Prevalence of Anal Human Papillomavirus (HPV) and Performance of Cepheid Xpert and Hybrid Capture 2 (hc2) HPV Assays in South African HIV-Infected Women

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ABSTRACT

Objectives: *This study investigated anal high-risk HPV (HR-HPV) prevalence in HIV-infected women using the Cepheid Xpert HPV assay and compares its performance with that of Hybrid Capture-2 (hc2).*

Methods: *A total of 199 HIV-infected women were recruited from Helen Joseph Hospital, Johannesburg. Stored ThinPrep anal swabs that had previously been tested using hc2 were tested for HPV using Xpert.*

Results: *The HR-HPV prevalence by Xpert was 40.8% and similar to hc2 (41.8%) with overall agreement of 86.7%; Cohen's kappa 0.73 (95% CI 0.63-0.82). High grade squamous intraepithelial lesions (HSIL) was associated with increasing number of multiple HPV infection (*P < *.001). Xpert and hc2 were similarly sensitive (77.4% and 77.4%, respectively) and specific (66.1% and 64.8% respectively) for HSIL detection. HPV16 (OR: 14.0, 95% CI: 3.9-48.0,* P < *.0001), HPV39/68/56/66 (OR: 4.1, 95% CI: 1.4-12,* P = *.01) and HPV51/59 (OR: 2.8, 95% CI: 1.1-7.6,* P = *.04) were independently associated with anal HSIL.*

Conclusions: *Xpert HPV typing is a promising anal screening test in HIV-infected women that performs similarly to hc2.*

Persistent human papillomavirus (HPV) infection is associated with cancers of the cervix, anus, vulva, vagina, penis, and head and neck.[1] Incidence of anal cancer is increasing in both women and men, and HPV is detected in 80% to 90% cases of anal cancer, with HPV 16 and HPV 18 being the dominant HPV types.[2] Anal cancer is more prevalent in women than in men.[3] It is more prevalent in individuals with a history of anal condyloma, cervical cancer, vulvovaginal cancer, and immunosuppression, including human immunodeficiency virus (HIV) infection.[4,5] The incidence of anal cancer remains elevated among HIV-infected individuals despite effective antiretroviral therapy (ART). It is hypothesized that anal cancer incidence will increase among HIV-infected populations with decreased risk of other AIDS-related illnesses and longer life expectancy.[1,6]

According to a 2015 systematic review, the incidence of anal cancer among HIV-infected women ranged from 3.9 to 30.0 per 100,000 person years compared with 0.55 to 2.4 per 100,000 person years among a general population of women.[1] Risk factors for anal HPV infection in women include cervical HPV infection, CD4 counts less than 200, smoking, anal intercourse, greater number of lifetime partners, and history of perianal and/or vulvar condyloma.[1,7-9] Anal HPV acquisition in women is reported even in women without a history of anal intercourse.[1] Among

women in South Africa, anal cancer age-standardized incidence in 2011 was reported to be 0.48 per 100,000 (95% confidence interval [CI], 0.39-0.57) according to the National Cancer Registry, which collects statistics for histologically diagnosed cancers in South Africa. These data, released in July 2016, are the most current cancer data available from the National Cancer Registry. The number of anal cancer cases was found to increase between 2000 and 2011 among South African women.[10]

In other countries as well, the incidence of anal cancer is reported to have increased in the past decades.[1,11] The observed increased anal cancer in women suggests that further investigation on anal cancer risk factors, natural history, screening, and treatment is needed. Data on anal HPV infection among HIV-infected women are very limited in sub-Saharan Africa. In South Africa, there are no standard guidelines on anal cancer prevention in either HIV-infected or uninfected women and men. Investigation of anal cancer screening methods among HIV-positive women may be necessary given the high anal cancer burden among HIV-infected individuals in the Unites States and Europe and the high prevalence of HIV in South Africa. Currently, no anal cancer statistics are stratified according to HIV status in South Africa. Performance of anal cancer screening for high-risk populations is recommended.[11-13] Therefore, the aim of this study was to investigate anal HPV prevalence in South African HIV-infected women using the Xpert HPV assay (Cepheid, Sunnyvale, CA) and compare its performance with that of Hybrid Capture 2 (hc2 [Qiagen, Germantown, MD], a test approved by the US Food and Drug Administration) for detection of high-grade squamous intraepithelial lesion (HSIL).

Materials and Methods

Study Population and Design

The current study used stored anal ThinPrep (Hologic, Bedford, MA) specimens obtained from HIV-infected women aged 25 to 65 years who were recruited from Themba Lethu Clinic (TLC), Helen Joseph Hospital, Johannesburg, South Africa. The parent study was conducted between June 2012 and August 2014. The study was described to women, and signed informed consent to participate in study-related activities was received from all participants. The University of Witwatersrand Human Research Ethics Committee, University of Cape Town Human Research Ethics Committee, and the University of North Carolina Internal Review Board approved all aspects of the study.

Women were ineligible to participant in the study if they were pregnant, had clinically active sexually transmitted infections (STIs) (participation was allowed after the STI treatment was completed), or had significant medical/mental illness. Three anal swabs were collected from each woman (one for conventional cytology and two for HPV testing). Anal cytology and high-resolution anoscopy (HRA) were performed as described in the parent study.[14,15]

HPV Genotyping

High-risk HPV testing was performed on ThinPrep anal swab specimens using Digene hc2 for the parent study. ThinPrep anal swabs were stored at −20°C in ThinPrep. A total of 1 mL ThinPrep anal specimen was used to run the Xpert HPV assay according to the manufacturer's instructions. Xpert HPV gives results from six separate channels: (1) sample adequacy control, (2) P1–HPV 16, (3) P2–HPV 18/45, (4) P3–HPV 31/33/35/52/58, (5) P4–HPV 51/59, and (6) P5–HPV 39/68/56/66.

Specimens with discordant Xpert HPV and hc2 results were further processed using the Roche (Indianapolis, Indiana) Linear Array HPV genotyping test. A total volume of 5 mL ThinPrep anal specimen was centrifuged at 8,000*g* for 30 minutes at −4°C, and cell pellet was resuspended to 400 µL phosphate-buffered saline. DNA from resuspended cells was extracted by a MagNA Pure Compact (Roche) using the MagNA Pure Compact Nucleic Acid Isolation Kit (Roche). HPV genotyping was performed using the Roche Linear Array HPV genotyping test, which identifies 37 different HPV genotypes. High-risk (HR)–HPV types included HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59; probable or possible HR-HPV types included HPV 26, 53, 66, 67, 68, 70, 73, and 82; and low-risk HPV types 6, 11, 40, 42, 54, 55, 61, 62, 64, 69, 71, 72, 81, 83, 84, 89 (HPV-CP6108), and IS39.

Statistical Analysis

Logistic regression was used to evaluate the relationship of the five Xpert channels to the presence of anal HSIL (defined as HSIL on cytology or histology or atypical squamous cells suggestive of HSIL on cytology). A multivariable model was fitted using stepwise logistic regression. The comparison of hc2 relative light units and numbers of Xpert channels among discordant specimens was done using the Student *t* test. The 95% CIs around estimated test characteristics were calculated using Clopper-Pearson binominal CIs. All statistical analysis was conducted using SAS version 9.4 (SAS Institute, Cary, NC).

Results

A total of 200 women were enrolled in the parent study. All women were HIV infected with a median CD4 count of 430 cells/mm^3 (interquartile range, 311-600), 97% (193/200) were taking ART, and 89% (166/200) had plasma HIV RNA levels of less than 400 copies/mL. A total of 196 women had anal Xpert HPV results (four specimens were missing). The overall HR-HPV prevalence was 40.8% (80/196) by Xpert and 41.8% (82/196) by hc2, with overall agreement of 86.7%; Cohen's κ was 0.73 (95% CI, 0.63-0.82), indicating substantial agreement. In total, 7.1% (14/196) were HPV 16 positive, 8.7% (17/196) were HPV 18/45 positive, 23.0% (45/196) were HPV 31/33/35/52/58 positive, 11.2% (22/196) were HPV 51/59 positive, and 16.3% (32/196) were HPV 39/68/56/66 positive **Figure 1**. Forty-four (22%) were positive for a single channel, 25 (13%) were positive for two channels, and 11 (6%) were positive for three channels.

HSIL by anal cytology or high-resolution anoscopy-directed biopsies was found in 15.8% (31/196). HPV positivity on both hc2 (odds ratio [OR], 6.3; 95% CI, 2.6-15.6; $P < .0001$) and HPV Xpert (OR, 6.7; 95% CI, 2.7-16.4; $P < .0001$) was significantly associated with HSIL. HPV 16 (OR, 13.1; 95% CI, 4.0-42.6; $P < .0001$), HPV 31/33/35/52/58 (OR, 4.2; 95% CI, 1.9-9.5; $P = .001$), HPV 51/59 (OR, 4.8; 95% CI, 1.8-12.5; $P = .001$), and HPV 39/68/56/66 (OR, 3.1; 95% CI, 1.3-7.4; $P = .012$) were significantly associated with HSIL but not HPV 18/45 (OR, 2.5; 95% CI, 0.8-7.5; $P = .12$). In multivariable analysis, HPV 16 (OR, 14.0; 95% CI, 3.9-48.0; $P < .001$), HPV 51/59 (OR, 4.1; 95% CI, 1.4-12.0; $P = .01$), and HPV 39/68/56/66 (OR, 2.8; 95% CI, 1.1-7.6; $P = .04$) were independently associated with HSIL **Table 1**. HSIL was associated with an increasing number of multiple HPV infections ($P < .001$, **Table 2**).

Xpert and hc2 were similarly sensitive (77.4% and 77.4%, respectively) and specific (66.1% and 64.8%, respectively) for HSIL **Table 3**. Sensitivity and specificity, respectively, were 29% and 97% for HPV 16, 16% and 93% for HPV 18/45, 48% and 82% for HPV 31/33/35/52/58, for 29% and 92% HPV 51/59, and 32% and 87% for HPV 39/68/56/66.

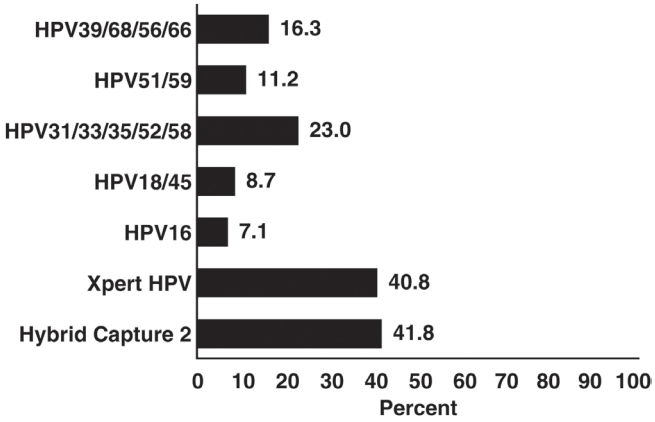

Figure 1 Anal human papillomavirus (HPV) prevalence among women infected with human immunodeficiency virus.

Six participants with HSIL were negative by Xpert and hc2. Two participants with HSIL had discordant results (one was Xpert positive/hc2 negative and one was Xpert negative/hc2 positive). There were 24 specimens with discordant HPV Xpert and hc2 results, and 23 of these specimens were further investigated using the Roche Linear Array HPV genotyping assay (remaining sample was not enough for one specimen). Thirteen specimens were positive by hc2 and negative by Xpert, and these specimens had lower HPV DNA detected compared with those with HPV DNA detected by both assays (relative light units [RLUs], 2.6 vs 48, $P < .0001$). Among 12 specimens with Roche Linear Array HPV genotyping results, three (25%) were HPV positive when considering only the HR-HPV types targeted by hc2. Eleven specimens were positive by Xpert and negative by hc2. These specimens had fewer channels with HPV detected than specimens positive by both tests (1.1 vs 1.7 channels, $P = .008$). Among these specimens,

Table 1
Association of Anal Human Papillomavirus With HSIL in Women Infected With Human Immunodeficiency Virus[a]

	Univariate Analysis OR for HSIL		Multivariable Analysis OR for HSIL	
Characteristic	**OR (95% CI)**	***P* Value**	**OR (95% CI)**	***P* Value**
Hybrid Capture 2	6.3 (2.6-15.6)	<.0001		
Xpert HPV	6.7 (2.7-16.4)	<.0001		
HPV 16	13.1 (4.0-42.6)	<.0001	14.0 (3.9-48.0)	<.0001
HPV 18/45	2.5 (0.8-7.5)	.12		
HPV 31/33/35/52/58	4.2 (1.9-9.5)	.001		
HPV 51/59	4.8 (1.8-12.5)	.001	4.1 (1.4-12.0)	.01
HPV 39/68/56/66	3.1 (1.3-7.4)	.012	2.8 (1.1-7.6)	.04

CI, confidence interval; HPV, human papillomavirus; HSIL, high-grade squamous intraepithelial lesion; OR, odds ratio.
[a] *P* values assess the statistical significance of the relationship between the characteristic and anal HSIL.

Table 2
Association of HSIL With Number of Human Papillomavirus Xpert Channel Positivity[a]

Xpert Channel	Xpert Channel, No. (%)	No. With HSIL	Prevalence of HSIL (%)
0	116 (59.2)	7	6.0
1	44 (22.4)	10	22.7
2	25 (12.8)	7	28.0
≥3	11 (5.6)	7	63.6
$P_{\text{trend for positivity}}$			<.001

HSIL, high-grade squamous intraepithelial lesion.
[a]Number of channels is strongly related to HSIL, Cochran-Mantel-Haenszel $P < .0001$.

four (36.4%) of 11 were HPV positive by the Roche Linear Array HPV assay (considering only the HR-HPV types targeted by all assays, Table 4).

Discussion

To our knowledge, this is the first published report on performance of anal HPV testing using the Xpert HPV assay. The GeneXpert technology has been widely available in the South African public health sector, and using it could be cost-effective and practical for HPV detection. This assay performed well in comparison to hc2, and we demonstrated substantial agreement between the two tests. Discordant results were related to lower HPV DNA amounts as demonstrated by lower RLU values by hc2 or a lower number of HPV channels detected by Xpert. This finding was observed in our previous study on cervical specimens.[16] Xpert has the advantage over hc2 of providing HPV typing. Observed anal HPV prevalence of 41% for only HR-HPV types is of concern as HR-HPV is among the risk factors for anal cancer. The prevalence of anal HR-HPV among HIV-infected women is reported to range between 16% and 85%.[1] A 42.9% (57/133) prevalence of anal HR-HPV was observed in HIV-infected women of sub-Saharan Africa origin in France taking ART.[17]

HPV 16 was strongly related to anal HSIL in our study. This is expected as HPV 16 is the predominant HPV type found in anal cancer.[2,3] In addition, the number of channels with HPV detected was related to the risk of HSIL: 63% of participants with three or more channels with HPV detection had anal HSIL compared with 23% and 28% of those with one and two channels with HPV detection, respectively. Patel et al[18] previously suggested that in a population with a high HPV burden, detection of multiple infections could be used as a marker to identify women at risk of developing precancerous lesions. Other analyses from our group have found that cervical HSIL is related to higher quantities of HPV DNA as measured by the cycle threshold from Xpert.[16] We did not investigate cycle thresholds within this analysis because we had relatively limited numbers of anal HSIL cases. Both Xpert and hc2 have been found to have similar sensitivity and specificity for detecting cervical intraepithelial neoplasia grades 2+ and 3+.[16,19-22]

There are limitations to this analysis. We performed the HPV detection on frozen specimens rather than in real time, as described in the package insert for this assay. It is therefore important to note that this study may be undercalling the prevalence of HPV as frozen specimens were used and fresh specimens may have had a higher detection rate. However, currently, no validation studies have been performed to determine the performance of the Cepheid Xpert HPV on frozen specimens compared with fresh specimens. Anal cytology was performed using conventional glass-slide cytology rather than liquid-based cytology as liquid-based cytology is not currently available within the South African public health sector. Strategies using HPV cotesting or triage strategies would likely use liquid-based cytology. Our providers performing high-resolution anoscopy were new to this procedure, and this likely resulted in an underestimate of anal HSIL. Thus,

Table 3
Performance of HPV Xpert and Hybrid Capture 2 for High-Grade Squamous Intraepithelial Lesion in Women Infected With Human Immunodeficiency Virus[a]

Characteristic	No./Total No. (%; 95% CI)			
	Sensitivity	Specificity	PPV	NPV
Hybrid Capture 2	24/31 (77; 59-90)	107/165 (65; 57-72)	24/82 (29; 20-40)	107/114 (94; 88-98)
Xpert HPV	24/31 (77; 59-90)	109/165 (66; 58-73)	24/80 (30; 20-41)	109/116 (94; 88-98)
HPV 16	9/31 (29; 14-48)	160/165 (97; 93-99)	9/14 (64; 35-87)	160/182 (88; 82-92)
HPV 18/45	5/31 (16; 5-34)	153/165 (93; 88-96)	5/17 (29; 10-56)	153/179 (85; 79-90)
HPV 31/33/35/52/58	15/31 (48; 30-67)	135/165 (82; 75-87)	15/45 (33; 20-49)	135/151 (89; 83-94)
HPV 51/59	9/31 (29; 14-48)	152/165 (92; 87-96)	9/22 (41; 21-64)	152/174 (87; 81-92)
HPV 39/68/56/66	10/31 (32; 17-51)	143/165 (87; 81-91)	10/32 (31; 16-50)	143/164 (87; 81-92)

CI, confidence interval; HPV, human papillomavirus; HSIL, high-grade squamous intraepithelial lesion; NPV, negative predictive value; PPV, positive predictive value.
[a]Xpert considered positive if any channel is positive.

Table 4
Analysis of Discordant Results Between Xpert HPV and Hybrid Capture 2 Compared With Roche HPV Linear Array Genotyping Results[a]

	Hybrid Capture 2			
Sample ID	RLU	Hybrid Capture 2 Positive/Negative	Xpert HPV Type	Roche LA HPV Type
SID 1	0.37	Negative	16 (Ct: 36.1), 31/33/35/52/58 (Ct: 33.8)	**16**, **33**, 53, 61, 71
SID 2	0.14	Negative	18/45 (Ct: 39.1)	Negative
SID 3	0.33	Negative	18/45 (Ct: 32.0)	Negative
SID 4	0.12	Negative	18/45 (Ct: 39.0)	Negative
SID 5	0.15	Negative	31/33/35/52/58 (Ct: 37.1)	62, 83
SID 6	0.51	Negative	31/33/35/52/58 (Ct: 36.9)	**35**, **52/33/35/58**, 71
SID 7	0.56	Negative	31/33/35/52/58 (Ct: 34.3)	Negative
SID 8	0.41	Negative	31/33/35/52/58 (Ct: 37.9)	55
SID 9	0.53	Negative	39/68/56/66 (Ct: 34.4)	**66**
SID 10	0.35	Negative	39/68/56/66 (Ct: 38.0)	**66**, 69
SID 11	0.88	Negative	51/59 (Ct: 36.3)	**51, 52/33/35/58**
SID 12	3.29	Positive	Negative	Negative
SID 13	9.26	Positive	Negative	81, 82
SID 14	12.41	Positive	Negative	Negative
SID 15	3.73	Positive	Negative	61, 70, 81
SID 16	1.74	Positive	Negative	Negative
SID 17	4.09	Positive	Negative	53, **58**
SID 18	3.29	Positive	Negative	Negative
SID 19	7.99	Positive	Negative	Negative
SID 20	1.5	Positive	Negative	**52/33/35/58, 68**
SID 21	1.69	Positive	Negative	Negative
SID 22	1.24	Positive	Negative	**52/33/35/58**
SID 23	1.31	Positive	Negative	72

Ct; cycle threshold; HPV, human papillomavirus; LA, Linear Array; RLU, reactive light unit; SID, sample ID.
[a]HPV types detected by Hybrid Capture 2, Xpert, and Roche Linear Array: HPV 16/18/31/33/35/39/45/51/ 52/56/58/59/66/68. The bold HPV types are those targeted by Hybrid Capture 2 or Xpert.

our reported test characteristics of Xpert for HSIL should be interpreted with caution as cases of HSIL were likely missed. It is also important to indicate that HPV 66 is targeted by the Cepheid Xpert platform but not hc2; however, hc2 has been reported to cross-react with HPV 66.[23]

In conclusion, Xpert HPV is a promising anal cancer screening test in HIV-infected women that performs similarly to hc2. The typing information provides additional data for determining HSIL risk and may be able to risk stratify who should proceed to diagnostic anoscopy alone or in combination with cytology. Future studies should investigate Xpert HPV as a primary or adjunctive test for anal cancer screening programs.

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