What Drives the Number of High-Risk Human Papillomavirus Types in the Anal Canal in HIV-Positive Men Who Have Sex With Men?

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We estimated the effect of sexual behavior, age, and immunodeficiency on the number of high-risk human papillomavirus (HR-HPV) types in the anal canal among human immunodeficiency virus–positive men who have sex with men (MSM). Anal samples were genotyped with the Linear Array HPV Genotyping Test, and risk factors were investigated with Poisson regression. Of 586 MSM, 69% were Spanish, and 25.6% were Latin American; the median age was 34.9 years (interquartile range [IQR], 30.1–40.8). The median number of recent sex partners was 6 (IQR, 2–24 sex partners), and the median $CD4^+$ T-cell count was 531.5 cells/mm^3 (IQR, 403–701 cells/mm^3). The prevalence of any and multiple HR-HPV infections was 83.4% and 60.5%, respectively. The most common types were HPV-16 (42%), HPV-51 (24%), HPV-39 (23.7%), and HPV-59 (23.5%). Age had a statistically significant, nonlinear association with the number of types, with the highest number detected around 35 years of age ($P < .001$). The number of recent sex partners had a statistically significant, fairly linear association on the log scale ($P = .033$). The high prevalence of HR-HPV types is associated with recent sexual behavior and age.

Keywords. HR-HPV; HIV; MSMS; sexual behavior; anal cancer.

Infection with high-risk human papillomavirus (HR-HPV) among human immunodeficiency virus (HIV)–positive men who have sex with men (MSM) is extremely common [1–5]. Around 90% of HIV-positive MSM are coinfected with HR-HPV [1–5], a prevalence that is considerably higher than that among HIV-negative MSM [2, 6, 7]. Furthermore, the prevalence of multiple HR-HPV types among HIV-positive MSM has also been reported to be very high, at nearly 60% [2, 7], which is important because infection with multiple HR-HPV types is associated with a higher prevalence of anal intraepithelial neoplasia in this population [8–11].

Infection with HR-HPV types is a necessary cause of anal carcinoma, an emerging tumor whose incidence is increasing among MSM, particularly those infected with HIV [12–19]. Anal carcinoma is considered an opportunistic tumor, although it is not part of the AIDS case definition, in contrast with cervical carcinoma, which became an AIDS-defining condition in 1993 [20].

The very high prevalence of infection with multiple HR-HPV types among HIV-positive MSM could be driven by an increased persistence of HR-HPV infections due to compromised immunity and/or to a high incidence of new infections driven by sexual behavior, but to date, this has not been established. To address this question, we investigated the effect of self-reported past and current sexual behavior, age, and immunodeficiency on the number of baseline HR-HPV types in the anal canal in HIV-positive MSM.

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METHODS

CoRIS-HPV is a cohort study within CoRIS, the cohort of the Spanish Network of Excellence on HIV/AIDS Research. CoRIS is an open and multicenter cohort established in January 2004 that consists of adult patients with confirmed HIV infection who were naive to combined antiretroviral therapy (cART) at study entry. Patients are followed periodically according to routine clinical practice, usually every 4 months. Ethical approval and signed informed consent were obtained from each CoIRIS participant [21]. CoRIS-HPV was set up in January 2007 to study the epidemiology of HR-HPV coinfection in 12 of the 28 sites that contribute data to CoRIS. Study subjects are informed about the nature of the study and are required to provide written informed consent specific to CoRIS-HPV, in addition to the consent for the main CoRIS study.

Specific ethical approval for this study has been obtained, as well (ISCIII Ethical Comite reference number PI-43). Besides the variables collected in CoRIS, subjects are requested to answer a questionnaire on sexual behavior (age at first sexual intercourse; lifetime number of sex partners; number of sex partners in the past 12 months; and frequency of unsafe sex, measured by the frequency of condom use during anal intercourse in the past 12 months), history of genital warts, and smoking history. Anal samples are processed for HR-HPV DNA detection and cytological analyses.

We restrict this article to the analysis of baseline data, which were obtained at cohort entry. The outcome variable for current analyses was the number of HR-HPV types at baseline. Separate analyses for single HPV-16 and HPV-18 infections were also performed. The variables capturing self-reported past sexual behavior were age at first sexual intercourse and lifetime number of sex partners, and variables for current sexual behavior were number of sex partners in the past 12 months and having had unsafe sex. The variable capturing immunodeficiency was $CD4^+$ T-cell count at baseline (ie,within 6 months of collection of the HR-HPV anal sample). The following variables were conceptualized as potential confounders for the relation between age, sexual behavior, and immune status and the outcome: geographic origin (categorized as Europe, Latin-America, and other), education level (categorized as none/primary, secondary, and university), and smoking history (categorized as current smoker, past smoker, and never smoker).

HPV DNA Detection and Genotyping

Samples were collected with a citobrush and placed in 1 mL of specimen transport medium (Qiagen, Gaithersburg, MD), sent to the Retroviruses and Papillomavirus Unit of the National Center for Microbiology in Madrid, and stored at −20°C until required for testing. Anal HR-HPV infection was genotyped using polymerase chain reaction (PCR) amplification, followed by reverse line blot hybridization, using the Linear Array HPV Genotyping test (Roche Molecular Systems, Branchburg, NJ). DNA was extracted from a 200-μL aliquot of the original anal samples, using an automatic DNA extractor (Biorobot M48 Robotic Workstation, Qiagen). For quality control, each extraction run included 10 samples, 1 negative control (water of PCR quality) and 4 positive controls (SiHa cells infected with HPV 16). The results were considered satisfactory if there were a low and high B-globin levels or if HPV was detectable and the controls results for the run were valid. HPV-16, -18, -31, -33, -35, -39, -45, -51, -52, -56, -58, -59 and -68 were considered as HR-HPV types using the Munoz et al 2003 classification [22].

Statistical Analysis

We present descriptive data on overall HR-HPV prevalence and number of HR-HPV types by covariate categories. For every covariate, we present the *P* value for its effect on HR-HPV prevalence and number of HR-HPV types, based on univariable logistic regression models for overall HR-HPV prevalence and univariable Poisson regression models for the number of HR-HPV types.

We used multivariable Poisson regression to establish the effect of exposure variables on the number of HR-HPV infections. We considered past and current sexual behavior, current age, and immunodeficiency as the main potential causes for the increased number of HR-HPV and treated the previously described variables as confounders. The number of sex partners had a very skewed distribution, so these values were transformed to the logarithmic scale. Similarly, $CD4^+$ T-cell count was transformed to a square root scale, and HIV load was transformed to a logarithmic scale. We also extended the model with an interaction between $CD4^+$ T-cell count and 3 variables: (1) the number of sex partners in the past 12 months, (2) unsafe anal intercourse, and (3) age at baseline. First, missing values were imputed using the MICE (multiple imputation by chained equations) technique [23]. This was based on a model that, besides the variables in Table 1, also included information on number of cigarettes smoked per day, history of vaginal sex, and results of anal cytology (either conventional or liquid). The effect of all continuous variables was allowed to vary smoothly by using natural cubic splines [24]. We also fit a negative binomial regression model, and results of the parameter estimates did not change, although the overall fit of the model was better. The R statistical computing environment was used for the analyses [25].

RESULTS

The study included 586 HIV-positive MSM, of whom 405 (69%) were Spanish. The median age was 34.9 years (interquartile range [IQR], 30.1–40.8 years), the median age at first sexual intercourse was 17 years (IQR, 15–18 years), the median lifetime number of sex partners was 100 (IQR, 40–300

Table 1. Descriptive Baseline Characteristics of 586 Human Immunodeficiency Virus–Positive Men Who Have Sex With Men, Overall and High-Risk Human Papillomavirus (HR-HPV) Positivity, and Association With the Number of HR-HPV Types Detected

Variable	All MSM, No. (%) (n = 586)	HR-HPV–Positive MSM, No. (%) (n = 489)	P[a]	HR-HPV Types Detected, No., Mean	P[a]
Age , y					
≤30	178 (30.4)	148 (83.2)	.05	2.10	<.001
31–35	152 (26)	131 (86.2)		2.47	
36–41	128 (22)	108 (84.4)		2.24	
≥42	128 (22)	102 (79.7)		1.81	
Geographic origin					
Europe	417 (71.2)	358 (86)	.69	2.10	.20
Latin America	150 (25.6)	130 (86.7)		2.35	
Other	19 (3.2)	17 (89.5)		2.21	
Education level					
None/primary	100 (17)	86 (84)	.98	2.40	.16
Secondary	240 (41)	204 (83.3)		2.06	
University	238 (40.6)	208 (83.2)		2.17	
Unknown	8 (1.4)	7 (87.5)		2.00	
Smoking history					
Current smoker	253 (43.2)	217 (85.8)	.36	2.17	.30
Past smoker	47 (8)	39 (83)		1.85	
Never smoker	270 (46)	219 (81)		2.21	
Unknown	16 (2.7)	14 (87.5)		2.13	
Age at first sexual intercourse, y					
≤14	119 (20.3)	96 (80.7)	.62	2.00	.85
15–16	135 (23)	118 (87.4)		2.42	
17–18	162 (27.7)	131 (81)		2.10	
>19	137 (23.4)	115 (84)		2.12	
Unknown	33 (5.6)	29 (88)		2.18	
Sex partners, lifetime no.					
≤40	157 (26.8)	124 (79)	.14	1.83	<.001
41–100	163 (28)	135 (83)		2.28	
101–300	87 (15)	75 (86.2)		2.49	
≥301	136 (23.2)	117 (86)		2.25	
Unknown	43 (7.4)	38 (88.4)		2.00	
Sex partners in past 12 mo, no.					
≤2	159 (27.2)	128 (80.5)	.15	1.87	<.001
3–6	120 (20.5)	95 (79.2)		2.04	
7–25	129 (22)	109 (84.5)		2.11	
≥26	132 (22.5)	119 (90.2)		2.70	
Unknown	46 (8)	38 (82.6)		2.04	
Condom use during anal intercourse in past 12 mo					
Never	196 (33.5)	165 (84.2)	.75	2.07	.63
Occasionally	235 (40)	204 (87)		2.22	
Frequently	36 (6)	32 (89)		2.36	
Always	111 (19)	90 (81)		2.15	
Unknown	8 (1.4)	6 (75)		2.14	
$CD4^+$ T-cell count, cells/mm^3					
≤200	24 (4)	21 (87.5)	.72	2.13	.65
201–350	80 (13.7)	67 (83.8)		2.24	
351–500	150 (25.6)	126 (84)		2.18	
≥501	329 (56.2)	272 (82.7)		2.14	
Unknown	3 (0.5)	3 (100)		2.33	

Table 1 Continued.

Variable	All MSM, No. (%) (n = 586)	HR-HPV–Positive MSM, No. (%) (n = 489)	P^a	HR-HPV Types Detected, No., Mean	P^a
cART use at study entry					
No	437 (74.6)	360 (82.4)	.24	2.11	.16
Yes	149 (25.4)	129 (86.6)		2.31	

Abbreviation: cART, combination antiretroviral therapy.

[a] Based on univariable logistic regression and univariable Poisson regression models.

partners), and the median number of sex partners in the preceding year was 6 (IQR, 2–24 partners). The median time since HIV diagnosis was 4.9 months (IQR, 1.4–12.7 months), and the median $CD4^+$ T-cell count and HIV load at study entry were 531.5 cells/mm^3 (IQR, 403–701 cells/mm^3) and 15 672 HIV-RNA copies/mL (IQR, 3020–46 697 copies/mL), respectively. A total of 149 participants (25%) were receiving cART.

Overall, 489 MSM were infected with HR-HPV, with a prevalence of 83.4% (95% confidence interval [CI], 80.2%–86.4%). There were no statistically significant differences in HR-HPV prevalence according to the different variables described in Table 1, except for age. Multiple infections were observed in 355 men, with a prevalence of 60.5% (95% CI, 56.5%–64.6%). The median number of HR-HPV types was 2 (range, 0–10 HR-HPV types), and the mean was 2.2. A total of 134 MSM (22.9%) had 1 HR-HPV type, 137 (23.4%) had 2 types, 95 (16.2%) had 3 types, 66 (11.3%) had 4 types, and 57 (9.7%) had >4 HR-HPV types. The most common HR-HPV types were HPV-16 (42% of MSM), HPV-51 (24%), HPV-39 (23.7%), and HPV-59 (23.5%). The mean number of HR-HPV types according to the different baseline variables is summarized in Table 1.

In the multivariable model, the overall interaction effect with $CD4^+$ T-cell count was not significant ($P = .53$). Therefore, we only present results with the interaction terms left out. The number of sex partners in the preceding year had a significant effect on the number of HR-HPV types ($P = .033$); the expected number of types increased linearly with the logarithm of the number of sex partners in the past 12 months (Figure 1). Multivariable analyses also showed that age had a very strong and nonlinear effect on the number of HR-HPV types ($P \leq .001$); the number of HR-HPV infections peaked at age 35 years, with an expected number of 2.3 for those who had 1 partner in the past year and 2.8 for those who had 50 partners in the past year (Figure 2). There was no statistically significant effect of baseline $CD4^+$ T-cell count ($P = .474$) on the number of HR-HPV types (Figure 3).

In the multivariable models for infections with HPV-16 and HPV-18 separately, none of the variables considered reached statistical significance (data not shown).

DISCUSSION

The presence of multiple HR-HPV types in the anal canal in a sample of HIV-positive MSM is very frequent and seems to be driven by recent sexual behavior and age. There is a strong nonlinear association between the number of HR-HPV types and age, with a peak in the mid-thirties, and a positive association between the number of HR-HPV types and the number of recent sex partners.

The high prevalences of HR-HPV and multiple infections found in this study (83.4% and 60.5%, respectively) are consistent with previous reports from studies conducted in Canada, the United States, and Europe [1–5]. The most common type found in our study, HPV-16, is also the most common in all

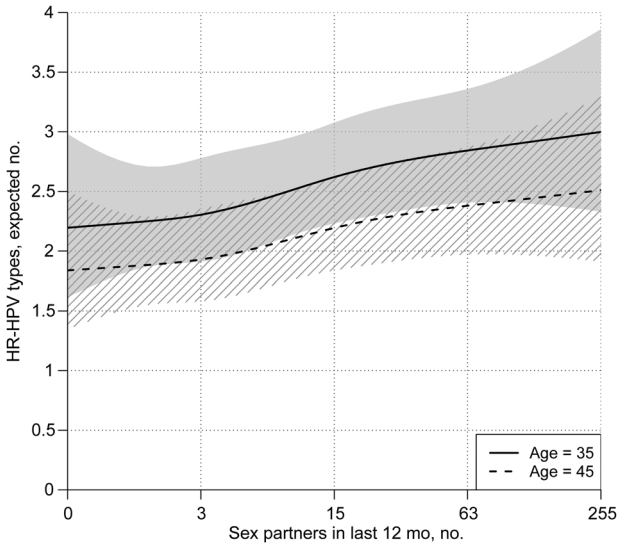

Figure 1. Expected number of high-risk human papillomavirus (HR-HPV) types, according to the number of sex partners in the past 12 months, among men aged 35 and 45 years. The analysis was adjusted for reference values of the other variables ($CD4^+$ T-cell count, ≥501 cells/mm^3; age at first sexual intercourse, 17 years; condom use during anal intercourse in past 12 months, occasionally; smoking history, never; geographic origin, Europe; and education level, university). Shaded regions are 95% confidence intervals.

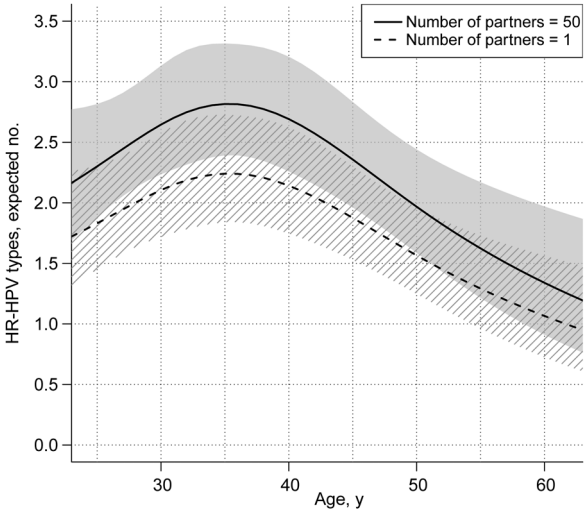

Figure 2. Expected number of high-risk human papillomavirus (HR-HPV) types, according to age, among men with 1 and 50 sex partners in the past 12 months. The analysis was adjusted for reference values of the other variables ($CD4^+$ T-cell count, ≥501 cells/mm^3; age at first sexual intercourse, 17 years; condom use during anal intercourse in past 12 months, occasionally; smoking history, never; geographic origin, Europe; and education level, university).

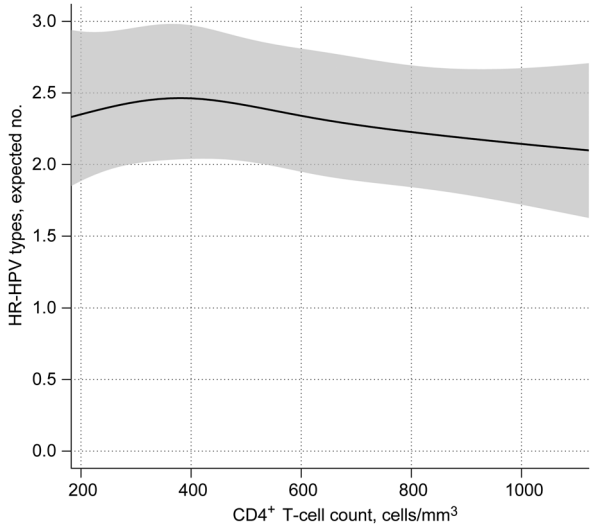

Figure 3. Expected number of high-risk human papillomavirus (HR-HPV) types, according to $CD4^+$ T-cell count. The analysis was adjusted for reference values of the other variables (age, 35 years; number of sex partners in past 12 months, 6; age at first sexual intercourse, 17 years; condom use during anal intercourse in past 12 months, occasionally; smoking history, never; geographic origin, Europe; and education level, university).

worldwide reports [1, 2, 4, 26] and is included in the vaccine licenced for the prevention of anal carcinoma in HIV-negative population [27]. We have shown that recent sexual behavior, measured by the number of sex partners in the past year, is a strong risk factor for the number of HR-HPV types. Nitray et al have also reported recent sexual behavior to be a risk factor for HR-HPV in HIV-negative MSM [28]. Similar to other publications, we failed to elicit a relationship with immunodeficiency, as measured by $CD4^+$ T-cell count [29, 30]. We also looked for effect modification and did not find it. The high burden of anal HR-HPV infection among MSM is no surprise given that HPV is sexually transmitted, but its apparent independence from the host immunological status is surprising given that anal carcinoma is an opportunistic tumor, that cervical carcinoma is an AIDS-defining condition [20], and that the HR-HPV prevalence in cervix has an inverse association with $CD4^+$ T-cell count [31–33]. The lack of variability in the $CD4^+$ T-cell count in our sample, with the majority of MSM having high values, could account for the lack of observed associations. Therefore, we conclude that, in the early stages of HIV infection, when immunity is well preserved, the higher prevalence found in HIV-positive MSM is related to recent sexual behavior. Follow-up of this cohort will allow us to explore whether the decline in $CD4^+$ T-cell count, together with other factors, such as HR-HPV type, number of HR-HPV types, age, and ongoing high-risk sexual behavior, has a role in persistence of HR-HPV infection.

As far as we know, this is the first study to describe the shape of the relationship between age and the number of HR-HPV types in HIV-positive MSM. We have identified a nonlinear association, which has a different shape from the age-specific curves of the HR-HPV prevalence among HIV-negative MSM, among whom an equal prevalence across all age groups has been reported [6]. The age-specific curve for the prevalence of HR-HPV in our sample was virtually identical for that of the number of HR-HPV types (data not shown). A number of potential explanations for these differences can be put forward. Subjects in our cohort were slightly younger than those in EXPLORE study [6] and were infected with HIV, and our results were adjusted for sexual behavior variables. However, it is likely that there is residual confounding by ongoing exposure through unaccounted sexual behavior. Our study has a large sample size, compared with that of most related publications. Recall bias associated with the number of partners is a limitation of most sexual behavior studies, and to minimize this we asked for the number of recent sex partners. Furthermore, we lacked information on whether unprotected anal sex was receptive. These analyses, as well as the study design, did not allow differentiation between recent and past HR-HPV infections, although follow-up of the cohort will. Nevertheless, the fact that the number of types is associated with recent sexual behavior supports the hypothesis that a large number of these infections are also recent.

This study contributes to the increasing body of knowledge that highlights the burden of anal HPV-associated disease and

the need to implement primary and secondary prevention interventions. Our findings have implications for clinical and public health practice since these data underscore the potential impact of prophylactic HR-HPV vaccines among HIV-positive MSM, given that, soon after HIV diagnosis, the proportion already infected with at least 1 of the 2 HR-HPV types contained in the vaccines is very high. From a preventive point of view, these data support the need to implement anal carcinoma screening programs in this population.

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Notes

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Potential conflicts of interest. All authors: No reported conflicts.

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.

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