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Incidence, Clearance, Persistence and Factors Related with High-risk Anal HPV Persistence in South-East Asian MSM and Transgender Women

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Abstract

Objectives: Persistent anal high-risk human papillomavirus (HR-HPV) infection is a major risk factor for anal cancer among men who have sex with men (MSM) and transgender women (TGW). We aimed to estimate incidence, clearance, and persistence of anal HR-HPV in HIV-positive and HIV-negative MSM and TGW, and to assess factors for HR-HPV persistent.

Design: Prospective cohort study.

Methods: MSM and TGW aged ≥18 years, were enrolled from Indonesia, Malaysia, and Thailand, then followed-up 6 monthly for 12 months. Anal swabs were collected at every visit for HR-HPV genotypes to define anal HR-HPV incidence, clearance, and persistence. Logistic regression was used to evaluate factors associated with HR-HPV persistence.

Results: 325 MSM and TGW were included in this study, of whom 72.3% were HIV-positive. The incidence of anal HR-HPV persistence was higher in HIV-positive than HIV-negative MSM participants (28.4/1000 vs 13.9/1000 person-months). HIV-positive participants had HR-HPV lower clearance rate than HIV-negative participants (OR 0.3; 95% CI 0.1-0.7). The overall

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EY, TPP, NP, IA, SN, JMP and PP planned the study, EY wrote the manuscript, NT, WSJ, IAY, HN, IKAS, MDDS, LR, TP, KATA, and NH did acquisition of data, NP, EY, RR and DT designed the analysis, DT and EY analysed the data, EY, NP and SN interpreted the data, all authors read and approved the final manuscript, and NP, JMP and PP critically revised the paper.

persistence of HR-HPV was 39.9% in HIV-positive and 22.8% HIV-negative participants. HPV-16 was the most persistent HR-HPV in both HIV-positive and HIV-negative participants. HIV infection (aOR 2.87; 95% CI 1.47-5.61), living in Kuala Lumpur (aOR 4.99; 95% CI 2.22-11.19) and Bali (aOR 3.39; 95% CI 1.07-10.75), being employed/freelance (aOR 3.99; 95% CI 1.48-10.77), and not being circumcised (aOR 2.29; 95% CI 1.07-4.88) were independently associated with anal HR-HPV persistence.

Conclusion: HIV-positive MSM and TGW had higher risk of persistent anal HR-HPV infection. Prevention program should be made available and prioritized for HIV-positive MSM and TGW where resources are limited.

Keywords

Incidence; clearance; persistence; anal; Human Papilloma Virus; men who have sex with men; transgender

INTRODUCTION

Persistent infection with high-risk human papillomavirus (HR-HPV) is a known cause of cervical, oral, penile and anal cancers. Men who have sex with men (MSM) have about 20 times higher chance to develop anal cancer than heterosexual men.[1,2] The risk is even greater in HIV-positive MSM. The pooled annual anal cancer incidence rate is 45.9 per 100000 in HIV-positive MSM (95% confidence interval, CI 31.2–60.3), compared with 5.1 per 100000 person (95% CI 0-11.5) in HIV-negative MSM. With longer survival due to the availability of antiretroviral therapy (ART), the incidence of anal cancer increased in the ART era compared with the pre-ART era [77.8 (95% CI 59.4–96.2) vs 21.8 (95% CI 8.2–35.4) per 100000].[2,3].

HPV-associated cancers, where tracked, are very common in South East Asia. Age-standardized rate (ASR) of cervical cancer was 17.2 per 100,000 (10.5 in Malaysia, 16.2 in Thailand, and 23.4 in Indonesia per 100,000). ASR of anal cancer was 0.3 per 100,000 (0.39 in Malaysia, 0.31 in Thailand, and 0.27 in Indonesia per 100,000).[4] We previously demonstrated a high prevalence (68%) of anal HR-HPV infection among MSM and transgender women (TGW) in Indonesia, Malaysia and Thailand.[5] Anal HR-HPV prevalence in HIV-positive participants was similar to the pooled prevalence reported in the meta-analysis done by Machalek, et al. (76.6% vs 73·5%), but the prevalence in HIV-negative participants was much higher than those reported in the same meta-analysis (53.5% vs 37.2%).

Longitudinal information on incidence, clearance, and persistence of anal HR-HPV infection and related diseases in Asia is needed to further elucidate disease burden among MSM and TGW, in order to guide the implementation of prevention programs in this region. This study aims to define incidence, clearance and persistence of anal HR-HPV infection in a longitudinal cohort of HIV-positive and HIV-negative MSM and TGW in Indonesia, Malaysia, and Thailand over a one-year period. Additionally, we assessed factors related with persistence of anal HR-HPV in all participants and specifically in HIV-positive MSM and TGW.

METHODS

Enrollment and follow-up of study participants

MSM and TGW, aged 18 years or more, who reported ever had sex with men were recruited to two cohort studies (MSM-VCT and ANSAP) conducted in Cipto Mangunkusumo Hospital Jakarta, Sanglah Hospital Bali, Thai Red Cross Anonymous Clinic Bangkok, and University of Malaya Medical Center Kuala Lumpur (for ANSAP study only). ANSAP was the continuity of MSM-VCT study which used the same inclusion and exclusion criteria and the exact same study procedures. Study sites were HIV testing and treatment centres which worked in close collaborations with local community-based organizations serving MSM and TGW for recruitment.

Exclusion criteria included history of anal cancer treatment; anal cytology or high-resolution anoscopy (HRA) or infrared coagulation within 12 months prior to enrollment; trichloroacetic acid/podophyllin application of the intraanal area in the past month; evidence of active concurrent intraanal or perianal bacterial or herpes simplex infection; and history of medical or psychiatric disorders that would preclude compliance with the study protocol.

Both MSM-VCT (NCT01637324) and ANSAP (NCT02155231) studies were conducted with approvals from ethical committees/institutional review boards at all study sites. All study procedures and data collection were performed after participants provided their written informed consent. Participants were asked to complete a baseline questionnaire containing information about demographic and behavioural risk data. HIV-specific data, including ART use, CD4 count and viral load, were also collected from participants with HIV infection. All participants were scheduled to come back at 6 months and 12 months after the baseline visit. Digital anorectal examination, anal swab collection, and high-resolution anoscopy were performed on all participants by trained study physicians at baseline, month 6 and month 12 visits.

Human papillomavirus (HPV) genotyping

A Dacron swab was used to collect anal sample from anal canal and placed in 20 mL liquid-based cytology fluid (Liqui-PREP fluid, LGM International, Inc, Melbourne, FL for MSM-VCT participants and ThinPrep fluid, Hologic, Boxborough, MA, USA for ANSAP participants). All samples were stored in −80° C refrigerator before being tested. The human b-globin gene was used to ensure DNA sufficiency and negative β-globin specimens were excluded from the analysis. By using the LINEAR ARRAY HPV Genotyping Test (Roche Molecular Systems, Inc, NJ), we amplified target DNA within the L1 region of the HPV genome. Nucleic acid hybridization with biotin-labelled DNA probes was used to determine 37 HPV genotypes, including HPV type 6, 11, 16, 18, 26, 31, 33, 35, 39, 40, 42, 45, 51, 52, 53, 54, 55, 56, 58, 59, 61, 62, 64, 66, 67, 68, 69, 70, 71, 72, 73, 81, 82, 83, 84, IS39 (variant of 82), and CP6108 (89).

Other testing

All HIV-negative or participants of unknown HIV status were tested for HIV antibodies at regular interval every 6 months and received pre- and post-test counselling, including risk

reduction counselling. Blood tests for CD4 count and plasma HIV RNA quantification were performed for HIV-positive participants.

Statistical analysis

All statistical analyses were conducted using STATA version 14 (StataCorp, College Station, TX). Anal HR-HPV types included in this analysis were 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68.

Incidence of anal HR-HPV type was calculated exclusively among participants whose baseline anal HR-HPV test result were negative for that particular type. Incidence was defined as the detection of a specific anal HR-HPV type at month 6 or month 12 visit. Clearance of specific anal HR-HPV types present at baseline was considered at the first follow-up visit at which that infection was no longer detected. Participant visits with an invalid anal HR-HPV test were excluded from the analysis. The incidence and clearance densities were calculated per participant time at risk, along with the incidence rate ratios (IRR) and the clearance rate ratios (CRR) between participants who were HIV-positive and HIV-negative. Person-time was calculated using the actual visit dates of participants in the risk set, and 95% CI around the incidence or clearance rate estimates and ratios were calculated using the quadratic approximation to the Poisson log likelihood for the log rate. Anal HR-HPV persistence was defined as having the same specific anal HR-HPV type at 2 consecutive visits. A logistic regression model was used to study factors associated with any anal HR-HPV persistence during a one-year follow up period. All covariates with $P < 0.25$ were included and adjusted for in multivariate models. A separate analysis was performed to also include HIV-specific covariates into the model for HIV-positive participants.

RESULTS

Participant characteristics

As shown in Table 1, we studied 392 participants (235 HIV-positive and 157 HIV-negative; 344 MSM and 48 TGW; 96 from Jakarta, 36 from Bali, 52 from Kuala Lumpur, and 208 from Bangkok) were enrolled and followed up between January 2011 to November 2012 in the MSM-VCT study and between June 2013 to April 2015 in the ANSAP study. Most of the participants (84.4%) were employed or were freelance workers. More than a quarter (26.5%) were current smokers. HIV-positive participants were older than HIV-negative participants [mean age 35.8 (standard deviation, SD 9.0) vs 32.1 (SD 9.2)], were less likely to be circumcised (35.3% vs 45.9%), and were less likely to report current use of alcohol (32.8% vs. 37.6%). Mean (SD) age at first anal sex was similar between HIV-positive and HIV-negative participants [18.1 (SD 4.3) and 18.4 (SD 4.3) years]. 63% of HIV-positive participants were on ART at baseline, with a median duration of 3 years (IQR 1.8-5.8) and had a median CD4 count at baseline of 375.5 (IQR 274-543) cells/mm^3.

Total number of participants in MSM-VCT study that completed 3 study visits was 203 of 239 participants (84.9%) and in ANSAP study was 132 of 153 participants (86.3%). The median time from baseline to month 6 visit was 5.90 (IQR 5.25-6.39) months and to month 12 visit was 11.21 (IQR 10.75-12.52) months.

At baseline, anal HR-HPV was detected in 66.5% of HIV-positive and 50.8% of HIV-negative individuals (data not shown). The mean number of anal HR-HPV types was 1.86 per person in HIV-positive participants and 1.69 per person in HIV-negative participants. The most common HR-HPV genotypes were HPV 16 (16.9%) followed by HPV 51, HPV 18 and HPV 59 (13.1%, 11.9% and 11.6%, respectively).

Anal HR-HPV incidence and clearance

Incidence rate of any anal HR-HPV types in HIV-positive persons was higher than incidence in HIV-negative persons although it was not statistically significant (28.4 per 1000 person-months; 95% CI 16.5-48.9 vs 13.9 per 1000 person-months; 95% CI 6.9-27.7), as seen in Table 2. Incidence rates in HIV-positive participants ranged from 0.6 (95% 0.1-4) per 1000 person-months for HPV 31 to 6.8 (95% CI 3.7-12.7) per 1000 person-months for HPV 16. The other high incident anal HR-HPV types included HPV 59 (incidence rate 6.3 per 1000 person-months; 95% CI 3.4-11.8), HPV 18 (incidence rate 4.4 per 1000 person-months; 95% CI 2.1-9.2), and HPV 52 (incidence rate 4.2 per 1000 person-months; 95% CI 2-8.7). For HIV-negative participants, HPV 16 (2.8 per 1000 person-months; 95% CI 0.9-8.7) and HPV 68 (2.6 per 1000 person-months; 95% CI 0.8-8) were the two HR-HPV types with the highest incidence rates.

There was less clearance of any anal HR-HPV types among HIV-positive participants than HIV-negative participants (0.3; 95% CI 0.1-0.7, Table 3). Clearance rate ratios varied by type. Clearance rate of HPV 16 was also lower in HIV-positive than HIV-negative participants (14.1 (95% CI 5.9-33.9) per 1000 person-months vs 47.1 (95% CI 21.1-104.7) per 1000 person-months). Among HIV-negative participants, HPV 18 was the least cleared anal HR-HPV infection (18.8 per 1000 person-months).

Anal HR-HPV persistence

The overall persistence of any anal HR-HPV types was 33.3% (39.9% among HIV-positive vs. 22.8% among HIV-negative participants). HPV 16 was the most persistent type in both HIV-positive and HIV-negative participants (12.3% and 5.9%, respectively). HPV 68 and HPV 58 were more persistent in HIV-positive than HIV-negative participants while HPV 52 tended to be more persistent in HIV-negative participants.

Factors associated with persistence of anal HR-HPV types

In a multivariate model, being HIV-positive (adjusted odds ratio, aOR 2.87; 95% CI 1.47-5.61), living in Kuala Lumpur (aOR 4.99; 95% CI 2.22-11.19) and Bali (aOR 3.39; 95% CI 1.07-10.75), being employed or freelance workers (aOR 3.99; 95% CI 1.48-10.77), and not being circumcised (aOR 2.29; 95% CI 1.07-4.88) increased the risk of having any anal HR-HPV persistence. Younger age, age at sexual debut, gender, partner status, education, monthly income, smoking and alcohol use were not associated with any anal HR-HPV persistence.

For HIV-positive participants, multivariate analysis shown that living in Kuala Lumpur (aOR 5.69; 95% CI 1.56-20.74), being employed or freelance workers (aOR 5.41; 95% CI 1.39-21.09), and having higher income (aOR 3.04; 95% CI 1.16-7.95) were risk factors for

persistence of any anal HR-HPV infection. Baseline CD4 count less than 350 cells/mm^3 showed a trend towards increased risk of any anal HR-HPV persistence (aOR 2.10; 95% CI 0.96-4.59), while ART use and plasma HIV RNA had no association with any anal HR-HPV persistence.

Persistence of HPV 16 infection also had significant association with HIV-positive status (aOR 3.00; 95% CI 1.09-8.19) and living in Kuala Lumpur (aOR 6.99; 95% CI 2.42-20.28). HIV-positive participants with baseline CD4 count less than 350 cells/mm^3 had 4.48 times (95% CI 1.35-14.86) higher risk of HPV 16 persistence. No other HIV-related factor was found to be related to the persistence of HPV 16.

DISCUSSION

Our study is one of a few cohorts evaluating incidence, clearance, and persistence of anal HR-HPV infection in HIV-positive and HIV-negative MSM and TGW in Asia. Most studies reported higher anal HR-HPV prevalence among MSM with HIV Infection than those without HIV.[1,6] Our study adds to limited data available in Asia and confirm higher incidence and persistence of anal HR-HPV in Asian HIV-positive MSM and TGW. As MSM and TGW currently contribute to the majority of new HIV infections in South East Asia, high burden of anal HR-HPV prevalence, incidence and persistence points to urgent need for countries in the region to integrate HPV prevention services as part of long-term sexual health care for these populations.

In this study, incidence rates of any anal HR-HPV infections among HIV-positive and HIV-negative participants were comparable to those found in other previous studies (ranged 9.5-28.2 per 1000 person-month in HIV-negative MSM and 15.9-64.9 in HIV-positive MSM), even though definitions of incidence, laboratory methods for HPV genotyping and study population were not consistent.[6–9] However, the incidence rates for HIV-positive and HIV-negative participants was lower than a previous study in Bangkok which was one of our study sites.[10] In HIV-positive participants, HPV 16 was the highest incident anal HR-HPV type, although the rate (6.8 per 1000 person-months) in our study was lower than a range of 9.1-64.9 per 1000 person-months reported in other studies. We found HPV 59 to be the second highest incident type in HIV-positive participants while other studies did not find many HPV 59 HPV infections. Similar findings were also seen among HIV-negative participants for HPV 16.[10–13]

HIV-positive participants exhibited a much lower anal HR-HPV clearance rate compared with HIV-negative participants (CRR 0.3; 95% CI 0.1-0.7). Our data were consistent with those from a MSM cohort in Amsterdam (CRR 0.7; 95%CI 0.6–0.9), but with much lower anal HR-HPV clearance rate in HIV-positive participants.[12] Overall clearance rates in our study were also lower than in a previous study in Bangkok (6 vs 30 per 1000 person-months in HIV-positive participants and 23.8 vs 39.9 per 1000 person-months in HIV-negative participants).[10] The clearance rate of HPV 16 in HIV-positive participants (14.1 per 1000 person-months) was much lower than that of HIV-positive MSM in Amsterdam and the previous Bangkok cohort (38 and 52 per 1000 person-months, respectively) but still

comparable with HIPVIRG cohort study in Montreal (12.2 per 1000 person-months) and a recent study in Australia (12.2 per 1000 person-months).[14]

One third of participants with any prevalent HR-HPV at baseline showed persistence over six months period. The high anal HR-HPV prevalence of 68%, as demonstrated in our previous report, combined with a high persistence among HIV-positive participants could therefore lead to clinically important events in this population. We could see similar patterns of high prevalence and persistence of several anal HR-HPV types. In HIV-positive participants, HPV types 16, 58, 59, and 68 that had high prevalence in our previous report also shown high persistence in this study.[5] HPV types 59 and 68 are not prevented by the current quadrivalent HPV vaccine nor by 9-valent HPV vaccine.[15]

Consistent with many other studies, our study showed that HIV infection was the main factor related to any anal HR-HPV type persistence, as well as HPV 16 persistence.[7,8,10,14,16] The only HIV-related covariates that showed a clear relationship to HPV 16 persistence was CD4 count below 350 cells/mm^3 (aOR 4.48; 95% CI 1.35-14.86), which also showed a trend toward association with persistence of any anal HR-HPV types. FHDH-ANRS 004 cohort study revealed that the risk of anal cancer increased with the longer duration of time with CD4 count less than 200 cells/mm^3.[17] The impact of HIV viral load on anal cancer has been inconsistent in previous studies.[17,18],[18] Our study did not find an association between HIV viral load and persistence of anal HR-HPV infection.

Sixty three percent of HIV-positive participants in this study reported ART use at baseline, but ART used was not related with the persistence of anal HR-HPV infection. This is consistent with the lack of clear impact of ART use on the reducing anal cancer incidence. It is possible that many HIV-positive participants started ART late and did not achieve complete reconstitution of the immune systems at the time of enrollment.[19] Unfortunately, we did not have their nadir or baseline CD4 count before starting ART. Earlier HIV diagnosis and treatment for all policy that is widely being implemented could potentially lower the risk of anal HR-HPV persistence in this population, but this will need to be demonstrated in future studies.

Interestingly, sustainable and higher income in our study was associated with increased risk of anal HR-HPV persistence. Our data also revealed that participants living in Kuala Lumpur had higher persistence of any anal HR-HPV infection and HPV 16 infection, regardless of their HIV status. Participants in Kuala Lumpur had higher income than other sites, as 79.3% of them had income more than 2000 MYR while only 48.6% in Bangkok, 3.1% in Jakarta, and 2.8% in Bali had the same amount of income. Although there were no supporting behavioural data, it is possible that economic factors influence the number of sex partners or unsafe sexual behaviour. Lifetime number of male sex partners is an important risk factor for anal HPV infection and has been shown to be a proxy for HPV exposure in previous studies.[20,21] Since the data of this report combining 2 cohort studies that had different questionnaires regarding behaviour practice, we did not analyse behaviour data to avoid bias.

We found not being circumcised to be associated with the increased risk of any anal HR-HPV persistence, but not HPV 16. However, circumcision practice varied greatly among

sites in our study, from 13% in Bangkok to almost 90% in Jakarta. In a meta-analysis by Albero, et al, male circumcision was associated with significant reduction of genital HPV prevalence, including HR-HPV prevalence. Most studies included in the analysis were using sample from the penis and surrounding areas. There was no evidence that male circumcision was associated with HPV clearance and incidence.[22,23] Nyitray, et al did not find an association between male circumcision and anal HPV persistence.[7]

There were several limitations in this study. The number of HIV-negative participants was limited, which hampered statistical analysis for the persistence of each anal HR-HPV type. However, we were able to evaluate the persistence of HPV type 16, the most common and highest incidence of anal HR-HPV. As with many other previous studies, we could not differentiate between reactivation and new infection in participants who previously cleared anal HR-HPV since we only had 6 monthly follow-up visits in a year duration.[10–12] HPV clearance was defined based on one negative sample collection, which might have overestimated the clearance rate. More frequent visits (every 3 months) and longer follow-up duration may give more accurate estimation of incidence and clearance of anal HR-HPV. In addition, we did not assess HPV viral load as a predictor of persistence of anal HR-HPV infection. Several studies have found associations between HPV viral load with persistent cervical HPV, penile HPV, and anal HPV infections.[16,24,25]

In summary, we demonstrated that HIV-positive MSM and TGW in Indonesia, Malaysia and Thailand had a trend toward higher incidence, significantly higher persistence, and lower clearance rate of anal HR-HPV than those without HIV infection. Our data highlight the need to establish affordable and accessible primary and secondary prevention programs for HPV infections and its associated pre-cancerous and cancerous diseases for MSM and TGW in Southeast Asia. These programs should be made available and prioritized for HIV-positive MSM and TGW where resources are limited.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Conflict of Interest and Source of Funding

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REFERENCES

1. Patel P, Bush T, Kojic EM, Conley L, Unger ER, Darragh TM, et al. Prevalence, incidence, and clearance of anal high-risk human papillomavirus infection among HIV-infected men in the SUN Study. J Infect Dis 2018; 217:953–963. [PubMed: 29211874]

2. Daling JR, Madeleine MM, Johnson LG, Schwartz SM, Shera KA, Wurscher MA, et al. Human papillomavirus, smoking, and sexual practices in the etiology of anal cancer. Cancer 2004; 101:270–280. [PubMed: 15241823]

3. Machalek DA, Poynten IM, Jin F, Fairley CK, Farnsworth A, Garland SM, et al. Anal human papillomavirus infection and associated neoplastic lesions in men who have sex with men: A systematic review and meta-analysis. Lancet Oncol 2012; 13:487–500. [PubMed: 22445259]

4. Bruni L, Albero G, Serrano B, Mena M, Gómez D, Muñoz J, et al. ICO/IARC Information Centre on HPV and Cancer (HPV Information Centre). Human papillomavirus and related diseases report Asia. Summary Report 17 6 2019 [accessed 21 May2020].

5. Somia IKA, Teeratakulpisarn N, Jeo WS, Yee IA, Pankam T, Nonenoy S, et al. Prevalence of and risk factors for anal high-risk HPV among HIV-negative and HIV-positive MSM and transgender women in three countries at. Medicine (Baltimore) 2018; 97:1–10.

6. Glick SN, Feng Q, Popov V, Koutsky LA, Golden MR. High rates of incident and prevalent anal human papillomavirus infection among young men who have sex with men. J Infect Dis 2018; 209:369–376.

7. Nyitray AG, Carvalho RJ, Chang M, Baggio ML, Ingles DJ, Abrahamsen M, et al. Incidence, duration, persistence, and factors associated with high-risk anal human papillomavirus persistence among HIV-negative men who have sex with men: A multinational study. Clin Infect Dis 2016; 62:1367–1374. [PubMed: 26962079]

8. Liu Z, Nyitray AG, Hwang LY, Swartz MD, Abrahamsen M, Lazcano-Ponce E, et al. Acquisition, persistence, and clearance of human papillomavirus infection among male virgins residing in Brazil, Mexico, and the United States. J Infect Dis 2018; 217:767–776. [PubMed: 29165581]

9. Hernandez AL, Efird JT, Holly EA, Berry JM, Jay N, Palefsky JM. Incidence of and risk factors for type-specific anal human papillomavirus infection among HIV-positive MSM. AIDS 2014; 28:1341–1349. [PubMed: 24959962]

10. Phanuphak N, Teeratakulpisarn N, Pankam T, Hongchookiat P, Chomchey N, Phanuphak P. Anal human papillomavirus infection among Thai men who have sex with men with and without HIV infection: prevalence, incidence, and persistence. J Acquir Immune Defic Syndr 2013; 63:472–479. [PubMed: 23514956]

11. De Pokomandy A, Rouleau D, Ghattas G, Vézina S, Coté P, Macleod J, et al. Prevalence, clearance, and incidence of anal human papillomavirus infection in HIV-infected men: The HIPVIRG cohort study. J Infect Dis 2009; 199:965–973. [PubMed: 19239366]

12. Van Santen K Geskus RB, Mooij SH, Van Der Sande MAB, Coutinho RA, Stolte IG, et al. The effect of HIV infection on anal and penile human papillomavirus incidence and clearance: a cohort study among MSM. AIDS 2016; 30:121–132. [PubMed: 26474302]

13. Geskus RB, Gonza C, Del J, Viciana P, Masia M, Herna B, et al. Incidence and clearance of anal high-risk human papillomavirus in HIV-positive men who have sex with men: estimates and risk factors. AIDS 2015; 30:37–44.

14. Ong JJ, Walker S, Grulich A, Hoy J, Read TRH, Bradshaw C, et al. Incidence, Clearance, and Persistence of Anal Human Papillomavirus in Men Who Have Sex With Men Living With Human Immunodeficiency Virus: Implications for Human Papillomavirus Vaccination. Sex Transm Dis 2019; 46:229–233. [PubMed: 30870323]

15. Van Damme P, Meijer CJLM, Kieninger D, Schuyleman A, Thomas S, Luxembourg A, et al. A phase III clinical study to compare the immunogenicity and safety of the 9-valent and quadrivalent HPV vaccines in men. Vaccine 2016; 34:4205–4212. [PubMed: 27354258]

16. Grabowski MK, Gray RH, Serwadda D, Kigozi G, Gravitt PE, Nalugoda F, et al. High-risk human papillomavirus viral load and persistence among heterosexual HIV-negative and HIV-positive men. Sex Transm Infect 2014; 90:337–343. [PubMed: 24482488]

17. Guiguet M, Boué F, Cadranel J, Lang J, Rosenthal E, Costagliola D, et al. Effect of immunodeficiency, HIV viral load, and antiretroviral therapy on the risk of individual malignancies (FHDH-ANRS CO4): a prospective cohort study. Lancet Oncol 2009; 10:1152–1159. [PubMed: 19818686]

18. Silverberg MJ, Chao C, Leyden WA, Xu L, Horberg MA, Klein D, et al. HIV infection, immunodeficiency, viral replication, and the risk of cancer. Cancer Epidemiol Biomarkers Prev 2011; 20:2551–2560. [PubMed: 22109347]

19. Okoye AA, Picker LJ. CD4(+) T-cell depletion in HIV infection: mechanisms of immunological failure. Immunol Rev 2013; 254:54–64. [PubMed: 23772614]

20. Giuliano AR, Anic G, Nyitray AG. Epidemiology and pathology of HPV disease in males. Gynecol Oncol 2010; 117:S15–S19. [PubMed: 20138345]

21. Heywood W, Smith AMA. Anal sex practices in heterosexual and male homosexual populations: a review of population-based data. Sex Health 2012; 9:517. [PubMed: 22951046]

22. Albero G, Castellsagué X, Giuliano AR, Bosch FX. Male circumcision and genital human papillomavirus: A systematic review and meta-analysis. Sex Transm Dis 2011; 39:104–113.

23. Larke N, Thomas SL, Dos Santos Silva I, Weiss HA. Male circumcision and human papillomavirus infection in men: A systematic review and meta-analysis. J Infect Dis 2011; 204:1375–1390. [PubMed: 21965090]

24. Marra E, King A, van Logchem E, van der Weele P, Mooij SH, Heijman T, et al. Anal HPV 16 and 18 viral load: A comparison between HIV-negative and positive MSM and association with persistence. J Med Virol 2018; 90:76–83. [PubMed: 28700080]

25. Winer RL, Xi LF, Shen Z, Stern JE, Newman L, Feng Q, et al. Viral load and short-term natural history of type-specific oncogenic human papillomavirus infections in a high-risk cohort of midadult women. Int J Cancer 2014; 134:1889–1898. [PubMed: 24136492]

Table 1.

Characteristics at baseline by HIV Status

	Total (n = 392)	HIV-positive (n = 235)	HIV-negative (n = 157)	p-value
DEMOGRAPHIC DATA				
Mean age (SD), years	34.3(9.2)	35.8(9.0)	32.1(9.2)	<0.001
Self-identified gender (%)				0.05
MSM	344(87.8)	200(85.1)	144(91.7)	
Transgender women	48(12.2)	35(14.9)	13(8.3)	
Partner status (%)				0.54
Single	313(79.9)	190(80.9)	123(78.3)	
Living together	79(20.2)	45(19.2)	34(21.7)	
Education (%)				0.27
Lower than secondary/vocational low school	53(13.5)	39(16.6)	14(8.9)	
Secondary school/vocational low school	114(29.1)	68(28.9)	46(29.3)	
Vocational high school/certificate	49(12.5)	29(12.3)	20(12.7)	
Bachelor's degree/university	145(37.0)	82(34.9)	63(40.1)	
Higher than bachelor	31(7.9)	17(7.2)	14(8.9)	
Occupation (%)				0.11
Unemployed/home duties/retired/street singer	36(9.2)	19(8.1)	17(10.8)	
Student	9(2.3)	5(2.1)	4(2.6)	
Employed/freelance	331(84.4)	197(83.8)	134(85.4)	
Sex worker	16(4.1)	14(6.0)	2(1.3)	
Monthly income				0.66
<10,000 THB/<3.2M IDR/<1,000 MYR	149(38.0)	93(39.6)	56(35.7)	
10,000-20,000 THB/3.2-6.4M IDR/1,000-2,000 MYR	101(25.8)	56(23.8)	45(28.7)	
20,001-50,000 THB/6.4-15.9M IDR/2001-5,000 MYR	107(27.3)	66(28.1)	41(26.1)	
>50,000 THB/15.9M IDR/5,000 MYR	34(8.7)	19(8.1)	15(9.6)	
Missing	1(0.3)	1(0.4)	0(0.0)	
Current smoker (%)				0.75
No	254(64.8)	164(69.8)	90(57.3)	
Yes	104(26.5)	69(29.4)	35(22.3)	
Missing	34(8.7)	2(0.9)	32(20.4)	
Current alcohol use (%)				0.02
No	227(57.9)	156(66.4)	71(45.2)	
Yes	136(34.7)	77(32.8)	59(37.6)	
Missing	29(7.4)	2(0.9)	27(17.2)	
Circumcision history (%)				0.04
Not circumcised	237(60.5)	152(64.7)	85(54.1)	
Circumcised	155(39.5)	83(35.3)	72(45.9)	
RISK BEHAVIOUR AT BASELINE				
Mean age of sexual debut (SD) (years)	18.2(4.3)	18.1(4.3)	18.4(4.3)	0.51
Had anal receptive in the past 6 mo (%)				0.07

	Total (n = 392)	HIV-positive (n = 235)	HIV-negative (n = 157)	p-value
No	41(10.5)	27(11.5)	14(8.9)	
Yes	220(56.1)	120(51.1)	100(63.7)	
Missing	132(33.4)	88(37.4)	43(27.4)	
Condom used in the past 6 months (%)				<0.001
Safe sex	93(23.7)	52(22.1)	41(26.1)	
Unprotected sex	128(32.7)	61(26.0)	67(42.7)	
Missing	171(43.6)	122(51.9)	49(31.2)	
ANAL HPV AT BASELINE				
Prevalence of high-risk HPV types	208 (60.5)	141 (66.5)	67 (50.8)	0.004
Mean number of high-risk HPV types	1.80	1.86	1.68	
HIV SPECIFIC FACTORS AT BASELINE				
ART used at baseline (%)				
No		79(33.6)		
Yes		148(63.0)		
Median (IQR) of ART duration		3.0(1.8-5.8)		
Median (IQR) CD4 count (cells/mm^3)		375.5(274-543)		
Median (IQR) log10 plasma HIV RNA (copies/ml)		2.0(1.6-4.3)		
Undetectable HIV RNA < 50 copies/ml (%)		110(47.0)		

SD, standard deviation; IQR, interquartile range; MSM, men who have sex with men; STI, sexually transmitted infection; HPV, human papillomavirus; ART, antiretroviral therapy; THB, Thai bath; IDR, Indonesian rupiah; MYR, Malaysian ringgit

Table 2.

Incidence of high-risk human papillomavirus types in HIV-positive and HIV-negative participants (N=264)

	HIV-Positive (n=163)					HIV-Negative (n=101)						
HPV Type	**Baseline n(%)**	**Incidence (number)**	**Person-Months**	**Incidence/1000 Person-Months (95% CI)**	**12-Month Incidence(%) (95% CI)**	**Baseline n(%)**	**Incidence (number)**	**Person-Months**	**Incidence/1000 Person-Months (95% CI)**	**12-Month Incidence(%) (95% CI)**	**IRR (95% CI)**	**p-value**
HPV16	40(18.9)	10	1460.6	6.8(3.7-12.7)	8.2(4.4-15.2)	18(13.6)	3	1074.0	2.8(0.9-8.7)	3.3(1.1-10.4)	2.5(0.6-13.9)	0.17
HPV18	28(13.2)	7	1600.8	4.4(2.1-9.2)	5.2(2.5-11)	13(9.9)	2	1130.7	1.8(0.4-7.1)	2.1(0.5-8.5)	2.5(0.5-24.4)	0.27
HPV31	10(4.7)	1	1796.7	0.6(0.1-4)	0.7(0.1-4.7)	2(1.5)	1	1241.3	0.8(0.1-5.7)	1(0.1-6.8)	0.7(0-54.2)	0.82
HPV33	13(6.1)	2	1732.3	1.2(0.3-4.6)	1.4(0.3-5.5)	0(0)	0	0.0	0(0-0)	0(0-0)		
HPV35	9(4.3)	1	1775.1	0.6(0.1-4)	0.7(0.1-4.8)	1(0.8)	0	0.0	0(0-0)	0(0-0)		
HPV39	17(8)	4	1675.6	2.4(0.9-6.4)	2.9(1.1-7.6)	8(6.1)	0	0.0	0(0-0)	0(0-0)		
HPV45	15(7.1)	1	1742.5	0.6(0.1-4.1)	0.7(0.1-4.9)	7(5.3)	0	0.0	0(0-0)	0(0-0)		
HPV51	30(14.2)	5	1582.8	3.2(1.3-7.6)	3.8(1.6-9.1)	15(11.4)	2	1113.2	1.8(0.4-7.2)	2.2(0.5-8.6)	1.8(0.3-18.5)	0.53
HPV52	16(7.6)	7	1683.2	4.2(2-8.7)	5(2.4-10.4)	17(12.9)	0	0.0	0(0-0)	0(0-0)		
HPV56	9(4.3)	3	1784.6	1.7(0.5-5.2)	2(0.6-6.2)	2(1.5)	0	0.0	0(0-0)	0(0-0)		
HPV58	25(11.8)	5	1607.4	3.1(1.3-7.5)	3.7(1.6-8.9)	9(6.8)	0	-	-	0(0-0)		
HPV59	29(13.7)	10	1579.0	6.3(3.4-11.8)	7.6(4.1-14.1)	11(8.3)	0	-	-	0(0-0)		
HPV68	21(9.9)	2	1656.4	1.2(0.3-4.8)	1.4(0.4-5.8)	10(7.6)	3	1161.0	2.6(0.8-8)	3.1(1-9.6)	0.5(0-4.1)	0.44
Any high-risk HPV	**141(66.5)**	**13**	**457.7**	**28.4(16.5-48.9)**	**34(19.8-58.6)**	**67(50.8)**	**8**	**576.5**	**13.9(6.9-27.7)**	**16.6(8.3-33.2)**	**2(0.8-5.7)**	**0.056**

HPV, human papillomavirus; CI, confidence interval; IRR, incidence rate ratio.

Table 3.

Clearance of high-risk human papillomavirus types in HIV-positive and HIV-negative participants (N=264)

	HIV-positive (n=163)			HIV-negative (n=101)				
HPV Type	**Cleared infection (n)**	**Person-Months**	**Clearance/1000 Person-Months (95% CI)**	**Cleared infection (n)**	**Person-Months**	**Clearance/1000 Person-Months (95% CI)**	**CRR (95%CI)**	**p-value**
HPV16	5	354.6	14.1(5.9-33.9)	6	127.5	47.1(21.1-104.7)	0.3(0.1-1.2)	0.055
HPV18	7	228.8	30.6(14.6-64.2)	2	106.4	18.8(4.7-75.2)	1.6(0.3-16.1)	0.58
HPV31	4	80.4	49.8(18.7-132.6)	-	-	-	-	-
HPV33	3	137.9	21.8(7.0-67.5)	-	-	-	-	-
HPV35	4	97.2	41.1(15.4-109.6)	-	-	-	-	-
HPV39	5	170.7	29.3(12.2-70.4)	5	37.2	134.5(56-323.1)	0.2(0.1-0.9)	0.02
HPV45	6	110.6	54.2(24.4-120.7)	2	45.4	44.1(11-176.2)	1.2(0.2-12.5)	0.85
HPV51	6	256.8	23.4(10.5-52)	4	108.7	36.8(13.8-98.1)	0.6(0.2-3.1)	0.49
HPV52	6	152.9	39.2(17.6-87.4)	5	155.0	32.3(13.4-77.5)	1.2(0.3-5)	0.76
HPV56	1	97.0	10.3(1.5-73.2)	2	10.9	184.3(46.1-736.9)	0.1(0-1.1)	0.03
HPV58	6	226.9	26.4(11.9-58.9)	3	78.4	38.3(12.3-118.7)	0.7(0.1-4.3)	0.60
HPV59	8	229.2	34.9(17.5-69.8)	4	90.2	44.3(16.6-118.1)	0.8(0.2-3.6)	0.68
HPV68	2	215.3	9.3(2.3-37.1)	3	63.5	47.2(15.2-146.4)	0.2(0-1.7)	0.09
Any high-risk HPV	**8**	**1336.9**	**6.0(3.0-12.0)**	**13**	**546.7**	**23.8(13.8-41.0)**	**0.3(0.1-0.7)**	**0.002**

HPV, human papillomavirus; CI, confidence interval; CRR, clearance rate ratio

Table 4.

Type-specific persistence of anal high-risk human papillomavirus, by HIV status

HPV Type	Overall (n=264) n(%)	HIV-positive (n=163) n(%)	HIV-negative (n=101) n(%)	p-value
HPV16	26(9.9)	20(12.3)	6(5.9)	0.09
HPV18	11(4.2)	8(4.9)	3(3.0)	0.54
HPV31	2(0.8)	2(1.2)	0(0.0)	0.53
HPV33	3(1.1)	3(1.8)	0(0.0)	0.29
HPV35	4(1.5)	3(1.8)	1(1.0)	>0.99
HPV39	5(1.9)	4(2.5)	1(1.0)	0.65
HPV45	5(1.9)	4(2.5)	1(1.0)	0.65
HPV51	13(4.9)	8(4.9)	5(5.0)	0.99
HPV52	8(3.0)	2(1.2)	6(5.9)	0.057
HPV56	3(1.1)	3(1.8)	0(0.0)	0.29
HPV58	11(4.2)	10(6.1)	1(1.0)	0.056
HPV59	14(5.3)	10(6.1)	4(4.0)	0.44
HPV68	14(5.3)	13(8.0)	1(1.0)	0.01
Any high-risk HPV	88(33.3)	65(39.9)	23(22.8)	0.004

HPV, human papillomavirus

Table 5.

Univariate and multivariate analyses of factors associated with persistence of any anal high-risk human papillomavirus types and HPV-16 only

Covariates	All high-risk HPV types				HPV-16			
	Univariate		Multivariate		Univariate		Multivariate	
	OR (95% CI)	p-value	OR (95%CI)	p-value	OR (95% CI)	p-value	OR (95%CI)	p-value
All participants								
Baseline HIV-positive vs negative	2.25 (1.24-4.1)	0.004	2.87 (1.47- 5.61)	0.002	2.21 (0.86-5.72)	0.08	3.00 (1.09-8.19)	0.03
Sites		<0.001				0.004		
Bangkok	1				1			1
Jakarta	1.14 (0.54-2.39)		0.86 (0.31-2.41)	0.775	2.24 (0.68-7.43)		1.90 (0.47-7.72)	0.37
Kuala Lumpur	4.59 (2.32-9.07)		4.99 (2.22-11.19)	<0.001	6.09 (2.24-16.54)		6.99 (2.42-20.28)	<0.001
Bali	2.18 (0.89-5.35)		3.39 (1.07-10.75)	0.038	1.75 (0.34-8.99)		1.99 (0.33-1.05)	0.45
Age, ≥30 years	1.42 (0.82-2.45)	0.20	0.91 (0.48-1.70)	0.758	1.59 (0.64-3.94)	0.30	0.99 (0.95-1.05)	0.93
MSM vs transgender women	1.58 (0.65-3.75)	0.26			0.68 (0.15-3.04)	0.60		
Living together vs single	0.90 (0.46-1.73)	0.74			0.99 (0.36-2.78)	0.99		
Bachelor degree and above	1.05 (0.63-1.75)	0.86			1.14 (0.51-2.57)	0.74		
Employed/freelance	1.63 (1.09-2.45)	0.01	3.99 (1.48-10.77)	0.006	1.63 (0.78-3.41)	0.14	3.00 (0.63-14.41)	0.17
Monthly income >20,000 THB/6.4M IDR/2,000 MYR	1.97 (1.17-3.32)	0.01	1.55 (0.77-3.13)	0.223	1.31 (0.58-2.96)	0.51		
Current smoking	1.42 (0.81-2.51)	0.19	1.11 (0.76-1.62)	0.601	1.05 (0.43-2.53)	0.92		
Current alcohol Use	0.91 (0.54-1.55)	0.74			0.93 (0.4-2.15)	0.86		
Circumcision	1.48 (0.84-2.60)	0.15	2.29 (1.07-4.88)	0.031	1.69 (0.68-4.14)	0.21	1.60 (0.59-4.41)	0.34
Age of sexual debut <18 years	1.00 (0.60-1.67)				0.73 (0.32-1.67)	0.45		
HIV-positive participants only								
Sites		<0.001				0.003		
Bangkok	1		1		1		1	
Jakarta	1.18 (0.47-2.94)		0.83 (0.21-3.25)	0.79	2.55 (0.66-9.80)		1.47 (0.30-7.12)	0.633
Kuala Lumpur	9.43 (3.22-27.63)		5.69 (1.56-20.74)	0.008	8.25 (2.58-26.38)		5.36 (1.39-20.57)	0.014
Bali	2.10 (0.73-5.99)		4.49 (0.91-22.07)	0.065	0.92 (0.1-8.13)		0.89 (0.07-11.32)	0.933
Age, ≥30 years	1.69 (0.83-3.45)	0.14	0.92 (0.38-2.20)	0.852	1.33 (0.43-4.98)	0.59		
MSM vs transgender women	1.27 (0.50-3.26)	0.62			0.34 (0.04-2.72)	0.24	0.54 (0.05-6.48)	0.630

Covariates	All high-risk HPV types				HPV-16			
	Univariate		Multivariate		Univariate		Multivariate	
	OR (95% CI)	p-value	OR (95%CI)	p-value	OR (95% CI)	p-value	OR (95%CI)	p-value
Living together vs single	1.11 (0.50-2.46)	0.79			0.93 (0.27-4.13)	0.90		
Bachelor degree and above	1.18 (0.91-1.52)	0.21	0.79 (0.31-2.03)	0.635	1.23 (0.43-3.53)	0.66		
Employed/freelance	1.41 (0.87-2.27)	0.14	5.41 (1.39-21.09)	0.015	2.09 (0.45-14.63)	0.33		
Monthly income >20,000 THB/6.4M IDR/2,000 MYR	2.81 (1.47-5.39)	0.002	3.04 (1.16-7.95)	0.024	1.23 (0.48-3.17	0.66		
Current smoking	1.52 (0.78-2.97)	0.22	1.11 (0.63-1.96)	0.725	2.32 (0.81-6.77)	0.08	1.61 (0.89-2.89)	0.115
Current alcohol Use	0.94 (0.49-1.81)	0.86			1.20 (0.39-3.44)	0.71		
Circumcision	1.56 (0.76-3.20)	0.19	1.79 (0.67-4.78)	0.246	1.46 (0.48-4.17)	0.45		
Age of sexual debut <18 years	0.84 (0.45-1.57)	0.58			0.71 (0.24-2.04)	0.49		
CD4 count at baseline (<350 cells/mm^3)	1.45 (0.77-2.75)	0.25	2.10 (0.96-4.59)	0.062	3.02 (1.04-9.48)	0.02	4.48 (1.35-14.86)	0.014
Plasma HIV RNA at baseline (>400 copies/ml)	1.43 (0.71-2.91)	0.28			0.34 (0.08-1.14)	0.06	0.82 (0.15-4.46)	0.819
ART used at baseline		0.05				0.01		
No ART	1		1		1		1	
ART <1 years	1.6 (0.55-4.62)	0.385	2.34 (0.67-8.14)	0.810	3.9 (0.34-45.52)	0.276	3.15 (0.24-41.47)	0.383
ART >1 years	2.3 (1.06-5.00)	0.035	2.17 (0.79-5.96)	0.134	9.3 (1.21-72.86)	0.032	2.17 (0.44-44.96	0.207

HPV, human papillomavirus; OR, odds ratio; CI, confidence interval; MSM, men who have sex with men; ART, antiretroviral therapy; THB, Thai bath; IDR, Indonesian rupiah; MYR, Malaysian ringgit.