Point-of-care HPV molecular diagnostics for a test-and-treat model in high-risk HIV populations

Strategies for cervical cancer prevention and control in low-income and middle-income countries (LMICs) require concerted efforts to improve screening and access to treatment, especially in high-risk HIV populations. LMICs bear the largest burden of HIV infection, human papillomavirus (HPV) infection is common among HIV-infected women, risk of cervical cancer is increased in women with HIV/AIDS, and HIV clinics provide opportunities to screen and treat for cervical cancer in this population.

A cluster randomised trial from India has shown that one round of HPV screening reduced advanced cervical cancer and mortality compared with the standard care group, whereas the so-called see and treat method (visual inspection of the cervix with acetic acid, VIA) did not show such benefit.[1] Furthermore, overtreatment and undertreatment due to the low sensitivity and specificity of the current screening tests are a real problem and they reduce the impact of screening in health systems that are already overstretched and under-resourced.

Implementation of the traditional Pap smear in national screening programmes is not sustainable in under-resourced LMIC settings with a limited skilled cytologist workforce[2] and where, despite a high prevalence of cervical cancer,[3] loss to follow-up and poor adherence to treatment are major impediments for programmatic success. The current WHO recommendation for HPV testing as a primary cervical cancer screening tool has been adopted by countries such as Kenya, where it forms part of the national cancer screening guidelines.

However, a concern with the HPV screen-and-treat approach is the overtreatment of high-risk HPV-positive women. There is a need for innovative point-of-care molecular diagnostic tools that are sensitive and specific and can be integrated into primary health settings in LMICs as screen-and-treat models. These point-of-care platforms can further be used to diagnose multiple conditions and monitor therapy on a single device.[4]

There are multiple HPV point-of-care testing platforms in the market (eg, the careHPV test, Qiagen), but none of these has been fully validated in the clinical setting. Devices such as the GeneXpert (Cepheid, Sunnyvale, CA, USA), which has been endorsed by WHO for molecular diagnosis of tuberculosis and rifampicin resistance[5] and which requires minimum training, have created opportunities for disease diagnostic testing; GeneXpert is currently the only validated HPV point-of-care device. The GeneXpert, developed by Cepheid for rapid molecular diagnostics,[6] combines cartridge-based microfluidic sample preparation with RT-PCR-based fluorescent signal detection with the capacity to perform RNA isolation, reverse transcription, and quantitative PCR in about 35 min.[8] To date, there are over 7000 GeneXpert platforms globally, the majority of which are in low-income and middle-income countries and are being used almost exclusively for tuberculosis diagnosis.[7]

However, for the point-of-care HPV tests to be adopted, they must be widely applicable, specifically in high-risk HIV populations. In *The Lancet Global Health*, Louise Kuhn and colleagues[8] describe a clinical study from South Africa and provide a comprehensive background of the current limitation of the GeneXpert for screening a high-risk HIV positive population. They describe a novel modification of the test that would increase the specificity of detecting cervical intraepithelial neoplasia of grade 2 (CIN2+) on the same device by up to 26% without compromising the sensitivity of the test in high-risk HIV-positive women. Furthermore, by restricting the channels to the eight high-risk HPV genotypes (HPV 16, 18, 45, 31, 33, 35, 52, and 58), they demonstrate that specificity increased by about 4·4% in the HIV-negative population and by 17·1% in the HIV-positive population. The positive predictive value increased by 2·2–3·6% for CIN2+.

Specificity is important in a screening test to avoid overtreatment. New studies[9] suggest that loop electrosurgical excision procedure (LEEP) might be better than cryotherapy (ie, lower recurrence of CIN2+ lesions) among HIV-infected women, but overtreatment with LEEP might have worse consequences than cryotherapy given the side-effects associated with LEEP such as cervical stenosis and bleeding. A more specific test is thus welcome. Kuhn and colleagues also suggest that the HPV screen-and-treat method can leverage on the VIA or Lugol's Iodine (VILI) infrastructure already in

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For more on the **burden of HIV infection** see https://www.who.int/gho/hiv/en/

For more on **cancer in women with HIV/AIDS** see https://www.cancer.net/cancer-types/hivaids-related-cancer/introduction

For **Kenya's National Screening Guidelines** see http://www.health.go.ke/wp-content/uploads/2019/02/National-Cancer-Screening-Guidelines-2018.pdf

place in many LMICs—a point that we agree with given that minimal training is required to perform the HPV test on the GeneXpert platform.

However, it is crucial that any new point-of-care test is easy to perform, sensitive, and specific, and that it is not vulnerable to user error like VIA, which has performed poorly in LMICs (the test is subjective and requires regular refresher training to maintain accuracy). The new HPV test modification reported on the Gene Xpert by Kuhn and colleagues[8] might be able to overcome this. But, before LMICs adopt point-of-care technologies that can surpass fragile health systems and allow for testing in the absence of traditional laboratory settings, multiple implementation studies examining cost-effectiveness, feasibility, and acceptability by health-care workers and by women of HPV screen-and-treat methods are needed. More importantly, it would be useful to understand how HPV test specificity might be affected by immune status, ART use, and age, as these variables might reduce specificity of the test.[10]

We declare no competing interests.

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