

Unique Human Papillomavirus–Type Distribution in South African Women With Invasive Cervical Cancer and the Effect of Human Immunodeficiency Virus Infection

Matthys Cornelis van Aardt, FCOG(SA),^{1} Greta Dreyer, PhD,¹
Hannelie Francina Pienaar, FCOG(SA),¹ Frank Karlsen, PhD,² Siri Hovland, Cand. Scient,³
Karin Louise Richter, FC Path(SA) Viro,⁴ and Piet Becker, PhD⁵*

¹Gynaecologic Oncology Unit, Department of Obstetrics & Gynaecology, University of Pretoria, Pretoria, South Africa;

²Buskerud and Vestfold University College, Borre;

³NorChip AS, Klokkestua, Norway;

⁴Department of Medical Virology University of Pretoria; National Health Laboratory Service; and

⁵Biostatistics Unit, South African Medical Research Council, Departments of Medical Virology, and Gynaecology, University of Pretoria, Pretoria, South Africa.

*Address correspondence and reprint requests to Matthys Cornelis van Aardt, FCOG(SA), Department of Obstetrics and Gynaecology, Steve Biko Academic Hospital, Dr Savage Rd, Pretoria 0001, South Africa. E-mail: mc@vanaardt.net.

The authors declare no conflicts of interest.

Objectives: Cervical cancer is the most common cause of cancer-related deaths among South African women. Viral types associated with cervical cancer may differ not only between countries and regions, but possibly also between human immunodeficiency virus (HIV)–infected and noninfected women.

Methods: In a population with high HIV prevalence, human papillomavirus (HPV)–type infections detected with DNA analyses were reported in a cohort of 299 women diagnosed with invasive cervical cancer.

Results: One hundred fifty-four women tested HIV negative, 77 tested HIV positive, and HIV status was unknown for 68 women. The mean age for HIV-positive women was 41.3 years, and that for HIV-negative women was 55.8 years ($P < 0.001$). Ninety-two percent of women tested HPV-DNA positive. Human papillomavirus types 16 and/or 18 were present in 62% of HIV-negative women and 65% of HIV-positive women. The 5 most common HPV types in HIV-positive women were, in decreasing frequency, HPV 16, 18, 45, 33, and 58. In HIV-negative women, the most common HPV types were HPV 16, 18, 35, and 45, followed by HPV 33 and 52. Human papillomavirus type 45 was more likely in the HIV positive compared with the HIV negative (odds ratio, 3.07; 95% confidence interval, 1.07–8.77). The HIV-positive women had more multiple high-risk HPV-type infections than did the HIV-negative women (27% vs 8%, $P = 0.001$).

Conclusions: A high number of women in South Africa with cervical cancer are HIV positive. Without viral cross-protection, HPV vaccines should prevent around 65% of cervical cancers in this population. Human papillomavirus type 45 infection is significantly linked to HIV and important for future vaccine developments.

Key Words: Cervical cancer, Human papillomavirus, Human immunodeficiency virus

*

Among all South African women, cervical cancer is the second most common malignancy and the most common cancer in women between the ages of 15 and 44 years.¹ In South Africa, it is estimated that annually 7735 women are newly diagnosed with cervical cancer, and 4248 women die as a result of it.¹ The age-standardized annual incidence rate of cervical cancer in sub-Saharan Africa and South Africa ranges between 31.0 and 40.3 per 100,000 women.¹⁻⁴

Cervical cancer has a huge impact on society, because death often occurs at a young age while women are raising families.⁵ Unless current preventive policies change, an estimated 140,000 women will be newly diagnosed with cervical cancer by 2030, and at least 95,000 women will die as a direct result.⁶

In 2007, it was reported that around 67% of the estimated 33 million people around the globe infected with human immunodeficiency virus (HIV) reside in sub-Saharan Africa, and around three-quarters of AIDS-related deaths occur in the region.⁷ Secondary to an HIV-mediated increase in persistent and recurrent human papillomavirus (HPV) infections, women infected with human immunodeficiency virus (HIV) have a greater chance to develop cervical neoplasia.^{8,9}

Comparing women in the general population with HIV-infected women, HIV-infected women may have more than a 20-fold increased risk for developing invasive cervical cancer.¹⁰ Compared with other high-risk HPV (hrHPV) types, HPV 16 infections and associated premalignant cervical changes appear to be less reliant on the immune status of a woman.¹¹ A meta-analysis found HPV 16 less frequently in HIV-infected women with normal Papanicolaou smears, low-grade as well as high-grade cervical disease compared with non-HIV-infected women.¹²

Although HPV types associated with invasive cervical cancer are known for many countries and regions, there still remains a lack in knowledge on HPV type distribution in many areas worldwide. Especially in developing countries, the question of which HPV types are prevalent among women with invasive cervical cancer is still largely unanswered, and the effect of HIV coinfection on the prevalence of specific HPV types is also clearly missing.¹³

MATERIALS AND METHODS

Study Design

This retrospective descriptive study was performed at the gynecologic oncology unit, University of Pretoria. It consisted of data obtained during 2 study periods. The first study period started in January 2003 and ended in December 2004. The second collection period was initiated in 2008 and lasted until July 2011. Patients included in the study were women 18 years or older, referred for staging and treatment of histologically confirmed invasive cervical cancer.

Consent Process and Ethical Considerations

Patients received counseling and an information document that explained the method and voluntary nature of the study. During counseling by trained nursing personnel, patients were motivated to undergo HIV testing as per standard

departmental management protocols, but it was explained clearly that testing was voluntary. Written informed consent and standard management protocols were the same for both study periods. This study was approved by the Research Ethics Committee of the Faculty of Health Sciences of the University of Pretoria (27/2008, 108/2008, 189/2012).

Patient Recruitment

One hundred twelve consecutive women were invited during 2003 and 2004, of whom 106 patients fulfilled the inclusion criteria. Starting in 2008, another 201 consecutive patients were recruited, of whom 193 patients were included in the study. Women finally included with proven invasive cervical cancer were 299. Fourteen patients were excluded, of whom 9 patients had endometrial cancers, 3 had cervical intraepithelial neoplasia grade III, 1 had carcinosarcoma, and 1 had only severe cervicitis on the final histological diagnoses. Patients excluded were treated according to standard departmental treatment protocols for the specific disease diagnosed.

Sample Collection and Transport

Tissue biopsies for histological confirmation of the diagnosis were taken with punch biopsy forceps in the outpatient clinic from each cervical tumor and placed in buffered formalin. The samples were transported to the Department of Anatomical Pathology at the University of Pretoria, where histological examination was performed.

During the initial study period, DNA sampling was performed using tampons and transported in phosphate-buffered saline and 10% methanol solution. During the second study period, HPV DNA analysis was performed on cervical tumor tissue preserved in a methanol-based buffer solution (PreTect [NorChip AS, Norway]).

HPV DNA Testing

DNA extraction was accomplished during the first study period by means of the DNA Isolation Kit (Roche Molecular Systems, Branchburg, NJ) on the MagNa Pure automated extraction system. Human papillomavirus linear array genotyping kit (Roche Molecular Systems) was used to determine the HPV type. MagNa Pure extractions and linear array genotyping were performed at the University of Pretoria. Fifteen high-risk types (HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, and 82), 3 probable high-risk types (HPV 26, 53, and 66), and 19 low-/undetermined-risk types (HPV 6, 11, 40, 42, 54, 55, 61, 62, 64, 67, 69, 70, 71, 72, 81, 83, 84, IS39, and CP6108) were tested for.¹⁴

NucliSENS manual extraction kit (bioMerieux, Marcy l'Etoile, France) was used for isolation of nucleic acid during the second study period. Human papillomavirus DNA analysis, testing for 39 individual HPV types (ie, HPV 6, 11, 16, 18, 26, 30, 31, 33, 34, 35, 39, 40, 42, 43, 44, 45, 51, 52, 53, 54, 55, 56, 57, 58, 59, 61, 64, 66, 67, 68, 69, 70, 71, 72, 73, 81, 82/MM4, 82/IS39, and CP6108) and 6 rare HPV types (ie, HPV 32, 83, 84, 85, 86, and JC9710) as a pool, was performed on GP5⁺/6⁺ polymerase chain reaction products using reverse line blot assay. Polymerase chain reaction toward the β -globin gene was included as DNA control for all HPV-negative samples.^{15,16} NucliSens extraction, GP5⁺/6⁺ polymerase chain

reaction and RLB genotyping were performed at NorChip AS, Norway.

Data Capturing and Analysis

Data were captured on Microsoft Excel datasheets, and analysis performed using Stata statistical software (StataCorp, College Station, TX). The distribution of HPV types was expressed in terms of frequencies, percentages, and 95% confidence intervals and displayed in table form and bar charts. The HIV groups were compared with respect to proportion of HPV infections using Fisher exact test at the 0.05 level of significance. The risk of HPV infection associated with HIV status was determined from the crude odds ratio along with its 95% confidence interval.

RESULTS

Age Distribution and HIV Status

Among the 299 patients included in the total study population, 154 (51.5%) were non-HIV infected, 77 (25.8%) HIV infected, and for 68 patients (22.7%), the HIV status was not known. Although the patients in the different study periods were similar, there were more HIV positive patients in the second study period and more multiple-type infections in the first study period (Table 1).

The ages of women ranged from 23 to 89 years, with the largest group between the ages of 50 and 59 years. The mean age for the total study population was 50.7 years. The mean ages for non-HIV-infected women were 55.8 (SD, 12.5) years and 41.4 (SD, 11.4) years for women infected with HIV. The HIV-infected women were significantly younger than non-HIV-infected women (P for mean age < 0.0001). Figure 1 illustrates the age distribution and HIV prevalence for the total study population.

Histological Distribution

The majority of patients had squamous cell carcinoma (277/299, 92.6%). Twenty-two patients (7.4%) had

nonsquamous cervical cancer. This number included 9 patients with adenocarcinoma, 10 patients with adenosquamous, and 3 patients with small cell neuroendocrine carcinoma. Of the 22 patients with nonsquamous cervical cancer, 3 patients were HIV infected, 11 were non-HIV infected, and the remainder unknown.

HPV Results

HPV Prevalence

Human papillomavirus DNA was demonstrated in 91.7% of all study samples. The prevalence of confirmed HPV infection was 90.9% for both non-HIV-infected and HIV-infected women and 94.1% among women with unknown HIV status.

Single and Multiple hrHPV-Type Infections

In total, 264 (88.3%) of 299 tumors tested positive for hrHPV, and 194 (64.9%) of 299 were positive for a single hrHPV type. These 2 groups form the basis for describing the HPV-type contribution in this study (Table 2).

The prevalence of hrHPV infections was 86.4% among HIV-negative women and 87.0% among the HIV-positive group. The HIV-infected women had significantly more multiple hrHPV-type infections ($P = 0.001$). Figure 2 illustrates the difference between HIV-positive and HIV-negative women regarding the number of hrHPV types present in women with invasive cervical cancer. There were more multiple hrHPV-type infections during the first study period. This is likely due to different HPV testing methods. However, HIV-positive patients had significantly more multiple high-risk HPV-type infections in both the first ($P = 0.049$) and second ($P = 0.0001$) study periods.

Distribution of hrHPV Types in Order of Prevalence for the Total Study Population

Including women with single and multiple HPV-type infections, the most common hrHPV-type infection was

TABLE 1. Comparison between patients included in the study

		Study Period 1	Study Period 2	Total
No. patients		106	193	299
Mean age		53.0	49.4	50.7
HIV	Unknown	31 (29.2%)	37 (19.2%)	68 (22.7%)
	Negative	58 (54.7%)	96 (49.7%)	154 (51.5%)
	Positive	17 (16.1%)	60 (31.1%)	77 (25.8%)
Histology	Squamous	102 (96.2%)	175 (90.7%)	277 (92.6%)
	Nonsquamous	4 (3.8%)	18 (9.3%)	22 (7.4%)
HIV negative	hrHPV negative	15.5%	12.5%	13.6%
	Single hrHPV	65.5%	85.4%	77.9%
	Multiple hrHPV	19.0%	2.1%	8.5%
HIV positive	hrHPV negative	11.8%	13.3%	13.0%
	Single hrHPV	41.1%	65.0%	59.7%
	Multiple hrHPV	47.1%	21.7%	27.3%

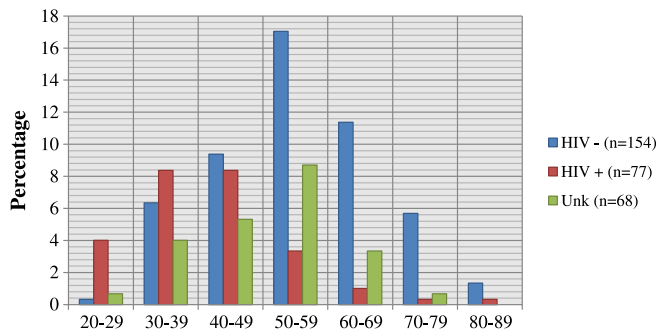


FIGURE 1. Age distribution and HIV prevalence for the study population.

HPV 16, followed by HPV 18, 45, 35, and 33. In the non-HIV-infected group, in order of decreasing frequency, the 5 most common hrHPV types were HPV 16, 18, 35, 45, and 33/52 (equally fifth most prevalent).

The most prevalent hrHPV-type infections were slightly different in the HIV-infected group, with HPV 16 infections the most common, followed by HPV 18, 45, 33, and 58. Compared with HIV-negative women, a higher percentage of HIV-positive women were infected with HPV 45 ($P = 0.015$). Table 1 tabulates the prevalence of different hrHPV-type infections among the total study population and women with single hrHPV-type infections. The table also shows the distribution among HIV-infected and non-HIV-infected women.

Single HPV-Type Infections

A single HPV infection was present in 197 patients (65.9%) and is illustrated in Table 1. The most prevalent single HPV types were, in decreasing order, HPV 16, 18, 45, 35, and 33. The distribution of single-HPV-type infections among HIV-infected and non-HIV-infected women is illustrated in Figure 3. The prevalence of HPV 45 was more than 3 times higher in HIV-positive women with single HPV-type infections compared with HIV-negative women ($P = 0.045$).

Figure 4 illustrates the hrHPV-type distribution for all women with hrHPV-positive tumors (264/299; 88.3%) and for women with single hrHPV-type positive tumors (194/299; 64.9%). Considering HPV types as oncogenic when present as part of multiple infections in patients with invasive cervical cancer seems inaccurate. This consideration probably overestimates the oncogenic potential and contribution to cancer cases. Single hrHPV-type infection may be more important when wanting to prove oncogenicity of the specific virus. However, patients with invasive cervical cancer may still have acquired transient infections after they have developed invasive cancer.

Comparing single hrHPV-type infections with all hrHPV-type infections, it appears as if the prevalence remains similar for HPV 16, 31, and 35 between the 2 groups and HPV 18 and 45 slightly more representative among women with single and multiple hrHPV-type infection. The other hrHPV types are markedly more representative among women with 1 or more hrHPV-type infections. This finding is likely the

TABLE 2. Summary of hrHPV-type infections among total population, single hrHPV-type infections, and distribution among HIV-infected and non-HIV-infected patients

HPV Type	hrHPV Type Distribution for Total Population				hrHPV Type Distribution for Single Type Infections					
	HIV Negative (n = 154)	HIV Positive (n = 77)	P (Fisher Exact)	Total (n = 299)	Total (%)	HIV Negative (n = 106)	HIV Positive (n = 46)	P (Fisher Exact)	Total (n = 197)	Total %
16	74	32	0.635	136	45.5	55	21	0.597	97	49.2
18	22	18	0.212	53	17.7	16	9	0.485	32	16.2
31	5	2	0.463	7	2.3	4	1	1.000	5	2.6
33	8	8	0.158	18	6.0	6	1	0.676	8	4.1
35	12	7	0.798	26	8.7	10	3	0.755	18	9.1
39	1	1	0.794	3	1.0	0	0	—	0	0
45	9	13	0.015*	32	10.7	5	7	0.045*	19	9.6
51	4	2	1.000	7	2.3	0	1	1.000	1	0.5
52	8	2	0.413	15	5.0	5	1	0.668	7	3.6
56	1	0	0.192	3	1.0	1	0	1.000	1	0.5
58	5	8	0.082	16	5.4	2	0	1.000	5	2.6
59	0	1	0.234	2	0.7	0	0	—	0	0
68	2	0	0.264	4	1.3	0	0	—	0	0
73	1	1	0.105	5	1.7	0	1	1.000	1	0.5
82	2	1	1.000	3	1.0	0	0	—	0	0
Non-hrHPV	36	32	—	90	30.1	2	1	—	3	1.5

*Statistically significantly more prevalent among HIV-infected women.

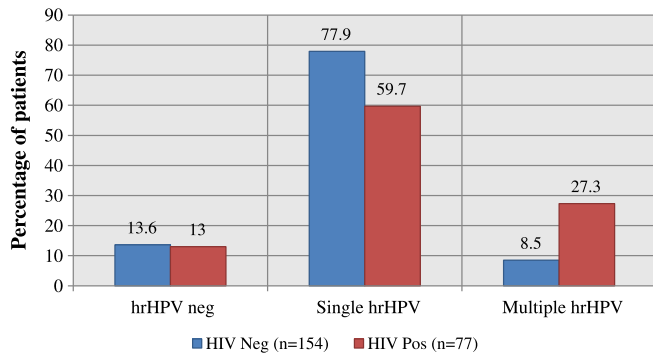


FIGURE 2. Absent, single, and multiple hrHPV-type infections among HIV-positive and HIV-negative patients ($P = 0.001$).

result of different methods having been used to detect HPV DNA, with more multiple-type infections among tampon collections compared with biopsy samples. However, HPV DNA methods may detect transient hrHPV infection not associated with the disease.

Histological Subtypes and hrHPV-Type Distribution

The most striking difference is that HPV 18 (54.6%) was most prevalent among women with non-squamous cell cervical cancer, followed by HPV 16 (13.6%). Among women with squamous cell cancer, HPV 16 (48%) was most prevalent followed by HPV 18 (14.8%). Despite a relatively small number of patients with non-squamous cell cervical cancer, there was a statistically significant difference in relation to the prevalence of HPV 16 ($P = 0.002$) and HPV 18 ($P < 0.001$) between the 2 groups.

DISCUSSION

A growing number of studies focus on HPV prevalence in women with invasive cervical cancer in South and sub-Saharan Africa. This study adds valuable information toward understanding the interaction between HPV infections, HIV,

and invasive cervical cancer in our population. To our knowledge, this is the largest study in our defined population to date.

Age Distribution and HIV Status

In this study, HIV-infected women with invasive cervical cancer were on average 14 years younger than non-HIV infected, which is comparable to previous reported South African data.² The prevalence of HIV infections was higher in this study (25.8%) than the reported prevalence by van Bogaert (13.6%),² but similar to the South African sub-group (27.6%) reported by Denny et al.⁴

HPV Prevalence

The prevalence of HPV infections among women with invasive cervical cancer was similar to the reported prevalence of 90% from the meta-analysis by Li et al.¹⁷ In contrast to other reports on HIV-positive women,^{4,7} the prevalence of HPV infections in this study was the same (90.9%) for both HIV-infected and non-HIV-infected women. However, HIV-infected women had significantly more multiple high-risk HPV types compared with non-HIV-infected women ($P = 0.001$). The number of women with multiple HPV-type infections, especially among HIV-infected women, is more than the previously reported data from South Africa and Kenya for all HPV-type infections and considerably higher than that reported in Europe.^{10,18,19} This might be because of tampon sampling.

All HPV-Type Infections

Human papillomavirus types 16 and/or 18 were present in 63.21% of the entire population, but only 61.20% had either HPV 16 or 18. The prevalence of either HPV 16 or 18 is considerably lower than the globally reported 73%, but similar to South African data reported by Bruni et al.^{1,17} Human papillomavirus types 16 and/or 18 were present in 69.9% of women with single and multiple types reported by Denny et al⁴ and 69.2% reported by Louie et al³ for sub-Saharan African women with invasive cervical cancer. In this study, no significant difference was found between HIV-infected, non-HIV-infected, and HIV-unknown patients with regard to HPV 16 ($P = 0.635$) or HPV 18 ($P = 0.212$) infections. These findings

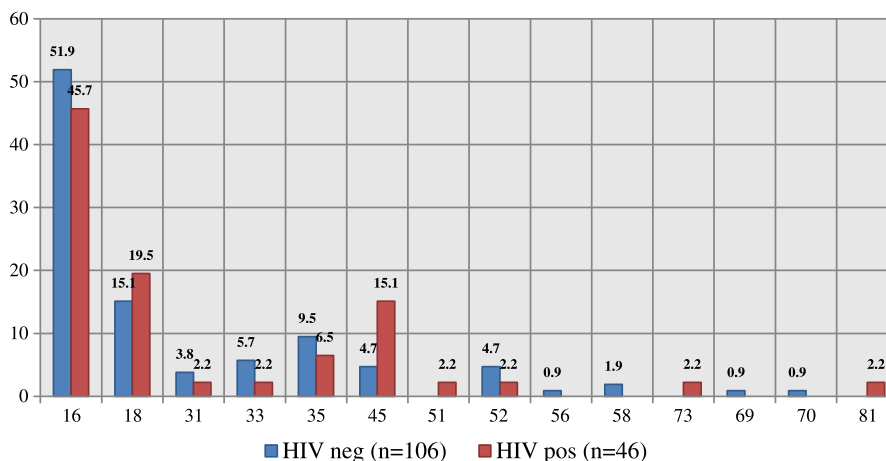


FIGURE 3. Single HPV-type infections among HIV-infected and non-HIV-infected women.

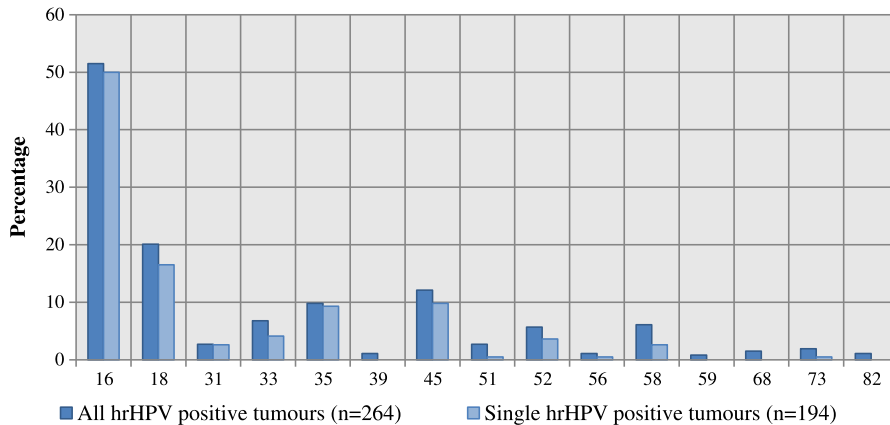


FIGURE 4. Type distribution among all hrHPV-positive tumors and single hrHPV-positive tumors.

are similar to those from Mozambique, South Africa, and Kenya.^{10,20}

Another Kenyan study also showed little difference in the prevalence of HPV 16 in cervical cancer specimens between HIV-positive and HIV-negative women.²¹ These findings and findings from the current study reestablish confidence in possible effects of current HPV 16/18 vaccines on women infected with HIV.¹⁰

Comparing the most prevalent single and multiple HPV-type infections to the meta-analysis by Li et al¹⁷ (HPV 16, 18, 58, 33, 45, 31, 52, 35), HPV 45, 35, and 33 were more prevalent than HPV 58, reported as the third most common globally. However, the HPV type sequence of the current study compares better with the African sub-group in the meta-analysis. The top 5 HPV types are identical, except that HPV 33 and 35 are swapped around and that HPV 58 did not feature among the top 8 most prevalent viruses.¹⁷ The order of the 5 most prevalent HPV types in this study was exactly the same as reported by Denny et al.⁴ The higher prevalence of HPV 35 does not appear to be related to HIV coinfection and is most likely a regional difference.

The odds ratio for a HPV 45 infection was triple for HIV-positive compared with HIV-negative women (odds ratio, 3.07; 95% confidence interval, 1.07–8.77). In contrast to findings published by de Vuyst et al,¹⁰ HIV-positive patients in this study had 3 times higher infection rates for HPV 45 compared with HIV-negative women ($P = 0.015$). Human papillomavirus type 45 is therefore not only important among South African women but especially in HIV-infected women, who are currently not directly covered by HPV vaccines, but only by some cross-protection.

Single HPV-Type Infections

In women infected with a single HPV type, the sequence of the most common types were similar to the findings from a large European study,¹⁹ except HPV 33 and 31 that were fourth and fifth most common. In sub-Saharan women, the most prevalent single HPV-type infections were reported as HPV 16, 18, 35, 45, 33, and 52.⁴ The percentage of women infected with HPV 16 or 18, however, was similar to findings by Denny et al.⁴ Women in this study, coinfecting

with HIV and a single HPV type, had significantly more HPV 45 infections compared with non-HIV-infected women. The importance of HPV 45 infections in Africa was also highlighted by another study.⁶ Current bivalent HPV vaccine demonstrated significant cross-protection against HPV 45 in clinical trials, which might be particularly important in this population.²²

Histological Subtypes and HPV Type Distribution

In agreement with global data, HPV 16 infections in this study were significantly more prevalent in patients with squamous cell cancer ($P = 0.002$), whereas HPV 18 was the most prevalent HPV type among women with non-squamous cell carcinoma ($P < 0.001$).^{17,19} Denny et al⁴ also found HPV 18 as most prevalent among women with adenocarcinoma in sub-Saharan Africa. Although HPV 45 is globally reported as the third most common HPV-type infection in women with adenocarcinoma, in this study HPV 35 was more common among patients with non-squamous cell carcinoma. Because of the small sample size, the significance of this finding is questionable.

Study Limitations

Limitations of this study were the combination of 2 study populations and the absence of a standard method of testing samples for all women included. Although the 2 HPV tests may have different specificity and cutoff of values for single and multiple types, because of limited sample size, statistical analysis was not performed separately for the different HPV testing methods. However, both study groups included highly sensitive methods to detect type-specific HPV DNA, and the main objective of this study was to compare HPV types in HIV-infected and non-HIV-infected patients and not the different HPV assays. Some women did not have HIV results that might have influenced findings. Although the center where the study was performed serves a large referral area, the study did not include patients from all regions of South Africa. The effect of CD4 cell count could not be evaluated because of lack of information. Lastly, because HIV-positive women were significantly younger than HIV-negative women, age may influence HPV prevalence.

CONCLUSIONS

Regardless of HIV status, HPV 16 and 18 were the most prevalent hrHPV types present among women with cervical cancer in this study. Disregarding cross-protection, current bivalent and quadrivalent HPV vaccines could directly prevent cervical cancer in 65% or more of women in this population. Human papillomavirus types 45 and 35 are important in the South African context and HPV 45 even more relevant among HIV-infected women. This study highlights the need for future vaccines to target HPV 45 and 35 in women infected with HIV. It is also important to take these findings in consideration when screening strategies for cervical cancer are being developed in our population, especially in HIV-infected women.

ACKNOWLEDGMENTS

The authors thank Discovery Foundation for funding and grant support, as well as E. Janse van Rensburg, M. Wolvaardt, and the laboratory personnel who were involved in testing samples to ensure accurate and reliable results.

REFERENCES

1. Bruni L, Barrionuevo-Rosas L, Serrano B, et al. ICO Information Centre on HPV and Cancer (HPV Information Centre). Human papillomavirus and related diseases in South Africa. Summary Report. Available at: <http://www.hpvcentre.net/statistics/reports/XWX.pdf>. Accessed March 17, 2014.
2. van Bogaert LJ. Age at diagnosis of preinvasive and invasive cervical neoplasia in South Africa: HIV-positive versus HIV-negative women. *Int J Gynecol Cancer*. 2011;21:363–366.
3. Louie KS, de Sanjose S, Mayaud P. Epidemiology and prevention of human papillomavirus and cervical cancer in sub-Saharan Africa: a comprehensive review. *Trop Med Int Health*. 2009;14:1287–1302.
4. Denny L, Adewole I, Anorlu R, et al. Human papillomavirus prevalence and distribution in invasive cervical cancer in sub-Saharan Africa. *Int J Cancer*. 2014;134:1389–1398.
5. Schiffman M, Castle PE, Jeronimo J, et al. Human papillomavirus and cervical cancer. *Lancet*. 2007;370:890–907.
6. Ndiaye C, Alemany L, Ndiaye N, et al. Human papillomavirus distribution in invasive cervical carcinoma in sub-Saharan Africa: could HIV explain the differences? *Trop Med Int Health*. 2012;17:1432–1440.
7. Pantanowitz L, Michelow P. Review of human immunodeficiency virus (HIV) and squamous lesions of the uterine cervix. *Diagn Cytopathol*. 2011;39:65–72.
8. Maiman M. Cervical neoplasia in women with HIV infection. *Oncology*. 1994;8:83–94.
9. Didelot-Rousseau MN, Nagot N, Costes-Martineau V, et al. Human papillomavirus genotype distribution and cervical squamous intraepithelial lesions among high-risk women with and without HIV-1 infection in Burkina Faso. *Br J Cancer*. 2006;95:355–362.
10. de Vuyst H, Ndirangu G, Moodley M, et al. Prevalence of human papillomavirus in women with invasive cervical carcinoma by HIV status in Kenya and South Africa. *Int J Cancer*. 2012;131:949–955.
11. Strickler HD, Palefsky JM, Shah KV, et al. Human papillomavirus type 16 and immune status in human immunodeficiency virus-seropositive women. *J Natl Cancer Inst*. 2003;95:1062–1071.
12. Clifford GM, Gonçalves MA, Franceschi S, HPV and HIV Study Group. Human papillomavirus types among women infected with HIV: a meta-analysis. *AIDS*. 2006;20:2337–2344.
13. de Sanjose S, Quint WG, Alemany L, et al. Human papillomavirus genotype attribution in invasive cervical cancer: a retrospective cross-sectional worldwide study. *Lancet Oncol*. 2010;11:1048–1056.
14. Muñoz N, Bosch FX, de Sanjosé S, et al. Epidemiologic classification of human papillomavirus types associated with cervical cancer. *N Engl J Med*. 2003;348:518–527.
15. Snijders PJ, van den Brule AJ, Jacobs MV, et al. HPV DNA detection and typing in cervical scrapes by general primer GP5⁺/6⁺ PCR. In: Davy CEDJE, Doorbar J, eds. *Methods in Molecular Medicine: Human Papillomaviruses—Methods and Protocols*. Totowa, Ontario, Canada: Humana Press; 2005:101–114.
16. van den Brule AJ, Pol R, Fransen-Daalmeijer N, et al. GP5⁺/6⁺ PCR followed by reverse line blot analysis enables rapid and high-throughput identification of human papillomavirus genotypes. *J Clin Microbiol*. 2002;40:779–787.
17. Li N, Franceschi S, Howell-Jones R, et al. Human papillomavirus type distribution in 30,848 invasive cervical cancers worldwide: variation by geographical region, histological type and year of publication. *Int J Cancer*. 2011;128:927–935.
18. Mariani L, Monfulledda N, Alemany L, et al. Human papilloma virus prevalence and type-specific relative contribution in invasive cervical cancer specimens from Italy. *BMC Cancer*. 2010;10:259.
19. Tjalma WA, Fiander A, Reich O, et al. Differences in human papillomavirus type distribution in high-grade cervical intraepithelial neoplasia and invasive cervical cancer in Europe. *Int J Cancer*. 2013;132:854–867.
20. Naucler P, Mabota da Costa F, da Costa JL, et al. Human papillomavirus type-specific risk of cervical cancer in a population with high human immunodeficiency virus prevalence: case-control study. *J Gen Virol*. 2011;92(pt 12): 2784–2791.
21. de Vuyst H, Gichangi P, Estambale B, et al. Human papillomavirus types in women with invasive cervical carcinoma by HIV status in Kenya. *Int J Cancer*. 2008;122:244–246.
22. Tay SK. Cervical cancer in the human papillomavirus vaccination era. *Curr Opin Obstet Gynecol*. 2012;24:3–7.