Prevalence of HPV genitalia and oral infection in an unvaccinated population of MSM-HIV in Northwest Spain

Prevalencia de la infección genital y oral por VPH en población no vacunada de HSH-VIH en el noroeste de España

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ABSTRACT

Introduction: Human papillomavirus (HPV) infection is the most common sexually transmitted infection (STI), and it is a major risk factor for penile, oropharyngeal and anal cancer. HPV anal infection is common in men-who-have-sex-with-men (MSM), especially in patients living with HIV (MSM-HIV). HPV can also be detected in genitalia and oral tissues. The objective of this cross-sectional study is to analyze the prevalence of HPV genital and oral infection in a HIV-MSM cohort.

Methods: This cross-sectional study of HPV infection included 107 HIV-MSM subjects recruited in a HIV follow-up unit of Northwest Spain.
HPV-vaccinated subjects were excluded. HPV-DNA was detected with Anyplex™ II HPV28 method. Participants completed a questionnaire on lifestyle and sexual behavior.

Results: Median age was 43 years (range 35-54 years); 97 patients received antiretroviral treatment (ART); 81 (75.7%) had undetectable HIV-RNA; median CD4-lymphocyte count was 746 cell/mm^3; 70 (65.4%) participants had a previous STI. Genitalia HPV-DNA was detected in n=37 (34.6%) subjects and oral HPV-DNA was detected in 26 (24.3%). In 12 (11.2%) patients, HPV-DNA was detected in both locations. High risk HPV (hrHPV) genotypes were detected in 24 (22.4%) and 15 (14%) patients in genitalia and oral samples respectively. Genitalia HPV-DNA isolation was more common in HIV virologically non-suppressed patients (65.4% vs 24.7%; p<0.001).

Conclusions: HPV genitalia and oral infection is common in unvaccinated HIV-MSM patients. Detectable HIV-RNA was associated with higher HPV prevalence in genitalia. High oncogenic risk HPV genotypes were more common in genitalia than in oral cavity.

Keywords: HPV, HIV, papillomavirus, prevalence, men who have sex with men.

RESUMEN

Introducción: La infección por el virus del papiloma humano (VPH) es la infección de transmisión sexual (ITS) más común; y es factor de riesgo para el desarrollo de cáncer de pene, orofaringe y ano. La infección por VPH es frecuente en hombres-que-tienen-sexo-con-hombres (HSH), especialmente en pacientes infectados por VIH (HSH-VIH). Asimismo, el VPH puede infectar genitales y cavidad oral. El objetivo de este estudio transversal es estimar la prevalencia de la infección orogenital por VPH en una cohorte HSH-VIH.

Métodos: se incluyeron 107 pacientes de una Unidad de VIH del noroeste de España. Los pacientes vacunados fueron excluidos. El material genético del VPH (ADN-VPH) fue detectado mediante Anyplex™-II HPV-28. Los participantes completaron un cuestionario sobre hábitos sexuales.

Resultados: la mediana de edad fue 43 años (rango 35-54); 97 pacientes recibían tratamiento antirretroviral (TAR); 81 (75,7%) presentaban carga viral del VIH suprimida, la mediana de linfocitos-CD4 era de 746 células/mm^3, 70 (65,4%) habían padecido una ITS. Se detectó VPH en los genitales de 37 (34.6%) sujetos, en la cavidad oral de 26 (24.3%) y en 12 (11,2%) en ambas localizaciones. Se detectaron genotipos de alto riesgo oncogénico (AR-VPH) en 24 (22,4%) y 15 (14%) sujetos en genitales y cavidad oral respectivamente. El aislamiento del VPH fue más común en pacientes virológicamente no-suprimidos (65.4% vs 24.7%).

Conclusiones: la infección orogenital por VPH es frecuente en pacientes HSH-VIH no vacunados. La no-supresión virológica del VIH se asoció con mayor prevalencia de infección genital por VPH. La detección de genotipos AR-VPH fue más común en genitales que cavidad oral.

Palabras clave: VPH, VIH, papilomavirus, prevalencia, HSH

INTRODUCTION

Human papillomavirus (HPV) infection is the most common sexually transmitted infection (STI) in many countries, including United States[1] and some South European regions[2]. HPV is the main cause of cervical cancer in woman[3] and anal cancer in HIV-MSM([4]). Moreover, HPV is a major cause of penile cancer[5] and oropharyngeal carcinoma[6]. HPV genotypes are classified in four categories based on their oncogenic risk: high oncogenic risk (i.e., HPV-16, HPV-18), probably high-risk (i.e., HPV-53), low risk (i.e., HPV-6, HPV-11) and indeterminate risk (i.e., HPV-25)[7]. Prior studies have reported an incidence of HPV anal infection in MSM-HIV patients between 24 and 33/100 person-years, higher than MSM HIV negative subjects[8]. On the other hand, previous studies reported an HPV penile incidence around 11/100 persons-year in people living with HIV (PLWH)[9]. Incidence is also higher in HIV-MSM individuals compared to men-who-have-sex-with-women (MSW). In regard of oral HPV infection, our research group reported a prevalence of 13.4% in a MSM-HIV cohort[10]. HPV-16 and HPV-18 are the most detected HPV genotypes in anal and genitalia samples. However, several cross-sectional studies did not fin concordance between HPV genotypes across anatomic locations[11]. Sexual behavior plays a key role in the acquisition of HPV infection. In addition, specific sexual practices (i.e., oral sex, multiple sexual partners) may increase the risk of HPV infection in genitalia or oral cavity[9]. Also, a great number of sexual partners and a younger age of first sexual intercourse increase the risk of HPV infection[9].

Currently, the interaction between HPV and HIV is not yet fully understood but several studies have found a higher risk of HPV related carcinomas in PLWH[7]. This may be attributed to several mechanisms, such as the immunosuppression state induced by HIV, disruptions of the mucosal epithelial barrier and low clearance of HPV[12].

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Coinfection of HPV, HIV and other STIs is also frequent[13]. Indeed, *Chlamydia trachomatis* coinfection may increase HPV-related cancer in males[14] and infertility[15]. Furthermore, *Ureaplasma* and other bacterial STIs could increase the HPV carcinogenity[13].
To date, few studies have analyzed concurrent infection in the genitalia and the oral cavity. We performed a cross-sectional hospital-based study to evaluate the prevalence of HPV DNA in a HIV-MSM cohort from Northwest Spain.

METHODS

Study design

This cross-sectional study was performed in Vigo, Spain, from January 2019 to December 2019. Patients were recruited in the HIV follow-up Unit of Alvaro Cunqueiro Hospital, in Northwest Spain (population area around 540,000 inhabitants). HPV-vaccinated subjects were excluded. HIV virological suppression was defined as a HIV viral load under 50 copies per milliliter. The study was approved by Ethics Committee of Pontevedra-Vigo-Ourense (reference 217/2019). Written informed consent was obtained from each participant.

Data collection

Subjects were recruited during their follow-up at HIV unit. A questionnaire was used to collect sexual behavior data, including condom usage, age of sexual intercourse and number of sexual partners. Demographical and clinical data were obtained from the medical records.

Sample collection and laboratory test

Samples were collected in the HIV follow-up unit. Genitalia samples were obtained with a cytologic brush (Endobrush®, Covaca S.A., Madrid, Spain) from glans, coronal sulcus and scrotum, and stored in TrisEDTA pH8 molecular grade at 4 ºC. Oral samples were taken after one hour fast. Patients were asked to make two rinses with 5 mL of sodium chloride. First rinse was safely disposed while the second was sent to laboratory in a sterile bottle at ambient temperature.

In addition, anal, oral and genitalia swabs were obtained for bacterial STI detection and stored in PCR media (Roche Diagnostics®, Basel, Switzerland). Samples were tested for *Chlamydia trachomatis* and *Neisseria gonorrhoeae*. Serum was obtained for *Treponema pallidum* study (enzyme immunoassay, LIAISON®, Diasorin; rapid plasma reagin, Biomerieux®, France).

HPV-DNA was extracted from genitalia and oral samples employing the QIAcube automated extraction system (Qiagen, Hilden, Germany). The HPV genotypes were identified by applying the Anyplex™ II HPV28 detection method (Seegene, Seoul, South Korea), following the manufacturer's recommendations. This test simultaneously detects 19 types of high-risk HPV (HPV-16, HPV-18, HPV-26, HPV-31, HPV-33, HPV-35, HPV-39, HPV-45, HPV-51, HPV-52, HPV-53, HPV-56, HPV-58, HPV-59, HPV-66, HPV-68, HPV-69, HPV-73, HPV-82) and 9 types of low-risk HPV (HPV-6, HPV-11, HPV-40, HPV-42, HPV 43, HPV-44, HPV-54, HPV-61, HPV-70). The system performs 3 real-time multiplex polymerase chain reactions per sample using DPO™ Technology and the TOCETM technology melting curve analysis method.

Statistical analyses

Quantitative variables are expressed as median and interquartile range. Qualitative variables are shown as absolute value and percentages. Categorical variables were compared with χ-square test or Fischer exact test as appropriate. For quantitative variables comparison we used U Man Whitney test. A p value less than 0.05 was considered significant. Statistical analysis was performed with Statistical Package for Social Sciences (SPSS), IBM, version 22.

Ethics

All patients signed an informed consent form. Study was approved by Ethics Committee of Pontevedra-Vigo-Ourense (reference 217/2019).

RESULTS

A total of 107 HIV-MSM subjects were recruited. The median age was 43 years (IQR, 35-54) and most of them were Spanish (n=80, 74.8%). Demographic and clinical characteristics are shown in Table 1.

Table 1. Baseline characteristics of study population

Ethnicity, n (%)	
Spanish	80 (74.8%)
Latin-American	25 (23.4%)
Other	2 (1.8%)
Age in years, median (range)	43 (35 – 54)
Subjects receiving ART	97 (90.7%)
Naive to ART	10 (9.3%)
Nadir CD4 lymphocyte (cell/mm3; median and range)	326 (197 – 456)
CD4 nadir less than 200 (cell/mm3), n (%)	25 (23.4%)
CDC C stage, n (%)	21 (19.6%)
CD4 lymphocyte at recruitment (cell/mm3; median and range	746 (447 – 966)
HIV RNA < 50 copies/mL	81 (75.7%)
Time since HIV diagnosis (years; median and interquartile range)	8 (4 – 13)
Circumcision, n (%)	22 (20.6%)
Anogenital condylomata acuminata	17 (15.9%)
Prior HPV anal infection, high risk genotype	68 (63.6%)
Tobacco consumption	
Current smoker, n (%)	34 (31.8%)
Former smoker, n (%)	19 (17.8%)
Never smoker, n (%)	53 (49.5%)
Previous sexually transmitted infection, n (%)	70 (65.4%)
Syphilis, n (%)	64 (59.8%)
Gonorrhea, n (%)	21 (19.6%)
Chlamydia trachomatis infection, n (%)	10 (9.3%)

HIV: human immunodeficiency virus; ART: anti-retroviral treatment, CDC: Centers for Disease Control and Prevention, HIV-RNA: human immunodeficiency viral load; HPV: human papillomavirus

Sexual behavior questionnaire

Consistent use of condom in penetration was reported by 55 patients (51.4%), but only 5 (4.7%) used condom in oral sex. The median number of lifetime sexual partners was 100 (IQR,40-300) and 4 in the past year (IQR, 1-10). The median age of first sexual intercourse was 17 years (IQR, 15-18) (Table 2). The sexual behavior questionnaire is attached as supplementary material.

Table 2. Results of sexual behavior questionnaire

Age of first sexual intercourse, median (range)	17 (15 – 18)
Lifetime number of sexual partners, median (range)	100 (40 - 300)
Sexual partners last year, median (range)	4 (1 - 10)
Consistent condom use (penetration), n (%)	55 (51.4%)
Consistent condom use (oral sex), n (%)	5 (4.7%)

Bacterial STI samples

A total of 24 patients tested positive for another STI excluding HPV infection. The most frequent bacterial STI was *Chlamydia trachomatis* infection with 12 cases (11.2%), followed by *Neisseria gonorrhoeae* (9 cases, 8.4%) and *Haemophilus parainfluenzae* (2 subjects, 1.9%). *Chlamydia* spp. and gonococcus spp. coinfection was detected in 2 subjects (1.9%). Ten subjects (9.3%) tested positive for anal infection, followed by oral cavity (5 cases, 4.7%) and urethra (4 cases, 3.7%). One subject (0.9%) tested positive in two locations: anal conduct and oral cavity. Ten patients (9.3%) tested positive for active syphilis. HPV infection prevalence did not vary between patients who tested positive for a concurrent bacterial STI (27.5% vs. 17.9% respectively).

HPV prevalence and distribution

HPV prevalence results are shown in Table 3, Table 4 and Figure 1. A total of 51 subjects (47.7%) tested positive for HPV-DNA in one or both locations. HPV DNA was detected in 37 genitalia samples (34.6%). HPV DNA was isolated from oral samples of 26 participants (24.3%).

The distribution of HPV genotypes was different between genitalia and oral samples. HPV-51 was the most common in genitalia samples (n=9; 8.4%), followed by HPV-16 (n=7, 6.5%) and HPV-68 (n=6, 5.6%). However, HPV-66 was the most frequent strain in oral samples, reaching 6 cases (5.6%) tied with HPV-16 (6 cases, 5.6%). HPV-51 and HPV-68 were not detected in oral samples. Coinfection of more than one HPV genotype was more common in genitalia than oral cavity (52.8% vs 30.8% respectively).

Overall, prevalence of HPV-DNA detection was higher in non-virologically suppressed patients. However, after stratification by anatomical site, only genitalia infection was associated with detectable HIV RNA (65.4% vs 24.7%; p<0.001). No difference was observed in HPV oral infection between virologically suppressed and non-suppressed patients (24.9% and 23.1%, respectively). Age, number of sexual partners and age of first sexual intercourse did not differ between HPV positive and HPV negative patients.

HPV genitalia infection did not vary between smokers and non-smokers. Regarding oral cavity, there was no significant differences in HPV prevalence in smokers and ex-smokers vs. never smokers (30.2% and 20.5%, respectively). HPV oral infection pre-

Table 3. Study population characteristics stratified by HPV infection status

	HPV negative (n=56)	HPV positive (n=51)	*p value*
Demographic characteristics			
Age, median (range), years	49 (16)	43 (28)	*p=0.512*
Spanish origin, n (%)	43 (76.8%)	37 (72.5%)	*p=0.461*
Clinic and HIV characteristics			
Time of known HIV, median (range), years	9 (8.3)	7 (10.0)	*p=0.154*
CDC stage C, n (%)	8 (13.3%)	13 (25.5%)	*p=0.223*
HIV viral load < 50 copies/mL, n (%)	48 (85.7%)	33 (64.7%)	*p=0.014*
CD4 nadir less than 200 (cell/mm3), n (%)	10 (17.9%)	15 (29.4%)	*p=0.258*
CD4 lymphocyte at recruitment (cell/mm3; median and interquartile range)	747 (473)	746 (632)	*p=0.772*
Naive to ART, n (%)	2 (3.6%)	8 (15.7%)	*p=0.045*
Current smoker, n (%)	22 (39.3%)	12 (23.5%)	*p=0.098*
Circumcision, n (%)	9 (16.1%)	13 (25.5%)	*p=0.261*
Sexual questionnaire			
Age of first sex intercourse, median (range), years	17 (3)	17 (4)	*p=0.260*
Lifetime number of sexual partners, n (%)	100 (227)	150 (413)	*p=0.752*
Sexual partners last year, median (range)	3 (8)	4 (11)	*p=0.534*
Consistent condom use (penetration), n (%)	31 (59.6%)	24 (57.1%)	*p=0.836*
Consistent condom use (oral sex), n (%)	3 (5.8%)	2 (4.8%)	*p=1.000*
History of sexually transmitted infection, n (%)	39 (69.6%)	31 (60.8%)	*p=0.417*
Current sexually transmitted infection, n (%)	10 (17.9%)	14 (27.5%)	*p=0.255*

valence did not differ between patients with a history of a previous STI. In both locations, prevalence was not related with HIV stage C nor a CD4 cell count less than 200 cell/mm^3. Age, circumcision status, number of lifetime sexual partners, consistent condom use, age of first sexual intercourse, CD4 lymphocyte count, nadir CD4 lymphocyte count and tobacco consumption did not differ between HPV positive and HPV negative subjects.

Table 4. HPV results stratified by anatomical site

Location	Genitalia	Oral Cavity
Coinfection of more than one genotypes	19 (17.8%)	8 (7.5%)
At least one high-risk genotype	24 (22.4%)	15 (14.0%)
High-risk genotypes		
HPV-16	7 (6.5%)	6 (5.6%)
HPV-18	5 (4.7%)	1 (0.9%)
HPV-26	2 (1.9%)	0
HPV-31	2 (1.9%)	3 (2.8%)
HPV-33	4 (3.7%)	1 (0.9%)
HPV-35	1 (0.9%)	0
HPV-45	2 (1.9%)	0
HPV-51	9 (8.4%)	0
HPV-52	3 (2.8%)	0
HPV-56	1 (0.9%)	3 (2.8%)
HPV-58	2 (1.9%)	2 (1.9%)
HPV-59	3 (2.8%)	0
HPV-66	2 (1.9%)	6 (5.6%)
HPV-68	6 (5.6%)	0
HPV-69	0	2 (1.9%)
HPV-73	3 (2.8%)	1 (0.9%)
HPV-83	0	1 (0.9%)
HPV-84	1 (0.9%)	0
HPV-89	1 (0.9%)	0
Probably high-risk genotypes		
HPV-53	2 (1.9%)	0
Indeterminate risk genotypes		
HPV-25	0	1 (0.9%)
Low-risk genotypes		
HPV-6	3 (2.8%)	1 (0.9%)
HPV-11	2 (1.9%)	0
HPV-40	1 (0.9%)	0
HPV-42	3 (2.8%)	2 (1.9%)
HPV-43	5 (4.7%)	0
HPV-44	4 (3.7%)	1 (0.9%)
HPV-61	2 (1.9%)	2 (1.9%)
HPV-62	1 (0.9%)	1 (0.9%)
HPV-70	4 (3.7%)	0
HPV-72	0	1 (0.9%)
HPV-81	0	1 (0.9%)

DISCUSSION

In this cross-sectional study we analyzed the prevalence of HPV-DNA in genitalia and oral samples in a Spanish HIV-MSM cohort. The study results are similar to previous research in another European countries (between 20% and 31%.) ([11,16]). However, the estimated incidence of HPV genital and oral infection varies widely across different studies, due to several reasons. Firstly, the study population may vary between studies. For example, studies focused in PLWH reveal a higher prevalence of HPV-DNA detection than HIV negative populations. In addition, there is not a clear consensus about how to collect genitalia and oral samples. The lack of a standard criteria may over or underestimate the real prevalence of HPV infection. Thirdly, vaccination programs may reduce the prevalence rate of some HPV genotypes (i.e., HPV-16, HPV-18). In our study, we excluded HPV vaccinated subjects. Therefore, our study could report a higher prevalence compared to studies including vaccinated patients. Finally, geographical and regional variations may influence the results of unicentric studies.

Overall prevalence of HPV infection was higher in genitalia than oral cavity, including hrHPV, similar to previous research[17]. We could not find any studies in Spanish population that compared HPV infection prevalence between genitalia and oral samples.

Distribution of genotypes also varied between both locations, maybe signaling different tropism based on the genotype. The cause of this variability remains unknown, but the interactions between HPV and mucosal surface, microbiome and local immunity could play a significant role[12].

HPV-16 was the only genotype detected in a similar rate in both locations (6.5% vs. 5.6%). The prevalence in our study is slightly higher than previous research[18].

On the other hand, HPV-66 was the most detected genotype in oral samples, tied with HPV-16. HPV-66 is classified as probable high risk oncogenic strain with an estimated prevalence in woman around 16%[19]. The prevalence and relevance of this genotype in HIV-MSM is still unknown.

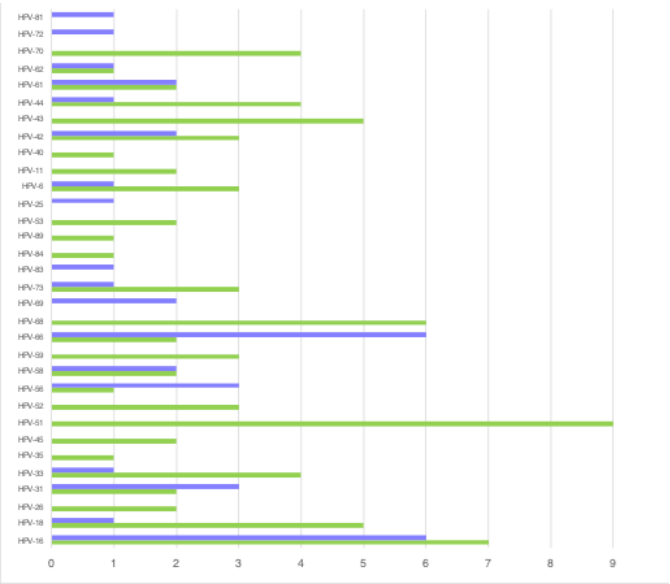
HPV-51 was the most common genotype isolated from genital samples; however, it was not detected in any oral sample. HPV-51 is a hrHPV, which anal prevalence in a nationwide Spanish cohort was around 20%[20].

HPV-18, HPV-33, HPV-52 and HPV-68 were also more commonly detected in genitalia than oral samples. All of them are considered hrHPV. Most of the previous studies have been focused on anal samples[20], while real prevalence and incidence of these genotypes outside anal conduct remains unknown.

Coinfection of multiple genotypes was also more common in genitalia than in oral cavity. HPV coinfection is frequent in HIV-MSM[21]. HIV enhance individual susceptibility to HPV infection through various mechanisms. Firstly, HIV decrease the number of CD4 lymphocytes, which increases the risk of HPV infection. Secondly, cells exposed to HIV produce many inflammatory substances, damaging epithelial barriers and other defensive mechanisms. Finally, HIV infection lowers the rate of HPV clearance[12].

We found no correlation between HPV genotypes in genitalia and oral cavity. Our previous research showed no concordance between anal and oral HPV genotypes[10]. The lack of concordance between locations have been reported in several previous cross-sec-

Figure 1. HPV distribution stratified by anatomical site



tional studies[22]. The absence of concordance between genital and oral samples may be due to different interactions between HPV and both tissues. Furthermore, anatomic alterations in oral or genitalia mucosa may increase or diminish de risk of HPV infection. For example, a cross-sectional study in Denmark found a lower risk of HPV genitalia infection in circumcised males[9]. In our study, we did not found difference in circumcised and uncircumcised patients, but this could be due to a lower sample size compared to previous research.

Consistent use of condom was similar to a previous study of Tao et al in Chinese MSM-HIV population[23]. Consistent use of condom during penetration was not associated with a lower HPV infection prevalence. This could be attributed to two factors. Firstly, HPV can be transmitted by direct contact with unprotected areas, such as scrotum, perineum and lips[24]. Secondly, low sample size may limit the statistical analysis. Moreover, use of condom during oral sex was very low. We did not find any study regarding the use of condom in oral sex in HIV-MSM. However, Hollway *et al*. found a rate use around 9% in males[25].

Previous research showed an increased risk of HPV anal and genitalia infection in patients with detectable HIV-RNA or low CD4 lymphocyte count[22]. However, in our study, CD4 lymphocyte count was not associated with an increased HPV prevalence. On the other hand, a detectable HIV-RNA was associated with a higher prevalence of genitalia infection, but not within the oral cavity. In addition, age, number of sexual partners and age of initial sexual intercourse were not associated with a higher HPV infection prevalence. Although the interactions between HIV and HPV are not yet fully understood, several studies showed an increase of HPV incidence in PLWH[26,27]. Multiple reasons for this have emerged in the recent years. Firstly, the immunosuppresed state induced by HIV impairs the host defense against HPV and another virus. Secondly, epithelial damage caused by HIV-related inflammation could facilitate the infection of some HPV genotypes.

CONCLUSIONS

Genital and oral HPV infection is frequent in HIV-MSM, including hrHPV. HPV 16 was the most common genotype in the study population. Prevalence and distribution of genotypes varied based on anatomic location, but no correlation was found between genitalia and oral samples. A detectable HIV-RNA was associated with a higher HPV genital prevalence but not with HPV oral infection rate. CD4 lymphocyte count, circumcision status, age and number of sexual partners were not associated with a higher prevalence of HPV infection.

Our study has several limitations. Firstly, the study of HPV infection prevalence outside anal conduct is challenging due to lack of commercial validated kits and a clear standard of sample collection. Moreover, management of this specimens in the Microbiology Department does not follow well established indications. Each laboratory uses a customized routine in order to detect HPV-DNA. We used the most common technique for each location (triple sample collection in genitalia and rinse in oral cavity) but both procedures are not validated. These two elements could explain the great variability of results between different research studies. Our research group has used these two techniques in previous studies, increasing our experience in HPV-DNA detection outside anal conduct[10,28,29]. Secondly, sample size is relatively small, so many comparisons could not be accurate (e.g., condom usage). Finally, only 10 patients were naïve to ART, so comparisons between naive and treated subjects may not be significant due to low sample size.

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CONFLICT OF INTEREST

The Author(s) declare(s) that there is no conflict of interest.

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ETHICAL ASPECTS

The study was approved by Ethics Committee of Pontevedra-Vigo-Ourense (reference 217/2019). Written informed consent was obtained from each participant.

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