# Prevalence of HPV infection and cervical intraepithelial lesions in HIV positive and negative women in the city of Florianopolis

## *Prevalência da infecção pelo HPV e lesões intraepiteliais cervicais em mulheres HIV positivas e negativas na cidade de Florianópolis*

*Pâmela Raquel Conradesque[1], Iane Dagostin[1], Edison Natal Fedrizzi[2], Sérgio Murilo Steffens[2], Paula Fernanda Santos[3], Daniella Serafin Couto Vieira[4], Ana Paula Farina Pasinato[5], Adriane Pogere[6], Maria Elizabeth Menezes[3]*

**ABSTRACT**

**Introduction:** The human papillomavirus (HPV) is the most common sexually transmitted infection among women. The HPV of high oncogenic risk, associated with other factors, presents a risk of progressing to a precancerous lesion of the uterus and even cancer. Such an evolution is related to the persistence of the infection and other factors, mainly those that interfere with women's immunity. The immunosuppression caused by HIV infection is an important factor for viral persistence and the onset of these lesions. **Objectives:** To compare the prevalence of HPV infection and cervical intraepithelial lesions in HIV-positive and negative women and describe the possible associated risk factors. **Methods:** The sample consisted of 50 HIV positive women (study group) and 50 HIV negative women (control group) recruited from the public health system of Florianópolis from January to April 2022. Cervical samples were collected for cytological analysis and for the detection of high-risk oncogenic HPV DNA by polymerase chain reaction (PCR). Categorical variables were compared using the chi-square test, with a significance level set at 5% **Results:** HPV infection was more prevalent in the control group; however, HIV positive women presented higher frequency of intraepithelial lesions diagnosed on cytology. Factors such as higher number of sexual partners, depression and smoking were more frequent in the group of HIV positive women. CD4 T cells lower than 200 cells/mm$^3$ was associated with a higher number of altered Pap smears and a positive HPV DNA test. The use of combination antiretroviral therapy and undetectable viral load were associated with more frequent normal cytology and undetected HPV DNA. Conclusion: The prevalence of cervical intraepithelial lesions in HIV-infected women is higher than among women without the infection. The presence of HIV infection was the most important risk factor associated with the development of cervical lesions.
**Keywords:** HPV; HIV; coinfection; cervical intraepithelial lesions; prevalence.

**RESUMO**

**Introdução:** O Papilomavírus Humano (HPV) é a infecção de transmissão sexual mais frequente na mulher. O HPV de alto risco oncogênico, associado a outros fatores, apresenta risco de evoluir para uma lesão pré-cancerosa do colo de útero e até mesmo para o câncer. Essa evolução está relacionada à persistência da infecção e outros fatores, principalmente os que interferem na imunidade da mulher. A imunossupressão causada pela infecção HIV é um fator importante para a persistência viral e o aparecimento destas lesões. **Objetivos:** Comparar a prevalência da infecção pelo HPV e das lesões intraepiteliais do colo de útero em mulheres HIV positivas e negativas, e descrever os possíveis fatores de risco associados. **Métodos:** A amostra foi composta por 50 mulheres HIV positivas (grupo de estudo) e 50 mulheres HIV negativas (grupo controle) recrutadas no sistema público de saúde de Florianópolis durante os meses de janeiro a abril de 2022. Foram coletadas amostras cervicais para análise citológica e para detecção do DNA HPV de alto risco oncogênico por reação em cadeia da polimerase (PCR). As variáveis categóricas foram comparadas pelo teste qui-quadrado, com nível de significância estabelecido em 5%. **Resultados:** A infecção pelo HPV foi mais prevalente no grupo controle, entretanto, as mulheres HIV positivas tiveram uma maior frequência de lesões intraepiteliais diagnosticadas na citologia. Os fatores como maior número de parceiros sexuais, depressão e tabagismo foram mais frequentes no grupo de mulheres HIV positivas. O número de células TCD4 inferior a 200 células/mm$^3$ esteve associado a maior número de colpocitologias alteradas e teste DNA HPV positivo. O uso da terapia antirretroviral combinada e a carga viral indetectável estiveram associadas a um número elevado de citologias normais e DNA HPV não detectado. **Conclusão:** A prevalência de lesões intraepiteliais do colo do útero em mulheres infectadas pelo HIV foi maior que em mulheres soronegativas. A presença de infecção pelo HIV foi o fator de risco mais importante associado ao desenvolvimento de lesões cervicais.
**Palavras-chave:** HPV. HIV. coinfecção. lesões intraepiteliais escamosas cervicais. prevalência.

[1]Universidade Federal de Santa Catarina, Department of Health Sciences – Florianópolis (SC), Brazil.
[2]Universidade Federal de Santa Catarina, Department of Ginecology and Obstetrics, Clinical Research Center – Project HPV – Florianópolis (SC), Brazil.
[3]Universidade Federal de Santa Catarina, Programa Nacional de Controle de Qualidade – Rio de Janeiro (RJ), Brazil.
[4]Universidade Federal de Santa Catarina, Pathology Department – Florianópolis (SC), Brazil.
[5]Universidade Federal de Santa Catarina, Pathological Anatomy laboratory – Florianópolis (SC), Brazil.
[6]Universidade Federal de Santa Catarina, Lower Genital Tract Pathology and Colposcopy Sector – Florianópolis (SC), Brazil.

## INTRODUCTION

The Human Papillomavirus (HPV) is considered as the most prevalent sexually transmitted disease in the world[1] and is associated with the development of lesions that precede cervical cancer, especially among immunosuppressed women, such as the ones who live with the human immunodeficiency virus (HIV)[2].

The natural history of high oncogenic risk HPV involves cellular changes that can lead to invasive carcinoma[3]. The cervical intraepithelial lesions caused by the HPV virus are classified as high and low grade, according to the level of cellular change and the chances of progression

to invasive lesions[4]. The low-grade squamous intraepithelial lesion (LSIL) presents high potential for regression to a normal state, but it can eventually progress to a high-grade lesion (HSIL) and invasive cancer[5]. The cytological term HSIL includes cervical intraepithelial neoplasias grades 2 and 3 (CIN 2 and CIN 3), and these are mainly caused by types of high oncogenic risk HPV[6,7]. When left untreated, these damages can progress to more severe lesions or invasive carcinoma[8].

Cervical cancer is the second most common type of cancer among women aged from 25 to 64 years around the world, with approximately 466 thousand new cases and 227 thousand deaths a year, being the third most common cause of death by cancer in women in 2020[9].

As to the chances of a women being in contact with the virus, the probability increases according to the number of sexual partners, inadequate use of condoms, early beginning of sexual activity, marital status and schooling. Other risk factors, such as the prolonged use of contraceptives for more than ten years, smoking and changes in the immune system lead to viral persistence[10], especially among immunosuppressed women, such as the ones with[11].

Individuals with inherited immunodeficiency, autoimmune disorders, who underwent transplant of solid organs or bone marrow and infected by HIV present with high risk of infection by HPV. Chronic immunosuppression provides an environment for the persistence of the HPV infection, leading to higher risk of evolution to a malignant lesion[12].

When compared to HIV-negative women, patients with HIV are more prone to being infected with HPV and its persistence, presenting a high number of high grade intraepithelial lesion and higher risks of progression to invasive cervical carcinoma, which is a defining factor of the Acquired Immunodeficiency Syndrome (AIDS) for this group[11]. Besides, the estimation is that more than one third of the HIV-positive women with normal cervical cytology are infected by HPV, including multiple viral genotypes[13,14]. The low CD4 T lymphocyte count (<200 cells/mm$^3$) is also directly related with the lower elimination of HPV in comparison to women with higher CD4 T cells or HIV negative patients[15]. Besides, the low CD4 T lymphocyte count is associated with approximately four times more chances of progression of intraepithelial lesions[16].

Antiretroviral therapy (ART), by acting on viral suppression and on the improvement of the immune function, especially of the CD4 T cells, has significantly impacted the incidence, the management and the prognosis of opportunistic and malignant diseases related to HIV. Besides changing the natural history of HIV infection in relation to incidence and survival, ART has drastically reduced the incidence of some malignant conditions associated with HIV, mediated by viral infections[17,18].

# OBJECTIVE

The objective of this study was to assess the prevalence of the Human Papillomavirus infection and the cytological changes in the Pap smear in HIV-positive and negative women from Florianópolis.

# METHODS

## Study design and participants

This is a prospective, cross-sectional, observational study carried out in the city of Florianópolis, Santa Catarina, from January to March, 2022. Women assisted at the outpatient clinics of ginecology and infectology at Hospital Universitário Polydoro Ernani de São Thiago and Hospital Nereu Ramos, respectively, were invited to participate. The sample was comprised of 50 women in the control group (HIV-negative) and 50 women in the study group (HIV-positive).

The study included sexually active women who accepted to fill out a questionnaire with questions about socioeconomic, behavioral and clinical status; to undergo a complete physical and gynecological examination, besides the collection of samples for oncotic colpocytology tests and polymerase chain reaction (PCR) for the detection of the Papillomavirus.

Exclusion criteria were:

1. women diagnosed with genital infection by HPV before entering the study;
2. women undergoing or waiting for treatment for genital warts or intraepithelial lesions in the lower genital tract;
3. previous treatment for any cervical lesion in the past six months;
4. women who had undergone oncotic colpocytology in less than one year;
5. women with severe chronic conditions; and
6. ongoing pregnancy or breastfeeding.

The informed consent form was read, discussed and signed by all study participants. A copy of the document was handed to the participants, and the other copy remained with the research team. Then, there was a standardized interview. Besides, they were all submitted to collection of cervical samples for cytological analysis, and PCR for HPV.

## Procedures

The samples were collected from the endocervical and ectocervical region for cytopathological examinations and HPV DNA. The Pap smear collection was performed with an Ayre spatula and a cervical brush. A swab was used for the PCR, and the sample was stored in a sterile tube without culture, frozen at -1°C and sent for analysis.

These samples were sent for a molecular biology study using *the Bio Clin multiplex PCR kit for high-risk HPV* to detect HPV DNA. This kit is sensitive to detect from 10 copies per reaction and, in an isolated manner, recognizes HPV 16 and 18 and together with the other types (31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 60).

## Statistical analysis

The sample size was calculated considering the previous study carried out in Florianópolis, in 2011, by Fedrizzi and cols[19], who found a 71% prevalence of HPV-DNA among women infected with HIV, and 21% among women without HIV. For a statistical power of 80%, a 5% significance level ($p<0.05$) and control-to-case ratio of 1:1, it was observed that a sample of 38 women (19 HIV-positive and 19 HIV-negative women) would be sufficient for this study. Therefore, two samples were selected; one composed of 50 HIV-positive women assisted at the outpatient Infectology clinic of Hospital Nereu Ramos (HNR); and the other composed of 50 HIV-negative women assisted at the outpatient Gynecology clinic of Hospital Universitário Polydoro Ernani de São Thiago.

The obtained data were stored in a database using the entry software EpiData®, version 3.1, and the statistical analysis was carried out using the SPSS® software, version 17.0, and Stat Calc®. The frequency measure we used was prevalence, whereas the measures of association were prevalence ratio, $\chi^2$ and Fisher's exact test, with a 95% Confidence Interval. The result was considered significant for the probability of error ≤5% ($p<0.05$).

This study was approved by the Human Research Ethics Committee of UFSC, CAAE record: 52671521.7.0000.012.

## RESULTS

Both groups had similar sociodemographic characteristics, such as age, schooling, marital status and Family income. The age mean and variance were 39.4 years, 107,78 for the study group; and 42.9 years and 141,87 for the control group. Regarding gynecological history, the control group began their sexual activity earlier (before the age of 12) in comparison to the group of cases (after the age of 13). On the other hand, HIV-positive women had more partners (6 or more) in relation to HIV-negative women (56% and 24%, respectively) and history of vulvovaginal candidiasis (72% versus 42%). Regarding current sexual activity, HIV-negative women were more active (94%) than HIV-positive ones (70%) ($p<0.05$), as well as the unprotected intercourse (63.7% in the control group and 20% in the case group). Besides, the two groups differed in relation to the occurrence of previous sexually transmitted disease (STD), with prevalence of 36% among HIV-positive women, and 57.14% among HIV-negative women ($p<0.05$). Among behavioral variables, HIV-positive women presented a significant difference, especially for smoking and depression ($p<0.05$). Even though HIV-positive women had been more often vaccinated against HPV, there was no statistical difference between the groups (**Table 1**).

**Table 1 –** Characteristics of the study population.

| | HIV (+) n (%) | HIV (-) n (%) | p |
|---|---|---|---|
| **Sociodemographic** | | | |
| Age | | | |
| 18–25 | 3 (6.00) | 6 (12.00) | |
| 26–35 | 9 (18.00) | 12 (24.00) | 0.379 |
| >35 | 38 (76.00) | 32 (64.00) | |
| Schooling | | | |
| Elementary school | 23 (46.00) | 14 (28.00) | |
| High school | 16 (32.00) | 21 (42.00) | 0.175 |
| Higher education | 11 (22.00) | 15 (30.00) | |
| Marital status | | | |
| Single | 21 (42.00) | 17 (34.69) | |
| Married | 21 (42.00) | 26 (53.06) | 0.415 |
| Divorced | 4 (8.00) | 5 (10.20) | |
| Widow | 4 (8.00) | 1 (2.04) | |
| Family income | | | |
| Lower than 1 minimum wage | 6 (12.00) | 7 (14.00) | |
| From 2 to 3 minimum wages | 39 (78.00) | 36 (72.00) | 0.767 |
| More than 4 minimum wages | 5 (10.00) | 7 (14.00) | |
| **Gynecological history** | | | |
| Beginning of sexual activity | | | |
| ≤12 years old | 0 (0.00) | 4 (8.00) | |
| 13–15 years old | 11 (22.00) | 7 (14.00) | 0.023 |
| ≥16 years old | 39 (78.00) | 39 (78.00) | |
| Number of sexual partners | | | |
| 1–2 | 4 (8.00) | 19 (38.00) | |
| 3–5 | 18 (36.00) | 19 (38.00) | <0.001 |
| 6 or more | 28 (56.00) | 12 (24.00) | |
| Use of condoms in the past 12 months | | | |
| Without sexual intercourse | 15 (30.00) | 0 (0.00) | |
| Always | 21 (42.00) | 9 (18.37) | <0.001 |
| Sometimes | 4 (8.00) | 9 (18.37) | |
| Not once | 10 (20.00) | 31(63.27) | |

Continue...

**Table 1 –** Continuation.

| | HIV (+) n (%) | HIV (-) n (%) | p |
|---|---|---|---|
| Number of sexual partners in the past 12 months | | | |
| None | 15 (30.00) | 3 (6.00) | 0.018 |
| 1 | 32 (64.00) | 42 (84.00) | |
| 2–3 | 2 (4.00) | 4 (8.00) | |
| ≥4 | 1 (2.00) | 1 (2.00) | |
| History of STD | | | |
| Yes | 18 (36.00) | 28 (57.14) | 0.035 |
| No | 32 (64.00) | 21 (42.86) | |
| Candidiasis | | | |
| Yes | 36 (72.00) | 21(42.00) | 0.002 |
| No | 14 (28.00) | 29 (58.00) | |
| Parity | | | |
| Up to 3 | 31 (62.00) | 38 (77.55) | 0.092 |
| 3 or more | 19 (38.00) | 11 (22.45) | |
| **Behavioral** | | | |
| Depression | | | |
| Yes | 18 (36.00) | 4 (8.00) | 0.001 |
| No | 32 (64.00) | 46 (92.00) | |
| Smoking | | | |
| Yes | 15 (30.00) | 5 (10.20) | 0.014 |
| No | 35 (70.00) | 44 (89.80) | |
| Vaccination against HPV | | | |
| Yes | 16 (32.00) | 8 (16.00) | 0.061 |
| No | 34 (68.00) | 42 (84.00) | |

Source: Hospital Universitário/UFSC; Hospital Nereu Ramos, 2022.

Regarding oncotic colpocytology, HIV-positive women presented twice and a half more changes when compared to HIV-negative women, with a proportion of 4:1 and 3:1 for HSIL and atypical squamous cells cannot exclude high-grade lesion (ASC-H), respectively. In the result of the HPV-DNA of high oncogenic risk, detected by the PCR technique, the prevalence was higher among HIV-negative women (52.9% versus 45.5%), but not statistically significant. Among the 17 positive cases for HPV in the control group, only one woman (5%) presented a major change in the cytopathological examination (HSIL), whereas in the 11 positive cases of HPV in the case group, 7 (63%) of the women presented with this change (HSIL and ASC-H). There was no case of HPV 16 and 18 detected in the control group (**Table 2**).

When we assess the cytological changes and the presence of HPV DNA in HIV-positive women, we observe that women whose CD4 T cells is lower than 200 cells/ $mm^3$ were the ones that presented more cytological changes (75%) and positive HPV DNA (27%), being statistically significant ($p<0,05$) (**Table 3**). Women whose CD4 T cells is higher than 500 cells/$mm^3$ had the same positivity of cytological changes as HIV-negative women (86%) (**Tables 2 and 3**). Regarding HPV DNA, 63% of the women who demonstrated the presence of high oncogenic risk HPV presented CD4 T cells up to 500 cells/$mm^3$, almost twice as much as the observed among women whose CD4 T cells was higher than 500 $mm^3$ (36%). Of the 45 women with undetectable viral load, most (75%) had no changes in cytology and negative HPV DNA (81%). Most women on antiretroviral therapy (ART) had normal results for the oncotic colpocytology (73%) and negative HPV DNA (79%), which was statistically significant in comparison to those with detectable viral load. There was no relation between the time of HIV infection and cytological changes and the HPV infection (**Table 3**).

**Table 2 –** Cytology and PCR for HPV DNA among HIV-positive and negative women.

| Examination | HIV + n (%) | HIV- n (%) | p |
|---|---|---|---|
| Cytology | | | |
| Without changes | 36 (72.00) | 43 (86.00) | 0.086 |
| Altered | 14 (36.00) | 7 (14.00) | 0.439 |
| LSIL | 4 (8.00) | 3 (6.00) | 0.538 |
| ASC-US | 3 (6.00) | 2 (4.00) | |
| HSIL | 4 (8.00) | 1 (2.00) | 0.081 |
| ASC-H | 3 (6.00) | 1 (2.00) | |
| HPV DNA | | | |
| Negative | 38 (77.55) * | 29 (63.04)** | 0.121 |
| Positive | 11 (22.44) | 17 (36.95) | 0.342 |
| HPV 16 | 1 (9.09) | 0 (0.00) | 0.206 |
| HPV 18 | 1 (9.09) | 0 (0.00) | 0.206 |
| Multiple infection | 5 (45.45) | 9 (52.94) | 0.699 |
| Others | 4 (36.36) | 8 (47.06) | 0.576 |

*Missing: 1; **Missing: 4.
Source: Hospital Universitário/UFSC; Hospital Nereu Ramos, 2022.

**Table 3 –** Prevalence of cytological and HPV DNA changes in relation to the CD4 T cell count, viral load, use of ART and time of HIV infection in the group of HIV-positive women.

| | | Cytology | | | HPV DNA | | |
|---|---|---|---|---|---|---|---|
| | N (%) | Normal n (%) | Altered n (%) | | Negative n (%) | Positive n (%) | p |
| CD4 T (cell/mm3) | | | | **0.013** | | | **0.024** |
| <200 | 4 (8.0) | 1 (25.0) | 3 (75.0) | **0.029** | 1 (2.63) | 3 (27.27) | **0.009** |
| 200–500 | 17(34.0) | 10 (58.82) | 7 (41.18) | 0.136 | 13 (34.21) | 4 (36.36) | 0.895 |
| >500 | 29(58.0) | 25 (86.21) | 4 (13.79) | **0.009** | 24 (63.16) | 4* (36.36) | 0.114 |
| Viral load (copies/mL) | | | | | | | |
| Undetectable | 45(90.0) | 34 (75.56) | 11 (24.44) | **0.032** | 36 (81.82) | 8* (18.18) | **0.010** |
| Detectable | 5 (10.0) | 2 (40.0) | 3 (60.0) | | 2 (40.0) | 3 (60.0) | |
| ART | | | | | | | |
| Yes | 49(98.0) | 36 (73.47) | 13 (26.53) | 0.105 | 38 (79.17) | 10*(20.83) | 0.060 |
| No | 1(2.0) | 0 (0.00) | 1 (100.0) | | 0 (0.00) | 1 (100.0) | |
| Time of HIV infection | | | | 0.748 | | | 0.453 |
| Vertical transmission | 5 (10.0) | 4 (11.11) | 1 (7.14) | 0.675 | 4 (10.53) | 1 (9.09) | 0.890 |
| 1–7 years | 11(22.0) | 7 (19.44) | 4 (28.57) | 0.484 | 7 (18.42) | 4 (36.36) | 0.209 |
| ≥8 years | 34(68.0) | 25 (69.44) | 9 (64.29) | 0.726 | 27 (71.05) | 6*(54.55) | 0.304 |

*Missing: 1; ART: antirretroviral therapy. Bold: valores com p significativo
Source: Hospital Nereu Ramos, 2022

## DISCUSSION

Even if our study shows higher prevalence of HPV infection in the control group, of the 17 HIV-positive women, only one presented with one alteration at oncotic colpocytology. On the other hand, of the 11 HIV-positive women, 7 (63.6%) presented changes. Similarly to this finding, the study by Wang et al showed, through cytological examinations, that 77.5% of HIV-positive women infected with HPV had detectable cervical lesions in comparison to only 4.9% of the HIV-negative women infected with HPV[20].

The group of HIV-positive women presented twice and a half more cytological changes when compared to the control group, with higher frequency of HSIL and ASC-H among HIV-positive women (ratio of 4:1 and 3:1, respectively). These results are similar to others that were previously published, which show an increased risk for the development of these lesions in women living with HIV. The study by Moodley et al emphasizes that viral coinfection, high risk HPV and HIV, increases in about 40 times the chances of evolution to cervical intraepithelial lesion[21]. Liu et al also reported higher incidence of low-grade (RR 3.73) and high-grade (RR 1.32) squamous intraepithelial lesions in HIV-positive women, mostly associated with the increasing persistence of HPV, related to immunosuppression[22].

Castellsagué et al observed there are several cofactors that increase the probability of being infected by HPV and its progress to cervical cancer. The most common ones were coinfection with other sexually transmitted agents, multiple sexual partners and younger age at the first sexual intercourse[23]. Our study showed that HIV-negative women who began their sexual activities earlier (12 years of age or less), with an active sexual life, number of partners and non-use of condoms were the factors associated with the increasing changes of contamination with HPV.

Even though other studies[24,25] show higher changes of previous or concomitant STD in women with HIV, this analysis identified a high rate of STD in the control group, probably due to the low use of condoms and multiple sexual partners in the past year.

Regarding the vaccination rate against HPV among women living with HIV, we observed that only 32% had been immunized; more than half of the women who had not been vaccinated are aged less than 45 years and would be able to be vaccinated according to the National Program of Immunization of the Ministry of Health[26]. The vaccine Against HPV is extremely important for this group of women, since they present with higher risk of infection by this virus and HPV-induced cancer in comparison to HIV-negative women. All vaccines against HPV available in the market show high immunogenicity, efficacy and safety in HIV-infected individuals, according to a recent systematic review and meta-analysis by Staadegaard et al[27].

As to infections, we observed a high number of cases of candidiasis (72%) in HIV-positive women. The study by Alczuk et al, which included 178 HIV-positive and 200 HIV-negative women, showed higher frequency of vaginal infection by Candida sp in the HIV group in comparison to the control group[28]. Holanda et al.[29] and Peixoto et al.[30] also associated HIV as a potential risk factor for vulvovaginal candidiasis. Reda observed there is a change in the vaginal medium of HIV-positive women, especially changes in pH. There was also an increased prevalence of vulvovaginal candidiasis, especially among those whose CD4 T cells was <200 cells/mm$^3$ and/or with higher viral load[31]. Besides, HPV infection seems to change genital homeostasis, with greater diversity of species in the vaginal microbiota of HPV-positive women when compared to HPV-negative women[32].

We did not observe differences as to parity and the risk of HPV infection and/or cytological change, even though the hormonal changes induced by pregnancy can also influence the immune response to the HPV infection, its persistence and progression[33].

Munõz described the association of hormonal changes related to pregnancy and parity, and how both of them influence the

transformation zone of the ectocervix, thus facilitating the direct exposure to HPV and other cofactors[33].

Psychosocial factors have been associated with immunological changes, which, on the other hand, demonstrated a role in the disease progression due to HIV and neoplasms associated with HPV. One of these conditions is depression, considered as a powerful immunosuppressant factor. This was the statistically most frequent clinical condition in the group of HIV-positive women in our study. Grinsztejn et al demonstrated higher rates of depression symptoms among women infected by HIV and/or HPV than among those that were not infected[34].

Smoking is another factor associated with genital immunosuppression and higher risk of the HPV infection progression. Our study also showed higher frequency of smoking among HIV-positive women. The relation between smoking and HPV infection and cytological atypia was not assessed. Some researchers showed the presence of nicotine and specific tobacco-related carcinogens in the endocervical mucus of smokers, pointing to a probable direct mitogenic action, causing damage to DNA and the development of neoplastic lesions[35,36].

Most studies show that HPV infection is more prevalent among HIV-positive women. Moodley et al observed a risk about 5 times higher among women living with HIV of presenting with a high oncogenic risk Human Papillomavirus infection when compared to HIV-negative women[21]. This association was also observed by Monteiro et al, who showed that coinfection was present in 63% of the sample[37]. A previous study also carried out in Florianópolis showed higher prevalence of HPV infection among HIV-positive women (70%), in comparison to HIV-negative women (21%)[19]. However, such an association was not observed in this study, that presented no significant difference between the two groups (p=0.342). A possible explanation for that is in the fact that most HIV-positive women use antiretroviral drugs (98%). Combination antiretroviral therapy is a protective factor in relation to HPV infection and the onset of cervical intraepithelial neoplasm due to the reduction in the viral load (undetectable) and improved immunity because of the increase in CD4 T cells.

In the group of HIV-positive women, two factors have been associated with the lower prevalence of HPV infection: the level of CD4 T cells and the viral load of the participants. Of the HIV-positive women who presented with cytological changes, the CD4 T cells count was up to 500 cells/ mm³ for 70% of them. HIV infection leads to an immunological dysfunction caused by the reduction of CD4 T cells, and the result is a lower elimination rate of the HPV, whose persistence is responsible for the development of precancerous lesions[38,39]. The study by Denny et al showed that women infected by the HIV whose CD4 T cells count was higher than 500 cells/mm³ had a 57% reduction in the risk of developing a precancerous cervical lesion when compared to CD4 T cells count lower than 200 cells/mm³[39].

In our study, we observed that the undetectable viral load has been associated with a lower number of altered oncotic colpocytology results (24%) and positivity for the HPV DNA (18%). The same was observed by Delory et al, who demonstrated that only 19% of HIV-positive women, with undetectable viral load, were infected by the HPV, and, of these, less than half progressed with some type of neoplasm[40].

We observed that women on ART had lower percentages of altered oncotic colpocytology results (21%) and detection of HPV DNA (20%). In a systematic review and meta-analysis conducted by Kelly et al, women living with HIV and on regular ART had lower prevalence of high-risk HPV than those who were not on therapy, as well as reduced risk of incidence of HSIL cytological changes[41]. Another study corroborating this association is the analysis performed by Menon et al, who assessed antiretroviral therapy in the mediation of cervical disease. The 22 studies included in this review suggested a positive impact of the use and duration of ART, both in the CD4 T cells count and in the reduction of high oncogenic risk HPV[42]. The results of Liu et al also showed a significant association between ART and the lower rate of HPV infection, suggesting the increased depuration and, therefore, the reduced progress of cervical lesions, probably through immunological reconstitution[22]. A study conducted by Abel et al with 439 women infected by HIV, in which approximately 90% were on antiretroviral therapy and undetectable plasma concentrations of HIV, showed that they all had lower risks of HPV infection[43].

This study had some limitations. The sample was small, since several results demonstrated a tendency to statistical significance, which was not demonstrated probably due to the number of participants. These results reflect what we observe for the city of Florianópolis, and not necessarily the same reality is seen in other cities of Brazil or in other countries. The fact that most HIV-positive women were on ART, leading to an undetectable viral load and good levels of CD4 T cells makes them similar to HIV-negative women, thus reducing the risk of HPV infection and cytological changes. A study with more women from different locations in Brazil is necessary to reach a result that can be reproduceable in the entire country.

## CONCLUSION

The prevalence of intraepithelial cervical lesions was higher among HIV-positive women, even though uninfected women presented higher rates of HPV infection, probably due to more frequent sexual activity, thus demonstrating that the presence of HIV was the most important risk associated with the development of these lesions.

### Positive aspects of the study

With this study, we can demonstrate that HPV infection is more associated with higher sexual activity, when the immune system is preserved, regardless of the association of an HIV infection. However, when we assess the presence of precancerous cervical lesions, in which the persistent HPV infection plays a determinant role, we observe that the reduced immunity is the most important factor for the evolution of these cases.

### Approval by the Human Research Ethics Committee

This study was approved by the Human Research Ethics Committee at UFSC (CEPSH UFSC) CAAE record: 52671521.7.0000.012.

### Participation of each author

PRC: Conceptualization, data curation, formal analysis, investigation, methodology, project administration, resources, supervision, validation, visualization, writing – original draft, writing – review & editing. ID: Conceptualization, data curation, formal analysis, investigation,

methodology, project administration, resources, supervision, validation, visualization, writing – original draft, writing – review & editing. ENF: Conceptualization, data curation, formal analysis, investigation, methodology, project administration, resources, supervision, validation, visualization, writing – original draft, writing – review & editing. SMS: Data curation, formal analysis, investigation, validation, visualization, writing – review & editing. PFS: Data curation, formal analysis, investigation, validation, visualization, writing – review & editing. DSCV: Data curation, formal analysis, investigation, validation, visualization, writing – review & editing. APFP: Data curation, formal analysis, investigation, writing – review & editing. AP: Data curation, formal analysis, investigation, writing – review & editing. MEM: Data curation, formal analysis, investigation, writing – review & editing.

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## Conflict of interests

The authors declare there is no conflict of interest.

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**Address for correspondence**
***EDISON NATAL FEDRIZZI***
Rua Profª Maria Flora Pausewang, s/n – Campus Universitário – Bairro Trindade
Florianópolis (SC), Brazil
CEP: 88036 800
E-mail: edison.fedrizzi@ufsc.br

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