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Performance of Xpert HPV on Self-collected Vaginal Samples for Cervical Cancer Screening Among Women in South Africa

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Objectives: Self-sampling may increase access to cervical cancer screening in low-resource settings. Using Xpert HPV, we compared test performance of self- and clinician-collected samples in HIV-positive and HIV-negative women in South Africa.

Materials and Methods: Three hundred thirty HIV-positive and 375 HIV-negative women in the screening group and 202 HIV-negative and 200 HIV-positive women in the referral group, aged 30–65 years, participated in the study. All women self-collected a vaginal sample, and then, a cervical sample was collected by a clinician (both tested using Xpert HPV), followed by colposcopic examination and collection of histologic specimens.

Results: There was good agreement between self- and clinician-collected samples for detection of any high-risk human papillomavirus (HPV, $\kappa = 0.72$ [95% CI = 0.669–0.771]). Prevalence of HPV and sensitivity of the test to detect cervical intraepithelial neoplasia 2+ was similar in self- and clinician-collected samples. Specificity was lower in self-collected than in clinician-collected samples in both HIV-negative (self: 77.5% [95% CI = 72.8–81.8] vs clinician: 86.9% [95% CI = 82.9–90.2]) and HIV-positive (self: 44.0% [95% CI = 38.0–50.1] vs clinician: 59.7% [95% CI = 53.6–65.6]) women. Restricting the definition of screen-positive to 3 of 5 channels on HPV Xpert improved specificity in both HIV-negative (self: 83.2% [95% CI = 78.8–87.0] vs clinician: 89.7% [95% CI = 86.1–92.7]) and HIV-positive (self: 54.2% [95% CI = 48.1–60.2] vs clinician: 67.4% [95% CI = 61.5–72.9]) women.

Conclusions: The self-collected sample had good agreement with the clinician-collected sample for the detection of HPV, and restricting the HPV types may improve the specificity in HIV-positive women.

Key Words: South Africa, self-sampling, clinician-sampling, human papilloma virus, human immune deficiency virus, HPV testing, cervical cancer screening

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Cervical cancer ranks as the fourth most frequently diagnosed and the fourth leading cause of cancer death among women worldwide.[1] In many low- and middle-income countries (LMIC), particularly in Sub-Saharan Africa, cervical cancer ranks as the second most frequently diagnosed cancer and the leading cause of cancer death among women.[1] Providing appropriate and effective screening can prevent women from getting and dying from cervical cancer. Cytology-based screening programs have been less successful in LMIC, because of the complex logistical, technological, and human resource requirements, hence the need for new approaches to overcome the obstacles to effective screening.

The World Health Organization has recommended molecular testing for human papillomavirus (HPV) for primary screening for cervical cancer in LMIC.[2] Human papillomavirus testing has better sensitivity than cytology and visual inspection with acetic acid for the detection of cervical neoplasia.[3,4] The standard method of obtaining samples for HPV testing is by a clinician who collects a cervical sample during a gynecological examination. An additional advantage of HPV testing is that samples can be collected by the woman herself through self-sampling techniques.[5,6] Self-sampling offers the opportunity to screen women who might be reluctant to go for screening or women in hard to reach areas and has the potential to overcome shortages of staff in health centers across LMIC.[7–9] Many studies have shown self-sampling to be highly acceptable to women in many different settings.[5,10–13] Previous studies have also shown good performance characteristics of self-collected samples in detecting high-risk (HR) HPV.[3,14–17] In a meta-analysis/systematic review in 2007, Petignat et al.[17] reported that self-collected samples were equivalent to clinician-collected samples for detection of HR HPV.

This study aimed to evaluate the performance of HPV testing with Xpert HPV to detect cervical cancer precursor lesions comparing performance of the test using self- and clinician-collected samples in HIV-positive and HIV-negative women.

METHODS

We conducted a prospective observational study in Cape Town, South Africa. Participants were recruited from 2 populations: (1) a screening population composed of women from the general population seeking primary screening and (2) a referral population composed of women referred for colposcopy because of abnormal screening test results.

Participant Recruitment

Women from the screening population were recruited at the Khayelitsha Site B Primary Health Care Clinic, a large public

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This study was approved by the human research ethics committee of the University of Cape Town and the institutional review board of Columbia University.

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clinic serving a disadvantaged population resident in this community on the outskirts of Cape Town. Women from the referral population were recruited from the routine colposcopy services at Groote Schuur Hospital, one of the leading university teaching hospitals in Cape Town. A total of 1,121 woman enrolled in the study (715 women from the screening clinic and 406 from the referral colposcopy clinic). Approximately half of the study population (535) was HIV-positive by design. Information on HIV status was collected from all women. Any documentation of HIV-positive status (eg, documented test result, receiving antiretroviral therapy, etc) was accepted as proof of being HIV-positive. Women with a documented HIV-negative antibody test within the prior 3 months were accepted as HIV-negative. For women who wished to join the study but who did not have documentation of their most recent HIV status or a negative test done within 3 months before enrolment, we referred to the standard voluntary counseling and testing services at our site to be tested before joining the study.

Self-collected Sample Collection

Women performed the self-collection in a private clinical examination room, after instructions given to them by a community health worker before the pelvic examination. The self-collected sample was collected by the study participant inserting and rotating a standard flock tip swab (Puritan, Guilford, ME) into the vagina and then placing it in a 5-mL vial (Globe Scientific, Paramus, NJ) containing 4 mL of PreservCyt solution (Hologic, Bedford, MA).

Clinician-Collected Sample

Women had a pelvic examination performed by a physician on the study team. After visualization of the cervix with a speculum, 2 cervical samples were obtained using an extended tip plastic spatula (Medscand, Berlin, Germany) and an endocervical cytobrush (Medscand, Berlin, Germany) for each sample. The cervical samples were placed in 2 separate ThinPrep vials (Hologic) each filled with 20 mL of PreservCyt solution.

Colposcopy and Histologic Sample Collection

After sample collection, the physician then performed a colposcopic examination. The Reid Colposcopy scoring system was used to define normal and abnormal colposcopic findings.[18] All acetowhite areas were biopsied. If there were colposcopic features of high-grade squamous intraepithelial lesion, then an excisional procedure, loop electrosurgical excision procedure (LEEP), was carried out. Endocervical curettage samples were collected if there were no visible lesions on the cervix.

All women in the screening population were asked to return 6 weeks after the enrolment visit for histology results (biopsy or LEEP). Women with abnormal results on biopsy had LEEP at this time. All HPV-positive women and those not initially identified as having cervical intraepithelial neoplasia grade 2 or worse (CIN 2+) had a repeat colposcopy with histological sampling to minimize missed disease at initial colposcopy. Random biopsies were done if no lesion could be seen on colposcopy. They were seen again 6 weeks later for a third colposcopy with histological sampling. All women who had treatment were referred for long-term follow-up at Groote Schuur Hospital.

Human Papillomavirus Testing

Both clinician-collected samples and self-collected samples were tested with Xpert HPV (CE-IVD) on the GeneXpert instrument system (Cepheid, Sunnyvale, CA), according to manufacturer's instructions at the Khayelitsha site. The Xpert HPV test is a real-time polymerase chain reaction assay with integrated sample preparation that detects 14 types of HR HPV DNA, grouped into 5 channels HPV 16; HPV 18 and/or 45; HPV 31, 33, 35, 52, and/or 58 (P3); HPV 51 and/or 59 (P4); and HPV 39, 56, 66, and/or 68 (P5). One milliliter of sample was pipetted into the Xpert HPV cartridge, which was then slotted into the GeneXpert machine. The advantages of this test are that it does not require specialized skills to operate and does not require batching of samples, and the result of the test is available in an hour making it an appropriate point-of-care test in a screen-and-treat setting. Human papilomavirus testing of self-collected samples with a point-of-care test may significantly increase access to cervical screening for women in low-resource countries. Xpert HPV is a World Health Organization prequalified test and has European Conformity Marking (CE marking). It is available globally and is registered for use in many countries.

Histology Examination

All histological samples were initially reviewed by a certified pathology laboratory in Cape Town. All the pathology slides were then shipped to Columbia University, New York, for rereview by an expert gynecologic pathologist who was blinded to all clinical and laboratory information including prior Cape Town diagnoses. All discordant diagnoses were rereviewed by a third expert gynecologic pathologist at Columbia University, and the final histologic diagnosis was reached by consensus. The end point for evaluating the performance the HPV test was CIN 2+.

Ethics Approval and Data Management

Regulatory approval was obtained from the institutional review boards at the University of Cape Town and Columbia University to undertake the study. All women provided written informed consent to participate.

Statistical Analysis

Analyses were done for detection of any HR HPV result (positivity on any of the 5 channels) and each of the 5 channels separately on the Xpert HPV. The percent agreement and Cohen κ were calculated to determine the agreement between self- and clinician-collected samples to detect HPV. The prevalence of HPV was described only in the screening population. Sensitivity calculations combined data from the screening and referral populations. Specificity, positive predictive values (PPVs), negative predictive values (NPVs), and percent screen-positive calculations included only data from the screening population. Comparisons of proportions between groups were tested using χ^2 tests. Comparisons between self- and clinician-collected samples in the same woman were made using the McNemar test. The data were analyzed using SPSS 25.

Role of the Funding Source

The funder of the study had no role in study design and conduct, data collection, data analysis, data interpretation, or manuscript drafting, review, and final approval.

RESULTS

Demographic and clinical characteristics of the 705 women recruited from the screening population are shown in Table 1. The median age of the women was 42 years, a quarter had completed grade 12, 44% used contraception, and most had never smoked. Most (80%) of the HIV-positive women were on antiretroviral therapy. The HIV-positive women were significantly younger; more of the HIV-positive women also used a condom always and had a previous cervical cylology test than HIV-negative women (see Table 1).

TABLE 1. Demographic and Clinical Characteristics of 705 Women Recruited From the Screening Population Stratified by HIV Status

Variable	*N* = 705	HIV-negative (*n* = 375)	HIV-positive (*n* = 330)	*p*
Age, median (IQR), y	42 (36–49)	44 (36–52)	39 (35–46)	<.001
Parity, median (IQR)	2 (2–3)	3 (2–4)	2 (1–3)	<.001
Age categories, y				
<42	350 (49.6%)	156 (41.6%)	194 (58.8%)	<.001
≥42	355 (50.4%)	219 (58.4%)	136 (41.2%)	
Educational status				
None	8 (1.1%)	6 (1.6%)	2 (0.6%)	.07
<Grade 12	520 (73.8%)	264 (70.4%)	256 (77.6%)	
≥Grade 12	177 (25.1%)	105 (28.0%)	72 (21.8%)	
Tobacco use				
Never	593 (84.1%)	316 (84.3%)	277 (83.9%)	.97
Current	77 (10.9%)	40 (10.7%)	37 (11.2%)	
Former	35 (5.0%)	19 (5.1%)	16 (4.9%)	
Contraception				
None	395 (56.0%)	210 (56.0%)	185 (56.1%)	.99
Yes	310 (44.0%)	165 (44%)	145 (43.9%)	
Injectable	137 (44.2%)	59 (35.8%)	78 (53.8%)	
Tubal ligation	115 (37.1%)	72 (43.6%)	43 (29.7%)	
Implant	34 (11.0%)	18 (10.9%)	16 (11.0%)	
IUCD	13 (4.2%)	7 (4.2%)	6 (4.1%)	
Oral	9 (2.9%)	7 (4.2%)	2 (1.4%)	
Other	2 (0.6%)	2 (1.2%)	0	
Condom use				
Always	220 (31.2%)	80 (21.3%)	140 (42.4%)	<.001
Never	211 (29.9%)	152 (40.5%)	59 (17.9%)	
Abstinent	160 (22.7%)	92 (24.5%)	68 (20.6%)	
Sometimes	114 (16.2%)	51 (13.6%)	63 (19.1%)	
Prior cervical cytology				
Yes	487 (69.1%)	240 (64.0%)	247 (74.9%)	.001
No	218 (30.9%)	135 (36.0%)	83 (25.1%)	

IQR indicates interquartile range; IUCD, intrauterine contraceptive devices.

Prevalence of HPV

The prevalence of any HR HPV infection was higher in self-collected samples (61.5%) than in clinician-collected samples (48.2%) from HIV-positive women. Similarly, 25.1% of the self-collected samples from HIV-negative women and 16.3% of the clinician-collected samples were positive for any HR HPV. This pattern was also observed considering positivity for each Xpert HPV channel separately (see Table 2). The pattern of higher HPV prevalence in self-collected versus clinician-collected samples was also observed when stratified by the median age (42 years) of the population (Supplementary Table 1 http://links.lww.com/LGT/A186).

Agreement Between Self- and Clinician-Collected Samples

Overall, the percent agreement for detection of any HR HPV was 86.8%, and the Cohen κ coefficient was 0.72 (0.669–0.771) for agreement between self- and clinician-collected samples in the screening population. This is considered a good agreement.[19]

When analyzed by channel, there was a good agreement between self- and clinician-collected samples in the first 3 channels of the Xpert HPV test. There was a very good agreement between the 2 sampling methods in the HPV 16 channel in both screening and referral population groups ($k = 0.815$ and 0.923, respectively). The agreement between self- and clinician-collected samples was also good in the HPV 18, 45 and HPV 31, 33, 35, 52, 58 channels (see Table 3). There was a moderate agreement in the channels detecting HPV 51, 59 and HPV 39, 56, 66, 68 (see Table 3). The agreement between self- and clinician-collected samples was similar in both screening and referral populations, regardless of HIV status. When the analysis was restricted to the 3 channels detecting HPV types 16, 18, 45, 31, 33, 35, 52, 58, there was a slight increase in both the % agreement and the κ values (see Supplementary Table 2 http://links.lww.com/LGT/A187).

Sensitivity and Specificity of the Self-collected HPV Test

Using the final histology result as the criterion standard, the sensitivity of Xpert HPV test (defining screen-positive as positivity on any of the 5 channels) to detect CIN 2+ was similar in self- and clinician-collected samples. In HIV-positive women, sensitivity to detect CIN 2+ was 95.8% (95% CI = 91.6–98.3) in self-collected samples and 93.5% (95% CI = 88.6–96.7) in clinician-collected samples. In HIV-negative women, sensitivity was 87.7% (95% CI = 80.7–93.0) in self-collected samples and

TABLE 2. Prevalence of HPV Infection Detected by Xpert HPV Overall and in Each Channel Among 705 Women Recruited From the Screening Population by Sampling Method (Self vs Clinician) and HIV Status

Sampling method	HIV-negative $n = 375$, n (%)	HIV-positive $n = 330$, n (%)	p HIV-pos vs HIV-neg, χ^2 test	p CS vs SS in HIV-neg, McNemar test	p CS vs SS in HIV-pos, McNemar test
HPV 16, 18, 45, 31, 33, 35, 52, 58, 51, 59, 39, 56, 66, 68 (all 14 genotypes)					
Self	94 (25.1)	203 (61.5)	<.001	<.001	<.001
Clinician	61 (16.3)	159 (48.2)	<.001		
HPV 16					
Self	14 (3.7)	50 (15.2)	<.001	.5	<.001
Clinician	12 (3.2)	35 (10.6)	<.001		
HPV 18, 45					
Self	24 (6.4)	77 (23.3)	<.001	.009	.001
Clinician	13 (3.5)	59 (17.9)	<.001		
HPV 31, 33, 35, 52, 58					
Self	45 (12.0)	100 (30.3)	<.001	.003	.005
Clinician	30 (8.0)	84 (25.5)	<.001		
HPV 51, 59					
Self	20 (5.3)	48 (14.5)	<.000	.003	<.001
Clinician	11 (2.9)	22 (6.7)	.019		
HPV 39, 56, 66, 68					
Self	28 (7.5)	74 (22.4)	<.001	.001	<.001
Clinician	14 (3.7)	36 (10.9)	<.001		

88.5% (95% CI = 81.5–93.6) in clinician-collected samples (see Table 4).

Specificity was slightly lower in self-collected samples than in clinician-collected samples. In HIV-positive women, specificity was 44.0% (95% CI = 38.0–50.1) in self-collected samples and 59.7% (95% CI = 53.6–65.6) in clinician-collected samples. In HIV-negative women, the specificity was also lower (77.5%, 95% CI = 72.8–81.8) in self-collected samples compared with clinician-collected samples (86.9%, 95% CI = 82.9–90.2; see Table 4).

Next, using positivity from each of the channels separately, we examined sensitivity and specificity. This approach yielded excellent specificity but poor sensitivity (see Table 4).

We then defined screen-positive as only those with positive results on the first 3 channels of Xpert, i.e., HPV types 16, 18, 45, 31, 33, 35, 52, 58. Compared with identifying all 14 HR HPV genotypes, the restricted definition of screen-positive led to only minor reductions in sensitivity in both the self- and clinician-collected samples with an appreciable increase in specificity in both HIV-positive and HIV-negative women (see Table 5). The sensitivity in self-collected samples reduced to 84.4% from 87.7% among HIV-negative women and reduced 90.5 from 95.8 among HIV-positive women. In clinician-collected samples, the sensitivity reduced to 86.9% from 88.5% among HIV-negative women and reduced to 90.5% from 93.5% among HIV-positive women. In self-collected samples, restricting to the first 3 channels improved the specificity to 83.2% from 77.5% in HIV-negative women and to 54.2% from 44.0% in HIV-positive women. In clinician-collected samples, the specificity improved to 89.7% from 86.9% among HIV-negative women and to 67.4% from 59.7% in HIV-positive women (see Table 5).

Self-collected sample HPV testing had a lower PPV compared with clinician-collected samples both overall and according

TABLE 3. Consistency of HPV Results Detected by Xpert HPV Overall and in Each Channel (% Agreement and κ Coefficient) Between Self- and Clinician-Collected Samples in 705 Women From the Screening Population and 402 Women From the Referral Population

	Screening population ($n = 705$)			Referral population ($n = 402$)		
HPV channel	% agreement	κ	95% CI	% agreement	κ	95% CI
Xpert HPV (all 14 genotypes)[a]	86.8%	0.720	0.669–0.771	89.3%	0.622	0.476–0.726
Selected 3 channels[b]	89.4%	0.751	0.699–0.803	89.8%	0.690	0.602–0.778
HPV 16	97.3%	0.815	0.734–0.895	97.1%	0.923	0.880–0.966
HPV 18, 45	94.5%	0.744	0.668–0.82	91.8%	0.755	0.677–0.833
HPV 31, 33, 35, 52, 58	93.1%	0.769	0.708–0.83	91.3%	0.824	0.769–0.879
HPV 51, 59	94.5%	0.588	0.472–0.704	77.9%	0.696	0.590–0.802
HPV 39, 56, 66, 68	91.8%	0.578	0.484–0.694	67.6%	0.670	0.579–0.761

[a]Positive for HPV 16, and/or HPV 18, 45, and/or HPV 31, 33, 35, 52, 58, and/or HPV 51, 59, and/or HPV 39, 56, 66, 68.

[b]Positive for HPV 16, and/or HPV 18, 45, and/or HPV 31, 33, 35, 52, 58.

TABLE 4. Comparison of Sensitivity and Specificity of Xpert HPV Overall and Each Channel Separately to Detect CIN 2+ Using Self- or Clinician-Collected Samples by HIV Status

	Sensitivity (95% CI)[a]			Specificity (95% CI)[a]		
HIV status	**Self**	**Clinician**	***p* McNemar test**	**Self**	**Clinician**	***p* McNemar test**
HPV 16, 18, 45, 31, 33, 35, 52, 58, 51, 59, 39, 56, 66, 68 (all 14 genotypes)[b]						
HIV-neg	87.7 (80.7–93.0)	88.5 (81.5–93.6)	.7	77.5 (72.8–81.8)	86.9 (82.9–90.2)	<.001
HIV-pos	95.8 (91.6–98.3)	93.5 (88.6–96.7)	.2	44.0 (38.0–50.1)	59.7 (53.6–65.6)	<.001
HPV 16						
HIV-neg	42.6 (33.7–51.9)	41.8 (32.9–51.1)	.6	97.2 (94.8–98.6)	97.7 (95.6–99.0)	.2
HIV-pos	32.7 (25.7–40.4)	31.0 (24.1–38.5)	.2	88.6 (84.3–92.2)	93.0 (89.3–95.8)	.001
HPV 18, 45						
HIV-neg	13.1 (7.7–20.4)	13.9 (8.33–21.4)	.7	93.4 (90.3–95.8)	96.6 (94.1–98.2)	.001
HIV-pos	33.9 (26.8–41.6)	28.6 (21.9–36.0)	.02	79.9 (74.6–84.4)	85.3 (80.6–89.3)	.002
HPV 31, 33, 35, 52, 58						
HIV-neg	45.9 (36.8–55.2)	45.9 (36.8–55.2)	1.0	90.0 (86.4–93.0)	94.0 (91.0–96.3)	.005
HIV-pos	65.5 (57.8–72.6)	64.9 (57.2–72.1)	.7	75.1 (69.5–80.1)	81.3 (76.2–85.8)	.002
HPV 51, 59						
HIV-neg	4.9 (1.83–10.4)	6.6 (2.87–12.5)	.3	94.9 (92.0–96.9)	97.2 (94.8–98.6)	.005
HIV-pos	26.2 (19.7–33.5)	11.9 (7.43–17.8)	<.001	89.0 (84.7–92.5)	93.8 (90.2–96.3)	.002
HPV 39, 56, 66, 68						
HIV-neg	12.3 (7.1–19.5)	6.6 (2.87–12.5)	.008	93.2 (90.0–95.6)	96.9 (94.5–98.4)	.002
HIV-pos	39.3 (31.9–47.1)	25.0 (18.7–32.3)	<.001	79.9 (74.6–84.4)	90.5 (86.4–93.7)	<.001

[a]By design, sensitivity is calculated by combining data from the screening and referral study populations, and specificity, PPV and NPV, and percent screen-positive from the screening population only.

[b]Positive for HPV 16, and/or HPV 18, 45, and/or HPV 31, 33, 35, 52, 58, and/or HPV 51, 59, and/or HPV 39, 56, 66, 68.

to HIV status. There was a slight increase in the PPV when the analysis was restricted to HPV types 16, 18, 45, 31, 33, 35, 52, 58 (see Table 5).

DISCUSSION

With a high prevalence of HIV infection among women in South Africa, it is essential to understand the accuracy of self-sampling in HIV-positive women to determine its clinical utility as ancillary screening modality in this setting. In this study, the prevalence of detecting HR HPV infection was higher in self-collected samples (61.5%) than in clinician-collected samples (48.2%) from HIV-positive women. Palmisano et al.[20] in 2003 and Petignat et al.[21] in 2005 reported similar findings. The HIV-infected women have a higher prevalence of HPV infection[22] as a result of which they might have increased shedding of HPV-infected cells in the vagina, hence the increase in detection of HR HPV in the self-collected sample.

We found a good agreement between self-collected vaginal specimens with clinician-collected cervical specimens for the detection of HR HPV infection in both HIV-positive and HIV-negative

TABLE 5. Comparison of Sensitivity and Specificity of Xpert HPV Overall (All 5 Channels) and Restricted to the Selected 3 Channels (HPV 16, HPV 18, 45 and HPV 31, 33, 35, 52, 58) to Detect CIN 2+ Using Self- or Clinician-Collected Samples by HIV Status

Sampling method	**HIV status**	**Sensitivity[a] (95% CI)**	**Specificity[a] (95% CI)**	**PPV (95% CI)**	**NPV (95% CI)**	**% screen-positive (95% CI)**
HPV 16, 18, 45, 31, 33, 35, 52, 58, 51, 59, 39, 56, 66, 68 (all 14 genotypes)[b]						
Self	Neg	87.7 (80.7–93.0)	77.5 (72.8–81.8)	15.1 (8.48–24.0)	97.8 (95.4–99.2)	25.0 (21.0–29.8)
	Pos	95.8 (91.6–98.3)	44.0 (38.0–50.1)	24.3 (18.5–30.8)	96.8 (91.9–99.1)	62.0 (56.0–67.3)
Clinician	Neg	88.5 (81.5–93.6)	86.9 (86.9–90.2)	23.3 (13.4–36.0)	98.1 (95.8–99.3)	16.0 (13.0–20.3)
	Pos	93.5 (88.6–96.7)	59.7 (53.6–65.6)	30.4 (23.3–38.2)	97.0 (93.2–99.0)	48.0 (43.0–54)
HPV 16, 18, 45, 31, 33, 35, 52, 58 (selected 3 channels)[c]						
Self	Neg	84.4 (76.8–90.4)	83.2 (78.9–87.0)	19.2 (10.9–30.1)	98.0 (95.7–99.3)	20.0 (16.0–24.7)
	Pos	90.5 (85.0–94.5)	54.2 (48.1–60.2)	26.5 (20.0–33.7)	94.9 (90.1–97.8)	52.0 (47.0–57.7)
Clinician	Neg	86.9 (79.6–92.3)	89.7 (86.1–92.7)	28.0 (16.2–42.5)	98.1 (96.0–99.3)	13.0 (10.0–17.4)
	Pos	90.5 (85.0–94.5)	67.4 (61.5–72.9)	33.6 (25.7–42.2)	95.8 (92.0–98.2)	41.0 (36.0–46.7)

[a]By design, sensitivity is calculated by combining data from the screening and referral study populations, and specificity, PPV and NPV, and percent screen-positive from the screening population only.

[b]Positive for HPV 16, and/or HPV 18, 45, and/or HPV 31, 33, 35, 52, 58, and/or HPV 51, 59, and/or HPV 39, 56, 66, 68.

[c]Positive for HPV 16, and/or HPV 18, 45, and/or HPV 31, 33, 35, 52, 58.

women. Toliman et al.[23] in 2016 in a study of 1,005 women using Xpert HPV also reported excellent percentage agreement (93.4%) for any HR HPV using self- and clinician-collected samples among a screening population in Papua New Guinea.[23] Catarino et al.[24] in 2017, also using Xpert HPV, reported 82.2% agreement in samples collected from women attending colposcopy clinic in Geneva. Using COBAS 4800 HPV platform, Ketelaars et al.[25] in 2017 reported a 96.8% agreement between self- and clinician-collected samples from a screening population in the Netherlands. Few studies have examined the level of agreement between self- and clinician-collected samples among HIV-positive women. In this study, we found good agreement between self- and clinician-collected samples in HIV-positive women in detecting any HR HPV infection among both the screening (82.4%, $\kappa = 0.65$) and referral (94.0%, $\kappa = 0.59$) populations. Petignat et al.,[21] in 2005 in a study among HIV-positive women in Canada, reported a good agreement (91.8%, $\kappa = 0.88$), higher than that from our study. Differences in the sampling device and clinical settings may explain the slightly higher agreement in the Canadian study.

The sensitivity for predicting CIN 2+ was similar for both self- and clinician-collected samples in our study as has been reported by other studies.[3,7,24,26] Arbyn et al.[7,14] in a meta-analysis in 2014 and a follow-up meta-analysis in 2018 by the same author, reported that self-collected samples were similarly sensitive but slightly less specific than clinician-collected samples for detection of HR HPV in polymerase chain reaction–based HPV assays but not in signal-amplification or RNA detection tests. Among HIV-positive women, however, the specificity of the Xpert HPV test in both self- and clinician-collected samples and, in particular, of the self-collected sample was much lower than that reported by others.[3,7,24,26,27] Although the type of sampling device and testing platform may play a role, differences in the populations studied (in this case, HIV-positive women) are the most likely explanation for our results. Previous studies have consistently shown that HPV testing has the inherent weakness of a low specificity in HIV-positive populations, an area of concern in regions with a high prevalence of HIV infection.[28,29]

We have previously reported from this study that changes in the definition of screen-positive to include only the 3 channels of Xpert HPV that detect HPV 16, 18, 45, 31, 33, 35, 52, 58 leads to improvement in specificity with only minor reductions in sensitivity.[30,31] Here, we confirm that this improvement in the sensitivity/specificity balance with type restriction is also attained when Xpert HPV is run on self-collected samples. Type restriction also improves the PPV in the self-collected samples, reducing the number of false-positive results. Although improved, the worse specificity associated with self-collected samples, especially in HIV-positive women, suggests that further evaluation and/or testing may be necessary before treatment if only self samples are used for primary screening in a screen-and-treat model.

Restricting the HPV genotypes in Xpert HPV to 3 channels can be an effective way to improving the balance between sensitivity and specificity of HPV tests especially among the HIV-positive population. As well as reducing false-positive screening results and unnecessary treatment, achieving this balance is important in low-resource settings, where there is also a high burden of cervical cancer and HIV infections, together with limited resources capacity for optimal screening, treatment of screen positive women, and subsequent follow-up.

Because it is costly to recruit adequate numbers of CIN 2+ from a screening population, one of the limitations of this study is that we combined women from both the screening and the referral populations in the calculation of the sensitivity. This combination was to enable us to get enough numbers of those women with the desired endpoint of CIN 2+. This approach of enriching a study population by a referral population to get enough numbers was also for a sensitivity calculation was also applied previously in the VALGENT HPV test validation protocol.[32] Another weakness is that most of the women are from the same area and are of the same ethnicity, hence the need to carry out a more extensive study across the country.

CONCLUSIONS

We demonstrated that self-collected samples were comparable with clinician-collected samples in identifying HR HPV infection using Xpert HPV, irrespective of the HIV status of the woman. We also demonstrated that although the specificity of self-collected sample to predict CIN 2+ is lower than clinician sample, especially in HIV-positive women, restricting the definition of a positive Xpert HPV test to include only the 3 channels comprising HPV 16, 18, 45, 31, 33, 35, 52, 58 increased the specificity without compromising the sensitivity of the test. This is important, especially in low resource settings with a high burden of HIV infection, because this approach reduces the number of women requiring further evaluation, thereby reducing the cost of screening.

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REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018;68:394–424.
2. WHO. *WHO guidelines: WHO guidelines for screening and treatment of precancerous lesions for cervical cancer prevention*. Geneva, Switzerland: WHO; 2013.
3. Porras C, Hildesheim A, Gonzalez P, et al. Performance of self-collected cervical samples in screening for future precancer using human papillomavirus DNA testing. *J Natl Cancer Inst* 2015;107:400.
4. Sankaranarayanan R. Screening for cancer in low- and middle-income countries. *Ann Glob Health* 2014;80:412–7.
5. Berner A, Hassel SB, Tebeu P-M, et al. Human papillomavirus self-sampling in cameroon: women's uncertainties over the reliability of the method are barriers to acceptance. *J Low Genit Tract Dis* 2013;17:235–41.
6. Quincy BL, Turbow DJ, Dabinett LN, et al. Diagnostic accuracy of self-collected human papillomavirus specimens as a primary screen for cervical cancer. *J Obstet Gynaecol* 2012;32:795–9.
7. Arbyn M, Smith SB, Temin S, et al, Collaboration on Self-Sampling and HPV Testing. Detecting cervical precancer and reaching underscreened women by using HPV testing on self samples: updated meta-analyses. *BMJ* 2018;363:k4823.
8. Petignat P, Vassilakos P. Is it time to introduce hpv self-sampling for primary cervical cancer screening? *J Natl Cancer Inst* 2012;104:166–7.
9. Gupta S, Palmer C, Bik EM, et al. Self-sampling for human papillomavirus testing: increased cervical cancer screening participation and incorporation in international screening programs. *Front Public Health* 2018;6:77.
10. Saidu R, Moodley J, Tergas A, et al. South African women's perspectives on self-sampling for cervical cancer screening: a mixed-methods study. *S Afr Med J* 2018;109:47–52.
11. Ma'som M, Bhoo-Pathy N, Nasir NH, et al. Attitudes and factors affecting acceptability of self-administered cervicovaginal sampling for human

papillomavirus (HPV) genotyping as an alternative to Pap testing among multiethnic Malaysian women. *BMJ Open* 2016;6:e011022.

12. Sultana F, Mullins R, Murphy M, et al. Women's views on human papillomavirus self-sampling: focus groups to assess acceptability, invitation letters and a test kit in the Australian setting. *Sex Health* 2015;12: 279–86.
13. Bansil P, Wittet S, Lim JL, et al. Acceptability of self-collection sampling for HPV-DNA testing in low-resource settings: a mixed methods approach. *BMC Public Health* 2014;14:596.
14. Arbyn M, Verdoodt F, Snijders PJF, et al. Accuracy of human papillomavirus testing on self-collected versus clinician-collected samples: a meta-analysis. *Lancet Oncol* 2014;15:172–83.
15. Zhao FH, Lewkowitz AK, Chen F, et al. Pooled analysis of a self-sampling HPV DNA test as a cervical cancer primary screening method. *J Natl Cancer Inst* 2012;104:178–88.
16. Obiri-Yeboah D, Adu-Sarkodie Y, Djigma F, et al. Self-collected vaginal sampling for the detection of genital human papillomavirus (HPV) using careHPV among Ghanaian women. *BMC Womens Health* 2017;17:86.
17. Petignat P, Faltin DL, Bruchim I, et al. Are self-collected samples comparable to physician-collected cervical specimens for human papillomavirus DNA testing? A systematic review and meta-analysis. *Gynecol Oncol* 2007;105:530–5.
18. Sellors JW, Sankaranarayanan R. Chapter 7, Colposcopic assessment of cervical intraepithelial. In: *Colposcopy and Treatment of Cervical Intraepithelial Neoplasia: A Beginners' Manual*. Lyon, France: International Agency for Research on Cancer; 2003/2004:55–68.
19. Brennan P, Silman A. Statistical methods for assessing observer variability in clinical measures. *BMJ* 1992;304:1491–4.
20. Palmisano ME, Gaffga AM, Daigle J, et al. Detection of human papillomavirus DNA in self-administered vaginal swabs as compared to cervical swabs. *Int J STD AIDS* 2003;14:560–7.
21. Petignat P, Hankins C, Walmsley S, et al. Self-sampling is associated with increased detection of human papillomavirus DNA in the genital tract of HIV-seropositive women. *Clin Infect Dis* 2005;41:527–34.
22. Joshi S, Babu JM, Jayalakshmi D, et al. Human papillomavirus infection among human immunodeficiency virus-infected women in Maharashtra, India. *Vaccine* 2014;32:1079–85.
23. Toliman P, Badman SG, Gabuzzi J, et al. Field evaluation of Xpert HPV point-of-care test for detection of human papillomavirus infection by use of self-collected vaginal and clinician-collected cervical specimens. *J Clin Microbiol* 2016;54:1734–7.
24. Catarino R, Vassilakos P, Bilancioni A, et al. Accuracy of self-collected vaginal dry swabs using the Xpert human papillomavirus assay. *PLoS One* 2017;12:e0181905.
25. Ketelaars PJW, Bosgraaf RP, Siebers AG, et al. High-risk human papillomavirus detection in self-sampling compared to physician-taken smear in a responder population of the Dutch cervical screening: results of the VERA study. *Prev Med* 2017;101:96–101.
26. Polman NJ, Ebisch RMF, Heideman DAM, et al. Performance of human papillomavirus testing on self-collected versus clinician-collected samples for the detection of cervical intraepithelial neoplasia of grade 2 or worse: a randomised, paired screen-positive, non-inferiority trial. *Lancet Oncol* 2019;20:229–38.
27. Toliman PJ, Kaldor JM, Badman SG, et al. Performance of clinical screening algorithms comprising point-of-care HPV-DNA testing using self-collected vaginal specimens, and visual inspection of the cervix with acetic acid, for the detection of underlying high-grade squamous intraepithelial lesions in Papua New Guinea. *Papillomavirus Res* 2018;6:70–6.
28. Mbulawa ZZA, Wilkin TJ, Goeieman B, et al. Xpert human papillomavirus test is a promising cervical cancer screening test for HIV-seropositive women. *Papillomavirus Res* 2016;2:56–60.
29. Mapanga W, Girdler-Brown B, Feresu SA, et al. Prevention of cervical cancer in HIV-seropositive women from developing countries through cervical cancer screening: a systematic review. *Syst Rev* 2018;7:198.
30. Kuhn L, Saidu R, Boa R, et al. Clinical Evaluation of modifications to a human papillomavirus assay to optimise its utility for cervical cancer screening in low-resource settings: a diagnostic accuracy study. *Lancet Glob Health* 2020;8:e296–304.
31. Johnson LG, Saidu R, Mbulawa Z, et al. Selecting human papillomavirus genotypes to optimize the performance of screening tests among South African women. *Cancer Med* 2020;9:6813–6824.
32. Arbyn M, Depuydt C, Benoy I, et al. VALGENT: a protocol for clinical validation of human papillomavirus assays. *J Clin Virol* 2016;76(suppl 1): S14–21.

