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**Cervical Infection with Human Papillomavirus (HPV) 6 or 11 in High-Risk Women in Burkina Faso**

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**Key words:** Low-risk Human Papillomavirus (LR-HPV); HIV-1; genital warts; genital ulcer disease; Africa.

## **Abstract**

**Objectives:** Human papillomavirus (HPV) types 6 and 11 are known agents of genital warts but little is known about their epidemiology in Africa. We present data on the prevalence of, and risk factors for, cervical HPV 6 and 11 in high-risk women in Burkina Faso.

**Methods:** 306 women were enrolled. HIV status and CD4+ counts were determined. Among other genital samples, a cervical swab (Cervex) was collected for liquid-based cytology and HPV genotyping using MY09/MY11 and GP5+/GP6+ PCRs, and INNO-LiPA genotyping v2. Risk factors were examined using logistic regression.

**Results:** HIV-1 seroprevalence was 40% (123/306). Cervical HPV DNA was detected in 55% (100/183) of HIV-uninfected women, 84% (78/93) of HIV-1 infected women with CD4+ T-cell counts >200 cells/ $\mu$ l and 97% (29/30) of HIV-1 infected women with CD4+ T-cell counts  $\leq$ 200 cells/ $\mu$ l ( $p_{\text{trend}} < 0.001$ ). HPV 6 prevalence was 6% (18/306), HPV 11 prevalence 4% (13/306), and overall HPV 6/11 prevalence 9% (28/306), which increased with HIV infection and immuno-suppression. Genital warts were associated with HPV 6 (adjusted OR=4.12, 95% CI: 1.17-14.53) but not with HPV 11. Genital ulcerations were associated with HPV 6/11 but not with other HPV types. There was a protective effect for vaginal douching and the follicular phase of the menstrual cycle. Condom use, HIV-1 plasma viral load, and other STI/RTIs were not associated with HPV 6/11.

**Conclusions:** Prevalence of HPV 6/11 was high in this population, with predominance of HPV 6. HPV 6/11 were found more frequently in women with genital ulcers and in those with HIV-related immunosuppression.

## **Introduction**

Human papillomaviruses (HPV) are the most common sexually transmitted infections worldwide.[1] The low oncogenic risk types HPV (LR-HPV) 6 and 11 are the major causative agents of genital warts.[2] The epidemiology of these HPV types is poorly described in Africa. As HPV vaccines become more widely available, it becomes important to understand the epidemiology of vaccine-associated HPV types. We present data on the prevalence of, and risk factors for, cervical HPV 6 and 11 in high-risk women in Burkina Faso.

## **Methods**

Data were obtained from a cross-sectional survey of high-risk women nested within the Yerelon Cohort study, which has been evaluating interventions to reduce the risk of HIV infection among sex workers in Bobo-Dioulasso since 1998.[3]

Between December 2003 and March 2004, cohort participants were asked for permission to collect a cervical swab (Cervex) for liquid-based cytology and HPV-DNA detection using MY09/MY11 and GP5+/GP6+ PCRs and genotyping with INNO-LiPA genotyping v2 (Innogenetics).[4, 5] Vaginal and cervical swabs were collected for the diagnosis of *Trichomonas vaginalis* and bacterial vaginosis (BV) by microscopy, and *Candida albicans* and *Neisseria gonorrhoeae* by culture. Blood samples were collected for HIV, syphilis, and HSV-2 serologies, and HIV-1 plasma viral load and CD4+ count in HIV-1 seropositive women. Statistical analysis was conducted using logistic regression. Ethical approval was obtained from the Ethics Committees of the Burkina Faso Ministry of Health and the London School of Hygiene & Tropical Medicine.

## Results

Of 379 cohort participants enrolled during the study period, 306 had data on HPV and concurrent clinical and laboratory information. The median age was 26 years (range 15-54 years), median age at first intercourse was 17 years (range 10-24), and 64 women (21%) described themselves as full-time sex workers. HIV-1 seroprevalence was 40% (123/306), syphilis seroprevalence was 3% (9/303) and HSV-2 seroprevalence was 68% (195/285).

Cervical HPV DNA was detected in 55% (100/183) of HIV-uninfected women, 84% (78/93) of HIV-1 infected women with CD4+ counts >200 cells/ $\mu$ l and 97% (29/30) of HIV-1 infected women with CD4+ counts  $\leq$ 200 cells/ $\mu$ l ( $p_{\text{trend}} < 0.001$ ). HPV 6 prevalence was 6% (18/306), HPV 11 prevalence 4% (13/306), and overall HPV 6/11 prevalence 9% (28/306), which increased with HIV infection and immunosuppression (Table 1).

Among the 18 women with genital warts, 4 were positive for HPV 6 (adjusted OR=4.12, 95% CI: 1.17-14.53,  $p=0.03$ ) but none were positive for HPV 11. Genital ulcerations were positively associated with cervical HPV 6/11 but not with other HPV types. Regular vaginal douching and the follicular phase of the menstrual cycle were associated with lower HPV 6/11 prevalence. Condom use, HIV-1 plasma viral load, and other STI/RTIs were not associated with HPV 6/11.

**Table 1. Multivariate associations with cervical HPV 6/11 and other HPV types in 306 high-risk women in Burkina Faso**

Characteristic	N	Women with HPV 6/11 n (%)	HPV 6 or 11 adjusted OR (95%CI) <sup>a</sup>	P-value	Other HPV types adjusted OR (95% CI) <sup>a</sup>	P-value
Age groups, years						
15-24	123	10 (8)	1.0		1.0	
25-34	119	10 (8)	1.00 (0.32-3.08)	0.99	1.15 (0.65-2.04)	0.64
>34	64	8 (12)	1.99 (0.65-6.05)	0.23	1.33 (0.67-2.63)	0.42
Practices regular vaginal douching	279	22 (8)	0.25 (0.07-0.88)	0.03	2.47 (0.83-7.33)	0.10
Last menstruation <15 days <sup>b</sup>	146	8 (6)	0.37 (0.15-0.92)	0.03	0.94 (0.57-1.54)	0.80
Genital warts on exam	18	4 (22)	3.01 (0.70-12.87)	0.14	0.71 (0.25-2.06)	0.53
Genital ulceration on exam	12	4 (33)	5.22 (1.21-22.57)	0.03	0.61 (0.17-2.19)	0.45
HSV-2 seropositivity	195	19 (10)	1.03 (0.36-2.95)	0.36	0.71 (0.39-1.27)	0.25
Bacterial vaginosis	131	14 (11)	1.08 (0.44-2.69)	0.86	1.15 (0.69-1.91)	0.60
HIV status:						
HIV seronegative	183	13 (7)	1.0		1.0	
HIV-1 +, CD4 >200 cells/ $\mu$ L	93	9 (10)	1.06 (0.39-2.88)	0.90	2.13 (1.22-3.70)	0.007

HIV-1 +, CD4 $\leq$ 200 cells/ $\mu$ L	30	6 (20)	2.64 (0.75-9.33)	0.13	2.32 (0.91-5.94)	0.08
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NOTE: determined by logistic regression. OR, odds ratio; CI, confidence interval;

<sup>a</sup> odds ratio adjusted for HIV status, genital ulceration, regular vaginal douching, and last menstrual period less than 15 days prior to visit; <sup>b</sup> women with amenorrhea and menopause were excluded from this group

## **Discussion**

The prevalence of cervical HPV 6/11 was high in this population and increased with immunosuppression. Unlike overall cervical HPV types, which had a strong association with both HIV and CD4+ count in this setting,[4] the association with HPV 6/11 was weaker, likely due in part to the smaller numbers of subjects who were HPV 6/11 positive.

Our data suggest that HPV 6 is more prevalent in women with genital warts than HPV 11, which was already reported from an aetiological study in Australia.[2] However, any relationship might be obscured by the fact that HPV DNA was recovered from the cervix and not directly from genital lesions.

The presence of genital ulcers, mainly caused by HSV-2 in Burkina Faso,[6] was strongly associated with HPV 6/11 but not with other HPV types. This suggests that HPV 6/11 may either cause or be acquired or transmitted through breaches of the genital mucosal surface, possibly induced by HSV-2 reactivations, although any biological differences between types remains unclear at this point. Conversely, we did not detect any association between HPV 6/11 and the presence of BV, often implicated in the acquisition of STIs and which might allow for persistence of HPV.[7] Regular vaginal douching, linked to disturbances of the vaginal milieu and increased STI risk in other settings,[8] was found to be protective for HPV 6/11 in this study. This might be secondary to mechanical factors which decrease DNA detection, although the sensitivity of HPV DNA detection does not seem impaired after washing.[9] Another African study has suggested a protective effect of douching on genital warts.[10] The follicular phase of the menstrual cycle was protective for HPV



6/11, which might be due to an oestrogenic effect on HPV persistence,[11] although the role of hormonal factors on STIs remains poorly characterized in African women.

In conclusion, HPV 6/11 prevalence was high in this high-risk population, with a predominance of HPV 6. HPV 6/11 were found more frequently in women with genital ulcers and in those with HIV-related immunosuppression.

**Key Messages:**

1. The prevalence of low-risk-HPV types 6 and 11 was relatively high (9%) in this cohort of 306 high-risk women in Burkina Faso.
2. HIV infection and immune suppression were predictive of the presence of cervical HPV 6 and 11 and other HPV types.
3. HPV types 6 and 11, but not other HPV types, were strongly associated with concurrent genital ulcer disease, suggesting a role either in clinical presentation or transmission of HPV 6/11.

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**Competing interests:** We have no conflicts of interest to declare.

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**Roles:** N Nagot, P Mayaud and P Van de Perre designed the study, which was carried out by I Konaté, A Ouédraogo, and supervised by N Nagot. HPV testing was performed by MN Didelot-Rousseau and M Segondy in Montpellier. Statistical analyses were performed by A Low and reviewed by T Clayton and P Mayaud. First manuscript was drafted by A Low and P Mayaud with inputs and reviews from all co-authors, who approved the final version.

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