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SHORT REPORT

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Human papillomavirus prevalence, genomic diversity and related risk factors in HIV-positive women from a countryside city in the state of Rio de Janeiro

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ABSTRACT

Human papillomavirus (HPV) can cause genital warts and HPV-related cancer.People living with human immunodeficiency virus (HIV)are more symptomatic for HPV infections.Campos dos Goytacazes,a municipality of Rio de Janeiro,introduced the quadrivalent HPV vaccine (4vHPV)for HIV-positive women four years before initiation of a public vaccination program.This study analyzed the prevalence of HPV infection in HIV-positive women and the variables associated with infectionTwo groups were evaluated: group 1,with Pap smear and HPV-negative polymerase chain reaction (PCR);group 2, individuals with at least one positive result for HPV in PCR or pap smear.PCR was performed in endocervical samples using generic primers, and the LCD-Array Kit was used for genotyping.Univariate and multivariate analyzes were performed.Results in 109 women (Group 1 n = 70; group 2 n = 39)showed an overall HPV prevalence of 36%.Results also showed that 88% (n = 23) and 96% (n = 25)of typed viruses (total of typed viruses n = 26) were included in 4vHPV and 9vHPV (nonavalent HPV),respectively.In univariate analysis,age less than 45 years, a high number of sexual partners,and HIV-viral load were risk factors for infection.However, a CD4 indicator was associated with protection.Although HIV infection is generally related to multiple and rare types of HPV,this study showed that a vast majority of the HPV types found are included in 4vHPV. Considering that age less than 45 years is a risk factor, the use of 4vHPV in Brazil should be extended in the public vaccination program to HIV seropositive women up to age 45 years

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Introduction

Human papillomavirus (HPV) is a DNA virus that act by infecting the basal epithelial cells of the skin and mucous membranes. Their main outcomes are genital warts and HPV-related cancers.[1–3]

HPV infection can be considered a sexually transmitted disease, with a prevalence of about 11–12% worldwide, ranging from 16% to 24% among females.[4,5] In the Brazilian population, preliminary data from a nationally conducted study on 5,812 women estimated a 54.6% prevalence of HPV infection, which is in agreement with studies conducted in the state of Rio de Janeiro (54.5%). In addition, high-risk HPV types were found in 38.4% of the cases analyzed.[6]

HPV-related tumors account for 5.2% of all cancer cases in the world. The second most prevalent HPV-related cancer worldwide is cervical cancer, which occurs annually in nearly 569,847 cases, with 311,365 related deaths.[6] Data from the National Cancer Institute (INCA) in Brazil reported 16,370 new cases of cervical carcinoma, with 6,385 deaths.[7] Other HPV-related cancers are anus, vulva, vagina, penis and oropharynx tumors.

Genital HPV infection has a number of consequences in women infected with the human immunodeficiency virus (HIV). We must consider not only the increased risk of HPV infection, but also the persistence of HPV infection, the occurrence of different genotypes and the greater chance of developing invasive malignant lesions.[1,8]

The portfolio of HPV prevention measures includes condoms, Pap smears and sex education. Moreover, two HPV vaccines are available in Brazil: the bivalent Cervarix® vaccine (2vHPV) and the quadrivalent Gardasil® vaccine (4vHPV). Both vaccines prevent infection by HPV types 16 and 18, which account for 70% of cervical cancer cases and 50% of high-risk precancerous lesions. HPV types 6 and 11 are also prevented by the 4vHPV, and are associated with genital warts and low-risk cervical lesions.[9] The Gardasil 9-valent vaccine (9vHPV) was

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In this paper, we report data from Campos dos Goytacazes, the first municipality in Brazil to introduce free of charge the quadrivalent HPV vaccine GARDASIL® for women HIV positive until 45 years old, 4 years before its introduction by the Brazilian Government. The study was focused in HIV women who were interviewed and had endocervical samples collected for molecular tests. The results show that the women analyzed before vaccination had HPV genotypes included in the vaccine, so the Brazilian Government should consider change the schedule for women beyond 26 years old, because HIV people are immunosuppressed and need protection. This is significant, because it is the unique study in Brazil to analyze trends of HPV infection in HIV people vaccinated beyond 26 years old. This short communication shows the data before vaccination. After 3 years we collected new samples to analyze vaccination effectiveness, which will be disclosed in the future.
The authors have other published papers
The authors declare that there is any conflict of interest.

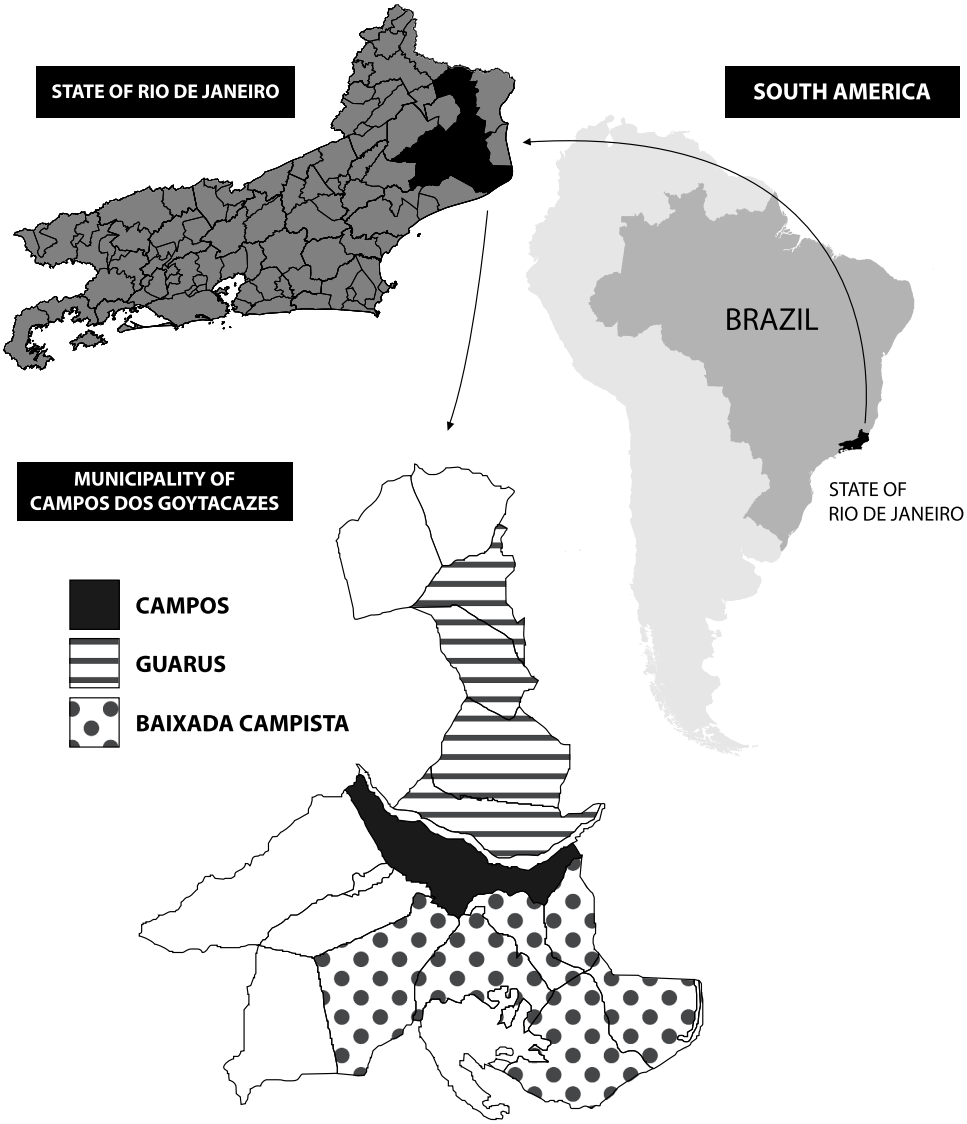

Figure 1. South America Map showing Brazil. State of Rio the Janeiro showing Campos dos Goytacazes. Campos dos Goytacazes and the 3 most important districts: Campos, Guarus and Baixada Campista

licensed in Brazil in December 2017, and provides complementary protection against HPV types 31, 33, 45, 52 and 58, although it is not available in private clinics or in the public vaccination program.[10]

The 4vHPV was introduced by the National Immunization Program (PNI) in March 2014, free of charge for Brazilian adolescents 11–13 years of age. The municipality of Campos dos Goytacazes, state of Rio de Janeiro, was the first city in Brazil to introduce a 4vHPV in September 2010 for adolescents 11–15 years of age, using the 0-2-6 months regimen. In 2011, the same municipality pioneered the vaccination of HIV-positive women 9–45 years of age. The Brazilian Ministry of Health only introduced it in 2015, for women 9–26 years of age.[11]

Considering the relationship between HIV-positive women and the unfavorable disease progression of HPV, this article presents the preliminary results of the prevalence of HPV infection in a cohort of HIV-positive women attended at the municipal infectious and parasitic disease center (CEDIP) in Campos dos Goytacazes, and correlates the findings regarding the infection with various variables of interest.

Methods

Characterization of study population

The municipality of Campos dos Goytacazes (Figure 1) is the main city in the state of Rio de Janeiro, the main national producer of petroleum. It has 4,032 square kilometers distributed over urban and rural areas, with an estimated population of 503,424 inhabitants. Of these, about 240,000 are women.[12] Campos dos Goytacazes is the largest municipality outside the metropolitan region of Rio de Janeiro, which has with

approximately 280,000 properties. The three main districts of the municipality are Campos, Guarus and Baixada Campista.

Study type

This was a prospective cohort study with intervention and prevention, which is non-randomized, controlled and single-blinded.

Inclusion criteria

(a) Women HIV-positive over 18 years of age
(b) Served by the municipal program CEDIP
(c) Agreed to participate in serial sample collection

Exclusion criteria

(a) Lack of HIV test results in sample collection
(b) Samples not suitable for analysis
(c) Lack of Pap smear results

Risks

Because it was an intervention study, the possible risks were inherent to the procedures performed on the patients. These included possible complications in the collection of the Pap smear/PCR and possible adverse reactions to the vaccine applied after the collection of the Pap smear/PCR.

Benefits

The characterization of HPV genotypes in HIV women has several benefits, such as elucidating the real burden of the disease in the seropositive population, correlating data from literature about HPV infection caused by multiple and rare genotypes and understanding the benefit of vaccination in this population.

Instruments and procedures for data collection

(a) Interviewed participants at the time of entry into the study and provided informed consent protocol, which was read, discussed and signed by the individuals.
(b) At the time of entry into the protocol, the informed consent is signed. After the gynecology workup, the sample collection occurs.
(c) Formed two groups inside the population studied:
Group 1 – Negative PCR for HPV and all results negative for Pap smear
Group 2 – Positive PCR for HPV and/or any result positive for Pap smear
(d) Collected a preventive brush for molecular biology at the 'T1' moment.
(e) Variables to be analyzed in the questionnaire were age, address, marital status, family income, sexually activity, age at first intercourse, contraceptive use, whether participants had children or not and number of children
(f) Investigated other variables in the medical records, such as:
- CD4 value
- HIV viral load
- Pap smear results in the last 5 years before the study

Laboratory tests

CD4+ count and HIV viral load

The CD4 + T-cell count was performed by flow cytometry using FACSCalibur (Becton-Dickinson, New Jersey, USA). The viral load for HIV was determined by PCR using Abbott Real Time HIV-1 (Abbott Diagnostics). The results were presented as base 10 logarithms. The minimum detection value for the HIV viral load was 50 copies/mL.

Pap smear

A Pap smear consists of scraping the endocervical and ectocervical cells. This procedure is performed by means of three collection devices: a speculum ('duckbill'), an Ayres spatula and a small brush. This proceeding is performed by the doctor or nurse during a complete clinical gynecologic evaluation. In CEDIP, like other public services in Brazil, the chosen method is the conventional one.

HPV detection

DNA extraction. All samples used for the study were collected in TRIS-EDTA buffer pH 7.2 and frozen at −20°C. After thawing, the samples were placed in the Thermoblock at 56°C for 2 hours. The samples were submitted to the digestion process of their material through contact with 100 µL of proteinase K-containing a digestion buffer. The extraction protocol used was phenol-chloroform (Thermo Fisher®). The aqueous phase was transferred to a new tube, and the DNA was precipitated with 3 M sodium acetate (pH 6.0; 1/10 volumes) and absolute ethanol (2.5 volumes). The DNA was suspended in 50 L of miliQ water and stored at −20°C.[13]

PCR using generic primers. Consensus primers (MY09/11) were used to detect generic HPV DNA. Amplification was carried out as previously described, using 50 ng of DNA sample in 50 µL of reaction mixture.[14,15] HeLa DNA was used as an HPV-positive control. The beta-actin primers were used as an internal control. Negative controls for checking contamination were included in all reactions. The PCR products were analyzed on 1.3% agarose gel stained with ethidium bromide for visualization of DNA under UV light, and a 100-bp DNA ladder was used as the molecular weight control pattern.

Microarray technique for HPV typing by the LCD-Array Kit. Samples positive for generic PCR but not genotyped by specific PCR were submitted to genotyping by the HPV 3.5® LCD-Array Kit (CHIPRON GmbH, Berlin, DE) according to the manufacturer's instruction. Briefly, PCR was performed using Primer Mix A (MY11/09) and B ('125') provided by the kit. The hybridization mix was composed of 5 µL of each amplified PCR product A and B. This mix was added to the LCD-Array slide. After staining and washing, the hybridization spots were scanned and analyzed by Slide Reader Software (CHIPRON GmbH, Berlin, DE).

Statistical analysis

The sample studied was HIV-positive women treated at the CEDIP of the municipality of Campos dos Goytacazes. For statistical purposes, using a test power of 90%, the OpenEpi network tool (an epidemiological calculator) was used, and the

female population 18–60 years of age was the target of the study (116,000 women were in this age group).[16] Therefore, considering a 30% prevalence of HPV, a sample of at least 78 individuals was needed for the study.

Patients and data were allocated in continuous and dichotomous variables in the EPIDATA® database, with posterior univariate and multivariate analyses by the free web tool "The comprehensive R Archive Network" (R Foundation, ISSN 2973–4859). Analyses were made between groups 1 and 2 and paired to investigate the relationship between HPV positivity and the weight of specific variables. The strength of association was measured using odds ratios (ORs) with 95% confidence intervals (95% CIs); logistic regression was used for ordinal data to estimate adjusted ORs. All hypothesis tests were set at the 0.05 significance level. The "Comprehensive R Archive Network" tool was also used for all statistical procedures.

Ethics

The project and the free and informed consent form were sent to the Research Ethics Committee of the Faculdade de Medicina de Campos through the Plataforma Brasil system, and were approved on 16 March 2014, with reference opinion 558.338, issued on 28 February 2014.

Results

Demographics and prevalence

This study describes a preliminary analysis of HPV infection among 109 HIV-positive women. The study population consisted of 43 (39%) participants aged 45 years and older and 66 (61%) participants aged between 18 and 45 years. Group 1 was represented by 70 women (64%) not infected with HPV and group 2 was represented by 39 women (36%) infected with HPV (MY09/11 PCR and/or Pap smear). Regarding the HPV positivity of group 2 in relation to the laboratory method, the study showed 30 patients who were confirmed positive by PCR and 9 who were confirmed positive by Pap smear. The main types of HPV and patients with single and multiple HPV infections are described in Table 1. We observed a total of 9 patients presenting with a single virus infection and 17 patients with multiple genotype infections, some of which are rare among an HIV-negative population. The remaining four infections were untyped. Of the 26 infected patients with recognized HPV types in group 2, 23 (88%) had a genotype included in the 4vHPV distributed by the Brazilian Ministry of Health. When 9vHPV coverage was considered, 25 (96%) patients had genotypes contained in the vaccine.

Univariate analysis

A univariate analysis was conducted as part of our study and is presented in Table 2. A p-value < 0.05 was considered significant. In the univariate analysis, the variables most statistically associated with HPV positivity were an age of less than or equal to 45 years, a high number of sexual partners and the quantitative viral load. On the other hand, a higher concentration of

Table 1. HPV types found in single or multiple infection(s) for HIV-positive women.

HPV infection presentation	HPV type(s)	No. of patients with microarray technique finding
Single infection	6	2
	11	3
	16	2
	81	1
	18	1
Multiple infections	06 – 11 – 44 – 61	2
	06 – 11 – 44	1
	11–39	1
	11 – 68 – 90	1
	53 – 58 – 90	1
	45–70	1
	16 – 18 – 44	1
	06 – 11 – 53 – 58 – 70	1
	06–11	1
	06–18	6
	16 – 42 – 52	1
Untyped HPV		4
Total		30

Footnotes:
HPV = Human papillomavirus
Single infection = only 1 HPV
Multiple infection = 2 or more HPV
Microarray technique – HPV 3.5® LCD-Array Kit (CHIPRON GmbH, Berlin, DE)

Table 2. Univariate analysis of HPV PCR positivity variables in HIV-positive women.

Variable (intercept: PCR)	Odds ratio (95% CI)	CI (Inf-Sup)	*p-value*
Age group (years)			
Age < or = 45 years	1.37	1.34–8.94	0.01*
Marital status			
Married	0.72		0.51
Widow	0.4	0.26–1.90	0.27
Divorced	0.57	0.07–2.0	0.38
		0.16–2.0	
Sexually active life			
No	1.00	0.28–1.1	0.1
Yes	0.62	0.26–1.4	0.27
Sexual Partners			
> 3	0.58	0.58–1.06	0.08
≤ 3	0.44	0.44–1.00	< 0.05*
Family income			
1–3 MW	1.00	0.17–1.5	0.23
3–5 MW	3.6	0.0–1.0	0.99
Age at first intercourse			
> 16	1.00	0.19–1.07	0.719
≤ 16	1.2	0.52–2.8	0.64
Condom use			
Yes	0.35	0.21–0.58	5.5
No	1.29	0.5–3.2	5.7
Number of children			
> 2	0.56	0.29–1.07	0.08
≤ 2	0.53	0.21–1.29	0.16
CD4 score			
< 500	1.00	0.31–1.00	0.09
≥ 500	0.3	0.15–0.9	0.03*
Viral load			
Not detectable	1.00	0.3–0.7	1.58
Detectable	1.2	1.00–1.59	< 0.05*

*Statistical significance
PCR – polymerase chain reaction
CI (inf-sup) – Confidence interval (inferior-superior)
MW – minimum wages
CD4 – T cell count
Viral load – minimum detection value for the HIV viral load of 50 copies/mL.

Table 3. Logistic regression model of factors associated with HPV PCR positivity in HIV-positive women.

Variable (intercept: PCR)	Odds ratio (95% CI)	IC (Inf-Sup)	*p-value*
Age < or = 45 years	1.55	1.48–12.9	0.01*
CD4 ≥ 500 cells	0.50	0.28–1.28	0.15

*Statistical significance
PCR – polymerase chain reaction
CI (inf-sup) – Confidence interval (inferior-superior)
CD4 – T cell count

CD4 was associated with a protective factor against HPV infection.

Logistic regression

We performed a preliminary multivariate analysis with significant age-related risk factors. In this model, patients aged 45 years or younger remained at higher risk of HPV infection. However, CD4 values lost significance. Table 3 demonstrates this.

Discussion

In this preliminary study, the overall prevalence of HPV infection in HIV-positive patients was 36%, with 39 positive cases. A multi-center study conducted by Miranda et al. in Brazil, which considered the prevalence of HPV lesions in 802 women, had results close to ours with a prevalence of 28.4%.[17] Nevertheless, Silva Martins and colleagues described a more comprehensive cohort in a study involving three Brazilian research centers. In that study, about 450 HIV-positive women were recruited and studied using oncologic cytology, colposcopy with biopsy, and viral typing with PCR. The results showed an HPV prevalence of 47.5% in the HIV-positive women.[18] This great variability in HPV prevalence may be due to the methodologies used or the population studied.

Regarding socio-demographic variables, we observed that HPV infection was more closely related to an age of 45 years or less, a high number of sexual partners and an HIV detectable viral load, as shown in Table 2. CD4 value was initially associated with a protection factor for HPV but lost the significance in logistic regression. As in our study, Ortiz and colleagues showed that a high number of sexual partners and low CD4 count was associated with HPV infection.[19] Similar results were also found in other studies.[20,21] However, in most different studies, the variable age as a risk factor for HPV had a different cutoff; this varied from 30 years, in studies by Silva and colleagues[22] and Travassos and colleagues,[23] to 35 years, in studies by Silva Martins[18] and Chakravarty.[21] In our study the cutoff was 45 years. This could be speculated because of the specificity of our sample, in which almost 40% of the HIV-positive women were aged over 45 years.

Regarding genotype detection, our results showed 15 different genotypes, with a greater prevalence of HPV 6, 11, 16 and 18. It is interesting to observe that multiple HPV infections were prevalent (56.7%), although high-risk HPV genotypes were detected in only 38.5% of HPV typed samples. Other studies have also shown that HIV-positive women have a higher frequency of multiple HPV infections and greater genotypic diversity, but have a tendency for greater distribution of oncogenic viral types, mainly 16, 18, 31, 33 and 45.[24–26] Similarly, Castilho and colleagues published hrHPV prevalence results of 65% in a cohort of 590 HIV-positive women by using hybrid capture-based genome testing. Besides, they also showed that 32% of the women studied had more than one type of high-risk HPV detected. The most commonly detected HPV types were 58, 53 and 16.[27] In our study, multiple infections showed a more benign HPV genotype profile. We can argue that the patients from this countryside municipality are at a lower risk for HPV infection and the development of malignant diseases because of the CEDIP program; this program offers a complete and specialized gynecology service for this population, and so it is possible to quickly track and treat HPV lesions.

One point to highlight about HPV infection in HIV-seropositive women is viral persistence and the continued risk of the development of malignant and even invasive lesions, such as cervical cancer. Despite the use of HAART – that is, despite the elevation of cellular immunity and antibodies – there is still a high and consistent risk of malignancy associated with HPV.[1,28] An example of this association is the cross-sectional study conducted by Mujuni et al., which evaluated 255 HIV-positive women and showed the presence of HPV-positive DNA in about 54% of patients, with high-risk HPV genotypes present in 48.6% of patients, culminating in a higher incidence of HPV positivity in patients with CD4 levels below 100 and the presence of intraepithelial lesions.[29]

Our study also demonstrated the HPV genotype coverage inside the available vaccines. Although HIV-positive people generally show infection with multiple forms of HPV, we found that of 26 patients with genotypes identified, 23 (88.4%) and 25 (96.1%) of them had at least one genotype included in 4vHPV and 9vHPV, respectively. Two studies addressed the potential benefits of vaccination in preventing lesions related to HPV in HIV-positive people. In the first article, Thorsteinsson and colleagues analyzed the prevalence and distribution of lesions related to HPV and the genotype coverage included in vaccines. For cervical lesions, the coverage included in 4vHPV and 9vHPV was 17.8% and 50% respectively.[30] In another study, Fusco and others demonstrated that HPV was present in 50.2% of a sample of 321 HIV+ women. Based on the genotypes identified, the use of 2vHPV, 4vHPV and 9vHPV would prevent lesions in 19%, 33% and 48%, respectively.[31]

HPV infection is a public health problem due to the extent of its spread and its adverse outcomes, such as the occurrence of oncogenic lesions. Regarding the female population living with HIV, this issue is still more complex due to the context of immunosuppression. This study confirms the high prevalence and genomic diversity of HPV in the investigated population and further strengthens the need for indications of the vaccine, given the high prevalence of HPV types contained in the vaccine. The implementation of 9vHPV would improve genotype coverage in almost 10% of HIV-positive women.

However, the vaccination policy in Brazil should be first prepared to broaden the 4vHPV vaccination age schedule for the HIV-positive people and ensuring elevated vaccine coverage. Then, in a second step, it would be plausible to implement 9vHPV to improve protection for HPV.

This work has several limitations. First, the study chose to look at only patients aged 18 years and older; this was intended to resolve two possible initial limitations of the study: small sample size and the fact that almost all teenagers would have already received the first dose of the vaccine initiated by the municipality before the study started. It is noticeable that the small sample size does not allow for a more significant multivariate analysis. We had difficulties performing follow-up of some patients, so the authors started active surveillance of the sample through the use of phone calls and conversation during basic care attendance. Other limitations of the analysis involve subjective data collected in a questionnaire. It is possible to have varying degrees of bias, such as recall bias or interviewer bias, which may impact univariate statistical analysis. However, new collections and an increase in the number of patients should be expected to make the logistic regression model more robust for further analysis.

Based on the worldwide experience of HPV vaccine use, the success of vaccination is undeniable, especially among people living with HIV who particularly need vaccination in moments of HIV suppression. In conclusion, the results of this study demonstrate that the public vaccination program in Brazil should consider changing the 4vHPV schedule for HIV-positive women to include an on-label extension of indication until patients reach 45 years of age.

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