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Visual Inspection with Acetic Acid as a Screening Test for Cervical Cancer

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Visual inspection with acetic acid (VIA) has been extensively investigated and accepted as potential alternative to cytology or Human Papilloma Virus (HPV) screening in limited resource settings. In developing countries, VIA may have several advantages over cytology or HPV screening. The consumables of the test are low-cost and readily available. VIA has potential of achieving large population coverage, as the test can be performed by a wide range of trained health care personnel and requires basic health infrastructure. It is a real-time test and offers logistic advantage of providing treatment for screen positive women during the same visit leading to high treatment coverage. The sensitivity and specificity estimates of VIA generally fall within the range of those reported for cytology and HPV testing. Randomized controlled trials evaluating test performance of VIA have demonstrated reduction in cervical cancer incidence and mortality in study population. The major limitation of VIA is that it is a subjective test and accuracy is dependent on the skill of trained providers. Low specificity and sub-optimal positive predictive value results in unnecessary referrals and/or treatment which can offset the perceived low cost of the test. VIA based screening programs are required to have clearly defined measurable indicators and a framework to identify the program strengths and weaknesses. Quality assurance of VIA is challenging specially because there is limited information on the test performance in multi-provider real programmatic setting. High quality training, periodic refresher courses, expertise of trained providers and close monitoring of performance indicators are required to ensure good quality VIA.

INTRODUCTION

Visual screening for cervical neoplasia

Visual screening for cervical neoplasia includes visual inspection with acetic acid (VIA) and visual inspection with Lugol's iodine (VILI). VIA involves naked eye examination of the uterine cervix under bright light (preferably a halogen focus lamp) one minute after application of 5% dilute acetic acid. Use of magnification does not improve the performance of VIA (Sankaranarayanan, 2004b). VIA is currently being used as a screening test for the national cervical cancer screening programs of many low and medium resource countries in South Asia like Bangladesh (Ahmed, 2008). Visual screening tests are simple, widely feasible and affordable. The test provides immediate results enabling diagnosis and/or treatment to be carried out in the same session for screen positive women. They can be provided by a wide range of health professionals including

Key words: Cervical cancer screening, Cervical neoplasia, Visual Inspection with Acetic Acid (VIA), VIA accuracy, VIA limitations, VIA performance indicators, VIA quality control, VIA provider performance.
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doctors, nurses, midwives and primary health care workers after a short period of training. The infrastructural need is minimal and the consumables are universally available.

Accuracy of VIA: range in sensitivity and specificity

A systematic review of the accuracy of conventional cytology reported that, in 12 studies with the least biased estimates, sensitivity ranged from 30–87% and specificity from 86–100% (Nanda, 2000). A critical review by Pan American Health Organization (PAHO) in 2003 observed the sensitivity of VIA to range from 29–95.8% and specificity to range from 64.1–97.7% with CIN 2 as the threshold for positive diagnosis (PAHO, 2003). Most of these studies had verification bias since all the women with negative test were not evaluated by the reference standard. International Agency for Research on Cancer (IARC) conducted cross-sectional studies involving 56,939 women aged 25–65 years in Burkina Faso, Congo, Guinea, India, Mali and Niger to evaluate the accuracy of VIA performed by health workers (Sankaranarayanan, 2004a). In all these studies same definitions were used to characterize the test outcomes and all the VIA negative women had gold standard test of Colposcopy to avoid verification bias. The pooled sensitivity, specificity, positive and negative predictive values for VIA in these multi-centric studies were 76.8% (95% CI: 74.2–79.4%), 85.5% (95% CI: 85.2–85.8%), 9.4% (95% CI: 8.8–10.8%) and 99.5% (95% CI: 99.4–99.6%), respectively. The accuracy of VIA was similar or higher than that of Pap smear in such studies where both visual tests and cytology were concurrently evaluated.

Comparative efficacy of VIA with cytology and HPV DNA testing

Randomized Controlled Trials (RCT) provides realistic evidences on efficacy of various cervical cancer screening tests and the resulting impact they have on reduction of disease burden. In India a large cluster randomized trial (Sankaranarayanan, 2009) investigated the effect of single round of screening with VIA, cytology and HPV DNA tests among women aged 30-59 years. The study demonstrated that a single round of HPV testing was associated with a significant reduction in number of advanced cervical cancer cases and deaths as compared to the unscreened control group. No such effect was seen in either the VIA or cytology screened group. The findings of the trial indicated that HPV testing could be used as a primary screening technique in low resource settings as it is less demanding in terms of training and quality assurance. Presently, the major drawback is the high cost involved in implementing such a program.

In another cluster RCT (Sankaranarayanan, 2007) in South India, more than 49,000 women aged 30–59 years were followed for 7 years after a single round of VIA screening. The study observed an overall 25% reduction in cervical cancer incidence and 35% reduction in mortality in the intervention group as compared to the unscreened control group. Furthermore, the

maximum benefit of VIA screening was observed in the 30–39 age groups with 38% reduction in cervical cancer incidence and 66% reduction in cervical cancer mortality. The study concluded that in the presence of good training and sustained quality assurance, VIA is an effective method to prevent cervical cancer in developing countries.

The safety and efficacy of 'screen and treat' approach to prevent cervical cancer were evaluated in an RCT (Denny, 2005) at South Africa in which the screen positive women were treated by cryotherapy without resorting to colposcopy. The study demonstrated that 'screen and treat' approach of treating the HPV positive women with cryotherapy was superior to the immediate treatment of the VIA positive women. Treatment of the HPV positive women resulted in 77% lower prevalence of CIN 2+ in subsequent follow up as compared to 37% lower prevalence of CIN 2+ in the women treated for positive VIA. This landmark trial showed that treating women with positive HPV DNA test or VIA with cryotherapy is safe and has a significant impact on the prevalence of CIN 2+ among women participating in such a program.

Limitations of VIA

The visual tests are subjective in nature and provider dependent, resulting in a wide variation of performance in different settings. Quality assurance for visual screening is a challenging task specially because there is limited information on the test performance in multi-provider real programmatic setting. VIA is dependent on the full visibility of the transformation zone of the cervix. However, the transformation zone moves into the endocervical canal after menopause and may be totally invisible with aging, limiting the utility of visual tests in postmenopausal women. Moreover, the interpretation of VIA is difficult in postmenopausal women due to the atrophy of the cervical epithelium. Reasons for false positive and false negative results of VIA are summarized in Table 1. Low specificity and suboptimal positive predictive value of VIA will result in unnecessary referrals and/or treatment which can offset the perceived low cost of the tests. There are several training issues related to VIA such as the duration of training, structure and content of the competency based course and post-course evaluation need to be standardized.

VIA TEST PROCEDURES

Pre-test counseling

The test procedure and the implications of the test results are explained to the woman before proceeding to examine her. She is assured that the discomfort associated with the procedure is minimal. Adequate privacy should be maintained in the examination room. Such measures will ensure that the woman is fully relaxed during pelvic examination. Some programs may require the woman to sign an informed consent prior to the procedure.

Steps of VIA

The woman is made to lie in lithotomy position or dorsal supine position with legs flexed. A good focusing light, preferably one containing a halogen bulb should be used to

Table 1: Reasons for false positive and false negative result of VIA

False positive	False negative
Immature squamous metaplasia	Inability to identify acetowhite area
HPV infection	Inability to categorize acetowhite area
Blanching of columnar epithelium	Endocervical lesion
Inflammation	
Post-menopausal atrophy	

visualize the genitalia and cervix. The external genitalia are inspected for any excoriation, skin changes, ulceration, wart or growth before proceeding to insert the lubricated self-retaining bivalve speculum. The cervix is gently exposed and any evidence of infection such as purulent, curdy white or greenish yellow or malodorous discharge, vesicles, redness and inflammation are investigated. The cervical os and the squamo-columnar junction (SCJ) are identified. If there is any cervical polyp or ulcer or growth it should be noted. A cotton swab is used to apply 5% freshly prepared acetic acid generously on the entire cervix for one minute before the acetowhite changes are looked for. If there is any discharge or mucus on cervix, it is gently removed while applying the acetic acid. The cervix is examined for any well-defined, well-demarcated, opaque acetowhite areas abutting the SCJ or the external os or extending into the endocervical canal. After the completion of examination any acetic acid collected in the posterior vaginal fornix should be removed with a dry swab. The speculum should be gently withdrawn. The test findings should be explained to the woman and she should be appropriately advised if any abnormality is detected. Meticulous attention should be given to ensure infection control.

Reporting VIA test results

VIA test results are interpreted one minute after application of acetic acid. Acetowhitening is not specific to neoplasia. It can be associated with immature metaplasia, inflammation, regenerating epithelium and HPV infection. Acetowhitening associated with cervical neoplasia are localised in the transformation zone of the cervix, invariably arising from the SCJ, have a smooth well demarcated margin and are densely white.

Different authors have used different criteria to define the VIA outcome. In the present document we have used the test definitions as per the technical manual by IARC where VIA is reported as negative, positive or invasive cancer (Sankaranarayanan, 2003). A negative report implies that screening test is normal and no further evaluation is necessary. The woman should be referred for Colposcopy if VIA is reported positive. The suspected invasive cancers on VIA may be directly referred for diagnosis and treatment.

VIA test definitions as per criteria set by IARC, Lyon

VIA is reported negative when any of the following features are seen:

- No acetowhite lesions on the cervix
- Thin transparent acetowhite lesions or

faint patchy lesions or lesions without definite margins
- Polyp protruding from the os taking up acetowhite
- Nabothian cysts taking up acetowhite and appearing as whitish acne
- Faint line-like acetowhitening at the junction of columnar and squamous epithelium
- Acetowhite lesions away from the transformation zone
- Streak-like acetowhitening
- Dot like areas in the endocervix, which are due to grape-like columnar epithelium transiently staining with acetic acid

VIA is reported positive when any of the following features are seen:
- Distinct, well defined, dense, opaque or dull white or oyster white acetowhite areas touching the SCJ or touching the external os (if SCJ not seen)
- The lesion with a well-defined margin may or may not be raised from the surface

VIA is reported suspicious of invasive cancer when any of the following features are seen:
- Visible growth or ulcer on the cervix that bleeds on touch
- The growth or ulcer may or may not be acetowhite after acetic acid application

QUALITY CONTROL AND QUALITY ASSURANCE FOR VIA

Principles of quality control for cervical cancer screening program

To make the cervical cancer screening program efficient and cost-effective appropriate monitoring and periodic performance evaluation should be done. The ultimate 'impact' of cervical cancer screening program is the reduction of incidence of cervical cancer and mortality from the disease. Initially the program is likely to detect many of the undiagnosed prevalent cancers that may be reflected as an apparent increase in the incidence. There will be a stage-shift of the detected invasive cancers with more cases being diagnosed at earlier stages. As the cervical precancers are detected and treated, there will be a gradual reduction in new cases of invasive disease. However, reduction in incidence and mortality as an impact of screening program may take a decade to be evident. In the meantime, evaluation of performance of the program can be done by assessing the following performance indicators:
- Coverage of the target population
- VIA positivity and positive predictive value
- System capacity (time to colposcopy, compliance to colposcopy, etc.)
- Colposcopy performance (i.e., biopsy rate, colposcopy-histology agreement)
- Pre-cancer detection rate
- Disease extent at diagnosis
- Treatment performance (compliance to treatment, cure rate after treatment)

Objectives of quality control for VIA

VIA being an observer dependent test requires stringent quality control for optimum performance. The quality standards and the

performance indicators should take into consideration all the components of a VIA-based screening program rather than the test in isolation. The Quality Control and Quality Assurance document for a VIA-based screening program should:

- Clearly define the measurable indicators that will help assess the performance of the program in achieving the stated targets and goals
- Provide a framework to identify the strengths and weaknesses of the ongoing program as well as report and resolve problems at the earliest
- Help continuous improvement in quality for all aspects of cervical screening service delivery

The performance indicators should cover all levels of services – public education and outreach, screening facilities, colposcopy and treatment facilities, pathology laboratories and training program. Some of the quality standards may not be universal and may vary from one programmatic setting to another. Over time, with regular monitoring and reporting of the various performance indicators, an evidence base will generate that will permit the setting of targets for individual program. Data obtained from a well-designed pilot study prior to launching a population based screening program can serve as quality standards for future evaluation of the program.

Performance indicators for VIA based screening program

Coverage of the eligible population

- Definition: Percentage of eligible women in the target population with at least one VIA test in a three to five years period depending on the specified screening interval
- Method of calculation: (Number of women who have had VIA in last N years ÷ Number of eligible women) × 100
  N = Specified screening interval in the program

Explanation: Ensuring the participation of majority of eligible women in the screening program is one of the key determinants of success of the program. The age at which screening will be initiated and the age at which screening will be discontinued need to be predetermined depending on the capacity and the resources available. Similarly, the interval between two rounds of screening may vary from program to program. The program manager should ensure that all women within the specified age group have access to VIA and a majority undergo the test on regular basis. In an opportunistic program with low participation rate, usually the low risk women undergo frequent rounds of screening, while those with significantly higher risk are left out. For significant reduction of mortality from cervical cancer, 70-80% eligible women should have regular cervical screening.

VIA test positivity

- Definition: Percentage of women reported positive/invasive cancer on VIA.
- Method of calculation: (Number of women reported positive/invasive cancer on VIA ÷ Number of women screened) × 100

- Explanation: The positivity of VIA depends on the age distribution of the screened women, prevalence of cervical neoplasia in the target population, skill and experience of the VIA providers. The test positivity will be high in younger women, especially those below 30 years due to the metaplastic changes in the cervix and high prevalence of low grade intraepithelial lesions. In various studies it has been observed that the test providers tend to report higher positivity initially. As they acquire skill and gain confidence, the test positivity tends to come down and stabilizes at a rate appropriate for the population. The optimum VIA test positivity is 5–10% in women between 30–60 years of age. The providers need retraining if the test positivity becomes too low (possibility of missing disease) or too high (possibility of high false positives). If possible, the test positivity should be calculated by 10-year age groups.

Compliance to colposcopy

- Definition: Percentage of VIA positive women undergoing colposcopy following a positive VIA test.
- Method of calculation: (Number of VIA positive women who had colposcopy within N months ÷ Number of Women reported positive on VIA in a 12 month period) × 100

  N = 1–3 months of index VIA test, depending on the program capacity and specification
- Explanation: Ideally all screen positive women should have colposcopy for confirmation of the disease status that will lead to appropriate treatment. Linkage between screening and colposcopy/treatment is essential for the success of the screening program. A major advantage of VIA is that the report is immediately available and the positive women can have colposcopy in the same sitting or can be advised for colposcopy immediately. The program managers will have to decide on the permissible interval between VIA test and colposcopy depending on the program capacity. More than 80% of the VIA positive women should have colposcopy within the specified time.

Biopsy rate and adequacy of biopsy specimens

- Definition: Percentage of VIA positive women who received a histological diagnosis in a 12 month period is defined as the biopsy rate. The proportion of all the biopsies obtained during colposcopy that are reported unsatisfactory by the histopathologist is the measure of inadequate biopsies.
- Method of calculating biopsy rate: (Number of women with a histological diagnosis after VIA ÷ Number of VIA positive women in a 12 month period) × 100
- Method of calculating inadequate biopsy rate: (Number of women with a diagnosis of inadequate biopsy ÷ Number of VIA positive women in a 12 month period)

× 100

- Explanation: Punch biopsies are obtained from cervix if cervical neoplasias are suspected during colposcopy of the VIA-positive women. Biopsy is obtained through loop excision if 'see and treat' policy is practiced during colposcopy. A low biopsy rate usually indicates poor predictive value of VIA or inadequate follow up. The biopsy rate also depends on the skill and thoroughness of the colposcopist to rule out neoplasias. Sometimes the women themselves refuse biopsy. The minimum biopsy rate acceptable as a performance measure is to be specified in individual program setting and to be monitored over time. High inadequate biopsy rate indicates use of inappropriate punch biopsy forceps or inadequate skill of colposcopist to obtain a good biopsy. Failure to preserve the specimen or to process the specimen correctly in the laboratory can also lead to a report of unsatisfactory biopsy. The rate of inadequate biopsies should be as low as possible and corrective measures should be taken promptly if a high rate is detected.

Detection rate for cervical cancer precursors

- Definition: Number of pre-cancerous lesions detected per 1,000 women who had a VIA test in a 12 month period. Commonly the detection rate of CIN 2 and CIN 3 are calculated due to the clinical and programmatic relevance of the high grade precursor lesions.
- Method of Calculation: (Number of women with CIN 2 and CIN 3 on histology ÷ Number of women who had VIA in a 12 month period) × 1000
- Explanation: Detection rate of CIN, especially CIN 2 and CIN 3 lesions, can serve as a surrogate for the sensitivity estimate of VIA test. The detection rate of CIN 2+ lesions in the population also depends on the prevalence of the disease in the population and capability of the colposcopist to identify the disease correctly. The detection rate has to be monitored over time. A decline in the rate indicates suboptimal sensitivity of VIA or inadequate work up of the VIA positive women. The detection rate of CIN 2 and CIN 3 usually varies from 3–10 per 1000 screened population.

Stage of invasive cancer at diagnosis

- Definition: Proportion of screen detected invasive cancers in early stage (stage I; confined to cervix)
- Explanation: One of the major indicators of effectiveness of screening program is the ability to detect cervical cancers in the preclinical or early stage when the cancer is curable in more than 90% cases. In an unscreened population the majority of cancers are detected in advanced stage. With implementation of screening program the number should come down gradually.
- Method of calculation: (Number of cancers of cervix in stage I ÷ Number of

cancers detected in a 12 month period) × 100

Incidence of cervical cancer

- Definition: Age standardized incidence of cervical cancer in the screened population.
- Explanation: As organized screening program become established the rates of cervical cancers come down eventually due to intervention at the precancer stage of the disease. The incidence rate is recorded by a population based cancer registry operating among the screened women and is expressed as age-standardized rate. A reduction in incidence (and mortality) rate of cervical cancer is the best outcome indicator for cervical cancer screening program but may not be feasible to obtain in many of the low/medium resource settings due to non-availability of population based cancer registry.
- Method of calculation: To calculate age standardized incidence rate, information regarding the number of cancers detected in one year, their age distribution and the age distribution of a standard population is necessary.

Appropriate infection control and sterilization procedures should be practiced and should be monitored as part of standard quality control measure.

In addition, following practical issues also influence accuracy of the test:

- Use of correct concentration of acetic acid (5%)
- Use of a good quality light source, preferably a halogen lamp
- Use of a stop-watch to monitor the time (one minute) required for interpretation of test following application of acetic acid

Individual VIA provider performance evaluation

VIA is an observer dependent test. For correct interpretation of the post acetic acid application changes, appropriate training of the test providers is essential. VIA training manuals developed by IARC (Sankaranarayanan, 2003) or JHPIEGO (McIntosh, 2001) may be used. The duration of training varies between 5–10 days (JHPIEGO, 2001a; Blumenthal, 2005), during which the candidates should have exposure to adequate number of VIAs being performed by the trainer as well as by the trainee. The minimum number of VIAs required to be observed and to be performed under supervision to gain adequate competency to perform the procedure independently is not yet standardized. It is generally agreed that the number should be 50–100, of which at least half of the procedures should be done by the trainee.

It is essential that after completion of training each trainee should undergo competency based evaluation. During such evaluation the trainee should perform adequate number of VIAs while being observed by a trainer. The trainer has to evaluate the trainee using a checklist that can assess the trainee's skill in counseling (before and after VIA), positioning of the woman, steps of VIA, interpretation of the appearance

of the cervix before and after application of acetic acid and following appropriate infection control measures. All VIA providers need a reorientation training at least once a year. The agreement between the VIA results obtained by the provider and those obtained by the trainer can be assessed during such reorientation training. Such agreement should be at least 80%.

CONCLUSION

For implementing successful cervical cancer screening programs, it is essential to have sufficient resources to cover the entire target population and provide diagnostic as well as treatment facilities to all women identified as positive by screening tests. Evidences from various studies suggest use of HPV DNA testing as a primary screening tool as it is objective, reproducible, highly sensitive and demonstrates a high negative predictive value. Due to logistic and fiscal constraints many of the low and medium resource countries have not been able to introduce HPV based screening program.

On the other hand VIA is feasible, effective and an inexpensive alternative to cytology or HPV DNA based screening programs in countries with limited resources. Moreover, it offers logistic advantage in providing diagnosis and/or treatment for screen positive women during the same visit leading to high treatment coverage. VIA quality control is challenging but when performed by well trained and experienced providers under good monitoring and supervision, it is an effective alternative screening method for prevention of cervical cancer in a low resource setting.

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CONFLICT OF INTEREST

The authors claim no conflict of interest.

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