# Human Papillomavirus (HPV) Infection in HIV Positive Women of Florianópolis, State of Santa Catarina, Brazil

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**ABSTRACT**

**Introduction:** HPV infection is the most prevalent sexually transmitted disease worldwide. The disease induced by this virus is dependent on several other factors that affect the host. The main factor is immunosuppression, mainly associated with HIV infection. **Objective:** research the presence of HPV infection (HPV DNA) in a group of HIV positive women and compare it with the HIV negative women group; analyse the prevalence of viral groups of oncogenic high-risk, low-risk; the relation between these findings to socioeconomic, demographic and behavioural characteristics, as well as variables related to HIV infection, such as CD4 level, viral load and HAART use. **Methods:** a total of 20 HIV positive and 99 HIV negative women were enrolled in a cross-sectional and descriptive study, where genital samples were analysed by the hybrid capture method for detection of HPV DNA. Other data from charts and from a questionnaire have been collected from the patients. **Results:** the prevalence of HPV infection was 70% among the HIV positive group, and 21.2% among the HIV negative group. High-risk HPV was found in 71.4% of HPV positive cases of both groups, and both viral types were found in 35.7% of HIV positive women. HPV infection was associated with age above 35 years, low education level, CD4 between 200 to 500 cells/mm$^3$, and HAART use in HIV positive women. Other variables studied did not show any association with HPV infection. **Conclusion:** the prevalence of HPV was about 3.3 times higher among HIV positive women, and high-risk HPV types were the most prevalent virus.

**Keywords:** human papillomavirus infection (HPV), HIV infection, hybrid capture, immunosupression, STD.

## INTRODUCTION

Infection with HPV is the most frequent sexually transmitted disease (STD) in the world. The World Health Organization (WHO) estimates around 630 million new cases per year, and 30 million of these are associated with *Condyloma acuminatum*, 30 million with low-grade lesions, 10 million with high-grade lesions, and 500 thousand with cervical cancer. The development of these lesions is directly related to the presence of different HPV types[1].

Cervical cancer is the most common death cause of adult women in developing countries, and the second more common cancer in women worldwide[1], with an estimate of half a million new cases and 274,000 deaths/year, according to WHO[2]. In Brazil, the estimate for 2010 was 19,603 new cases and 8,286 deaths resulting from the disease[3]. Immunosuppression, mainly acquired, is the major cause of the manifestation of HPV infection. Currently, the HIV infection is considered a pandemic problem, especially in developing countries. This disease has increased the prevalence of HPV infection, increasing the risk to cervical neoplasia.

In 1993, invasive cervical cancer was added to the list of defining diseases of Acquired Immunodeficiency Syndrome (AIDS) by the *Centers for Disease Control and Prevention* (CDC) in the USA[4]. The role of HPV in the genesis of cervical cancer is biologically and epidemiologically well established[5], although HIV aetiological contribution to co-infection in the genesis of cervical cancer remains uncertain[6].

Studies have shown that HIV positive women have a higher prevalence of infection with HPV[6-13], and these women are often infected with a greater number of types of viruses than the HIV negative women[7-10,12]. The presence of multiple viral types[1] and viral types of high oncogenic risk[14] is related to adverse outcomes, such as persistent infection, and increase of both prevalence and lesion progression. In addition, there is evidence of a greater prevalence of intraepithelial neoplasia among HIV positive women when compared with the HIV negative women[6,12,13].

In general, the prevalence of HPV increases with progressive reduction of CD4 cells[6,12,13] and the presence of multiple types can also increase with the progressive CD4[12] reduction. Furthermore, the infection with this virus is also more persistent in the HIV positive population[6,12,13], which can contribute to its greater prevalence and also to a higher risk of cervical epithelial lesions. Some factors have been associated with the progression of these lesions, such as the prolonged use of hormonal contraceptives (more than 10 years), multiparity, smoking, co-infection with other STD (such as HIV itself, herpes simplex 2, and *Chlamydia trachomatis*), and immunosuppression[1,5].

However, it is unclear if HIV infection increases the susceptibility to a genital HPV infection, no matter the epidemiolocal risk patterns, or if it modifies the associations with specific types of HPV and the cervical disease documented in general population[9]. It is also important to remember that factors related to HPV-HIV co-infection, such as viral types, variation in the immune status, and presence of citopathological changes, when crossed with different populations, show conflicting results, revealing the importance of regional, ethnic, and demographic characteristics, and also studies planning.

## OBJECTIVE

Compare the positivity of HPV genital infection in both HIV positive and negative women, evaluating the prevalence of high-

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-risk and low-risk viral types among the groups, as well as the relation with socioeconomic, demographic, and behavioural factors, in addition to variables related to HIV infection, such as CD4 cells level, viral load (VL), and use of Highly Active Anti-Retroviral Therapy (HAART).

## METHODS

This is an observational and transversal study, performed in the city of Florianópolis, state of Santa Catarina, Brazil, from December, 2007, to April, 2010. The samples size calculation was based on the Brazilian study by Campos *et al.*[16], which found HPV DNA prevalence of 73% among women HIV infected, and 24% among HIV negative women.

Considering a statistics power of 80%, a significance level of 5% ($p < 0.05$), and a 1:1 case-control relation, it was observed that a sample of 38 women (19 HIV positive and 19 HIV negative women) would be enough for this study. Therefore, two samples were selected: the first one was composed of 20 HIV positive women of the Hospital Nereu Ramos (HNR), specialized in infectious diseases hospital; the second sample consisted of 99 HIV negative women of the gynecology clinic at the University Hospital Polydoro Ernani de São Thiago. All subjects of this study have searched for the infectious disease or gynecology services for regular appointments or complaints not related to a possible sexually transmitted disease. All women infected with HPV before starting the study were excluded.

All volunteers who have agreed to participate of this study have read, discussed with investigator and signed the Consent Term, for interview and records, and to collect genital samples. Collection of samples (endocervical and ectocervical region) for HPV DNA detection and its oncogenic risk was performed using the *Female Swab Specimen Collection Kit*™ (Digene Corporation). Samples were obtained from endocervix (with 360° rotation movements) and ectocervix as well, using the same swab. They were then stored in specific means of transport (*Sodium azide* 0.05%, 1 mL), properly identified (identification number and initials) and frozen. These Samples were submitted to a molecular biology study by Digene & Co. Hybrid Capture Method II™, in the DNAnálise laboratory, in Florianópolis, for the HPV DNA detection. This method has a clinic sensitivity of 1 pg/mL, equivalent to 0.1 copy of virus per cell, and can detect 70% of low-risk HPV types (6, 11, 42, 43, and 44) and 99% of high oncogenic risk types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 60).

The test was considered positive when RLU (Relative Light Units) ratio of two positive controls was equal to 1 pg/mL of HPV DNA or more. According to recent studies, this cutting point value adds greater sensitivity and specificity to the exame[15]. After, registered data were collected and charts filled up with the interview with patients, such as schooling level, race, parity, tobacco smoking, oral contraceptives (OC) use, and antirretroviral therapy.

The obtained data were stored in a database EpiData® software, version 3.1, and the statistical analysis carried out by SPSS®, version 17.0, and StatCalc® software programs. A case-controle type analysis was performed, where cases were represented by 20 HIV positive women, and controls by 99 HIV negative women. The measure of frequency used was the prevalence, while the measures of association were the ratio of prevalence, the Chi-square ($X^2$), and the Fisher exact test, with a confidence interval of 95%. The result was considered significant if the error probability was ≤ 5% ($p < 0.05$). The current procedures are in accordance with the ethical principles set out by the National Commission of Ethics in Research and approved by the Ethics Committee in Research with Human Beings from UFSC. This study has been approved by this Committee under registry 325/2007 and 330/2009.

## RESULTS

Infection with HPV (HPV DNA) was found in 70% of HIV positive women, while in HIV negative women the infection was present in 21.2% ($p < 0.001$), with a ratio of prevalence of 3.3 (IC 95%; [2.05-5.3]), as shown in **Table 1**. High oncongenic risk HPV was found in 71.4% of HIV positive women, while the low oncogenic risk were found in 64.3%. Both types were concomitantly found in 35.7% of HIV positive women, and in 23.8% of HIV negative women. The high-risk HPV was observed in 71.4% of HIV negative patients (**Table 2**).

The average age of HIV positive women group was 44.7 years old (varying from 28 to 56 years old), and in the control group was of 36.3 years old (varying from 17 to 63 years old). In the HIV positive women group, HPV was significantly more frequent in women over 35 years old (78.5%). In control group, the prevalence of HPV infection was also more frequent over 35 year old women (42.8%), however, it was distributed in a more uniform way (**Table 3**).

With regard to schooling, most HIV positive women infected with HPV had only elementary school (57.1%), while in the HIV negative women the same percentage (57.1%) was observed on women with high school graduation. Among women with elementary school graduation, the prevalence for HPV DNA was significantly greater (72.7%) among HIV positive women than in the control group (23.5%). Those who attended high school and college showed a HPV DNA greater prevalence in HIV positive women, but not significantly (**Table 3**).

In relation to ethnicity, HPV DNA prevalence was higher among white HIV positive women group (92.8%), and also in white HIV negative women (85.7%). With regard to parity, the HPV DNA was more common in nulliparous women of both groups (85.7% HIV positive, and 66.6% negative). HPV infection was more common in non-smokers of both groups (64.2% HIV positive, and 76.1% HIV negative). In the HIV positive group, HPV was more common in oral contraceptive non-users (85.7%), while in the control group it was more frequent in OC users (76.1%) with statistical

**Table 1** – Prevalence of HPV among HIV positive and negative women.

| HIV | HPV (+) (n = 35) | | RR | 95% IC | p* |
|---|---|---|---|---|---|
| | n | %† | 3.3 | 2.05-5.30 | 0.000012 |
| Positive | 14 | 70.0 | | | |
| Negative | 21 | 21.2 | | | |

* Chi-square test.

† Percentage of groups' total women.

**Tabela 2** – Prevalência dos tipos virais de alto e baixo riscos entre os grupos.

| HPV | HIV (+) (n = 14) | | HIV (–) (n = 21) | | p |
|---|---|---|---|---|---|
| | n | %* | n | %* | |
| High-risk | 10 | 71.4 | 15 | 71.4 | 0.496919† |
| Low-risk | 09 | 64.3 | 11 | 52.4 | 0.485667‡ |
| Both | 05 | 35.7 | 05 | 23.8 | 0.445008‡ |

* Percentage of groups' total women.
† Fisher's test.
‡ Chi-square test.

**Table 3** – HPV prevalence in relation to interest variables among groups.

| | HPV (+) | | | | |
|---|---|---|---|---|---|
| Variables | HIV (+) (n = 14) | | HIV (–) (n = 21) | | |
| | n | %* | n | %* | p |
| ***Age (years old)*** | | | | | |
| 15-25 anos | – | – | 07 | 36.8 | - |
| 26-35 anos | 03 | 100.0 | 05 | 15.2 | 0.602335† |
| > 35 anos | 11 | 64.7 | 09 | 19.1 | 0.036269‡ |
| ***Schooling*** | | | | | |
| Elementary | 08 | 72.7 | 04 | 23.5 | 0.024990† |
| High school | 05 | 62.5 | 12 | 28.6 | 0.214005‡ |
| College | 01 | 100.0 | 05 | 21.2 | 0.208944† |
| ***Ethnic group*** | | | | | |
| White | 13 | 76.5 | 18 | 20.2 | 0.469919† |
| Other | 01 | 33.3 | 03 | 30.0 | |
| ***Parity*** | | | | | |
| Nulliparous | 02 | 100.0 | 07 | 18.4 | 0.194374† |
| Non-nulliparous | 12 | 66.7 | 14 | 23.0 | |
| ***Smoking*** | | | | | |
| Yes | 05 | 71.4 | 05 | 16.1 | 0,348350† |
| No | 09 | 69.2 | 16 | 23.5 | |
| ***Oral conceptive*** | | | | | |
| Yes | 02 | 100.0 | 16 | 22.5 | 0,000330‡ |
| No | 12 | 66.7 | 05 | 17.9 | |

* Percentage of groups' total women.
† Fisher's test.
‡ Chi-square test.

significance. **Table 3** describes the prevalence of HPV per category among both HIV positive and negative women in relation to the discussed variables.

When we analyse the group of women infected with HIV, we verified that most HPV positive cases were found in those with CD4 cell levels > 500 cells/mm$^3$ (57.1%), however, among women with CD4 < 200 cells/mm$^3$, all were positive for HPV infection (100%). When we compared the HPV infection between groups, a significant association with this infection was observed for women with CD4 cells counting between 200 and 500 cells/mm$^3$. Among women with undetectable viral load, 66.6% were HPV DNA positive.

The remaining HIV positive women showed variable viral loads (between 840 and 42,373), and only one of them did not present HPV, totalling a prevalence of 80%. Among women receiving HAART, the HPV DNA prevalence was 87.5%. The HPV DNA was negative among all women who were not in use of HAART, which were a statistically significant difference (**Table 4**).

# DISCUSSION

It was found a significantly higher prevalence of HPV infection (HPV DNA) in HIV positive women (70%) when we compare with the HIV negative women (21.2%). This difference represents a 3.3 times higher risk for the HIV positive women. World data demonstrate different results for HPV prevalence among these groups. However, the tendency to a greater prevalence among HIV positive groups is invariably observed.

In Sun *et al.*[9] study, HPV DNA was found in 60% of HIV positive women, while among the HIV negative women the prevalence was 36%. Minkoff *et al.*[10] found a prevalence of 73% *versus* 43%, respectively.

A meta-analysis[11] that included important studies about HIV showed a prevelance of 64% *versus* 28% in HERS (HIV Epidemiology Research Study, 1999) study, and 63% *versus* 30% in WHIS (Women's Interagency HIV Study, 1999) study for both HIV positive and negative women, respectively. Brazilian studies, however, such as Campos *et al.*[16], found significant differences between both groups, showing a HPV DNA prevalence in 73.2% of HIV infected women, and 23.7% among HIV negative women, a result very similar to our study.

Nevertheless, Levi *et al*.[17] showed 87% of HIV positive women and 100% of HIV negative women positive to HPV DNA. In this study, control group women were selected in a cervical pathology clinic, and a high positivity was expected to HPV DNA.

The investigators of a study from the specific region of Brazil (state of Bahia[7]) found a prevalence of 100% of HPV DNA among HIV positive women, predominantly in Afro-descendants' individuals. Similarly, a prevalence of 98% for HPV was found in a study using the polymerase chain reaction (PCR), which included only HIV positive women in São Paulo[11]. However, another study of the same authors using the hybrid capture method showed the HPV prevalence of 64.5% among positive HIV women.

**Table 4** – Prevalence of HPV in relation to CD4 cells counting, viral load (VL), and use of HAART among HIV positive women.

| | HIV (+) | | | | |
|---|---|---|---|---|---|
| Variables | HPV (+) (n = 14) | | HPV (–) (n = 6) | | |
| | n | %* | n | %* | p† |
| ***CD4 (cell/mm$^3$)*** | | | | | |
| < 200 | 03 | 100.0 | – | – | 0.319298 |
| 200-500 | 03 | 37.5 | 05 | 62.5 | 0.018059 |
| > 500 | 08 | 88.9 | 01 | 11.1 | 0.119195 |
| ***VL (copies/mL)*** | | | | | |
| Undetectable | 10 | 66.6 | 5 | 33.4 | 0.516511 |
| Detectable | 04 | 80.0 | 1 | 20.0 | |
| ***HAART*** | | | | | |
| Yes | 14 | 87.5 | 2 | 12.5 | 0.003096 |
| No | – | – | 4 | 100.0 | |

* Percentage of groups' total women.
† Fisher's test.

A possible reason for the higher prevalence of HPV infection in HIV positive women could be explained by the mechanism of the disease: an immune system failure would bring prejudice to the eradication of the HPV infection, increasing the persistent infection rate. Viral replication can be more efficient in immunocompromised individuals, contributing to higher rates of both viral persistence and detection. The different design of the studies and the use of viral DNA identification techniques of different sensitivities[1,19,20] can be partially blamed for the variation in prevalences found in several studies. However, the greater HPV positivity in HIV women is observed regardless of the test performed.

The results in our observations showed a high prevalence of high oncogenic risk viral types in both groups (71.4%), besides a greater prevalence of both types in HIV positive women, with 35.7% versus 23.8% in the HIV negative women.

In several studies, the multiple infection was predominant among HIV positive women[7,9,12,16], and the prevalence of high-risk viral types was significant[7,8,10,12,18], revealing a correlation with the data found in the results of this study. Greater infection with low-risk viral types was also found among HIV positive women, reinforcing the tendency to a higher prevalence of HPV in this group, regardless of type.

Some studies verified that young women are exposed to a greater risk of infection with HPV[1] and thus have a higher prevalence, with an important decline after the 25-30 years of age[1,21]. In this study, a greater HPV prevalence in women above 35 years old was observed in both groups, and significantly higher in the HIV positive (78.5%) than in the HIV negative (42.8%). Other studies[1,19-21] showed another HPV prevalence, with a second peak in postmenopausal age (> 50 years old), but only in some regions studied. This new pattern, bimodal, is explained by a decrease in the immune response by postmenopausal hormonal changes that could reactivate latent infections[19-21], and also increase the vulnerability to HPV. A second mechanism would be the change in sexual behavior among women and their partners, resulting in new infections with the virus[19].

High HPV DNA prevalences were found among HIV positive women who received only elementary education, (72.7%), as well as in those who attended high school (62.5%). Both results agree with the expectation of a higher prevalence in lower socioeconomic *status* groups. According to meta-analysis involving studies of all continents (except Oceania), HPV prevalence was higher in developing countries (15.5%) than in developed ones (10%)[19]. Cavalcanti *et al.*[22], in a Brazilian study of samples of population in general, they found a prevalence of 10.7% among high socioeconomic status women (private service users), while among low socioeconomic status women (public service users) the prevalence was 31.1% The risk of HPV infection increased 1.72 time in this group. A significant association of HPV infection was observed among HIV positive women who attended only elementary school, outlining a synergistic effect of HPV and HIV infection risks, which are higher in low social *status* women.

Some studies showed a greater risk of HPV infection in Afro-descendants' women[1,22], as well as an association between the increase of cervical cancer risk and multiparity[5,23], tobacco smoking[5,24-26], and oral contraceptive use[5,20,27]. In this study, these variables were not related to HPV presence among HIV positive women.

In the Palefsky *et al.*[13] prospective study involving women infected with both HIV and HPV, a higher incidence of HPV was found in women with a viral load below than 100.000 copies/mL or CD4 counting less than 200 cells/mm$^3$, and it is known that these women are at greater risk for any type of infection.

In our study, all women with CD4 < 200 cells/mm$^3$ were positive for HPV infection, showing the correlation with previous studies. Hankins *et al.*[28] verified a significant association among HPV and CD4 > 200 cells/mm$^3$, with OR = 1.9. We observed a statistical significance among HPV infection in women with CD4 between 200 and 500 cells/mm$^3$. Furthermore, a high prevalence of HPV infection was observed in those with CD4 > 500 cells/mm$^3$ (88.9%). No significant association between viral load and presence of HPV was observed in our study. The prevalence of HPV infection was higher in the group with viral load undetected, and lower in the group with a viral load above 50 copies/mL.

Studies have shown controversial results regarding prevalence and progression of HPV infection in women with combined antirretroviral therapy[6,12]. In our study, we observed 80% of HIV positive women were using HAART, with a significant prevalence of 87.5% of HPV infection. The HPV DNA research was negative for all women who not were using HAART, who probably had more efficient immunological mechanisms, since they did not need antirretroviral use.

We observed that the prevalence of HPV infection in HIV positive women is significantly higher than in the HIV negative women, and that high oncogenic risk viruses are the most common. We have also verified a greater HPV positivity in HIV positive women with age above 35 years old who had only attended elementary school and had used combined antirretroviral therapy.

In our study, we were limited by the size of the sample, which may have hindered, in part, our results. In addition, most of the available data on the HIV and HPV co-infection are consequence of large multicentre studies involving HIV infected patients, resulting in a shortage of studies concerning these two infections.

Therefore, new population studies with an increased number of individuals are needed to better understand the association of these two sexual transmitted viral infections and their repercussion, mainly on the female genital area.

## CONCLUSION

The prevalence of HPV infection was 3.3 times greater in HIV positive women (70%) than in HIV negative women (21.2%), and most of them with the high oncogenic risk HPV.

### Conflict of interest

The authors declare no conflict of interest.

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