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Cervical and anal HPV infection: cytological and histological abnormalities in HIV-infected women in Thailand

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Abstract

Background: Women infected with human immunodeficiency virus (HIV) have higher rates of persistent infection with high-risk human papillomavirus (hr-HPV) and cervical and anal dysplasia. We describe the epidemiology of hr-HPV, and cervical and anal intra-epithelial abnormalities in HIV-infected women in Thailand.

Methods: HIV-infected women aged 18–49 years, either HAART-naïve or -experienced, were enrolled in Bangkok, Thailand. A demographic and sexual-risk behaviour questionnaire was administered and a pelvic examination with colposcopy was performed on every woman. Cervical and anal samples were tested for cytology and HPV genotyping.

Results: A total of 256 women were enrolled with a median [interquartile range (IQR)] age of 35 (32–40) years. Ninety (35.2%) had detectable cervical hr-HPV. Being post-menopausal was associated with increased risk for cervical hr-HPV, while years since HIV diagnosis and plasma HIV RNA <40 copies/mL were significantly associated with decreased risk in multivariable regression analyses. Abnormal cervical cytology was detected in 6.3%. Cervical biopsies that were taken from 99 women (39.3%) owing to abnormalities seen during colposcopy showed cervical intra-epithelial neoplasia (CIN) in 22.6%. The sensitivity of cervical cytology to detect CIN2+ was 10.0%. Among 102 women enrolled in the anal substudy, 18.8% had anal HPV infection and 11.1% had anal hr-HPV. Two women had abnormal anal cytology.

Conclusion: We found cervical and anal hr-HPV in 35.2% and 11.1% of Thai HIV-infected women, respectively. Moreover, the observed poor agreement between cervical cytology and histology results could indicate current cervical cancer screening programs for HIV-infected women might not be optimal for the detection of pre-neoplastic lesions.

Keywords: cervical HPV, anal HPV, women, Pap smear, HIV, Thailand

Introduction

Persistent infection with carcinogenic 'high-risk' types of the human papillomavirus (hr-HPV) is necessary for the development of cervical dysplasia and malignancies [1]. Worldwide, about 70% of all cervical cancers are caused by infection with HPV type 16 or 18 [2]. Cervical cancer is a preventable disease: in countries where screening programmes using Pap smears have been implemented, prevalence of invasive cervical cancer and cervical cancer-related mortality has reduced dramatically [3,4]. In developing countries, the implementation of widespread use of prophylactic vaccine, as well as cervical cancer screening programmes, is difficult owing to financial and logistic restrictions, and therefore the burden of disease is disproportionately high [5].

Women infected with HIV have higher rates of cervical HPV infection and more rapid progression to high-grade squamous intra-epithelial lesions (HSIL) and cervical cancer [6,7].

Furthermore, anal HPV infection in HIV-infected women is highly prevalent, with some studies reporting rates of 80–90% [8,9].

There are approximately 1.4 million women infected with HIV in Asia [10]; however, data on cervical and anal HPV are severely lacking. In Thailand, approximately 250,000 women are currently infected with HIV, but information on the burden of cervical HPV infection in this population is scarce, and data on anal HPV infection in this population are not available. We conducted this study to assess the prevalence of cervical and anal HPV infection in HIV-infected women in Thailand.

Methods

This is a cross-sectional analysis of cervical and anal HPV and intra-epithelial neoplasia of a study conducted at the Thai Red Cross AIDS Research Centre, Bangkok, Thailand. Non-pregnant, HIV-infected women aged 18–49 years were invited to enrol if they did not have a history of cervical cancer, hysterectomy or current cervical infection. HAART-naïve women were eligible for enrolment if they had a CD4 cell count >350 cells/mm^3, whereas HAART-experienced women were eligible if they had been using antiretroviral therapy for at least 6 months. After providing informed consent, an extensive questionnaire to assess demographics and sexual behaviour was administered by a trained study nurse. Blood samples for CD4 cell count and HIV RNA were collected. A pelvic exam was performed by a gynaecologist, during which cervical samples for cytology and HPV DNA testing were taken. At the same visit, prior to Pap smear results, colposcopy was performed on all patients, including application of acetic acid, and cervical biopsies were taken as necessary. A sub-study to assess anal HPV was also performed. Separate consent was required; patients who provided consent answered

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Table 1. Baseline characteristics by cervical hr-HPV status (*n*=256). Characteristics are given in *n* (%) or median (IQR) where appropriate

Characteristic	Overall (*n*=256)	No hr-HPV infection (*n*=166)	hr-HPV infection (*n*=90)	*P* value
Age (years)	35 (32–40)	36 (33–40)	34 (30–40)	0.09
Marital status				
Unmarried	8 (3.1)	3 (1.8)	5 (5.6)	0.11
Married	195 (76.2)	128 (77.1)	67 (74.4)	
Separated/divorced	32 (12.5)	18 (10.8)	14 (15.6)	
Widowed	21 (8.2)	17 (10.2)	4 (4.4)	
Age at marriage (years)	21 (19–26)	21 (18–25)	21 (19–27)	0.33
HIV-status current partner				
Uninfected	88 (34.4)	61 (36.7)	27 (30)	0.21
Infected	79 (30.9)	49 (29.5)	30 (33.3)	
No partner	45 (17.6)	33 (19.9)	12 (13.3)	
Unknown status	44 (17.2)	23 (13.9)	21 (23.3)	
Level of education				
No formal education	5 (2.0)	3 (1.8)	2 (2.2)	0.81
Primary school	91 (35.5)	56 (33.7)	35 (38.9)	
Secondary school	99 (38.7)	69 (41.6)	30 (33.3)	
Tech. certificate	25 (9.8)	15 (9.0)	10 (11.1)	
Bachelor	33 (12.9)	20 (12.0)	13 (14.4)	
Masters	3 (1.2)	3 (1.8)	—	
Total monthly family income (THB)				0.36
≤20,000	203 (79.2)	136 (82.9)	67 (74)	
>20,000	48 (18.9)	27 (16.3)	21 (23.3)	
Refused to answer	5 (1.9)	3 (1.8)	2 (2.2)	
Current smoking	6 (2.3)	2 (1.2)	4 (4.4)	0.12
Past smoking	19 (7.5)	10 (6.1)	9 (10.1)	0.25
Current alcohol use	29 (11.5)	14 (8.6)	15 (16.7)	0.054
Past alcohol use	61 (24.2)	35 (21.6)	26 (28.9)	0.20
Post-menopausal	9 (3.5)	2 (1.2)	7 (7.9)	0.01
Age first intercourse (years)	19 (18–23)	19 (18–23)	19 (18–22)	0.46
Number sexual partners last 30 days				0.45
0	43 (16.8)	29 (17.5)	14 (15.6)	
1	202 (79.2)	134 (80.7)	68 (76.4)	
2–4	3 (1.2)	0	3 (3.4)	
>5	5 (2.0)	3 (1.8)	2 (2.2)	
Lifetime number sexual partners				0.45
1	67 (26.2)	45 (27.1)	22 (24.4)	
2–4	132 (51.8)	89 (53.6)	43 (48.3)	
5–20	36 (14.1)	21 (12.7)	15 (16.9)	
>20	8 (3.1)	4 (2.4)	4 (4.5)	
Commercial sex work	15 (5.9)	6 (3.6)	9 (10.1)	0.052
Current OC use	25 (10.1)	13 (8.1)	12 (13.6)	0.18
Past OC use	177 (73.4)	109 (69.4)	68 (81.0)	0.14
Condom use during VI with regular partner	*n*=223	*n*=144	*n*=79	0.03
Consistent	189 (84.8)	128 (88.9)	61 (77.2)	
Inconsistent	19 (8.5)	7 (4.9)	12 (15.2)	
Never	15 (6.7)	9 (6.3)	6 (7.6)	
Current genital ulcer	7 (2.8)	1 (0.6)	6 (6.6)	0.009
Past genital ulcer	19 (7.5)	8 (4.9)	11 (12.2)	0.08
Current genital warts	1 (0.4)	—	1 (1.1)	0.58
Ever genital warts	8 (3.2)	2 (1.2)	6 (6.7)	0.034
Time since HIV diagnosis (years)	7.0 (4.9–10.1)	7.5 (5.4–10.5)	5.9 (4.0–8.3)	0.0001
HIV transmission category				0.18
Sex with husband	237 (92.6)	156 (94.0)	81 (90.0)	
Other	18 (7.0)	9 (5.5)	9 (10.0)	
Current CD4 count (cells/mm^3)	482 (376–623)	488 (378–617)	464 (372–651)	0.81
CD4 count <350 cells/mm^3	46 (18.1%)	28 (17.1%)	18 (20.0%)	0.56
HAART use, *n* (%)	189 (73.8)	129 (77.7)	60 (66.7)	0.055
Time since start HAART (years)	4.9 (3.1–6.3)	5.0 (3.2–6.4)	4.3 (2.8–6.2)	0.31
Plasma HIV RNA <40 copies/mL				
All patients	149/238 (62.6)	109/159 (68.6)	40/79 (50.6)	0.006
On HAART	145/180 (80.6)	107/124 (86.3)	38/56 (67.9)	0.004

THB: Thai Baht, OC: oral contraceptives, VI: vaginal intercourse, HAART: highly active antiretroviral therapy

questions regarding anal intercourse, and underwent anal examination, during which, samples for anal cytology and HPV DNA testing were collected. High-resolution anoscopy by an experienced physician was offered to all women with evidence of abnormalities from anal cytology. The study was approved by Chulalongkorn University Institutional Review Board. Informed consents were obtained in Thai language from all patients.

Cervical cytology and histology

Cytology was performed on cervical specimens using conventional Pap smear, and classified according to the 2001 revised Bethesda system [11] as negative for intra-epithelial lesion or malignancy, atypical squamous cells of undetermined significance (AS-CUS), low-grade squamous intra-epithelial lesions (LSIL), high-grade squamous intra-epithelial lesions (HSIL) and squamous cell carcinoma. Histological diagnoses were classified as normal and cervical intra-epithelial neoplasia (CIN) grades 1–3. The Pap smears and cervical biopsies were read by gynaecological pathologists at the Chulalongkorn University Hospital, Bangkok, Thailand. Abnormal slides and a randomly selected 10% of normal slides were re-read by a senior cytopathologist, who gave the final result. Samples that were found to be unsatisfactory were excluded from analysis.

Cervical HPV testing

Liquid-based cytology samples were screened first with the Amplicor HPV test (Roche Molecular Systems, Alameda, CA, USA), a polymerase chain reaction (PCR) testing positive if at least one of 13 hr-HPV types is present (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68). Invalid samples (negative internal control) were excluded from analysis. Positive samples were processed further using the Linear Array HPV genotyping test (Roche Molecular Systems, Alameda, CA, USA), which detects up to 37 HPV genotypes (the above mentioned 13 hr-HPV types, and additionally 24 other HPV types that are possibly carcinogenic, non-carcinogenic or of unknown carcinogenicity (6, 11, 26, 40, 42, 53, 54, 55, 61, 62, 64, 66, 67, 69, 70, 71, 72, 73, 81, 82, 83, 84, IS39 and CP6108).

Anal cytology

Cytology was performed on anal specimens by conventional Pap smear, and were classified according to the 2001 revised Bethesda system [11] as described above. The anal Pap smears were read by gynaecological pathologists at the Chulalongkorn University Hospital, Bangkok, Thailand. Abnormal slides and a randomly selected 10% of normal slides were re-read by a senior cytopathologist, who gave the final result. Samples that were found to be unsatisfactory were excluded from analysis. Women with squamous cell abnormalities were offered high-resolution anoscopy at our centre.

Anal HPV testing

Anal swabs were collected and were tested for HPV using the Linear Array HPV genotyping test as described above.

Statistical methods

Statistical analysis was conducted using Stata Version 12 (Statacorp, College Station, TX, USA). Demographic characteristics were analysed using descriptive statistics [frequency and percentage or median and interquartile range (IQR) as appropriate]. Women without cervical hr-HPV infection were compared to women with cervical hr-HPV infection using Chi-squared tests or Kruskal–Wallis tests as appropriate. Factors associated with cervical hr-HPV infection were analysed using univariable and multivariable logistic regression analyses using a backward selection process retaining terms in the model significant at $P<0.05$.

Results

Demographic, sexual and HIV characteristics

A total of 256 women were enrolled, of whom 90 (35.2%) had cervical hr-HPV using the Amplicor HPV test (Table 1). Overall, the median age was 35 years (IQR 32–40 years). The majority of women (76.2%) were married. Very few women were past or current smokers (9.8%); this did not differ between women with, and without cervical hr-HPV. The median age at first sexual intercourse was 19 years, and a minority ($n=15$, 5.9%) reported current or ever commercial sex work. A total of 189 (73.8%) women were currently using HAART for a median time of 4.9 years, the median time since HIV diagnosis was 7.0 years, 7.5 years among women without cervical hr-HPV and 5.9 years for women with cervical hr-HPV ($P<0.001$). The majority of women (92.6%) reported to have been infected with HIV by their current or previous husband. Median CD4 cell counts were similar between HAART-naïve (460 cells/mm^3; IQR 396–584 cells/mm^3) and HAART–experienced women (CD4 483 cells/mm^3; IQR 359–626 cells/mm^3).

Prevalence of cervical hr-HPV

After excluding three (1.2%) invalid samples, we found cervical hr-HPV infection in 90 (35.6%) women using the Amplicor HPV test. These samples were then processed to identify the HPV genotypes present and the results are shown in Table 2.

Of the 90 women, no HPV DNA was detected with the Linear Array test for 16. The most common hr-HPV genotypes identified were HPV-51 ($n=12$, 4.7%), HPV-58 ($n=12$, 4.7%), HPV-16 ($n=11$, 4.3%), HPV-52 ($n=11$, 4.3%), HPV-18 ($n=6$, 2.3%), HPV-33 ($n=6$, 2.3%) and HPV-39 ($n=6$, 2.3%) (Figure 1). Because the probe that hybridises HPV-52 in the Linear Array test is cross-reactive with HPV types 33, 35 and 58, we examined further for the presence of one of these three types in the samples positive for HPV-52. HPV-52 was present exclusively in 10 (3.9%), while in one (0.4%) sample HPV-33 was also present.

Cervical cytology and histology

After excluding four unsatisfactory samples (1.6%), cytological results were available for 252 women. Of the samples that were satisfactory for evaluation, organisms were detected in 15 samples (5.9%), 56 samples (22.2%) lacked an endocervical/transformation zone component and 42 samples (16.7%) were partially obscured by blood. Furthermore, 97 (38.5%) samples showed reactive cellular changes associated with inflammation. Of the 252 samples, 236 (93.7%) were negative for intra-epithelial abnormalities, nine (3.6%) had ASCUS, six (2.4%) had LSIL and one (0.4%) had HSIL. All women underwent colposcopy, but biopsies were performed on 99/252 (39.3%) of

Table 2. Number of HPV genotypes present by individuals using the Amplicor HPV test

Number of HPV genothypes present	Number of women (%)
1	45 (50)
2	14 (15.6)
3	11 (12.2)
4	1 (1.1)
5	1 (1.1)
6	2 (2.2)

the women owing to colposcopic abnormalities. The biopsies showed no intra-epithelial abnormalities in 42 women, CIN1 in 47 (18.7%), CIN2 in two (0.8%) and CIN3 in eight women (3.2%). Of the 57 women with CIN1+, 45 (78.9%) had normal cytology, five (8.8%) had ASCUS, six (10.5%) had LSIL and one (1.8%) had HSIL (Table 3), resulting in a Cohen's kappa of 0.11. The sensitivity of abnormal cervical cytology from ASCUS and above to detect histology confirmed CIN1+ was 12.7% (95%CI 5.3–24.5%), and the corresponding sensitivity to detect CIN2+ was 10.0% (95%CI 0.3–44.5%). The specificity was 100% (95%CI 91.8–100%) and 100% (95%CI 95.9–100%), respectively.

Risk factors for cervical hr-HPV infection

Factors that were significantly associated with cervical hr-HPV infection in the univariable regression analysis were being post-menopausal, years since HIV diagnosis, plasma HIV RNA <40 copies/mL, self-reported inconsistent condom use during vaginal intercourse, current or ever having genital ulcer (self-reported) and ever having genital warts (self-reported). These factors were included in a multivariable regression model, except for self-reported genital ulcers and genital warts due to collinearity. In this multivariable regression model, being post-menopausal (OR 12.47, 95%CI 2.34–66.29, P=0.003), years since HIV diagnosis (OR 0.88, 95%CI 0.81–0.96, P=0.003) and plasma HIV-RNA <40 copies/mL (OR 0.42, 95%CI 0.23–0.79, P=0.007) remained significantly associated with cervical hr-HPV infection (Table 4). After adding self-reported genital ulcers and genital warts to this model, both factors were significantly associated with the presence of hr-HPV (OR 11.75, 95%CI 1.14–121.19, P=0.038 and OR 6.82, 95%CI 1.07–43.38, P=0.042, respectively). However, the OR for the other risk factors from the multivariable model did not significantly change (data not shown).

Anal sub-study

A total of 102 women consented to the anal sub-study. Of these, four (3.9%) reported to ever having engaged in anal intercourse, of whom one reported consistent condom use during anal intercourse, one inconsistent condom use, and two never having used condoms during anal intercourse. Five unsatisfactory Pap smears were excluded (4.9%). Two women showed abnormalities on anal cytology: one ASCUS and one LSIL-AIN. Both women were offered high-resolution anoscopy at our centre. The woman with ASCUS did not return for further examination. The women with LSIL-AIN underwent high-resolution anoscopy during which a biopsy was taken. Histological analysis of this specimen showed anal condylomata.

After excluding 12 (11.8%) invalid HPV test results, 90 anal HPV results were available. Anal HPV infection was detected in 17 women (18.8%); of whom 10 (11.1%) had hr-HPV. Among these 90 women who had cervical and anal HPV results available, 26 (28.9%) had only cervical hr-HPV infection, seven (8%) had only anal HPV-infection, and nine (10%) had cervical as well as anal HPV infection (Table 5). In women with anal hr-HPV, the odds of having cervical hr-HPV was 2.03 (95%CI 0.67–6.11, P=0.21).

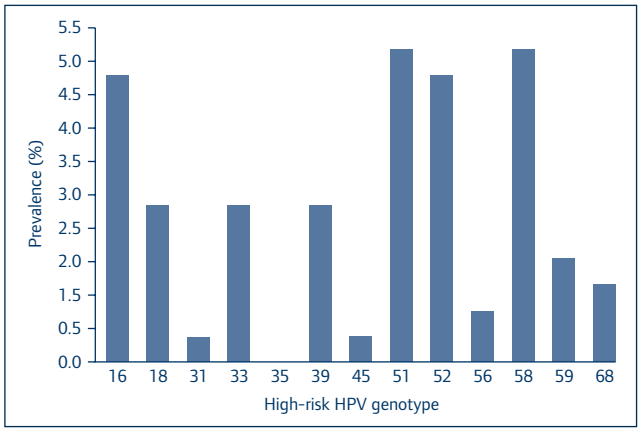

Figure 1. Cervical high-risk HPV genotype distribution in HIV-infected women in Thailand.

Discussion

We found cervical hr-HPV infection in 35.2% of HIV-infected women in Thailand. Furthermore, we found cervical squamous intra-epithelial lesions of any grade in 6.3%, as determined by Pap smear. All women underwent colposcopy, which was abnormal in 99 women and, as a result, histological specimens were taken. Histology revealed that 22.6% of women had CIN. To our knowledge, we also provide the first data on anal HPV infection in HIV-infected women in Asia. Among 102 women in our sub-study, we found anal hr-HPV infection in 11.1%, and abnormal anal cytology in two women.

The prevalence of cervical hr-HPV in our cohort is similar to the prevalence of 38.6% reported from a previous study in HIV-infected women in Bangkok [12], but lower than the prevalence in studies in HIV-infected women from other countries, which ranged from 46.7% to 70% [9,13].

Furthermore, in our cohort HPV types 51, 58, 16, 52, 18, 33 and 39 were the most common high-risk types found. This is consistent with a recent study involving over 5,906 Thai women, where HPV 52, 16 and 51 were the most prevalent cervical HPV types found, although whether any of the women in this latter study were HIV-infected was not reported [14]. HIV-infected women might have a different HPV type distribution in cervical dysplasia compared to HIV-uninfected women, with HPV types 18, 33, 51, 52 and 58 found more commonly than HPV 16 [15,16]. While other studies do not confirm this, nevertheless they tend to show a higher HPV prevalence in HIV-negative women [17–19]. The clinical significance of this, and the potential impact on HPV-vaccine efficacy remains to be elucidated.

In our and other resource-limited settings, Pap smear for cervical cancer screening is not routinely performed owing to logistical and financial restrictions. Testing for the presence of hr-HPV as a triage has been suggested for settings where the availability of histopathological analysis is limited, due to the higher sensitivity to detect lesions with a high potential for malignant transformation, and has been shown to be feasible for these settings [20,21]. We found a poor agreement between cytology and histology findings, and the sensitivity of Pap smears to detect either CIN1+ or CIN2+ in our study was rather low. This is in line with other reports suggesting that routine colposcopy should be performed in HIV-infected women [22–24]. The quality of cytology is dependent upon various operational and logistical requirements, which are often not optimal in resource-limited settings. However, in our study we assured quality control by the re-reading of all abnormal slides and a random selection of normal slides by a second cytopathologist. Collection technique significantly influences the sensitivity of cervical cytology. Although the rate of unsatisfactory samples was relatively low (four samples), 22.2% of samples lacked an endocervical/transformation zone component. An endocervical/transformation zone component is not required by the Bethesda criteria for a sample to be classified as satisfactory, but its presence improves the overall specimen quality [11]. The importance of this component is controversial, but it has been

Table 3. Cytology versus histology

Biopsy	Cervical cytology				
	Total	Normal	ASC-US	LSIL	HSIL
ND	153	150	3	0	0
No intraepithelial abnormalities	42	41	1	0	0
CIN	47	40	2	5	0
CIN2	2	1	1	0	0
CIN3	8	4	2	1	1
Total		236	9	6	1

ND: not done; CIN1: cervical intra-epithelial neoplasia grade 1; CIN2: cervical intra-epithelial neoplasia grade 2; CIN3: cervical intra-epithelial neoplasia grade 3; ASCUS: atypical squamous cells of undetermined significance; LSIL: low grade squamous intra-epithelial lesions; HSIL: high grade squamous intra-epithelial lesions

Table 4. Unadjusted and adjusted odds ratios for factors associated with cervical hr-HPV

Characteristic	Unadjusted OR (95% CI)	*P* value	Adjusted OR (95% CI)	*P* Value
Age (years)	0.96 (0.92–1.01)	0.11		
Age at marriage (years)	1.03 (0.98–1.08)	0.31		
Current smoking	3.77 (0.68–20.98)	0.13		
Past smoking	1.73 (0.68–4.44)	0.25		
Current alcohol use	2.13 (0.98–4.64)	0.057		
Past alcohol use	1.47 (0.82–2.66)	0.20		
Postmenopausal	7.00 (1.42–34.45)	0.02	12.47 (2.34–66.29)	0.003
HAART use	0.57 (0.32–1.02)	0.056		
Years since HIV diagnosis	0.87 (0.80–0.94)	<0.001	0.88 (0.81–0.96)	0.003
Years since start HAART	0.93 (0.83–1.06)	0.29		
Current plasma HIV RNA <40 copies/mL	0.47 (0.27–0.82)	0.008	0.42 (0.23–0.79)	0.007
Current CD4 count				
<350 cells/mm^3 (reference)	1.0			
350–499 cells/mm^3	0.87 (0.42–1.79)	0.70		
≥500 cells/mm^3	0.79 (0.39–1.60)	0.51		
Marital status				
Unmarried (reference)	1.0			
Married	0.31 (0.07–1.35)	0.12		
Separated/divorced	0.47 (0.09–2.29)	0.35		
Widowed	0.14 (0.02–0.85)	0.03		
HIV status partner				
HIV-uninfected (reference)	1.0			
HIV-infected	1.38 (0.73–2.63)	0.32		
No partner	0.82 (0.37–1.83)	0.63		
Unknown	2.06 (0.98–4.35)	0.057		
Lifetime number of sex partners				
1 (reference)	1.0			
2–9	1.08 (0.59–1.97)	0.81		
20–100	1.02 (0.09–11.90)	0.99		
More than 100	3.07 (0.48–19.72)	0.24		
Refused	1.46 (0.42–5.13)	0.55		
Number of sex partners in last 30 days				
0 (reference)	1.0			
1–4	1.10 (0.55–2.21)	0.79		
5–19	0.69 (0.07–7.25)	0.76		
Ever commercial sex work	2.65 (0.89–7.83)	0.08		
Condom use during vaginal intercourse				
Consistent (reference)	1.0			
Inconsistent	3.60 (1.35–9.59)	0.01		
Never	1.40 (0.48–4.11)	0.54		
Current genital ulcer	11.64 (1.38–98.29)	0.02		
Ever genital ulcer	2.72 (1.05–7.02)	0.04		
Ever genital wart	5.86 (1.16–29.65)	0.03		

OR: odds ratio; 95%CI: 95% confidence interval; HAART: highly active antiretroviral therapy

Table 5. HPV genotype distribution in women with anal and cervical HPV infection

Age (years)	CD4 (cells/mm^3)	HAART use	Anal HPV types	Anal Pap	Cervical HPV types
26	317	+	16	Neg	16
34	303	+	33, 66	Neg	33
33	465	+	18, 51, 52	Neg	51, 53
35	352	+	59	Neg	59, 62, 71
32	445	-	16, 58, 59, 73, CP6108	Neg	16, 54, 58, 70, 73, CP6108
21	396	-	45	Neg	16, 40, 45, 58, 59, 66
44	394	-	16	Neg	16
25	395	-	62	Neg	52, 53, 55, 56, 62
29	728	-	72	Neg	High-risk positive, could not be typed

HAART: highly active antiretroviral therapy; Neg: negative for intra epithelial abnormalities

found that abnormal cells are less often found in samples lacking the endocervical/transformation zone component [25]. This could explain the lower sensitivity of cervical cytology found in our study. We did not perform wet mount in this study, and therefore it might have been possible that local inflammation leading to cellular obscuration played an important role. Further research on screening tests to evaluate ideal combinations of sensitivity and specificity must be pursued, such as hr-HPV testing and/or the use of other biomarkers such as HPV E6/E7 oncoprotein in HIV-infected women in resource-limited settings, and particularly in Thailand [26].

Women with undetectable plasma HIV RNA had a decreased risk of having cervical hr-HPV infection. Immune recovery after starting HAART, resulting in a better clearance of HPV-infection could explain this phenomenon [27]. Although the use of HAART as a factor was not significantly associated with cervical hr-HPV in our cohort, this difference might be explained by an adherence effect, and persistent undetectable viral load may be a more appropriate marker. Minkoff *et al*. investigated the effect of adherent and effective HAART use on the prevalence of cervical HPV infection and squamous intra-epithelial lesions [28]. Adherent HAART use was defined as self-reported use of HAART as prescribed ≥95% of the time, while effective HAART use was defined as a reduction in HIV RNA by >90% or to undetectable levels. In adherent HAART users, the prevalence of cervical hr-HPV infection was reduced in multivariable models, although the association was not significant. In our study, HAART use was not associated with prevalent hr-HPV in multivariate models, but an undetectable viral load, which reflects good adherence in the period before testing, was associated with a significant 58% reduction in prevalent hr-HPV.

Longer duration of diagnosed HIV-infection was also associated with a decreased risk of cervical hr-HPV infection. This could reflect a higher likelihood of these women to have started HAART, leading to immune recovery, and facilitating the clearance of HPV infection. However, a change in sexual risk behaviour after diagnosis of HIV-infection cannot be excluded [25].

Although we were limited by the sample size, our estimates indicate that post-menopausal women had an increased risk of cervical hr-HPV infection. This is in line with previous evidence, showing a 'second peak' of HPV infection among older, post-menopausal women, in addition to the first peak in adolescence [29]. Likely explanations for this are a weakened immune response with older age, hormonal changes leading to higher vulnerability of the epithelium, or changes in sexual activity [30].

Official anal cancer screening guidelines have not been adopted, but the routine screening of HIV-infected men and women with anal Pap smear has been suggested [31]. In our cohort the prevalence of anal HPV infection and of anal hr-HPV infection was 18.8% and 11.1%, respectively, which is relatively low compared to the recently reported results of the Study to Understand the Natural History of HIV/AIDS in the Era of Effective Therapy (the SUN study) [9]. In the SUN cohort, 90% of HIV-infected women had anal HPV, and 85% had anal hr-HPV infection. However, the SUN cohort was quite different from ours: 52% of women were current smokers, compared to 2.3% in our cohort, and 38% of the women in the SUN study reported a history of anal intercourse, compared to 3.9% in our cohort. Furthermore, we found a relatively low prevalence of cytological abnormalities, which may be explained by the fact that anal cytology, similar to cervical cytology, has low sensitivity to detect abnormalities [32] and that we only performed high-resolution anoscopy on women who had abnormal anal cytology. The Women's Interagency HIV Study (WIHS) cohort recently reported 16% prevalence of anal intra-epithelial neoplasia in HIV-infected women, which is similar to the prevalence of CIN in the same cohort [8].

Our study has several limitations. Although the colposcopy performed in all women was a strength of our study, biopsy was only performed in women with abnormal findings; hence the sensitivity and specificity estimates are not adjusted for verification bias. Furthermore, longitudinal data are needed to elucidate the influence of suppressed plasma HIV RNA on the acquisition or clearance of cervical hr-HPV infection.

In conclusion, we found a prevalence of cervical hr-HPV of 35% in Thai HIV-infected women; with virologically suppressed women and women with a longer time since HIV diagnosis having a lower risk of having cervical hr-HPV infection, indicating that early diagnosis and treatment of HIV is beneficial. Furthermore, we found a poor agreement between the results of cervical Pap smear testing and results of cervical histology, suggesting Pap smear for cervical cancer screening might not be an optimal method for cervical cancer screening in HIV-infected women in our setting. Further research on evaluating efficacy of HPV-based screening among HIV-infected women in our setting is warranted.

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Conflicts of interest

None were declared.

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Disclaimer

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