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Time Trend Analysis of Cervical High-Risk HPV in HIV-Infected Women in an Urban Cohort from Rio de Janeiro, Brazil: The Rise of Non-16/18 HPV

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Abstract

Objectives—HIV-infected women are at increased risk of HPV infection. We assessed time trends in annual prevalences of cervical high-risk human papillomavirus (HR-HPV) genotypes from 2006-2012 among a non-vaccinated, HIV-infected female cohort in urban Brazil.

Study Design—Cervical specimens for HPV genotyping were collected yearly between January 2006 and December 2012 in a cross-sectional analysis of participants ≥18 years enrolled in the Women's HIV Cohort at Fiocruz in Rio de Janeiro, Brazil. Age-adjusted generalized estimating equation models with an exchangeable matrix were used to estimate odds ratios (OR) and 95% confidence intervals (CI) for annual HPV positivity (reference year: 2006).

Results—Among 590 participants: median age 35.5-40.0 from 2006-2012; any HR-HPV prevalence ≥53% every year; HR-HPV 16, 58, 59, and 68 prevalences ≥24% in at least one year. Odds of HPV 16 and 68 decreased in 2012. HPV 58 prevalences followed a U-shape, beginning

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Ethical Approval

The IPEC Women's HIV Cervical HPV Genotyping Study was approved by the Institutional Review Board of IPEC at Fiocruz, Rio de Janeiro, Brazil. Written informed consent was obtained from all participants prior to enrollment and initiation of study procedures.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

and ending with >20%. HPV 59 prevalences followed a linear trend, with increased odds in 2012 (OR 16.0, 95% CI [3.8 – 67.3], Bonferroni-adjusted p-value<0.01).

Conclusions—The prevalences of HR-HPV 58, 59 and 68 were high in this cohort. Given current HR-HPV vaccine coverage and availability, further investigation is needed to optimize vaccine recommendations for this population.

Keywords

HIV; Women; Cervical HPV; High-Risk HPV; HPV Vaccine; Epidemiology

Background and Objectives

HIV-infected (HIV+) women are at increased risk of HPV-associated invasive cervical carcinoma (ICC)(1), an AIDS-defining illness and vaccine-preventable disease. Despite routine screening in Brazil, the Instituto Nacional de Câncer estimated 15,590 new ICC cases in 2014, with a 33% fatality rate. High-risk Human Papillomavirus (HR-HPV) genotypes 16 and 18 are associated with 70% of ICC cases worldwide, while the other thirteen HR-HPV genotypes account for the remaining cases(2).

The HPV vaccine was proposed as a method to effectively reduce ICC prevalence on a population level. Three FDA-approved HR-HPV vaccines are currently available: the bivalent, quadrivalent and nine-valent vaccines. The bivalent and quadrivalent vaccines protect against only HPV 16 and 18 of the HR-HPV genotypes, although the impact of these vaccines on non-16/18 HR-HPV genotypes remains unclear(3-5). Non-16/18 HR-HPV genotypes are detected at higher rates in HIV+ women(2), and we are uncertain if a single sample traditionally used in cross-sectional studies accurately captures HPV infection patterns in this population. We performed a time trend analysis of annual cervical HR-HPV genotype prevalences from 2006 to 2012 among a non-vaccinated, HIV+ female cohort in urban Brazil to establish a pre-vaccine baseline.

Study Design

Data Collection

We conducted an annual, cross-sectional analysis of participants in the Evandro Chagas Clinical Research Institute (IPEC) Women's HIV Cervical HPV Genotyping Study at Fiocruz (Rio de Janeiro, Brazil). Cohort procedures have previously been published(6). Participants in the IPEC Women's HIV Cohort (est. 1996) ≥18 years of age were invited to participate in the IPEC Women's HIV Cervical HPV Genotyping Study. On-site gynecologists collected specimens for cytology and HPV genotyping yearly. Cervical HPV genotyping and cytology analysis procedures have previously been published(7). The IPEC Women's HIV Cervical HPV Genotyping Study was approved by the Institutional Review Board of IPEC at Fiocruz, Rio de Janeiro, Brazil. Written informed consent was obtained from all participants prior to enrollment and initiation of study procedures.

Statistical Analysis

Descriptive analysis of the following was performed yearly (2006-2012), using clinical data and cervical specimens closest to the July 1 marker of the mid-year: current age, CD4+ T cell count, HIV-1 viral load, cervical cytology, cervical treatments, and prevalences of the 15 HR-HPV genotypes. The clinical data for each year reflects that of the participants who contributed an HPV sample in that given year. Women who underwent hysterectomies were excluded from analysis in the years post-procedure.

Odds ratios (OR) and 95% confidence intervals (CI) for HPV positivity were estimated for each genotype using generalized estimating equation models with an exchangeable matrix to account for patient clustering. The year was the independent predictor, with 2006 as the reference category. The final model was adjusted for age as a continuous variable, given the inverse association between age and HPV positivity(8). Bonferroni-adjusted p-values were calculated to account for multiple comparisons. Statistical analysis was performed using R version 3.01, with statistical significance defined using a two-sided $\alpha<0.05$

Results

Five hundred ninety-one women met inclusion criteria, with one excluded for prior hysterectomy (final N=590). Table 1 describes the characteristics and annual HR-HPV genotype prevalences by year (2006-2012). Table 2 provides ORs for HR-HPV positivity in those years. The prevalences of HR-HPV 16, 58, 59 and 68 were ≥24% in at least one year, while the prevalence of HPV 18 never surpassed 13%. The odds of HPV 16 and 68 significantly decreased in 2012 compared to 2006, starting with prevalences of 25% and 24% for HPV 16 and 68, respectively, and ending with 12% and 10%. While the odds of HPV 58 decreased from 25% in 2006 to 12% in 2008, it rebounded to 21% by 2012. The odds of HPV 59 increased sixteen-fold between 2006 and 2012, with prevalence increasing from 2% to 24%.

Conclusions

In this cohort of 590 HIV+ women, the high prevalences of HPV 58 and 59 are concerning, given HPV 58 is associated with pre-malignant cervical lesions among HIV-uninfected women in Brazil(9, 10) and both genotypes are commonly identified in HIV+ women worldwide(2). Additionally, neither the bivalent nor the quadrivalent vaccine cover HPV 58 and 59, leading to questions regarding their efficacy against non-16/18 genotypes(4, 5).

Our study has both strengths and limitations. While it is unclear which factors influenced fluctuating HPV prevalences, current clinical and cervical data remained relatively unchanged. We analyzed HPV prevalences over a seven-year period, compared to most studies utilizing a single time point. Additionally, our study is one of the largest HPV/HIV co-infection studies in the Americas. However, the individual sample sizes for each HPV genotype are relatively small, and additional studies with larger sample sizes and longer follower-up are needed to further explore temporal trends of HR-HPV prevalences.

Continued monitoring of HR-HPV epidemiology and further investigation into the effects of HPV vaccination on non-16/18 HR-HPV genotypes is needed to optimize HPV vaccine recommendations for HIV+ women in Brazil.

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Table 1

Annual Characteristics of Participants in the IPEC Women's HIV Cervical HPV Genotyping Study at Time of Cervical Specimen Collection (2006-2012)

		2006	2007	2008	2009	2010	2011	2012
	N = 590	**102**	**167**	**240**	**282**	**256**	**260**	**225**
	First Appointment [a]	**75 (74%)**	**55 (33%)**	**69 (29%)**	**105 (37%)**	**71 (28%)**	**59 (23%)**	**66 (29%)**
Age								
	Median (IQR)	35.5 (29.3 - 42.0)	36.0 (30.0 - 43.0)	37.0 (30.8 - 44.3)	36.5 (31.0 - 45.8)	38.0 (31.0 - 46.0)	38.0 (31.0 - 46.0)	40.0 (32.0 - 47.0)
	<30	26 (25%)	40 (24%)	53 (22%)	60 (21%)	51 (20%)	56 (22%)	39 (17%)
	30 - 39	41 (40%)	61 (37%)	88 (37%)	110 (39%)	86 (34%)	84 (32%)	71 (32%)
	40 - 49	28 (27%)	51 (31%)	72 (30%)	74 (26%)	80 (31%)	77 (30%)	74 (33%)
	≥50	7 (7%)	15 (9%)	27 (11%)	38 (13%)	39 (15%)	42 (16%)	41 (18%)
	Unknown	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (<1%)	0 (0%)
Current CD4 Count (cells/mm^3)								
	>350	55 (54%)	96 (57%)	156 (65%)	201 (71%)	178 (70%)	193 (74%)	172 (77%)
	≤350	31 (30%)	58 (35%)	71 (30%)	59 (21%)	56 (22%)	46 (18%)	40 (18%)
	Unknown	16 (16%)	13 (8%)	13 (5%)	22 (8%)	22 (8%)	21 (8%)	13 (5%)
Current HIV Viral Load (copies/mL) [b]								
	Detectable	45 (44%)	79 (47%)	98 (41%)	106 (38%)	79 (31%)	103 (40%)	83 (37%)
	Undetectable	35 (34%)	60 (36%)	121 (50%)	136 (48%)	146 (57%)	129 (50%)	125 (56%)
	Unknown	22 (22%)	28 (17%)	21 (9%)	40 (14%)	31 (12%)	28 (10%)	17 (7%)
Cervical Cytology								
	Negative	77 (75%)	130 (78%)	190 (79%)	200 (71%)	193 (75%)	187 (72%)	179 (80%)
	ASC-US	10 (10%)	12 (7%)	26 (11%)	29 (10%)	24 (9%)	28 (10%)	21 (9%)
	AGC	0 (0%)	1 (<1%)	0 (0%)	0 (0%)	1 (<1%)	2 (1%)	0 (0%)
	ASC-H	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	LSIL	15 (15%)	18 (11%)	21 (9%)	42 (15%)	34 (13%)	33 (13%)	23 (10%)
	HSIL	0 (0%)	4 (2%)	2 (<1%)	8 (3%)	2 (1%)	7 (3%)	1 (<1%)

		2006	2007	2008	2009	2010	2011	2012
	N = 590	**102**	**167**	**240**	**282**	**256**	**260**	**225**
	First Appointment [a]	**75 (74%)**	**55 (33%)**	**69 (29%)**	**105 (37%)**	**71 (28%)**	**59 (23%)**	**66 (29%)**
	Cervical Cancer	0 (0%)	0 (0%)	1 (<1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Unknown	0 (0%)	2 (1%)	0 (0%)	3 (1%)	2 (1%)	3 (1%)	1 (<1%)
Cervical Treatment								
	Hysterectomy	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (<1%)
	Cone	1 (1%)	1 (<1%)	2 (<1%)	3 (1%)	3 (1%)	4 (2%)	3 (1%)
	Cauterization	0 (0%)	0 (0%)	0 (0%)	4 (1%)	6 (2%)	5 (2%)	4 (2%)
	LEEP	4 (4%)	4 (2%)	5 (2%)	2 (<1%)	1 (<1%)	2 (1%)	0 (0%)
Any HPV								
	≥One HPV	72 (71%)	88 (53%)	135 (56%)	170 (60%)	180 (70%)	187 (72%)	159 (71%)
	No HPV	30 (29%)	79 (47%)	105 (44%)	112 (40%)	76 (30%)	73 (28%)	66 (29%)
HR-HPV Genotype Prevalence (%)								
	16	25	13	10	12	12	15	12
	18	12	13	7	6	11	7	8
	31	11	7	3	7	8	9	12
	33	1	7	5	5	6	4	3
	35	6	7	9	9	11	13	13
	39	10	3	4	6	7	7	12
	45	4	6	5	7	5	4	10
	51	7	5	5	8	13	15	7
	52	6	7	9	6	6	8	6
	56	10	7	4	5	5	5	11
	58	25	13	12	19	20	26	21
	59	2	7	8	7	11	19	24
	68	24	8	5	5	8	9	10
	73	0	4	5	4	5	3	7

	2006	2007	2008	2009	2010	2011	2012
N = 590	**102**	**167**	**240**	**282**	**256**	**260**	**225**
First Appointment [a]	**75 (74%)**	**55 (33%)**	**69 (29%)**	**105 (37%)**	**71 (28%)**	**59 (23%)**	**66 (29%)**
82	1	2	2	1	3	2	5

[a] 90 of the 590 women had their first appointment in 2005

[b] Detectable defined as ≥400 copies/mL from 2006 - 2010, and ≥50 copies/mL from 2011 - 2012, based on assays used

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Table 2

Odds Ratios for HR-HPV Positivity (2006-2012)[a]

Year	2006	2007		2008		2009		2010		2011		2012	
	Baseline	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
HPV 16	1	0.4 (0.2 - 0.8)	0.05	0.3 (0.2 - 0.6)	<0.01	0.4 (0.2 - 0.8)	<0.05	0.4 (0.2 - 0.8)	<0.05	0.5 (0.3 - 0.9)	0.18	0.4 (0.2 - 0.8)	<0.05
HPV 18	1	1.2 (0.5 - 2.5)	1.00	0.6 (0.3 - 1.2)	0.87	0.5 (0.2 - 1.1)	0.51	1.0 (0.5 - 2.0)	1.00	0.6 (0.3 - 1.4)	1.00	0.7 (0.3 - 1.6)	1.00
HPV 58	1	0.5 (0.3 - 0.9)	0.12	0.4 (0.2 - 0.8)	<0.05	0.7 (0.4 - 1.3)	1.00	0.8 (0.5 - 1.4)	1.00	1.1 (0.7 - 1.9)	1.00	0.9 (0.5 - 1.5)	1.00
HPV 59	1	3.6 (0.8 - 16.4)	0.63	4.6 (1.1 - 20.1)	0.25	4.1 (0.9 - 17.8)	0.36	6.3 (1.5 - 27.0)	0.08	12.0 (2.9 - 50.3)	<0.01	16.0 (3.8 - 67.3)	<0.01
HPV 68	1	0.3 (0.1 - 0.6)	<0.01	0.2 (0.1 - 0.3)	<0.01	0.2 (0.1 - 0.4)	<0.01	0.3 (0.2 - 0.5)	<0.01	0.3 (0.2 - 0.6)	<0.01	0.4 (0.2 - 0.7)	<0.01

[a]Odds Ratios were calculated for all 15 HR-HPV genotypes. HPV 16 and 18 are presented given their associations with cervical cancer. HPV 58, 59 and 68 are presented given the prevalence of each genotype >20% in at least one year