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MAJOR ARTICLE

Prevalence, Incidence, and Clearance of Human Papillomavirus Types Covered by Current Vaccines in Men With Human Immunodeficiency Virus in the SUN Study

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(See the Editorial Commentary by Ellsworth and Wilkin, on pages 171–2.)

Background. High-risk anal human papillomavirus (HPV) infection is prevalent among men living with human immunodeficiency virus (HIV); the association between 9-valent (9v) high-risk HPV (HR-HPV) vaccine types and abnormal cytology has not been well characterized.

Methods. We followed a prospective cohort study of persons with HIV at 7 HIV clinics in 4 US cities from March 2004 through June 2012. Annually, providers collected separate anal swabs for HPV detection and cytopathologic examination. Among men, we examined prevalence, incidence, and clearance of 9v HR-HPV vaccine types, compared with other HR types, and associations with abnormal cytology to assess potential vaccine impact.

Results. Baseline prevalence of any anal 9v HR-HPV type among men who have sex with men (MSM) and men who have sex with women (MSW) was 74% and 25% ($P < .001$), respectively. Among 299 MSM, abnormal cytology was detected in 161 (54%) MSM and was associated with the presence of any 9v HR-HPV (relative risk [RR], 1.8 [95% confidence interval {CI}, 1.3–2.6]; $P < .001$). Among 61 MSW, abnormal anal cytology was detected in 12 (20%) and was associated with the presence of any 9v HR-HPV (RR, 4.3 [95% CI, 1.6–11.5]; $P < .001$).

Conclusions. Among men with HIV, the prevalence of the 7 HR-HPV types in the 9v vaccine was high and was associated with abnormal cytology. These findings indicate that men with HIV could benefit from prophylactic administration of the 9v HPV vaccine.

Keywords. HIV; human immunodeficiency virus; HPV; human papillomavirus; HPV vaccine.

Annually, 40 000 new cases of anal cancer are diagnosed worldwide, of which 88% are attributable to human papillomavirus (HPV) infection [1, 2]. HPV-16 is by far the most carcinogenic type [2]. Persons with human immunodeficiency virus (HIV), particularly men who have sex with men (MSM), are at higher risk of having anal HPV infection, anal cancer precursors, and anal cancer compared with persons who do not have HIV [3–7]. Pooled prevalence of any anal HPV in a recent meta-analysis of 53 studies was 92.6% among MSM with HIV and 63.9% among MSM without HIV [8]. Anal HPV infection, specifically HPV-16, is less likely to clear among MSM with HIV compared with MSM without HIV [9]. Studies have shown that the persistence of high-risk (HR) HPV types, specifically HPV-16, is an important risk factor for the development of anal cancer [10, 11].

HPV vaccination can prevent anal HR-HPV infection; however, vaccination was initially recommended for males <27 years of age and wide uptake has not yet been seen [12, 13]. There are 3 HPV vaccines licensed in the United States (US), all of which have been shown to be safe and immunogenic in men and women [14]; however, only the 9-valent (9v) HPV vaccine is currently available. Gardasil 9 (Merck & Co, Inc) was approved for prevention of infection with the 4 HPV types (6, 11, 16, and 18) in the quadrivalent vaccine among persons aged 9–26 years and an additional 5 HR-HPV types (31, 33, 45, 52, and 58) in December 2014 [12]. It is now approved for women and men aged 27–45 years, although the Advisory Committee on Immunization Practices recommendations do not currently extend beyond age 26 because data are lacking to support the indication [15, 16]. It is important to understand the epidemiology of HPV infection and associated pathology, including abnormal cytology, to develop evidence-based HPV vaccination and screening programs for anal cancer prevention, particularly for men with HIV.

To better characterize the clinical epidemiology of vaccine-preventable HPV infection among men with HIV, we examined the prevalence, incidence, and clearance of the HR-HPV types covered and not covered by the 9v vaccine using data from the

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Study to Understand the Natural History of HIV/AIDS in the Era of Effective Therapy (SUN Study).

METHODS

Study Design and Population

From March 2004 through June 2006, the SUN Study enrolled 700 adults with HIV from 7 clinics in 4 US cities into a prospective observational cohort study sponsored by the Centers for Disease Control and Prevention (CDC) (ClinicalTrials.gov identifier NCT00146419). The participants were followed through June 2012. The study's design and its data collection and management methods have been described previously [17]. Participants were adults (aged ≥18 years) with HIV receiving routine outpatient care and whose entire antiretroviral experience consisted only of highly active combination antiretroviral therapy (cART). Data were collected at a baseline visit through physical examination, an audio computer-assisted self-interview (ACASI), routine laboratory examination (eg, CD4 cell count, HIV RNA) that included comprehensive testing for sexually transmitted infections, medical records abstraction for all diagnoses and treatments, and collection of a variety of additional study-specific biological specimens. The ACASI collected extensive behavioral information, including sexual behavior. Participants were classified as MSM or men who have sex with women (MSW) according to self-report on the ACASI. Data abstracted from medical charts were entered into an electronic database (Clinical Practice Analyst, Cerner Corporation) by trained staff. None of the participants received HPV vaccination as it was not standard of care during the duration of the study. These data were reviewed for quality and analyzed centrally. All participants provided informed consent. The study protocol was approved and reviewed annually by the institutional review boards of the CDC and each participating site.

Anal Sample Collection and Examination

Two swab specimens were collected annually; the first for anal cytopathologic examination (to optimize quality of cytology sample) and the second for HPV DNA testing. Each collection used a Dacron swab moistened with tap water that was inserted 3–5 cm into the anus to the distal rectum and rotated at least twice while applying outward pressure while being withdrawn. The cytology sample was placed into PreservCyt (Thin Prep vial) transport medium. The swab for HPV testing was placed into Digene Specimen Transport Medium (STM; Qiagen). Cytology specimens were evaluated by a single pathologist with expertise in the interpretation of anal cytology (T. M. D.). All cytologic results were classified according to the Bethesda System terminology. Abnormal cytology was defined as presence of atypical squamous cells of undetermined significance; low-grade squamous intraepithelial lesions; high-grade squamous intraepithelial lesions (HSIL); or atypical squamous cells, cannot exclude HSIL.

The STM samples were stored at 4°C and mailed weekly at ambient temperature to the CDC where they were stored at –4°C until DNA was extracted from 150 μL using a Roche MagNA Pure automated extractor with external lysis and DNA isolation kit III (Roche Diagnostics). The 100-μL extract was stored at –20°C until use.

HPV Detection and Typing

The Roche HPV Linear Array research-use-only kit (Roche Diagnostics) was used following the manufacturer's protocol, with the exception that 10 μL of extract was used in the 100-μL reaction and hybridization and detection were automated. The assay uses L1 consensus polymerase chain reaction (PCR) with biotinylated primers and type-specific hybridization detecting 37 different HPV types (14 HR types [16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68]; 23 other types [6, 11, 26, 40, 42, 53, 54, 55, 61, 62, 64, 67, 69, 70, 71, 72, 73, 81, 82, 83, 84, 89, and IS39]; and an endogenous control gene [β-globin]). Each assay batch included controls for extraction and PCR contamination, as well as a low-copy positive control (50 copies) for HPV-16. Results for HPV-52 may be ambiguous because of cross-hybridization of the HPV-52 probe with types 33, 35, and 58. To unambiguously determine the presence of HPV-52 in samples with 1 or more of the 3 other types, an HPV-52–specific real-time PCR assay was used [18].

Statistical Methods

Univariate associations were explored using either Mantel–Haenszel χ^2 or Fisher exact test for categorical variables and the Student *t* test for continuous variables. We evaluated the prevalence, incidence, and clearance of HR-HPV types covered (9v HR-HPV; HPV types 16, 18, 31, 33, 45, 52, and 58) and not covered (non-9v HR-HPV; types 35, 39, 51, 56, 59, 66, and 68) by the 9v HPV vaccine at the anus and compared these rates between MSM and MSW. We defined detection of an HPV type at baseline as prevalent infection, expressed as a percentage. We defined incident infection as the new detection of an HPV type that was not detected at the previous visit, and calculated incidence rate per 100 person-years (PY) of observation. Incidence was estimated among men who did not have the HPV type of interest at baseline regardless of other HPV types. We assessed the percentage of participants who cleared HPV infection(s) in follow-up, and estimated the rate (probability) of HPV clearance at 4 years of observation using Kaplan–Meier survival analysis; clearance was defined as 2 consecutive annual visits where a prevalent HPV type was not detected again. We assessed the association of prevalent and incident infection, and clearance of prevalent infection, with selected baseline behavioral and clinical characteristics. Eight men (5 MSM and 3 MSW) were excluded from this analysis due to missing survey data. To assess the potential impact of the vaccination, we also investigated the relative risk of abnormal anal cytology given prevalent HPV infection and assessed the

sensitivity and specificity, of 9v HR-HPV detected at baseline as a predictive factor for any baseline anal cytological abnormality.

All statistical analysis was performed using SAS version 9.3 software (SAS Institute); *P* values <.05 were considered statistically significant.

Ethical Considerations

The investigation followed the guidelines of the US Department of Health and Human Services regarding protection of human subjects. The study protocol was approved and renewed annually by each participating institution's ethical review board. All study participants provided written informed consent.

RESULTS

Patient Characteristics

Of the 390 men included in this analysis, 325 (83%) were MSM and 65 (17%) were MSW. The median follow-up time for MSM and MSW was 59 (interquartile range [IQR], 51–60) months and 60 (IQR, 58–62) months, respectively. Overall, median age was 42 (IQR, 36–47) years. Compared with MSM, MSW were less likely to be non-Hispanic white (77% vs 32%, respectively; $P < .001$) and more likely to be married (36% vs 51%, respectively; $P = .004$; Table 1). Two hundred fifty-four (78%) MSM and 53 (82%) MSW were prescribed cART. Median baseline CD4 counts were 462 (IQR, 308–659) cells/μL for MSM and 418 (IQR, 290–555) cells/μL for MSW ($P = .156$). Seventy-three percent of MSM and 77% of MSW were virologically suppressed (HIV RNA <400 copies/mL) at baseline. MSM and MSW did not differ markedly in terms of behavioral characteristics, except that MSM were more likely to have had ≥4 sex partners in the last 6 months than MSW (22% vs 3%; $P < .001$).

HPV Prevalence

Among all men, the prevalence of 9v HR-HPV types was higher than non-9v HR-HPV types over the entire study period. Although there were more 9v types compared with non-9v HR-HPV types, the prevalence of the non-9v types was substantial. Prevalence of both 9v and non-9v HR-HPV types decreased over time (all $P < .01$).

The baseline prevalence of any 9v HR-HPV type in the anus was higher among MSM than MSW (74% vs 25%, respectively; $P < .001$); the same pattern was present when the 9v HR-HPV types were divided as HPV-16 or -18 (49% vs 12%, respectively; $P < .001$) and the other 5 HR types (58% vs 17%, respectively; $P < .001$). Of the 9v HR-HPV types, HPV-16 was the most common HR type detected among MSM and MSW (36% and 8%, respectively; Table 2). For MSM, HPV-16 was the most common and persistent type for the entire study period (Figure 1). Of the non-9v HR-HPV types, type 51 (24%) was most prevalent among MSM and type 39 (14%) was most prevalent among MSW. The baseline prevalence of each individual HR-HPV type is shown in Table 2.

HPV Incidence

Incidence of any 9v HR-HPV type was different among MSM and MSW (15.6 vs 7.6 per 100 PY, respectively, $P = .003$). Among MSM and MSW, the most common incident 9v HR-HPV types were 52 and 16 (6.1 and 6.0 per 100 PY, respectively) and 45 and 16 (2.0 and 1.6 per 100 PY, respectively). Incidence of type 16 or 18 was higher among MSM compared with MSW (8.1 vs 2.1 per 100 PY, respectively; $P < .001$). Incidence of any non-9v HR-HPV type was higher among MSM compared with MSW (18.5 vs 4.9 PY, respectively; $P < .001$) (Table 2).

HPV Clearance Rate

By Kaplan–Meier analysis with estimates at 4 years of follow-up, among MSM and MSW, the estimated probability of clearance of any 9v HR-HPV type was similar to any non-9v HR-HPV type (25% vs 29%, $P = .143$ and 58% vs 54%, $P = .872$, respectively). HPV-16 was the most prevalent 9v HR-HPV type among both MSM and MSW, and the clearance rate of HPV-16 was similar among MSM compared with MSW (42 vs 60, respectively; $P = .192$).

Anal Cytology

Among all men, 299 MSM and 61 MSW provided anal swab samples adequate for assessment of cytology. Anal cytology was abnormal in 161 (54%) MSM and 12 (20%) MSW and the distribution of cytology grade is shown (Table 3). While HSIL cytology was prevalent in MSM, no MSW participant had HSIL cytology. Among MSM and MSW with prevalent 9v HR-HPV types, 61% and 47% had abnormal anal cytology, respectively. Among MSM and MSW with prevalent 9v HR-HPV types not 16 or 18, 62% and 40% had abnormal anal cytology, respectively. Among MSM, abnormal cytology was associated with the presence of any 9v HR-HPV (relative risk [RR], 1.8 [95% confidence interval {CI}, 1.3–2.6]; $P < .001$), with 9v HR-HPV not types 16 or 18 (RR, 1.5 [95% CI, 1.2–1.9]; $P < .001$), and with 5 or more 9v HR-HPV types (RR, 1.8 [95% CI, 1.4–2.4]; $P < .001$). Among MSW, abnormal anal cytology was significantly associated with the presence of any 9v HR-HPV (RR, 4.3 [95% CI, 1.6–11.5]; $P = .003$), but not significantly associated with other 9v HR-HPV types excluding 16 or 18 (RR, 2.6 [95% CI, .6–11.0]; $P = .077$), nor with 5 or more 9v HR-HPV types (RR, 2.6 [95% CI, .9–7.3]; $P = .107$) (Table 4).

Among MSM and MSW with any non-9v HR-HPV type, 63% and 26%, respectively, had abnormal anal cytology. Unlike MSW, among MSM, abnormal anal cytology was associated with the presence of any non-9v HR-HPV type (RR, 1.7 [95% CI, 1.3–2.2]; $P < .001$; Table 4).

Among MSM and MSW, sensitivity of anal 9v HR-HPV detection for the presence of coincident anal cytologic abnormalities was 84% (95% CI, 77%–89%) and 58% (95% CI, 29%–84%), respectively. Specificity among MSM was 38% (95% CI, 30%–46%) and among MSW was 84% (95% CI, 70%–82%).

Table 1. Baseline Characteristics, Male Participants (N = 390)[a], SUN Study, 2004–2006

Characteristics	MSM (n = 325)	MSW (n = 65)	*P* Value
Demographics			
Median age at enrollment, y (IQR)	42 (36–47)	43 (38–48)	.233
Race/ethnicity			
White, not Hispanic	250 (77)	21 (32)	< .001
Black, not Hispanic	40 (12)	30 (46)	
Hispanic	30 (9)	11 (17)	
Other	5 (2)	3 (5)	
High school graduate[b]	286 (94)	49 (81)	.002
Marital/partner status[c]			
Married/partnered	100 (36)	31 (51)	.004
Single/separated/divorced/widowed	178 (64)	30 (49)	
Clinical characteristics			
Antiretroviral-naive	43 (13)	5 (8)	.313
Prescribed cART	254 (78)	53 (82)	.543
HIV RNA <400 copies/mL[d]	236 (73)	49 (77)	.587
Median $\log_{10}$ viral load if detectable (IQR)	4.04 (3.37–4.78)	3.70 (3.18–4.43)	.239
$CD4^+$ T-lymphocyte count[d]			
<200 cells/μL	29 (9)	11 (17)	.127
200–500 cells/μL	161 (50)	31 (48)	
>500 cells/μL	133 (41)	22 (34)	
Median cells/μL (IQR)	462 (308–659)	418 (290–555)	.156
Nadir $CD4^+$ T-lymphocyte count[d]			
<50 cells/μL	53 (16)	19 (30)	.010
50–199 cells/μL	99 (31)	23 (36)	
≥200 cells/μL	171 (53)	22 (34)	
Median cells/μL (IQR)	213 (100–329)	119 (34–265)	.001
Rectal *Neisseria gonorrhoeae* diagnosed by NAAT	8 (2)	0 (0)	.221
Rectal *Chlamydia trachomatis* diagnosed by NAAT	24 (8)	0 (0)	.013
Syphilis	7 (2)	0 (0)	.287
Behavioral characteristics			
Cigarette smoking			
Ever	215 (66)	42 (65)	.811
Current	127 (39)	27 (42)	.711
Alcohol consumption in last 6 mo			
0–13 drinks/wk	304 (94)	58 (89)	.219
≥14 drinks/wk	21 (6)	7 (11)	
≥5 drinks on 1 occasion	103 (32)	18 (28)	.505
No. of sexual partners in last 6 mo			
0	55 (18)	31 (48)	< .001
1	104 (35)	27 (42)	
2–3	73 (25)	5 (8)	
≥4	66 (22)	2 (3)	
Receptive anal sex in the past 6 mo	160 (52)	1 (2)	< .001
Receptive anal sex ever[e]	289 (93)	8 (13)	< .001

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: cART, combination antiretroviral therapy; IQR, interquartile range; MSM, men who have sex with men; MSW, men who have sex with women; NAAT, nucleic acid amplification test; SUN, Study to Understand the Natural History of HIV/AIDS in the Era of Effective Therapy.

[a]n = 390 unless otherwise noted.

[b]n = 365.

[c]n = 339.

[d]n = 387.

[e]n = 369.

DISCUSSION

Among all men with HIV in our study, the anal prevalence of 9v HR-HPV types was higher than non-9v HR-HPV types over the entire study period. The anal prevalence of 9v HR-HPV types was higher among MSM (74%) compared with MSW (25%), but similar to women with HIV (67%) [19]. A prior study also found higher prevalence of HR-HPV among MSM (85%) than MSW (48%) [20]. In our study, HPV-16 was the most prevalent

Table 2. Prevalence, Clearance, and Incidence of Human Papillomavirus Types Among Male Participants, SUN Study Baseline and Follow-up, 2004–2012 (N = 390)

	MSM (n = 325)				MSW (n = 65)			
HPV Type	Prevalence, No. (%)	Clearance, No. (%)	Estimated Clearance Rate[a] (95% CI)	Incidence per 100 PY (95% CI)	Prevalence, No. (%)	Clearance, No. (%)	Estimated Clearance Rate[a] (95% CI)	Incidence per 100 PY (95% CI)
HR-HPV in 9v								
16	118 (36)	39 (33)	42 (32–53)	6.0 (4.4–8.0)	5 (8)	3 (60)	60 (25–95)	1.6 (.5–3.8)
18	71 (22)	37 (52)	62 (49–75)	3.3 (2.3–4.7)	4 (6)	1 (25)	25 (4–87)	0.7 (.1–2.5)
31	70 (22)	31 (44)	58 (45–72)	3.1 (2.1–4.4)	1 (2)	1 (100)	Undetermined	1.1 (.3–2.9)
33	52 (16)	22 (42)	49 (36–65)	3.8 (2.7–5.2)	0 (0)	0 (0)	0	1.4 (.4–3.4)
45	77 (24)	33 (43)	53 (39–69)	4.0 (2.8–5.2)	3 (5)	2 (67)	67 (23–99)	2.0 (1.4–5.7)
52	67 (21)	35 (52)	60 (46–74)	6.1 (4.7–7.9)	4 (6)	4 (100)	Undetermined	0.7 (.1–2.5)
58	55 (17)	23 (42)	51 (36–68)	3.8 (2.7–5.2)	4 (6)	3 (75)	75 (33–99)	1.5 (.5–3.7)
16 or 18	159 (49)	48 (30)	39 (30–49)	8.1 (5.9–10.8)	8 (12)	3 (38)	38 (14–77)	2.1 (.8–4.6)
HR 9v, not 16 or 18	190 (58)	55 (29)	37 (29–46)	13.8 (10.5–17.8)	11 (17)	8 (73)	80 (44–99)	5.7 (3.1–9.7)
Any HR 9v	240 (74)	48 (20)	25 (19–33)	15.6 (11.1–23.2)	16 (25)	9 (56)	58 (33–84)	7.6 (4.3–12.4)
HR-HPV not in 9v								
35	62 (19)	35 (56)	67 (53–80)	4.8 (3.0–5.5)	6 (9)	2 (33)	33 (10–81)	0.8 (.1–2.6)
39	57 (18)	30 (53)	69 (54–82)	4.1 (3.0–6.4)	9 (14)	7 (78)	87 (56–99)	2.1 (.8–4.6)
51	77 (24)	42 (55)	70 (57–83)	4.7 (3.4–6.3)	4 (6)	2 (50)	50 (16–94)	3.2 (1.5–6.0)
56	40 (12)	27 (68)	81 (65–92)	3.9 (2.8–5.2)	3 (5)	3 (100)	Undetermined	1.9 (.7–4.1)
59	57 (18)	30 (53)	66 (50–80)	4.7 (3.4–6.2)	7 (7)	2 (67)	50 (9–99)	1.9 (.7–4.1)
66	44 (14)	27 (61)	71 (55–86)	3.9 (2.8–5.3)	3 (5)	2 (67)	67 (23–99)	0.7 (.1–2.4)
68	57 (18)	30 (53)	78 (45–98)	3.7 (2.6–5.1)	7 (11)	4 (57)	57 (27–90)	0.8 (.1–2.6)
Any HR non-9v	203 (62)	52 (26)	29 (22–37)	18.5 (14.3–23.6)	24 (37)	11 (46)	54 (33–78)	4.9 (2.3–9.3)
No. of types								
Median HR 9v (IQR)	2 (1–3)	…	…	…	1 (0–1)	…	…	…
Median HR non-9v (IQR)	1 (0–2)	…	…	…	1 (0–1)	…	…	…

Abbreviations: 9v, 9-valent; CI, confidence interval; HPV, human papillomavirus; HR, high-risk; IQR, interquartile range; MSM, men who have sex with men; MSW, men who have sex with women; PY, person-years; SUN, Study to Understand the Natural History of HIV/AIDS in the Era of Effective Therapy.

[a]Estimated rate (probability) of clearance was calculated using Kaplan–Meier survival analysis and reported at 4 years of observation.

HR-HPV type among both MSM and MSW, which has been shown to be the most oncogenic type of HPV [2].

Among MSM, HPV-16 had a higher prevalence and incidence rate, and a lower clearance rate compared with MSW. Comparable published data of incidence and clearance of HPV are sparse. In the HPV Infection in Men (HIM) cohort of men without HIV, incident anal HPV infections declined with advancing age; however, incidence rates of 9v HPV–type infections remained constant across the lifespan [21]. In the cART era, among MSM, the most common incident HPV infections were HPV-18 and HPV-16 (3.7 and 3.5 per 100 PY, respectively) [22]. We found lower incidence rates and higher clearance rates than was previously reported among men with HIV. One study has reported that among men with HIV, the incidence of HPV-16 was 13% per year, and of HPV-18 was 5.3% per year; clearance of HPV-16 was 14.6% per year, and of HPV-18 was 24.5% per year [8]. The majority of the SUN Study cohort participants were on cART and achieved high levels of viral suppression, and this may explain the difference.

Among both MSM and MSW with HIV and with prevalent 9v HR-HPV types, the presence of abnormal anal cytology was substantial, approximately 50%. This finding suggests that both MSM and MSW had been exposed to 9v HR-HPV types, particularly the most oncogenic type (HPV-16), which is a priority target for anal cancer prevention [2], that renders them at risk for developing precancerous lesions and cancer. The prevalence of abnormal anal cytology among men with HIV was high compared with that for women with HIV in the SUN Study [18], which is not surprising. Among MSM, sensitivity of anal 9v HR-HPV detection for the presence of anal cytologic abnormalities was good; however, specificity was poor among MSM and good among MSW. Furthermore, these data suggest that men with HIV, especially MSM, may benefit from anal cancer screening programs [23].

Modeling has shown that targeted anal cancer screening of MSM and persons with low CD4 cell counts may have a substantial effect on anal cancer incidence. However, with increasing cART and HPV vaccination coverage, the benefit of anal cancer screening may be limited. Substantial reductions in anal cancer incidence among MSM in the next 15 years are expected, even in the absence of screening and without further increases in cART coverage [23]. Nevertheless, the number needed to screen

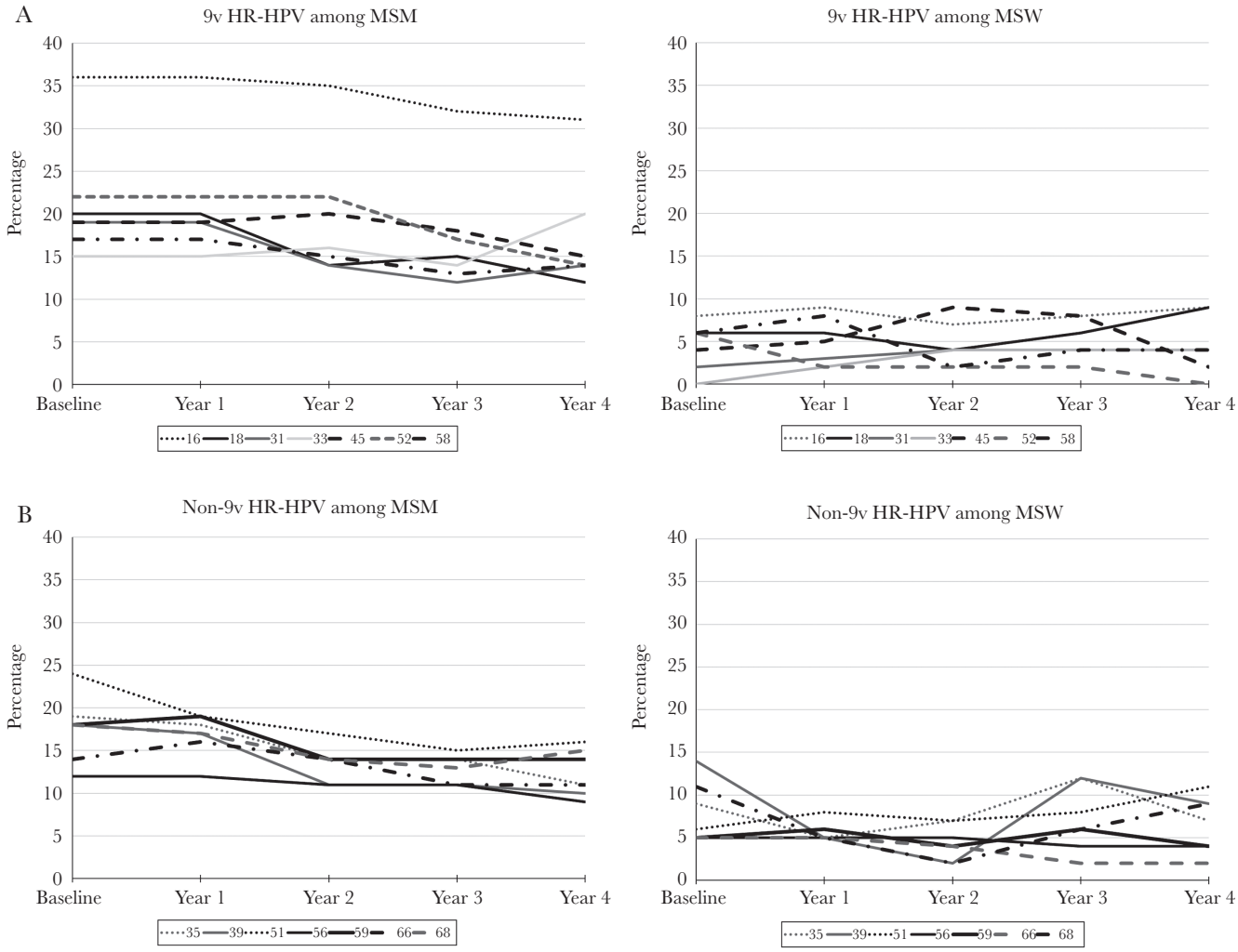

Figure 1. Prevalence of 9-valent (9v) (*A*) and non-9v (*B*) high-risk human papillomavirus (HR-HPV) types in men who have sex with men (MSM) and men who have sex with women (MSW), SUN Study baseline and follow-up, 2004–2012.

to prevent 1 invasive anal cancer in MSM with HIV appears to be lower than the number needed to screen to prevent 1 invasive cervical cancer in women without HIV, in whom screening is well established [24]. Anal cancer prevention with screening among high-risk populations may have similar benefits to cervical cancer screening programs. Studies to validate anal cancer screening are under way [25].

Our data suggest that the 9v HPV vaccine given consistent with recommendations and optimally before sexual debut may be beneficial in preventing anal cancer among men with HIV. This may be particularly true among MSM, who were less likely to clear HPV-16 over time in our study and who were more likely than MSW to have abnormal anal cytology attributable to 9v HR-HPV types other than 16 or 18. The additional protection offered by the 9v vaccine vs the bivalent and quadrivalent vaccines, however, may be smaller for anal cancer than for cervical cancer [1]. Additionally, in our study the prevalence of abnormal anal cytology associated with any 9v HR-HPV type was similar to any non-9v HR-HPV type among MSM. Furthermore, while regional variation in prevalent HPV types exists [2], recent data from Europe suggest that the proportion of anal cancers among persons with HIV that are not due to HPV-16 or -18 is higher than previously recognized [26]. The 9v HPV vaccine would provide greater reductions in HPV infections that cause anal cancer in persons with HIV compared with persons without HIV [2], and the widespread use of the 9v vaccine is important as well, being the only available primary prevention modality for anal cancer.

Our study had a number of limitations. We did not have a cohort of men without HIV for comparison and some MSW, who self-identified as MSW, reported receptive anal intercourse, which may have led to classification bias. Anal specimens in the SUN study were collected annually, and therefore HPV incidence and clearance estimates may be affected as natural progression of HSIL show that approximately one-third will clear lesions in 1 year. Similarly, we were unable to distinguish HPV

Table 3. Distribution of Anal Cytology Results by Human Papillomavirus Status, Male Participants, SUN Study Baseline, 2004–2006 (N = 360)

	Anal Cytology					
Characteristic	Normal	Any Abnormal[a]	ASC-US	LSIL	ASC-H	HSIL
MSM	n = 138	n = 161	n = 40	n = 87	n = 8	n = 26
Any HPV	126 (91)	159 (99)	38 (95)	87 (100)	8 (100)	26 (100)
Any HR-HPV	110 (80)	152 (94)	37 (38)	82 (94)	8 (100)	25 (96)
HPV type 16 or 18	53 (38)	91 (57)	17 (43)	52 (60)	7 (88)	15 (58)
Any 9v HR-HPV	86 (62)	135 (84)	30 (75)	73 (84)	8 (100)	24 (92)
9v HR-HPV not 16 or 18	68 (49)	112 (70)	26 (23)	59 (53)	7 (6)	20 (18)
Any non-9v HR-HPV	69 (50)	120 (75)	29 (73)	62 (71)	7 (88)	22 (85)
≥5 types any HPV	61 (44)	118 (73)	26 (65)	64 (74)	8 (100)	20 (77)
MSW	n = 49	n = 12	n = 6	n = 4	n = 2	n = 0
Any HPV	26 (53)	12 (100)	6 (100)	4 (100)	2 (100)	NA
Any HR-HPV	22 (45)	10 (83)	6 (100)	3 (75)	1 (50)	NA
HPV type 16 or 18	3 (6)	5 (42)	3 (50)	1 (25)	1 (50)	NA
Any 9v HR-HPV	8 (16)	7 (58)	5 (83)	1 (25)	1 (50)	NA
9v HR-HPV not 16 or 18	6 (12)	4 (33)	3 (75)	0 (0)	1 (25)	NA
Any non-9v HR-HPV	17 (35)	6 (50)	3 (50)	2 (50)	1 (50)	NA
≥5 types any HPV	4 (8)	3 (25)	1 (17)	1 (25)	1 (50)	NA

Data are presented as No. (%).

Abbreviations: 9v, 9-valent; ASC-H, atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesions; ASC-US, atypical squamous cells of undetermined significance; HPV, human papillomavirus; HSIL, high-grade squamous intraepithelial lesions; HR, high-risk; LSIL, low-grade squamous intraepithelial lesions; MSM, men who have sex with men; MSW, men who have sex with women; NA, Not applicable; SUN, Study to Understand the Natural History of HIV/AIDS in the Era of Effective Therapy.

[a]Abnormal defined as presence of ASC-US, LSIL, HSIL, or ASC-H.

reinfection from failure to clear. Furthermore, given the low specificity of abnormal anal cytology and since we did not have tissue biopsies with histology data to confirm the presence of abnormal cytology findings, we may have overestimated the number of abnormalities. Given the small number of abnormal cytology findings among MSW, analyses of these data were limited.

The high prevalence of 9v HR-HPV types among men with HIV in our study, and their correlation with abnormal anal cytology, support the use of the 9v HPV vaccine among men with

Table 4. Univariate Associations of Anal Human Papillomavirus Infection With Anal Cytological Abnormalities, Male Participants, SUN Study Baseline, 2004–2006 (N = 360)

	Anal Cytology				
Characteristic	Normal	Abnormal[a]			
MSM	n = 138	n = 161	RR	(95% CI)	*P* Value
Any HPV	126 (91)	159 (99)	3.9	(1.1–14.1)	< .001
Any HR-HPV	110 (80)	152 (94)	2.4	(1.3–4.3)	< .001
HPV type 16 or 18	53 (38)	91 (57)	1.4	(1.2–1.8)	.002
Any 9v HR-HPV	86 (62)	135 (84)	1.8	(1.3–2.6)	< .001
9v HR-HPV not 16 or 18	68 (49)	112 (70)	1.5	(1.2–1.9)	< .001
Any non-9v HR-HPV	69 (50)	120 (75)	1.7	(1.3–2.2)	< .001
≥5 types any HPV	61 (44)	118 (73)	1.8	(1.4–2.4)	< .001
MSW	n = 49	n = 12			
Any HPV	26 (53)	12 (100)	15.4	(.95–248)	.002
Any HR-HPV	22 (45)	10 (83)	4.5	(1.1–19.0)	.001
HPV type 16 or 18	3 (6)	5 (42)	4.7	(2.0–11.3)	.006
Any 9v HR-HPV	8 (16)	7 (58)	4.3	(1.6–11.5)	.003
9v HR-HPV not 16 or 18	6 (12)	4 (33)	2.6	(.6–11.0)	.077
Any non-9v HR-HPV	17 (35)	6 (50)	1.7	(.6–4.5)	.160
≥5 types any HPV	4 (8)	3 (25)	2.6	(.9–7.3)	.107

Data are presented as No. (%).

Abbreviations: 9v, 9-valent; CI, confidence interval; HPV, human papillomavirus; HR, high risk; MSM, men who have sex with men; MSW, men who have sex with women; RR, relative risk; SUN, Study to Understand the Natural History of HIV/AIDS in the Era of Effective Therapy.

[a]Abnormal defined as presence of atypical squamous cells of undetermined significance; low-grade squamous intraepithelial lesions; low-grade squamous intraepithelial lesions (HSIL); or atypical squamous cells, cannot exclude HSIL.

HIV, particularly in younger age groups. The benefits of using the extended age indication (HPV vaccination through age 45 years) in this high-risk population should be studied further. The high prevalence of HPV-16, the most oncogenic type [2], among our male participants indicates that the 9v HPV vaccine may still offer substantial benefit in preventing anal cancer despite the notable cytologic abnormalities associated with HPV types not covered by the vaccine. Among MSM, HPV-16 was also the most persistent HR-HPV (ie, having lowest rates of clearance), which increases their risk of developing anal cancer. Primary prevention with the currently available 9v HPV vaccine, which has been demonstrated to be immunogenic among men with HIV [11], may substantially reduce their risk for anal cancer [27] by preventing HR-HPV infection of the anus. The association between 9v HR-HPV and abnormal cytology demonstrates that more research is needed to inform recommendations for HR-HPV testing in anal cancer screening.

Notes

Disclaimer. The findings and conclusions from this review are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention (CDC).

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