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Prevalence of human papillomavirus in men who have sex with men in the era of an effective vaccine; a call to act

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Objectives

The incidence of human papillomavirus (HPV)-associated anal cancer is increasing. Men who have sex with men (MSM), particularly those coinfected with HIV, are disproportionately affected. Documenting the molecular epidemiology of HPV infection is important in guiding policy makers in formulating universal and/or targeted vaccine guidelines.

Methods

A prospective cohort study was conducted. HIV-positive and HIV-negative MSM > 18 years old were invited to participate. Provider-performed anal swabs were collected and anal HPV infection was detected using consensus primer solution phase polymerase chain reaction (PCR) followed by type-specific PCR for high-risk (HR)-HPV types 16, 18 and 31. Between-group differences were analysed using χ^2 tests and Wilcoxon rank tests.

Results

One hundred and ninety-four MSM [mean (standard deviation (SD)) age 36 (10) years; 51% HIV-positive) were recruited. The median number of sexual contacts in the preceding 12 months was 4 (interquartile range 2-10). HIV-positive subjects had a mean (SD) CD4 count of 557 (217) cells/μL, and 84% were on highly active antiretroviral therapy (HAART). Thirty-one samples were *B*-globin negative and thus excluded from further analysis. A total of 113 subjects (69%) had detectable HPV DNA. Sixty-eight subjects (42%) had an HR-HPV type detected. HR HPV type 16 was detected in 44 samples (27%), HR-HPV type 18 in 26 samples (16%) and HR-HPV type 31 in 14 samples (23%). Twenty-eight subjects (17%) had more than one type of HR-HPV type detected. When HPV and HR-HPV were stratified by age, those > 35 years had a higher prevalence ($P = 0.001$ and $P = 0.028$, respectively). HIV-positive subjects were more likely than HIV-negative subjects to have any detectable HPV (77% *vs.* 61%, respectively; $P = 0.04$), to have HR-HPV type 18 or 31 ($P = 0.05$ and $P = 0.006$, respectively) and to be infected with more than one HR-HPV type (31% *vs.* 3%, respectively; $P < 0.001$). Within the HIV-positive group, the prevalence of HPV was higher in those not on HAART ($P = 0.041$), although it did not differ when stratified by CD4 count.

Conclusions

The identified prevalence of anal HPV infection was high. Emerging patterns of HPV-related disease strengthen the call for universal vaccination of boys and girls with consideration of catch-up and targeted vaccination of high-risk groups such as MSM and those with HIV infection.

Keywords: HIV, HPV, MSM, prevalence, vaccine

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Introduction

Human papillomavirus (HPV) infection is the most common sexually transmitted infection (STI); it is highly prevalent in the sexually active population and is rapidly acquired after sexual debut [1]. Over 90 serotypes of HPV have been identified; low-risk (LR)-HPV types (predominantly 6 and 11) can cause genital warts, while high-risk (HR)-HPV types (predominantly 16 and 18) can cause cancer of the cervix, anus and oropharynx [2].

Following the introduction of screening programmes in the developed world, the incidence of cervical cancer has decreased; however, the incidences of HPV-associated anal and oropharyngeal cancers have increased dramatically in the past decade [3]. Noncervical HPV-associated cancers, while individually relatively rare, now collectively parallel the burden of cervical cancers in developed countries. HR-HPV is now thought to cause over 5% of all cancers world-wide [4].

Certain 'at-risk' groups such as men who have sex with men (MSM), particularly those with HIV infection, are disproportionately affected. The incidence of anal cancer is 1–2/100 000 in the general population, 35/100 000 in HIV-negative MSM and up to 70/100 000 in HIV-positive MSM [5–8].

Since the advent of highly active antiretroviral therapy (HAART), the HIV-positive population is living longer. In the Department of GU Medicine and Infectious Diseases (GUIDE), the largest HIV centre in Ireland, HIV-related mortality has fallen over tenfold from 16.8 deaths per 100 active patient-years in 1995 to 1.4 deaths per 100 active patient-years in 2012 [9]. With increased survival there are an increasing number of non- AIDS-defining illnesses contributing to morbidity and mortality. Malignancy and in particularly anal cancer is a major driver of this trend [10].

Strategies to curtail the increase in anal cancer include screening, the benefits of which remain to be determined, and HPV vaccination.

Two vaccines have been developed to protect against HPV infection, a quadrivalent vaccine which targets HPV 6, 11, 16 and 18 (Gardasil®, HPV-6/11/16/18, Merck, Whitehouse Station, NJ, USA) and a bivalent vaccine which targets HPV 16 and 18 (Cervarix®, HPV-16/18, GlaxoSmithKline Biologicals, GSK, Brentford, London, UK).

Both vaccines have demonstrated efficacy against the development of cervical intraepithelial neoplasia (CIN) 2 or 3, adenocarcinoma in situ or cervical cancer among HPV-naïve women [11–14]. Gardasil has in addition demonstrated efficacy against genital warts in male and female individuals and anal intraepithelial neoplasia related to HPV 6, 11, 16 and 18 in male individuals [15].

Despite the substantial clinical benefit of the HPV vaccine in male individuals, mathematical models suggest that HPV vaccination of male individuals would exceed cost-effectiveness thresholds [16]. Cost effectiveness, however, has been demonstrated in models looking at specific 'at-risk' male populations such as MSM and those infected with HIV over a range of assumptions [17].

Although no therapeutic benefit of the HPV vaccine has been demonstrated for the treatment of active disease present at the time of vaccination, there are early data suggesting a possible benefit of HPV vaccination in the setting of previous disease which could represent an important opportunity for intervention in older high-risk patient groups such as HIV-positive MSM [18].

In addition, if the HPV vaccine proved efficacious in the HIV-positive population against vaccine subtypes, the potential reduction in anal cancer rates could be upwards of 60% [19].

The primary objective of this study was to document the prevalence of anal HPV infection and the prevalence of infection with HR-HPV types 16, 18 and 31 in HIV-positive and HIV-negative MSM. Secondary objectives were to identify factors associated with HPV and HR-HPV infection.

Understanding the prevalence of HPV and HR-HPV infection in the MSM population may help inform strategies for primary and secondary prevention of HPV-associated anal cancer in this at-risk group.

Methods

HIV-positive and HIV-negative MSM were recruited from the GUIDE clinic in St James's Hospital, Dublin, Ireland, a dedicated HIV clinic, and from the GMHS (Gay Men's Health Service), a community-based gay men's sexual health clinic. Participants were recruited from April 2012 to May 2012. Basic demographic data along with information regarding sexual behaviour were collected by means of a self-completed questionnaire. Trained medical providers at each site collected anal samples by rotating a Dacron swab in the anal canal without direct visualization. DNA was extracted using the QIA amp Mini kit (Qiagen, Hilden, Germany). HPV was detected using consensus primer solution phase polymerase chain reaction (PCR) followed by type-specific PCR for HR-HPV types 16, 18 and 31. Between-group differences were analysed using χ^2 tests and the Wilcoxon rank test. At enrolment, each participant provided written informed consent. The study received approval from the local research ethics committee.

Results

One hundred and ninety-four MSM participated in the study (51% HIV-positive; 77% Irish; mean age 36 years)

Table 1 Baseline characteristics of the study cohort and human papillomavirus (HPV) DNA positivity

	Total cohort	HIV positive	HIV negative	*P*-value
n (%)	194	99 (51)	95 (49)	
Age (years) [mean (SD)]	36 (10)	40 (10)	32 (8)	< 0.001
Region of birth [*n* (%)]				
Ireland	149 (77)	74 (75)	75 (79)	
Western Europe	13 (7)	9 (9)	4 (4)	
Eastern Europe	13 (7)	7 (7)	6 (6)	
Other	19 (10)	9 (9)	10 (10)	
Number of partners in past 12 months [mean (SD)]	8 (11)	7 (10)	8 (12)	
Type of intercourse [*n* (%)]				
Anal intercourse only	6 (3)	4 (4)	2 (2)	
Oral intercourse only	26 (13)	12 (12)	15 (15)	
Both oral and anal intercourse	146 (75)	69 (70)	77 (81)	
No sexual contacts in past 12 months [*n* (%)]	14 (6)	12 (12)	2 (2)	0.012
Condom use in past 12 months [*n* (%)]				
Always	81 (42)	43 (43)	38 (40)	
Sometimes	96 (50)	44 (44)	52 (55)	
Never	11 (6)	7 (7)	4 (4)	
Previous STI [*n* (%)]	109 (56)	67 (70)	42 (44)	0.001
History of anogenital warts [*n* (%)]	52 (27)	39 (39)	13 (14)	< 0.001
Smoker [*n* (%)]	74 (38)	45 (45)	29 (30)	0.038
B-globin [*n* (%)]	163 (84)	83 (84)	80 (84)	
HPV DNA detected [*n* (%)]	113 (69)	64 (77)	49 (61)	0.04
HR-HPV 16	44 (27)	26 (31)	18 (23)	0.23
HR-HPV 18	26 (16)	18 (22)	8 (10)	0.05
HR-HPV 31	23 (14)	18 (22)	5 (6)	0.006
Any HR-HPV type	68 (42)	39 (47)	29 (36)	0.146
Individuals with > 1 HR-HPV type [*n* (%)]	28 (17)	26 (31)	2 (3)	< 0.001
HR-HPV 16 and 18	10 (6)	10 (12)	0 (0)	0.0016
HR-HPV 16 and 31	11 (7)	10 (12)	1 (1)	0.009
HR-HPV 18 and 31	7 (4)	6 (7)	1 (1)	0.1
HR-HPV 16, 18 and 31	3 (2)	3 (4)	0 (0)	0.2

HR, high risk; SD, standard deviation; STI, sexually transmitted infection.

(Table 1). The mean number of reported sexual contacts in the preceding 12 months was 8; 75% of individuals reported both oral and anal intercourse, while 42% reported always using condoms. Fifty-six per cent reported a previous diagnosis of an STI, 27% reported a history of anogenital warts and 36% were smokers.

HIV-positive participants were more likely than HIV-negative participants to be older (mean age 40 *vs.* 32 years, respectively; $P < 0.001$), to report no sexual contacts in the preceding 12 months (12% *vs.* 2%, respectively; $P = 0.012$), to report a history of an STI (67% *vs.* 42%, respectively), and to be a current smoker (49% *vs.* 25%, respectively; $P = 0.038$).

Of the 194 MSM recruited, 163 contributed interpretable HPV data (*B*-globin positive), with no significant differences in *B*-globin detection rates between the HIV-positive and HIV-negative groups (Table 1). Only those with detectable *B*-globin were included in further analysis.

One hundred and thirteen participants (69%) had detectable HPV DNA, while 68 subjects (42%) had any HR-HPV type detected.

HR-HPV 16 was detected in 44 samples (27%), HR-HPV 18 in 26 samples (16%) and HR-HPV 31 in 27 samples (17%). Ten subjects (6%) had both HR-HPV types 16 and 18 detected, 11 (7%) had both HR-HPV types 16 and 31 detected, and seven (4%) had both HR-HPV types 18 and 31 detected. Three subjects (2%) had HR-HPV types 16, 18 and 31 detected.

HIV-positive participants were significantly more likely than HIV-negative participants to have HPV DNA detected (64% *vs.* 49%, respectively; $P = 0.04$) and to be infected with HR-HPV type 18 (22% *vs.* 10%, respectively; $P = 0.05$) or HR-HPV type 31 (22% *vs.* 6%, respectively; $P = 0.006$). In addition, those with HIV infection were more likely than those without HIV infection to be infected with multiple types of HR-HPV (31% *vs.* 3%, respectively; $P < 0.001$) (Table 2). All three subjects who tested positive for HR-HPV types 16, 18 and 31 were HIV infected.

HPV DNA and HR-HPV types were more likely to be detected in subjects over 35 years of age ($P = 0.001$ and 0.028, respectively) (Table 2). In addition, subjects who reported a previous STI were more likely to have HPV DNA and HR-HPV detected ($P = 0.01$). A reported history of anogenital warts was positively associated with detectable HPV DNA, although this was of borderline significance ($P = 0.085$).

Table 2 Factors associated with human papillomavirus (HPV) DNA positivity

	B-globin detected	HPV DNA	*P*	HR-HPV	*P*
Total [*n* (%)]	163	113 (69)		68 (42)	
Age [*n* (%)]					
18–24 years	17	14 (82)	< 0.001	4 (24)	0.028
25–29 years	32	13 (41)		8 (25)	
30–35 years	32	22 (69)		14 (44)	
> 35 years	82	64 (78)		42 (51)	
Region of birth [*n* (%)]					
Ireland	117	79 (68)	0.456	50 (43)	0.526
Western Europe	13	10 (77)		7 (54)	
Eastern Europe	11	8 (73)		3 (27)	
Other	22	16 (73)		8 (36)	
Sexual partners in past 12 months [*n* (%)]					
≤5	93	60 (65)	0.178	42 (45)	0.517
> 5	64	48 (75)		25 (39)	
Unknown	6	6 (83)		1 (8)	
Type of intercourse [*n* (%)]					
Anal intercourse only	5	3 (60)	0.693	1 (20)	0.323
Oral intercourse only	21	17 (81)		6 (29)	
Both oral and anal intercourse	124	83 (67)		56 (45)	
Unknown	13	10 (77)		5 (38)	
Condom use in past 12 months [*n* (%)]					
Always	69	44 (64)	0.239	25 (36)	0.366
Sometimes	73	51 (70)		32 (44)	
Never	9	8 (89)		5 (56)	
Unknown	12	10 (83)		6 (50)	
Previous STI [*n* (%)]	94	70 (74)	0.013	48 (51)	0.01
History of anogenital warts [*n* (%)]	47	36 (77)	0.085	23 (49)	0.291
Smoker [*n* (%)]	63	44 (69)	0.844	24 (38)	0.59
Nonsmoker [*n* (%)]	76	44 (58)		35 (46)	
Past smoker [*n* (%)]	22	14 (64)		9 (41)	
HIV-positive [*n* (%)]	83	64 (77)	0.04	39 (47)	0.146
HIV-negative [*n* (%)]	80	49 (61)		29 (36)	

HR, high risk; STI, sexually transmitted infection.

Within the HIV-positive group, the prevalence of HPV was higher in those not on HAART ($P = 0.041$), although it did not differ when stratified by CD4 count.

Discussion

The incidence of HPV infection in our study was high (69% of participants had detectable HPV DNA and 42% had HR-HPV detected). HR-HPV type 16, which was found in 27% of subjects participating in our study, has been shown to be associated with over 80% of anal cancers [20].

While our study did not investigate the persistence of HPV infection, 14 participants self-reported no sexual contacts in the preceding 12 months. Nine of these 14 (64%) were found to have detectable anal HPV DNA, while seven of the 14 (50%) had an HR-HPV type detected, which probably represents persistence of infection. Larger international studies have reported a similar prevalence of HR-HPV infection, with persistence of HR-HPV infection in 50–70% of MSM and a higher persistence rate in HIV-infected subjects [21–23].

HIV infection was positively associated with detection of HPV DNA ($P = 0.04$) and HR-HPV DNA (47% *vs.* 36% in HIV-negative individuals; $P = 0.146$) in our study. The high prevalence of HPV infection in HIV-infected subjects may be driven by an increased persistence of HPV infection as a consequence of compromised immunity and/or by a high incidence of new infections as a consequence of sexual behaviour.

We identified a higher prevalence of HPV infection in subjects reporting more than five sexual partners in the preceding 12 months (75% *vs.* 65% in those reporting five or fewer sexual partners; $P = 0.178$). In addition, individuals with a self-reported history of a previous STI were more likely to have HPV or HR-HPV detected ($P = 0.013$ and 0.01, respectively). Sexual behaviours, including a greater number of sexual partners and receptive anal intercourse, and smoking have been shown to be positively associated with anal HPV infection and anal cancer in a number of studies [22–24].

In our study, rates of infection with HPV in those reporting not using condoms consistently in the preceding 12

months were greater than in those who reported always using condoms: 73% *vs.* 60% for HPV DNA and 36% *vs.* 43% for HR-HPV, respectively. A number of studies have shown that consistent use of condoms prevents or decreases the risk of HPV infection [25,26].

Our study has a number of limitations. Study participants were recruited from a sexual health clinic and an HIV clinic, and so MSM recruited may not be representative of the general MSM population. As this was a point prevalence study, anal swabs were taken at one time-point only and we cannot thus comment reliably on the duration or persistence of HPV infection. Planned follow-up of this cohort will look to clarify this issue. Data on sexual behaviour and history were collected by means of a self-completed questionnaire and therefore may be subject to recall bias.

Our study highlights the burden of anal HPV infection in MSM and those with HIV coinfection. A significant proportion (73%) of participants in our study did not have evidence of infection with HR-HPV type 16 or 18. This indicates that a large proportion of sexually active MSM could potentially benefit from HPV vaccination. There is a growing body of knowledge supporting targeted vaccination of MSM.

STI and HIV clinics would be well placed to facilitate HPV vaccination of risk groups such as MSM given previous experience and successes with hepatitis B virus vaccination [27]. In addition, provision of HPV vaccination in STI clinics may encourage young MSM to access sexual health services earlier, which may provide an opportunity for education interventions targeting HIV prevention.

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