Carcinogenicity of Human Papillomavirus (HPV) Types in HIV-Positive Women: A Meta-Analysis From HPV Infection to Cervical Cancer

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Background. Data on the relative carcinogenic potential of human papillomavirus (HPV) types among women infected with human immunodeficiency virus (HIV) (WHIV) are needed to inform prevention programs for this population.

Methods. A systematic literature review and meta-analysis of high-risk HPV-type distribution in 19 883 HIV-positive women was performed. The women, from 86 studies worldwide, included 11 739 with normal cytological findings; 1784 with atypical squamous cells of undetermined significance (ASCUS); 2173 with low-grade and 1282 with high-grade squamous intraepithelial lesions (HSILs) diagnosed cytologically; 1198 with cervical intraepithelial neoplasia grade 1 (CIN1), 456 with CIN2, and 455 with CIN3 diagnosed histologically; and 796 with invasive cervical cancers (ICCs). A large proportion of WHIV, and almost all with ICCs, were from Africa.

Results. In Africa, HPV 16 accounted for 13% of HPV-positive WHIV with normal cytological findings, but this proportion increased through ASCUS, low-grade squamous intraepithelial lesions, CIN1, and CIN2 (18%–25%), up to 41%–47% for CIN3 and ICCs. Only HPV 16, HPV 18, and HPV 45 accounted for a greater proportion of HPV infections in ICCs compared with normal cytological findings (ICC:normal ratios, 3.68, 2.47, and 2.55, respectively). Other high-risk types accounted for important proportions of low- and/or high-grade lesions, but their contribution dropped in ICCs, with ICC:normal ratios in Africa ranging from 0.79 for HPV 33 down to 0.38 for HPV 56. Findings for HPV 16 and HPV 18 in Europe/North America, Asia, and Latin America were compatible with those from Africa.

Conclusions. HPV 16 and HPV 18 in particular, but also HPV 45, at least in Africa, warrant special attention in WHIV. Broad consistency of findings with those in HIV-uninfected population would suggest that the risk stratification offered by partial HPV genotyping tests also have relevance for HIV-positive women.

Keywords. human papillomavirus; human immunodeficiency virus; cervical cancer; epidemiology.

The 13 human papillomavirus (HPV) types classified as carcinogenic, or probably carcinogenic to humans (group 1/2A carcinogens) [1], hereafter referred to as high-risk (HR) types, are known to differ greatly in their carcinogenic potential [2, 3]. Judged on their prevalence in invasive cervical cancer (ICC) relative to that in normal cytological findings [2, 3] and/or prospective risks for cervical intraepithelial neoplasia grade 3+ (CIN3+) [4–6], HPV 16 is clearly the most potent, followed by HPV 18. This knowledge informed HPV vaccine formulations and has led to approval of screening tests that include at least

HPV 16/18 genotyping to improve risk stratification among HPV-positive women [5].

Human immunodeficiency virus (HIV)–related immunodeficiency is known to have an unfavorable impact on HPV natural history, being associated with increased acquisition [7], and persistence [8] of HPV infection, as well as with increased risk of CIN2 and CIN3 [9, 10] and ICC [10–12]. However, HIV may affect some HR HPV types more unfavorably than others. In particular, HPV 16 was reported to be less affected by changes in immunodeficiency levels than other HR HPV types [13, 14] and to be underrepresented relative to other HR HPV types in women infected with HIV (WHIV), compared with HIV-uninfected women with similar cytological and/or histological cervical diagnoses [15–17].

No recommendations exist on the relevance of partial HPV genotyping algorithms to triage the high proportion of WHIV who test HPV positive, owing to scant prospective data in this population. Therefore, our objective was to perform a systematic literature review and meta-analysis to fully characterize the available information on cross-sectional HPV type distribution

across the spectrum of cytopathological and histopathological cervical diagnoses, from normal cytological findings to ICC. This approach is of practical use for identifying types that might merit differential management in HPV-based screening programs.

METHODS

We updated a previous systematic review of HPV type-specific prevalence in WHIV published in 2006 [15]. We extended the MEDLINE and EMBASE search to June 2016, using the key words "human immunodeficiency virus," "human papillomavirus," "cervical intraepithelial neoplasia," "cervical neoplasia," "squamous intraepithelial lesions," "human," and "female" in combination with "polymerase chain reaction" or "PCR." Additional relevant studies were identified in the reference lists of selected articles and in abstract books of international HPV conferences. Eligible studies had to report HPV-type specific prevalence stratified by cytological and/or histological cervical diagnosis, detected using PCR-based assays. If study methods suggested that additional relevant information was available (eg, additional HPV types and/or more detailed stratification by cervical diagnosis), data requests were made to authors.

Cases were classified into 8 grades of cervical diagnosis: those diagnosed cytologically as (1) normal, (2) atypical squamous cells of undetermined significance (ASCUS), (3) low-grade squamous intraepithelial lesion (LSIL), or (4) high-grade squamous intraepithelial lesion (HSIL); and those diagnosed histologically as (5) CIN1, (6) CIN2, (7) CIN3 (including squamous carcinoma in situ), or (8) ICC, which includes squamous cell carcinoma, adeno/adenosquamous carcinoma (ADC), or cervical cancer of other/unspecified histology. To retain appropriate sample sizes for certain analyses, cervical diagnoses were collapsed from 8 into 4 categories: (1) normal, including normal cytological findings only; (2) low grade, including ASCUS, LSIL, and CIN1; (3) high grade, including HSIL, CIN2, and CIN3; and (4) ICC.

Subjects were initially classified into 5 geographic regions (Africa, Asia, Europe, North America, and Latin America), but Europe and North America were combined for HPV type-specific analyses. Of note, the 770 ICC cases from Africa have been described in depth, and compared with ICC cases in HIV-negative subjects from the same continent, in a previous publication [17].

Overall HPV DNA prevalence is reported as a percentage of all women tested by consensus PCR. Data were extracted for 13 HPV types judged to be HR (group 1/2A) by an International Agency for Research on Cancer working group on the evaluation of carcinogenic risks to humans (HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68) [1]. Prevalence was estimated only among those studies that both genotyped and reported the HPV type in question, and thus denominators can vary by type. Type-specific positivity is presented as the proportion of HPV-positive cases in which the particular HPV type was detected, as in previous meta-analyses [2], and includes that contributed by single and multiple HPV infections.

Type-specific positivity was compared between HPV-positive ICC and HPV-positive normal cytological findings (and HPV-positive CIN3), using prevalence ratios, which are referred to hereafter as normal:ICC (and CIN3:ICC) ratios, calculated using generalized linear models, with 95% confidence intervals, as in previous meta-analyses in the general female population [2]. For Africa, ratios were calculated for all HR HPV types, whereas for Europe and North America, they were only calculated for HPV 16, 18, and 45. Standard errors of type-specific positivity estimates and prevalence ratios were calculated assuming the nonindependence of cases within the same study, using cluster-correlated robust variance estimates.

RESULTS

Eighty-six studies met inclusion criteria (see details in Supplementary Table 1), including a total of 19 883 WHIV. The majority of WHIV had been tested for HPV using MY09/11 primers (n = 7747; 39%), followed by PGMY09/11 (n = 4011, 20%), SPF10 (n = 1837; 9%), and GP5$^+$/6$^+$ (n = 1105; 6%), whereas 1743 (9%) had been tested with a combination of these, and 3440 (17%) with other PCR primers. The distribution of WHIV by grade of cervical disease and geographic region is given in Table 1. WHIV with normal cytological findings contributed the majority of samples (n = 11 739; 59%), and those with ASCUS (9%), LSIL (11%), HSIL (6%), CIN1 (6%), CIN2 (2%), CIN3 (2%), and ICC (4%) each contributed smaller fractions. The 796 ICC cases included 560 squamous cell carcinomas, 27 ADCs, and 209 ICCs of unspecified histology. Africa was the best-represented region (n = 6578; 33%), accounting for nearly all ICC cases (770 of 796), followed by North America (n = 4699; 24%), the only other region that contributed a sizeable number of CIN1–3 cases. A total of 11 455 WHIV were HPV positive. Overall HPV prevalence increased with severity of cervical disease, from 41% in normal cytological findings to 96% in CIN3, dropping slightly to 91% in ICC (Table 1).

Figure 1 shows overall HPV prevalence in all included WHIV, across 8 cervical disease grades by region. Among WHIV with normal cytological findings, HPV prevalence varied substantially by region, ranging from 25%–34% in Asia, Europe, and North America, up to 57%–64% in Africa and Latin America. In comparison with findings in Africa, the HPV prevalence in WHIV with normal cytological findings was significantly (approximately 2-fold) lower in Asia, Europe, and North America. The significance of these differences was not materially affected by adjustment for PCR primers and/or publication year (data not shown). Differences in HPV positivity by region tended to diminish with increasing severity of lesions (Figure 1).

For Africa, the proportion of HPV-positive WHIV in which individual HR HPV types were detected is shown by 8 cervical

Table 1. Number of HIV-Infected Women Tested and Positive for HPV (HPV⁺), by Cervical Disease Grade and Region

Region	Studies, No.	All Studies (n = 86) Total	HPV⁺	Normal (n = 63) Total	HPV⁺	ASCUS (n = 47) Total	HPV⁺	LSIL (n = 53) Total	HPV⁺	HSIL (n = 56) Total	HPV⁺	CIN1 (n = 14) Total	HPV⁺	CIN2 (n = 13) Total	HPV⁺	CIN3 (n = 19) Total	HPV⁺	ICC (n = 28) Total	HPV⁺
Africa	42	6578	4886	2986	1692	300	219	791	704	863	810	471	382	228	217	169	160	770	702
Asia	9	3003	1005	2523	636	94	62	121	94	51	47	98	61	39	34	71	65	6	6
Europe	15	3285	1424	2137	591	391	201	444	347	202	187	47	37	11	10	39	38	14	13
North America	9	4699	2534	2427	821	680	399	555	463	107	86	575	439	175	151	175	172	5	3
Latin America	11	2318	1606	1666	1058	319	253	262	233	59	53	7	6	3	2	1	1	1	0
Overall	86	19 883	11 455	11 739	4798	1784	1134	2173	1841	1282	1183	1198	925	456	414	455	436	796	724

Abbreviations: ASCUS, atypical squamous cells of undetermined significance; CIN, cervical intraepithelial neoplasia (by grade); HIV, human immunodeficiency virus; HPV, human papillomavirus; HSIL, high-grade squamous intraepithelial lesion; ICC, invasive cervical cancer; LSIL, low-grade squamous intraepithelial lesion.

disease grades in Figure 2. HPV 16 positivity increased consistently with severity of cervical diagnosis, from 12.6% in normal cytological findings, through 18.3% and 24.7% for ASCUS and LSIL, respectively, to 32.1% in HSIL; and from 18.3% in CIN1, through 23.0% and 40.6% for CIN2 and CIN3, respectively, to reach 46.6% in ICC (ICC:normal ratio, 3.68) (Figure 2A). HPV 18 and HPV 45 also increased substantially in positivity with severity of cervical diagnosis (although both were relatively underrepresented in CIN3) and, together with HPV 16, were the only HR types found more frequently in ICC than in cytologically normal samples, with ICC:normal ratios of 2.47 and 2.55, respectively. Types 16, 18, and 45 were also the only HPV types to be more frequently detected in ICC than in CIN3 (ICC:CIN3 ratio, 1.15, 1.86, and 2.48, respectively).
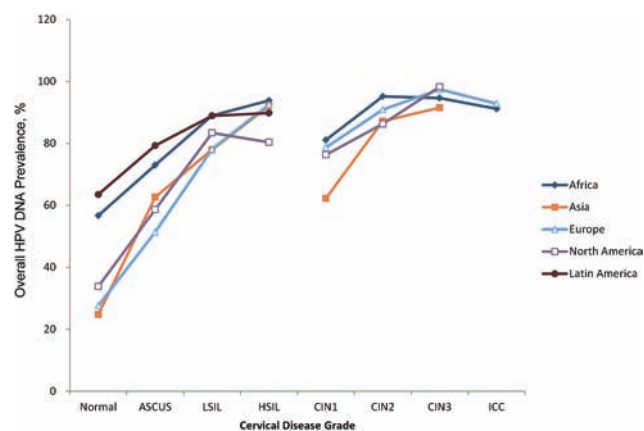
In HPV-positive WHIV in Africa, each of the remaining 10 HR types was substantially underrepresented in ICC compared

Figure 1. Prevalence of human papillomavirus DNA among women infected with human immunodeficiency virus, by 8 cervical disease grades and region. (Disease grades including <10 tested women within an individual region are not shown.) Abbreviations: ASCUS, atypical squamous cells of undetermined significance; CIN, cervical intraepithelial neoplasia; HPV, human papillomavirus; HSIL, high-grade squamous intraepithelial lesion; ICC, invasive cervical cancer; LSIL, low-grade squamous intraepithelial lesion.

with normal cytological findings (Figure 2B and 2C), with ICC:normal ratios ranging from 0.79 for HPV 33 down to 0.38 for HPV 56. However, whereas each of the 10 types tended to increase with severity of cytological diagnoses, their pattern of positivity by severity of histological diagnoses varied: some types, most notably HPV 35 and HPV 58, were more frequent in HPV-positive CIN3 than in CIN1, whereas others, most notably HPV 51, were most frequently detected in HPV-positive CIN1 and 2. All of these types, however, were less frequently detected in ICC than in CIN3.
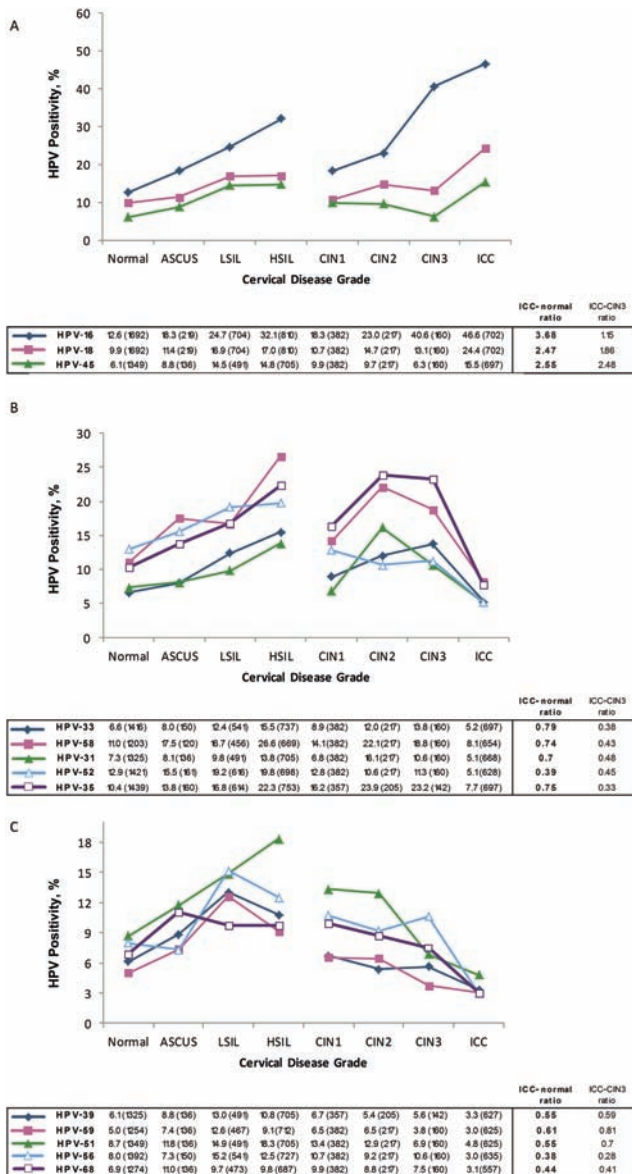
For Europe/North America, the proportion of HPV-positive WHIV in whom HPV 16, HPV 18, and HPV 45 were detected is shown by 8 cervical disease grades in Figure 3. Of note, there were few HPV-positive WHIV with ICCs (n = 16). There was no apparent trend in HPV 16 positivity between normal cytological findings and LSIL, but it did increase through HSIL/CIN2/CIN3 to reach 62.5% in ICC. The HPV 16 ICC:normal ratio was 3.42. The HPV 18 and HPV 45 ICC:normal ratios (1.37 and 1.01, respectively) were lower than in Africa. HPV 16 and HPV 18, but not HPV 45, were more frequently detected in ICCs than in CIN3 (ICC:CIN3 ratio, 1.85, 1.31, and 0.76, respectively).

For HPV-positive WHIV in Europe/North America, the remaining 10 HR types are described in Figure 2B and 2C, although ICC:normal and ICC:CIN3 ratios are not shown owing to small numbers of ICC cases, given the expected frequency of these types in ICC. In contrast to their pattern in Africa, there was no increase in positivity by severity of cytological diagnoses, with the exception of HPV 33. All of these types were less frequently detected in ICCs compared with normal cytological findings (or CIN3), again with the exception of HPV 33, which was more frequently detected (12.5%, similar to HPV 18) than HPV 45 (6.3%) in ICCs from Europe/North America.

HPV type-specific positivity for each of the 13 HR types is shown by 4 grades of cervical disease in Table 2, stratified by region. Data on severe lesions from WHIV in Asia and Latin

Cervical Disease Grade	Normal	ASCUS	LSIL	HSIL	CIN1	CIN2	CIN3	ICC	ICC-normal ratio	ICC-CIN3 ratio
HPV-16	12.6 (1692)	18.3 (219)	24.7 (704)	32.1 (810)	18.3 (382)	23.0 (217)	40.6 (160)	46.6 (702)	3.68	1.15
HPV-18	9.9 (1692)	11.4 (219)	16.9 (704)	17.0 (810)	10.7 (382)	14.7 (217)	13.1 (160)	24.4 (702)	2.47	1.86
HPV-45	6.1 (1349)	8.8 (136)	14.5 (491)	14.8 (705)	9.9 (382)	9.7 (217)	6.3 (160)	15.5 (697)	2.55	2.48

Cervical Disease Grade	Normal	ASCUS	LSIL	HSIL	CIN1	CIN2	CIN3	ICC	ICC-normal ratio	ICC-CIN3 ratio
HPV-33	6.6 (1416)	8.0 (150)	12.4 (549)	15.5 (737)	8.9 (382)	12.0 (217)	13.8 (160)	5.2 (697)	0.79	0.38
HPV-58	11.0 (1203)	17.5 (120)	16.7 (456)	26.6 (669)	14.1 (382)	22.1 (217)	18.8 (160)	8.1 (654)	0.74	0.43
HPV-31	7.3 (1325)	8.1 (106)	9.8 (491)	13.8 (705)	6.8 (382)	16.1 (217)	10.6 (160)	5.1 (668)	0.7	0.48
HPV-52	12.9 (1421)	15.5 (151)	19.2 (616)	19.8 (698)	12.8 (382)	10.6 (217)	11.3 (160)	5.1 (628)	0.39	0.45
HPV-35	10.4 (1439)	13.8 (150)	16.8 (614)	22.3 (753)	16.2 (357)	23.9 (205)	23.2 (142)	7.7 (697)	0.75	0.33

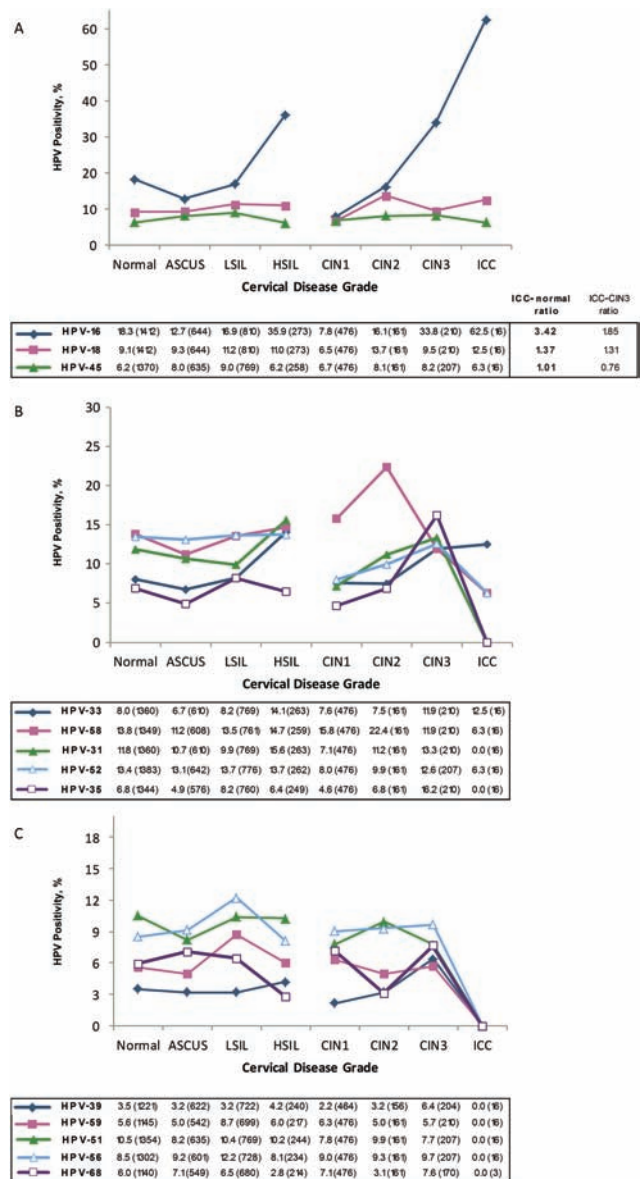| Cervical Disease Grade	Normal	ASCUS	LSIL	HSIL	CIN1	CIN2	CIN3	ICC	ICC-normal ratio	ICC-CIN3 ratio
HPV-39	6.1 (1325)	8.8 (136)	13.0 (491)	10.8 (705)	6.7 (357)	5.4 (205)	5.6 (142)	3.3 (627)	0.55	0.59
HPV-59	5.0 (1254)	7.4 (106)	12.6 (467)	9.1 (712)	6.5 (382)	6.5 (217)	3.8 (160)	3.0 (625)	0.61	0.81
HPV-51	8.7 (1349)	11.8 (136)	14.9 (491)	16.3 (705)	13.4 (382)	12.9 (217)	6.9 (160)	4.8 (625)	0.55	0.7
HPV-56	8.0 (1392)	7.3 (150)	15.2 (549)	12.5 (727)	10.7 (382)	9.2 (217)	10.6 (160)	3.0 (635)	0.38	0.28
HPV-68	6.9 (1274)	11.0 (136)	9.7 (473)	9.8 (887)	9.9 (382)	8.8 (217)	7.5 (160)	3.1 (557)	0.44	0.41

Figure 2. Positivity for human papillomavirus (HPV) types in women infected with human immunodeficiency virus (HIV) in Africa, as a proportion of HPV-positive samples (denominators in parentheses), by cervical disease grade for HPV types 16, 18, and 45 (*A*) 33, 58, 31, 52, and 35 (*B*), and 39, 59, 51, 56, and 68 (*C*). Abbreviations: ASCUS, atypical squamous cells of undetermined significance; CIN, cervical intraepithelial neoplasia (by grade); HSIL, high-grade squamous intraepithelial lesion; ICC, invasive cervical cancer; LSIL, low-grade squamous intraepithelial lesion.

Cervical Disease Grade	Normal	ASCUS	LSIL	HSIL	CIN1	CIN2	CIN3	ICC	ICC-normal ratio	ICC-CIN3 ratio
HPV-16	18.3 (1412)	12.7 (644)	16.9 (810)	35.9 (273)	7.8 (476)	16.1 (161)	33.8 (210)	62.5 (16)	3.42	1.85
HPV-18	9.1 (1412)	9.3 (644)	11.2 (810)	11.0 (273)	6.5 (476)	13.7 (161)	9.5 (210)	12.5 (16)	1.37	1.31
HPV-45	6.2 (1370)	8.0 (635)	9.0 (769)	6.2 (258)	6.7 (476)	8.1 (161)	8.2 (207)	6.3 (16)	1.01	0.76

Cervical Disease Grade	Normal	ASCUS	LSIL	HSIL	CIN1	CIN2	CIN3	ICC
HPV-33	8.0 (1360)	6.7 (610)	8.2 (769)	14.1 (263)	7.6 (476)	7.5 (161)	11.9 (210)	12.5 (16)
HPV-58	13.8 (1349)	11.2 (608)	13.5 (761)	14.7 (259)	15.8 (263)	22.4 (161)	11.9 (210)	6.3 (16)
HPV-31	11.8 (1360)	10.7 (610)	9.9 (769)	15.6 (263)	7.1 (476)	11.2 (161)	13.3 (210)	0.0 (16)
HPV-52	13.4 (1383)	13.1 (642)	13.7 (776)	13.7 (262)	8.0 (476)	9.9 (161)	12.6 (207)	6.3 (16)
HPV-35	6.8 (1344)	4.9 (576)	8.2 (760)	6.4 (249)	4.6 (476)	6.8 (161)	16.2 (210)	0.0 (16)

Cervical Disease Grade	Normal	ASCUS	LSIL	HSIL	CIN1	CIN2	CIN3	ICC
HPV-39	3.5 (1221)	3.2 (622)	3.2 (722)	4.2 (240)	2.2 (464)	3.2 (156)	6.4 (204)	0.0 (16)
HPV-59	5.6 (1145)	5.0 (542)	8.7 (699)	6.0 (217)	6.3 (476)	5.0 (161)	5.7 (210)	0.0 (16)
HPV-51	10.5 (1054)	8.2 (635)	10.4 (769)	10.2 (244)	7.8 (476)	9.9 (161)	7.7 (207)	0.0 (16)
HPV-56	8.5 (1002)	9.2 (601)	12.2 (728)	8.1 (234)	9.0 (476)	9.3 (161)	9.7 (207)	0.0 (16)
HPV-68	6.0 (1140)	7.1 (549)	6.5 (680)	2.8 (214)	7.1 (476)	3.1 (161)	7.6 (170)	0.0 (3)

Figure 3. Positivity for human papillomavirus (HPV) types in women infected with human immunodeficiency virus (HIV) in Europe/North America, as a proportion of HPV-positive samples (denominators in parentheses), by cervical disease grade for HPV types 16, 18, and 45 (*A*), 33, 58, 31, 52, and 35 (*B*), and 39, 59, 51, 56, and 68 (*C*). Abbreviations: ASCUS, atypical squamous cells of undetermined significance; CIN, cervical intraepithelial neoplasia (by grade); HSIL, high-grade squamous intraepithelial lesion; ICC, invasive cervical cancer; LSIL, low-grade squamous intraepithelial lesion.

America were limited, but findings for HPV 16 and HPV 18 were compatible with those of Africa and Europe/North America, with HPV 16 and HPV 18 positivity tending to increase with severity of cervical diagnosis.

DISCUSSION

This meta-analysis describes HPV types across the complete spectrum of cervical disease, from infection to cancer, in WHIV.

The aim was to use cross-sectional prevalence of HR HPV types from a large systematic review to study HPV natural history in this population, given previous evidence that it is altered by HIV. We judged the ratio of positivity in HPV-positive ICC to that in HPV-positive normal cytological findings to be particularly informative, because it captures the complete carcinogenic process and avoids variations due to different quality standards of cytology and histology for intermediate lesions. In this respect,

Table 2. Number of HPV-Positive and HIV-Positive Women Tested and Proportion Positive for Individual HR HPV Types, by 4 Cervical Disease Grades and Region[a]

Type	Region	Normal No. Tested	Normal Positive, %	Low Grade No. Tested	Low Grade Positive, %	High Grade No. Tested	High Grade Positive, %	ICC No. Tested	ICC Positive, %
HPV 16	Africa	1692	12.6	1377	21.9	1104	31.3	702	46.6
	Europe/NA	1412	18.3	1485	15.6	473	34.9	16	62.5
	Asia	689	22.2	257	21.8	108	37.0	6	50.0
	Latin America	1058	23.5	492	24.8	56	37.5	0	…
HPV 18	Africa	1692	9.9	1377	13.5	1104	15.6	702	24.4
	Europe/NA	1412	9.1	1485	10.2	473	10.6	16	12.5
	Asia	689	14.7	257	11.3	108	11.1	6	33.3
	Latin America	1058	9.1	492	14.2	56	17.9	0	…
HPV 31	Africa	1325	7.3	1081	8.4	999	13.9	668	5.1
	Europe/NA	1360	11.8	1410	10.0	463	15.1	16	0.0
	Asia	683	15.2	245	10.6	104	14.4	6	33.3
	Latin America	1057	11.0	457	14.7	54	13.0	0	…
HPV 33	Africa	1416	6.6	1145	10.0	1031	14.5	697	5.2
	Europe/NA	1360	8.0	1410	7.4	463	13.4	16	12.5
	Asia	665	8.6	245	7.3	100	14.0	6	0.0
	Latin America	1058	7.1	492	8.3	56	7.1	0	…
HPV 35	Africa	1439	10.4	1203	15.8	1017	21.8	697	7.7
	Europe/NA	1344	6.8	1367	6.8	449	10.9	16	0.0
	Asia	665	6.6	248	7.3	100	2.0	6	0.0
	Latin America	760	8.9	409	8.3	44	13.6	0	…
HPV 39	Africa	1325	6.1	1056	9.5	969	9.7	627	3.3
	Europe/NA	1221	3.5	1344	3.2	429	5.1	16	0.0
	Asia	683	10.1	245	7.8	104	7.7	6	0.0
	Latin America	480	2.9	391	4.6	33	6.1	0	…
HPV 45	Africa	1349	6.1	1081	11.3	999	13.0	697	15.5
	Europe/NA	1370	6.2	1435	8.5	455	7.5	16	6.3
	Asia	689	4.6	257	5.1	108	2.8	6	0.0
	Latin America	911	4.4	454	7.0	37	8.1	0	…
HPV 51	Africa	1349	8.7	1081	13.2	999	15.8	625	4.8
	Europe/NA	1354	10.5	1416	9.5	441	9.1	16	0.0
	Asia	665	11.7	248	10.9	100	6.0	6	0.0
	Latin America	479	9.6	356	11.8	31	16.1	0	…
HPV 52	Africa	1421	12.9	1231	16.8	992	17.4	628	5.1
	Europe/NA	1383	13.4	1449	13.4	459	13.5	16	6.3
	Asia	683	12.7	251	12.7	100	17.0	6	0.0
	Latin America	898	2.9	406	15.3	40	10.0	0	…
HPV 56	Africa	1392	8.0	1145	11.8	1021	11.9	635	3.0
	Europe/NA	1302	8.5	1341	11.1	431	9.0	16	0.0
	Asia	683	9.7	248	11.7	100	7.0	6	0.0
	Latin America	762	5.4	376	13.8	31	16.1	0	…
HPV 58	Africa	1203	11.0	1030	15.2	963	24.2	654	8.1
	Europe/NA	1349	13.8	1400	12.4	459	14.2	16	6.3
	Asia	665	12.3	248	11.3	100	10.0	6	0.0
	Latin America	1057	12.4	457	18.8	54	24.1	0	…
HPV 59	Africa	1254	5.0	1057	8.6	1006	8.0	625	3.0
	Europe/NA	1145	5.6	1253	7.0	417	5.8	16	0.0
	Asia	665	8.9	245	3.3	100	4.0	6	0.0
	Latin America	822	6.1	386	17.4	40	5.0	0	…
HPV 68	Africa	1274	6.9	1063	9.4	981	9.1	557	3.1
	Europe/NA	1140	6.0	1241	6.7	374	5.6	3	0.0
	Asia	665	10.2	245	10.6	100	6.0	6	0.0
	Latin America	762	5.1	376	15.2	31	0.0	0	…

Abbreviations: HIV, human immunodeficiency virus; HPV, human papillomavirus; HR, high risk; ICC, invasive cervical cancer; NA, North America.

[a]Low and high grade include diagnoses by cytology and/or histology combined (see Methods).

we show that the clearest differences in HR HPV carcinogenicity that have supported HPV 16/18 genotyping algorithms for HPV-based screening for the HIV-uninfected population [2], and HPV 16/18 valency as the priority for HPV vaccines also hold true in WHIV, as does a particular importance of HPV 45 over other HR HPV types in Africa.

The steady rise in HPV 16 positivity through increasing severity of cervical disease from normal cytological findings to ICC confirmed HPV 16 to be by far the most carcinogenic HR HPV type in WHIV worldwide. This extends evidence of a high CIN3^{+} risk for HPV 16, versus other HR types in WHIV [14, 18], to risk of ICC. So despite evidence that HPV 16 is somewhat less affected by HIV-related immunodeficiency than other types [13, 16] and that high-grade lesions [15, 16] and ICCs [17] among WHIV are relatively more frequently infected with non-HPV 16 types than in equivalent diagnoses among HIV-uninfected women, HPV 16 remains the clear priority for prevention of ICC in WHIV worldwide.

HPV 18 is also enriched in ICC in WHIV compared with all lower grades of diagnosis, both in Africa and elsewhere, confirming a higher carcinogenic potential relative to all other non-HPV 16 types, as seen in similar meta-analyses in HIV-uninfected women [2]. In WHIV in Africa, HPV 45 was also clearly more carcinogenic than all other non-HPV 16/18 types, with an ICC:normal ratio similar to that for HPV 18. Of note, findings for HPV 18 and HPV 45 are not driven by their known propensity to cause ADC, because ADC accounted for only 27 (<4%) of ICC cases (among which HPV types 16, 18, 45, and 35 were detected in 6, 10, 6, and 2 cases, respectively). Rather, the underrepresentation of HPV 18 and HPV 45 in CIN3 in WHIV, as seen in the HIV-uninfected population [2], supports the evidence that HPV 18 and HPV 45 have a tendency to cause endocervical glandular lesions that are harder to detect by cytological screening [19]. This could partly explain why risks for CIN3 with HPV 18 do not seem clearly higher than with other HR HPV in prospective studies of HIV-uninfected women [4–6], and why no HPV 18–positive CIN2 or higher-grade lesions were detected in the only relevant prospective study of WHIV to date [18]. Of note, the relative importance of HPV 18 and HPV 45 increase between CIN3 and ICC and the HPV 18–positive fraction for ICC in Africa has been shown to be even higher in WHIV than in the HIV-negative population [17].

In Europe/North America, HPV 45 did not stand out from many other HR types. Indeed, in Europe/North America, HPV 33 (together with HPV 18) was the most common type in ICC after HPV 16. Although these findings need to be taken with the caveat that ICC cases were few, they nevertheless mirror those from the HIV-uninfected population, among whom HPV 45 is of particular importance in Africa, and the ICC:normal ratio for HPV 33 is higher than all other non-HPV 16/18 types, including HPV 45, in both Europe and North America [2].

In prospective studies from HIV-uninfected populations in North America [4], Europe [6], and Asia [20] HPV types 31, 33, 35, and/or 58 have each been reported to confer higher absolute risks for CIN3 than other non–HPV 16 HR types. We confirmed a strong enrichment of these types between normal cytological findings and high-grade lesions in WHIV in Africa, but their importance relative to HPV 16/18/45 dropped in cancer (ie, low ICC:CIN3 ratios).

We did not undertake a formal regional comparison of HPV type-distribution within specific lesion grades, owing to relatively small numbers other than for normal cytological findings. Nevertheless, the most consistent regional heterogeneity seen in similar meta-analyses of HIV-uninfected women—namely, a higher prevalence of HPV 35 and HPV 45 in Africa compared with elsewhere [2] —was also apparent across all lesions in WHIV.

Neither did we compare type-specific prevalence in WHIV with that in HIV-uninfected women by lesion grade because such a comparison is best performed restricted to studies that include both HIV-positive and HIV-negative women, to control for different HPV genotyping protocols. Indeed, 358 African WHIV with ICC were previously compared with 790 African women with ICC in the HIV-uninfected population from the same 7 studies [17], showing that HIV infection does indeed alter the relative carcinogenicity of HR HPV types: the fraction of ICC caused by HPV 16 was significantly lower, and that of HPV 18 concomitantly higher, in HIV-positive women.

Evidence of a higher burden of HPV in WHIV than in the HIV-uninfected population can be seen by region-specific comparisons with a meta-analysis of women with normal cytological findings [21]: HPV prevalence was 62% for HIV-positive versus 24% for HIV-negative women in sub-Saharan Africa, 30% versus 14% in Europe, and 30% versus 5% in North America.

General limitations associated with such cross-sectional meta-analyses include the variation in PCR-based HPV detection protocols, age ranges, and quality of diagnosis and cervical screening practices across included countries and studies. All these potential problems are mitigated, however, by restriction of HPV type-specific comparisons to women testing HPV-positive, and adjustment of ICC:normal ratios for PCR primers did not materially affect main findings (data not shown). A particular limitation of the current meta-analysis, however, was the scarcity of data on HIV-positive ICC outside Africa, limiting the interpretation of relative carcinogenicity for non–HPV 16 types in non-African regions, for which there may be some heterogeneity in HPV type distribution and/or relative carcinogenicity [2]. We were not able to evaluate the specific propensity of HPV 58 to cause ICC in East Asian populations [2, 20], owing to the underrepresentation of East Asian WHIV. Furthermore, we did not have information on level of immunodeficiency of HIV-positive women, and it is possible that the moderate lack

of HPV 16 among HPV-positive women would be stronger among those that were the most immunosuppressed [13].

Finally, because of the lack of individual-level data on the type-specific breakdown of multiple infections, type-specific estimates include types present in multiple HPV infections. This is a problem for all such meta-analyses, but is a particularly important issue in WHIV, among whom the prevalence of multiple HPV infections is known to be higher than in the HIV-negative population [17]. Of note, in a subset of studies with the relevant data available, the proportion of HPV-positive women infected with multiple HPV infections was 41% in normal cytological findings versus 30% in cervical cancer, but rose to 55% and 67% of low- and high-grade lesions, respectively, highlighting problems of attributing type-specific causality in intermediate lesions in WHIV. Of note, testing for HPV from biopsy specimens is known to reduce the prevalence of multiple infections [2], but only for cervical cancer were a majority of cases derived from biopsy specimens (78%); all other diagnoses were tested almost uniquely from cervical cells (see Supplementary Table 1).

With respect to improving risk stratification among HPV-positive WHIV, referring HPV 16– and HPV 18–positive women for special management will be promoted via the existence of clinical guidelines, in the framework of cotesting with cytology [22] or primary screening [23], and the development of Food and Drug Adminstration–approved [24, 25] tests relevant to such algorithms. For a small increase in the number of women being referred, however, adding HPV 45–positive WHIV for special management might be particularly justifiable for Africa and is inherent in certain partial genotyping tests [26].

The World Health Organization currently recommends HPV-based screen and treat algorithms to be applied irrespective of HIV status [27], and CIN2$^+$ and CIN3$^+$ risks among HR HPV–negative women with normal cytological findings are similarly low in WHIV as in HIV-uninfected women, suggesting that HPV cotesting algorithms are also relevant to WHIV [28]. Given the broad consistency of the current findings on the relative carcinogenicity of HR HPV types in WHIV compared with those in HIV-uninfected population, most notably for HPV 16/18, but also for HPV 45 and HPV 33, there would also seem no reason to change partial genotyping protocols according to HIV status. Although absolute risks for cervical cancer associated with any given HPV type may be higher in WHIV than in women uninfected with HIV, type-specific risk stratification remains relevant.

In conclusion, although HIV-associated immunosuppression is known to alter the relative carcinogenicity of HR HPV types [17], the risk stratification offered by partial HPV genotyping tests still has relevance to HIV-positive women and may be of particular utility for prioritizing the diagnostic workup of WHIV in low-infrastructure settings [29, 30], which would be otherwise overburdened with the management of all HR HPV–positive women.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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