Risk of Human Papillomavirus–Associated Cancers Among Persons With AIDS

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Background Although risk of human papillomavirus (HPV)–associated cancers of the anus, cervix, oropharynx, penis, vagina, and vulva is increased among persons with AIDS, the etiologic role of immunosuppression is unclear and incidence trends for these cancers over time, particularly after the introduction of highly active antiretroviral therapy in 1996, are not well described.

Methods Data on 499 230 individuals diagnosed with AIDS from January 1, 1980, through December 31, 2004, were linked with cancer registries in 15 US regions. Risk of in situ and invasive HPV-associated cancers, compared with that in the general population, was measured by use of standardized incidence ratios (SIRs) and 95% confidence intervals (CIs). We evaluated the relationship of immunosuppression with incidence during the period of 4–60 months after AIDS onset by use of CD4 T-cell counts measured at AIDS onset. Incidence during the 4–60 months after AIDS onset was compared across three periods (1980–1989, 1990–1995, and 1996–2004). All statistical tests were two-sided.

Results Among persons with AIDS, we observed statistically significantly elevated risk of all HPV-associated in situ (SIRs ranged from 8.9, 95% CI = 8.0 to 9.9, for cervical cancer to 68.6, 95% CI = 59.7 to 78.4, for anal cancer among men) and invasive (SIRs ranged from 1.6, 95% CI = 1.2 to 2.1, for oropharyngeal cancer to 34.6, 95% CI = 30.8 to 38.8, for anal cancer among men) cancers. During 1996–2004, low CD4 T-cell count was associated with statistically significantly increased risk of invasive anal cancer among men (relative risk [RR] per decline of 100 CD4 T cells per cubic millimeter = 1.34, 95% CI = 1.08 to 1.66, $P = .006$) and non–statistically significantly increased risk of in situ vagina or vulva cancer (RR = 1.52, 95% CI = 0.99 to 2.35, $P = .055$) and of invasive cervical cancer (RR = 1.32, 95% CI = 0.96 to 1.80, $P = .077$). Among men, incidence (per 100 000 person-years) of in situ and invasive anal cancer was statistically significantly higher during 1996–2004 than during 1990–1995 (61% increase for in situ cancers, 18.3 cases vs 29.5 cases, respectively; RR = 1.71, 95% CI = 1.24 to 2.35, $P < .001$; and 104% increase for invasive cancers, 20.7 cases vs 42.3 cases, respectively; RR = 2.03, 95% CI = 1.54 to 2.68, $P < .001$). Incidence of other cancers was stable over time.

Conclusions Risk of HPV-associated cancers was elevated among persons with AIDS and increased with increasing immunosuppression. The increasing incidence for anal cancer during 1996–2004 indicates that prolonged survival may be associated with increased risk of certain HPV-associated cancers.

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Human papillomavirus (HPV) infection causes essentially all cervical cancers and is etiologically related to a subset of cancers of the anus, oropharynx, penis, vagina, and vulva (1,2). Individuals with HIV or AIDS are at increased risk of HPV-associated cancers (3–7). This increased risk among persons with HIV or AIDS is consistent with a high incidence and persistence of HPV infections (8–14). Incidence of HPV-associated cancers is also increased among transplant recipients (3,15), another immunosuppressed population.

The extent to which HIV-related immunosuppression plays a role in the increased risk of HPV-associated cancers remains unclear. Among HIV-infected individuals, the incidence of invasive HPV-associated cancers has not appeared to be related to the CD4 T-cell count, a measure of immune status (4,6,9,16). However, most previous analyses have included small numbers of cancers and small numbers of subjects with available markers of immunosuppression and thus may not have had the power to

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detect statistically significant differences (4,6,16). Furthermore, most previous analyses have been restricted to calendar periods before 1996, when highly active antiretroviral therapy (HAART) against HIV was introduced (4,16).

Understanding the associations of immunosuppression and HAART with the risk of HPV-associated cancers is particularly important because immune restoration with HAART is only partial and the prolonged survival of HIV-infected individuals with reduced immune competence could be associated with increased incidence of cancers that are not strongly related to immunosuppression (6,8,9,17). Indeed, an increased incidence of anal cancer has been reported among individuals with HIV or AIDS in the HAART era (1996–2004) (18–21). In a recent study (22) of AIDS-associated cancers that was restricted to the 2 years after the onset of AIDS, the risk of invasive cervical cancer was not associated with immunosuppression and the incidence of cervical cancer was stable in the HAART era. In this study, we further investigated the risk of cervical cancer and other HPV-associated cancers over a longer follow-up period among 499 230 persons with AIDS in the United States (23). We assessed risk of both in situ and invasive cancers of the anus, cervix, oropharynx, penis, vagina, or vulva. We characterized the relationship of immunosuppression with the risk of HPV-associated cancers and investigated changes in the incidence of these cancers in the HAART era.

CONTEXT AND CAVEATS

Prior knowledge

Risk of human papillomavirus (HPV)–associated cancers is increased among persons with AIDS.

Study design

Retrospective study that used data from persons diagnosed with AIDS that were linked to cancer registry data to estimate risks for in situ and invasive HPV-associated cancers, including cancers of the anus, cervix, oropharynx, penis, vagina, and vulva. These risks were compared with those of the general population. Immunosuppression was investigated by use of the CD4 T-cell count at AIDS onset.

Contribution

Statistically significantly elevated risks for all HPV-associated cancers were observed among persons with AIDS. From 1996 (when highly active antiretroviral therapy was introduced) through 2004, a low CD4 T-cell count was associated with a statistically significantly increased risk of invasive anal cancer among men and incidence of anal cancer was statistically significantly higher in 1996–2004 than in 1990–1995.

Implications

Increased incidence of anal cancer was observed among persons with AIDS and it increased with increasing immunosuppression. Prolonged survival of persons with AIDS may be associated with their increased risk for some HPV-associated cancers.

Limitations

Information on risk factors, such as cigarette smoking, was not available. Persons with AIDS receive increased medical surveillance. One CD4 T-cell count measured at the onset of AIDS probably does not reflect fluctuations in immunosuppression over time.

From the Editors

Subjects and Methods

Subjects and Cancer Outcomes

Records on 499 230 adolescents and adults aged 15 years or older who were diagnosed with AIDS from January 1, 1980, through December 31, 2004, were linked with cancer registry data in nine US states (Colorado, Connecticut, Florida, Georgia, Illinois, Massachusetts, Michigan, New Jersey, and Texas) and six US metropolitan regions (Atlanta, Los Angeles, New York, San Diego, Seattle, and San Francisco). We assessed cancer risk across a 10-year period including 5 years before AIDS onset to 5 years after AIDS onset. As in previous analyses (4,7), we used the time of AIDS onset as a reference to classify this 10-year period into the following five risk intervals: 60–25 months before AIDS onset, 24–7 months before AIDS onset, 6 months before to 3 months after AIDS onset (ie, the AIDS onset interval), 4–27 months after AIDS onset, and 28–60 months after AIDS onset. For each risk interval, follow-up began at the later of the start of cancer registry coverage or at the first month of the interval and ended at the earliest occurrence of death, end of cancer registry coverage, or the end of the interval.

From previous epidemiological and molecular evidence (2), the following cancers were considered to be HPV associated: anus, anal canal, and anorectum (*International Classification of Diseases for Oncology*, 3rd edition topography [ICD-O-3 codes C210–218]); uterine cervix (ICD-O-3 codes C530–539); oropharynx (as a composite site, including base of tongue [ICD-O-3 code C019], lingual tonsil [ICD-O-3 code C024], tonsil [ICD-O-3 codes C090–099], oropharynx [ICD-O-3 codes C100–109], and Waldeyer ring [ICD-O-3 code C142]); penis (ICD-O-3 codes C600–609); and both vagina and vulva (ICD-O-3 codes C529 and C510–519). We included all histological subtypes of cervical cancer but restricted other cancer outcomes to squamous cell histology (ICD-O-3 codes 8050–8076, 8078, 8083, 8084, and 8094). For each HPV-associated cancer, we analyzed in situ and invasive cancers separately. Additionally, we analyzed anal cancers separately for men and women. We could not analyze in situ cervical cancers after 1996 or in situ head and neck cancers (for all calendar years) because cancer registry data were unavailable.

Statistical Methods

To compare risk of HPV-associated cancers among individuals with AIDS with that of the general population, we focused on incident cancers that were diagnosed from 4 to 60 months after AIDS onset. We calculated the expected number of cancers for each outcome by use of age, calendar year, race, registry, and sex-specific general population cancer incidence rates. The standardized incidence ratio (SIR) was calculated as the ratio of observed to expected number of cancers, and exact 95% Poisson confidence intervals (CIs) were also calculated. Standardized incidence ratios for each in situ and invasive HPV-associated cancer were calculated overall and separately by HIV-risk group (ie, men who have sex with men, injection drug user, men who have sex with men and injection drug user, heterosexual, and other or unknown HIV transmission modes).

We used two strategies to assess the association between HIV-related immunosuppression and risk of each HPV-associated cancer. First, we assessed trends in standardized incidence ratios from 5 years before to 5 years after AIDS onset by use of Poisson regression (4). An increasing trend in standardized incidence ratios across time periods relative to AIDS onset would indicate that cancer risk increased with increasing intensity or duration of immunosuppression. Standardized incidence ratios for prevalent cancers that were diagnosed before AIDS onset used expected numbers of cancers that account for mortality after a diagnosis of cancer (4). In these trend analyses, we excluded the AIDS onset period from 6 months before to 3 months after the diagnosis of AIDS to avoid potential biases arising from overascertainment of cancers at AIDS diagnosis (4).

Second, we assessed the relationship of CD4 T-cell count with cancer incidence during the 4–60 months after AIDS onset. Associations of cancer incidence with CD4 T-cell count measured at AIDS onset were calculated for the entire period of 4–60 months after AIDS onset and separately for the period of 4–27 months after AIDS onset and the period of 28–60 months after AIDS onset. The relative risk (RR) for each decline in CD4 T-cell count of 100 cells per cubic millimeter (scaled by dividing the CD4 T-cell count by a value of 100 and modeled as a continuous covariate) was estimated by use of Poisson regression after adjustment for age at AIDS diagnosis, race, and a combination of sex and mode of HIV acquisition (men who have sex with men, other men, and women). Because previous analyses have addressed the association of CD4 T-cell count with HPV-associated cancer risk in the pre-HAART era (4,16), we restricted the CD4 T-cell count evaluations to the 185 781 individuals who were diagnosed with AIDS during the HAART era (1996–2004). Additionally, these models were restricted to the 159 005 individuals with available data on CD4 T-cell count who also had a CD4 T-cell count in the range of 0–499 cells per cubic millimeter. To evaluate the validity of a log-linear relationship between CD4 T-cell count and HPV-associated cancer incidence during the 4–60 months after AIDS onset, we categorized CD4 T-cell counts into the following five levels: 0–99, 100–199, 200–299, 300–399, and 400–499 cells per cubic millimeter. We then compared models that incorporated CD4 T-cell count as a categorical variable (4 *df*) with models that incorporated CD4 T-cell count as an ordinal variable (1 *df*) by use of the likelihood ratio goodness-of-fit test. No models that incorporated an ordinal CD4 variable exhibited lack of fit (data not shown), indicating that a log-linear assumption was appropriate.

To assess changes in the incidence of HPV-associated cancers over calendar time, we classified subjects by their attained calendar year into three categories: 1980–1989, when no effective therapies were available; 1990–1995, when single and dual therapies were available; and 1996–2004, the HAART era. The attained calendar year was calculated in a time-dependent manner so that individuals could contribute person-years to more than one calendar period. These analyses evaluated risk during the 4–60 months after AIDS onset. Using the 1990–1995 period as reference, we compared incidence of HPV-associated cancers across the three calendar periods in Poisson regression models after adjustment for age at AIDS onset, race, combination of sex and mode of HIV acquisition (men who have sex with men, other men, and women), and risk period relative to AIDS onset (4–27 months after AIDS onset vs 28–60 months after AIDS onset).

We incorporated a dispersion parameter in all Poisson regression models to account for overdispersion or underdispersion. All statistical tests were two-sided, and statistical significance required a P value of less than .05. Additionally, because of the multiple statistical comparisons in our analyses, we conducted sensitivity analyses by assessing statistical significance at Bonferroni-corrected P-value thresholds. These Bonferroni-corrected P values were based on the number of cancer outcomes in each set of comparisons—10 outcomes (in situ cancers of the anus among men, anus among women, cervix, penis, and vagina or vulva, and invasive cancers of the anus among men, anus among women, oropharynx, penis, and vagina or vulva) for the analyses of trends in standardized incidence ratios across time periods relative to AIDS onset and for the relationship of CD4 T-cell count with cancer incidence during the periods of 4–27, 28–60, and 4–60 months after AIDS onset (Bonferroni $P = .005$) and 11 outcomes (in situ cancers of the anus among men, anus among women, cervix, penis, and vagina or vulva, and invasive cancers of the anus among men, anus among women, cervix, oropharynx, penis, and vagina or vulva) for analyses of changes in incidence across calendar periods (Bonferroni $P = .004$). All statistical tests were two-sided.

Results

The characteristics of 499 230 individuals across three calendar periods of AIDS diagnoses (1980–1989, 1990–1995, and 1996–2004) are shown in Table 1. From the early AIDS period (1980–1989) through the HAART era (1996–2004), the proportion of women and the median age at AIDS diagnosis increased. The proportion of African Americans and Hispanics with AIDS increased, as did the proportion of those who acquired HIV through heterosexual contact. The availability of CD4 T-cell counts at AIDS onset increased from 5.7% during 1980–1989 to 87% for individuals diagnosed with AIDS during 1996–2004, with the median CD4 T-cell counts at AIDS onset across the three periods being 138 (interquartile range [IQR] = 57–191), 100 (IQR = 31–173), and 108 (IQR = 35–177) cells per cubic millimeter, respectively. Survival during the 2 years after AIDS onset increased dramatically over time from 49.2% (95% CI = 48.8% to 49.5%) during 1980–1989 to 90.2% (95% CI = 90.1% to 90.3%) during 1996–2004.

Risk of HPV-Associated Cancers Among Persons With AIDS

During the 4–60 months after AIDS onset, 699 in situ and 602 invasive incident HPV-associated cancers were diagnosed in study subjects. Compared with the general population, persons with AIDS were at statistically significantly increased risk for all in situ HPV-associated cancers (SIRs ranged from 8.9, 95% CI = 8.0 to 9.9, for cervical cancer to 68.6, 95% CI = 59.7 to 78.4, for anal cancer among men) and for invasive HPV-associated cancers (SIRs ranged from 1.6, 95% CI = 1.2 to 2.1, for oropharyngeal cancer to 34.6, 95% CI = 30.8 to 38.8, for anal cancer in men) (Table 2). For each site of HPV-associated cancer, risks for in situ cancers were higher than risks for invasive cancers. Although risks for in situ and invasive anal cancer were statistically significantly increased among men and women and among all HIV-risk groups, this risk was particularly high among men who have sex with men (for in situ

Table 1. Characteristics of persons with AIDS in the United States from 1980 through 2004 (n = 499 230)*

Characteristic	AIDS diagnosis year		
	1980–1989 (n = 85 621)	1990–1995 (n = 227 828)	1996–2004 (n = 185 781)
Sex, No. (%)			
Male	76 213 (89.0)	186 959 (82.1)	139 755 (75.2)
Female	9408 (11.0)	40 869 (17.9)	46 026 (24.8)
Age at AIDS onset, No. (%)			
15–29 y	14 821 (17.3)	32 554 (14.3)	21 879 (11.8)
30–39 y	40 975 (47.9)	103 190 (45.3)	73 651 (39.6)
40–49 y	20 480 (23.9)	65 764 (28.9)	61 246 (33.0)
≥50 y	9345 (10.9)	26 320 (11.5)	29 005 (15.6)
Median age (range), y	36 (15–89)	37 (15–90)	39 (15–93)
Race or ethnicity, No. (%)			
White	44 677 (52.2)	93 004 (40.8)	54 193 (29.2)
Black	25 839 (30.2)	85 649 (37.6)	87 621 (47.1)
Hispanic	14 303 (16.7)	46 712 (20.5)	39 127 (21.1)
Other or unknown	802 (0.9)	2463 (1.1)	4840 (2.6)
HIV-risk group, No. (%)			
MSM	49 612 (57.9)	104 198 (45.7)	66 036 (35.6)
IDU	21 332 (24.9)	66 966 (29.4)	38 419 (20.7)
MSM and IDU	5892 (6.9)	13 625 (6.0)	8331 (4.5)
Heterosexual	3447 (4.0)	23 994 (10.5)	34 277 (18.4)
Other or unknown	5338 (6.2)	19 045 (8.4)	38 718 (20.8)
CD4 T-cell count at AIDS onset, No. (%)			
0–99 cells per cubic millimeter	1751 (2.0)	71 205 (31.3)	75 094 (40.4)
100–199 cells per cubic millimeter	2019 (2.4)	55 304 (24.3)	62 189 (33.5)
≥200 cells per cubic millimeter	1076 (1.3)	19 705 (8.6)	24 176 (13.0)
Missing	80 775 (94.3)	81 614 (35.8)	24 322 (13.1)
Median count, cells per cubic millimeter (interquartile range)	138 (57–191)	100 (31–173)	108 (35–177)
Life table estimate of survival at 2 years after AIDS onset, % (95% CI)	49.2 (48.8 to 49.5)	68.1 (67.8 to 68.3)	90.2 (90.1 to 90.3)

* MSM = men who have sex with men; IDU = injection drug user; CI = confidence interval.

cancers, SIR = 89.7, 95% CI = 76.8 to 104.1; and for invasive cancers, SIR = 51.8, 95% CI = 45.3 to 59.0).

Relationship Between HPV-Associated Cancers and Immunosuppression

In the 10-year period from 5 years before to 5 years after the onset of AIDS, 1611 in situ and 1468 invasive HPV-associated cancers were diagnosed among persons with AIDS in this study. Among in situ cancers, statistically significant increasing trends in risk were observed across this 10-year period for cancers of the anus among men, cervix, penis, and vagina or vulva (Figure 1) but not for anal cancer among women. Among invasive cancers, statistically significant increasing trends in risk were observed for cancers of the anus among both men and women and for vagina or vulva cancers (Figure 2). We did not assess trends in risk for invasive cervical cancer because it is an AIDS-associated cancer and thus, by definition, no cases can occur before AIDS onset (24). No statistically significant trend in risk across the 10-year period from 5 years before to 5 years after the onset of AIDS was observed for invasive cancers of the penis or oropharynx.

For individuals who were diagnosed with AIDS during the HAART era (1996–2004), we assessed the relationship of CD4 T-cell count at AIDS onset with risk of incident cancers during the entire period of 4–60 months after AIDS onset and separately for the periods of 4–27 and 28–60 months after AIDS onset (Figure 3 and Table 3). A low CD4 T-cell count at AIDS onset was associated with a non–statistically significantly increased risk of invasive cervical cancer during the 4–27 months after AIDS onset (P = .080). During the 28–60 months after AIDS onset, a low CD4 T-cell count was associated with a statistically significantly increased risk of invasive anal cancer among men (RR per 100 cells per cubic millimeter decline in CD4 T-cell count = 1.59, 95% CI = 1.09 to 2.34, P = .016) and in situ (RR = 1.59, 95% CI = 1.01 to 2.49, P = .041) and invasive (RR = 4.91, 95% CI = 1.02 to 23.60, P = .046) vagina or vulva cancers and with a statistically significantly decreased risk of invasive oropharyngeal cancer (RR = 0.58, 95% CI = 0.44 to 0.76, P < .001). For the entire period of 4–60 months after AIDS onset, a low CD4 T-cell count was associated with statistically significantly increased risk of invasive anal cancer among men (RR = 1.34, 95% CI = 1.08 to 1.66, P = .006) and non–statistically significantly increased risks of invasive cervical cancer (RR = 1.32, 95% CI = 0.96 to 1.80, P = .077) and in situ vagina or vulva cancer (RR = 1.52, 95% CI = 0.99 to 2.35, P = .055).

Changes in the Incidence of HPV-Associated Cancers Over Time

We compared incidence of HPV-associated cancers during the 4–60 months after AIDS onset across three calendar periods (1980–1989, 1990–1995, and 1996–2004) (Table 4). Across all three periods, the incidence of both in situ and invasive anal cancer among men increased. Specifically, for in situ anal cancer among men, the incidence was 1.7 cases per 100 000 person-years in

Table 2. Risk of in situ and invasive human papillomavirus–associated cancers among persons with AIDS in the 4–60 months after AIDS onset*

Category	Anal cancer (men)		Anal cancer (women)		Cervical cancer		Cancer of the penis		Cancer of the vagina or vulva†		Oropharyngeal cancer‡	
	No.	SIR (95% CI)	No.	SIR (95% CI)	No.	SIR (95% CI)	No.	SIR (95% CI)	No.	SIR (95% CI)	No.	SIR (95% CI)
In situ cancers												
Overall	214	68.6 (59.7 to 78.4)	9	33.0 (15.1 to 62.7)	324	8.9 (8.0 to 9.9)	29	19.7 (13.2 to 28.3)	123	27.2 (22.6 to 32.5)		
HIV-risk group												
MSM	173	89.7 (76.8 to 104.1)	—	—	—	—	17	21.8 (12.7 to 35.0)	—	—		
IDU	6	11.7 (4.2 to 25.5)	4	38.0 (10.3 to 97.3)	181	9.6 (8.3 to 11.1)	8	25.8 (11.1 to 50.9)	41	22.8 (16.4 to 31.0)		
MSM and IDU	27	89.3 (58.8 to 130.0)	—	—	—	—	0	0.0 (0.0 to 39.9)	—	—		
Heterosexual	3	20.8 (4.2 to 60.8)	3	24.9 (5.1 to 73.0)	111	8.1 (6.7 to 9.8)	3	25.7 (5.3 to 75.3)	64	32.6 (25.1 to 41.6)		
Other or unknown	5	21.5 (6.9 to 50.2)	2	42.3 (5.1 to 153.0)	32	8.3 (5.6 to 11.7)	1	5.8 (0.1 to 32.3)	18	23.8 (14.1 to 37.6)		
Invasive cancers												
Overall	295	34.6 (30.8 to 38.8)	20	14.5 (8.8 to 22.4)	192	5.6 (4.8 to 6.5)	20	5.3 (3.2 to 8.2)	16	5.8 (3.3 to 9.5)	59	1.6 (1.2 to 2.1)
HIV-risk group												
MSM	229	51.8 (45.3 to 59.0)	—	—	—	—	8	4.4 (1.9 to 8.7)	—	—	19	1.1 (0.7 to 1.8)
IDU	18	8.9 (5.3 to 14.1)	7	13.7 (5.5 to 28.3)	101	7.0 (5.7 to 8.5)	3	3.2 (0.6 to 9.4)	9	8.4 (3.8 to 16.0)	21	2.1 (1.3 to 3.2)
MSM and IDU	26	44.0 (28.7 to 64.5)	—	—	—	—	1	4.8 (0.1 to 27.0)	—	—	2	1.0 (0.1 to 3.7)
Heterosexual	8	14.0 (6.0 to 27.6)	9	15.1 (6.9 to 28.7)	62	4.3 (3.3 to 5.6)	5	14.7 (4.8 to 34.5)	5	4.3 (1.4 to 10.2)	12	3.2 (1.6 to 5.7)
Other or unknown	14	15.2 (8.3 to 25.5)	4	14.6 (3.9 to 37.3)	29	5.2 (3.5 to 7.5)	3	6.5 (1.3 to 19.1)	2	3.8 (0.4 to 13.7)	5	1.0 (0.3 to 2.5)

* No. = observed number of patients diagnosed with the corresponding cancer; SIR = standardized incidence ratio; CI = confidence interval; MSM = men who have sex with men; IDU = injection drug user; — = not applicable.

† In situ vagina or vulva cancers include 23 vagina cancers and 100 vulva cancers, and invasive vagina or vulva cancers include zero vagina cancer and 16 vulva cancers.

‡ Oropharyngeal cancers include cancers of the base of tongue, lingual and palatine tonsils, oropharynx, and Waldeyer ring.

1980–1989, 18.3 cases per 100 000 person-years in 1990–1995, and 29.5 cases per 100 000 person-years in 1996–2004. The increased incidence of in situ cancer was statistically significant between 1980–1989 and 1990–1995 (difference = 976%; RR = 0.08, 95% CI = 0.01 to 0.61, $P = .014$) and between 1990–1995 and 1996–2004 (difference = 61%; RR = 1.71, 95% CI = 1.24 to 2.35, $P < .001$). For invasive anal cancer among men, the incidence was 10.5 cases per 100 000 person-years in 1980–1989, 20.7 cases per 100 000 person-years in 1990–1995, and 42.3 cases per 100 000 person-years in 1996–2004. The incidence of invasive anal cancer among men increased non–statistically significantly between 1980–1989 and 1990–1995 (difference = 97%; RR = 0.48, 95% CI = 0.21 to 1.06, $P = .071$) and increased again statistically significantly between 1990–1995 and 1996–2004 (difference = 104%; RR = 2.03, 95% CI = 1.54 to 2.68, $P < .001$). For both in situ and invasive anal cancer, the increases were similar for the groups of men who have sex with men and groups of other men. Incidence of in situ cervical cancer increased statistically significantly from 1980–1989 to 1990–1995 but could not be assessed during 1996–2004. Specifically, incidence was 177.3 cases per 100 000 person-years in 1980–1989 and 448.9 cases per 100 000 person-years in 1990–1995 (difference = 153%; RR = 0.34, 95% CI = 0.17 to 0.66, $P = .002$). Incidence for other in situ and invasive HPV-associated cancers did not change statistically significantly over time.

We also assessed changes in incidence between the 4–27 and the 28–60 months after AIDS onset, after adjustment for calendar period (1980–1989, 1990–1995, or 1996–2004) (Table 4). Incidence of in situ cervical cancer was lower in the 28–60 months after AIDS onset than in the 4–27 months after AIDS onset, but not statistically significantly so ($P = .055$). In contrast, incidences in the 28–60 months after AIDS onset of invasive anal cancer among men ($P = .043$), in situ penile cancer ($P = .028$), and in situ vagina or vulva cancer ($P = .025$) were statistically significantly higher than incidences in the 4–27 months after AIDS onset. The incidence of in situ anal cancer among men was non–statistically significantly higher in the 28–60 months than in the 4–27 months after AIDS onset ($P = .093$).

Cancers detected through screening would be expected to be diagnosed at earlier stages than those diagnosed clinically. To assess whether increased screening could explain the increased incidence of invasive anal cancer among men during 1996–2004, we compared the stage at diagnosis for this cancer in 1990–1995 with that in 1996–2004. Stage information was available for 80% of invasive anal cancers; the stage distribution was similar for 1990–1995 (63% local, 30% regional, and 7% distant) and 1996–2004 (65% local, 30% regional, and 5% distant). Likewise, the proportions of in situ anal cancer among men in 1990–1995 and in 1996–2004 were similar (47% during 1990–1995 and 41% during 1996–2004).

To evaluate the possibility of chance associations arising from multiple statistical testing, we conducted sensitivity analyses by assessing statistical significance at Bonferroni-corrected *P*-value thresholds of less than .005 for trends in risk from 5 years before to 5 years after AIDS onset and for relationships of cancer incidence with CD4 T-cell count and a Bonferroni-corrected *P*-value threshold of less than .004 for evaluations of incidence trends across time. Our results for increasing trends in risk from 5 years before to 5 years after AIDS onset for in situ cancers of the anus

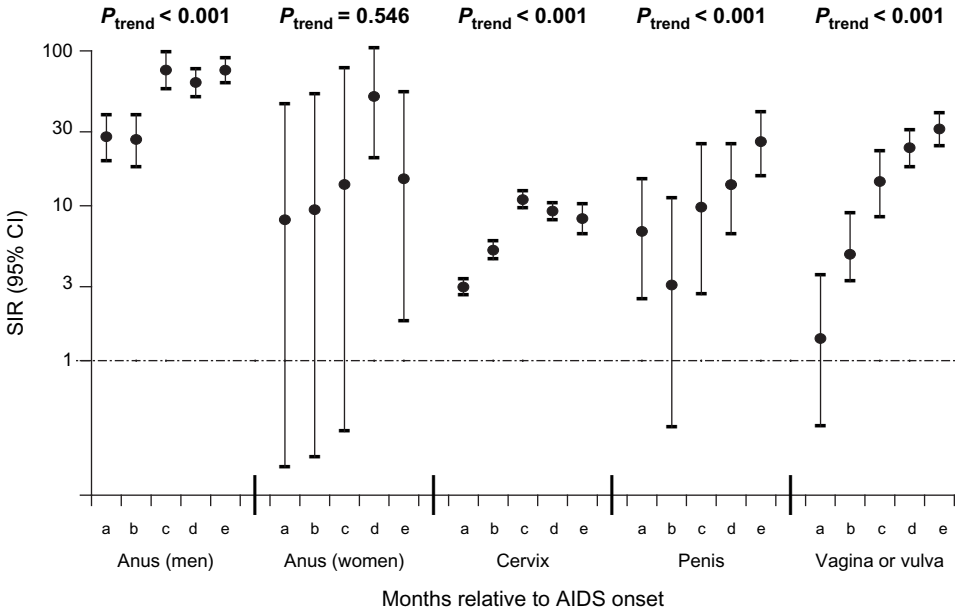

Figure 1. Risk of in situ human papillomavirus (HPV)–associated cancers among persons with AIDS, according to time relative to AIDS onset. Standardized incidence ratios (SIRs) and 95% confidence intervals (CIs) for in situ HPV-associated cancers are presented across the following five risk periods relative to AIDS onset: a = 60–25 months before AIDS; b = 24–7 months before AIDS; c = 6 months before to 3 months after AIDS (the AIDS onset period); d = 4–27 months after AIDS; and e = 28–60 months after AIDS. The AIDS onset period was excluded from trend analyses. P_{trend} values were calculated by use of Poisson regression. All statistical tests were two-sided.

among men, cervix, penis, and vagina or vulva, as well as for invasive cancers of the anus among men and women and vagina or vulva, were robust even at a Bonferroni-corrected *P*-value threshold of less than .005 (Figures 1 and 2). At the same threshold, during the 28–60 months after AIDS onset, associations of CD4 T-cell count with incidence of invasive anal cancer among men ($P = .016$) and in situ ($P = .041$) and invasive ($P = .046$) vagina or vulva cancers were not statistically significant (Table 3). During the 28–60 months after AIDS onset, the association of CD4 T-cell count with incidence of oropharyngeal cancer ($P < .001$) was robust even at a Bonferroni-corrected threshold of less than .005. During the 4–60 months after AIDS onset, the association of CD4 T-cell count with incidence of invasive anal cancer among men ($P = .006$) had borderline statistical significance at a Bonferroni-corrected *P* value of less than .005. If we used a Bonferroni-corrected *P*-value threshold of less than .004, our observations of increasing incidence of in situ and invasive anal cancer among men during the HAART era (1996–2004) (both $P < .001$; Table 4) remained statistically significant.

Discussion

To our knowledge, this study is the largest to date to systematically evaluate risk of HPV-associated cancers among persons with AIDS. We found that risks for cancers of the anus, cervix, oropharynx, penis, and vagina or vulva were statistically significantly higher among persons with AIDS than among the general population. Risks of all HPV-associated in situ cancers and risks of invasive cancers of the anus and vagina or vulva increased statistically significantly from 5 years before to 5 years after AIDS onset. Furthermore, a low CD4 T-cell count at AIDS onset was associated with statistically significantly increased risks of invasive cancers of the anus among men and of in situ and invasive vagina or vulva cancers but with a non–statistically significant increased risk of

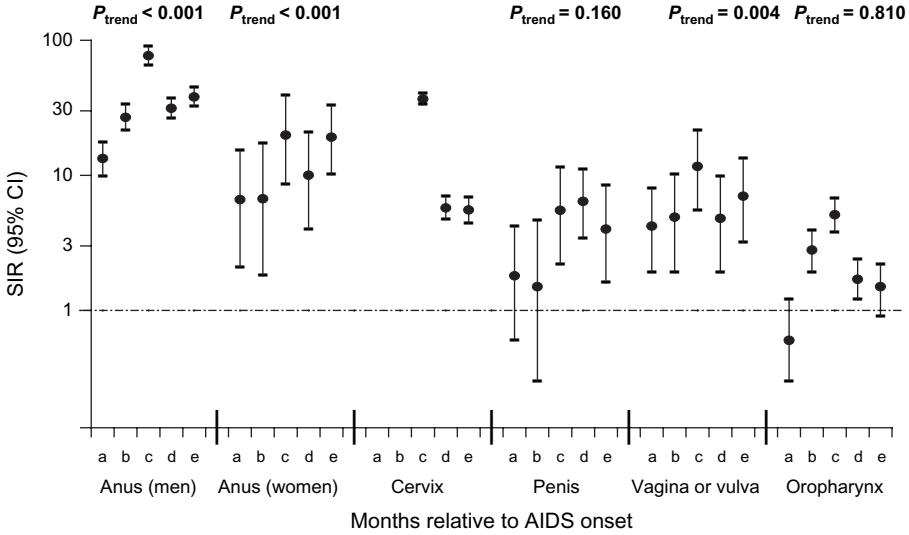

Figure 2. Risk of invasive human papillomavirus (HPV)–associated cancers among persons with AIDS, according to time relative to AIDS onset. Standardized incidence ratios (SIRs) and 95% confidence intervals (CIs) for invasive HPV-associated cancers are presented across the following five risk periods relative to AIDS onset: a = 60–25 months before AIDS; b = 24–7 months before AIDS; c = 6 months before to 3 months after AIDS (the AIDS onset period); d = 4–27 months after AIDS; and e = 28–60 months after AIDS. The AIDS onset period was excluded from trend analyses. P_{trend} values were calculated by use of Poisson regression. All statistical tests were two-sided.

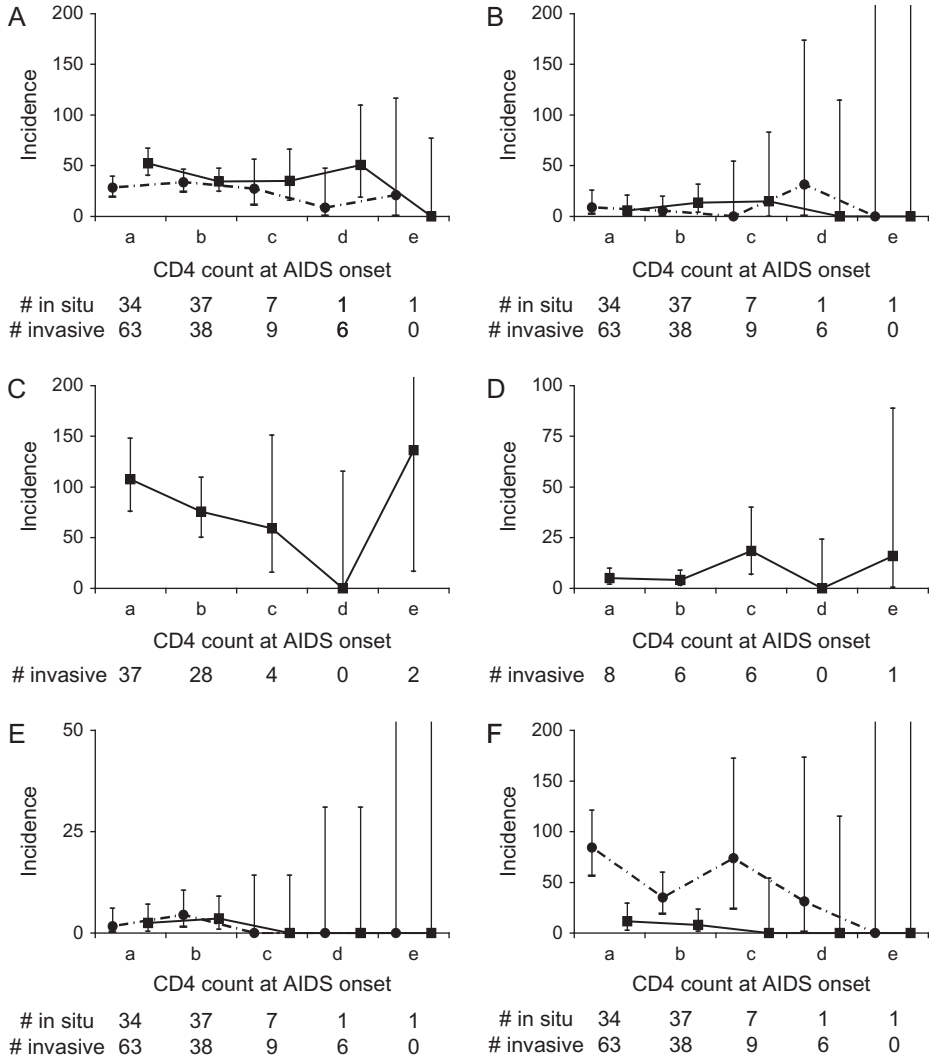

Figure 3. Incidence of in situ and invasive human papillomavirus (HPV)–associated cancers in the 4- to 60-month period after AIDS, according to CD4 T-cell count at AIDS onset. Incidence of HPV-associated cancers per 100 000 person-years is shown according to the following five CD4 T-cell count categories: a = 0–99 cells per cubic millimeter; b = 100–199 cells per cubic millimeter; c = 200–299 cells per cubic millimeter; d = 300–399 cells per cubic millimeter; and e = 400–499 cells per cubic millimeter. Analyses were restricted to persons diagnosed with AIDS during the era of highly active antiretroviral therapy (1996–2004). **A**) Anal cancer among men. **B**) Anal cancer among women. **C**) Cervical cancer. **D**) Oropharyngeal cancer. **E**) Cancer of the penis. **F**) Cancer of the vagina or vulva. **Broken lines** = in situ cancers; **solid lines** = invasive cancers. The number of cancer patients in each CD4 T-cell count category is also shown. **Error bars** = 95% confidence intervals.

invasive cervical cancer. Finally, in the HAART era (1996–2004), we found that incidence of anal cancer among men increased statistically significantly but that incidences of cancers of the cervix, oropharynx, penis, and vagina or vulva have remained stable.

The elevated risk of HPV-associated cancers among persons with AIDS that we observed is consistent with results from several previous studies (3–7) and reflects the increased incidence, prevalence, and persistence of HPV infections as well as a high prevalence of cofactors for such cancers, such as cigarette smoking, among persons infected with HIV (9–11,13,14,25). The increased risk of cervical cancer among women with AIDS may also reflect limited access to or use of screening programs for cervical cancer. The degree of immunosuppression, as reflected by a low CD4 T-cell count, is associated with increased HPV persistence and progression in severity of precursor lesions (9,11,26,27). Furthermore, increasing time after AIDS onset has been associated with an increased risk of in situ HPV-associated cancers (4). We might expect these associations of immunosuppression with earlier stages of HPV-associated carcinogenesis to also translate to associations with risk of invasive cancers. Previous analyses (4–6,16,22), however, have not found a direct relationship between immunosuppression and risk of invasive cancer.

In this study, a low CD4 T-cell count at AIDS diagnosis was associated with a statistically significantly increased risk of invasive cancer of the anus (among men) and with a non–statistically significantly increased risk of invasive cervical cancer. These associations of CD4 T-cell count with risk of HPV-related invasive cancers in the HAART era (1996–2004) are in contrast to observations from our previous analyses (4,16), which were restricted to the pre-HAART era (before 1996). We hypothesize that high mortality among individuals with a low CD4 T-cell count during the pre-HAART era masked an association between immunosuppression and the risk of HPV-related invasive cancer and that the increased survival during the HAART era provides adequate time for progression of premalignant or in situ lesions to invasive cancers. It should be noted that we used the CD4 T-cell count at AIDS onset as a marker for the degree of immunosuppression. However, during the HAART era, CD4 T-cell counts at AIDS onset would be expected to increase during the 4–60 months after AIDS onset. Systematic data on CD4 T-cell counts were not available and so repeated CD4 T-cell counts from individuals with AIDS could not be analyzed. Nonetheless, previous studies (28,29) have shown that improvements in CD4 T-cell counts that were related to HAART were strongly associated with the baseline CD4

Table 3. Association of human papillomavirus–associated cancer incidence in the 4–60 months after AIDS onset with CD4 T-cell count measured at AIDS onset (1996–2004)*

Cancer type	4–27 months after AIDS onset		28–60 months after AIDS onset		4–60 months after AIDS onset	
	RR (95% CI)†	*P* value‡	RR (95% CI)†	*P* value	RR (95% CI)†	*P* value
Anus (men)						
In situ	1.00 (0.75 to 1.34)	.967	1.10 (0.80 to 1.51)	.528	1.04 (0.84 to 1.29)	.666
Invasive	1.16 (0.88 to 1.51)	.278	1.59 (1.09 to 2.34)	.016	1.34 (1.08 to 1.66)	.006
Anus (women)						
In situ	1.20 (0.50 to 2.88)§	.673	—	—	1.23 (0.42 to 3.58)§	.693
Invasive	1.21 (0.27 to 5.37)§	.795	0.82 (0.40 to 1.68)§	.594	0.92 (0.42 to 2.01)§	.844
Cervix, invasive	1.46 (0.95 to 2.23)	.080	1.14 (0.75 to 1.73)	.522	1.32 (0.96 to 1.80)	.077
Oropharynx,‖ invasive	0.94 (0.50 to 1.76)	.853	0.58 (0.44 to 0.76)	<.001	0.72 (0.47 to 1.12)	.151
Penis						
In situ	0.84 (0.28 to 2.44)§	.748	1.18 (0.40 to 3.49)§	.757	1.00 (0.48 to 2.09)§	.989
Invasive	1.15 (0.47 to 2.79)§	.756	2.71 (0.28 to 25.99)§	.386	1.39 (0.56 to 3.47)§	.471
Vagina or vulva						
In situ	1.47 (0.75 to 2.87)	.251	1.59 (1.01 to 2.49)	.041	1.52 (0.99 to 2.35)	.055
Invasive	0.89 (0.36 to 2.17)§	.804	4.91 (1.02 to 23.60)§	.046	1.46 (0.61 to 3.50)§	.392

* RR = relative risk; CI = confidence interval; MSM = men who have sex with men.

† All relative risks per decline in CD4 T-cell count of 100 cells per cubic millimeter were adjusted for age at AIDS onset (15–29, 30–39, 40–49, or ≥50 years), race (white or nonwhite), and sex or mode of HIV infection (heterosexual or other modes among women; MSM or other modes among men; or women, MSM, or other men for non–sex-specific outcomes).

‡ Threshold for statistical significance was less than .05. *P* values were from Poisson regression models. All statistical tests were two-sided.

§ The relative risk was not adjusted for demographic factors because of the small number of events.

‖ Oropharynx includes cancers of the base of tongue, lingual and palatine tonsils, oropharynx, and Waldeyer ring.

T-cell count at the initiation of HAART (ie, individuals with a low CD4 T-cell count at the initiation of therapy continued to remain relatively more immunosuppressed than those with a high CD4 T-cell count).

For many individuals in the HAART era (1996–2004), the CD4 T-cell count at AIDS onset can be considered the "nadir" level of immunosuppression. Likewise, increased risk of HPV-associated cancers observed with increased time relative to the onset of AIDS (Figures 1 and 2 and Table 4) might occur because of prolonged but somewhat stable immunosuppression rather than to strictly advancing immunosuppression. Under either scenario, our observations indicate that HIV-related immunosuppression can influence later stages of the development of HPV-related cancers. It should, however, be noted that the association of CD4 T-cell count with invasive cancer risk over an extended period of time (eg, the 4–60 months after AIDS) is in contrast to results for Kaposi sarcoma and non-Hodgkin lymphoma, for which associations were strongest in the 6 months after the CD4 T-cell count was measured and then weakened statistically significantly thereafter (22). Therefore, given the long time interval between CD4 T-cell count and cancer incidence, it is unclear when immunosuppression is etiologically relevant during carcinogenesis of an HPV-related cancer. It is possible that poor immune control of premalignant lesions (eg, during earlier stages of HIV infection or at AIDS onset) facilitates the development of cancer and that later progression to invasive cancer is not affected by immunosuppression (9).

In contrast to the high risk of other HPV-associated cancers (SIRs of 5.3–34.6), the risk of invasive oropharyngeal cancer was only modestly statistically significantly elevated among persons with AIDS when compared with the general population (SIR = 1.6, 95% CI = 1.2 to 2.1). This modest increase in risk may reflect the fact that only a subset of oropharyngeal cancers is caused by HPV. Contemporary estimates (30) indicate that 60%–70% of oropharyngeal cancers may be HPV related; however, this proportion may have varied over calendar time (31). Furthermore, although unrelated to AIDS-relative time (5 years before to 5 years after AIDS onset), we observed that risk of oropharyngeal cancer was higher among persons with a relatively higher CD4 T-cell count at AIDS onset than among those with a lower count. The reasons for this paradoxical observation are unclear, but these results are consistent with reports (32–34) of increased oral HPV prevalence and persistence among HAART users and the increased incidence of oral warts among HIV-infected individuals after initiation of HAART regimens. Additional studies with information on the HPV status of individual tumors are needed to fully characterize the risk of HPV-associated oropharynx cancers among persons with AIDS.

HAART has not substantially altered HPV persistence or the rates of progression or regression of premalignant anogenital lesions (35–38), indicating that HAART may not restore HPV-specific immunity (9,35). Consequently, it has been speculated that the incidence of HPV-associated cancers may increase as persons with AIDS live longer in the HAART era (6,9,17). Consistent with this hypothesis and with recent reports (18–21), we observed that the incidence of in situ and invasive anal cancer among men was statistically significantly higher in the HAART era (1996–2004) than in the pre-HAART era (1980–1995). The incidence of in situ and invasive anal cancer was non–statistically significantly higher among women during the HAART era than during the pre-HAART era, although these analyses may not have had sufficient power to detect statistically significant differences. The increase in anal cancer in the HAART era may reflect the possibility that in the pre-HAART era, individuals at highest risk of anal cancer would have died from other causes. In addition, the increased

Table 4. Incidence of human papillomavirus–associated cancers in the 4–60 months after AIDS onset, according to calendar period and time period after AIDS onset*

	Calendar year								Time after AIDS onset 28–60 vs 4–27 mo	
	1980–1989			1990–1995		1996–2004				
Cancer	Incidence per 100 000 person-years	RR (95% CI)†	*P* value‡	Incidence per 100 000 person-years	RR (95% CI)†	Incidence per 100 000 person-years	RR (95% CI)†	*P* value	RR (95% CI)†	*P* value
Anus (men)										
In situ	1.7	0.08 (0.01 to 0.61)	.014	18.3	1.00 (ref)	29.5	1.71 (1.24 to 2.35)	<.001	1.26 (0.96 to 1.67)	.093
Invasive	10.5	0.48 (0.21 to 1.06)	.071	20.7	1.00 (ref)	42.3	2.03 (1.54 to 2.68)	<.001	1.26 (1.00 to 1.57)	.043
Anus (women)										
In situ	0.0	—	—	1.7	1.00 (ref)	5.2	3.89 (0.65 to 23.13)‡	.134	0.29 (0.07 to 1.12)‡	.072
Invasive	0.0	—	—	5.2	1.00 (ref)	11.2	1.75 (0.25 to 11.90)‡	.562	2.07 (0.49 to 8.69)‡	.316
Cervix										
In situ	177.3	0.34 (0.17 to 0.66)	.002	448.9	1.00 (ref)	—	—	—	0.74 (0.54 to 1.00)	.055
Invasive	70.9	0.81 (0.27 to 2.39)	.706	89.0	1.00 (ref)	90.4	1.03 (0.72 to 1.47)	.832	0.97 (0.71 to 1.32)	.858
Oropharynx,§ invasive	0.0	—	—	3.9	1.00 (ref)	6.5	1.34 (0.79 to 2.27)	.280	0.97 (0.62 to 1.53)	.907
Penis										
In situ	1.7	1.26 (0.21 to 7.58)	.794	1.7	1.00 (ref)	4.2	1.95 (0.85 to 4.45)	.111	2.09 (1.08 to 4.05)	.028
Invasive	0.0	—	—	1.3	1.00 (ref)	2.9	2.12 (0.65 to 6.82)	.207	0.58 (0.22 to 1.56)	.288
Vagina or vulva‖										
In situ	17.7	0.34 (0.04 to 2.40)	.279	54.1	1.00 (ref)	60.0	1.01 (0.67 to 1.53)	.939	1.51 (1.05 to 2.16)	.025
Invasive	0.0	—	—	6.9	1.00 (ref)	7.9	1.03 (0.37 to 2.90)	.942	1.61 (0.66 to 3.93)	.294

* RR = relative risk; CI = confidence interval; ref = referent; MSM = men who have sex with men.

† Multivariable models included terms for attained calendar year and AIDS-relative time period (28–60 months after AIDS onset vs 4–27 months after AIDS onset). The relative risks were adjusted for age at AIDS onset (15–29, 30–39, 40–49, or ≥50 years), race (white or nonwhite), and sex or mode of HIV infection (heterosexual or other modes among women; MSM or other modes among men; or women, MSM, or other men for non–sex-specific outcomes).

‡ These relative risks were not adjusted for demographic factors because of low event numbers.

§ Oropharynx includes cancers of the base of tongue, lingual and palatine tonsils, oropharynx, and Waldeyer ring.

‖ In situ vagina or vulva cancers included 23 vagina cancers and 100 vulva cancers; invasive vagina or vulva cancers included zero vagina cancer and 16 vulva cancers.

incidence of anal cancer among persons with AIDS could partly reflect temporal changes in the general population such as a birth cohort effect (39).

Another explanation for the recent rise in the incidence of anal cancers may relate to changes in screening practices. Among cancers that we evaluated, only cervical cancer and anal cancer have screening methods, and an apparent increase in incidence for anal cancer could have arisen if persons with AIDS were screened more intensively for this cancer in the HAART era than in the pre-HAART era. However, our findings of a similar stage at diagnosis and similar proportions of in situ anal cancers in 1990–1995 and in 1996–2004 argue against more intensive screening being involved.

Our study had several strengths. These strengths include its large size and the systematic evaluation of the risk of HPV-associated cancers among a representative sample of persons with AIDS in the United States.

Our study also had several limitations. We did not have information on cofactors for HPV-related cancers, such as cigarette smoking. The strategies that we used to assess relationships with immunosuppression also have limitations. For example, an increase in cancer incidence across AIDS-relative time (5 years before to 5 years after AIDS onset) may partly reflect an increase in medical surveillance after an AIDS diagnosis. Although we found associations between CD4 T-cell count measured at AIDS onset and the risk of HPV-related cancers for up to 5 years after the onset of AIDS, one CD4 T-cell count will not reflect fluctuations in immunosuppression over an extended period. Additionally, because all subjects in our study had AIDS, the low range of CD4 T-cell counts could have masked some associations. We did not have systematic information on HIV viral load, which is another marker of the degree of immunosuppression (40) that may be particularly relevant in the natural history of HPV infections and associated premalignant lesions (12). Finally, testing of multiple hypotheses in our analyses could have led to some chance associations, and our results must be interpreted in light of our sensitivity analyses that incorporated Bonferroni corrections. Nevertheless, we note that most associations that were statistically significant at the threshold of a P value of less than .05 were robust even at conservative Bonferroni-corrected thresholds of less than .005 or .004, including the increased incidence of in situ and invasive anal cancer among men during the HAART era.

In conclusion, we found an elevated risk of HPV-associated cancers among persons with AIDS. The increasing incidence for anal cancer during 1996–2004 indicates that prolonged survival may be associated with increased risk of certain HPV-associated cancers. This increase and the lack of decline in incidence of other HPV-associated cancers indicate that the risk of HPV-associated cancers among persons with AIDS remains high in the HAART era. Given that individuals currently infected with HIV infection may obtain little benefit from available HPV vaccines (because of a low proportion of individuals presumably being naive to vaccine-targeted HPV types) (17,41), our results underscore the need for effective screening for cervical cancer and anal cancer among persons with HIV infection or AIDS.

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