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Seroconversion following anal and genital HPV infection in men: *The HIM study*

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ABSTRACT

Background: Protection from naturally acquired human papillomavirus (HPV) antibodies may influence HPV infection across the lifespan. This study describes seroconversion rates following genital, anal, and oral HPV 6/11/16/18 infections in men and examines differences by HPV type and anatomic site.
Methods: Men with HPV 6/11/16/18 infections who were seronegative for those genotypes at the time of DNA detection were selected from the HPV Infection in Men (HIM) Study. Sera specimens collected ≤ 36 months after detection were analyzed for HPV 6/11/16/18 antibodies using a virus-like particle-based ELISA. Time to seroconversion was separately assessed for each anatomic site, stratified by HPV type.
Results: Seroconversion to ≥ 1 HPV type (6/11/16/18) in this sub-cohort ($N=384$) varied by anatomic site, with 6.3%, 18.9%, and 0.0% seroconverting following anal, genital, and oral HPV infection, respectively. Regardless of anatomic site, seroconversion was highest for HPV 6 (19.3%). Overall, seroconversion was highest following anal HPV 6 infection (69.2%). HPV persistence was the only factor found to influence seroconversion.
Conclusions: Low seroconversion rates following HPV infection leave men susceptible to recurrent infections that can progress to HPV-related cancers. This emphasizes the need for HPV vaccination in men to ensure immune protection against new HPV infections and subsequent disease.

Introduction

Human papillomavirus (HPV) infection is the cause of multiple cancers in both men and women [1]. The rate of HPV acquisition appears to differ by gender and by anatomic site of infection [2]. A high prevalence of genital HPV has been observed in men across the lifespan, with the rate of new genital HPV acquisition remaining constant in men with age [3]. This age pattern is significantly different than what has been observed in women, where rates of new infection decrease with age [4,5]. Similarly, anal HPV prevalence in men appears constant across the lifespan [6,7], and oral HPV prevalence may actually increase with age in men [8–10]. The factors that underlie the association between age and HPV infection at multiple anatomic sites in men remain unknown. Differences in sexual behavior across the lifespan of men and women may contribute to differences in HPV prevalence observed between the sexes by age. A proportion of newly detected infections may also be due to reactivation of a latent infection or fluctuations in the level of viral replication in individuals with a persistent infection. Another factor that may influence HPV prevalence across the lifespan is protection conferred from naturally acquired HPV antibodies.

HPV seroprevalence studies have consistently demonstrated that a smaller proportion of heterosexual men are HPV seropositive compared to men who have sex with men (MSM) or to women [11]. In addition, the anatomic site of HPV infection may influence immune response, as infection at mucosal epithelia such as the cervix and anal canal may induce stronger immune responses compared to infection at keratinized epithelia such as the genital skin [12–14]. To date, few studies have examined the proportion of men who seroconvert following HPV infection and the rate at which men seroconvert following natural HPV infection at the genitals [15,16]. Only one study

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examined the rate of seroconversion following infection at multiple anatomic sites [16], but this study was conducted among a highly select group of men who have sex with men (MSM), some of whom were HIV-positive, factors known to influence HPV infection and antibody status [17,18].

The purpose of this study was to describe the rate of seroconversion following HPV infection at the anal canal, oral epithelium, and genitals in men ages 18–70 years participating in the *HPV Infection in Men (HIM) Study* and to examine differences in antibody response by HPV type and anatomic site of infection.

Materials and methods

Men were recruited in São Paulo, Brazil, Cuernavaca, Mexico, and Tampa, Florida from June 2005 to September 2009 for the prospective *HIM Study*. Inclusion criteria included an age of 18–70 years, no plans to relocate during the four year study, no self-reported history of penile or anal cancer or genital warts, and no current sexually transmitted infections (STIs), including HIV. Additional details of the study design have been described previously [3,9]. The Human Subjects Committees of the University of South Florida (Tampa, FL, USA), Ludwig Institute for Cancer Research (São Paulo, Brazil), Centro de Referência e Treinamento em Doenças Sexualmente Transmissíveis e AIDS (São Paulo, Brazil), and Instituto Nacional de Salud Pública de México (Cuernavaca, Mexico) approved all study procedures (IRB approval numbers 102660 [U.S.], 028/2004 [Brazil], and CI440 [Mexico]). All participants provided written informed consent.

Study protocol

A total of 4123 men enrolled in the *HIM Study*. Follow-up occurred at six-month intervals for a total of four years. A total of 72 men acknowledged HIV infection after enrollment and were removed from further analysis. Of the remaining 4051 men, 3661 (90.4%) men returned for at least the first six-month follow-up visit.

Participants completed an 88-item computer-assisted self-interview (CASI) at each visit, written in the region's primary language (Portuguese, Spanish, or English). The validated CASI questionnaire elicited information about participant demographics, substance use, and sexual behaviors [19].

At each study visit, a clinician examined participants for STI symptoms, including anogenital warts and lesions, and genital, anal, and oral specimens were obtained. For genital HPV sampling, the clinician used a saline-wetted swab to sweep 360° around the coronal sulcus and glans penis, and if present, a retracted prepuce. A second swab was used to sample the entire surface of the penile shaft, while a third was used to sample the scrotum. Finally, the clinician used a separate swab to sample the anal canal. Each swab was placed in a vial of transport media (STM, Qiagen) and stored at −80 °C. For detection of genital HPV, swabs from the coronal sulcus/glans, shaft, and scrotum were combined. Oral gargle specimens were collected by a 30-s rinse/gargle with 15 mL of locally available mouthwash and processed as previously published by our group and others [9,10]. All specimens were stored at −80 °C until PCR analyses and genotyping were conducted.

At each study visit, study staff drew 10 mL of blood. Blood was processed at the clinic site and later aliquoted into cryovials and placed in a −20 °C freezer pending transfer to long-term storage at −80 °C. Sera were sent on dry ice to Johns Hopkins University for HPV antibody testing. Enrollment serostatus of the *HIM Study* cohort has been previously reported [20].

HPV DNA analyses

DNA was extracted from specimens using the QIAamp DNA Mini Kit (Qiagen) and underwent PCR and HPV genotyping as previously described using the Linear Array method (Roche Diagnostics) [3,13,20–22] to detect 37 genital HPV types: 6, 11, 16, 18, 26, 31, 33, 35, 39, 40, 42, 45, 51 – 56, 58, 59, 61, 62, 64, 66 – 73, 81 – 84, IS39, and CP6108 [21]. Accuracy and potential contamination were assessed using non-template negative controls and CaSki DNA-positive controls. β-globin positivity at enrollment and all follow-up visits was greater than 97%. Specimens that were negative for β-globin and all HPV types were considered invalid and were excluded from this analysis.

Seroconversion study population

Participants selected for inclusion in this analysis of HPV seroconversion: (1) had HPV 6, 11, 16, or 18 DNA detected at the genital, anal, or oral site; (2) were seronegative for HPV 6, 11, 16, or 18 at the visit at which the relevant type-specific HPV DNA detection occurred and up to two visits prior; and, (3) had no prior detection of the same HPV type at the other two anatomic sites.

Archived serum specimens for HPV antibody analyses were available for all men in the seroconversion sub-cohort. To ensure attribution of the antibody response to infection at a specific anatomic site, men with prior detection of a specific HPV type at a different anatomic site were removed from analyses for the anatomic site under consideration. For example, a man with HPV 6 DNA detected first at the genitals and later at the anal canal was included in the genital seroconversion analysis but not the anal seroconversion analysis. Men with concurrent same type HPV infection at multiple anatomic sites were excluded from this analysis. As a single participant could have infections with multiple HPV types, there were more infections than men included in this analysis.

HPV antibody testing

HPV serum samples collected at the time of HPV DNA detection, up to 12 months prior to HPV detection, and at subsequent six-month intervals for up to 36 months post-DNA detection were evaluated for the presence of HPV antibodies to HPV 6, 11, 16, and 18 – the types that cause a majority of HPV-related disease in men – using a previously described type-specific method [14,20]. Briefly, serum antibodies to these four HPV types were individually measured using a virus-like particle (VLP)-based ELISA. Serum samples were tested using a single lot of reagents. To further ensure reliability of results, specimens were tested in duplicate on separate plates, with results from retesting of specimens exceeding a preset coefficient of variation. To minimize inter-assay variation, serial samples from the same subject were tested on the same day. Cutoff values for seropositivity were determined using optical density (OD) values greater than the mean OD value plus five standard deviations (SDs) and were 0.3, 0.3, 0.2, and 0.2 for HPV 6, 11, 16, and 18, respectively. Antibody titers below these values were not classified as seroconverters. Means and SDs were estimated using serum samples from children 1 to 10 years of age after exclusion of outliers. Quality control was assured through preparation of positive and negative controls in each of the serology assays.

Statistical analysis

Selected baseline characteristics, including age, circumcision status, smoking status, and sexual orientation, were compared between those who did and did not seroconvert using the Chi Square exact and Wilcoxon rank sum tests. The time-to-event approach was applied to assess the time from type-specific infection at one of three

anatomic sites to seroconversion to the same HPV type that was detected using the Kaplan–Meier method. Infections that did not result in seroconversion were censored at the last visit. Time-to-event analyses were stratified by HPV type (6, 11, 16, 18) at each anatomic site. Viral infection was categorized as transient (one-time HPV DNA detection) or persistent (HPV DNA detected at two or more consecutive visits, spaced ~6 months apart). To investigate potential heterogeneity by country, age group, sexual orientation, circumcision, and viral persistence (transient HPV DNA detection vs. infections persisting for ≥6 months), stratified Kaplan–Meier curves were estimated for HPV 16 and HPV 6, the HPV types with sufficient events to support these analyses. The log-rank test was used to compare the probability of seroconversion between groups. Data were analyzed using SAS 9.3 (SAS Institute Inc., Cary, North Carolina, USA).

Results

A total of 384 men with HPV 6, 11, 16, or 18 infections at the genital, anal canal, or oral cavity qualified for the *HIM Study* seroconversion sub-cohort, with their characteristics presented in Table 1. No statistically significant differences were noted between participants who seroconverted to at least one HPV type ($n=35$) following an HPV infection compared to men who did not seroconvert ($n=349$) (Table 1). However, the mean age of men who seroconverted following HPV 16 infection was marginally lower compared to those who did not (27.0 vs. 32.6 years, $p=0.059$) (data not shown). Among men with anal HPV infections, 33% (16/48) were classified as men who have sex with men (MSM) and 8.3% (4/48) were classified as men who have sex with women and men (MSWM).

The majority of HPV infections detected at the oral site were preceded by an infection with the same HPV type at either the genital or anal anatomic sites. As genital HPV prevalence is known to be higher than prevalence observed at the anal canal or oral epithelium,[2] among this cohort of predominantly heterosexual men, genital infections predictably comprised the largest sample ($n=399$), followed by anal infections ($n=53$) and oral infections ($n=3$). An interesting question we attempted to address was whether seroconversion differed among men who had the same HPV type concurrently at multiple anatomic sites compared to one anatomic site only. Only 16 participants had HPV DNA detected simultaneously at the genitals and anal canal, none of whom seroconverted to that HPV type (data not shown).

Overall, 24-month seroconversion varied by anatomic site of HPV detection: 6.3%, 18.9%, and 0.0% seroconverted following infection with any of the four HPV types (6, 11, 16, or 18) at the anal canal, genitals, and oral epithelium, respectively (Table 2). All men who seroconverted following an anal HPV infection did so by month 12. Among men who seroconverted to HPV 6, 11, 16, or 18 within 24 months following a genital HPV infection, 83.3%, 66.7%, 62.5%, and 50% seroconverted by 12 months. Regardless of anatomic site of infection, seroconversion was highest among participants with HPV 6 (19.3%) and lowest among those with HPV 16 (3.6%) or 18 (3.4%) infections. Seroconversion was highest following HPV 6 infection at the anal canal (69.2%).

Among men who seroconverted to one or more HPV types, the median time to seroconversion following any HPV DNA detection at the genitals was 257 days (min, max=163, 1003). Although probability of seroconversion following genital HPV DNA detection differed by HPV type ($p<0.05$), the median time to seroconversion did not differ significantly by HPV type (Fig. 1a). However, a shorter time to seroconversion was noted for HPV types 6 and 11 (223 and 182 days [7.4 and 6.1 months], respectively), compared to HPV types 16 and 18 (317 and 311 days [10.6 and 10.4 months], respectively).

At the anal canal, the median time to seroconversion following any HPV DNA detection was 200 days (min, max=181, 263). Similar to seroconversion at the genitals, the median time to seroconversion following an anal HPV 6 infection was 197 days (6.6 months). Median time to seroconversion following an anal HPV 18 infection was 219 days [7.3 months] (Fig. 1b). Regardless of anatomic site of infection, a shorter time to seroconversion following HPV 6 infection (197 days) was observed compared to other HPV types (266 days). However, these differences did not reach statistical significance ($p=0.2$).

Overall, seroconversion following genital or anal infection did not differ by age, country of residence, race, circumcision status, smoking status, or sexual orientation (data not shown). However, men who had persistent genital HPV 6 infection were more likely to seroconvert compared to those with transient infections (Fig. 2a). Seroconversion did not differ when men with transient and persistent genital HPV 16 infections were compared (Fig. 2b).

Among men who seroconverted following genital HPV 6 infections, men with infections persisting ≥6 months also had a significantly ($p<0.005$) more rapid rate of seroconversion (median time=223 days) compared to men with transient HPV 6 genital infections (median time=586 days) (Fig. 2a). Viral persistence did not influence median time to seroconversion following genital HPV type 11, 16, or 18 infections.

Discussion

In this multinational study of men ages 18–70 years, we demonstrate a low rate of seroconversion following HPV infection, regardless of anatomic site of infection. Overall, only 7.7% of men developed detectable serum HPV antibodies. Type-specific HPV seroconversion was higher and faster following HPV 6 infection (19.3%, regardless of anatomic site) compared with HPV 11, 16, and 18 infections and was highest following HPV 6 infection at the anal canal (69.2% seroconverted). In addition, persistent HPV 6 infection at the genitals was more likely to result in seroconversion compared to transiently detected infection.

We previously reported low HPV 6, 11, 16, and 18 seroprevalence among men participating in the *HIM Study* cohort [20], an observation consistent with reports from studies conducted in different world regions with varying sexual behaviors and characteristics [11,17,18,22–24]. Among studies that included both males and females, HPV seroprevalence in men is consistently lower (typically twofold lower for HPV 16) than that reported among women [11]. This lower HPV seroprevalence, combined with the observation that genital HPV DNA prevalence is high and remains relatively constant across the lifespan of men [3], has led to the hypothesis that seroconversion following HPV infection in men is lower than that reported among women. However, prior reports of higher HPV seroprevalence among MSM and men with anal HPV infections compared with genital infections in cross-sectional analyses [14,17,24] suggested that the immune response to HPV in men may differ by anatomic site of infection.

As suspected, the percentage of men who seroconverted following HPV infection was low, approximately four- to tenfold lower than that observed among women following cervical infection [25]. For example, in the current study, 4.1% of men seroconverted following genital HPV 16 detection compared to 60% of women following cervical HPV 16 detection [25], regardless of whether the infection was persistent or transient. Two other studies have examined seroconversion following genital HPV infection in men, both documenting similarly low rates. Among young university male students, 13.0% seroconverted within 24 months following genital HPV 16 infection [15]. In a study of MSM recruited from infectious disease and STI clinics in Amsterdam, 8.2% of HIV-negative and 12.4% of HIV-positive men seroconverted within 12 months following HPV 16 detection [16]. This low antibody response to genital HPV infections in men may partially explain the observation of recurrent HPV infection with the same type in men and the constant prevalence and incidence rates across the lifespan [3].

Table 1
Characteristics of HIM Study seroconversion sub-cohort ($N=384$) by seroconversion status to HPV types 6, 11, 16, or 18 within 36 months post HPV infection.

	Entire cohort ($N=384$)	Seroconverted[a] ($N=35$)	No Seroconversion ($N=349$)
Age, in years			
Mean (SD)	32.8 (10)	33.1 (11)	32.7 (9.9)
Median (range)	31 (20–71)	32 (20–70)	31 (20–71)
Age, in years			
18–30	187 (48.7)	17 (48.6)	170 (48.7)
31–44	149 (38.8)	14 (40)	135 (38.7)
45–70	48 (12.5)	4 (11.4)	44 (12.6)
Country			
U.S.	148 (38.5)	13 (37.1)	135 (38.7)
Brazil	153 (39.8)	12 (34.3)	141 (40.4)
Mexico	83 (21.6)	10 (28.6)	73 (20.9)
Race			
White	207 (53.9)	17 (48.6)	190 (54.4)
Black	70 (18.2)	6 (17.1)	64 (18.3)
Asian/Native American/ Native Alaskan	13 (3.4)	1 (2.9)	12 (3.4)
Mixed race	94 (24.5)	11 (31.4)	83 (23.8)
Education			
≤ 12 years	160 (41.7)	16 (45.7)	144 (41.3)
13–15 years	116 (30.2)	13 (37.1)	103 (29.5)
≥ 16 years	108 (28.1)	6 (17.1)	102 (29.2)
Marital status			
Single/never married	208 (54.2)	17 (48.6)	191 (54.7)
Married	92 (24)	10 (28.6)	82 (23.5)
Cohabitating	49 (12.8)	6 (17.1)	43 (12.3)
Divorced/separated/widowed	35 (9.1)	2 (5.7)	33 (9.5)
Circumcision			
None	203 (52.9)	17 (48.6)	186 (53.3)
Full	176 (45.8)	17 (48.6)	159 (45.6)
Partial	5 (1.3)	1 (2.9)	4 (1.1)
Smoking status			
Current	98 (25.5)	10 (28.6)	88 (25.2)
Former	60 (15.6)	4 (11.4)	56 (16.0)
Never	226 (58.9)	21 (60.0)	205 (58.7)
Sexual orientation[b]			
MSW	337 (87.8)	28 (80)	309 (88.5)
MSM	41 (10.7)	6 (17.1)	35 (10)
MSWM	6 (1.6)	1 (2.9)	5 (1.4)
Lifetime no. female partners			
0–1	39 (10.2)	8 (22.9)	31 (8.9)
2–9	122 (31.8)	8 (22.9)	114 (32.7)
10–49	176 (45.8)	12 (34.3)	164 (47.0)
≥ 50	21 (5.5)	2 (5.7)	19 (5.4)
Refused	26 (6.8)	5 (14.3)	21 (6.0)
Lifetime no. male partners			
0	305 (79.4)	24 (68.6)	281 (80.5)
1–9	44 (11.5)	5 (14.3)	39 (11.2)
≥ 10	17 (4.4)	1 (2.9)	16 (4.6)
Recent[c] no. female partners			
0	92 (24.0)	10 (28.6)	82 (23.5)
1	139 (36.2)	14 (40.0)	125 (35.8)
2	57 (14.8)	1 (2.9)	56 (16.0)
≥ 3	83 (21.6)	7 (20.0)	76 (21.8)
Refused	13 (3.4)	3 (8.6)	10 (2.9)
Recent[c] no. male partners			
0	344 (89.6)	28 (80.0)	316 (90.5)
≥ 1	25 (6.5)	4 (11.4)	21 (6.0)
Refused	15 (3.9)	3 (8.6)	12 (3.4)

[a] Includes all men who seroconverted to one or more of HPV types 6, 11, 16, or 18.
[b] MSW=Men having sex with women; MSM=men having sex with men; MSWM= men having sex with women and men.
[c] Within past six months. P values were derived using Monte Carlo estimation of the exact Pearson chi-squared test (for categorical variables) and the Wilcoxon test (for continuous variables) and were not significant ($p > 0.05$) for any variables.

Differences in the immune response to HPV were observed by HPV type, similar to prior reports that focused on high-risk HPV types [15,24]. However, to our knowledge, the current study is the only to examine seroconversion to low-risk HPV types 6 and 11 in men. Following HPV 6 infection at the genitals, 12.5% of men seroconverted, compared with only 4.1% and 2.6% in response to HPV 16 and 18 infections, respectively. In contrast, only slight differences in seroconversion by HPV type were observed

Table 2
Percent of men who seroconverted within 36 months following HPV DNA detection of an genital, anal, or oral infection with HPV 6, 11, 16, or 18.

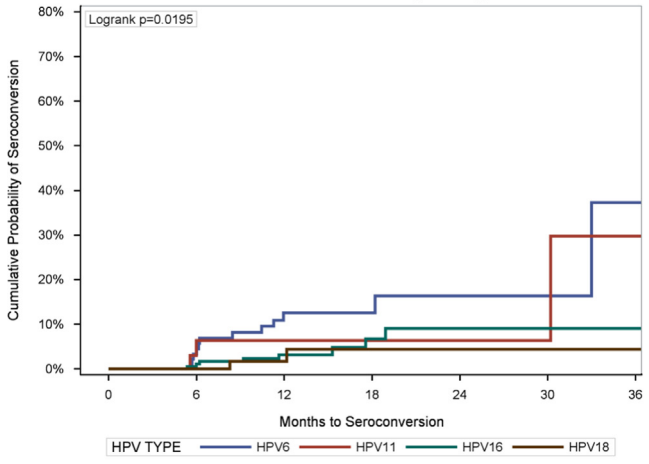
	HPV 6 n/N (%)	HPV 11 n/N (%)	HPV 16 n/N (%)	HPV 18 n/N (%)	Overall[a] n/N (%)
All sites[b]	21/109 (19.3)	3/35 (8.6)	8/223 (3.6)	3/88 (3.4)	35/455 (7.7)
Genital	12/96 (12.5)	3/33 (9.1)	8/193 (4.1)	2/77 (2.6)	25/399 (18.9)
Anal	9/13 (69.2)	0/2 (0.0)	0/27 (0.0)	1/11 (9.1)	10/53 (6.3)
Oral	0/0 (0.0)	0/0 (0.0)	0/3 (0.0)	0/0 (0.0)	0/3 (0.0)

n=number of men per HPV type per anatomic site who seroconverted; *N*=total number of men per HPV type per anatomic site.

[a] HPV DNA-positive for HPV 6, 11, 16, or 18.

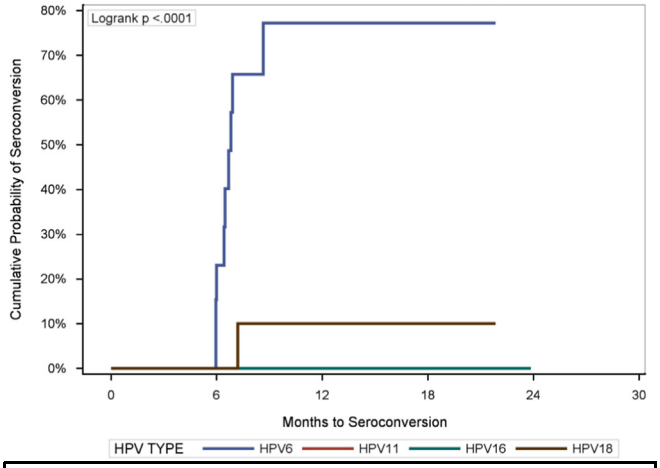
[b] Infection at genital, anal, or oral site.

A



Percent seroconversion by genital HPV type			
	N	%	median time (in days)
HPV6	12	12.5	223
HPV11	3	9.1	182
HPV16	8	4.2	317
HPV18	2	2.6	311

B



Percent seroconversion by anal HPV type			
	N	%	median time (in days)
HPV6	9	69.2	197
HPV11	0	0	
HPV16	0	0	
HPV18	1	9.1	219

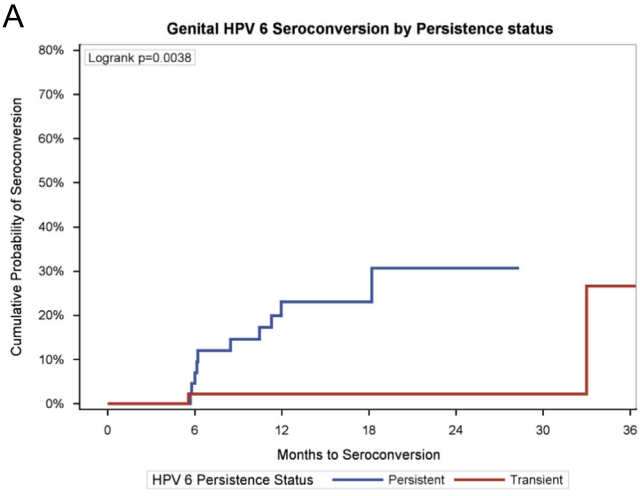
Fig. 1. Time to seroconversion following: (a) genital or (b) anal infection with HPV 6, 11, 16, or 18.

following cervical infection in women (60% and 69% following HPV 16 and 6 infections, respectively) [25]. Interestingly, while seroconversion following HPV 16 infection did not differ by anatomic site of infection, seroconversion following HPV 6 infection at the anal canal was significantly higher than at the genitals (69.2% compared to 12.5%), similar to the 69% reported among women following cervical HPV 6 infection [25]. HPV 16 is known to evade immunity and is more likely to persist compared to HPV 6 [26]. As genital HPV 6 has a high rate of progression to condyloma (~25% of HPV 6 infections progress in men) [27], we examined whether condyloma incidence might influence seroconversion following genital HPV 6 infection. Although a slightly higher rate of seroconversion was observed among men who developed HPV 6-related condyloma, differences between groups did not reach statistical significance; 16% vs. 11.3% of men with and without condyloma, respectively, seroconverted to HPV 6. To adequately address whether seroconversion is higher subsequent to lesion development, studies among a larger sample of men with HPV-related anal and genital lesions need to be conducted. The low rate of seroconversion among men may be due to a poor immune response or may simply reflect that HPV detected is deposition and not true infection in men. Regardless, our study and the other two studies published among men have shown that circulating antibodies to HPV do not confer protection against subsequent HPV infection in men, in contrast to the partial protection observed among females. [14,28,29].

Few factors influenced seroconversion and the rate at which men seroconverted following HPV infection in the current study. We examined rates of seroconversion for the four vaccine HPV types by age, race, sexual orientation, circumcision, smoking status, and infection persistence. No demographic or behavioral factors evaluated were associated with seroconversion. The only factor that influenced seroconversion was viral persistence, with a higher and faster rate of seroconversion observed following persistent HPV 6 infection at the genitals. Similar results have been reported among HIV-negative MSM, in which a higher probability of seroconversion was observed following anal infection but not penile infection [16]. Among university-aged men, those who reported ever smoking and men with HPV detected at multiple genital anatomic sites were at significantly higher risk of seroconversion [15]. Differences in population characteristics likely contributed to differences in factors associated with seroconversion across studies.

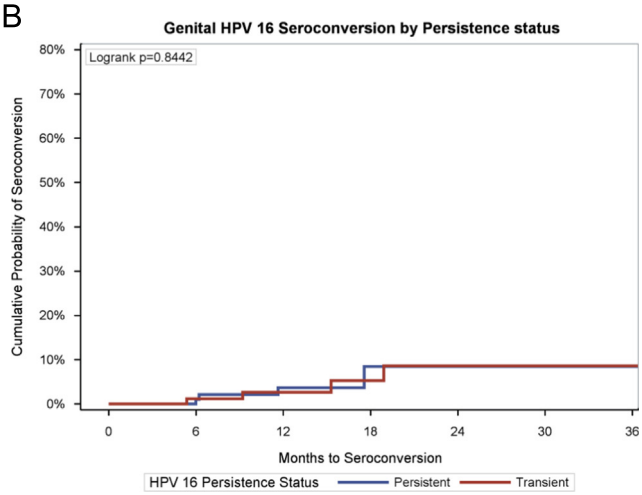
As with any epidemiologic study, there are limitations that need to be considered when interpreting the findings. The low prevalence and incidence of oral HPV infections [9] resulted in a small sample size to evaluate seroconversion following oral HPV detection. Larger studies and/or longer follow-up of existing male cohorts will be required to adequately assess rates of seroconversion following oral HPV detection. Additionally, as only a subset of anal HPV genotyping data was available for this study, we were unable to compare seroconversion following transient vs. persistent anal HPV infection. It is also possible that seroconversion would be different when examining recurrent type-specific HPV infections or restricting to incident infections only, and that by excluding information from subsequent infections, there is a potential formisclassification of seroconversion to the first site of HPV DNA detection. However, a major strength of our analysis is that we evaluated men with infections detected at the first anatomic site of detection in an attempt to evaluate differences in seroconversion by anatomic site of infection. Other studies only evaluated seroconversion at one anatomic site, regardless of whether infection first occurred at this anatomic site or at another [15]. In the only other publication that examined HPV infection at multiple anatomic sites in men [16], it is unclear how consecutive infections with the same HPV type at different anatomic sites were analyzed. The current study also focused only on the HPV types that cause the majority of disease in men (HPV 6, 11, 16, 18). While other HPV types are commonly detected in men,

A



HPV 6 seroconversion by persistence status			
	N	%	median time (in days)
Persistent	10	10.4	223
Transient	2	2.1	586

B



HPV 16 seroconversion by persistence status			
	N	%	median time (in days)
Persistence	4	4.6	271.5
Transience	4	4.6	372.5

Fig. 2. Time to seroconversion following transient or persistent ($\geq$ 6 month duration) genital infections with (a) HPV 6 or (b) HPV 16.

these rarely progress to disease in men [30]. To our knowledge, this is the only study that examined seroconversion following HPV 6 and 11 infections in men, the types that cause 90% of genital warts.

Conclusions

In conclusion, low rates of seroconversion following HPV infection in men, coupled with a lack of demonstrated protection against infection among those that do seroconvert, may leave men susceptible to recurrent infections, especially with HPV type 16, the cause of anal, oropharyngeal, oral, and penile cancers in men. In contrast, nearly 100% seroconversion to all included types following HPV vaccination has been documented in men. Thus, HPV vaccination is the only reliable method to ensure immune protection against new HPV infections and subsequent disease in males [18,31].

Conflicts of interest

A.R.G. and L.L.V. are members of the Merck Advisory Board. No conflicts of interest were declared for the remaining authors.

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