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Authors

Hernandez, Alexandra L
Efird, Jimmy T
Holly, Elizabeth A
et al.

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Risk factors for anal human papillomavirus infection type 16 among HIV-positive men who have sex with men in San Francisco

Alexandra L. Hernandez, PHD, MPH[1,2], **Jimmy T. Efird, PHD, MSc**[3], **Elizabeth A. Holly, PHD, MPH**[4], **J. Michael Berry, MD**[1], **Naomi Jay, N.P., PHD**[1], and **Joel M. Palefsky, MD**[1]

[1]Department of Medicine, University of California, San Francisco, San Francisco, CA

[2]School of Public Health, Department of Epidemiology, University of California, Berkeley, Berkeley, CA

[3]Center for Health Disparities Research and Department of Public Health, Brody School of Medicine, Greenville, NC

[4]Department of Epidemiology and Biostatistics, University of California, San Francisco, San Francisco, CA

Abstract

Background and Objective—HIV-positive men who have sex with men (MSM) are at high risk of anal cancer compared with the general population. Human papillomavirus (HPV) infection, particularly HPV 16, is causally associated with anal cancer. However, risk factors for anal HPV 16 infection are poorly understood. We determined the prevalence and risk factors for anal HPV 16 infection in a population of HIV-positive MSM, most of whom were being treated with antiretroviral therapy.

Design—Cross-sectional data from the baseline visit of a 4-year prospective cohort study.

Methods—348 HIV-positive MSM were recruited in San Francisco and received a detailed sexual behavior risk-factor questionnaire. An anal swab was used to collect specimens for HPV type-specific DNA testing using L1 HPV DNA PCR. We used log-binomial multivariable models to determine risk factors for anal HPV 16 infection.

Corresponding author and requests for reprints: Alexandra L. Hernandez, PhD, MPH, Division of Infectious Diseases, University of California, San Francisco, Box 0654, 513 Parnassus Ave, Room S420, San Francisco CA 94143, Tel: 415-502-0515, Fax: 415-476-9364, alexandra.hernandez@ucsf.edu.

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Results—92% of HIV-positive MSM had at least one anal HPV type, 80% had at least one oncogenic HPV type and 42% had HPV 16. Non-Hispanic white race and higher level of education were associated with a decreased risk of HPV 16 infection. A higher number of total male partners was associated with HPV 16 (RR: 1.6, 95%CI 1.1–2.4, p=0.01) for 201–1000 partners compared with 1–200. Injection drug use (IDU) was independently associated with anal HPV 16 infection (RR: 1.5, 95%CI 1.2–1.9, p=0.003).

Conclusions—The prevalence of anal HPV infection, including HPV 16, is high in HIV-positive MSM. HIV-positive MSM should be counseled about the risk associated with increased partners and IDU.

Keywords

Human papillomavirus; HPV; HIV/AIDS; men who have sex with men; MSM; anal cancer

Introduction

The incidence of anal cancer is substantially higher among HIV-negative men who have sex with men (MSM) than among men in the general population, with an incidence of up to 37 per 100,000 [1]. Among MSM who are also HIV-positive, the incidence rates have been reported to be even higher at 131 per 100,000 [2]. The high rates of anal cancer in this population have not been reduced by antiretroviral therapy (ART), and several papers have documented that the incidence of anal cancer has stayed high or continued to rise, even after the introduction of ART [2–7].

Similar to cervical cancer, which is preceded by high-grade cervical intraepithelial neoplasia (CIN 2 or 3), anal cancer is preceded by high-grade anal intraepithelial neoplasia (HGAIN, AIN 2 or 3). Consistent with the anal cancer data, HIV-positive MSM have higher rates of HGAIN than HIV-negative MSM [8–13]. Furthermore, anal cancer and AIN are associated with human papillomavirus (HPV) infection, particularly HPV 16 infection. Approximately 90% of anal cancers have detectable HPV DNA; two-thirds of those have HPV 16 and another 9 percent have HPV 18 [14]. The US Food and Drug Administration (FDA) recently approved an HPV vaccine that has been shown to be effective in preventing HGAIN and anal HPV 16 and 18 infection in healthy MSM [15], and thus a large proportion of anal cancers are potentially preventable through vaccination.

Consistent with the increased risk of anal cancer and HGAIN, multiple studies have shown that MSM are at high risk for anal HPV infection and that HIV-positive MSM are at even greater risk than HIV-negative MSM [11, 13, 16–21]. The prevalence of anal HPV infection in HIV-negative MSM has been reported to be between 32% and 60% [19, 22–25] and almost all HIV-positive MSM have detectable anal HPV infection [19, 26, 27]. A recent meta-analysis that included 21 studies of HIV -positive MSM reported a summary prevalence estimate of any HPV infection of 92.6% (90.8–94.5) [28].

Cervical HPV infection in women is sexually transmitted [29] and there is convincing evidence that penile HPV infection also is sexually transmitted in men. Younger age of first sexual experience [30], anal intercourse [19, 25, 31], and number of sexual partners [25, 32–

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34] all have been shown to increase the risk of penile HPV infection in both heterosexual men and MSM. However, there are few data available on risk factors for anal HPV infection among men, including anal HPV 16 specifically, but sexual routes such as receptive anal intercourse have been associated with increased risk of anal HPV infection [16, 19, 35].

Epidemiologic assessment of risk factors for anal HPV infection of any type has been limited by the high proportion of this population that is anal HPV positive. Most previous studies that investigated the relationship between sexual behaviors and anal HPV infections also have been limited in the number and types of sexual behaviors assessed, and often have not distinguished between insertive and receptive anal intercourse. Additionally, many studies have not controlled for potential confounding factors when assessing the relationship between sexual practices and anal HPV infection. We previously conducted a cross-sectional study prior to the introduction of antiretroviral therapy (ART) and showed that 93% of HIV-positive MSM had anal HPV infection and 38% were infected with HPV 16 [20]. Here we report the results from the baseline visit of a prospective study designed to assess the natural history of anal HPV infection among MSM to better understand sexual risk factors in the post-ART era. The goal of this analysis was to identify sexual behaviors associated with prevalent anal HPV infection in HIV-positive MSM, many of whom were receiving ART. We focused our analysis on HPV 16, because HPV 16 is the type most associated with anal cancer.

Methods

HIV-positive MSM were recruited to participate in a 4-year prospective follow-up study conducted by the University of California, San Francisco (UCSF), through newspaper advertisements and other community outreach. Participants were enrolled from 1998–2001. At the baseline visit, 348 participants completed an interviewer-administered questionnaire and clinical examination that included collection of two anal swabs to test for HPV and for cytology. All participants also had high-resolution anoscopy (HRA) to detect anal lesions. Blood was collected for CD4+ lymphocyte counts that were measured by standardized two- or three-color fluorescence methods. Plasma HIV viral load (HIV VL) was measured using the branched-chain Chiron assay (Chiron, Emeryville, California, USA). All procedures were performed after obtaining written informed consent from each study participant. The study was approved by the UCSF Committee on Human Research.

Tests for HPV anal infection were performed as described previously using the polymerase chain reaction (PCR) with L1 consensus primers and probes specific for 29 individual HPV types and a mixture of 10 other types [19]. Beta-globin-negative samples (n=30) were excluded from analysis. We report the prevalence of each type separately, the prevalence of infection with any oncogenic HPV type, and the prevalence any HPV infection defined as positive with the consensus probe mixture. We defined infection with an oncogenic HPV as a positive test for at least one of the following HPV types: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, and 82 [36]. No HPV vaccine was available for use in men at the time of participant enrollment.

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Assessment of potential risk factors

Demographics, lifestyle characteristics (including smoking, alcohol and recreational drug use), medical history including self-reported history of sexually transmitted infections, prescription medication use and history of sexual behavior were collected through an interviewer-administered questionnaire. We asked about sexual behaviors in two time periods: lifetime and within the past 30 days. Men were queried about multiple types of sexual behaviors including sex with men and women, “insertive” anal intercourse (participant inserts his penis into partner’s anus) and “receptive” anal intercourse (participant receives his partner’s penis into his anus), oral-anal contact (“rimming,” participant’s anus receives contact from partners mouth), and use of objects in the anus.

Statistical analysis

Characteristics thought to be related to prevalent HPV infection were examined for association with HPV 16. Bivariable associations between anal HPV infection (no oncogenic types, oncogenic types other than HPV 16, and HPV 16) were assessed through chi-square tests, analysis of variance (ANOVA) or ranked ANOVA as appropriate. Relative risks (RRs) for HPV 16 were estimated using log-binomial regression. Robust variance approximation was used to determine the 95% confidence intervals (CIs) for the RR estimates. We selected potential sexual risk factors to analyze, as well as potential confounders *a priori,* based on a review of the literature of existing risk factors for HPV infection in men and women. Because the sexual risk behaviors were correlated (r>=0.5) and thought to be on similar causal pathways, they were each evaluated in separate multivariable models. Multivariable models were constructed for the association of each of the selected sexual risk factors with HPV 16 adjusted for age, race, education, ever smoked 100+ cigarettes, and CD4+ level. Tests for trend were computed, where appropriate, by assigning ordinal dose-specific categories, fitting this variable as a continuous linear term and testing the significance of the regression coefficient using the likelihood ratio test. Model fit was assessed using the Hosmer-Lemeshow goodness-of-fit test for log-binomial models [37].

Results

A total of 348 HIV-positive men were evaluated for anal HPV infections and of these, samples from 30 (8.6%) were found to be β-globin negative and excluded from further analyses. The average age of the 318 men included in the analyses was 43 years, 88% were non-Hispanic white, 2% were black, 7% were Hispanic, and 1.6% were Asian (Table 1). Sixty-six percent of men had completed college, 52% reported smoking more than 100 cigarettes in their lifetime and 87% reported drinking alcohol in the past 12 months.

Only 9% of our study population had been diagnosed with HIV in the past 12 months. The mean CD4+ level was 446 cells/mL. Seventeen percent had a CD4+ level less than 200 cells/mL, 47% had 200–500 cells/mL, and 36% had more than 500 cells/mL. Most of our participants had HIV viral load levels of <500 (54%) copies/mL, the limit of detectability at the time of the study. Most participants (83%) were taking antiretroviral medications for their HIV disease at the time of the study.

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Participants self-reported a high number of lifetime sexual partners (Table 2). Over 70% said that they had more than 200 total lifetime male partners and 29% had more than 200 lifetime male partners with whom they were the receptive partner. Almost all men (93%) reported a history of receptive oral-anal contact (rimming) and 61% said that they had had objects inserted in the anus in the past 5 years.

Prevalence of anal HPV

The overall and type-specific prevalence of anal HPV infection are presented in Figure 1. 92% of men tested positive for at least one type of HPV. The five most common types were HPV 6 (45%), HPV 16 (42%), HPV 11 (31%), HPV 33 (30%) and HPV 18 (20%). Oncogenic HPV infection was very common with 80% of men positive for at least one oncogenic HPV type. Multiple HPV infections also were common with a mean of 5 HPV types among participants positive for at least one identifiable HPV type.

Risk factors for anal HPV 16 infection

Table 3 presents the unadjusted and adjusted associations of risk factors for anal HPV 16 infection. In unadjusted bivariable analyses, education, smoked 100+ lifetime cigarettes, history of IDU, history of anogenital gonorrhea infection, lower CD4+ level, higher total lifetime male partners, and higher total lifetime partners with whom the participant was the insertive partner were significantly associated with anal HPV 16 infection ($p \leq 0.05$). Bivariable associations between the above risk factors and anal HPV infection (no oncogenic types, oncogenic types other than HPV 16, and HPV 16) were similar to associations found in Table 3 (see Table, Supplemental Digital Content 1).

Non-Hispanic white participants had significantly lower risk of having anal HPV 16 infection after adjustment for age, education, smoking and CD4+ level (adjusted relative risk (aRR): 0.5, 95% CI: 0.03–1.0). Education was also associated with a lower risk of anal HPV 16 infection when participants who completed college were compared with those who did not (aRR 0.7, (0.5–0.9)). When participants who completed graduate school were compared with those who did not complete college, a similar aRR was found, although the 95% CI overlapped unity.

A history of IDU (intravenous drug use/intravenous drug users) was associated with an increased risk of anal HPV 16 infection with an aRR of 1.5 (1.1–1.9). Although other recreational drug use was prevalent in this population, none of the other drugs examined were found to be statistically significantly associated with anal HPV 16. A history of an anogenital gonorrhea infection also was associated with an increased risk of anal HPV 16 (aRR 1.7 (1.2–2.5)).

Among the sexual risk factors examined, total lifetime number of male partners increased risk of infection with an aRR of 1.6 (1.1 – 2.4) when 201–1000 partners was compared with 1–200 partners and an aRR of 1.5 (1.0 – 2.2) when 1000+ partners was compared with 1–200 partners (although the latter 95% CI overlapped unity).

A history of smoking more than 100 lifetime cigarettes and CD4+ level did not retain statistical significance in multivariable adjusted models. HIV VL, receptive male partners (in

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any time period), oral-anal contact, use of objects in the anus, and total male partners in the past 30 days were not associated with anal HPV 16 infection in either unadjusted or adjusted analyses. Tests for trend were not statistically significant in for any variable examined. The Hosmer-Lemeshow goodness-of-fit test showed no evidence of lack of fit (p-values all were above 0.05).

Discussion

The results of this study support the findings from our earlier pre-ART study of a high prevalence of anal HPV infection among HIV-positive MSM in San Francisco. In this population of HIV-positive men where 80% were taking ART, almost all men had a prevalent case of anal HPV infection and 80% were positive for at least one oncogenic HPV type. This is consistent with other recent studies that also found a high prevalence of anal HPV in HIV-positive MSM in the post-ART era. Chin-Hong (2008) found a prevalence of 88% among the HIV-positive MSM in their population-based San Francisco based study [24]. De Pokomandy et al (2009) found an even higher prevalence of anal HPV with 98% of their Canadian HIV-positive MSM [26]. An Australian study and a recent French study both also had similarly high prevalence of anal HPV in their HIV-infected MSM [27, 38] and a recent meta-analysis computed a summary prevalence estimate of 92.6% (90.8–94.5) [28]. This very high prevalence is of great concern in these populations given the strong correlation between anal HPV and anal cancer. Antiretroviral medications have not been shown to impact the risk of anal cancer in HIV-positive populations [39] and based on our data and those of others, ART also does not seem to impact the prevalence of anal HPV in HIV-positive MSM.

We chose to examine risk factors for HPV 16 as an individual type because it is biologically more aggressive than the other HPV types, it is the most common HPV type in anal cancer, and it is also more likely to be associated with HGAIN [40]. In our analysis, we found that HIV-positive MSM who reported being non-Hispanic white had a lower risk of anal HPV 16 infection than those of other racial/ethnic backgrounds. This is in contrast to reports where non-Hispanic whites in the general population generally have higher anal cancer incidence rates [41, 42]. Men who had completed college also had lower risk of HPV 16 infection. Race and education were correlated and non-Hispanic white men were more likely to have completed college and graduate school (data not shown). The associations seen with race and education may be markers of socio-economic status. Individuals with lower socio-economic status are known to have increased risks of many poor health outcomes [43–45]. However, there may be other factors not explored here or a direct association between race and HPV infection and more work is needed in this area before a conclusion can be made.

Having a self-reported history of any anogenital gonorrhea infection was associated with an increased risk of anal HPV 16 infection, although there was no increase in risk associated with anal gonorrhea, specifically. Having a sexually transmitted infection such as gonorrhea is likely to be a marker for having had a high number of sexual partners. Among our participants, men who had 1000 or more lifetime partners were 2.5 times more likely to have had an anogenital gonorrhea infection than men with 0–100 partners (data not shown, p=<0.01). However when a multivariable model was run that included anogenital gonorrhea

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and number of total male partners, anogenital gonorrhea remained significant in the model (data not shown). There may be some biological interaction between the two infections or perhaps in an immune response to the infections. Because this is a cross-sectional analysis, we do not know which infection came first and this relationship should be further evaluated in longitudinal analyses.

These analyses identified a potentially new risk factor for HPV 16 infection, injection drug use. In our multivariable model, IDU was associated with HPV 16 infection with a 50% increased risk of anal HPV 16 infection for HIV-positive MSM who are IDU. We ran secondary analyses including total number of male partners or total number of receptive partner to the final adjusted model including IDU. The addition of either variable did not change the RR or increase the p-value to a non-significant level (data not shown). This result is consistent with an earlier study that found that 46% of heterosexual HIV-positive IDU had anal HPV infection in the absence of receptive anal intercourse [21]. This same study reported that the median CD4+ level was significantly lower in the IDU group than the non-IDU HIV-positive MSM comparison group. Although our results were adjusted for CD4+ level this may suggest that there is a biological interaction between immune status and IDU. Another possibility is that IDU engaged in riskier sex behaviors. It has been observed that men who use injection drugs are less likely to use condoms than men who are not IDU [46]. Another study had findings consistent with ours, although among HIV-negative MSM [35]. Chin-Hong et al investigated risk factors for AIN and found an odds ratio of 17 for participants reporting IDU ≥2 times per month in the past 6 months than those who had never used injection drugs [35]. HIV-positive MSM who also are IDU may have an even higher risk of HPV 16 infection, and thus be at a higher risk for anal cancer than those who do not use injection drugs. This finding should be investigated in future studies and patients should be queried about injection drug use.

In our analysis, we found an increased risk of anal HPV 16 infection associated with an increased number of male partners, consistent with previously published studies [16, 47]. This increased risk was found for a higher number partners with whom the participants were the insertive partner but not the receptive partner. However in our population, only 3 of our participants reported never having had receptive anal sex and 93% had more than 10 lifetime receptive partners. Our study sample did not have a comparison group of men ‘unexposed’ to receptive anal sex. Thus, total number of partners may be a better marker for exposure because it captures both insertive and receptive intercourse, as well as other sexual behaviors that may provide anal exposure to HPV.

A limitation to this study was that we did not collect condom use as part of the sexual behavior history. This possible confounder could have masked an association with receptive intercourse. In addition, because drug users are known to engage in riskier sexual behavior, such as receptive sex without a condom, this may potentially explain our association with injection drug use. Men may also have over- or under-reported sexual behaviors to the interviewer which may have introduced some misclassification of exposure bias into our estimates, but because men were not aware of their HPV 16 status at the time of the interview, the bias would likely be toward the null. Also, we compared men with HPV 16 with men who did not have HPV 16, which may have also introduced misclassification bias

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because men with HPV types other than HPV 16 were included in our comparison group. This would have resulted in reduced RRs and our estimates should be considered conservative. Another limitation to these analyses is that it was cross-sectional. It is possible that the risk factors that we identified are not associated with acquisition of infection, but persistence of infection. Finally because our study focused on HIV-positive MSM living in San Francisco, a large urban area, our results may not be generalizable to all MSM living in other areas of the country.

In summary, our data are consistent with existing literature that anal HPV infection is common among HIV-positive MSM during the era of ART. The high prevalence of HPV 16, the most common HPV type associated with anal cancer, is of particular concern. Our risk factor analyses confirmed a role for sexual transmission of anal HPV 16 infection. The association between IDU and anal HPV 16 infection is notable and should be explored further. Based on our results and other recent publications, we recommend that HIV-positive MSM be counseled regarding anal cancer prevention strategies emphasizing safe-sex behaviors with all partners and include information on the increased risk of anal HPV infection with an increasing number of male partners. Additionally, public health efforts that focus on high-risk groups should consider targeting IDU and men of races other than non-Hispanic white and men who have not completed college.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. 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; 317:973–977. [PubMed: 2821396]
2. Silverberg MJ, Lau B, Justice AC, Engels E, Gill MJ, Goedert JJ, et al. Risk of Anal Cancer in HIV-Infected and HIV-Uninfected Individuals in North America. Clin Infect Dis. 2012
3. Bower M, Palmieri C, Dhillon T. AIDS-related malignancies: changing epidemiology and the impact of highly active antiretroviral therapy. Curr Opin Infect Dis. 2006; 19:14–19. [PubMed: 16374212]
4. Bower M, Powles T, Newsom-Davis T, Thirlwell C, Stebbing J, Mandalia S, et al. HIV-associated anal cancer: has highly active antiretroviral therapy reduced the incidence or improved the outcome? J Acquir Immune Defic Syndr. 2004; 37:1563–1565. [PubMed: 15577408]
5. Chiao EY, Krown SE, Stier EA, Schrag D. A population-based analysis of temporal trends in the incidence of squamous anal canal cancer in relation to the HIV epidemic. J Acquir Immune Defic Syndr. 2005; 40:451–455. [PubMed: 16280701]

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6. Palefsky JM, Holly EA, Ralston ML, Da Costa M, Bonner H, Jay N, et al. Effect of highly active antiretroviral therapy on the natural history of anal squamous intraepithelial lesions and anal human papillomavirus infection. J Acquir Immune Defic Syndr. 2001; 28:422–428. [PubMed: 11744829]
7. Hessol NA, Pipkin S, Schwarcz S, Cress RD, Bacchetti P, Scheer S. The impact of highly active antiretroviral therapy on non-AIDS-defining cancers among adults with AIDS. Am J Epidemiol. 2007; 165:1143–1153. [PubMed: 17344204]
8. 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; 46:203–206. [PubMed: 2166709]
9. Caussy D, Goedert JJ, Palefsky J, Gonzales J, Rabkin CS, DiGioia RA, et al. Interaction of human immunodeficiency and papilloma viruses: association with anal epithelial abnormality in homosexual men. Int J Cancer. 1990; 46:214–219. [PubMed: 2166710]
10. Critchlow CW, Holmes KK, Wood R, Krueger L, Dunphy C, Vernon DA, et al. Association of human immunodeficiency virus and anal human papillomavirus infection among homosexual men. Arch Intern Med. 1992; 152:1673–1676. [PubMed: 1323247]
11. 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; 7:43–49. [PubMed: 8382927]
12. Palefsky JM, Shiboski S, Moss A. Risk factors for anal human papillomavirus infection and anal cytologic abnormalities in HIV-positive and HIV-negative homosexual men. J Acquir Immune Defic Syndr. 1994; 7:599–606. [PubMed: 8176644]
13. 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; 17:320–326. [PubMed: 9525432]
14. Munoz N, Bosch FX, Castellsague X, Diaz M, de Sanjose S, Hammouda D, et al. Against which human papillomavirus types shall we vaccinate and screen? The international perspective. Int J Cancer. 2004; 111:278–285. [PubMed: 15197783]
15. Administration FaD. FDA: Gardasil approved to prevent anal cancer. 2010 FDA Press release.
16. 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; 12:1177–1184. [PubMed: 9677167]
17. Kiviat N, Rompalo A, Bowden R, Galloway D, Holmes KK, Corey L, et al. Anal human papillomavirus infection among human immunodeficiency virus-seropositive and - seronegative men. J Infect Dis. 1990; 162:358–361. [PubMed: 1973695]
18. 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; 17:314–319. [PubMed: 9525431]
19. 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; 177:361–367. [PubMed: 9466522]
20. 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. [PubMed: 9543448]
21. Piketty C, Darragh TM, Da Costa M, Bruneval P, Heard I, Kazatchkine MD, et al. High prevalence of anal human papillomavirus infection and anal cancer precursors among HIV-infected persons in the absence of anal intercourse. Ann Intern Med. 2003; 138:453–459. [PubMed: 12639077]
22. Dunne EF, Nielson CM, Stone KM, Markowitz LE, Giuliano AR. Prevalence of HPV infection among men: A systematic review of the literature. J Infect Dis. 2006; 194:1044–1057. [PubMed: 16991079]
23. van der Snoek EM, Niesters HG, Mulder PG, van Doornum GJ, Osterhaus AD, van der Meijden WI. Human papillomavirus infection in men who have sex with men participating in a Dutch gay-cohort study. Sex Transm Dis. 2003; 30:639–644. [PubMed: 12897686]

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24. Chin-Hong PV, Berry JM, Cheng SC, Catania JA, Da Costa M, Darragh TM, et al. Comparison of patient- and clinician-collected anal cytology samples to screen for human papillomavirus-associated anal intraepithelial neoplasia in men who have sex with men. Ann Intern Med. 2008; 149:300–306. [PubMed: 18765699]
25. Chin-Hong PV, Vittinghoff E, Cranston RD, Buchbinder S, Cohen D, Colfax G, et al. Age-Specific prevalence of anal human papillomavirus infection in HIV-negative sexually active men who have sex with men: the EXPLORE study. J Infect Dis. 2004; 190:2070–2076. [PubMed: 15551204]
26. de Pokomandy A, Rouleau D, Ghattas G, Vezina S, Cote P, Macleod J, et al. Prevalence, clearance, and incidence of anal human papillomavirus infection in HIV-infected men: the HIPVIRG cohort study. J Infect Dis. 2009; 199:965–973. [PubMed: 19239366]
27. Vajdic CM, van Leeuwen MT, Jin F, Prestage G, Medley G, Hillman RJ, et al. Anal human papillomavirus genotype diversity and co-infection in a community-based sample of homosexual men. Sex Transm Infect. 2009; 85:330–335. [PubMed: 19342375]
28. Machalek DA, Poynten M, Jin F, Fairley CK, Farnsworth A, Garland SM, et al. Anal human papillomavirus infection and associated neoplastic lesions in men who have sex with men: a systematic review and meta-analysis. Lancet Oncol. 2012; 13:487–500. [PubMed: 22445259]
29. zur Hausen H. Papillomaviruses in the causation of human cancers - a brief historical account. Virology. 2009; 384:260–265. [PubMed: 19135222]
30. Castellsague X, Ghaffari A, Daniel RW, Bosch FX, Munoz N, Shah KV. Prevalence of penile human papillomavirus DNA in husbands of women with and without cervical neoplasia: a study in Spain and Colombia. J Infect Dis. 1997; 176:353–361. [PubMed: 9237700]
31. Lajous M, Mueller N, Cruz-Valdez A, Aguilar LV, Franceschi S, Hernandez-Avila M, et al. Determinants of prevalence, acquisition, and persistence of human papillomavirus in healthy Mexican military men. Cancer Epidemiol Biomarkers Prev. 2005; 14:1710–1716. [PubMed: 16030106]
32. Kjaer SK, Munk C, Winther JF, Jorgensen HO, Meijer CJ, van den Brule AJ. Acquisition and persistence of human papillomavirus infection in younger men: a prospective follow-up study among Danish soldiers. Cancer Epidemiol Biomarkers Prev. 2005; 14:1528–1533. [PubMed: 15941967]
33. Franceschi S, Castellsague X, Dal Maso L, Smith JS, Plummer M, Ngelangel C, et al. Prevalence and determinants of human papillomavirus genital infection in men. Br J Cancer. 2002; 86:705–711. [PubMed: 11875730]
34. Svare EI, Kjaer SK, Worm AM, Osterlind A, Meijer CJ, van den Brule AJ. Risk factors for genital HPV DNA in men resemble those found in women: a study of male attendees at a Danish STD clinic. Sex Transm Infect. 2002; 78:215–218. [PubMed: 12238658]
35. Chin-Hong PV, Vittinghoff E, Cranston RD, Browne L, Buchbinder S, Colfax G, et al. Age-related prevalence of anal cancer precursors in homosexual men: the EXPLORE study. J Natl Cancer Inst. 2005; 97:896–905. [PubMed: 15956651]
36. Munoz N, Bosch FX, de Sanjose S, Herrero R, Castellsague X, Shah KV, et al. Epidemiologic classification of human papillomavirus types associated with cervical cancer. N Engl J Med. 2003; 348:518–527. [PubMed: 12571259]
37. Blizzard L, Hosmer DW. Parameter estimation and goodness-of-fit in log binomial regression. Biom J. 2006; 48:5–22. [PubMed: 16544809]
38. Damay A, Fabre J, Costes V, Didelot JM, Didelot MN, Boulle N, et al. Human papillomavirus (HPV) prevalence and type distribution, and HPV-associated cytological abnormalities in anal specimens from men infected with HIV who have sex with men. J Med Virol. 82:592–596. [PubMed: 20166175]
39. Palefsky J. Human papillomavirus-related disease in people with HIV. Curr Opin HIV AIDS. 2009; 4:52–56. [PubMed: 19339939]
40. IARC. Human papillomaviruss. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. 2007; 90
41. 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; 92:1500–1510. [PubMed: 10995805]

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42. Benard VB, Johnson CJ, Thompson TD, Roland KB, Lai SM, Cokkinides V, et al. Examining the association between socioeconomic status and potential human papillomavirus-associated cancers. Cancer. 2008; 113:2910–2918. [PubMed: 18980274]

43. Karlamangla AS, Merkin SS, Crimmins EM, Seeman TE. Socioeconomic and ethnic disparities in cardiovascular risk in the United States, 2001–2006. Ann Epidemiol. 2010; 20:617–628. [PubMed: 20609342]

44. Kondo N. Socioeconomic disparities and health: impacts and pathways. J Epidemiol. 2012; 22:2–6. [PubMed: 22156290]

45. Vona-Davis L, Rose DP. The influence of socioeconomic disparities on breast cancer tumor biology and prognosis: a review. J Womens Health (Larchmt). 2009; 18:883–893. [PubMed: 19514831]

46. Celentano DD, Latimore AD, Mehta SH. Variations in sexual risks in drug users: emerging themes in a behavioral context. Curr HIV/AIDS Rep. 2008; 5:212–218. [PubMed: 18838061]

47. Palefsky JM. Human papillomavirus infection and anogenital neoplasia in human immunodeficiency virus-positive men and women. J Natl Cancer Inst Monogr. 1998:15–20. [PubMed: 9709296]

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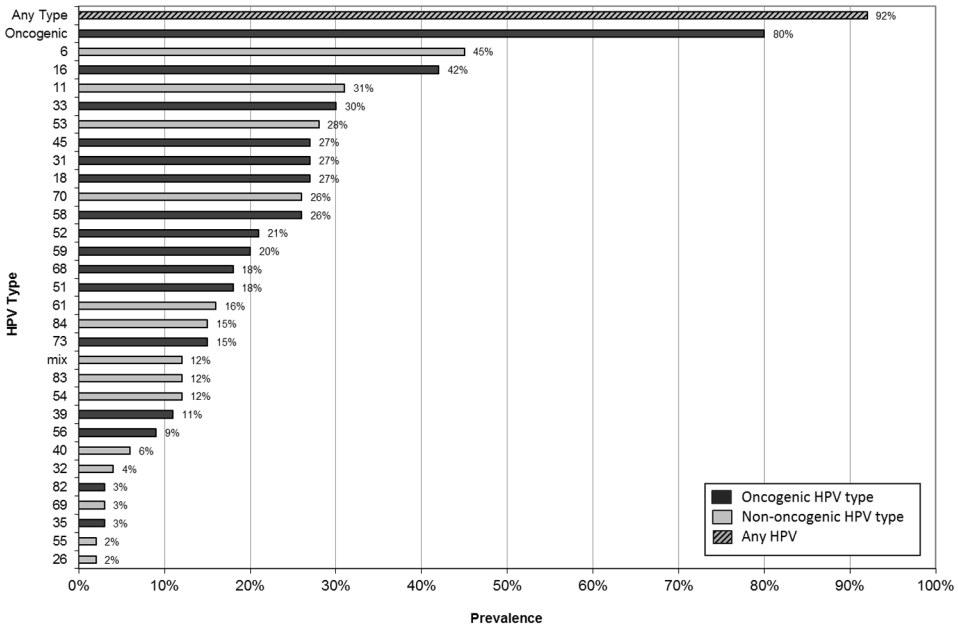

Figure 1.

Prevalence of HPV infection by type among HIV-positive men who have sex with men in San Francisco, CA. Figure includes only the 318 men whose anal swab specimens were β-globin DNA-positive. Men who had more than one prevalent HPV type are included in each prevalence calculation for which they were positive.

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Table 1

Socio-demographic and lifestyle characteristics of HIV-positive men who have sex with men (n=318)* in San Francisco, CA

Characteristic	(%)
Demographics	
Age (years), mean (± SD)	42.5 (±7.7)
Race/ethnicity	
Non-Hispanic white	281 (88.4)
Black	7 (2.2)
Asian	5 (1.6)
Hispanic	22 (6.9)
Other	3 (0.9)
Education	
Did not complete college	140 (44)
Completed college	91 (28.6)
Completed graduate school	87 (27.4)
Substance use	
Smoked >100 lifetime cigarettes	164 (51.6)
How many days per week drank alcohol	
<1 day/week	173 (54.4)
1–2 days/week	81 (25.5)
3–7 days/week	64 (20)
Ever used speed	222 (70)
Ever injection drug use (IDU)	67 (21.1)
Medical history	
Ever anal or genital warts	237 (74.5)
Ever any gonorrhea infection	226 (71.3)
CD4+ (cells/mL)	
<200	53 (16.9)
200–500	147 (46.8)
>500	114 (36.3)
HIV viral load (copies/mL)	
<500	169 (53.8)
500–4000	54 (17.2)
4001–20,000	49 (15.6)
>20,000	42 (13.4)
Currently taking antiretroviral therapy	
No	53 (16.9)
Yes	260 (83.1)

* Includes only those men whose anal swab specimens were β-globin DNA-positive.

When totals do not reach 318, data were missing; SD, Standard deviation

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Table 2

Sexual behavior of MSM (n=318)* in San Francisco, CA

Characteristic	N (%)
Lifetime sexual behavior	
Number of female partners	
0	113 (35.5)
1–4	135 (42.5)
5+	70 (22)
Number of male total partners	
1–200	92 (28.9)
201–1000	126 (39.6)
1000+	100 (31.4)
Number of partners with whom participant is the receptive partner	
0–50	142 (45.1)
51–200	80 (25.4)
201+	93 (29.5)
Number of anal sex partners with whom participant is the insertive partner	
0–50	136 (42.9)
51–200	95 (30)
201+	86 (27.1)
Ever had receptive oral-anal contact (been rimmed by) partner	296 (93.1)
Number of receptive oral-anal contact (rimming) partners	
0–10	128 (40.3)
11–50	103 (32.4)
51+	87 (27.4)
Sexual behavior in past 5 years	
Any objects inserted into anus	194 (61)
Sexual behavior in past 12 months	
Number of partners with whom participant is the receptive anal sex partner, mean (±SD)	7.5 (±17.3)
Number of partners with whom participant is the insertive anal sex partner, mean (±SD)	6.9 (±15.4)
Sexual behavior in past 30 days	
Number of partners with whom participant is the receptive anal sex partner, mean (±SD)	1.2 (±3.3)
Number of partners with whom participant is the insertive anal sex partner, mean (±SD)	1.2 (±2.9)

*Includes only those men whose anal swab specimens were β-globin DNA-positive.

When totals do not reach 318, data were missing; SD, Standard deviation

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Table 3

Risk factors for prevalent HPV 16 infection among MSM (n=318)*

	Unadjusted†		Adjusted‡	
Characteristic	**RR (95% CI)**	**P-value**	**RR (95% CI)**	**P-value**
Age in years	1.00 (0.98 – 1.02)	0.87	1.00 (0.99 – 1.02)	0.55
White race (compared with all others)	0.56 (0.32 – 1.02)	0.06	0.53 (0.29 – 0.95)	0.04
Education				
Did not complete college	1.0		1.0	
Completed college	0.73 (0.53 – 1.02)	0.06	0.67 (0.48 – 0.93)	0.02
Completed graduate school	0.70 (0.50 – 0.98)	0.04	0.70 (0.49 – 1.00)	0.05
Smoked 100+ lifetime cigarettes	1.3 (1.01 – 1.7)	0.05	1.2 (0.93 – 1.6)	0.14
History of injection drug use	1.6 (1.2 – 2.0)	0.0007	1.5 (1.1 – 1.9)	0.007
Used marijuana in past 12 months				
Did not use	1.0		1.0	
Used once	0.77 (0.52 – 1.2)	0.21	0.76 (0.52 – 1.1)	0.21
Used more than once	1.3 (0.95 – 1.8)	0.10	1.1 (0.81– 1.5)	0.53
History of speed use	1.2 (0.85 – 1.6)	0.40	1.1 (0.79 – 1.5)	0.65
History of anogenital gonorrhea infection	1.7 (1.2 – 2.4)	0.005	1.7 (1.2 – 2.5)	0.004
CD4+ level				
<200	1.0		1.0	
200–500	0.85 (0.61 – 1.2)	0.34	0.96 (0.68 – 1.3)	0.80
>500	0.68 (0.46 – 0.99)	0.04	0.74 (0.50 – 1.1)	0.12
HIV viral load§				
<500	1.0			
500–4,000	1.3 (0.94 – 1.8)	0.13		
4,001–20,000	0.96 (0.63 – 1.4)	0.79		

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	Unadjusted†		Adjusted‡	
Characteristic	**RR (95% CI)**	**P-value**	**RR (95% CI)**	**P-value**
>20,000	1.0 (0.66 – 1.5)	0.92		
Total lifetime male partners				
1–200	1.0		1.0	
201–1,000	1.6 (1.1 – 2.3)	0.01	1.6 (1.1 – 2.4)	0.01
1,000+	1.4 (0.95 – 2.1)	0.09	1.5 (0.99 – 2.2)	0.06
Lifetime partners with whom participant is the *insertive* partner				
1–50	1.0		1.0	
51–200	1.2 (0.84 – 1.7)	0.39	1.1 (0.77 – 1.5)	0.60
201+	1.5 (1.1 – 2.1)	0.009	1.6 (1.2 – 2.2)	0.001
Lifetime partners with whom participant is the *receptive* partner				
1–50	1.0		1.0	
51–200	0.99 (0.70 – 1.4)	0.94	0.79 (0.56 – 1.1)	0.21
201+	1.2 (0.89 – 1.6)	0.22	1.1 (0.83 – 1.5)	0.49
Lifetime partners from whom participant received oral-anal contact				
1–10	1.0		1.0	
11–50	0.93 (0.67 – 1.3)	0.65	0.90 (0.65 – 1.2)	0.51
51+	1.1 (0.79 – 1.5)	0.65	1.1 (0.85 – 1.5)	0.39
History of using objects in the anus	1.1 (0.85 – 1.5)	0.40	1.1 (0.85 – 1.5)	0.39
>4 male partners in the past 30 day	1.1 (0.96 – 1.2)	0.23	1.1 (0.97 – 1.2)	0.23
>0 male partners in the past 30 days with whom participant was the *insertive* partner	1.1 (0.86 – 1.5)	0.40	1.2 (0.90 – 1.5)	0.26
>0 male partners in the past 30 days with whom participant was the *receptive* partner	0.9 (0.71 – 1.2)	0.58	0.94 (0.72 – 1.2)	0.62

*Includes only those men whose anal swab specimens were β-globin DNA-positive.

†Relative risk (RR) and 95% confidence intervals (CI) from log-binomial regression.

‡Relative risk (RR) and 95% confidence intervals (CI) from multivariable log-linear models, adjusted for age, race, education, and ever smoked 100 cigarettes, and CD4+ level

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§HIV viral load could not be included in a multivariable model including CD4+ level because of co-linearity