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Original Article

Human papillomavirus prevalence in the anus and urine among HIV-infected Japanese men who have sex with men

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ABSTRACT

Background: The present study investigated human papillomavirus (HPV) prevalence in anal and urine samples, and evaluated cytological findings among human immunodeficiency virus (HIV)-infected Japanese men who have sex with men (MSM).
Methods: A total of 148 patients were enrolled. Anal and urine samples were collected from each participant, and a HPV-DNA test and genotyping were performed using flow-through hybridization. In addition, anal cytology was evaluated based on Papanicolaou staining. Questionnaires regarding lifestyle habits and sexual behavior were obtained.
Results: The β-globin gene was positive in 131 (88.5%) anal samples and 139 (94.0%) urine samples. Among the β-globin-positive samples, the HPV prevalence in anal and urine samples was 80.9% and 30.9%, respectively. High-risk HPV (HR-HPV) was detected in 57.3% of anal samples and 20.9% of urine samples. Among 122 adequate cytological samples, anal cytological abnormalities were observed in 99 cases (81.1%). Anal cytological tests revealed that atypical squamous cells of an undetermined significance (ASCUS) were detected in 57 (46.7%) patients, followed by low-grade squamous intraepithelial lesions (SIL) in 35 (28.7%), high-grade SIL in five (4.1%), and atypical squamous cells cannot exclude high-grade SIL (ASC-H) in two (1.6%), respectively. The nadir counts of CD4-positive T-lymphocyte less than 200 μL and anal HR-HPV infection were independent risk factors for anal cytological atypia over ASC-H.
Conclusions: The present study demonstrated high HPV prevalence in the anus and urine, and showed a high incidence of anal cytological atypia associated with HR-HPV infections among HIV-infected MSM patients.

1. Introduction

It is widely accepted that human papillomavirus (HPV) is the causative agent of cervical carcinoma in women. HPV can be passed onto the genitals, oral cavity, throat, urinary tract, and anus between all individuals through sexual contacts, and it is the most common pathogen of sexually transmitted infections (STIs). Men who have sex with men (MSM) have a high risk for human immunodeficiency virus (HIV), and present HPV infections in the anus much more than men who have sex with women (MSW). Some previous studies demonstrated that anal HPV prevalence rates were 4–10 times higher in MSM compared to MSW [1,2]. In particular, higher anal HPV infectious rates ranging from 47% to 96% have been reported in HIV-infected MSM [3–9], which are higher than ones reported in HIV-negative MSM [10,11]. Additionally, anal cancer cases are strongly correlated with HPV infection. The incidence of anal cancer is estimated to be 1.8 per 100,000 persons per year in the general population, whereas the highest risk population for anal cancer is HIV-infected MSM, among whom the incidence has been estimated to be 30–100 times the general population [10–12].

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Similar to cervical cancer screening, anal cytological testing and anoscopy have been widely used for the detection of anal intraneoplasia (AIN), a precancerous anal lesion [13]. Anal cytological abnormalities can be a predictor to anal dysplasia on histological analysis of biopsy samples [14]; however, a formal recommendation to use a cytological evaluation as a screening procedure for anal cancer for MSM has yet to be established. Further studies are likely required to clarify the relationship between anal HPV infection, cytological abnormalities, and AIN among the high-risk MSM population. Nevertheless, there is little information regarding anal HPV prevalence, type, distribution, and anal cytological findings within the MSM population in Japan.

In addition, some recent studies have suggested that the urinary tract can also be alternative site for HPV infection among men in addition to external genitalia and anus, and urine samples are used as a convenient tool for testing HPV infections in the urinary tract [15,16]. A broad range of HPV prevalence rate has been reported in urine samples of healthy men and urethritis men [16–18]. However few studies investigate HPV prevalence in urine among MSM population.

Hence, the present study aimed to investigate anal HPV prevalence and cytological findings within the HIV-infected Japanese MSM population. Additionally, we also investigated HPV prevalence in urine samples, and compared the HPV prevalence by anal and urine samples. Furthermore, we aimed to identify the critical factors affecting anal cytological abnormalities.

2. Patients and methods

2.1. Study population

The attending physicians recruited the Japanese HIV-infected MSM patients that visited the outpatient clinic of Kanazawa University Hospital, Ishikawa Prefectural Central Hospital, and the Shirakaba clinic, between April 2013 and August 2014, and a total of 148 patients enrolled in this study. All participants were MSM; MSW, and bisexual men were excluded.

The ethics committee of Kanazawa University Graduate School of Medical Science approved this study. Samples were collected from each subject after each provided a written informed consent.

2.2. Sampling procedures

Anal samples were obtained by rubbing the entire surface of anus and anal canal with a saline-wetted cotton swab, and were placed into separate tubes containing 2.5 mL of a preservative solution for liquid-based cytology (TACAS Amber; MBL Medical & Biological Laboratories Co., Ltd.). In addition, urine samples were provided in an individual urine cup, and were placed into a separate tube. Each urine sample (15 mL) was centrifuged at approximately 1500×*g* for 10 min, and the supernatant was discarded. The urine sediment was also placed into 2.5 mL of preservative solution for liquid-based cytology. All preservative solution samples were stored at 4 °C until testing.

2.3. HPV-DNA test and genotyping

After vortexing each sample, aliquots of 600 μL of anal samples and 800 μL of urine samples of the preservative solution containing cell samples were centrifuged at approximately 1500×*g* for 10 min, and the supernatants were discarded. The cell pellets were washed twice with 300 μL of 10 mmol/L Tris-HCl (pH 8.0). The DNA was extracted from the cells using a DNA Extraction Kit (SMI Test; G&G Science Co., Fukushima, Japan) according to the manufacturer's instructions. The β-globin gene was first amplified to confirm the adequacy of the extracted DNA in all samples.

HPV genotyping was performed using the Hybribio 37 HPV GenoArray Diagnostic Kit (HybriMax™; Chaozhou Hybribio Limited Corporation, Guangzhou, China). This kit can determine 37 HPV genotypes, consisting of 15 high-risk HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, 82), 10 low-risk HPV types (6, 11, 42, 43, 44, 54, 61, 70, 72, 81), and 12 unknown-risk types (26, 34, 40, 53, 55, 57, 66, 67, 69, 71, 83, 84), by flow-through hybridization and gene-chip methods using HPV-DNA amplified by PCR [17,19].

2.4. Cytological evaluation for anal samples

Aliquots of 700 μL of each liquid-based cytological sample were subjected to microtube centrifugation at 1500×*g* for 10 min and the supernatants were discarded. The residual cell pellets were mixed with 50 μL of a cellular base solution (LiquiPrep; LGM International Inc, Melbourne, FL, USA), and pipetted onto glass microscope slides. The slides were air-dried for more than 60 min and then subjected to Papanicolaou staining. All slides were assessed by two cytopathologists without previous knowledge of the molecular findings. All slides were evaluated based on the Bethesda system as follows: negative for an intraepithelial lesion or malignancy (NILM), atypical squamous cells of an undetermined significance (ASCUS), and atypical squamous cells that cannot exclude high-grade squamous intraepithelial lesions (ASC-H), low-grade squamous intraepithelial lesions (LSIL), and high-grade squamous intraepithelial lesions (HSIL).

2.5. Collection of clinical data and questionnaire

We collected data on the age at examination, the status of the HIV infection, nadir counts of CD4-positive T-lymphocytes, recent counts of CD4-positive T-lymphocytes, the time since HIV diagnosis, the duration of antiretroviral therapy (ART) for HIV infection, and recent HIV viral copies of all participants through medical chart review. Lifestyle habits, sexual behavior, data on smoking status, the past history of any genital warts, syphilis, urethritis, and the period of the latest receptive anal intercourse (RAI) were examined through patients' interviews from each attending physician. HIV-positive cases were clinically confirmed using the HIV-1/2 Western blot assay (HIV Blot 2.2 WB; Gene labs Diagnostics, Singapore).

2.6. Statistical analyses

The chi-square test was used to compare HPV-positive rates between the two anatomical sites among all 148 participants. Univariate and multivariate analysis using unconditional direct logistic regression analysis for all variables was performed to determine the risk factors for cytological atypia over ASC-H in anal samples, and the odds ratios (OR) and 95% confidence intervals (CI) were calculated. The SPSS statistical software package (version 17.0; SPSS Inc., Chicago, IL) was used for all analyses, and a $p < 0.05$ was taken to indicate statistical significance.

3. Results

3.1. Patients characteristics

The mean age of the participants was 39.0 ± 8.0 years (range; 24–62 years). All of the patients had received ART. The time from HIV diagnosis ranged from 509 to 6226 days (median 2000 days), and the duration of ART therapy ranged from 290 to 5102 days (median 1473 days). Mean (±standard deviation) of nadir and recent counts of CD4-positive T-lymphocyte were 221 ± 101/μL

(range; 7–440/μL) and 593 ± 185/μL (range 167–1051 μL), respectively. HIV viral load below 50 copies/mL of CD4-positive T-lymphocytes (suppressed state) was seen in 146 cases, whereas ≥50 copies/mL (unsuppressed state) was observed in 2 cases. More than 90% of patients experienced RAI in their lifetime, and more than 50% reported having RAI within last six months (Table 1). A few patients (5.4%) had a history of urethritis.

3.2. HPV-DNA analyses

The β-globin gene was positive in 131 (88.5%) anal samples and 139 (93.9%) urine samples (Table 2). Among the β-globin-positive samples, the HPV prevalence by anal and urine samples was 80.9% and 30.9%, respectively. High-risk HPV (HR-HPV) was detected in 57.3% of anal samples and 20.9% of urine sample. Any HPV types and HR-HPV prevalence was significantly higher in anal samples than in urine samples ($P < 0.05$). Multiple HPV types were frequently identified in anal samples (51.9%), whereas a single HPV-type infection was more frequent (87.8%) in urine samples ($P < 0.05$).

Focusing on HPV type distributions, HPV6 was most common in anal samples, followed by HPV16, HPV58, and HPV52. HPV6 was also most common in urine samples, followed by HPV52, HPV51, HPV33 and HPV58 (Table 3). HPV type distributions differed slightly between the anus and urinary tract. Although 35 (35/148 cases; 23.6%) patients showed HPV infection in both anal and urine samples, the detected HPV types were only partially consistent in 10 (10/148 cases; 6.8%) cases.

3.3. Cytological analyses

Cytological evaluation was performed in all 148 anal samples. However, twenty-four anal samples were excluded for cytological specimens due to classification as unsatisfactory for evaluation. All of β-globin negative samples by the prior PCR-based analysis included in these 24 samples, and the remaining samples had positive expression of the β-globin gene. Twenty-three (23/122 cases; 18.9%) patients had NILM by liquid based cytological evaluation. Any form of cytological abnormalities was observed in 99 cases (81.1%), with ASCUS the most commonly detected in 57 (46.7%) patients, followed by LSIL in 35 (28.7%), HSIL in 5 (4.1%), ASC-H in 2 (1.6%), respectively (Table 4).

3.4. Analyses of anal cytological abnormalities for identifying the critical factors

The univariate and multivariate analysis showed that a nadir count of CD4-positive T-lymphocytes lower than 200/μL (OR: 3.479; 95% CI: 1.500–8.068) and anal HR-HPV infection (OR: 2.562; 95% CI: 1.044–6.286) were independent risk factors for anal cytological atypia over ASC-H (Table 5). Conversely, age at examination,

Table 1
Patient characteristics in HIV-infected MSM.

Variables	*N*
Age (years)	
Median ± SD (Range)	39.0 ± 8.0 (24–59)
Nadir counts of CD4$^+$ T-lymphocyte (/μl)	
Median ± SD (Range)	221.0 ± 101.0 (7–404)
Recent counts of CD4$^+$ T-lymphocyte (/μl)	
Median ± SD (Range)	593.0 ± 185.0 (167–1051)
Duration of ART (days)	
Median ± SD (Range)	1472.5 ± 1029.7 (290–5102)
Time since HIV diagnosis (days)	
Median ± SD (Range)	1999.5 ± 1240.8 (509–6226)
Recent HIV viral copies	
Virally suppressed (<50 copies/ml)	146
Virally unsuppressed (≥50 copies/ml)	2
Smoking status	
Never/Past/Current	76/0/72
Brinkman Index[a]	
Median ± SD (Range)	220.0 ± 278.0 (12–1280)
Past history of any genital warts	
Yes/No	47/101
Past history of syphilis	
Yes/No	66/82
Past history of urethritis	
Yes/No	8/140
Time since recent RAI	
<1 month	48
1–6 months	34
6 months–5 years	38
>5 years	15
None	9
Unidentified	4

[a] Brinkman Index; number of cigarette smoking per day x duration (years); ART, antiretroviral therapy; HIV, human immunodeficiency virus; RAI, receptive anal intercourse.

Table 2
Results of PCR analysis of adequate anal samples and urine samples by liquid-based cytology.

	Anal (n = 131)	Urine (n = 139)	p value
Number of HPV detection (%)	106 (80.9%)	43 (30.9%)	<0.001
High-risk HPV detection rate (%)	75 (57.3%)	29 (20.9%)	<0.001
Multiple HPV detection rate (%)	68 (51.9%)	17 (12.2%)	<0.001

PCR, polymerase chain reaction; HPV, human papillomavirus.

Table 3
Type-specific prevalence rates of HPV in anal and urine samples.

Detected HPV type	Anus (n = 106) n (%)	Urine (n = 43) n (%)
High-risk HPV types		
HPV 16	21 (19.8)	5 (11.6)
HPV 18	5 (4.7)	1 (2.3)
HPV 31	16 (15.1)	0
HPV 33	10 (9.4)	6 (14.0)
HPV 35	1 (0.9)	0
HPV 39	9 (8.4)	4 (9.3)
HPV 45	8 (7.5)	0
HPV 51	10 (9.4)	7 (19.2)
HPV 52	18 (17.0)	9 (20.9)
HPV 56	1 (0.9)	0
HPV 58	20 (18.9)	6 (14.0)
HPV 59	2 (1.9)	0
HPV 68	5 (4.7)	2 (4.7)
HPV 73	2 (1.9)	0
HPV 82	4 (3.8)	0
Low-risk HPV types		
HPV 6	28 (26.4)	11 (25.6)
HPV 11	9 (8.4)	5 (11.6)
HPV 44	3 (2.8)	0
HPV 54	2 (1.9)	0
HPV 61	6 (5.7)	3 (7.0)
HPV 70	5 (4.7)	2 (4.7)
HPV 72	5 (4.7)	0
HPV 81	12 (11.3)	1 (2.3)
Unknown -risk HPV types		
HPV 34	1 (0.9)	0
HPV 53	7 (6.6)	0
HPV 55	1 (0.9)	0
HPV 57	1 (0.9)	2 (4.7)
HPV 66	3 (2.8)	1 (2.3)
HPV 69	3 (2.8)	0
HPV 71	5 (4.7)	1 (2.3)
HPV 83	2 (1.9)	0
HPV 84	6 (5.7)	1 (2.3)

HPV, human papillomavirus.

Table 4
Frequency of detected HPV according to cytology results in anal samples.

Status of detected HPV	Type of anal cytological atypia				
	NILM (%)	ASCUS (%)	ASC-H (%)	LSIL (%)	HSIL (%)
Any HPV types	14 (60.9)	45 (79.0)	2 (100)	29 (82.9)	5 (100)
High-risk HPV	9 (39.1)	30 (52.6)	2 (100)	23 (65.7)	4 (80.0)
Low-risk HPV	5 (21.7)	10 (17.5)	0	6 (17.1)	1 (20.0)
Total	23 (100)	57 (100)	2 (100)	35 (100)	5 (100)

HPV, human papillomavirus; NILM, negative for intraepithelial lesion or malignancy, ASCUS, atypical squamous cells of undetermined significance; ASC-H, atypical squamous cells cannot exclude high-grade squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion; HSIL, high-grade squamous intraepithelial lesion.

Table 5
Univariate and multivariate analyses of risk factors for anal cytological atypia greater than ASC-H.

Variables	Univariate analysis		Multivariate analysis	
	Odds ratio [95% CI]	p value	Odds ratio [95% CI]	p value
HR-HPV infection in anus[a]	2.366 [1.031–5.429]	0.042	2.562 [1.044–6.286]	0.040
Age: >40 years old	1.424 [0.666–3.047]	0.362	–	–
Past history of any genital warts	1.784 [0.826–3.857]	0.141	–	–
Brinkman Index (>220)	0.609 [0.244–1.519]	0.287	–	–
Past history of syphilis	1.093 [0.515–2.322]	0.816	–	–
Past history of urethritis	0.740 [0.137–3.988]	0.726	–	–
HPV infection in urine	0.642 [0.283–1.456]	0.289	–	–
Nadir $CD4^+$ T-lymphocyte counts: <200 μl[a]	2.760 [1.254–6.073]	0.012	3.479 [1.500–8.068]	0.004
Recent $CD4^+$ T-lymphocyte counts: <700 μL	0.861 [0.380–1.952]	0.720	–	–
Latest period of RAI: ≤6 months	1.661 [0.729–3.783]	0.227	–	–

ASC-H, atypical squamous cells-cannot exclude high-grade squamous intraepithelial lesion; HR, high-risk; HPV, human papillomavirus; RAI, receptive anal intercourse.
[a] Multivariate analysis.

Brinkman index, a past history of genital warts, syphilis, urethritis, recent counts of CD4-positive T-lymphocyte lower than 600/μL, latest RAI within six months, and HPV infection in urine samples were not associated with anal cytological abnormalities.

4. Discussion

We found a high anal prevalence of HPV (80.9%) and HR-HPV (57.3%) in the Japanese HIV-infected MSM population. Many epidemiological studies have been conducted to investigate anal HPV prevalence among HIV-infected MSM in several countries and regions. Anal HPV prevalence in HPV-infected MSM was 61.0% of 92 patients in the United States [3], 74.2% of 140 in Spain [4], 75.9% of 361 in Japan [5], 82.7% of 133 in Korea [6], 88.6% of 166 in Italy [7], 91.8% of 85 in South Africa [8], and 95.5% of 1439 in Spain [9]. The high prevalence of anal HPV infection observed in the present study is similar to that previously reported in other countries.

In addition, the present study revealed that the HPV infection was detected in 30.9% of urine samples. A previous Japanese study showed that HPV-DNA was detected in 21.0% of urine samples of 141 MSW with urethritis and in 3.3% of urine samples in 154 healthy men [16]. Nakashima et al. reported an HPV prevalence of 22.1% based on urine samples of 213 Japanese MSW attending a STIs clinic [18]. The HPV prevalence in urine samples of MSM in Japan was much higher than ones in heterosexual men with urethritis or healthy men. One previous study compared the HPV prevalence between anal and urine samples among the HIV-infected MSM population attending a clinical service in South Africa. HPV-DNA was detected in 91.8% and 14.8% of anal and urine specimens, respectively, in the study [8]. Another study demonstrated that HPV prevalence in the rectum and urine of 113 MSM attending a clinic in France was 64% and 6%, respectively [20]. HPV prevalence in urine samples in the present study was much higher than those reported previously, which may be explained by differences in the population, sexual activity, the HIV-infection status, and different sampling procedures.

A higher HPV prevalence in urine samples from the HPV-infected MSM population raises an important issue: some clinical studies and meta-analysis have indicated that HPV infection is likely to have a certain etiological correlation with development of urothelial carcinoma [15,21]. One previous report mentioned that bladder cancers in HIV-infected patients may occur in relatively young patients with a low nadir CD4 cell count [22], and suggested that the HPV infection might be associated with bladder cancer within HIV-infected patients [22]. The proportion of bladder cancer is increased by at least 5-fold in HIV-infected patients above 50 years old [23]. However, little information regarding the incidence of HPV-associated carcinomas of the urinary tract within the HIV-infected MSM population is currently available. Therefore, further studies are required to clarify a pathogenicity of urinary tract HPV infections for the HIV-infected MSM population.

The most common HPV-types detected in the anus of HIV-infected MSM were HPV6 and HPV16, which agrees with the highest HPV genotype distribution reported previously in other regions [7–9]. Conversely, HPV58 and 52, which are common type in Japanese women, were considerably prevalent in the anus of the Japanese MSM population. In addition to HPV6 and 16, HPV51 and 58 were also relatively frequent in South Africa [8], HPV11 and 61 in Italy [7], and HPV53 and 84 in Spain [9]. The distribution of HPV types is likely to slightly differ between different regions and populations. Furthermore, it is noteworthy that HPV16 was also a frequent oncogenic HPV type detected in anal samples. Indeed, many epidemiologic studies indicated that HPV16 is the most common HPV type detected from HPV-associated anal carcinoma [10,24].

We found that cytological abnormalities were observed in 81.1% of anal samples, and that anal HR-HPV infection was identified as a risk factor for anal cytological atypia higher grade than ASC-H. One previous study examined a correlation between the cytological findings and HR-HPV infection in the anus of 133 Korean MSM and 68 MSW; it was shown that 42.9% of the MSM presented abnormal cytological findings in the anus, and it was significantly higher in

MSW [6]. The most common atypia was LSIL (22.6%), followed by ASCUS (19.5%), and HSIL (0.8%). An epidemiological study conducted in Spain among HPV-infected MSM revealed a high HR-HPV prevalence (74.2%), and 54.2% of cytological atypia, such as LSIL (49.2%), ASCUS (2.5%), and HSIL (2.5%) [4]. Wilkin et al. also found that 47% of 85 HIV-infected men had abnormal results: LSIL (24%), ASCUS (18%), and HSIL (6%) [3]. We found a higher rate of cytological abnormalities compared those reported previously, and that ASCUS was the most frequent cytological abnormality. ASCUS is defined as a smear sample that reveals slightly abnormal squamous cells, but the changes do not clearly suggest that precancerous cells are present. Approximately 60% of the cases of ASCUS may be reclassified as NILM, based upon alternative samples in cervical cancer screening [25]. Indeed, HR-HPV was detected in only 52.6% of cases with ASCUS, which lower than in cases of LSIL (65.7%) and HSIL (80.0%). Alternatively, the improvement of recent diagnostic techniques by liquid-based cytology may contribute to an increase in ASCUS. Anal cytological atypia is likely to be frequently observed in the HIV-infected MSM population with HR-HPV, and anal cancer screening, such as HPV testing, and cytological evaluation should be considered for this population.

There are numerous epidemiological studies that analyzed risk factors for anal HPV infection among MSM [2,6–8], whereas limited information is available on predictors for anal cytological abnormalities. We found that a nadir count of CD4-positive T-lymphocyte lower than 200 μL was an independent risk factor for anal cytological atypia. Consistent with our findings, a lower nadir of CD4-positive T cells is an independent risk factor for cytological abnormalities and AIN [3,26,27]. However, recent counts of CD4-positive T-lymphocyte were not associated with cytological atypia.

Previous reports suggest that HIV-infected patients with lower nadir of CD4-positive cells may present with a decreased proliferative T cell response and to some types of immunosuppression compared to those with a higher nadir of CD4-positive cells, regardless of ART [10]. Immunosuppression can result in a persistent anal HPV infection, inducing cytological atypia and AIN. Furthermore in 2015, the World Health Organization recommended that all HIV-infected patients should undergo induction of ART, regardless of the CD4 count. An early induction of ART for HIV-infected patients resulted in reduced morbidity and in the reduction of the incidences of HIV infection of their partners [28]. Considering that nadir CD4-positive cells can correlate to anal cytological atypia, HIV-infected patients may benefit from early induction of ART.

However, there are some conflicting data regarding the effect of CD4-positive T cells on anal cytological changes. Yamada et al. demonstrated that not high-copy number of HIV amount but current lower CD4-positive T cells is associated with higher grade cervical lesions in Kenyan women who had no ART [29].Wilkin et al. reported that there was no association of current CD4-positive T cells and nadir CD4-positive T cells with abnormal anal cytology or high grade AIN [30]. Another previous study also found that HPV-DNA detection as well as cytological abnormalities were associated neither with HIV RNA detection in plasma nor with CD4-positive T cells [31]. Therefore, further studies, including large population samples and of longitudinal design, are required to clarify the risk factors associated with cytological abnormality by HPV infection among HIV-positive population.

There are some limitations in the present study. This study comprised a relatively small number of subjects and no HIV-negative population or a MSW population. A relatively large proportion of samples unsuitable for HPV testing and cytological evaluation were included in this study. In addition, some data regarding patients' background, including insertive or receptive partners of anal intercourse and the use of condoms were not collected. Additionally, the HPV type test used in the present study is not common, although it has shown good agreement in detection of HPV types compared to results by PCR-based methods [17,19]. Therefore, further studies should include a larger number of various participants and use a common HPV genotyping method to support the results of this study.

In conclusion, the present study found a high HPV prevalence in urine and a high prevalence of anal cytological atypia associated with HR-HPV infection in HIV-infected Japanese MSM. Currently, HPV vaccination programs and anal cancer screening guidelines have not been established in Japan, and HPV vaccination has been interrupted, even in women due to potential adverse effects. To prevent AIN and anal cancer among the MSM population, anal cancer screening, such as HPV testing and cytology evaluation, may need to be considered for MSM. Additionally, adaptation of the prophylactic HPV vaccine for the MSM population should be also discussed in Japan.

Conflicts of interests

The authors report no declarations of interest.

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