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Oral Human Papillomavirus Infection in HIV-infected Individuals- A Systematic Review and Meta-analysis

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Background: Human papillomavirus (HPV) is the most prevalent sexually transmitted infection globally. Some studies demonstrate that the prevalence and incidence of HPV infection are higher in HIV-infected patients compared to non-HIV controls. This study aims to conduct a systematic review with meta-analysis to assess 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

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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.

Results: A total of 925 studies were retrieved using our search strategy, with 26 studies meeting the inclusion criteria for this systematic review. The pooled analysis revealed an overall prevalence of oral HPV infection in HIV-infected individuals at 24.00% (95% confidence interval: 16.00-35.00).

Conclusion: This systematic review highlights a notable prevalence of oral HPV infection among individuals living with HIV. These findings underscore the importance of continued research and public health efforts to address the intersection of HIV and HPV, contributing to a comprehensive understanding of the epidemiology and potential implications for preventive strategies in this vulnerable population.

Keywords: Human papillomavirus; HIV; prevalence; oral cancer; oropharyngeal cancer.

1. INTRODUCTION

“The human papillomavirus (HPV) stands out as the most prevalent sexually transmitted viral infection worldwide” [1,2]. “HPV infections are transmitted through direct skin-to-skin or skin-to-mucosa contact. Furthermore, the number of sexual partners consistently identified as the primary determinant of HPV infection in both men and women” [1,2].

“In assessing the prevalence of HPV in the general population, Gillison et al. conducted an investigation into the presence of the HPV virus in the oral mucosa of 5579 individuals, revealing a prevalence of 6.9%, notably higher in men than in women” [3]. “Following an HPV infection, a substantial number of individuals spontaneously clear the virus after a certain period” [4].

“In individuals infected with the human immunodeficiency virus (HIV), oral HPV infection appears to persist for a longer duration compared to their healthy counterparts” [5,6]. “Multiple studies have consistently demonstrated a heightened prevalence and incidence of HPV infection in HIV-infected patients when compared to non-HIV controls” [7-9].

“Another significant consideration for individuals living with the HIV virus is the utilization of antiretroviral therapy (ART), the standard treatment for HIV infection, involving a combination of medications” [10]. “Notably, the initiation of ART in HIV-infected patients has been associated with HPV infection” [11].

Despite the critical intersection between HIV and HPV, limited research has been conducted on the prevalence of HPV in these individuals. In this context, investigating the prevalence of oral HPV infection in HIV-infected individuals becomes crucial. Therefore, the objective of our study is to conduct a systematic review with meta-analysis on the oral prevalence of HPV in individuals living with HIV, contributing to the understanding of this co-occurrence and potentially informing public health strategies and clinical interventions.

2. MATERIALS 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 Brigs 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 (> or = 70% of questions answered "yes") Moderate risk of bias (> or = 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.

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 Brigs 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%).

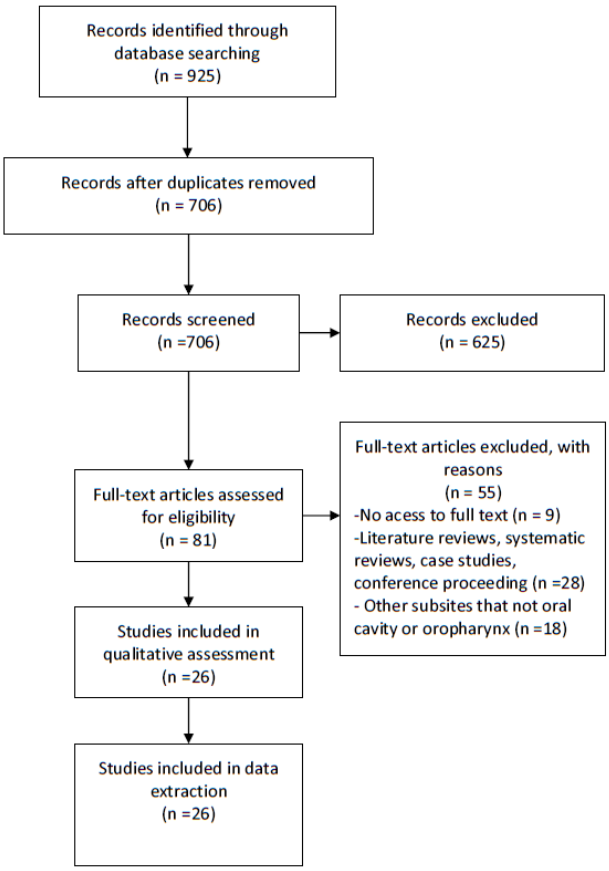

Fig. 1. PRISMA diagram of study identification and screening

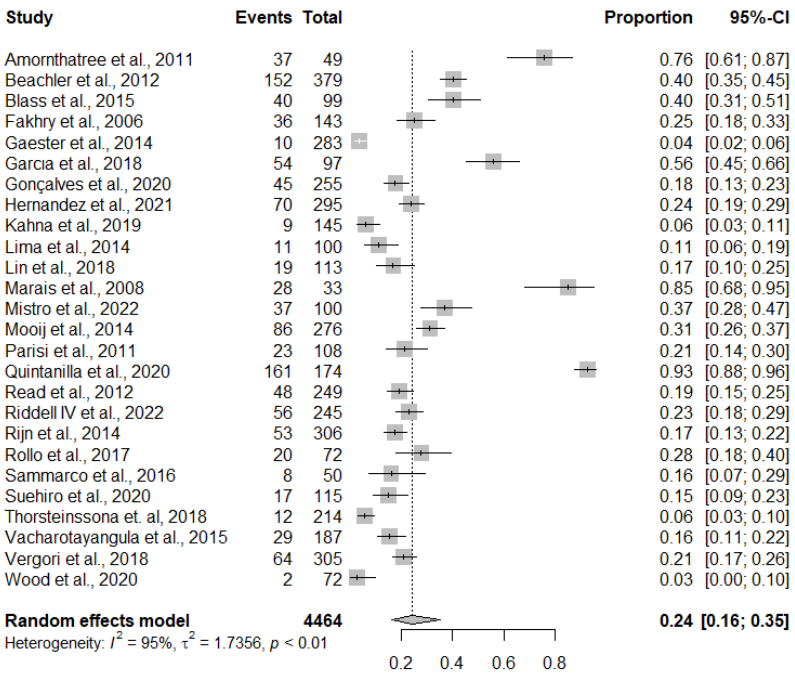

Fig. 2. Forest plots the prevalence of oral human papillomavirus infection in HIV-infected individuals

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., 2006 [16]	US	Cross-sectional	Female	36	143
Gaester et al., 2014 [17]	Brazil	Cross-sectional	Male	10	283
Garcıa 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

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

Authors/year	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Total (%of "yes")	Risk of bias
Amornthatree et al., 2011 [8]	Y	Y	Y	Y	Y	Y	Y	Y	Y	100	Low
Beachler et al., 2012 [6]	Y	Y	Y	Y	Y	Y	Y	Y	Y	100	Low
Blass et al., 2015 [15]	Y	Y	Y	Y	Y	Y	Y	Y	Y	100	Low
Fakhry et al., 2006 [16]	Y	Y	Y	Y	Y	Y	Y	Y	Y	100	Low
Gaester et al., 2014 [17]	Y	Y	Y	Y	Y	Y	Y	Y	Y	100	Low
Garcıa et al., 2018 [7]	Y	Y	Y	Y	Y	Y	Y	Y	Y	100	Low
Gonçalves et al., 2020 [18]	Y	Y	Y	Y	Y	Y	Y	Y	Y	100	Low
Hernandez et al., 2021 [19]	Y	Y	Y	Y	Y	Y	Y	Y	Y	100	Low
Kahna et al., 2019 [20]	Y	Y	Y	Y	Y	Y	N	Y	Y	88.89	Low
Lima et al., 2014 [21]	Y	Y	Y	Y	Y	Y	Y	Y	Y	100	Low
Lin et al., 2018 [22]	Y	N	Y	N	Y	Y	Y	Y	Y	77.78	Low
Marais et al., 2008 [9]	Y	Y	Y	Y	Y	Y	Y	Y	Y	100	Low
Mistro et al., 2022 [23]	Y	Y	Y	N	Y	Y	Y	Y	Y	88.89	Low
Mooij et al., 2014 [24]	Y	Y	Y	Y	Y	Y	Y	Y	Y	100	Low
Parisi et al., 2011 [25]	Y	Y	Y	Y	Y	Y	Y	Y	Y	100	Low
Quintanilla et al., 2020 [26]	Y	Y	Y	N	Y	Y	Y	Y	Y	88.89	Low
Read et al., 2012 [27]	Y	Y	Y	Y	Y	Y	Y	Y	Y	100	Low
Riddell IV et al., 2022 [28]	Y	Y	Y	Y	Y	Y	Y	Y	Y	100	Low
Rijn et al., 2014 [29]	Y	Y	Y	Y	Y	Y	Y	Y	Y	100	Low
Rollo et al., 2017 [30]	Y	Y	Y	Y	Y	Y	Y	Y	Y	100	Low
Sammarco et al., 2016 [31]	Y	N	Y	Y	Y	Y	Y	Y	Y	88.89	Low
Suehiro et al., 2020 [32]	Y	Y	Y	Y	Y	Y	Y	Y	Y	100	Low
Thorsteinssona et. al, 2018 [33]	Y	Y	Y	N	Y	Y	Y	Y	Y	88.89	Low
Vacharotayangula et al., 2015 [34]	Y	N	Y	N	Y	Y	Y	Y	Y	77.78	Low
Vergori et al., 2018 [35]	Y	N	Y	Y	Y	Y	Y	Y	Y	88.89	Low
Wood et al., 2020 [36]	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

Typically, an HPV infection resolves within 4 to 20 months in healthy individuals [37,38]. However, immune dysfunction in HIV-infected individuals hinders HPV clearance [39,40]. “The elevated incidence of oral HPV among those with HIV remains uncertain—whether it is linked to HIV-related immunosuppression or higher-risk sexual behavior. Consequently, the prevalence of oral HPV infection varies from 1% to 5% in immunocompetent individuals to 14% to 45% in those with HIV” [3,41].

In contemporary times, with the widespread use of combined antiretroviral therapy (ART) for treating HIV patients, tumors have emerged as the primary cause of mortality in HIV-positive individuals [42,43]. Individuals with HIV experience a higher incidence of head and neck squamous cell carcinoma than the general population [44], with most oropharyngeal squamous cell carcinomas being HPV-related tumors [45].

Our systematic review, conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) protocol, utilized R Studio for statistical analysis. Pooled results from all included studies indicated that the prevalence of oral HPV infection in HIV-infected individuals ranged from 3.00% to 93.00%, with an overall pooled prevalence of 24.00% (95% CI: 16.00-35.00). These findings align with prior studies [16,18,19,24,25,27,28,29,30,34,35] reporting prevalences of 25%, 18%, 24%, 31%, 21%, 19%, 23%, 17%, 28%, 16%, and 21%, respectively.

Interestingly, our review revealed a prevalence increase of 2 to 4 times in most studies compared to Gillison et al.'s findings in 5579 individuals without the HIV virus , who reported a prevalence of 6.9%. This suggests a substantial elevation in HPV prevalence among HIV patients.

In contrast, the studies of Gaester et al. [17], Kahna et al. [20], Lima et al. [21], Thorsteinssona et. [33] and Wood et al. [36] found 4, 6, 11, 6, 3 % respectively.

On the other hand, some studies evidenced a very high prevalence in Amornthatree et al. [8], Beachler et al. [6], Blass et al. [15], Marais et al. [9] and Quintanilla et al. [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.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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