Title

Prevalence and Incidence of Anal and Cervical High-Risk Human Papillomavirus (HPV) Types Covered by Current HPV Vaccines Among HIV-Infected Women in the SUN Study.

Journal

The Journal of infectious diseases, 217(10)

ISSN

0022-1899

Authors

Kojic, Erna Milunka
Conley, Lois
Bush, Tim
et al.

Publication Date

2018-04-01

DOI

10.1093/infdis/jiy087

Peer reviewed

The Journal of Infectious Diseases

MAJOR ARTICLE

Prevalence and Incidence of Anal and Cervical High-Risk Human Papillomavirus (HPV) Types Covered by Current HPV Vaccines Among HIV-Infected Women in the SUN Study

Erna Milunka Kojic,[1] Lois Conley,[2] Tim Bush,[2] Susan Cu-Uvin,[3] Elizabeth R. Unger,[4] Keith Henry,[5] John Hammer,[6] Gerome Escota,[7] Teresa M. Darragh,[8] Joel M. Palefsky,[8] John T. Brooks,[2] and Pragna Patel[2]

[1]Division of Infectious Diseases, Mount Sinai St Luke's and West Hospitals, New York; [2]Divisions of HIV/AIDS Prevention, Centers for Disease Control and Prevention, Atlanta, Georgia; [3]The Miriam Hospital, Providence, Rhode Island; [4]Division of High-Consequence Pathogens and Pathology, Centers for Disease Control and Prevention, Atlanta, Georgia; [5]Hennepin County Medical Center, Minneapolis, Minnesota; [6]Denver Infectious Disease Consultants, Rose Medical Center, Colorado; [7]Washington University School of Medicine, St Louis, Missouri; and [8]University of California, San Francisco

Background: Nonavalent (9v) human papilloma virus vaccine targets high-risk human papillomavirus (HR-HPV) types 16, 18, 31, 33, 45, 52, 58, and low-risk 6, 11. We examined prevalence, incidence, and clearance of anal and cervical HR-HPV in HIV-infected women.

Methods: The SUN Study enrolled 167 US women in 2004–2006. Anal and cervical specimens were collected annually for cytology and identification of 37 HPV types: 14 HR included: 9v 16, 18, 31, 33, 45, 52, 58; non-9v 35, 39, 51, 56, 59, 66, 68.

Results: Baseline characteristics of 126 women included: median age 38 years; 57% non-Hispanic black; 67% HIV RNA < 400 copies/mL; 90% CD4 counts ≥200 cells/mm^3. HPV prevalence at anus and cervix was 90% and 83%; for 9v HR-HPV types, 67% and 51%; non-9v HR-HPV, 54% and 29%, respectively. The 9v and non-9v HR-HPV incidence rates/100 person-years were similar (10.4 vs 9.5; 8.5 vs 8.3, respectively); 9v clearance rates were 42% and 61%; non-9v 46% and 59%, in anus and cervix, respectively.

Conclusions: Anal HR-HPV prevalence was higher than cervical, with lower clearance; incidence was similar. Although prevalence of non-9v HR-HPV was substantial, 9v HR-HPV types were generally more prevalent. These findings support use of nonavalent vaccine in HIV-infected women.

Keywords. HIV; HPV; nonavalent HPV vaccine prevalence; incidence; SUN Study.

Persons with human immunodeficiency virus (HIV) infection are living longer owing to effective combination antiretroviral therapy (ART), and non-acquired immune deficiency syndrome (non-AIDS)–defining conditions, including cancers, are increasingly diagnosed among them [1]. Despite the immunologic reconstitution associated with ART, the prevalence of anogenital human papillomavirus (HPV) infections and associated diseases remains high [1–4]. Persistent infection with high-risk HPV causes squamous dysplasia and cancer of the cervix, and 40%–90% of anal, vulvar, vaginal, penile, and oropharyngeal cancers [5, 6]. Of the estimated 14 million new cancers occurring in 2012 worldwide, almost 5% were attributable to HPV infection [7].

Anogenital HPV infection is multicentric, and anal HPV infection may be a reservoir causing cervical infection and vice versa [8, 9]. Several studies have shown that, among HIV-infected women, prevalence of anal HPV infection is greater than that of cervical infection [8–12], and HPV-infected women are at higher risk for HPV-associated cancers than HIV-uninfected women [13]. The North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) showed a significant, increasing trend in incidence of anal cancer of 6% per year in HIV-infected persons. The incidence of anal cancer among HIV-infected women ranged from 3.9 to 30 per 100 000 women [4, 12].

While secondary cervical cancer prevention strategies, such as cytology and HPV testing, have successfully reduced cervical cancer incidence, there is no current consensus on anal cancer prevention methods among women. Over the last few years, focus has been placed on implementing primary preventive strategies, specifically vaccine development. There are 3 HPV vaccines licensed in the United States, although currently only the nonavalent vaccine is available. The quadrivalent HPV vaccine Gardasil (Merck & Co., Inc.) was approved in June 2006 to prevent infection due to HPV types 6, 11, 16,

Received 27 November 2017; editorial decision 8 February 2018; accepted 13 February 2018; published online February 14, 2018.

Presented in part: IDWeek 2012, San Diego, CA, 17–21October 2012, abstract #36821. ID Week 2015, San Diego, CA, 7–11 October 2015, presentation #1563.

Correspondence: E. M. Kojic, MD, Mount Sinai St. Lukes/ Mount Sinai West, 1111 Amsterdam Ave, New York, NY 10025 (erna.kojic@mountsinai.org).

The Journal of Infectious Diseases® 2018;217:1544–52

DOI: 10.1093/infdis/jiy087

and 18. The bivalent HPV vaccine Cervarix (GlaxoSmithKline) was approved in October 2009 to prevent infection due to HPV types 16 and 18. In December 2014, a nonavalent HPV vaccine, Gardasil 9, was approved for prevention of infection with the 4 HPV types in the quadrivalent vaccine and an additional 5 high-risk (HR) HPV types, 31, 33, 45, 52, and 58 (9v-HPV; Merck & Co., Inc.), increasing type-specific protection from 70% up to 90% of HPV types that cause cervical cancer [14, 15]. The quadrivalent HPV vaccine is safe and immunogenic in HIV-infected persons [16, 17], and the 9v vaccine has been shown to have comparable immunogenicity rates to the quadrivalent vaccine for the 4 types found in both vaccines [18].

We examined the prevalence, incidence, and clearance of the 7 HR-HPV types covered by the nonavalent vaccine (9v HR-HPV; HPV 16, 18, 31, 33, 45, 52, 58), and the 7 HR-HPV types not covered (non-9v HR-HPV; HPV 35, 39, 51, 56, 59, 66, 68), in HIV-infected women in the 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 HIV-infected adults, including 167 women, from 7 clinics in 4 US cities, into a prospective observational cohort study. Data on anal and cervical HPV infection and cytology were available for 126 of 167 women. The study design, and data collection and management methods, have been described previously [19]. Participants were generally healthy, HIV-infected patients receiving routine outpatient care, who were either antiretroviral (ARV)-naive or whose antiretroviral experience consisted only of effective combination ART. Patient data were abstracted from medical charts, entered into an electronic database (Clinical Practice Analyst; Cerner Corporation, Vienna, VA) by trained staff, reviewed for quality, and analyzed centrally. Additional data were collected through physical examination, noninvasive imaging, testing for sexually transmitted infections (syphilis, trichomonas, and oral, rectal, and urine gonococcal and chlamydial infections), and an audio computer-assisted self-interview (ACASI). Cervical and anal samples for cytology, and HPV detection and genotyping, were collected at baseline and annually. 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.

Anal and Cervical Sample Collection and Examination

Sample collection, processing, and HPV testing have been described previously [3]. Two anal swabs were collected, the first placed into PreservCyt collection medium for preparation of a ThinPrep slide (Marlborough, MA) for cytology, and the second into Digene Specimen Transport Medium (STM, Qiagen Incorporated, Valencia, CA) for HPV testing. Cervical cytology specimens were collected, per study clinic protocol as part of each participant's routine care; only data from samples collected within 90 days of the appropriate visit were included. Cervical HPV specimens for detection and genotyping were obtained using a cytobroom or cytobrush, and transferred into PreservCyt collection medium (Hologic Incorporated, Marlborough, MA, www.thinprep.com) and were only done as part of the study.

All cytologic results were classified according to the Bethesda System terminology [20]. We defined abnormal cytology as the presence of atypical squamous cells (ASC-US or ASC-H), low-grade squamous intraepithelial lesions (LSIL), or high-grade intraepithelial lesions (HSIL). Anal cytology specimens were evaluated by a single pathologist with expertise in the interpretation of anal cytology (T.M. Darragh). Cervical cytology specimens were evaluated per local protocol. Women with abnormal cytology were referred to care per prevailing guidelines for anogenital cancer prevention. Anal and cervical STM samples for HPV detection were stored at 4°C and mailed weekly at ambient temperature to CDC, and 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, Indianapolis, IN). The 100-μL extract was stored at −20°C.

HPV Detection and Typing

The Roche HPV Linear Array research-use-only kit (Roche Diagnostics) was used following the manufacturer's protocol, except that 10 μL of extract was used in the 100 μL reaction, and hybridization and detection was automated. The assay used L1 consensus polymerase chain reaction (PCR) with biotinylated primers and type-specific hybridization detecting 37 different HPV types (14 HR: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68; 23 other: 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). Each assay batch included controls for extraction and PCR contamination, and a low-copy positive control (50 copies) for HPV 16. Results for HPV type 52 may have been ambiguous because of cross-hybridization of the HPV type 52 probe with types 33, 35, and 58. To unambiguously determine the presence of type 52 in samples with any combination of the 3 other types, an HPV type-52-specific real-time PCR assay was used [21].

Statistical Methods

Statistical analysis was performed using SAS, version 9.3 (SAS Institute, Inc., Cary, NC). We defined incident infection as detection of a HR-HPV type not found at baseline, and clearance as 2 consecutive visits when the respective HPV type was not detected. Overall clearance was determined by the percentage of women who cleared all prevalent HPV types from an anatomic site, while individual rates were the clearance of each individual type. We calculated incidence rates per 100

person-years with associated 95% confidence intervals (CI). We used McNemar's test for correlated proportions to assess differences in the detection of HPV, and the various types of HPV, identified from paired anal and cervical specimens from the baseline visit.

Ethical Considerations

The investigation followed the guidelines of the United States 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.

RESULTS

We included data from 126 (75%) of the 167 female SUN Study participants; median follow-up was 59.4 months with a total of 472 person-years of follow up. The remainder were excluded due to history of hysterectomy (n = 21), unsatisfactory HPV or cytology sample from either the anus or cervix (n = 17, 10 missing both anal and cervical data; 3 cervical only; and 4 anal only), or incomplete ACASI data (n = 3). The excluded women had similar HPV prevalences and demographics. At baseline, among the 126 women (median age 38 years), 57% were non-Hispanic black, 32% non-Hispanic white, 11% Hispanic or other race/ethnicity, and 52% current cigarette smokers. Thirteen percent were ARV-naive, 67% had a plasma HIV RNA viral load < 400 copies/mL, and median enrollment and nadir CD4 cell counts were 402 and 203 cells/mm^3, respectively. Thirty-six percent reported no sexual partners in the 6 months prior to enrollment, and only 2% reported having ≥4 sexual partners during the same period; 40% reported ever having anal sex (Table 1) [19].

Table 1. Selected Baseline Characteristics, Female Participants, the SUN Study, 2004–2006 (n = 126)

Characteristics	Value[a]
Demographics	
Median age at baseline, years (IQR)	38 (31–44)
Race/ethnicity, n (%)	
Non-Hispanic White	40 (32)
Non-Hispanic Black	72 (57)
Hispanic	9 (7)
Other	5 (4)
High school graduate[b], n (%)	91 (74)
Marital status[c], n (%)	
Currently married	23 (19)
Single	77 (62)
Separated/divorced/widowed	24 (19)
Clinical characteristics	
Antiretroviral naive, n (%)	16 (13)
HIV RNA viral load < 400 copies/mL, n (%)	85 (67)
CD4 cell count, cells/mm^3, n (%)	
<200	12 (10)
200–500	76 (60)
>500	38 (30)
Median (IQR)	402 (297–595)
Nadir CD4 cell count, cells/mm^3, n (%)	
<200	62 (49)
200–500	57 (45)
>500	7 (6)
Median (IQR)	203 (103–283)
Behavioral characteristics	
Cigarette smoking, n (%)	
Ever	83 (66)
Current	65 (52)
Ever hormonal contraceptive use, n (%)	82 (65)
Hormone replacement therapy[d], n (%)	4 (3)
Number of sexual partners in past 6 months, n (%)	
0	45 (36)
1	67 (53)
2–3	11 (9)
≥4	3 (2)
Receptive anal sex in the past 6 months[e], n (%)	12 (10)
Receptive anal sex ever, n (%)	46 (40)

Abbreviations: IQR, interquartile range; SUN, Study to Understand the Natural History of HIV/AIDS in the Era of Effective Therapy.

[a] N = 126 unless otherwise noted: [b] N = 123; [c] N = 124; [d] N = 119; [e] N = 115.

HPV Prevalence

As seen in our initial prevalence analysis [3], baseline HPV infection was more prevalent at the anus (90%) than the cervix (83%) (P = .088), including infection with both HR (79% vs 61%, respectively, P < .001) and other (81% vs 63%, respectively, P < .001) HPV types (Table 2). The prevalence did not differ significantly between women in different age groups, with different nadir or current CD4 cell counts, by number of sexual partners, or by anal sex [3].

The prevalence of 9v HR-HPV types was likewise higher in the anus than the cervix: 67% versus 51% (P = .002) and non-9v HPV types 54% and 29% (P < .001), respectively. Of the 9v types, HPV 16 (25%) and 45 (23%) were the most common types detected in the anus, whereas 16 (19%) and 58 (14%) were most common in the cervix. The most prevalent non-9v types were HPV 35 (19%) and 51 (17%) in the anus, and 39 (9%) and 66 (8%) in the cervix. The prevalence of each individual HR-HPV type is shown in Tables 2 and 3.

At baseline, 31 women (25%) had no 9v HR-HPV types in either anus or cervix; 42 (33%) had 1 or more 9v type in either only the anus or only the cervix, and 53 (42%) had 9v types in both anatomical areas concurrently (Table 4). During 5 years of follow-up, the annual point prevalence of anal 9v HR-HPV types was 43%–58%, and cervical 27%–38%, and for non-9v HR-HPV types, 28%–45% and 11%–23%, respectively (Figure 1).

HPV Incidence

In the anus and cervix, overall incidence rates for a new HR-HPV type infection, including 9v and non-9v, were 15.4 and 14.4 per 100 person-years, respectively. Both 9v and non-9v incidence rates were similar (9v: 10.4 vs 9.5 per 100 person-years) and (non-9v: 8.5 vs 8.3 per 100 person-years),

Table 2. Human Papillomavirus Types Identified in Anal and Cervical Specimens at Baseline, in Women, the SUN Study, 2004–2006 (N = 126)

	Anatomical Site				
HPV type identified	Anal n (%)	Cervical n (%)	*P* value	Anal Only n (%)	Cervical Only n (%)
Any type	113 (90)	105 (83)	.088	15 (12)	7 (6)
Any HR	100 (79)	77 (61)	<.001	31 (25)	8 (6)
Any 9v HR	84 (67)	64 (51)	.002	31 (25)	11 (9)
16	31 (25)	24 (19)	.194	18 (14)	11 (9)
18	23 (18)	7 (6)	<.001	18 (14)	2 (2)
31	19 (15)	12 (10)	.090	12 (10)	5 (4)
33	14 (11)	10 (8)	.206	7 (6)	3 (2)
45	29 (23)	11 (9)	<.001	20 (16)	2 (2)
52	27 (21)	15 (12)	.014	18 (14)	6 (5)
58	20 (16)	18 (14)	.655	11 (9)	9 (8)
Any non-9v HR	68 (54)	29 (29)	<.001	39 (31)	8 (6)
35	24 (19)	9 (7)	<.001	16 (13)	1 (1)
39	12 (10)	11 (9)	.781	7 (6)	6 (5)
51	22 (17)	7 (6)	.001	18 (14)	3 (2)
56	7 (6)	7 (6)	.739	4 (3)	5 (4)
59	14 (11)	1 (1)	<.001	13 (10)	0 (0)
66	14 (11)	10 (8)	.248	8 (6)	4 (3)
68	9 (7)	3 (2)	.034	7 (6)	1 (1)
Other type, any	102 (81)	79 (63)	<.001	32 (25)	9 (7)
6	18 (14)	9 (7)	.039	14 (11)	5 (4)
11	4 (3)	3 (3)	.564	2 (2)	1 (1)
26	3 (2)	1 (1)	.157	2 (2)	0 (0)
40	6 (5)	2 (2)	.046	4 (3)	0 (0)
42	11 (9)	8 (6)	.405	8 (6)	5 (4)
53	34 (27)	13 (10)	<.001	24 (19)	3 (2)
54	19 (15)	16 (13)	.405	8 (6)	5 (4)
55	20 (16)	4 (3)	<.001	18 (14)	2 (2)
61	27 (21)	19 (15)	.088	15 (12)	7 (6)
62	18 (14)	13 (10)	.166	9 (7)	4 (3)
64	1 (1)	0 (0)	N/A	0 (0)	1 (1)
67	7 (6)	2 (2)	.025	5 (4)	0 (0)
69	3 (3)	2 (2)	.564	2 (2)	1 (1)
70	12 (10)	10 (8)	.593	8 (6)	6 (5)
71	8 (6)	7 (6)	.655	3 (2)	2 (2)
72	8 (6)	7 (6)	.655	3 (2)	2 (2)
73	14 (11)	5 (4)	.013	11 (9)	2 (2)
81	14 (11)	14 (11)	1.00	7 (6)	7 (6)
82	9 (7)	2 (2)	.035	9 (7)	2 (2)
83	17 (13)	17 (13)	1.00	10 (8)	10 (8)
84	18 (14)	12 (10)	.134	11 (9)	5 (4)
89	16 (13)	9 (7)	.071	11 (9)	4 (3)
IS39	3 (2)	1 (1)	.157	2 (2)	0 (0)

Abbreviations: HPV, human papillomavirus; HR, high risk; SUN, Study to Understand the Natural History of HIV/AIDS in the Era of Effective Therapy.

at the anus and cervix, respectively (Table 3). Incidence rates for individual HR-HPV types did not differ significantly by anatomical site. Additionally, incidence rates specifically for HPV 16 or 18 did not differ (4.0 and 3.0 per 100 person-years, respectively).

HPV Clearance

Overall clearance of any anal HR-HPV type was 71%, and cervical HR-HPV type, 89%. Clearance rates for both 9v and non-9v types were generally lower in the anus compared with the cervix (Table 3). Clearance of any anal 9v HR-HPV types was 42%, compared with cervical, 61%. Clearance rates for anal non-9v HR-HPV were 46%, and cervical 59%. (Table 3). Though small numbers limited analyses of clearance of 1 HR type compared with 2 or more, for both 9v and non-9v HR-HPV, women having 2 or more types were less likely to clear HPV compared with those having only 1 type, both in the anus and in the cervix (Table 3).

Table 3. Prevalence, Clearance, and Incidence of HR-HPV Types in Women, SUN Study, 2004–2012

	HPV, Anus			HPV, Cervix		
	Prevalence (n = 126) No. (%)	Incidence (per 100 py)	Clearance[a] No. (%)	Prevalence (n = 126) No. (%)	Incidence (per 100 py)	Clearance[a] No. (%)
Any HR-HPV	100 (79)	15.4 (11.7–20.0)	63 (71)	77 (61)	14.4 (10.8–18.8)	54 (89)
9v HR-HPV						
16	31 (25)	2.8 (1.1–4.5)	12 (50)	24 (19)	1.8 (0.5–3.2)	12 (60)
18	23 (18)	1.6 (0.3–2.8)	10 (59)	7 (6)	1.6 (0.4–2.8)	4 (57)
31	19 (15)	2.8 (1.2–4.5)	11 (69)	12 (10)	1.9 (0.6–3.2)	5 (50)
33	14 (11)	1.2 (0.1–2.3)	6 (46)	10 (8)	1.4 (0.3–2.5)	6 (60)
45	29 (23)	1.9 (0.5–3.3)	12 (57)	11 (9)	1.2 (0.1–2.2)	6 (75)
52	27 (21)	2.9 (1.2–4.7)	8 (40)	15 (12)	3.2 (1.4–4.9)	7 (58)
58	20 (16)	1.8 (0.5–3.1)	6 (40)	18 (14)	1.0 (0.0–1.9)	9 (75)
16 or 18	45 (36)	4.0 (2.3–6.5)	16 (43)	29 (23)	3.0 (1.6–5.1)	15 (58)
Any 9v HR	84 (67)	10.4 (7.5–14.2)	27 (42)	64 (51)	9.5 (6.7–13.0)	31 (61)
1 type	33 (26)		20 (80)	39 (31)		24 (80)
2 types	27 (21)	3.1 (1.7–5.3)	5 (26)	18 (14)	1.7 (0.7–3.4)	7 (47)
3 or more types	24 (19)		2 (10)	7 (6)		0 (0)
Non-9v HR-HPV						
35	24 (19)	1.6 (0.3–2.9)	11 (55)	9 (7)	2.1 (0.7–3.4)	5 (62)
39	12 (10)	1.6 (0.4–2.8)	6 (67)	11 (9)	0.7 (0.0–1.5)	7 (87)
51	22 (17)	2.3 (0.8–3.8)	10 (59)	7 (6)	2.5 (1.0–3.9)	4 (67)
56	7 (6)	1.1 (0.1–2.1)	4 (80)	8 (6)	0.7 (0.0–1.4)	5 (100)
59	14 (11)	1.7 (0.4–3.0)	6 (50)	1 (1)	1.7 (0.5–2.9)	0 (0)
66	14 (11)	1.9 (0.6–3.3)	8 (67)	10 (8)	1.8 (0.5–3.1)	6 (75)
68	9 (7)	0.9 (0.0–1.8)	4 (80)	3 (2)	0.9 (0.0–1.7)	2 (67)
Any non-9v HR	68 (54)	8.5 (5.9–11.9)	28 (46)	37 (29)	8.3 (5.7–11.6)	20 (59)
1 type	42 (33)		21 (57)	27 (21)		16 (62)
2 types	19 (15)	2.2 (1.1–4.1)	5 (29)	8 (6)	2.2 (1.0–4.0)	3 (43)
3 or more types	7 (6)		2 (29)	2 (2)		1 (100)

Abbreviations: HPV, human papillomavirus; HR, high risk; py, person-year; SUN, Study to Understand the Natural History of HIV/AIDS in the Era of Effective Therapy; 9v, nonavalent vaccine high-risk HPV type.

[a]Overall clearance was determined by the percentage of women who cleared all HPV types from an anatomic site, while individual rates were the clearance of each individual type.

Anal and Cervical Cytology

During 5 years of follow-up, 5 women had no anal and 3 had no cervical cytology collected; the median number collected from each site was 4 (anal interquartile range [IQR] 3–5, cervical IQR 2–6). An abnormality was detected in 141 (29%) anal and 127 (26%) cervical cytologies; 63 (13%) women had both. The majority of HR-HPV types detected in both anal and cervical cytological abnormalities had both 9v and non-9v HR-HPV types, or 9v types, only; 8% of abnormal anal and 12% of abnormal cervical cytologies had no 9v HR-HPV. Specifically, most women with HSIL/ASC-H, about two-thirds, also had concurrent 9v and non-9v HPV infections (Figure 2).

DISCUSSION

In our ethnically diverse population of HIV-infected women, the prevalence of anal HR-HPV infection was higher than cervical [3], and for most HPV types, cleared more slowly. The prevalence of anal and cervical HR-HPV infection in our cohort is consistent with, or even higher than, prevalence estimates reported in other studies of HIV-infected women from different geographic areas [8, 12, 22]. Our data are consistent with other studies where HPV infection differs between anatomical compartments, possibly due to local mucosal environment, different sexual behaviors and transmission, or efficacy of the immune response to clear infection [8, 23]. As previously reported, history of anal sex was not associated with HPV prevalence [3]. Overall, the prevalence of cervical 9v HR-HPV types was much higher in our HIV-infected cohort, 51% compared with 14.1%, among a nationally representative sample of women in the National Health and Nutrition Examination Survey [24]. Although the prevalence of HR-HPV types included in the vaccine was higher in both the anus and cervix as compared with non-9v HR-HPV types, the prevalence of non-9v types was still substantial: 54% and 29% in anus and cervix, respectively. Furthermore, 23% of women in our cohort had a non-9v HR-HPV in the anus and the cervix, concurrently. The most common anal non-9v type was HPV 35, and cervical HPV 39.

The incidence rates of HR-HPV types were similar in the anus and cervix, both for 9v and non-9v types. Few studies have reported incidence rates among HIV-infected women; even

Table 4. Anal and Cervical HR-HPV in Women, SUN Study, 2004–2012 (n = 126)

	Anus Only	Cervix Only	Both Anus and Cervix	Neither Anus nor Cervix
Any HR-HPV	31 (25%)	8 (6%)	69 (55%)	18 (14%)
9v HR-HPV	31 (25%)	11 (9%)	53 (42%)	31 (25%)
Non-9v HR-HPV	39 (31%)	8 (6%)	29 (23%)	50 (40%)

Abbreviations: HPV, human papillomavirus; HR, high risk; SUN, Study to Understand the Natural History of HIV/AIDS in the Era of Effective Therapy; 9v, nonavalent vaccine high-risk HPV type.

fewer have compared rates at the anus and cervix. Incidence rates of anal and cervical HPV 16 were lower in our study than other published studies of HIV-infected persons. In a prospective study including 153 women, 168 men who have sex with men (MSM), and 69 men who have sex with women (MSW), anal HPV 16 incidence rates were 8.28 per 100 person-years (6.9 per 1000 person-months) [23] compared with 2.8 per 100 person-years in our cohort. A more recent study of 215 HIV-infected and uninfected women from India likewise showed higher rates of cervical HPV 16 and 58 infection (2.51 and 2.75 per 100 person-years, respectively) compared with 1.8 and 1.0 per 100 person-years in our cohort, although rates of other types were lower [25]. Among HIV-infected men, incidence of anal HPV 16 infection was 3.5 per 100 person-years [26] compared with 2.8 per 100 person-years in our female cohort. These differences likely reflect variation in sexual behaviors and demographics among the study populations, and varying geographic distributions of individual HPV types [24, 27]. In the HPV Infection in Men (HIM) cohort of HIV-uninfected men, lower rates of incident anal HPV infections were observed with advancing age, except rates of 9v HPV-type infections, which remained constant across the lifespan [28].

We report a HR-HPV clearance rate of 71% and 89% in anus and cervix, respectively. Clearance rates were lower in the anus than the cervix for most HR-HPV types. Anal and cervical 9v HR-HPV types had similar clearance rates compared with non-9v HR-HPV types. There are limited data about HPV clearance rates in HIV-infected women, and definitions of clearance, and HPV types included in the analyses, differ and therefore cannot be readily compared with our data [25, 29]. Among an HIV-uninfected Hawaiian cohort of 1363 women, 69% of HR-HPV infections cleared within 1 year [30, 31]. In a study including HIV-infected women, MSM, and MSW, Beachler et al reported clearance rates, using 2 negative HPV results, of 31% and 55% for prevalent and incident HPV infection, both oncogenic and nononcogenic, over a mean of 24 months; women had clearance rates similar to the MSM [23].

Our analysis shows that women with more than 1 concurrent HR-HPV type have a lower clearance rate than women with a single type, particularly in the anus, where the clearance rate of multitype HR-HPV infections was about half that of

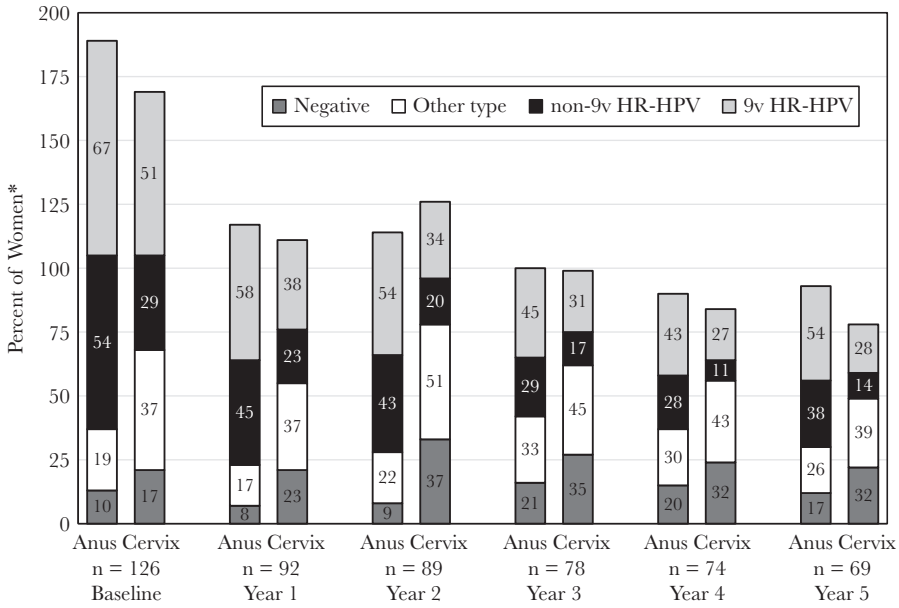

Figure 1. Human papillomavirus (HPV) point prevalence in women, in the anus and cervix, by year of follow-up, SUN Study, 2004–2012. Abbreviations: HR, high risk; 9v HR-HPV, nonavalent vaccine high-risk HPV type; non-9v HR-HPV, HR-HPV type not included in the nonavalent vaccine; SUN, Study to Understand the Natural History of HIV/AIDS in the Era of Effective Therapy. *HPV categories are not mutually exclusive.

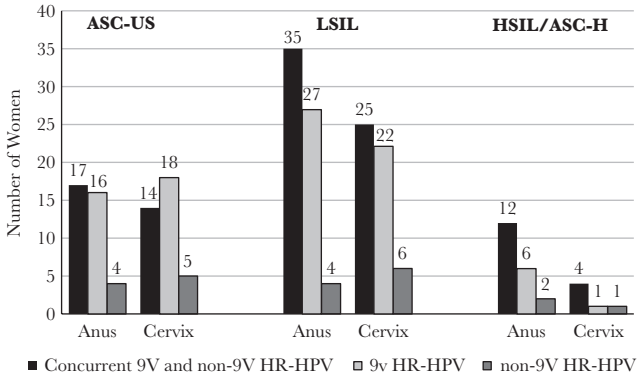

Figure 2. Cumulative cytologic findings in anus and cervix in women, by 9v HR-HPV status, during 5 years of follow-up, SUN Study, 2004–2012 (n = 126). Abbreviations: ASC-H, atypical squamous cells, potentially high-risk squamous intraepithelial lesion; ASC-US, atypical squamous cells of unknown significance; HR, high risk; HPV, human papillomavirus; HSIL, high-risk squamous intraepithelial lesion; LSIL, low-risk squamous intraepithelial lesion; SUN, Study to Understand the Natural History of HIV/AIDS in the Era of Effective Therapy; 9v, nonavalent vaccine high-risk HPV type.

single HR-HPV type infections. The dynamics of multitype HPV infection in the cervix have been examined, with some studies reporting the acquisition of multiple HPV types exceeded that expected by chance [30]. If acquisition of multiple HPV types is biologically favored, then clearance of multitype infections could be more difficult. Furthermore, there seems to be an association between incident HPV infections between the 2 anatomical sites. Goodman et al found that among generally healthy women, presence of multiple HPV types in the cervix was associated with a 2.5-fold increased likelihood of subsequent anal infection [30]. These dynamics may have implications for vaccine effectiveness. Conceivably, the vaccine could increase clearance rates of HPV types by decreasing the number of concurrent HPV types in either the anus or cervix. The multifactorial mechanisms of HPV incidence and clearance have been studied by others [32, 33].

Most abnormal cytologies, including HSIL and ASC-H, had 9v HR-HPV types detected, either alone or with non-9v HR types, but 8% of abnormal anal and 12% of abnormal cervical cytologies had only non-9v HR-HPV types identified. It is not clear from these data what role, if any, these types may have in causing high-grade abnormalities leading to cancer; the HPV types covered by the current nonavalent vaccine have a higher likelihood of causing cytological abnormalities than other HR types [27]. Because infection with multiple, concurrent HPV types appears to decrease the likelihood of HPV clearance, the fact that a significant number of women had both 9v and non-9v HR types concurrently might lead to more persistent infection and a greater likelihood of developing abnormal anogenital cytology. Most importantly, this was noted among women with HSIL/ASC-H where the potential for disease progression is greatest [34].

Our study had a number of limitations. We did not have an HIV-uninfected cohort of women for comparison, nor quantified amounts of HPV detected. Also, due to limited sample size, we were unable to evaluate risk factors for HPV acquisition in multivariable analyses. Furthermore, we did not have histology data to confirm the presence of abnormal cytology findings, and may have underestimated the number of abnormalities. We did not collect data on treatment of abnormal anal or cervical cytology. Women with cervical abnormalities were treated as per standards of care and those with anal abnormalities were monitored with repeat sampling. Strengths of our study include annual testing for 37 HPV types and relatively long follow-up, up to 5 years, to assess incidence and clearance.

In summary, we found that the prevalence of anal HR-HPV infection was higher than cervical and, for most HPV types, cleared more slowly. The HR-HPV types covered by the nonavalent HPV vaccine had similar clearance rates to HR-HPV types not included, and women infected with multiple anogenital HR-HPV types had lower rates of clearance than women infected with only 1 type. The majority of HR-HPV types we detected in abnormal anogenital cytologies were types included in the 9v vaccine, and because its use might impact the clearance rates of HR-HPV by decreasing the overall burden of anogenital HPV infection in HIV-infected women, these findings further support use of the nonavalent vaccine.

Notes

Acknowledgments. We thank the staff at each of the SUN Study sites and collaborating laboratories, and most importantly the SUN study participants, who have devoted their time and effort to this research project.

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.

Financial support. This work was supported by Centers for Disease Control and Prevention (grant numbers: 200-2002-00610, 200-2002-00611, 200-2002-00612, 200-2002-00613, 200-2007-23633, 200-2007-23634, 200-2007-23635, and 200-2007-23636).

Potential conflicts of interest. T. M. D. research support (supplies) from Hologic, consulting fees from Roche, BD, TheVax, and Antiva. K. H. has the following disclosures: Janssen, Merck, GSK/ViiV, and Gilead. 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.

References

1. Patel P, Hanson DL, Sullivan PS, et al. Incidence of types of cancer among HIV-infected persons compared with the general population in the United States, 1992–2003. Ann Intern Med **2008**; 148:728–36.
2. Denny LA, Franceschi S, de Sanjosé S, Heard I, Moscicki AB, Palefsky J. Human papillomavirus, human

immunodeficiency virus and immunosuppression. Vaccine **2012**; 30 (Suppl 5):F168–74.
3. Kojic EM, Cu-Uvin S, Conley L, et al. Human papillomavirus infection and cytologic abnormalities of the anus and cervix among HIV-infected women in the study to understand the natural history of HIV/AIDS in the era of effective therapy (the SUN study). Sex Transm Dis **2011**; 38:253–9.
4. Silverberg MJ, Lau B, Achenbach CJ, et al.; North American AIDS Cohort Collaboration on Research and Design of the International Epidemiologic Databases to Evaluate AIDS. Cumulative incidence of cancer among persons with HIV in North America: a cohort study. Ann Intern Med **2015**; 163:507–18.
5. Bosch FX, Broker TR, Forman D, et al.; authors of ICO Monograph Comprehensive Control of HPV Infections and Related Diseases Vaccine Volume 30, Supplement 5, 2012. Comprehensive control of human papillomavirus infections and related diseases. Vaccine **2013**; 31 (Suppl 7):H1–31.
6. Parkin DM. The global health burden of infection-associated cancers in the year 2002. Int J Cancer **2006**; 118:3030–44.
7. Plummer M, de Martel C, Vignat J, Ferlay J, Bray F, Franceschi S. Global burden of cancers attributable to infections in 2012: a synthetic analysis. Lancet Glob Health **2016**; 4:e609–16.
8. Hessol NA, Holly EA, Efird JT, et al. Concomitant anal and cervical human papillomavirusV infections and intraepithelial neoplasia in HIV-infected and uninfected women. AIDS **2013**; 27:1743–51.
9. Palefsky JM, Holly EA, Ralston ML, Da Costa M, Greenblatt RM. Prevalence and risk factors for anal human papillomavirus infection in human immunodeficiency virus (HIV)-positive and high-risk HIV-negative women. J Infect Dis **2001**; 183:383–91.
10. Baranoski AS, Tandon R, Weinberg J, Huang FF, Stier EA. Risk factors for abnormal anal cytology over time in HIV-infected women. Am J Obstet Gynecol **2012**; 207:107 e1–8.
11. Gonçalves MA, Randi G, Arslan A, et al. HPV type infection in different anogenital sites among HIV-positive Brazilian women. Infect Agent Cancer **2008**; 3:5.
12. Stier EA, Sebring MC, Mendez AE, Ba FS, Trimble DD, Chiao EY. Prevalence of anal human papillomavirus infection and anal HPV-related disorders in women: a systematic review. Am J Obstet Gynecol **2015**; 213:278–309.
13. Choudhury SA, Choudhury NA, Humphrey AD, et al. Higher prevalence of human papillomavirus-related cervical precancerous abnormalities in HIV-infected compared to HIV-uninfected women. J Natl Med Assoc **2016**; 108:19–23.
14. de Sanjose S, Quint WG, Alemany L, et al.; Retrospective International Survey and HPV Time Trends Study Group. Human papillomavirus genotype attribution in invasive cervical cancer: a retrospective cross-sectional worldwide study. Lancet Oncol **2010**; 11:1048–56.
15. Hartwig S, St Guily JL, Dominiak-Felden G, Alemany L, de Sanjosé S. Estimation of the overall burden of cancers, precancerous lesions, and genital warts attributable to 9-valent HPV vaccine types in women and men in Europe. Infect Agent Cancer **2017**; 12:19.
16. Kojic EM, Kang M, Cespedes MS, et al. Immunogenicity and safety of the quadrivalent human papillomavirus vaccine in HIV-1-infected women. Clin Infect Dis **2014**; 59:127–35.
17. Wilkin T, Lee JY, Lensing SY, et al. Safety and immunogenicity of the quadrivalent human papillomavirus vaccine in HIV-1-infected men. J Infect Dis **2010**; 202:1246–53.
18. Joura EA, Giuliano AR, Iversen OE, et al.; Broad Spectrum HPV Vaccine Study. A 9-valent HPV vaccine against infection and intraepithelial neoplasia in women. N Engl J Med **2015**; 372:711–23.
19. Vellozzi C, Brooks JT, Bush TJ, et al.; SUN Study Investigators. The study to understand the natural history of HIV and AIDS in the era of effective therapy (SUN Study). Am J Epidemiol **2009**; 169:642–52.
20. Solomon D, Davey D, Kurman R, et al. The 2001 Bethesda system: terminology for reporting results of cervical cytology. JAMA **2002**; 287:2114–9.
21. Onyekwuluje JM, Steinau M, Swan DC, Unger ER. A real-time PCR assay for HPV52 detection and viral load quantification. Clin Lab **2012**; 58:61–6.
22. Heard I, Poizot-Martin I, Potard V, et al.; ANRS-C017 VIHGY Study Group. Prevalence of and risk factors for anal oncogenic human papillomavirus infection among HIV-infected women in France in the combination antiretroviral therapy era. J Infect Dis **2016**; 213:1455–61.
23. Beachler DC, D'Souza G, Sugar EA, Xiao W, Gillison ML. Natural history of anal vs oral HPV infection in HIV-infected men and women. J Infect Dis **2013**; 208:330–9.
24. Liu G, Unger ER, Hariri S, Steinau M, Markowitz LE. Prevalence of 9-valent human papillomavirus types by race/ethnicity in the prevaccine era, United States, 2003–2006. Sex Transm Dis **2016**; 43:633–6.
25. Mane A, Sahasrabuddhe VV, Nirmalkar A, et al. Rates and determinants of incidence and clearance of cervical HPV genotypes among HIV-seropositive women in Pune, India. J Clin Virol **2017**; 88:26–32.
26. Hernandez AL, Efird JT, Holly EA, Berry JM, Jay N, Palefsky JM. Incidence of and risk factors for type-specific anal human papillomavirus infection among HIV-positive MSM. AIDS **2014**; 28:1341–9.
27. Hariri S, Unger ER, Schafer S, et al.; HPV-IMPACT Working Group. HPV type attribution in high-grade cervical lesions: assessing the potential benefits of vaccines in a population-based evaluation in the United States. Cancer Epidemiol Biomarkers Prev **2015**; 24:393–9.
28. Ingles DJ, Lin HY, Fulp WJ, et al. An analysis of HPV infection incidence and clearance by genotype and age in men:

The HPV Infection in Men (HIM) Study. Papillomavirus Res **2015**; 1:126–35.
29. Jalil EM, Bastos FI, Melli PP, et al. HPV clearance in postpartum period of HIV-positive and negative women: a prospective follow-up study. BMC Infect Dis **2013**; 13:564.
30. Goodman MT, McDuffie K, Hernandez BY, et al. The influence of multiple human papillomavirus types on the risk of genotype-concordant incident infections of the anus and cervix: the Hawaii HPV cohort study. J Infect Dis **2011**; 203:335–40.
31. Moscicki AB, Darragh TM, Berry-Lawhorn JM, et al. Screening for anal cancer in women. J Low Genit Tract Dis **2015**; 19:S27–42.
32. Sudenga SL, Wiener HW, King CC, et al. Dense genotyping of immune-related loci identifies variants associated with clearance of HPV among HIV-positive women in the HIV epidemiology research study (HERS). PLoS One **2014**; 9:e99109.
33. Syrjänen K. Mechanisms and predictors of high-risk human papillomavirus (HPV) clearance in the uterine cervix. Eur J Gynaecol Oncol **2007**; 28:337–51.
34. Conley LJ, Bush TJ, Darragh TM, et al.; SUN Study Group. Incidence and predictors of abnormal anal cytology findings among HIV-infected adults receiving contemporary antiretroviral therapy. J Infect Dis **2016**; 213:351–60.