

High Prevalence of Anal Human Papillomavirus Infection and Anal Cancer Precursors among HIV-Infected Persons in the Absence of Anal Intercourse

Christophe Piketty, MD; Teresa M. Darragh, MD; Maria Da Costa, MSc; Patrick Bruneval, MD; Isabelle Heard, MD; Michel D. Kazatchkine, MD, PhD; and Joel M. Palefsky, MD

Background: Anal cancer and its precursor lesion, anal squamous intraepithelial lesions (SILs), are associated with human papillomavirus (HPV) infection. Anal HPV infection and anal SIL are common in HIV-positive men who have sex with men; receptive anal intercourse is presumed to be the mode of acquisition of HPV.

Objective: To assess the prevalence and risk factors for anal HPV infection and anal SIL in HIV-positive men with no history of anal intercourse.

Design: Cross-sectional study.

Setting: Hôpital Européen Georges Pompidou outpatient clinic, Paris, France.

Patients: 118 HIV-infected men.

Measurements: 50 HIV-positive heterosexual male injection drug users with no history of anal intercourse and 67 HIV-infected men who had sex with men were evaluated by using anal cytologic, anal histologic, and anal HPV DNA testing.

Results: 23 of the 50 heterosexual injection drug users (46%) had anal HPV infection. Low-grade SIL (LSIL) was found in 8 patients (16%) and high-grade SIL (HSIL) in 9 patients (18%).

Among the 67 men who had sex with men, anal HPV infection was found in 57 patients (85%), LSIL in 33 patients (49%), and HSIL in 12 patients (18%). In univariate analysis, risk factors for abnormal anal cytologic or histologic findings in injection drug users included CD4⁺ cell counts less than 250 × 10⁶ cells/L (odds ratio, 5.7 [95% CI, 1.6 to 20.4]), plasma HIV RNA viral load greater than 1.7 log copies/mL (odds ratio, 8.9 [CI, 1.1 to 76.0]), previous AIDS-defining event (odds ratio, 4.3 [CI, 1.2 to 15.6]), and anal HPV detection (odds ratio, 5.7 [CI, 1.6 to 20.4]). Risk factors among men who had sex with men included having more than 10 lifetime receptive anal intercourse episodes (odds ratio, 5.6 [CI, 1.6 to 19.8]) and anal HPV detection (odds ratio, 8.7 [CI, 1.9 to 39.0]).

Conclusions: Anal HPV infection and anal SIL may be acquired in the absence of anal intercourse in HIV-positive men. The prevalence of HSIL is high among HIV-positive injection drug users. All HIV-positive men with CD4⁺ cell counts less than 500 × 10⁶ cells/L, regardless of history of anal intercourse, should be considered for anal cytologic screening; however, additional studies are needed to determine the efficacy of this procedure to prevent anal cancer in these populations.

Ann Intern Med. 2003;133:453-459.

www.annals.org

For author affiliations, see end of text.

The incidence of anal cancer among men with a history of receptive anal intercourse before the HIV epidemic was several times higher than the current rate of cervical cancer in women in the United States; the incidence of anal cancer is estimated to be as high as 35 per 100 000 in this population (1, 2). Anal cancer is associated with human papillomavirus (HPV) infection (3, 4). Earlier studies of the risk for anal cancer in HIV-negative populations showed that a history of receptive anal intercourse was an important risk factor (2, 5), presumably because it increased the risk for acquiring anal HPV infection.

Both anal squamous intraepithelial lesions (SILs) and anal HPV infection are more common in HIV-positive than in HIV-negative men who have sex with men (6–13). Recent studies estimated that the incidence of anal cancer was twofold higher in HIV-infected than in HIV-negative men who had sex with men (14, 15); in addition, the relative risk for developing anal cancer among HIV-positive men was 37-fold higher than in the general population (16). Human immunodeficiency virus–positive men who had sex with men were at 60-fold higher risk. Human immunodeficiency virus–positive injection drug users were also at increased risk (6-fold), although less so than the HIV-positive men who had sex with men. In HIV-positive

men who have sex with men, it is difficult to ascertain the role of anal intercourse as a risk factor for anal HPV infection or anal SIL, given the high prevalence of this behavior in this population. Immunosuppression probably plays a role, as indicated in studies showing an association between anal SIL and low CD4⁺ cell counts (6, 10, 13). In addition, evidence shows that the risk for anal SIL is increased in renal allograft recipients in the absence of receptive anal intercourse (17–19).

Cervical cytologic screening to detect cervical high-grade SIL (HSIL) followed by treatment of the lesions substantially reduces the incidence of cervical cancer. Studies of anal cytologic screening to determine whether the incidence of anal cancer can similarly be reduced have not yet been done. However, according to cost–benefit modeling over a wide range of assumptions, anal cytologic screening in HIV-positive men who have sex with men has been projected to be cost-effective for preventing anal cancer (20, 21).

In this cross-sectional study, we compared the prevalence of and risk factors for abnormal anal histologic or cytologic findings in HIV-positive men who have sex with men with male HIV-positive injection drug users who reported no history of anal intercourse. This was done to

Context

Anal cancer is associated with human papillomavirus (HPV) infection and receptive anal intercourse and is more common in HIV-positive than HIV-negative homosexual men. Little is known about HPV infection and anal lesions in HIV-positive men with no history of receptive anal intercourse.

Contribution

In this cross-sectional study of HIV-positive men, 46% of 50 heterosexual men who reported no history of receptive anal intercourse had anal HPV infection and 36% had anal squamous intraepithelial lesions. Low CD4⁺ cell counts were associated with an increased risk for anal lesions.

Implications

Anal HPV infection and precancerous lesions occur without receptive anal intercourse in HIV-positive men.

—The Editors

assess the role of HIV-related immunodeficiency in detecting anal HPV infection and anal disease in the absence of anal intercourse. In addition, we sought to determine whether the prevalence of anal HPV infection and anal SIL was high enough in HIV-positive injection drug users to warrant additional studies of potential benefit from anal cytologic screening in this population.

METHODS**Study Design**

Between June 1999 and October 2000, 120 HIV-seropositive men attending the outpatient clinic of Hôpital Européen Georges Pompidou, Paris, France, were recruited in a cross-sectional study of anal HPV infection and anal SIL in HIV-seropositive men. Men were eligible for the study if they had acquired HIV through homosexual or bisexual contact or through injection drug use, were older than 18 years of age, and had absolute CD4⁺ cell counts less than 500×10^6 cells/L. Injection drug users who had sex with men were excluded from the study. The patients were recruited from a cohort of 1198 HIV-infected patients who were followed at the Clinical Immunology unit of Hôpital Européen Georges Pompidou. All patients were consecutively enrolled into the study. No eligible patient declined participation. The Ethics Review Board of Hôpital Pitié-Salpêtrière, Paris, and the Committee on Human Research of the University of California, San Francisco, approved the protocol and written informed consent documents. Patients provided signed written consent before inclusion in the study.

All men were interviewed by using a standardized, comprehensive, self-administered questionnaire that included questions on age, education status, professional ac-

tivity, tobacco use, route of HIV infection, medical history, history of sexually transmitted diseases, history of HPV-related disease, history of treatment for anal disease, drug use, age at first intercourse, total number of sexual partners, total number of receptive and insertive anal intercourse, and history of commercial sex work with men. The questionnaire was a French translation of a questionnaire used in other published studies conducted at the University of California, San Francisco (10). The questionnaires were self-administered, and the investigators were blinded to the results to better ensure patient privacy and accuracy of the data.

Cytologic and Histologic Analyses

Patients had a thorough anal examination that included insertion of a Dacron swab (Eurotubo, Rubi, Spain) for anal cytologic and HPV testing. The swab was immediately rinsed in a vial of PreservCyt fixative fluid (Cytyc Corp., Boxborough, Massachusetts). Each vial was used for HPV testing and ThinPrep cytologic screening (Cytyc Corp.). An aliquot was taken from the vial for HPV testing; slides were then prepared from the vial by using the ThinPrep 2000 processor (Cytyc Corp.). When cytologic abnormalities were found, consenting patients underwent anoscopic examination and biopsy with the use of a colposcope (22). Biopsy specimens were fixed in 10% formalin for routine histopathologic examination. Anal cytologic and histologic results were evaluated independently of each other, without knowledge of clinical status and HIV risk group of the patient or HPV results. Anal cytologic results were classified as normal, atypical squamous cell of undetermined significance (ASCUS), low-grade squamous intraepithelial lesion (LSIL), or HSIL by using the Bethesda system criteria for evaluation of cervical cytologic results. If both cytologic and histologic results were available for analysis, a patient's diagnosis was categorized as the more severe result.

Detection of Anal HPV DNA

Polymerase chain reaction (PCR) for anal HPV DNA detection was performed in a blinded fashion. To determine specimen adequacy, genomic DNA was isolated from the ThinPrep vial and amplified by using MY09/MY11 consensus HPV L1 primers as well as primers to amplify the human β -globin gene (9). After 40 amplification cycles, specimens were probed with a biotin-labeled HPV L1 consensus probe mixture. A separate membrane was probed with biotin-labeled probes for the human β -globin gene.

We performed type-specific probing for the following HPV types individually: 6; 11; 16; 18; 26; 31; 32; 33; 35; 39; 40; 45; 51; 52; 53; 54; 55; 56; 58; 59; 61; 66; 68; 69; 70; 73; Pap 155; Pap 291; AE2; and a mix containing 2, 13, 34, 42, 57, 62, 64, 67, 72, and W13B. We designated samples that were positive with the consensus probes but negative with the individual type-specific probes as having one or more "other" types.

Polymerase chain reaction can be used to discriminate

Table 1. Characteristics of the Study Sample

Variable	Men Who Have Sex with Men (n = 67)	Injection Drug Users (n = 50)	P Value*
Median age (range), y	38.5 (27–73)	38 (28–45)	0.01
Previous AIDS-defining-event, n (%)	18 (27)	15 (30)	>0.2
Antiretroviral treatment, n (%)	61 (91)	42 (84)	>0.2
Protease inhibitor treatment, n (%)	46 (69)	30 (60)	>0.2
Median duration of antiretroviral treatment (range), mo	43.4 (3.5–151.3)	49.7 (1–123.4)	>0.2
Median duration of protease inhibitor treatment (range), mo	32.2 (3.5–53.7)	31.2 (4.9–56.4)	>0.2
Median CD4 ⁺ cell count (range), × 10 ⁶ cells/L	324 (8–621)	263 (4–633)	0.01
CD4 ⁺ cell count <200 × 10 ⁶ cells/L, n (%)	13 (19)	18 (36)	0.06
Median nadir of CD4 ⁺ cell count (range), × 10 ⁶ cells/L	146 (4–500)	99 (4–378)	0.05
Median plasma HIV RNA level (range), log copies/mL	2.9 (1.7–5.8)	3.6 (1.7–5.7)	0.10
History of anogenital warts, n (%)	29 (43)	9 (18)	0.005
History of gonorrhea, syphilis, or anogenital herpes, n (%)	39 (58)	15 (30)	0.003
History of hepatitis B, n (%)	45 (67)	31 (62)	0.7
Heterosexual contact, n (%)	39 (58)	50 (100)	<0.001
Median age at first vaginal intercourse, y	18 (13–38)	15 (13–21)	<0.001
Lifetime female sexual partners, n (%)			
0	28 (42)	0	
1–4	26	2	
5–9	8	10	
10–19	3	13	
20–39	1	13	
>40	1	12	
Homosexual contact, n (%)	67 (100)	0	
Lifetime male sexual partners, n			
0	0	50	
1–4	2		
5–9	3		
10–19	6		
20–39	12		
>40	44		
Median age at first receptive anal intercourse, y	20 (12–37)	Not applicable	
Total receptive anal intercourse episodes, n			
0	0	50	
1–10	15		
11–50	16		
51–100	12		
101–200	7		
201–500	11		
501–1000	1		
>1000	5		
Smoking status, n (%)			
Current smoker	40 (60)	47 (94)	0.001
Former smoker	58 (87)	50 (100)	0.009
Drug use status, n (%)			
Current injection drug use	0	12 (24)	
Opioid maintenance treatment	0	22 (44)	
Former injection drug user	2 (3)	50 (100)	<0.001

* Fisher exact test for categorical variables and Mann–Whitney U test for continuous variables.

between low-level HPV infection and high-level HPV infection on the basis of intensity of the PCR signal on Southern blot analysis (23), which was recorded on a scale from 0 (negative) to 5. For the purpose of the analysis, a sample that was positive for more than one HPV high-risk types was categorized as the higher PCR signal from the sample.

CD4⁺ Cell Count and Plasma HIV RNA Viral Load

We used the CD4⁺ cell counts and plasma HIV RNA viral loads closest to the period within 2 months of the anal examination. The nadir CD4⁺ cell count was defined as the lowest count recorded before the study. Absolute numbers of CD4⁺ T cells were determined by standard flow cytometry. Plasma HIV RNA levels were determined by

the branched-chain DNA signal amplification assay (Quantiplex HIV-RNA, Chiron Diagnostics Corp., Emeryville, California).

Statistical Analysis

We analyzed data by using StatView 5 software (SAS Institute, Inc., Cary, North Carolina). Because most variables had skewed distribution, data are presented as median and ranges. Differences across HIV risk groups were tested with the Fisher exact test (categorical variables) and the nonparametric Mann–Whitney U test (continuous variables). Patients with HPV infection and histologic or cytologic abnormalities were compared with patients with no evidence of HPV infection or anal disease. To identify risk factors for histologic or cytologic abnormalities, the follow-

Table 2. Proportion of Anal Histologic or Cytologic Abnormalities, Stratified by HIV Risk Group*

Anal Lesion Status	Men Who Have Sex with Men (n = 67), n (%)	Injection Drug Users (n = 50), n (%)	P Value†
Normal	19 (28)	32 (64)	<0.001
Abnormal			
ASCUS	3 (5)	1 (2)	0.14
LSIL	33 (49)	8 (16)	
HSIL	12 (18)	9 (18)	
Total	67 (100)	50 (100)	

* When both cytologic and histologic results were available for analysis, a patient's diagnosis was categorized in terms of the most severe result. ASCUS = atypical squamous cells of undetermined significance; HSIL = high-grade squamous intraepithelial lesions; LSIL = low-grade squamous intraepithelial lesions.

† Fisher exact test.

ing dichotomous variables were entered into a logistic regression model: age (<35 vs. ≥35 years), age at first intercourse (<16 vs. ≥16 years), number of lifetime sexual partners (<40 vs. ≥40), number of receptive anal intercourse episodes (<10 vs. ≥10), current smoking, history of anogenital warts, history of sexually transmitted disease (including anogenital herpes, gonorrhea, and syphilis), CD4⁺ cell count less than 250 × 10⁶ cells/L, nadir CD4⁺ cell count less than 100 × 10⁶ cells/L, plasma HIV RNA viral load greater than 1.7 log copies/mL, previous AIDS-defining event, current antiretroviral treatment, current protease inhibitor treatment, presence of HPV, and presence of one or more high-risk HPV types in HPV-positive men. All significant predictive factors in univariate analysis ($P \leq 0.1$) were then entered into multivariate analysis.

Role of the Funding Sources

The funding sources had no role in the collection, analysis, or interpretation of the data or in the decision to submit the manuscript for publication.

RESULTS

Patient Characteristics

The study included 50 male HIV-1–positive injection drug users and 67 HIV-1–positive men who had sex with men. Three of the injection drug users were excluded from the study because they reported having had sex with men. Table 1 presents the characteristics of the two groups. Because the patients were followed at the clinic since they were known to be HIV positive, the median follow-up was 119.4 months (range, 1 to 187.8 months). The median CD4⁺ cell count and median nadir CD4⁺ cell count were significantly lower in the injection drug users than in the men who had sex with men (263 vs. 324 × 10⁶ cells/L [$P = 0.01$] and 99 vs. 146 × 10⁶ cells/L [$P = 0.05$], respectively), as was the proportion with a history of anogenital warts and a history of gonorrhea, syphilis, or anogenital herpes. The proportion of current smokers was significantly higher in the injection drug users than the men who had sex with men (94% vs. 60%; $P = 0.001$).

Prevalence of Anal SIL and Anal HPV Infection

Of the 117 anal cytologic samples obtained, 66 (56%) were abnormal and included 9 samples with ASCUS, 41 with LSIL, and 16 with HSIL. Anoscopy and anal biopsy of a visible lesion were performed in 46 of the patients with cytologic abnormalities. Among the 20 patients who declined anoscopy and biopsy, 13 were injection drug users and 7 were men who had sex with men. These patients did not differ from the overall study sample with respect to age, stage of HIV disease (based on the Centers for Disease Control and Prevention criteria), CD4⁺ cell count, HIV RNA level, or HPV status. Table 2 presents the results of cytologic and histologic testing. The proportion of histologic or cytologic abnormalities was higher in men who had sex with men than in injection drug users (72% vs. 36%; $P < 0.001$). The distribution of grade did not significantly differ between the two groups with anal SIL ($P = 0.14$). Although the prevalence of LSIL was threefold higher in men who had sex with men than in injection drug users (49% vs. 16%), the prevalence of HSIL did not differ between the two groups (12 of 67 men who had sex with men [18%] vs. 9 of 50 injection drug users [18%]). The median CD4⁺ cell count did not differ between injection drug users who exhibited HSIL and those who did not (235 vs. 265 × 10⁶ cells/L; $P > 0.2$). However, the mean nadir CD4⁺ cell count was significantly lower in injection drug users who exhibited HSIL than in those who did not (16 vs. 140 × 10⁶ cells/L; $P = 0.03$).

Anal HPV DNA was detected in 80 of the 117 patients (68%). One or more high-risk HPV types was present in 47 of the 80 positive samples (59%). Table 3 presents data on HPV in the two groups. Human papillomavirus was detected more often in men who had sex with men than in injection drug users (85% vs. 46%; $P < 0.001$). Of the HPV-infected men who had sex with men, 61% had infection with more than one HPV type compared with 26% of the HPV-infected injection drug users ($P = 0.006$).

Table 3. Proportion of Patients with Anal HPV Infection, Stratified by HIV Risk Group*

Variable	Men Who Have Sex with Men (n = 67), n/n (%)	Injection Drug Users (n = 50), n/n (%)	P Value†
HPV positive	57 (85)	23 (46)	<0.001
>1 HPV type	35/57 (61)	6/23 (26)	0.006
≥3 Different HPV types	25/57 (44)	2/23 (8)	0.003
≥1 High-risk HPV type	37/57 (65)	10/23 (44)	0.08
≥2 High-risk HPV types	24/37 (65)	1/10 (10)	0.003
PCR intensity of high-risk HPV types ≥2	33/37 (89)	9/10 (90)	>0.2
Low-risk HPV types only	20/57 (35)	10/23 (44)	0.08
Unidentified HPV types	6/57 (10)	6/23 (26)	>0.2

* High-risk HPV types included types 16, 18, 31, 45, 33, 35, 39, 51, 52, 56, 58, 59, 68, 70, and 73; low-risk types included types 6, 11, 26, 40, 53, 54, 55, 61, 66, Pap 155, Pap 291, and AE2. HPV = human papillomavirus; PCR = polymerase chain reaction.

† Fisher exact test.

Table 4. Risk Factors for Abnormal Anal Histologic or Cytologic Findings in HIV-Positive Men Who Have Sex with Men and HIV-Positive Injection Drug Users*

Variable	Men Who Have Sex with Men			Injection Drug Users				
	Anal Histology or Cytology		Odds Ratio (95% CI)	P Value	Anal Histology or Cytology		Odds Ratio (95% CI)	P Value
	Abnormal	Normal			Abnormal	Normal		
	n/n				n/n			
Age <35 y	12/48	7/19	0.6 (0.2–1.8)	>0.2	4/18	6/32	1.2 (0.3–5.1)	>0.2
Current smoking	28/48	12/19	0.9 (0.3–3.1)	>0.2	16/18	31/32	0.3 (0.2–3.0)	>0.2
Age at first intercourse <16 y	11/48	6/18	0.6 (0.2–1.9)	>0.2	10/18	16/32	1.2 (0.4–3.9)	>0.2
Lifetime sexual partners ≥40	34/48	12/18	1.2 (0.4–3.8)	>0.2	10/18	15/32	1.4 (0.4–4.5)	>0.2
>10 Lifetime episodes of receptive anal intercourse	42/48	10/18	5.6 (1.6–19.8)	0.007	–	–	NA	
History of anogenital warts	23/48	6/19	1.9 (0.6–6.1)	0.2	5/18	4/32	2.7 (0.6–11.7)	0.2
History of gonorrhea, syphilis, or anogenital herpes	29/48	10/19	1.4 (0.5–4.0)	>0.2	4/18	11/32	0.5 (0.1–2.1)	>0.2
CD4 ⁺ cell count <250 × 10 ⁶ cells/L	15/48	6/19	0.9 (0.3–3.1)	>0.2	13/18	10/32	5.7 (1.6–20.4)	0.007
Nadir CD4 ⁺ cell count <100 × 10 ⁶ cells/L	16/48	5/19	1.4 (0.4–4.6)	>0.2	14/18	11/32	6.7 (1.8–25.2)	0.005
Plasma HIV RNA >1.7 log copies/mL	38/48	12/19	2.2 (0.7–7.1)	0.2	17/18	21/32	8.9 (1.1–76.0)	0.04
Previous AIDS-defining event	15/48	3/19	2.4 (0.6–9.6)	0.2	9/18	6/32	4.3 (1.2–15.6)	0.02
Current antiretroviral treatment	44/48	17/19	1.3 (0.2–7.7)	>0.2	15/18	27/32	0.9 (0.2–4.4)	>0.2
Current protease inhibitor treatment	33/48	13/19	1.0 (0.3–3.2)	>0.2	12/18	18/32	1.6 (0.5–5.1)	>0.2
Presence of HPV	45/48	12/19	8.7 (1.9–39.0)	0.004	13/18	10/32	5.7 (1.6–20.4)	0.007
Presence of high-risk HPV type in patients with positive HPV detection	30/45	7/12	1.4 (0.4–5.3)	>0.2	6/13	4/10	1.2 (0.2–6.8)	>0.2

* HPV = human papillomavirus; NA = not appropriate.

The proportion of men exhibiting at least one high-risk HPV type and a high-risk PCR signal (≥2) did not differ between the HPV-infected men who had sex with men and the HPV-infected injection drug users (65% vs. 44% [*P* = 0.08] and 89% vs. 90% [*P* > 0.2], respectively). Overall, 27 different genotypes were detected. Human papillomavirus 16 was the most common high-risk genotype found in the two groups (30% in the men who had sex with men and 22% in the injection drug users; *P* > 0.2). Human papilloma virus 18 was found in 16% of the men who had sex with men and 4% of the injection drug users; *P* > 0.2). Human papillomavirus 6 was the most common low-risk genotype found in the two groups (32% in the men who had sex with men and 17% in the injection drug users; *P* > 0.2). Among the patients with histologic or cytologic abnormalities, HPV was detected in 13 of 18 injection drug users (72%) and 45 of 48 men who had sex with men (94%) (*P* = 0.03).

Risk Factors for Abnormal Anal Cytologic and Histologic Findings and Anal HPV Infection

Table 4 presents univariate analyses of risk factors for abnormal anal histologic or cytologic findings among injection drug users. All factors significant in the univariate analysis remained significant in the multivariate models that incorporated these factors. These included CD4⁺ cell counts less than 250 × 10⁶ cells/L, nadir CD4⁺ cell count less than 100 × 10⁶ cells/L, a previous AIDS-defining event, plasma HIV RNA level greater than 1.7 log copies/mL, and positive results on HPV PCR (Table 4). Overall, no significant risk factors were observed for HPV when defined by positivity with the consensus primers. In univariate analysis, CD4⁺ cell counts less than 250 × 10⁶

cells/L and a previous AIDS-defining event were risk factors for HPV 16 or 18 infection.

Among the men who had sex with men, abnormal anal histologic or cytologic findings were associated in univariate analysis with HPV infection and with more than 10 lifetime episodes of receptive anal intercourse (Table 4). In univariate analysis, no significant risk factors for HPV 16 or 18 infection or HPV overall were identified.

DISCUSSION

We studied men with CD4⁺ cell counts less than 500 × 10⁶ cells/L who acquired HIV through injection drug use and who reported no history of receptive anal intercourse. Our results demonstrate a high prevalence of abnormal anal histologic or cytologic findings and anal HPV infection in this group. Among HIV-infected injection drug users, 36% had histologic or cytologic abnormalities. Half of these abnormalities were HSIL, and the overall prevalence of HSIL was similar among HIV-positive injection drug users and men who had sex with men. Risk factors for abnormal anal histologic or cytologic findings in the injection drug users included immunosuppression, high plasma HIV RNA level, and anal HPV infection. Although our study did not include HIV-negative injection drug users, these data indicate that immunosuppression plays an important role in detecting anal HPV infection and anal histologic or cytologic abnormalities in HIV-positive men in the absence of anal intercourse.

Our findings are consistent with data previously reported in renal allograft recipients in the absence of receptive anal intercourse (17–19). The mechanisms by which

anal HPV infection is acquired in the absence of anal intercourse are not known but could include insertion of transiently infected fingers or toys as well as shedding from other infected genital sites. Immunosuppression may permit replication of what may otherwise have been low-level, possibly undetectable HPV infection, with subsequent development of anal SIL. Anal HPV infection may therefore behave as both a sexually transmitted infection and an opportunistic infection during HIV disease.

A wide range of HPV types were detected in the anal canal of HIV-positive injection drug users. As in the group of HIV-positive men who had sex with men, the single most frequently detected type was HPV 16. However, infection with several HPV types was seen less frequently in injection drug users than in the men who had sex with men.

In contrast to injection drug users, the most important risk factors for anal lesions in HIV-infected men who had sex with men were anal HPV infection and the number of lifetime episodes of receptive anal intercourse. The prevalence of anal SIL and anal HPV infection observed in our cohort of 67 HIV-infected men who had sex with men was within the range observed in previous studies (7, 9, 10, 24, 25).

Our study has several limitations. An anal biopsy was performed only in patients with cytologic abnormalities. Because some of the men with normal cytologic findings may have had a false-negative cytology result (26), the true prevalence of anal SIL may be even higher than what we observed. Comparisons between the injection drug users and men who had sex with men may have been biased toward overestimating their similarities because the CD4⁺ cell counts were significantly lower and the prevalence of current smokers was significantly higher in the injection drug users than in the men who had sex with men. However, these limitations do not alter the interpretation of our findings, which show a high prevalence of anal HPV infection and anal SIL in the absence of anal intercourse.

Some of the injection drug users enrolled in the study may have had receptive anal intercourse, although they did not report this in the self-administered questionnaire. However, we consider this unlikely because most of the injection drug users were followed at the clinic for years and were not known by their treating physicians to have had anal intercourse, even by means of commercial sex work. Injection drug users were not interrogated for history of incarceration and homosexual rape in prison. However, the prevalence of homosexual rape during imprisonment is estimated to be as low as 1% in French prisons (27). If the patients under-reported anal intercourse, our results may have overestimated the importance of acquisition of anal HPV infection through other means.

Finally, our data indicate that possibly all HIV-positive men with a CD4⁺ cell count less than 500×10^6 cells/L, especially those with severe immunodeficiency, should be considered for anal cytologic screening, regard-

less of history of receptive anal intercourse. However, our sample size was small, and additional studies are needed to determine the efficacy of anal cytologic screening to prevent anal cancer in injection drug users and men who have sex with men. Notably, the prevalence of HSIL was similar to that of HIV-positive men who had sex with men, for whom screening is projected to be cost-effective (20). Many factors that have not yet been defined may affect the efficacy of screening among injection drug users; one of these is the rate of progression from HSIL to cancer in this group.

Additional studies are needed to better understand the natural history of anal SIL in HIV-positive injection drug users. In addition, studies of anal SIL and anal HPV infection in other groups, such as women and HIV-negative heterosexual persons, will provide necessary data.

From INSERM U 430 and Hôpital Européen Georges Pompidou, Paris, France; and University of California, San Francisco, San Francisco, California.

Acknowledgments: The authors thank Drs. Laurence Weiss, Gustavo Gonzalez-Canali, Dominique Batisse, Marina Karmochkine, Martin Buisson, and Didier Jayle for their help in enrolling patients in the study; Helena Bonner and Daniel Felmlee for their technical assistance; and Gilles Chatellier for his help in statistical analysis.

Grant Support: SIDACTION-ENSEMBLE CONTRE LE SIDA provided funding to design the study, collect the data, and send the samples from Paris to San Francisco; to perform the histologic, cytologic, and HPV PCR analyses; and to perform the statistical analysis. Cytyc Corp., France, provided vials of PreservCyt fixative fluid and TransCyt filters used in the study. The National Center for Research Resources, National Institutes of Health, U.S. Public Health Service (5 M01-RR-00079), provided additional funding for performing HPV PCR.

Requests for Single Reprints: Christophe Piketty, MD, Hôpital Européen Georges Pompidou, 20 rue Leblanc 75015 Paris, France; e-mail, Christophe.piketty@egp.ap-hop-paris.fr.

Potential Financial Conflicts of Interest: *Consultancies:* T.M. Darragh (Cytyc Corp.); *Honoraria:* T.M. Darragh (Cytyc Corp.); *Grants received:* T.M. Darragh (Cytyc Corp.), J. Palefsky (Cytyc Corp.); *Other:* T.M. Darragh (Speaker's Bureau for Cytyc Corp.).

Current author addresses and author contributions are available at www.annals.org.

References

1. Qualters JR, Lee NC, Smith RA, Aubert RE. Breast and cervical cancer surveillance, United States, 1973-1987. *MMWR CDC Surveill Summ.* 1992;41:1-7. [PMID: 1594012]
2. Daling JR, Weiss NS, Hislop TG, Maden C, Coates RJ, Sherman KJ, et al. Sexual practices, sexually transmitted diseases, and the incidence of anal cancer. *N Engl J Med.* 1987;317:973-7. [PMID: 2821396]
3. Melbye M, Sprøgel P. Aetiological parallel between anal cancer and cervical cancer. *Lancet.* 1991;338:657-9. [PMID: 1679474]
4. Palefsky JM, Holly EA, Gonzales J, Berline J, Ahn DK, Greenspan JS. Detection of human papillomavirus DNA in anal intraepithelial neoplasia and anal cancer. *Cancer Res.* 1991;51:1014-9. [PMID: 1846314]

5. Holly EA, Whittemore AS, Aston DA, Ahn DK, Nickloff BJ, Kristiansen JJ. Anal cancer incidence: genital warts, anal fissure or fistula, hemorrhoids, and smoking. *J Natl Cancer Inst.* 1989;81:1726-31. [PMID: 2810388]
6. Palefsky JM, Holly EA, Ralston ML, Arthur SP, Hogeboom CJ, Darragh TM. Anal cytological abnormalities and anal HPV infection in men with Centers for Disease Control group IV HIV disease. *Genitourin Med.* 1997;73:174-80. [PMID: 9306896]
7. Palefsky JM, Holly EA, Ralston ML, Arthur SP, Jay N, Berry JM, et al. Anal squamous intraepithelial lesions in HIV-positive and HIV-negative homosexual and bisexual men: prevalence and risk factors. *J Acquir Immune Defic Syndr Hum Retrovirol.* 1998;17:320-6. [PMID: 9525432]
8. Palefsky JM, Holly EA, Hogeboom CJ, Ralston ML, DaCosta MM, Botts R, et al. Virologic, immunologic, and clinical parameters in the incidence and progression of anal squamous intraepithelial lesions in HIV-positive and HIV-negative homosexual men. *J Acquir Immune Defic Syndr Hum Retrovirol.* 1998;17:314-9. [PMID: 9525431]
9. Palefsky JM, Holly EA, Ralston ML, Jay N. Prevalence and risk factors for human papillomavirus infection of the anal canal in human immunodeficiency virus (HIV)-positive and HIV-negative homosexual men. *J Infect Dis.* 1998;177:361-7. [PMID: 9466522]
10. Palefsky JM, Holly EA, Ralston ML, Jay N, Berry JM, Darragh TM. High incidence of anal high-grade squamous intra-epithelial lesions among HIV-positive and HIV-negative homosexual and bisexual men. *AIDS.* 1998;12:495-503. [PMID: 9543448]
11. Palefsky JM. Anal squamous intraepithelial lesions: relation to HIV and human papillomavirus infection. *J Acquir Immune Defic Syndr.* 1999;21 Suppl 1:S42-8. [PMID: 10430218]
12. Critchlow CW, Hawes SE, Kuypers JM, Goldbaum GM, Holmes KK, Surawicz CM, et al. Effect of HIV infection on the natural history of anal human papillomavirus infection. *AIDS.* 1998;12:1177-84. [PMID: 9677167]
13. Critchlow CW, Surawicz CM, Holmes KK, Kuypers J, Daling JR, Hawes SE, et al. Prospective study of high grade anal squamous intraepithelial neoplasia in a cohort of homosexual men: influence of HIV infection, immunosuppression and human papillomavirus infection. *AIDS.* 1995;9:1255-62. [PMID: 8561979]
14. Goedert JJ, Côté TR, Virgo P, Scoppa SM, Kingma DW, Gail MH, et al. Spectrum of AIDS-associated malignant disorders. *Lancet.* 1998;351:1833-9. [PMID: 9652666]
15. Goedert JJ. The epidemiology of acquired immunodeficiency syndrome malignancies. *Semin Oncol.* 2000;27:390-401. [PMID: 10950365]
16. Frisch M, Biggar RJ, Goedert JJ. Human papillomavirus-associated cancers in patients with human immunodeficiency virus infection and acquired immunodeficiency syndrome. *J Natl Cancer Inst.* 2000;92:1500-10. [PMID: 10995805]
17. Blohmé I, Brynner H. Malignant disease in renal transplant patients. *Transplantation.* 1985;39:23-5. [PMID: 3880960]
18. Ogunbiyi OA, Scholefield JH, Raftery AT, Smith JH, Duffy S, Sharp F, et al. Prevalence of anal human papillomavirus infection and intraepithelial neoplasia in renal allograft recipients. *Br J Surg.* 1994;81:365-7. [PMID: 8173899]
19. Penn I. Cancers of the anogenital region in renal transplant recipients. Analysis of 65 cases. *Cancer.* 1986;58:611-6. [PMID: 3524788]
20. Goldie SJ, Kuntz KM, Weinstein MC, Freedberg KA, Welton ML, Palefsky JM. The clinical effectiveness and cost-effectiveness of screening for anal squamous intraepithelial lesions in homosexual and bisexual HIV-positive men. *JAMA.* 1999;281:1822-9. [PMID: 10340370]
21. Goldie SJ, Kuntz KM, Weinstein MC, Freedberg KA, Palefsky JM. Cost-effectiveness of screening for anal squamous intraepithelial lesions and anal cancer in human immunodeficiency virus-negative homosexual and bisexual men. *Am J Med.* 2000;108:634-41. [PMID: 10856411]
22. Jay N, Berry JM, Hogeboom CJ, Holly EA, Darragh TM, Palefsky JM. Colposcopic appearance of anal squamous intraepithelial lesions: relationship to histopathology. *Dis Colon Rectum.* 1997;40:919-28. [PMID: 9269808]
23. Morrison EA, Goldberg GL, Kadish AS, Burk RD. Polymerase chain reaction detection of human papillomavirus: quantitation may improve clinical utility. *J Clin Microbiol.* 1992;30:2539-43. [PMID: 1328278]
24. Kiviat NB, Critchlow CW, Holmes KK, Kuypers J, Sayer J, Dunphy C, et al. Association of anal dysplasia and human papillomavirus with immunosuppression and HIV infection among homosexual men. *AIDS.* 1993;7:43-9. [PMID: 8382927]
25. Melbye M, Palefsky J, Gonzales J, Ryder LP, Nielsen H, Bergmann O, et al. Immune status as a determinant of human papillomavirus detection and its association with anal epithelial abnormalities. *Int J Cancer.* 1990;46:203-6. [PMID: 2166709]
26. Palefsky JM, Holly EA, Hogeboom CJ, Berry JM, Jay N, Darragh TM. Anal cytology as a screening tool for anal squamous intraepithelial lesions. *J Acquir Immune Defic Syndr Hum Retrovirol.* 1997;14:415-22. [PMID: 9170415]
27. Observatoire Régional de la Santé Provence Alpes Côte d'Azur. Réduction des risques de l'infection à VIH et des hépatites en milieu carcéral: prévalence des pratiques à risques et analyse des contraintes et de la faisabilité des programmes de réduction des risques en milieu carcéral. 1998. Accessed at www.orspaca.org on 17 January 2003.

Current Author Addresses: Drs. Piketty, Heard, and Kazatchkine: Department of Immunology, INSERM U 430 and Université Pierre et Marie Curie, Hôpital Européen Georges Pompidou, 20 rue Leblanc, 75015 Paris, France.

Dr. Bruneval: Department of Pathology, INSERM U 430 and Université Pierre et Marie Curie, Hôpital Européen Georges Pompidou, 20 rue Leblanc, 75015 Paris, France.

Dr. Palefsky and Ms. Da Costa: Department of Medicine, University of California, San Francisco, 505 Parnassus Avenue, San Francisco, CA 94143.

Dr. Darragh: Department of Pathology, University of California, San Francisco, 505 Parnassus Avenue, San Francisco, CA 94143.

Author Contributions: Conception and design: C. Piketty, I. Heard, J.M. Palefsky.

Analysis and interpretation of the data: C. Piketty, T.M. Darragh, M. Da Costa, P. Bruneval, I. Heard, M.D. Kazatchkine, J.M. Palefsky.

Drafting of the article: C. Piketty, I. Heard, M.D. Kazatchkine, J.M. Palefsky.

Critical revision of the article for important intellectual content: C. Piketty, T.M. Darragh, M. Da Costa, P. Bruneval, I. Heard, M.D. Kazatchkine, J.M. Palefsky.

Final approval of the article: C. Piketty, T.M. Darragh, M. Da Costa, P. Bruneval, I. Heard, M.D. Kazatchkine, J.M. Palefsky.

Provision of study materials or patients: C. Piketty, M.D. Kazatchkine. Statistical expertise: C. Piketty.

Obtaining of funding: C. Piketty, M.D. Kazatchkine, J.M. Palefsky.

Administrative, technical, or logistic support: C. Piketty, T.M. Darragh, M. Da Costa, P. Bruneval, I. Heard, M.D. Kazatchkine, J.M. Palefsky.

Collection and assembly of data: C. Piketty, T.M. Darragh, M. Da Costa, P. Bruneval, I. Heard, M.D. Kazatchkine, J.M. Palefsky.