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MAJOR ARTICLE

Prevalence, Incidence, and Clearance of Anal High-Risk Human Papillomavirus Infection Among HIV-Infected Men in the SUN Study

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Background. The natural history of anal human papilloma virus (HPV) infection among human immunodeficiency virus (HIV)-infected men is unknown.

Methods. Annually, from 2004 to 2012, we examined baseline prevalence, incidence, and clearance of anal HPV infection at 48 months, and associated factors among HIV-infected men.

Results. We examined 403 men who have sex with men (MSM) and 96 men who have sex with women (MSW) (median age 42 years for both, 78% versus 81% prescribed cART, median $CD4^+$ T-lymphocyte cell count 454 versus 379 cells/mm^3, and 74% versus 75% had undetectable viral load, respectively). Type 16 prevalence among MSM and MSW was 38% versus 14% ($P < .001$), and incidence 24% versus 7% ($P = .001$). Type 18 prevalence was 24% versus 8% ($P < .001$), and incidence 13% versus 4% ($P = .027$). Among MSM and MSW, clearance of prevalent HPV 16 and HPV 18 was 31% and 60% ($P = .392$), and 47% and 25% ($P = .297$), respectively. Among MSM, receptive anal sex (with or without a condom) was associated with persistent HPV 16 (OR 2.24, $P < .001$).

Conclusions. MSM had higher prevalence and incidence of HPV than MSW, but similar clearance. Receptive anal sex may predict cancer risk among HIV-infected MSM.

Keywords. HIV; human immunodeficiency virus; HPV; human papillomavirus; anal cytology.

Human papillomavirus (HPV) is a recognized cause of anal cancer [1–3]. Gay, bisexual, and other men who have sex with men (MSM) are about 20 times as likely as heterosexual men to develop anal cancer [3–7] and are also at higher risk for anal squamous intraepithelial lesions (SIL) and genital warts [7–11]. Human immunodeficiency virus (HIV)-infected MSM are at higher risk for anal cancer compared with HIV-uninfected MSM or women [12, 13]. A recent analysis from the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) showed that HIV-infected MSM had the highest risk for anal cancer; incidence rates were 80.3 times as high among HIV-infected MSM compared with HIV-uninfected men [7]. The highest reported incidence of anal cancer among HIV-infected MSM since the introduction of combination antiretroviral therapy (cART), 137 per 100 000 person-years, exceeds the highest reported incidence of cervical cancer anywhere in the world [4–8, 14]. Studies have shown a high prevalence of anal HPV (up to 90%) among MSM [15, 16], often with multiple types, regardless of $CD4^+$ T-lymphocyte cell count [17, 18]. The increased burden of anal cancer among MSM, and especially among HIV-infected MSM, likely results from the higher prevalence of anal HPV in these populations, compared with other men and women [14, 19].

Anal HPV infection is cleared less frequently by HIV-infected MSM compared with HIV-uninfected MSM [20], specifically for HPV type 16 [21]. Persistence of high-risk HPV types 16 and 18 is an important risk factor for the development of anal cancer [22–24]. HPV vaccination can prevent anal high-risk HPV infection; however, vaccination is limited to males younger than 27 years of age, and wide uptake has not yet been seen [25, 26]. HPV vaccination of HIV-infected men age 27 years or older has not been shown to alter risk for incident anal HPV infection, most likely due to increased risk of prior HPV exposure and decreased risk of infection among older men [27]. Additionally, HPV vaccination recommendations and anal cancer screening protocols that involve HPV testing [28] may benefit from epidemiological data that examine the natural history and risk factors of anal HPV infection and its consequences among HIV-infected men.

To better characterize the clinical epidemiology of HPV infection in a cohort of HIV-infected men, we examined

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prevalence, incidence, and clearance of infection among MSM compared with men who have sex with women (MSW). We further examined factors associated with clearance of HPV to potentially identify modifiable factors to reduce anal cancer risk in this population. Additionally, we assessed the association of HPV persistence with abnormal anal cytology.

METHODS

Study Design and Population

From March 2004 through June 2006 (the "baseline" period), the Study to Understand the Natural History of HIV/AIDS in the Era of Effective Therapy (the SUN study) enrolled 700 HIV-infected adults from 7 clinics in 4 US cities into a prospective observational cohort study sponsored by the Centers for Disease Control and Prevention (CDC) (http://clinicaltrials.gov/show/NCT00146419). The study design, data collection, and management methods have been described previously [29]. Participants were generally healthy HIV-infected patients 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 viral load) that included comprehensive testing for sexually transmitted diseases (STDs), medical chart 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 MSW according to self-report on the ACASI. Data abstracted from medical charts were entered into an electronic database (Clinical Practice Analyst; Cerner Corporation, Vienna, VA) by trained staff. 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 Centers for Disease Control and Prevention (CDC) and each participating site. The study follow-up period for remaining participants ended in 2012.

Anal Sample Collection and Examination

Two swab specimens were collected annually for the first 5 years of follow-up; 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 centimeters 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 (Marlborough, MA). The swab for HPV testing was placed into Digene Specimen Transport Medium (STM, Qiagen Incorporated, Valencia, CA). Cytology specimens were evaluated by a single pathologist with expertise in the interpretation of anal cytology (T.M. Darragh). All cytologic results were classified according to the Bethesda System terminology [30]. If the anal sample was satisfactory (ie, of sufficient cellularity), results were reported as negative, atypical squamous cells of undetermined significance (ASCUS), atypical squamous cells, cannot exclude SIL or carcinoma. We defined abnormal anal cytology as any result other than negative. Based on these results, participants were referred for appropriate follow-up per their institution's standard of practice.

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 a DNA isolation kit III (Roche Diagnostics, Indianapolis, IN). 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 the hybridization and detection steps were automated. The assay uses L1 consensus PCR with biotinylated primers and type-specific hybridization detecting 37 different HPV types (14 high-risk [HR] types: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 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, IS39; and an endogenous control gene [β-globin]). Samples negative for both β-globin and HPV were considered inadequate for evaluation and not included. 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 type 52 may be ambiguous because of cross-hybridization of the HPV type 52 probe with types 33, 35, and 58. To unambiguously determine the presence of HPV type 52 in samples with 1 or more of the 3 other types, an HPV type-52-specific real-time PCR assay was used [31].

Statistical Methods

Baseline prevalence of the 37 detectable HPV types was determined. We compared baseline behavioral and clinical characteristics in MSM, including bisexual men, and MSW using either Mantel-Hanzel X^2 or Fisher's exact test for categorical variables and the Student's *t* test or Kruskal-Wallis test for continuous variables, and logistic regression to assess factors associated with HPV. We evaluated the incidence and clearance of HPV types 16 and 18 at the anus collected at baseline, and annually over 60 and 48 months, respectively, using Kaplan-Meier survival analysis; *P* values were determined using the log-rank test. We defined incident infection as detection of HPV 16 or 18 not found on previous specimen collection. For those with prevalent or incident HPV 16 or HPV 18, we defined clearance as 2 consecutive visits where the respective HPV type

was not detected. Persistence was defined as HPV infection that did not clear, per the definition above. Incidence per 100 person-years, and 95% Poisson confidence intervals (CIs), were estimated among men who did not have HPV 16 or 18 at baseline, regardless of other HPV types. We used Mantel-Hanzel X^2 to assess univariate associations of incident types 16 and 18 infection, and clearance of prevalent type 16 and 18 infection, with selected baseline behavioral and clinical characteristics. We evaluated the number of HR and other types using the classification described above. We also investigated the relative risk of prevalent HPV infection and assessed the sensitivity, specificity, and positive and negative predictive values of HPV detected at baseline as a predictive factor for any subsequent anal cytological abnormality.

All statistical analysis was performed using SAS, version 9.3 (SAS Institute, Inc., Cary, North Carolina, www.sas.com); *P* values < .05 were considered statistically significant.

RESULTS

Patient Characteristics

Of the 700 participants enrolled in the SUN Study, 525 were men; of these, 499 had an adequate HPV result at baseline. Of the 499 men included in this analysis, 403 (81%) were MSM and 96 (19%) were MSW. Overall, median age was 42 years (interquartile range [IQR] 36–48). Compared with MSM, MSW were less likely to be white non-Hispanic (75% vs 33%, $P < .001$) and more likely to be married (33% vs 50%, $P = .004$) (Table 1). Three-hundred and sixteen (78%) MSM and 78 (81%) MSW were prescribed cART. Median baseline CD4 cell counts were 454 cells/mm^3 (IQR, 312–655) for MSM and 379 cells/mm^3 (IQR, 237–555) for MSW, $P = .055$; 74% of MSM and 75% of MSW were virologically suppressed (HIV RNA VL < 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 more than 4 sex partners and to report receptive anal sex (with or without a condom) in the last 6 months (51% vs 2%, $P < .001$) compared with MSW.

Anal HPV Prevalence

Anal prevalence of HPV was 95% for MSM and 59% for MSW (Table 2). High-risk HPV types were detected in 342 (85%) MSM and 46 (48%) MSW. Other HPV types were detected in 357 (89%) MSM and 42 (44%) MSW. Among MSM with detectable HPV, the median number of HPV types was 6 (IQR, 3–8) for any, 3 (IQR, 1–4) for high-risk, and 3 (IQR, 2–4) for other types. Among MSW, the corresponding medians were 2 (IQR, 2–4), 1 (IQR, 1–2), and 1 (IQR, 0–2). MSM were significantly more likely to be infected with a greater number of high-risk HPV types (3 versus 1, $P < .001$) compared with MSW.

The most common HPV types were 16 and 6 among both MSM (38% and 29%) and MSW (14% and 11%). The combined prevalence of any HPV types 6, 11, 16, or 18 among MSM was 67%, and 26% among MSW (Table 3). Forty-nine percent of MSM and 82% of MSW had neither HPV type 16 nor 18 detected. Among MSM and MSW, anal prevalences of HPV type 16 were 38% (n = 152) and 14% (n = 13) ($P < .001$), and of HPV type 18 were 24% (n = 97) and 8% (n = 8), ($P < .001$), respectively. Ten percent (n = 42) of MSM and 4% (n = 4) of MSW were coinfected with both HPV 16 and 18 types.

The prevalence of HR HPV and median number of HR HPV types for men with detectable HPV differed for MSW with CD4 cell count >500 cells/mm^3 (Figure 1*A*, *B*). The median number of HPV types also did not vary by age. The median numbers of types among age groups 20–29, 30–39, 40–49, and ≥50 years were 5, 6, 6, and 5 ($P = .168$), respectively, for MSM, and they were 3, 3, 2, and 2.5 ($P = .735$), respectively, for MSW.

Factors Associated With Prevalent Anal HPV Infection

MSW who were current smokers had a higher risk of HPV infection than nonsmokers (odds ratio [OR] = 2.50, 95% CI, 1.08–6.03, $P = .036$) (Supplementary Table). In men with detectable HPV, the mean numbers of HPV types among smokers compared with nonsmokers were 6.3 and 5.8 ($P = .115$) among MSM, and were 3.6 and 2.9 ($P = .127$) among MSW. The mean numbers of anal HPV types in smokers compared with nonsmokers were 3.3 versus 2.8 ($P = .017$) for HR types and 3.1 versus 3.0 ($P = .542$) for other types among MSM; correspondingly, they were 1.8 versus 1.7 ($P = .830$) for HR types and 1.7 versus 1.1 ($P = .030$) for other types among MSW.

MSM who injected drugs were more likely than those who did not inject drugs to have prevalent infection with HPV 16 (53% vs 36%, $P = .024$). Compared with MSM without the corresponding characteristics, those with rectal *Neisseria gonorrhea* infection (67% vs 24%, $P = .009$), CD4 cell count <500 cells/mm^3 (29% vs 17%, $P = .004$), and ≥4 sex partners during the 6 months before baseline (33% vs 21%, $P = .012$) were more likely to be infected with prevalent HPV 18.

Anal Incidence of High-Risk 16 and 18 HPV Types

Over 48 months, 45 MSM and 4 MSW had an incident HPV type 16 detected, while 33 and 2 had an incident type 18 detected, respectively. The estimated incidence of HPV type 16 at 48 months was 24% (95% CI, 18%–31%) for MSM and 7% (95% CI, 3%–18%) for MSW ($P = .001$). For HPV type 18, the incidence was 13% (95% CI, 9%–18%) for MSM and 4% (95% CI, 1%–15%) for MSW ($P = .027$). Anal sex in the 6 months before baseline (30% vs 11%, $P = .010$) and consuming alcohol in 30 days before baseline (21% vs 9%, $P = .026$) were associated with incident HPV 16; marijuana use in 6 months before baseline was associated with incident HPV 18 (20% vs 10%, $P = .031$).

Anal Clearance of High-Risk 16 and 18 Types

Clearance, at 48 months, of prevalent HPV type 16 was 31% (95% CI, 23%–41%) of MSM and 60% (95% CI, 25%–95%) of

Table 1. Baseline Characteristics of Male Participants (n = 499)[a], the SUN Study, 2004–2006

Characteristics	MSM (n = 403)	MSW (n = 96)	*P* value
Demographics			
Median age at enrollment, years (IQR)	42 (36–47)	42 (36.5–48)	.543
Median years since HIV diagnosis (IQR)	5.0 (2.2–7.9)	3.9 (1.7–7.8)	.264
Race/ethnicity, n (%)			
White, not Hispanic	304 (75)	32 (33)	<.001
Black, not Hispanic	58 (14)	46 (48)	
Hispanic	36 (9)	14 (15)	
Other	5 (1)	4 (4)	
High school graduate[b], n (%)	354 (94)	68 (81)	<.001
Marital/partner status[c], n (%)			
Married/partnered	116 (33)	43 (50)	.004
Single/separated/divorced/widowed	231 (67)	43 (50)	
Clinical Characteristics			
Antiretroviral naive, n (%)	53 (13)	9 (9)	.313
Prescribed cART	316 (78)	78 (81)	.540
HIV RNA viral load <400 copies/mL, n (%)	295 (74)	71 (75)	.874
Median viral load, $\log_{10}$ copies/mL, if detectable (IQR)	4.08 (3.40–4.78)	3.90 (3.28–4.47)	.465
$CD4^+$ T-lymphocyte count[d], n (%)			
<200 cells/mm^3	36 (9)	16 (17)	.050
200–500 cells/mm^3	203 (51)	50 (52)	
>500 cells/mm^3	161 (40)	30 (31)	
Median cells/mm^3 (IQR)	454 (312–655)	379 (237–555)	.055
Nadir $CD4^+$ T-lymphocyte count[d], n (%)			
<50 cells/mm^3	64 (16)	23 (24)	.032
50–199 cells/mm^3	125 (31)	36 (37)	
≥200 cells/mm^3	211 (53)	37 (39)	
Median cells/mm^3 (IQR)	209.5 (100–326.5)	137.5 (54–272)	.002
Rectal *Neisseria gonorrhoeae* diagnosed by NAAT (%)	9 (2)	0 (0)	.155
Rectal *Chlamydia trachomatis* diagnosed by NAAT (%)	31 (8)	0 (0)	.003
Behavioral Characteristics			
Cigarette smoking, n (%)			
Ever	269 (67)	65 (68)	.858
Current	160 (40)	42 (44)	.468
Alcohol consumption in last 6 months, n (%)			
None	87 (22)	41 (43)	<.001
1–13 drinks per week	287 (71)	47 (49)	
≥14 drinks per week	29 (7)	8 (8)	
≥5 drinks on one occasion	134 (33)	28 (29)	.452
Number of sexual partners in last 6 months, n (%)			
0	72 (18)	41 (43)	<.001
1	129 (32)	46 (48)	
2–3	88 (22)	7 (7)	
≥4	113 (28)	2 (2)	
Receptive anal sex (with or without a condom) in the past 6 months, n (%)	195 (51)	2 (2)	<.001
Receptive anal sex (with or without a condom) ever[e], n (%)	356 (93)	10 (11)	<.001

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 = 499 unless otherwise noted.

[b]n = 460.

[c]n = 433.

[d]n = 496.

[e]n = 470.

MSW (*P* = .392) (Figure 2*A*); for prevalent HPV type 18 anal infection, it was 53% (95% CI, 39%–64%) of MSM and 25% (95% CI, 4%–87%) of MSW (*P* = .297) (Figure 2*B*). Only a history of anal sex (with or without a condom) at baseline was associated with failure to clear prevalent HPV type 16 in MSM (OR 2.24 [95% CI, 1.39–3.60], *P* < .001). At 48 months, among

Table 2. Prevalence of Anal Human Papillomavirus Infection Among Male Participants, the SUN Study, 2004–2006

Characteristic	MSM (n = 403)	MSW (n = 96)	*P* value
Any HPV (%)	384 (95)	57 (59)	<.001
Any high-risk HPV types (%)	342 (85)	46 (48)	<.001
Any other HPV types (%)	357 (89)	42 (44)	<.001
Any HPV types 16 or 18 (%)	207 (51)	17 (18)	<.001
Any high-risk types other than HPV 16 or 18 (%)	135 (34)	29 (30)	.537
Any HPV types 6 or 11	164 (41)	14 (15)	<.001
Any other types, other than HPV 6 or 11 (%)	193 (48)	28 (29)	<.001
Median number of types (IQR)	6 (3–8)	2 (2–4)	<.001
Median number of high-risk types (IQR)	3 (1–4)	1 (1–2)	<.001
Median number of other types (IQR)	3 (2–4)	1 (0–2)	<.001

Abbreviations: HPV, human papillomavirus; IQR, interquartile range; MSM, men who have sex with men; MSW, men who have sex with women; SUN, Study to Understand the Natural History of HIV/AIDS in the Era of Effective Therapy.

the subset of MSM who reported history of anal sex (with or without a condom), 31% (95% CI, 22%–41%) cleared prevalent HPV 16 and 31% (95% CI, 11%–54%) cleared HPV 18.

At 48 months, after an incident HPV type 16 anal infection, 34% (95% CI, 17%–61%) of MSM cleared their infection; for incident HPV type 18 anal infection, 64% (95% CI, 42%–89%) of MSM cleared their infection. There was no significant difference between clearance of incident HPV 16 and incident HPV 18 at 48 months among MSM (34% vs 64%, $P = .536$) (Figure 2*C*). MSM who reported ever using club drugs, including methamphetamine, compared with those who did not were less likely to clear incident HPV 16 (20% vs 40%, $P = .031$).

SIL was more frequently detected in MSM with versus those without persistent infection, whether with HPV 16 (42% vs 29%, $P = .013$) or with HPV 18 (63% vs 49%, $P = .024$).

Abnormal Anal Cytology

Among 455 men with adequate anal cytology specimens, abnormal cytology (ASCUS or worse) was detected in 206 (56%) MSM and 17 (20%) MSW ($P < .001$), and was correlated with the presence of HPV (MSM: relative risk [RR] = 3.9, 95% CI, 1.2–12.4, $P < .001$; MSW: RR = 23.8, 95% CI, 1.5–382, $P < .001$). Abnormal anal cytology also correlated with detection of a HR-HPV type in the anus in both MSM (RR = 2.2, 95% CI, 1.4–3.3, $P < .001$) and MSW (RR = 4.6, 95% CI, 1.6–13.8, $P < .001$) (Table 4). Detection of anal HPV was sensitive, as a predictive factor, for the presence of anal cytologic abnormalities (99.0% for MSM, 100% for MSW) but was not specific (8.6% for MSM, 50.0% for MSW); however, the absence of detectable HPV had a high negative predictive value for cytologic abnormalities (88% for MSM and 100% for MSW) (Figure 3).

Table 3. Human Papillomavirus Types Identified in Anal Specimens at Baseline, Male Participants, the SUN Study, 2004–2006 (n = 499)

HPV type identified	MSM (n = 403)	MSW (n = 96)
Any type (%)	384 (95)	57 (59)
High-risk type, any (%)	342 (85)	46 (48)
16	152 (38)	13 (14)
18	97 (24)	8 (8)
31	89 (22)	5 (5)
33	58 (14)	1 (1)
35	73 (18)	9 (9)
39	79 (20)	10 (10)
45	97 (24)	7 (7)
51	95 (24)	9 (9)
52	87 (22)	6 (6)
56	49 (12)	5 (5)
58	67 (17)	9 (9)
59	77 (19)	7 (7)
66	59 (15)	3 (3)
68	65 (16)	9 (9)
Other type, any (%)	357 (89)	42 (44)
6	116 (29)	11 (11)
11	64 (16)	4 (4)
26	11 (3)	0 (0)
40	16 (4)	3 (3)
42	74 (18)	4 (4)
53	89 (22)	3 (3)
54	68 (17)	5 (5)
55	71 (18)	7 (7)
61	72 (18)	5 (5)
62	79 (20)	3 (3)
64	2 (1)	0 (0)
67	21 (5)	3 (3)
69	26 (6)	3 (3)
70	66 (16)	1 (1)
71	1 (<1)	1 (1)
72	32 (8)	5 (5)
73	55 (14)	3 (3)
81	31 (8)	1 (1)
82	27 (7)	1 (1)
83	40 (10)	5 (5)
84	99 (25)	10 (10)
89	87 (22)	4 (4)
IS39	14 (3)	1 (1)

Abbreviations: HPV, human papillomavirus; MSM, men who have sex with men; MSW, men who have sex with women; SUN, Study to Understand the Natural History of HIV/AIDS in the Era of Effective Therapy

DISCUSSION

In this cohort of HIV-infected men, the prevalence of anal HPV infection and the number of detected types was lower among MSW than MSM. In both groups, each measure correlated with the presence of cytologic abnormalities. Compared with HIV-infected MSW, MSM were more likely to have abnormal anal cytology. As expected, the prevalence and number of types of HR HPV and other types were higher among MSM than MSW. MSM reported a significantly greater number of sex partners compared

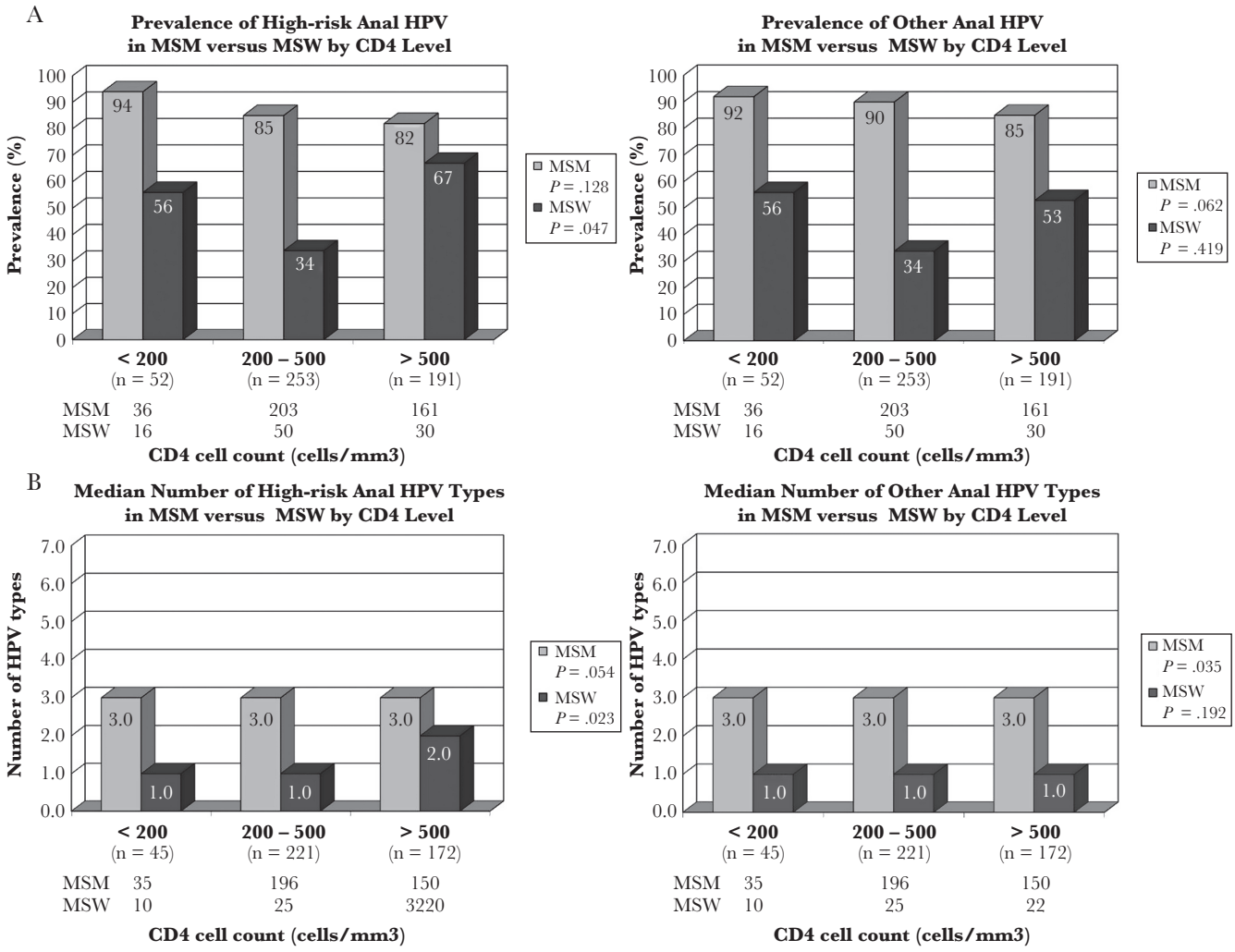

Figure 1. *A,* Prevalence of anal human papillomavirus (HPV) infection among human immunodeficiency virus (HIV)-infected men in the SUN study by CD4 cell count, high-risk versus other, 2004–2006 (n = 496). *B,* Number of anal HPV types among men with detectable HPV in the SUN study by CD4 cell count at baseline, high-risk versus other, 2004–2006 (n = 438). Abbreviations: MSM, men who have sex with men; MSW, men who have sex with women.

with MSW. These data indicate that HIV-infected MSM are at increased risk for high-risk anal HPV infection and subsequent abnormal cytology compared with HIV-infected MSW.

Risk factors for anal HPV infection differed among MSM and MSW. Smoking was the strongest risk factor for HPV infection among MSW. Several studies have shown that smoking is associated with HPV infection, abnormal anal cytology, and anal cancer among HIV-infected men [32–34]. Although smoking has been reported to be a significant risk factor for anal disease among HIV-infected MSM [35, 36], our data did not corroborate this finding; however, current smokers were more likely to have HPV infection in our cohort [36]. This is likely due to the high prevalence of HPV in our cohort of MSM. Smoking, however, was associated with the detection of a greater mean number of HPV types among MSM, and the mean number of anal other HPV types (not high risk) was higher among MSW smokers compared with nonsmokers. Smoking cessation should be encouraged among HIV-infected persons, particularly MSM, given the increased risk of HPV-related disease among HIV-infected smokers.

Injection drug use was associated with prevalent HPV 16 infection among MSM in our cohort, and rectal *Neisseria gonorrhea* infection, CD4 cell count <500 cells/mm^3, and >4 sex partners in the last 6 months were associated with prevalent HPV 18 infection. The finding of the effect of low CD4 cell count has been previously reported [36]. Injection drug use, number of sex partners, and rectal *Neisseria gonorrhea* infection are likely surrogates for high-risk behavior that could lead to increased risk of exposure to HPV. Clinicians should consider these factors when evaluating HIV-infected MSM for potential HPV infection and/or anal SIL.

Clearance and persistence of high-risk types 16 and 18 did not differ between MSM and MSW. However, HPV infection persisted longer among the HIV-infected men in our cohort compared with HIV-uninfected men in a previous study [37].

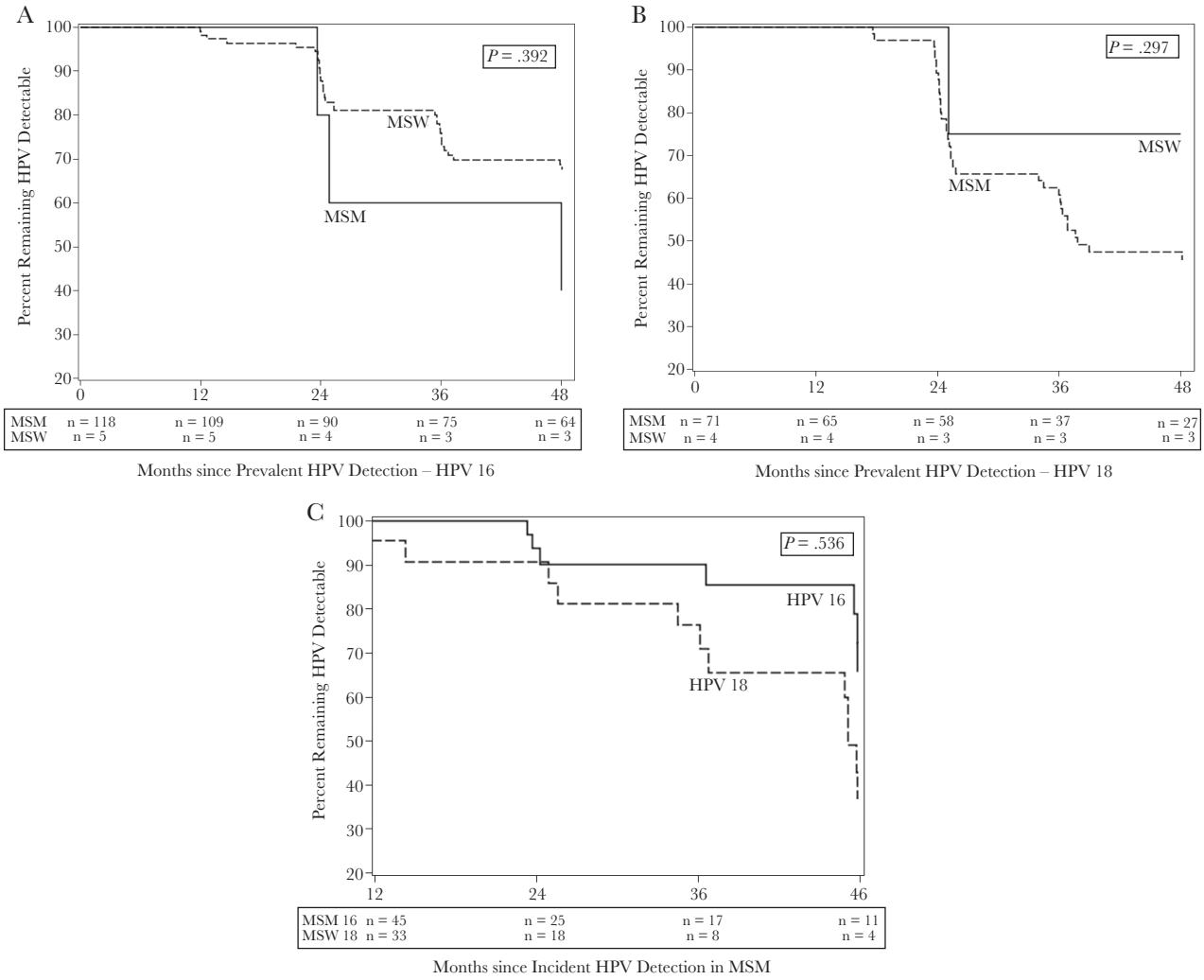

Figure 2. Clearance of prevalent high-risk anal human papillomavirus (HPV) infection among men who have sex with men (MSM) and men who have sex with women (MSW) for: (*A*) HPV type 16 infection; (*B*) HPV type 18 infection; and (*C*) clearance of incident high-risk anal HPV type 16 and type 18 infection among human immunodeficiency virus (HIV)-infected MSM, 2004–2012.

Among MSM with persistent HPV 16 or 18, SIL in the anus was significantly more likely to be detected compared with MSM without persistent HPV 16 or 18. Failure to clear prevalent HPV 16 was associated with receptive anal sex (with or without a condom) and use of club drugs, including methamphetamine. Those who reported methamphetamine use were also less likely to clear HPV 16. Condomless receptive anal sex is an indicator of risky sexual behavior and of increased exposure to HPV. Therefore, failure to clear HPV could be related to re-exposure or reinfection through sexual contacts. The association with methamphetamine use is a new finding and relevant because use of this drug has been associated with risky sexual behavior [38, 39]. As a general practice, MSM should be screened and counseled about drug use, which may also help prevent HPV-related anal disease.

The high negative predictive value of HPV nondetection for the presence of cytologic abnormalities, especially among MSW (for whom predictive values were comparable to those of cervical HPV detection to detect cervical SIL among HIV-infected women) [40], suggests that HPV testing and genotyping might be useful in a staged anal cancer screening program to identify men who may not require anal cytologic examination. Use of the HPV vaccine for prevention of infection with multiple high-risk HPV types warrants investigation, especially among MSW over 26 years of age in whom the opportunities for benefit might be greater due to lower rates of prevalent anal infection.

Our study has a number of limitations. Although we enrolled relatively few MSW, the number was comparable to or exceeded the number included in previous reports, but was not sufficient to evaluate risk factors associated with incidence or clearance of HPV among MSW. Additionally, we did not have an HIV-negative cohort of men for comparison, nor did we quantify the amount of HPV (ie, number and quantification of virions)

Table 4. Univariate Associations of Anal Human Papillomavirus Infection at Baseline With Subsequent Anal Cytological Abnormalities, Male Participants, the SUN Study, 2004–2006 (n = 455)

Characteristic	Anal Cytology		RR	95% CI	*P* value
	Normal	Abnormal[a]			
MSM	**n = 162**	**n = 206**			
Any HPV (%)	148 (91)	204 (99)	3.94	1.25–12.4	<.001
Any high-risk type (%)	123 (76)	191 (93)	2.16	1.40–3.32	<.001
Only other type (%)	25 (15)	13 (6)	0.59	0.38–0.92	.013
HPV type 16 or 18 (%)	63 (39)	124 (60)	1.46	1.21–1.77	<.001
>5 types any HPV	57 (35)	125 (61)	1.57	1.30–1.90	<.001
MSW	**n = 70**	**n = 17**			
Any HPV (%)	35 (50)	17 (100)	23.8	1.48–382	<.001
Any high-risk type (%)	27 (39)	14 (82)	4.64	1.56–13.8	<.001
Only other type (%)	6 (9)	3 (18)	1.64	0.61–4.49	.173
HPV type 16 or 18 (%)	6 (9)	9 (53)	5.10	2.41–10.8	<.001
>5 types any HPV	3 (4)	7 (41)	5.06	2.53–10.1	<.001

Abbreviations: CI, confidence interval; HPV, human papillomavirus; 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; low-grade squamous intraepithelial lesions (SIL) or high-grade.

MSW: HPV detection for abnormal cytology (n = 368)

		Abnormal cytology		
		Yes	No	
HPV detected	Yes	204 a	148 b	352
	No	2 c	14 d	16
		206	162	368

Sensitivity of HPV+ for abnormal anal cytology: a / a+c = 204/206 = 99.0%
Specificity of HPV– for abnormal anal cytology: d / b+d = 14/162 = 8.6%
Positive predictive value of HPV+ for abnormal anal cytology: a / a+b = 204/352 = 58.0%
Negative predictive value of HPV– for normal predictive value: d / c+d = 14/16 = 87.5%

MSW: HPV detection for abnormal cytology (n = 87)

		Abnormal cytology		
		Yes	No	
HPV detected	Yes	17 a	35 b	52
	No	0 c	35 d	35
		17	70	87

Sensitivity of HPV+ for abnormal anal cytology: a / a+c = 17/17 = 100%
Specificity of HPV– for abnormal anal cytology: d / b+d = 35/70 = 50.0%
Positive predictive value of HPV+ for abnormal anal cytology: a / a+b = 17/52 = 32.7%
Negative predictive value of HPV– for normal predictive value: d / c+d = 35/35 = 100%

Figure 3. Performance characteristics for human papillomavirus (HPV) detection at baseline as a predictor of abnormal anal cytology, 2004–2006. Abbreviations: MSM, men who have sex with men; MSW, men who have sex with women.

detected. Anal specimens in the SUN study were collected annually, and therefore HPV incidence may be overestimated and may reflect transient carriage of HPV in some instances. Similarly, we were unable to distinguish reinfection from failure to clear. Our analysis of SIL was based on cytology and not on high-resolution anoscopy-guided tissue biopsies. We therefore cannot correlate anal cytology with detection of biopsy-proven anal SIL, which is considered to be the gold standard for determining disease severity. We also cannot determine the causal relationships between abnormal anal cytology and either the presence of HPV or the number of HPV types detected.

In conclusion, we assessed HPV prevalence, incidence, and clearance among contemporary HIV-infected MSM compared with MSW. We also examined risk factors among MSM for prevalent, incident, and cleared anal HPV infection. Early treatment of HIV infection to limit the degree of immunosuppression experienced by the patient, as well as HPV vaccination [28, 41, 42], are 2 important prevention strategies for anal SIL and cancer. HIV-infected men should also be counseled on drug use, safe sex practices, and smoking cessation to reduce modifiable risk factors for anal disease. Lastly, these data may be relevant for anal screening protocols and may support the use of HPV testing and genotyping in men at high risk for developing anal cancer.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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 institutions' ethical review board. All study participants provided written, informed consent.

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