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# Sexual behaviours associated with incident high-risk anal human papillomavirus among gay and bisexual men

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## ABSTRACT

**Objective** High-risk human papillomavirus (HRHPV) causes anal cancer, which disproportionately affects gay and bisexual men (GBM). We examined sexual behaviours associated with incident anal HRHPV in an observational cohort study of GBM in Sydney, Australia.

**Methods** GBM aged 35 years and above were enrolled in the Study of the Prevention of Anal Cancer. Detailed information on sexual practices in the last 6 months, including receptive anal intercourse (RAI) and non-intercourse receptive anal practices, was collected. Anal human papillomavirus (HPV) testing was performed at the baseline and three annual follow-up visits. Risk factors for incident HRHPV were determined by Cox regression using the Wei-Lin-Weissfeld method.

**Results** Between 2010 and 2015, 617 men were recruited and 525 who had valid HPV results at baseline and at least one follow-up visit were included in the analysis. The median age was 49 years (IQR 43–56) and 188 (35.8%) were HIV-positive. On univariable analysis, incident anal HRHPV was associated with being HIV-positive (p<0.001), having a higher number of recent RAI partners regardless of condom use (p<0.001 for both), preference for the receptive position during anal intercourse (p=0.014) and other non-intercourse receptive anal sexual practices, including rimming, fingering and receptive use of sex toys (p<0.05 for all). In multivariable analyses, being HIV-positive (HR 1.46, 95% CI 1.09 to 1.85, p=0.009) and reporting condom-protected RAI with a higher number of sexual partners (p<0.001) remained significantly associated with incident HRHPV. When stratified by recent RAI, non-intercourse receptive anal practices were not associated with incident HRHPV in men who reported no recent RAI.

**Conclusion** GBM living with HIV and those who reported RAI were at increased of incident anal HRHPV. Given the substantial risk of anal cancer and the difficulty in mitigating the risk of acquiring anal HRHPV, HPV vaccination should be considered among sexually active older GBM.

**Trial registration number** ANZCTR365383.

## INTRODUCTION

High-risk human papillomavirus (HRHPV) infection-related cancers, including squamous cell carcinomas of the cervix and anus, accounted for approximately 4.5% of all cancers globally in 2012.[1] While rates of cervical cancer have declined in countries with organised cervical screening programmes,[2] anal cancer incidence has increased in most industrialised countries over the last three decades.[3]

Several distinct populations experience anal cancer at markedly higher rates than the general population. These groups include people with high exposure to anal human papillomavirus (HPV) infection, such as gay and bisexual men (GBM),[4] and individuals with immunodeficiency, including people living with HIV and solid organ transplant recipients.[4] HIV-positive GBM have the highest risk of developing anal cancer with an estimated incidence of 85 cases per 100 000,[4] compared with 19 per 100 000 in HIV-negative GBM[4] and less than 1 per 100 000 in the general population.[3]

A high prevalence of anal HRHPV infection is the main driver of the elevated risk of anal cancer in GBM. A recent meta-analysis estimated that 30% of HIV-positive GBM were positive for anal HPV16, the HRHPV type that causes the majority (80.7%) of anal cancer,[5] compared with 14% and 3% of HIV-negative GBM and heterosexual men, respectively.[6]

The sexual practices of GBM contribute to the high burden of anal HRHPV infection, as having a high number of sexual partners[7] and receptive anal intercourse (RAI)[8] are common among GBM. The role of other non-intercourse receptive anal sexual practices, such as rimming, fingering, fisting and receptive use of toys, in anal HRHPV transmission is less clear.[9 10]

We examined the association between incident anal HRHPV and recent sexual behaviours among a cohort of GBM aged 35 and older participating in a natural history study of anal HPV infection in Sydney, Australia.

## METHODS

### Participants

Detailed methods of the Study of the Prevention of Anal Cancer (SPANC) have been previously described.[11] In brief, men aged 35 years or older

who reported having had sex with other men in their lifetime were eligible to participate.[11] Men were excluded if they had a history of anal cancer or had previously undergone high-resolution anoscopy.[11] Participants were recruited between 2010 and 2015, primarily from community settings in Sydney, and followed up to 2018. Signed informed consent was obtained from all participants. The study was registered in the Australian New Zealand Clinical Trial Registry.

### Data collection

Participants in SPANC underwent three annual clinical visits after the baseline visit. Detailed information on recent sexual exposures (in the last 6 months) was collected at each study visit through a computer-assisted self-interview. Participants were asked about the number of recent male sexual partners and the practice of receptive and/or insertive anal intercourse with and without condoms. The questions also covered a range of non-intercourse receptive anal practices, including digital anal penetration (fingering), receiving a hand into the anal canal (fisting), receptive analingus (rimming), receptive use of toys and insertion of recreational drugs into the anal canal (shelving).

### Study procedures

At each study visit, participants underwent HPV DNA genotyping. The methods of HPV testing in SPANC have previously been described.[11] A moistened Dacron swab was used to sample the anal canal before it was deposited into 20 mL of PreservCyt fixative (Hologic, Marlborough, Massachusetts, USA). An aliquot of PreservCyt was forwarded to the Regional HPV Lab Net Reference Laboratory in Melbourne for HPV testing. The Roche Linear Array (Roche Molecular Systems, Alameda, California, USA) and Anyplex HPV HR Detection systems (Seegene, Seoul, South Korea) were used to identify HRHPV types, which included HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68. Specimens positive for any HRHPV type on either Linear Array or Anyplex were considered positive. Samples were deemed unassessable if they had a negative test result for the 254 bp region of the human β-globin gene on the Roche Linear Array.

### Statistical analysis

STATA V.16 was used to conduct statistical analyses. Participants who tested negative to any of the 13 HRHPV types at baseline and had at least one follow-up visit with a valid HPV test were included in the longitudinal analyses. Type-specific incident HRHPV was defined as a negative baseline test for a specific HRHPV type and a subsequent positive test for the same HPV type at an annual follow-up visit. For each type of HRHPV, person-years (PY) were calculated as the time from study entry to the date of the first positive test, or the last study visit for the participants who remained negative. The exact binomial method was used to calculate 95% CIs for type-specific PY-weighted average incident HRHPV rates.

Risk factors for type-specific incident anal HRHPV were identified with univariable and multivariable Cox regression models using the Wei-Lin-Weissfeld method,[12] which allows incident anal HPV of multiple types at the same study visit to be included in the analysis.[12] HRs and their corresponding 95% CIs were presented. Demographic and HIV characteristics, all surveyed sexual practices and partner numbers in the prior 6 months were analysed for associations with incident HRHPV. Data on missing report of sexual behaviour were treated as missing data, while those with an invalid HPV test result were excluded from the analysis. P values for trend were reported for ordinal variables, such as age group, the number of sex partners and frequencies of specific sexual behaviours. Multivariable Cox regression models using backward stepwise elimination were developed to determine risk factors independently associated with incident HRHPV. All variables with a p value of less than 0.10 in univariable analyses were considered. Age and HIV status were included a priori in the multivariable analyses.

Non-intercourse receptive anal practices (fingering, rimming, fisting and use of toys) were stratified by RAI to assess whether associations between incident HRHPV and non-intercourse receptive anal practices were independent of RAI. Non-intercourse receptive practices found to be significant on univariable analysis underwent stratified analysis individually and as a combined variable.

HIV status and report of consistent condom use were also stratified by report of recent RAI to assess whether they predicted incident HRHPV infection independent of RAI.

## RESULTS

### Cohort characteristics

Between 2010 and 2015, 617 men were recruited, and 525 who had valid HPV results at baseline and at least one follow-up visit were included in the analysis. The median age at enrolment was 49 years (IQR: 43–56). The majority identified as gay, homosexual (499, 95.0%); a further 2.8% identified as bisexual. Just above one-third (n=188, 35.8%) were HIV-positive and 337 (64.2%) were HIV-negative. Among HIV-positive participants, the majority were receiving antiretroviral therapy (94.1%), had an undetectable viral load (89.4%) and a CD4 T-cell count above 350 cell/μL (84.9%) at the baseline visit. A total of 299 men developed incident HRHPV infection; 156 men developed one incident infection; 86 had two incident infections; 37 had three incident infections; 12 had four incident infections; 5 had five incident infections; 2 had six infections; and 1 participant had eight incident infections throughout the study period.

### Factors associated with incident HRHPV

For all 13 HRHPV types, the total cumulative follow-up during the study period was 16 262.4 PY, and there were 532 new HRHPV detections. The type-specific incidence ranged from 1.9 per 100 PY (95% CI 1.3 to 2.8) for HPV31 to 4.9 per 100 PY (95% CI 3.8 to 6.3) for HPV68 (table 1). Overall, the PY weighted average anal HRHPV incidence was 3.3 per 100 PY (95% CI 3.0 to 3.6) (table 1).

In univariable analyses, incident anal HRHPV was more common among HIV-positive than HIV-negative men (4.1 vs 2.9 per 100 PY, HR 1.59, 95% CI 1.25 to 2.02; table 2). There were no differences in the incidence of HRHPV across age groups (p=0.613). Anal HRHPV incidence was significantly higher in men who reported a preference for the receptive position compared with those who preferred the insertive position for anal intercourse (p=0.014), but incidence remained substantial (2.8 per 100 PY) among those who reported preferring the insertive position. HRHPV incidence was higher in men who reported having RAI compared with those who reported no RAI (p<0.001) and men who reported having RAI with a higher number of partners regardless of condom use (p-trend<0.001 for RAI both with and without a condom). Incident HRHPV was also associated with a range of non-intercourse receptive anal practices including rimming (p=0.002), fingering (p=0.030) and using sex toys (p=0.001). Receptive fisting (p=0.129) and

**Table 1** Incidence of type-specific anal HRHPV infection in the Study of the Prevention of Anal Cancer

| HPV type | Incident cases (n) | PY | Incidence (per 100 PY) | 95% CI |
|---|---|---|---|---|
| 16 | 32 | 927.1 | 2.3 | 2.3 to 4.6 |
| 18 | 33 | 1262.7 | 2.6 | 1.9 to 3.7 |
| 31 | 25 | 1316.2 | 1.9 | 1.3 to 2.8 |
| 33 | 27 | 1337.6 | 2.0 | 1.4 to 2.9 |
| 35 | 32 | 1341.8 | 2.4 | 1.7 to 3.4 |
| 39 | 40 | 1286.9 | 3.1 | 2.3 to 4.2 |
| 45 | 55 | 1222.2 | 4.5 | 3.5 to 5.9 |
| 51 | 46 | 1227.1 | 3.7 | 2.8 to 5.0 |
| 52 | 57 | 1266.9 | 4.5 | 3.5 to 5.8 |
| 56 | 41 | 1330.7 | 3.1 | 2.3 to 4.2 |
| 58 | 43 | 1242.7 | 3.5 | 2.6 to 4.7 |
| 59 | 43 | 1259.1 | 3.4 | 2.5 to 4.6 |
| 68 | 58 | 1190.3 | 4.9 | 3.8 to 6.3 |
| Any HRHPV | 532 | 16 262.4 | 3.3 | 3.0 to 3.6 |

HRHPV, high-risk human papillomavirus; PY, person-years.

receptive shelving of drugs (p=0.815) were not associated with anal HRHPV incidence.

### Multivariable analyses

In multivariable analyses, HIV infection (HR 1.42, 95% CI 1.09 to 1.85) and engaging in condom-protected RAI with a higher number of partners (p-trend<0.001, table 3) remained independently associated with incident anal HRHPV. The association with condomless RAI with a higher number of partners was of borderline significance (p-trend=0.074). After adjusting for these variables, no non-intercourse receptive anal practices remained independently associated with incident anal HRHPV.

### Stratified analyses

#### Condom use

In men who reported having RAI in the 6 months before a study visit, consistent condom use did not significantly reduce the incidence of anal HRHPV compared with men who did not report consistent condom use (p=0.837, table 4).

#### HIV status

Being HIV-positive rather than HIV-negative was associated with a higher incidence of anal HRHPV in those who reported no recent RAI (HR 2.27, 95% CI 1.44 to 3.58) and those who reported having recent RAI (HR 1.45, 95% CI 1.10 to 1.91) (table 4).

#### Non-intercourse anal receptive practices

Fingering (p=0.374), rimming (p=0.077) and receptive use of toys (p=0.262) were not significantly associated with incident anal HRHPV in men who reported having no RAI in the 6 months before the study visit (table 4). In men who reported having recent RAI, only rimming (p=0.006) was associated with a higher incidence of anal HRHPV.

## DISCUSSION

In this cohort of mainly community-recruited GBM in Sydney, incident anal HRHPV was more common in HIV-positive men than in HIV-negative men and in men who reported RAI with a higher number of recent sexual partners, independent of condom use. The practice of RAI was, therefore, a major behavioural driver of anal HRHPV acquisition in GBM. Nevertheless, the incidence of anal HRHPV remained substantial in those men whose preference was mostly for the insertive position in anal sex. Non-intercourse receptive anal practices were not independently associated with incident anal HRHPV after adjustment for RAI.

Most studies that have examined the relationship between RAI and anal HPV infection have been cross-sectional. The present study is one of only a few longitudinal studies that have specifically linked incident anal HRHPV with a higher number of recent RAI partners.[9 13] The elevated risk of incident anal HPV infection with a higher number of RAI partners likely results from increased exposure to different HPV types with new sexual partners.[9 13 14]

Condom use did not mitigate the risk of incident anal HRHPV with no difference in anal HRHPV incidence observed between men who consistently used condoms during RAI compared with those who engaged in condomless RAI. Other longitudinal studies have also shown no significant association of incident anal HRPV infection with condom use.[10 15 16] A cohort of 442 HIV-negative Italian GBM found consistent condom use was not associated with a decreased incidence of any HPV, HRHPV and HPV16/18 infection in the anal canal.[17] Similar findings were observed in a Baltimore cohort of HIV-positive men and women which found no difference in the risk of incident anal HRHPV between people who reported condomless RAI and people who used condoms consistently.[15]

Although they were not significant in multivariate or stratified analyses, non-intercourse receptive anal practices may partially account for the lack of efficacy of condom use. These sexual practices often occur in conjunction with RAI.[18] Some non-intercourse sexual behaviours are implicated in the spread of other sexually transmitted diseases such as anorectal gonorrhoea.[19]

Several longitudinal cohort studies have associated non-intercourse receptive practises with anal HPV transmission. A San Francisco-based cohort of HIV-positive GBM showed that receptive rimming with new sexual partners increased the risk of incident anal HPV infection.[9] The Dutch H2M study identified receptive rimming and fisting in combination with multiple anal sexual partners as a substantial risk factor for acquiring new anal HRHPV infection.[10] Similarly, a large cohort of community recruited GBM in Sydney identified fingering and fisting as risk factors for anal warts, a condition that is caused by low-risk HPV infection.[20] Most of these studies, however, did not adequately adjust for the effect of RAI on anal HRHPV transmission through either multivariable or stratified analyses.

This study did not establish HPV transmission via non-intercourse receptive practices in those who did not report RAI. The stratified analyses thus suggest that RAI has the primary role in anal HPV transmission. The analysis did, however, suggest that rimming may increase the risk of incident anal HRHPV when RAI was also reported. Men who reported RAI and being rimmed had a 63% higher risk of incident HRHPV compared with those who only engaged in recent RAI.

HIV infection was an important predictor for incident anal HRHPV in this study, independent of recent sexual practice. The incidence of anal HRHPV was 1.6 times higher in HIV-positive (4.1 per 100 PY) than in HIV-negative men (2.9 per 100 PY). The elevated risk of incident HRHPV in HIV-positive GBM remained after adjustment for recent sexual behaviour

**Table 2** Univariable analysis of predictors of incident anal HRHPV in the Study of the Prevention of Anal Cancer

| Objectives | N | PY | Incidence (per 100 PY) | HR | 95% CI | P value |
|---|---|---|---|---|---|---|
| Age (years) | | | | | | 0.613* |
| 35–44 | 124 | 3426.0 | 3.6 | 1 | – | |
| 45–54 | 205 | 6640.1 | 3.1 | 0.87 | 0.64 to 1.18 | |
| 55–64 | 155 | 4056.6 | 3.8 | 1.33 | 0.95 to 1.85 | |
| >65 | 48 | 2139.7 | 2.2 | 0.80 | 0.52 to 1.24 | |
| HIV status | | | | | | <0.001 |
| Negative | 312 | 10 889.9 | 2.9 | 1 | – | |
| Positive | 220 | 5372.5 | 4.1 | 1.59 | 1.25 to 2.02 | |
| Sexual position preference for anal intercourse | | | | | | 0.014* |
| Mostly insertive | 155 | 5577.1 | 2.8 | 1 | – | |
| Versatile | 254 | 7164.5 | 3.5 | 1.32 | 1.00 to 1.75 | |
| Mostly receptive | 118 | 3428.3 | 3.4 | 1.45 | 1.06 to 1.99 | |
| RAI with and without condom use in the last 6 months | | | | | | <0.001* |
| No RAI | 115 | 5597.4 | 2.1 | 1 | | |
| Condom protected RAI only | 103 | 2849.1 | 3.6 | 1.84 | 1.31 to 2.58 | |
| Any condomless RAI | 311 | 7701.6 | 4.0 | 1.90 | 1.44 to 2.50 | |
| Number of RAI partners with a condom in the last 6 months | | | | | | <0.001* |
| 0 | 175 | 8166.6 | 2.1 | 1 | – | |
| 1 | 102 | 3034.9 | 3.4 | 1.69 | 1.23 to 2.33 | |
| 2–5 | 172 | 3275.1 | 5.3 | 2.69 | 2.04 to 3.54 | |
| >5 | 80 | 1671.4 | 4.8 | 2.23 | 1.57 to 3.16 | |
| Number of RAI partners without a condom in the last 6 months | | | | | | <0.001* |
| 0 | 218 | 8446.4 | 2.6 | 1 | – | |
| 1 | 143 | 4650.2 | 3.1 | 1.12 | 0.85 to 1.47 | |
| ≥2 | 168 | 3051.4 | 5.5 | 2.07 | 1.57 to 2.73 | |
| Insertive anal intercourse with condom in the last 6 months | | | | | | 0.061* |
| Never | 264 | 9113.6 | 2.9 | 1 | – | |
| Occasionally | 182 | 5118.2 | 3.6 | 1.17 | 0.90 to 1.52 | |
| Often | 83 | 1916.3 | 4.3 | 1.36 | 0.96 to 1.92 | |
| Insertive anal intercourse without condom in the last 6 months | | | | | | 0.547* |
| Never | 259 | 8810.9 | 2.9 | 1 | – | |
| Occasionally | 183 | 4940.3 | 3.7 | 1.23 | 0.95 to 1.60 | |
| Often | 87 | 2396.8 | 3.6 | 1.01 | 0.74 to 1.38 | |
| Rimmed in the last 6 months | | | | | | 0.002 |
| No | 139 | 5638.6 | 2.5 | 1 | – | |
| Yes | 390 | 10 509.5 | 3.7 | 1.50 | 1.16 to 1.93 | |
| Receptive fingering in the last 6 months | | | | | | 0.030 |
| No | 153 | 5694.2 | 2.7 | 1 | – | |
| Yes | 376 | 10 453.9 | 3.6 | 1.32 | 1.03 to 1.70 | |
| Receptive fisting in the last 6 months | | | | | | 0.129 |
| No | 453 | 14 436.7 | 3.1 | 1 | – | |
| Yes | 76 | 1688.8 | 4.5 | 1.34 | 0.92 to 1.95 | |
| Shelved drugs in the last 6 months | | | | | | 0.815 |
| No | 509 | 15 699.7 | 3.2 | 1 | – | |
| Yes | 20 | 448.3 | 4.5 | 1.09 | 0.53 to 2.24 | |
| Receptive use of toys in the last 6 months | | | | | | 0.001 |
| No | 333 | 11 258.8 | 3.0 | 1 | – | |
| Yes | 196 | 4829.7 | 4.1 | 1.49 | 1.17 to 1.91 | |
| Non-intercourse receptive sexual practices combined (rimming, fingering and use of toys) | | | | | | 0.015 |
| No | 100 | 3983.6 | 2.5 | 1 | – | |
| Yes | 432 | 12 278.8 | 3.5 | 1.41 | 1.07 to 1.85 | |

*P value for trend.
HRHPV, high-risk human papillomavirus; PY, person-years; RAI, receptive anal intercourse.

and despite most HIV-positive participants having an undetectable HIV viral load and CD4 count in the normal range. This finding is consistent with other studies which have reported anal HRHPV to be more prevalent[21] and incident infection more common in HIV-infected GBM compared with HIV-negative GBM.[10 22 23]

The elevated risk of anal HRHPV in HIV-positive GBM is likely to be multifactorial. HIV infection may directly facilitate anal

**Table 3** Multivariable analysis of predictors of incident anal HRHPV in the Study of the Prevention of Anal Cancer

| | HR | 95% CI | P value |
|---|---|---|---|
| Age (years) | | | 0.076 |
| 35–44 | 1 | – | |
| 45–54 | 1.00 | 0.73 to 1.36 | |
| 55–64 | 1.52 | 1.08 to 2.14 | |
| >65 | 1.07 | 0.68 to 1.68 | |
| HIV status | | | 0.009 |
| Negative | 1 | – | |
| Positive | 1.42 | 1.09 to 1.85 | |
| Number of RAI partners with a condom in the last 6 months | | | <0.001 |
| 0 | 1 | – | |
| 1 | 1.72 | 1.26 to 2.35 | |
| 2–5 | 2.42 | 1.81 to 3.23 | |
| >5 | 2.01 | 1.41 to 2.86 | |
| Number of RAI partners without a condom in the last 6 months | | | 0.074 |
| 0 | 1 | – | |
| 1 | 1.04 | 0.79 to 1.38 | |
| ≥2 | 1.37 | 0.99 to 1.90 | |

HRHPV, high-risk human papillomavirus; RAI, receptive anal intercourse.

HPV infection through disruption of anal epithelial tight junction[24] and may impair the ability to control and clear acquired HPV infection as a result of relative immunodeficiency.[10] The sexual behaviours of HIV-positive GBM may also contribute to the elevated incidence of anal HRHPV by increasing their exposure to different HRHPV types. A community survey of GBM in Sydney demonstrated that HIV-positive GBM reported a higher number of recent sexual partners compared with their HIV-negative counterparts.[25] As an HIV risk reduction strategy, HIV-positive men may be more likely to be the receptive partner with partners whose HIV status is negative or unknown,[26] thus increasing their risk of anal HRHPV infection.

A limitation of the study was that sexual behaviour was self-reported and thus subject to imprecise recall and under-reporting, given the sensitive nature of sexual behavioural data. The sexual behaviours reported by SPANC participants, however, were similar to those in other studies conducted among GBM in Sydney[27] and may represent the sexual activities of gay community-attached GBM in Sydney. The SPANC study also used computer-assisted self-interviews, which may result in more accurate disclosure of sensitive sexual behaviours compared with interviews conducted by clinicians.[28]

The 12-month testing interval may also result in some incident HRHPV infections resolving before detection and may account for some of the differences in incidence between HIV-positive and HIV-negative populations. The estimated median time for clearance of HPV ranges between 4 months for HPV 18 and 10 months for HPV16 in HIV-negative GBM.[16] HIV-positive individuals have a longer HRHPV clearance time compared with HIV-negative individuals,[22] and this may partially account for the higher HRHPV detection in the HIV-positive population. In SPANC, however, HIV status was not associated with HRHPV clearance.[29] The 12-month HPV testing interval also differs from the 6-month time period during which sexual behaviours were examined. Although the sexual behaviours of GBM do not vary markedly in the short term,[30] it is likely that some participants who did not report RAI in the 6 months prior to HPV testing might have engaged in RAI in intervals that were not covered by the study questionnaire. This could lead to an overestimation of anal HRHPV risk in those who did not report RAI.

Finally, the detection of anal HRHPV may also not necessarily represent incident HRHPV infection. The men in this study were a sexually active cohort with the majority having multiple recent sexual partners. A positive HPV test result may, in some

**Table 4** Stratified analysis of HIV status, condom use and non-intercourse receptive anal practices by RAI for incident anal HRHPV

| Factors | RAI In the last 6 months | Factor outcome | N | PY | Incidence (per 100 PY) | HR | 95% CI | P value |
|---|---|---|---|---|---|---|---|---|
| HIV status | No | Negative | 60 | 3717.8 | 1.6 | 1 | – | <0.001 |
| | | Positive | 58 | 1993.9 | 2.9 | 2.27 | 1.44 to 3.58 | |
| | Yes | Negative | 252 | 7172.1 | 3.5 | 1 | – | 0.009 |
| | | Positive | 162 | 3378.6 | 4.8 | 1.45 | 1.10 to 1.91 | |
| Rimming | No | No | 81 | 3550.1 | 2.3 | 1 | – | 0.077 |
| | | Yes | 34 | 2047.2 | 1.7 | 0.63 | 0.38 to 1.05 | |
| | Yes | No | 58 | 2088.5 | 2.8 | 1 | – | 0.006 |
| | | Yes | 356 | 8562.2 | 4.2 | 1.63 | 1.15 to 2.31 | |
| Fingering | No | No | 85 | 3817.3 | 2.3 | 1 | – | 0.374 |
| | | Yes | 30 | 1780.0 | 1.7 | 0.77 | 0.43 to 1.38 | |
| | Yes | No | 68 | 1876.9 | 3.6 | 1 | – | 0.847 |
| | | Yes | 346 | 8673.8 | 4.0 | 1.03 | 0.74 to 1.44 | |
| Receptive use of toys | No | No | 97 | 4916.1 | 2.0 | 1 | – | 0.262 |
| | | Yes | 18 | 681.2 | 2.6 | 1.59 | 0.71 to 3.55 | |
| | Yes | No | 236 | 6342.7 | 3.7 | 1 | – | 0.128 |
| | | Yes | 178 | 4148.4 | 4.3 | 1.23 | 0.94 to 1.62 | |
| Non-intercourse receptive practices combined (rimming/fingering, toys) | No | No | 71 | 3173.8 | 2.2 | 1 | – | 0.461 |
| | | Yes | 47 | 2537.9 | 1.9 | 0.84 | 0.52 to 1.34 | |
| | Yes | No | 29 | 809.8 | 3.6 | 1 | – | 0.585 |
| | | Yes | 385 | 9740.9 | 4.0 | 1.12 | 0.74 to 1.71 | |
| Consistent condom use reported during RAI in the last 6 months | Yes | No | 311 | 7701.6 | 4.0 | 1 | – | 0.837 |
| | | Yes | 103 | 2849.1 | 3.6 | 0.97 | 0.72 to 1.30 | |

HRHPV, high-risk human papillomavirus; PY, person-years; RAI, receptive anal intercourse.

circumstances, represent reactivation of latent infection or transient anal HPV deposition if the participant had RAI close to the time of testing.

The major strength of this study is that as a natural history study, SPANC is one of a few large longitudinal studies that is able to link sexual behaviour with incident anal HPV over a prolonged follow-up period. Participants were asked detailed questions about their sexual behaviour, including questions about a comprehensive range of non-intercourse receptive anal practices allowing for a clearer delineation of the roles of non-intercourse receptive practices in incident anal HRHPV. The recruitment of participants primarily from community-based settings and the inclusion of both HIV-positive and HIV-negative individuals also allow the findings to be more generalisable to the Sydney GBM population and other gay communities of similar settings.

Incident anal HRHPV was common in this cohort of older GBM, and high incidence rates persisted well into the sixth decade of life. HIV infection and recent RAI with a higher number of partners increased the risk of incident anal HRHPV. Of note, non-intercourse receptive sexual behaviours were not independently associated with HRHPV incidence. Condom use appears to have no protective effect against incident HRHPV, whereas just above half of all incident HRHPV detected are potentially preventable with the current nonavalent HPV vaccine. Given the ongoing high rates of incident anal HRHPV, the substantially higher risk of anal cancer and the difficulty in mitigating the risk of acquiring anal HRHPV in this population, HPV vaccination should be considered among sexually active older GBM.

## Key messages

- HIV-positive gay and bisexual men (GBM) and men who engage in receptive anal intercourse (RAI) with a higher number of recent sexual partners have an elevated risk of incident anal high-risk human papillomavirus (HRHPV) infection.
- Non-intercourse receptive anal practices are not independently associated with incident anal HRHPV infection.
- Condom use during RAI may not protect against incident anal HRHPV infection in GBM.

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**Data availability statement** Data are available upon reasonable request. Sharing of study data for research collaboration will be reviewed on a case-by-case basis by the study chief investigators. Requests can be made to the project leader, IMP, who is a coauthor in the submission.



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## REFERENCES

1 Plummer M, de Martel C, Vignat J, *et al*. Global burden of cancers attributable to infections in 2012: a synthetic analysis. *Lancet Glob Health* 2016;4:e609–16.
2 Yang DX, Soulos PR, Davis B, *et al*. Impact of widespread cervical cancer screening: number of cancers prevented and changes in race-specific incidence. *Am J Clin Oncol* 2018;41:289–94.
3 Kang Y-J, Smith M, Canfell K. Anal cancer in high-income countries: increasing burden of disease. *PLoS One* 2018;13:e0205105.
4 Clifford GM, Georges D, Shiels MS, *et al*. A meta-analysis of anal cancer incidence by risk group: toward a unified anal cancer risk scale. *Int J Cancer* 2021;148:38–47.
5 Alemany L, Saunier M, Alvarado-Cabrero I, *et al*. Human papillomavirus DNA prevalence and type distribution in anal carcinomas worldwide. *Int J Cancer* 2015;136:98–107.
6 Marra E, Lin C, Clifford GM. Type-Specific anal human papillomavirus prevalence among men, according to sexual preference and HIV status: a systematic literature review and meta-analysis. *J Infect Dis* 2019;219:590–8.
7 Torres-Ibarra L, Conde-Glez CJ, Salmerón J, *et al*. Risk factors for anal HPV-16/18 infection in Mexican HIV-infected men who have sex with men. *Prev Med* 2014;69:157–64.
8 Donà MG, Palamara G, Di Carlo A, *et al*. Prevalence, genotype diversity and determinants of anal HPV infection in HIV-uninfected men having sex with men. *J Clin Virol* 2012;54:185–9.
9 Hernandez AL, Efird JT, Holly EA, *et al*. Incidence of and risk factors for type-specific anal human papillomavirus infection among HIV-positive MSM. *AIDS* 2014;28:1341–9.

10 Twisk DE, van der Sande MAB, van Eeden A, *et al*. Detection of incident anal high-risk human papillomavirus DNA in men who have sex with men: incidence or reactivation? *J Infect Dis* 2018;218:1018–26.
11 Machalek DA, Grulich AE, Hillman RJ, *et al*. The study of the prevention of anal cancer (SPANC): design and methods of a three-year prospective cohort study. *BMC Public Health* 2013;13:946.
12 Wei LJ, Lin DY, Weissfeld L. Regression analysis of multivariate incomplete failure time data by modeling marginal distributions. *J Am Stat Assoc* 1989;84:1065–73.
13 Glick SN, Feng Q, Popov V, *et al*. High rates of incident and prevalent anal human papillomavirus infection among young men who have sex with men. *J Infect Dis* 2014;209:369–76.
14 Alberts CJ, Heard I, Canestri A, *et al*. Incidence and Clearance of Anal Human Papillomavirus (HPV)-16 and HPV-18 Infection, and Their Determinants, Among Human Immunodeficiency Virus-Infected Men Who Have Sex With Men in France. *J Infect Dis* 2020;221:1488–93.
15 Beachler DC, D'Souza G, Sugar EA, *et al*. Natural history of anal vs oral HPV infection in HIV-infected men and women. *J Infect Dis* 2013;208:330–9.
16 Marra E, Kovaleva A, Bruisten SM, *et al*. Incidence and clearance of anal high-risk human papillomavirus infections and their determinants over 5 years among human immunodeficiency virus-negative men who have sex with men. *Clin Infect Dis* 2019;68:1556–65.
17 DonMG, Vescio MF, Latini A. Anal human papillomavirus in HIV-uninfected men who have sex with men: incidence and clearance rates, duration of infection, and risk factors. *Clinical Microbiology and Infection* 2016;22:1004.e1–1004.e7.
18 Chow EPF, Cornelisse VJ, Read TRH, *et al*. Saliva use as a lubricant for anal sex is a risk factor for rectal gonorrhoea among men who have sex with men, a new public health message: a cross-sectional survey. *Sex Transm Infect* 2016;92:532–6.
19 Jin F, Prestage GP, Mao L, *et al*. Incidence and risk factors for urethral and anal gonorrhoea and Chlamydia in a cohort of HIV-negative homosexual men: the health in men study. *Sex Transm Infect* 2007;83:113–9.
20 Jin F, Prestage GP, Kippax SC, *et al*. Risk factors for genital and anal warts in a prospective cohort of HIV-negative homosexual men: the him study. *Sex Transm Dis* 2007;34:488–93.
21 Machalek DA, Poynten M, Jin F, *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.
22 Mooij SH, van Santen DK, Geskus RB, *et al*. The effect of HIV infection on anal and penile human papillomavirus incidence and clearance: a cohort study among MSM. *AIDS* 2016;30:121–32.
23 Phanuphak N, Teeratakulpisarn N, Pankam T, *et al*. 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;63:472–9.
24 Tugizov SM, Herrera R, Chin-Hong P, *et al*. Hiv-Associated disruption of mucosal epithelium facilitates paracellular penetration by human papillomavirus. *Virology* 2013;446:378–88.
25 Chan C, Broady T, Bavinton B. *Gay community periodic survey: Sydney*. Sydney: Centre for Social Research in Health UNSW Sydney, 2020.
26 Kramer SC, Schmidt AJ, Berg RC, *et al*. Factors associated with unprotected anal sex with multiple non-steady partners in the past 12 months: results from the European Men-Who-Have-Sex-With-Men Internet survey (EMIS 2010). *BMC Public Health* 2016;16:47.
27 Vajdic CM, van Leeuwen MT, Jin F, *et al*. Anal human papillomavirus genotype diversity and co-infection in a community-based sample of homosexual men. *Sex Transm Infect* 2009;85:330–5.
28 Richens J, Copas A, Sadiq ST, *et al*. A randomised controlled trial of computer-assisted interviewing in sexual health clinics. *Sex Transm Infect* 2010;86:310–4.
29 Poynten IM, Jin F, Garland SM, *et al*. HIV, immune dysfunction and the natural history of anal high-risk human papillomavirus infection in gay and bisexual men. *J Infect Dis* 2020. doi:10.1093/infdis/jiaa723. [Epub ahead of print: 21 Nov 2020].
30 Prestage G, Maher L, Grulich A, *et al*. Brief report: changes in behavior after PreP initiation among Australian gay and bisexual men. *J Acquir Immune Defic Syndr* 2019;81:52–6.