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ORIGINAL ARTICLE

Human papillomavirus infection in human immunodeficiency virus-positive Taiwanese women incarcerated for illicit drug usage

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Background: The number of female injection drug users infected with human immunodeficiency virus (HIV) is increasing in Taiwan. Their human papillomavirus (HPV) infection has not been fully discussed.
Methods: A cross-sectional study was conducted in a prison for women. Both HIV-positive and HIV-negative women were enrolled voluntarily. All patients answered self-administered questionnaires, had a Pap smear, and underwent linear array HPV genotype tests.
Results: A total of 72 female patients infected with HIV and 76 women who were not infected with HIV were enrolled in this cross-sectional study (mean age, 33.4 years). HPV infection was detected in 63.9% of patients infected with HIV and 47.4% of HIV-negative counterparts ($p = 0.043$). Oncogenic HPV was detected in 41.6% of patients infected with HIV and 28.9% of their counterparts ($p = 0.10$). A mean of 2.41 types of HPV were detected in HIV-positive women and 1.53 types were detected in the HIV-negative counterparts ($p = 0.014$). HPV 52 was the most commonly encountered oncogenic type. Only 10.2% of the patients (10.9% of HIV-positive patients) had vaccine-preventable HPV types. Patients with abnormal cytology (81.3%) tended to have oncogenic types of HPV infection. HIV serostatus was the significant factor associated with oncogenic HPV infection (odds ratio = 2.583, 95% confidence interval 1.071–6.231, $p = 0.0347$).

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Conclusion: Drug-using women infected with HIV had significantly higher rates of HPV infections, justifying the aggressive screening for cervical dysplasia.

Introduction

Human papillomavirus (HPV) is a widespread sexually transmitted infection, with at least 60% of sexually active adults having experienced a genital HPV infection once in their lifetime.[1] Studies have consistently shown that HPV infections are detected more frequently in human immunodeficiency virus (HIV)-seropositive women than in their HIV-negative counterparts, with HPV positivity being reported in approximately 58% of a large group of women infected with HIV as part of the Women's Interagency HIV Study that has been ongoing since 1994.[2] HPV prevalence rates varied in different geographic areas.[3,4] In addition, HPV is more likely to be persistent or reactivated in the setting of HIV infection.[5] There is an accelerated risk of progression to malignancy in women coinfected with HIV and HPV.[6]

In Taiwan, the proportion of newly diagnosed HIV-infected cases attributed to injection drug users surged drastically from less than 10% in 2003 to more than 70% in 2005. A previous prevalence study showed that the proportion of HIV infection in male injection drug users in Taiwan was 0.23% from 1994 to 2003[7] and 25.6% in 2005.[8] At the end of 2011, there were more than 22,000 reported patients infected with HIV in Taiwan, one-third (29.85%) of whom were injection drug users.[9] Sharing of injection equipment and drug paraphernalia was thought to be the main mode of HIV transmission among injection drug users.[8]

An increase in the number of women with HIV was also noted in Taiwan. The man-to-woman ratio of patients infected with HIV decreased from 20:1 in 2003 to 7:1 in 2005, and half of these HIV-positive women (54.4%) were injection drug users.[10] A previous study showed that female injection drug users infected with HIV were of lower socioeconomic status, had frequent common sexual and drug partners, and received poor parental support after several instances of recidivism.[11] Among the female injection drug users infected with HIV in that study, 64% had never used condoms and 88% had multiple sexual partners.[11] At the end of 2005, Taiwan's government launched a harm reduction program that included a needle exchange program and methadone maintenance therapy, and the outbreak was under control in 2 years.[8,9]

One study showed that HPV could be detected in 48.4% of Taiwanese HIV-positive women,[12] but their cohort comprised no injection drug users. Thus, the prevalence of HPV infection in HIV-positive female injection drug users in Taiwan is still unknown. The objectives of this study were to understand the prevalence of HPV infection in female illicit drug users who are HIV-positive, and to develop a sex-specific approach to the prevention, diagnosis, and treatment of HPV infection in such cases.

Patients and methods

Study population and collection of specimens

Under Taiwan law, all detainees should be tested for the presence of HIV-I/II antibodies upon admission to the detention facility, and those infected with HIV are segregated from HIV-negative detainees. The prevalence of HIV infection among incarcerated women was 8.5% in 2007.[13] This study was conducted in a womens' prison where, of approximately 1400 inmates, more than 75% of the incarcerations were directly or indirectly associated with illicit drug usage. During the 2008 annual Pap smear screening, 76 women infected with HIV were invited for testing after complete information about HPV was provided. Simultaneously, an approximately equal number of HIV-negative patients who were age-matched within $\pm$ 3 years were enrolled consecutively after informed consent was obtained. Self-administered questionnaires, thin-preparation Pap smear, and HPV genotyping tests were provided for both groups. CD4+ T-cell counts using flow cytometry (Coulter Epics XL, Beckman Coulter, CA, USA) were also evaluated for all HIV-positive patients. The study was reviewed and certified by the institutional review boards of Taoyuan General Hospital, Department of Health (IRB No: TYGH97019) and Far Eastern Memorial Hospital (FEMH No: 96049).

HIV serologic determination

Initial HIV-I/II antibodies testing was performed using microparticle enzyme immunoassay (HIV 1/2 gO, Abbott Diagnostic Division, IL, USA). Samples with positive results were run in duplicate, and the results were confirmed by Western blot HIV-1 and HIV-2 assays (New LAV Blot-I and II, Bio-Rad Fugirebio Inc, Tokyo, Japan).

Cervical cytology

Thin preparation Pap smears (ThinPrep, Hologic Inc, Marlborough, MA, USA) were prepared and sent to a certified laboratory where two cytopathology technicians and two cytopathologists performed a blind evaluation of the Pap smears. The results were classified according to the 2001 Bethesda System terminology.[14] The cervical cells were preserved in PreservCyt solution (Cytyc Corp., Marlborough, Massachusetts, USA) and stored at -70°C for DNA testing.

HPV genotyping

Reverse line blot methods (Linear Array HPV genotyping test, Roche Molecular System, Branchburg, NJ, US) were

applied. In brief, biotinylated primers were used in multiplex polymerase chain reactions to define a nucleotide sequence in the polymorphic L1 region within the HPV genome. An additional primer pair targeted at the human β-globin gene was added as the internal control. The denatured amplicon was hybridized to a linear array strip with probes detecting 37 genotypes of the HPV genome (13 types of oncogenic HPV: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68; and 24 types of nononcogenic HPV: 6, 11, 26, 40, 42, 53, 54, 55, 61, 62, 64, 66, 67, 69, 70, 71, 72, 73, 81, 82, 83, 84, IS39, and CP2108) and the human β-globin gene.[15] The assay provided 96% of sensitivity and 99% of specificity.[15]

Statistical analysis

According to the previous study,[2–4] HPV prevalence is 50% among HIV-positive women and 20% among the general female population. Sample size is estimated to at least 77 individuals to achieve 0.8 of desired power and 0.05 of significance level. Demographic data are presented as mean (standard deviation) for continuous variables and as a percentile for discrete variables. Prevalence rates of HPV in each group were calculated. In univariate analysis, odds ratios comparing cases and controls were calculated using the Fisher exact test for 2×2 comparisons. The chi square test was used for 2×3 or more comparisons when appropriate. Those variables with $p < 0.1$ were included in the following multiple regression. A multiple logistic regression analysis with best subsets selection using SAS 9.1 software (SAS Institute Inc, Cary, NC, USA) was applied for the association between significant variables and HPV infections. A p value < 0.05 was considered statistically significant.

Results

Of the 148 female inmates (mean age [standard deviation, SD], 33.4 [5.1] years) who were successfully enrolled, 72 were HIV-positive and 76 were HIV-negative. Of the HIV-positive women, four patients with either physiologic or social reasons did not join the study. All of the enrolled women were illicit drug users (included noninjection-type drugs, such as amphetamine, ketamine, marijuana, flunitrazepam, etc., or the injection type of heroin). As shown in Table 1, more than 70% of the HIV-positive cases had ≤ 9 years of education and more than 70% of them were single or divorced. Most of the HIV-positive patients (95.8%) were recidivists. For HIV-positive women, the mean age (SD) at their first sexual encounter was 16.31 (2.03) years, and the median number of lifetime sexual partners was three. Of these women, 15.3% had been sex workers at some time in their lives. More than 60% of the HIV-positive patients never or rarely used a condom during sexual intercourse.

Table 1 Demographic characteristics of 72 incarcerated HIV-positive female illicit drug users and 76 HIV-negative counterparts

	HIV-positive	HIV-negative	*p* value
No. of cases	72	76	
Demographics			
Mean age, years (SD)	32.7 (6.7)	34.2 (2.8)	> 0.1
Education years			
≤ 9, n (%)	53 (73.6%)	37 (48.9%)	0.004
> 9, n (%)	19 (26.4%)	38 (50.0%)	
Marital status			
Married, n (%)	17 (23.6%)	28 (36.8%)	0.08
Single, separated, divorced, n (%)	55 (76.4%)	48 (63.2%)	
Median duration of incarceration, days (25^{th}–75^{th} percentile)	244 (150–570)	315 (120–600)	> 0.1
Recidivism, n (%)	69 (95.8%)	53 (69.7%)	0.104
Sexual behavior			
Mean age at first sexual encounter, years (SD)	16.23 (2.14)	17.59 (3.13)	> 0.1
Median lifetime sexual partners (range)	3 (1–numerous)	4 (1–numerous)	> 0.1
Monogamous, lifetime, n (%)	12 (16.7%)	14 (18.4%)	> 0.1
Ever been a sex worker, n (%)	11 (15.3%)	9 (11.8%)	> 0.1
Ever had sexually transmitted disease, n (%)	19 (26.4%)	29 (38.2%)	> 0.1
Practicing anal sex, n (%)	7 (9.7%)	11 (14.5%)	> 0.1
Never/rarely use condoms with primary sexual partner, n (%)	45 (62.5%)	51 (67.1%)	> 0.1
Never/rarely use condoms with casual sexual partners, n (%)	44 (61.1%)	30 (39.5%)	0.013
Substance-taking behavior			
Smoking history, n (%)	66 (91.7%)	66 (86.8%)	> 0.1
Using illicit drugs, n (%)	72 (100%)	76 (100%)	-
Mean age of starting drugs, years (SD)	19.52 (5.89)	19.2 (5.03)	> 0.1
Mean no. of drugs used, n (SD)	2.83 (1.54)	2.74 (2.37)	> 0.1
Mean age of starting injections, years (SD)	23.84 (5.55)	24.35 (5.04)	> 0.1

HIV = human immunodeficiency virus; SD = standard deviation.

Table 2 Prevalence of HPV in 72 incarcerated HIV-positive female illicit drug users and their 76 HIV-negative counterparts

	HIV-positive	HIV-negative	*p* value
No. of cases	72	76	
Cases with any HPV, n (%)	46 (63.9%)	36 (47.4%)	0.043
Cases with any oncogenic HPV, n (%)	30 (41.6%)	22 (28.9%)	0.10
Mean types of HPV infection in HPV-positive cases	2.41	1.53	0.014

HIV = human immunodeficiency virus; HPV = human papillomavirus.

Compared with their counterparts, more of the HIV-positive individuals had fewer educational years and never or rarely used a condom ($p < 0.05$).

HPV infection was detected in 55.4% (82 of 148) of the study patients, 63.9% (46 of 72) of HIV-positive women, and 47.4% (36 of 76) of the HIV-negative ones ($p = 0.043$). Oncogenic types of HPV were identified in 41.6% (30 of 72) of HIV-positive women and in 28.9% (22 of 76) of HIV-negative ones ($p = 0.10$). In total, 166 episodes of HPV infections were detected, 43.4% (72 of 166) of which were oncogenic. A mean of 2.41 (111 of 46) types of HPV were detected in HIV-positive women and 1.53 (55 of 36) types were detected in their HIV-negative counterparts ($p = 0.014$) (Table 2). HPV 52, 51, and 58 were the most commonly encountered oncogenic types, whereas HPV 62, 81, 84, and 72 were the most commonly encountered nononcogenic types. Vaccine-preventable types (6, 11, 16, 18) were 5.4% (Fig. 1). Only 10.2% (10.9% of HIV-positive patients) of the patients had been infected with vaccine-preventable types.

A total of nine HIV-positive women (12.5%) and seven HIV-negative ones (9.5%) had abnormal cervical cytology. Patients with abnormal cytology (81.25%) tended to have oncogenic types of HPV infection. Atypical squamous cells of unknown significance were found in four case group individuals (5.5%) and three control patients (4.1%). Low-grade squamous intraepithelial lesion was found in four case group individuals (5.5%) and two control patients (2.7%). Atypical squamous cells cannot exclude high-grade squamous intraepithelial lesion, which were found in one HIV-positive individual (1.39%) and two HIV-negative women (2.8%). Trichomoniasis (9.5%), bacterial vaginosis (6.8%), and candidiasis (3.4%) were the frequently encountered infections.

HIV-positive patients with $<$ 350 CD4+ T cells/μL did not have a higher rate of any type (13 of 22, 59%) or oncogenic type (8 of 22, 36.4%) of HPV infection in comparison with patients with $>$ 350 CD4+ T cells/μL (31 of 48, 64.6% for any HPV and 21 of 48, 43.8% for oncogenic HPV, both $p > 0.05$).

Multiple logistic regression analysis revealed that HIV serostatus was the only significant factor (odds ratio = 2.583, 95% confidence interval 1.071- 6.231, $p = 0.0347$) associated with oncogenic HPV infection (Table 3).

Discussion

Although high prevalence rates of HPV in women infected with HIV have been observed in many Western and African countries, few studies have focused on women in the Western Pacific Rim.[2–4] In studies in Korea, low rates (10.4%) of HPV infection were observed for both women and men in the general population, but the living situations of

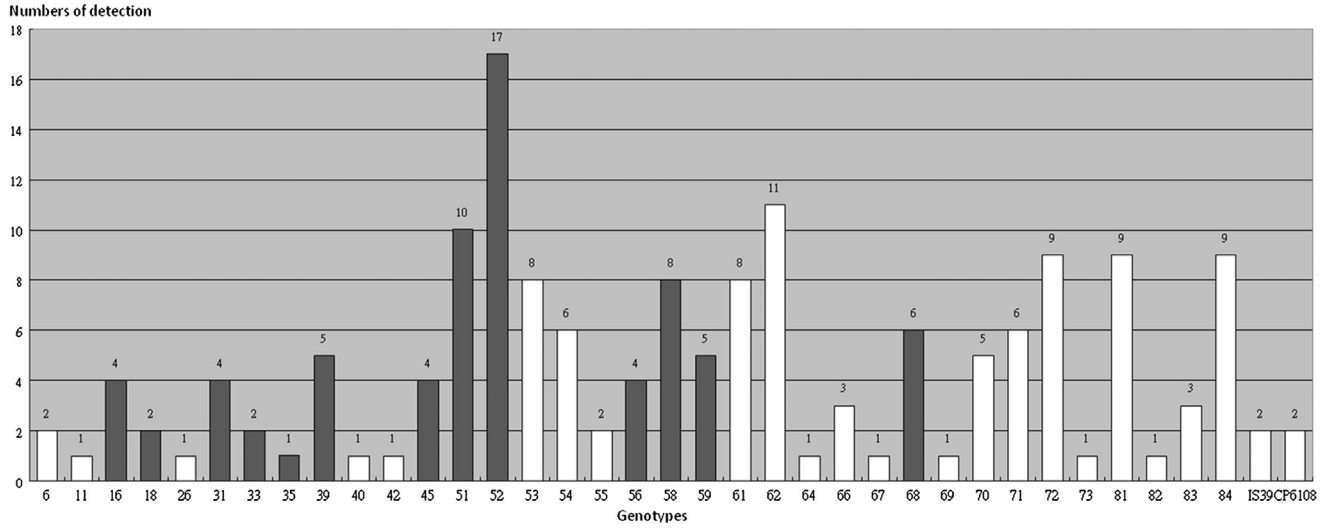

Figure 1. Genotypic distribution of 166 times of detection of human papillomavirus among 46 human immunodeficiency virus (HIV)-positive incarcerated female illicit drug users and 36 HIV-negative counterparts. (Types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68 are considered oncogenic [dark bar]).

Table 3 Multivariate logistic regression analysis for the prediction of any type of HPV infection and oncogenic HPV infection among female illicit drug users

	Any HPV		Oncogenic HPV	
	Odds ratio	95% CI (range)	Odds ratio	95% CI (range)
HIV status	1.963	0.886, 4.345	2.583*	1.071, 6.231
Age	0.567	0.285, 1.127	0.853	0.433, 1.080
Education	1.669	0.768, 3.629	1.985	0.856, 4.601
Marriage	1.344	0.599, 3.012	0.894	0.383, 2.087
Recidivism	0.976	0.347, 2.748	0.471	0.154, 1.437
Never/rarely use condoms with casual partners	1.072	0.509, 2.255	0.770	0.354, 1.676

CI = confidence interval; HIV = human immunodeficiency virus; HPV = human papillomavirus.
*$p = 0.0347$.

people infected with HIV were largely unknown.[16] In Taiwan, according to a study done before the HIV epidemics related to injection drug usage, 48.4% (15/31) of 31 HIV-positive women were infected with HPV.[12] Until now, the status of HPV infection in HIV-positive female drug users was unknown.

This study demonstrated that HIV serostatus was the most important attributor to oncogenic HPV infection in female illicit drug users. Many studies have also reported high rates of persistence of detectable oncogenic HPV DNA in women who were infected with HIV.[5,6] The study findings indicated that HIV-related immunocompromised status would contribute to the persistence of HPV infection. However, the mechanisms by which immunosuppression contributes to the increased risks of HPV-related diseases is not well understood. CD4+ T-cell levels were used as a marker of immunosuppression, but the markers for HPV-specific immunity were not known.[17]

In Taiwan, the general prevalence of HPV alone and oncogenic HPV infection in adult women is 19.85%[18] and 11.1%,[19] respectively. In this study, higher rates of HPV infections were observed in incarcerated HIV-negative women (47.4%) in comparison with the general population (19.85%).[18] Therefore, the characteristics of illicit drug users, including low number of years of education, unstable marital status, low rate of condom usage, and high numbers of sexual partners, were considered risk factors for HPV infection among female drug users.[11]

The median duration of incarceration for these women inmates was approximately 1 year in both groups in this study, so the detected HPV infections implicated possible persistent infections. Previous studies had demonstrated HPV infections would not abate for a median of 8 months[1,20,21]; thus, this point prevalence rate would approximate the rate of persistent infection, considered to be the major risk factor in the development of precancerous and cancer lesions.[6,17]

HPV types 52, 51, and 58 were the most commonly encountered oncogenic types in this study. Research has also demonstrated that HPV types 52 and 58 were the most prevalent oncogenic types in Taiwan.[19] Distribution of different HPV types may vary across areas. For example, in the United States, HPV types 53, 52, and 59 were the most commonly encountered oncogenic HPV genotypes.[22] HPV type 16 was the most commonly detected type in Brazil, type 52 in Uganda, and type 33 in Zimbabwe.[3,4,23] HPV types included in available HPV vaccines (types 6, 11, 16, and 18) comprised only 5.4% of the total infections in this study; therefore, these HPV vaccines may not provide enough protection for female drug users in Taiwan.

Previous studies had confirmed that immunosuppression may accelerate the progression of HPV-associated precursor lesions,[2,17] and HIV-positive patients with CD4+ T-cell counts less than 100 cells/μL were reported to have a twofold relative risk of developing cervical cancer.[24] However, because the patients in this study were young and not in a severe immunosuppressive status, and the number of cases was small, an association between cervical dysplasia and CD4+ cell counts could not be established.

There are several limitations of this study. First, this study focused on the incarcerated female population, and hence, no generalizations could be made. Second, this cross-sectional study did not reveal the outcome of HPV infection, for which longitudinal follow-up would be necessary. Third, the general women population was not enrolled in this study. However, the prevalence of HPV infection in the general population and patient demographics has already been reported in previous large-scale studies in Taiwan[18,19]; the value of this study could not be neglected despite the limitations.

This study demonstrated that HPV infections are common in female illicit drug users. Women infected with HIV were found to be more susceptible to HPV and oncogenic HPV infections in comparison with those without HIV infections. This study revealed that the burden of HPV infection among female illicit drug users is high. Thus, aggressive screening and early detection for cervical dysplasia are highly recommended.

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