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LETTER TO THE JOURNAL

Evaluation of cervical cancer screening strategies in women living with HIV in Thailand

Women living with human immunodeficiency viruses (WLHIV) are six times more likely to develop cervical cancer than the general population; they represent less than 1% of the world's population, but account for more than 5% of cervical cancers [1]. WLHIV also have higher prevalence of human papilloma virus (HPV) infection with high-risk oncogenic genotypes (HR-HPV) than the general population [2]. In Asia, an estimated 35% (95% confidence interval [95% CI]: 30%-39%) of WLHIV carry HR-HPV infection [3]. Before 2021, Thailand's national cervical cancer screening program recommended cervical cytology. Since then, the Thai Ministry of Public Health, in line with the World Health Organization (WHO), has approved screening of all women aged 30-60 years (including those living with HIV) with standalone (primary) HPV test every 5 years [4].

In this context, to determine the optimal cervical cancer screening strategy for WLHIV, we used data from the PapilloV cohort (NCT01792973) in which WLHIV had yearly screening for cervical cancer using cytology, HPV-DNA testing with full genotype subtyping (PapilloCheck®, Greiner Bio-One, Germany), and histology if necessary. Women in the cohort were all receiving antiretroviral therapy (ART), their HIV infection was well-controlled and they were highly compliant with the screening study protocol: 90% with at least 2 visits and 81% with at least 3 visits.

List of abbreviations: WHO, World Health Organization; PCR, polymerase chain reaction; HPV, human papillomavirus; HR-HPV, high risk-HPV; HIV, human immunodeficiency virus; ART, antiretroviral therapy; CIN, cervical intraepithelial neoplasia; NILM, negative for intraepithelial lesion malignancy; ASC-US, atypical squamous cells of undetermined significance; ASC-US+, atypical squamous cells of undetermined significance or higher-grade lesions; AGC, Atypical glandular cell; LSIL, Low-grade squamous intraepithelial lesion; ASC-H, Atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesion; HSIL, High-grade squamous intraepithelial lesion; AIS, Adenocarcinoma in situ; PPV, positive predictive value; NPV, negative predictive value; WLHIV, Women living with human immunodeficiency virus.

Patumrat Sripan and Myrtille Prouté contributed equally to this work and are considered as co-first authors.

We designed 17 screening strategies (Supplementary Figure S1), including cytology alone, primary HPV testing alone, reflex HPV testing (HPV test after abnormal cytology), reflex cytology (cytology after positive HPV testing), and co-testing (simultaneous cytology and HPV testing). For HPV testing, we considered four genotype combinations, among those prevalent in Asia and associated with cancer: "HR-HPV 16/18", "HR-HPV 16/18/31/33/52", "any HR-HPV", and "any HR-HPV or potentially HR (pHR)-HPV" [3, 5–7]. Methods are detailed in Supplementary Materials and Methods.

Among 179 WLHIV who underwent a total of 251 check-up visits with three interpretable screening tests (cytology, HPV test, and biopsy) over the 3-year follow-up, we diagnosed 40 (15.9%, 95% CI: 11.9%-20.9%) cervical intraepithelial neoplasia grade 2 or higher (CIN2+) and 24 (9.6%, 95% CI: 6.5%-13.8%) CIN3+ at biopsy. The population selection and its characteristics including HIV infection history, cytology, histology and HPV testing results are detailed in Supplementary Tables S1-S2 and Supplementary Figure S2.

We estimated the diagnostic performance of each screening strategy and its probability of not detecting high-grade cervical lesions. Depending on the strategy, 4 to 40 CIN2+ lesions could be detected with a sensitivity ranging from 16% to 100%, specificity from 3% to 93%, positive predictive value from 16% to 53%, and negative predictive value from 77% to 100% (Supplementary Table S3). The CIN2+ detection rate was greater than 75% for five strategies: (1) primary HPV test for any HR-HPV (78%); (2) primary HPV test for any HR-HPV or pHR-HPV (82%); (3) co-testing with HPV test for HPV16/18/31/33/52 (88%); (4) co-testing with HPV test for any HR-HPV (98%); and (5) co-testing with HPV test for any HR-HPV or pHR-HPV (100%) (Figure 1A).

The probability of missing CIN2+ lesions ranged from 8% to 15% for standalone strategies, from 10% to 23% for reflex strategies, and from 0% to 9% for co-testing strategies (Figure 1B). Reflex strategies led to the lowest number of colposcopies to detect one CIN2+ (2 to 3) compared with primary HPV testing (3 to 6) or co-testing strategies (4 to 6) (Supplementary Table S3). It also led to the

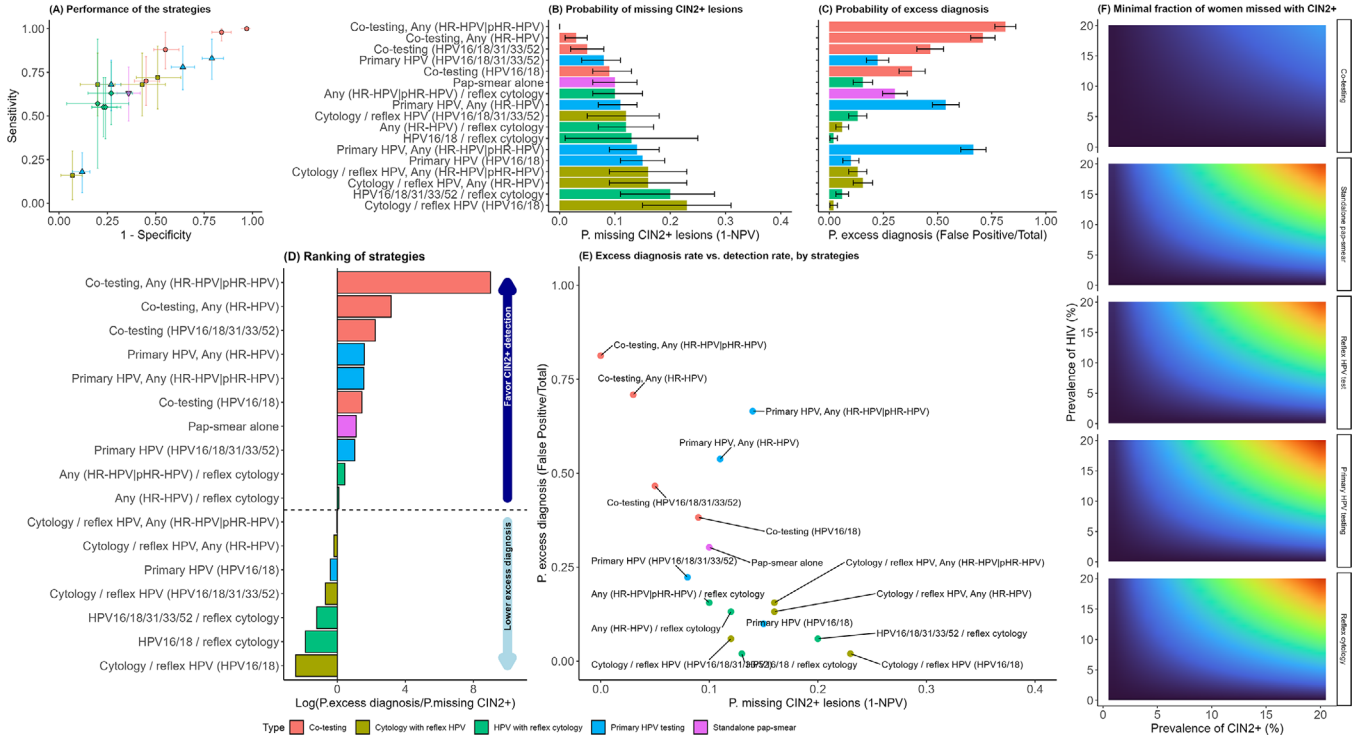

FIGURE 1 Strategies associated with a lower probability of missing women with CIN2+ lesions. (A) Performance of the 17 screening strategies in terms of sensitivity and specificity and their associated 95% CI. Red circles represent strategies based on co-testing; dark green squares represent strategies based on cytology with reflex HPV testing; green diamonds represent strategies based on HPV testing with reflex cytology; blue triangles represent strategies based on primary HPV testing; the purple triangle represents the strategy based on pap-smear alone. Vertical lines represent the 95% CI for sensitivity and horizontal lines the specificity. (B) Probability of missing CIN2+ lesions (1-Negative Predictive Value) for each of the 17 strategies, with their 95% CI represented by error bars. (C) Probability of excess diagnosis (False Positive/Total) for each of the 17 strategies, with their 95% CI represented by error bars. The *y*-axis between Figure (B) and (C) is shared. (D) Ranking of the 17 strategies by descending order, based on a log-transformation of the ratio of the probabilities of excess diagnosis over missing CIN2+ lesions. Strategies with positive log-transformation favor the detection of CIN2+ lesions, while those with negative ones reduce excess diagnosis. (E) Probability of excess diagnosis over the probability of missing CIN2+ lesions for each of the 17 strategies. (F) Number of women with CIN2+ lesions that are not detected per 100,000 women screened in the population, by screening strategy, and according to the size of the HIV epidemic and the prevalence of CIN2+ cervical lesions in women living with HIV. In this figure, the HPV test detects all HR-HPV or potential HR-HPV. Abbreviations: 95% CI, 95% Confidence Interval; HPV, human papillomavirus; CIN, cervical intraepithelial neoplasia; NPV, Negative Predictive Value; HIV, human immunodeficiency virus; HR-HPV, high risk-human papillomavirus; pHR-HPV, Potentially high risk-human papillomavirus.

lowest probability of excess diagnosis (Figure 1C, Supplementary Table S4). Results for CIN3+ lesions are provided in Supplementary Materials.

Policy makers have to strike the right balance between the need to detect high-grade lesions and the need to avoid over-diagnosis. Thus, we ranked strategies according to whether they favor the detection of high-grade lesions (co-testing and primary HPV testing) or limit over-diagnosis (reflex-based strategies) (Figure 1D), based on the comparison of the probabilities of excess diagnosis over missing CIN2+ lesions (Figure 1E).

As strategy's performance may vary according to the burden of HIV infection and cervical lesions, the proportion of women with undetected precancerous/cancerous lesions at the population level may be substantial. It is essential to identify needs-based regional strategies to translate the progress of the cervical cancer prevention strategies into implementation, uptake and further integration into population-based health programs. Therefore, we applied our results to different settings worldwide depending on the prevalence of HIV (from 0.1% to 20%) and CIN2+ lesions (from 0% to 20%) in WLHIV to project the number of women with undetected CIN2+ lesions at population-level [1]. We found that with any strategy other than co-testing, the fraction of women with CIN2+ lesions missed would increase at least 4-fold. At most, using HPV testing to screen for any HR-HPV or pHR-HPV, in settings where HIV and CIN2+ prevalence is 20%, the number of women with undetected CIN2+ lesions in the population would be between 2,462 and 2,651 per 100,000 women

with standalone or reflex strategies, compared with 606 per 100,000 women with co-testing (Figure 1F).

In our analysis among WLHIV, the current screening strategy using primary HPV testing, as recommended by WHO [8], offers a good balance between benefits and harms of colposcopy/biopsy. However, its sensitivity was relatively low compared with co-testing, particularly when the number of HPV genotypes targeted was small, as with HPV 16/18 alone. Even when the range of HPV genotypes was extended to the most potent HR-HPV (HPV 16/18/31/33/52), the percentage of missed CIN2+ lesions remained lower with co-testing than with primary HPV testing (5% versus 8%). Therefore, using primary HPV testing in settings with a wide variety of HR-HPV genotypes, such as in Asia or sub-Saharan Africa, a large number of CIN2+ lesions may go undetected [3]. To improve the detection of high-grade lesions, an HPV-based screening program should ideally use a wide range of alpha-genus genotypes, encompassing those identified as involved in most cancers [7]. Markers for HPV integration such as E6/E7 oncoproteins are being tested as alternative primary test or triage strategies.

Screening guidelines and practices involve difficult trade-offs, involving considerations of costs, resources and access constraints, as well as potential harms and benefits for women's health. Referral for colposcopy/biopsy represents a bottleneck in the care cascade, as colposcopes are sometimes only available in tertiary hospitals, far from women's home. Over-diagnosis may lead to over-referral for colposcopy and over-treatment of healthy women. Our results suggest that reflex-based strategies could be a good alternative to co-testing and primary HPV testing, in line with the latest WHO recommendations (conditional) among WLHIV [8].

The robustness of cytology for high-grade lesion detection, regardless of immune status or ART duration, was highlighted in a previous study in Kenya in which all WLHIV underwent colposcopy/biopsy [9]. It is not possible to compare with our results because women with cytology and HR-HPV tests both negative were included, ART coverage was lower and overall prevalence of CIN2+ lesions was higher.

In conclusion, our results suggest that in regions where the HIV epidemic and the prevalence of CIN2+ are lowest, primary HPV testing may achieve the same results as complex population-based co-testing programs, in line with the latest WHO recommendations (strong) [8]. In resource-limited settings, when the burden of both HIV and cervical cancer is highest [10], co-testing may be the best screening strategy to limit the number of missed precancerous/cancerous lesions in WLHIV.

AUTHOR CONTRIBUTIONS

Sophie Le Coeur and Tristan Delory conceived and designed the project. Samreung Rangdaeng performed quality control of all cytological and histological samples. Nicole Ngo-Giang-Huong performed the HPV testing analyses. Myrtille Prouté and Patumrat Sripan analyzed the data. Chaiwat Putiyanun, Guttiga Halue, Prattana Leenasirimakul, Suchart Thongpaen, and Sudanee Buranabanjasatean collected patient samples. Patumrat Sripan, Myrtille Prouté, Sophie Le Coeur, and Tristan Delory drafted the manuscript. All authors reviewed and approved the final manuscript.

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CLINICAL TRIAL REGISTRATION

The PapilloV study was registered on clinicaltrials.gov (NCT01792973).

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study protocol was approved by the ethics committees of the Institute for the Development of Human Research Protections, Ministry of Public Health, Thailand (SKM 1420/2554); the Faculty of Associated Medical Sciences, Chiang Mai University, Thailand (019E/55); the Research Institute for Development (IRD), and the 24 local hospitals. All women provided written informed consents.

DATA AVAILABILITY STATEMENT

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.