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ABCD Criteria to Improve Visual Inspection with Acetic Acid (VIA) Triage in HPV-positive Women

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ABCD Criteria to Improve Visual Inspection with Acetic Acid (VIA) Triage in HPV-positive

Women

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ABSTRACT

Objectives A simple system for visual inspection with acetic acid (VIA) assessment, named ABCD criteria, has been developed to increase accuracy for triaging of high-risk human papillomavirus (HPV)-positive women. The present study aimed to determine the accuracy of ABCD criteria for the detection of histologically confirmed cervical intraepithelial neoplasia grade 2 or worse (CIN2+) in HPV-positive women living in a low-resource setting.

Design Prospective study of diagnostic accuracy

Setting Cervical cancer screening program based on a 3T-Approach (Test, Triage, and Treat) in the Health District of Dschang, West Cameroon.

Participants Asymptomatic non-pregnant women aged 30–49 years were eligible to participate. Exclusion criteria included history of CIN treatment, anogenital cancer or hysterectomy. A total of 1980 women were recruited (median age, 40 years; interquartile range, 35–45 years), of whom 361 (18·4%) were HPV-positive and 340 (94·2%) completed the trial.

Interventions HPV-positive women underwent a pelvic examination for visual assessment of the cervix according to ABCD criteria. The criteria comprised A for Acetowhitiness, B for Bleeding, C for Colouring, and D for Diameter. The ABCD criteria results were codified as positive or negative and compared with histological analysis findings (reference standards).

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3 **Primary and secondary outcome measures** Diagnostic performance of ABCD criteria for

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6 **CIN2+, defined as sensitivity, specificity, negative and positive predictive values.**

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9 **Results** ABCD criteria had a sensitivity of 77.5% (95% CI, 61.3%–88.2%), specificity of
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12 42.0% (95% CI, 36.5%–47.7%), positive predictive value of 15.1% (95% CI, 10.8%–20.8%),
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15 and negative predictive value of 93.3% (95% CI, 87.6%–96.5%) for detection of CIN2+
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18 lesions. Most (86.7%) of the ABCD-positive women were treated on the same day.

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21 **Conclusions** ABCD criteria can be used in the context of a single-visit approach and may be
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23
24 the preferred triage method for management of HPV-positive women in a low-income
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29 context.

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32 **Trial registration** The trial was registered under ClinicalTrials.gov (number NCT03757299).

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35 **Key words:** cervical cancer screening, low- and middle-income countries, visual inspection
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37
38 with acetic acid (VIA), visual inspection with Lugol's iodine (VILI), human papillomavirus,
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41 triage

42 43 44 45 46 47 48 **Strengths and limitations of this study**

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51 • Using ABCD criteria for D-VIA interpretation is a simple test with binary results
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53 (positive or negative) that are immediately available, allowing initiation of therapy
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55 without delay.
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- Because all HPV-positive women underwent biopsy and cervical brushing regardless of the ABCD criteria results, there was no risk of verification bias in the calculations of sensitivity and specificity.
 - A limitation of the study was its setting in a single centre in a district hospital in West Cameroon with five clinicians administering all screening and treatment procedures.

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INTRODUCTION

More than 80% of cervical cancer (CC) deaths occur in low- and middle-income countries (LMICs), mainly due to lack of prevention.¹ Cytology-based CC screening programs and more recent HPV-based programs have been successfully implemented in high-income countries and have been associated with important reductions in deaths from CC.² However, these strategies have not been implemented in LMICs, predominantly because of financial and logistical limitations. Alternative methods such as visual inspection of the cervix after application of acetic acid (VIA) are considered suitable for use in LMICs.^{3,4}

The World Health Organization (WHO) recommendations for screening in resource-limited settings include a strategy of HPV-screening followed by VIA and treatment, or a strategy of HPV-screening and treatment.³ Although no recommendations are given for the approach that should be prioritized, sub-Saharan Africa has a high HPV prevalence rate of 15%–30% and most HPV-positive women have no lesions.^{3,7,8} In this context, HPV testing followed by immediate treatment can represent significant overtreatment in women with an HPV-positive test, which by itself may not confer a high risk of cervical intraepithelial neoplasia grade 2 or worse (CIN2+).^{5–9} In sub-Saharan Africa, the prevalence of CIN2+ was reported to be 2%–4% in women aged 30–49 years and 7%–11% in an HPV-positive population with a low HIV

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3 prevalence rate (<10%).⁷⁻⁹ A triage system is only a valid option if it can conserve the high
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6 sensitivity of the HPV test for identifying CIN2+ disease.
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10 Triage by VIA and/or visual inspection with Lugol's iodine (VILI) requires accurate criteria to
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13 decide whether or not the findings are positive, which are generally based on the
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16 International Agency for Research against Cancer (IARC) manual.¹⁰ However, in this setting,
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19 VIA triage in HPV-positive populations appears to be associated with an important loss of
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22 sensitivity, suggesting that triage by VIA using traditional criteria may not be of benefit.⁷⁻¹⁰
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26 Previous studies using histology as reference standard and having excluded verification bias
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29 had sensitivities ranging from 25.0% to 45.5%.^{7,9,11} In a pilot study having used relaxed
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32 criteria for VIA interpretation in HPV-positive women, sensitivity increased to 80%.⁸
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36 Interpreting VIA with naked eye alone is subjective and is highly variable between health
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39 care providers.¹²⁻¹⁴ This issue may be improved with continuous supervision and medical
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42 education thanks to the use of digital VIA and VILI (D-VIA/D-VILI). This includes acquisition
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45 of cervical images, native and after VIA and VILI application, through a camera or
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48 smartphone. These technologies provide an alternative to colposcopy in the context of
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51 LMICs and may constitute an important step in the improvement of VIA/VILI interpretation.¹⁵⁻
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55 ¹⁷ Although the image quality is probably lower than that with high-resolution colposcopy,
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58 there are significant benefits for healthcare providers, because they can move through and
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3 compare the native, VIA, and VILI images, and can also magnify suspicious lesions, before
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6 deciding whether treatment is needed.^{15,16}
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10 To improve VIA/D-VIA interpretation as a triage test in HPV-positive populations, we
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12 introduced a set of criteria, termed ABCD criteria. These criteria constitute a simple structure
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14 that may contribute to preventing CC in an LMIC context. The aim of the present study was
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16 to provide a rationale for the ABCD criteria and determine their performance in identifying
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18 histology-proven CIN2+.
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29 METHODS

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32 **Study design** – This prospective study was carried out between September 2018 and March
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34 2020 in the health district of Dschang (West Cameroon). Asymptomatic non-pregnant women
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36 aged 30-49 years were eligible to participate in the study on a voluntary basis and were
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38 included in a consecutive manner upon presentation to the screening site. Exclusion criteria
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40 included history of CIN treatment, anogenital cancer or hysterectomy. The study was
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42 conducted within a larger trial aiming to recruit 6,000 women in a 5-year screening
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44 program.¹⁷ At the baseline visit, after obtaining written informed consent and providing
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46 guidance to participants on the procedure for vaginal self-sampling, participants undertook
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48 an HPV self-test (Self-HPV) that was subsequently analyzed by a point-of-care assay
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3 (GeneXpert®) on the same day. HPV-negative women were reassured and advised to repeat
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6 the test in 5 years, while HPV-positive women were invited to undergo visual triage and
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9 thermal ablation or large loop excision of the transformation zone (LLETZ) if needed.
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12 **ABCD criteria (Figure 1)** – The ABCD criteria were chosen from a synthesis of published
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14 results as well as our own experience in VIA and VILI interpretation.^{3,10,18–22} We considered
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16 acetowhitening as the most important predictor for CIN and noted that Lugol's iodine can be
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18 used to identify thin acetowhite lesions not seen on the initial VIA assessment (Figure 1).
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25 Similar to the IARC criteria, the pathological area should be located within or in contact with
26
27 the transformation zone (TZ). The ABCD criteria are codified as positive (present) or
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29 negative (absent). To be considered ABCD-positive, at least one of the following conditions
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31 needs to be fulfilled: presence of criteria A (acetowhitening) and D (diameter) combined, or
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33 criterion B (bleeding) with or without presence of A, C (colouring) or D.
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41 ABCD criteria were independently evaluated by one of three trained midwives and
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43 supervised by two experienced Cameroonian gynaecologists. ABCD criteria interpretations
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45 were performed first in real-time during VIA/VILI, and on smartphone images, before deciding
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48 whether or not to perform treatment. A set of three images (native, acetic acid, Lugol's
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51 iodine) were obtained on a Galaxy S5 smartphone (Samsung, Seoul, South Korea).
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Diagnosis and treatment were based on combined results of VIA/VILI and smartphone-

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3 enhanced D-VIA, using aids such as zooming in on lesions and performing comparisons
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6 between the native, VIA, and VILI images. A positive ABCD result by either one of VIA/VILI
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9 or D-VIA/D-VILI warranted treatment.
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13 Eligibility criteria for thermal ablation were women being positive for ABCD criteria.
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16 Indications for referral to a gynecologist to determine treatment modalities were (i) lesions
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18 extending into the endocervix which could not be covered by the probe tip, (ii) suspicion of
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20 carcinoma, in-situ adenocarcinoma or invasive adenocarcinoma, (iii) presence of bleeding
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22 and (iv) presence of acetowhite lesions covering more than 75% of the ectocervix. Our
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24 management of HPV-positive women with a TZ type 3 was as follows: (i) those having no
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26 lesion on visual assessment were offered follow-up, (ii) those having a lesion which could be
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28 covered by thermal ablation tips were treated, and (iii) those with an endocervical lesion
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30 which could not be fully covered by the probe were referred for LLETZ. Cervical liquid-based
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32 cytology, biopsy at the TZ and endocervical curettage (ECC) were performed on all HPV-
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34 positive women prior to treatment.
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48 **Cytology** – Cervical liquid-based cytology was performed using the SurePath (September
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50 2018 to July 2019) and ThinPrep (July 2019 to March 2020) techniques. All vials were
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52 analyzed in Switzerland (CytoPath, Unilabs, Geneva, and University Hospital of Geneva).
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57 The slides were independently read by qualified cytotechnologists and classified according to
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3 the Bethesda classification system: negative for intraepithelial lesion or malignancy (NILM),
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6 inflammatory atypical squamous cells of undetermined significance (ASC-US), inflammatory
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9 atypical squamous cells that cannot exclude HSIL (ASC-H), atypical glandular cells with low-
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12 grade squamous intraepithelial lesion (LSIL), high-grade squamous intraepithelial lesion
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16 (HSIL), and invasive cancer.

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19 **Histology findings (reference standard)** – Cervical biopsies were performed using biopsy
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22 forceps, and ECC was carried out with an endocervical brush. Cervical biopsies were
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25 performed at 6 o'clock in the TZ when ABCD criteria were negative. If ABCD criteria were
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28 positive, one or more biopsies were performed at the most suspicious areas. All samples
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31 were stored in formalin. Biopsy slides and ECC samples were read by two experienced
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34 gynaecologic pathologists who were blinded to the screening test results and ABCD criteria
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37 findings. The histological results were classified as normal, CIN1, CIN2, CIN3,
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40 adenocarcinoma *in situ* (AIS), invasive carcinoma, or adenocarcinoma. The cut-off for a
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43 pathological result was set at CIN2+. When histological results varied within the samples of
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46 one participant, only the worst result was considered as the reference standard.

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51 **Patient and public involvement** – Preferences of and experience with former patients of a
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54 preliminary research study on cervical cancer screening in Dschang, Cameroon, were
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57 considered in the design and conduction of this study. During the study, focus groups were
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3 organized with members of the community (women and men), health care workers and
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6 community health workers, to explore barriers to cervical cancer screening and further
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9 improve the program and recruitment strategy. Patients are also involved at their arrival at
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12 the screening center where they are offered a one-hour information session on cervical
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15 cancer and sexual health by trained midwives. Furthermore, the public is kept informed about
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18 the progress of our research through the publication of yearly newsletters disseminated
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21 among health workers and the general community.
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25 **Statistical analysis** – Initially, we planned a sample of 6,000 women. However, the COVID-19
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28 pandemic and public health measures to control the virus have impacted on-site clinical
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31 activity since mid-March 2020. In this context, we decided to consider an interim analysis to
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34 the trial of the primary endpoints which included performance of the ABCD criteria.
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38 Descriptive statistics were used to analyse the baseline characteristics of the study
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41 population. Sensitivity, specificity, positive predictive value (PPV), and negative predictive
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44 value (NPV) plus their 95% confidence intervals (95% CIs) were calculated. Student's *t*-test,
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47 Mann–Whitney test, or Pearson's chi-square test were used, where appropriate, to identify
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50 sociodemographic and reproductive characteristics of the patients that could differ between
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53 ABCD criteria results. A P-value of <0.05 was considered statistically significant. An
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56 exploratory analysis was performed to assess the relationships between each independent
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3 variable and the correct prediction of the ABCD criteria. This correct prediction score was
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6 equal to 1 when ABCD criteria were positive and there was a CIN2+ on histology or if the
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9 ABCD criteria were negative and histology was also negative. All other incorrect predictions
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12 were assigned the value 0. Univariate and multivariate logistic regression analyses were
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15 carried out to identify predictors of a correct ABCD criteria score according to histology.
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18 Participants with missing or indeterminate results for ABCD criteria or histopathology were
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21 excluded from the analysis. Odds ratios (ORs) were adjusted for potential confounders, such
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24 as age, marital status, number of lifetime sexual partners, age at first sexual intercourse, age
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27 at first delivery, parity, HIV status, and type of TZ, and 95% CIs were calculated. All data
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30 analyses were conducted using Stata Statistical software Release 13 (StataCorp LP, College
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33 Station, TX).
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38 **Ethical considerations** – The study obtained approval from the Cantonal Ethics Board of
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41 Geneva, Switzerland (Commission cantonale d'éthique de la recherche [CCER], No. 2017-
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44 0110) and the Cameroonian National Ethics Committee for Human Health Research (No.
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47 2018/07/1083/CE/CNERSH/SP). The trial was registered under ClinicalTrials.gov (number
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50 NCT03757299). The full study protocol can be provided upon request to the first author.
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54 55 56 57 **RESULTS** 58 59 60

A total of 1980 women aged 30–49 years were enrolled (median age: 41 years; interquartile range [IQR], 36–50 years). Overall, 1964 women performed Self-HPV, of whom 361 (18.5%) had an HPV-positive test and underwent pelvic examination, three were excluded from the results analysis for lack of ABCD criteria assessment, and 340 (94.2%) had interpretable histology findings and constituted the study population (**Figure 2**). **Table 1** provides details of the baseline sociodemographic, reproductive, and clinical characteristics of the participants. Median age at first sexual intercourse was 18 years (IQR, 16–19 years) and median number of sexual lifetime partners was 3 (IQR, 2–5).

Table 1: Baseline sociodemographic, reproductive health, and clinical characteristics according to ABCD criteria (N=358)*

Variable	ABCD criteria-negative	ABCD criteria-positive	Total	P-value
Participants recruited. n (%)	140 (39.1)	218 (60.9)	358	
Age (years). median (IQR)	41 (35–45)	40 (34–45)	40 (34–45)	0.4464
Marital status. n (%)				0.8910
Single	15 (10.7)	20 (9.2)	35 (9.8)	
With partner	109 (77.9)	173 (79.3)	282 (78.8)	
Divorced/widowed	16 (11.4)	25 (11.5)	41 (11.4)	
Education. n (%)				0.3900
Unschooling	1 (0.7)	5 (2.3)	6 (1.7)	
Primary education	37 (26.4)	66 (30.3)	103 (28.8)	
Secondary education	67 (47.9)	105 (48.2)	172 (48.0)	
Tertiary education	35 (25.0)	42 (19.2)	77 (21.5)	
Employment status. n (%)				0.1750
Employed	50 (35.7)	57 (26.2)	107 (29.9)	
Independent	39 (27.9)	56 (25.7)	95 (26.5)	
Housewife	23 (16.4)	41 (18.8)	64 (17.9)	
Unemployed	7 (5.0)	12 (5.5)	19 (5.3)	
Farmer	21 (15.0)	52 (23.8)	73 (20.4)	
Age at menarche (years). mean ± SD	14.7±1.8	14.7±1.9	14.7±1.8	0.8914
Age at first intercourse. median (IQR)	17 (16–19)	18 (16–20)	18 (16–19)	0.2390
Number of sexual partners. median	4 (3–6)	3 (2–5)	3 (2–5)	0.0008
Contraception. n (%)				0.5950
None	93 (66.9)	142 (65.5)	235 (66.0)	
Condom	18 (13.0)	25 (11.5)	43 (12.1)	

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3	Hormonal null	1 (0.7)	7 (3.2)	8 (2.3)	
4	DIU/ implant/ injection	25 (18.0)	41 (18.9)	66 (18.5)	
5	Other	2 (1.4)	2 (0.9)	4 (1.1)	
6	HIV status. n (%)				0.9420
7	Negative	128 (92.7)	198 (93.0)	326 (92.9)	
8	Positive	10 (7.3)	15 (7.0)	25 (7.1)	
9	Age at first delivery (years). mean \pm SD	21.4 \pm 3.7	21.4 \pm 2.5	21.4 \pm 3.8	0.9137
10	Parity. n (%)				0.0080
11	Nulliparous	11 (7.9)	3 (1.4)	14 (3.9)	
12	1-4	66 (47.1)	108 (49.5)	174 (48.6)	
13	>4	63 (45.0)	107 (49.1)	170 (47.5)	
14	Transformation zone. n (%)				<0.0001
15	TZ1	76 (57.1)	150 (73.5)	226 (67.1)	
16	TZ2	26 (19.6)	45 (22.1)	71 (21.1)	
17	TZ3	31 (23.3)	9 (4.4)	40 (11.8)	
18	HPV testing results. n (%)				
19	HPV-16	11 (7.9)	23 (10.6)	34 (9.5)	0.3890
20	HPV-18/45	22 (15.8)	31 (14.2)	53 (14.9)	0.6770
21	Other HPV	114 (82.0)	186 (85.3)	300 (84.0)	0.4060
22	Cytology. n (%) (Total= 343)				0.0990
23	Normal	108 (82.5)	161 (75.9)	269 (78.4)	
24	ASC-US	7 (5.3)	10 (4.7)	17 (5.0)	
25	LSIL	10 (7.6)	15 (7.1)	25 (7.3)	
26	HSIL	4 (3.1)	21 (9.9)	25 (7.3)	
27	ASC-H	0	4 (1.9)	4 (1.2)	
28	Cancer	2 (1.5)	1 (0.5)	3 (0.8)	
29	Histology. n (%) (Total=340)				0.0040
30	Normal	108 (80.0)	129 (62.9)	237 (69.7)	
31	CIN1	18 (13.3)	45 (21.9)	63 (18.5)	
32	CIN2	1 (0.7)	12 (5.9)	13 (3.8)	
33	CIN3	6 (4.4)	18 (8.8)	24 (7.1)	
34	Invasive cancer	2 (1.5)	1 (0.5)	3 (0.9)	

Abbreviations: SD = standard deviation; IQR = interquartile range; CIN1 = cervical intraepithelial neoplasia grade 1; CIN2 = cervical intraepithelial neoplasia grade 2; CIN3 = cervical intraepithelial neoplasia grade 3; HIV = human immunodeficiency virus; HPV = human papillomavirus.

*Data from the 358 participants may be missing for some variables.

Thirty-four (9.5%) samples were positive for HPV-16, 53 (14.9%) for HPV-18/45 and 300 (84.0%) for other HPV types. Overall, 218 (60.9%) participants were classified as ABCD criteria-positive. All patients positive for ABCD were treated with thermal ablation with the exception of one patient who underwent LLETZ and one patient suspicious of cancer who was biopsied and referred for multimodal therapy. Thermal ablation was provided on the same day as HPV screening in 86.7% of cases. Reasons for delaying treatment included

referral for further evaluation, technical issues, bleeding at the time of screening, or choice of the patients themselves. No serious adverse event occurred as a result of the screening procedure.

Among all 358 women with HPV-positive results, 343 samples with valid cytological results and 340 samples with valid histological results were obtained. Of the 343 valid cytological results, 21.6% had abnormal cytology (ASC-US+). Four patients had ASC-H, 25 had HSIL, and three had cytology suggesting cancer. All three cancers identified by cytology were confirmed by histology. Of the 340 valid histological results, 63 (18.5%) CIN1 were identified, 13 (3.8%) CIN2, 24 (7.1%) CIN3, and 3 (0.9%) invasive cancers. The prevalence of CIN2+ and CIN3+ was 11.8% and 7.9%, respectively. Details for the disease prevalences are also shown in **Table 1**.

Table 2 shows demographic and pathological characteristics associated with a correct prediction of the ABCD criteria.

Table 2: Demographic and pathological characteristics associated with a correct prediction of the ABCD criteria (N=340)*

Variable	Total	Unadjusted OR (95% CI)	P-value	Adjusted OR (95% CI)**	P-value
Age (years) n (%)					
30–40	186 (54.7)	1.00 (Reference)		1.00 (Reference)	
41–50	154 (45.3)	1.39 (0.90–2.14)	0.133	1.51 (0.87–2.60)	0.140
Marital status. n (%)					
Single	34 (10.0)	1.00 (Reference)		1.00 (Reference)	
With partner	265 (77.9)	1.15 (0.56–2.36)	0.706	1.07 (0.43–2.63)	0.887
Divorced/widowed	41 (12.1)	0.81 (0.32–2.04)	0.656	0.63 (0.19–2.04)	0.442
Education. n (%)					
Unschooling/primary education	101 (29.7)	1.00 (Reference)		1.00 (Reference)	
Secondary/tertiary education	239 (70.3)	1.04 (0.65–1.65)	0.879	0.92 (0.47–1.82)	0.818
Employment status. n (%)					

Employed	104 (30.6)	1.00 (Reference)		1.00 (Reference)	
Independent	93 (27.3)	0.90 (0.51–1.57)	0.706	0.73 (0.38–1.43)	0.363
Housewife	58 (17.1)	0.81 (0.43–1.55)	0.528	0.74 (0.34–1.63)	0.461
Unemployed	19 (5.6)	0.72 (0.27–1.95)	0.528	0.89 (0.27–2.91)	0.852
Farmer	66 (19.4)	0.69 (0.37–1.29)	0.248	0.41 (0.18–0.95)	0.037
Age at first intercourse (years). n (%)					
≤17	154 (45.6)	1.00 (Reference)		1.00 (Reference)	
≥18	184 (54.4)	0.70 (0.46–1.08)	0.106	0.75 (0.43–1.31)	0.315
Number of sexual partners†. median	3 (2–5)	1.08 (1.01–1.16)	0.031	1.06 (0.97–1.17)	0.176
1–2. n (%)	98 (28.8)	1.00 (Reference)		1.00 (Reference)	
3–5. n (%)	177 (52.1)	1.39 (0.84–2.30)	0.195	1.22 (0.67–2.22)	0.506
>5. n (%)	65 (19.1)	1.96 (1.04–3.70)	0.038	1.53 (0.70–3.38)	0.284
Contraception. n (%)					
No	225 (66.6)	1.00 (Reference)		1.00 (Reference)	
Yes	113 (33.4)	0.84 (0.54–1.33)	0.466	0.92 (0.54–1.85)	0.769
HIV status. n (%)					
Negative	309 (92.8)	1.00 (Reference)		1.00 (Reference)	
Positive	24 (7.2)	1.21 (0.53–2.77)	0.657	0.95 (0.36–2.53)	0.589
Age at first delivery (years). n (%)					
≤20	157 (47.7)	1.00 (Reference)		1.00 (Reference)	
≥21	172 (52.3)	0.70 (0.45–1.08)	0.102	0.60 (0.34–1.07)	0.085
Parity. n (%)					
Nulliparous	14 (4.1)	1.00 (Reference)		1.00 (Reference)	
1–4	165 (48.5)	0.21 (0.06–0.79)	0.020	0.26 (0.02–2.91)	0.274
>4	161 (47.4)	0.23 (0.06–0.86)	0.029	0.28 (0.02–3.22)	0.307
Transformation zone. n (%)					
TZ1	210 (65.8)	1.00 (Reference)		1.00 (Reference)	
TZ2	70 (22.0)	1.17 (0.68–2.02)	0.575	1.24 (0.67–2.26)	0.492
TZ3	39 (12.2)	6.72 (2.84–15.93)	<0.0001	6.47 (2.59–16.21)	<0.0001
HPV testina results. n (%)					
Other HPV (without co-infection)	264 (77.9)	1.00 (Reference)		1.00 (Reference)	
HPV-16/18/45	75 (22.1)	1.19 (0.70–1.98)	0.514	1.18 (0.64–2.17)	0.605
Cytoloav. n (%)					
High-grade+***	29 (8.9)	2.47 (1.11–5.49)	0.027	3.37 (1.35–8.44)	0.009
Histoloav. n (%)					
CIN2+	40 (11.8)	4.76 (2.18–10.4)	<0.0001	6.05 (2.47–14.77)	<0.0001

Abbreviations: 95% CI = 95% confidence interval; CIN2+ = cervical intraepithelial neoplasia grade 2 or worse.

*Data from the 340 participants may be missing for some variables.

†ORs for continuous variables indicate the change in odds for an increase of one standard deviation.

**Adjusted for age, marital status, age at first intercourse, number of lifetime sexual partners, age at first delivery, parity, HIV status, and type of transformation zone.

***High-grade lesions include ASC-H, HSIL, AIS, and cancer.

Bold values are statistically significant.

ABCD criteria were more likely to be correct in the presence of TZ type 3 (aOR = 6.47; 95% CI, 2.59–16.21; P<0.001), high-grade lesions on cytology (aOR = 3.37; 95% CI, 1.35–8.44; P<0.009) and a CIN2+ on histology (aOR = 6.05; 95% CI, 2.47–14.77; P<0.001). Overall, a

correct prediction of the ABCD criteria was not impacted by the multiple sociodemographic characteristics of the population in the multivariate analysis.

Performance of ABCD and cytology for detection of high-grade cervical lesions (CIN2+ and CIN3+) is shown in **Table 3**.

Table 3: Diagnostic accuracy of ABCD criteria, cytology, and HPV for detection of CIN2+ and CIN3+

Variable	CIN2+ (N=40, 11.8%)			
	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV % (95% CI)	NPV % (95% CI)
ABCD criteria- positive	77.5 (61.3–88.2)	42.0 (36.5–47.7)	15.1 (10.8–20.8)	93.3 (87.6–96.5)
Cytology ASC-US+	80.0 (64.0–89.9)	87.5 (83.1–90.7)	47.1 (35.3–59.2)	96.9 (93.9–98.5)
Cytology LSIL+	70.0 (53.5–82.6)	91.3 (87.4–94.1)	52.8 (39.1–66.2)	95.6 (92.4–97.5)
Cytology HSIL+	62.5 (46.1–76.5)	98.6 (96.3–99.5)	86.2 (67.0–95.1)	95.0 (91.8–97.0)
HPV-16/18/45+	37.5 (23.5–53.9)	79.9 (74.9–84.1)	20.9 (12.3–30.8)	90.5 (86.3–93.5)
Variable	CIN3+ (N=27, 7.9%)			
	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV % (95% CI)	NPV % (95% CI)
ABCD criteria- positive	70.4 (49.6–85.2)	40.6 (35.2–46.1)	9.3 (6.0–14.1)	94.1 (88.5–97.0)
Cytology ASC-US+	88.9 (68.9–96.7)	85.4 (80.9–89.0)	35.3 (24.7–47.6)	98.8 (96.4–99.7)
Cytology LSIL+	81.5 (60.9–92.5)	89.7 (85.7–92.7)	41.5 (28.7–55.5)	98.2 (95.7–99.2)
Cytology HSIL+	74.1 (53.2–87.8)	97.0 (94.3–98.4)	68.9 (49.0–83.7)	97.7 (95.2–98.9)
HPV-16/18/45+	44.4 (26.2–64.3)	79.8 (75.0–83.9)	16.0 (9.2–26.4)	94.3 (90.8–96.6)

Abbreviations: CIN2+ = cervical intraepithelial neoplasia grade 2 or worse; CIN3+ = cervical intraepithelial neoplasia grade 3 or worse; Cytology ASC-US+ = ASC-US, LSIL, ASC-H, HSIL, AIS, and cancer; Cytology LSIL+ = LSIL, ASC-H, HSIL, AIS, and cancer; Cytology HSIL+ = ASC-H, HSIL, AIS, and cancer; HPV = human papilloma virus; HPV-16/18/45+ = HPV DNA test positive for HPV-16, HPV-18, and HPV-45; 95% CI = 95% confidence interval; PPV = positive predictive value; NPV = negative predictive value.

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3 ABCD criteria for CIN2+ detection showed a sensitivity of 77.5% (95% CI, 61.3%–88.2%),
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6 specificity of 42.0% (95% CI, 36.5%–47.7%), PPV of 15.1% (95% CI, 10.8%–20.8%), and
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9 NPV of 93.3% (95% CI, 87.6%–96.5%). Cytology-classified HSIL+ for CIN2+ detection
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12 showed lower sensitivity of 62.5% (95% CI, 46.1%–76.5%), but higher specificity of 98.6%
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15 (95% CI, 96.3%–99.5%), PPV of 86.2% (95% CI, 67.0%–95.1%), and NPV of 95.0% (95%
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18 CI, 91.8%–97.0%). Meanwhile, cytology-classified ASC-US+ showed improved sensitivity of
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21 80.0% (95% CI, 64.0%–89.9%) and specificity of 87.5% (95% CI, 83.1%–90.7%). Screening
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24 by HPV 16/18/45 genotyping alone had a much lower sensitivity of 37.5% (95% CI, 23.5–
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27 53.9) and a specificity of 79.9% (95% CI 74.9–84.1). ABCD criteria for CIN3+ lesion
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30 identification showed a sensitivity of 70.4% (95% CI, 49.6%–85.2%), specificity of 40.6%
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33 (95% CI, 35.2%–46.1%), PPV of 9.3% (95% CI, 6.0%–14.1%), and NPV of 94.1% (95% CI,
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36 88.5%–97.0%).

DISCUSSION

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48 The ABCD criteria were established as part of our efforts to improve the performance of
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51 visual-based approaches for triage of HPV-positive women. Previous studies conducted in
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54 LMICs indicated that traditional VIA criteria were not satisfactory for the detection of CIN2+
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57 lesions, with a trend toward reduced sensitivity compared with HPV testing alone.^{7–9} The
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3 challenge for VIA screeners lies in interpreting the wide variability of cervical presentations,
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6 in populations where obstetric trauma to the cervix and history of infection are frequent, and
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9 in which CIN2+ may be difficult to identify by the naked eye alone.

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12 The most important finding of this study is that the ABCD criteria appeared to be highly
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15 sensitive for detection of high-grade lesions in an HPV-positive population. We used both (i)
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18 a magnification technique with smartphone digital imaging that allows more detailed
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21 examination compared with naked eye alone and (ii) a lower VIA/D-VIA threshold positivity to
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24 optimize identification of lesions. The ABCD criteria provided improved VIA sensitivity for
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27 triage of HPV-positive women compared to most studies published using a comparable
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30 methodology (sensitivities ranging from 25% to 45.5%), and the weakness was the low
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33 specificity (42%, with previous specificities ranging from 44% to 98%).^{7-9,11,23} This can be
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36 explained by the fact that the IARC criteria require extensive VIA changes before being
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39 considered positive, thus limiting their sensitivity, while a reduced positivity threshold can
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42 contribute to improved sensitivity for CIN2+ detection.^{10,20}

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47 The low specificity arises because we considered any whitening to be positive, meaning
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50 many benign conditions (metaplasia, inflammation or other benign cervical changes) could
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53 produce false-positive results for the ABCD criteria. Criterion C (VILI/D-VILI), though
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56 dependent on criteria A and D, may contribute to the high false positive rate by categorizing
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3 benign conditions as ABCD-positive through the identification of iodine-negative areas
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6 compatible with thin, transparent or patchy acetowhite lesions on D-VIA. The lack of
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10 association between multiple socio-demographic variables and a correct prediction of the
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13 ACBD criteria (**Table 2**) supports the generalizability of these criteria to the overall population
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16 of women aged 30 to 49 years.

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19 Compared to screening by HPV-16/18/45 genotyping without triage, the sensitivity of the
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22 ABCD criteria was much higher, at the cost of a lower specificity. PPV was also slightly lower
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25 with triage by ABCD criteria (15.1%) than with HPV genotyping. Overall, 54.4% of normal
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28 histology results and 71.4% of CIN1 were considered ABCD criteria positive and
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31 consequently underwent unnecessary treatment. Thus, 85% (174 of 205) of women who
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34 screened positive were treated unnecessarily. However, when considering all women
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37 screened for CC, including HPV-negative, 174 were treated unnecessarily out of 1964
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40 screened by Self-HPV, corresponding to an overall 8.9% overtreatment rate in the total
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43 population screened. Despite the low specificity, our 3T-Approach in a single visit may be
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46 acceptable in an LMIC context because it reduces cost and loss to follow-up. Furthermore,
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49 treatment by thermal ablation has low risks of side effects and morbidity.²⁴ Therefore,
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52 treatment of a significant number of false-positive cases may be considered an acceptable
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55 strategy for effective control of CC in an LMIC setting. The second limitation is that the study
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3 was conducted in a single centre in a district hospital in West Cameroon with five clinicians
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6 (three midwives and two gynaecologists) administering all screening and treatment
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10 procedures.

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13 It should be noted that two out of three cervical cancers were assessed as ABCD-negative
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16 on site by the frontline health care providers and did not receive immediate treatment. After
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19 reviewing the smartphone images of these two cases off-site, it was determined that criterion
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22 B (bleeding) was present in both cases, which should have led to a positive ABCD result and
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25 subsequent treatment (**Supplement, Figure S1**).

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29 The strength of ABCD criteria is that they comprise a simple tool that can alert healthcare
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32 professionals to the clinical features of CIN2+, and the use of “relaxed IARC criteria” may
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35 greatly decrease the risk of missing CIN2+ lesions. Using ABCD criteria for D-VIA
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38 interpretation is a simple test with binary results (positive or negative) that are immediately
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41 available, allowing initiation of therapy without delay. In our series, 86.7% of participants
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44 underwent the 3T-Approach in one day.

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48 Furthermore, because all HPV-positive women underwent biopsy and cervical brushing
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51 regardless of the ABCD criteria results, there was no risk of verification bias in the
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54 calculations of sensitivity and specificity for ABCD criteria.
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3 In conclusion, ABCD criteria can improve CIN2+ diagnosis in HPV-positive women using VIA
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6 and D-VIA. This approach may provide a unique opportunity to improve cervical cancer
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10 screening programs in LMICs using a one-visit approach. This strategy may be particularly
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13 beneficial because the criteria are easily remembered and easy to use for healthcare
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16 providers.
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34 manuscript.
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42 **Competing Interests**

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45 All authors declare that they have no competing interests.
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5
6 and conduct of the study; collection, management, analysis, and interpretation of the data;
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9 preparation, review, or approval of the manuscript; and decision to submit the manuscript for
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12 publication.
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19 **Data access, analysis and responsibility**

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22 The principal investigator had full access to all the data in the study and takes responsibility
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24
25 for the integrity of the data and the accuracy of the data analysis. Data used in the study is
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28 available upon request to the first author.
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35 **Contributors**

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38 PP, BK, and PV designed the study protocol, implemented the study, oversaw the data
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40
41 collection, analysed the data, and drafted and revised the paper. AW and RC conducted data
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43
44 analysis, interpreted the data, and revised the draft paper. BK, ET, and JF trained the study
45
46
47 staff, assumed the quality control (supervision and mentorship), supported the data
48
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50 collection, interpreted the data, and revised the draft paper. JCT and ES analysed the
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53 pathological specimens, interpreted the data, and revised the draft paper.
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3 **Figure 1:** ABCD criteria for VIA interpretation in HPV-positive women
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5 **Figure 2:** Flowchart of participants for the 3T-Approach in Cameroon
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3 **Figure 1: ABCD criteria for VIA interpretation in HPV-positive women**

4
5 **Criterion A** – Acetowhite area touching the transformation zone (absent on the native view and
6 apparent after acetic acid application) is considered positive.

7
8 **Criterion B** – Bleeding without touching or after lightly touching (with a swab or speculum) the cervix
9 is considered positive.

10
11 **Criterion C (optional)** – Colouring with VILI contributes to confirmation or identification of a faint
12 acetowhite lesion.

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14 **Criterion D** – Diameter of >5 mm (about the size of a pencil eraser) in an acetowhite area is
15 considered positive.
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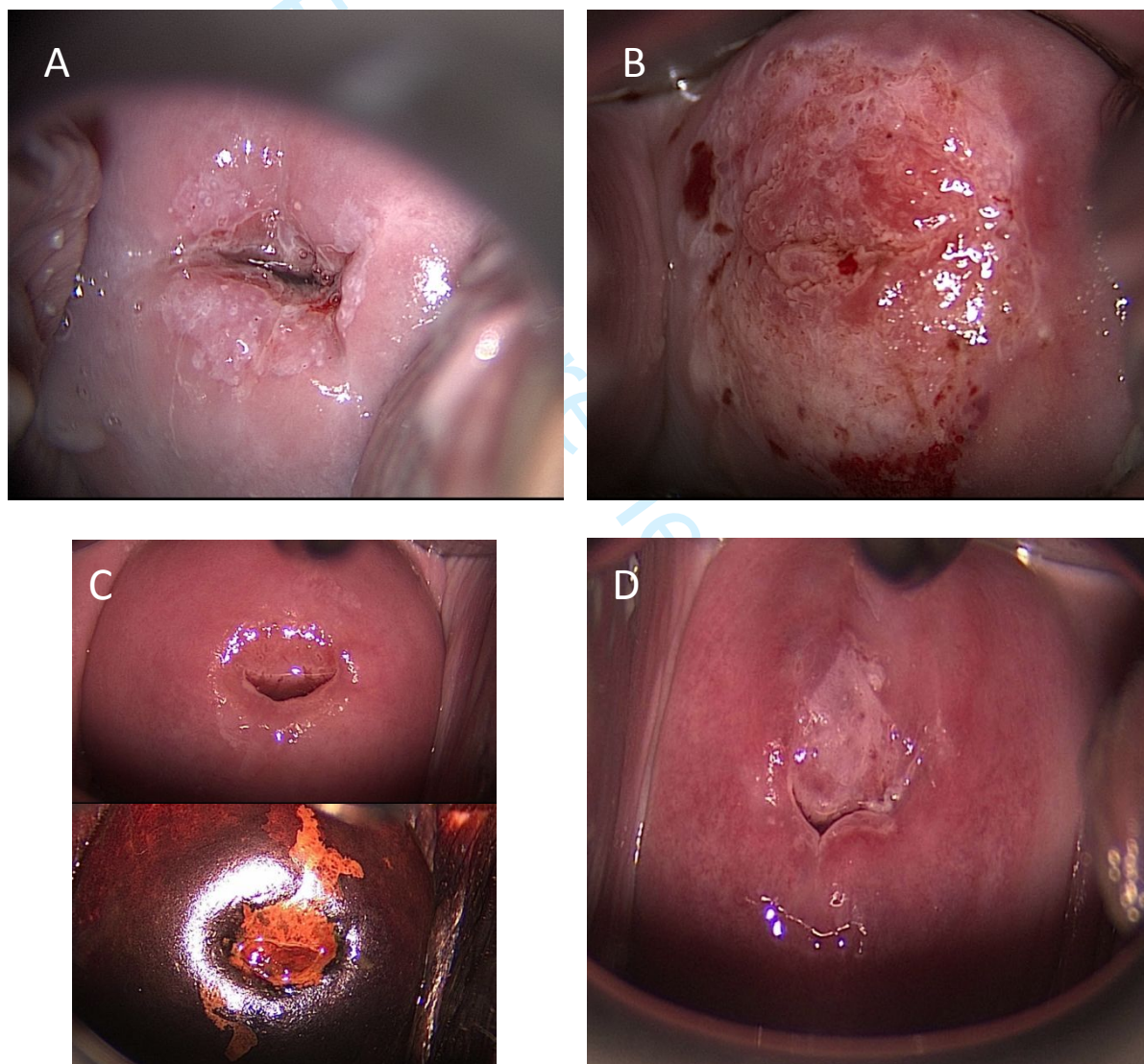
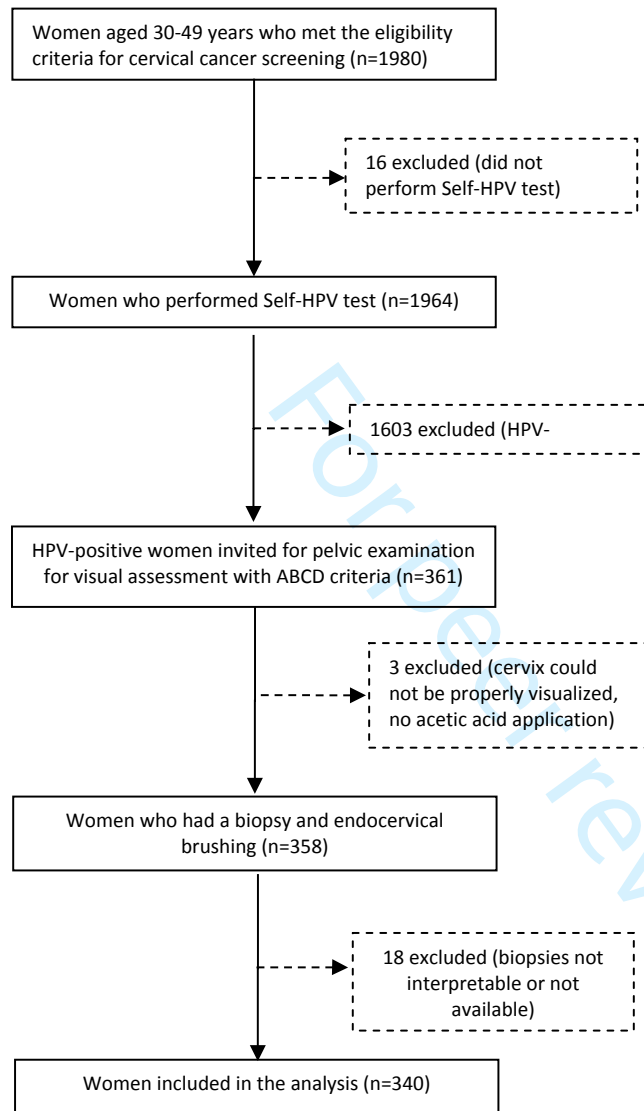


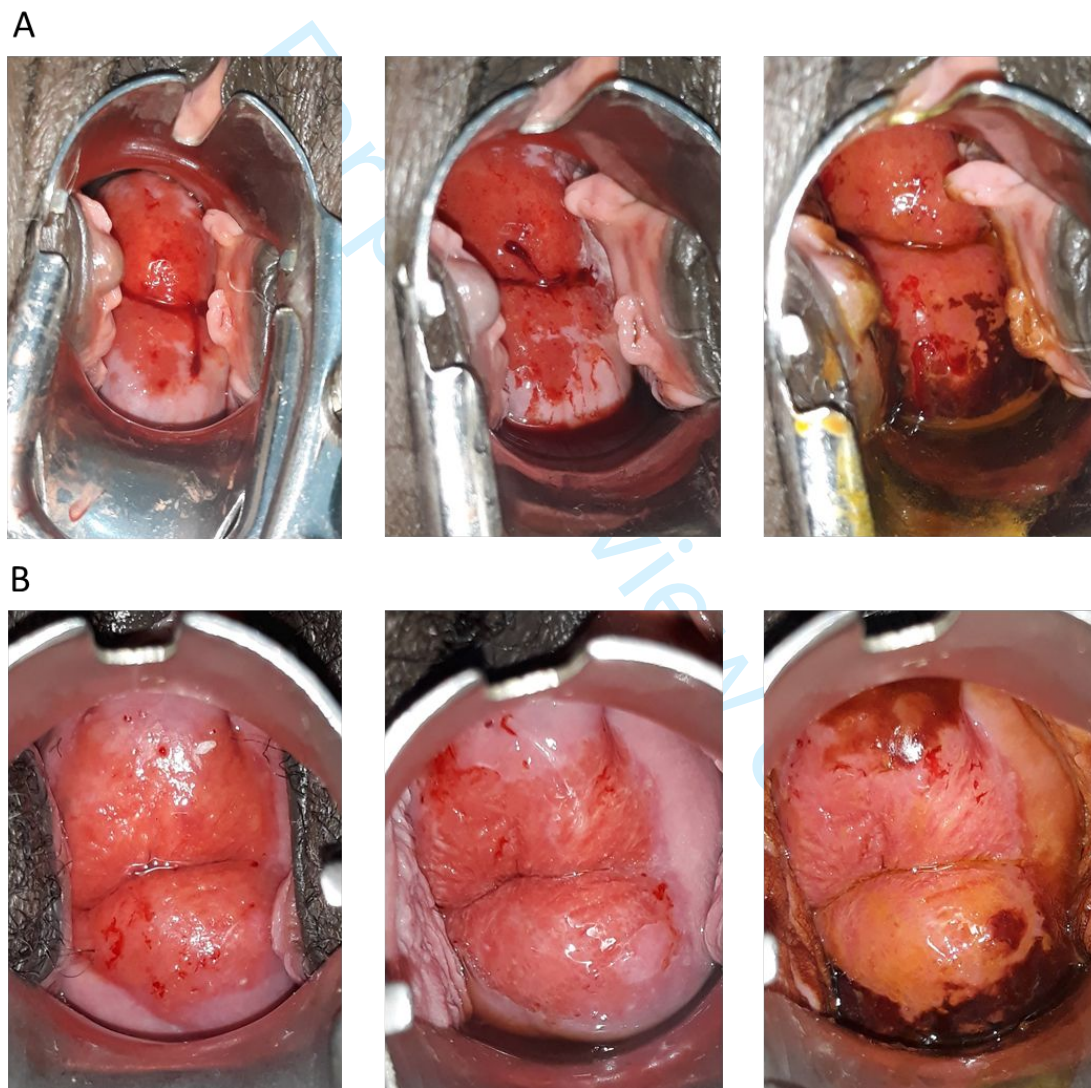
Figure 2: Flowchart of participants for the 3T-Study in Cameroon

Supplementary Material

ABCD Criteria to Improve Visual Inspection with Acetic Acid (VIA) Triage in HPV-positive Women: a prospective analysis

Patrick Petignat, Bruno Kenfack, Ania Wisniak, Essia Saiji, Jean-Christophe Tille, Jovanny Tsuala Fouogue, Rosa Catarino, Evelyn Foguem Tincho and Pierre Vassilakos

Figure S1. Cases of cervical cancer not identified by ABCD criteria on site



A. Poorly differentiated carcinoma, positive for criterion B (bleeding); B. Invasive adenocarcinoma, positive for criterion B. From left to right, smartphone photos of (i) the native cervix, (ii) after application of acetic acid and (iii) after application of Lugol's iodine.

Section & Topic	No	Item	Reported on page #
TITLE OR ABSTRACT			
	1	Identification as a study of diagnostic accuracy using at least one measure of accuracy (such as sensitivity, specificity, predictive values, or AUC)	2
ABSTRACT			
	2	Structured summary of study design, methods, results, and conclusions (for specific guidance, see STARD for Abstracts)	2
INTRODUCTION			
	3	Scientific and clinical background, including the intended use and clinical role of the index test	4-5
	4	Study objectives and hypotheses	5
METHODS			
<i>Study design</i>	5	Whether data collection was planned before the index test and reference standard were performed (prospective study) or after (retrospective study)	5
<i>Participants</i>	6	Eligibility criteria	5
	7	On what basis potentially eligible participants were identified (such as symptoms, results from previous tests, inclusion in registry)	5
	8	Where and when potentially eligible participants were identified (setting, location and dates)	5
	9	Whether participants formed a consecutive, random or convenience series	5
<i>Test methods</i>	10a	Index test, in sufficient detail to allow replication	6 + figure 1
	10b	Reference standard, in sufficient detail to allow replication	7
	11	Rationale for choosing the reference standard (if alternatives exist)	na
	12a	Definition of and rationale for test positivity cut-offs or result categories of the index test, distinguishing pre-specified from exploratory	6
	12b	Definition of and rationale for test positivity cut-offs or result categories of the reference standard, distinguishing pre-specified from exploratory	7
	13a	Whether clinical information and reference standard results were available to the performers/readers of the index test	6
	13b	Whether clinical information and index test results were available to the assessors of the reference standard	7
<i>Analysis</i>	14	Methods for estimating or comparing measures of diagnostic accuracy	8
	15	How indeterminate index test or reference standard results were handled	8
	16	How missing data on the index test and reference standard were handled	8
	17	Any analyses of variability in diagnostic accuracy, distinguishing pre-specified from exploratory	na
	18	Intended sample size and how it was determined	8
RESULTS			
<i>Participants</i>	19	Flow of participants, using a diagram	Figure 2
	20	Baseline demographic and clinical characteristics of participants	9
	21a	Distribution of severity of disease in those with the target condition	10-11
	21b	Distribution of alternative diagnoses in those without the target condition	na
	22	Time interval and any clinical interventions between index test and reference standard	na
<i>Test results</i>	23	Cross tabulation of the index test results (or their distribution) by the results of the reference standard	10 (table 1)
	24	Estimates of diagnostic accuracy and their precision (such as 95% confidence intervals)	12 (table 3)
	25	Any adverse events from performing the index test or the reference standard	10
DISCUSSION			
	26	Study limitations, including sources of potential bias, statistical uncertainty, and generalisability	15
	27	Implications for practice, including the intended use and clinical role of the index test	14-15
OTHER INFORMATION			
	28	Registration number and name of registry	9
	29	Where the full study protocol can be accessed	9
	30	Sources of funding and other support; role of funders	16

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STARD 2015

AIM

STARD stands for “Standards for Reporting Diagnostic accuracy studies”. This list of items was developed to contribute to the completeness and transparency of reporting of diagnostic accuracy studies. Authors can use the list to write informative study reports. Editors and peer-reviewers can use it to evaluate whether the information has been included in manuscripts submitted for publication.

EXPLANATION

A **diagnostic accuracy study** evaluates the ability of one or more medical tests to correctly classify study participants as having a **target condition**. This can be a disease, a disease stage, response or benefit from therapy, or an event or condition in the future. A medical test can be an imaging procedure, a laboratory test, elements from history and physical examination, a combination of these, or any other method for collecting information about the current health status of a patient.

The test whose accuracy is evaluated is called **index test**. A study can evaluate the accuracy of one or more index tests. Evaluating the ability of a medical test to correctly classify patients is typically done by comparing the distribution of the index test results with those of the **reference standard**. The reference standard is the best available method for establishing the presence or absence of the target condition. An accuracy study can rely on one or more reference standards.

If test results are categorized as either positive or negative, the cross tabulation of the index test results against those of the reference standard can be used to estimate the **sensitivity** of the index test (the proportion of participants *with* the target condition who have a positive index test), and its **specificity** (the proportion *without* the target condition who have a negative index test). From this cross tabulation (sometimes referred to as the contingency or “2x2” table), several other accuracy statistics can be estimated, such as the positive and negative **predictive values** of the test. Confidence intervals around estimates of accuracy can then be calculated to quantify the statistical **precision** of the measurements.

If the index test results can take more than two values, categorization of test results as positive or negative requires a **test positivity cut-off**. When multiple such cut-offs can be defined, authors can report a receiver operating characteristic (ROC) curve which graphically represents the combination of sensitivity and specificity for each possible test positivity cut-off. The **area under the ROC curve** informs in a single numerical value about the overall diagnostic accuracy of the index test.

The **intended use** of a medical test can be diagnosis, screening, staging, monitoring, surveillance, prediction or prognosis. The **clinical role** of a test explains its position relative to existing tests in the clinical pathway. A replacement test, for example, replaces an existing test. A triage test is used before an existing test; an add-on test is used after an existing test.

Besides diagnostic accuracy, several other outcomes and statistics may be relevant in the evaluation of medical tests. Medical tests can also be used to classify patients for purposes other than diagnosis, such as staging or prognosis. The STARD list was not explicitly developed for these other outcomes, statistics, and study types, although most STARD items would still apply.

DEVELOPMENT

This STARD list was released in 2015. The 30 items were identified by an international expert group of methodologists, researchers, and editors. The guiding principle in the development of STARD was to select items that, when reported, would help readers to judge the potential for bias in the study, to appraise the applicability of the study findings and the validity of conclusions and recommendations. The list represents an update of the first version, which was published in 2003.

More information can be found on <http://www.equator-network.org/reporting-guidelines/stard>.



BMJ Open

ABCD Criteria to Improve Visual Inspection with Acetic Acid (VIA) Triage in HPV-positive Women: a Prospective Study of Diagnostic Accuracy

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3 **ABCD Criteria to Improve Visual Inspection with Acetic Acid (VIA) Triage in HPV-positive**
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6 **Women: a Prospective Study of Diagnostic Accuracy**
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3 **1 ABSTRACT**
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6 **2 Objectives** A simple system for visual inspection with acetic acid (VIA) assessment, named
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10 **3** ABCD criteria, has been developed to increase accuracy for triaging of high-risk human
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13 **4** papillomavirus (HPV)-positive women. The present study aimed to determine the accuracy of
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16 **5** ABCD criteria for the detection of histologically confirmed cervical intraepithelial neoplasia
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19 **6** grade 2 or worse (CIN2+) in HPV-positive women living in a low-resource setting.
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22
23 **7 Design** Prospective study of diagnostic accuracy
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26 **8 Setting** Cervical cancer screening program based on a 3T-Approach (Test, Triage, and
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29 **9** Treat) in the Health District of Dschang, West Cameroon.
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33 **10 Participants** Asymptomatic non-pregnant women aged 30-49 years were eligible to
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36 **11** participate. Exclusion criteria included history of CIN treatment, anogenital cancer or
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39 **12** hysterectomy. A total of 1980 women were recruited (median age, 40 years; interquartile
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42 **13** range, 35-45 years), of whom 361 (18.4%) were HPV-positive and 340 (94.2%) completed
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45 **14** the trial.
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49 **15 Interventions** HPV-positive women underwent a pelvic examination for visual assessment of
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52 **16** the cervix according to ABCD criteria. The criteria comprised A for Acetowhitiness, B for
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55 **17** Bleeding, C for Colouring, and D for Diameter. The ABCD criteria results were codified as
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58 **18** positive or negative and compared with histological analysis findings (reference standards).
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4 19 **Primary outcome measure** Diagnostic performance of ABCD criteria for CIN2+, defined as
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7 20 sensitivity, specificity, negative and positive predictive values.
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10 21 **Results** ABCD criteria had a sensitivity of 77.5% (95% CI, 61.3%–88.2%), specificity of
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13 22 42.0% (95% CI, 36.5%–47.7%), positive predictive value of 15.1% (95% CI, 10.8%–20.8%),
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16 23 and negative predictive value of 93.3% (95% CI, 87.6%–96.5%) for detection of CIN2+
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19 24 lesions. Most (86.7%) of the ABCD-positive women were treated on the same day.
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22 25 **Conclusions** ABCD criteria can be used in the context of a single-visit approach and may be
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25 26 the preferred triage method for management of HPV-positive women in a low-income
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28 27 context.
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32 28 **Trial registration** The trial was registered under ClinicalTrials.gov (number NCT03757299).
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35 29 **Key words:** cervical cancer screening, low- and middle-income countries, visual inspection
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38 30 with acetic acid (VIA), visual inspection with Lugol's iodine (VILI), human papillomavirus
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41 31 (HPV), triage
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48 33 **Strengths and limitations of this study**

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- 52 34 • Using ABCD criteria for VIA interpretation is a simple test with binary results (positive
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55 35 or negative) that are immediately available, allowing a screen-and-treat approach .
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3 36 • Because all HPV-positive women underwent biopsy and endocervical curettage
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6 37 regardless of the ABCD criteria results, there was no risk of verification bias in the
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9 38 calculations of sensitivity and specificity.
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13 39 • A limitation of the study was its setting in a single centre in a district hospital in West
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16 40 Cameroon with five clinicians administering all screening and treatment procedures.
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42 INTRODUCTION

43 More than 90% of cervical cancer (CC) deaths occur in low- and middle-income countries

44 (LMICs), mainly due to lack of prevention.(1) Cytology-based CC screening programs and

45 more recent HPV-based programs have been successfully implemented in high-income

46 countries and have been associated with important reductions in deaths from CC.(2)

47 However, these strategies have not been implemented in LMICs, predominantly because of

48 financial and logistical limitations. Alternative methods such as visual inspection of the cervix

49 after application of acetic acid (VIA) and more recently, HPV primary screening, are

50 considered suitable for use in LMICs.(3,4)

51 A global strategy for the elimination of cervical cancer has been launched by the World

52 Health Organization (WHO) in 2020, which relies upon the screening of 70% of women using

53 a high-performance test and the treatment of 90% of women identified with cervical

54 disease.(5) Recommendations adopted by the WHO for screening in resource-limited

55 settings include a strategy of HPV-screening followed by VIA triage and treatment, or a

56 strategy of HPV-screening followed by treatment.(3) Although no recommendations are given

57 for the approach that should be prioritized, sub-Saharan Africa has a high HPV prevalence

58 rate of 15%–30% and most HPV-positive women have no lesions.(3,6,7) In this context, HPV

59 testing followed by immediate treatment can represent significant overtreatment in women

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4 60 with an HPV-positive test, which by itself may not confer a high risk of cervical intraepithelial
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7 61 neoplasia grade 2 or worse (CIN2+).(4,8,9) In sub-Saharan Africa, the prevalence of CIN2+
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10 62 was reported to be 2%–4% in women aged 30–49 years and 7%–11% in an HPV-positive
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13 63 population with a low HIV prevalence rate (<10%).(6,7,10) A triage system is only a valid
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16 64 option if it can improve the positive predictive value (PPV) for CIN2+ and minimize the
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19 65 referral rate, while conserving the high sensitivity of the HPV test. The achievement of a high
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22 66 PPV at the cost of limited sensitivity may be considered a reasonable option when the loss to
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25 67 follow-up of women requiring surveillance is minimal. However, in low-resource settings, high
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28 68 levels of loss to follow-up constitute an important barrier to cervical cancer screening, which
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31 69 is why programs having no follow-up visits or as few as possible are preferable to achieve a
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34 70 high degree of participation.(11)
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38 71 Triage by VIA and/or visual inspection with Lugol's iodine (VILI) requires accurate criteria to
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41 72 decide whether or not the findings are positive, which are generally based on the
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44 73 International Agency for Research against Cancer (IARC) manual.(12) However, in this
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47 74 setting, VIA triage in HPV-positive populations appears to be associated with an important
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50 75 loss of sensitivity, suggesting that triage by VIA using traditional criteria may not be of
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53 76 benefit.(6,7,10,13) Previous studies using histology as reference standard and having
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56 77 excluded verification bias had sensitivities ranging from 25.0% to 45.5%.(6,10,14)
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3 78 Interpreting VIA with naked eye alone is subjective and is highly variable between health
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6 79 care providers.(15–17) This issue may be improved with continuous supervision and medical
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10 80 education thanks to the use of digital VIA and VILI (D-VIA/D-VILI). This includes acquisition
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13 81 of cervical images, native and after VIA and VILI application, through a camera or
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16 82 smartphone. These technologies provide an alternative to colposcopy in the context of
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19 83 LMICs and may constitute an important step in the improvement of VIA/VILI
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22 84 interpretation.(18–20) Although the image quality is probably lower than that with high-
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25 85 resolution colposcopy, there are significant benefits for healthcare providers, because they
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28 86 can move through and compare the native, VIA, and VILI images, and can also magnify
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32 87 suspicious lesions, before deciding whether treatment is needed.(18,19)
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35 88 To improve VIA/D-VIA interpretation as a triage test in HPV-positive populations, we
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38 89 introduced a set of criteria, termed ABCD criteria for “Acetowhiteness”, “Bleeding”,
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41 90 “Colouring” (with Lugol’s iodine) and “Diameter” of the lesion. These criteria constitute a
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44 91 simple structure that may contribute to preventing CC in an LMIC context. The aim of the
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47 92 present study was to provide a rationale for the ABCD criteria and determine their
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51 93 performance in identifying histology-proven CIN2+.

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95 **METHODS**

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4 96 **Study design** – This prospective study was carried out between September 2018 and March
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7 97 2020 in the health district of Dschang (West Cameroon) as part of a 5-year cervical cancer
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10 98 screening programme. The screening strategy consisted of the “3T-Approach”, in which
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13 99 Testing with HPV, Triage with VIA and Treatment are provided within one visit.
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16 100 Asymptomatic non-pregnant women aged 30-49 years were eligible to participate in the
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19 101 study on a voluntary basis and were included in a consecutive manner upon presentation to
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22 102 the screening site. Exclusion criteria included history of CIN treatment, anogenital cancer or
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25 103 hysterectomy. The study was conducted within a larger trial aiming to recruit 6,000 women in
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28 104 a 5-year screening program.(20) At the baseline visit, after obtaining written informed
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32 105 consent and providing guidance to participants on the procedure for vaginal self-sampling,
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35 106 participants undertook an HPV self-test (Self-HPV) that was subsequently analyzed by a
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38 107 point-of-care assay (GeneXpert®) in one hour. HPV-negative women were reassured and
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41 108 advised to repeat the test in 5 years, while HPV-positive women were invited to undergo
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44 109 visual triage and thermal ablation or large loop excision of the transformation zone (LLETZ) if
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47 110 needed. Healthcare providers performed gynecologic examination with VIA/VILI, assessment
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50 111 of ABCD criteria and transformation zone (TZ) type, and determined treatment modalities in
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54 112 a single visit.
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3 113 **ABCD criteria (Figure 1)** – The ABCD criteria were chosen from a synthesis of published
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6 114 results as well as our own experience in VIA and VILI interpretation.(3,12,21–25) We
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9 115 considered acetowhiteness as the most important predictor for CIN and noted that Lugol's
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12 116 iodine can be used to identify thin acetowhite lesions not seen on the initial VIA assessment
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16 117 (Figure 1). Similar to the IARC criteria, the pathological area should be located within or in
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19 118 contact with the TZ. The ABCD criteria are codified as positive (present) or negative
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22 119 (absent). To be considered ABCD-positive, at least one of the following conditions needs to
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25 120 be fulfilled: presence of criteria A (acetowhiteness) and D (diameter) combined, or criterion B
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28 121 (bleeding) with or without presence of A, C (colouring) or D.
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32 122 ABCD criteria were independently evaluated by one of three trained midwives and
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35 123 supervised by two experienced Cameroonian gynaecologists..
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37
38 124 • *Criterion A for Acetowhiteness* – Criterion A is obtained after application of 3%–5% acetic
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40 125 acid. Any acetowhite area touching the TZ and having a diameter of >5 mm (criterion D)
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42 126 is considered positive. Compared with the IARC criteria, which require a degree of
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44 127 whiteness combined with the presence of a sharp, distinct, well defined, dense
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46 128 (opaque/dull or oyster white) acetowhite area,(12) we considered here any acetowhite
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48 129 lesion exceeding 5 mm to be positive.
49
50
51 130 • *Criterion B for Bleeding on touch* – Criterion B is obtained upon native examination or
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53 131 after acetic acid application. Presence of cervical bleeding without touching or after lightly
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55 132 touching the cervix in the TZ area is considered positive. This means that any bleeding
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57 133 from the surface of the cervix, after excluding bleeding of intra-uterine origin, can be
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59 134 associated with CIN2+ lesions. Although bleeding can also be caused by ulceration or
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3 135 infection, any signs should be thoroughly investigated to rule out the possibility of early
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5 136 preclinical invasive cancer. This sign is easy to recognize and is considered a high-risk
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7 137 finding for precancerous lesions and cervical cancer.(24,25) Presence of bleeding in
8
9 138 association with criteria A and C may require referral for further testing like biopsy and
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11 139 colposcopy.

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13 140 • *Criterion C for Colouring with Lugol's iodine* – Criterion C is optional. Lugol's iodine
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15 141 staining can be used as an adjunct to VIA to recognize epithelial change that would
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17 142 otherwise be difficult to identify by VIA only. The colour changes with VILI can be easier
18
19 143 to appreciate than those after VIA and may contribute to identification of a missed thin
20
21 144 acetowhite lesion. To be considered positive, an iodine-negative lesion should
22
23 145 correspond to a VIA lesion having criteria A and D. Compared with the IARC criteria,
24
25 146 which require the presence of a well-defined, bright yellow, iodine non-uptake area,(12)
26
27 147 we consider any non-iodine uptake areas to be positive, providing they match an
28
29 148 acetowhite lesion.
- 30
31 149 • *Criterion D for Diameter* – Criterion D is evaluated after application of acetic acid (or
32
33 150 Lugol's iodine). An acetowhite lesion measuring >5 mm in diameter (about the size of a
34
35 151 pencil eraser) is considered positive. Defining a minimal size of 5 mm allows exclusion of
36
37 152 benign conditions such as dot-like, line-like, or streak-like areas.(23)

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39 153 A set of three images (native, acetic acid, Lugol's iodine) were obtained on a Galaxy S5
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44 154 smartphone (Samsung, Seoul, South Korea). Diagnosis and treatment were based on
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48 155 combined results of VIA/VILI and smartphone-enhanced D-VIA, using aids such as zooming
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51 156 in on lesions and performing comparisons between the native, VIA, and VILI images.
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54 157 Eligibility criteria for thermal ablation were women being positive for ABCD criteria.

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57 158 Indications for referral to determine further treatment modalities were (i) lesions extending
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3 159 into the endocervix which could not be covered by the probe tip, (ii) suspicion of carcinoma,
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6 160 in-situ adenocarcinoma or invasive adenocarcinoma Our management of HPV-positive
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8
9 161 women with a TZ type 3 was as follows: (i) those having no lesion on visual assessment
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11
12 162 were offered follow-up, (ii) those having a lesion which could be covered by thermal ablation
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15 163 tips were treated, and (iii) those with an endocervical lesion which could not be fully covered
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18 164 by the probe were referred for LLETZ. Cervical liquid-based cytology, biopsy at the TZ and
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21 165 endocervical curettage (ECC) were performed on all HPV-positive women prior to treatment.
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25 166 **Cytology** – Cervical liquid-based cytology was performed using the SurePath (September
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27
28 167 2018 to July 2019) and ThinPrep (July 2019 to March 2020) techniques. All vials were
29
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31 168 analyzed in Switzerland (CytoPath, Unilabs, Geneva, and University Hospital of Geneva).
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35 169 The slides were independently read by qualified cytotechnologists and classified according to
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38 170 the Bethesda classification system: negative for intraepithelial lesion or malignancy (NILM),
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41 171 inflammatory atypical squamous cells of undetermined significance (ASC-US), inflammatory
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44 172 atypical squamous cells that cannot exclude HSIL (ASC-H), atypical glandular cells with low-
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47 173 grade squamous intraepithelial lesion (LSIL), high-grade squamous intraepithelial lesion
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50 174 (HSIL), and invasive cancer.
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54 175 **Histology findings (reference standard)** – Cervical biopsies were performed using biopsy
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57 176 forceps, and ECC was carried out with an endocervical brush. Cervical biopsies were
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3 177 performed at 6 o'clock in the TZ when ABCD criteria were negative. If ABCD criteria were
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6 178 positive, one or more biopsies were performed at the most suspicious areas. All samples
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9 179 were stored in formalin. Biopsy slides and ECC samples (processed by cellular block) were
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13 180 read by two experienced gynaecologic pathologists of the Geneva University Hospitals,
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16 181 Switzerland, who were blinded to the screening test results and ABCD criteria findings. There
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19 182 was no external review of histological analyses. The histological results were classified as
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22 183 normal, CIN1, CIN2, CIN3, adenocarcinoma *in situ* (AIS), invasive carcinoma, or
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25 184 adenocarcinoma. The cut-off for a pathological result was set at CIN2+. When histological
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28 185 results varied within the samples of one participant, only the worst result was considered as
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31
32 186 the reference standard.

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35 187 **Patient and public involvement** – Preferences of and experience with former patients of a
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38 188 preliminary research study on cervical cancer screening in Dschang, Cameroon, were
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41 189 considered in the design and conduction of this study. During the study, focus groups were
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44 190 organized with members of the community (women and men), health care workers and
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47 191 community health workers, to explore barriers to cervical cancer screening and further
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50 192 improve the program and recruitment strategy. Patients were also involved at their arrival at
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53 193 the screening center where they were offered a one-hour information session on cervical
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56 194 cancer and sexual health by trained midwives. Furthermore, the public is kept informed about
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3 195 the progress of our research through the publication of yearly newsletters disseminated

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6 196 among health workers and the general community.

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9 197 **Statistical analysis** – Initially, we planned a sample of 6,000 women. However, the COVID-19

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12 198 pandemic and public health measures to control the virus have impacted on-site clinical

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15 199 activity since mid-March 2020. In this context, we decided to consider an interim analysis to

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18 200 the trial of the primary endpoints which included performance of the ABCD criteria.

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21 201 Descriptive statistics were used to analyse the baseline characteristics of the study

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24 202 population. Sensitivity, specificity, positive predictive value (PPV), and negative predictive

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27 203 value (NPV) plus their 95% confidence intervals (95% CIs) were calculated. Student's *t*-test,

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30 204 Mann–Whitney test, or Pearson's chi-square test were used, where appropriate, to identify

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33 205 sociodemographic and reproductive characteristics of the patients that could differ between

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36 206 ABCD criteria results. A P-value of <0.05 was considered statistically significant. An

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39 207 exploratory analysis was performed to assess the relationships between each independent

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42 208 variable and the correct prediction of the ABCD criteria. This correct prediction score was

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45 209 equal to 1 when ABCD criteria were positive and there was a CIN2+ on histology or if the

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48 210 ABCD criteria were negative and histology was also negative. All other incorrect predictions

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51 211 were assigned the value 0. Univariate and multivariate logistic regression analyses were

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54 212 carried out to identify predictors of a correct ABCD criteria score according to histology.

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3 213 Participants with missing or indeterminate results for ABCD criteria or histopathology were
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6 214 excluded from the analysis. Odds ratios (ORs) were adjusted for potential confounders, such
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9 215 as age, marital status, number of lifetime sexual partners, age at first sexual intercourse, age
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12 216 at first delivery, parity, HIV status, and type of TZ, and 95% CIs were calculated. All data
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16 217 analyses were conducted using Stata Statistical software Release 13 (StataCorp LP, College
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19 218 Station, TX).

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23 219 **Ethical considerations** – The study obtained approval from the Cantonal Ethics Board of
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26 220 Geneva, Switzerland (Commission cantonale d'éthique de la recherche [CCER], No. 2017-
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29 221 0110) and the Cameroonian National Ethics Committee for Human Health Research (No.
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32 222 2018/07/1083/CE/CNERSH/SP). The trial was registered under ClinicalTrials.gov (number
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35 223 NCT03757299). The full study protocol can be provided upon request to the first author.
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40 41 225 **RESULTS**

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45 226 A total of 1980 women aged 30–49 years were enrolled (median age: 41 years; interquartile
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48 227 range [IQR], 36–50 years). Overall, 1964 women performed Self-HPV, of whom 361 (18·5%)
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51 228 had an HPV-positive test and underwent pelvic examination, three were excluded from the
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54 229 results analysis for lack of ABCD criteria assessment, and 340 (94·2%) had interpretable
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58 230 histology findings and constituted the study population (**Figure 2**). **Table 1** provides details of
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231 the baseline sociodemographic, reproductive, and clinical characteristics of the participants.

232 Median age at first sexual intercourse was 18 years (IQR, 16–19 years) and median number

233 of sexual lifetime partners was 3 (IQR, 2–5).

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Table 1: Baseline sociodemographic, reproductive health, and clinical characteristics according to ABCD criteria (N=358)*

Variable	ABCD criteria- negative	ABCD criteria- positive	Total	P-value
Participants recruited. n (%)	140 (39.1)	218 (60.9)	358	
Age (years). median (IQR)	41 (35–45)	40 (34–45)	40 (34–45)	0.4464
Marital status. n (%)				0.8910
Single	15 (10.7)	20 (9.2)	35 (9.8)	
With partner	109 (77.9)	173 (79.3)	282 (78.8)	
Divorced/widowed	16 (11.4)	25 (11.5)	41 (11.4)	
Education. n (%)				0.3900
Unschooling	1 (0.7)	5 (2.3)	6 (1.7)	
Primary education	37 (26.4)	66 (30.3)	103 (28.8)	
Secondary education	67 (47.9)	105 (48.2)	172 (48.0)	
Tertiary education	35 (25.0)	42 (19.2)	77 (21.5)	
Employment status. n (%)				0.1750
Employed	50 (35.7)	57 (26.2)	107 (29.9)	
Independent	39 (27.9)	56 (25.7)	95 (26.5)	
Housewife	23 (16.4)	41 (18.8)	64 (17.9)	
Unemployed	7 (5.0)	12 (5.5)	19 (5.3)	
Farmer	21 (15.0)	52 (23.8)	73 (20.4)	
Age at menarche (years). mean ± SD	14.7±1.8	14.7±1.9	14.7±1.8	0.8914
Age at first intercourse. median (IQR)	17 (16–19)	18 (16–20)	18 (16–19)	0.2390
Number of sexual partners. median	4 (3–6)	3 (2–5)	3 (2–5)	0.0008
Contraception. n (%)				0.5950
None	93 (66.9)	142 (65.5)	235 (66.0)	
Condom	18 (13.0)	25 (11.5)	43 (12.1)	
Hormonal pill	1 (0.7)	7 (3.2)	8 (2.3)	
DILU/implant/injection	25 (18.0)	41 (18.9)	66 (18.5)	
Other	2 (1.4)	2 (0.9)	4 (1.1)	
HIV status. n (%)				0.9420
Negative	128 (92.7)	198 (93.0)	326 (92.9)	
Positive	10 (7.3)	15 (7.0)	25 (7.1)	
Age at first delivery (years). mean ± SD	21.4±3.7	21.4±2.5	21.4±3.8	0.9137
Parity. n (%)				0.0080
Nulliparous	11 (7.9)	3 (1.4)	14 (3.9)	
1–4	66 (47.1)	108 (49.5)	174 (48.6)	
>4	63 (45.0)	107 (49.1)	170 (47.5)	
Transformation zone. n (%)				<0.0001
TZ1	76 (57.1)	150 (73.5)	226 (67.1)	
TZ2	26 (19.6)	45 (22.1)	71 (21.1)	
TZ3	31 (23.3)	9 (4.4)	40 (11.8)	
HPV testing results. n (%)				0.3890
HPV-16	11 (7.9)	23 (10.6)	34 (9.5)	

HPV-18/45	22 (15.8)	31 (14.2)	53 (14.9)	0.6770
Other HPV	114 (82.0)	186 (85.3)	300 (84.0)	0.4060
Cytoloav. n (%) (Total= 343)				0.0990
Normal	108 (82.5)	161 (75.9)	269 (78.4)	
ASC-US	7 (5.3)	10 (4.7)	17 (5.0)	
LSIL	10 (7.6)	15 (7.1)	25 (7.3)	
HSIL	4 (3.1)	21 (9.9)	25 (7.3)	
ASC-H	0	4 (1.9)	4 (1.2)	
Cancer	2 (1.5)	1 (0.5)	3 (0.8)	
Histoloav. n (%) (Total=340)				0.0040
Normal	108 (80.0)	129 (62.9)	237 (69.7)	
CIN1	18 (13.3)	45 (21.9)	63 (18.5)	
CIN2	1 (0.7)	12 (5.9)	13 (3.8)	
CIN3	6 (4.4)	18 (8.8)	24 (7.1)	
Invasive cancer	2 (1.5)	1 (0.5)	3 (0.9)	

235 **Abbreviations:** SD = standard deviation; IQR = interquartile range; CIN1 = cervical intraepithelial
 236 neoplasia grade 1; CIN2 = cervical intraepithelial neoplasia grade 2; CIN3 = cervical intraepithelial
 237 neoplasia grade 3; HIV = human immunodeficiency virus; HPV = human papillomavirus.

238 *Data from the 358 participants may be missing for some variables.

239

240 Thirty-four (9.5%) samples were positive for HPV-16, 53 (14.9%) for HPV-18/45 and 300

241 (84.0%) for other HPV types. Overall, 218 (60.9%) participants were classified as ABCD

242 criteria-positive. All patients positive for ABCD were treated with thermal ablation with the

243 exception of one patient who underwent LLETZ and one patient suspicious of cancer who

244 was biopsied and referred for multimodal therapy. Thermal ablation was provided on the

245 same day as HPV screening in 86.7% of cases. Reasons for delaying treatment included

246 referral for further evaluation, technical issues, bleeding at the time of screening, or choice of

247 the patients themselves. No serious adverse event occurred as a result of the screening

248 procedure.

249 Among all 358 women with HPV-positive results, 343 samples with valid cytological results

250 and 340 samples with valid histological results were obtained. Of the 343 valid cytological

251 results, 21.6% had abnormal cytology (ASC-US+). Four patients had ASC-H, 25 had HSIL,
 252 and three had cytology suggesting cancer. All three cancers identified by cytology were
 253 confirmed by histology. Of the 340 valid histological results, 63 (18.5%) CIN1 were identified,
 254 13 (3.8%) CIN2, 24 (7.1%) CIN3, and 3 (0.9%) invasive cancers. The prevalence of CIN2+
 255 and CIN3+ was 11.8% and 7.9%, respectively. Details for the disease prevalences are also
 256 shown in **Table 1**.

257 **Table 2** shows demographic and pathological characteristics associated with a correct
 258 prediction of the ABCD criteria.

Table 2: Demographic and pathological characteristics associated with a correct prediction of the ABCD criteria (N=340)*

Variable	Total	Unadjusted OR (95% CI)	P- value	Adjusted OR (95% CI)**	P-value
Age (years). n (%)					
30–40	186 (54.7)	1.00 (Reference)		1.00 (Reference)	
41–50	154 (45.3)	1.39 (0.90–2.14)	0.133	1.51 (0.87–2.60)	0.140
Marital status. n (%)					
Single	34 (10.0)	1.00 (Reference)		1.00 (Reference)	
With partner	265 (77.9)	1.15 (0.56–2.36)	0.706	1.07 (0.43–2.63)	0.887
Divorced/widowed	41 (12.1)	0.81 (0.32–2.04)	0.656	0.63 (0.19–2.04)	0.442
Education. n (%)					
Unschool/primary education	101 (29.7)	1.00 (Reference)		1.00 (Reference)	
Secondary/tertiary education	239 (70.3)	1.04 (0.65–1.65)	0.879	0.92 (0.47–1.82)	0.818
Employment status. n (%)					
Employed	104 (30.6)	1.00 (Reference)		1.00 (Reference)	
Independent	93 (27.3)	0.90 (0.51–1.57)	0.706	0.73 (0.38–1.43)	0.363
Housewife	58 (17.1)	0.81 (0.43–1.55)	0.528	0.74 (0.34–1.63)	0.461
Unemployed	19 (5.6)	0.72 (0.27–1.95)	0.528	0.89 (0.27–2.91)	0.852
Farmer	66 (19.4)	0.69 (0.37–1.29)	0.248	0.41 (0.18–0.95)	0.037
Age at first intercourse (years). n (%)					
≤17	154 (45.6)	1.00 (Reference)		1.00 (Reference)	
≥18	184 (54.4)	0.70 (0.46–1.08)	0.106	0.75 (0.43–1.31)	0.315
Number of sexual partner†. median	3 (2–5)	1.08 (1.01–1.16)	0.031	1.06 (0.97–1.17)	0.176
1–2. n (%)	98 (28.8)	1.00 (Reference)		1.00 (Reference)	
3–5. n (%)	177 (52.1)	1.39 (0.84–2.30)	0.195	1.22 (0.67–2.22)	0.506
>5. n (%)	65 (19.1)	1.96 (1.04–3.70)	0.038	1.53 (0.70–3.38)	0.284
Contraception. n (%)					
No	225 (66.6)	1.00 (Reference)		1.00 (Reference)	
Yes	113 (33.4)	0.84 (0.54–1.33)	0.466	0.92 (0.54–1.85)	0.769
HIV status. n (%)					
Negative	309 (92.8)	1.00 (Reference)		1.00 (Reference)	

Positive	24 (7.2)	1.21 (0.53–2.77)	0.657	0.95 (0.36–2.53)	0.589
Age at first delivery (years). n (%)					
≤20	157 (47.7)	1.00 (Reference)		1.00 (Reference)	
≥21	172 (52.3)	0.70 (0.45–1.08)	0.102	0.60 (0.34–1.07)	0.085
Parity. n (%)					
Nulliparous	14 (4.1)	1.00 (Reference)		1.00 (Reference)	
1–4	165 (48.5)	0.21 (0.06–0.79)	0.020	0.26 (0.02–2.91)	0.274
>4	161 (47.4)	0.23 (0.06–0.86)	0.029	0.28 (0.02–3.22)	0.307
Transformation zone. n (%)					
TZ1	210 (65.8)	1.00 (Reference)		1.00 (Reference)	
TZ2	70 (22.0)	1.17 (0.68–2.02)	0.575	1.24 (0.67–2.26)	0.492
TZ3	39 (12.2)	6.72 (2.84–15.93)	<0.0001	6.47 (2.59–16.21)	<0.0001
HPV testina results. n (%)					
Other HPV (without co-infection)	264 (77.9)	1.00 (Reference)		1.00 (Reference)	
HPV-16/18/45	75 (22.1)	1.19 (0.70–1.98)	0.514	1.18 (0.64–2.17)	0.605
Cytology. n (%)					
High-grade+***	29 (8.9)	2.47 (1.11–5.49)	0.027	3.37 (1.35–8.44)	0.009

259 **Abbreviations:** 95% CI = 95% confidence interval; CIN2+ = cervical intraepithelial neoplasia grade 2 or
 260 worse.

261 *Data from the 340 participants may be missing for some variables.

262 †ORs for continuous variables indicate the change in odds for an increase of one standard deviation.

263 **Adjusted for age, marital status, age at first intercourse, number of lifetime sexual partners, age at
 264 first delivery, parity, HIV status, and type of transformation zone.

265 ***High-grade lesions include ASC-H, HSIL, AIS, and cancer.

266 Bold values are statistically significant.

268 ABCD criteria were more likely to be correct in the presence of TZ type 3 (aOR = 6.47; 95%
 269 CI, 2.59–16.21; P<0.001), high-grade lesions on cytology (aOR = 3.37; 95% CI, 1.35–8.44;
 270 P<0.009) and a CIN2+ on histology (aOR = 6.05; 95% CI, 2.47–14.77; P<0.001). Overall, a
 271 correct prediction of the ABCD criteria was not impacted by the multiple sociodemographic
 272 characteristics of the population in the multivariate analysis.

273 Performance of ABCD and cytology for detection of high-grade cervical lesions (CIN2+ and
 274 CIN3+) is shown in **Table 3**.

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Table 3: Diagnostic accuracy of ABCD criteria, cytology, and HPV for detection of CIN2+ and CIN3+

Variable	CIN2+ (N=40, 11.8%)				
	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV % (95% CI)	NPV % (95% CI)	Positivity rate* % (95% CI)
ABCD criteria-positive	77.5 (61.3–88.2)	42.0 (36.5–47.7)	15.1 (10.8–20.8)	93.3 (87.6–96.5)	60.9 (55.6–65.9)
Cytology ASC-US+	80.0 (64.0–89.9)	87.5 (83.1–90.7)	47.1 (35.3–59.2)	96.9 (93.9–98.5)	21.6 (17.4–26.4)
Cytology LSIL+	70.0 (53.5–82.6)	91.3 (87.4–94.1)	52.8 (39.1–66.2)	95.6 (92.4–97.5)	16.6 (12.9–21.1)
Cytology HSIL+	62.5 (46.1–76.5)	98.6 (96.3–99.5)	86.2 (67.0–95.1)	95.0 (91.8–97.0)	9.3 (6.6–13.0)
HPV-16/18/45+	37.5 (23.5–53.9)	79.9 (74.9–84.1)	20.9 (12.3–30.8)	90.5 (86.3–93.5)	23.3 (19.1–28.1)
Variable	CIN3+ (N=27, 7.9%)				
	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV % (95% CI)	NPV % (95% CI)	
ABCD criteria-positive	70.4 (49.6–85.2)	40.6 (35.2–46.1)	9.3 (6.0–14.1)	94.1 (88.5–97.0)	
Cytology ASC-US+	88.9 (68.9–96.7)	85.4 (80.9–89.0)	35.3 (24.7–47.6)	98.8 (96.4–99.7)	
Cytology LSIL+	81.5 (60.9–92.5)	89.7 (85.7–92.7)	41.5 (28.7–55.5)	98.2 (95.7–99.2)	
Cytology HSIL+	74.1 (53.2–87.8)	97.0 (94.3–98.4)	68.9 (49.0–83.7)	97.7 (95.2–98.9)	
HPV-16/18/45+	44.4 (26.2–64.3)	79.8 (75.0–83.9)	16.0 (9.2–26.4)	94.3 (90.8–96.6)	

* Positivity rate calculated on total HPV-positive cases (CIN threshold not applicable).

Abbreviations: CIN2+ = cervical intraepithelial neoplasia grade 2 or worse; CIN3+ = cervical intraepithelial neoplasia grade 3 or worse; Cytology ASC-US+ = ASC-US, LSIL, ASC-H, HSIL, AIS, and cancer; Cytology LSIL+ = LSIL, ASC-H, HSIL, AIS, and cancer; Cytology HSIL+ = ASC-H, HSIL, AIS, and cancer; HPV = human papilloma virus; HPV-16/18/45+ = HPV DNA test positive for HPV-16, HPV-18, and HPV-45; 95% CI = 95% confidence interval; PPV = positive predictive value; NPV = negative predictive value.

ABCD criteria for CIN2+ detection showed a sensitivity of 77.5% (95% CI, 61.3%–88.2%), specificity of 42.0% (95% CI, 36.5%–47.7%), PPV of 15.1% (95% CI, 10.8%–20.8%), and NPV of 93.3% (95% CI, 87.6%–96.5%). Cytology-classified HSIL+ for CIN2+ detection showed lower sensitivity of 62.5% (95% CI, 46.1%–76.5%), but higher specificity of 98.6% (95% CI, 96.3%–99.5%), PPV of 86.2% (95% CI, 67.0%–95.1%), and NPV of 95.0% (95% CI, 91.8%–97.0%). Meanwhile, cytology-classified ASC-US+ showed improved sensitivity of

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3 290 80.0% (95% CI, 64.0%–89.9%) and specificity of 87.5% (95% CI, 83.1%–90.7%). Screening
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7 291 by HPV 16/18/45 genotyping alone had a much lower sensitivity of 37.5% (95% CI, 23.5–
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10 292 53.9) and a specificity of 79.9% (95% CI 74.9–84.1). ABCD criteria for CIN3+ lesion
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13 293 identification showed a sensitivity of 70.4% (95% CI, 49.6%–85.2%), specificity of 40.6%
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16 294 (95% CI, 35.2%–46.1%), PPV of 9.3% (95% CI, 6.0%–14.1%), and NPV of 94.1% (95% CI,
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19 295 88.5%–97.0%).

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24 25 26 297 **DISCUSSION**

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29 298 The ABCD criteria were established to improve the performance of visual-based approaches
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32 299 for triage of HPV-positive women. Previous studies conducted in LMICs indicated that triage
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35 300 using traditional VIA criteria was not satisfactory for the detection of CIN2+ lesions, as the
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38 301 gain in specificity when adding VIA to HPV testing was obtained at the expense of an
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41 302 important loss in sensitivity.(6,7,10) The challenge for VIA screeners lies in interpreting the
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44 303 wide variability of cervical presentations, in populations where obstetric trauma to the cervix
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47 304 and history of infection are frequent, and in which CIN2+ may be difficult to identify.

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51 305 The most important finding of this study is that the ABCD criteria appeared to be highly
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54 306 sensitive for detection of high-grade lesions in an HPV-positive population. We used both (i)
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57 307 a magnification technique with smartphone digital imaging that allows more detailed
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3 308 examination compared with naked eye alone and (ii) a lower VIA/D-VIA threshold positivity to
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6 309 optimize identification of lesions. The ABCD criteria provided improved VIA sensitivity for
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9 310 triage of HPV-positive women compared to most previous studies using a comparable
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12 311 methodology (histology as reference standard) (6,10,14,25,26) This can be explained by the
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16 312 fact that the IARC criteria require dense VIA changes before being considered positive, thus
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19 313 limiting their sensitivity, while a reduced positivity threshold can contribute to improved
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22 314 sensitivity for CIN2+ detection.(12,23)
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25 315 The low specificity arises because we considered any whitening to be positive, meaning
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28 316 many benign conditions (metaplasia, inflammation or other benign cervical changes) could
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31 317 produce false-positive results for the ABCD criteria. Criterion C (VILI/D-VILI), though
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34 318 dependent on criteria A and D, may contribute to the high false positive rate by categorizing
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37 319 benign conditions as ABCD-positive through the identification of iodine-negative areas
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41 320 compatible with thin, transparent or patchy acetowhite lesions. The lack of association
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44 321 between multiple socio-demographic variables and a correct prediction of the ACBD criteria
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47 322 (**Table 2**) supports the generalizability of these criteria to the overall population of women
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50 323 aged 30 to 49 years in West Cameroon. However, the limited sample size and the fact that
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53 324 the study was conducted in a single center, do not allow to extend these results to the overall
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56 325 female population, especially considering the differences in HPV prevalence in other regions.
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3 326 Compared to screening by HPV-16/18/45 genotyping without triage, the sensitivity of the
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6 327 ABCD criteria was much higher, at the cost of a lower specificity. PPV was also slightly lower
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9 328 with triage by ABCD criteria (15.1%) than with HPV genotyping (20.9%). Overall, 54.4% of
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12 329 normal histology results and 71.4% of CIN1 were considered ABCD criteria positive and
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15 330 consequently underwent unnecessary treatment. Thus, 85% (174 of 205) of women who
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18 331 screened positive were treated unnecessarily. However, when considering all women
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21 332 screened for CC, including HPV-negative, 174 were treated unnecessarily out of 1964
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24 333 screened by Self-HPV, corresponding to an overall 8.9% overtreatment rate in the total
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27 334 population screened. Despite the low specificity, our 3T-Approach in a single visit may be
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30 335 acceptable in an LMIC context because it reduces cost and loss to follow-up, which are
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33 336 recognized barriers to effective cervical cancer screening.(11,27) Indeed, studies in
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36 337 Uganda(28) and South Africa(27) have shown loss to follow-up rates between 21% and 25%
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39 338 after the first visit, up to 50% at 24 months. Furthermore, treatment by thermal ablation is
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42 339 associated with very low risks of side effects and morbidity.(29) Therefore, treatment of a
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45 340 significant number of false-positive cases may be considered an acceptable strategy for
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48 341 effective control of CC in an LMIC setting and may contribute to reaching the target of the
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51 342 WHO's elimination initiative.(3,5) However, the use and integration of the ABCD criteria in
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54 343 the cervical cancer screening process warrants multidisciplinary discussion with involved
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3 344 stakeholders, taking into account the local context and resources, as well as regional HPV
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6 345 prevalence, prevalence of CIN2+ in HPV-positive participants, level of risk including HIV
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10 346 prevalence, availability of treatment modalities on site, and the possibility to offer further
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13 347 investigation when required. According to the context, the decision to refer has
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16 348 consequences for the patients and the health care system, requiring additional time and
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19 349 resources, and increasing the risk of loss to follow-up. Recognizing the limitations of the
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22 350 ABCD criteria with regard to PPV and overtreatment rates, other triaging strategies merit
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25 351 further investigation. The use of extended HPV genotyping (HPV 16, 18, 45, 31, 33, 35, 52
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28 352 and/or 58) for the triaging of HPV-positive women is one alternative that should also be
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32 353 explored.

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35 354 The second limitation is that the study was conducted in a single centre in a district hospital
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38 355 in West Cameroon with five clinicians (three midwives supervised by two gynaecologists)
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41 356 administering all screening and treatment procedures.

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44 357 It should be noted that two out of three cervical cancers were assessed as ABCD-negative
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47 358 on site by the frontline health care providers and did not receive immediate treatment. After
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50 359 reviewing the digital images of these two cases off-site, it was determined that criterion B
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53 360 (bleeding) was present in both cases, which should have led to a positive ABCD result
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56 361 **(Supplement, Figure S1).**

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3 362 ABCD criteria comprise a simple tool that can alert healthcare professionals to the clinical
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6 363 features of CIN2+, and the use of “relaxed IARC criteria” may greatly decrease the risk of
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10 364 missing CIN2+ lesions. Using ABCD criteria is a simple test with binary results (positive or
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13 365 negative) that are immediately available, allowing initiation of therapy without delay. In our
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16 366 series, 86.7% of participants underwent the 3T-Approach in one day. Strengths of our study
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19 367 included the application of ABCD criteria upon VIA examination in real-life conditions with
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22 368 immediate treatment when necessary, therefore supporting the feasibility of a “screen-and-
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25 369 treat” strategy. Furthermore, because all HPV-positive women underwent biopsy and cervical
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28 370 brushing regardless of the ABCD criteria results, there was no risk of verification bias in the
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32 371 calculations of sensitivity and specificity for ABCD criteria.
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35 372 In conclusion, ABCD criteria can improve CIN2+ diagnosis in HPV-positive women and may
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38 373 provide a unique opportunity to improve cervical cancer screening programs in LMICs using
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41 374 a one-visit approach. This strategy may be particularly beneficial because the criteria are
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44 375 easily remembered and to use for healthcare providers.
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53
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57 379 nurses who examined the women. We would also like to thank Alison Sherwin, PhD, from
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3 380 Edanz Group (<https://en-author-services.edanzgroup.com/ac>) for editing a draft of this
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6 381 manuscript.

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11 12 13 383 **Competing Interests**

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15
16 384 All authors declare that they have no competing interests.

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19 385

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24
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26
27
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29
30
31 389 University Hospital of Geneva (Switzerland). The funding sponsors played no role in design

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34 390 and conduct of the study; collection, management, analysis, and interpretation of the data;

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37 391 preparation, review, or approval of the manuscript; and decision to submit the manuscript for

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40 392 publication.

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44 45 46 394 **Data access, analysis and responsibility**

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49 395 The principal investigator had full access to all the data in the study and takes responsibility

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52 396 for the integrity of the data and the accuracy of the data analysis. Data used in the study is

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55 397 available upon request to the first author.

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67 399 **Contributors**

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9
10 400 PP, BK, and PV designed the study protocol, implemented the study, oversaw the data
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12
13 401 collection, analysed the data, and drafted and revised the paper. AW and RC conducted data
14
15
16 402 analysis, interpreted the data, and revised the draft paper. BK, ET, and JF trained the study
17
18
19 403 staff, assumed the quality control (supervision and mentorship), supported the data
20
21
22 404 collection, interpreted the data, and revised the draft paper. JCT and ES analysed the
23
24
25
26 405 pathological specimens, interpreted the data, and revised the draft paper.
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29 406 **References**

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34 497 ablation versus cryotherapy or loop excision to treat women positive for cervical
35 498 precancer on visual inspection with acetic acid test: pilot phase of a randomised
36 499 controlled trial. *Lancet Oncol*. 2020;21(1):175–84.

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4 501 **Figure 1: ABCD criteria for VIA interpretation in HPV-positive women**

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6 502 **Criterion A** – Acetowhite area touching the transformation zone (absent on the native view
7 503 and apparent after acetic acid application) is considered positive.

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10 504 **Criterion B** – Bleeding without touching or after lightly touching (with a swab or speculum) the
11 505 cervix is considered positive.

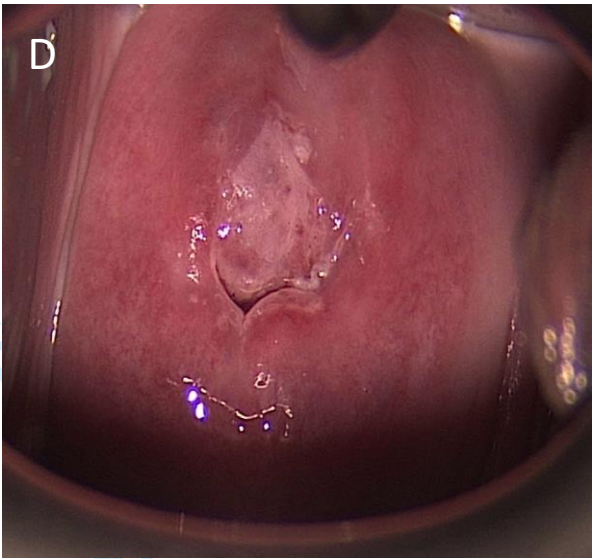
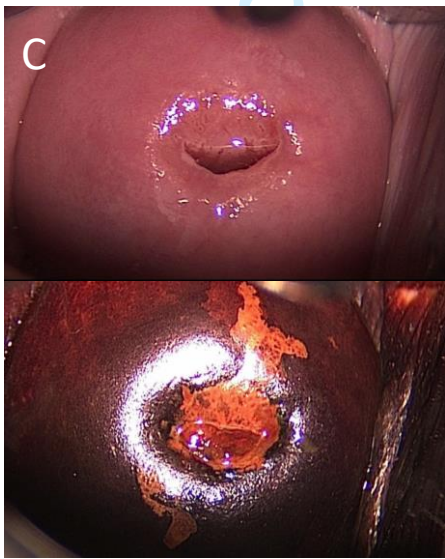
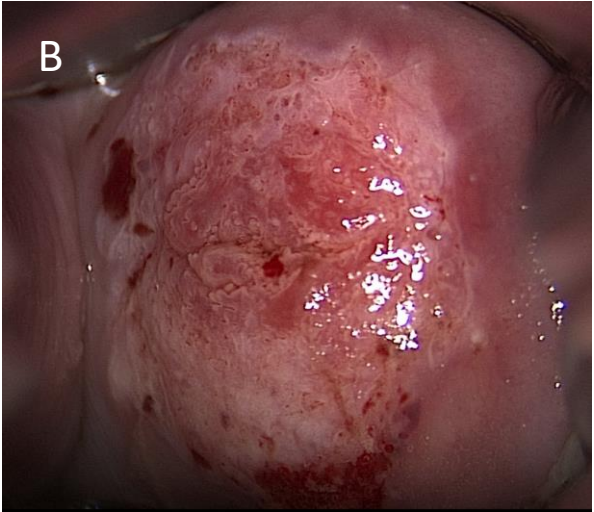
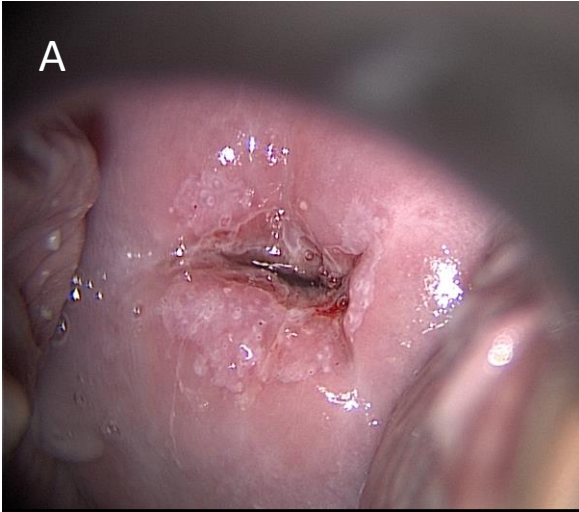
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14 506 **Criterion C (optional)** – Colouring with VILI contributes to confirmation or identification of a
15 507 faint acetowhite lesion.

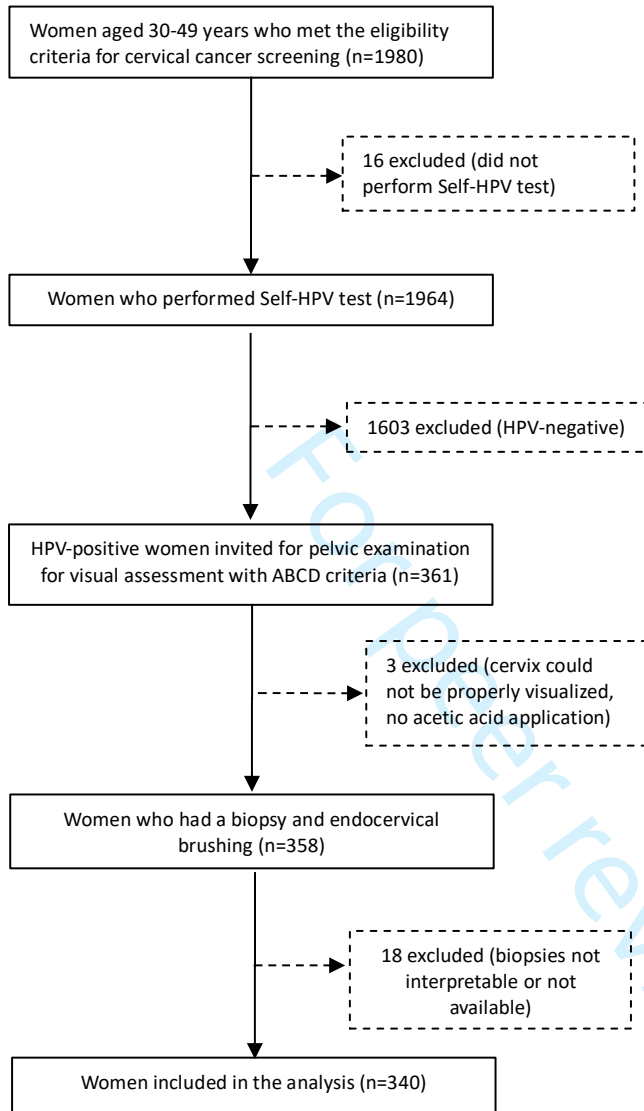
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18 508 **Criterion D** – Diameter of >5 mm (about the size of a pencil eraser) in an acetowhite area is
19 509 considered positive.

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23 511 **Figure 2: Flowchart of participants for the 3T-Approach in Cameroon**

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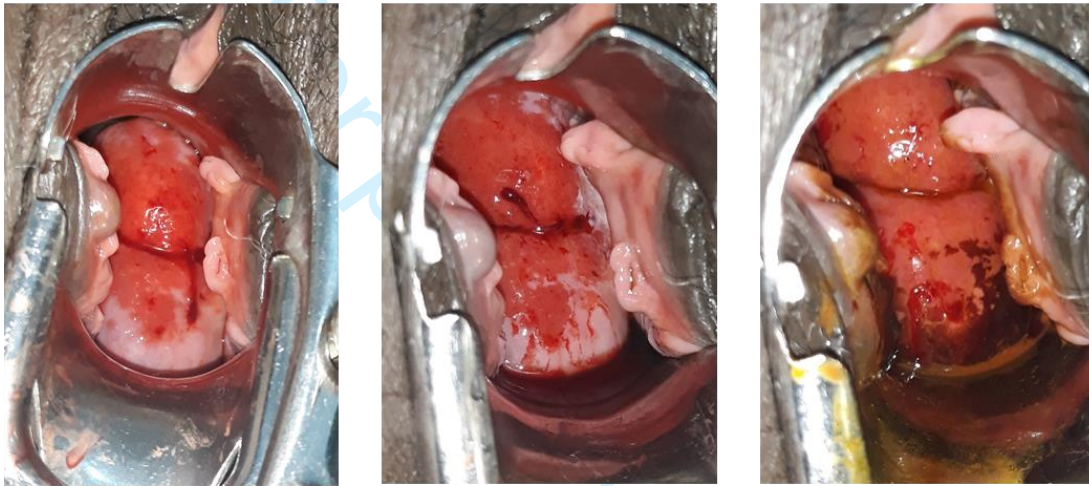
Supplementary Material

ABCD Criteria to Improve Visual Inspection with Acetic Acid (VIA) Triage in HPV-positive Women: a prospective analysis

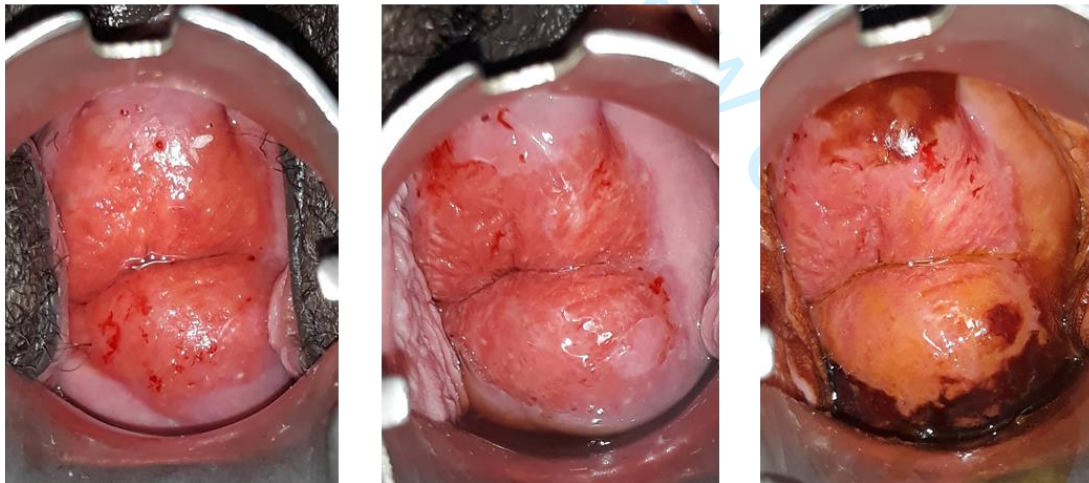
Patrick Petignat, Bruno Kenfack, Ania Wisniak, Essia Saiji, Jean-Christophe Tille, Jovanny Tsuala Fouogue, Rosa Catarino, Evelyn Foguem Tincho and Pierre Vassilakos

Figure S1. Cases of cervical cancer not identified by ABCD criteria on site

A



B



A. Poorly differentiated carcinoma, positive for criterion B (bleeding); B. Invasive adenocarcinoma, positive for criterion B. From left to right, smartphone photos of (i) the native cervix, (ii) after application of acetic acid and (iii) after application of Lugol's iodine.

Section & Topic	No	Item	Reported on page #
TITLE OR ABSTRACT			
	1	Identification as a study of diagnostic accuracy using at least one measure of accuracy (such as sensitivity, specificity, predictive values, or AUC)	2
ABSTRACT			
	2	Structured summary of study design, methods, results, and conclusions (for specific guidance, see STARD for Abstracts)	2
INTRODUCTION			
	3	Scientific and clinical background, including the intended use and clinical role of the index test	4-5
	4	Study objectives and hypotheses	5
METHODS			
<i>Study design</i>	5	Whether data collection was planned before the index test and reference standard were performed (prospective study) or after (retrospective study)	5
<i>Participants</i>	6	Eligibility criteria	5
	7	On what basis potentially eligible participants were identified (such as symptoms, results from previous tests, inclusion in registry)	5
	8	Where and when potentially eligible participants were identified (setting, location and dates)	5
	9	Whether participants formed a consecutive, random or convenience series	5
<i>Test methods</i>	10a	Index test, in sufficient detail to allow replication	6 + figure 1
	10b	Reference standard, in sufficient detail to allow replication	7
	11	Rationale for choosing the reference standard (if alternatives exist)	na
	12a	Definition of and rationale for test positivity cut-offs or result categories of the index test, distinguishing pre-specified from exploratory	6
	12b	Definition of and rationale for test positivity cut-offs or result categories of the reference standard, distinguishing pre-specified from exploratory	7
	13a	Whether clinical information and reference standard results were available to the performers/readers of the index test	6
	13b	Whether clinical information and index test results were available to the assessors of the reference standard	7
<i>Analysis</i>	14	Methods for estimating or comparing measures of diagnostic accuracy	8
	15	How indeterminate index test or reference standard results were handled	8
	16	How missing data on the index test and reference standard were handled	8
	17	Any analyses of variability in diagnostic accuracy, distinguishing pre-specified from exploratory	na
	18	Intended sample size and how it was determined	8
RESULTS			
<i>Participants</i>	19	Flow of participants, using a diagram	Figure 2
	20	Baseline demographic and clinical characteristics of participants	9
	21a	Distribution of severity of disease in those with the target condition	10-11
	21b	Distribution of alternative diagnoses in those without the target condition	na
	22	Time interval and any clinical interventions between index test and reference standard	na
<i>Test results</i>	23	Cross tabulation of the index test results (or their distribution) by the results of the reference standard	10 (table 1)
	24	Estimates of diagnostic accuracy and their precision (such as 95% confidence intervals)	12 (table 3)
	25	Any adverse events from performing the index test or the reference standard	10
DISCUSSION			
	26	Study limitations, including sources of potential bias, statistical uncertainty, and generalisability	15
	27	Implications for practice, including the intended use and clinical role of the index test	14-15
OTHER INFORMATION			
	28	Registration number and name of registry	9
	29	Where the full study protocol can be accessed	9
	30	Sources of funding and other support; role of funders	16

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STARD 2015

AIM

STARD stands for “Standards for Reporting Diagnostic accuracy studies”. This list of items was developed to contribute to the completeness and transparency of reporting of diagnostic accuracy studies. Authors can use the list to write informative study reports. Editors and peer-reviewers can use it to evaluate whether the information has been included in manuscripts submitted for publication.

EXPLANATION

A **diagnostic accuracy study** evaluates the ability of one or more medical tests to correctly classify study participants as having a **target condition**. This can be a disease, a disease stage, response or benefit from therapy, or an event or condition in the future. A medical test can be an imaging procedure, a laboratory test, elements from history and physical examination, a combination of these, or any other method for collecting information about the current health status of a patient.

The test whose accuracy is evaluated is called **index test**. A study can evaluate the accuracy of one or more index tests. Evaluating the ability of a medical test to correctly classify patients is typically done by comparing the distribution of the index test results with those of the **reference standard**. The reference standard is the best available method for establishing the presence or absence of the target condition. An accuracy study can rely on one or more reference standards.

If test results are categorized as either positive or negative, the cross tabulation of the index test results against those of the reference standard can be used to estimate the **sensitivity** of the index test (the proportion of participants *with* the target condition who have a positive index test), and its **specificity** (the proportion *without* the target condition who have a negative index test). From this cross tabulation (sometimes referred to as the contingency or “2x2” table), several other accuracy statistics can be estimated, such as the positive and negative **predictive values** of the test. Confidence intervals around estimates of accuracy can then be calculated to quantify the statistical **precision** of the measurements.

If the index test results can take more than two values, categorization of test results as positive or negative requires a **test positivity cut-off**. When multiple such cut-offs can be defined, authors can report a receiver operating characteristic (ROC) curve which graphically represents the combination of sensitivity and specificity for each possible test positivity cut-off. The **area under the ROC curve** informs in a single numerical value about the overall diagnostic accuracy of the index test.

The **intended use** of a medical test can be diagnosis, screening, staging, monitoring, surveillance, prediction or prognosis. The **clinical role** of a test explains its position relative to existing tests in the clinical pathway. A replacement test, for example, replaces an existing test. A triage test is used before an existing test; an add-on test is used after an existing test.

Besides diagnostic accuracy, several other outcomes and statistics may be relevant in the evaluation of medical tests. Medical tests can also be used to classify patients for purposes other than diagnosis, such as staging or prognosis. The STARD list was not explicitly developed for these other outcomes, statistics, and study types, although most STARD items would still apply.

DEVELOPMENT

This STARD list was released in 2015. The 30 items were identified by an international expert group of methodologists, researchers, and editors. The guiding principle in the development of STARD was to select items that, when reported, would help readers to judge the potential for bias in the study, to appraise the applicability of the study findings and the validity of conclusions and recommendations. The list represents an update of the first version, which was published in 2003.

More information can be found on <http://www.equator-network.org/reporting-guidelines/stard>.



BMJ Open

ABCD Criteria to Improve Visual Inspection with Acetic Acid (VIA) Triage in HPV-positive Women: a Prospective Study of Diagnostic Accuracy

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3 **ABCD Criteria to Improve Visual Inspection with Acetic Acid (VIA) Triage in HPV-positive**
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6 **Women: a Prospective Study of Diagnostic Accuracy**
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1 ABSTRACT

2 **Objectives** A simple system for visual inspection with acetic acid (VIA) assessment, named
3 ABCD criteria, has been developed to increase accuracy for triaging of high-risk human
4 papillomavirus (HPV)-positive women. The present study aimed to determine the accuracy of
5 ABCD criteria for the detection of histologically confirmed cervical intraepithelial neoplasia
6 grade 2 or worse (CIN2+) in HPV-positive women living in a low-resource setting.

7 **Design** Prospective study of diagnostic accuracy

8 **Setting** Cervical cancer screening program based on a 3T-Approach (Test, Triage, and
9 Treat) in the Health District of Dschang, West Cameroon.

10 **Participants** Asymptomatic non-pregnant women aged 30-49 years were eligible to
11 participate. Exclusion criteria included history of CIN treatment, anogenital cancer or
12 hysterectomy. A total of 1980 women were recruited (median age, 40 years; interquartile
13 range, 35-45 years), of whom 361 (18.4%) were HPV-positive and 340 (94.2%) completed
14 the trial.

15 **Interventions** HPV-positive women underwent a pelvic examination for visual assessment of
16 the cervix according to ABCD criteria. The criteria comprised A for Acetowhitiness, B for
17 Bleeding, C for Colouring, and D for Diameter. The ABCD criteria results were codified as
18 positive or negative and compared with histological analysis findings (reference standards).

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4 19 **Primary outcome measure** Diagnostic performance of ABCD criteria for CIN2+, defined as
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7 20 sensitivity, specificity, negative and positive predictive values.
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10 21 **Results** ABCD criteria had a sensitivity of 77.5% (95% CI, 61.3%–88.2%), specificity of
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13 22 42.0% (95% CI, 36.5%–47.7%), positive predictive value of 15.1% (95% CI, 10.8%–20.8%),
14
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16 23 and negative predictive value of 93.3% (95% CI, 87.6%–96.5%) for detection of CIN2+
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19 24 lesions. Most (86.7%) of the ABCD-positive women were treated on the same day.
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22 25 **Conclusions** ABCD criteria can be used in the context of a single-visit approach and may be
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24
25 26 the preferred triage method for management of HPV-positive women in a low-income
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28 27 context.
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32 28 **Trial registration** The trial was registered under ClinicalTrials.gov (number NCT03757299).
33
34

35 29 **Key words:** cervical cancer screening, low- and middle-income countries, visual inspection
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38 30 with acetic acid (VIA), visual inspection with Lugol's iodine (VILI), human papillomavirus
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41 31 (HPV), triage
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48 33 **Strengths and limitations of this study**

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- 52 34 • Using ABCD criteria for VIA interpretation is a simple test with binary results (positive
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55 35 or negative) that are immediately available, allowing a screen-and-treat approach .
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3 36 • Because all HPV-positive women underwent biopsy and endocervical brushing
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6 37 regardless of the ABCD criteria results, there was no risk of verification bias in the
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10 38 calculations of sensitivity and specificity.
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13 39 • A limitation of the study was its setting in a single centre in a district hospital in West
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16 40 Cameroon with five clinicians administering all screening and treatment procedures.
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42 INTRODUCTION

43 More than 90% of cervical cancer (CC) deaths occur in low- and middle-income countries

44 (LMICs), mainly due to lack of prevention.(1) Cytology-based CC screening programs and

45 more recent HPV-based programs have been successfully implemented in high-income

46 countries and have been associated with important reductions in deaths from CC.(2)

47 However, these strategies have not been implemented in LMICs, predominantly because of

48 financial and logistical limitations. Alternative methods such as visual inspection of the cervix

49 after application of acetic acid (VIA) and more recently, HPV primary screening, are

50 considered suitable for use in LMICs.(3,4)

51 A global strategy for the elimination of cervical cancer has been launched by the World

52 Health Organization (WHO) in 2020, which relies upon the screening of 70% of women using

53 a high-performance test and the treatment of 90% of women identified with cervical

54 disease.(5) Recommendations adopted by the WHO for screening in resource-limited

55 settings include a strategy of HPV-screening followed by VIA triage and treatment, or a

56 strategy of HPV-screening followed by treatment.(3) Although no recommendations are given

57 for the approach that should be prioritized, sub-Saharan Africa has a high HPV prevalence

58 rate of 15%–30% and most HPV-positive women have no lesions.(3,6,7) In this context, HPV

59 testing followed by immediate treatment can represent significant overtreatment in women

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4 60 with an HPV-positive test, which by itself may not confer a high risk of cervical intraepithelial
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7 61 neoplasia grade 2 or worse (CIN2+).(4,8,9) In sub-Saharan Africa, the prevalence of CIN2+
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9
10 62 was reported to be 2%–4% in women aged 30–49 years and 7%–11% in an HPV-positive
11
12
13 63 population with a low HIV prevalence rate (<10%).(6,7,10) A triage system is only a valid
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15
16 64 option if it can improve the positive predictive value (PPV) for CIN2+ and minimize the
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19 65 referral rate, while conserving the high sensitivity of the HPV test. The achievement of a high
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22 66 PPV at the cost of limited sensitivity may be considered a reasonable option when the loss to
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25 67 follow-up of women requiring surveillance is minimal. However, in low-resource settings, high
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28 68 levels of loss to follow-up constitute an important barrier to cervical cancer screening, which
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30
31 69 is why programs having no follow-up visits or as few as possible are preferable to achieve a
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33
34 70 high degree of participation.(11) A '3T-Approach' (Test, Triage and Treat) combining testing
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37 71 with a rapid HPV test, triage of HPV-positive women with VIA, and treatment by thermal
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40 72 ablation of VIA-positive patients within the same day, has been previously used to further
41
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43 73 reduce the risk of loss to follow-up.(12)
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48 74 Triage by VIA and/or visual inspection with Lugol's iodine (VILI) requires accurate criteria to
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51 75 decide whether or not the findings are positive, which are generally based on the
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54 76 International Agency for Research against Cancer (IARC) manual.(13) However, in this
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57 77 setting, VIA triage in HPV-positive populations appears to be associated with an important
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3 78 loss of sensitivity, suggesting that triage by VIA using traditional criteria may not be of
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6 79 benefit.(6,7,10,14) Previous studies using histology as reference standard and having
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8
9 80 excluded verification bias had sensitivities ranging from 25.0% to 45.5%.(6,10,15)
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11
12 81 Interpreting VIA with naked eye alone is subjective and is highly variable between health
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15 82 care providers.(16–18) This issue may be improved with continuous supervision and medical
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18 83 education thanks to the use of digital VIA and VILI (D-VIA/D-VILI). This includes acquisition
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21 84 of cervical images, native and after VIA and VILI application, through a camera or
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24 85 smartphone. These technologies provide an alternative to colposcopy in the context of
25
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27 86 LMICs and may constitute an important step in the improvement of VIA/VILI
28
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30 87 interpretation.(19–21) Although the image quality is probably lower than that with high-
31
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33 88 resolution colposcopy, there are significant benefits for healthcare providers, because they
34
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36 89 can move through and compare the native, VIA, and VILI images, and can also magnify
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39 90 suspicious lesions, before deciding whether treatment is needed.(19,20)
40
41
42 91 To improve VIA/D-VIA interpretation as a triage test in HPV-positive populations, we
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44
45 92 introduced a set of criteria, termed ABCD criteria for “Acetowhiteness”, “Bleeding”,
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48 93 “Colouring” (with Lugol’s iodine) and “Diameter” of the lesion. These criteria constitute a
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51 94 simple structure that may contribute to preventing CC in an LMIC context. The aim of the
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3 95 present study was to provide a rationale for the ABCD criteria and determine their
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6 96 performance in identifying histology-proven CIN2+.
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11 12 13 98 **METHODS**

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16 99 **Study design** – This prospective study was carried out between September 2018 and March
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19 100 2020 in the health district of Dschang (West Cameroon) as part of a 5-year cervical cancer
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22 101 screening programme. The screening strategy consisted of the “3T-Approach”, in which
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25 102 Testing with HPV, Triage with VIA and Treatment are provided within one visit.
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29 103 Asymptomatic non-pregnant women aged 30-49 years were eligible to participate in the
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32 104 study on a voluntary basis and were included in a consecutive manner upon presentation to
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35 105 the screening site. Exclusion criteria included history of CIN treatment, anogenital cancer or
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38 106 hysterectomy. The study was conducted within a larger trial aiming to recruit 6,000 women in
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42 107 a 5-year screening program.(21) At the baseline visit, after obtaining written informed
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45 108 consent and providing guidance to participants on the procedure for vaginal self-sampling,
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48 109 participants undertook an HPV self-test (Self-HPV) that was subsequently analyzed by a
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51 110 point-of-care assay (GeneXpert®), with most results available within an hour. HPV-negative
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54 111 women were reassured and advised to repeat the test in 5 years, while HPV-positive women
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57 112 were invited to undergo visual triage and thermal ablation or large loop excision of the
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3 113 transformation zone (LLETZ) if needed. Trained midwives performed gynecologic
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6 114 examination with VIA/VILI, assessment of ABCD criteria and transformation zone (TZ) type,
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10 115 and determined treatment modalities in a single visit. Two gynaecologists were available on
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13 116 call for a second opinion or advice.

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16 117 **ABCD criteria (Figure 1)** – The ABCD criteria were chosen from a synthesis of published
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19 118 results as well as our own experience in VIA and VILI interpretation.(3,13,22–26) We
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21
22 119 considered acetowhiteness as the most important predictor for CIN and noted that Lugol's
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24
25 120 iodine can be used to identify thin acetowhite lesions not seen on the initial VIA assessment
26
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28 121 (Figure 1). Similar to the IARC criteria, the pathological area should be located within or in
29
30
31 122 contact with the TZ. The ABCD criteria are codified as positive (present) or negative
32
33
34 123 (absent). To be considered ABCD-positive, at least one of the following conditions needs to
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36
37 124 be fulfilled: presence of criteria A (acetowhiteness) and D (diameter) combined, or criterion B
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40 125 (bleeding) with or without presence of A, C (colouring) or D.

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44 126 ABCD criteria were independently evaluated by one of three trained midwives and
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47 127 supervised by two experienced Cameroonian gynaecologists.

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51 128 • *Criterion A for Acetowhiteness* – Criterion A is obtained after application of 3%–5% acetic
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53 129 acid. Any acetowhite area touching the TZ and having a diameter of >5 mm (criterion D)
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55 130 is considered positive. Compared with the IARC criteria, which require a degree of
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57 131 whiteness combined with the presence of a sharp, distinct, well defined, dense
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3 132 (opaque/dull or oyster white) acetowhite area,(13) we considered here any acetowhite
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5 133 lesion exceeding 5 mm to be positive.

6
7 134 • *Criterion B for Bleeding on touch* – Criterion B is obtained upon native examination or
8
9 135 after acetic acid application. Presence of cervical bleeding without touching or after lightly
10
11 136 touching the cervix in the TZ area is considered positive. This means that any bleeding
12
13 137 from the surface of the cervix, after excluding bleeding of intra-uterine origin, can be
14
15 138 associated with CIN2+ lesions. Although bleeding can also be caused by ulceration or
16
17 139 infection, any signs should be thoroughly investigated to rule out the possibility of early
18
19 140 preclinical invasive cancer. This sign is easy to recognize and is considered a risk finding
20
21 141 for precancerous lesions and cervical cancer.(25,26) Presence of bleeding in association
22
23 142 with criteria A and C may require referral for further testing like biopsy and colposcopy.

24
25 143 • *Criterion C for Colouring with Lugol's iodine* – Criterion C is optional. Lugol's iodine
26
27 144 staining can be used as an adjunct to VIA to recognize epithelial change that would
28
29 145 otherwise be difficult to identify by VIA only. The colour changes with VILI can be easier
30
31 146 to appreciate than those after VIA and may contribute to identification of a missed thin
32
33 147 acetowhite lesion. To be considered positive, an iodine-negative lesion should
34
35 148 correspond to a VIA lesion having criteria A and D. Compared with the IARC criteria,
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37 149 which require the presence of a well-defined, bright yellow, iodine non-uptake area,(13)
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39 150 we consider any non-iodine uptake areas to be positive, providing they match an
40
41 151 acetowhite lesion.

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43 152 • *Criterion D for Diameter* – Criterion D is evaluated after application of acetic acid (or
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45 153 Lugol's iodine). An acetowhite lesion measuring >5 mm in diameter (about the size of a
46
47 154 pencil eraser) is considered positive. Defining a minimal size of 5 mm allows exclusion of
48
49 155 benign conditions such as dot-like, line-like, or streak-like areas.(24)

50
51 156 A set of three images (native, acetic acid, Lugol's iodine) were obtained on a Galaxy S5
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57 157 smartphone (Samsung, Seoul, South Korea). Diagnosis and treatment were based on
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3 158 combined results of VIA/VILI and smartphone-enhanced D-VIA, using aids such as zooming
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7 159 in on lesions and performing comparisons between the native, VIA, and VILI images.
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10 160 Women with positive ABCD criteria were eligible for treatment by thermal ablation, with the
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13 161 exception of (i) lesions extending into the endocervix which could not be covered by the
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16 162 probe tip, and (ii) suspicions of carcinoma, in-situ adenocarcinoma or invasive
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19 163 adenocarcinoma, which were referred to a gynaecologist to determine the need for further
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22 164 treatment (LLETZ or oncological management). Cervical liquid-based cytology, biopsy at the
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26 165 TZ and endocervical brushing (ECB) were performed on all HPV-positive women prior to
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29 166 treatment.

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32 167 **Cytology** – Cervical liquid-based cytology was performed using the SurePath (September
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35 168 2018 to July 2019) and ThinPrep (July 2019 to March 2020) techniques. All vials were
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38 169 analyzed in Switzerland (CytoPath, Unilabs, Geneva, and University Hospital of Geneva).
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41 170 The slides were independently read by qualified cytotechnologists and classified according to
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45 171 the 2014 Bethesda classification system: negative for intraepithelial lesion or malignancy
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48 172 (NILM), inflammatory atypical squamous cells of undetermined significance (ASC-US),
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51 173 inflammatory atypical squamous cells that cannot exclude HSIL (ASC-H), atypical glandular
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54 174 cells with low-grade squamous intraepithelial lesion (LSIL), high-grade squamous
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57 175 intraepithelial lesion (HSIL), and invasive cancer. The cytotechnologists were aware of the
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3 176 HPV-positive status (but not of the HPV type) of participants but were blinded to the ABCD

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6 177 criteria interpretation.

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9 178 **Histology findings (reference standard)** – Cervical biopsies were performed using biopsy

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13 179 forceps, and ECB was carried out with an endocervical brush. Cervical biopsies were

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16 180 performed at 6 o'clock in the TZ when ABCD criteria were negative. If ABCD criteria were

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19 181 positive, one or more biopsies were performed at the most suspicious areas. All samples

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22 182 were stored in formalin. Biopsy slides and ECB samples (processed by cellular block) were

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25 183 read by two experienced gynaecologic pathologists of the Geneva University Hospitals,

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29 184 Switzerland, who were blinded to the screening test results and ABCD criteria findings. There

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32 185 was no external review of histological analyses. The histological results were classified as

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35 186 normal, CIN1, CIN2, CIN3, adenocarcinoma *in situ* (AIS), invasive carcinoma, or

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38 187 adenocarcinoma. The cut-off for a pathological result was set at CIN2+. When histological

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41 188 results varied within the samples of one participant, only the worst result was considered as

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44 189 the reference standard.

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47 190 **Patient and public involvement** – Preferences of and experience with former patients of a

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51 191 preliminary research study on cervical cancer screening in Dschang, Cameroon, were

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54 192 considered in the design and conduction of this study. During the study, focus groups were

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57 193 organized with members of the community (women and men), health care workers and

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3 194 community health workers, to explore barriers to cervical cancer screening and further
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6 195 improve the program and recruitment strategy. Patients were also involved at their arrival at
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10 196 the screening center where they were offered a one-hour information session on cervical
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13 197 cancer and sexual health by trained midwives. Furthermore, the public is kept informed about
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16 198 the progress of our research through the publication of bi-annual newsletters disseminated
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19 199 among health workers and the general community. Newsletters will be published until the
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22 200 end of the 3T study.

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25 201 **Statistical analysis** – Initially, we planned a sample of 6,000 women. However, the COVID-19
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28 202 pandemic and public health measures to control the virus have impacted on-site clinical
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32 203 activity since mid-March 2020. In this context, we decided to consider an interim analysis to
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35 204 the trial of the primary endpoints which included performance of the ABCD criteria.
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38 205 Descriptive statistics were used to analyse the baseline characteristics of the study
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42 206 population. Sensitivity, specificity, positive predictive value (PPV), negative predictive value
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45 207 (NPV), and positivity rate plus their 95% confidence intervals (95% CIs) were calculated for
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47
48 208 each triaging test. Student's *t*-test, Mann–Whitney test, or Pearson's chi-square test were
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51 209 used, where appropriate, to identify sociodemographic and reproductive characteristics of the
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54 210 patients that could differ between ABCD criteria results. A P-value of <0.05 was considered
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57 211 statistically significant. An exploratory analysis was performed to assess the relationships
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3 212 between each independent variable and the correct prediction of the ABCD criteria. This
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6 213 correct prediction score was equal to 1 when ABCD criteria were positive and there was a
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9 214 CIN2+ on histology or if the ABCD criteria were negative and histology was also negative. All
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13 215 other incorrect predictions were assigned the value 0. Univariate and multivariate logistic
14
15
16 216 regression analyses were carried out to identify predictors of a correct ABCD criteria score
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19 217 according to histology. Participants with missing or indeterminate results for ABCD criteria or
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22 218 histopathology were excluded from the analysis. Odds ratios (ORs) were adjusted for
23
24
25 219 potential confounders, such as age, marital status, number of lifetime sexual partners, age at
26
27
28 220 first sexual intercourse, age at first delivery, parity, HIV status, and type of TZ, and 95% CIs
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31
32 221 were calculated. All data analyses were conducted using Stata Statistical software Release
33
34
35 222 13 (StataCorp LP, College Station, TX).

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38 223 **Ethical considerations** – The study obtained approval from the Cantonal Ethics Board of
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40
41 224 Geneva, Switzerland (Commission cantonale d'éthique de la recherche [CCER], No. 2017-
42
43
44 225 0110) and the Cameroonian National Ethics Committee for Human Health Research (No.
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46
47 226 2018/07/1083/CE/CNERSH/SP). The trial was registered under ClinicalTrials.gov (number
48
49
50
51 227 NCT03757299). The full study protocol can be provided upon request to the first author.
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54 228

57 229 **RESULTS**

230 A total of 1980 women aged 30–49 years were enrolled (median age: 41 years; interquartile
 231 range [IQR], 36–50 years). Overall, 1964 women performed Self-HPV, of whom 361 (18.5%)
 232 had an HPV-positive test and underwent pelvic examination, three were excluded from the
 233 results analysis for lack of ABCD criteria assessment, and 340 (94.2%) had interpretable
 234 histology findings and constituted the study population (**Figure 2**). **Table 1** provides details of
 235 the baseline sociodemographic, reproductive, and clinical characteristics of the participants.
 236 Median age at first sexual intercourse was 18 years (IQR, 16–19 years) and median number
 237 of sexual lifetime partners was 3 (IQR, 2–5).
 238

Table 1: Baseline sociodemographic, reproductive health, and clinical characteristics according to ABCD criteria (N=358)*

Variable	ABCD criteria-negative	ABCD criteria-positive	Total	P-value
Participants recruited. n (%)	140 (39.1)	218 (60.9)	358	
Age (years). median (IQR)	41 (35–45)	40 (34–45)	40 (34–45)	0.4464
Marital status. n (%)				0.8910
Single	15 (10.7)	20 (9.2)	35 (9.8)	
With partner	109 (77.9)	173 (79.3)	282 (78.8)	
Divorced/widowed	16 (11.4)	25 (11.5)	41 (11.4)	
Education. n (%)				0.3900
Unschooling	1 (0.7)	5 (2.3)	6 (1.7)	
Primary education	37 (26.4)	66 (30.3)	103 (28.8)	
Secondary education	67 (47.9)	105 (48.2)	172 (48.0)	
Tertiary education	35 (25.0)	42 (19.2)	77 (21.5)	
Employment status. n (%)				0.1750
Employed	50 (35.7)	57 (26.2)	107 (29.9)	
Independent	39 (27.9)	56 (25.7)	95 (26.5)	
Housewife	23 (16.4)	41 (18.8)	64 (17.9)	
Unemployed	7 (5.0)	12 (5.5)	19 (5.3)	
Farmer	21 (15.0)	52 (23.8)	73 (20.4)	
Age at menarche (years). mean \pm SD	14.7 \pm 1.8	14.7 \pm 1.9	14.7 \pm 1.8	0.8914
Age at first intercourse. median (IQR)	17 (16–19)	18 (16–20)	18 (16–19)	0.2390
Number of sexual partners. median	4 (3–6)	3 (2–5)	3 (2–5)	0.0008
Contraception. n (%)				0.5950
None	93 (66.9)	142 (65.5)	235 (66.0)	
Condom	18 (13.0)	25 (11.5)	43 (12.1)	

3	Hormonal pill	1 (0.7)	7 (3.2)	8 (2.3)	
4	DIU/ implant/ injection	25 (18.0)	41 (18.9)	66 (18.5)	
5	Other	2 (1.4)	2 (0.9)	4 (1.1)	
6	HIV status. n (%)				0.9420
7	Negative	128 (92.7)	198 (93.0)	326 (92.9)	
8	Positive	10 (7.3)	15 (7.0)	25 (7.1)	
9	Age at first delivery (years). mean ± SD	21.4±3.7	21.4±2.5	21.4±3.8	0.9137
10	Parity. n (%)				0.0080
11	Nulliparous	11 (7.9)	3 (1.4)	14 (3.9)	
12	1–4	66 (47.1)	108 (49.5)	174 (48.6)	
13	>4	63 (45.0)	107 (49.1)	170 (47.5)	
14	Transformation zone. n (%)				<0.0001
15	TZ1	76 (57.1)	150 (73.5)	226 (67.1)	
16	TZ2	26 (19.6)	45 (22.1)	71 (21.1)	
17	TZ3	31 (23.3)	9 (4.4)	40 (11.8)	
18	HPV testing results. n (%)				
19	HPV-16	11 (7.9)	23 (10.6)	34 (9.5)	0.3890
20	HPV-18/45	22 (15.8)	31 (14.2)	53 (14.9)	0.6770
21	Other HPV	114 (82.0)	186 (85.3)	300 (84.0)	0.4060
22	Cytology. n (%) (Total= 343)				0.0990
23	Normal	108 (82.5)	161 (75.9)	269 (78.4)	
24	ASC-US	7 (5.3)	10 (4.7)	17 (5.0)	
25	LSIL	10 (7.6)	15 (7.1)	25 (7.3)	
26	HSIL	4 (3.1)	21 (9.9)	25 (7.3)	
27	ASC-H	0	4 (1.9)	4 (1.2)	
28	Cancer	2 (1.5)	1 (0.5)	3 (0.8)	
29	Histology. n (%) (Total=340)				0.0040
30	Normal	108 (80.0)	129 (62.9)	237 (69.7)	
31	CIN1	18 (13.3)	45 (21.9)	63 (18.5)	
32	CIN2	1 (0.7)	12 (5.9)	13 (3.8)	
33	CIN3	6 (4.4)	18 (8.8)	24 (7.1)	
34	Invasive cancer	2 (1.5)	1 (0.5)	3 (0.9)	

239 **Abbreviations:** SD = standard deviation; IQR = interquartile range; CIN1 = cervical intraepithelial
 240 neoplasia grade 1; CIN2 = cervical intraepithelial neoplasia grade 2; CIN3 = cervical intraepithelial
 241 neoplasia grade 3; HIV = human immunodeficiency virus; HPV = human papillomavirus.

242 *Data from the 358 participants may be missing for some variables.

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244 Thirty-four (9.5%) samples were positive for HPV-16, 53 (14.9%) for HPV-18/45 and 300
 245 (84.0%) for other HPV types. Overall, 218 (60.9%) participants were classified as ABCD
 246 criteria-positive. All patients positive for ABCD were treated with thermal ablation with the
 247 exception of one patient who underwent LLETZ and one patient suspicious of cancer who
 248 was biopsied and referred for multimodal therapy. Thermal ablation was provided on the
 249 same day as HPV screening in 86.7% of cases. Reasons for delaying treatment included

250 referral for further evaluation, technical issues, bleeding at the time of screening, or choice of

251 the patients themselves. No serious adverse event occurred as a result of the screening

252 procedure.

253 Among all 358 women with HPV-positive results, 343 samples with valid cytological results

254 and 340 samples with valid histological results were obtained. Of the 343 valid cytological

255 results, 21.6% had abnormal cytology (ASC-US+). Four patients had ASC-H, 25 had HSIL,

256 and three had cytology suggesting cancer. All three cancers identified by cytology were

257 confirmed by histology. Of the 340 valid histological results, 63 (18.5%) CIN1 were identified,

258 13 (3.8%) CIN2, 24 (7.1%) CIN3, and 3 (0.9%) invasive cancers. The prevalence of CIN2+

259 and CIN3+ was 11.8% and 7.9%, respectively. Details for the disease prevalences are also

260 shown in **Table 1**.

261 **Table 2** shows demographic and pathological characteristics associated with a correct

262 prediction of the ABCD criteria.

Table 2: Demographic and pathological characteristics associated with a correct prediction of the ABCD criteria (N=340)*

Variable	Total	Unadjusted OR (95% CI)	P- value	Adjusted OR (95% CI)**	P-value
Age (years) n (%)					
30–40	186 (54.7)	1.00 (Reference)		1.00 (Reference)	
41–50	154 (45.3)	1.39 (0.90–2.14)	0.133	1.51 (0.87–2.60)	0.140
Marital status. n (%)					
Single	34 (10.0)	1.00 (Reference)		1.00 (Reference)	
With partner	265 (77.9)	1.15 (0.56–2.36)	0.706	1.07 (0.43–2.63)	0.887
Divorced/widowed	41 (12.1)	0.81 (0.32–2.04)	0.656	0.63 (0.19–2.04)	0.442
Education. n (%)					
Unschooler/primary education	101 (29.7)	1.00 (Reference)		1.00 (Reference)	
Secondary/tertiary education	239 (70.3)	1.04 (0.65–1.65)	0.879	0.92 (0.47–1.82)	0.818
Employment status. n (%)					

3	Employed	104 (30.6)	1.00 (Reference)		1.00 (Reference)	
4	Independent	93 (27.3)	0.90 (0.51–1.57)	0.706	0.73 (0.38–1.43)	0.363
5	Housewife	58 (17.1)	0.81 (0.43–1.55)	0.528	0.74 (0.34–1.63)	0.461
6	Unemployed	19 (5.6)	0.72 (0.27–1.95)	0.528	0.89 (0.27–2.91)	0.852
7	Farmer	66 (19.4)	0.69 (0.37–1.29)	0.248	0.41 (0.18–0.95)	0.037
8	Age at first intercourse (years). n (%)					
9	≤17	154 (45.6)	1.00 (Reference)		1.00 (Reference)	
10	≥18	184 (54.4)	0.70 (0.46–1.08)	0.106	0.75 (0.43–1.31)	0.315
11	Number of sexual partners†. median	3 (2–5)	1.08 (1.01–1.16)	0.031	1.06 (0.97–1.17)	0.176
12	1–2. n (%)	98 (28.8)	1.00 (Reference)		1.00 (Reference)	
13	3–5. n (%)	177 (52.1)	1.39 (0.84–2.30)	0.195	1.22 (0.67–2.22)	0.506
14	>5. n (%)	65 (19.1)	1.96 (1.04–3.70)	0.038	1.53 (0.70–3.38)	0.284
15	Contraception. n (%)					
16	No	225 (66.6)	1.00 (Reference)		1.00 (Reference)	
17	Yes	113 (33.4)	0.84 (0.54–1.33)	0.466	0.92 (0.54–1.85)	0.769
18	HIV status. n (%)					
19	Negative	309 (92.8)	1.00 (Reference)		1.00 (Reference)	
20	Positive	24 (7.2)	1.21 (0.53–2.77)	0.657	0.95 (0.36–2.53)	0.589
21	Age at first delivery (years). n (%)					
22	≤20	157 (47.7)	1.00 (Reference)		1.00 (Reference)	
23	≥21	172 (52.3)	0.70 (0.45–1.08)	0.102	0.60 (0.34–1.07)	0.085
24	Parity. n (%)					
25	Nulliparous	14 (4.1)	1.00 (Reference)		1.00 (Reference)	
26	1–4	165 (48.5)	0.21 (0.06–0.79)	0.020	0.26 (0.02–2.91)	0.274
27	>4	161 (47.4)	0.23 (0.06–0.86)	0.029	0.28 (0.02–3.22)	0.307
28	Transformation zone. n (%)					
29	TZ1	210 (65.8)	1.00 (Reference)		1.00 (Reference)	
30	TZ2	70 (22.0)	1.17 (0.68–2.02)	0.575	1.24 (0.67–2.26)	0.492
31	TZ3	39 (12.2)	6.72 (2.84–15.93)	<0.0001	6.47 (2.59–16.21)	<0.0001
32	HPV testina results. n (%)					
33	Other HPV (without co-infection)	264 (77.9)	1.00 (Reference)		1.00 (Reference)	
34	HPV-16/18/45	75 (22.1)	1.19 (0.70–1.98)	0.514	1.18 (0.64–2.17)	0.605
35	Cytology. n (%)					
36	High-grade+***	29 (8.9)	2.47 (1.11–5.49)	0.027	3.37 (1.35–8.44)	0.009

263 **Abbreviations:** 95% CI = 95% confidence interval; CIN2+ = cervical intraepithelial neoplasia grade 2 or

264 worse.

265 *Data from the 340 participants may be missing for some variables.

266 †ORs for continuous variables indicate the change in odds for an increase of one standard deviation.

267 **Adjusted for age, marital status, age at first intercourse, number of lifetime sexual partners, age at
268 first delivery, parity, HIV status, and type of transformation zone.

269 ***High-grade lesions include ASC-H, HSIL, AIS, and cancer.

270 Bold values are statistically significant.

272 ABCD criteria were more likely to be correct in the presence of TZ type 3 (aOR = 6.47; 95%

273 CI, 2.59–16.21; P<0.001) and high-grade lesions on cytology (aOR = 3.37; 95% CI, 1.35–

274 8.44; P<0.009). Overall, a correct prediction of the ABCD criteria was not impacted by the

275 multiple sociodemographic characteristics of the population in the multivariate analysis, apart

276 from women working as farmers who were less likely to have a correct prediction of ABCD
 277 criteria than employed women (OR 0.41, 95% CI 0.18-0.95).
 278 Performance of ABCD and cytology for detection of high-grade cervical lesions (CIN2+ and
 279 CIN3+) is shown in **Table 3**.
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Table 3: Diagnostic accuracy of ABCD criteria, cytology, and HPV for detection of CIN2+ and CIN3+

Variable	CIN2+ (N=40, 11.8%)				HPV+ (N=358)
	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV % (95% CI)	NPV % (95% CI)	Positivity rate % (95% CI)
ABCD criteria-positive	77.5 (61.3–88.2)	42.0 (36.5–47.7)	15.1 (10.8–20.8)	93.3 (87.6–96.5)	60.9 (55.6–65.9)
Cytology ASC-US+	80.0 (64.0–89.9)	87.5 (83.1–90.7)	47.1 (35.3–59.2)	96.9 (93.9–98.5)	21.6 (17.4–26.4)
Cytology LSIL+	70.0 (53.5–82.6)	91.3 (87.4–94.1)	52.8 (39.1–66.2)	95.6 (92.4–97.5)	16.6 (12.9–21.1)
Cytology HSIL+	62.5 (46.1–76.5)	98.6 (96.3–99.5)	86.2 (67.0–95.1)	95.0 (91.8–97.0)	9.3 (6.6–13.0)
HPV-16/18/45+	37.5 (23.5–53.9)	79.9 (74.9–84.1)	20.9 (12.3–30.8)	90.5 (86.3–93.5)	23.3 (19.1–28.1)
Variable	CIN3+ (N=27, 7.9%)				
	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV % (95% CI)	NPV % (95% CI)	
ABCD criteria-positive	70.4 (49.6–85.2)	40.6 (35.2–46.1)	9.3 (6.0–14.1)	94.1 (88.5–97.0)	
Cytology ASC-US+	88.9 (68.9–96.7)	85.4 (80.9–89.0)	35.3 (24.7–47.6)	98.8 (96.4–99.7)	
Cytology LSIL+	81.5 (60.9–92.5)	89.7 (85.7–92.7)	41.5 (28.7–55.5)	98.2 (95.7–99.2)	
Cytology HSIL+	74.1 (53.2–87.8)	97.0 (94.3–98.4)	68.9 (49.0–83.7)	97.7 (95.2–98.9)	
HPV-16/18/45+	44.4 (26.2–64.3)	79.8 (75.0–83.9)	16.0 (9.2–26.4)	94.3 (90.8–96.6)	

281 **Abbreviations:** CIN2+ = cervical intraepithelial neoplasia grade 2 or worse; CIN3+ = cervical
 282 intraepithelial neoplasia grade 3 or worse; Cytology ASC-US+ = ASC-US, LSIL, ASC-H, HSIL, AIS, and
 283 cancer; Cytology LSIL+ = LSIL, ASC-H, HSIL, AIS, and cancer; Cytology HSIL+ = ASC-H, HSIL, AIS,
 284 and cancer; HPV = human papilloma virus; HPV-16/18/45+ = HPV DNA test positive for HPV-16, HPV-
 285 18, and HPV-45; 95% CI = 95% confidence interval; PPV = positive predictive value; NPV = negative
 286 predictive value.

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3 288 ABCD criteria for CIN2+ detection showed a sensitivity of 77.5% (95% CI, 61.3%–88.2%),
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6 289 specificity of 42.0% (95% CI, 36.5%–47.7%), PPV of 15.1% (95% CI, 10.8%–20.8%), and
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9 290 NPV of 93.3% (95% CI, 87.6%–96.5%). Cytology-classified HSIL+ for CIN2+ detection
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12 291 showed lower sensitivity of 62.5% (95% CI, 46.1%–76.5%), but higher specificity of 98.6%
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15 292 (95% CI, 96.3%–99.5%), PPV of 86.2% (95% CI, 67.0%–95.1%), and NPV of 95.0% (95%
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18 293 CI, 91.8%–97.0%). Meanwhile, cytology-classified ASC-US+ showed improved sensitivity of
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21 294 80.0% (95% CI, 64.0%–89.9%) and specificity of 87.5% (95% CI, 83.1%–90.7%). Screening
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24 295 by HPV 16/18/45 genotyping alone had a much lower sensitivity of 37.5% (95% CI, 23.5–
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27 296 53.9) and a specificity of 79.9% (95% CI 74.9–84.1). When combining HPV 16/18/45 partial
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30 297 genotyping with VIA triage of other HPV types, sensitivity rose to 85.0% (95% CI, 70.2%–
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33 298 94.3%) and NPV to 94.4% (95% CI, 88.2%–97.9%), while specificity decreased to 33.7%
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36 299 (95% CI 28.3%–39.3%) and PPV to 14.6% (95% CI 10.3%–19.8%). ABCD criteria for CIN3+
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39 300 lesion identification showed a sensitivity of 70.4% (95% CI, 49.6%–85.2%), specificity of
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42 301 40.6% (95% CI, 35.2%–46.1%), PPV of 9.3% (95% CI, 6.0%–14.1%), and NPV of 94.1%
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45 302 (95% CI, 88.5%–97.0%).

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54 304 **DISCUSSION**
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3 305 The ABCD criteria were established to improve the performance of visual-based approaches
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6 306 for triage of HPV-positive women. Previous studies conducted in LMICs indicated that triage
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9 307 using traditional VIA criteria is not satisfactory for the detection of CIN2+ lesions, as the gain
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12 308 in specificity when adding VIA to HPV testing is obtained at the expense of an important loss
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16 309 in sensitivity.(6,7,10) The challenge for VIA screeners lies in interpreting the wide variability
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19 310 of cervical presentations, in populations where obstetric trauma to the cervix and history of
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22 311 infection are frequent, and in which CIN2+ may be difficult to identify.
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26 312 The most important finding of this study is that the ABCD criteria appeared to be highly
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29 313 sensitive for detection of high-grade lesions in an HPV-positive population. We used both (i)
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32 314 a magnification technique with smartphone digital imaging that allows more detailed
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35 315 examination compared with naked eye alone and (ii) a lower VIA/D-VIA threshold positivity to
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38 316 optimize identification of lesions. The ABCD criteria provided improved VIA sensitivity for
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41 317 triage of HPV-positive women compared to most previous studies using a comparable
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44 318 methodology (histology as reference standard) (6,10,15,26,27) This can be explained by the
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47 319 fact that the IARC criteria require dense VIA changes before being considered positive, thus
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51 320 limiting their sensitivity, while a reduced positivity threshold can contribute to improved
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54 321 sensitivity for CIN2+ detection.(13,24)
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3 322 The low specificity and PPV, leading to higher overtreatment rates, arise because we
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6 323 considered any whitening to be positive, meaning many benign conditions (metaplasia,
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9 324 inflammation or other benign cervical changes) could produce false-positive results for the
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12 325 ABCD criteria. Criterion C (VILI/D-VILI), though dependent on criteria A and D, may
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15 326 contribute to the high false positive rate by categorizing benign conditions as ABCD-positive
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18 327 through the identification of iodine-negative areas compatible with thin, transparent or patchy
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21 328 acetowhite lesions. Overall, 54.4% of normal histology results and 71.4% of CIN1 were
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24 329 considered ABCD criteria positive and consequently underwent unnecessary treatment.
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27 330 Thus, 85% (174 of 205) of women who screened positive were treated without CIN2+.
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30 331 However, when considering all women screened for CC, including HPV-negative, 174 were
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33 332 treated unnecessarily out of 1964 screened by Self-HPV, corresponding to an overall 8.9%
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36 333 overtreatment rate in the total population screened. Despite the low specificity, our 3T-
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39 334 Approach in a single visit may be acceptable in an LMIC context because it reduces cost and
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42 335 loss to follow-up, which are recognized barriers to effective cervical cancer screening.(11,28)
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45 336 Indeed, studies in Uganda(29) and South Africa(28) have shown loss to follow-up rates
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48 337 between 21% and 25% after the first visit, up to 50% at 24 months. Furthermore, treatment
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51 338 by thermal ablation is associated with very low risks of side effects and morbidity.(30)
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54 339 Therefore, treatment of a significant number of false-positive cases in this context may be
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3 340 considered an acceptable strategy for effective control of CC in an LMIC setting and may
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6 341 contribute to reaching the target of the WHO's elimination initiative.(3,5) However, the use
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9 342 and integration of the ABCD criteria in the cervical cancer screening process warrants
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12 343 multidisciplinary discussion with involved stakeholders, taking into account the local context
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16 344 and resources, as well as regional HPV prevalence, prevalence of CIN2+ in HPV-positive
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19 345 participants, level of risk including HIV prevalence, availability of treatment modalities on site,
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22 346 and the possibility to offer further investigation when required. According to the context, the
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25 347 decision to refer has consequences for the patients and the health care system, requiring
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28 348 additional time and resources, and increasing the risk of loss to follow-up. Recognizing the
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31 349 limitations of the ABCD criteria with regard to PPV and overtreatment rates, other triaging
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34 350 strategies merit further investigation. The use of extended HPV genotyping (HPV 16, 18, 45,
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37 351 31, 33, 35, 52 and/or 58) for the triaging of HPV-positive women is one alternative that
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41 352 should also be explored.
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44 353 Compared to screening by HPV-16/18/45 genotyping without triage, the sensitivity of the
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47 354 ABCD criteria was much higher, at the cost of a lower specificity. PPV was also slightly lower
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50 355 with triage by ABCD criteria (15.1%) than with HPV partial genotyping (20.9%). One of the
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53 356 screening strategies currently recommended by the WHO is combined HPV 16/18/45
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56 357 genotyping (treated immediately) and VIA triage of non-16/18/45 HPV genotypes.(3) In our
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3 358 study population, this combined strategy resulted in an increased sensitivity of 85.0%, but
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6 359 even further decreased the specificity and PPV, which would therefore even further increase
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10 360 overtreatment rates. On the contrary, triage by cytology (using a threshold of ASC-US for a
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13 361 positive triage) improved both sensitivity (80.0%, 95% CI 64.0-89.9) and specificity (87.5,
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16 362 95% CI 83.1-90.7) compared to the ABCD criteria. However, although this strategy may be
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19 363 adapted to higher-middle and high-income countries, the lack of trained cytotechnicians and
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22 364 well-equipped laboratories in low-income countries, the higher cost, and the inability to
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25 365 provide same-day treatment to patients positively triaged with cytology, render this triaging
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29 366 strategy unsuitable for low-resource settings. In comparison, the ABCD criteria require only
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32 367 basic equipment at a low cost, and allow initiation of therapy without delay. In our series,
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35 368 86.7% of participants underwent the 3T-Approach in one day. ABCD criteria comprise a
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38 369 simple tool with binary results (positive or negative) that can alert healthcare professionals to
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41 370 the clinical features of CIN2+, and the use of “relaxed IARC criteria” may greatly decrease
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44 371 the risk of missing CIN2+ lesions. While digital imaging by smartphone may facilitate ABCD
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47 372 interpretation and enhance diagnostic performance, it may result in slightly prolonged
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50 373 examination time and may not be accessible in all settings.
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54 374 Having a TZ3 was associated with a better prediction of ABCD criteria compared to TZ1
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57 375 (**Table 2**), which is unexpected as VIA is generally considered inadequate for the evaluation
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3 376 of TZ3 cervixes. This may be due to the use of B, C and D criteria in addition to
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6 377 acetowhiteness, enabling the detection of lesions extending to the ectocervix and bleeding in
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9 378 the absence of visible lesions. However, as A, B, C and D criteria were not assessed
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12 379 separately within this study sample, it is currently not possible to determine which criterion
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15 380 contributes most to a correct interpretation of VIA. A study is currently underway to assess
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18 381 each criterion individually for the detection of CIN2+. The lack of association between
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21 382 multiple socio-demographic variables and a correct prediction of the ACBD criteria (**Table 2**)
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24 383 supports the generalizability of these criteria to the overall population of women aged 30 to
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27 384 49 years in West Cameroon. However, the limited sample size and the fact that the study
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30 385 was conducted in a single center, do not allow to extend these results to the overall female
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33 386 population, especially considering the differences in HPV prevalence in other regions.
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36 387 A further limitation is that the study was conducted in a single centre in a district hospital in
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39 388 West Cameroon with five health care providers administering all screening and treatment
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42 389 procedures.

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45 390 It should be noted that two out of three cervical cancers were assessed as ABCD-negative
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48 391 on site by the frontline health care providers and did not receive immediate treatment. After
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51 392 reviewing the digital images of these two cases off-site, it was determined that criterion B
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3 393 (bleeding) was present in both cases, which should have led to a positive ABCD result
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6 394 **(Supplement, Figure S1).**
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10 395 Strengths of our study included the application of ABCD criteria upon VIA examination in
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13 396 real-life conditions with immediate treatment when necessary, therefore supporting the
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16 397 feasibility of a “screen-and-treat” strategy. Furthermore, because all HPV-positive women
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19 398 underwent biopsy and cervical brushing regardless of the ABCD criteria results, there was no
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22 399 risk of verification bias in the calculations of sensitivity and specificity for all diagnostic
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25 400 strategies assessed.
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29 401 In conclusion, ABCD criteria can improve CIN2+ diagnosis in HPV-positive women and may
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32 402 provide a unique opportunity to improve cervical cancer screening programs in LMICs using
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35 403 a one-visit approach. This strategy may be particularly beneficial because the criteria are
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38 404 easily remembered and to use for healthcare providers.
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51 408 nurses who examined the women. We would also like to thank Alison Sherwin, PhD, from
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54 409 Edanz Group (<https://en-author-services.edanzgroup.com/ac>) for editing a draft of this
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6 412 **Contributors**
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10 413 PP, BK, and PV designed the study protocol, implemented the study, oversaw the data
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13 414 collection, analysed the data, and drafted and revised the paper. AW and RC conducted data
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16 415 analysis, interpreted the data, and revised the draft paper. BK, ET, and JF trained the study
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18
19 416 staff, assumed the quality control (supervision and mentorship), supported the data
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21
22 417 collection, interpreted the data, and revised the draft paper. JCT and ES analysed the
23
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25 418 pathological specimens, interpreted the data, and revised the draft paper.
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32 420 **Competing Interests**

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35 421 All authors declare that they have no competing interests.
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49
50
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54 427 and conduct of the study; collection, management, analysis, and interpretation of the data;
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3 428 preparation, review, or approval of the manuscript; and decision to submit the manuscript for
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6 429 publication.
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11 12 13 431 **Data access, analysis and responsibility**

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16 432 The principal investigator had full access to all the data in the study and takes responsibility
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19 433 for the integrity of the data and the accuracy of the data analysis. Data used in the study is
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22 434 available upon request to the first author.
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27 28 29 436 **Data sharing statement**

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32 437 Data are available upon reasonable request to the principal investigator of the study.
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37 38 39 439 **References**

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3 537 **Figure 1: ABCD criteria for VIA interpretation in HPV-positive women**

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6 538 **Criterion A** – Acetowhite area touching the transformation zone (absent on the native view
7 539 and apparent after acetic acid application) is considered positive.

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10 540 **Criterion B** – Bleeding without touching or after lightly touching (with a swab or speculum) the
11 541 cervix is considered positive.

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14 542 **Criterion C (optional)** – Colouring with VILI contributes to confirmation or identification of a
15 543 faint acetowhite lesion.

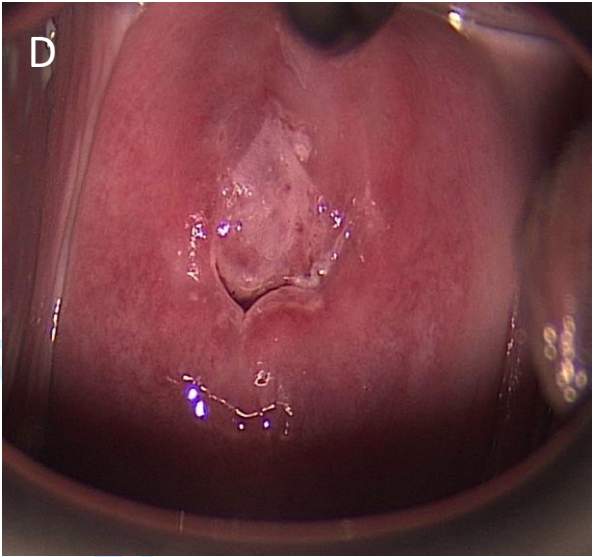
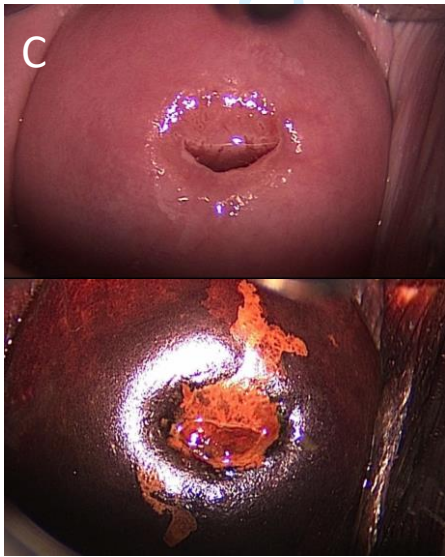
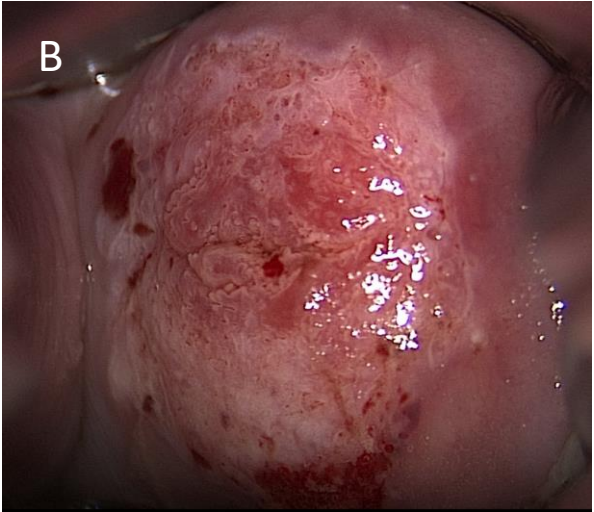
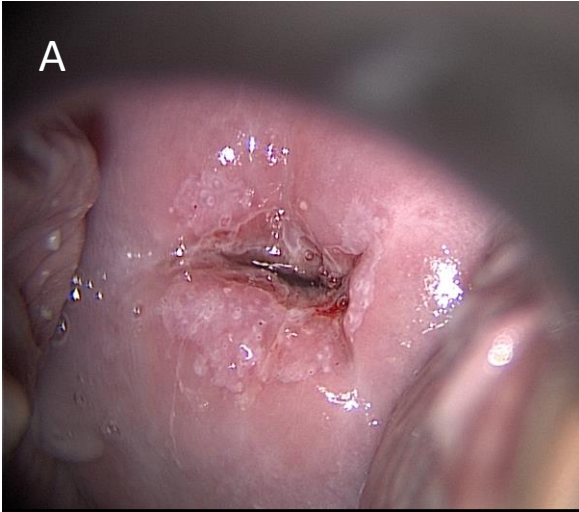
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18 544 **Criterion D** – Diameter of >5 mm (about the size of a pencil eraser) in an acetowhite area is
19 545 considered positive.

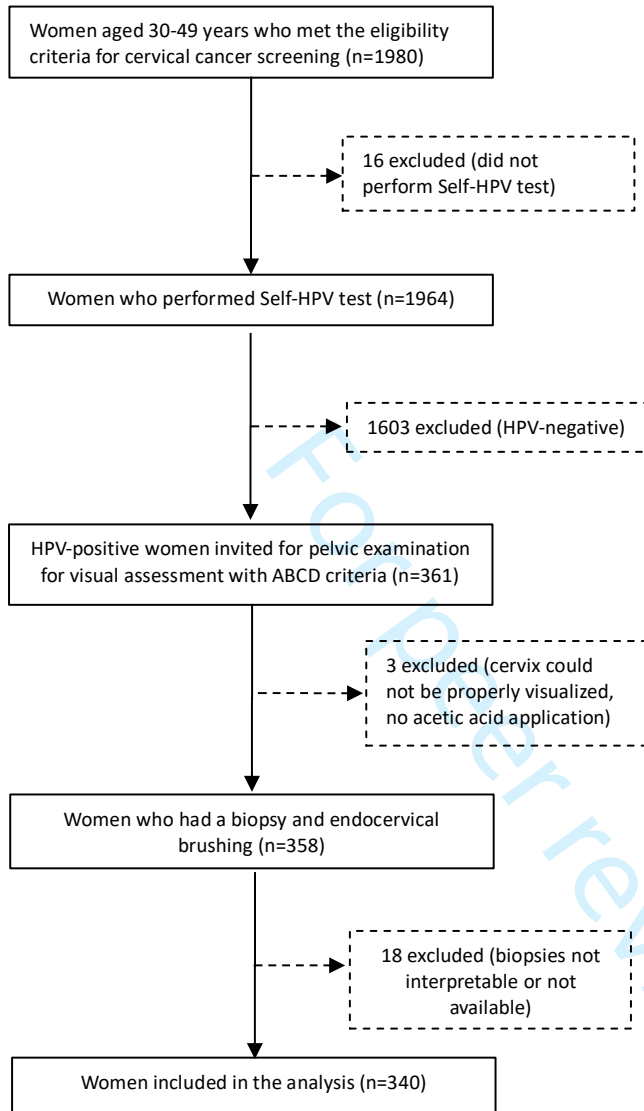
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23 547 **Figure 2: Flowchart of participants for the 3T-Approach in Cameroon**

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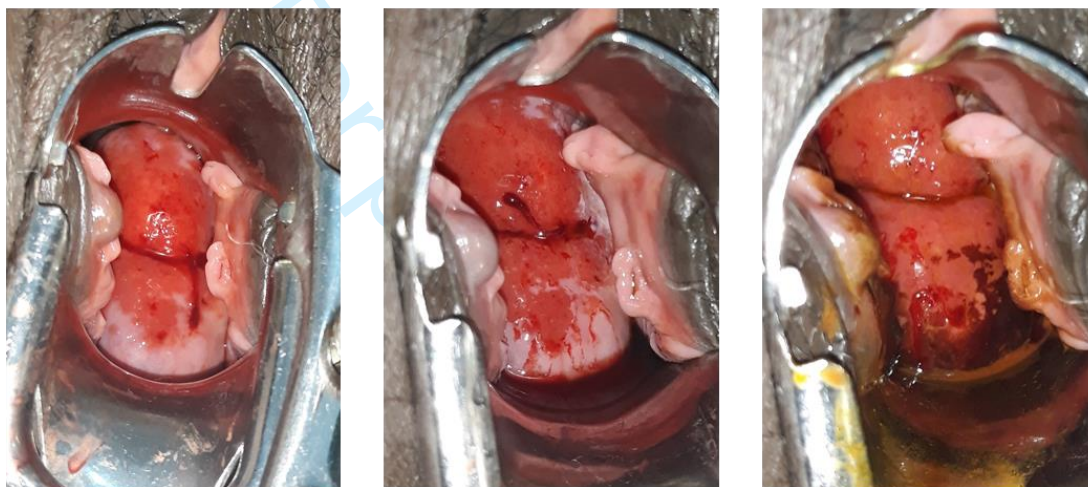
Supplementary Material

ABCD Criteria to Improve Visual Inspection with Acetic Acid (VIA) Triage in HPV-positive Women: a prospective analysis

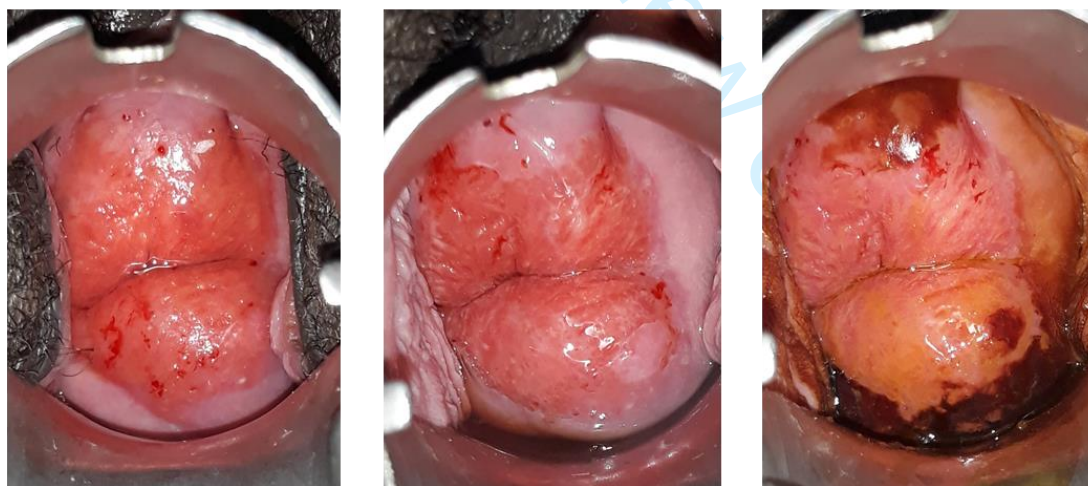
Patrick Petignat, Bruno Kenfack, Ania Wisniak, Essia Saiji, Jean-Christophe Tille, Jovanny Tsuala Fouogue, Rosa Catarino, Evelyn Foguem Tincho and Pierre Vassilakos

Figure S1. Cases of cervical cancer not identified by ABCD criteria on site

A



B



A. Poorly differentiated carcinoma, positive for criterion B (bleeding); B. Invasive adenocarcinoma, positive for criterion B. From left to right, smartphone photos of (i) the native cervix, (ii) after application of acetic acid and (iii) after application of Lugol's iodine.

Section & Topic	No	Item	Reported on page #
TITLE OR ABSTRACT			
	1	Identification as a study of diagnostic accuracy using at least one measure of accuracy (such as sensitivity, specificity, predictive values, or AUC)	2
ABSTRACT			
	2	Structured summary of study design, methods, results, and conclusions (for specific guidance, see STARD for Abstracts)	2
INTRODUCTION			
	3	Scientific and clinical background, including the intended use and clinical role of the index test	4-5
	4	Study objectives and hypotheses	5
METHODS			
<i>Study design</i>	5	Whether data collection was planned before the index test and reference standard were performed (prospective study) or after (retrospective study)	5
<i>Participants</i>	6	Eligibility criteria	5
	7	On what basis potentially eligible participants were identified (such as symptoms, results from previous tests, inclusion in registry)	5
	8	Where and when potentially eligible participants were identified (setting, location and dates)	5
	9	Whether participants formed a consecutive, random or convenience series	5
<i>Test methods</i>	10a	Index test, in sufficient detail to allow replication	6 + figure 1
	10b	Reference standard, in sufficient detail to allow replication	7
	11	Rationale for choosing the reference standard (if alternatives exist)	na
	12a	Definition of and rationale for test positivity cut-offs or result categories of the index test, distinguishing pre-specified from exploratory	6
	12b	Definition of and rationale for test positivity cut-offs or result categories of the reference standard, distinguishing pre-specified from exploratory	7
	13a	Whether clinical information and reference standard results were available to the performers/readers of the index test	6
	13b	Whether clinical information and index test results were available to the assessors of the reference standard	7
<i>Analysis</i>	14	Methods for estimating or comparing measures of diagnostic accuracy	8
	15	How indeterminate index test or reference standard results were handled	8
	16	How missing data on the index test and reference standard were handled	8
	17	Any analyses of variability in diagnostic accuracy, distinguishing pre-specified from exploratory	na
	18	Intended sample size and how it was determined	8
RESULTS			
<i>Participants</i>	19	Flow of participants, using a diagram	Figure 2
	20	Baseline demographic and clinical characteristics of participants	9
	21a	Distribution of severity of disease in those with the target condition	10-11
	21b	Distribution of alternative diagnoses in those without the target condition	na
	22	Time interval and any clinical interventions between index test and reference standard	na
<i>Test results</i>	23	Cross tabulation of the index test results (or their distribution) by the results of the reference standard	10 (table 1)
	24	Estimates of diagnostic accuracy and their precision (such as 95% confidence intervals)	12 (table 3)
	25	Any adverse events from performing the index test or the reference standard	10
DISCUSSION			
	26	Study limitations, including sources of potential bias, statistical uncertainty, and generalisability	15
	27	Implications for practice, including the intended use and clinical role of the index test	14-15
OTHER INFORMATION			
	28	Registration number and name of registry	9
	29	Where the full study protocol can be accessed	9
	30	Sources of funding and other support; role of funders	16

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STARD 2015

AIM

STARD stands for “Standards for Reporting Diagnostic accuracy studies”. This list of items was developed to contribute to the completeness and transparency of reporting of diagnostic accuracy studies. Authors can use the list to write informative study reports. Editors and peer-reviewers can use it to evaluate whether the information has been included in manuscripts submitted for publication.

EXPLANATION

A **diagnostic accuracy study** evaluates the ability of one or more medical tests to correctly classify study participants as having a **target condition**. This can be a disease, a disease stage, response or benefit from therapy, or an event or condition in the future. A medical test can be an imaging procedure, a laboratory test, elements from history and physical examination, a combination of these, or any other method for collecting information about the current health status of a patient.

The test whose accuracy is evaluated is called **index test**. A study can evaluate the accuracy of one or more index tests. Evaluating the ability of a medical test to correctly classify patients is typically done by comparing the distribution of the index test results with those of the **reference standard**. The reference standard is the best available method for establishing the presence or absence of the target condition. An accuracy study can rely on one or more reference standards.

If test results are categorized as either positive or negative, the cross tabulation of the index test results against those of the reference standard can be used to estimate the **sensitivity** of the index test (the proportion of participants *with* the target condition who have a positive index test), and its **specificity** (the proportion *without* the target condition who have a negative index test). From this cross tabulation (sometimes referred to as the contingency or “2x2” table), several other accuracy statistics can be estimated, such as the positive and negative **predictive values** of the test. Confidence intervals around estimates of accuracy can then be calculated to quantify the statistical **precision** of the measurements.

If the index test results can take more than two values, categorization of test results as positive or negative requires a **test positivity cut-off**. When multiple such cut-offs can be defined, authors can report a receiver operating characteristic (ROC) curve which graphically represents the combination of sensitivity and specificity for each possible test positivity cut-off. The **area under the ROC curve** informs in a single numerical value about the overall diagnostic accuracy of the index test.

The **intended use** of a medical test can be diagnosis, screening, staging, monitoring, surveillance, prediction or prognosis. The **clinical role** of a test explains its position relative to existing tests in the clinical pathway. A replacement test, for example, replaces an existing test. A triage test is used before an existing test; an add-on test is used after an existing test.

Besides diagnostic accuracy, several other outcomes and statistics may be relevant in the evaluation of medical tests. Medical tests can also be used to classify patients for purposes other than diagnosis, such as staging or prognosis. The STARD list was not explicitly developed for these other outcomes, statistics, and study types, although most STARD items would still apply.

DEVELOPMENT

This STARD list was released in 2015. The 30 items were identified by an international expert group of methodologists, researchers, and editors. The guiding principle in the development of STARD was to select items that, when reported, would help readers to judge the potential for bias in the study, to appraise the applicability of the study findings and the validity of conclusions and recommendations. The list represents an update of the first version, which was published in 2003.

More information can be found on <http://www.equator-network.org/reporting-guidelines/stard>.

