Anal HPV prevalence in a cohort of individuals infected with HIV-1

Prevalência de HPV anal em uma coorte de indivíduos infectados pelo HIV-1

Nathalia Silva Oliveira[1], David William Provance Jr.[1,2], Beatriz Grinsztejn[3], Ruth K Friedman[3], Valdileia Gonçalves Veloso[3], Jose Ricardo Coutinho[3], Cynthia Braga da Cunha[3], Dennis de Carvalho Ferreira[4], Alcina Frederica Nicol[1]

ABSTRACT

Introduction: Human Papillomavirus (HPV) is the primary etiologic agent of anogenital tract cancer. A higher prevalence and incidence of developing cancer and diseases associated with HPV have been observed in individuals infected with the human immunodeficiency virus (HIV). The natural history of HPV infection has not been completely elucidated, as well as the immune response that occurs as coinfection with HIV/HPV, particularly in the anal mucosa. **Objective**: To analyze the HPV prevalence and clinical, epidemiological, and behavioral data in a cohort of HIV-seropositive individuals from the National Institute of Infectious Diseases, FIOCRUZ, RJ. **Methods**: The study included a total of 114 individuals from the histopathological diagnosis of anal biopsy. PCR and sequencing was performed for HPV DNA identification in anal discharge. Statistical analysis was performed using SPSS 15.0 software. **Results:** Patients Infected with HIV with anal intraepithelial neoplasia (AIN) II/III had nadir CD4 + <50 cells/mm³ compared to normal patients (p=0.01). The most prevalent HPV types in the anal secretion (by Papillocheck) were HPV 16 (29.2%), followed by HPV 52 (23.1%), both high-risk oncogenic, followed by HPV 44 and 55 (21.5%) that are low-risk type. A total of 53.3% HIV-infected individuals analyzed have already been exposed to the four HPV types targeted by the current quadrivalent vaccine (MSDm – HPV types 6, 11, 16, and 18). **Conclusion**: The data suggest that vaccination against HPV could be regarded as a prophylactic measure to reduce the risk of anal intraepithelial lesions in HIV-infected individuals.

Keywords: Papillomaviridae; vaccines; homosexuality; women; anal cancer.

RESUMO

Introdução: O papilomavírus humano (HPV) é o principal agente etiológico do câncer do trato anogenital. A maior prevalência e incidência de desenvolvimento de câncer e doenças associadas ao HPV têm sido observadas em indivíduos infectados pelo vírus da imunodeficiência humana tipo 1 (HIV-1). A história natural da infecção pelo HPV não foi completamente elucidada, assim como a resposta imune que ocorre na coinfecção pelo HIV/HPV, particularmente na mucosa anal. **Objetivo:** Analisar a prevalência de HPV, dados clínicos, epidemiológicos e comportamentais em uma coorte de indivíduos infectados pelo HIV do Instituto Nacional de Infectologia (INI), FIOCRUZ, RJ. **Métodos:** Foi incluído um total de 114 indivíduos com diagnóstico histopatológico de biópsia anal. A tipagem do DNA de HPV foi realizada através da secreção anal. A análise estatística foi realizada utilizando o software SPSS 15.0. **Resultados**: Pacientes HIV positivos com Neoplasia intraepitelial anal de alto grau (NIA II/III) apresentaram CD4+ nadir <50 células/mm³ , comparados a pacientes sem displasia anal (p=0,01). Os tipos de HPV mais prevalentes na secreção anal (pelo *Papillocheck*) foram HPV 16 (29,2%), seguido do HPV 52 (23,1%), ambos de alto risco oncogênico, seguido de HPV 44 e 55 (21,5%), que são baixo risco oncogênico. Um total de 53,3% dos indivíduos infectados pelo HIV já analisados foi exposto aos 4 tipos de HPV, que são alvos da vacina quadrivalente corrente (MSD – HPV 6, 11, 16 e 18). **Conclusão**: Os dados sugerem que a vacinação contra o HPV pode ser considerada como uma medida profilática para reduzir o risco de lesões intraepiteliais anais em indivíduos infectados pelo HIV.

Palavras-chave: Papilomavírus humano; vacinas; homossexualidade; mulheres; câncer anal.

INTRODUCTION

Human Papillomavirus (HPV) is the main causative agent for the development of neoplastic lesions in uterine cervix. In anal tissue, the progression of HPV-positive high-grade lesions to an invasive cancer can require years. This progression can occur more rapidly in young HIV-infected individuals. However, there is a paucity of information on the consequences of HIV/HPV coinfections with regard to neoplastic lesions. Prospective studies can better clarify on the factors that may contribute to the severity and progression of disease surrounding HIV/HPV coinfection. Few studies have reported on the major risk factors associated with HIV/HPV coinfections such as unprotected sex and a high number of sexual partners[1,2]. The aim of this study was to evaluate the HPV prevalence and to cross-analyze clinical, sociodemographic, and behavioral data from HIV-infected subjects diagnosed with anal intraepithelial lesions.

OBJECTIVE

To analyze the HPV prevalence, clinical, epidemiological, and behavioral data in a cohort of HIV-seropositive individuals from the National Institute of Infectious Diseases, FIOCRUZ, RJ.

Work conducted at *Laboratório de Pesquisa Clínica em DST/AIDS* (LapClin DST/AIDS), *Instituto Nacional de Infectologia* (INI), *Fundação Oswaldo Cruz* (Fiocruz) and *Laboratório Interdisciplinar de Pesquisas Médicas* (LIPMED), *Instituto Oswaldo Cruz* (IOC), Fiocruz – Rio de Janeiro (RJ), Brazil.

[1]*Laboratório Interdisciplinar de Pesquisas Médicas* (LIPMED), IOC, Fiocruz – Rio de Janeiro (RJ), Brazil.

[2]*Centro de Desenvolvimento Tecnológico em Saúde* (CDTS), *Instituto Nacional de Ciência e Tecnologia de Inovação em Doenças Negligenciadas* (INCT-IDN), Fiocruz – Rio de Janeiro (RJ), Brazil.

[3]LapClin DST/AIDS, *Instituto Nacional de Infectologia* (INI), Fiocruz – Rio de Janeiro (RJ) Brazil

[4]Department of Endodontics, Postgraduate Program in Dentistry, Universidade Estácio de Sá – Rio de Janeiro (RJ) Brazil.

METHODS

Study Population

The study received approval prior to recruiting participants from the institutional ethical review board at the Evandro Chagas National Institute of Infectious Diseases (INI) of the Oswaldo Cruz Foundation (Fiocruz) in Rio de Janeiro, Brazil (protocol CAE 0044.0.009.000-09). The study enrolled 114 individuals being followed within cohort studies at the INI/Fiocruz-RJ[3]. Participants were either HIV positive (86.8%; 99/114) or negative (13.2%; 15/114). Written informed consent for participation in the study was obtained from all participants in strict compliance with the ethical guidelines involving human subjects in Brazil as required by Resolution No. 466/2012 of the National Health Council.

Anal examination and tissue biopsies

An anal examination through a high-resolution anoscopy was performed by an experienced proctologist, which consisted of a visual inspection of the margin and anal canal using an anoscope. Acetowhite staining was performed to increase the visibility of intraepithelial lesions. Two separate biopsies were obtained for conducting histopathological evaluations and analyses for the presence of HPV. Histopathological findings were categorized as the absence of anal squamous intraepithelial lesions (without dysplasia), atypia, condyloma, AIN I (anal intraepithelial neoplasia I), AIN II/III, and invasive cancer.

Sociodemographic, clinical, and behavioral variables

Sociodemographic, clinical, and behavioral information was extracted from the Audio Computer-Assisted Self-Interview (ACASI) database of the INI/Fiocruz consisting of answers received from each cohort member[3]. The following lifestyle variables were retrieved: smoking status with current exposure to second-hand smoke, illicit drug use, anal sex history, number of sexual partners of the female participants over the last 6 months with distinctions for anal or vaginal sex and number of sexual partners of the male participants over the last 12 months for men. The HPV-associated variables obtained included the history for anal and/or cervical lesions, treatments, and HPV genotyping of anal secretion samples. The variables related to HIV infections recorded were status of HIV serology tests, length of time since a positive HIV diagnosis, $CD4^+$ nadir; $CD4^+$ T lymphocyte levels closest to the anal biopsy date, HIV-1 viral load (detectable at ≥49 copies/IU), use of combination antiretroviral therapy (cART) at the time of performing anal biopsies and the use of two or more analog reverse transcriptase inhibitors and nucleoside reverse transcriptase inhibitor or a non-nucleoside analog and at least one protease inhibitor along with the duration of treatment with highly active antiretroviral therapy (HAART).

Statistical Analysis

Two separate analyses were performed based on HIV status and histopathological diagnosis. The categorical variables that included sex, smoking, illicit drug use, anal sex history, and HPV variables were analyzed by χ^2 test and Fisher's exact test. Continuous variables that included age, number of partners, and HIV variables were analyzed by the non-parametric Kruskal–Wallis test. Statistical analysis was performed with SPSS 15.0 software.

RESULTS

Study population

Age of the patients included in this study ranged from 33.5 to 48.1 years. Average age of the HIV-infected individuals was 42 (±0.9) years and that for the non HIV-infected individuals was 33.6 (±2.5) years. Among the biopsies from HIV-positive patients, 21 presented with normal squamous epithelium, 39 with low-grade neoplasia (AIN I), and 39 samples with high-grade neoplasia (AIN II/III). In the HIV-positive group, the average age of individuals with normal squamous epithelium was 38.5 (±1.8) years; that for low-grade AIN was 41.5 (±1.4) years; and for high-grade AIN, the average was 44.4 (±1.6) years.

In all of the samples collected, high-risk HPV was detected in 78.5% of biopsies while non-high-risk HPV was seen in 44.6% **(Table 1)**. Based on HIV status, more than 80% of the samples from positive individuals showed high-risk HPV compared to 40% for negative patients. Of the individual HPV high-risk genotypes, HPV 16 showed the greatest prevalence with a total of 18 different types identified **(Table 1)**. HIV-1-positive individuals with high-grade AIN had a higher prevalence of high-risk HPV types in the anal secretion specimens compared to individuals without lesions (normal) and low-grade AIN; however there was no statistically significant difference ($p>0.05$).

For non-high-risk HPV, detection was more frequently observed in AIN I or AIN II/III tissue samples than normal tissue (**Table 1**). When examining for infections by multiple HPV genotypes (**Table 2**), it is clear that a large number of samples were positive for two or more HPV genotypes. Surprisingly, we found poor agreement between the two methods analyzed (Papillocheck and PCR), except for the diagnosis of HPV 11, which showed moderate agreement ($k=0.57$; $p=0.000$) and a high specificity for genotypes 31, 43, and 53 (**Table 3**). A graphical representation of the HPV genotype data is shown in **Figure 1**.

DISCUSSION

HPV is the main etiologic agent related to cervical cancer and its association with the development of anal intraepithelial neoplasia is more frequently observed with HIV-1 infections. Over 90% of anal carcinoma in HIV-infected individuals is associated with a persistent HPV infection by at least one HPV genotype with multiple infections being common[4,5].

Some studies have reported age as an important factor in HPV infection[6]. In this study, the average age among HIV-infected individuals was 42 years and 33.6 years for those individuals not infected with HIV, such that this group only provided tissue samples that were diagnosed as being without lesions by histopathology. However, in this study, the average age of participants who were HIV positive and diagnosed with anal lesions showed a slight increase in relation to the lesion severity. The mean age of the subjects with normal samples, AIN I and II/III were 38.5; 41.5, and 44.4 years, respectively, with a statistically significant difference. Our results agree with data reported in our previous study[7].

Table 1 – HPV genotypes found on the anal secretion by Papillocheck according the Histopathology diagnostic (2010–2013).

HPV type	HIV serology Histopathology – n (%)				Total
	HIV-negative	HIV-positive			
	No lesion (n=15)	No lesion (n=21)	AIN I (n=39)	AIN II/III (n=39)	
High risk HPV	6 (40.0)	5 (83.3)	19 (86.4)	21 (95.5)	1 (78.5)
Low risk HPV	3 (20.0)	3 (50.0)	12 (54.5)	11 (50.0)	29 (44.6)
High risk					
HPV 16	-	2 (33.3)	6 (27.3)	11 (50.0)	19 (29.2)
HPV 18	-	1 (16.7)	3 (13.6)	3 (13.6)	7 (10.8)
HPV 31	1 (6.7)	1 (16.7)	2 (9.1)	3 (13.6)	7 (10.8)
HPV 33	-	-	2 (9.1)	3 (13.6)	5 (7.7)
HPV 35	1 (6.7)	-	1 (4.5)	2 (9.1)	4 (6.2)
HPV 39	1 (6.7)	-	2 (9.1)	3 (13.6)	6 (9.2)
HPV 45	-	-	5 (22.7)	3 (13.6)	8 (12.3)
HPV 51	1 (6.7)	3 (50.0)	1 (4.5)	1 (4.5)	6 (9.2)
HPV 52	-	3 (50.0)	7 (31.8)	5 (22.7)	15 (23.1)
HPV 56	1 (6.7)	2 (33.3)	6 (27.3)	3 (13.6)	12 (18.5)
HPV 58	-	-	4 (18.2)	6 (27.3)	10 (15.4)
HPV 59	-	1 (16.7)	4 (18.2)	3 (13.6)	8 (12.3)
HPV 68	-	-	6 (27.3)	3 (13.6)	9 (13.8)
HPV 73	-	-	3 (13.6)	-	3 (4.6)
HPV 82	-	1 (16.7)	1 (4.5)	3 (13.6)	5 (7.7)
Probable hr					
HPV 53	1 (6.7)	3 (50.0)	2 (9.1)	5 (22.7)	11 (16.9)
HPV 66	-	1 (16.7)	5 (22.7)	2 (9.1)	8 (12.3)
Low risk					
HPV 6	-	1 (16.7)	3 (13.6)	6 (27.3)	10 (15.4)
HPV 11	-	-	5 (22.7)	2 (9.1)	7 (10.8)
HPV 40	2 (13.3)	-	1 (4.5)	-	3 (4.6)
HPV 42	-	1 (16.7)	4 (18.2)	5 (22.7)	10 (15.4)
HPV 43	-	-	1 (4.5)	2 (9.1)	3 (4.6)
HPV 44, 55	1 (6.7)	2 (33.3)	4 (18.2)	7 (31.8)	14 (21.5)
HPV 70	-	1 (16.7)	3 (13.6)	2 (9.1)	6 (9.2)

HPV: human papillomavirus; HIV: human immunodeficiency virus; AIN: anal intraepitherlial neoplasia; hr: high risk.

In that study conducted in Brazil, it was found that, in cervical cancer cases, women with HIV/HPV coinfection had an average age of 51.1 years. Another study of HIV-infected women in a Brazilian cohort also analyzed samples of AIN and the association with HPV. In this study, women diagnosed with AIN had an average age of 42 years[8]. In a recent study with the same cohort patients, Nicol and colleagues found that HIV-positive women with <30 years of age had a higher prevalence of HPV 6, 11, 16, and 18 with a tendency for HPV seroprevalence of the genotypes 6, 16 in HIV-negative women above 30 years[8].

Some other known risk factors for the development of HPV-associated lesions have been preestablished, such as an early initiation of sexual activity, multiple sexual partners, history of sexually transmitted diseases, teenage pregnancy, and smoking[6]. When analyzing the number of sexual partners of individuals included in the study, we found that the average number of sexual partners for women was 1 over the last 6 months, and that for men was 14.1 in the last 12 months. Even if the analysis time has been different for men and women, the largest number of sexual partners among men compared to women is remarkable; mainly in the number of male sexual partners reported by men. Given that this corroborates the literature, in which studies have shown that men who have sex with men (MSM) are up to 37 times more likely to progress to anal cancer and are considered risk group[9].

Among patients who reported smoking, approximately 38% had pathological diagnosis of high-grade AIN, and all were infected with HIV. As for the report of receptive anal sex, most patients were infected with HIV and were diagnosed with either low- or high-grade AIN. This feature is consistent with previous studies on AIN where men and women are considered to display risk factors for the development of AIN and anal cancer through their receptive anal sex history, high number of sexual partners, and smoking. For women, these same risk factors apply to cervical cancer[4].

Table 2 – Multiple HPV types in anal secretions by Papillocheck according the Histopathology diagnostic (2010-2013).

HPV types	HIV-negative	HIV-positive			Total n (%)
	Nondysplastic (n=15)	Nondysplastic (n=21)	Low-grade AIN (n=39)	High-grade AIN (n=39)	
Multiple infection					
HPV 16, 52	-	4 (66.7)	11 (50.0)	13 (59.1)	28 (43.1)
HPV 39, 66	1 (6.7)	1 (16.7)	7 (31.8)	4 (18.2)	13 (20.0)
HPV 16, 56	1 (6.7)	3 (50.0)	10 (45.5)	13 (59.1)	27 (41.5)
HPV 16, 56	1 (6.7)	3 (50.0)	10 (45.5)	13 (59.1)	27 (41.5)
HPV 11, 45	-	-	9 (40.9)	5 (22.7)	14 (21.5)
HPV 31, 39	2 (13.3)	1 (16.7)	3 (13.6)	5 (22.7)	11 (16.9)
HPV 16, 45	-	2 (33.3)	9 (40.9)	12 (54.5)	23 (35.4)
HPV 68, 70	-	1 (16.7)	6 (27.3)	5 (22.7)	12 (18.5)
HPV 56, 58	1 (6.7)	2 (33.3)	9 (40.9)	7 (31.8)	19 (29.2)
HPV 56, 66	1 (6.7)	2 (33.3)	8 (36.4)	4 (18.2)	15 (23.1)
HPV 16, 53, 58	1 (6.7)	4 (66.7)	9 (40.9)	16 (72.7)	30 (46.2)
HPV 18, 52, 59	-	3 (50.0)	8 (36.4)	6 (27.3)	17 (26.2)
HPV 16, 33, 68	-	2 (33.3)	12 (54.5)	13 (59.1)	27 (41.5)
HPV 16, 44, 55, 52	1 (6.7)	4 (66.7)	12 (54.5)	15 (68.2)	32 (49.2)
HPV 16, 43, 44, 55, 58	1 (6.7)	3 (50.0)	10 (45.5)	15 (68.2)	29 (44.6)
HPV 56, 58, 66, 68	1 (6.7)	2 (33.3)	12 (54.5)	11 (50.0)	26 (40.0)
HPV 44, 55, 51, 52, 59	2 (13.3)	5 (83.3)	10 (45.5)	9 (40.9)	26 (40.0)
HPV 11, 33, 56, 82	1 (6.7)	3 (50.0)	9 (40.9)	10 (45.5)	23 (35.4)
HPV 51, 53, 56, 66	3 (20.0)	4 (66.7)	10 (45.5)	8 (36.4)	25 (38.5)
HPV 16, 44, 55, 52, 53, 58	2 (13.3)	5 (83.3)	14 (63.6)	16 (72.7)	37 (56.9)
HPV 16, 18, 42, 45, 59	-	4 (66.7)	11 (50.0)	15 (68.2)	30 (46.2)
HPV 11, 31, 33, 43, 66	1 (6.7)	2 (33.3)	9 (40.9)	10 (45.5)	22 (33.8)
HPV 16, 18, 52, 58, 59	-	4 (66.7)	12 (54.5)	16 (72.7)	32 (49.2)
HPV 39, 42, 44, 55, 45, 51	3 (20.0)	4 (66.7)	9 (40.9)	12 (54.5)	28 (43.1)
HPV 6, 16, 31, 42, 45	1 (6.7)	3 (50.0)	12 (54.5)	17 (77.3)	33 (50.8)
HPV 33, 39, 42, 44, 55, 45, 58	2 (13.3)	3 (50.0)	12 (54.5)	16 (72.7)	33 (50.8)
HPV 16, 18, 44, 55, 51, 53, 68	3 (20.0)	5 (83.3)	12 (54.5)	15 (68.2)	35 (53.8)
HPV 42, 44, 55, 53, 56, 58, 66	3 (20.0)	4 (66.7)	12 (54.5)	15 (68.2)	34 (52.3)
HPV 6, 42, 45, 52, 58, 66	-	4 (66.7)	16 (72.7)	14 (63.6)	34 (52.3)
HPV 11, 31, 39, 52, 59, 68	2 (13.3)	4 (66.7)	16 (72.7)	12 (54.5)	34 (52.3)
HPV 6, 16, 53, 56, 58, 68	2 (13.3)	4 (66.7)	14 (63.6)	17 (77.3)	37 (56.9)
HPV 16, 31, 44, 55, 51, 53, 56	5 (33.3)	5 (83.3)	13 (59.1)	17 (77.3)	40 (61.5)
HPV 11, 40, 53, 56, 68, 70, 73	4 (26.7)	3 (50.0)	12 (54.5)	9 (40.9)	28 (43.1)
HPV 6, 18, 42, 52, 53, 70, 82	1 (6.7)	5 (83.3)	14 (63.6)	14 (63.6)	34 (52.3)
HPV 16, 42, 44, 55, 56, 66, 68, 70, 73	2 (13.3)	5 (83.3)	15 (68.2)	17 (77.3)	39 (60.0)
HPV 6, 11, 35, 44, 55, 52, 53, 59, 68	3 (20.0)	5 (83.3)	17 (77.3)	15 (68.2)	40 (61.5)
HPV 6, 11, 16, 33, 43, 44, 55, 52, 59, 70	1 (6.7)	4 (66.7)	18 (81.8)	16 (72.7)	39 (60.0)
HPV 6, 16, 18, 35, 44, 55, 52, 58, 59, 68, 73	1 (6.7)	4 (66.7)	16 (72.7)	17 (77.3)	(58.5)

Fisher's exact test, p<0,005; HPV: human papillomavirus; HIV: human immunodeficiency virus; AIN: anal intraepitherlial neoplasia.

Table 3 – Sensitivity and specificity of HPV genotypes found in the biopsies of anal secretion (Papillocheck) (2010–2013).

HPV genotypes	Kappa				
	Sensitivity	Specificity	Coefficient	n	p-value
HPV 6	20.0	92.0	0.14	60	0.248
HPV 11	57.1	96.2	0.57	60	0.000
HPV 16	55.6	73.8	0.28	60	0.029
HPV 18	16.7	96.3	0.17	60	0.167
HPV 31	28.6	100.0	0.41	60	0.000
HPV 33	-	-	-	-	-
HPV 35	25.0	98.2	0.30	60	0.012
HPV 39	0.0	98.2	-0.03	60	0.761
HPV 40	-	-	-	-	-
HPV 42	0.0	98.0	-0.03	60	0.652
HPV 43	33.3	100.0	0.49	60	0.000
HPV 51	-	-	-	-	-
HPV 52	7.1	97.8	0.07	60	0.364
HPV 53	9.1	100.0	0.14	60	0.033
HPV 56	-	-	-	-	-
HPV 58	33.3	98.0	0.41	60	0.001
HPV 59	57.1	84.9	0.32	60	0.009
HPV 66	12.5	96.2	0.12	60	0.296

HPV: human papillomavirus.

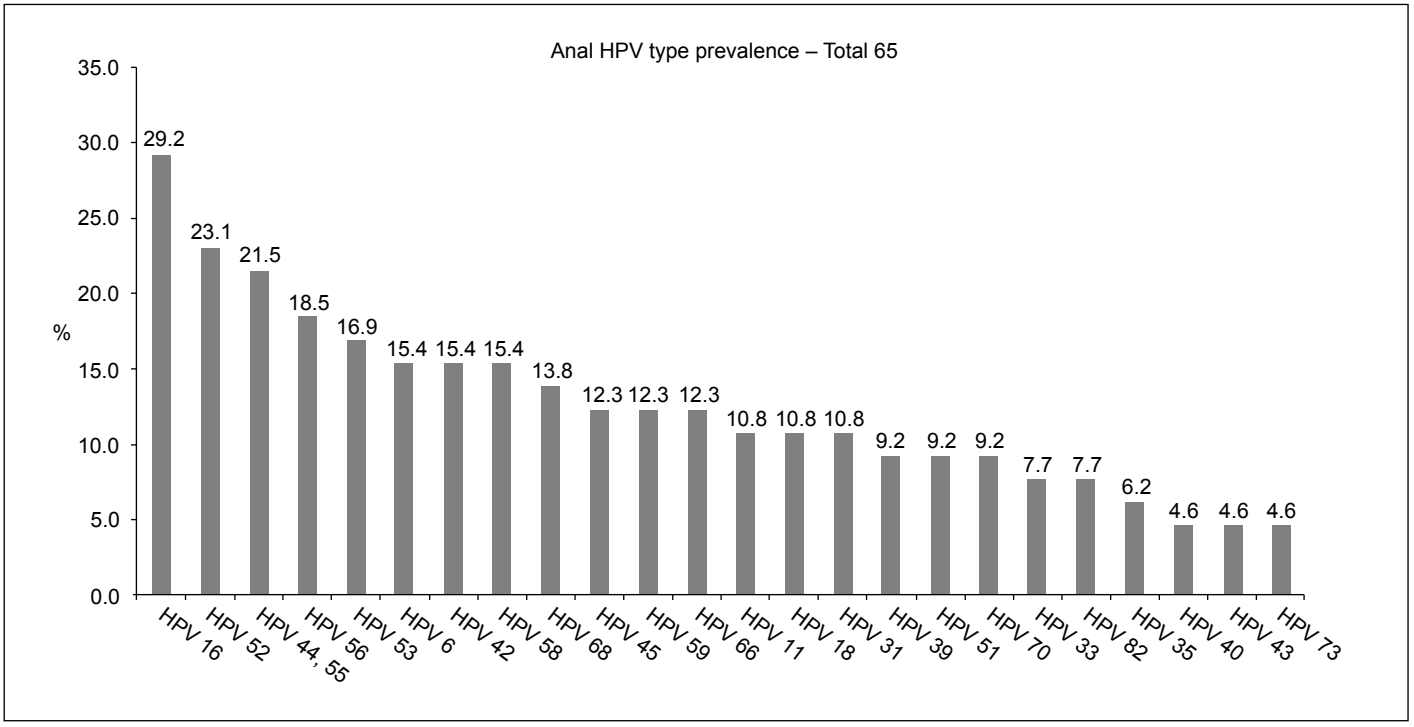

Figure 1 – HPV prevalence found in the anal secretion.

Data from this study showed a high prevalence (94.4%) of patients with $CD4^+$ nadir <50 cells/mm³ who were diagnosed with high-grade AIN. However, the results disagree with one particular study that found that 14.8% of individuals with a high-grade AIN had CD4 nadir below 50 cells/mm³ in a cohort in Brazil of HIV-infected women[10]. In another study, where multivariate analysis was performed, it was observed that a low $CD4^+$ count (≤200 cells/mm³) does not show a strong predictor of high-risk HPV infection[2].

Currently, the increased life span of HIV-infected individuals may be explained due to the impact of treatment with cART. In this study, 81.8% of HIV-1-infected patients were under cART treatment and 42.9% had detectable viral load. No correlation was found between peripheral levels of $CD4^+$ and the use of HAART. In our previous study with cervical samples, this type of correlation was also not observed[11].

HIV/HPV coinfections lead to important biological changes that entail the development of progression of AIN to anal cancer. While most studies that address the immune response against HPV/HIV are directed to cervical cancer, it has been shown that the infection by only HPV displayed no activation of the immune response mediated by Th1 lymphocytes, whereas in the coinfection a profile shift to Th2 occurs[12].

Among the HPV genotypes detected in anal secretion of HIV-infected individuals, HPV 51 showed statistical differences in the samples without lesion. Studies show that infection with high-risk HPV is common in anal samples of HIV-infected individuals, and usually HPV 51 appears moderately associated with anal lesions. In this study, a weak association was found between the HPV types detected in the anal secretion and biopsies, which indicates that HPV detected in secretion is not necessarily of the same type of those underlying the intraepithelial lesion[13].

Of the population analyzed, more than 45% of HIV-negative and 57% of HIV-positive subjects had already been exposed to the four HPV types covered by the current quadrivalent HPV vaccine, suggesting that HPV vaccination should be considered as a prophylactic approach to reduce the risk of anal intraepithelial lesion development on this population. Further studies should be done in a larger population of individuals. The present study has as limitation the nonavailability of some analyzed variables for all patients. However, the data suggest some important clinical approaches.

CONCLUSION

This study showed that there was a strong association in HIV-1-infected individuals between the development of anal intraepithelial lesions to stage AIN II/III with the increasing age and peripheral blood $CD4^+$ nadir <50 cells/mm³. In addition, most HIV-infected individuals analyzed have already been exposed to the four HPV types targeted by the current quadrivalent vaccine (MSD—HPV types 6, 11, 16, and 18) suggesting that vaccination against HPV could be regarded as a prophylactic measure to reduce the risk of anal intraepithelial lesions in HIV-infected individuals.

Conflict of interests

The authors reported no conflict of interests.

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Address for correspondence:
ALCINA F. NICOL
Av. Brasil, 4365 – Manguinhos
Rio de Janeiro (RJ), Brazil
CEP: 21045-900
Phone: +55 (21) 2562-1037
E-mail: nicol@ioc.fiocruz.br; afnnicol@gmail.com

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