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article

Association of human papillomavirus with HIV and CD4 cell count in women with high or low numbers of sex partners

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Objective: To explore whether HIV serostatus (HIV-1, HIV-2, and dual (HIV-D) reactivity) and CD4 cell count affect human papillomavirus (HPV) in two groups of women from Côte d'Ivoire.

Methods: We conducted a cross sectional study of two groups of women. One group had low numbers of lifetime sex partners (maternal women, n=258) and were enrolled based on HIV serostatus. The other group had high numbers of sex partners (female sex workers, n=278) and all consenting self identified sex workers were admitted to this study. We collected epidemiological and clinical data, and cervicovaginal lavage for HPV testing.

Results: The groups had different distributions of HIV seroreactivity, but the rates of HPV DNA detection were similar. Most of the HPV DNAs detected in both groups were high risk types. A strong association of high risk HPV DNA and HIV-1 seropositivity was found in both maternal women (adjusted odds ratio (OR) 7.5 (95% CI 3.2–17.4)) and in sex workers (OR 5.0 (2.1–12.0)). The maternal group also showed an association of high risk HPV DNA detection with HIV-2 (OR 3.7 (1.6–8.5)) and HIV-D (OR 12.7 (4.3–37.5)) that was not observed in the sex workers. In addition, the association of high risk HPV DNA with HIV-1 in the maternal group was independent of low CD4 cell count, while in the sex workers the association depended on CD4 cell counts $\leq 500 \times 10^6/l$.

Conclusions: We found that an association between HPV and HIV varied depending on the sexual behaviour and CD4 cell count of the population examined.

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Introduction

An association of human papillomavirus (HPV) DNA detection with HIV infection has been described in several studies.^{1–10} High risk HPV types linked to cervical neoplasia have been more strongly associated with HIV infection than have low risk HPV types.^{7–11} Most studies have found the association of HIV and HPV in the setting of HIV associated immune suppression.^{6–8, 12} A few studies have examined the two viruses in the absence of measurable immune suppression, and have still found the association between HIV and HPV to be strong.^{9–13} Because HIV and HPV infections can be sexually transmitted and are associated with similar risk factors (for example, high number of sexual partners), a strong trend for co-infection with or without immune suppression could be expected. Another explanation for the association between HIV and HPV in the absence of immune suppression could be interaction of the viruses. For example, HIV-1 tat has been demonstrated to stimulate HPV in vitro.^{14–15}

Two biologically similar, sexually transmitted viruses, HIV-1 and HIV-2, circulate in west Africa.¹⁶ HIV-2 appears to be less virulent and disease progresses more slowly than with HIV-1.¹⁷ Serum can have dual serological reactivity to both HIV-1 and HIV-2, and in Côte d'Ivoire most of this dual serological reactivity is caused by mixed HIV-1/HIV-2 infections rather than serological cross reactivity.¹⁸ One

other group has examined the relation of HPV to HIV-1, HIV-2, and dual HIV-1 and 2 (HIV-D) infections in women. They found that HIV-2 and HIV-D infections conferred a similar risk of HPV DNA detection as HIV-1 infection.^{7–9} In an attempt to examine further the association of HPV with HIV types and immune suppression, we studied two groups of women with different sexual risk behaviours in Abidjan, Côte d'Ivoire.

Materials and methods

STUDY POPULATIONS

Women enrolled from 1990 to 1992 into a longitudinal study of mother to child HIV transmission¹⁹ were asked to participate in this study. We were interested in studying this cohort because we anticipated they would have a low number of lifetime sexual partners. The original enrolment criteria have been described.¹⁹ Briefly, a total of 18 099 women delivering at the maternal and child health centre in Abidjan, Côte d'Ivoire, were tested for HIV-1 and HIV-2 antibodies. Women positive for HIV-1, HIV-2, and HIV-D were asked to participate. For every HIV seropositive woman enrolled, two HIV seronegative women delivering at the centre were also invited to participate. If a woman declined to participate, the next individual with appropriate serostatus was asked. Routine medical care has been provided to women of this cohort since enrolment. Of those cohort members still receiving routine

medical care, 57 HIV-1 seropositive women, 57 HIV-2 seropositive women, 22 HIV-D seropositive women, and 122 seronegative women gave informed consent and agreed to participate in this study.

We were also interested in studying women with high numbers of sexual partners. Sex workers in Abidjan were contacted at sex work sites through a network of community based peer educators and invited to come to the Clinique de Confiance²⁰ for a physical examination, including a STD assessment and HIV counselling and testing. All consenting self identified sex workers who presented to the clinic were admitted to the study. None of the sex workers presenting to the clinic declined enrolment but some women declined to have an HIV test. The sex worker group included 109 HIV-1 seropositive, four HIV-2 seropositive, 63 HIV-D seropositive, 68 seronegative, and 34 women whose sera was not tested for HIV.

This study began in April 1994 and ended November 1994. Following counselling and informed consent, a standard questionnaire on sociodemographics and sexual behaviour was administered during an interview with a female nurse. The standard questionnaires were from the two separate studies^{19, 20}; however, additional questions related to obstetric and gynaecological history were added specifically for this study. A general, as well as gynaecological, examination was performed by a physician. Blood and cervicovaginal lavage samples were collected.

HIV SEROLOGY

Sera were tested for antibodies to HIV-1 and HIV-2 by a whole virus enzyme linked immunosorbent assay (ELISA) (Genetic Systems, Seattle, WA, USA) or a mixed antigen ELISA (Genelavia-mix, Diagnostics Pasteur, Paris); HIV serotyping was done by using a synthetic peptide based test (Pepti-LAV, Diagnostics Pasteur, Paris) and western blot (New-LAV blot, Diagnostics Pasteur, Paris, and HIV blot 2.2; Diagnostic Biotechnology, Geneva) only when ELISA and Pepti-LAV results were discordant. Women's HIV serostatus was classified as HIV-1, HIV-2, or HIV-D based on serological reactivity.²¹ Flow cytometry (FACScan; Becton Dickinson, Franklin Lakes, NJ, USA) was used for lymphocyte subset typing and counting.

LAVAGE SPECIMENS

We used cervicovaginal lavage to sample exfoliated cells from all areas of the lower genital tract. The cervix was visualised with a disposable plastic speculum, and the cervix and vagina were irrigated with 10 ml of normal saline. Samples were concentrated by low speed centrifugation. Cells were resuspended at 1:10 dilution in phosphate buffered saline (volume:volume), frozen, and shipped to the Centers for Disease Control and Prevention in Atlanta.

DETECTION OF HPV BY HYBRID CAPTURE

Hybrid capture tube assays for HPV DNA detection were performed according to the method provided by the manufacturer (Digene Diagnostics, Silver Spring, MD, USA). A volume of 100 µl of concentrated lavage sample was tested separately with probe A (low risk HPV types 6, 11, 42, 43, 44) and probe B (high risk HPV types 16, 18, 31, 33, 35, 45, 51, 52). A sample was considered positive when the relative light unit (RLU) ratio (RLU of sample/mean RLU of three positive controls) was ≥ 1 .

DATA ANALYSIS

HIV-1, HIV-2, and HIV-D were treated as separate independent variables in all analysis. Because few sex workers were HIV-2 seropositive, HIV-2 was not analysed for this group. Thirty four sex workers were not tested for HIV and were excluded from the analysis of HIV serostatus with HPV detection. Few women from the maternal group had ever smoked, and therefore this variable was not used in the analysis of this group.

All analysis were performed using PC-SAS version 6.10/6.11 (SAS Institute, Cary, NC, USA). The χ^2 test or Student's *t* test was used to compare differences between women with and without each type of HIV infection within each group. The associations of HPV with HIV, age, education, number of lifetime sex partners (maternal group), and smoking (sex workers) were estimated with univariate odds ratios; the precision of the estimates was evaluated with the χ^2 test and test based confidence intervals (CI) for the odds ratio, or by Fisher's exact test (two tailed). Logistic regression was used to adjust the estimates of the association (adjusted odds ratio, OR) between HIV types and demographic and behavioural variables. Age at first intercourse was not tested for association with HPV and was not used as a potential confounder because more than 30% of women in each group did not report this information. We categorised CD4 cell counts as $\leq 500 \times 10^6/l$ or $>500 \times 10^6/l$ to increase the number per category for analysis; results were similar if categories of $<200 \times 10^6/l$ and $200-500 \times 10^6/l$ were compared with those of >500 . The significance of the resulting ORs was determined by 95% CI and corresponding *p* values of <0.05 .

Results

CHARACTERISTICS OF THE STUDY POPULATIONS

Table 1 summarises the frequency distributions of the variables analysed for this study. Enrolment procedures determined the distributions of HIV-1, HIV-2, and HIV-D serological reactivity in the two groups of women. The frequency of HPV DNA detection was similar for both groups and most HPV DNAs detected were high risk types. The sex workers had a lower overall CD4 cell count and in general more HIV related symptoms than the maternal group (data not shown).

To evaluate possible differences on key demographic characteristics between the HIV sero-

Table 1 Descriptive statistics for the maternal group and sex workers

Variable description	Maternal group Frequency (%)	Sex workers Frequency (%)
HIV-1	57/258 (22.1)	109/278 (39)
HIV-2	57/258 (22.1)	4/278 (1)
HIV-D	22/258 (8.5)	63/278 (23)
Negative	122/258 (47.3)	68/278 (24)
Not tested	—	34/278 (12)
High risk HPV DNA	74/258 (29)	81/273 (30)
Low risk HPV DNA	15/258 (6)	19/273 (7)
Negative	168/258 (65)	173/273 (63)
Undetermined	1/258 (0.4)	5/273 (2)
Age at first intercourse (years)		
<14	22/170 (13)	44/168 (25)
15–16	64/170 (38)	75/168 (43)
17–18	56/170 (33)	39/168 (22)
>19	28/170 (16)	17/168 (10)
>2 lifetime sex partners	74/238 (31)	—
Median No clients previous day (SD)	—	2.8 (2.1)
Mean age (range)	29 (18–48)	29 (15–54)
Secondary education (v primary or none)	30/258 (12)	31/251 (12)
Smoking (ever)	4/258 (2)	107/251 (43)

Table 2 Association of high or low risk HPV DNA detection with HIV serostatus

	Maternal group		Sex workers†	
	Freq (%)	OR* (95% CI)	Freq (%)	OR* (95% CI)
High risk HPV				
HIV-1	29/56 (52)	7.5 (3.2–17.4)	43/98 (44)	5.0 (2.1–12.0)
HIV-2	18/56 (32)	3.7 (1.6–8.5)	—	—
HIV-D	13/21 (62)	12.7 (4.3–37.5)	16/59 (27)	2.7 (0.9–6.5)
HIV-NEG	14/109 (13)	reference	9/66 (14)	reference
Low risk HPV‡				
HIV-1	1/28 (4)	0.3 (0.1–2.1)	11/66 (17)	5.7 (1.4–23.4)
HIV-2	1/39 (2)	0.2 (0.1–1.4)	—	—
HIV-D	1/9 (11)	1.0 (0.1–8.7)	4/47 (8)	2.6 (0.5–14.4)
HIV-NEG	12/107 (11)	reference	2/59 (3)	reference

*Adjusted for age, education, number of lifetime sex partners (maternal group), and smoking (sex workers).

†The 34 women who did not receive an HIV test are excluded.

‡Excludes women who tested positive for high risk HPV, values shown are crude odds ratios.

— indicates not analysed.

Table 3 Association of high risk HPV DNA detection among HIV positive women with CD4 cell counts $\leq 500 \times 10^6/l$

	Maternal group		Sex workers	
	Freq (%)	OR* (95% CI)	Freq (%)	OR* (95% CI)
CD4 ≤ 500	25/44 (57)	1.9 (0.9–4.4)	55/115 (48)	3.7 (1.8–7.5)
CD >500	35/89 (39)	reference	17/73 (23)	reference

*Adjusted for age, education, number of lifetime sex partners (maternal group), and smoking (sex workers).

Table 4 Association of high risk HPV DNA detection in women with CD4 cell counts $>500 \times 10^6/l$

	Maternal group		Sex workers	
	Freq (%)	OR* (95% CI)	Freq (%)	OR* (95% CI)
HIV-1	12/29 (41)	5.4 (2.0–14.8)	10/33 (30)	2.2 (0.7–6.9)
HIV-2	14/47 (30)	3.2 (1.3–7.8)	—	—
HIV-D	9/13 (69)	17.0 (4.4–64.8)	3/31 (10)	0.8 (0.2–3.5)
HIV-neg	13/105 (12)	reference	9/64 (14)	reference

*Adjusted for age, education, number of lifetime sex partners (maternal group), and smoking (sex workers).

— indicates not analysed.

positive and seronegative women of each group, we examined age, education, numbers of clients per day (female sex workers), or number of lifetime sex partners (maternal group) stratified by HIV serostatus. No significant differences were detected for either group. HIV-1 and HIV-D seropositive sex workers were significantly more likely to smoke than were HIV seronegative sex workers ($p \leq 0.002$), and HIV-D seropositive sex workers were older than HIV-1 seropositive or seronegative sex workers ($p = 0.02$).

ASSOCIATION BETWEEN HIV TYPES AND HIGH AND LOW RISK HPV

A strong association of high risk HPV DNA detection with HIV-1, HIV-2, HIV-D was found in the maternal group (table 2). Detection of low risk HPV DNA was not associated with any of the HIV seropositive categories. In female sex workers, there was an association of high risk HPV DNA detection with HIV-1 (table 2). In contrast with results for the maternal group, HIV-1 seropositivity in sex workers was also associated with detection of low risk HPV DNA. HPV DNA detection was not associated with age, education, number of lifetime sex partners (maternal group) and smoking (sex workers) (data not shown).

EFFECT OF HIV ASSOCIATED IMMUNE SUPPRESSION ON HPV

Decreased CD4 cell count is a direct consequence of HIV infection, and thus cannot be included in a regression analysis that includes HIV as a risk variable. We limited the analysis of CD4 cell count to HIV seropositive women only (seronegative women from both groups were excluded). An association of HPV DNA detection with CD4 cell counts $\leq 500 \times 10^6/l$ was noted among HIV positive sex workers but not HIV positive women of the maternal group (table 3).

In an attempt to minimise the effect of low CD4 cell count, we analysed the relation of high risk HPV DNA to HIV in all women with CD4 cell counts of $>500 \times 10^6/l$ (table 4). Among the maternal group women with CD4 counts of $>500 \times 10^6/l$, high risk HPV DNA detection was associated with HIV-1, HIV-2, and HIV-D. However, among sex workers with CD4 counts of $>500 \times 10^6/l$, detection of high risk HPV was not associated with HIV-1 or HIV-D.

Discussion

In this cross sectional study, we examined the relation of HPV to HIV-1, HIV-2, HIV-D, and CD4 cell count in two groups of women with either high or low numbers of sex partners. We anticipated that the female sex workers, given greater sexual exposure, would have higher rates of HPV DNA detection than women in the maternal group. Unexpectedly, the two groups had similar rates of both high and low risk HPV DNA. This result was true whether we examined overall HPV DNA prevalence (table 1) or HPV DNA prevalence by HIV serostatus (table 2).

One explanation for this finding may be that because of frequent exposure to HPV, sex workers develop an immune response to HPV, resulting in a lower overall HPV prevalence relative to exposure. Additionally, the sex workers may be at a later stage in the natural history of HPV infection than women in the maternal group. HPV prevalence varies with age, usually being highest in younger women near the onset of coitus and declining with increasing age. Svare *et al*²² studied HPV detection in two populations with different average ages of sexual debut. The peak HPV

prevalence occurred at a younger age in the population that had initiated sexual activity at an earlier age. The authors hypothesised that exposure frequency and exposure time are important elements in acquiring immunity to HPV.

Our study is the first to demonstrate a relation of HPV DNA detection to HIV infection in a group of women with low numbers of lifetime sex partners. In the maternal group, detection of high risk HPV was associated with HIV-1, HIV-2, or HIV-D. In parallel with the results of numerous studies of high risk populations,²³ increased detection of high risk HPV DNA was also seen among HIV-1 infected female sex workers. For the sex workers, detection of low and high risk HPV DNA was associated with HIV-1 seropositivity (OR 5.7 versus 5.0, respectively). However, in the maternal group, detection of low risk HPV was not associated with HIV serostatus. This result may reflect different risk profiles for the high versus low risk HPV types. Detection of low risk HPV has been shown to correlate with numbers of new recent sex partners.²⁴

Since HIV infection and immune suppression are related, it has been difficult to separate the effect of HIV infection from that of HIV induced immunosuppression. Most studies of HIV and HPV in high risk populations included women with significant AIDS related immunosuppression. In general, the magnitude of increased HPV prevalence was proportionate to the severity of immunosuppression. Since iatrogenic immunosuppression increases the risk of HPV associated neoplasias,²⁵ it is reasonable to suspect that HIV induced immunosuppression would increase HPV DNA detection rates. To limit the confounding effect of HIV induced immunosuppression, we restricted the analysis to women with CD4 counts of $>500 \times 10^6/l$ and found that the association between HIV and HPV was lost in sex workers, but maintained in the maternal group. Further, when we examined the association of HPV with CD4 cell count $\leq 500 \times 10^6/l$ among HIV positive women, an association with high risk HPV DNA was noted only in the sex workers. Both observations suggest that in the sex workers, the association of HPV with HIV could be predominantly accounted for by HIV induced immunosuppression. As further evidence that HIV induced immunosuppression accounts for the association between HIV and HPV, no association of HPV and HIV was observed in predominantly asymptomatic, and presumably immune competent, HIV infected Nairobi prostitutes.²

What accounts for the association of HPV with HIV-1, HIV-2, and HIV-D in the maternal group if not HIV induced immunosuppression? It would be tempting to speculate direct interactions between HIV and HPV, as has been demonstrated *in vitro*.^{14 15} However, the association with HPV was observed with both HIV-1 and HIV-2 and direct interactions between HIV-2 and HPV have not been demonstrated *in vitro*.¹⁴ Microbiological and immunological microenvironments influence susceptibility, infectiousness, and sequelae of

STDs including HIV infection.²⁶ Women from the maternal group who have acquired one infection (HIV first or HPV first) may be less likely to acquire the second infection on the basis of exposure alone; rather, the second infection may be acquired as a result of altered susceptibility caused by the first infection. In our companion paper, we show that HIV-1 was associated with squamous intraepithelial neoplasia (SIL) independent of HPV,²⁷ which suggests that HIV-1 may be influencing the microenvironment of the cervix in ways not yet understood.

We found that numbers of sex partners and CD4 cell count can affect the association between HPV and HIV; however, several limitations of our study lend caution to generalising these findings. The cross sectional study design allows only for presentation of baseline information. Perhaps as HIV disease progresses in the maternal group a stronger influence of immune suppression on HPV may become evident. In addition, we clearly did not measure all demographic and behavioural variables that could influence HPV DNA detection. Factors such as nutrition and behaviour of male partners are known to be important HPV risk factors and should be taken into consideration for further investigations of HPV and HIV interactions in women.

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All study participants were volunteers who gave informed consent. Complete study protocols were approved by the Ivorian Ministry of Health and the Centers for Disease Control and Prevention human subjects committees. Human experimentation guidelines of the US Department of Health and Human Services were followed in the conduct of this study.

None of the authors has commercial or other associations that might pose a conflict of interest.

Contributors: SD Vernon, ER Unger, and WC Reeves conceived the study and, together with SZ Wiktor and AE Greenberg, implemented the study design and carried it out. ST Severin and PD Ghys ran the clinics and cared for the women. IR Horowitz provided gynaecological training. DL Miller provided laboratory expertise and performed HPV tests. MA Piper performed statistical analysis and in collaboration with all coauthors interpreted the results and wrote the first draft of the manuscript. SD Vernon, ER Unger, and WC Reeves collaborated to finalise the manuscript for publication.

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