

# Performance of Direct Visual Inspection of the Cervix with Acetic Acid and Magnification in a Previously Screened Population

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## ■ Abstract

**Objective.** To assess the screening performance of direct visual inspection with acetic acid and  $\times 2$  magnification (VIAM) in a previously screened population, as performed by experienced gynecologic nurses with minimal training in VIAM.

**Patients and Methods.** Performance of VIAM was evaluated in 2,080 women from a population-based cohort in Guanacaste, Costa Rica, 5 years after they had negative enrollment results of conventional and liquid-based cytologic analysis, cervigram, and human papillomavirus DNA by Hybrid Capture Tube Test (Digene Corporation, Gaithersburg, MD). The VIAM results were compared with repeat conventional Pap smears, liquid-based cytologic examinations, and cervicography, with adjudication of differences by reference

to MY09/MY11 L1 consensus primer polymerase chain reaction detection of oncogenic human papillomavirus DNA.

**Results.** Less than 5% of women were classified as having positive results using VIAM. The VIAM positivity was also very low among women with high-grade squamous intraepithelial lesion conventional Pap smear results (8.3%), high-grade squamous intraepithelial lesion liquid-based cytologic results (6.3%), or cervigrams suggesting cervical intraepithelial neoplasia 2,3 or cancer (30%). The VIAM positivity was not associated with human papillomavirus DNA positivity.

**Conclusions.** As we practiced it, VIAM was not sensitive for detection of possibly serious incident cervical lesions in this previously screened population where cytologic screening is in place. ■

**Key Words:** screening, direct visual inspection, VIAM, human papillomavirus, cervical cancer

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Cervical cancer is a leading cause of morbidity and mortality among women worldwide, but especially in areas with limited access to medical resources [1, 2]. Screening programs based on cytologic smears

stained with the Papanicolaou technique have proven effective in several countries for detecting treatable cervical cancer precursor lesions [3]. Despite notable exceptions [4], it has been difficult to maintain high-quality cytology-based cervical screening programs in limited access areas of the world. Problems with costs, reagent quality, and training of cytotechnologists and pathologists result in substandard cytology-based screening programs. Even in regions with moderate resources such as Costa Rica, which has had an established nationwide cervical cancer cytologic screening program since 1970, cervical cancer incidence (age standardized rate (ASR) 24.96 per 100,000 women) and mortality (ASR 12.13 per 100,000) remain high compared with the average rates of the developed countries (6.45 per 100,000 and 4.08 per 100,000, respectively) [5].

Alternatives to cytologic sampling of the cervix are being tested, including direct visual inspection without or with magnification and application of acetic acid (VIAM) to highlight abnormalities. The VIAM technique has received considerable attention given its simplicity and low cost. Early evaluations suggested good sensitivity in populations with high prevalence of cervical cancer, detecting between 65% and 90% of cervical cancer and its immediate intraepithelial precursors (cervical intraepithelial neoplasia grade 2 or 3 [CIN 2,3]) [6–10]. Recent studies have suggested the technical feasibility and acceptability of a 1-day screen-and-treat program using VIAM followed by cryotherapy of VIAM-positive women [11]. However, the specificity of VIAM has been poor, with a quarter or more of screened women being classified as VIAM positive using the same threshold that generated the high sensitivity previously mentioned. Recent thorough cost-utility analyses [12, 13] suggested that to reduce cervical cancer mortality substantially, a program of repeated VIAM would be required, albeit at long intervals. Therefore, the performance of the technique in previously screened populations is relevant.

We hoped to increase the specificity of VIAM while maintaining the sensitivity of detection of CIN 2,3 and cancer. We also wished to examine the possible use of VIAM as part of a program of repeat screening in Costa Rica, using our existing personnel. We therefore evaluated the performance of VIAM as performed by experienced gynecologic nurses, who received informal training on VIAM, for detecting incident CIN 2,3 and cancer in a population that having negative results on intensive screening 5 years earlier. We compared VIAM with two kinds of cytologic examination and cervicography (an-

other visual screening technique). We adjudicated differences by reference to human papillomavirus (HPV) DNA test results.

## PATIENTS AND METHODS

### Study Population

A population-based cohort was established in 1993–1994 in Guanacaste, Costa Rica, to study the natural history of HPV and cervical neoplasia and the performance of different screening methods, including visual inspection, to detect cervical cancer and its precursor lesions [14, 15]. After a census enumeration in the Guanacaste province that was chosen for its perennially high incidence of cervical cancer, all women who agreed to participate in the study signed informed consent forms. The protocol was cleared by the Institutional Review Boards of the National Cancer Institute, National Institutes of Health, Bethesda, MD, and an ad hoc ethical committee of Fundación Castarricense para la Docencia de la Salud (FUCODOCSA), in accordance with the revised Helsinki Declaration of 1983. After signing informed consent, a total of 10,049 women were enrolled (93.6% participation). A pelvic exam and HPV testing were performed for cervical cancer screening on 9,175 women (96.9% of sexually active women eligible for pelvic examination).

As part of the cohort follow-up, 2,926 women with a reported history of fewer than 5 lifetime sexual partners and negative enrollment screening results (negative conventional and liquid-based cytologic results, negative cervigram results, and negative HPV DNA results by Hybrid Capture Tube Test [Digene Corporation, Gaithersburg, MD] [16]) were called back 5 years after enrollment for a second study visit using the same screening methods. We used MY09/MY11 L1 consensus primer polymerase chain reaction using Ampli Taq Gold Polymerase (Perkin-Elmer Applied Biosystems, Foster City, CA) for HPV DNA detection at the second evaluation. Of these, 359 women (12%) did not attend because of intervening death, serious illness, hysterectomy, current pregnancy, migration, or declined participation (accounting for only 47 persons, or 1.6% of this group). We conducted the VIAM study during the first, most intense 11 months of the 18-month complete rescreening period, during which time 2,100 women (82% of the eligible rescreened women) were examined by VIAM in addition to the standard study methods. Analysis was restricted to 2,080 because 18 women were virgins and no screening tests were taken and two other women had

severe uterine prolapse and only cervigrams were taken at the time of the return visit.

#### Limited Training for Direct Visual Inspection with Acetic Acid and $\times 2$ Magnification

A senior nurse, who had already performed thousands of study screening examinations, received a 3-day training in colposcopy before this VIAM project from an experienced colposcopist (JTC) looking at colposcopic images of women referred to a colposcopy clinic. The more junior nurse was less experienced, having performed several hundred cervical examinations at the initiation of the VIAM component of the project, without additional training by the experienced colposcopist (JTC). Additionally, in Costa Rica, both nurses received 1-day training with normal and abnormal cervicographic and colposcopic images, conducted by the Guanacaste Project colposcopist (JM) and spent 2 more days reviewing approximately 200 previously interpreted cervicographic photographs. The nurses did not attend formal VIAM courses (with theoretical lessons and supervised clinical practice) and were not supervised regarding the quality of their calls afterward as described by other VIAM research groups [9, 11]. The senior nurse performed 1,063 VIAM examinations and the junior nurse performed 1,017 VIAM examinations. Each woman was classified as having a cervix VIAM-positive or VIAM-negative; no attempt was made to identify different thresholds of severity of the acetowhite lesion. The criterion to define a cervix as VIAM-positive was persistent, definite acetowhitening near or in the transformation zone, with or without extension into the endocervical canal, regardless of the size. We also considered as VIAM positive any woman having a lesion suggestive of cancer (such as an erosion bleeding on touch, or a mass) even before applying acetic acid or magnification.

#### Pelvic Examination

All examinations were performed by one of the two nurses. After collecting cells for cytologic screening and HPV testing, a 4% acetic acid solution was applied to the cervix for 1 minute followed by inspection with an Aviscope (O’Ryan Industries, Vancouver, WA), a low-power ( $\times 2$ ), monocular, magnifying device with a built-in light source. The nurses’ impressions were recorded. After reapplying acetic acid solution, two cervigrams were taken.

#### Cytologic Examination

Conventional Pap smears were stained and read in Costa Rica by an experienced team of cytotechnologists and an expert cytopathologist (MA). The liquid-based slides were prepared, stained, and read in the United States by experienced cytotechnologists and a cytopathologist expert in that technique (MH). Cytologic results were reported using the Bethesda system. Sixty-eight women were missing conventional cytologic interpretations and 50 women were missing liquid-based cytologic interpretations, with 30 women missing both interpretations.

#### Cervigrams

Cervicographic photographs were evaluated by National Testing Laboratories Worldwide (Fenton, MO) and were reported using the company’s standard terminology. A cervigram of P2 (possible high-grade squamous intraepithelial lesion [HSIL]) or P3 (possible carcinoma) were considered positive for this analysis. There were 67 missing cervigram results.

#### Human Papillomavirus DNA Testing

Cervical specimens obtained the same day as the other screening tests were tested for more than 40 types of HPV DNA using consensus primer polymerase chain reaction [17]. We considered positive for this analysis those specimens containing 1 or more oncogenic type (types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, or 68). Forty-one women were missing HPV DNA test results.

#### Colposcopy Referral and Treatment

Women were referred to colposcopy if either cytologic result was interpreted as HSIL, if the cervigram was P2 (possible HSIL) or P3 (possible carcinoma), or if unaided direct visual inspection suggested cancer, but they were not referred for lesser VIAM positivity alone. Histologic examination is not the reference standard of this analysis as described below. The colposcopy clinic followed an aggressive biopsy and treatment protocol to maximize the safety of the participants [15].

#### Pathologic Examination

All specimens were evaluated by a local pathologist (Dr. Diego Guillén, Cartago Hospital, Caja Costarricense de Seguro Social, Cartago, Costa Rica) who was masked to the screening tests but not to the colposcopic impression. Histologic results were grouped as less than CIN 1, CIN 1, or CIN2+.

### Statistical Analysis

We compared the relative, not absolute, performance of VIAM compared with conventional cytologic analysis, liquid-based cytologic analysis, and cervigram. We estimated the proportion of women classified as VIAM positive or VIAM negative within each result category of the comparison screening tests. To test for statistical significance ( $p < .05$ ) of relationships between VIAM positivity and severity of cytologic abnormalities and cervigram results, we used Pearson  $\chi^2$  tests and, when appropriate, the Mantel-Haenszel extension test for trend ( $p_{\text{Trend}}$ ). To adjudicate the meaning of these comparisons, we estimated the proportion of women with VIAM-positive or VIAM-negative cervical results for oncogenic HPV DNA positivity stratified by each of the comparison methods. To test for difference between oncogenic HPV DNA positivity by VIAM outcome for each screening test interpretation, a Pearson  $\chi^2$  test was used.

For comparing the performance between the two nurses, we grouped all comparison screening test results into two categories, lesions suspicious of HSIL or worse ( $\geq$ HSIL) and the rest ( $<$ HSIL), based on the worst of the two cytologic and the one cervigram interpretation. We estimated the proportion of VIAM positive or negative by each grouped screening test result category stratified by nurse. The significance of this difference was tested using a Pearson  $\chi^2$  test ( $p < .05$ ). We also calculated the

odds ratio and 95% CI for the VIAM detection of the  $\geq$ HSIL for each nurse, and differences in the odds ratio were tested for statistical significance by calculating a Pearson  $\chi^2$  test ( $p < .05$ ).

### RESULTS

At the enrollment interview, 92.6% of women in this subcohort reported having attended elementary school; of these, 7.8% completed high school, and 13.7% attended additional schooling after high school. Parity was high in this rural population, with 38.5% having five or more children. The median number of sexual partners was one.

The age range of this subcohort of women at the fifth anniversary visit was 23 to 97 years, with a mean age of 46 years (median, 43). Almost 70% of women had at least one conventional cytologic examination outside of the project between enrollment and the VIAM visit, although only 108 (7.4%) had received treatment.

The main results are shown in Table 1. The VIAM positivity was uncommon overall (4.7%). The negative conventional cytologic group had the lowest proportion of VIAM-positive women (4.1%). Women with atypical squamous cells of undetermined significance cytologic results had the highest proportion of VIAM positivity (16.9%), followed by the low-grade squamous intraepithelial lesion and HSIL groups, with 12.8% and 8.3%, respectively.

**Table 1. Performance of VIAM Compared with Conventional and Liquid-Based Cytologic Analysis and Cervigram**

| Screening method                | Total women | VIAM negative |      | VIAM positive |      | <i>p</i> value     |
|---------------------------------|-------------|---------------|------|---------------|------|--------------------|
|                                 |             | <i>n</i>      | %    | <i>n</i>      | %    |                    |
| Conventional cytologic analysis |             |               |      |               |      |                    |
| Negative                        | 1,922       | 1,843         | 95.9 | 79            | 4.1  | .0001 <sup>a</sup> |
| ASCUS                           | 59          | 49            | 83.1 | 10            | 16.9 |                    |
| LSIL                            | 39          | 34            | 87.2 | 5             | 12.8 |                    |
| HSIL                            | 12          | 11            | 91.7 | 1             | 8.3  |                    |
| Total/mean                      | 2,032       | 1,937         | 95.3 | 95            | 4.7  |                    |
| Liquid-based cytologic analysis |             |               |      |               |      |                    |
| Negative                        | 1,940       | 1,852         | 95.5 | 88            | 4.5  | .5 <sup>a</sup>    |
| ASCUS                           | 68          | 63            | 92.6 | 5             | 7.4  |                    |
| LSIL                            | 26          | 25            | 96.2 | 1             | 3.8  |                    |
| HSIL                            | 16          | 15            | 93.8 | 1             | 6.3  |                    |
| Total/mean                      | 2,050       | 1,955         | 95.4 | 95            | 4.6  |                    |
| Cervigram                       |             |               |      |               |      |                    |
| Negative                        | 2,023       | 1,930         | 95.4 | 93            | 4.6  | .0001 <sup>b</sup> |
| Positive                        | 10          | 7             | 70.0 | 3             | 30.0 |                    |
| Total/mean                      | 2,033       | 1,937         | 95.3 | 96            | 4.7  |                    |

VIAM, visual inspection without or with magnification and application of acetic acid; ASCUS, atypical squamous cells of undetermined significance; LSIL, low-grade squamous intraepithelial lesion; HSIL, high-grade squamous intraepithelial lesion.

<sup>a</sup> $\chi^2$  tests for trend for screening method versus VIAM outcome.

<sup>b</sup>Pearson  $\chi^2$  test for screening method versus VIAM outcome.

The VIAM results were not associated with severity of interpretation of liquid-based cytologic analysis. The VIAM positivity was strongly associated with cervicography, the other visual technique. However, only 3 of 10 women with P2 or P3 cervigrams were VIAM positive (Table 1).

We estimated the meaning of VIAM evaluations, and disagreements with the other screening tests, by reference to HPV testing (Table 2). There was no association of VIAM with HPV positivity, either overall or within groups, defined by conventional cytologic analysis, liquid-based cytologic analysis, or cervicography.

As shown in Table 3, the more experienced nurse was more likely to detect lesions suspicious of HSIL (classified as the worst of the two cytologic and cervicography results) than the less experienced nurse. The more experienced nurse classified fewer women as VIAM positive, but recognized 3 of 19 cases (15.8%) of HSIL P2 or P3 as positive ( $p < .001$ , Pearson  $\chi^2$ ). By comparison, the less experienced nurse called many more women VIAM positive, but was unable to distinguish any lesions suspicious of HSIL (0 of 12; 0.0%;  $p = .3$ , Pearson  $\chi^2$ ). The odds ratio associating HSIL with VIAM positivity was 9.6 (95% CI, 1.7–37) for the more experienced nurse compared with an odds ratio of 0.0 (95% CI, 0–4.6) for the less experienced nurse, and the difference between the nurses was statistically significant.

## DISCUSSION

The two nurses in our study were unable using VIAM to detect a large percentage of worrisome cytologic or cervicographic cases using criteria that attempted specifically to detect CIN 2, CIN 3, or cancer. We conclude that despite the highly qualified nurses, VIAM would not be useful as part of screening for serious incident cervical neoplasia in Costa Rica, where cytologic screening is already established, unless significant modifications in criteria or training greatly improved its performance.

Our study has some limitations and differs in several important aspects from earlier VIAM projects. We did not estimate the performance of VIAM compared with a reference standard of colposcopically directed biopsy, raising the possibility of verification bias, although the sensitivity of colposcopy itself is not optimal [18]. The prevalence of CIN 2,3 and cancer in this population was low because of previous cohort screening. We hypothesize that those incident high-grade lesions that did occur were likely to be smaller and more difficult to detect than large prevalent lesions typically found in unscreened populations. We believe that any program including repeated VIAM should take into account some degree of decreased performance in sequential screens,

**Table 2. Oncogenic HPV DNA Positivity for VIAM Outcome Stratified by Conventional Pap Smear, Liquid-Based Cytologic, or Cervigram Results**

| Screening method                       | VIAM negative |          |      | VIAM positive |          |       | $p^a$ |
|--|---------------|----------|------|---------------|----------|-------|-------|
|  | Total women   | HPV+     |      | Total women   | HPV+     |       |       |
|  | <i>n</i>      | <i>n</i> | %    | <i>n</i>      | <i>n</i> | %     |       |
| <b>Conventional cytologic analysis</b> |               |          |      |               |          |       |       |
| Negative                               | 1,828         | 95       | 5.2  | 75            | 5        | 6.7   | .6    |
| ASCUS                                  | 48            | 6        | 12.5 | 10            | 0        | 0.0   | .2    |
| LSIL                                   | 34            | 6        | 17.7 | 5             | 0        | 0.0   | .3    |
| HSIL                                   | 11            | 4        | 36.4 | 1             | 1        | 100.0 | .2    |
| Total/mean                             | 1,921         | 111      | 5.8  | 91            | 6        | 6.6   |       |
| <b>Liquid-based cytologic analysis</b> |               |          |      |               |          |       |       |
| Negative                               | 1,836         | 77       | 4.2  | 84            | 2        | 2.4   | .4    |
| ASCUS                                  | 63            | 10       | 15.9 | 5             | 1        | 20.0  | .8    |
| LSIL                                   | 25            | 12       | 48.0 | 1             | 1        | 100.0 | .3    |
| HSIL                                   | 15            | 12       | 80.0 | 1             | 1        | 100.0 | .6    |
| Total/mean                             | 1,939         | 111      | 5.7  | 91            | 5        | 5.5   |       |
| <b>Cervigram</b>                       |               |          |      |               |          |       |       |
| Negative                               | 1,913         | 105      | 5.5  | 89            | 3        | 3.4   | .4    |
| Positive                               | 6             | 4        | 66.7 | 3             | 2        | 66.7  | 1.0   |
| Total/mean                             | 1,919         | 109      | 5.7  | 92            | 5        | 5.4   |       |

HPV, human papillomavirus; VIAM, visual inspection without or with magnification and application of acetic acid; ASCUS, atypical squamous cells of undetermined significance; LSIL, low-grade squamous intraepithelial lesion; HSIL, high-grade squamous intraepithelial lesion.

<sup>a</sup>Pearson  $\chi^2$  tests for differences between oncogenic HPV DNA positivity by VIAM outcome for each interpretation.

**Table 3. Comparison of Performance of the Two Nurses**

| Screening tests   | Junior nurse             |          |      |          |     |                       | Senior nurse |          |      |          |      |                       |
|-------------------|--------------------------|----------|------|----------|-----|-----------------------|--------------|----------|------|----------|------|-----------------------|
|                   | Total women <sup>a</sup> | Negative |      | Positive |     | <i>p</i> <sup>c</sup> | Total women  | Negative |      | Positive |      | <i>p</i> <sup>c</sup> |
|                   |                          | <i>n</i> | %    | <i>n</i> | %   |                       |              | <i>n</i> | %    | <i>n</i> | %    |                       |
| HSIL              | 1,004                    | 930      | 92.6 | 74       | 7.4 |                       | 1,044        | 1,024    | 98.1 | 20       | 1.9  |                       |
| HSIL <sup>b</sup> | 12                       | 12       | 100  | 0        |     | .3                    | 19           | 16       | 84.2 | 3        | 15.8 | <.001                 |
| Total             | 1,016                    | 942      |      | 74       |     |                       | 1,063        | 1,040    |      | 23       |      |                       |

HSIL, high-grade squamous intraepithelial lesion.

<sup>a</sup>One with three screening test results missing.

<sup>b</sup>Any indication of HSIL or more severe by conventional or liquid-based cytologic analysis or Cervigram.

<sup>c</sup>Pearson  $\chi^2$  test.

depending on the projected efficacy of each screen and the time between screens [12, 13].

The number of screeners in this study was small, only two, and no measure of interobserver variability was carried out. One of our nurse clinicians was more highly trained and educated concerning cervical examinations than most evaluators likely to be included in VIAM projects. However, our training for this VIAM project was neither formal nor extensive. The better performance of the more senior nurse suggests that training may improve VIAM, although the technique was still not adequate in her hands. We provided some ongoing feedback to the nurses on their performance relative to colposcopy (including a small number of patients referred based on VIAM positivity alone who proved to be virtually all negative; data not shown). However, more extensive training and continued supervision probably would have improved performance by an unknown amount. Given the difficulty of mastering colposcopy [19–21] and how insensitive it is compared with follow-up clinical history [18], a useful VIAM program will require very good ongoing training and simple criteria, even when the evaluators are motivated and competent.

It is highly likely that to reach adequate sensitivity using VIAM will require much less stringent criteria for positivity that, in turn, greatly will decrease specificity. In fact, in previous studies suggesting high sensitivity of visual inspection for detection of prevalent CIN 2,3 or cancer, as many as 30% of women were called positive [7, 8, 22]. A priori, we were not interested in a nonspecific strategy, but conclude that a successful strategy would necessarily be less specific than the one we used. Other ongoing projects (the Trivandrum in India and the TATI project in Peru; Alliance for Cervical Cancer Prevention webpage) [23] will determine whether a viable tradeoff between sensitivity and specificity can be obtained using VIAM as a stand-alone technique, and under what circumstances. We continue to research pos-

sible applications of visual screening techniques in combination with cytologic examination or HPV testing [19, 24].

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