Short Communication

Time trend analysis of cervical high-risk human papillomavirus (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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SUMMARY

Objectives: HIV-infected women are at increased risk of human papillomavirus (HPV) infection. Time trends in annual prevalences of cervical high-risk human papillomavirus (HR-HPV) genotypes among a non-vaccinated, HIV-infected female cohort in urban Brazil were assessed for the period 2006–2012.
Methods: Cervical specimens were collected for HPV genotyping yearly between January 2006 and December 2012 in a cross-sectional analysis of participants aged ≥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 the 590 participants, the median age across all study years ranged from 35.5 to 40.0 years. The prevalence of any HR-HPV was ≥53% every year; prevalences of HR-HPV 16, 58, 59, and 68 were ≥24% in at least 1 year. The odds of HPV 16 and 68 decreased in 2012. HPV 58 prevalence followed a U-shape, beginning and ending at >20%. HPV 59 prevalence 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 investigations are needed to optimize vaccine recommendations for this population.

1. Introduction

HIV-infected women are at increased risk of human papillomavirus (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 HPV (HR-HPV) genotypes 16 and 18 are associated with 70% of ICC cases worldwide, while the other 13 HR-HPV genotypes account for the remaining cases.[2]

The HPV vaccine was proposed as a method to effectively reduce ICC prevalence at the population level. Three US Food and Drug Administration (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, and 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-infected women,[2] and it is uncertain whether a single sample traditionally used in cross-sectional studies accurately

captures HPV infection patterns in this population. A time trend analysis of annual cervical HR-HPV genotype prevalences from 2006 to 2012 among a non-vaccinated, HIV-positive female cohort in urban Brazil was performed to establish a pre-vaccine baseline.

2. Methods

2.1. Data collection

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) was conducted. Cohort procedures have been published previously.[6] Participants in the IPEC Women's HIV Cohort (est. 1996) aged ≥18 years 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 been published previously.[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.

2.2. Statistical analysis

A 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

Table 1
Annual characteristics of participants in the IPEC Women's HIV Cervical HPV Genotyping Study at the 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, years							
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/mm³							
>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%)
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							
≥1 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
82	1	2	2	1	3	2	5

IPEC, Evandro Chagas Clinical Research Institute; HPV, human papillomavirus; IQR, interquartile range; ASC-US, Atypical squamous cells of undetermined significance; AGC, Atypical glandular cells; ASC-H, Atypical squamous cells; LSIL, Low-grade squamous intraepithelial lesion; HSIL, High-grade squamous intraepithelial lesion; LEEP, loop electrosurgical excision procedure; HR, high-risk.

[a] Ninety of the 590 women had their first appointment in 2005.
[b] Detectable defined as ≥400 copies/ml for 2006–2010, and ≥50 copies/ml for 2011–2012, based on assays used.

Table 2
Odds ratios for HR-HPV positivity (2006–2012)[a]

Year	2006	2007		2008		2009		2010		2011		2012	
	Baseline	OR (95% CI)	p-Value[b]	OR (95% CI)	p-Value	OR (95% CI)	p-Value	OR (95% CI)	p-Value	OR (95% CI)	p-Value	OR (95% CI)	p-Value
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

HR-HPV, high-risk human papillomavirus; OR, odds ratio; CI, confidence interval.

[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 1 year.

[b] Bonferroni-adjusted p-values were calculated to account for multiple comparisons.

each year reflect those of the participants who contributed an HPV sample in that given year. Women who underwent hysterectomies were excluded from the 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. The statistical analysis was performed using R version 3.01, with statistical significance defined using a two-sided $\alpha < 0.05$.

3. Results

Five hundred ninety-one women met the 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 1 year, while the prevalence of HPV 18 never surpassed 13%. The odds of HPV 16 and 68 decreased significantly 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 16-fold between 2006 and 2012, with prevalence increasing from 2% to 24%.

4. Discussion

In this cohort of 590 HIV-positive women, the high prevalences of HPV 58 and 59 are concerning, given that 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-positive 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]

This study has both strengths and limitations. While it is unclear which factors influenced the fluctuating HPV prevalences, current clinical and cervical data remained relatively unchanged. HPV prevalences were analyzed over a 7-year period, compared to most studies utilizing a single time point. Additionally, the present 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 follow-up are needed to further explore temporal trends in HR-HPV prevalences.

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

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