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ASSOCIATION BETWEEN HIV INFECTION AND ONCOGENIC HPV SUBTYPES IN CISGENDER WOMEN

ASSOCIAÇÃO ENTRE A INFECÇÃO POR HIV E OS SUBTIPOS ONCOGÊNICOS DO HPV EM MULHERES CISGÊNERO

HIV and Oncogenic HPV in Cisgender Women

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ABSTRACT:

Introduction: Women living with HIV/AIDS (WLHA) are more vulnerable to human papillomavirus (HPV) infection, particularly by high-risk oncogenic subtypes, due to HIV-associated immunosuppression. **Objective:** To assess the prevalence and distribution profile of HPV subtypes in WLHA, correlating findings with CD4 levels and age group. **Methods:** A cross-sectional study was conducted with 184 WLHA receiving care at a public referral center in Juiz de Fora, Minas Gerais, from May 2021 to May 2022. Self-collected vaginal samples were analyzed by RT-PCR to detect HPV subtypes. Associations between HPV infection, CD4 counts, and age were assessed using the chi-square test ($p<0.05$). **Results:** HPV infection was detected in 72% of the participants. Oncogenic subtypes not included in the quadrivalent vaccine were identified in 49.3% of the infected individuals, with HPV 52 and 58 being the most prevalent. A higher frequency of infection was observed in women with CD4 counts <500 cells/mm³, although no statistical association was found between CD4 levels and specific viral types. There was no significant association between age and the prevalence of major subtypes. **Conclusion:** WLHA show a high prevalence of HPV, particularly high-risk subtypes not covered by the quadrivalent vaccine. The findings support expanding immunization with the nonavalent vaccine and strengthening cervical cancer screening and control strategies in this population.

Keywords: HIV; Human Papillomavirus; Coinfection; Vaccines; Women’s Health.

RESUMO:

Introdução: Mulheres vivendo com HIV/AIDS (MVHA) são mais vulneráveis à infecção pelo papilomavírus humano (HPV), especialmente pelos subtipos oncogênicos de alto risco, devido à imunossupressão associada ao HIV. Objetivo: Avaliar a prevalência e o perfil de distribuição dos subtipos de HPV em MVHA, correlacionando os achados com os níveis de CD4 e a faixa etária. Métodos: Foi realizado um estudo transversal com 184 MVHA atendidas em um centro público de referência em Juiz de Fora, Minas Gerais, entre maio de 2021 e maio de 2022. Amostras vaginais autocoletadas foram analisadas por RT-PCR para detecção dos subtipos de HPV. As associações entre infecção por HPV, contagem de CD4 e idade foram avaliadas pelo teste do qui-quadrado ($p<0,05$). Resultados: A infecção por HPV foi detectada em 72% das participantes. Subtipos oncogênicos não contemplados pela vacina quadrivalente foram identificados em 49,3% das mulheres infectadas, sendo os HPV 52 e 58 os mais prevalentes. Observou-se maior frequência de infecção em mulheres com contagem de CD4 <500 células/mm³, embora não tenha sido encontrada associação estatisticamente significativa entre os níveis de CD4 e tipos virais específicos. Não houve associação significativa entre idade e prevalência dos principais subtipos. Conclusão: MVHA apresentam alta prevalência de HPV, particularmente de subtipos de alto risco não cobertos pela vacina quadrivalente. Os achados reforçam a necessidade de ampliação da imunização com a vacina nonavalente e do fortalecimento das estratégias de rastreamento e controle do câncer do colo do útero nessa população.

Palavras-chave: HIV; Papilomavírus Humano; Coinfecção; Vacinas; Saúde da Mulher.

INTRODUCTION

Human papillomavirus (HPV) infection is one of the most prevalent sexually transmitted infections (STIs) worldwide. It is estimated that a substantial portion of the global population will be exposed to HPV at some point in life. With over 228 identified variants, HPV has been the focus of numerous studies due to the association between persistent infection by oncogenic subtypes and the development of dysplasias in

various anatomical sites such as the larynx, anorectal junction, and cervix—the latter being directly associated with invasive cervical carcinoma[1,2].

Among the known variants, at least 12 are considered oncogenic and carry a higher risk of causing persistent infections and precursor lesions of cervical cancer[3]. Subtypes 16, 18, 31, 33, 45, 52, and 58 are the most prevalent, especially types 16 and 18, which are found in 70% of cervical cancer cases. In contrast, HPV 6 and 11, although present in 90% of genital warts and laryngeal papillomas, are considered non-oncogenic[3,4].

Although the epidemiological link between HPV and cancer incidence is well established, infection with the Human Immunodeficiency Virus (HIV) is also recognized as a risk factor for the development of cervical dysplasia and invasive cervical carcinoma in people living with HIV/AIDS (PLWHA)[5,6,7].

In most HPV-infected individuals without comorbidities leading to immunosuppression, viral clearance is typically achieved—a process by which the virus is eliminated or reduced to levels below the detection threshold of standard molecular assays. PLWHA, on the other hand, show greater persistence of oncogenic subtypes throughout the natural history of infection, due to impaired immune clearance of subtypes that would normally be controlled in the absence of immunosuppression[6,7], even among patients on highly active antiretroviral therapy[7]. These findings may be explained by enhanced HPV replication and progression to cervical squamous intraepithelial lesions[8].

As such, immunosuppressed individuals may develop treatment-refractory and progressive HPV-related diseases, including cutaneous and mucosal warts, and cervical, anogenital, and oropharyngeal carcinomas[9]. Moreover, they are 4 to 5 times more likely to develop invasive cervical cancer compared to women without HIV[10].

Although the quadrivalent vaccine—which protects against oncogenic subtypes 16 and 18—has demonstrated efficacy in the general population, it remains unclear whether women living with HIV/AIDS (WLHA) are equally protected, given the potential for a different distribution of oncogenic subtypes in PLWHA[11]. A systematic review by Parana et al.[12] found a similar prevalence of HPV-16 in WLHA and HIV-negative women, but higher prevalence of HPV-58, HPV-31, and HPV-52 among WLHA, whereas HPV-18 was more frequent among HIV-negative women.

Furthermore, few studies have explored the relationship between HPV subtype distribution, CD4 levels, and age in WLHA, representing a significant gap in the literature. Women with CD4 counts below 200 cells/mm³ are known to be more susceptible to complications from HPV infection than those with higher counts[13], but the level of protection in women with higher counts remains underexplored.

In addition, retrospective studies have shown age-related variations in the prevalence of high-risk HPV subtypes. Grinsztejn et al.[8] observed that women under the age of 30 had approximately 50% higher prevalence of these subtypes compared to those over 40. Complementing these findings, Wei et al.[14] showed that the prevalence of HPV-16 tends to decrease significantly with age in both HIV-negative women and WLHA. However, it remains unclear whether these differences are attributable to behavioral or biological factors. Understanding these associations may support tailored screening and vaccination strategies for WLHA.

OBJECTIVE

In this context, the objective of this study was to analyze the epidemiological distribution of HPV subtypes in cisgender WLHA, investigating possible associations with CD4 levels and age groups. The findings are expected to contribute to the improvement of HPV prevention and control strategies in this vulnerable population.

METHODS

This study aimed to analyze the prevalence and factors associated with HPV DNA detection in cisgender WLHA who were followed between May 2021 and May 2022 at a clinical outpatient service providing specialized care in the city of Juiz de Fora, Minas Gerais. This is a reference center for the treatment of infectious diseases in the metropolitan area and is specialized in the care and management of PLWHA.

The inclusion criteria comprised all cisgender WLHA receiving regular care at the outpatient clinic, aged 18 years or older, undergoing continuous antiretroviral therapy (ART), and who consented to participate in the study. Pregnant women, women with a history of hysterectomy, and those diagnosed with gynecologic cancer were excluded from the study.

Participants were approached in a standardized manner by a trained researcher, received detailed information about the study, and were invited to participate by voluntarily signing the informed consent form. They were assured of the confidentiality of their data and its use exclusively for scientific purposes, ensuring no harm to the participants. They were also informed of guaranteed anonymity, the voluntary nature of their participation, and their right to withdraw from the study at any time, in accordance with Resolution No. 466/12 of the Brazilian National Health Council.

Upon consent, self-collection kits for vaginal samples were distributed to the 184 women enrolled in the study. Samples were received by a healthcare professional at the service and sent to a national reference laboratory. The testing technique used was RT-PCR A (Anyplex™ II HPV28 Detection kit – Seegene, Seoul, South Korea) for identification of HPV subtypes present in the samples at the time of infection. The test detected 19 high-risk HPV types (16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 69, 73, and 82) and 9 low-risk types (6, 11, 40, 42, 43, 44, 54, 61, and 70).

Additionally, medical records were reviewed to collect CD4+ T cell counts, CD8, CD4/CD8 ratio, CD45, and viral load based on the most recent laboratory results available, regardless of proximity to the self-sampling date. Information was also collected about the initials of their names and their mothers' names (used for tracking HPV test results), and participants' dates of birth to calculate age—one of the study variables. All data were entered into a Microsoft Excel spreadsheet for statistical analysis. Data were analyzed using Pearson's chi-square test, with a 95% confidence interval (CI) and significance level set at $p<0.05$.

This study was previously submitted to and approved by the Research Ethics Committee of SUPREMA – Sociedade Universitária para o Ensino Médico Assistencial Ltda (CEP/FCMS-JF), regulated by the National Research Ethics Committee (CONEP), under approval number 4.718.416 and CAAE: 43223521.7.2009.5103. The study was initiated only after ethics approval was obtained.

RESULTS

Among the 184 WLHA analyzed, 134 women (72.8%) tested positive for HPV DNA. The most prevalent oncogenic subtypes were HPV 52 and 58, each present in 18 women (13.4% of the HPV-positive cases and 9.8% of the total sample), followed

by subtype 16 detected in 14 women (10.4% of HPV-positive cases and 7.6% of the total sample).

Among the non-oncogenic subtypes, subtypes 6 and 11 were detected in six (4.5%) and two (1.5%) WLHA, respectively. See Table 1.

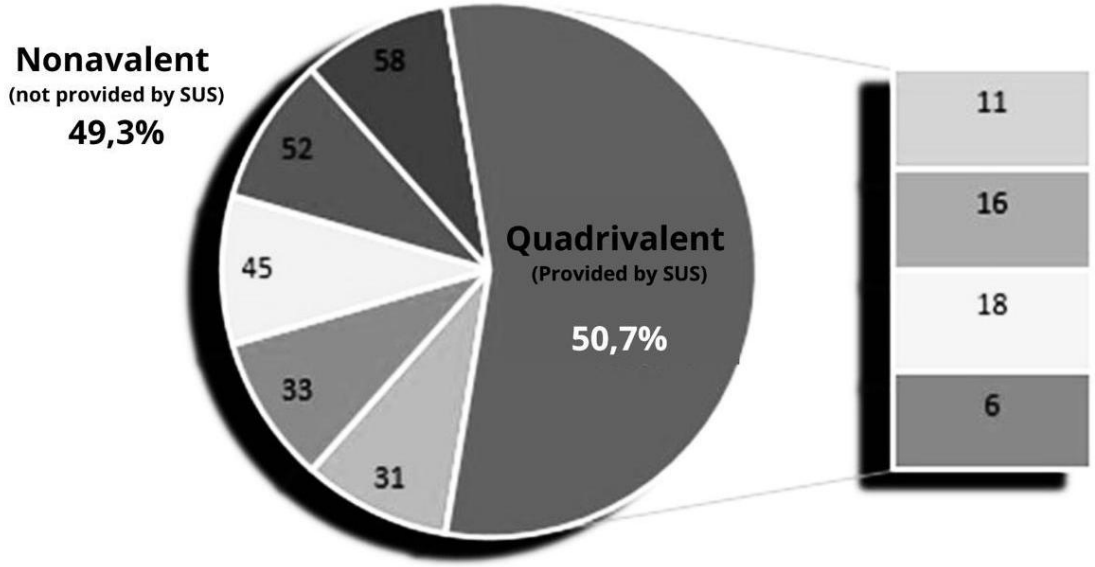
Table 1. Prevalence of main oncogenic and non-oncogenic HPV subtypes in the sample

HPV Subtypes	Nº of WLHA with detectable HPV-DNA	% among HPV-positive cases (n=134)	% of total sample (n=184)
52	18	13.4%	9.8%
58	18	13.4%	9.8%
16	14	10.4%	7.6%
45	12	8.9%	6.5%
31	11	8.2%	6.0%
33	7	5.2%	3.8%
18	7	5.2%	3.8%
6	6	4.5%	3.3%
11	2	1.5%	1.1%

WLHA: Women living with HIV/AIDS
% among HPV-positive cases: number of cases per subtype divided by 134
% of total sample: number of cases per subtype divided by 184

Of the 134 WLHA with detectable HPV-DNA, 66 (49.25%) presented at least one oncogenic subtype not covered by the quadrivalent vaccine, but included in the nonavalent vaccine. Coinfections involving more than one oncogenic subtype were also observed.

Graph 1. Vaccine coverage against different HPV subtypes identified in WLHA: Quadrivalent vaccine (available via public health system) vs. Nonavalent vaccine



The most frequent coinfections were observed between subtypes HPV 31 and HPV 58 (5 cases),, followed by HPV 16 and HPV 58 (4 cases). The distribution of additional combinations is detailed in Table 2.

Table 2. Coinfection between oncogenic HPV subtypes in the sample

Coinfection pair	Number of cases
HPV 31 + HPV 58	5
HPV 16 + HPV 58	4
HPV 31 + HPV 45	2
HPV 31 + HPV 52	2
HPV 33 + HPV 52	2
HPV 33 + HPV 58	2

HPV 52 + HPV 58	1
HPV 31 + HPV 16	1
HPV 31 + HPV 33	1

Note: Some participants presented more than one coinfection combination.

Of the total 134 samples with DNA-HPV positive, 79 (59.0%) had available CD4 data, while 55 (41.0%) had no updated immunophenotyping results in the laboratory system. Among women with available CD4 counts, 25 had CD4 counts above 500 and 54 had CD4 counts below 500. In the group of 50 women without detectable HPV-DNA, 29 had available CD4 data. Of these, 26 (89.7%) had CD4 counts above 500 cells/mm³. Table 3 summarizes the distribution of CD4 counts according to HPV detection status.

Table 3. Distribution of CD4 cell counts by immunophenotyping

Group	CD4 < 350	CD4 350–500	CD4 > 500	Data not available	Total
HPV-DNA detected	—	54 (40.3%)	25 (18.7%)	55 (41.0%)	134
HPV-DNA not detected	1 (2.0%)	2 (4.0%)	26 (52.0%)	21 (42.0%)	50

These results suggest that higher CD4 counts were more frequently associated with participants without HPV detection, while lower counts were predominant among women with detected HPV infection. However, statistical analysis (chi-square test) did not show a significant association between the different CD4 strata and HPV detection ($p = 0.8$).

To evaluate the association between CD4 levels and HPV subtype distribution, data from the 79 WLHA with detectable HPV-DNA and available CD4 counts were

analyzed. No statistically significant association was identified between CD4 categories and the distribution of HPV subtypes ($p > 0.05$).

Regarding HIV viral load, among the 134 WLHA with a positive DNA-HPV result, 58 (43.2%) had undetectable viral loads, 19 (14.1%) had detectable viral loads, and 57 had no data available in the laboratory system.

In the sample with a negative result for DNA-HPV detection, 27 (54%) had undetectable viral loads, two had detectable viral loads and 21 had no data available in the system.

The association between age group and HPV subtype distribution was also evaluated among the 134 WLHA with detectable HPV-DNA. Participants were categorized into two age groups (18–45 years and ≥46 years), and the prevalence of HPV types included in the quadrivalent and nonavalent vaccines was analyzed. Among HPV-positive women, 51 (38.0%) were between 18 and 45 years old, while 42 (31.0%) were aged 46 years or older.

Table 4. Distribution of main high-risk HPV types covered by quadrivalent and nonavalent vaccines among HPV-DNA positive WLHA, by age group

HPV Type	18-45 years n absolute (%)	≥46 years absolute n (%)	Total n (%)
HPV 16	9 (17,6%)	5 (11,9%)	14 (10,4%)
HPV 18	3 (5,9%)	4 (9,5%)	7 (5,2%)
HPV 31	7 (13,7%)	4 (9,5%)	11 (8,2%)
HPV 33	4 (7,8%)	3 (7,1%)	7 (5,2%)
HPV 45	4 (7,8%)	6 (14,3%)	10 (7,5%)
HPV 52	10 (19,6%)	8 (19,0%)	18 (13,4%)

HPV 58	9 (17,6%)	9 (21,4%)	18 (13,4%)
HPV 6	3 (5,9%)	3 (7,1%)	6 (4,5%)
HPV 11	2 (3,9%)	0 (0%)	2 (1,5%)
Total WLHA	**51 (38%)**	**42 (31%)**	**93 (69%)**

No association was found between age group (18–45 vs. 46+) and the distribution of the main HPV subtypes (p = 0.55).

DISCUSSION

The HPV DNA detection rate of 72% in vaginal self-collected samples from WLHA in this study aligns with recent data reporting prevalence rates between 55% and 80% of this infection among PLWHA in Brazil[15]. These figures highlight the increased immunological vulnerability of this population to HPV infection, especially when compared to the general population, where recent studies have shown significantly lower prevalence rates, ranging from 37% to 55%[15,16].

Although there is no concrete data on the vaccination history of these participants, prior HPV vaccination should be interpreted in light of the historical context of the implementation of this vaccine in the Brazilian Unified Health System (SUS). In Brazil, HPV vaccination was introduced only in 2014, initially targeting female adolescents, and was later expanded to include people living with HIV/AIDS within restricted age groups. During the study collection period, the expansion of vaccination for immunosuppressed women up to 45 years of age was still recent, while a significant portion of the sample was already above the age range covered by the vaccination strategies in force at the time. Furthermore, 31% of participants with detectable HPV-DNA were aged 46 years or older, an age group that had never been included in public HPV vaccination campaigns in Brazil. Therefore, the age profile of the studied population suggests a high probability of low or absent prior vaccination coverage in this sample, despite a large proportion of participants being unaware of their vaccination status.

Oncogenic subtypes 16 and 18, historically the main types associated with cervical carcinogenesis, were found in only 10.4% and 5.2% of the samples, respectively. In contrast, the most prevalent high-risk subtypes were types 52 and 58, both detected in 13.4% of the samples, appearing twice as frequently as subtype 18. Other high-risk types, such as 31 and 45, also showed higher prevalence than type 18. These findings suggest a distinct HPV subtype distribution pattern among WLHA, with predominance of oncogenic subtypes not included in the quadrivalent vaccine currently available through the Brazilian public health system[11,12,18].

The lower prevalence of subtypes 16 and 18 observed in this cohort may reflect the natural epidemiological distribution of HPV in this population, contrasting with findings from previous studies that suggested a possible relationship between the reduction of these subtypes and the impact of immunization[11,18]. However, in the absence of vaccination records, the influence of prior immunization cannot be excluded, and its impact on subtype distribution remains uncertain[8,18]. Therefore, future studies should include vaccination history to better assess the relationship between immunization and HPV subtype distribution among WLHA[8,11,18]. .

Subtypes HPV 52 and HPV 58 are strongly associated with high-grade squamous intraepithelial lesions, such as CIN2 and CIN3, which may progress to invasive cervical cancer[17]. The same applies to HPV 31 and HPV 33[17], which were also prevalent in the sample. These findings reinforce the potential relevance of broader vaccine coverage for WLHA. Even with the availability of vaccines covering additional oncogenic subtypes, continued cervical screening remains essential. Molecular biology-based tests are currently considered the most effective tools for screening, as recommended by WHO guidelines[19]. From a clinical and public health perspective, the combined use of molecular HPV testing and reflex cytology may contribute to earlier detection of precursor lesions and reduction of HPV-related neoplasms among WLHA.

Additionally, co-infection with multiple oncogenic subtypes was observed in this study. Most HPV-positive women had infections with more than one subtype, often including types associated with cervical dysplasia. This finding is consistent with epidemiological hypotheses reported in other studies, such as the meta-analysis by Menon et al.[26], which identified multiple HPV infections as a frequent feature among WLHA.

Regarding CD4 counts, 89% of women without HPV detection had CD4 counts above 500 cells/mm³, while lower CD4 levels were more frequently observed among women with detectable HPV DNA, indicating an association between greater immune protection and elevated CD4 levels, even though other factors may contribute to susceptibility to infection. This pattern was also presented in previous studies, such as the meta-analysis by Silva et al.[26], which emphasized the link between advanced immunosuppression and increased risk of high-risk HPV infections, particularly HPV 16 and 58. However, statistical analysis did not reveal a significant association between CD4 strata and HPV detection ($p = 0.8$). This finding should be interpreted with caution, given the substantial proportion of missing immunological data, the limited sample size available for subgroup analyses, and the lack of temporal standardization between laboratory proportions and HPV sample collection, factors that may have limited the statistical power to detect possible associations. Laboratory parameters were found in the most recent available records and were not necessarily obtained concomitantly with HPV sample collection. Although causality cannot be established in this cross-sectional study, previous evidence suggests that severe immunosuppression may contribute to persistent HPV infection and reduced viral shedding.[26]

In analyzing the association between CD4 levels and the prevalence of specific HPV subtypes, no statistically significant differences were found. This result suggests that, at least in this sample, immune status may not play a determining role in the distribution of viral subtypes. However, the lack of statistical significance may be due to the limited sample size.

Based on the data analyzed, the distribution of different HPV types appeared similar across age groups, suggesting that age alone is not a determining factor for the presence of specific HPV types. This finding contradicts some expectations, as previous studies, including those by Grinsztejn et al.[8] and Wei et al.[14], indicated that the prevalence of certain HPV types may vary with age, particularly among younger women at the beginning of their sexual lives. Nevertheless, the lack of a significant association in the present study could be due to factors such as the insufficient sample size or the use of a single age cut-off point (45 years). Overall, the interaction between immunity and HPV infection is complex, involving multiple variables, such as sexual practices, number of partners, and access barriers to healthcare. In this context, understanding HPV infection among WLHA requires a broader perspective that

includes not only immunological status, but also behavioral and social determinants that may influence viral exposure, persistence, and access to preventive healthcare services. These factors may contribute to the maintenance of HPV circulation and reinforce the need for more integrated preventive approaches in this population.

The incomplete vaccination records and limited availability of cervical screening data observed in this study may reflect challenges in the integration of gynecological preventive care among WLHA. In this context, strategies such as self-sampling may be crucial for expanding access to HPV screening, especially in healthcare services lacking proper gynecological infrastructure.

Future multicenter studies including detailed vaccination history, sexual behavior variables, and longitudinal follow-up are necessary to better understand the dynamics of HIV/HPV coinfection in WLHA. In addition, investigations evaluating the potential epidemiological and cost-effectiveness impact of broader access to the nonavalent vaccine in the Brazilian public health system may help support future prevention strategies in this high-risk population.

Strengths:

This study presents important strengths, particularly by investigating a vulnerable population that remains underrepresented in the national literature, evaluating the distribution of HPV subtypes among WLHA receiving care at a public referral center. The use of molecular RT-PCR methodology allowed a more sensitive and comprehensive analysis of circulating viral subtypes, including the identification of coinfections and oncogenic types not covered by the quadrivalent vaccine currently available through the Brazilian public health system. Furthermore, the findings provide relevant epidemiological data on the profile of HPV infection in this population, contributing to discussions regarding screening strategies, prevention measures, and the expansion of vaccine coverage among immunosuppressed women.

Limitations:

This study has some limitations that should be considered. First, the absence of information regarding participants' HPV vaccination histories limited the evaluation of the impact of immunization on HPV subtype distribution. In addition, incomplete availability of updated CD4 and viral load data for part of the sample may have reduced

the statistical power of some analyses. Additionally, laboratory parameters were not always collected concurrently with HPV sampling, which may have limited the accuracy of the associations between immunological status and HPV detection. The cross-sectional design also prevents establishing causal relationships between immunological status and HPV infection persistence. Furthermore, the lack of oncotic colpocitology data limited the assessment of the association between HPV subtypes and cervical lesion severity. Finally, the relatively limited sample size may have reduced the statistical power to detect statistically significant associations across different age stratifications.

CONCLUSION

This study demonstrated a high prevalence of HPV infection among cisgender WLHA, with a predominance of oncogenic HPV subtypes 52 and 58, followed by subtype 16. A substantial proportion of HPV-positive women presented high-risk subtypes not covered by the quadrivalent vaccine currently available through the Brazilian Unified Health System (SUS), highlighting the epidemiological relevance of broader vaccine coverage in this population.

A high frequency of coinfections involving oncogenic HPV subtypes was also observed, especially among subtypes included only in the nonavalent vaccine. Although no statistically significant association was found between HPV subtype distribution and CD4 levels or age groups, women without detectable HPV infection more frequently presented CD4 counts above 500 cells/mm³, suggesting a possible relationship between better immune status and lower HPV detection.

These findings suggest the importance of continuous cervical cancer screening and targeted preventive strategies for WLHA, particularly considering the high prevalence of oncogenic HPV subtypes associated with persistent infection and cervical carcinogenesis.

Approval by the Human Research Ethics Committee

This project was approved by the Research Ethics Committee of SUPREMA – Sociedade Universitária para o Ensino Médico Assistencial Ltda (CEP/FCMS-JF), under approval number 4.718.416 and CAAE: 43223521.7.2009.5103.

Conflict of interests

The authors declare no conflicts of interest.

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Participation of each author:

SMSG: Conceptualization, Methodology, Project administration, Writing – original draft, Writing – review & editing. PCAS: Conceptualization, Methodology, Project administration, Writing – original draft, Writing – review & editing. CFR: Conceptualization, Formal analyses, Methodology, Writing – original draft, Writing – review & editing. YVOA: Conceptualization, Investigation, Methodology, Writing – original draft, Writing – review & editing. MAM: Conceptualization, Data curation, Project administration, Resources, Writing – review & editing, Supervision. MLB: Conceptualization, Data curation, Resources, Writing – review & editing, Supervision. MFS: Conceptualization, Data curation, Resources, Writing – review & editing, Supervision

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