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Diverse and High Prevalence of Human Papillomavirus Associated with a Significant High Rate of Cervical Dysplasia in Human Immunodeficiency Virus–Infected Women in Johannesburg, South Africa

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Abstract

Objective—To evaluate the epidemiology of the human papillomavirus (HPV) type and correlate it with the Papanicolaou smears in human immunodeficiency virus–seropositive women in Johannesburg, South Africa.

Study Design—In a cohort of 148 women, HPV DNA testing was performed with the Roche HPV genotyping test (Branchburg, New Jersey, U.S.A.). Papanicolaou smears were performed by standard cytology utilizing 2001 Bethesda reporting guidelines.

Results—The average age and CD4 count of the participants was 35 years and 255 cells per mm^3, respectively. Fifty-four percent had abnormal Papanicolaou smears; 66% of the abnormal cytology was low grade changes, with 33% assessed as having high grade changes. HPV DNA was found in 95% of the 148 subjects assessed, with 83% having 1 or more HPV oncogenic types. Common oncogenic types were 16, 35, 53 and 18. When HPV results were stratified by CD4, there was a significant risk of an oncogenic HPV type in women with CD4 <200. Significant odds ratios for high grade lesions were seen in HPV types 16, 35, 51, 66, 69 and 73.

Conclusion—The results of HPV typing illustrate the diverse range of oncogenic HPV and high prevalence of oncogenic type. These results highlight the need for improved access to Papanicolaou smear screening for this population.

Keywords

cervical dysplasia; HIV; human papillomavirus type 16; uterine cervical diseases

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The human papillomavirus (HPV) is the etiologic agent for cervical cancer and precursor lesions.[1] In human immunodeficiency virus (HIV)–negative women, the majority of HPV viral infections are cleared within 8–10 months. However, some infections do evade the immune system through a complicated cascade of events and become persistent. Persistent HPV infection is the first step towards cervical dysplasia and cancer. The E6 and E7 proteins of oncogenic HPV types are known to facilitate the degradation of tumor suppression proteins.[2] Factors that increase the risk of persistent infection and cell dysregulation include immune suppression, cigarette smoking, multiple sexual partners, age at first intercourse, hormonal birth control and possibly other sexually transmitted infections, such as *Chlamydia*.[3]

Invasive cervical cancer is an AIDS-defining malignancy. The role of immune suppression from the HIV and the effect of highly active antiretroviral therapy (la Stavudine, Lamivudine, Efavirenz; Ib Stavudine, Lamivudine, Nevirapine; 2 Zidovudine, Didanosine, Lopinavir/Ritonavir) (HAART) on HPV disease progression remains uncertain.[4] The advent of 2 new preventive HPV vaccines directed towards types 16 and 18 has generated much hope that a vaccine might prevent cervical disease in women in developing countries, where HIV is pandemic and access to Papanicolaou smears and colposcopies is very limited.[5,6]

The prevalence of HIV infection is reported to be 12% in South Africa, with the major burden carried by women.[7] Cervical cancer is one of the most common cancers in black South African women; 31.2% of all cancers are cervical in this population. A black South African woman carries a 1 in 34 lifetime risk of developing cervical cancer as compared to a white South African woman, whose lifetime risk is 1 in 93.[8] In HIV-positive women cervical cancer presents between the ages of 35 and 40, which is 10–15 years earlier than expected in HIV-negative women.[9,10] In a Cape Town study, HIV-positive women were nearly 5 times more likely to have high-risk HPV infection present as compared to HIV-negative women. Women infected with both HIV and high-risk HPV had a more than 40-fold higher risk of squamous intraepithelial lesions (SILs) than women infected with neither of these viruses.[11] Little is known about the prevalence of HIV/HPV coinfection in Southern African women. In this paper, we present the results of cervical screening using

Papanicolaou smears and HPV typing in 148 women seen at the Themba Lethu Clinic, Helen Joseph Hospital, in Johannesburg, South Africa.

Materials and Methods

The women were recruited from an adult HIV government outpatient clinic in a tertiary teaching hospital in Johannesburg. Women in this clinic were indigent, with an average of grade 8 education. Many were unemployed or worked in lower economic service industry jobs. Women were offered a Papanicolaou smear in the clinic after an educational session presented in English and Zulu. In addition, women were offered HPV testing. Women participating in the cohort were 18–65 years of age, HIV infected, had a cervix and not severely ill. Women who were pregnant or had a clinically active sexually transmitted disease were excluded. The study was approved by the University of Witwatersrand Human Research Ethics Committee (Medical).

HPV testing was done using the Roche Linear Array HPV genotyping test (Roche Molecular Systems Inc., Branchburg, New Jersey, U.S.A.) according to the manufacturer's instructions. This technique detects 37 types; HPV classification is per Muñoz etal.[12] Fifteen HPV types were classified as high-risk types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73 and 82), 3 were classified as probable high-risk types (26, 53 and 66) and 12 were classified as low-risk types (6, 11, 40, 42, 43, 44, 54, 61, 70, 72, 81 and CP6108). Muñoz's probable high-risk types 26, 53 and 66 and the types 67, 69 and IS39 (per the Roche Linear Array) were added to the high-risk category for convenience of analysis.

Conventional cervical smears were performed as liquid-based cytology is currently not available in South Africa. The slides were read and analyzed according to the Bethesda 2001 reporting guidelines.[13] Atypical squamous cells of undetermined significance (ASCUS) and low grade SIL (LSIL) results were followed by repeat Papanicolaou smears. Women with atypical squamous cell, cannot rule out high grade (ASCH) and high grade SIL (HSIL) results were referred for colposcopy. One atypical glandular Papanicolaou smear was found in this cohort of 148. Women with low grade lesions had the Papanicolaou smear repeated in 1 year if their CD4 count was >200, and, if CD4 was <200, the Papanicolaou smear was repeated in 6 months. The women were referred for colposcopy if there were 3 consecutive LSILs over a period of 18 months to 3 years. For quality control, 10% of the Papanicolaou smears were sent to the University of North Carolina, and a high rate of concordance (81%) was found between the pathology departments. The concordance found between Papanicolaou smear and colposcopy results was approximately 76% (Table I).

Data were analyzed using SAS 9.1 software with SAS Enterprise Guide 3.1 (SAS Institute Inc., Cary, North Carolina, U.S.A.). Associations between categorical variables were assessed using χ^2 tests and Cochran-Mantel-Haenszel methods. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated using logistic regression models adjusted for confounding effects where applicable. Analysis of variance was used to compare continuous variables in groups using Duncan's multiple-range test to compare means. All p values are 2 sided.

Results

Demographics and Cytology

The demographic features of this cohort were similar to those of the other women attending the clinic. The average age of the cohort was 35 and average CD4 count of 255.5 ± 209.5 cells per mm^3 (Table II). A standard of care sexual history was taken at each visit. The use of condoms was reported in 83% of the women, and 14% used hormonal birth control. Over

90% of women had fewer than 10 lifetime sexual partners, and more than half of these had fewer than 5. Twelve percent reported having sexual intercourse before the age of 15 years, but for the majority this occurred between 15 and 18 years. Sixty percent of the women were on HAART at the time of the study.

The results of the cervical smear cytology in the 148 subjects in whom HPV types were determined are shown in Table III. One case reported as "glandular epithelium" on cytology was not classifiable and was omitted from the analysis but is included in the description of HPV types. Of the remaining 147 subjects, 83 (56%) had abnormal cytology. Two thirds of these (60) had LSIL and ASCUS, while in the remainder (23) the lesions were high grade lesions (HSIL and ASCH). An analysis of variance showed that there was a significant difference between the CD4 counts in these 3 groups (p = 0.042), with the lowest mean CD4 count seen in patients with high grade cytology. While there was no significant difference between CD4 counts in the low and high grade cytology groups, the difference between the normal and high grade cytology was significant (p < 0.05) (Table III, footnote 4). In a multiple logistic regression model to assess the contribution of sexual history, age, infection with oncogenic HPV and the percentage of subjects on HAART on the cytology grade, only the presence of an oncogenic HPV type (OR 15.4, 95% CI 4.3–55.6) and the number of sexual partners (OR 1.4, 95% CI 1.0–2.1) entered the model. Age at first intercourse, use of hormonal birth control, condom use, HAART, use of tobacco products and age were not statistically significant.

HPV Types

HPV infection was demonstrated in 95% of the women, and 83% had 1 or more oncogenic HPV types (Table IV). The 5 most common oncogenic HPV types encountered were 16, 35, 53, 18 and 45. All oncogenic types according to Muñoz et al[12] were detected in this cohort. The median number of oncogenic HPV types was 3, with > 1 oncogenic type identified in 73% of the women. Two women had 8 oncogenic types, and 1 woman had a total of 13 HPV types. HPV types 6 and 11, which have been associated with genital warts, were each encountered in 8% of this cohort.

A comparison of the prevalence of HPV type in women with differing cervical cytology is shown in Table V. All 8 women in whom HPV was not detected had normal Papanicolaou smears. All 23 women with high grade cervical lesions had oncogenic HPV types, and the 5 most prevalent oncogenic HPV types (Table IV) were found in 19 of these. Of these 23 women with high grade lesions, 14 (61%) had HPV 16, while only 2 women had 18. Both of these women were coinfected with 16. Overall, HPV 16 was found in 44/148 women (30%) and type 18 in 27 of 148 women (18%). Both types were found in only in 10 of 148 (6.8%) women. Of great concern is the high prevalence of oncogenic HPV types in women with normal cytology (67%). The prevalence of oncogenic HPV types in women with low-risk lesions was 94%.

Statistical analysis found significant differences in the prevalence of oncogenic HPV types between cytology groups (normal, low and high grade) χ^2_{trend} = 22.9, p < 0.0001), reflecting the high prevalence of oncogenic types in high grade Papanicolaou smears. When results were stratified by CD4 count above and below 200 cells/μL (the level defining AIDS), there was a significant risk of an oncogenic HVP type in patients with a CD4 count below 200 cells/μL (χ^2 = 7.1, p < 0.008; OR 3.9, 95% CI 1.4–11.0). Adjusting for HAART did not alter the results.

The ORs and 95% CIs, adjusted for the number of sexual partners, of a specific high-risk HPV type being associated with either low or high grade Papanicolaou smears are shown in

Table VI. Significant ORs for high grade Papanicolaou smears were seen in HPV types 16, 35, 51, 66, 69 and 73. Significant ORs for low-risk smears were seen with types 18 and 73.

Discussion

Throughout the developed world HPV types 16 and 18 have accounted for most cases of cervical cancer. A quadrivalent preventive vaccine for high-risk HPV types 16, 18, 6 and 11 has been approved.[5] Trials to test this vaccine in HIV-positive women are being planned.

Little has been published regarding HPV typing in HIV-positive women in sub-Saharan, Africa. A study from rural Zimbabwe looking at 236 HIV-positive women found that HPV DNA was detected in 54% of HIV-positive women and in only 27% of HTV-negative women.[14] A recent study in HIV-infected women from Zambia showed SILs to be present in up to 76% of women.[15] Another study in 150 HIV-infected Zambian women showed that 98% harbored HPV with a median of 4 types per participant and that 85% had 1 or more oncogenic HPV types.[16] Early data from Brazil and Thailand show high rates of HPV infection in HIV-positive women (38.6% and 51%, respectively).[17,18] Studies from other developing countries have also shown a large diversity of oncogenic HPV types (including 16 and 18) but also other types, such as 33, 35, 52, 53 and 81.[18,19] One small study in South Africa showed that HIV-positive women had a significantly higher level of cervical anti-VLP-16 IgG antibodies (33%) as compared to HIV-negative women (10%, p = 0.002).[20] A meta-analysis published in late 2006 looking at HPV typing from around the world, including Africa (Ivory Coast, Kenya, Senegal, Tanzania and Zimbabwe), showed that types 31 and 35 were high, with an HPV prevalence overall at 56.6% in HIV-seropositive women, a much lower rate and slightly different HPV types than found in our cohort.[21] The present study is the first to describe cervical HPV typing in HIV-positive women from South Africa.

Three aspects of this study deserve special attention. First, >65% of the women with normal cervical cytology had cervical infection with oncogenic HPV types. How to best follow HIV-infected women with normal Papanicolaou smears is a vexing question, particularly in resource-limited communities. However, the statistically significant finding that women with CD4 counts <200 cells/μL are more likely to be infected with oncogenic HPV types than women with CD4 counts >200 cells/mm^3 suggests that such women should be followed with at least yearly cervical smears instead of the current policy of every 10 years. The second aspect is the disturbing finding that only 61% of women with high grade Papanicolaou smears were infected with either HPV type 16 or 18 and that these women were infected with a wide spectrum of other oncogenic types. Overall, only 51 women (34%) were infected with either type 16 or type 18, and 83% of the women had additional oncogenic HPV types. In addition, the OR illustrated that other HPV types were significantly associated with high grade cytology results. It is of concern that the impact of recently developed vaccines against types 16 and 18 may be less than hoped for in this vulnerable population. With >80% of women in this study infected with oncogenic HPV types it is evident that vaccines with a broader spectrum may need to be developed for use in the developing world. Last, it is of interest that apart from the number of sexual partners, sexual history and other known risk factors were not significant in the development of cytologic abnormalities. It is possible that HIV immune suppression may override these traditional risk factors.

This cross-sectional study did not show any significant differences in cervical cytology or HPV type with or without HAART; however, the numbers are small. Women with high grade lesions were found to have a statistically significant lower CD4 count, indicating that the status of the immune system is important in this setting for increased risk of dysplasia. The correlation of significant dysplasia on Papanicolaou smear results with HPV is

consistent with previous results in women without HIV. When results were stratified by CD4 count > and < 200 cells/mm^3 (the level defining AIDS), there was a significant risk of an oncogenic HPV type in patients with a CD4 count < 200 cell/mm^3. Adjusting for HAART did not alter the result. This finding illustrates a relation between the state of immune deterioration and HPV disease progression, underscoring an association between immune function, giving possibly a little more fuel to the argument of starting HAART earlier to prevent development of this opportunistic infection. The impact of HAART and CD4 count on the progression of cervical pathology and HPV infection will be addressed by a 5-year longitudinal study, currently under development, of a larger cohort.

In southern Africa, where access to Papanicolaou smears and colopscopy is limited and HIV infection is pandemic, a preventive vaccine against only HPV types 16 and 18 will help reduce the burden of cervical dysplasia and cancer but may have a limited impact. These data, in addition to those from Zambia, show a disturbingly high prevalence and diversity of oncogenic HPV, suggesting that HIV-infected women from urban areas in southern Africa are at significant risk for cervical dysplasia and cancer.[15,16] A broader-coverage vaccine may be more effective in this vulnerable group of women. In addition, developing a wide-reaching cervical screening program to complement the new antiretroviral program is also essential to augment the improvement of quality and quantity of health that these program bring to southern Africa.

Acknowledgments

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Table I

Colposcopy Results *vs.* Pap Smear Results in Cohort to Date

Pap smear results	Not done[a]	Normal	LSIL	HSIL	Total
LSIL	233	N/A	N/A	N/A	233
HSIL	99[a]	1	20	66	186
Total	332	1	20	66	419

[a]Continuing attempts to recall these patients for colposcopy.

N/A = not applicable. Per protocol—if a patient has had 3 or more LSILs, a colposcopy is required. This scenario has not occurred in the present study.

Correlation rate = 76%.

Table II

Demographics and Sexual History of a Cohort of the South African Cervical Cancer Cohort Who Underwent HPV Typing

	Cohort (n = 148)	
Demographics and sexual history	No.	%
No. of lifetime sexual partners		
< 5	71	48
5–10	64	43
11–15	7	6
16–20	4	3
> 20	2	1
Total	148	100
Age at first sexual intercourse (yr)		
< 15	18	12
15–18	82	55
19–21	37	25
> 21	11	8
Total	148	100
HAART[*]		
None	57	39
1a	66	45
1b	9	6
2	8	5
Other	8	5
Total	148	100
Age (mean ± SD) (yr)	36 ± 7	
CD4 (most recent at time of Pap smear)	257 ± 199	
Condom use (consistent use)	83%	
Hormonal contraception	14%	

[*] 1a Stavudine, Lamivudine, Efavirenz; 1b Stavudine, Lamivudine, Nevirapine; 2 Zidovudine, Didanosine, Lopinavir/Ritonavir.

Table III

Effect of CD4 Count, Antiretroviral Treatment and Sexual History on the Cervical Cytology in HIV-Positive Women (n = 147)[*]

| | Cervical cytology | | | |
	Normal (n = 64)	LSIL (n = 60)	HSIL (n = 23)	Significance
CD4 (mean ± SD) cells/mm^3	301 ± 243.8^{a}	$236.2 \pm 170.4^{a,c}$	$188 \pm 131^{b,c}$	F = 3.24; p < 0.04
Percentage on HAART	52	66	56	$\chi^2 = 2.95$; p > 0.2
Age (yr) (mean ± SD)	37 ± 7	36 ± 8	35 ± 6	F = 1.06; p > 0.3
Time on HAART (median, IQR)	6.6, 2.2–9,0	6.1, 1.6–8.4	4.8, 2.5–7.5	$\chi^2 = 0.97$; p > 0.6
Age at first intercourse				
< 15	5 (8%)		10 (17%)	3 (13%)
16–18	42 (65%)	25 (42%)	15 (65%)	
19–21	12 (19%)	20 (33%)	4 (18%)	
> 21	5 (8%)	5 (8%)	1 (4%)	$\chi^2 = 9.2$; p > 0.1
No. of lifetime partners				
< 5	27 (42%)	29 (48%)	14 (61%)	
5–10	32 (50%)	23 (38%)	9 (39%)	
11–15	3 (5%)	4 (7%)	0	
16–20	1 (2%)	3 (5%)	0	
> 20	1 (2%)	1 (2%)	0	
$c^2=6.35$: p >0.6				
Smokers (%)	8	3	0	Fisher's exact; p > 0.4
Snuff takers (tobacco orally chewed) (%)	8	10	9	$\chi^2 = 0.18$; p > 0.9

[*] One subject with cytology reported as "glandular epithelium" is not included in the table or in the statistical analysis.

[a,b,c] Means not sharing superscript letter significantly different (p < 0.05) Duncan's multiple-range test.

HAART is defined in a footnote to Table II.

Table IV

Prevalence of HPV Types in Cervical Samples from 148 HIV Positive Women

	HPV Types		High-risk HPV types > 10% frequency										
Type	**Any**	**High risk**	**16**	**35**	**53**	**18**	**45**	**56**	**51**	**52**	**66**	**59**
Frequency	140	123	45	30	29	27	25	22	20	20	18	16
Percentage	94.6	83.1	30.4	20.3	19.6	18.2	16.9	14.9	13.5	13.5	12.2	10.8

	High-risk HPV types < 10% frequency									
Type	**39**	**58**	**73**	**33**	**68**	**69**	**31**	**82**	**IS39**	**26**	**67**
Frequency	14	14	12	12	12	12	11	10	9	4	2
Percentage	9.5	9.5	8.1	8.1	8.1	8.1	7.4	6.8	6.1	2.7	1.4

Table V

Relationship Between Cytology and HPV Type in HIV-Positive Women (N = 147[*])

HPV type	Cervical cytology		
	Normal (n = 63, 43%)	Low grade lesions (n = 61, 41%)	High grade lesions (n = 23, 7%)
No. of HPV	8 (13%)	0	0
Any low-risk HPV	50 (78%)	53 (88%)	19 (83%)
Any high-risk HPV	42 (67%)	57 (94%)	23 (100%)

[*] One subject with cytology reported as "glandular epithelium" but did have high-risk HPV is not included in the table or in the statistical analysis.

Table VI

Frequency of All 22 High-Risk HPV Types Encountered in Women with Normal Cervical Cytology, Low and High Grade Cervical Dysplasia

HPV type		Cytology grade				Significance (2 *df*)
		Normal	Low grade lesion	High grade lesion	Total	
16	Frequency (%)	16 (25%)	14 (23%)	14 (61%)	44 (30%)	**p < 0.002**
	OR	1	0.9 (0.4–2.1)	4.7 (1.70–12.8)		
18	Frequency (%)	8 (13%)	17 (28%)	2 (9%)	26 (18%)	**p < 0.04**
	OR	1	2.8 (1.1–7.0)	0.7 (0.1–3.4)		
26	Frequency (%)	1 (2%)	1 (2%)	1 (4%)	3 (2%)	p > 0.7
	OR	1	1.1 (0.1–17.5)	1.1 (0.1–17.5)		
31	Frequency (%)	4 (6%)	4 (6%)	3 (13%)	11 (7%)	p > 0.5
	OR	1	1.1 (0.3–4.5)	2.3 (0.5–10.9)		
33	Frequency (%)	2 (3%)	7 (12%)	3 (13%)	12 (8%)	p > 0.1
	OR	1	4.1 (0.8–20.6)	0.9 (0.3–2.2)		
35	Frequency (%)	8 (13%)	11 (18%)	10 (43%)	29 (20%)	**p < 0.006**
	OR	1	1.6 (0.6–4.2)	5.9 (1.9–18.2)		
39	Frequency (%)	4 (6%)	6 (10%)	3 (13%)	13 (9%)	p > 0.5
	OR	1	1.7 (0.4–6.2)	2.3 (0.5–10.9)		
IS39	Frequency (%)	2 (3%)	5 (8%)	2 (9%)	9 (6%)	p > 0.4
	OR	1	2.8 (0.5–15.11)	3.0 (0.4–22.3)		
45	Frequency (%)	11 (17%)	9 (15%)	4 (17%)	24 (16%)	p > 0.9
	OR	1	0.9 (0.3–2.2)	1.0 (0.3–3.6)		
51	Frequency (%)	5 (8%)	9 (15%)	6 (26%)	20 (14%)	p > 0.08
	OR	1	2.1 (0.7–6.6)	4.2 (1.1–15.3)		
52	Frequency (%)	7 (11%)	8 (13%)	5 (22%)	20 (14%)	p > 0.4
	OR	1	1.3 (0.4–3.7)	2.3 (0.6–8.0)		
53	Frequency (%)	12 (19%)	13 (22%)	3 (13%)	28 (19%)	p > 0.6
	OR	1	1.3 (0.4–3.7)	2.3 (0.6–8.0)		
56	Frequency (%)	6 (9%)	10 (17%)	6 (26%)	22 (15%)	p > 0.1
	OR	1	1.9 (0.7–5.7)	3.4 (0.9–12.0)		
58	Frequency (%)	4 (6%)	6 (10%)	4 (17%)	14 (10%)	p > 0.2
	OR	1	1.7 (0.4–6.2)	3.2 (0.7–13.9)		

Cytology grade

HPV type		Normal	Low grade lesion	High grade lesion	Total	Significance (2 *df*)
59	Frequency (%)	5 (8%)	7 (12%)	4 (17%)	16 (11%)	p > 0.4
	OR	1	1.6 (0.5–5.2)	2.5 (0.6–10.2)		
66	Frequency (%)	3 (5%)	9 (15%)	6 (26%)	18 (12%)	**p < 0.02**
	OR	1	3.6 (0.9–14.0)	7.2 (1.6–31.7)		
67	Frequency (%)	0	0	2 (9%)	2 (1%)	—
	OR	—	—	—		
68	Frequency (%)	5 (8%)	5 (8%)	2 (9%)	12 (8%)	p > 0.9
	OR	1	1.1 (0.3–3.9)	1.1 (0.2–6.2)		
69	Frequency (%)	3 (5%)	4 (7%)	5 (22%)	12 (8%)	**p < 0.04**
	OR	1	1.5 (0.3–6.8)	5.6 (1.2–26.0)		
73	Frequency (%)	1 (2%)	7 (12%)	4 (17%)	12 (8%)	**p < 0.03**
	OR	1	8.3 (1.0–69.7)	13.3 (1.4–125.8)		
82	Frequency (%)	1 (2%)	5 (8%)	3 (13%)	9 (6%)	p > 0.09
	OR	1	5.7 (0.6–50.5)	9.4 (0.9–96.0)		

The OR and 95% CI of a specific high-risk HPV being associated with low and high grade dysplasia, adjusted for the number of sexual partners, are shown.

Bold p values indicate the level is significant.