Research Article

The SDGs Perspective of TeleDoVIA Reliability for Cervical Cancer Elimination in 2030: A Cross-Sectional Study in Indonesia

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Abstract

Objective: To describe the prevalence of HPV infection in women with negative Visual Inspection with Acetic Acid (VIA) and introduce Teleconsultation of Documented VIA (TeleDoVIA) as an objective test and provide a rationalization for recommending TeleDoVIA as a "high-performance" test for cervical cancer screening in lower resource settings, from SDGs perspective, to accelerate the achievement of second pillar elimination and the third SDGs target in 2030.

Methods: This is a 7-year cross-sectional study. Subjects were recruited consecutively from several public and private health providers in Jakarta. VIA test was documented and consulted with the experts panel (TeleDoVIA). Negative VIA women underwent HPV-DNA testing using SPF10-DEIA-LiPA25 for PCR and electrophoresis.

Results: A total of 1,397 negative VIA subjects were collected, including 52 HPV-DNA positive. The false-negative for VIA was 3.7% (95% CI 0.027–0.047).

Conclusion: VIA is a reliable screening method with a low false-negative rate. TeleDoVIA could be recommended as a reliable cervical cancer screening method in low-resource settings such as Indonesia, which is in line with the third SDG: good health and well-being.

Keywords: asia, public health, southeast asia.

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INTRODUCTION

Cervical cancer is the leading cause of gynecological death worldwide, especially in developing countries or LMICs. The 5-year prevalence of cervical cancer globally and in Indonesia, based on GLOBOCAN 2020, is 1,495,211 and 92,930, respectively.[1-3] The World Health Organization (WHO) has set a triple intervention target of 90% vaccination coverage before age 15.70% screening with high-performance tests, and 90% treatment to be achieved in 2030.[4] In addition, eliminating cervical cancer is consistent with the third goal of the SDGs stated by the United Nations (UN): good health and well-being.[5] HPV-DNA testing is a high-performance test generally used as a cervical cancer screening test.[6-8] It has been recommended by the WHO as the primary screening tool over the other screening methods.[9] However, in LMICs, where facilities and resources are limited, this method is unreachable due to higher costs.[10-12] VIA is a screening method for cervical cancer precancerous lesions recommended by WHO for low-resource settings because it is simple, inexpensive, and sensitive.[13-15] In the

WHO decision-making flowchart for program managers, VIA is no longer just a screening test but a triage for treatment implementation after a positive HPV-DNA test.9 In order to avoid subjectivity of VIA expertise, in Indonesia, we have developed Documented VIA (TeleDoVIA): a method of documenting VIA results using a cell phone camera and a specific technique that provides results comparable to colposcopy. The Documentated VIA (DoVIA) results are consulted and discussed by gynecologists oncologist experts panel on the easy-to-use Whatsapp Messenger telecommunication system, which is called Teleconsultation of Documented VIA (TeleDoVIA). These experts' responses have been reported to be immediate or, at maximum, within six hours, providing accurate VIA interpretations.[16,17] A study by Utami et al. reported a low false positive rate of 3.21% for DoVIA, suggesting that TeleDoVIA is likely also to maintain a low false negative rate. Given this, our primary concern with this teleconsultation platform remains the potential for false positives.[18]

This modality is expected to provide an alternative screening method with comparable performance to the HPV-DNA test. Hence, the goal of cervical cancer elimination can be achieved in LMICs. Poverty is a significant risk factor for non-communicable diseases, including cancer.[18] Poverty is the first goal of SDGs. This study aims to describe the prevalence of HPV-DNA positive in the negative VIA women and rationalize the recommendation of TeleDoVIA as an objective, even as a "high-performance" test for cervical cancer screening in lower resource settings, from SDGs perspective, to accelerate the achievement of second pillar elimination and the third SDGs target in 2030.

METHODS

The research method is a descriptive cross-sectional study conducted for approximately seven years (January 2012 - July 2018). The subjects were women enrolled in primary health care (PHC) and other health care facilities appointed in the "See and Treat" Female Cancer Program (FCP) Jakarta, as well as gynecologists, colposcopies, and gynecological outpatients from the private clinic of the Department of Obstetrics and Gynaecology of Dr. Cipto Mangunkusumo General Hospital (RSCM).

Ethical approval for this study was obtained from the University of Indonesia Review Boards. Subjects were recruited consecutively, and the inclusion criteria were: married or sexually active, residing in Jakarta, the squamocolumnar junction (SCJ) was fully seen, and willingness to participate in the study. The exclusion criteria were pregnancy, recent genital infection, SCJ was not fully seen, and cervical cancer or precancerous lesion. With an assumed proportion of positive HPV in the hostile VIA population of 5 % and a precision of 1.25 %, a minimum of 1,167 subjects were required.

After ethical approval was obtained, the data were collected. The information about the study was explained to the patients by trained medical staff. Each subject who participated in this study signed an informed consent form. Before a thorough physical examination, each woman was administered a structured socio-demographic and complications and medical history questionnaire. The questions addressed socio-demographic variables such as age, occupation, education level, smoking, contraceptive use, age at menarche, previous cervical screening history, and sexual behaviour questions.

A well-trained general practitioner or midwife performed the procedures under the direct supervision of an oncological gynecologist. The subject was in the lithotomy position after being informed about the indications, the procedure, possible side effects, and the treatment. The examiner inserted a speculum into the vagina to expose the cervix. Before the VIA test, an initial inspection was performed to assess whether the cervix was normal, severely inflamed, or suspicious for precancerous or invasive cervical cancer. In addition, the examiner applied a 5% acetic acid solution to the cervix, especially in the transformation zone, including the squamocolumnar junction site. The result was evaluated after 60 seconds. We make documentation of VIA (DoVIA) using a cell phone camera and a specific technique that provides results comparable to colposcopy. The DoVIA results are consulted and discussed by an expert panel on the Whatsapp Messenger telecommunication system (TeleDoVIA).

The result was considered positive VIA due to the presence of white epithelial lesions (WEL). Meanwhile, the absence of WEL was stated as a negative VIA. Patients with negative VIA results were then subjected to HPV-DNA testing.

HPV-DNA tests were performed by Leiden University Medical Center (LUMC) and KALGen Laboratory Jakarta. HPV-DNA status was defined

as a positive or negative HPV-DNA test result determined by PCR SPF10-DEIA-LiPA25. A standardized protocol was used for cervical sampling.

Samples from cervical mucus were collected by swabbing with a cytobrush rotated 2x360° and then placed in a tube containing a 20 ml volume buffer solution. The tubes were centrifuged at 4,500 rpm for 10 min the same day. The residue was then placed in a 2 ml save-lock tube and stored at -50°C for further analysis.

HPV-DNA detection. The assay was performed in the pre-PCR laboratory, specifically in the HPV cabinet, to avoid contamination. Each well (A1-H9) contained 20 ul SPF10 PCR, 2 l H2O, and 3 ul DNA samples; the H10 well contained 20 ul SPF10 PCR and 5 ul H2O; the H11 well contained 20 ul SPF 10 PCR and 5 ul Siha; the H12 well contained 20 ul SPF 10 PCR and 5 ul SPF 10 positive control. After all, well were ready, the plate was covered with the Bio-rad RT-PCR shield, and short centrifugation was performed (± 1 min). Then the thermal cycle PCR process was performed with an additional LIPA program in the PCR lab. Subsequently, electrophoresis is continued to determine HPV-positive samples.

DNA quality PCR (Q-PCR). All A1-H9, H10, and H11 were prepared. Each well (A1-H9) contained 11 ul qPCR mix and 1 ul DNA samples; the H10 well contained 11 ul qPCR and 1 ul H2O; the H11 well contained 11 ul qPCR and 1 ul Siha 3 cell line as a positive control. After all, well were ready, the plate was covered with the Bio-rad RT-PCR shield, and short centrifugation (± 1 min) was performed. Then the thermal cycle PCR process was performed with an additional LIPA program in the PCR lab. Subsequently, electrophoresis is continued to determine HPV-positive samples.

Electrophoresis. First, the 3% agarose gel was prepared. Then the electrophoresis equipment and the samples were prepared. The PCR plate was removed from the freezer. Then the samples were melted and centrifuged. The gel was run at 120V for 45-60 minutes.

After data collection, the data were reviewed, edited, and coded. Data analysis was done using the Statistical Program for Social Sciences (SPSS) for Windows version 20.0. The data obtained were presented descriptively for categorical variables. The results of the analysis were presented in terms of number (n) and percentage (%) (proportion). The descriptive data presentation was in tabular form. Missing data were not calculated.

RESULTS

A total of 1,504 subjects met the inclusion criteria in the study period. Sixty-two subjects from FCP and PHC forty-two subjects from RSCM were excluded due to incomplete data (age), while three subjects were excluded due to duplicate subjects. Finally, 1,397 subjects were enrolled and processed (Figure 1).

As described in Table 1, the median subjects' age was 41, while the mean age of marriage was 22. The HPV-DNA test result were described in Table 2.

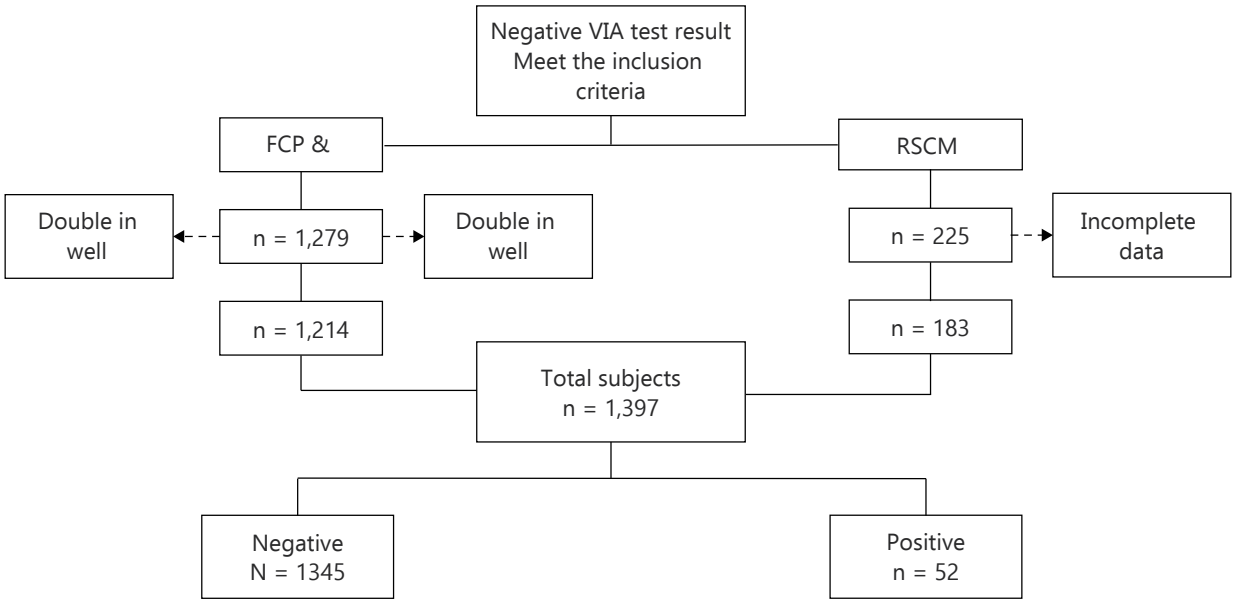

Figure 1. Subjects Flow Diagram FCP, Female Cancer Program; PHCs, Public Health Care; RSCM Clinics, Dr. Cipto Mangunkusumo General Hospital

Table 1. Demographic characteristics

	Description (n=1,397)	
Age (years old)		41 (19-84)
Age category	≤ 40 years old	681 (48.7)
	> 40 years old	716 (51.3)
Marital age (years old) *		22 (13-48)
First menstruation age (years old) **		13 (9-20)

Numeric variables for abnormal data distribution are presented with the median (minimum - maximum); Categorical variables are expressed as n (%).
*n = 1391, as many as six subjects missing data
**n = 543, as many as 854 subjects missing data

Table 2. HPV-DNA Test Results

Variabel	Category	n (%)
Status	Positive	52 (3.7)
	Negative	1.345(96.3)
Genotyping (n=52)	Hr-HPV	29 (55.7)
	Non Hr-HPV	7 (13.5)
	HPV X	16 (30.8)
Number of infections (n=52)	Single infection	35 (67.3)
	Multiple infection	17 (32.7)

Hr-HPV: High risk HPV

DISCUSSION

This study collected 1,397 subjects with negative VIA were collected. Fifty-two subjects (3.7%) had positive HPV-DNA results (95% CI 0.027-0.047). Of the 52 subjects, 55.7% were infected with high-risk HPV, regardless of single or multiple infections. These results showed that the false-negative of VIA testing could be considered low.

The sensitivity of VIA is lower in postmenopausal women than in premenopausal women but has higher specificity.[19-21] The cohort of the study consists of 51.3% women over 40 years. However, we did not have data on the menopausal status of the subjects. Therefore, the percentage of postmenopausal women cannot be presented. In this study, 228 out of 1397 subjects (16,32%) were > 50 years of age, while 8 of them (3.52%) were HPV positive. In Contrast, 1168 out of 1397 subjects (83,67%) were ≤ 50 years of age, while 44 subjects of this group (3,76%) were HPV positive. If we agrees that women aged > 50 years were considered postmenopausal, the false-negative VIA in premenopausal and postmenopausal women groups was very low, illustrating that it was an excellent screening method.

A similar study refers to HPV-DNA positive in VIA-hostile populations was limited. Instead, however, more studies refer to HPV-DNA positives in cytologically negative populations. In Pakistan, the study presented the same result (4.74%) with a similar total of subjects (1,011 subjects) compared to this study. The study assessed the prevalence of HPV infection in a population with normal cytologic results.[22] Then, the study reported that the prevalence of HPV in 1,859 subjects with normal cytology results in Colombia was 14.8%, with 9% of the women infected by hrHPV.[23] Worldwide HPV prevalence in women with normal cytology at any given point in time is approximately 10%.[24] The higher prevalence of HPV in normal cytology results was reported, which is 51%.[25]

The most comprehensive available data on HPV prevalence in women with normal cytology derives from a large, global meta-analysis of the literature published and compiled by the WHO. The study includes 157,897 women with normal cytology and specifically excludes data on women with any abnormality. Only women with reported normal cytology were included in the analysis. The results indicate that 10.4% (95% CI: 10.2–10.7) of the women worldwide are positive for HPV-DNA. HPV prevalence is higher in the less developed world (13.4%; 95% CI: 13.1–13.7) than in more developed regions (8.4%; 95% CI: 8.3–8.6). African women (22.1%; 95% CI: 20.9–23.4), in particular women in Eastern Africa, have the highest HPV prevalence rates (31.6%; 95% CI: 29.5–33.8), while the lowest estimates are identified in Southeast Asia (6.2%; 95% CI:

5.5–7.0).[26] Compared to these studies, if the HPV-DNA test is a gold standard, this study showed a very low false-negative VIA test in detecting HPV infection than using cytology with 5-40% false-negative rate. This allows us to conclude that the VIA test can provide results comparable to or maybe even better than the cytology test.

In this study, married individuals were considered sexually active because asking about sexual activity status was taboo in the Indonesian population. Therefore, we included married women as inclusion criteria instead of expanding the inclusion criteria to include sexually active womaen even though they are not yet married, which would lead to biased responses.

The VIA examination in this study was performed by a well-trained general practitioner or midwife. To avoid the subjectivity of VIA expertise, we use TeleDoVIA: teleconsultation to an experts panel on the Whatsapp Messenger telecommunication system of documented VIA with a specific technique that provides results comparable to colposcopy.

Of the 17 points of SDGs, cervical cancer elimination is in line with the third goal, specifically target 3.4, 3.7, and 3.8.[27-29] Target 3.4 aimed to reduce premature mortality from noncommunicable diseases, including cervical cancer, by one-third through prevention and treatment.[27] Target 3.7 ensures universal access to sexual and reproductive health services and the inclusion of reproductive health in national policies and programs.[29] Target 3.8 aimed to achieve universal health coverage. These targets are expected to be achieved by 2030.[30]

WHO defines premature NCDs-related death as the unconditional possibility of mortality from cardiovascular disease, cancer, diabetes, and chronic respiratory disease between 30 and 70 years old.[31]

Globally, 41 million people (71% of global mortality) die annually from non-communicable diseases. The number of annual premature deaths (between 30 and 69 years) due to NCDs is over 15 million worldwide. Unfortunately, low- and middle-income countries account for 77% and 85% of total NCD- and premature NCD-related mortality, respectively. Cancer is the second leading NCD-related mortality, which causes 9.3 million deaths annually.[32] Cervical cancer is the fourth most common cancer in women. In 2020, 341,831 women died from this disease (2.8% of total NCD-related mortality).[33] In Indonesia, 73% of deaths were caused by NCDs, while NCDs caused 26% of the probability of premature death.[34] Screening, early detection, treatment, and palliative care of NCDs are essential to the success of the 3.4 SDGs by 2030.[35]

The first SDG target, to end poverty in all its forms everywhere, is also in line with the cervical cancer elimination. Target 1.4 of this goal is to ensure that all men and women, in particular the poor and vulnerable, have equal rights to economic resources, as well as access to basic services, ownership and control over land and other forms of property, inheritance, natural resources, appropriate new technologies, and financial services, including microfinance. Basic services also include access to basic health services, including preventive health services. This goal is consistent with target 3.8.1 of the third goal.[36] Unfortunately, among the SDGs' various goals, targets, and indicators, there are several aspects that LMICs have not been able to implement due to several limitations. Therefore, LMICs need to focus on implementable goals.

The introduction of VIA as a national screening in Indonesia 7 has been in place since 2008. However, the screening coverage in Indonesia is still 21%.[37] Hence, achieving 70% HPV-DNA coverage in 9 years will considered difficult under Indonesian conditions. Although WHO has reduced the coverage for screening with high-performance testing from 80% to 70%, Indonesia, as a big island country with more than 17,000 islands[38], 34 provinces[39], and more than 40 million women between 30-50 years old[40] among more than 270 million of population[41], could not conduct HPV-DNA testing because laboratory facilities are not available throughout the Indonesian archipelago, except on the major islands, insufficient human resources, and lack of funding. In Indonesia, HPV DNA is currently proposed to be introduced as a national screening in 2022. In preparing for the introduction of the HPV-DNA screening program in Indonesia, based on the results of this study, the VIA can be used as an alternative "high-performance test". A screening method is called a gold standard if it has a sensitivity of 100% and a specificity of 100%.[42] False-negative VIA is considered low if HPV-DNA test is the gold standard. In several cases, we found positive VIA with histopathologic confirmed as high-grade lesions in negative HPV-DNA. Thus, we suggest a combination of HPV-DNA and TeleDoVIA test ("Co-testing") as the national cervical cancer screening program in Indonesia.

Although VIA is not a gold standard due to its subjectivity[43], the objectivity of VIA can be increased by introducing tiered supervision by an experienced oncologic-gynecologist. According to WHO, high-performance tests must have similar or better performance characteristics than the HPV-DNA test. However, new technologies may become available in the future.[4] In Indonesia, the tiered supervision is implemented using the DoVIA, which is the documentation of the cervix that underwent VIA using cell phone camera devices with special techniques (filling light mode, without backlight). The DoVIA is a material for communication and consultation between practitioners and the experts (gynecologic-oncologist). The expert panel consultation is called Portal Teleconsultation of DoVIA (TeleDoVIA). This photography-based consulting model utilizes a teleconsultation system via WhatsApp Messenger, which was immediately discussed with the experts and received feedback within 15 minutes, even less than 10 minutes.[17] DoVIA is effortless to implement, cost-effective and provides better images than colposcopy.[16] Hence, VIA, as well as DoVIA and TeleDoVIA, are reliable methods that could be considered as a "high-performance test" in Indonesia as a low-resource country to accelerate the achievement of the second pillar of the triple intervention to eliminate cervical cancer by 2030.[43]

This study has several strengths. First, it is recognized that the HPV-DNA testing was done in two different locations and at two different times, but the authors used standardized protocols, so these two results should be reliable. Second, all recruited patients were tested for HPV-DNA with no loss to follow-up. However, this study has a limitation; there was a random error in the collection of subjects. So that occurred three times in the whale data, but we excluded all of that to avoid bias.

In this study, the results can be generalized to the Indonesian population. The objectivity of the VIA test can be increased with TeleDoVIA. Further diagnostic studies are needed for "co-testing" of HPV-DNA and VIA test as a more accurate screening test with a lower cost than the existing co-testing.

CONCLUSION

VIA has a low false-negativity rate. TeleDoVIA could be recommended as a reliable cervical cancer screening method in low-resource settings, which is in line with the third SDG, paticularly targets 3.4, 3.7, and 3.8. However, further diagnostic studies on "co-testing" of HPV-DNA and VIA tests are needed.

DATA AVAILABILITY

The data supporting this study's finding are available from the corresponding author upon reasonable request.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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