

Review Article

Oral human papillomavirus infection in HIV-infected individuals – a systematic review and meta-analysis

ABSTRACT

Background:The human papillomavirus (HPV) is the most common sexually transmitted infection in the world. Our study aimed to conduct a systematic review with meta-analysis on the prevalence of HPV among HIV-positive individuals.

Methodology:We followed the guidelines of the preferred reporting items for systematic reviews and meta-analyses (PRISMA) to conduct a thorough review. We searched for published literature in MEDLINE/PubMed, EMBASE and Scopus, using the following keywords: “HPV”, “papillomavirus”, “papillomaviridae”, “head and neck”, “oropharynx”, “oropharyngeal”, “tongue”, “mouth”, “oral”, “oral cavity”, “HIV”, “Acquired Immunodeficiency Syndrome” and “AIDS”. Out of 925 studies, we included 26 in our analysis. Our results showed that the overall pooled prevalence of oral HPV infection in HIV-infected individuals was 24.00% (with a 95% confidence interval between 16.00-35.00).

Results:A total of 925 studies were retrieved with our search strategy. After removing duplicate articles, 706 studies remained. Reading the titles and abstracts of these studies, 81 studies were eligible to read the full article. After reading the full text of the selected articles, we excluded 55 articles for reasons such as no access to full text (n=9) and literature reviews, systematic reviews, case studies, and conference proceedings (n=28). We also exclude articles concerning other subsites that are not oral cavity or oropharynx. There were 26 studies left that were included in this systematic review.

Conclusion: This systematic review revealed a high prevalence of oral HPV infection in positive HIV individuals.

*Keywords:*human papillomavirus, HIV, prevalence, oral

1. INTRODUCTION

The human papillomavirus (HPV) represents the viral sexually transmitted infection most frequent in the world [1,2]. HPV infections are transmitted through direct contact skin-to-skin or skin-to-mucosa and the number of sexual partners has been repeatedly demonstrated as the main determining condition of HPV infection, both in men and women [1,2].

Regarding the prevalence of HPV in the general population, Gillison et al. investigated the presence of the HPV virus in the oral mucosa of 5579 individuals, showing a prevalence of 6.9%, which is higher in men than in women [3]. After a period of time following HPV infection, most individuals clear the virus spontaneously [4].

In Human immunodeficiency virus (HIV) infected individuals, oral HPV infection appears to persist longer than in healthy individuals [5,6]. Several studies have shown that the prevalence and incidence of HPV infection have been shown to be higher in HIV-infected patients when compared to non-HIV controls [7,8,9]

Another important point for patients living with the HIV virus is that they use antiretroviral therapy (ART), which is the standard treatment for HIV infection, and consists of a combination of medications [10]. HPV infection in HIV-infected patients after ART initiation has been associated. [11].

Few studies have been published on the prevalence of HPV in these individuals. In this context, it is important to investigate the prevalence of oral HPV infection in HIV-infected individuals. Thus, the objective of our study was to carry out a systematic review with meta-analysis on the oral prevalence of HPV in HIV individuals.

2. MATERIAL AND METHODS

2.1 Searching strategies

We conducted a systematic review according to the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [12]. We searched published literature in MEDLINE/PubMed, EMBASE and Scopus for articles published up to February 2023. The following terms were used to search in the titles, abstracts, and keywords: “HPV”, “papillomavirus”, “papillomaviridae”, “head and neck”, “oropharynx”, “oropharyngeal”, “tongue”, “mouth”, “oral”, “oral cavity”, “HIV”, “Acquired Immunodeficiency Syndrome” and “AIDS”.

2.2 Inclusion and exclusion criteria

We searched for articles reporting the prevalence of oral HPV in HIV individuals. We included articles in English, Portuguese or Spanish. Any type of study design was considered and no restriction on the publication date of the article. We excluded review articles, meta-analyses, case reports, animal studies and articles with incomplete information.

2.3 Selection of studies

Two researchers (MEAS and GFSJ) independently screened titles and abstracts for eligibility in the period from January to February 2023. Any discrepancies between all investigators

were resolved by the third investigator (CCF). A PRISMA workflow diagram was created to show how the studies were included (Fig 1.)

2.4 Data extraction

Two investigators (MEAS and GFSJ) independently extracted data from the selected studies which were subsequently reviewed by a third investigator. We used a form to extract the following data from each study: author name, year of publication, study design, HPV prevalence, sample size, findings and conclusions.

2.5 Statistical analysis

All the statistical analyses for the meta-analysis were developed in R software (version 4.2.2 and package meta version 6.2-0). I^2 statistics were applied for the evaluation of study heterogeneity, where 25, 50, and 75% represented low, moderate, and severe heterogeneity, respectively. A random-effect model was employed to conduct the meta-analysis because of high heterogeneity. We use the random effect model, with a 95% confidence interval to estimate the pooled prevalence because of the high heterogeneity of the included studies (99%) [13].

2.6 Quality assessment and publication bias

The quality of the different papers included in this systematic review was evaluated following the checklist proposed by the Joanna Briggs Institute Critical Appraisal Checklist for Studies Reporting Prevalence Data. The checklist contains 9 questions with four answering options including Yes, No, Unclear, and Not applicable; studies were characterized as follows: low risk of bias ($\geq 70\%$ of questions answered "yes") Moderate risk of bias ($\geq 50\%$ and $<70\%$) of questions answered "yes" and high risk of bias ($<50\%$ of questions answered "yes"). In our review, all 26 studies included in this study were considered to present a low risk of bias as shown in Table 2 [14].

3. RESULTS

3.1 Search results

A total of 925 studies were retrieved with our search strategy. After removing duplicate articles, 706 studies remained. Reading the titles and abstracts of these studies, 81 studies were eligible to read the full article. After reading the full text of the selected articles, we excluded 55 articles for reasons such as no access to full text ($n=9$) and literature reviews, systematic reviews, case studies, and conference proceedings ($n=28$). We also exclude articles concerning other subsites that are not oral cavity or oropharynx. There were 26 studies left that were included in this systematic review. Fig 1. shows the flow of studies throughout the review. A summary of study characteristics is presented in Table 1. Included studies evaluated 4464 participants from 26 studies that provided data for quantitative analysis.

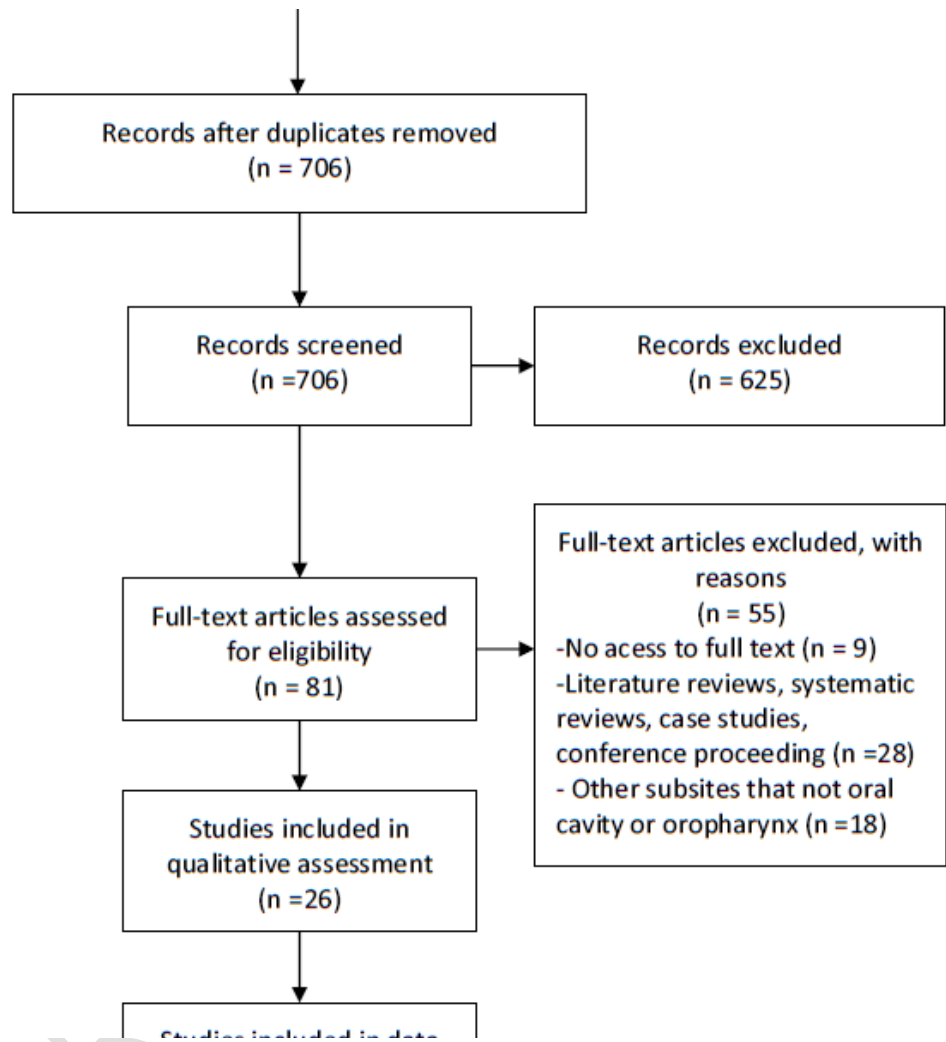


Fig. 1 PRISMA diagram of study identification and screening.

Table 1 Characteristics of studies

Autor/Year	Country	Study design	Gender	Overall HPV (n)	Total (n)
Amornthatree et al., 2011[8]	Thailand	Cross-sectional	Male and Female	37	49
Beachler et al., 2012[6]	US	Cohort	Male and Female	152	379
Blass et al., 2015[15]	Peru	Cross-sectional	Male	40	99
Fakhry et al.,	US	Cross-sectional	Female	36	143

2006[16]					
Gaester et al., 2014[17]	Brazil	Cross-sectional	Male	10	283
Garcia et al., 2018[7]	Mexico	Cohort	Male	54	97
Gonçalves et al., 2020[18]	Portugal	Cross-sectional	Male	45	255
Hernandez et al., 2021[19]	India	Cross-sectional	Male	70	295
Kahna et al., 2019 [20]	US	Clinical trial	Male	9	145
Lima et al., 2014[21]	Brazil	Cross-sectional	Female	11	100
Lin et al., 2018[22]	Tawan	Cross-sectional	Male	19	113
Marais et al., 2008[9]	South Africa	Cross-sectional	Female	28	33
Mistro et al., 2022 [23]	Italy	Cross-sectional	Male and Female	37	100
Mooij et al., 2014 [24]	Holland	Cross-sectional	Male	86	276
Parisi et al., 2011 [25]	Italy	Cohort	Male	23	108
Quintanilla et al., 2020 [26]	Mexico	Cross-sectional	Female	161	174
Read et al., 2012 [27]	Australia	Cross-sectional	Male	48	249
Riddell IV et al., 2022 [28]	US	Cross-sectional	Male and Female	56	245
Rijn et al., 2014 [29]	Holland	Cross-sectional	Male	53	306
Rollo et al., 2017 [30]	Italy	Cross-sectional	Male	20	72
Sammarco et al., 2016 [31]	Italy	Cross-sectional	Male	8	50
Suehiro et al., 2020 [32]	Brazil	Cohort	Female	17	115
Thorsteinssona et. al, 2018 [33]	Denmark	Cohort	Female	12	214
Vacharotayangula et al., 2015 [34]	Thailand	Cross-sectional	Male and Female	29	187
Vergori et al., 2018 [35]	Italy	Cross-sectional	Male	64	305
Wood et al., 2020 [36]	South Africa	Cohort	Male and Female	2	72

3.2 Characteristics of included studies

26 studies with 4464 participants were included in this study. These studies were conducted in different countries. As depicted in Table 1, a total of 19 Cross-sectional studies [8,9,15-19,21-24,26-31,34,35], 6 Cohort studies [6,7,25,32,33,36] and 1 Clinical trial [20].

Regarding the sample size of included studies, 49 is the smallest number of participants and 379 is the maximum number of participants.

3.3 Quality and publication bias of included studies

The quality of the papers included in this systematic review was evaluated following the checklist proposed by the Joanna Briggs Institute Critical Appraisal Checklist for Studies Reporting Prevalence Data. In our systematic review, all 26 studies were considered as presenting a low risk of bias, as shown in Table 2.

3.4 Meta-analysis of the prevalence of oral human papillomavirus infection in HIV-infected individuals

In our study, the prevalence of oral human papillomavirus infection in HIV-infected individuals ranged from 3.00% to 93.00%. The pooled amount of oral human papillomavirus infection in this study was 26% (95% CI, 16 - 35) among HIV-infected individuals. Fig 2. shows the forest plot illustrating the individual prevalence of each study and the pooled prevalence of this systematic review and meta-analysis. The studies had high heterogeneity ($I^2 = 95\%$).

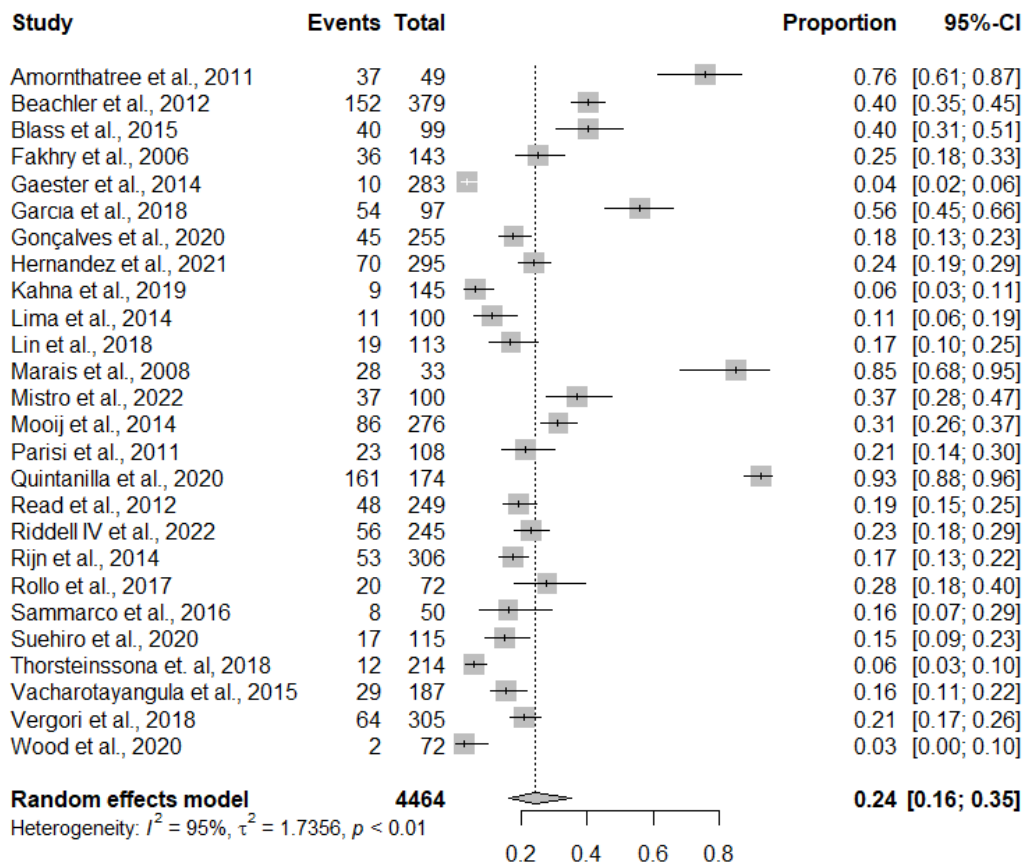


Fig. 2 Forest plot the prevalence of oral human papillomavirus infection in HIV-infected individuals.

Table 2 Risk of bias assessment according to the Joanna Briggs Institute critical appraisal tool for prevalence studies

Authors/year	Q 1	Q 2	Q 3	Q 4	Q 5	Q 6	Q 7	Q 8	Q 9	Total (% of "yes")	Risk of bias
Amornthatree et al., 2011	Y	Y	Y	Y	Y	Y	Y	Y	Y	100	Low
Beachler et al., 2012	Y	Y	Y	Y	Y	Y	Y	Y	Y	100	Low
Blass et al., 2015	Y	Y	Y	Y	Y	Y	Y	Y	Y	100	Low
Fakhry et al., 2006	Y	Y	Y	Y	Y	Y	Y	Y	Y	100	Low
Gaester et al., 2014	Y	Y	Y	Y	Y	Y	Y	Y	Y	100	Low
Garcia et al., 2018	Y	Y	Y	Y	Y	Y	Y	Y	Y	100	Low
Gonçalves et al., 2020	Y	Y	Y	Y	Y	Y	Y	Y	Y	100	Low
Hernandez et al., 2021	Y	Y	Y	Y	Y	Y	Y	Y	Y	100	Low
Kahna et al., 2019	Y	Y	Y	Y	Y	Y	N	Y	Y	88.89	Low
Lima et al., 2014	Y	Y	Y	Y	Y	Y	Y	Y	Y	100	Low
Lin et al., 2018	Y	N	Y	N	Y	Y	Y	Y	Y	77.78	Low
Marais et al., 2008	Y	Y	Y	Y	Y	Y	Y	Y	Y	100	Low
Mistro et al., 2022	Y	Y	Y	N	Y	Y	Y	Y	Y	88.89	Low
Mooij et al., 2014	Y	Y	Y	Y	Y	Y	Y	Y	Y	100	Low
Parisi et al., 2011	Y	Y	Y	Y	Y	Y	Y	Y	Y	100	Low
Quintanilla et al., 2020	Y	Y	Y	N	Y	Y	Y	Y	Y	88.89	Low

Read et al., 2012	Y	Y	Y	Y	Y	Y	Y	Y	Y	100	Low
Riddell IV et al., 2022	Y	Y	Y	Y	Y	Y	Y	Y	Y	100	Low
Rijn et al., 2014	Y	Y	Y	Y	Y	Y	Y	Y	Y	100	Low
Rollo et al., 2017	Y	Y	Y	Y	Y	Y	Y	Y	Y	100	Low
Sammarco et al., 2016	Y	N	Y	Y	Y	Y	Y	Y	Y	88.89	Low
Suehiro et al., 2020	Y	Y	Y	Y	Y	Y	Y	Y	Y	100	Low
Thorsteinsson et al., 2018	Y	Y	Y	N	Y	Y	Y	Y	Y	88.89	Low
Vacharotayan gula et al., 2015	Y	N	Y	N	Y	Y	Y	Y	Y	77.78	Low
Vergori et al., 2018	Y	N	Y	Y	Y	Y	Y	Y	Y	88.89	Low
Wood et al., 2020	Y	Y	Y	Y	Y	Y	Y	Y	Y	100	Low

Note 1: Q1 = Was the sample frame appropriate to address the target population? - Q2 = Were study participants sampled in an appropriate way? - Q3 = Was the sample size adequate? - Q4 = Were the study subjects and the setting described in detail? - Q5 = Was the data analysis conducted with sufficient coverage of the identified sample? - Q6= Were valid methods used for the identification of the condition? - Q7 = Was the condition measured in a standard, reliable way for all participants? - Q8 = Was there appropriate statistical analysis? - Q9 = Was the response rate adequate, and if not, was the low response rate managed appropriately? Note 2: Y = yes; N = no; U = Unclear; NA = not applicable

4. DISCUSSION

In most cases, an HPV infection is resolved within 4 to 20 months in healthy individuals [37,38]. However, immune dysfunction in HIV-infected individuals impairs HPV clearance [39,40]. It is unclear whether the increased incidence of oral HPV among HIV-infected persons is due to HIV-related immunosuppression or higher sexual risk behaviour. Thus the prevalence of oral HPV infection ranges from 1% to 5% in immunocompetent people and from 14% to 45% in those with HIV [3, 41].

In current times due to combined antiretroviral therapy used to treat HIV patients, tumors have become the main cause of mortality in HIV-positive individuals [42,43]. HIV-positive individuals have a higher incidence of head and neck squamous cell carcinoma than the general population [44]. Furthermore, most oropharyngeal squamous cell carcinomas are HPV-related tumours [45].

We performed this systematic review following the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) protocol and we used the R Studio for the statistics analysis.

The pooled analysis of all included studies indicated that the prevalence of oral HPV infection in HIV-infected individuals ranged from 03.00% to 93.00%, with an overall pooled prevalence of 24.00% (95% CI: 16.00-35.00). These results are similar to the findings by Fakhry et al. (2006) [16], Gonçalves et al. (2020) [18], Hernandez et al. (2021) [19], Mooij et al. (2014) [24], Parisi et al. (2011) [25], Read et al. (2012) [27], Riddell IV et al. (2022) [28], Rijn et al. (2014) [29], Rollo et al. (2017) [30], Vacharotayangula et al. (2015) [34] and Vergori et al. (2018) [35]. Which found 25, 18, 24, 31, 21, 19, 23, 17, 28, 16 and 21 % respectively.

We observed that the majority of the studies included in this systematic review evidenced an increase in the prevalence of 2 to 4 times comparatively to the findings of Gillison et al. that investigated the presence of oral HPV in 5579 individuals, showing a prevalence of 6.9%. This suggests that the prevalence of HPV in HIV patients is really increased.

In contrast, the studies of Gaester et al. (2014) [17], Kahna et al. (2019) [20], Lima et al. (2014) [21], Thorsteinsson et al. (2018) [33] and Wood et al. (2020) [36] found 4, 6, 11, 6, 3 % respectively.

On the other hand, some studies evidenced a very high prevalence in Amornthatree et al. (2011) [8], Beachler et al. (2012) [6], Blass et al. (2015) [15], Marais et al. (2008) [9] and Quintanilla et al. (2020) [26]. That found 76, 40, 40, 85 and 93 %. A possible explanation for this might be due to all studies evidencing a high prevalence in non-HIV patients.

This study has certain limitations. One significant limitation is the possibility of publication bias, which arises when studies with positive or statistically significant results are more likely to get published. This can result in an overestimation of the overall occurrence of the phenomenon under investigation. Furthermore, variations in study designs, sample sizes, and geographical locations can introduce heterogeneity, making it challenging to arrive at definitive conclusions.

The human papillomavirus (HPV) is a well-recognized sexually transmitted infection and is a major public health concern worldwide. In this systematic review and meta-analysis, we aimed to investigate the prevalence of oral HPV infection in individuals living with HIV, as this population is particularly vulnerable to infections and associated diseases.

Our analysis revealed an overall pooled prevalence of 24.00% (95% CI: 16.00-35.00) for oral HPV infection among HIV-infected individuals. This finding indicates a substantial burden of oral HPV in this population, which is notably higher compared to individuals without HIV. Several factors may contribute to this higher prevalence in HIV-infected individuals.

One explanation for the increased prevalence of oral HPV in HIV-infected individuals could be the compromised immune system resulting from HIV infection. HIV weakens the immune response, making it less effective in controlling and clearing viral infections, including HPV. This weakened immune response allows HPV to persist for more extended periods in the oral cavity.

Furthermore, the initiation of antiretroviral therapy (ART), while essential for managing HIV infection, might paradoxically increase the prevalence of oral HPV infection in these individuals. Our findings suggest that ART was associated with a higher prevalence of oral HPV. This phenomenon could be due to immune reconstitution inflammatory syndrome (IRIS), where the recovering immune system may overreact to latent HPV infections, causing them to become active.

Our study also assessed the quality of the included studies, and all 26 studies were deemed to present a low risk of bias. This strengthens the reliability of our findings and the validity of our conclusions.

5. CONCLUSIONS

In conclusion, our systematic review and meta-analysis highlight a considerably higher prevalence of oral HPV in HIV-infected individuals compared to the general population. This underscores the importance of regular screening, early detection, and HPV vaccination in this vulnerable population to mitigate the potential risks of HPV-associated oral cancers. Further research is needed to better understand the mechanisms underlying the persistence of oral HPV in HIV-infected individuals and to develop strategies for prevention and management. This study serves as a valuable contribution to the field, shedding light on the unique challenges faced by HIV-infected individuals in the context of oral HPV infection.

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