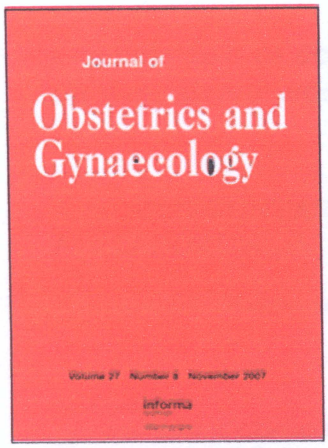

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Correlation of cervical cytology and visual inspection with acetic acid in HIV-positive women

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Summary
The prevalence of squamous intraepithelial lesion is higher among human immunodeficiency virus (HIV)-positive women. These lesions when they occur in these patients are also more difficult to treat. A total of 205 consenting HIV-seropositive women were recruited. A cervical cytology (Pap smear) was taken, followed by visual inspection with freshly prepared 5% acetic acid and cervical biopsy taken from the squamocolumnar junction as the reference for diagnosis to avoid verification bias. The sensitivity of VIA was 76.0% (95% CI 52.0–91.0); specificity 83.0% (95% CI 77.0–88.0); positive predictive value 34.0% (95% CI 21.0–49.0). The sensitivity of cervical cytology (Pap smear) was 57.0% (95% CI 34.0–77.0), specificity of 95.0% (95% CI 90.0–97.0), and positive predictive value of 55.0% (95% CI 33.0–75.0). In HIV-seropositive women, the sensitivity of VIA is 76.0%, making it a useful screening test for preinvasive lesion of the cervix in low resource settings.

Keywords
HIV positive, Pap smear, VIA

Introduction

Cancer of the cervix is the most common malignant tumour of the female reproductive tract and the leading cause of death from cancers among women in the developing world (Parkin et al. 1999; Adewole et al. 2005). Cervical cancer is an important public health problem. An estimated 466,000 new cases occur annually worldwide, with the vast majority occurring in the developing countries. Over 80% of the estimated 231,000 deaths that occur annually due to cervical cancer also occur in these countries (Parkin et al. 1999).

The incidence and mortality vary widely between countries with an up to 10-fold difference between high and low risk regions (Thomas et al. 2002). The high incidence areas include Latin America, sub-Saharan Africa and South-east Asia, while low incidence areas are Western Europe, North America, the Middle East and China. Many of the patients in these high incidence areas present in advanced stages of cervical cancer (Adelusi 1997).

In developed countries, the reduction in cervical cancer incidence and mortality is a direct result of widespread cytological screening (Pap smears) and diagnostic biopsy coupled with treatment of cervical cancer precursor lesions (Sigurdsson 1999; Austoker 1999). These precursor lesions, referred to by a variety of names (e.g. dysplasia, cervical intraepithelial neoplasia (CIN) or squamous intraepithelial lesions (SIL) usually develop slowly. Several studies have shown that the prevalence of SIL and of the multifocal HPV-related lesions (Korn and Landers 1995) is higher among HIV-positive women than in HIV-negative women (Sun et al. 1995). These precursor lesions are often more difficult to treat in HIV-positive women than in HIV-negative women (Fructcher et al. 1996).

Cervical cancer screening programmes in low resource countries, such as Nigeria are difficult to implement and maintain (Denny et al. 2000). These have led to the need for developing alternative methods such as direct visual inspection (DVI) of the cervix. A substantial body of evidence has accumulated on the use of DVI as a screening test for premalignant lesions of the cervix (Cullins et al. 1999). DVI involves painting the cervix with 3–5% acetic acid (vinegar) and then inspecting with the naked eye for evidence of disease (aceto-white lesion) at the squamocolumnar junction. This has tremendous advantages in low resource setting as the test can be done by well-trained non-physician health provider.

In Nigeria, the HIV seroprevalence rate according to the 2005 survey was 4.4%. It is currently estimated that there are about 4 million people living with HIV in Nigeria with heterosexual transmission accounting for nearly 80% of all infections (UNAIDS/WHO 2005). HIV is a well-known risk factor for development of cervical intraepithelial neoplasia (CIN). Women who are HIV-positive most often have a co-infection with human papilloma virus (HPV) a causative agent in the aetiology of cancer of the cervix. Cervical cancer is an AIDS-defining neoplasm in women (Matos et al. 2003). Cytology-based screening programmes and/or DNA typing of HPV is beyond the capacity of many health services

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in developing countries, although this may change as rapid, accurate and inexpensive HPV screening diagnostics become available (Denny et al. 2000; Denny 2001).

Methodology

Study facility and area

The study was conducted in the cytology room in the antenatal clinic of the University College Hospital (UCH), a tertiary health institution, located in Ibadan, the capital of Oyo State, Nigeria. It is an 800 bed facility. The cervical cytology room is a well-equipped multipurpose facility with three colposcopes, loop electrosurgical and cryotherapy equipment to allow for integrated management of women with a premalignant lesion of the cervix.

Study population

These were HIV-seropositive women attending the HIV clinic of the University College Hospital, Ibadan, Oyo state.

Study design

This is a descriptive study carried out between November 2006 and March 2007. Ethical approval was obtained from the University of Ibadan/University College Hospital Institutional Review Committee. The women were educated on what the study was about and the procedures were explained. A written informed consent was obtained from each patient recruited into the study.

Inclusion criteria

- Non-pregnant HIV-positive women with no history suggestive of carcinoma of the cervix
- HIV-positive women with no history suggestive of previous hysterectomy.

Each patient was placed in the lithotomy position; the external genitalia was inspected for the presence of lesions, such as papules, vesicles, ulcerations, condylomata, discharge, redness, swelling and excoriations. A bivalve speculum was slowly and carefully inserted into the vagina to expose the cervix and adjusted so that the entire cervix was in view and the halogen angle poised light adjusted as needed. The cervix was inspected for discharge, ulcers, ectopy, nabothian cysts, ulcers, warts, polyps, leucoplakia (thickened white patches).

The Aylesbury spatula was introduced into the external os of the cervix and rotated 360° to obtain ectocervical cells from the transformation zone. These were then smeared on appropriately labeled slides. A cytobrush was used to obtain endocervical cells and smeared over the earlier smear. The cells are then fixed with 95% alcoholic spray.

Visual inspection with freshly prepared acetic acid (VIA) involved liberally swabbing the cervix with 5% acetic acid solution and waiting for 2 min for the acetic acid solution to be absorbed (using a stopwatch). The VIA for this study was conducted by a trained gynaecologist. The transformation zone was carefully checked, especially near the squamocolumnar junction for any dense, non-movable aceto-white areas of the epithelium.

The results of VIA are reported as VIA-negative, VIA-positive or suspicious for cancer. VIA negative meant that there are no significant aceto-white lesions. A positive result meant that there are sharp, distinct, well-defined, dense (opaque/dull white) aceto-white areas with or without raised margins, close to the squamocolumnar junction near the transformation zone. There may be dense aceto-white lesions in the columnar epithelium, near the cervical os. Findings that are suspicious for cancer include an ulcerative, proliferative growth that may bleed easily when touched (JHPIEGO 2000).

For the VIA positive lesions, two cervical biopsies are taken with re-usable punch biopsy forceps at the site of the lesion. For VIA negative patients, one biopsy each is taken at positions 6 and 12 o'clock of the transformation zone. The biopsy forceps are sterilised after each patient's use. The cytology and histology evaluation were done by two independent pathologists skilled in cytopathology. Any differences in results were jointly reconciled with the help of a third and most senior pathologist in the hospital.

The main variables were the cytology, visual inspection with acetic acid and histology of cervical biopsy. The degree of sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy of cervical cytology (Pap smear) and visual inspection with 5% acetic acid in HIV-positive women were assessed using the cervical biopsy report as the reference test. The degree of agreement of each of the screening tests compared with biopsy was determined using the kappa statistics. The closer the value to 1.0, the better the test as a diagnostic tool. The level of significance was $p<0.05$ (or 95% CI).

Any patient with moderate or severe cervical dysplasia confirmed with biopsy, i.e. CIN II–CIN III was recommended for treatment.

Results

A total of 205 women were recruited for the study. Data were available for all the study participants.

The age range of the study population was 17–60 years, with a mean age of 33.9 years (SD 7.5 years). Duration of diagnosis of HIV at the time of study ranges from 1 month to 6 years. The number of lifetime sexual partners was 1–7 male partners with a median of two partners. Marital status of the participants is as follows: single 17 (8.3%); monogamous 105 (51.2%); polygamous 40 (19.5%); divorced 4 (2.0%); separated 9 (4.4%); and widowed 30 (14.4%).

The reports of the cervical cytology (Pap smear) and histology of the cervical biopsy are shown in Table I.

Table I. Results of biopsy and cytology.

	Biopsy		*Cytology*	
Findings	*n*	(%)	*n*	(%)
Normal	103	50.2	100	48.8
Inflammatory	61	29.8	72	35.1
HPV changes	20	9.8	11	5.4
CIN 1	10	4.9	13	6.3
CIN 2	11	5.4	9	4.4
CIN 3	–	–	–	–
Total	205	100.0	205	100.0

Cervical cytology was normal in 100 (48.8%) subjects; inflammatory in 72 (35.1); HPV associated changes in 11 (5.4%); CIN 1 in 13 (6.3%) and CIN 2 in nine (4.4%). The histology report was normal in 103 (50.2%) subjects; inflammatory in 61 (29.8%); HPV associated changes in 20 (9.8%); CIN 1 in 10 (4.9%) and CIN 2 in 11 (5.4%). There was no case of grade worse than moderate dysplasia (CIN 2) in this study. A total of 47 of the 205 subjects had VIA positive reports (aceto-whitening) after painting the cervix with 5% acetic acid as shown in Table II. The prevalence of CIN based on the histology report from the study was 10.2%.

Table II shows the sensitivity and specificity of VIA to be 76.0% (95% CI, 52.0–91.0) and 83.0% (95% CI 77.0–88.0), respectively. The positive predictive value (PPV) is 34.0% (95% CI, 21.0–49.0), while the negative predictive value (NPV) is 97.0% (95% CI, 92.0–99.0). The diagnostic accuracy of VIA is 82.0% (95% CI, 76.0–87.0). There was a fair agreement between VIA reports and cervical biopsy (κ statistics 0.383, significant $p = 0.000$).

Table III shows the sensitivity of cervical cytology (Pap smear) to be 57.0% (95% CI 34.0–77.0) and a specificity of 95.0% (95% CI 90.0–97). The PPV is 55.0% (95% CI 33.0–75.0) with a NPV of 95.0% (95% CI 91.0–98.0). The diagnostic accuracy is 91.0% (95% CI 86.0–98.0). There was a good agreement with the cervical biopsy (κ statistics 0.506, $p = 0.000$).

Discussion

An effective cervical cancer screening programme would help in reducing the morbidity and mortality associated with the disease in a developing country like Nigeria. The HIV pandemic had made it more relevant as cervical carcinoma is an AIDS-defining disease, hence the need to screen for the premalignant lesion. Conventional cytology screening is not widely available and it is cost intensive and requires a high level of technical competence, which is not readily available in this environment. Therefore, there is the need to look into alternative screening methods such as VIA for pre-invasive lesions of the cervix.

Table II. Comparison of results from biopsy and visual inspection with acetic acid.

	Biopsy		
VIA	CIN	Non-CIN	Total
Positive	16	31	47
Negative	5	153	158
Total	21	184	205

Sensitivity 76.0%; Specificity 83.0%.
Measure of agreement, $\kappa = 0.383$; $p = 0.000$.
Diagnostic accuracy = 82%; 95% CI, 76.0–87.0.
Non-CIN, normal, inflammatory and HPV changes.

Table III. Comparison of results from biopsy and cervical cytology.

	Biopsy		
Cytology results	CIN	Non-CIN	Total
CIN	12	10	22
Non-CIN	9	174	183
Total	21	184	205

Sensitivity 57.0%; Specificity 95%.
Measure of agreement, $\kappa = 0.506$; $p = 0.000$.
Diagnostic accuracy = 91.0%; CI 86.0–98.0
Non-CIN, normal, inflammatory and HPV changes.

A suitable reference investigation chosen in this study for all the patients was cervical biopsy, to distinguish patients who are truly positive from those that are negative. Any study assessing sensitivity and specificity will suffer 'verification bias' if the reference investigation is restricted to test positive individuals only or additionally to a sample of test negative persons. Such bias is known to inflate sensitivity estimates and may be avoided if all individuals receive the reference investigation irrespective of the test results. This was applied in this study.

The sensitivity and specificity of VIA from this study is 76.0% and 83.0%, respectively. This compares favourably with sensitivities and specificities from other studies: Doh et al. (2005); 70.4% and 77.6%, Elit et al. (2006); 82.9% and 88.6%, Abdel-Hady et al. (2006) and De Vuyst et al. (2005); 94.4% and 73.9%, respectively. Though, the HIV serostatus of the patients in these other studies were not stated. The PPV for VIA in this study is 34.0% and the NPV being 97.0%. Doh et al. (2005) reported a PPV and NPV of 44.0% and 91.3%, respectively and Elit et al. (2006) had 12.2% and 99.7% in another study. Sankaranarayanan et al. (2004) in a multicentred study conducted in India and some part of Africa also reported similar findings.

From this study, the cervical cytology (Pap smear) sensitivity and specificity were 57.0% and 95.0%, respectively. Wright et al. (1994) in a similar study in HIV-positive patients reported sensitivity and specificity of the Pap smear as 81% and 87%, respectively. In Cameroun, Doh et al. in (2005) reported the sensitivity and specificity of Pap smear as 47.7% and 94.2%. The reported PPV and NPV are also similar in these other studies.

The sensitivity of VIA appears better than that of the conventional Pap smear; 76.0% vs 57.0% in this study among HIV-positive women, although the specificity is lower, 83.0% vs 95.0%. This agrees with the common knowledge as expressed in several earlier studies (Blumenthal et al. 2001; Sankaranarayanan et al. 2003). Hence, VIA can be proposed as a screening test for pre-invasive lesions of the cervix and is helpful in reducing referrals for colposcopy without compromising the quality of care.

The lower diagnostic accuracy of 82.0% of VIA compared with the 91.0% of Pap smear further emphasises VIA as a screening rather than diagnostic tool for pre-invasive cervical lesions. The κ statistics 0.506 of Pap smear compared with 0.383 of VIA showed a better agreement between Pap smear and cervical biopsy than VIA and biopsy as a diagnostic test. The prevalence of 10.2% of CIN among these HIV-positive women in this study is much less than the 23.8% reported by Saidu et al. (2006) from Ilorin, Nigeria. This is because a confirmatory diagnosis of CIN in this study was done with cervical biopsy, while the Ilorin study had only Pap smear screening with no further confirmatory test.

Conclusion

This study shows that visual inspection with acetic acid (VIA) is a sensitive screening test for pre-cancerous cervical lesions in HIV-positive women. Thus, it is a good

alternative to the conventional cervical cytology (Papanicolaou) test in low resource settings. The cost-effectiveness of this screening test is also well documented (Goldie et al. 2005).

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