

Is HIV Infection a Cofactor for Cervical Squamous Cell Neoplasia?¹

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Abstract

The objective of this study was to test the hypothesis that HIV interacts with human papilloma virus (HPV) to increase the odds of cervical neoplasia.

The study design was a meta-analysis using data pooled from published sources. Studies published between January 1986 and March 1998 were eligible for inclusion if they included data on neoplasia (cytology-based), HIV (defined by laboratory and/or standard clinical criteria), and HPV (assessed by PCR, Southern blot, dot-blot hybridization, or cytology of an otherwise well designed study) among nonpregnant women. Blinded data abstraction was performed independently by the investigators.

There were 15 studies that were eligible and presented data in a format that could be abstracted for analysis. Data were pooled using a Mantel-Haenszel summary odds ratio (OR); generalized estimation regression equations were used to examine independent effects of HIV and HPV. Overall, based on the Mantel-Haenszel ORs, there was a strong overall association between HPV and neoplasia [OR, 8.1; 95% confidence interval (CI), 6.5–10.1]. Stratifying by HIV status, HIV-positive women had higher odds of disease (OR, 8.8; 95% CI, 6.3–12.5) than HIV-negative women (OR, 5.0; 95% CI, 3.7–6.8). In the regression model, there was an interaction between HPV and HIV ($P = 0.01$); immunosuppression also tended to predict neoplasia ($P = 0.058$).

HIV seems to be a cofactor in the association between HPV and cervical neoplasia; this effect may vary

by level of immune function. These speculations are biologically plausible. Additional data from large, well designed studies are needed to confirm these hypotheses.

Introduction

More than one-third of the 8 million persons infected with the HIV virus worldwide are women (1), and AIDS is rapidly becoming a leading cause of death in women, especially in developing countries (2). Likewise, worldwide, cervical cancer is a leading cancer cause of death in women, particularly in developing countries (3).

Numerous studies of HIV infection in association with CN³ (4) prompted the CDC to add invasive cervical cancer to their revised definition of AIDS-related conditions (5). However, the meaning of observed associations between HIV and CN is not clear. Several researchers have suggested that the relationship is not etiological because, in the United States where data are most complete, there has yet to be an increase in the incidence of cervical cancer parallel to the increasing rates of HIV infection in women (6). Others have suggested that the association between HIV and CN is due to uncontrolled confounding by factors such as HPV, or other sexual and reproductive variables (7). Alternatively, the relationship between HIV and CN may be causal, either directly via depressed cellular immunity, or as a cofactor with HPV (8, 9).

Because there are few controlled studies testing the relationships between HIV, HPV, and CN, we pooled data from published sources to explore these relationships. We hypothesized that the relationship between HPV and neoplasia would be modified by HIV, with HIV-positive women demonstrating higher odds of disease in the presence of HPV than HIV-negative women. Moreover, we postulated that among HIV-infected women, women with higher levels of immunosuppression would have higher odds of neoplasia in the face of HPV infection than women with lower levels of immunosuppression.

Materials and Methods

A meta-analysis was conducted pooling data from published sources to address the research objectives. Meta-analysis is a technique that can be used to summarize results of studies performed in diverse settings with differing methodologies (10–13). Such analyses are useful when no one study has sufficient power to address a particular question; meta-analysis is also useful to answer questions that were not posed in the original studies. All of these issues were considered in our choice of meta-analysis. However, given the post-hoc nature of these analyses, the results should be considered as hypothesis-generating (12).

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³ The abbreviations used are: CN, cervical neoplasia; CDC, Centers for Disease Control; HPV, human papilloma virus; SIL, squamous intraepithelial lesion; OR, odds ratio; CI, confidence interval; MH, Mantel-Haenszel; SIL, squamous intraepithelial lesion.

Data Sources. Multiple sources were used to identify all potential research for inclusion in the analysis. First, a Medline search was conducted for all English language articles published between January 1986 and March 1998. The earlier date of 1986 was selected because AIDS was not well described or reported in women before this time period. The following key words were used for the search: Pap smear, cervical cytology, cervical cancer, CN, cervical intraepithelial neoplasia, SIL, or invasive cervical cancer, and AIDS, HIV, and HPV. Second, to ensure complete ascertainment (14), the search was supplemented by a review of *Current Contents* (1997–98) and bibliographies of all pertinent original and review articles.

Third, given the rapidly evolving database in this subject area, all meeting abstracts of the Annual International Conferences on AIDS and Annual Papillomavirus Workshops were reviewed for titles containing the same key words. For identified abstracts, all author names were searched on Medline and authors and titles were searched in *Current Contents* to identify potential published journal sources of these data. Finally, for articles that appeared eligible, but did not contain data in a format that permitted abstraction and reanalysis, the authors were contacted to provide the raw data.

Study Selection. “Methods” and “Results” sections were reviewed for eligibility by three investigators (J. S. M., P. K., L. E.) using a standardized abstraction form (15, 16). Reviewers were blinded to author names, journal, and the discussion sections. Study inclusion criteria included having data available on HIV, HPV, and CN among nonpregnant women; if pregnancy status was not included, it was assumed that the subjects were not pregnant. Additional inclusion criteria included having appropriate comparison groups, laboratory measurement of HIV infection and degree of HIV immunosuppression, HPV infection and types, and an adequate Pap smear classification schema. If data, or data subsets, had been published in more than one forum or time period, the largest data set that contained the highest quality of information was selected for the final sample. Review articles, case reports, and animal studies were excluded from consideration.

HIV infection was defined serologically (from ELISA and Western blot tests) or clinically, using standardized criteria (1, 17, 18). All HIV viral types were considered (*i.e.*, HIV-1 and HIV-2). Cellular immune suppression among women with HIV infection was defined either clinically by CDC class (class III and IV, symptomatic *versus* class II, asymptomatic; Refs. 1, 17, 18), or by laboratory measures (CD4+ count, <500 *versus* \geq 500; 19). HPV positivity and types were measured by Southern blot, PCR, or dot-blot hybridization. Studies diagnosing HPV by the clinical presence of condyloma (on physical examination or colposcopy), cytological interpretation of a Pap smear, histological interpretation of a biopsy specimen, or filter *in situ* hybridization were only considered if the remainder of the study was of high quality. CN was defined as low-grade SILs or more severe (Bethesda system) or the equivalent; histological diagnoses were not available from the majority of studies. There were insufficient numbers of cases to stratify analyses by level of neoplasia (*i.e.*, low *versus* high-grade SIL) or HPV type. Adenocarcinomas of the cervix were excluded.

Data Abstraction. For studies eligible for inclusion, the following data were abstracted: the study setting; country/city; design, number, and age of subjects; source of control population; mode of HIV transmission; type of HIV virus, if specified; sexual and reproductive risk factors; sexually transmitted disease history or concurrence; degree of HIV immunosuppres-

sion; and numbers of subjects in each exposure and disease subcategory.

The concordance between investigators was 100% for final sample inclusion/exclusion status, and 95% for specific data items among the studies in the final study sample. Discrepancies were resolved by discussion, review of the methods and/or results, and consensus.

Statistical Analysis. Overall and strata-specific ORs and 95% CIs were calculated individually for each study 2×2 table using standard techniques (20). Because many studies had data tables with zero cell counts, 0.5 was added to each cell of all studies for calculation of an estimated OR and CI. The MH test for homogeneity of studies was conducted separately for the overall and sub-strata. In strata with zero cells, this test could not be calculated because we could not calculate variance. In these situations, the individual studies were examined for consistency. Rejection of the null hypothesis of heterogeneity implies that the effects are homogeneous across studies. If there was homogeneity of effects, the MH method was then used for calculating a summary OR based on the raw data, adding 0.5 to zero cells. This method weighs studies by the inverse of the within-study variance to provide a pooled estimate of the OR; thus the sample size of a study determines its contribution to the summary OR (20, 21). The MH summary OR for pooled data are still valid when data are heterogeneous, although the result is less powerful than in the condition of homogeneity (20). Interaction was considered to occur if the substratum ORs were unequal (21). In addition, to quantify the independent effects of HPV and HIV, and to formally test for interaction, we used a generalized estimation equation logistic regression model (22). This method takes the same form as a standard logistic regression, but adjusts parameter estimates for observation intercorrelation attributable to study observation clustering. The model-dependent variable was CN, and the independent variables were HPV infection, HIV infection (positive or negative), HIV immunosuppression (suppressed HIV positive, nonsuppressed HIV positive, and HIV negative), and interactions between HPV and HIV.

Results

There were 78 original research articles identified by the search; thirty (38.5%) of these met the criteria for study inclusion. The most common reason for exclusion included lack of one or more comparison groups ($n = 39$; Refs. 6, 23–44, 33, 45–58); the remainder were excluded due to a focus on non-HIV-related immunosuppression ($n = 3$; Refs. 59–61), pregnant women ($n = 1$; Ref. 62) or contained data reported more completely in another publication ($n = 4$; Ref. 63–66), or has substantial design flaws threatening validity ($n = 1$; Ref. 67). Among the 30 studies potentially eligible for inclusion, 11 included data that could be abstracted for analysis (7, 68–77); the remaining 19 study authors were contacted to provide raw data for analysis (26, 78–94). We received a response from 8 of 19 authors (78–82, 90–92); of these, four provided data in a manner that was amenable to analysis (81, 82, 91, 92); others provided data that did not correspond to the data in the original report (*i.e.*, included updated and unpublished data). We also contacted and received additional data from two of authors whose original studies included some raw data (72,70). One study (90) conducted additional analyses on specimens collected from an earlier study (89). Thus, we present results for a total of 15 studies (Table 1; Refs. 7, 68–77, 81, 82, 91, 92); the remaining 15 potentially eligible studies were excluded. The excluded studies were very similar to those included in design,

Table 1 Characteristics of final study sample^a

Author, year of publication	Place, year of data collection	Study design ^b	Sample size ^c	Mean age, (range)	Setting	Population	Method of SIL diagnosis	Method of HPV determination	Measure of immune function
Matorras <i>et al.</i> , 1991	Spain, 1986–89	Cross-sectional	83	31.8	Hospital colposcopy clinic	IVDU, ^d prostitutes, heterosexual transmission	Cytology	Cytologic	p24 antigen
Schafer <i>et al.</i> , 1991	Berlin, Germany	Cross-sectional	713	28.9 (21–34)	Hospital in- and out-patient	IVDU (76%), heterosexual transmission	Cytology and histology	Cytologic	CDC class and CD4+ count ^e
Vermund <i>et al.</i> , 1991	Bronx, NY, N/A	Cross-sectional	96	34.6 (N/A)	Methadone maintenance program, and medical center HIV programs	11.5% pregnant; 35.3% of HIV + asymptomatic	Cytology; Ayre's spatula and cotton swab	Cervico vaginal lavage collection; Southern blot; typing not done	CDC staging II, vs III and IV
Johnson <i>et al.</i> , 1992	Washington, DC, N/A	Cross-sectional	30	34.7 (20–64)	Hospital HIV and women's health clinic	37.5% IVDU 43.8% heterosexual; mean time since HIV diagnosis 2 yrs	Cytology and histology	Swab collection; dot-blot and PCR; typing done	CD4+ count
Kreiss <i>et al.</i> , 1992	Nairobi, Kenya, 1989	Cross-sectional	63	30.6 yrs (N/A)	Community HIV/STD research clinic	Prostitutes; 3% pregnant; 93% of HIV + CDC Class 2	Cytology; Ayre's spatula and cytobrush	Swab collection; Southern blot; typing done ^e	N/A
Laga <i>et al.</i> , 1992	Kinshasa, Zaire, 1989	Cross-sectional	82	26.4 yrs (N/A)	Community women's health clinic	Prostitutes; working for average of 4.6 yrs	Cytology; Ayre's spatula and cytobrush	Cervico-vaginal lavage collection; dot-blot; Southern blot; typing done ^e	N/A
Gentile <i>et al.</i> , 1993	Bologna, Spain, N/A	Cross-sectional	32	29 (20–35)	Hospital colposcopy clinic	IVDU (84%), heterosexual transmission	Cytology and histology	Cytologic and histologic	N/A
Williams <i>et al.</i> , 1994	San Francisco, CA, 1990–91	Cross-sectional	92	37 (20–62)	Hospital clinical OPD detox and methadone programs	IVDU	Cytology; Ayre's spatula and cytobrush	Swab collection; dot-blot and PCR; typing done	CD4+ count
Branca <i>et al.</i> , 1995	Rome, Italy, 1994	Cross-sectional	221	27.5 (N/A)	Hospital STD clinics; drug treatment program	HIV + HIV-IVDU; heterosexual transmission	Cytology	Cytology	CD4+ count ^e
Sun <i>et al.</i> , 1995 ^a	Newark, NJ, N/A	Cross-sectional	642	Median, 34	STD, HIV, and methadone clinics	HIV + HIV–	Cytology	PCR	CD4+ count ^e
Langley <i>et al.</i> , 1996	Senegal, Africa 1990–93	Cross-sectional	681	29 (22–40)	STD clinic	HIV _{1/2} + HIV–	Cytology	PCR	CD4+ count
Melbye <i>et al.</i> , 1996	Denmark, 1991–93	Cross-sectional	125	N/A (25–30)	Hospital HIV/infectious disease clinic	HIV + HIV–	Cytology	PCR	CD4+ count ^e
Shah <i>et al.</i> , 1997	Baltimore, MD, N/A	Cross-sectional	263	N/A	IVDU	HIV + HIV–	Cytology	PCR	CD4+ count
LaRuche <i>et al.</i> , 1998	W. African, 1995–96	Cross-sectional	595	Median, 28	Hospital and community gynecology clinics	HIV + HIV–	Cytology	PCR	CD4+ count ^e

^a All HIV determinations were done using ELISA and Western blot.

^b Study design classification was based on how data were collected that were used in this analysis. For example, if analyses were done on data obtained at one point in time from an on-going cohort, the study was classed as cross-sectional.

^c Sample size with complete data on HIV, HPV, SIL, or HIV severity level, HPV and SIL; may be fewer than total reported sample in original study.

^d IVDU, intravenous drug use; STD, sexually transmitted diseases; N/A, not available.

^e Raw data on immune function by HPV and neoplasia status could not be abstracted.

^f Raw data on HPV types not extractable from published tables.

^g Includes data previously published in Wright *et al.*, 1994.

year of publication, mean population age, sample size, settings, methods, and results [*i.e.*, magnitude of results and proportion with null results (data not shown)].

HIV Infection. Thirteen studies (7, 68–72, 74–77, 81, 91, 92) contained sufficient data for inclusion in analyses of the relationship between HIV, HPV, and SIL; two only included data for HIV-positive women (73, 82). The individual studies all demonstrated a significant association between HPV and SIL among HIV-infected and -noninfected women (Table 2). Together, the pooled data demonstrated that women who were HPV positive had odds of having SIL that were 8.1 times higher (95% CI, 6.5–10.1) than the odds for HPV-negative women. Stratifying by HIV status, the odds of SIL among HIV-positive women were generally higher than the odds for HIV-negative women. The pooled summary OR for the association between HPV and CN were 8.8 (95% CI, 6.3–12.5) and 5.0 (95% CI, 3.7–6.8), respectively, for HIV-positive and -negative women. These data suggest that HIV interacts with HPV to increase the odds of neoplasia; however, because the CIs overlap minimally (upper limit for HIV- 6.8 *versus* lower limit for HIV+ 6.3), we can rule out a lack of interaction effect.

Immune Function. Six articles (7, 72, 73, 81, 91, 92) contained sufficient data among HIV-positive women to evaluate the role of immunosuppression on the odds of neoplasia. When data were stratified by level of immunosuppression, the OR was higher for suppressed than nonsuppressed women in four of six studies; point estimates for the two studies with nonsignificant results (*i.e.*, CI includes 1) are more difficult to interpret (Table 3).

Logistic Regression Model. Table 4 summarizes the multivariate results. HPV was the strongest predictor of neoplasia, considering HPV, HIV, and immunosuppression among HIV-infected women. As suggested by the univariate summary ORs, there was a significant interaction between HPV and HIV infections; immunosuppressed women were also more likely to have neoplasia.

Discussion

The results of this meta-analysis suggest that HIV is a cofactor in the association between HPV and CN; this effect seems to vary by level of immune function. These hypotheses are biologically plausible and are supported by the general consistency of findings across studies and similar types of neoplasia (*i.e.*, anal) and the dose-response-like relationship for level of immunosuppression.

Although the precise biological mechanism underlying the interaction between HIV and HPV has yet to be determined, there are two potential mechanisms for the interaction: (a) HIV and its resultant effects on immune function affect the susceptibility to, severity of, and/or potential oncogenicity of HPV; and/or (b) there is a molecular interaction between HIV and HPV.

Biological mechanisms through which cellular immunosuppression could facilitate the oncogenic effects of HPV include prolonging the length of time of an HPV infection (95–97), increasing HPV viral load (96, 98), allowing for more rapid HPV replication (65), persistence (56), or progression (65), or impacting on Langerhans' cells (90). Enhanced oncogenicity of HPV in HIV-infected women is also supported by clinical observations of more rapidly progressive disease (37, 99) and higher rates of recurrence among HIV-positive compared with HIV-negative women with HPV (40, 100, 101). Indirect evidence also links cellular immune responses and HPV. For example, there are increases in both HPV and CN in transplant

patients, pregnant women, aged women, and women with AIDS (4, 6, 37, 61–63, 102–107). Cellular immune suppression also seems to increase the risk of anal neoplasia among HIV-positive men with anal HPV infection, where risk of neoplasia increases with increasing level of immunosuppression (108, 109). Preliminary data also suggest a molecular interaction between HIV and HPV, where the HIV-1 tat protein transactivates HPV and effects expression of HPV- E2 and the E6 and E7 oncoproteins (110, 111).

Our pooled results suggesting an interaction between HIV and HPV are consistent with the results of other investigations (65, 78). For example, Klein *et al.* (65) noted odds of neoplasia of 43.6 (95% CI, 2.3–818.7) and 20 (95% CI, 2.2–180.7) among HIV-infected women with moderate or severe immunosuppression, compared with odds of 3.9 (95% CI, 1.2–12.6) among HIV-negative women (65). In our study, 11 of 13 studies (85%) noted higher odds of neoplasia in HIV-positive women compared with HIV-negative women with HPV infection; the remaining two studies had wide CIs and nonsignificant results. Last, all but two of the studies that included data on immune function suggest that there is a dose-response relationship, with women having the lowest CD4+ counts having the highest risk of disease. In one study where the relationship was not significant for a cut-point of a CD4+ count of 500, there was an increased odds of disease in women with CD4+ counts below 200 compared with those with higher counts (73). In the other inconsistent study (91), nonsignificant results for suppression may be a result two factors. First, data from HIV-1- and HIV-2-infected women were combined, where CD4 counts for HIV-2-infected women were more similar to those in HIV-negative women, biasing results to the null. Second, there were only 15 women with CD4 counts of <500, and clinically apparent immunosuppression was rare in this group. Further study of HIV-1 and -2 infections in relation to HPV and neoplasia risk will be important (91).

Our conclusions must be considered in light of several caveats, including the post-hoc nature of the analysis, the inability to assess the role of uncontrolled confounding, power, inconsistent studies, possible misclassification, inability to separate types of HPV and degree of neoplasia (*i.e.*, preinvasive and invasive), and lack of data on temporality of effects.

A meta-analysis such as this, where the original data were collected for other purposes, should be considered preliminary; prospective data collection will be important to confirm our hypothesis. Also, meta-analyses are prone to “publication bias,” where studies with positive effects are more likely to be published than those with no association. Such bias may overestimate neoplasia risks, but should not have affected our conclusions regarding interactions.

Pooled ORs for the association of neoplasia and HPV showed clinically meaningful differences between HIV-positive and -negative women, and suggested an interaction of HIV and HPV, with minimal overlap in CIs; this interaction was significant in multivariate analysis ($P = .01$). As more quality data are published, it will be important to extend our analyses to confirm and explain interaction effects.

Several variables may confound or bias the relationships being explored, such as route of HIV transmission, type of HIV (91), anti-HIV medication use, other sexual risks, country, and HIV prevalence in the general population. Unfortunately, raw data were not presented in such a manner to allow for control of these variables in our analyses.

Some data from three studies were contradictory or inconclusive. There are several possible explanations of these apparently discordant findings, including true differences, lack of

Table 2 Odds of neoplasia by HIV status

Author, Year	Country	All women		HIV+ women		HIV- women		
		SIL+ ^a	SIL-	SIL+ ^a	SIL-	SIL+ ^a	SIL-	
Johnson <i>et al.</i> , 1992	USA	HPV+		7	4			
		HPV-		1	18			
		OR ^b		20.6				
		95% CI		2.7-157.0				
Van Doornum <i>et al.</i> , 1993	Netherlands	HPV+	0	11	0	8	0	3
		HPV-	2	56	0	17	2	39
		OR ^b	1		2.1		2.3	
		95% CI	0.04-21.9		0.04-112.9		0.09-56.9	
Matorras <i>et al.</i> , 1991	Spain	HPV+	38	20	11	1	27	19
		HPV-	1	24	0	2	1	22
		OR ^b	30.7		38.3		21.2	
		95% CI	5.4-173.6		1.2-1245.1	3.7-121.9		
Schaffer <i>et al.</i> , 1991	Germany	HPV+	47	82	36	17	11	65
		HPV-	27	557	10	48	17	509
		OR ^b	11.7		9.6		5.1	
		95% CI	6.9-19.7		4.0-23.2		2.3-11.2	
Vermund <i>et al.</i> , 1991	USA	HPV+	17	20	14	13	3	7
		HPV-	6	53	3	21	3	32
		OR ^b	7.0		6.6		4.3	
		95% CI	2.5-19.8		1.7-25.5		0.8-23.3	
Kreiss <i>et al.</i> , 1992	Kenya	HPV+	13	13	9	10	4	3
		HPV-	3	34	2	21	1	13
		OR ^b	9.9		7.8		11.6	
		95% CI	2.6-37.4		1.6-37.7		1.3-103.4	
Laga <i>et al.</i> , 1992	Zaire	HPV+	8	13	8	9	0	4
		HPV-	4	57	3	21	1	36
		OR ^b	8.1		5.5		2.7	
		95% CI	2.2-37.4		1.3-23.7		0.1-76.8	
Gentile <i>et al.</i> , 1993	Spain	HPV+			6	6		
		HPV-			1	19		
		OR ^b			13.0			
		95% CI			1.8-94.6			
Williams <i>et al.</i> , 1994	USA	HPV+	5	26	5	19	0	7
		HPV-	0	61	0	20	0	41
		OR ^b	25.5		11.6		5.5	
		95% CI	1.4-487.4		0.6-223.3		0.1-301.0	
Branca <i>et al.</i> , 1995	Italy	HPV+	29	52	23	35	6	17
		HPV-	10	130	5	58	5	72
		OR ^b	6.3		7.0		4.9	
		95% CI	2.9-13.5		2.5-19.5		1.4-17.0	
Sun <i>et al.</i> , 1995	USA	HPV+	77	222	66	126	11	96
		HPV-	9	334	6	128	3	206
		OR ^b	12.3		10.4		7.0	
		95% CI	6.1-24.6		4.5-24.1		2.1-23.8	
Melbye <i>et al.</i> , 1996	Denmark	HPV+	14	54	11	24	3	30
		HPV-	1	56	0	28	1	28
		OR ^b	10.0		26.8		2.2	
		95% CI	1.8-56.1		1.5-477.8		0.3-15.8	
Langley <i>et al.</i> , 1996	Africa	HPV+	32	261	10	60	22	201
		HPV-	14	374	1	54	13	320
		OR ^b	3.2		6.3		2.7	
		95% CI	1.7-6.1		1.1-36.3		1.3-5.3	
Shah <i>et al.</i> , 1997	USA	HPV+	22	122	21	102	1	20
		HPV-	3	116	2	55	1	61
		OR ^b	6.1		4.7		3.0	
		95% CI	1.9-19.4		1.2-18.0		0.3-30.0	
LaRuche <i>et al.</i> , 1998	Africa	HPV+	151	95	81	30	70	65
		HPV-	57	292	11	43	46	249
		OR ^b	8.1		10.1		5.8	
		95% CI	5.5-11.2		4.7-21.9		3.7-9.1	
MH test of homogeneity		NS ^c		NS				
MH summary OR ^d		8.1		8.8		5.0		
95% CI		6.5-10.1		6.3-12.5		3.7-6.8		

^a SIL includes high- and low-grade SILs diagnosed cytologically.

^b OR *not* controlled for potential confounders; 0.5 added to all cells to estimate the OR and CIs.

^c NS, not significant (*i.e.*, the hypothesis that the studies are not homogeneous can not be rejected).

^d In analyses excluding the four studies that diagnosed HPV on cytology/histology alone (Matorras, Schaffer, Gentile, and Branco), the MH summary OR for all women is 7.4 (95% CI, 5.7-9.6), for HIV+ women it is 8.7 (95% CI, 5.8-13.2), and the OR for HIV- women is 4.6 (3.3-6.4).

Table 3 Odds of neoplasia by level of immune function

Author, year	Country		All HIV+ women		Suppressed ^a		Nonsuppressed	
			SIL+ ^b	SIL-	SIL+	SIL-	SIL+	SIL-
Matorras <i>et al.</i> , 1991	Spain	HPV+	11	1	1	0	10	1
		HPV-	0	2	0	0	0	2
		OR ^c	38.3		NE ^d		35.0	
		95% CI	1.2-1245.1				1.1-1142.0	
Vermund <i>et al.</i> , 1991	USA	HPV+	14	13	13	10	1	3
		HPV-	3	21	1	9	2	12
		OR ^c	6.6		8.1		2.4	
		95% CI	1.7-25.5		1.2-54.5		0.21-22.4	
Johnson <i>et al.</i> , 1992 ^e	USA	HPV+	7	4	5	4	2	0
		HPV-	1	18	1	13	0	5
		OR ^c	20.6		11		55.0	
		95% CI	2.7-157.0		1.4-89.6		0.8-3651.0	
Williams <i>et al.</i> , 1994	USA	HPV+	5	19	4	9	1	10
		HPV-	0	20	0	10	0	10
		OR ^c	11.6		10.0		3.0	
		95% CI	0.6-223.3		0.5-210.2		0.1-82.4	
Langley <i>et al.</i> , 1996 ^f	Africa	HPV+	10	60	3	7	5	27
		HPV-	1	54	0	5	0	36
		OR ^c	6.3		4.9		14.6	
		95% CI	1.1-36.3		0.2-118.6		0.8-275.4	
Shah <i>et al.</i> , 1997	USA	HPV+	21	102	15	61	6	41
		HPV-	2	55	1	29	1	26
		OR ^c	4.7		5.0		2.8	
		95% CI	1.2-18.0		0.8-28.0		0.4-17.4	
MH test of homogeneity			NE		NE		NE	
MH summary OR			8.8 ^g		7.06		4.6	
95% CI			6.3-12.5		2.5-19.7		1.5-14.2	

^a Suppression defined as CD4+ count <500 or CDC class III or IV (symptomatic); nonsuppressed includes CD4+ counts ≥500 and CDC class II (asymptomatic).

^b SIL includes high- and low-grade SILs diagnosed cytologically.

^c OR not controlled for potential confounders; 0.5 added to all cells to estimate the OR and CIs.

^d NE, not estimatable.

^e If the data from the study by Johnson *et al.*, which shows differences in odds of cervical neoplasia by a somewhat different CD 4 count, but not for the level of 400 used here, is excluded the summary odds-ratio is.

^f Summary odds ratio excludes data from Langley *et al.*, since this study included HIV-1 and HIV-2 infected women, where HIV-2 patients were similar to HIV negative patient. See discussion.

^g Summary OR derived from all 15 studies in Table 2; summary OR's by level of suppression derived from 6 studies with data available.

power, chance, selection bias, confounding or differential misclassification, a short duration of HIV infection relative to the natural history of cervical carcinogenesis, competing mortality, and/or difficulty accurately diagnosing cervical cancer and its precursors in HIV-infected women. For example, in the study by Johnson *et al.* (73), although more than three-quarters of the HIV-infected women who were HPV positive had HPV types of high to moderate oncogenic potential, only one woman was diagnosed with high-grade SIL. The mean time from infection to evaluation was 24 months; thus, many of these women may still develop neoplasia. In two studies, failure to detect strata-specific differences between HIV-positive and -negative women may have been due to the facts that in one study 93% of the HIV positives were asymptomatic (CDC stage II; Ref. 68), and the other study had a small sample, sparse data, and limited power to detect effects (70).

Misclassification of subjects can effect risk estimates. Two-thirds of the included studies (six of nine) relied on a cytological diagnosis of CN; only three studies included histopathological results. If women with neoplasia are falsely labeled as normal, estimates will underestimate the true effect, if misclassification is random with respect to HPV or HIV infection status. If there is some systematic misclassification of women (differential misclassification), results may produce artificially high or low estimates of risk. It is difficult to ascertain the potential for differential misclassification in the studies

included in this analysis (28, 83, 85, 112, 113), although there is no reason to believe that any misclassification would be not differential with respect to HIV status, the variable of interest for this study.

It would have been interesting to further stratify our results by HPV type (*i.e.*, low versus high oncogenicity), numbers of HPV types, and viral load because these factors seem to be related to the risk of neoplasia (63, 65, 73, 92, 114, 115). Finally, our data were all cross-sectional and do not allow us to determine the temporality of effects. For instance, does having HPV and/or CN facilitate transmission of, and infection with, the HIV virus; or does having HIV immunosuppression enhance the effects of HPV in producing CN? The precise role of HPV in transmission of HIV is not yet known (9, 116-119). This is an important area for future research.

If HIV is further confirmed as a cofactor with HPV in cervical carcinogenesis, the roles or modifying influences of different HIV viral types and other potential cocarcinogens will need to be evaluated in well-controlled, prospective research (91, 120, 121). Examples of factors which have been suggested to modulate cervical cancer risk include repeated and/or concurrent exposure to sexually transmitted antigens, or cervical trauma (120, 121), cigarette-related carcinogens (122, 123), contraceptives (123, 124), and nutritional deficiencies (125), including B-carotene (126), folate (127), and vitamin C (128, 129). As more women are included in clinical trials and receive

Table 4 Adjusted odds of CN^a

Variable	Coefficient	OR	95% CI
HPV			
Positive	1.63	5.10	4.28–6.10
Negative		1.00	
HIV	0.57	1.76	1.31–2.38
		1.00	
HIV			
Positive, immunosuppressed ^b	0.22	1.24	1.04–1.49
Negative		1.00	
Interaction terms			
HPV*HIV	0.41	1.20	1.29–1.75
HPV*HIV, suppressed ^c	0.02	1.02	0.76–1.35

^a All variables and interactions adjusted for the remaining variables in a generalized estimation logistic regression equation.

^b Immunosuppressed is defined as having a CD4 count of ≤ 400 ; nonsuppressed is defined as a CD 4 count of >400 .

^c The referent group for interaction terms is HIV-negative women. Interactions are between having *versus* not having HPV, and being HIV immunosuppressed *versus* non-HIV infected; and having *versus* not having HPV, and being HIV+, but not immunosuppressed *versus* non-HIV infected.

primary preventive care for HIV infection, the observed relationships between HIV, HPV, and CN will need to be reevaluated, controlling for use of AZT or other drugs and access to care. Finally, if the role of cellular immunity is confirmed for HPV-mediated carcinogenesis, a critical question that must be addressed is whether less extreme immune depression, such as that seen with normal aging or chronic disease, also increases the risk of cervical cancer.

The elucidation of the relationships between immune function, HPV, and cervical carcinogenesis will be critical to efforts to preventive efforts, including HIV and HPV vaccinations. Such efforts will be key to decreasing the high burden of disease and deaths attributable to the dual epidemics of cervical cancer and HIV infection in medically under-served women worldwide.

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