Prevalence and determinants of oral infection by Human Papillomavirus in HIV-infected and uninfected men who have sex with men

Francesca Rollo, Alessandra Latini, Barbara Pichi, Manuela Colafigli, Maria Benevolo, Ilenia Sinopoli, Valentina Laquintana, Giulia Fabbri, Mirko Frasca, Antonio Cristaudo, Massimo Giuliani, Maria Gabriella Donà

1 Pathology Department, Regina Elena National Cancer Institute, IFO, IRCCS, Rome, Italy, 2 STI/HIV Unit, San Gallicano Dermatologic Institute, IFO, IRCCS, Rome, Italy, 3 Otolaryngology Head Neck Surgery Department, Regina Elena National Cancer Institute, IFO, IRCCS, Rome, Italy, 4 Biostatistics Unit, Regina Elena National Cancer Institute, IFO, IRCCS, Rome, Italy

These authors contributed equally to this work.

* mariagabriella.dona@ifo.gov.it

Abstract

Background
Oral Human Papillomavirus (HPV) infection is rare in the general population but common in high-risk individuals. Recent data indicate that oral HPV is associated with the development of head and neck carcinomas. HPV16 infection, in particular, increases the risk of oropharyngeal cancer.

Methods
We evaluated oral HPV prevalence and determinants of infection in cancer-free HIV-infected and uninfected men who have sex with men (MSM) recruited among attendees of an STI/HIV centre. Oral rinse and gargles were collected using a mouthwash and analyzed with the Linear Array HPV Genotyping Test. Socio-demographic and behavioral data were collected through face-to-face interviews.

Results
Overall, 170 MSM participated: 98 HIV-uninfected and 72 HIV-infected (91.7% under cART). Oral HPV was detected in 17.3% and 27.8% of the subjects, respectively (p = 0.13). Non-carcinogenic HPVs were significantly more common among HIV-infected MSM (18.1% vs. 5.1%, p = 0.01). Prevalence of the HPV types included in the quadrivalent HPV vaccine was similar (6.1% vs. 8.3% for the HIV-negative and positive MSM, respectively, p = 0.76). HPV16 was the most frequent type in HIV-negative (5.1%), and HIV-positive individuals, in the latter group together with HPV18, 72 and 84 (4.2% each). Older age at first sex (AOR: 4.02, 95% CI: 1.17–13.86 for those older than 18 years of age at first intercourse, p = 0.027) and a higher lifetime number of receptive oral sex partners (AOR: 9.14, 95% CI: 2.49–33.62...
such as HIV serostatus and sexual orientation. The dataset is however available from the corresponding author on reasonable request.

Funding: The work was funded by the Italian Ministry of Health (GR-2011-02349732 to MGD).

Competing interests: The authors have declared that no competing interests exist.

for those with >50 compared to ≤50 partners, p<0.001) were determinants of oral HPV among HIV-infected MSM.

Conclusion

Oral HPV infection among MSM attending an urban STI center is very frequent compared to the general population. Sexual behavior appears to be the major determinant of infection among the HIV-infected individuals.

Introduction

Oral infection by Human Papillomavirus (HPV) increases risk for the development of oropharyngeal squamous cell carcinoma (OPSCC). HPV16 represents the genotype involved in the etiology of the majority of HPV-related OPSCC. Remarkably, oral HPV16 infection is associated with a 22-fold increased risk of incident OPSCC [1].

Because of the role of HPV in the development of oropharyngeal cancer and the steady increase in the incidence of this neoplasia observed in several countries [2–4], interest in the epidemiology of oral HPV infection has been growing. This is an uncommon infection in the general population, as shown by large studies conducted on healthy individuals in the US [5] and China [6]. Gillison and collaborators found a prevalence of 6.9% for any HPV and 1% for HPV16 [5]. They also showed that oral infection is more frequent in men than women (10.1% vs. 3.6%). Being male is in fact an established risk factor for prevalent oral HPV [5,7].

Sexual behavior plays a major role in the acquisition of oral HPV infections and changes in sexual activity are probably contributing to the increase in the incidence of HPV-positive OPSCC, together with changes in smoking habits, particularly among some populations. Importantly, specific sexual practices (i.e., receptive oral sex) that may enhance the exposure of oropharyngeal mucosa to HPV infection represent important risk factors for HNSCC [8,9]. A greater number of partners for any and oral sex, a younger age at sexual debut and ever having had oral sex have been shown to be associated with risk of oropharyngeal cancer, despite the fact that differences have been found related to cancer subsite and gender [9]. Notably, same sex sexual contact has been shown to be associated with an almost 9-fold increased risk for base of the tongue cancer in men [9]. Due to their sexual practices, men who have sex with men (MSM), who also harbor the highest prevalence of anal HPV [10,11], show a significantly higher prevalence of oral HPV infection than the general population. Although data are very limited, their risk of HNSCC also seems to be higher in these subjects, as shown by a Danish study [12]. Notably, HIV-positive individuals harbor up to a 6-fold increase in risk for both oral HPV infection and HNSCC compared to their HIV-uninfected counterparts [13–15]. Although the data available on the natural history of oral HPV infection are very scarce, a higher incidence, however, has been reported for HIV-positive compared to HIV-negative MSM [16,17].

Despite the fact that the epidemiology of oral HPV in high-risk populations has been increasingly investigated, only few studies have been conducted in Europe [18–20]. Sparse data obtained have been gained in Italy but only on small to moderately-sized groups of MSM [21–23]. It is thus important to gather new data on this high-risk population.

We conducted a cross-sectional study to evaluate oral HPV infection in HIV-infected and uninfected cancer-free MSM attending an STI/HIV centre, and to investigate the determinants of infection in the two groups.
Materials and methods

Study population

From November 2014 to May 2016, all MSM attendees of the STI/HIV centre of the San Gallicano Dermatological Institute (Rome, Italy) were asked to participate in the OHMAR (Oral/ Oropharyngeal HPV in Men At Risk) study. Individuals that met the following inclusion criteria were included: 1. age ≥18 years; 2. sexual intercourse with a man in the preceding 6 months; 3. no history of HNSCC; 4. no clinically suspicious lesions for HNSCC, as ascertained during a full otolaryngology examination conducted at enrollment. HIV-infected MSM were also included in the study. Face-to-face interviews were used to collect socio-demographic data and risk factor information. Clinical, virological and immunological data of the HIV-infected patients were retrieved from their medical records. A written informed consent was obtained from the participants. All procedures were performed in accordance with the Helsinki Declaration. The study was cleared by the institutional Ethics Committee, I.F.O. Section (Istituti Regina Elena e San Gallicano)–Fondazione Bietti (CE/417/14).

Oral sample collection

Oral specimens were collected using 15 ml of Listerine mouthwash. Participants were asked to alternatively rinse and gargle for a total time of 30 seconds. Samples were immediately placed on ice, and within 15 min, centrifuged for 10 min at 3000xg, 4°C. The supernatant was removed and the pellet was washed twice with PreservCyt (Hologic, Pomezia, Italy). Subsequently, the pellet was resuspended in 2 ml of PreservCyt.

HPV testing

The Linear Array HPV genotyping test (Roche Diagnostics, Milan, Italy), which detects 37 genotypes (HPV 6, 11, 16, 18, 26, 31, 33, 35, 39, 40, 42, 45, 51, 52, 53, 54, 55, 56, 58, 59, 61, 62, 64, 66, 67, 68, 69, 70, 71, 72, 73, 81, 82, 83, 84, CP6108 and IS39) was used. Total nucleic acids were extracted from 250 μl of the PreservCyt sample using the Amplilute Liquid Media Extraction kit, part of the Linear Array HPV genotyping test, following the manufacturer’s instructions. 50 μl of the eluate was used for amplification. Automated detection was performed in a Profiblot T48 (Tecan, Männedorf, Switzerland). Results were interpreted as indicated by the producer. Samples with presence of one or more HPV hybridization bands, independently from the presence of the internal control, represented by β-globin, were considered as positive.

Data analysis

Descriptive statistics were computed for all the variables of interest in order to provide summarized descriptions of the study population. Regarding drinking habits, participants were asked to indicate their consumption of wine, beer, and spirits separately: 350 ml of beer, 120 ml of wine, and 50 of spirits were considered as one dose of alcoholic beverage (10–12 g of alcohol). Study subjects were then classified as follows: non-drinker (no alcohol consumption); light drinker (≤1 dose per day); moderate drinker (up to 3 doses per day); heavy drinker (>3 doses per day). Frequency of receptive oral sex was classified as follows: occasionally (<1 time per week), often (1–2 times per week), very often (≥3 times per week). The Mann-Whitney test was used for comparisons between median values. Socio-behavioral characteristics and lifestyle habits of HIV-positive and HIV-negative individuals were compared using Chi-square tests.
Participants were considered positive for any HPV whenever at least one of the 37 types detectable by the Linear Array was evidenced in the oral rinse. HPV genotypes were considered as carcinogenic, possibly carcinogenic, or non-carcinogenic based on the risk assigned to each genotype by the International Agency for Research on Cancer [24], and as previously specified [25], with the following modifications for purposes of analysis: HPV68, classified by IARC as a probably carcinogenic type, was included in the carcinogenic HPV group; HPV 55, 62, 64, 71, 83 and 84, classified by IARC as types with undetermined risk, were considered as non-carcinogenic types. The final HPV risk classification used in this study was: i) carcinogenic: HPVs 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68; ii) possibly carcinogenic: HPVs 26, 53, 66, 67, 69, 70, 73, 82; iii) non-carcinogenic: HPVs 6, 11, 40, 42, 54, 55, 61, 62, 64, 71, 72, 81, 83, 84, CP6108, IS39. Participants were considered positive for the types of the quadrivalent HPV vaccine (qHPV), if any of the 4 types included in the vaccine, i.e., HPVs 6, 11, 16, 18, was detected in the oral sample.

To assess the relationship between categorical variables, we used the Pearson’s Chi-square test and the Fisher Exact test, depending on the size of groups compared. A multivariate logistic regression model was generated for each of the two study groups. Both for the HIV-negative and positive MSM, the final model included: i) all the variables significant in the univariate assessment for any of the groups (p value <0.05): age at first sex with a man, number of lifetime partners for any sex and receptive oral sex, number of recent partners for any sex and receptive oral sex, history of ano-genital warts; ii) covariates known to be associated with oral HPV based on the literature, regardless of their significance in the univariate analysis: age, smoking status, occasional partners for any sex and receptive oral sex. The multivariate logistic regression models were built using a stepwise regression approach (forward selection) and the related estimates reported as Adjusted Odds Ratio (AOR) and 95% Confidence Interval (CI). The enter and remove limits were p = 0.10 and p = 0.15, respectively. Statistical analyses were carried out using SPSS software (SPSS version 21, SPSS Inc., Chicago, IL, USA).

Results

Study population

During the study period, a total of 170 MSM, mostly Caucasian (164, 96.5%), were recruited for this cross-sectional study: 98 (57.6%) HIV-uninfected and 72 HIV-infected individuals (42.4%).

The main socio-demographic and behavioral characteristics of the participants are shown in Table 1. The median age was 39 years (IQR: 32–45) for the HIV-negative and 44 years (IQR: 39–49) for the HIV-positive MSM (p = 0.04). Both groups of individuals had a similar median age at sexual debut (p = 0.13). Median numbers of lifetime partners for any sex (p = 0.87) and receptive oral sex (p = 0.56) were similar for both groups. Differently, HIV-infected MSM had a significantly lower number of recent partners both for any sex (p<0.001) and receptive oral sex (p = 0.005). HIV-negative and HIV-positive MSM were significantly different regarding education, alcohol consumption, partnership for any sex and receptive oral sex, and STI history. All the HIV-negative participants and 98.6% of the HIV-infected MSM reported to have engaged in receptive oral sex in their life, and the majority declared to have practiced receptive oral sex in the preceding 6 months (93.9% and 88.9%, respectively). Almost all the participants declared that they practiced condomless receptive oral sex both with their steady partner and with their occasional partners.

The 72 HIV-infected participants had a median nadir CD4+ count of 300 cells/mm3 (IQR: 200–391). At enrollment, the median CD4+ count was 622 cells/mm3 (IQR: 479–817). Only 4 patients (5.5%) had received a diagnosis of AIDS. The majority of the HIV-positive individuals
Table 1. Socio-demographic, behavioral and lifestyle characteristics at enrollment of the study population of 170 HIV-uninfected and infected MSM.

|                        | HIV-uninfected MSM | HIV-infected MSM | p value |
|------------------------|--------------------|------------------|---------|
| Age, years             | 39 (32–45)         | 44 (33–49)       | 0.04    |
| Age at first sex with a man, years | 19 (17–24) | 18 (17–20) | 0.13    |
| N. lifetime partners for any sex | 87 (45–150) | 100 (32–300) | 0.87    |
| N. recent partners for any sex | 8 (4–16) | 2 (1–9) | <0.001  |
| N. lifetime partners for receptive oral sex | 50 (20–95) | 50 (15–150) | 0.56    |
| N. recent partners for receptive oral sex | 4 (2–10) | 2 (1–6) | 0.0005  |
| Graduate education     | 51 % 52.0          | 22 % 30.6        | 0.005   |
| Medium/high incomea    | 63 % 64.3          | 45 % 62.5        | 0.81    |
| Alcohol consumption    | non drinker 40 % 40.8 | 40 % 55.6       | 0.02    |
|                       | light drinker 20 % 20.4 | 16 % 22.2       |         |
|                       | moderate drinker 34 % 34.7 | 14 % 19.4       |         |
|                       | heavy drinker 4 % 4.1 | 2 % 2.8         |         |
| Smoking status         | never 58 % 59.2    | 31 % 43.1       | 0.06    |
|                       | former 5 % 5.1     | 7 % 9.7         |         |
|                       | current 35 % 35.7  | 34 % 47.2       |         |
| Partnership for any sex | only steady partner 3 % 3.1 | 13 % 18.1     | 0.0004  |
|                       | steady and occasional partners 24 % 24.5 | 22 % 30.6 |         |
|                       | only occasional partners 71 % 72.4 | 37 % 51.4 |         |
| Receptive oral sex (ever) | 98 % 100.0 | 71 % 98.6 | 0.24    |
| Recent receptive oral sex | 92 % 93.9  | 64 % 88.9      | 0.24    |
| Frequency of recent receptive oral sex | occasionally 60 % 65.2 | 39 % 60.9 | 0.29    |
|                       | often 30 % 32.6   | 20 % 31.3       |         |
|                       | very often 2 % 2.2 | 5 % 7.8        |         |
| Partnership in recent receptive oral sex | only steady partner 5 % 5.1 | 19 % 26.4  | <0.0001 |
|                       | steady and occasional partners 15 % 15.3 | 13 % 18.1 |         |
|                       | only occasional partners 72 % 73.5 | 32 % 44.4 |         |
| Condomless receptive oral sex with steady partnerb | 19 % 95.0  | 32 % 100.0     | 0.21    |
| Condomless receptive oral sex with occasional partnersc | 72 % 82.8  | 34 % 75.6      | 0.32    |
| STI historyd           | 67 % 68.4         | 59 % 81.9       | 0.047   |
| Ano-genital wart historye | 30 % 30.6       | 28 % 38.9       | 0.26    |

STI, Sexually Transmitted Infections. Significant differences are highlighted in bold.

*a Income > 12,000 €/year.

*b For the participants with a steady partner (n = 20 for HIV-uninfected MSM; n = 32 for HIV-infected MSM).

*c For the participants with occasional partners (n = 87 for HIV-uninfected MSM; n = 45 for HIV-infected MSM).

*d Ano-genital warts, genital herpes, syphilis, gonorrhea (any site), diagnosed at least 6 months prior to enrollment.

https://doi.org/10.1371/journal.pone.0184623.t001
were on cART (66, 91.7%); almost all the cART-experienced MSM (60, 90.9%) were aviremic at enrollment.

Overall and type-specific oral HPV prevalence

A valid HPV test result was obtained for all the samples analyzed. Overall, HPV was detected in 37 of the 170 collected oral rinses (21.7%). Specifically, HPV infection was found in 17.3% and 27.8% of the HIV-negative and positive MSM, respectively (p = 0.13) (Table 2). No significant difference in the proportion of individuals positive for oncogenic types was observed for the two study groups, while non-oncogenic HPVs were significantly more common among HIV-infected subjects (18.1% vs. 5.1%, p = 0.01). Similar proportions of individuals were positive for the HPV types included in the quadrivalent HPV vaccine (p = 0.76). Multiple infections were twice as common among HIV-infected MSM, although this difference did not reach statistical significance (9.7% vs. 4.1%, p = 0.21). In HIV-positive individuals, up to 6 different types were found, compared to 4 types maximum for their HIV-negative counterparts (data not shown).

A total of 23 different HPV types were detected among HIV-infected MSM, while only 15 genotypes were found in the HIV-uninfected participants. Type-specific prevalence of all the genotypes found is shown in Fig 1. HPV16 was the most frequent type in HIV-negative MSM (5.1%). Among the HIV-positive individuals, HPV16, 18, 72 and 84 all showed the highest prevalence (4.2% each).

Determinants of oral HPV infection

Associations between oral HPV infection by any HPV genotype and sexual behavior, STI history, oral health, and lifestyle (smoking and drinking habits) were investigated separately for each study group. The results of the univariate and multivariate analyses by HIV status are shown in Table 3. Subset analyses for carcinogenic HPVs and HPV16 were not performed due to the limited number of positive individuals observed in each study group.

HIV-uninfected MSM who reported a history of ano-genital warts were significantly more likely to harbor oral HPV infection (COR: 3.21, 95% CI: 1.10–9.41, p = 0.033).

Among the HIV-infected MSM, the odds of oral infection increased with age at first sexual intercourse (COR: 3.44, 95% CI: 1.14–10.40 for those older than 18 years at first sex, p = 0.028), the number of lifetime partners for any sex (COR: 3.78, 95% CI: 1.20–11.95, for those with

Table 2. Distribution of oral HPV infection in the 170 study participants, stratified according to HPV group and HIV status.

|                        | HIV-uninfected MSM N = 98 | HIV-infected MSM N = 72 | p value |
|------------------------|---------------------------|-------------------------|---------|
| **Any HPV**            |                           |                         |         |
|                        | n    | %  | n    | %  |         |
| Carcinogenic HPV<sup>a</sup> | 17   | 17.3| 20   | 27.8| 0.13    |
| Possibly carcinogenic HPV<sup>b</sup> | 9    | 9.2 | 8    | 11.1| 0.79    |
| Non-carcinogenic HPV<sup>c</sup> | 7    | 7.1 | 7    | 9.7 | 0.58    |
| qHPV<sup>d</sup>       | 5    | 5.1 | 13   | 18.1| 0.01    |
| >1 HPV genotype        | 4    | 4.1 | 7    | 9.7 | 0.21    |

Significant differences are highlighted in bold.

<sup>a</sup> HPVs 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68.

<sup>b</sup> HPVs 26, 53, 66, 67, 69, 70, 73, 82.

<sup>c</sup> HPVs 6, 11, 40, 42, 54, 55, 61, 62, 64, 71, 72, 81, 83, 84, CP6108, IS39.

<sup>d</sup> HPVs 6, 11, 16, 18.

https://doi.org/10.1371/journal.pone.0184623.t002
≥100 compared to <100 partners, p = 0.019) and for receptive oral sex (COR: 8.23, 95% CI: 2.38–28.44, for those with >50 compared to ≤50 partners, p < 0.001). A significant increase in oral HPV prevalence was also observed among those who reported more than 4 recent partners for any sex (COR: 3.09, 95% CI: 1.06–8.97, p = 0.03) and receptive oral sex (COR: 3.32, 95% CI: 1.13–9.70, p = 0.02). HIV-positive MSM who referred to having sex with occasional partners also showed a higher prevalence of infection (COR: 4.37, 95% CI: 0.91–21.04, p = 0.066). Oral HPV was more frequent among HIV-infected MSM of more than 40 years of age (COR: 2.78, 95% CI: 0.88–8.76, p = 0.08). Regarding the HIV parameters, a borderline association was observed with the CDC-93 stage. In fact, oral HPV infection was more frequent among individuals in stage C compared to those in stage A/B (COR: 9.00, 95% CI: 0.88–92.40, p = 0.06).

Neither factors associated with oral health nor presence of tonsils appeared to modify the risk for oral HPV infection in the two study groups. After the beginning of the study, the otolaryngologist who performed the clinical examination was asked to rate the oral hygiene of the participants. This evaluation was available for 113 individuals. A non-significant increase in oral HPV infection was found for MSM with very poor/poor/fair hygiene.

For the HIV-uninfected MSM, none of the covariates was retained in the final adjusted model. For the HIV-infected MSM, an independent association for oral infection by any HPV was observed with age at first sex with a man (AOR: 4.02, 95% CI: 1.17–13.86, p = 0.027 for those reporting to be older than 18 years at first intercourse) and number of lifetime receptive oral sex partners (AOR: 9.14, 95% CI: 2.49–33.62, p < 0.001 for those with >50 partners).
Table 3. Univariate and multivariate analyses of the association between oral HPV infection (any HPV), socio-demographic factors, sexual behavior and HIV parameters.

|                              | HIV-uninfected MSM | HIV-infected MSM |
|------------------------------|--------------------|------------------|
|                              | HPV-positive COR (95% CI) | p value | AOR (95% CI) | p value | HPV-positive COR (95% CI) | p value | AOR (95% CI) | p value |
|                              | n/N (%)             |        |         |        | n/N (%)             |        |         |        |
| **Age, years**               |                    |        |         |        |                    |        |         |        |
| <40                          | 9/54 (16.7) Ref     |        |         |        | 5/30 (16.7) Ref     |        |         |        |
| ≥40                          | 8/44 (18.2) 1.11 (0.39–3.17) | 0.84 | not retained* |        | 15/42 (35.7) 2.78(0.88–8.76) | 0.08 | not retained* |
| **Education**                |                    |        |         |        |                    |        |         |        |
| graduate                     | 9/51 (17.6) Ref     |        |         |        | 6/22 (27.3) Ref     |        |         |        |
| ungraduate                   | 8/47 (17.0) 0.96 (0.34–2.73) | 0.94 |        |        | 14/50 (28.0) 1.04 (0.34–3.19) | 0.95 |        |
| **Annual income**            |                    |        |         |        |                    |        |         |        |
| medium/high                  | 12/63 (19.0) Ref    |        |         |        | 13/45 (28.9) Ref    |        |         |        |
| low                          | 5/35 (14.3) 0.71 (0.23–2.21) | 0.55 |        |        | 7/27 (25.9) 0.86 (0.29–2.52) | 0.79 |        |
| **Alcohol consumption**      |                    |        |         |        |                    |        |         |        |
| no/light                     | 9/60 (15.0) Ref     |        |         |        | 17/56 (30.4) Ref    |        |         |        |
| moderate/heavy               | 8/38 (21.1) 1.51 (0.53–4.33) | 0.44 |        |        | 3/16 (18.8) 0.53 (0.13–2.10) | 0.37 |        |
| **Smoking status**           |                    |        |         |        |                    |        |         |        |
| never/former                | 10/63 (15.9) Ref    |        |         |        | 9/38 (23.7) Ref     |        |         |        |
| current                      | 7/35 (20.0) 1.32 (0.45–3.86) | 0.61 | not retained* |        | 11/34 (32.4) 1.54 (0.55–4.35) | 0.41 | not retained* |
| **Age at first sex with a man, years** |                    |        |         |        |                    |        |         |        |
| <18                          | 9/43 (20.9) Ref     |        |         |        | 6/37 (16.2) Ref     |        |         |        |
| >18                          | 8/55 (14.5) 0.64 (0.22–1.84) | 0.41 | not retained* |        | 14/35 (40.0) 3.44 (1.14–10.40) | 0.028 | 4.02 (1.17–13.86) | 0.027 |
| **N. lifetime partner for any sex** |                    |        |         |        |                    |        |         |        |
| <100                         | 12/54 (22.2) Ref    |        |         |        | 5/34 (14.7) Ref     |        |         |        |
| ≥100                         | 5/44 (11.4) 0.45 (0.14–1.39) | 0.16 | not retained* |        | 15/38 (39.5) 3.78 (1.20–11.95) | 0.019 | not retained* |
| **N. recent partner for any sex** |                    |        |         |        |                    |        |         |        |
| ≤4                           | 7/31 (22.6) Ref     |        |         |        | 8/43 (18.6) Ref     |        |         |        |
| >4                           | 10/67 (14.9) 0.60 (0.20–1.77) | 0.35 | not retained* |        | 12/29 (41.4) 3.09 (1.06–8.97) | 0.03 | not retained* |
| **N. lifetime partners for receptive oral sex** |                    |        |         |        |                    |        |         |        |
| ≤50                          | 12/57 (21.0) Ref    |        |         |        | 4/39 (10.2) Ref     |        |         |        |
| >50                          | 5/41 (12.2) 0.52 (0.17–1.61) | 0.25 | not retained* |        | 16/33 (48.5) 8.23 (2.38–28.44) | <0.001 | 9.14 (2.49–33.62) | <0.001 |
| **N. recent partners for receptive oral sex** |                    |        |         |        |                    |        |         |        |
| ≤4                           | 12/52 (23.1) Ref    |        |         |        | 9/47 (19.1) Ref     |        |         |        |
| >4                           | 5/46 (10.9) 0.40 (0.13–1.26) | 0.11 | not retained* |        | 11/25 (44.0) 3.32 (1.13–9.70) | 0.02 | not retained* |
| **Occasional partner for any sex** |                    |        |         |        |                    |        |         |        |
| no                           | 1/3 (33.3) Ref      |        |         |        | 2/19 (10.5) Ref     |        |         |        |
| yes                          | 16/95 (16.8) 0.40 (0.03–4.74) | 0.47 | not retained* |        | 18/53 (34.0) 4.37 (0.91–21.04) | 0.07 | not retained* |
| **Occasional partner for receptive oral sex** |                    |        |         |        |                    |        |         |        |
| no                           | 0/5 (0.0) Ref       |        |         |        | 3/19 (15.8) Ref     |        |         |        |
| yes                          | 13/87 (14.9) 1.99 (0.10–38.18) | 0.64 | not retained* |        | 19/64 (29.7) 2.94 (0.74–11.64) | 0.12 | not retained* |

(Continued)
### Table 3. (Continued)

| HIV-uninfected MSM | HIV-infected MSM |  |
|--------------------|------------------|  |
|                     | HPV-positive COR (95% CI) | *p* value | AOR (95% CI) | *p* value | HPV-positive COR (95% CI) | *p* value | AOR (95% CI) | *p* value |
|---------------------|---------------------|-----------|-------------|-----------|---------------------|-----------|-------------|-----------|
| **Frequency recent receptive oral sex** | | | | | | | | |
| occasionally        | 11/60 (18.3) Ref    | 9/39 (23.1) Ref |  | | | | | |
| often/very often    | 2/32 (6.3) 0.29 (0.06–1.43) 0.13 | 10/25 (40.0) 2.22 (0.74–6.63) 0.15 | | | | | | |
| **Condomless receptive oral sex** | | | | | | | | |
| no                  | 0/2 (0.0) Ref       | 1/4 (25.0) Ref |  | | | | | |
| yes                 | 13/90 (14.4) 1.15 (0.05–29.26) 0.93 | 16/60 (30.0) 1.29 (0.12–13.21) 0.83 | | | | | | |
| **STI history** | | | | | | | | |
| no                  | 5/31 (16.1) Ref     | 3/13 (23.1) Ref |  | | | | | |
| yes                 | 12/67 (17.9) 1.13 (0.36–3.56) 0.83 | 17/59 (28.8) 1.35 (0.33–5.51) 0.68 | | | | | | |
| **Ano-genital warts history** | | | | | | | | |
| no                  | 8/68 (11.8) Ref     | 14/44 (31.8) Ref |  | | | | | |
| yes                 | 9/30 (30.0) 3.21 (1.10–9.41) 0.033 not retained | 6/26 (21.4) 0.58 (0.19–1.76) 0.34 not retained | | | | | | |
| **Presence of tonsils** | | | | | | | | |
| no                  | 5/25 (20.0) Ref     | 3/12 (25.0) Ref |  | | | | | |
| yes                 | 12/73 (16.4) 0.79 (0.25–2.51) 0.68 | 17/60 (28.3) 1.19 (0.29–4.92) 0.81 | | | | | | |
| **Gum bleeding (ever)** | | | | | | | | |
| no                  | 8/60 (13.3) Ref     | 17/56 (30.4) Ref |  | | | | | |
| yes                 | 9/36 (23.7) 2.02 (0.70–5.79) 0.19 | 3/16 (18.8) 0.90 (0.13–2.10) 0.53 | | | | | | |
| **Dental abscesses (ever)** | | | | | | | | |
| no                  | 15/78 (19.2) Ref    | 13/55 (23.6) Ref |  | | | | | |
| yes                 | 2/20 (10.0) 0.47 (0.09–2.23) 0.34 | 7/17 (41.2) 2.26 (0.72–7.13) 0.16 | | | | | | |
| **Toothache (ever)** | | | | | | | | |
| no                  | 13/69 (18.8) Ref    | 12/47 (25.5) Ref |  | | | | | |
| yes                 | 4/29 (13.8) 0.69 (0.20–2.32) 0.55 | 8/25 (32.0) 1.37 (0.47–3.98) 0.56 | | | | | | |
| **Tooth loss (ever)** | | | | | | | | |
| no                  | 12/74 (16.2) Ref    | 15/55 (27.3) Ref |  | | | | | |
| yes                 | 5/24 (20.8) 1.36 (0.42–4.35) 0.60 | 5/17 (29.4) 1.11 (0.33–3.69) 0.86 | | | | | | |
| **Dental cleaning per year** | | | | | | | | |
| ≥1                  | 16/63 (19.3) Ref    | 13/56 (23.2) Ref |  | | | | | |
| <1                  | 1/15 (6.7) 0.30 (0.04–2.44) 0.26 | 7/16 (43.8) 2.57 (0.80–8.26) 0.12 | | | | | | |
| **Mounth wash use** | | | | | | | | |
| often/always        | 7/44 (15.9) Ref     | 6/26 (23.1) Ref |  | | | | | |
| never/sometime      | 10/54 (18.5) 1.20 (0.42–3.47) 0.73 | 14/46 (30.4) 1.46 (0.48–4.41) 0.50 | | | | | | |
| **Oral hygiene** | | | | | | | | |
| good/very good      | 4/30 (13.3) Ref     | 4/17 (23.5) Ref |  | | | | | |
| very poor/poor/fair | 6/34 (17.6) 1.39 (0.35–5.50) 0.64 | 12/32 (37.5) 1.95 (0.52–7.37) 0.32 | | | | | | |

HIV-related parameters

| | HIV-positive COR (95% CI) | *p* value | AOR (95% CI) | *p* value |
|--------------------|---------------------|-----------|-------------|-----------|
| Stomatitis         | 12/60 (20.0) 1.31 (0.47–3.81) 0.61 | 18/59 (30.5) 1.73 (0.56–5.58) 0.34 |
| Recurrent mouth ulcer | 6/33 (18.2) 1.64 (0.42–6.55) 0.52 | 10/33 (30.3) 1.92 (0.58–5.92) 0.37 |

(Continued)
Discussion

This cross-sectional study provided data on the overall and type-specific prevalence of oral HPV infection in HIV-infected and uninfected MSM. It also evidenced differences in the correlates of infection for these two groups of individuals. To the best of our knowledge, this is the largest Italian study on this topic. Epidemiological data on oral HPV infection may be useful to evaluate the potential impact of HPV vaccination on MSM, although very few data on the efficacy of the HPV vaccines against oral infection have been provided to date. The Costa Rica Trial has shown a reduced prevalence in the vaccinated women compared to the control group [26], but we still lack data on the vaccine efficacy in HNSCC prevention.

In this study, we used oral rinse and gargles for the assessment of HPV infection. This type of sample, notwithstanding the inability to reveal the specific site of infection, has been shown to be better than other specimens for oral HPV detection [20,21,27,28].

Our estimates for the prevalence of any HPV among HIV-negative and HIV-positive MSM are 4 to 7-fold higher in comparison with the prevalence observed in young adults recruited in Italy [29], while they are similar to those found in other comparable cohorts of MSM [21,27].
Moreover, they almost perfectly overlap the pooled prevalence estimated for these individuals by a recent meta-analysis, i.e., 17.1% and 28.9%, respectively [30]. Similarly, the prevalence of carcinogenic HPV infection in HIV-negative MSM (9.2%) is very close to the pooled prevalence of this meta-analysis (9.1%), while the corresponding figure for HIV-positive individuals (11.1%) is lower than that estimated by King and collaborators (16.5%).

HPV16 was the most prevalent genotype in both study groups, confirming that HPV16 is the most common genotype in oral infections, besides being by far the most frequent type in HPV-associated oropharyngeal cancers [31]. Nevertheless, many other different HPVs were found in our participants, particularly among HIV-infected subjects, who also more frequently harbored multiple infections.

Our study confirmed that oral HPV is more common among MSM with HIV infection. Although statistical significance was not reached, others have shown that HIV status is independently associated with oral HPV [18,27]. The difference observed in our study does not seem to be attributable to a greater exposure to HPV for HIV-infected subjects through high risk sexual habits, since they were less likely to report receptive oral sex with occasional partners and had a lower number of recent partners both for any sex and receptive oral sex compared to their HIV-negative counterparts. However, it is noteworthy that the HIV-negative were significantly younger than the HIV-positive participants and this may partly explain our findings. In fact, some studies showed that oral HPV prevalence increases with age among HIV-negative men [32], and among HIV-negative MSM [18]. Additionally, we observed a higher prevalence of infection among HIV-positive participants who were more than 40 years of age, while other studies did not evidence any age effect for these subjects [18,32]. We found that HIV-positive individuals were significantly more likely to have non-carcinogenic HPVs, consistently with other studies [18,32].

We investigated socio-demographic variables, lifestyle, oral health and sexual habits in order to assess the determinants of oral HPV infection in the two study groups. We did not observe any association with recent oral sex behavior for the HIV-negative MSM, differently from other studies [32]. In the univariate analysis, a significant association was only found with having had ano-genital warts in the past. Consistently with previous studies [27,33], individuals reporting a history of ano-genital condylomatosis appeared to be at increased risk for prevalent oral HPV infection. In the multivariate analysis, a significant association was not evidenced for any of the factors investigated.

Number of lifetime partners for oral sex emerged as a determinant of prevalent oral HPV infection among HIV-infected MSM, in line with previous studies [7,27,32,34,35]. In particular, participants with more than 50 partners showed an almost 10-fold increased odds of oral HPV. Interestingly, we also observed a positive association with age at first intercourse. The odds for oral HPV increased 4-fold in those who reported an older age at first sexual experience with a man. Our observation may reflect a measurable age-cohort effect on age at first intercourse, due to the older age of the HPV-positive patients. Moreover, it must be noted that oral sex experiences may precede sexual debut.

This investigation failed to evidence a role for several other variables known to be associated with the risk for oral HPV infection, such as oral sex [7,34] and tobacco use, which has been demonstrated as a risk factor in men, MSM [18,27,32,35,36], as well as in the general population [5,7]. Regarding sex habits, the high frequency of risky behavior among MSM often limits the possibility of finding significant associations. For instance, we could not establish whether or not oral sex is associated with HPV infection, since very few individuals denied having ever practiced or having recently practiced receptive oral sex. Unfortunately, we did not collect data on oral-anal contacts, which may also play a role in the acquisition of oral HPV infection.
Indeed, a previous study observed that oral HPV prevalence increased significantly with the number of rimming partners among HIV-negative MSM [32].

We also investigated the possible role of oral hygiene, since a large cross-sectional study has previously identified four different indicators of scarce oral health as being associated with increased likelihood of oral HPV [7], and poor oral hygiene also represents a risk factor for head and neck carcinomas [37–39]. However, we did not observe any significant increase in the odds of oral HPV for MSM with poor oral hygiene in any of the two study groups.

As regards the HIV parameters, we observed that HIV-positive MSM in C-CDC 93 stage, i.e., subjects diagnosed with an AIDS-associated disease, had a higher prevalence of infection, at borderline significance. This finding seems to suggest that a severe immunocompromised status favors oral HPV infection. However, we did not observe any significant association with nadir and current CD4 counts, consistently with other studies [10,18,27,36,40]. Nevertheless, others have demonstrated increased risk of oral infection for HIV-positive individuals with lower nadir and current CD4 counts, with a particular association with HPV16 infection [27,32,33]. Being on cART did not seem to significantly affect the prevalence of oral HPV. Data from the literature have displayed conflicting results. A recent investigation showed no effect of cART initiation on oral HPV infection [41]. No significant differences in oral HPV prevalence between cART-naïve and -experienced subjects have been also observed by others [32,36].

Some limitations of the present study can be evidenced. Firstly, the analyses may have been underpowered due to the small size of the study groups. Secondly, the participants homogeneously reported a high risk sexual behavior, so our results may not be generalizable to all urban MSM. Finally, the group of HIV-infected MSM was largely lacking in individuals with severe immunosuppression and this may have limited the validity of the association measures between oral HPV infection and the parameters of immunodeficiency.

In conclusion, this study showed that the prevalence of oral HPV in MSM is 3–5 fold higher in comparison with the general population and the infection is particularly frequent even among aviremic and immunologically balanced HIV-infected MSM. However, the sample size needs to be increased to have reliable estimates for the predictors of this infection. Since no established screening programs for OPSCC exist, further studies are needed to clarify whether or not individuals with oral HPV infection have to undergo specific management.

**Acknowledgments**

We would like to thank Dr. Michael Kenyon for his review of the English language.

**Author Contributions**

**Conceptualization:** Francesca Rollo, Alessandra Latini, Antonio Cristaudo, Massimo Giuliani, Maria Gabriella Donà.

**Data curation:** Francesca Rollo, Massimo Giuliani, Maria Gabriella Donà.

**Formal analysis:** Isabella Sperduti, Massimo Giuliani, Maria Gabriella Donà.

**Funding acquisition:** Maria Gabriella Donà.

**Investigation:** Francesca Rollo, Barbara Pichi, Maria Benevolo, Ilenia Sinopoli, Valentina Laquintana, Giulia Fabbri.

**Methodology:** Francesca Rollo, Alessandra Latini, Maria Benevolo, Maria Gabriella Donà.

**Project administration:** Massimo Giuliani, Maria Gabriella Donà.
Resources: Alessandra Latini, Barbara Pichi, Manuela Colafigli, Maria Benevolo, Ilenia Sinopoli, Mirko Frasca.

Supervision: Massimo Giuliani, Maria Gabriella Donà.

Visualization: Francesca Rollo, Massimo Giuliani, Maria Gabriella Donà.

Writing – original draft: Francesca Rollo, Massimo Giuliani, Maria Gabriella Donà.

Writing – review & editing: Francesca Rollo, Alessandra Latini, Barbara Pichi, Manuela Colafigli, Maria Benevolo, Ilenia Sinopoli, Isabella Sperduti, Valentina Laquintana, Giulia Fabbrri, Mirko Frasca, Antonio Cristaudo, Massimo Giuliani, Maria Gabriella Donà.

References

1. Agalliu I, Gapstur S, Chen Z, Wang T, Anderson RL; Teras L, et al. Associations of oral alpha-, beta-, and gamma-human papillomavirus types with risk of incident head and neck cancer. JAMA Oncol. 2016. https://doi.org/10.1001/jamaoncol.2015.5504 PMID: 26794505

2. Chaturvedi AK, Engels EA, Pfeiffer RM, Hernandez BY, Xiao W, Kim E, et al. Human papillomavirus and rising oropharyngeal cancer incidence in the united states. J Clin Oncol. 2011; 29(32):4294–4301. https://doi.org/10.1200/JCO.2011.36.4596 PMID: 21969503

3. Tinnofer I, Johrens K, Keilholz U, Kaufmann A, Lehmann A, Weichert W, et al. Contribution of human papilloma virus to the incidence of squamous cell carcinoma of the head and neck in a european population with high smoking prevalence. Eur J Cancer. 2015; 51(4):514–521. https://doi.org/10.1016/j.ejca.2014.12.018 PMID: 25623438

4. Carlson AF, Gronhoj Larsen C, Jensen DH, Garnaes E, Kiss K, Andersen L, et al. Continuing rise in oropharyngeal cancer in a high HPV prevalence area: A Danish population-based study from 2011 to 2014. Eur J Cancer. 2017; 70:75–82. https://doi.org/10.1016/j.ejca.2016.01.015 PMID: 27886679

5. 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(7):693–703. https://doi.org/10.1001/jama.2012.101 PMID: 22282321

6. Hang D, Liu F, Liu M, He Z, Sun M, Liu Y, et al. Oral human papillomavirus infection and its risk factors among 5,410 healthy adults in china, 2009–2011. Cancer Epidemiol Biomarkers Prev. 2014; 23 (10):2101–2110. https://doi.org/10.1158/1055-9965.EPI-14-0084 PMID: 25033824

7. Bui TC, Markham CM, Ross MW, Mullin PD. Examining the association between oral health and oral HPV infection. Cancer Prev Res. 2013; 6(9):917–924.

8. 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(6):407–420. https://doi.org/10.1093/jnci/djn025 PMID: 18334711

9. Heck JE, Berthiller J, Vaccarella S, Winn DM, Smith EM, Shan’gina O, et al. Sexual behaviours and the risk of head and neck cancers: A pooled analysis in the international head and neck cancer epidemiology (INHANCE) consortium. Int J Epidemiol. 2010; 39(1):166–181. https://doi.org/10.1093/ije/dyp350 PMID: 20029296

10. Beachler DC, D’Souza G, Sugar EA, Xiao W, Gillison ML. Natural history of anal vs oral HPV infection in HIV-infected men and women. J Infect Dis. 2013; 208(2):330–339. https://doi.org/10.1093/infdis/ jjt170 PMID: 23596319

11. Nyitray AG, Carvalho da Silva RJ, Baggio ML, Lu B, Smith D, Abrahamson M, et al. Age-specific prevalence of and risk factors for anor human papillomavirus (HPV) among men who have sex with women and men who have sex with men: The HPV in men (HIM) study. J Infect Dis. 2011; 203(1):49–57. https://doi.org/10.1093/infdis/jjq201 PMID: 21148496

12. Frisch M, Smith E, Gruilich A, Johansen C. Cancer in a population-based cohort of men and women in registered homosexual partnerships. Am J Epidemiol. 2003; 157(11):966–972. PMID: 12777359

13. Patel P, Hanson DL, Sullivan PS, Novak RM, Moorman AC, Tong TC, et al. Incidence of types of cancer among HIV-infected persons compared with the general population in the United States, 1992–2003. Ann Intern Med. 2008; 148(10):728–736. PMID: 18490686

14. Chaturvedi AK, Madeleine MM, Biggar RJ, Engels EA. Risk of human papillomavirus-associated cancers among persons with AIDS. J Natl Cancer Inst. 2009; 101(16):1120–1130. https://doi.org/10.1093/jnci/djp205 PMID: 19648510
15. Shiels MS, Cole SR, Kirk GD, Poole C. A meta-analysis of the incidence of non-AIDS cancers in HIV-infected individuals. J Acquir Immune Defic Syndr. 2009; 52(5):611–622. https://doi.org/10.1097/QAI.0b013e3181b327a PMID: 19770804

16. Mooij SH, Boot HJ, Speksnijder AG, Meijer CJ, King AJ, Verhagen DW, et al. Six-month incidence and persistence of oral HPV infection in HIV-negative and HIV-infected men who have sex with men. PLoS One. 2014; 9(6):e89955. https://doi.org/10.1371/journal.pone.0089955 PMID: 24896848

17. van Aar F, Mooij SH, van der Sande MA, Meijer CJ, King AJ, Verhagen DW, et al. Twelve-month incidence and clearance of oral HPV infection in HIV-negative and HIV-infected men who have sex with men: The H2M cohort study. BMC Infect Dis. 2014; 14:668. https://doi.org/10.1186/s12879-014-0668-z PMID: 25551194

18. Mooij SH, Boot HJ, Speksnijder AG, Stolte IG, Meijer CJ, Sniijders PJ, et al. Oral human papillomavirus infection in HIV-negative and HIV-infected MSM. AIDS. 2013; 27(13):2117–2128. https://doi.org/10.1097/QAD.0b013e328362395c PMID: 24384590

19. van Rijn VM, Mooij SH, Mollers M, Sniijders AG, King AJ, et al. Anal, penile, and oral high-risk HPV infections and HPV seropositivity in HIV-positive and HIV-negative men who have sex with men. PLoS One. 2014; 9(3):e92208. https://doi.org/10.1371/journal.pone.0092208 PMID: 24651691

20. King EM, Gilson R, Beddows S, Soldan K, Panwar K, Young C, et al. Oral human papillomavirus (HPV) infection in men who have sex with men: Prevalence and lack of anogenital concordance. Sex Transm Infect. 2015; 91(4):284–286. https://doi.org/10.1136/sextrans-2014-051955 PMID: 25887283

21. Parisi SG, Cruciani M, Scaglione B, Boldrin C, Andreis S, Dal Bello F, et al. Anal and oral human papillomavirus (HPV) infection in HIV-infected subjects in northern Italy: A longitudinal cohort study among men who have sex with men. BMC Infect Dis. 2011; 11:150. https://doi.org/10.1186/1471-2334-11-150 PMID: 21612634

22. Del Mistro A, Baboci L, Frayle-Salamanca H, Trevisan R, Bergamo E, Lignitto L, et al. Oral human papillomavirus and human herpesvirus-8 infections among human immunodeficiency virus type 1-infected men and women in Italy. Sex Transm Dis. 2012; 39(11):894–896. https://doi.org/10.1097/OLQ.0b013e31826af2da PMID: 23064540

23. Sammarco ML, Ucciferri C, Tamburro M, Falasca K, Ripabelli G, Vecchiet J. High prevalence of human papillomavirus type 58 in HIV infected men who have sex with men: A preliminary report in Central Italy. J Med Virol. 2016; 88(5):911–914. https://doi.org/10.1002/jmv.24406 PMID: 26471111

24. IARC monographs on the evaluation of carcinogenic risks to humans. Volume 100B. A review of human carcinogens: Biological agents. Lyon: IARC; 2011.

25. Donà MG, Vescio MF, Latini A, Giglio A, Moretto D, Frasca M, et al. Anal human papillomavirus in HIV-uninfected men who have sex with men: Incidence and clearance rates, duration of infection, and risk factors. Clin Microbiol Infect. 2016; 22(12):1004.e1-1004.e7.

26. 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. 2015; 10(7):e0137610. https://doi.org/10.1371/journal.pone.0137610 PMID: 26133876

27. 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(11):e49324. https://doi.org/10.1371/journal.pone.0049324 PMID: 23173054

28. Darwich L, Canadas MP, Videla S, Coll J, Molina-López RA, Cobarsi P, et al. Oral human papillomavirus type-specific infection in HIV-infected men: A prospective cohort study among men who have sex with men infected and heterosexual men. Clin Microbiol Infect. 2014; 20(9):O585–9. https://doi.org/10.1111/cmi.12469 PMID: 24382308

29. Lupo P, Holzinger D, Hofler D, Menegaldo A, Giorgi Rossi P, Del Mistro A, et al. Prevalence and determinants of oral human papillomavirus infection in 500 young adults from Italy. PLoS One. 2017; 12(1): e0170091. https://doi.org/10.1371/journal.pone.0170091 PMID: 28103272

30. King EM, Oomeer S, Gilson R, Copas A, Beddows S, Soldan K, et al. Oral human papillomavirus infection in men who have sex with men: A systematic review and meta-analysis. PLoS One. 2016; 11(7): e0157976. https://doi.org/10.1371/journal.pone.0157976 PMID: 27384050

31. Castellsague X, Alemany L, Quer M, Halec G, Quiró B, Tous S, et al. HPV involvement in head and neck cancers: Comprehensive assessment of biomarkers in 3680 patients. J Natl Cancer Inst. 2016; 108(6):djv403. https://doi.org/10.1093/jnci/djv403 PMID: 26823521

32. 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(1):122–133. https://doi.org/10.1158/1055-9965.EPI-11-0734 PMID: 22045700
33. Videla S, Darwich L, Cañadas MP, Coll J, Piñol M, García-Cuyás F, et al. Natural history of human papillomavirus infections involving anal, penile, and oral sites among HIV-positive men. Sex Transm Dis. 2013; 40(1):3–10. https://doi.org/10.1097/OLQ.0b013e31827e87bd PMID: 23250297

34. D’Souza G, Cullen K, Bowie J, Thorpe R, Fakhry C. Differences in oral sexual behaviors by gender, age, and race explain observed differences in prevalence of oral human papillomavirus infection. PLoS One. 2014; 9(1):e86023. https://doi.org/10.1371/journal.pone.0086023 PMID: 24475067

35. Colon-Lopez V, Quinones-Avila V, Del Toro-Meijas LM, Reyes K, Rivera ME, Nieves K, et al. Oral HPV infection in a clinic-based sample of Hispanic men. BMC Oral Health. 2014; 14:7. https://doi.org/10.1186/1472-6831-14-7 PMID: 24460642

36. Gaester K, Fonseca LA, Luiz O, Assone T, Fontes AS, Costa F, et al. Human papillomavirus infection in oral fluids of HIV-1-positive men: Prevalence and risk factors. Sci Rep. 2014; 4:6592. https://doi.org/10.1038/srep06592 PMID: 25322857

37. Divaris K, Olshan AF, Smith J, Bell ME, Weissler MC, Funkhouser WK, et al. Oral health and risk for head and neck squamous cell carcinoma: The Carolina head and neck cancer study. Cancer Causes Control. 2010; 21(4):567–575. https://doi.org/10.1007/s10552-009-9486-9 PMID: 20049634

38. Eliot MN, Michaud DS, Langevin SM, McClean MD, Kelsey KT. Periodontal disease and mouthwash use are risk factors for head and neck squamous cell carcinoma. Cancer Causes Control. 2013; 24(7):1315–1322. https://doi.org/10.1007/s10552-013-0209-x PMID: 23568534

39. Mazul AL, Taylor JM, Divaris K, Weissler MC, Brennan P, Anantharaman D, et al. Oral health and human papillomavirus-associated head and neck squamous cell carcinoma. Cancer. 2017; 123(1):71–80. https://doi.org/10.1002/cncr.30312 PMID: 27571516

40. Ong JJ, Read TR, Vodstrcil LA, Walker S, Chen M, Bradshaw CS, et al. Detection of oral human papillomavirus in HIV-positive men who have sex with men 3 years after baseline: A follow up cross-sectional study. PLoS One. 2014; 9(7):e102138. https://doi.org/10.1371/journal.pone.0102138 PMID: 25033212

41. Shiboski CH, Lee A, Chen H, Webster-Cyriaque J, Seaman T, Landovitz RJ, et al. Human papillomavirus infection in the oral cavity of HIV patients is not reduced by initiating antiretroviral therapy. AIDS. 2016; 30(10):1573–1582. https://doi.org/10.1097/QAD.0000000000001072 PMID: 26919735