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Anal squamous intraepithelial lesions among HIV positive and HIV negative men who have sex with men in Thailand

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Abstract

Objectives—To evaluate the prevalence and risk factors of anal squamous intraepithelial lesions (ASIL), the putative anal cancer precursor, in Asian HIV positive and HIV negative men who have sex with men (MSM).

Methods—Men who underwent anal Pap smear reported clinical, sociodemographic and behavioural information collected through questionnaire and interview between January 2007 and April 2008. χ^2 and logistic regression were used to evaluate ASIL prevalence and risk factors among HIV positive and HIV negative MSM.

Results—Of the 174 MSM (mean age 32.1 years), 118 (67.8%) were HIV positive. Overall, 27% had abnormal anal cytology: 13.2% had atypical squamous cells of undetermined significance (ASC-US), 11.5% had low-grade squamous intraepithelial lesion (LSIL) and 2.3% had high-grade squamous intraepithelial lesion (HSIL). Prevalence of ASIL was higher among HIV positive than HIV negative MSM (33.9% vs 12.5%; $p=0.003$). Among HIV positive MSM, 16.1% had ASC-US, 14.4% had LSIL and 3.4% had HSIL and 7.1%, 5.4% and 0% in HIV negative MSM, respectively. Anal condyloma was detected in 22% of HIV positive and 16.1% (9/56) of HIV negative MSM ($p=0.5$). In HIV positive MSM, anal condyloma (OR 3.42, 95% CI 1.29 to 9.04; $p=0.01$) was a significant risk factor for ASIL. Highly active antiretroviral therapy use and CD4+ T cell count were not associated with ASIL.

Conclusions—One-third of HIV positive and 12.5% of HIV negative MSM had ASIL. Thus, as greater numbers of HIV positive MSM live longer due to increasing access to HAART worldwide, effective strategies to screen and manage anal precancerous lesions are needed.

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Men who have sex with men (MSM) are at increased risk for developing anal squamous intraepithelial lesions (ASIL) or anal squamous cell cancer (SCC),¹ which are associated with chronic infection with oncogenic (high-risk) human papillomavirus (HPV) genotypes.² The incidence of anal SCC among MSM in the USA is estimated to be 35 per 100 000 person-years^{3,4} and studies have indicated MSM with HIV infection are two times as likely as HIV negative MSM to develop anal SCC.⁵ HIV positive MSM represent one of the highest risk groups for the development⁶ and recurrence⁷ of high-grade squamous intraepithelial lesions (HSIL), the likely precursors of anal cancer.

Anal cancer and cervical cancer share a common associated aetiology: HPV infection, as well as patterns of cytological changes. These changes in cytology, graded by the revised Bethesda system, can be detected by using Papanicolaou (Pap) smear screening. Screening for ASIL is important from a clinical and public health point of view since men with abnormal results can be investigated further and their Pap results confirmed by high-resolution anoscopy and biopsied as necessary. Treatment of the precancerous lesions may be possible; thereby, minimising risk for progression to anal cancer.

Studies in the West have demonstrated ASIL prevalence ranging from 7–20%^{8–10} among HIV negative MSM and 27–81% among HIV positive MSM.^{11–13} Few studies have reported ASIL prevalence in MSM in Thailand or in other parts of Asia, largely as a result of lack of awareness among MSM about the excess risk of anal precancerous lesions as well as non-availability of routine anal Pap smear screening. The prevalence and incidence of anal SCC are also not well documented mainly due to limitations in population-based cancer registry reporting.

In January 2007, the Thai Red Cross AIDS Research Centre (TRC-ARC) began offering anal Pap smear as part of an annual health examination programme to HIV positive and HIV negative MSM. Our objective was to describe the prevalence of anal cytological abnormalities in HIV positive and HIV negative MSM in our centre and to identify risk factors for ASIL.

METHODS

This study was a cross-sectional study of anal Pap smear results and linked clinical, sociodemographic and behavioural information collected at the TRC-ARC in Bangkok. Participants were those receiving anal Pap smears between January 2007 and April 2008. Anal Pap smears were performed by one research nurse and slides fixed and stained in the clinic were sent to the Thai National Cancer Institute for assessment. A cytotechnician screened all slides and positive slides were re-screened by the head cytotechnician who had 3 years of experience in reading anal cytology slides. Cytology results were categorised according to the revised Bethesda System of cervical cytology, and were reported as normal, atypical squamous cells of undetermined significance (ASC-US), low-grade squamous intraepithelial lesion (LSIL) and HSIL.¹⁴ Participants reported medical, sexual, and behavioural history during a nurse-administered interview. Sociodemographic data, CD4+ T cell count, HIV-RNA viral load, history of opportunistic infections and highly active antiretroviral therapy (HAART) regimen data were extracted from the questionnaire and the patients' records if the information was not available at the time of the visit.

We defined our outcome variable, ASIL, as any abnormal squamous cells on Pap smear: ASC-US, LSIL, HSIL or SCC. We based our sample size calculations on the assumption of prevalence of ASIL derived from data from other published literature.^{11–13} Thus, the minimum sample size required to detect an 18% difference of ASIL prevalence between the HIV positive and HIV negative groups at 80% power was 152 assuming an alpha of 0.05.

Differences in baseline population characteristics by HIV status, including prevalence of anal cytological abnormality, were examined using the χ^2 test for categorical variables and Mann-Whitney U for comparing median values of continuous variables. Prevalence estimates and 95% Wilson confidence intervals (CI) of abnormal cytology were computed for both groups. We used multivariable logistic regression to explore the association between the presence of abnormal cytology in HIV positive MSM and risk factors while adjusting for potential confounders. In multivariable analysis, models were selected a priori using covariates deemed clinically relevant. Data were analysed using SPSS v15.0 and the statistical software package R (v2.7.1, The R Foundation for Statistical Computing).

RESULTS

Between January 2007 and April 2008, 189 Pap smears were performed at the TRC-ARC. Results for three men with reported heterosexual behaviour and nine men of Caucasian descent were excluded from the analysis. For three patients who received more than one anal Pap smear, the first Pap smear result during the study period was included for analysis. Sociodemographic information for 174 MSM is described in table 1.

Overall, the mean age (range) was 32.1 (19–57) years, and the majority were of Thai ethnicity while six (4.3%) were of other Asian ethnicity, including Singaporean and Chinese. The majority (63.3%, 81/128) had a bachelor's degree or higher and their median monthly income was US\$ 300 (range 150–800). Of 174 men, 118 were HIV positive (67.8%). HIV negative MSM were more likely to be students. Similar percentages of HIV negative and HIV positive MSM smoked cigarettes. Almost all practiced receptive anal intercourse and most had six or more lifetime sexual partners. A total of 15% (8/55) HIV negative MSM reported a history of anal warts compared with 23% (26/113) of HIV positive MSM ($p=0.2$). Among HIV positive MSM, the median CD4+ T cell count was 342 cells/ml (interquartile range (IQR) 216–437) and median duration since HIV diagnosis was 13 months (IQR 1–25). Of 58 patients with plasma HIV RNA test results available, the median HIV RNA was 4.1 log₁₀ copies/ml (IQR <1.7–4.7) and 27.8% had undetectable HIV RNA. Altogether, 34% (39/114) of the HIV positive participants were on HAART, while no data were available on four HIV positive participants.

Table 2 displays the results of anal cytology in all participants as well as results stratified by HIV serostatus. Overall, 27% had abnormal anal cytology: 13.2% had ASC-US, 11.5% had LSIL and 2.3% had HSIL. Anal condyloma was detected by physical examination in 20.1%. Prevalence of ASIL, but not anal condyloma, was significantly higher among HIV positive than HIV negative MSM (33.9% vs 12.5%; $p=0.003$). Among HIV positive MSM, 16.1% had ASC-US, 14.4% had LSIL and 3.4% had HSIL. These were 7.1%, 5.4% and 0% in HIV negative MSM, respectively. On unadjusted bivariate analysis with ASIL status as the outcome and HIV status as predictor, HIV positive MSM had significantly greater odds of having ASIL as compared with HIV negative MSM (OR 3.59, 95% CI 1.49 to 8.64; $p=0.004$).

Results of the analyses of risk factors for ASIL among HIV positive MSM are shown in Table 3. Age, education, occupation, CD4+ T cell counts and HAART status were not statistically associated with ASIL. The presence of anal condyloma on physical examination and reported history of anal condyloma were associated with ASIL in HIV positive MSM in bivariable analysis. Covariates deemed clinically relevant were included in the multivariable model. These included age, CD4+ T cell count, HAART status and presence of anal condyloma on clinical examination. Anal condyloma detected on physical exam was the only significant predictor of ASIL (OR 3.42, 95% CI 1.29 to 9.04) in HIV positive MSM.

DISCUSSION

To our knowledge, this study is one of the first to describe cytological prevalence of HPV-associated anal precancerous disease among MSM in Asia. We report a high (27%) prevalence of abnormal anal cytology among Asian MSM in Bangkok and an even higher (34%) prevalence within HIV positive Asian MSM. Self-reported history of anal condyloma and anal condyloma on physical examination were associated with ASIL on anal Pap smears among HIV positive MSM in bivariate analysis, but only the latter was an independent predictor of ASIL after controlling for other confounders in multivariable analysis.

Our findings suggest that HIV positive MSM were more than three times as likely as HIV negative MSM to have ASIL. These results support studies from other countries that have identified HIV infection as a risk factor for abnormal anal cytology.⁵⁶⁸ Although ASIL prevalence was significantly higher among HIV positive MSM compared with HIV negative MSM, the history of and presence on physical examination of perianal condyloma was not different in the two groups. Studies in western settings have not consistently demonstrated an association between HIV infection and increased risk of anal condyloma. However, HIV positive patients are more likely to experience recurrences of condyloma after treatment.¹⁵ In a French study, 16% of HIV positive MSM had anal condyloma on physical exam, and a remote history (average 8 years since last treatment) of condyloma was associated with presence of Histologically confirmed anal intraepithelial neoplasia.¹⁶ We also describe an association between history of anal condyloma and ASIL in bivariate analysis; however, this may represent a selection bias as those who were aware of anal disease symptoms might choose to undergo anal cancer screening at higher rates than those who did not have any anal disease symptoms. Furthermore, condyloma prevalence may have been underestimated because the anal canal is only incompletely visualised during the examination and endoanal condyloma may not have been detected.

Cytological abnormalities in HIV positive MSM in the USA and Europe have varied between 27% and 81%;¹²¹³ thus, the estimate in our study (34%) falls within the reported prevalence range worldwide. A recently published study in a similar clinical setting, an urban HIV clinic in the USA, reported 28% abnormal anal cytology.¹¹ Unfortunately, Pap smears, even by highly trained pathologists, have only a moderate sensitivity in detecting histological anal dysplasia (69%–93%);¹⁷¹⁸ thus, true disease prevalence may have, in fact, been underestimated. The MSM in our study reported high levels of sexual risk behaviour, suggesting high potential of exposure to HPV. During the study period, MSM with abnormal cytology were referred to outside hospitals for follow-up anoscopy and treatment; however, future studies will allow us to confirm histological prevalence of dysplasia. This information would be valuable given the decreased specificity of Pap smears (33%–59%).¹⁶¹⁷

Poorer immunological status, as reflected by low CD4+ T cell count, has been associated with the development of ASIL.¹⁹²⁰ We did observe a trend of lowering CD4+ T cell counts and increasing risk of ASIL in this study, but this difference did not reach statistical significance potentially due to the modest sample size in this study. Our study did not demonstrate an association between current HAART use and cytological abnormalities of the anal mucosa. Studies in the West offer conflicting results: ASIL prevalence was lower among men on HAART compared with untreated men;²¹ however, most studies have not demonstrated a protective effect of HAART.²²²³ In fact, HAART may prolong the life of HIV positive MSM long enough for anal squamous intraepithelial lesions to manifest and progress; thus, highlighting the importance of screening programs to detect precancerous lesions.

This study is subject to limitations. First, participants were part of a self-pay service cohort and may not be representative of all Thai MSM due to the cost of Pap smear screening (around 7 US\$). Our clients receiving anal Pap smears had on average twice the median household monthly income of all Thais surveyed at the TRC-ARC. This difference in socioeconomic status may result in lower ASIL prevalence due to better access to health care. In a study of Thai females attending the same clinic,²⁴ low income was a predictor of cervical squamous intraepithelial lesion. Conversely, prevalence of abnormal anal cytology may be overestimated due to patients' desire to seek care for observed anal condyloma or other perceived anal disease, such that the sample is self-selected. However, most ASIL is asymptomatic and all MSM seeking care at the TRC-ARC were offered anal Pap smears. Second, we did not undertake HPV testing in this cohort and, therefore, are not able to stratify the odds of having ASIL by HPV types. One study in Taiwan found HPV types 16 and 58 in histological specimens from HIV negative and positive men with ASIL and anal cancer.²⁵ Future studies need to explore this dimension, especially since a prophylactic vaccine is now available against human papillomavirus (HPV) types 6, 11, 16 and 18.²⁶ While the protective efficacy in men is not known as yet, studies are ongoing and efficacy has a strong biological plausibility.

The concept of MSM-specific care in Thailand emerged only recently after HIV prevalence among MSM in Bangkok rose from 17% in 2003 to 28% in 2005.²⁷ Between 3% and 16% of Thai men report same sex experience;^{28,29} thus, the population is vulnerable to HPV infection and ASIL development may be substantial. Currently, there are only two clinics in Thailand, both located in Bangkok, that offer anal Pap smears. The role of anal Pap smear screening in the Thai setting has not been examined previously. Effectiveness of screening and treatment strategies^{7,17,30} have been investigated in Western countries, and many centres in the USA and Europe have adopted anal cancer screening as a routine part of MSM or HIV care. Taken together, this information highlights the potential benefits of implementing anal cancer screening programmes for MSM in Thailand. Anal SCC, when detected at a localised stage, has a 78% 5-year survival rate compared with 56% for regional disease and 18% for metastatic disease.³¹ Thus, the early detection of anal cancer could potentially improve survival.

In summary, we have demonstrated that one-third of HIV positive Thai MSM have ASIL. Prospective studies are needed to evaluate the incidence and predictors of ASIL and HPV infection in HIV infected and HIV uninfected MSM in Asia. As greater numbers of MSM seek HIV testing and care, effective strategies to screen and manage anal precancerous disease will need to be developed.

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Key messages

- ▶ Anal Pap smear screening was implemented at a community based clinic in Bangkok, Thailand.
- ▶ Prevalence of abnormal anal cytology among HIV positive and HIV negative men who have sex with men (MSM) was high, similar to that reported in Western countries.
- ▶ HIV positive MSM were three times more likely to have abnormal cytology when compared with HIV negative MSM.
- ▶ Human papillomavirus-related anal disease is common in Thai MSM and represents an opportunity for screening and prevention of anal cancer.

Table 1

Sociodemographic characteristics of participants

Characteristic	All MSM n (%)	HIV positive MSM n (%)	HIV negative MSM n (%)	p Value
Total number	174 (100%)	118 (67.8%)	56 (32.2%)	
Age, years mean (SD)	32.1 (8.3)	32.7 (7.7)	30.7 (9.4)	0.139
Ethnicity (%)				0.665
Thai	168 (96.6)	113 (95.8)	55 (98.2)	
Other Asian *	6 (3.4)	5 (4.2)	1 (1.8)	
Income (US\$) median (IQR)	300 (150–800)	300 (150–610)	455 (150–910)	0.341
Education				0.922
High school or lower	47 (36.7)	30 (37.0)	17 (36.2)	
College or higher	81 (63.3)	51 (63.0)	30 (63.8)	
Occupation				0.022
Unemployed/daily wage earner	29 (21.0)	21 (23.9)	8 (16.0)	
Student	25 (18.1)	10 (11.4)	15 (30.0)	
Employed	84 (60.9)	57 (64.8)	27 (54.0)	
Smoking history				0.138
Never	95 (72.5)	64 (68.8)	31 (81.6)	
Ever	36 (20.7)	29 (31.2)	7 (18.4)	
Ever practiced receptive anal intercourse	129 (92.8)	90 (92.8)	39 (92.9)	0.988
6+ sexual partners in lifetime	74 (89.2)	54 (90.0)	20 (87.0)	0.690
3+ sexual partners in last 1 month	8 (9.6)	5 (7.8)	3 (15.8)	0.301
History of anal condyloma	34 (20.2)	26 (23.0)	8 (14.5)	0.200

* Other Asian describes ethnically Asian men who were not of Thai nationality. IQR, interquartile range; MSM, men who have sex with men.

Table 2

Prevalence of abnormal anal cytology and anal condyloma among overall MSM, HIV negative MSM and HIV positive MSM

Cytology	All MSM (n=174), % (n)	95% CI (%)	HIV positive MSM (n=118), % (n)	95% CI (%)	HIV negative MSM (n=56), % (n)	95% CI (%)	p Value
No abnormality	73.0 (127)	(65.9 to 79.0)	66.1 (78)	(57.2 to 74.0)	87.5 (49)	(76.4 to 93.8)	0.003
Abnormal (ASC-US)	27.0 (47)	(21.0 to 34.1)	33.9 (40)	(26.0 to 42.8)	12.5 (7)	(6.2 to 23.6)	0.003
ASC-US	13.2 (23)	(9.0 to 19.1)	16.1 (19)	(10.6 to 23.8)	7.1 (4)	(2.8 to 17.0)	
LSIL	11.5 (20)	(7.6 to 17.1)	14.4 (17)	(9.2 to 21.9)	5.4 (3)	(1.8 to 14.6)	
HSIL	2.3 (4)	(0.9 to 5.8)	3.4 (4)	(1.3 to 8.4)	– (0)	(0 to 6.4)	
Anal condyloma on physical exam	20.1 (35)	(14.8 to 26.7)	22.0 (26)	(15.5 to 30.3)	16.1 (9)	(15.5 to 30.3)	0.359

ASC-US, atypical squamous cells of undetermined significance; HSIL, high-grade squamous intraepithelial lesions; LSIL, low-grade squamous intraepithelial lesions; MSM, men who have sex with men.

Table 3

Analyses of risk factors for ASIL in HIV positive MSM (n=118)

Characteristic	Unadjusted (bivariable) analysis		Multivariable logistic regression analysis	
	OR	p Value	Adjusted OR	p Value
Age (per additional year)	1.0 (0.95 to 1.05)	0.87	1.01 (0.96 to 1.08)	0.629
Education			Not included	
High school or lower	0.73 (0.27 to 1.97)	0.531		
College education or higher	1.0			
Occupation			Not included	
Unemployed/daily wage earner	2.81 (0.96 to 8.23)	0.059		
Student	3.75 (0.93 to 15.11)	0.063		
Employed	1			
Smoking			Not included	
Never	1			
Ever	1.25 (0.49 to 3.18)	0.644		
CD4+ T cell count (per additional 100 cells)	0.89 (0.67 to 1.11)	0.28	0.91 (0.68 to 1.14)	0.409
Currently on HAART	1.57 (0.70 to 3.52)	0.27	1.26 (0.5 to 3.14)	0.625
History of anal warts	3.52 (1.31 to 8.04)	0.01	Not included	
Anal condyloma on physical exam	3.66 (1.48 to 9.02)	0.005	3.42 (1.29 to 9.04)	0.013

ASIL, anal squamous intraepithelial lesions; HAART, highly active antiretroviral therapy; MSM, men who have sex with men.