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Incidence, Clearance, and Persistence of Penile High-Risk Human Papillomavirus Among Rwandan Men Who Have Sex With Men

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Background. Little is known about penile high-risk human papillomavirus (hrHPV) among men who have sex with men (MSM) in low- and middle-income countries. We aimed to determine the incidence, clearance, and persistence of penile hrHPV among Rwandan MSM.

Methods. We enrolled 350 MSM (345 with valid human papillomavirus [HPV] results) aged ≥18 years. At each visit (6–12 months apart), we collected penile PreservCyt specimens and blood for HPV and HIV testing, as well as sociodemographic and behavioral variables. HPV testing was performed with the Ampfire assay. Penile hrHPV incidence and clearance per 1000 person-months of follow-up, as well as prevalent and incident persistence, were computed and compared by HIV status.

Results. The mean (SD) age was 27.7 (6.7) years and 19.4% were living with HIV. Penile hrHPV incidence was 34.8 (95% CI, 29.1–41.8) per 1000 person-months of follow-up. HPV-16 (11.7; 95% CI, 9.26–14.9) and HPV-59 (6.1; 95% CI, 4.52–8.39) had the highest incidence rates. Prevalent and incident persistence was 47.5% and 46.6%, respectively. HPV-66 (33.3%), HPV-52 (30.8%), and HPV-16 (29.2%) had the highest prevalent persistence and HPV-33 (53.8%), HPV-31 (46.7%), and HPV-16 (42.6%) the highest incident persistence. No differences were found by HIV status except for HPV-45 (higher in MSM with HIV).

Conclusions. We found high incidence and prevalent/incident persistence of penile hrHPV among Rwandan MSM. This highlights the importance of preventive strategies for HPV-associated anogenital cancers.

Keywords. HIV; MSM; penile HPV; Kigali; Rwanda.

BACKGROUND

Men who have sex with men (MSM) have an increased risk of anal and penile high-risk human papillomavirus (hrHPV) infection [1]. Although proportions vary widely, hrHPV is responsible for >50% of penile cancer [2, 3], with some reports showing even higher proportions up to 70% [4]. Penile cancer, although relatively rare, is increasing in incidence globally [5], with incidence from 0.45 to 1.7 per 100 000 men in high-income countries [6, 7]. Some low- and middle-income countries (LMICs), such as Uganda [8, 9], have reported higher incidence rates (4.4/100 000) when compared with high-income countries. The 2020 global cancer estimates reported 36 068 new cases and 13 211 deaths [10], with a slight increase from 34 475 new cases in 2018 [11].

There are limited data on penile hrHPV, squamous intraepithelial lesions, and cancer among MSM in LMICs, but previous studies have noted a relatively high prevalence of penile hrHPV in the general population [12] and in penile cancer tissue [2]. We previously found an overall prevalence of penile hrHPV of 29.7% among MSM who were HIV negative and 55.2% among MSM with HIV (MSMWH) in Rwanda [1], higher than among MSM with HIV-negative status in high-income countries [13].

The incidence and clearance of penile hrHPV have been studied in high-income countries. A study among Dutch MSM who were HIV negative cited overall hrHPV incidence and clearance rates of 32.8 and 118 per 1000 person-months of follow-up (PMF), respectively, with HPV-16 having

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incidence and clearance rates of 4.9 per 1000 PMF (the highest) and 90.6 per 1000 PMF (the second lowest after HPV-56) [14].

Similarly, the HPV in Men study, done in Brazil, Mexico, and the United States [15], reported an hrHPV incidence of 22.2 per 1000 PMF. Type-specific incidence rates from the same study were 4.4 per 1000 person-months for HPV-16 (second highest after HPV-51) and 1.9 per 1000 person-months for HPV-18 [16]. There is a paucity of data on the persistence of penile hrHPV, a critical step in the carcinogenesis of HPV-related cancers, including penile cancer.

A number of factors are known to be associated with the incidence and clearance of penile hrHPV, including the number of sex partners: individuals with 2 to 5 sex partners have a lower likelihood of clearing their infection as compared with those with 0 or 1 partner [14]. Studies that assessed the incidence, clearance, and persistence of anal hrHPV by HIV status found differences in MSMWH when compared with MSM who were HIV negative: MSMWH had higher incidence and lower clearance rates, and not being circumcised was associated with persistent anal hrHPV infection [17]. These factors might be similar or different for the penis and, given the relationship between the anatomic sites, perhaps comparable.

Owing to the scarcity of data on the incidence, clearance, and persistence of penile hrHPV in Rwanda and other countries in sub-Saharan Africa (SSA), as well as the relatively high incidence of penile cancer in some countries in SSA, such as Uganda [9], we sought to determine the incidence, clearance, and persistence of penile hrHPV among Rwandan MSM and to identify factors associated with persistent penile hrHPV infection.

METHODS

Study Design, Population, and Setting

This was a prospective cohort study of MSM. We recruited 300 MSM in Kigali, Rwanda, through community recruitment by reaching out to MSM community organizations as well as individuals known to the community who were not members of any MSM organization. We also recruited 50 MSM with known HIV from partner clinics in Kigali, making a total of 350. Snowball recruitment was used between 30 March 2016 and 25 October 2017 to reach the required number of participants. Eligibility criteria for inclusion in the study included being at least 18 years of age, living in the city of Kigali, reporting any type of sex with another man in the 6 months prior to study enrollment, undergoing an HIV viral load and CD4 cell count (for those with HIV), and expressing a willingness to have an HIV test and be contacted for follow-up visits.

Data Collection

Study visits were performed at Rwanda Military Hospital, Kigali, Rwanda. During the appointment, an automated computer-assisted self-interview was used to complete a questionnaire in the local language, Kinyarwanda. Questions included basic demographic and clinical information, such as history of HIV testing and sexually transmitted infections, as well as sexual behavior and behavioral factors (eg, tobacco, alcohol, and nonprescription drug use).

After the automated computer-assisted self-interview, 5 mL of blood was collected for HIV testing. A penile specimen for HPV testing was collected by retracting the foreskin if present and rubbing the entire penile skin, including the root, shaft, glans, and coronal sulcus, with a 600-grit emery paper (sandpaper), followed by swabbing the penile skin with a moist Dacron swab, which was then placed in PreservCyt (Hologic) and vigorously shaken. All collected specimens were transported to the Rwanda Military Hospital research laboratory for testing. Participants were followed-up for 5 visits (6–12 months apart) during which behavioral data were gathered and penile specimens collected for HPV testing.

Laboratory Testing: HIV and HPV

HIV Testing

Participants received standard HIV pretest counseling, followed by HIV testing according to Rwanda guidelines: rapid test with Alere HIV 1/2 Combo (Abbott) and second- and third-tier verification with HIV 1/2 STAT-PAK (CHEMBIO Diagnostic Systems Inc), depending on the initial result. Posttest counseling was provided and the result communicated to the participant. If the HIV test result was positive, HIV viral load and CD4 cell count measurements were performed.

HPV Testing

Penile swab specimens were tested by the AmpFire HPV Genotyping Assay (Atila Biosystems Inc) for real-time fluorescence detection of 15 HPV genotypes (16, 18, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, and 68) in 4 reaction tubes based on isothermal nucleic acid amplification. Testing was done according to the manufacturer's protocol. Briefly, an aliquot of the stored specimen in PreservCyt solution was pelleted by centrifugation; the supernatant was decanted; and pelleted cells were suspended in lysis buffer. The cell suspension incubated for 10 minutes at 95°C to lyse the cells. For each reaction, 2 μL of lysate was mixed with 12 μL of reaction mix and 11 μL of 1 of the 4 reaction mixes. The resulting 4 reaction tubes for every sample were incubated in a Powergene 9600 fluorescence real-time polymerase chain reaction machine at 60°C with fluorescence from FAM/HEX/ROX/CY5 channels measured every minute.

After approximately 1 hour, the amplification results were interpreted according to exponential curves developed during the process. If the negative control showed no exponential curves and positive control showed exponential curves, this experiment run was valid. The next step was to examine the set of 4 tubes corresponding to a specimen. If no exponential curve

other than internal control (Hex channel in PM-3 tube) was present for a sample, this sample was negative. If there was no exponential amplification curve in any of 4 tubes or any fluorescence channels, the sample failed the test. A failed sample usually indicated insufficient DNA in the sample, and it was reprocessed [18]. Findings of the baseline visit have been published [1].

Statistical Analysis

The following were computed and compared by HIV status:

Overall and type-specific penile hrHPV incidence: any hrHPV and type-specific new infection at any follow-up visit per 1000 PMF,

Overall and type-specific penile hrHPV clearance: any hrHPV and type-specific cleared infection at any follow-up visit per 1000 PMF,

Prevalent persistence: the proportion of persistent hrHPV infection at any follow-up visit for participants with hrHPV infection at the baseline visit and

Incident persistence: the proportion of persistent new infections of hrHPV at any follow-up visit for participants who were hrHPV negative at the baseline visit.

The incidence rate ratios and clearance rate ratios to compare HIV status were estimated, and their 95% CIs were calculated with the quadratic approximation to the Poisson log likelihood for the log rate. Logistic regression was used to calculate crude odds ratios and adjusted odds ratios with 95% CIs as a measure of association between various factors and persistence. All analyses were performed with SAS statistical software (version 9.4; SAS Institute). $P < .05$ was considered statistically significant.

Ethical Consideration

The study protocol was reviewed and approved by the Rwanda National Ethics Committee and the institutional review boards of the Albert Einstein College of Medicine and the University of California San Francisco. All study participants provided written informed consent prior to enrollment to the study.

RESULTS

Characteristics of the Study Population at Enrollment

Of the 350 participants enrolled in the study at visit 1, 284, 265, 222, and 215 were seen at visits 2, 3, 4, and 5, respectively. The median (IQR) time between visits was as follows: visits 1 to 2, 6.7 months (5.4–8.1); 2 to 3, 4.8 (4.6–6.5); 3 to 4, 6.3 (5.2–6.8); and 4 to 5, 10.9 (10.4–11.5). The mean (SD) age of our study population (n = 345 with valid HPV results) was 27.7 (6.7) years, and 67 (19.4%) had HIV. HIV infection was more common among older participants as compared with younger ones (≤24 vs >24 years, $P < .0001$) and among those who were not circumcised and were single ($P < .0001$ and $P = .025$). Further details of the baseline characteristics of the study population are shown in Supplementary Table 1 as previously published [1].

Penile hrHPV Incidence

During the 3329.4 PMF, 116 incident cases of hrHPV were recorded for an overall penile hrHPV incidence of 34.8 (95% CI, 29.1–41.8) per 1000 PMF. HPV-16 had the highest incidence at 11.7 per 1000 PMF (95% CI, 9.3–14.9), followed by HPV-59 and HPV-35 at 6.1 (95% CI, 4.5–8.4) and 5.7 (95% CI, 4.1–7.8) per 1000 PMF, respectively. No differences were found by HIV status except for HPV-45 (Table 1), for which MSMWH had a higher incidence with an incidence rate ratio of 3.63 (95% CI, 1.41–9.38).

Penile hrHPV Clearance

During the 1832.4 PMF, 43 cases were cleared of hrHPV, with an overall clearance rate of 23.5 (95% CI, 17.4–31.6) per 1000 PMF. HPV-18 (37.8; 95% CI, 17.0–84.0) and HPV-16 (45.8; 95% CI, 27.6–76.0) had the lowest clearance rates per 1000 PMF, and HPV-68 had the highest (92.4; 95% CI, 44.0–193.7). No differences were observed by HIV status (Table 2).

Penile hrHPV Prevalent and Incident Persistence

Of the 118 participants positive for hrHPV at baseline, 56 had a persistent infection at any follow-up visit. The overall HPV prevalent persistence was 47.5%, and HPV-66, HPV-52, and HPV-16 had the highest proportions (33.3%, 30.8%, and 29.2%, respectively). No differences were observed by HIV status for all HPV types (Table 3). Of the 116 participants negative for hrHPV at baseline, 54 had an incident infection persistent at any follow-up visit. The overall incident persistence was 46.6%, and HPV-33, HPV-31, and HPV-16 had the highest proportions (53.8%, 46.7%, and 42.6%). No differences were observed by HIV status for all HPV types (Table 4). We did not find any association of age, circumcision, marital status, income, and number of sex partners with penile hrHPV persistence (Supplementary Table 2).

DISCUSSION

Our study aimed to determine the incidence, clearance, and prevalent and incident persistence of penile hrHPV infection among Rwandan MSM. To our knowledge, this is among the first reports on those outcomes in SSA and especially Rwanda.

The overall penile hrHPV incidence in our study (34.8/1000 PMF) is similar to that in a study in the Netherlands (32.2/1000 PMF) [14] and higher than that in a study done in Spain (9.8/1000 PMF) [13]. The 3 most common incident hrHPV types in our study were HPV-16, HPV-59, and HPV-35 while those of the Dutch study were HPV-16, HPV-51, and HPV-18. In the Spanish study, HPV-33 had the highest incidence rate at 2.5 per 1000 PMF, and HPV-16 and HPV-59 had similar incidence rates to those in our study (1.4/1000 PMF) [13]. This highlights

Table 1. Overall and Type-Specific Incidence Rates by HIV Status

	HIV Positive (n = 67)				HIV Neg (n = 278)						Overall (n = 345)			
Type	Neg at Baseline, No. (%)	Incid	PM	Incid/1000 PM (95% CI)	Neg at Baseline, No. (%)	Incid	PM	Incid/1000 PM (95% CI)	IRR (95% CI)	*P* Value	Neg at Baseline, No. (%)	Incid	PM	Incid/1000 PM (95% CI)
HPV-16	61 (91.0)	12	888.9	13.5 (7.67–23.8)	255 (93.4)	56	4899.2	11.4 (8.80–14.8)	1.18 (.63–2.20)	.60	316 (92.9)	68	5788.2	11.7 (9.26–14.9)
HPV-18	60 (89.6)	3	1011.3	2.97 (.96–9.20)	268 (98.2)	24	5636.4	4.26 (2.85–6.35)	0.70 (.21–2.31)	.56	328 (96.5)	27	6647.7	4.06 (2.79–5.92)
HPV-31	62 (92.5)	4	1041.2	3.84 (1.44–10.2)	265 (97.1)	26	5464.5	4.76 (3.24–6.99)	0.81 (.28–2.31)	.69	327 (96.2)	30	6505.7	4.61 (3.22–6.60)
HPV-33	61 (91.0)	3	970.5	3.09 (1.00–9.58)	266 (97.4)	10	5724.0	1.75 (.94–3.25)	1.77 (.49–6.43)	.39	327 (96.2)	13	6694.5	1.94 (1.13–3.34)
HPV-35	61 (91.0)	9	953.3	9.44 (4.91–18.1)	267 (97.8)	28	5596.6	5.00 (3.45–7.25)	1.89 (.89–4.00)	.10	328 (96.5)	37	6549.8	5.65 (4.09–7.80)
HPV-39	60 (89.6)	6	966.2	6.21 (2.79–13.8)	262 (96.0)	23	5500.7	4.18 (2.78–6.29)	1.49 (.60–3.65)	.39	322 (94.7)	29	6466.9	4.48 (3.12–6.45)
HPV-45	65 (97.0)	7	996.6	7.02 (3.35–14.7)	266 (97.4)	11	5692.5	1.93 (1.07–3.49)	3.63 (1.41–9.38)	.008	331 (97.4)	18	6689.1	2.69 (1.70–4.27)
HPV-51	58 (86.6)	5	911.9	5.48 (2.28–13.2)	258 (94.5)	30	5375.9	5.58 (3.90–7.98)	0.98 (.38–2.53)	.97	316 (92.9)	35	6287.8	5.57 (4.00–7.75)
HPV-52	63 (94.0)	7	994.6	7.04 (3.36–14.8)	264 (96.7)	22	5548.6	3.96 (2.61–6.02)	1.78 (.76–4.16)	.19	327 (96.2)	29	6543.2	4.43 (3.08–6.38)
HPV-53	61 (91.0)	7	1005.9	6.96 (3.32–14.6)	268 (98.2)	24	5613.7	4.28 (2.87–6.38)	1.63 (.70–3.78)	.26	329 (96.8)	31	6619.6	4.68 (3.29–6.66)
HPV-56	61 (91.0)	5	988.5	5.06 (2.11–12.2)	265 (97.1)	17	5695.2	2.98 (1.86–4.80)	1.69 (.63–4.59)	.30	326 (95.9)	22	6683.8	3.29 (2.17–5.00)
HPV-58	62 (92.5)	5	1005.9	4.97 (2.07–11.9)	267 (97.8)	17	5778.5	2.94 (1.83–4.73)	1.69 (.62–4.58)	.30	329 (96.8)	22	6784.4	3.24 (2.14–4.92)
HPV-59	62 (92.5)	6	944.0	6.36 (2.86–14.2)	267 (97.8)	34	5552.0	6.12 (4.38–8.57)	1.04 (.44–2.47)	.93	329 (96.8)	40	6496.0	6.16 (4.52–8.39)
HPV-66	64 (95.5)	4	1061.2	3.77 (1.41–10.0)	258 (94.5)	22	5482.6	4.01 (2.64–6.09)	0.94 (.32–2.73)	.91	322 (94.7)	26	6543.7	3.97 (2.71–5.84)
HPV-68	62 (92.5)	4	1011.3	3.96 (1.48–10.5)	268 (98.2)	18	5687.7	3.16 (1.99–5.02)	1.25 (.423.69)	.69	330 (97.1)	22	6699.0	3.28 (2.16–4.99)
Any high-risk HPV	30 (44.8)	14	357.7	39.1 (23.2–66.1)	192 (70.3)	102	2971.7	34.3 (28.3–41.7)	1.14 (.65–1.99)	.65	222 (65.3)	116	3329.4	34.8 (29.1–41.8)

Abbreviations: HPV, human papillomavirus; incid, incidence; neg, negative; PM, person-months.

Table 2. Overall and Type-Specific Clearance Rates by HIV Status

	HIV Pos (n = 67)				HIV Negative (n = 278)						Overall (n = 345)			
Type	Pos at Baseline, No. (%)	Cleared Infection	PM	Clearance/1000 PM (95% CI)	Pos at Baseline, No. (%)	Cleared Infection	PM	Clearance/1000 PM (95% CI)	CRR (95% CI)	*P* Value	Pos at Baseline, No. (%)	Cleared Infection	PM	Clearance/1000 PM (95% CI)
HPV-16	6 (9.0)	3	107.6	27.9 (9.0–86.5)	18 (6.6)	12	219.8	54.6 (31.0–96.1)	0.51 (.14–1.81)	.30	24 (7.1)	15	327.4	45.8 (27.6–76.0)
HPV-18	7 (10.4)	4	73.7	54.3 (20.4–144.6)	5 (1.8)	2	85.2	23.5 (5.9–93.9)	2.31 (.42–12.6)	.33	12 (3.5)	6	158.9	37.8 (17.0–84.0)
HPV-31	5 (7.5)	3	32.6	92.0 (29.7–285.3)	8 (2.9)	4	92.0	43.5 (16.3–115.8)	2.12 (.47–9.46)	.33	13 (3.8)	7	124.5	56.2 (26.8–117.9)
HPV-33	6 (9.0)	4	85.6	46.7 (17.5–124.5)	7 (2.6)	7	55.6	125.9 (60.0–264.1)	0.37 (.11–1.27)	.11	13 (3.8)	11	141.2	77.9 (43.1–140.7)
HPV-35	6 (9.0)	3	50.1	59.9 (19.3–185.7)	6 (2.2)	3	46.1	65.1 (21.0–201.8)	0.92 (.19–4.56)	.92	12 (3.5)	6	96.2	62.4 (28.0–138.8)
HPV-39	7 (10.4)	5	59.1	84.6 (35.2–203.3)	11 (4.0)	8	82.4	97.1 (48.6–194.1)	0.87 (.29–2.66)	.81	18 (5.3)	13	141.4	91.9 (53.4–158.3)
HPV-45	2 (3.0)	2	16.2	123.5 (30.9–493.6)	7 (2.6)	4	101.7	39.3 (14.8–104.8)	3.14 (.57–17.1)	.19	9 (2.6)	6	117.8	50.9 (22.9–113.4)
HPV-51	9 (13.4)	5	107.2	46.6 (19.4–112.1)	15 (5.5)	10	159.7	62.6 (33.7–116.4)	0.74 (.25–2.18)	.59	24 (7.1)	15	266.9	56.2 (33.9–93.2)
HPV-52	4 (6.0)	1	31.3	31.9 (4.5–226.8)	9 (3.3)	6	104.6	57.4 (25.8–127.7)	0.56 (.07–4.63)	.59	13 (3.8)	7	135.9	51.5 (24.6–108.1)
HPV-53	6 (9.0)	2	52.0	38.5 (9.6–153.8)	5 (1.8)	2	26.0	76.9 (19.2–307.6)	0.50 (.07–3.55)	.49	11 (3.2)	4	78.0	51.3 (19.2–136.6)
HPV-56	6 (9.0)	2	66.3	30.2 (7.5–120.6)	8 (2.9)	6	70.7	84.9 (38.1–188.9)	0.36 (.07–1.76)	.20	14 (4.1)	8	137.0	58.4 (29.2–116.8)
HPV-58	5 (7.5)	2	56.5	35.4 (8.8–141.5)	6 (2.2)	3	34.8	86.2 (27.8–267.3)	0.41 (.07–2.46)	.33	11 (3.2)	5	91.3	54.8 (22.8–131.6)
HPV-59	5 (7.5)	4	76.6	52.2 (19.6–139.1)	6 (2.2)	4	74.3	53.8 (20.2–143.4)	0.97 (.24–3.88)	.97	11 (3.2)	8	150.9	53.0 (26.5–106.0)
HPV-66	3 (4.5)	1	18.6	53.8 (7.6–381.7)	15 (5.5)	8	173.5	46.1 (23.1–92.2)	1.17 (.15–9.32)	.88	18 (5.3)	9	192.1	46.9 (24.4–90.0)
HPV-68	5 (7.5)	4	39.7	100.8 (37.8–268.4)	5 (1.8)	3	36.2	82.9 (26.7–256.9)	1.22 (.27–5.43)	.80	10 (2.9)	7	75.8	92.4 (44.0–193.7)
Any high-risk HPV	37 (55.2)	12	482.7	24.9 (14.1–43.8)	81 (29.7)	31	1349.7	23.0 (16.2–32.7)	1.08 (.56–2.11)	.82	118 (34.7)	43	1832.4	23.5 (17.4–31.6)

Abbreviations: HPV, human papillomavirus; PM, person-months; pos, positive.

Table 3. Overall and Type-Specific Prevalent Persistence by HIV Status

Type	HIV Positive			HIV Negative				Overall		
	No. Positive at Baseline	No. With Persistence	%	No. Positive at Baseline	No. With Persistence	%	*P* Value	No. Positive at Baseline	No. With Persistence	%
HPV-16	6	3	50.0	18	4	22.2	.31	24	7	29.2
HPV-18	7	2	28.6	5	1	20.0	>.99	12	3	25.0
HPV-31	5	1	20.0	8	2	25.0	>.99	13	3	23.1
HPV-33	6	2	33.3	7	0	0.0	.19	13	2	15.4
HPV-35	6	1	16.7	6	1	16.7	>.99	12	2	16.7
HPV-39	7	0	0.0	11	1	9.1	>.99	18	1	5.6
HPV-45	2	0	0.0	7	2	28.6	>.99	9	2	22.2
HPV-51	9	2	22.2	15	1	6.7	.53	24	3	12.5
HPV-52	4	2	50.0	9	2	22.2	.53	13	4	30.8
HPV-53	6	2	33.3	5	0	0.0	.45	11	2	18.2
HPV-56	6	3	50.0	8	0	0.0	.05	14	3	21.4
HPV-58	5	2	40.0	6	2	33.3	>.99	11	4	36.4
HPV-59	5	1	20.0	6	0	0.0	.45	11	1	9.1
HPV-66	3	1	33.3	15	5	33.3	>.99	18	6	33.3
HPV-68	5	1	20.0	5	0	0.0	>.99	10	1	10.0
Any high-risk HPV	37	18	48.6	81	38	46.9	>.99	118	56	47.5

Abbreviation: HPV, human papillomavirus.

the importance of hrHPV types as an anogenital infection and risk factor for the development of penile cancer.

In addition, the HPV-16 incidence (11.7/1000 PMF) was higher than that in the Dutch study (4.9/1000 PMF), as well as other previously reported studies, including the Spanish study [13, 14]. Note that the study in the Netherlands was among MSM who were HIV negative and the Spanish study among MSMWH, whereas the MSMWH population in our study was only 19.4% and we found no differences by HIV status—hence, the potential for meaningful comparisons with both studies. The penile hrHPV incidence rates in our study are comparable to the anal rates found in some studies [16, 17, 19]. We did not find any study on penile hrHPV incidence and clearance rates among MSM in SSA and Rwanda.

Clearance rates in our study were lower than those in the Dutch study [14], which found an overall clearance rate of 118.4 per 1000 PMF vs 23.5 per 1000 PMF in our study. Furthermore, the 3 hrHPV types that cleared the least frequently in the same study were HPV-56, HPV-16, and HPV-59 vs HPV-52, HPV-33, and HPV-16 in the Spanish study [13], as compared with HPV-18, HPV-16, and HPV-66 in our study. With the much higher overall clearance in the Dutch study, it is expected that type-specific clearance for all types studied would be much higher than those in our study. For example, the clearance rate for HPV-16 was 45.8 per 1000 PMF for our study vs 90.6 per 1000 PMF for the Dutch study and an even lower clearance rate in the Spanish study (24.5/1000 PMF) [13].

Further studies are therefore required to understand how racial/ethnic, genetic, and sexual behavioral differences and HIV might contribute to these differences. Our study did not show any differences by HIV status. This has also been reported in 1 study [14], but other studies have found differences by HIV status for anal hrHPV [17, 19], indicating possible differences in hrHPV for both anogenital anatomic sites.

Persistence of hrHPV is a crucial step in HPV-related carcinogenesis, and our finding of relatively high proportions of penile hrHPV prevalent and incident persistent infection among Rwandan MSM warrants further evaluation. The overall penile hrHPV prevalent persistence in our study is, however, lower than that in a study by Silva et al, although their findings concur with ours in that there were no differences in persistence by HIV status [20]. Nonetheless, given the fact that penile cancer is increasing in SSA [9], the role of penile hrHPV in the carcinogenesis of penile cancer in Rwanda and SSA warrants further study.

We did not find any prior study reporting on incident persistence in the literature, but our overall and type-specific incident persistence proportions were similar to overall and type-specific prevalent persistence proportions with no differences by HIV status. We did not find any association of demographic and clinical factors—including age, circumcision, marital status, income, and number of sex partners—with penile hrHPV persistence. Other studies have reported the number of sex partners to be associated with incident persistent infections [14], but we tested associations only with prevalent persistent infections.

Our study has some limitations. First, follow-up visits and the time between them were not uniform for all participants, and this might introduce bias in our findings, especially for

Table 4. Overall and Type-Specific Incident Persistence by HIV Status

	HIV Positive			HIV Negative				Overall		
Type	Incid	No. With Incid Persistence	%	Incid	No. With Incid Persistence	%	*P* Value	Incid	No. With Incid Persistence	%
HPV-16	12	6	50.0	56	23	41.1	.75	68	29	42.6
HPV-18	3	1	33.3	24	8	33.3	>.99	27	9	33.3
HPV-31	4	2	50.0	26	12	46.2	>.99	30	14	46.7
HPV-33	3	2	66.7	10	5	50.0	>.99	13	7	53.8
HPV-35	9	3	33.3	28	9	32.1	>.99	37	12	32.4
HPV-39	6	2	33.3	23	4	17.4	.58	29	6	20.7
HPV-45	7	3	42.9	11	3	27.3	.63	18	6	33.3
HPV-51	5	2	40.0	30	9	30.0	.64	35	11	31.4
HPV-52	7	2	28.6	22	5	22.7	>.99	29	7	24.1
HPV-53	7	2	28.6	24	11	45.8	.67	31	13	41.9
HPV-56	5	2	40.0	17	2	11.8	.21	22	4	18.2
HPV-58	5	2	40.0	17	3	17.6	.55	22	5	22.7
HPV-59	6	1	16.7	34	8	23.5	>.99	40	9	22.5
HPV-66	4	2	50.0	22	6	27.3	.56	26	8	30.8
HPV-68	4	1	25.0	18	3	16.7	>.99	22	4	18.2
Any high-risk HPV	14	8	57.1	102	46	45.1	.41	116	54	46.6

Abbreviations: HPV, human papillomavirus; incid, incidence.

prevalent and incident persistence, which was measured as a proportion between visits. Second, the number of participants who attended each visit decreased over time, and some participants skipped some visits and returned later, which may have led to nonuniform observations. Third, the number of MSMWH was much lower than that of MSM who were HIV negative in our cohort, and it kept decreasing over time—hence, the possibility of not accumulating sufficient person-time to make robust comparisons by HIV status.

Nevertheless, our study has some strengths, such as being among the first studies in Rwanda and SSA to study penile hrHPV incidence, clearance, and persistence as well as incident persistent infection in a hard-to-reach population such as MSM. We were also able to make comparisons by HIV status and to measure incident persistence, which has not been previously studied. Our findings are therefore a valuable contribution to the scientific body of knowledge at a time when a single dose of the HPV vaccine is being proved to offer sufficient protection against hrHPV infection [21, 22]; this implies that without the logistical and cost constraints, gender-neutral HPV vaccination could be considered in SSA for the prevention of anogenital HPV infection, including penile hrHPV, which may in turn result in the prevention of penile cancer.

CONCLUSIONS

We found high incidence rates and high prevalent and incident persistence of penile hrHPV among Rwandan MSM, with HPV-16 being the type with the highest incidence. These findings highlight the importance of preventive strategies for HPV-associated anogenital cancers, such as gender-neutral HPV vaccination in SSA.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online (http://jid.oxfordjournals.org/). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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