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Journal

The Journal of Infectious Diseases, 229(3)

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Publication Date

2024-03-14

DOI

10.1093/infdis/jiad485

Peer reviewed

The Journal of Infectious Diseases

MAJOR ARTICLE

High Risk of New HPV Infection Acquisition Among Unvaccinated Young Men

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Background. International data on anogenital HPV infection incidence among men are limited.

Methods. Incidence of incident-persistent (IP) anogenital HPV infections was evaluated among 295 men who have sex with men (MSM) and 1576 heterosexual men (HM) aged 16–27 years in the placebo arm of a global, multicenter 4-valent (4v) HPV vaccine trial. We estimated IP incidence (penile/scrotal, perineal/perianal, anal) for 4vHPV and 9-valent (9v) HPV vaccine types and cumulative IP incidence over 36 months.

Results. IP infection incidence per 100 person-years (95% CI) among HM for 4vHPV and 9vHPV types was 4.1 (3.5–4.9) and 6.8 (5.9–7.6) at penile/scrotal, and 1.2 (.8–1.6) and 1.9 (1.5–2.4) at perineal/perianal sites, respectively; and among MSM, IP infection incidence was 2.3 (1.3–3.8) and 3.2 (2.0–4.9) at penile/scrotal, 6.8 (4.9–9.2) and 9.0 (6.9–11.6) at perineal/perianal, and 12.0 (9.4–15.1) and 16.8 (13.7–20.2) at anal sites, respectively. Cumulative IP incidence over 36 months (excluding anal canal; any 9vHPV type) was higher among MSM versus HM (24.1% vs 18.4%).

Conclusions. A substantial proportion of unvaccinated men of catch-up vaccination age developed IP 9vHPV-related infections. Gender-neutral vaccination could decrease male HPV infection, contribute to herd protection, and reduce disease burden.

Clinical Trials Registration. NCT00090285.

Keywords. human papillomavirus; HPV vaccines; HPV infection.

Anogenital human papillomavirus (HPV) infection is common in men and women. HPV infection is the cause of cervical, vulvar, and vaginal cancers in women, penile cancer in men, and anal cancer, head and neck cancer, anogenital warts, and recurrent respiratory papillomatosis in both sexes [1, 2].

The epidemiology of male HPV infection was studied in the prospective, multinational (United States, Brazil, and Mexico) HPV Infection in Men (HIM) study [3], which enrolled more than 4000 men aged 18–70 years with no previous diagnosis of genital or anal warts [3]. In the HIM study, a high incidence of new genital HPV infections was reported (38.4 per 1000 person-months) [3], along with high rates of incident anal HPV infection among men who have sex with men (MSM; 25.9 per 1000 person-months) [4]. Male HPV infection incidence data from other countries are limited. Data on incident-persistent (IP) HPV infection are needed, as it is a strong risk factor for incident HPV-related disease. Additional research is required to expand our understanding of male HPV infection across different geographic regions and in relation to multiple HPV types.

Using data from the placebo arm of a global, randomized, 4-valent HPV (4vHPV) vaccine efficacy trial (V501-020) in young men [5, 6], this study was conducted to estimate the incidence of IP anogenital HPV infections and associated risk factors separately, among heterosexual men (HM) and MSM.

METHODS

Data Source

Data in this analysis are from HM and MSM in the placebo arm of a global randomized controlled trial of the 4vHPV vaccine (V501-020; NCT00090285) [5, 6]. Details of the trial have been previously reported [5]. Between 3 September 2004 and 29 August 2008, HM (aged 16–23 years) and MSM (16–26 years) were enrolled from 18 countries in North America, Latin America, Asia-Pacific, Europe, and Africa [5, 6]. Briefly, key inclusion criteria were HM who had 1–5 lifetime exclusively female partners, or MSM with 1–5 lifetime sex partners who reported engaging in either insertive or receptive anal intercourse, or oral sex with another male partner within the past year [5, 6]. In addition, HM and MSM did not have a prior diagnosis of human immunodeficiency virus (HIV) infection, no clinical evidence of anogenital warts or dysplasia, and no

Received 03 July 2023; accepted 28 October 2023; published online 28 November 2023

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The Journal of Infectious Diseases® 2024;229:707–18

https://doi.org/10.1093/infdis/jiad485

history of these findings. HM and MSM found to be HIV positive before the first day of the study were excluded [5, 6]. During follow-up, HM from South Africa and all MSM were tested annually for HIV, whereas HM from other countries were only tested if clinically indicated; MSM residing in South Africa were not included in the study [5, 6].

The V501-020 trial was sponsored by Merck Sharp & Dohme LLC, a subsidiary of Merck & Co, Inc, Rahway, NJ, and was conducted in accordance with Good Clinical Practice Guidelines, Declaration of Helsinki, and all applicable country or local statutes and regulations regarding ethical committee review, informed consent, and the protection of the rights and welfare of human participants in biomedical research. Participants (or their legally authorized representatives) provided written informed consent at the start of the study.

HPV DNA Sampling and Assessment

On day 1, month 7, and at 6-month intervals thereafter through follow-up, scrotal, perineal/perianal, and penile specimens for all study participants (HM and MSM), and intra-anal specimens for MSM subjects only were obtained. All specimens were HPV genotyped using multiplex polymerase chain reaction (PCR)-based assays [7, 8] to detect 9 HPV types targeted by the 9-valent HPV (9vHPV) vaccine (6/11/16/18/31/33/45/52/58) and 5 additional oncogenic HPV types that are not vaccine targeted (35/39/51/56/59).

Statistical Analyses

This analysis comprised men from the placebo arm who were HPV naive to the relevant type (HNRT), defined as being naive at day 1 to the HPV type under consideration. For HPV types 6, 11, 16, and 18, HPV naive was defined as having a negative swab (ie, PCR negative across all anatomic sites) and serology negative to the relevant HPV type, whereas for HPV types 31, 33, 45, 52, and 58, serology information was not available for all participants and therefore HNRT was defined as having a negative swab to the relevant HPV type. Participants with missing PCR results at ≥1 anatomic site or missing serology results at day 1 were excluded from HNRT analyses.

An IP infection was defined as the detection of a new HPV type at 2 or more consecutive visits at the same anatomic site spaced approximately 6 months apart (± 1 month). A new HPV infection detected at the last available follow-up visit was not considered an IP infection because persistence could not be confirmed. Follow-up time in men with a non-IP HPV infection was defined as the time from day 1 to the last known visit at which a new infection was detected. Kaplan-Meier methods were used to estimate cumulative incidence of IP infections with HPV 16, HPV 16/18, 4vHPV types, or 9vHPV types over 36 months. While the visit following initial acquisition was used to confirm outcome, the visit at which IP infection was first detected was used as the event censoring time.

The association between baseline characteristics and IP infection was assessed by logistic regression analysis. A backward stepwise method was used to guide selection of relevant covariates in multivariable (adjusted) models [9]. Odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were estimated, with adjustment for age, geographic region, and number of lifetime female (for HM subjects) or male (for MSM subjects) sex partners. All analyses were conducted using SAS version 9.4.

RESULTS

Demographic and Behavioral Characteristics of Men in the HRNT Population for ≥1 HPV Type

A total of 4065 men participated in the V501-020 trial (3463 HM and 602 MSM) [5]. The current analysis was based on data from the 1871 men comprising the HNRT placebo arm population (1576 HM and 295 MSM).

Median follow-up was 35.7 months (range, 0–52.1) among HM and 28.7 months (range, 0–51.7) among MSM. A larger proportion of HM in the HNRT analysis population were in the younger age group of 16–20 years than MSM (56.6% vs 30.5%; Table 1). More HM than MSM were from Latin America (41.3% vs 22.7%), whereas more MSM were from North America (42.7% vs 22.3%). A substantial proportion of MSM had 4–5 lifetime male sex partners (46.8%).

Incidence of Incident-Persistent Anogenital HPV Infection

Among HM, the rate of penile/scrotal HPV IP infection was higher than perineal/perianal IP HPV infection for 4vHPV (4.1 vs 1.2 per 100 person-years, respectively) and 9vHPV (6.8 vs 1.9 per 100 person-years, respectively) vaccine types (Table 2). Furthermore, incidences of penile/scrotal and perineal/perianal IP HPV infections were highest for HPV type 16 (2.1 and 0.6 per 100 person-years, respectively), type 6 (1.4 and 0.5 per 100 person-years, respectively), and type 52 (1.3 and 0.4 per 100 person-years, respectively) (Table 2).

Among MSM, the rates of IP HPV infection for 4vHPV and 9vHPV vaccine types were highest at the anal site (12.0 and 16.8 per 100 person-years, respectively), followed by the perineal/perianal site (6.8 and 9.0 per 100 person-years, respectively), and the penile/scrotal site (2.3 and 3.2 per 100 person-years, respectively) (Table 2). HPV 6 was the most commonly detected type, with an IP infection incidence of 6.3 per 100 person-years at the anal canal, 4.3 at the perineal/perianal site, and 1.8 at the penile/scrotal site (Table 2).

Three-year cumulative incidence of IP HPV infection at the combined external genital sites (excluding infection within the anal canal) for 4vHPV and 9vHPV vaccine types was 17.7% and 24.1% among MSM, compared with 11.7% and 18.4% among HM, respectively (Figure 1*A* and Supplementary Table 1). High cumulative incidences of IP HPV 16 were observed among both MSM and HM (6.5% and 5.6%, respectively).

Table 1. Baseline Demographic and Behavioral Characteristics of HM and MSM From the Study (HRNT) Population[a] for ≥1 HPV Type

Characteristic	HM (n = 1576) No. (%)	MSM (n = 295) No. (%)
Age, y[b,c]		
16–20	892 (56.6)	90 (30.5)
21–27[d,e]	683 (43.4)	205 (69.5)
Geographic region		
North America[f]	352 (22.3)	126 (42.7)
Latin America[g]	651 (41.3)	67 (22.7)
Europe[h]	178 (11.3)	61 (20.7)
Asia-Pacific[i]	132 (8.4)	41 (13.9)
Africa[j]	263 (16.7)	0 (0.0)
Tobacco use on day 1		
Never used	903 (57.3)	147 (49.8)
Former	98 (6.2)	29 (9.8)
Current user	575 (36.5)	119 (40.3)
Age at first intercourse, y[c,k]		
<15	198 (12.6)	36 (12.6)
15–19	1248 (79.3)	195 (68.2)
≥20	128 (8.1)	55 (19.2)
Number of lifetime male sex partners[c]		
1–3	NA	150 (53.2)
4–5	NA	132 (46.8)
Number of lifetime female sex partners[c,k]		
1–3	1069 (68.0)	76 (98.7)
4–5	503 (32.0)	1 (1.3)
Number of lifetime partners with insertive anal intercourse[c]		
0	NA	33 (11.7)
1	NA	73 (26.0)
2	NA	54 (19.2)
3–5	NA	121 (43.1)
Number of lifetime partners with receptive anal intercourse[c]		
0	NA	31 (11.0)
1	NA	63 (22.4)
2	NA	70 (24.9)
3–5	NA	117 (41.6)
Number of new male partners in last 6 mo[c]		
0	NA	105 (37.2)
1	NA	109 (38.7)
≥2	NA	68 (24.1)
Number of new female partners in last 6 mo[c,k]		
0	931 (59.2)	72 (93.5)
1	519 (33.0)	4 (5.2)
≥2	123 (7.8)	1 (1.3)
Frequency of lifetime condom use[k]		
Always	594 (37.7)	107 (36.3)
More than half the time	516 (32.7)	133 (45.1)
Less than half the time	290 (18.4)	25 (8.5)
Never	173 (11.0)	18 (6.1)
Frequency of condom use in the last 6 mo[k]		
Always	567 (36.0)	114 (38.6)
More than half of the time	323 (20.5)	68 (23.1)
Less than half of the time	213 (13.5)	24 (28.1)
Never	436 (27.7)	74 (25.1)
Circumcision		
No	1017 (64.5)	166 (56.3)
Yes	559 (35.5)	129 (43.7)

Abbreviations: HPV, human papillomavirus; HM, heterosexual men; HNRT, HPV naive to relevant type; MSM, men who have sex with men; NA, not applicable; PCR, polymerase chain reaction.

[a]HRNT population defined as HPV naive at day 1 to the HPV type under consideration. For HPV 6, 11, 16, and 18, HPV naive was defined as having a negative swab (ie, PCR negative) and serology negative to the relevant HPV type. For HPV 31, 33, 45, 52, and 58, HPV naive was defined as having a negative swab to the relevant HPV type.

[b]The inclusion criteria for age was 16–26 years; however, some men aged 26 years at screening subsequently turned 27 years of age by the enrollment visit. One subject in the HM group was aged 15 years.

[c]Differences in age eligibility criteria were evident between HM (aged 16–23 years) and MSM (16–26 years).

[d]Owing to age eligibility criteria, the upper age category was 21–23 years for HM and 21–27 years for MSM.

[e]Among MSM, some participants aged 26 years at enrollment had turned 27 years before the start of the study (ie, prior to the day 1 visit); these participants were included in the analysis.

[f]North America included the United States and Canada.

[g]Latin America included Brazil, Mexico, Costa Rica, and Peru.

[h]Asia-Pacific included Australia, Philippines, and Taiwan.

[i]Europe included Croatia, Finland, Germany, Netherlands, Norway, Portugal, Spain, and Sweden.

[j]Africa included South Africa.

[k]Categories have missing values for HM and/or MSM.

Among MSM, cumulative IP HPV incidence at the anal canal was 26.4% for any 4vHPV vaccine type and 35.4% for any 9vHPV vaccine type, with a large proportion acquiring IP HPV 16 (10.7%) (Figure 1*B* and Supplementary Table 1). At the perineal/perianal site, cumulative IP HPV incidence rates were higher among MSM versus HM for any 4vHPV (16.5% vs 3.4%) and any 9vHPV (22.2% vs 5.5%) vaccine type (Figure 1*C* and Supplementary Table 1). Cumulative incidence of IP HPV at the penile/scrotal sites (excluding perineal/perianal and anal canal sites) were substantially lower among MSM compared with HM for any 9vHPV (8.2% vs 18.0%) and any 4vHPV (5.6% vs 11.4%) vaccine types (Figure 1*D* and Supplementary Table 1).

Among HM, overall 9vHPV vaccine type IP (excluding infection at the anal canal) incidence rates were highest in Africa (9.2 per 100 person-years) and lowest in Asia-Pacific (2.1 per 100 person-years) (Figure 2*A*). In contrast, among MSM, overall IP HPV incidence rates (excluding anal canal infections) were highest in Latin America and the Asia-Pacific (27.6 and 20.2 per 100 person-years, respectively) and lowest in North America and Europe (7.4 and 12.8 per 100 person-years, respectively) (Figure 2*B*). Similarly, overall incidence rates of IP anal HPV among MSM were highest in Latin America (30.4 per 100 person-years) and lowest in North America (7.4 per 100 person-years) (Figure 2*C*).

Table 2. Incidence (per 100 Person-Years) of Incident-Persistent Anogenital HPV Infections Among Men by Anatomic Site, HPV Type, and Sexual Orientation (HNRT Population[a]) (N = 1871, Including 1576 HM and 295 MSM)

	Penile/Scrotal			Perineal/Perianal			Anal		
HPV Type	No.	Person-Years	Incidence (95% CI)	No.	Person-Years	Incidence (95% CI)	No.	Person-Years	Incidence (95% CI)
Heterosexual men									
		(n = 341)[b]			(n = 98)[b]			NA	
6	50	3508.2	1.4 (1.06–1.87)	18	3550.1	0.5 (.30–.80)	NA	NA	NA
11	13	3556.0	0.4 (.19–.62)	5	3609.1	0.1 (.04–.32)	NA	NA	NA
16	72	3491.4	2.1 (1.62–2.59)	20	3533.5	0.6 (.35–.87)	NA	NA	NA
18	32	3661.4	0.9 (.60–1.23)	7	3715.5	0.2 (.08–.39)	NA	NA	NA
31	37	3661.2	1.0 (.71–1.39)	13	3706.3	0.4 (.19–.60)	NA	NA	NA
33	23	3726.2	0.6 (.39–.92)	4	3782.1	0.1 (.03–.27)	NA	NA	NA
45	17	3718.2	0.5 (.27–.73)	6	3758.7	0.2 (.06–.35)	NA	NA	NA
52	48	3587.9	1.3 (.99–1.77)	13	3638.3	0.4 (.19–.61)	NA	NA	NA
58	29	3659.4	0.8 (.53–1.14)	5	3710.0	0.1 (.04–.31)	NA	NA	NA
6/11/16/18	149	3591.7	4.1 (3.52–4.85)	44	3791.6	1.2 (.84–1.55)	NA	NA	NA
6/11/16/18/31/33/45/52/58	235	3480.0	6.8 (5.94–7.64)	72	3752.5	1.9 (1.50–2.41)	NA	NA	NA
Men who have sex with men									
		(n = 31)[b]		(n = 71)[b]			(n = 112)[b,c]		
6	8	455.7	1.8 (.76–3.43)	19	441.4	4.3 (2.61–6.64)	27	427.3	6.3 (4.21–9.06)
11	1	468.1	0.2 (.01–1.18)	6	466.2	1.3 (.47–2.78)	14	449.9	3.1 (1.71–5.17)
16	5	520.0	1.0 (.31–2.23)	12	498.5	2.4 (1.25–4.17)	24	490.1	4.9 (3.16–7.20)
18	5	577.8	0.9 (.28–2.01)	10	561.4	1.8 (.86–3.25)	18	544.0	3.3 (1.97–5.18)
31	3	603.3	0.5 (.10–1.45)	6	592.9	1.0 (.37–2.19)	13	576.8	2.3 (1.21–3.82)
33	0	…	…	4	617.6	0.6 (.18–1.65)	8	602.5	1.3 (.57–2.60)
45	2	605.2	0.3 (.04–1.19)	6	587.6	1.0 (.38–2.21)	12	566.1	2.1 (1.10–3.67)
52	2	604.5	0.3 (.04–1.19)	5	581.3	0.9 (.28–2.00)	14	568.0	2.5 (1.35–4.10)
58	0	…	…	3	619.9	0.5 (.10–1.41)	8	599.8	1.3 (.58–2.61)
6/11/16/18	14	608.2	2.3 (1.26–3.83)	40	584.4	6.8 (4.93–9.20)	65	540.9	12.0 (9.40–15.1)
6/11/16/18/31/33/45/52/58	20	626.4	3.2 (1.96–4.89)	54	597.8	9.0 (6.86–11.6)	89	530.9	16.8 (13.7–20.2)

Abbreviations: HM, heterosexual men; HNRT, HPV naive to relevant type; MSM, men who have sex with men; PCR, polymerase chain reaction.

[a]HNRT population defined as HPV naive at day 1 to the HPV type under consideration. For HPV 6, 11, 16, and 18, HPV naive was defined as having a negative swab (ie, PCR negative) and serology negative to the relevant HPV type. For HPV 31, 33, 45, 52 and 58, HPV naive was defined as having a negative swab to the relevant HPV type.

[b]Total number of men with incident-persistent HPV infection with any 9vHPV type (6/11/16/18/31/33/45/52/58).

[c]Anal specimens were only collected from MSM.

Baseline Characteristics Associated With IP Anogenital HPV Infection (9vHPV Types) by Anatomic Site Among HM and MSM

Factors independently associated with risk of perineal/perianal IP HPV infections among HM included age (16–20 vs 21–23 years: OR, 1.72; 95% CI, 1.03–2.86), geographic region (Africa vs North America: OR, 2.19; 95% CI, 1.02–4.71), frequency of lifetime condom use (less than half the time vs always: OR, 1.88; 95% CI, 1.08–3.28), and frequency of condom use in the

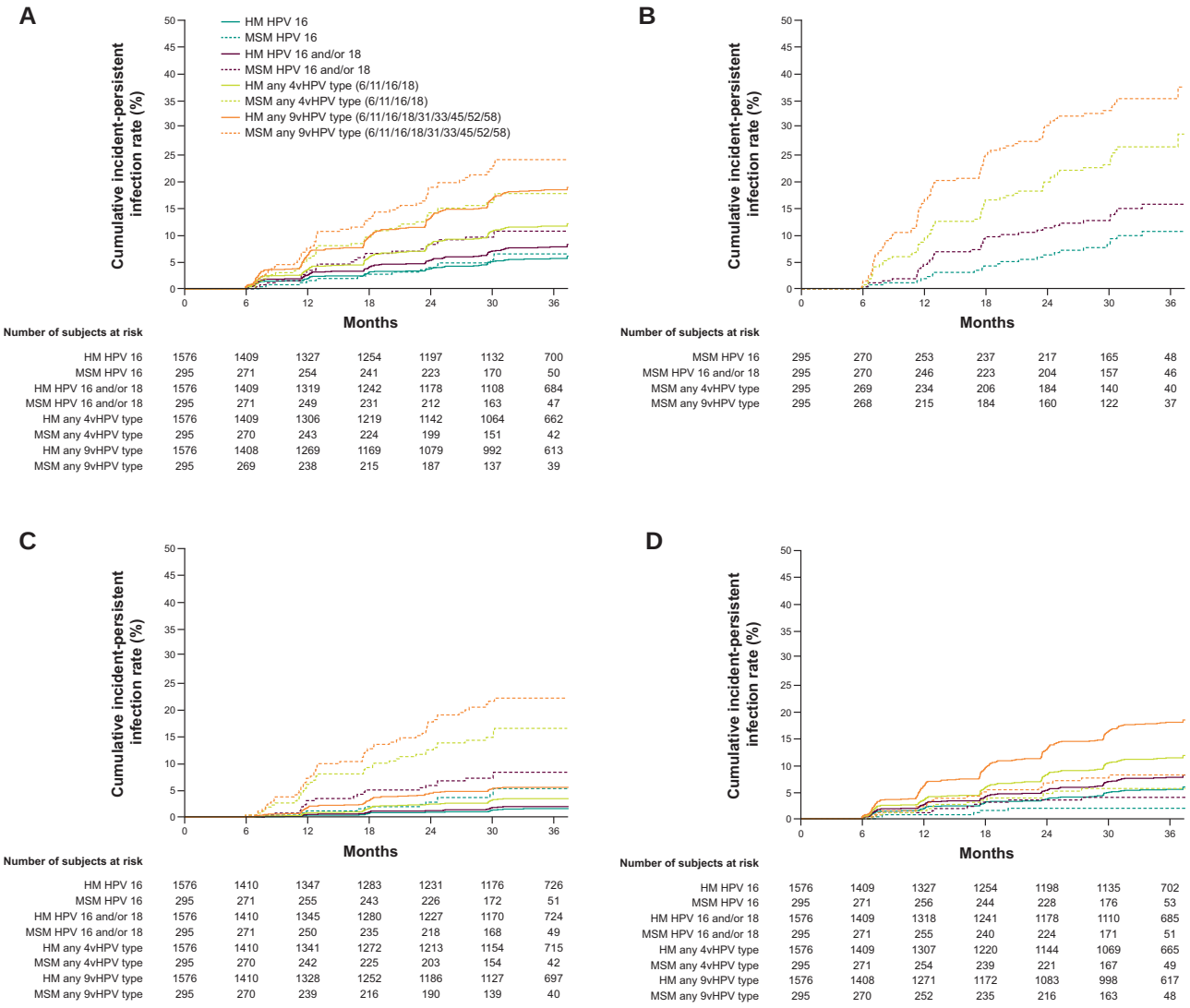

Figure 1. Kaplan-Meier estimates for the cumulative incidence of incident-persistent anogenital HPV infections for 4vHPV types (6/11/16/18) and 9vHPV types (6/11/16/18/31/33/45/52/58). *A*, Incident-persistent infections at all anatomic sites combined (excluding the anal canal) among HM and MSM. *B*, Incident-persistent infections at anal sites among MSM only. *C*, Incident-persistent infections at perianal/perineal sites among HM and MSM. *D*, Incident-persistent infections at penile/scrotal sites among HM and MSM. Abbreviations: 4vHPV, 4-valent HPV; 9vHPV, 9-valent HPV; HM, heterosexual men; HPV, human papillomavirus; MSM, men who have sex with men.

last 6 months (less than half the time vs always: OR, 2.12; 95% CI, 1.18–3.79) (Table 3). Among MSM, 2 or more new male partners in the last 6 months (≥2 vs 0: OR, 2.08; 95% CI, 1.01–4.28) was the only factor independently associated with an increased risk of perineal/perianal IP HPV infection, whereas 1 new male partner in the last 6 months was associated with a lower risk of IP infection (1 vs 0: OR, 0.40; 95% CI, .20–.82); however, no association was observed for age, geographic region, or frequency of condom use (Table 3). Factors independently associated with risk of penile/scrotal IP HPV infection among HM included younger age (16–20 vs 21–23 years: OR, 1.43; 95% CI, 1.07–1.92), geographic region (Latin America vs North America: OR, 1.67; 95% CI, 1.13–2.47; Africa vs North America: OR, 1.91; 95% CI, 1.20–3.02), and larger number of lifetime female sex partners (4–5 vs 1–3: OR, 1.65; 95% CI, 1.23–2.20). Among MSM, no factors were significantly associated with risk of penile/scrotal IP infection, whereas the number of new male partners in the last 6 months was associated with a lower risk of penile/scrotal IP infection (1 vs 0: OR, 0.14; 95% CI, .03–.65) (Table 3). Among MSM, factors significantly independently associated with an increased risk of anal IP HPV infection included geographic region (Latin America vs North America: OR, 4.30; 95% CI, 2.15–8.61; Asia-Pacific vs North America: OR, 3.44; 95% CI, 1.52–7.78; Europe vs North America: OR, 2.26; 95% CI, 1.07–4.75), larger number of lifetime male sex partners (4–5 vs 1–3: OR, 1.81; 95% CI, 1.06–3.11), and larger number of lifetime partners with receptive anal intercourse (2 vs 3–6: OR, 2.13; 95% CI, 1.12–4.05) (Table 3).

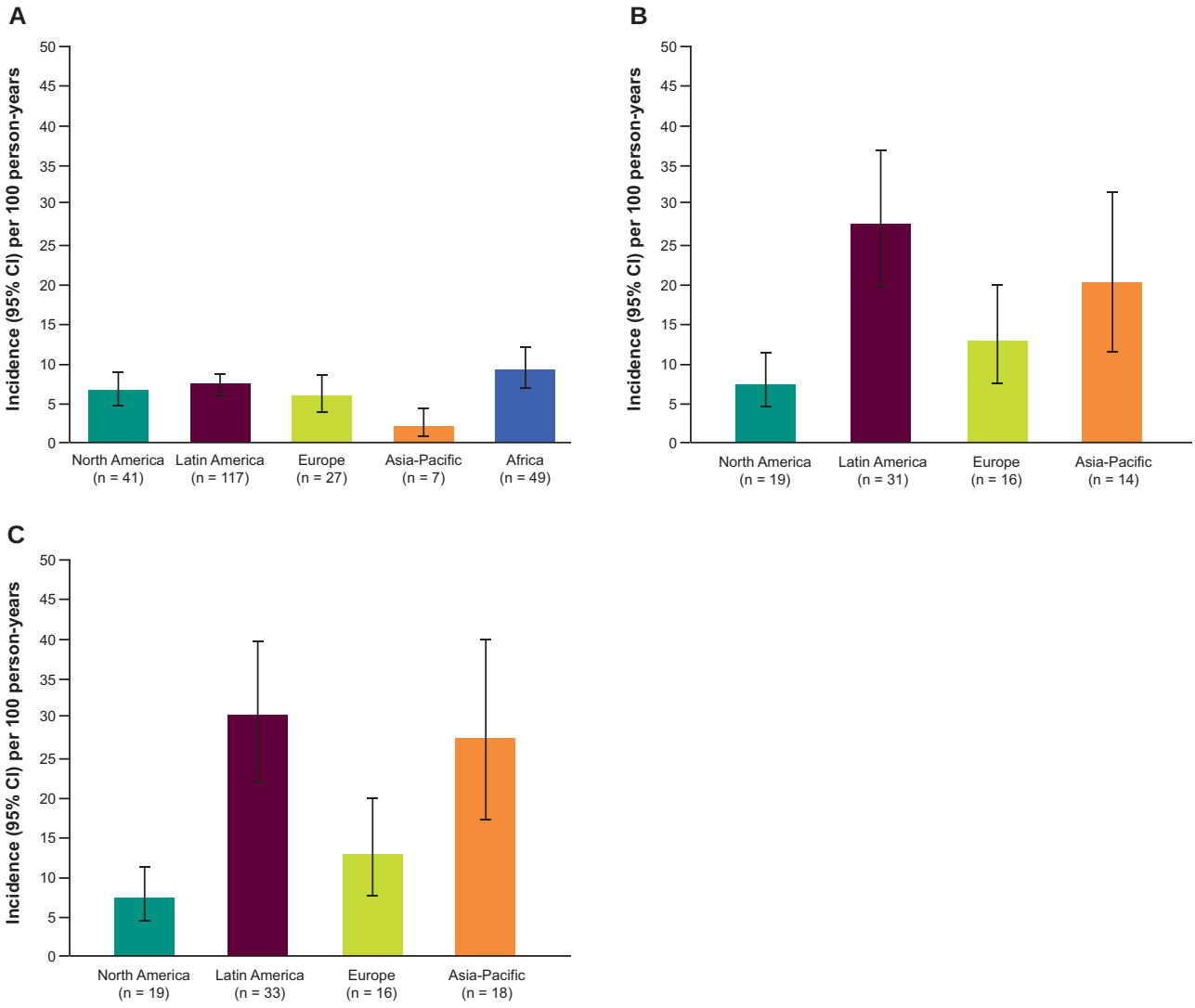

Figure 2. Incidence (per 100 person-years) of incident-persistent anogenital HPV infection with grouped 9vHPV types (6/11/16/18/31/33/45/52/58) in the study population by geographic region. *A*, Incident-persistent anogenital HPV infection (excluding the anal canal) among MSM HM. *B*, Incident-persistent anogenital HPV infection (excluding the anal canal) among HM MSM. *C*, Incident-persistent HPV infection at the anal canal among MSM. Abbreviations: 9vHPV, 9-valent HPV; CI, confidence interval; HM, heterosexual men; HPV, human papillomavirus; MSM, men who have sex with men.

DISCUSSION

This analysis of men enrolled in the placebo arm of a global 4vHPV vaccine clinical trial describes the high burden of IP infection with 9vHPV vaccine types among MSM and HM. The HPV infection burden is higher among MSM compared to HM and differs by sexual orientation, whereby IP incidence rates were higher at penile/scrotal sites compared to the perineal/perianal sites among HM, and highest at anal and perineal/perianal versus penile/scrotal sites among MSM. Furthermore, higher IP incidence rates were observed for MSM versus HM at the perineal/perianal site, whereas higher rates were observed for HM at the penile/scrotal sites. Among MSM, IP HPV 6 infection was the most commonly acquired HPV type at all anatomic sites examined, consistent with the high incidence of anal condyloma [10]. In contrast, HPV 16 was the most commonly acquired HPV type among HM. The high rate of new IP HPV infection among men highlights the high risk of HPV-related disease young unvaccinated men face potentially throughout their lifetime.

Results of our study add important data to the growing evidence of a high burden of HPV infection among men. For example, high incidence rates of anogenital HPV were reported in a Dutch study of HM (50.5 per 100 person-years for any HPV type) [11] and in a US cohort of HM (50.8 and 25.0 per 100 person-years for any and oncogenic HPV types, respectively) [12]. A US study of HM university students reported 24-month cumulative incidence rates of 62.4% for any HPV type and 47.9% for high-risk HPV vaccine types [13]. Anal canal HPV

Table 3. Association Between Baseline Characteristics and Incident-Persistent HPV Infection to 9vHPV Types (at the Perineal/Perianal, Penile/Scrotal, and Anal Sites) Among HM and MSM

	Perineal/Perianal Site				Penile/Scrotal Site				Anal Site	
	HM		MSM		HM		MSM		MSM	
Risk Factor	Rate of Infection, %[a]	Adjusted OR[b] (95% CI)	Rate of Infection, %[a]	Adjusted OR[c] (95% CI)	Rate of Infection, %[a]	Adjusted OR[b] (95% CI)	Rate of Infection, %[a]	Adjusted OR[c] (95% CI)	Rate of Infection, %[a]	Adjusted OR[c] (95% CI)
Age, y										
21–27[d,e]	3.51 (24/683)	1.0	17.6 (36/205)	1.0	12.6 (86/683)	1.0	6.83 (14/205)	1.0	29.8 (61/205)	1.0
16–20	5.38 (48/892)	**1.72 (1.03–2.86)**	20.0 (18/90)	1.34 (.70–2.57)	16.7 (149/892)	**1.43 (1.07–1.92)**	6.67 (6/90)	1.16 (.42–3.22)	31.1 (28/90)	1.16 (.65–2.06)
Geographic region										
North America	3.42 (12/351)	1.0	11.9 (15/126)	1.0	11.4 (40/351)	1.0	5.56 (7/126)	1.0	15.9 (20/126)	1.0
Latin America	4.61 (30/651)	1.39 (.70–2.76)	22.4 (15/67)	1.94 (.86–4.36)	17.5 (114/651)	**1.67 (1.13–2.47)**	5.97 (4/67)	1.10 (.30–4.11)	47.8 (32/67)	**4.30 (2.15–8.61)**
Europe	4.49 (8/178)	1.37 (.55–3.43)	23.0 (14/61)	2.18 (.95–4.98)	15.2 (27/178)	1.43 (.84–2.42)	13.1 (8/61)	2.77 (.90–8.51)	31.1 (19/61)	**2.26 (1.07–4.75)**
Asia-Pacific	3.79 (5/132)	1.40 (.48–4.13)	24.4 (10/41)	1.98 (.77–5.11)	4.55 (6/132)	0.45 (.18–1.09)	2.44 (1/41)	0.45 (.05–3.94)	43.9 (18/41)	**3.44 (1.52–7.78)**
Africa	6.46 (17/263)	**2.19 (1.02–4.71)**	NA	NA	18.3 (48/263)	**1.91 (1.20–3.02)**	NA	NA	NA	NA
Tobacco use on day 1										
Never used	4.43 (40/903)	1.0	17.7 (26/147)	1.0	14.3 (129/903)	1.0	6.12 (9/147)	1.0	27.9 (41/147)	1.0
Exuser	4.08 (4/98)	0.93 (.33–2.61)	27.6 (8/29)	1.86 (.75–4.60)	13.3 (13/98)	0.91 (.49–1.67)	6.90 (2/29)	0.98 (.21–4.64)	41.4 (12/29)	1.91 (.83–4.41)
Current user	4.88 (28/574)	1.04 (.63–1.70)	16.8 (20/119)	0.60 (.31–1.16)	16.2 (93/574)	1.09 (.82–1.46)	7.56 (9/119)	0.95 (.35–2.54)	30.3 (36/119)	0.60 (.34–1.06)
Age at first intercourse, y										
<15	6.09 (12/197)	1.18 (.61–2.31)	19.4 (7/36)	0.74 (.29–1.89)	19.8 (39/197)	1.14 (.76–1.70)	2.78 (1/36)	0.27 (.03–2.24)	38.9 (14/36)	0.85 (.39–1.88)
15–19	4.41 (55/1248)	0.82 (.46–1.45)	17.4 (34/195)	0.71 (.37–1.36)	14.5 (181/1248)	0.85 (.60–1.20)	8.72 (17/195)	2.63 (.74–9.41)	30.3 (59/195)	0.86 (.48–1.55)
≥20	3.91 (5/128)	1.0	21.8 (12/55)	1.0	11.7 (15/128)	1.0	3.64 (2/55)	1.0	27.3 (15/55)	1.0
No. of lifetime male sex partners										
1–3	NA	NA	14.7 (22/150)	1.0	NA	NA	6.00 (9/150)	1.0	23.3 (35/150)	1.0
4–5	NA	NA	22.7 (30/132)	1.55 (.83–2.90)	NA	NA	7.58 (10/132)	1.31 (.50–3.41)	39.4 (52/132)	**1.81 (1.06–3.11)**
No. of lifetime female sex partners										
1–3	4.03 (43/1068)	1.0	21.1 (16/76)	NE	12.8 (137/1068)	1.0	7.89 (6/76)	NE	NE	NE
4–5	5.77 (29/503)	1.56 (.95–2.54)	NE	NE	19.5 (98/503)	**1.65 (1.23–2.20)**	NE	NE	NE	NE
No. of lifetime partners with insertive anal intercourse										
0	NA	NA	24.2 (8/33)	1.48 (.61–3.57)	NA	NA	12.1 (4/33)	2.20 (.66–7.33)	36.4 (12/33)	1.31 (.59–2.94)
1	NA	NA	16.4 (12/73)	1.03 (.49–2.18)	NA	NA	1.37 (1/73)	0.14 (.02–1.11)	21.9 (16/73)	0.76 (.39–1.48)

Table 3. Continued

	Perineal/Perianal Site				Penile/Scrotal Site				Anal Site	
	HM		MSM		HM		MSM		MSM	
Risk Factor	Rate of Infection, %[a]	Adjusted OR[b] (95% CI)	Rate of Infection, %[a]	Adjusted OR[c] (95% CI)	Rate of Infection, %[a]	Adjusted OR[b] (95% CI)	Rate of Infection, %[a]	Adjusted OR[c] (95% CI)	Rate of Infection, %[a]	Adjusted OR[c] (95% CI)
2	NA	NA	11.1 (6/54)	0.60 (.23–1.54)	NA	NA	5.56 (3/54)	0.74 (.20–2.74)	18.5 (10/54)	0.62 (.28–1.36)
3–6	NA	NA	21.5 (26/121)	1.0	NA	NA	9.09 (11/121)	1.0	40.5 (49/121)	1.0
No. of lifetime partners with receptive anal intercourse										
0	NA	NA	6.45 (2/31)	0.34 (.08–1.52)	NA	NA	3.23 (1/31)	0.50 (.06–4.02)	16.1 (5/31)	0.50 (.17–1.44)
1	NA	NA	15.9 (10/63)	0.91 (.41–2.02)	NA	NA	9.52 (6/63)	1.65 (.57–4.82)	20.6 (13/63)	.63 (.30–1.29)
2	NA	NA	18.6 (13/70)	1.21 (.58–2.50)	NA	NA	4.29 (3/70)	0.55 (.15–2.05)	37.1 (26/70)	**2.13 (1.12–4.05)**
3–6	NA	NA	23.1 (27/117)	1.0	NA	NA	7.69 (9/117)	1.0	36.8 (43/117)	1.0
Frequency of lifetime condom use										
Always	4.55 (27/593)	1.0	16.8 (18/107)	1.0	13.3 (79/593)	1.0	7.48 (8/107)	1.0	27.1 (29/107)	1.0
More than half of the time	3.68 (19/516)	0.71 (.41–1.23)	21.1 (28/133)	1.12 (.59–2.11)	16.7 (86/516)	1.19 (.88–1.60)	6.02 (8/133)	0.68 (.25–1.82)	36.8 (49/133)	1.23 (.71–2.13)
Less than half of the time	6.90 (20/290)	**1.88 (1.08–3.28)**	20.0 (5/25)	1.23 (.43–3.50)	17.6 (51/290)	1.28 (.90–1.82)	4.00 (1/25)	0.57 (.07–4.57)	24.0 (6/25)	0.74 (.27–2.01)
Never	3.47 (6/173)	0.79 (.33–1.90)	11.1 (2/18)	0.69 (.15–3.18)	11.0 (19/173)	0.73 (.44–1.23)	16.7 (3/18)	3.97 (.95–16.6)	22.2 (4/18)	0.87 (.26–2.92)
No. of new male partners in the last 6 mo										
0	NA	NA	20.0 (21/105)	1.0	NA	NA	8.57 (9/105)	1.0	30.5 (32/105)	1.0
1	NA	NA	11.0 (12/109)	**0.40 (.20–.82)**	NA	NA	1.83 (2/109)	**0.14 (.03–.65)**	25.7 (28/109)	0.68 (.39–1.20)
≥2	NA	NA	29.4 (20/68)	**2.08 (1.01–4.28)**	NA	NA	13.2 (9/68)	2.38 (.81–7.00)	41.2 (28/68)	1.86 (.96–3.57)
No. of new female partners in the last 6 mo										
0	4.51 (42/931)	1.0	22.2 (16/72)	NE	13.6 (127/931)	1.0	8.33 (6/72)	NE	33.3 (24/72)	NE
1	3.86 (20/518)	0.77 (.45–1.33)	NE	NE	15.4 (80/518)	1.06 (.78–1.44)	NE	NE	NE	NE
≥2	8.13 (10/123)	1.85 (.87–3.97)	NE	NE	22.8 (28/123)	1.50 (.92–2.44)	NE	NE	NE	NE
Frequency of condom use in the last 6 mo										
Always	4.59 (26/566)	1.0	19.3 (22/114)	1.0	15.0 (85/566)	1.0	7.02 (8/114)	1.0	31.6 (36/114)	1.0
More than half of the time	4.02 (13/323)	0.84 (.45–1.56)	22.1 (15/68)	1.04 (.51–2.12)	16.1 (52/323)	1.11 (.78–1.56)	5.88 (4/68)	0.62 (.19–2.02)	42.6 (29/68)	1.54 (.83–2.86)
Less than half of the time	7.98 (17/213)	**2.12 (1.18–3.79)**	20.8 (5/24)	1.38 (.47–4.03)	19.7 (42/213)	1.44 (.98–2.11)	4.17 (1/24)	0.65 (.08–5.32)	29.2 (7/24)	1.24 (.46–3.31)
Never	3.67 (16/436)		14.9 (11/74)	0.84 (.39–1.81)	12.2 (53/436)		9.46 (7/74)		20.3 (15/74)	

Table 3. Continued

Risk Factor	Perineal/Perianal Site				Penile/Scrotal Site				Anal Site	
	HM		MSM		HM		MSM		MSM	
	Rate of Infection, % [a]	Adjusted OR [b] (95% CI)	Rate of Infection, % [a]	Adjusted OR [c] (95% CI)	Rate of Infection, % [a]	Adjusted OR [b] (95% CI)	Rate of Infection, % [a]	Adjusted OR [c] (95% CI)	Rate of Infection, % [a]	Adjusted OR [c] (95% CI)
		0.73 (.41–1.29)				0.73 (.52–1.03)		2.23 (.76–6.53)		0.52 (.26–1.04)
Circumcision										
No	5.11 (52/1017)	1.0	21.1 (35/166)	1.0	16.1 (164/1017)	1.0	8.43 (14/166)	1.0	36.1 (60/166)	1.0
Yes	3.58 (20/558)	0.59 (.31–1.13)	14.7 (19/129)	0.91 (.43–1.92)	12.7 (71/558)	0.85 (.57–1.26)	4.65 (6/129)	0.67 (.21–2.17)	22.5 (29/129)	0.97 (.50–1.86)

Bolded numbers refer to factors independently associated with the risk of perineal/perianal or penile/scrotal incident-persistent HPV infection (9vHPV types).

Abbreviations: 9vHPV, 9-valent HPV; HM, heterosexual men; MSM, men who have sex with men; NA, not applicable; NE, not estimable; OR, odds ratio.

[a]Numerator: total count of individuals who have persistent incidence of infection among those being HPV naive to relevant type, per each risk factor. Denominator: count of individuals who are HPV naive to relevant type, per each risk factor.

[b]Odds ratio of each risk factor is adjusted with age group, geographic regions, and number of lifetime female sex partners.

[c]Odds ratio of each risk factor is adjusted with age group, geographic regions, and number of lifetime male sex partners.

[d]Owing to age eligibility criteria, the upper age category was 21–23 years for HM and 21–27 years for MSM.

[e]Among MSM, some participants aged 26 years at enrolment had turned 27 years before the start of the study (ie, prior to the day 1 visit); these participants were included in the analysis.

incidence reports among MSM range from 16% for any oncogenic HPV type in the HIM study [4], to 29.8% for 4vHPV types in the US-based DASH study [14]. Additionally, incidence of anal HPV infection in a study of HIV-infected MSM in Montreal, Canada, was approximately 13 per 100 person-years for both HPV types 16 and 52, with 3-year cumulative incidence rates of 33% and 30%, respectively [15]. Collectively, these data highlight that substantial proportions of both HM and MSM develop anogenital HPV infection.

In the current analysis, cumulative IP incidence at all anatomic sites combined was higher among MSM versus HM. Cumulative incidence rates of IP HPV infection at the perineal/perianal site were significantly higher among MSM compared to HM. Consistent with our observation are reports of higher incidence of anal HPV infection and persistence among MSM than in HM [4], with receptive anal sex identified as a factor associated with anal HPV infection among MSM [16–18]. Similarly, a randomized, placebo-controlled trial of the 4vHPV vaccine that collected intra-anal swabs from young Japanese men reported a higher incidence of persistent intra-anal 4vHPV infections among MSM versus HM in the placebo arm [19]. In contrast, cumulative incidence of 4vHPV vaccine type IP HPV infection at the penile/scrotal site was higher among HM compared with MSM. In the HIM study, 12-month cumulative incidence of genital HPV was high among both MSM and HM [20], highlighting that the development of IP anogenital vaccine type HPV infection is common among unvaccinated MSM and HM.

As expected, factors related to sexual behavior were significantly associated with IP 9vHPV vaccine type anogenital infection. Previous studies have reported strong associations between sexual behaviors and anogenital HPV infection among men, including a higher number of lifetime sex partners or new/recent sex partners associated with anogenital HPV infection among both HM [13, 21, 22] and MSM [16, 21, 23]. Interestingly, the risk of IP HPV infection at the perineal/perianal or penile/scrotal sites was lower among MSM who had 1 versus 0 new male partners in the last 6 months, but higher for those with ≥2 new male partners. In the current analysis, approximately half the MSM with 0 new male partners in the last 6 months reported never using condoms in the last 6 months, compared with less than 20% of MSM with 1 new male sex partner in the last 6 months (data not shown). Frequency of condom use has also been identified as a risk factor for anogenital HPV infection [22, 24], but results have been inconsistent, particularly among MSM [16, 21]. Similarly, associations between inconsistent lifetime or recent condom use and HPV infection at the perineal/perianal site among HM were identified, but no associations were observed among MSM. The lack of consistent associations between condom use and anogenital HPV infection among men in the literature may be due to transmission during digital insertion or genital-to-genital contact without

penetration, inaccuracies in the reporting of condom use, the presence of HPV in areas of genitalia not covered by a condom (ie, perineal/perianal sites or anal canal), and the inability to determine condom use in the male sex partners of MSM having sex with multiple partners.

Key strengths of this study include the HPV testing methodology used in the V501-020 trial, frequent testing (every 6 months), diverse enrollment (18 countries), a large sample size, and high clinical trial retention rate. A limitation of this study is related to the restrictive eligibility criteria of the V501-020 trial, in which participants were of a limited age range (16–23 years for HM and 16–26 years for MSM), had no current or past history of HPV-related anogenital disease, and had no more than 5 lifetime sex partners. This may have selected for men with a lower likelihood of HPV exposure and thus may not be representative of the general population of sexually active men and may have also contributed to the low cumulative incidence of IP infection. In addition, focusing on IP infections to avoid the inclusion of cases due to HPV deposition may have resulted in a conservative incidence estimate, as HPV infections that were acquired and cleared more rapidly may not be detected using this approach. Serologic status at baseline, an indicator of prior exposure to HPV infection across anatomic sites, was not available for all 9vHPV vaccine types in all participants from this 4vHPV vaccine trial. Furthermore, HPV vaccination was introduced in some of the vaccine trial countries during trial follow-up, almost exclusively to adolescent girls after 2006 (United States, parts of Europe, and Australia). As such, this may have led to a lower estimate of anogenital HPV infection among men. Finally, the V501-020 trial did not include oral HPV infection outcomes, which will be of importance in future analyses, given that the incidence of HPV-associated oropharyngeal cancers in men has surpassed that of cervical cancer in women in many settings [25].

In this global study focusing on young men from the placebo arm of a global 4vHPV vaccine trial, a substantial proportion of both HM and MSM developed IP anogenital HPV infections to at least one 9vHPV vaccine type over 3 years. Given that IP HPV infections are strong risk factors and precede the development of HPV-related diseases, vaccination of men targeted for catch-up vaccination would be expected to prevent a substantial HPV-related disease burden attributable to these infections. The benefit of catch-up vaccination in men is evidenced by recent findings from an open-label extension study of the V501-020 trial, which reported no new cases of external genital warts or genital lesions after a median follow-up of 4.7 years in the catch-up vaccination group [26]. Due to the limited availability of screening procedures for HPV-related disease in men, primary prevention of anogenital HPV infection through vaccination is currently the only practical approach for prevention of HPV-related disease. Vaccination of men may also contribute to herd protection, which may be of value in settings of suboptimal vaccination coverage among women [27]. Furthermore, these data demonstrate the higher risk of IP HPV infection among MSM. While HM experience herd protection in settings of high female vaccination rates, MSM do not show a similar benefit. Therefore, gender-neutral vaccination is critical to reduce disease burden in men, especially among MSM. Lastly, we observed high rates of IP HPV infection in Africa (HM) and Latin America (MSM and HM), both of which are regions where the general population may have limited access to screening for and treatment of HPV-related disease. This highlights the importance of switching to gender-neutral vaccination in these regions.

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

Author contributions. A. R. G. contributed to the design of the parent trial, participated in data collection, and oversaw data analysis and manuscript preparation. All authors substantially contributed to the conception, design, or planning of the study, and were involved in the acquisition or analysis of the data, and interpretation of the results. All authors had access to all the relevant study data and related analyses, vouch for the completeness and accuracy of the data presented, and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors were involved in critically reviewing or revising the manuscript for important intellectual content and approved the final version for submission.

Acknowledgments. Medical writing assistance was provided by Maxwell Chang, BSc Hons, and Matthew Grzywacz, PhD, of ApotheCom (New York, NY). This assistance was funded by Merck Sharp & Dohme, LLC, a subsidiary of Merck & Co, Inc, Rahway, NJ.

Financial support. This work was supported by Merck Sharp & Dohme, LLC, a subsidiary of Merck & Co, Inc, Rahway, NJ.

Potential conflicts of interest. A. R. G. reports receipt of support in the form of medical writing for the current manuscript, grants, and consulting fees from Merck Sharp & Dohme LLC. J. M. P. reports receipt of consulting fees from Merck Sharp & Dohme, LLC, Vir Biotechnologies, Antiva Biosciences, and Roche Diagnostics; has received payment from Merck Sharp & Dohme LLC, for lectures, presentations, speakers' bureaus, and manuscript writing or educational

events; is an honorary board member of the International Papillomavirus Society; and holds stock or stock options in Virion Therapeutics. S. G. has received grants from Inovio and Franz Viral Technologies; consulting fees from THD America; and payment or honoraria from Merck Sharp & Dohme, LLC, for speakers' bureaus. S. G. and J. E. T. have received support from Merck Sharp & Dohme, LLC, for the present manuscript. A. L., B. D., A. S., C. V., and J. E. T. are employees of Merck Sharp & Dohme, LLC. A. L., B. D., A. S., and J. E. T. hold stock in Merck & Co, Inc, Rahway, NJ, USA.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

Data sharing. The data sharing policy, including restrictions, of Merck Sharp & Dohme, LLC, a subsidiary of Merck & Co, Inc, Rahway, NJ, is available at http://engagezone.msd.com/ds_documentation.php. Requests for access to the clinical study data can be submitted through the Engage Zone site or via email to Data Access mailbox.

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