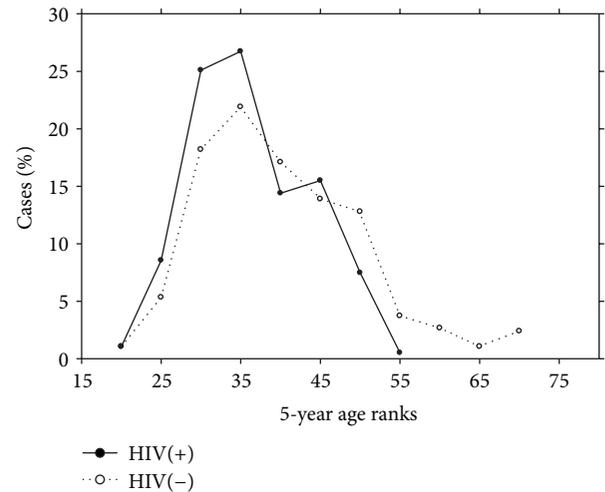


FIGURE 1: Relative age distribution of biopsy-confirmed CIN2+.

TABLE 1: Correlation between cytology and histopathology of colposcopy-directed LLETZ: HIV-uninfected versus HIV-infected women.

	HIV uninfected <i>n</i> = 399	HIV infected <i>n</i> = 389
Concordant		
HGSIL = CIN2+	249 (88.6%)	262 (89.1%)
LGSIL = CIN ≤ 1	13 (4.6%)	24 (8.2%)
Pap (+) = ICC*	19 (6.8%)	8 (2.7%)
Total	281 (65.7–74.9%)*	294 (71.0–79.8%)*
Discordant		
HGSIL = CIN ≤ 1	84 (71.2%)	79 (83.2%)
LGSIL = CIN2+	5 (4.2%)	8 (8.4%)
LGSIL = ICC	6 (5.1%)	5 (5.3%)
Pap (+) = CIN $\leq 2+$	3 (2.5%)	2 (2.1%)
Pap (-) = CIN2+	5 (4.2%)	—
Pap (-) = ICC	15 (12.7%)	1 (1.0%)
Total	118 (25.1–34.3%)*	95 (20.2–29.1%)*

*95% confidence intervals.

$P < 0.0001$). Figure 1 shows the relative age distribution of biopsy-confirmed CIN2+. In cases and controls, the peak prevalence occurred at 30–34 years of age.

Table 1 illustrates the correlation between cytology and histopathology of colposcopy-directed LLETZ in 389 HIV-infected and 399 HIV-uninfected women. The sensitivity (i.e., the fraction of all with a cytological diagnosis of minimal abnormality, HGSIL, or ICC who really have one of the conditions) for the lowest endpoint (minimal abnormality) was 92.7%. The specificity (i.e., the fraction of all with a cytological diagnosis of minimal abnormality, HGSIL, or ICC who do not have the condition) was only 18.5%, indicating a high false positive rate. Our low endpoint resulted in a low negative predictive value (i.e., the probability that a negative result is certain) of 45.1%. The positive predictive value (i.e., the proportion of diagnoses that are correct) was 77.9%. The cytohistopathological concordance/discordance (i.e., over- or

TABLE 2: Reported sensitivity and specificity of cervical cytology.

Endpoint	Sensitivity	Specificity	NPV	PPV	References
	30.0–87.0	86.0–100.0			[21]*
CIN (NOS)**	89.7	75.0			[22]
NM***				72.0	[3]
NM	78.0	94.0			[23]
CIN2+	55.4	96.8			[24]
ASCUS	57.0	93.0			[11]*
CIN3+	78.2	86.0			[25]
NM	54.0				[26]
NM	60.0	100.0	99.4		[27]
CIN2+	75.8	83.4			[28]
CIN2+	±56.0	±96.0	±86.0		[14, 20]
CIN3+	±87.0	±86.0			[29]

*Meta-analysis; ** not otherwise specified; *** not mentioned.

undercall) rate was similar in the controls and the cases. The false negative rate was double among controls as compared to cases (chi-square = 4.6; $P = 0.033$; odds ratio = 0.50, 95% CI –0.27–0.96) suggesting that the HIV status does not impact negatively the overall accuracy (or lack thereof) of cytological screening in our setting.

4. Discussion

In LRS, especially in sub-Saharan Africa, the burden of cervical cancer, HPV, and HIV carriage is high, and the human and financial resources are scarce [20]. In sub-Saharan Africa, the usage of Pap smear is low, and the facilities to manage abnormal Pap smears are insufficient [10]. This indicates the importance of cytological accuracy for the too few women undergoing cytological screening in general and in LRS in particular.

The reported sensitivity and specificity of cervical cytology vary widely worldwide from distressingly low to impressively high (Table 2) [3, 11, 14, 20–29]. However, these indicators are dependent on the endpoint that is used. Setting the endpoint high (\geq CIN2+) improves the sensitivity at the expense of specificity. Setting the endpoint low (\leq CIN1) results in a low negative predictive value, an important accuracy indicator of a screening test [3]. The importance is the prevalence of negative or minimally abnormal cytology that overlooks lesions that have the potential to progress, particularly in HIV-infected women. Khuakoonratt and colleagues found that 16.3% of 226 women who had a colposcopy for cytology-diagnosed LGSIL had in fact CIN2+ or worse lesions [30]. Another study reported a prevalence of 29.9% CIN1 and 32.2% CIN2+ in colposcopy-directed biopsies of 208 women with Pap-diagnosed LGSIL [31]. This shows the importance of action (e.g. “see and treat” in its broadest sense) for all minimally abnormal cytology, regardless of HIV status [15].

De Lemos and colleagues observed 12.1% abnormal cytology not otherwise specified (NOS) in 125 HIV-infected cases versus 5.4% in 112 controls ($P = 0.05$) [32]. A study of 276 unscreened HIV-infected women reported a 17.8% prevalence

of SIL NOS [33]. Dames and colleagues found 44% of cervical abnormalities NOS after Pap/HPV screening of 100 HIV-positive women [2]. Another study reported the presence of 14.3% of CIN NOS in colposcopy-directed biopsies of HIV-infected women with a normal Pap smear versus 1.2% in HIV-negative controls ($P < 0.01$) [34]. At variance with our findings, these studies suggest that cytological abnormalities are more common in HIV-infected women and that the false negativity rate of cervical cytology is higher among them. The limitations of these studies are that no distinction was made between low- and high-grade lesions.

The variability of cytological accuracy is well known and illustrated by the two following examples. Curry and colleagues found an odds ratio (OR) of 2.17 (95% CI 1.3–3.6) of biopsy-diagnosed CIN2+ in HIV-infected women with minimally abnormal cytology [35]. In a large series of 770 HIV-infected and 480 uninfected women who had a normal Pap at enrollment, the cumulative incidence of ASCUS and of progression into LSIL was 78 and 60% in the former and 38 and 25% in the latter ($P < 0.01$) [36]. At variance, another study reported an OR of only 1.2 (95% CI 0.6–2.4) for the risk for CIN2+ in 103 HIV-infected women with minimally abnormal cytology versus uninfected women [37]. This raises the question of the natural history of LSIL, defined as typically self-limited HPV infections that will resolve spontaneously, hence a benign nonpreinvasive lesion or even no pathology at all [19, 38]. In contrast, it has been shown that untreated LGSIL progressed in 53.6% of HIV-infected and 23.0% uninfected women [39]. Similarly, a South African study reported persistence and progression of LGSIL in HIV-positive and HIV-negative women [40]. These data support the concept that, in LRS, where HPV-DNA testing is not available, ASCUS is not to be underestimated as being innocuous and should be treated by ablation or excision [15]. This policy is supported by the fact that about 16% of LGSIL progress into CIN2+ and that more than half carry HR-HPV especially at the age of 30 and older [41, 42].

5. Conclusion

The present study does not show evidence of increased discordance between cytology and histology in HIV-infected women. Our data do indicate that HIV-infected women need earlier screening than HIV-uninfected women because high-grade preneoplastic lesions tend to develop at an earlier age in HIV-infected women. In LRS with high HIV and cervical cancer endemicity screening debut should start before the age of 30 years. Therefore, the South African screening policy should be reconsidered [43]. Our findings suggest that, in LRS, where cytology remains the primary screening tool and HPV testing out of reach, minimally abnormal cytology should trigger a “see and treat” intervention. The visualization and treatment modalities will depend on the local resources.

Conflict of Interests

The author declares that there is no conflict of interests.

References

- [1] P. Lehtovirta, J. Paavonen, and O. Heikinheimo, "Risk factors, diagnosis and prognosis of cervical intraepithelial neoplasia among HIV-infected women," *International Journal of STD and AIDS*, vol. 19, no. 1, pp. 37–41, 2008.
- [2] D. N. Dames, C. Ragin, A. Griffith-Bowe, P. Gomez, and R. Butler, "The prevalence of cervical cytology abnormalities and human papillomavirus in women infected with the human immunodeficiency virus," *Infectious Agents and Cancer*, vol. 4, no. 1, article S8, 2009.
- [3] L. S. Massad, G. D'Souza, F. Tian, H. Minkhoff, M. Cohen, R. L. Wright et al., "Negative predictive value of pap testing: implications for screening intervals for women with human immunodeficiency virus," *Obstetrics & Gynecology*, vol. 120, no. 4, pp. 791–797, 2012.
- [4] Centers for Disease Control and Prevention, "1993 revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults," *Morbidity Mortality Weekly Report Recommendation Report*, vol. 41, pp. 1–19, 1992.
- [5] W. K. Sekirime and R. Gray, "HIV infection among Uganda women with cervical cancer: a retrospective study," *Gynecologic and Obstetric Investigation*, vol. 63, no. 4, pp. 222–228, 2007.
- [6] J. R. Moodley, M. Hoffman, H. Carrara et al., "HIV and pre-neoplastic and neoplastic lesions of the cervix in South Africa: a case-control study," *BMC Cancer*, vol. 6, article 135, 2006.
- [7] A. K. Chaturvedi, M. M. Madeleine, R. J. Biggar, and E. A. Engels, "Risk of human papillomavirus-associated cancers among persons with AIDS," *Journal of the National Cancer Institute*, vol. 101, no. 16, pp. 1120–1130, 2009.
- [8] M. Bower, D. Mazhar, and J. Stebbing, "Should cervical cancer be an acquired immunodeficiency syndrome-defining cancer?" *Journal of Clinical Oncology*, vol. 24, no. 16, pp. 2417–2419, 2006.
- [9] L.-J. Van Bogaert and D. C. Knapp, "Opportunistic testing of medically underserved women for cervical cancer in south africa," *Acta Cytologica*, vol. 45, no. 3, pp. 313–316, 2001.
- [10] M. Hoffman, D. Cooper, H. Carrara et al., "Limited Pap screening associated with reduced risk of cervical cancer in South Africa," *International Journal of Epidemiology*, vol. 32, no. 4, pp. 573–577, 2003.
- [11] M. Arbyn, R. Sankaranarayanan, R. Muwonge et al., "Pooled analysis of the accuracy of five cervical cancer screening tests assessed in eleven studies in Africa and India," *International Journal of Cancer*, vol. 123, no. 1, pp. 153–160, 2008.
- [12] J. Cuzick, M. Arbyn, R. Sankaranarayanan et al., "Overview of human papillomavirus-based and other novel options for cervical cancer screening in developed and developing countries," *Vaccine*, vol. 26, no. 10, pp. K29–K41, 2008.
- [13] I. M. C. M. De Kok, J. Van Rosmalen, J. Dillner et al., "Primary screening for human papillomavirus compared with cytology screening for cervical cancer in European settings: cost effectiveness analysis based on a Dutch microsimulation model," *British Medical Journal*, vol. 344, no. 7847, article e670, 2012.
- [14] L. Kuhn, C. Wang, W.-Y. Tsai, T. C. Wright, and L. Denny, "Efficacy of human papillomavirus-based screen-and-treat for cervical cancer prevention among HIV-infected women," *AIDS*, vol. 24, no. 16, pp. 2553–2561, 2010.
- [15] L. J. van Bogaert, "Cervical cancer prevention in resource-limited settings with special emphasis on areas of high cervical cancer and human immunodeficiency virus endemicity," in *Human Papillomavirus: Prevalence, Detection and Management*, H. B. Smith, Ed., Novapublishers, New York, NY, USA, 2013.
- [16] G. Ronco, P. Giorgi-Rossi, F. Carozzi et al., "Results at recruitment from a randomized controlled trial comparing human papillomavirus testing alone with conventional cytology as the primary cervical cancer screening test," *Journal of the National Cancer Institute*, vol. 100, no. 7, pp. 492–501, 2008.
- [17] P. Naucler, W. Ryd, S. Törnberg et al., "Efficacy of HPV DNA testing with cytology triage and/or repeat HPV DNA testing in primary cervical cancer screening," *Journal of the National Cancer Institute*, vol. 101, no. 2, pp. 88–99, 2009.
- [18] S. H. van der Burg and J. M. Palefsky, "Human immunodeficiency virus and human papilloma virus—why HPV-induced lesions do not spontaneously resolve and why therapeutic vaccination can be successful," *Journal of Translational Medicine*, vol. 7, p. 108, 2009.
- [19] T. M. Darragh, T. J. Colgan, T. Cox, D. Heller, M. Henry, R. Luff et al., "The lower anogenital squamous terminology standardization project for HPV-associated lesions: background and consensus recommendations from the College of American Pathologists and the American Society for Colposcopy and Cervical Pathology," *International Journal of Gynecological Pathology*, vol. 32, no. 1, pp. 76–115, 2013.
- [20] V. V. Sahasrabudhe, R. A. Bhosale, A. N. Kavatkar et al., "Comparison of visual inspection with acetic acid and cervical cytology to detect high-grade cervical neoplasia among HIV-infected women in India," *International Journal of Cancer*, vol. 130, no. 1, pp. 234–240, 2012.
- [21] K. Nanda, D. C. McCrory, E. R. Myers et al., "Accuracy of the papanicolaou test in screening for and follow-up of cervical cytologic abnormalities: a systematic review," *Annals of Internal Medicine*, vol. 132, no. 10, pp. 810–819, 2000.
- [22] M. Branca, E. Rossi, M. Alderisio et al., "Performance of cytology and colposcopy in diagnosis of cervical intraepithelial neoplasia (CIN) in HIV-positive and HIV-negative women," *Cytopathology*, vol. 12, no. 2, pp. 84–93, 2001.
- [23] R. Sankaranarayanan, A. M. Budukh, and R. Rajkumar, "Effective screening programmes for cervical cancer in low- and middle-income developing countries," *Bulletin of the World Health Organization*, vol. 79, no. 10, pp. 954–962, 2001.
- [24] M.-H. Mayrand, E. Duarte-Franco, I. Rodrigues et al., "Human papillomavirus DNA versus Papanicolaou screening tests for cervical cancer," *The New England Journal of Medicine*, vol. 357, no. 16, pp. 1579–1588, 2007.
- [25] P. E. Gravitt, P. Paul, H. A. Katki et al., "Effectiveness of VIA, pap, and HPV DNA testing in a cervical cancer screening program in a Peri-Urban community in Andhra Pradesh, India," *PLoS ONE*, vol. 5, no. 10, Article ID e13711, 2010.
- [26] South African HPV advisory board, "Cervical cancer and human papillomavirus: South African guidelines for screening and testing," *Southern African Journal of Gynaecologic Oncology*, vol. 2, no. 1, pp. 23–26, 2010.
- [27] S. O. Albert, O. A. Oguntayo, and M. O. A. Samaila, "Comparative study of visual inspection of the cervix using acetic acid (VIA) and Papanicolaou (Pap) smears for cervical cancer screening," *Ecancer*, vol. 6, article 262.
- [28] C. Firnhaber, N. Mayisela, S. Williams, A. Swarts, M. Faesen, S. Levin et al., "Validation of cervical screening methods in HIV positive women from Johannesburg South Africa," *Plos ONE*, vol. 8, no. 1, Article ID e53494, 2013.
- [29] P. E. Castle, M. H. Stoler, T. C. Wright, A. Sharma, T. L. Wright, and C. M. Behrens, "Performance of carcinogenic human

- papillomavirus (HPV) testing and HPV16 or HPV18 genotyping for cervical cancer screening of women aged 25 years and older: a subanalysis of the ATHENA study,” *The Lancet Oncology*, vol. 12, no. 9, pp. 880–890, 2011.
- [30] N. Khuakoonratt, S. Tangjitgamol, S. Manusirivithaya et al., “Prevalence of high grade squamous intraepithelial lesion (HSIL) and invasive cervical cancer in patients with low grade squamous intraepithelial lesion (LSIL) at cervical pap smear,” *Asian Pacific Journal of Cancer Prevention*, vol. 9, no. 2, pp. 253–258, 2008.
- [31] R. Kiatiyosnusorn, P. Suprasert, J. Srisomboon, S. Siriaree, S. Khunamornpong, and C. Kietpeerakool, “High-grade histologic lesions in women with low-grade squamous intraepithelial lesion cytology from a region of Thailand with a high incidence of cervical cancer,” *International Journal of Gynecology and Obstetrics*, vol. 110, no. 2, pp. 133–136, 2010.
- [32] P. A. de Lemos, M. T. Garcia-Zapata, and S. B. Tavares, “Cervical cytopathology in a population of HIV-positive and HIV-negative women,” *Journal of Tropical Medicine*, vol. 2012, Article ID 869758, 4 pages, 2012.
- [33] J. Atashili, W. C. Miller, J. S. Smithy, P. M. Ndumbe, G. M. Ikomey, J. Eron et al., “Age trends in the prevalence of cervical squamous intraepithelial lesions among HIV-positive women in Cameroon: a cross-sectional study,” *BMC Research Notes*, vol. 5, article 590, 2012.
- [34] J. R. Anderson, P. Paramsothy, C. Heilig, D. J. Jamieson, K. Shah, and A. Duerr, “Accuracy of Papanicolaou test among HIV-infected women,” *Clinical Infectious Diseases*, vol. 42, no. 4, pp. 562–568, 2006.
- [35] C. L. Curry, Y. H. Sage, O. Vragovic, and E. A. Stier, “Minimally abnormal pap testing and cervical histology in hiv-infected women,” *Journal of Women’s Health*, vol. 21, no. 1, pp. 87–91, 2012.
- [36] A. Duerr, P. Paramsothy, D. J. Jamieson et al., “Effect of HIV infection on atypical squamous cells of undetermined significance,” *Clinical Infectious Diseases*, vol. 42, no. 6, pp. 855–861, 2006.
- [37] L. A. Boardman, K. Cotter, C. Raker, and S. Cu-Uvin, “Cervical intraepithelial neoplasia grade 2 or worse in human immunodeficiency virus-infected women with mildly abnormal cervical cytology,” *Obstetrics and Gynecology*, vol. 112, no. 2, pp. 238–243, 2008.
- [38] M. T. Galgano, P. E. Castle, K. A. Atkins, W. K. Brix, S. R. Nassau, and M. H. Stoler, “Using Biomarkers as objective standards in the diagnosis of cervical biopsies,” *American Journal of Surgical Pathology*, vol. 34, no. 8, pp. 1077–1087, 2010.
- [39] L. Nappi, C. Carriero, S. Bettocchi, J. Herrero, A. Vimercati, and G. Putignano, “Cervical squamous intraepithelial lesions of low-grade in HIV-infected women: recurrence, persistence, and progression, in treated and untreated women,” *European Journal of Obstetrics Gynecology and Reproductive Biology*, vol. 121, no. 2, pp. 226–232, 2005.
- [40] M. Zeier, M. H. Botha, F. H. van der Merwe et al., “Progression and persistence of low-grade cervical squamous intraepithelial lesions in women living with human immunodeficiency virus,” *Journal of Lower Genital Tract Disease*, 2012.
- [41] M. Alsharif, K. Kjeldahl, C. Curran, S. Miller, H. E. Gulbahce, and S. E. Pambuccian, “Clinical significance of the diagnosis of low-grade squamous intraepithelial lesion, cannot exclude high-grade squamous intraepithelial lesion,” *Cancer Cytopathology*, vol. 117, no. 2, pp. 92–100, 2009.
- [42] M. J. Thrall, D. A. Smith, and D. R. Mody, “Women ≥ 30 years of age with low grade squamous intraepithelial lesion (LSIL) have low positivity rates when cotested for high-risk human papillomavirus: should we reconsider HPV triage for LSIL in older women?” *Diagnostic Cytopathology*, vol. 38, no. 6, pp. 407–412, 2010.
- [43] “National Department of Health, South Africa “National Guideline on Cervical Cancer Screening Programme”, Pretoria,” 2003.



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