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EXPLORING INCLUSION OF RAPID HPV DNA TESTING IN PRIMARY CERVICAL CANCER SCREENING IN TANZANIA – ROLE OF HIV STATUS

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Abstract – *Objective:* *HPV DNA testing is currently used as primary cervical cancer screening method in most of high income countries and was shown to improve quality of screening services. However, this is not yet the case in low income countries. In this study, we investigate whether the value of HPV DNA testing in primary cervical cancer screening with VIA as triage test is the same among HIV positive and negative women.*

Subjects and Methods: *This cohort study included women attending routine cervical cancer screening clinics at Ocean Road Cancer Institute and Kilimanjaro Christian Medical Centre. At enrolment eligible women were interviewed tested for HIV, had a cervical sample taken, and finally VIA was performed. After 14 months, they were invited for follow-up visit and VIA was repeated.*

Results: *At enrolment, 938 women tested* careHPV *positive, of those 101 were VIA positive and were referred to further diagnostic work up and treatment. Among 837* careHPV *positive but VIA negative women, 333 attended follow-up as scheduled and 4.2% were VIA positive. However, this was not distributed equally according to HIV status. In 109 HIV positive women (hrHPV positive and VIA negative at enrolment), 9.2% were VIA positive at the 14 months follow-up whereas this only applied 1.8% of the HIV negative women follow-up.*

Conclusions: *The study shows that when HPV DNA testing is integrated in cervical cancer screening using triage with VIA, HIV status should be considered when considering further follow-up.*

KEYWORDS: *HPV DNA testing, Cervical cancer screening, HIV, Tanzania.*

INTRODUCTION

Cervical cancer ranks as the fourth most common cancer among women worldwide and is the fourth most common cancer related death[1]. Persistent infection with high risk HPV (hrHPV) is the main cause of cervical cancer and types 16 and 18 is associated with about 70% of cancer cases[2].

HPV is a common sexually transmitted infection, with most infections being cleared within 6 to 18 months[3]. In persistent infection, HPV can integrate into the host genome and trigger the expression of early proteins E1 and E2. These proteins enable viral replication by interacting with specific sequences in the viral genome and human cellular DNA replication factors. Then viral

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E6 induces cellular transformation by inhibiting tumor suppressor gene p53, and E7 binds and inactivates the retinoblastoma protein (pRb)[4,5]. They cause degradation and functional loss of the p53 and pRb genes leading to resistance to apoptosis, causing uncontrolled cell growth after cellular DNA damage. This can eventually result in malignant transformation[6]. One approach to prevention of cervical cancer is regular screening of eligible women in order to detect precancerous lesions that can be treated before progression into cancer. Visual inspection with acetic acid (VIA) is a widely used screening modality in most low and middle-income countries (LMICs) as it is cheap, easily available, and give results at the point of care which enable women to get treatment on the spot[7]. However, it is limited by subjectivity and low sensitivity[8]. Cytology, and most recently HPV DNA testing, are the screening methods used in high-income countries (HICs). These modalities are expensive to run and demand skilled staffs and good infrastructure, which most LMICs cannot afford. Rapid HPV DNA technology is a relatively new technology that can be used at the point of care with minimal training of available staffs[9].

As only a minor proportion of HPV infections progress to precancerous lesions, HPV DNA testing must be followed by a triage test of HPV positive women to increase specificity and avoid unnecessary follow-up and over treatment[10]. In HICs, follow-up is performed by colposcopy with biopsies to detect cervical precancerous lesions[11]. In LMICs, infrastructure for colposcopy and histological assessment of biopsies is not readily available, and it is currently not clear how rapid HPV DNA testing will be integrated into the available cervical cancer screening programs which rely on VIA[12,13].

In this study, we aim to investigate if the value of HPV DNA testing in primary cervical cancer screening with VIA as triage test is the same among HIV positive and negative women in Tanzania.

SUBJECTS AND METHODS

Study site

The study was part of the Comprehensive Cervical Cancer Prevention in Tanzania (CONCEPT) project, which is a collaboration between Ocean Road Cancer Institute (ORCI), Kilimanjaro Christian Medical Centre (KCMC), Southern University of Denmark and the Danish Cancer Society and conducted at cervical cancer screening clinics at ORCI, Dar es Salaam and KCMC, Kilimanjaro[14].

Study population

In this cross sectional study, we consecutively included women attending routine cervical cancer screening at ORCI and KCMC, respectively. Women were eligible if they were 25 – 60 years of age, gave informed consent, were not pregnant, and had no history of cervical precancerous lesion.

Data collection

Eligible women were interviewed using a structured questionnaire to obtain information on socio-demographic, behavioural and lifestyle characteristics. The women were then tested for HIV (on a voluntary basis) according to the Tanzanian guidelines[15]. We used the SD bio-line HIV test as primary test and in the event of a positive result, the Uni-Gold HIV test was used as confirmation test.

A gynaecological examination was performed where a cervical sample was obtained and kept in collection *care*HPV medium (QIAGEN GmbH,D-40724 Hilden, China) at room temperature. The samples stayed for a maximum of 14 days, waiting to reach a total number of 90 before being analysed for hrHPV (types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68)[9].

After taking the HPV cervical sample, VIA was done as per Tanzanian guidelines[16]. Using a cotton-tipped swab, 5% acetic acid was applied to the cervix. After around one-minute, potential cervical changes were assessed. Women who had distinct aceto-white lesions were defined as VIA positive (having signs of cervical precancerous lesion) and those without aceto-white lesions were regarded as VIA negative.

All women were invited to come back in 14 months for a follow-up visit, at which VIA was repeated as described above.

Ethical consideration

The study got ethical clearance from National Institute of Medical Research and MUHAS Ethical Committees (ref. no. NIMR/HQ/R.8a/Vol. IX/1955).

VIA positive women were treated with cryotherapy or loop electrosurgical excision procedure (LEEP) (depending on the extension of the lesion); and women who tested HIV positive were linked to care and treatment clinics at the respective hospitals. Women who were found to be VIA positive at the follow-up were referred to Oncology Department at KCMC and ORCI for further diagnosis and management.

TABLE 1. Distribution of women according to *care*HPV and VIA at enrolment.

	CareHPV		
VIA	***Negative (%)***	***Positive (%)***	***Total (%)***
Negative	2957 (73.2)	837 (20.8)	3794 (94.0))
Positive	143 (3.5)	101 (2.5)	244 (6.0)
Total (%)	3100 (76.8)	938 (23.2)	4038 (100.0)

RESULTS

A total of 4038 women were enrolled to participate in the study. The mean age was 40 years, 65.1% had primary education, and 70.8% were married. At enrolment, 938 women (23.2%) tested hrHPV positive by care HPV and 244 women (6.0%) were VIA positive (Table 1). Altogether, 101 women (2.5%) were positive for both hrHPV and VIA while 2957 women (73.2%) were negative on both tests.

Among the 837 women who were hrHPV positive and VIA negative at enrolment, 263 women did not show up for follow-up and 574 women (68.5%) attended the follow-up at 14 months. Of these, 333 women attended at the clinic as scheduled and VIA was performed, whereas 241 women were not able to come to the clinic and attended only from home.

In Figure 1, the VIA results at the 14 months follow-up are presented among women who were *care*HPV positive at enrolment and had a negative triage VIA result. Of the 333 women who attended follow-up and had a negative VIA at enrolment, overall, 14 women (4.2%) were VIA positive at follow-up. However, this was differently distributed according to HIV status. Among the 109 HIV positive women, 10 women (9.2%) had a positive VIA test at follow-up, whereas among the 224 HIV negative women, this only applied to 4 women (1.8%).

DISCUSSION

Our study shows that 4.2% of the women who at enrolment were *care*HPV positive but had a negative triage test (VIA), were VIA positive at follow-up. If

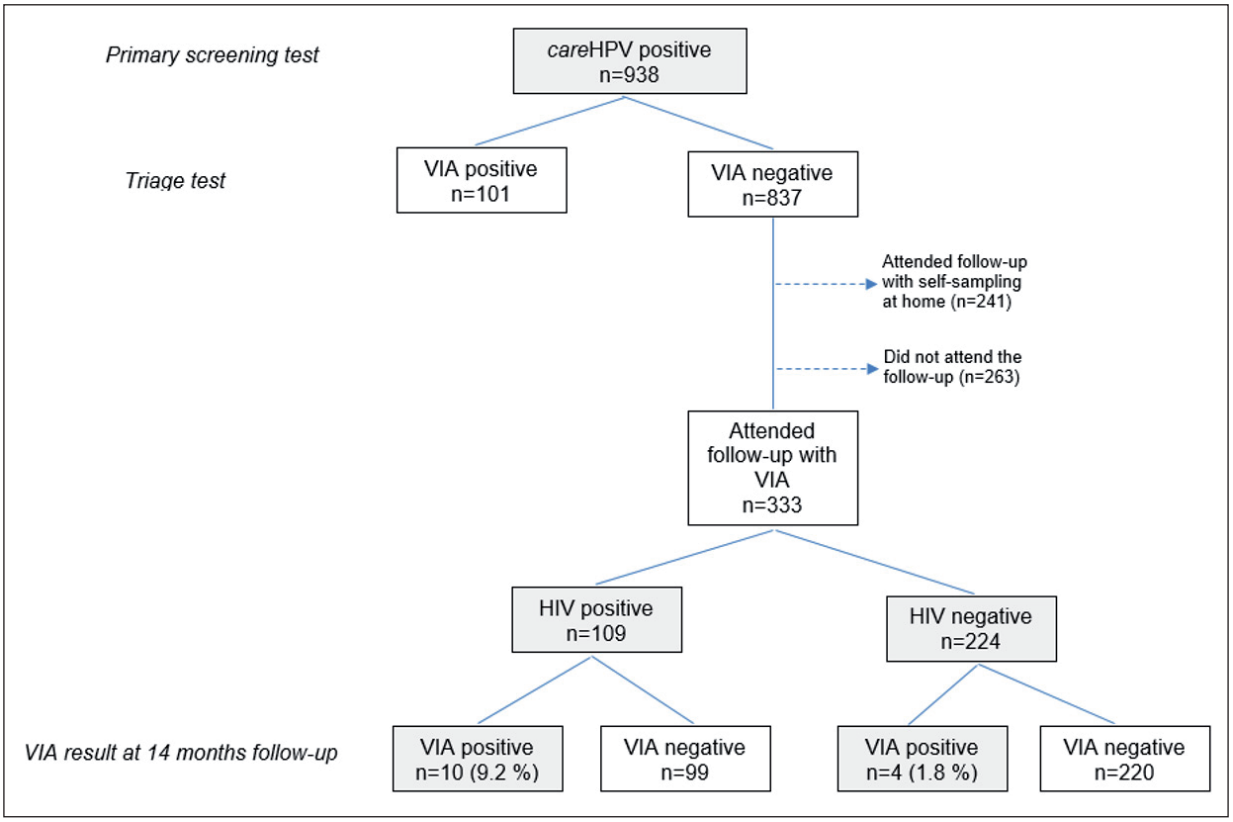

Fig. 1. Overview of the VIA results at 14 months follow-up among women positive on *care*HPV and negative triage VIA test according to HIV status.

the screening program only relies on the positive primary screening result and the negative triage result, the findings of our study indicate that with current 3 years screening interval, these 4.2% women would have been missed, potentially leading to development of high-grade lesions. We find that the occurrence of VIA positivity at follow-up differed substantially according to HIV status, being 9.2% among HIV positive and only 1.8% among HIV negative. In Tanzania, the National Cervical Cancer Screening Service guidelines stipulate that women who are VIA negative should re-attend in 3 years and those who are VIA negative with HIV should attend in 1 year [16].

The fact that most of the participants who were VIA positive at follow-up were HIV positive is supported by other studies, which show positive association between HIV and occurrence of precancerous lesions[17]. HIV may potentiate the persistence of HPV infection by decreasing the ability to clear the infection and thereby increase the risk of carcinogenic development. In addition, it has been suggested that HIV can imply a change in the cervical microbiome, which may influence the outcome of an HPV infection[17,18]. Thus, in HIV endemic areas, it is vital to consider HIV status in cervical cancer screening programs, and special regime considerations for yearly screening should be given to HIV positive women.

The strength of this study is we have used new HPV DNA testing (*care*HPV) technology in our cervical cancer screening activities. It was feasible to perform HPV testing at the laboratory of respective hospitals with staff that got a minimal training. It is also a strength that we used experienced nurses to do VIA and cervical sample collection, who before the start of the study, had a refresher training in order to get as reliable results for our study as possible.

In contrast, it is a limitation of the study that we did not have the possibility to perform rapid HPV DNA testing or cytology at follow-up.

CONCLUSIONS

The results showed that with rapid HPV DNA testing as the primary screening test and triage by VIA in cervical cancer screening programs, it is recommendable to consider HIV status in relation to the follow-up strategy.

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Conflict of interest:
The Authors declare no conflict of interest

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