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Detecting anal human papillomavirus infection in men who have sex with men living with HIV: implications of assay variability

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ABSTRACT

Background Incidence of anal cancer (AC) caused by persistent human papillomavirus (HPV) infection has risen in the last years in men who have sex with men (MSM) living with HIV. There is consensus that this population should be screened for anal precancerous lesions, but the role of HPV DNA testing in AC screening programmes is still under debate.

Objectives This study employed two molecular test to detect anal HPV DNA and compared assay performance and prognostic value for the diagnosis of histology proven high-grade intraepithelial anal lesions.

Methods MSM living with HIV attended their regular check-up visits consisting of detection of anal HPV infection, anal cytology, digital anorectal examination and high resolution anoscopy. HPV DNA was detected using Hybrid Capture 2 High-Risk test (HC2, total assay) and LINEAR ARRAY HPV Genotyping Test (LA, type-specific assay)

Results Among 274 participant, prevalence of HPV DNA was 48.5% by HC2 and 89.4% by LA. HPV16 (30.6%) and HPV6 (19.6%) were the most common genotypes identified. Prevalence of multiple HPV infections was 56.2%. Agreement between HPV DNA assays was 75.2% ($\kappa=0.51$; 95% CI 0.42 to 0.60). Total HPV detection demonstrated high sensitivity (90%; 95% CI 68.3 to 98.8) and moderate specificity (58.4%; 95% CI 50.2 to 66.3), while type-specific HPV16/18 genotyping provided an increase in specificity and showed the highest area under the curve (0.81; 95% CI 0.74 to 0.89) and Youden's index (0.63).

Conclusions Both methodologies identified a high prevalence of anal HPV infection and multiple HPV infections in MSM living with HIV, showing a moderate overall agreement between them. Either total HPV detection or type-specific HPV16/18 detection together with a threshold \geq atypical squamous cells of undetermined significance for abnormal cytology showed an acceptable diagnostic accuracy.

INTRODUCTION

Chronic infection with oncogenic HPV is associated with precancerous lesions that may progress to invasive anal cancer (AC). Among MSM living with HIV, AC incidence is 131 per 100 000 person-year and the relative risk is 80 times higher than expected for the general population.¹

Currently, the gold standard for the histopathological evaluation of suspect lesions is the biopsy

directed by high-resolution anoscopy (HRA), a technically complex procedure that requires highly trained clinicians. Tests for HPV DNA detection are the recommended primary tools for cervical cancer screening,² but their use in MSM living with HIV is under discussion mainly due to the high HPV infection prevalence.³ There are numerous molecular tests available for HPV detection. Hybrid Capture 2 (HC2; Qiagen, Germany) and Linear Array Genotyping Test (LA; Roche Diagnostics, USA) have been widely validated in cervical samples²; however, few studies have compared their performance in anal samples. This study estimated anal HPV prevalence in MSM living with HIV by employing two HPV DNA detection tests and compared their performance and prognostic value for the diagnosis of histology proven high-grade intraepithelial anal lesions.

METHODS

MSM aged 18 years or older living with HIV who attended their check-up visit were offered to participate in an AC prevention programme consisting of detection of HPV DNA detection, anal cytology, digital anorectal examination (DARE) and HRA between May 2014 and June 2017. Anal samples were collected with circulatory rotatory movements for at least 40 s and then introduced in ThinPrep[®] Pap test vial containing PreservCyt[®] liquid-based medium (Hologic, Marlborough, Massachusetts, USA). Samples were stored at room temperature. Anal cytology was performed using the automatised system ThinPrep method (Hologic) and classified as negative for intraepithelial lesion and malignancy, atypical squamous cells of undetermined significance, low-grade squamous intraepithelial lesion (LSIL), high-grade squamous intraepithelial lesion (HSIL), atypical squamous cells cannot exclude HSIL (ASC-H) and squamous cell carcinoma.⁴ HRA was performed employing an anoscope coated with a lubricant inserted into the anal canal that was visualised using a colposcope. From 2014 until June 2016, HRA was performed a few days later after anal sample collection; from June 2016 onwards, HRA was performed at the same visit. Biopsies of any suspicious lesion were taken and were reported as negative, LSIL-AIN1, HSIL-AIN2 or HSIL-AIN3. HPV DNA detection was done using both HC2 and LA; discordant result were further tested with Anyplex II HPV28 (Seegene, Seoul, Korea). Agreement was determined using Cohen's kappa (κ) index and McNemar's χ^2 test. Histology



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Table 1 Performance of HPV DNA detection using HC2, LA and anal cytology for identification of HGAIN lesions results among HIV-infected men who have sex with men

	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	PLR (95% CI)	NLR (95% CI)	Area under ROC curve (95% CI)	Youden's index
HPV DNA detection								
HC2	90.0% (68.3 to 98.8)	58.4% (50.2 to 66.3)	22.0% (13.6 to 32.5)	97.8% (92.4 to 99.7)	2.2 (1.7 to 2.7)	0.2 (0.5 to 0.6)	0.74 (0.66 to 0.82)	0.484
LA (oncogenic HPV genotypes)	95.0% (75.1 to 99.9)	27.3% (20.4 to 35.0)	14.5% (9.0 to 21.7)	97.7% (87.7 to 99.9)	1.3 (1.1 to 1.5)	0.2 (0.0 to 1.3)	0.61 (0.55 to 0.67)	0.223
LA HPV16	70.0% (45.7 to 88.1)	76.6% (69.1 to 83.1)	28.0% (16.2 to 42.5)	95.2% (89.8 to 98.2)	3.0 (2.0 to 4.5)	0.4 (0.2 to 0.8)	0.73 (0.63 to 0.84)	0.466
LA HPV18	25.0% (8.7 to 49.1)	91.6% (86.0 to 95.4)	27.8% (9.7 to 53.5)	90.4% (84.6 to 94.5)	3.0 (1.2 to 7.4)	0.8 (0.6 to 1.1)	0.58 (0.48 to 0.68)	0.166
LA HPV16/18*	90.0% (68.3 to 98.8)	72.7% (65.0 to 79.6)	30.0% (18.8 to 43.2)	98.2% (93.8 to 99.8)	3.3 (2.4 to 4.4)	0.1 (0.0 to 0.5)	0.81 (0.74 to 0.89)	0.627
LA HPV6 and/or 16 and/or 18	95.0% (75.1 to 99.9)	61.0% (52.9 to 68.8)	24.1% (15.1 to 35.0)	98.9% (94.3 to 100)	2.4 (1.9 to 3.0)	0.1 (0.0 to 0.6)	0.78 (0.72 to 0.84)	0.560
LA HPV genotypes frequently identified in anal cancer (HPV16, 18, 33, 35, 58)	90.0% (68.3 to 98.8)	59.1% (50.9 to 66.9)	22.2% (13.7 to 32.8)	97.8% (92.4 to 99.7)	2.2 (1.7 to 2.8)	0.2 (0.5 to 0.6)	0.745 (0.67 to 0.82)	0.491
Anal cytology								
Abnormal	95.0% (75.1 to 99.9)	56.4% (48.0 to 64.5)	22.6% (14.2 to 33.0)	98.8% (93.6 to 100.0)	2.2 (1.8 to 2.7)	0.1 (0.0 to 0.6)	0.76 (0.69 to 0.82)	0.514
HSIL	45.0% (23.1 to 68.5)	96.0% (91.4 to 98.5)	60.0% (32.3 to 83.7)	92.9% (87.6 to 96.4)	11.2 (4.4 to 28.1)	0.6 (0.4 to 0.9)	0.70 (0.59 to 0.82)	0.410
HPV DNA detection and anal cytology								
HC2 and abnormal	85.0% (62.1 to 96.8)	72.5% (64.6 to 79.5)	29.3% (18.1 to 42.7)	97.3% (92.3 to 99.4)	3.1 (2.3 to 4.3)	0.2 (0.1 to 0.6)	0.79 (0.70 to 0.88)	0.575
HPV16/18 and abnormal	85.0% (62.1 to 96.8)	81.9% (74.7 to 87.7)	38.6% (24.4 to 54.5)	97.6% (93.1 to 99.5)	4.7 (3.2 to 6.9)	0.2 (0.1 to 0.5)	0.83 (0.75 to 0.92)	0.669
HC2 and HSIL	45.0% (23.1 to 68.5)	96.0% (91.4 to 98.5)	60.0% (32.3 to 83.7)	92.9% (87.6 to 96.4)	11.2 (4.5 to 28.1)	0.6 (0.4 to 0.9)	0.71 (0.59 to 0.82)	0.410
HPV16/18 and HSIL	45.0% (23.1 to 68.5)	97.3% (93.3 to 99.3)	69.2% (38.6 to 90.9)	92.9% (87.7 to 96.4)	16.8 (5.7 to 49.4)	0.6 (0.4 to 0.8)	0.71 (0.60 to 0.82)	0.423

Abnormal: ASC-US or ASC-H or LSIL.

Table created by the authors.

*Presence of HPV16, HPV18 or both HPV genotypes.

ASC-H, atypical squamous cells cannot exclude HSIL; ASC-US, atypical squamous cells of undetermined significance; HC2, Hybrid Capture 2 HPV DNA test; HGAIN, high-grade anal intraepithelial neoplasia; HPV, human papillomavirus; HSIL, high-grade squamous intraepithelial lesion; LA, Linear Array Genotyping Test; LSIL, low-grade squamous intraepithelial lesion; NLR, negative likelihood ratio; NPV, negative predictive value; PLR, positive likelihood ratio; PPV, positive predictive value; ROC, receiver operating characteristic.

results were grouped as negative for a normal appearance on HRA or LSIL-AIN1 cases, and high-grade anal intraepithelial neoplasia (HGAIN) for HSIL-AIN2 and HSIL-AIN3 cases. The prognostic value of the assays was calculated employing HGAIN histology result as the end point.

RESULTS

274 participants were enrolled in the study. All samples rendered a valid HPV detection result; 113 samples (48.5%) were positive by HC2 and 245 (89.4%) were positive by LA. Multiple HPV genotypes were detected in 207 (75.5%) participants; the median number of oncogenic and non-oncogenic HPV genotypes was 3 (IQR: 1–4) and 2 (IQR: 1–2), respectively. A valid anal cytology result was obtained in 269 samples (98.2%). Among 176 (64.2%) participants who underwent HRA, 95 (53.4%) had no anoscopically visible abnormalities and 81 (29.6%) were biopsied. Online supplemental table 1 shows the cytology and histology results. HPV prevalence by HC2 was 41.6% (64/154) in men with negative histology and 90% (18/20) in men with HGAIN ($p < 0.0001$). HPV prevalence by LA was 85.7% (132/154) and 100% (20/20) ($p = 0.0806$), respectively. HPV16 (70% (14/20)) and HPV6 (45% (13/20)) were the most prevalent genotypes in patients with HGAIN results. Differences regarding HPV type-specific prevalence according to HGAIN and negative results were identified for HPV16 (70% (14/20) vs 23.4% (36/154); $p < 0.0001$), HPV18 (25% (5/20) vs 8.4% (13/154); $p = 0.0384$), HPV39 (30% (6/20) vs 11% (17/154); $p = 0.0303$), HPV42 (25% (5/20) vs 8.4% (13/154); $p = 0.0384$) and HPV58 (30% (6/20) vs 11% (18/154); $p = 0.0374$). Similarly, differences were observed for the prevalence of multiple oncogenic (85% (17/20) vs 54% (83/154); $p = 0.0081$) and non-oncogenic (75% (15/20) vs 44.8% (69/154); $p = 0.0160$) HPV genotypes. The agreement between assays was 75.2% ($\kappa = 0.51$; 95% CI 0.42 to 0.60). Discordant results corresponded to 61 samples (22.3%) that tested negative by HC2 and positive by LA and 7 samples (2.6%) that tested a positive result by HC2 and negative by LA ($p < 0.001$). Anyplex II HPV28 detection identified at least one oncogenic HPV genotype targeted by HC2 in 6/7 (85.7%) samples. The performance characteristics of the HPV DNA detection tests and the anal cytology in identifying HGAIN results are presented in table 1.

DISCUSSION

In our study of anal samples, the agreement between two HPV DNA detection assays was slightly lower than described for cervical samples, although the presence of lubricants, stool or even a lower DNA levels in anal samples could interfere with their performance.⁵ Although most discordant results may be explained by the higher analytical sensitivity of the LA, there were also identified samples classified as analytically false positive or false negative. HC2 false positivity may be attributed to the cross-reactivity with genotypes not targeted by the probe, which may have been the case in our sample, in which HPV61 was identified. LA false negativity may be explained by a higher analytical sensitivity for the detection of specific HPV genotypes due to the overcoming of masking effects to the competition for the use of consensus primers *versus* specific primers (eg, Anyplex II HPV28).⁶ Moreover, the size of the amplicons would also be associated with increased detection because longer amplicons may result in more negative samples. Despite the fact that Anyplex II HPV28 test does not provide information about the amplicon size, LA amplifies a fragment that can be considered long (450 bp). Interestingly, four of these six LA false negative samples harboured HPV genotypes frequently reported as cross-reactive in HC2.

The role of HPV DNA testing in AC screening programmes in people living with HIV or MSM is still under debate.³ We identified that total HPV DNA detection demonstrated a high sensitivity but a low specificity for HGAIN, mainly as a consequence of the high prevalence of anal HPV.⁷ In contrast to earlier studies, we identified that the use of HC2 *versus* LA showed higher specificity, PPV and area under the curve (AUC), while having a slight impact on sensitivity.⁸ This better overall performance of HC2 may be explained by the analytical sensitivity and the association of a higher HPV viral load of persistent infection with a higher risk of HGAIN.⁷ Indeed, we observed that the median values of RLU/CO increased with the grade of abnormality in the histology results. Previous studies have reported how the inclusion of HPV genotyping *versus* total HPV DNA detection provided an increase in clinical specificity, and a decrease in the clinical sensitivity.⁷ Our findings support these results, and we found that the identification of selected combinations of HPV genotypes demonstrated higher sensitivity, specificity and NPV than individual genotyping. HPV16/18 genotyping showed the highest Youden's index and AUC, which could be mainly explained because 90% of men histologically diagnosed with HGAIN enrolled in this study were positive for at least one of the two genotypes. In our study, the HPV detection-cytology cotesting decreased the sensitivity but increased the specificity and the PPV when we employed as the definition of an abnormal cytology a threshold of HSIL *versus* \geq ASC US, confirming that the anal cytology screening seems to underestimate the true level of histological dysplasia.⁹ Previous reports on cotesting demonstrate high sensitivity and a low specificity¹⁰ that improves with the HPV16 and/or HPV18 genotyping.⁷ In our population, global HPV detection by HC2 or HPV16/18 genotyping by LA showed similar clinical performance, and the use of a threshold \geq ASC US for abnormal cytology provided the highest diagnostic accuracy for detecting anal precancer, suggesting that either HPV DNA-based tests could be used for detection of HGAIN lesions.

This study is subject to several limitations. The prevalence of HGAIN results reported in our study is lower compared with other works. The expertise in the use of the anoscope to identify visually suspicious areas of the anal canal, characterised by a long learning curve, might have conditioned the number of biopsies. Moreover, not all men included in the study completed the protocol because, during the first period, the anal sample collection was performed in the first visit but the HRA was programmed some days later. Whether the low detection of lesions is attributable to a false low indication of biopsies remains to be seen in the future evaluation of the study subjects. In addition, all parameters evaluated are cross-sectional and it would be more relevant to have a prospective indication of the value of HPV DNA-based detection. Finally, the relatively small sample size might also have underpowered the study.

The advantage of this study was the use of fresh anal samples to compare the performance of two frequently employed HPV

Key messages

- ⇒ Anal HPV prevalence in a population of MSM living with HIV attending their check-up visit was very high employing either a total or type-specific HPV detection assay.
- ⇒ Oncogenic HPV16 and non-oncogenic HPV6 were the most prevalent genotypes among men histologically diagnosed with high-grade anal intraepithelial neoplasia.
- ⇒ The overall agreement between the two HPV DNA assays for the identification of anal HPV infection was moderate.

DNA-based assays along with cytology and HRA from a homogeneous population of MSM living with HIV. All results were tested blindly. To further our research, we are performing a long-term follow-up of the cohort to perform both longitudinal and cost-effectiveness analyses to discriminate potential HPV biomarkers with prognostic value to predict the persistent anal precancerous lesions.

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Competing interests Cancer Epidemiology Research Program (ST, AE, SdS and MT) has received sponsorship for grants from Merck and Co, GlaxoSmithKline, Hologic and Seegene.

Patient consent for publication Not applicable.

Ethics approval This study was approved by Ethics Committee for Research of Bellvitge University Hospital (Barcelona, Spain) (ID: PR345/14). Participants gave informed consent to participate in the study before taking part.

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Supplemental Table 1. Cytology and histology results among men who have sex with men living with HIV.

Cytology	HRA					
	No biopsy (n=95) n (%)	Negative (n=45) n (%)	LSIL-AIN1 (n=14) n (%)	HSIL-AIN2 (n=14) n (%)	HSIL-AIN3 (n=6) n (%)	Unsatisfactory (n=2) n (%)
NILM	57 (60)	21 (46.7)	6 (42.9)	1 (7.1)	0 (0.0)	2 (100)
ASC-US	13 (13.7)	10 (22.2)	2 (14.3)	2 (14.3)	0 (0.0)	0 (0.0)
LSIL	18 (18.9)	8 (17.8)	6 (42.9)	5 (35.7)	1 (16.7)	0 (0.0)
ASC-H	2 (2.1)	0 (0.0)	0 (0.0)	1 (7.1)	1 (16.7)	0 (0.0)
HSIL	1 (1.1)	5 (11.1)	0 (0.0)	5 (35.7)	4 (66.7)	0 (0.0)
Unsatisfactory	4 (4.2)	1 (2.2)	0 (0.0)	0 (0.0)	0 (0)	0 (0.0)

NILM: negative for intraepithelial lesion and malignancy; ASC-US: atypical squamous cells of undetermined significance, ASC-H: atypical squamous cells cannot exclude HSIL; LSIL: low grade squamous intraepithelial lesion; HSIL: high grade squamous intraepithelial lesion. HRA: High resolution anoscopy. AIN: Anal intraepithelial neoplasia.

Table created by the authors

Antecedentes: En los últimos años ha aumentado la incidencia de cáncer anal (CA) causado por el virus de papiloma humano (VPH) en hombres que tienen sexo con hombres (HSH) que viven con VIH. A pesar de que existe consenso en que esta población debe ser sometida al cribado de lesiones precancerosas anales, sigue siendo objeto de debate el empleo de pruebas de detección de VPH en los programas de cribado.

Objetivos: Este estudio empleó dos pruebas moleculares para la detección del ADN del VPH, y comparó el rendimiento de las mismas así como su valor pronóstico en el diagnóstico de lesiones anales intraepiteliales de alto grado.

Métodos: HSH que viven con VIH y que acudieron a visitas control que consistían en la detección de VPH anal, citología anal, examen rectal digital y anoscopia de alta resolución (AAR) con toma de biopsia de zonas sospechosas de lesión. El ADN del VPH fue detectado empleando *Hybrid Capture® 2 High-Risk test* (HC2, detección total) y *Linear Array HPV test* (LA, detección tipo-específica).

Resultados: En 274 participantes identificamos una prevalencia de infección por VPH del 48,5% empleando HC2 y del 89,4% con LA. VPH16 (30,6%) y VPH6 (19,6%) fueron los genotipos más prevalentes. La prevalencia de infecciones múltiples fue del 56,2%. La concordancia entre las pruebas de detección de VPH fue del 75,2% ($\kappa=0,51$; intervalo de confianza [IC] del 95%: 0,42-0,60). La detección total de VPH demostró una elevada sensibilidad (90%; IC 95%: 68,3-98,8) y una especificidad moderada (58,4%; IC 95%: 50,2-66,3), mientras que la detección tipo-específica VPH16/18 proporcionó un aumento de la especificidad y mostró el mayor AUC (0,81; IC 95%: 0,74-0,89) e índice de Youden (0,63).

Conclusiones: Ambas metodologías identificaron una elevada prevalencia de infección e infección múltiple en HSH que viven con VIH, observándose una concordancia moderada entre ellas. Tanto la detección total de VPH como la detección tipo-específica de VPH16/18, con un resultado \geq ASC-US para la citología anal, mostraron una precisión diagnóstica aceptable.