HHS Public Access

Author manuscript

Sex Transm Dis. Author manuscript; available in PMC 2016 May 01.

Published in final edited form as:

Sex Transm Dis. 2015 May ; 42(5): 246–252. doi:10.1097/OLQ.0000000000000264.

Behavioral, Immunologic, and Virologic Correlates of Oral Human Papillomavirus Infection in HIV-Infected Youth

Jessica A. Kahn, MD MPH[a], **Bret J. Rudy, MD**[b], **Jiahong Xu, MPH**[c], **Elizabeth A. Secord, MD**[d], **Bill G. Kapogiannis, MD**[e], **Sarah Thornton, BA**[f], and **Maura L. Gillison, MD PhD**[g]

[a]Cincinnati Children's Hospital Medical Center and the University of Cincinnati College of Medicine, 3333 Burnet Avenue, Cincinnati, OH, 45229, U.S.

[b]New York University School of Medicine, 550 First Avenue, New York, NY 10016, U.S., bret.rudy@nyumc.org

[c]Westat, 1600 Research Boulevard, Rockville, MD, 20850, U.S., jiahong.xu@westat.com

[d]Wayne State University, 540 E Canfield St, Detroit, MI 48201, U.S., esecord@wayne.med.edu

[e]Maternal and Pediatric Infectious Disease Branch, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, National Institutes of Health, Rockville, MD, U.S. kapogiannisb@mail.nih.gov

[f]Westat, 1600 Research Boulevard, Rockville, MD, 20850, U.S., SarahThornton@westat.com

[g]Ohio State University, 410 W 10th Ave, Columbus, OH 43210, U.S., Maura.gillison@osumc.edu

Abstract

Background—Little is known about the epidemiology or risk factors for oral human papillomavirus (HPV) in HIV-infected youth. The objectives of this study were to determine the

Corresponding author Jessica Kahn, MD MPH Division of Adolescent Medicine, Cincinnati Children's Hospital Medical Center, MLC 4000 3333 Burnet Avenue, Cincinnati, OH 45229 P (513) 803-4539 F (513)636-1129 jessica.kahn@cchmc.org.

Conflicts of Interest

Drs. Kahn and Rudy have co-chaired two HPV vaccine clinical trials in HIV-positive individuals, for which Merck & Co., Inc., provided vaccine and immunogenicity titers. Dr. Kahn chaired a grant review committee for the Society for Adolescent Health and Medicine evaluating public health demonstration project proposals to improve adolescent vaccination; grant funding for this program was from Merck, Inc. For the remaining authors none were declared.

Principal contributions made by each of the authors

Jessica A. Kahn: Dr. Kahn conceptualized and designed the study, supervised the data collection and analyses, drafted the manuscript, and approved the final manuscript as submitted.

Bret Rudy: Dr. Rudy made substantial contributions to conception and design as well as interpretation of data, revised the article critically for important intellectual content, and approved the final manuscript as submitted.

Jiahong Xu: Ms. Xu analyzed and interpreted the data, revised the manuscript critically for important intellectual content, and approved the final manuscript as submitted.

Elizabeth Secord: Dr. Secord made substantial contributions to the design of the study, supervised data collection, revised the article critically for important intellectual content, and approved the final manuscript as submitted.

Bill G. Kapogiannis: made substantial contributions to conception and design as well as interpretation of data, revised the article critically for important intellectual content, and approved the final manuscript as submitted.

Sarah Thornton: Ms. Thornton made substantial contributions to design of the study and acquisition of data, revised the article critically for important intellectual content, and approved the final manuscript as submitted.

Maura L. Gillison: Dr. Gillison made substantial contributions to conception and design as well as interpretation of data, supervised HPV analyses in her laboratory, revised the article critically for important intellectual content, and approved the final manuscript as submitted.

prevalence and correlates of oral HPV infection, and explore the association between HPV vaccination and oral infection, in HIV-infected youth.

Methods—Youth 12-24 years of age with behaviorally-acquired HIV were recruited for this cross-sectional study. Procedures involved medical chart review, survey, and collection of an oral rinse sample. Univariable and multivariable logistic regression models were used to determine whether demographic, behavioral, immunologic and virologic factors and history of vaccination were significantly associated with oral HPV infection.

Results—Mean age of the 272 participants was 21.5 years; 64% were non-Hispanic Black and 20.2% Hispanic; and 10.8% of men compared to 20.3% of women were fully vaccinated. HPV prevalence in men was 19.7% and in women 18.6% (p=1.0). Only men were positive for vaccine-type HPV: 5.6% were positive for HPV-6, -11, -16, and/or -18, and 4.2% were positive for HPV-16 and/or -18. Among men who were fully vaccinated, none were positive for HPV-6, -11, -16, and/or -18, compared to 12 (6.3%) of men who were not fully vaccinated (p=.37). Two variables were marginally associated with oral HPV ($p < .10$): marijuana use in the previous 3 months and lower CD4+ T cell count.

Conclusions—Prevalence rates of oral HPV were relatively high in this population of HIV-infected youth and were similar in male and female youth. No fully vaccinated men were infected with vaccine-type HPV.

Keywords

Human Immunodeficiency Virus; Papillomavirus Infections; Adolescents; Youth

Background

Human papillomavirus (HPV) is a common sexually transmitted infection (STI) that may cause significant morbidity and mortality.[1] Infection with low-risk types such as HPV-6 and HPV-11 may cause anogenital or oral condylomata, while infection with high-risk types such as HPV-16 and HPV-18 may cause anogenital or oropharyngeal cancers.[2] The oral cavity is an important reservoir for HPV infection, especially in HIV-positive individuals.[3, 4] Oral infection with high-risk HPV types is the principal cause of oropharyngeal cancers, a subset of head and neck squamous cell carcinomas (HNSCC).[5] Incidence rates of HPV-related oropharyngeal cancers have more than doubled in the past few decades.[6] HIV-infected individuals are at a 2- to 6-fold increased risk for oropharyngeal cancers compared to the general population, and the risk of cancer increases with the severity of AIDS-related immunosuppression.[7]

Little is known about the epidemiology, natural history, or risk factors for oral HPV in HIV-infected youth. In addition, it has not yet been established that HPV vaccination is effective in preventing oral infection with types targeted by the vaccines, though a study completed four years after HPV vaccination in a clinical trial demonstrated that vaccine-type oral HPV infection was significantly lower in the vaccine arm compared to the control arm.[8] The natural history and risk factors for oral HPV infection in youth may differ from adult populations: incidence and clearance rates may be higher, and behaviors such as cigarette smoking, marijuana use, and oral sex may be more common. Therefore, we conducted a

cross-sectional study in a sample of HIV-infected youth with the following aims: 1) to examine the prevalence of oral HPV infection in this population; 2) to define the behavioral, immunologic and virologic correlates of oral HPV infection; and 3) to explore the association between HPV vaccination and oral HPV infection.

Methods

Study participants

All participants in an observational study of youth ages 12 to 24 years with behaviorally-acquired HIV were invited to participate in this cross-sectional sub-study. The primary inclusion criterion was behaviorally acquired HIV infection. Exclusion criteria included serious psychiatric symptoms or intoxication with alcohol or drugs. Participants were recruited from five U.S. sites participating in the Adolescent Medicine Trials Network for HIV/AIDS Interventions (ATN). This protocol was approved by the Institutional Review Boards (IRB) of each site and the institution where the central laboratory was located. Signed informed consent/assent to participate was obtained from the subject or from the parent/legal guardian for subjects who could not consent for themselves.

Study design and procedures

Audio computer-assisted self-interviewing (paper-and-pencil surveys were available in Spanish) was used to assess demographic information, substance use, mental health history, sexual behaviors, and adherence to HIV medications. A medical chart abstraction was conducted to assess HIV-1 viral load and CD4+ T-cell count and HPV vaccination history. An oral rinse sample was collected for HPV testing: participants swished and gargled with 10mL of Scope mouthwash (or sterile saline if requested) for 30 seconds and then spit into a collection cup. This method is described in more detail in D'souza et al., 2005.[9] DNA purification was accomplished by processing a 1.5 mL aliquot using the Qiagen Virus/Bacteria Midi Kit (Qiagen Inc.; Hilden, Germany) on the Qiasymphony SP instrument.[10] The presence of any of 37 HPV DNA types and beta-globin was detected in the purified DNA by PGMY primer polymerase chain reaction (PCR), followed by reverse line blot hybridization (Roche Linear Array HPV Genotyping Test, Roche Molecular System, Inc.).[11] Beta-globin positive samples were considered evaluable and classified as HPV-positive if any of the 37 HPV DNA types were detected.

Statistical analyses

The primary outcome variable was oral HPV infection, defined as at least one HPV type identified. Prevalence of single HPV types, high-risk types HPV-16 and -18, any high-risk type, and multiple (≥ 2) types was also assessed. The main independent variables were demographic characteristics (gender, age, race, ethnicity, marital status, education and sexual orientation), behavioral factors (substance use, sexual behaviors, HIV medication adherence), immunologic factors (CD4+ T-cell count), and virologic factors (length of time since HIV diagnosis, route of HIV infection, and HIV viral load). HPV vaccination status was assessed by a complete review of the medical record and self-report; if either indicated HPV vaccination the participant was considered to be vaccinated. Univariable and multivariable logistic regression was used to examine the associations between independent

variables and oral HPV infection. Independent variables associated with HPV infection at p < 0.15 in univariable analysis were included in the initial multivariable model, and retained in the final model only if the p-value was < 0.05.

Results

A total of 272 participants (213 male and 59 female) were enrolled in the study between August 2011 and June 2012 (**Table 1**). Mean age was 21.5 years and the majority (64%) was non-Hispanic Black. Most men (89.7%) reported they were gay or bisexual, while most women (84.7%) reported they were heterosexual. Approximately half (50.8%) of women and 33.3% of men had received at least one HPV vaccine dose (all quadrivalent): 20.3% of women and 10.8% of men had received at least three doses. The correlations between medical record confirmation and self-report of HPV vaccination (for receipt of one, two, three, or at least three doses) were moderate: they ranged from 0.44 to 0.64 when measured using a Kappa statistic, and from 0.47 to 0.68 using a Spearman's correlation coefficient.

Overall HPV prevalence was 19.5% and was slightly higher in men (19.7%) than women (18.6%) (**Table 2**). Only men were positive for vaccine-type HPV (HPV-6, -11, -16, or HPV-18): 5.6% were positive for at least one vaccine type HPV, 3 (1.4%) for HPV-6, 2 (0.9%) for HPV-11, 8 (3.8%) for HPV-16, and 1 (0.5%) for HPV-18. Among men, 4.2% were positive for HPV-16 and/or -18. Another common type in men was HPV-59, identified in 8 (3.8%); the most common types identified in women were HPV-84, identified in 3 (5.1%) participants, and HPV-52 and HPV-81, both identified in 2 (3.4%) of participants (data not shown). Of those participants positive for oral HPV, approximately half had at least one high-risk type, and more than one-third had multiple types, with a range of 0-4 types for men and 0-3 types for women. All samples were positive for beta-globin, indicating an adequate sample for detecting HPV DNA.

In univariable analyses, no demographic, behavioral, immunologic or virologic factors were significantly associated ($p < .05$) with oral HPV prevalence (**Table 3**). However, two variables were associated with oral HPV infection at a marginal level of significance: recent marijuana use (almost daily/daily vs. weekly or less, $p = .069$) and CD4+ T cell count (< 350 vs. ≥ 350 cells/mm3, $p = .066$). Results were similar when sexual behaviors were analyzed as continuous (vs. categorical) variables and when these analyses were stratified by gender. When variables associated at $p < .15$ with oral HPV in univariable models were included in a multivariable model, no variables contributed significantly to predicting the occurrence of oral HPV ($p > .05$). Although receipt of an HPV vaccine was not associated with oral HPV infection among men and women combined (**Table 3**), gender-stratified analyses demonstrated that prevalence of HPV-16 and/or -18 was 0 among men who had received ≥ 3 HPV vaccine doses, compared to 9 (4.7%) among men who had received < 3 doses (p=.60). Similarly, prevalence of HPV-6, -11, -16, and/or -18 was 0 among men who completed ≥ 3 vaccine doses, compared to 12 (6.3%) among men who had not (p=.37).

Discussion

In this study, we examined the cross-sectional prevalence of oral HPV in HIV-infected youth and the behavioral, immunologic, and virologic correlates of oral HPV infection. Given the greater potency and tolerability of newer antiretroviral regimens, many youth will live for decades with HIV and will therefore be at-risk for long-term complications. Thus, understanding co-infections in this population and identifying specific contributions resulting from HIV infection in the development and pathogenesis of HPV-related cancers is important, as earlier interventions may be needed to impact diseases that could be decades away.

In this study sample, the overall prevalence of oral HPV was 19.5% and was similar in men and women. In previous studies of HIV-uninfected adults, cross-sectional prevalence for oral HPV ranged widely, from 4.0% to 31.1%, and no consistent association between gender and oral HPV has been demonstrated though prevalence is higher in men than in women in some studies.[4, 12-18] In a systematic review of 18 published studies that detected oral HPV DNA in 4,581 healthy individuals, 3.5% were positive for a high-risk HPV type and 4.5% for any HPV type.[13] Rates are generally higher in HIV-infected individuals, ranging from 7% to 47% in published studies of adult populations.[12, 15, 19, 20] For example, in the Women's Interagency HIV Study, HIV-positive women had substantially higher rates of oral HPV compared to HIV-negative women (point prevalence of 25% vs. 9% and 6-month cumulative prevalence of 33% vs. 15%, respectively),[4] and in a study of men and women who were HIV-infected or HIV-uninfected but at risk, the prevalence of any HPV was 35% vs. 18% in HIV-infected vs. HIV-uninfected women, and 45% vs. 28% in HIV-infected vs. HIV-uninfected men.[15]

Few studies have examined the prevalence of oral HPV infection in youth, though several studies have examined rates of oral HPV infection in infants and young children, who are at risk for recurrent respiratory papillomatosis caused by vertically-transmitted low-risk HPV types.[21-23] Youth may be at relatively high risk for oral HPV infection given that oral sexual behaviors and smoking are common in this age group and adolescents/young adults have the highest age-specific rates of STIs.[24] Tobacco use is a well-established risk factor for HPV persistence, viral load, and neoplastic progression in the cervix. [25-27] In two studies of healthy individuals that examined the prevalence of oral HPV among the subset of study subjects who were adolescents, the authors estimated that the prevalence of oral HPV in this age group was approximately 5%.[21, 28] In a larger study of healthy children and adolescents recruited from several community- and hospital-based sites, Smith et al. reported that the prevalence of oral HPV was 1.5% among 12-15 year-olds (N=200), and 3.3% among 16-20 year-olds (N=336).[23] In a study of adolescents and young adults recruited from a university setting, HPV prevalence was 2.4%.[17] In contrast, HPV prevalence was substantially higher – and similar to the rates found in our study – in two studies of HIV-uninfected adolescents and young adults at relatively high risk for STIs. In a study of sexually active urban young women in the U.S. who were 14-20 years of age, 19.6% were positive for oral HPV[29] and in a study of youth in Sweden attending a clinic for contraception and STI treatment, 9.3% were positive for oral HPV.[30]

In summary, HPV prevalence in our study sample of HIV-infected youth are generally similar to or lower than the prevalence in HIV-infected adults,[4, 12, 15, 19, 20] higher than the prevalence in most studies of HIV-uninfected children, adolescents and adults,[4, 12-18, 21-23, 31] and comparable to oral HPV prevalence in adolescents and young adults at high risk for STIs.[29, 30] The findings suggest that important risk factors for oral HPV in youth are riskier sexual behaviors and immunosuppression, and the high rates of oral HPV are concerning in terms of their potential to impact rates of oropharyngeal cancers later in life. Longitudinal data are needed to determine the natural history and persistence of oral HPV in HIV-infected individuals, and factors associated with the development of HNSCC.

The most commonly-detected HPV types in men and women differed in this study sample: HPV-16 and HPV-59 were the most common in men, while HPV-52, -81 and -84 were the most common in women. In previous studies and across age groups, HPV-16 has usually been identified as the most commonly detected HPV type;[16, 23, 30, 32] however, most of the participants in these studies were unvaccinated. In a systematic review of HPV prevalence in healthy individuals, 1.3% were positive for HPV-16 and this accounted for 28% of all HPV infections.[13] An unexpected finding in our study was that only men were infected with HPV-6, -11, -16, and -18. One previous study of HIV-infected adults demonstrated a slightly higher rate of HPV-16 in men compared to women (6.8% vs. 5.4%), and a national study of oral HPV infection in 14- to 69-year-old individuals demonstrated that the prevalence of oral HPV was approximately 3-fold higher in men than women and the prevalence of HPV-16 was more than 5-fold higher in men than women.[16] Higher rates of HPV-16 in men vs. women are concerning in that they may explain the substantially higher risk for HPV-positive oropharyngeal cancers in men. The fact that only men were positive for vaccine-type HPV in our study may reflect the fact that significantly more women than men had ever received an HPV vaccine, and none of the men who were fully vaccinated were positive for at least one vaccine-type HPV, vs. 6.3% of men who were not fully vaccinated. This preliminary finding must be confirmed in studies with larger sample sizes.

Finally, we examined behavioral, immunologic and virologic correlates of oral HPV infection in HIV-infected youth. In univariable analyses, no factors were significantly associated with oral HPV prevalence. However, two variables were associated with oral HPV infection at a marginal level of significance: marijuana use in the previous 3 months and lower CD4+ T cell count. Marijuana use and lower CD4+ T cell count among HIV-infected individuals have been associated with oral HPV positivity in some previous studies,[15, 16] and are important in that they are potentially modifiable factors to prevent oral HPV infection. Marijuana use was shown to be associated with HPV-16-positive HNSCC in a previous study.[33] The authors note that it is biologically plausible that marijuana could promote the development of HPV-positive HNSCC, as marijuana smoke contains carcinogens that can cause molecular changes in the airway epithelium and cannabionoids suppress humoral and cell-mediated immune responses and may suppress anti-tumor immunity. Alternatively, marijuana use could be an indicator of other behaviors that would put youth at risk for HPV. The marginal reverse association between CD4+ T-cell count and oral HPV infection suggests that immunosuppression may be associated with increased

susceptibility to oral virus infection or replication, and is consistent with previous work demonstrating higher HPV prevalence in HIV-infected individuals.[34-37]

There are a number of limitations to this study. The number of participants enrolled was relatively small, limiting statistical power to detect associations between independent variables and oral HPV prevalence. HPV prevalence was measured at only one point in time, and the prevalence may have been underestimated because of issues with oral sampling or transient fluctuation of the HPV viral load below the lower limit of detection. If the proportion of those with HPV was underestimated, analyses examining factors associated with HPV infection may have been biased toward the null. Prevalence of oral HPV may be underestimated because the Roche assay was designed to detect the HPV types most strongly associated with cervical cancer, while the types found in the oral cavity may differ from those found in the anogenital area. Differences in HPV prevalence across studies may be due to differences in sampling methods, HPV testing methods, and study design. Finally, oral sexual behaviors were only assessed for the prior three months; oral HPV prevalence may be associated with lifetime, but not recent, number of oral sexual partners in this population.

Despite these limitations, this study provides novel data regarding the prevalence of oral HPV infection in HIV-infected youth and the possible behavioral, immunologic and virologic correlates of infection. Additional research will be important to determine why vaccine-type HPV was only identified among men in this study, to further examine whether HPV vaccination prevents oral HPV infection, to explore mechanisms by which marijuana might increase the risk of oral HPV, to examine the natural history of oral HPV and determinants of HNSCC risk in HIV-infected individuals, and to develop interventions to prevent oral HPV and its sequelae in this population.

Acknowledgements

This work was supported by The Adolescent Trials Network for HIV/AIDS Interventions (ATN; U01-HD040533) from the National Institutes of Health through the National Institute of Child Health and Human Development (B. Kapogiannis, C. Worrell), with supplemental funding from the National Institutes of Drug Abuse (S. Kahana) and Mental Health (P. Brouwers): 5 U01 HD 40533 and 5 U01 HD 40474. The study was scientifically reviewed by the ATN's Therapeutic Leadership Group. Network, scientific, and logistical support was provided by the ATN Coordinating Center (C. Wilson, C. Partlow) at the University of Alabama at Birmingham. Network operations and data management support was provided by the ATN Data and Operations Center at Westat, Inc. (J. Korelitz, B. Driver). Laboratory testing was supported by a grant from the Viral Oncology Program, Ohio State University Comprehensive Cancer Center. We acknowledge the contribution of the investigators and staff at the following ATN 114 sites that participated in this study: Baylor Collect of Medicine (Mary E. Paul, M.D., Nancy Calles, MSN, RN, PNP, ACRN, MPH, Norma Cooper, RN); Wayne State University Children's Hospital of Michigan (Elizabeth Secord, M.D., Monique L Green-Jones, MPH, Charnell Cromer, MSN); Johns Hopkins University (Allison George Agwu, M.D., Thuy C Anderson, BSN, Kaye Park, MPH); The Fenway Institute (Kenneth Mayer, M.D., Marcy S Gelman, CRNP, Emily George, RN); University of Colorado Denver (Elizabeth McFarland, M.D., Kerry A Hahn, BS, CCRP, Emily A Barr, CPNP,CNM,MSN); We sincerely thank the ATN 114 Protocol Team Members (Nancy Calles, MSN, RN, PNP, ACRN, MPH and Charnell Cromer, MSN), and the youth who participated in the study. An oral presentation of portions of this study was made at the biannual Adolescent Medicine Trials Network for HIV/AIDS Intervention Meeting in Bethesda, MD, on October 2, 2012.

References

1. Xea, CastellsagueHPV and Cervical Cancer in the World 2007. Report. Vaccine. 2007; 25(Suppl 3):C1–230.

2. 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. New England Journal of Medicine. 2003; 348:518–527. [PubMed: 12571259]

3. Herrero R, Castellsague X, Pawlita M, Lissowska J, Kee F, Balaram P, et al. Human papillomavirus and oral cancer: the International Agency for Research on Cancer multicenter study. J Natl Cancer Inst. 2003; 95:1772–1783. [PubMed: 14652239]

4. D'Souza G, Fakhry C, Sugar EA, Seaberg EC, Weber K, Minkoff HL, et al. Six-month natural history of oral versus cervical human papillomavirus infection. Int J Cancer. 2007; 121:143–150. [PubMed: 17354235]

5. Gillison ML, Lowy DR. A causal role for human papillomavirus in head and neck cancer. Lancet. 2004; 363:1488–1489. [PubMed: 15135592]

6. Chaturvedi AK, Engels EA, Anderson WF, Gillison ML. Incidence trends for human papillomavirus-related and -unrelated oral squamous cell carcinomas in the United States. J Clin Oncol. 2008; 26:612–619. [PubMed: 18235120]

7. Gillison ML. Oropharyngeal cancer: a potential consequence of concomitant HPV and HIV infection. Curr Opin Oncol. 2009; 21:439–444. [PubMed: 19587593]

8. Herrero R, Quint W, Hildesheim A, Gonzalez P, Struijk L, Katki HA, et al. Reduced prevalence of oral human papillomavirus (HPV) 4 years after bivalent HPV vaccination in a randomized clinical trial in Costa Rica. PLoS One. 2013; 8:e68329. [PubMed: 23873171]

9. D'Souza G, Sugar E, Ruby W, Gravitt P, Gillison M. Analysis of the effect of DNA purification on detection of human papillomavirus in oral rinse samples by PCR. J Clin Microbiol. 2005; 43:5526–5535. [PubMed: 16272481]

10. Broutian TR, He X, Gillison ML. Automated high throughput DNA isolation for detection of human papillomavirus in oral rinse samples. J Clin Virol. 2011; 50:270–275. [PubMed: 21273118]

11. Gravitt PE, Peyton CL, Apple RJ, Wheeler CM. Genotyping of 27 human papillomavirus types by using L1 consensus PCR products by a single-hybridization, reverse line blot detection method. J Clin Microbiol. 1998; 36:3020–3027. [PubMed: 9738060]

12. Fakhry C, D'Souza G, Sugar E, Weber K, Goshu E, Minkoff H, et al. Relationship between prevalent oral and cervical human papillomavirus infections in human immunodeficiency virus-positive and -negative women. J Clin Microbiol. 2006; 44:4479–4485. [PubMed: 17021055]

13. Kreimer AR, Bhatia RK, Messeguer AL, Gonzalez P, Herrero R, Giuliano AR. Oral human papillomavirus in healthy individuals: a systematic review of the literature. Sex Transm Dis. 2010; 37:386–391. [PubMed: 20081557]

14. Kreimer AR, Villa A, Nyitray AG, Abrahamsen M, Papenfuss M, Smith D, et al. The epidemiology of oral HPV infection among a multinational sample of healthy men. Cancer Epidemiol Biomarkers Prev. 2011; 20:172–182. [PubMed: 21148755]

15. Beachler DC, Weber KM, Margolick JB, Strickler HD, Cranston RD, Burk RD, et al. Risk factors for oral HPV infection among a high prevalence population of HIV-positive and at-risk HIV-negative adults. Cancer Epidemiol Biomarkers Prev. 2012; 21:122–133. [PubMed: 22045700]

16. Gillison ML, Broutian T, Pickard RK, Tong ZY, Xiao W, Kahle L, et al. Prevalence of oral HPV infection in the United States, 2009-2010. JAMA. 2012; 307:693–703. [PubMed: 22282321]

17. Pickard RK, Xiao W, Broutian TR, He X, Gillison ML. The prevalence and incidence of oral human papillomavirus infection among young men and women, aged 18-30 years. Sex Transm Dis. 2012; 39:559–566. [PubMed: 22706220]

18. Paolini F, Rizzo C, Sperduti I, Pichi B, Mafera B, Rahimi SS, et al. Both mucosal and cutaneous papillomaviruses are in the oral cavity but only alpha genus seems to be associated with cancer. J Clin Virol. 2013; 56:72–76. [PubMed: 23092620]

19. Fakhry C, Sugar E, D'Souza G, Gillison M. Two-week versus six-month sampling interval in a short-term natural history study of oral HPV infection in an HIV-positive cohort. PLoS One. 2010; 5:e11918. [PubMed: 20689835]

20. Read TR, Hocking JS, Vodstrcil LA, Tabrizi SN, McCullough MJ, Grulich AE, et al. Oral human papillomavirus in men having sex with men: risk-factors and sampling. PLoS One. 2012; 7:e49324. [PubMed: 23173054]

21. Summersgill KF, Smith EM, Levy BT, Allen JM, Haugen TH, Turek LP. Human papillomavirus in the oral cavities of children and adolescents. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2001; 91:62–69. [PubMed: 11174573]
22. Smith EM, Ritchie JM, Yankowitz J, Swarnavel S, Wang D, Haugen TH, et al. Human papillomavirus prevalence and types in newborns and parents: concordance and modes of transmission. Sex Transm Dis. 2004; 31:57–62. [PubMed: 14695959]
23. Smith EM, Swarnavel S, Ritchie JM, Wang D, Haugen TH, Turek LP. Prevalence of human papillomavirus in the oral cavity/oropharynx in a large population of children and adolescents. Pediatr Infect Dis J. 2007; 26:836–840. [PubMed: 17721381]
24. Halpern-Felsher BL, Cornell JL, Kropp RY, Tschann JM. Oral versus vaginal sex among adolescents: perceptions, attitudes, and behavior. Pediatrics. 2005; 115:845–851. [PubMed: 15805354]
25. Wang SS, Schiffman M, Herrero R, Carreon J, Hildesheim A, Rodriguez AC, et al. Determinants of human papillomavirus 16 serological conversion and persistence in a population-based cohort of 10 000 women in Costa Rica. Br J Cancer. 2004; 91:1269–1274. [PubMed: 15292929]
26. Trottier H, Franco EL. The epidemiology of genital human papillomavirus infection. Vaccine. 2006; 24(Suppl 1):S1–15. [PubMed: 16406226]
27. Smith EM, Rubenstein LM, Haugen TH, Hamsikova E, Turek LP. Tobacco and alcohol use increases the risk of both HPV-associated and HPV-independent head and neck cancers. Cancer Causes & Control. 2010; 21:1369–1378. [PubMed: 20401530]
28. Marais DJ, Sampson C, Jeftha A, Dhaya D, Passmore JA, Denny L, et al. More men than women make mucosal IgA antibodies to Human papillomavirus type 16 (HPV-16) and HPV-18: a study of oral HPV and oral HPV antibodies in a normal healthy population. BMC Infect Dis. 2006; 6:95. [PubMed: 16762074]
29. Schlecht NF, Burk RD, Nucci-Sack A, Shankar V, Peake K, Lorde-Rollins E, et al. Cervical, anal and oral HPV in an adolescent inner-city health clinic providing free vaccinations. PLoS One. 2012; 7:e37419. [PubMed: 22624027]
30. Du J, Nordfors C, Ahrlund-Richter A, Sobkowiak M, Romanitan M, Nasman A, et al. Prevalence of oral human papillomavirus infection among youth, Sweden. Emerg Infect Dis. 2012; 18:1468–1471. [PubMed: 22932445]
31. Kero K, Rautava J, Syrjanen K, Grenman S, Syrjanen S. Oral mucosa as a reservoir of human papillomavirus: point prevalence, genotype distribution, and incident infections among males in a 7-year prospective study. Eur Urol. 2012; 62:1063–1070. [PubMed: 22771267]
32. Schlecht NF, Rojas M, Lorde-Rollins E, Nucci-Sack A, Strickler HD, Burk RD, et al. Burden of cervical, anal, and oral HPV in an inner-city pre-vaccine adolescent population. J Urban Health. 2013; 90:141–146. [PubMed: 22932952]
33. Gillison ML, D'Souza G, Westra W, Sugar E, Xiao W, Begum S, et al. Distinct risk factor profiles for human papillomavirus type 16-positive and human papillomavirus type 16-negative head and neck cancers. J Natl Cancer Inst. 2008; 100:407–420. [PubMed: 18334711]
34. Hille JJ, Webster-Cyriaque J, Palefski JM, Raab-Traub N. Mechanisms of expression of HHV8, EBV and HPV in selected HIV-associated oral lesions. Oral Dis. 2002; 8(Suppl 2):161–168. [PubMed: 12164651]
35. Ferenczy A, Coutlee F, Franco E, Hankins C. Human papillomavirus and HIV coinfection and the risk of neoplasias of the lower genital tract: a review of recent developments. CMAJ. 2003; 169:431–434. [PubMed: 12952805]
36. Clifford GM, Goncalves MA, Franceschi S. Human papillomavirus types among women infected with HIV: a meta-analysis. Aids. 2006; 20:2337–2344. [PubMed: 17117020]
37. McLemore MS, Haigentz M Jr. Smith RV, Nuovo GJ, Alos L, Cardesa A, et al. Head and neck squamous cell carcinomas in HIV-positive patients: a preliminary investigation of viral associations. Head Neck Pathol. 2010; 4:97–105. [PubMed: 20333562]

Summary

Oral HPV prevalence in HIV-infected youth was 19.5%. No fully vaccinated men were positive for HPV-6, -11, -16, or 18. Demographics, immunologic factors, and behaviors were not associated with HPV.

Sex Transm Dis. Author manuscript; available in PMC 2016 May 01.

Table 1

Characteristics of Study Participants by Birth Gender

	Total N=272	Male N=213	Female N=59	p-value[a]
Demographic factors				
Age in years [Mean (SD)]	21.5 (2.0)	21.6 (1.9)	21.2 (2.2)	0.19
Race/Ethnicity [N (%)]				
Non-Hispanic White	43 (15.8)	35 (16.4)	8 (13.6)	0.38
Non-Hispanic Black/African American/Non-Hispanic, Other	174 (64.0)	130 (61.0)	44 (74.6)	
Hispanic	55 (20.2)	48 (22.5)	7 (11.9)	
Marital status [N (%)]				
Single	209 (77.4)	170 (80.2)	39 (67.2)	0.0034
Living with a steady partner	43 (15.9)	33 (15.6)	10 (17.2)	
Married	10 (3.7)	3 (1.4)	7 (12.1)	
Separated, divorced, widowed, or other	8 (3.0)	6 (2.8)	2 (3.4)	
Sexual orientation [N (%)]				
Straight	72 (26.5)	22 (10.3)	50 (84.7)	<.0001
Gay/Bisexual/Other	200 (73.5)	191 (89.7)	9 (15.3)	
HIV related factors				
Age at HIV diagnosis [Mean (SD)]	19.3 (2.3)	19.5 (2.2)	18.6 (2.4)	0.0058
Length of time since HIV diagnosis [Mean (SD)]	1.9 (1.9)	1.8 (1.8)	2.4 (2.2)	0.035
Self-reported route of HIV infection [N (%)]				
Perinatal	1 (0.4)	1 (0.5)	0 (0.0)	0.09
Sex with a man	241 (88.6)	189 (88.7)	52 (88.1)	
Sex with a woman	11 (4.0)	11 (5.2)	0 (0.0)	
Other/Don't know	19 (7.0)	12 (5.6)	7 (11.9)	
CD4+ T cell count (cells/mm^3) [Mean (SD)]	515.5 (252.1)	500.2 (240.0)	570.4 (286.9)	0.10
CD4+ T cell count (cells/mm^3) [N (%)]				
< 350	70 (25.8)	56 (26.4)	14 (23.7)	0.74
≥ 350	201 (74.2)	156 (73.6)	45 (76.3)	
Viral load (copies/mL) [Mean (SD)]	74528.6 (385987.7)	89689.1 (435026.3)	20053.5 (35044.8)	0.32
Viral load (copies/mL) [N (%)]				

	Total N=272	Male N=213	Female N=59	p-value[a]
< 400	101 (37.3)	80 (37.7)	21 (35.6)	0.88
≥ 400	170 (62.7)	132 (62.3)	38 (64.4)	
Viral load (copies/mL) [N (%)]				
Detectable	208 (76.8)	164 (77.4)	44 (74.6)	0.73
Non-detectable	63 (23.2)	48 (22.6)	15 (25.4)	
HPV Vaccination Status [N (%)]				
Ever received HPV vaccine	101 (37.1)	71 (33.3)	30 (50.8)	0.015
Completed one dose only	34 (12.5)	25 (11.7)	9 (15.3)	0.51
Completed two doses only	32 (11.8)	23 (10.8)	9 (15.3)	0.36
Completed three doses or more	35 (12.9)	23 (10.8)	12 (20.3)	0.076

[a] P-value is derived from a two-sample t-test or Kruskal-Wallis test for continuous variables, and a Fisher's exact test with Monte Carlo estimations for categorical variables, comparing genders.

Table 2

Overall and Type-Specific Oral HPV Prevalence by Birth Gender

	Overall (N=272)		Male (N=213)		Female (N=59)		
	n (%)	95% CI[a]	n (%)	95% CI[a]	n (%)	95% CI[a]	p-value[b]
Overall HPV prevalence							
Positive for ≥ 1 HPV type	53 (19.5)	15.0-24.7	42 (19.7)	14.6-25.7	11 (18.6)	9.7-30.9	1.00
High-risk HPV types in the bivalent and quadrivalent vaccines							
Positive for 16 and/or 18	9 (3.3)	1.5-6.2	9 (4.2)	2.0-7.9	0 (0.0)	0.0-6.1	0.21
Low-risk HPV types in the quadrivalent vaccine							
Positive for 6 and/or 11	4 (1.5)	0.4-3.7	4 (1.9)	0.5-4.7	0 (0.0)	0.0-6.1	0.58
HPV types in the quadrivalent vaccine							
Positive for 6, 11, 16 and/or 18	12 (4.4)	2.3-7.6	12 (5.6)	2.9-9.6	0 (0.0)	0.0-6.1	0.085
HPV types in the nonavalent vaccine							
Positive for 6, 11, 16, 18, 31, 33, 45, 52 and/or 58	20 (7.4)	4.6-11.1	18 (8.5)	5.1-13.0	2 (3.4)	0.4-11.7	0.26
High-risk HPV types							
Positive for 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and/or 68	30 (11.0)	7.6-15.4	25 (11.7)	7.7-16.8	5 (8.5)	2.8-18.7	0.64
Multiple type HPV infection (among those who are HPV positive)							
≥ 2 HPV types	20 (37.7)	24.8-52.1	15 (35.7)	21.6-52.0	5 (45.5)	16.8-76.6	0.73
Number of HPV types identified							
0	219 (80.5)		171 (80.3)		48 (81.4)		0.89
1	33 (12.1)		27 (12.7)		6 (10.2)		
2	13 (4.8)		9 (4.2)		4 (6.8)		
3	5 (1.8)		4 (1.9)		1 (1.7)		
4	2 (0.7)		2 (0.9)		0 (0.0)		
Number of HPV types identified (continuous)							
Mean (SD), median	0.3 (0.7), 0		0.3 (0.7), 0		0.3 (0.7), 0		
Minimum - maximum	0 - 4		0 - 4		0 - 3		

[a] Exact 95% CI confidence interval reported.

[b] P-value is from a Fisher's exact test, comparing prevalence between genders.

Table 3

Association between Independent Variables and Oral HPV Infection (N=53)

	≥1 HPV+ N (%)/Mean (SD)[c]	Unadjusted	
		OR (95% CI)[a]	p-value[b]
Demographic factors			
Age (years)	21.6 (1.9)[c]	1.02 (0.88 - 1.20)	0.77
Current gender			
Male	39 (19.2)	1.00	
Female	11 (19.0)	0.98 (0.47 - 2.07)	0.97
Transgender	3 (30.0)	1.80 (0.45 - 7.29)	0.41
Race/ethnicity			
Non-Hispanic White	6 (14.0)	1.00	
Non-Hispanic Black/African American, Non-Hispanic, Other	37 (21.3)	1.67 (0.65 - 4.25)	0.29
Hispanic	10 (18.2)	1.37 (0.46 - 4.12)	0.58
Marital status			
Single	41 (19.6)	1.00	
Not single	11 (18.0)	0.90 (0.43 - 1.88)	0.78
Highest level of education or grade completed			
Did not graduate high school	11 (17.7)	1.00	
High school graduate	42 (20.0)	1.16 (0.56 - 2.42)	0.69
Sexual orientation			
Heterosexual	15 (20.8)	1.00	
Gay/Bisexual/Other	38 (19.0)	0.89 (0.46 - 1.74)	0.74
Behavioral factors			
Substance use			
Tobacco use (lifetime)			
No	18 (20.9)	1.00	
Yes	35 (18.8)	0.88 (0.46 - 1.65)	0.68
Tobacco use (past 3 months)			
Weekly or less	38 (20.3)	1.00	
Almost daily or daily	15 (17.6)	0.84 (0.43 - 1.63)	0.61

	≥1 HPV+ N (%)/Mean (SD)[c]	Unadjusted	
		OR (95% CI)[a]	p-value[b]
Alcohol use (lifetime)			
No	8 (25.0)	1.00	
Yes	45 (18.8)	0.70 (0.29 - 1.65)	0.41
Alcohol use (past 3 months)			
Weekly or less	51 (20.2)	1.00	
Almost daily or daily	2 (10.5)	0.46 (0.10 - 2.07)	0.31
Marijuana use (lifetime)			
No	18 (24.0)	1.00	
Yes	35 (17.8)	0.68 (0.36 - 1.30)	0.25
Marijuana use (past 3 months)			
Weekly or less	35 (17.0)	1.00	
Almost daily or daily	18 (27.3)	1.83 (0.95 - 3.52)	0.069
Sexual behaviors: heterosexual			
Number of male (female) partners with whom participant has had sexual contact (oral, anal, vaginal), past 3 months			
1 +	14 (20.6)	1.00	
0	38 (18.8)	0.89 (0.45 - 1.77)	0.75
Number of male (female) partners known to be HIV positive, lifetime			
1 +	4 (20.0)	1.00	
0	10 (21.3)	1.08 (0.29 - 3.96)	0.91
Number of male (female) partners known to be HIV negative/unknown HIV status, lifetime			
1 +	9 (20.0)	1.00	
0	5 (23.8)	1.25 (0.36 - 4.33)	0.72
Number of times performed/received oral sex, past 3 months			
1 +	11 (22.9)	1.00	
0	2 (16.7)	0.67 (0.13 - 3.54)	0.64
Number of times had vaginal sex, past 3 months			
1 +	11 (21.6)	1.00	
0	2 (25.0)	1.21 (0.21 - 6.86)	0.83
Sexual behaviors: homosexual			
Number of male (female) partners with whom participant has had sexual contact (oral, anal, vaginal), past 3 months			

	≥1 HPV+ N (%)/Mean (SD)[c]	Unadjusted	
		OR (95% CI)[a]	p-value[b]
1 +	30 (17.8)	1.00	
0	22 (22.0)	1.31 (0.71 - 2.42)	0.39
Number of male (female) partners known to be HIV positive, lifetime			
1 +	16 (19.8)	1.00	
0	14 (16.5)	0.80 (0.36 - 1.77)	0.58
Number of male (female) partners known to be HIV negative/unknown HIV status, lifetime			
1 +	21 (17.4)	1.00	
0	9 (18.8)	1.10 (0.46 - 2.61)	0.83
Number of times performed/received oral sex, past 3 months			
1 +	26 (17.9)	1.00	
0	3 (27.3)	1.72 (0.43 - 6.91)	0.45
Number of times had oral, vaginal (females only) or anal sex WITH a condom or washing sex toys in between uses, past 3 months			
1 +	24 (19.4)	1.00	
0	5 (15.6)	0.77 (0.27 - 2.21)	0.63
Adherence to medication			
Currently taking antiretroviral therapy			
Yes	30 (22.7)	1.00	
No	22 (15.9)	0.64 (0.35 - 1.19)	0.16
Weekday antiretroviral therapy adherence			
≥ 90%	19 (22.1)	1.00	
< 90%	8 (20.5)	0.91 (0.36 - 2.30)	0.84
Weekend antiretroviral therapy adherence			
≥ 90%	20 (23.0)	1.00	
< 90%	7 (19.4)	0.81 (0.31 - 2.12)	0.67
Immunologic factors			
CD4 T cell count (cells/mm^3)			
≥ 350	34 (16.9)	1.00	
< 350	19 (27.1)	1.83 (0.96 - 3.48)	0.066
Virologic factors			
Length of time since HIV diagnosis (years)	2.2 (2.0)[c]	1.08 (0.93 - 1.26)	0.31

	≥1 HPV+ N (%)/Mean (SD)[c]	Unadjusted	
		OR (95% CI)[a]	p-value[b]
Length of time since HIV diagnosis			
≥ 1 year	33 (20.9)	1.00	
< 1 year	20 (17.5)	0.81 (0.44 - 1.49)	0.49
Self-reported route of HIV infection			
Sex with a man	44 (18.3)	1.00	
Sex with a woman	4 (36.4)	2.56 (0.72 - 9.12)	0.15
Perinatal/Other/Don't know	5 (25.0)	1.49 (0.52 - 4.32)	0.46
Viral load (copies/mL)			
< 400	17 (16.8)	1.00	
≥ 400	36 (21.2)	1.33 (0.70 - 2.51)	0.38
Viral load (copies/mL)			
Non-detectable	12 (19.0)	1.00	
Detectable	41 (19.7)	1.04 (0.51 - 2.13)	0.91
HPV vaccination status			
Receipt of an HPV vaccine			
Yes	18 (17.8)	1.00	
No	35 (20.5)	1.19 (0.63 - 2.23)	0.59
Received at least one dose			
Yes	5 (14.7)	1.00	
No	48 (20.2)	1.46 (0.54 - 3.98)	0.45
Received at least two doses			
Yes	3 (9.4)	1.00	
No	50 (20.8)	2.54 (0.74 - 8.69)	0.14
Received three doses or more			
Yes	10 (28.6)	1.00	
No	43 (18.1)	0.55 (0.25 - 1.24)	0.15

[a] OR = odds ratio; CI = confidence interval

[b] p-values obtained from univariable logistic regression models

[c] Mean (SD or standard deviation) for continuous variables, and N (%) for all other categorical variables