High-risk HPV Clustering and Cervical Outcomes in HIV-Infected Women in Rio de Janeiro, Brazil

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Introduction

- Despite the availability of screening, morbidity and mortality from cervical cancer remain high in Latin America[1].
- Prevalence of high risk HPV among HIV-infected women in Latin America is higher than in HIV-infected women in Europe and North America[2].
- HPV vaccines are effective and immunogenic in HIV-infected women but are not yet widely available in Latin America, including Brazil[1,3,4].
- As new HPV vaccines are developed, knowledge of high risk HPV epidemiology, including in HIV-infected women, is of critical importance.

Methods

- We performed a study of 562 HIV-infected women in Rio de Janeiro, Brazil, who underwent cervical cytology and HPV genotyping between 2005-2013.
- Patient characteristics at the time of the exam were compared by HPV genotypes.
- We examined prevalence of high risk HPV types by cytology outcomes and patterns of high risk HPV clustering in women with abnormal (ASC-US and higher) cytology.
- Logarithmic binomial regression models calculated prevalence ratios for abnormal cytology by individual high risk HPV types, adjusting for presence of multiple high risk types, age, and CD4 lymphocyte count. After correcting for multiple comparisons, $p < 0.004$ was measured as statistically significant in these models.

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Results

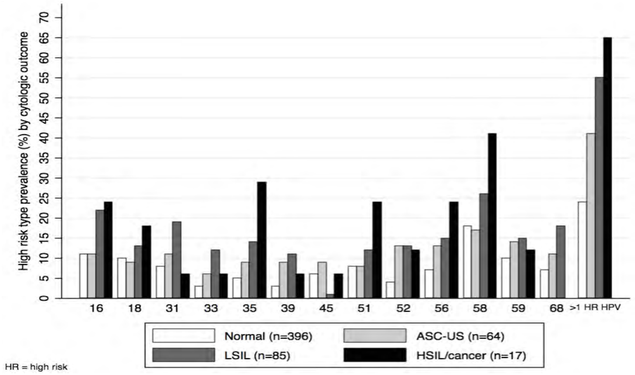
Table 1: Demographic, social, and clinical characteristics of women by HPV genotype result (N=562)

	No HPV	Only low risk HPV types	One high risk HPV type	>1 high risk HPV type
N (%)	64 (11)	134 (24)	183 (33)	181 (32)
Age in years, median (IQR)	37 (30-41)	39 (31-46)	36 (30-44)	33[b] (27-41)
Non-white race (%)	50 (79)	99 (74)	129 (71)	124 (69)
Condom with last sex (%)	37 (58)	86 (66)	117 (65)	118 (66)
HIV-infected sexual partner (%)	9 (14)	38 (28)[a]	28 (15)	50 (28)[a,b]
CD4 lymphocyte count, median (IQR)	528 (326-827)	512 (309-679)	433 (309-631)	398[a,b] (251-549)
Undetectable HIV RNA (%)	27 (42)	63 (47)	74 (40)	62 (34)
HPV 16 or 18 detected (%)	-	-	42 (23)	82 (45)[b]
Abnormal cervical cytology (%)	7 (11)	22 (16)	53 (24)[a]	84 (46)[a,b]

[a] Comparison with No HPV group $p<0.05$
[b] Comparison with one high risk HPV group $p<0.05$

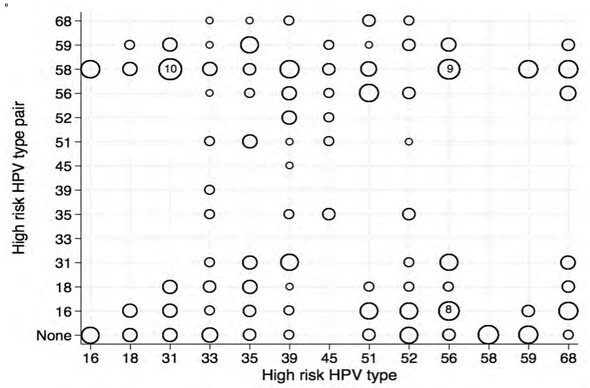
- Overall, HPV 58 was the most prevalent HPV type detected (prevalence = 19.8%, 95% CI 16.4-23.1).
- HPV 16 was the second most frequent high risk HPV type observed (prevalence = 13%, 95% CI 10.2-15.8).

Figure 1: Prevalence of high risk HPV types and presence of more than one high risk HPV types by cervical cytology



HR = high risk

Figure 2: Relative frequencies of high risk HPV pairings in women with abnormal cytology (N=166)



Circle size reflects relative frequency of occurrence such that smaller circles reflect less frequent observations. The most frequently observed pairings are labeled (HPV 31 and HPV 58, n=10 occurrences; HPV 56 and HPV 58, n=9 occurrences; HPV 56 and HPV 16, n=8 occurrences). Pair = None refers to HPV type frequency without another high risk HPV type.

Table 2: Univariate and multivariate prevalence ratios for abnormal cytology of high risk HPV types

HR HPV type	Univariate PR		Multivariate PR[a,b]		
	HR type PR [95% CI]	*P* value	HR type aPR [95% CI]	*P* value	More than one HR HPV aPR [95% CI]	*P* value
16	1.48 [1.08-2.01]	0.013	1.14 [0.83-1.54]	0.418	1.94 [1.50-2.52]	<0.001[c]
18	1.19 [0.81-1.74]	0.369	0.83 [0.57-1.20]	0.321	2.04 [1.57-2.66]	<0.001[c]
31	1.53 [1.09-2.13]	0.013	0.97 [0.70-1.37]	0.882	1.98 [1.51-2.59]	<0.001[c]
33	2.13 [1.51-3.02]	<0.001	1.47 [1.10-1.97]	0.009	1.89 [1.45-2.46]	<0.001[c]
35	1.89 [1.38-2.59]	<0.001	1.20 [0.88-1.64]	0.246	1.88 [1.43-2.48]	<0.001[c]
39	2.03 [1.43-2.88]	<0.001	1.09 [0.74-1.61]	0.665	1.95 [1.49-2.53]	<0.001[c]
45	0.80 [0.44-1.50]	0.507	0.58 [0.32-1.06]	0.079	2.07 [1.60-2.68]	<0.001[c]
51	1.35 [0.93-1.97]	0.116	1.00 [0.70-1.43]	0.993	1.97 [1.52-2.56]	<0.001[c]
52	2.05 [1.50-2.81]	<0.001	1.35 [1.00-1.84]	0.051	1.89 [1.45-2.46]	<0.001[c]
56	1.74 [1.27-2.38]	0.001	1.06 [0.76-1.47]	0.726	1.94 [1.48-2.55]	<0.001[c]
58	1.29 [0.97-1.72]	0.084	0.90 [0.68-1.21]	0.488	2.04 [1.56-2.68]	<0.001[c]
59	1.34 [0.95-1.89]	0.097	1.00 [0.72-1.38]	0.976	1.97 [1.51-2.57]	<0.001[c]
68	1.53 [1.09-2.16]	0.015	1.04 [0.74-1.46]	0.834	1.96 [1.50-2.56]	<0.001[c]

[a] Due to missing CD4+ lymphocyte values in 37 women, 525 women were included in multivariate models.
[b] All multivariate models included individual high-risk HPV type, age, CD4+ lymphocyte count at HPV test, and presence of more than one high risk HPV types. CD4 lymphocyte count and presence >1 high-risk HPV types remained statistically significant. Age was not statistically significant in multivariate models.
[c] *p* value significant at Bonferroni threshold (0.004) for correction of multiple comparisons

Conclusions

- In this large cohort study of HIV-infected women in Brazil, infection by high risk HPV and infection by multiple high risk HPV types was common.
- HPV 58 was the most frequent HPV type detected and has been observed at high prevalence rates in studies of HIV-infected women in other parts of Brazil and in Africa[5,6].
- Women infected with >1 high risk HPV type were younger, had lower CD4 lymphocyte counts, and were more likely to report a known HIV-infected sexual partner.
- The clustering patterns of high risk HPV types in women were varied and appeared random.
- After adjusting for age, CD4 lymphocyte count, and presence of >1 high risk type, no individual high risk HPV type was statistically associated with abnormal cytology. However, the presence of multiple high risk HPV remained associated with abnormal cervical cytology in every model.
- As future HPV vaccine effectiveness may be compromised by infection by multiple high risk types, further development of multivalent vaccines is needed.
- Additional study of the longitudinal clinical outcomes of women infected by multiple high risk HPV types is also needed.

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