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# ORAL HPV IN YOUTH FROM THE PEDIATRIC HIV/AIDS COHORT STUDY (PHACS)

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## Abstract

In contrast to high rates of oral HPV found in HIV-infected adults, only 2% of 209 perinatally HIV-infected youth had oral HPV. This rate was similar in HIV exposed but uninfected youth. No association was found with sexual activity; however, low CD4 counts were associated with oral HPV.

### Keywords

oral human papillomavirus; HIV-infected; children and adolescents

Approximately 25% of all head and neck squamous cell carcinomas and 45–90% of oropharyngeal cancers are associated with human papillomavirus (HPV), particularly tonsillar lesions and those at the base of the tongue [1]. HPV 16 is the predominant genotype found in these cancers. Individuals with HPV-associated head and neck squamous cell carcinomas have similar risk factors as those with HPV associated anogenital cancers including a greater lifetime number of sex partners and HIV infection [2, 3]. Despite these similarities, oral HPV infections are much less common than genital infections.

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Approximately 10% of men and 4% of women in the general population will have oral HPV compared to 20%–50% with genital HPV [4] ; 14 to 35% of HIV infected persons have oral HPV [5]. The higher rates of HPV in HIV-infected persons are thought to be due to a deficient immune response to HPV resulting in higher rates of persistence.

There is considerable debate whether HPV is always sexually transmitted or if it is acquired by other routes. Although HPV DNA can be detected on the hand, it remains unknown whether the hand is a mode of transmission during sexual play [6]. Other modes may include perinatal or hygienic (i.e. through caretaking) transmission [7]. It is plausible that perinatally HIV-infected children as well as HIV-exposed but uninfected children are at high risk of acquiring oral HPV at either birth or later since HIV-infected parents have high rates of vaginal and oral HPV. However, we would expect that HPV is more likely to persist in HIV-infected children than their immunocompetent HIV-exposed but uninfected counterparts. In this study, we examined the prevalence of and factors associated with oral HPV in perinatally HIV-infected youth compared to perinatally HIV-exposed but uninfected youth.

We conducted a cross-sectional study within the Adolescent Master Protocol of the Pediatric HIV/AIDS Cohort Study (PHACS). Adolescent Master Protocol is a prospective cohort study of perinatally HIV-infected and perinatally HIV-exposed but uninfected youth [8]. Regularly scheduled visits included audio-computer assisted structured interviews (ACASI) to obtain data on sexual and substance use history, and chart reviews for medication, diagnoses, CD4 counts and viral load (VL) [8]. Participants were enrolled into the Oral health substudy at 11 participating sites. Institutional Review Boards at clinical sites and the Harvard T.H. Chan School of Public Health approved the study. Parents/legal guardians and youth provided written informed consent/assent.

Sites scheduled the Oral Health study visit within 3 months of the regularly scheduled AMP annual visit. At the visit, subjects were asked to gargle and swish alternatively (5 second intervals) for 30 seconds with 10 CC of sterile saline and expectorate into a 50 CC conical tube. The gargle was put on ice and transported to the laboratory within 2 hours where it was processed and frozen at −70 C. A 1 cc aliquot from the gargle samples was tested for HPV DNA at a centralized laboratory using Roche linear Array (Roche Molecular Systems, Pleasanton, CA) which types for 37 different HPV genotypes: 6, 11, 16, 18, 26, 31, 33, 35, 39, 40, 42, 45, 51–59, 61, 62, 64, 66–73, 81–84, IS39, and 89 as well as high and low beta-globin concentrations to verify higher and lower limits of sample adequacy [9]. No samples were found to be inadequate.

For HPV vaccination history, doses given at least 21 days before the oral health visit were considered. Participants were considered to have ever had sex if oral, vaginal, or anal sexual activity was reported on any ACASI before a cutoff date of 90 days after the oral health visit. Recent substance and cigarette use was defined using the ACASI closest to the oral health visit date and before a cutoff date of 90 days after the oral health visit. The 95% exact confidence intervals (C.I.) of the prevalence of oral HPV were evaluated using the approach of Clopper and Pearson.

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If CD4 and VL measurements were not available within 90 days of the oral study visit, sites were asked to draw blood at the time of the Oral Health substudy visit for these studies. CD4 nadir measurements were restricted to those obtained before or at the oral health visit.

Characteristics of the HIV-infected and HIV-uninfected youth are shown in Table 1. The median time between the closest ACASI and the oral health visit was 56 days before oral health visit (IQR 180, 4 days before oral health visit) and in 15% the ACASI used was within 90 days after the visit. HPV was detected in 4 (2%, 95% exact C.I.: 0.5%, 4.8%) of the HIV-infected youth and 2 (2%, 95% exact C.I.: 0.2%, 5.7%) of the HIV-uninfected youth. Only 1 HPV vaccine type (16) was detected in one HIV-uninfected youth. Boys had a slightly higher prevalence of oral HPV than girls (3% vs 1%, respectively). None of the 104 youth who had 2 or more doses of the HPV vaccine had oral HPV. No differences for HPV status were found by sexual behavior (data not shown). Among the HIV-infected youth, low nadir and current CD4 counts had an association with oral HPV with marginal statistical significance (Table 2).

HPV was uncommon in both HIV-infected and uninfected youth. The rate of detection of HPV in the oral cavity of neonates ranges from 4% to 87% [10]. However, most studies show that HPV persistence in healthy immunocompetent children is quite rare over 1–2 years of follow up suggesting that the HPV initially detected does not represent a true infection [7, 10]. Persistent oral HPV infection in infants has been associated with persistent oral HPV infection in the mother. It might be suspected that once the mother has a lesser role in feeding and hygiene, rates of HPV may decrease. As seen in neonates, the rates in children have varied widely, ranging from 1% to 50% [11, 12]. One of the larger studies [11] found a bimodal distribution with highest prevalence in those <1 year (2.5%) and again in those 16–20 years (3.3%) and rates less than 1% in-between. The finding for females is inconsistent with adult studies that show men to have prevalence 2–3 times that of women [4]. In part the wide variability seen in children may be due to different sampling techniques. HPV is rarely seen in buccal swabs whereas gargles, tonsillar swabs or tissue yield much higher rates [4, 13].

We were surprised by the low rate found in this group of HIV-infected youth, specifically among those reporting sexual activity. The lack of correlation with sexual activity may in part have been due to the gap between the day of the oral visit and the day of the ACASI or underreporting. In addition, oral and vaginal sex may have been practiced infrequently among those reporting sex in this young population. No data is available for frequency of intercourse, or cervical or anal HPV in our cohort for comparison.

The rates of oral HPV were by far lower than HIV-infected adults or sexually active high risk adolescents where rates have ranged from 16% to 38.5% with the highest being found in HIV-infected men who have sex with men [2, 3, 5]. Despite our low rate of detection, we did find associations with low CD4 count and high VL similar to that reported in adults [2, 3, 5]. In a recent study of 388 treatment-naïve HIV-infected adults, men showed a higher rate of oral HPV than women (20% vs 11%, respectively, p=0.06) however, no difference was seen with respect to oral shedding of oncogenic HPV subgenotypes (4% and 5%, respectively) similar to our findings [14]. Another possible reason we observed low rates of HPV is that

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these sexually active HIV-infected youth entered puberty on ART with relatively well controlled HIV infection. In contrast, HIV infected adults often go undiagnosed for years during which there is oral HIV shedding which may enhance susceptibility to HPV acquisition. Surprisingly those who were fully HPV vaccinated in our study had no cases. Studies of children, adolescents and adults show that the HPV vaccine types make up a relatively small percentage of oral HPV types detected, hence we would have expected a similar higher prevalence of these non-vaccine types. [4, 15] Only 2 small studies have previously examined HIV-infected children. Pinheiro et al [16] found oral HPV in 12% of 50 HIV-infected children with a mean age of 9.1 years compared to 6% in the 50 uninfected children (mean age 7.6 years). Samples for this study were obtained from the palate, tongue and buccal mucosa. In a study with 100 non-sexually active HIV-infected and HIV-exposed but uninfected children, HPV was found in 17% of tonsil/buccal/tongue specimens of the HIV-infected girls compared to none in the HIV-uninfected girls [9]. In the 50 non-sexually active boys, oral HPV was found in only 2 - one HIV-infected and the other uninfected. Of note, the mean age of the HIV-infected group was 14.3 years compared to 6.2 years in the uninfected. Neither study found an association with CD4 counts.

In conclusion, the detection of HPV DNA was uncommon from perinatally HIV-infected and HIV-exposed but infected youth. As these youth age, it will be important to monitor oral HPV acquisition, as head and neck squamous cell carcinomas are higher in HIV-infected adults. HPV vaccination of this group remains critical as it may protect against the development of these cancers as well as other HPV-associated cancers.

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## Table 1

Characteristics of HIV-infected and HIV-uninfected youth.

| Characteristic | HIV Status | | P-Value[a] |
|---|---|---|---|
| | HIV-infected (N=209) | HIV-uninfected (N=125) | |
| **HPV positive**[b] | 4 (1.9%) | 2 (1.6%) | 1.00 |
| **Median age (IQR)**[c] | 17.3 (14.9, 18.8) | 14.5 (12.6, 16.4) | <0.01 |
| **Male gender** | 99 (47%) | 61 (49%) | 0.82 |
| **History of ever having sex**[d,e] | 99 (47%) | 40 (32%) | <0.01 |
| **History of ever having oral sex**[f] | 86 (41%) | 34 (27%) | <0.01 |
| **Number of HPV vaccine doses received** | | | <0.01 |
| **0** | 39 (19%) | 47 (38%) | |
| **1** | 87 (42%) | 57 (46%) | |
| **2+** | 83 (40%) | 21 (17%) | |

[a] Fisher's Exact Test for discrete measures. Wilcoxon test for continuous age.

[b] HPV genotypes 16, 35, 59, 68, 69, 71, 72 were detected.

[c] Interquartile range.

[d] Sex included vaginal, oral or anal. There were 7 participants without sexual behavior information (5 HIV-infected, 2 HIV-uninfected).

[e] Among those reporting vaginal sex, the median [first (Q1) and third (Q3) quartiles] number of lifetime vaginal sexual partners was 2 (0, 5).

[f] Among those reporting oral sex, the median (Q1, Q3) number of lifetime partners with whom the adolescent had oral exposure during sex was 1 (0, 3).

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**Table 2**

HIV disease markers by number of HPV vaccine doses and detection of HPV.

| **Number of Vaccine Doses** | | **0** | | | **1** | | **2+** |
|---|---|---|---|---|---|---|---|
| **Positive for Any HPV Genotype**[a] | **No (n = 38)** | **Yes (n = 1)** | | **No (n = 84)** | **Yes (n = 3)** | | **No (n = 83)** |
| **Characteristic** | **Median (IQR)** | **Actual Values**[b] | **P-Value**[c] | **Median (IQR)** | **Actual Values**[b] | **P-Value**[c] | **Median (IQR)** |
| **CD4+ Nadir (cells/mm$^3$)** | 406.5 (292.0, 496.0) | 16 | 0.120 | 322.5 (169.5, 467.0) | 205<br>33<br>217 | 0.111 | 237 (100, 369) |
| **CD4+ current (cell/mm$^3$)** | 613 (472, 885) | 127 | 0.120 | 658.5 (493.5, 880.5) | 267<br>426<br>498 | 0.068 | 605 (329, 783) |
| **HIV Viral Load (copies/mL)**[d] | 40 (20, 3,923) | 1,020,000 | 0.094 | 40.0 (20.0, 924.5) | 5,187<br>75<br>57 | 0.341 | 40 (20, 2,143) |

IQR: interquartile range

[a] HPV genotypes 16, 35, 59, 68, 69, 71, 72 were detected. Vaccine type 16 was detected in HIV-uninfected patient receiving 1 HPV dose.

[b] Actual values for CD4 count and viral load are given for each subject.

[c] Wilcoxon test.

[d] 2 missing in HPV negative participants.