Anal human papillomavirus infection and associated neoplastic lesions in men who have sex with men: a systematic review and meta-analysis

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Summary

Background **Men who have sex with men (MSM) are at greatly increased risk of human papillomavirus (HPV)-associated anal cancer. Screening for the presumed cancer precursor, high-grade anal intraepithelial neoplasia (AIN), followed by treatment in a manner analogous to cervical screening, has been proposed. We aimed to assess available data for anal HPV disease that can inform pre-cancer screening programmes.**

Methods **We searched PubMed, OVID Medline, and Embase for all studies published before Nov 1, 2011, that reported prevalence and incidence of anal HPV detection, AIN, and anal cancer in MSM. We calculated summary estimates using random-effects meta-analysis.**

Findings **53 studies met the inclusion criteria, including 31 estimates of HPV prevalence, 19 estimates of cytological abnormalities, eight estimates of histological abnormalities, and nine estimates of anal cancer incidence. Data for incident HPV and high-grade AIN were scarce. In HIV-positive men, the pooled prevalence of anal HPV-16 was 35·4% (95% CI 32·9–37·9). In the only published estimate, incidence of anal HPV-16 was 13·0% (9·6–17·6), and clearance occurred in 14·6% (10·2–21·2) of men per year. The pooled prevalence of histological high-grade AIN was 29·1% (22·8–35·4) with incidences of 8·5% (6·9–10·4) and 15·4% (11·8–19·8) per year in two estimates. The pooled anal cancer incidence was 45·9 per 100 000 men (31·2–60·3). In HIV-negative men, the pooled prevalence of anal HPV-16 was 12·5% (9·8–15·4). Incidence of HPV-16 was 11·8% (9·2–14·9) and 5·8% (1·9–13·5) of men per year in two estimates. The pooled prevalence of histological high-grade AIN was 21·5% (13·7–29·3), with incidence of 3·3% (2·2–4·7) and 6·0% (4·2–8·1) per year in two estimates. Anal cancer incidence was 5·1 per 100 000 men (0–11·5; based on two estimates). There were no published estimates of high-grade AIN regression.**

Interpretation **Anal HPV and anal cancer precursors were very common in MSM. However, on the basis of restricted data, rates of progression to cancer seem to be substantially lower than they are for cervical pre-cancerous lesions. Large, good-quality prospective studies are needed to inform the development of anal cancer screening guidelines for MSM.**

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Introduction

Infection with high-risk types of human papillomavirus (HPV) causes more than 80% of cases of anal cancer,[1] and is recognised as a necessary cause of nearly 100% of cases of cervical cancer.[2,3] During the past 20–30 years, the incidence of anal cancer has been increasing. Populations at increased risk include women with previous cervical HPV-related disease,[4] immune suppressed transplant recipients, and HIV-positive individuals.[5] Incidence of anal cancer is highest in men who have sex with men (MSM), who are about 20 times more likely than heterosexual men to develop the disease.[6] HIV-positive MSM are at even greater risk.[7] In view of the increasing health burden of anal cancer in MSM and its similarities to cervical cancer, some researchers have proposed an anal cancer screening programme for this population.[8] It would be based on cytological detection of HPV-related abnormalities, or possibly by direct detection of HPV-related biomarkers, followed by histological confirmation of the presumed cancer-precursor lesion high-grade intraepithelial neoplasia (AIN), and treatment. Since the implementation of population-based screening programmes for cervical cancer, there has been a substantial reduction in the incidence and mortality from this malignancy.[9] In the past 5 years, HPV vaccination has been introduced for women in several countries, with the aim of further reducing the incidence of cervical cancer. In Australia, where there has been a rapid and widespread uptake of the quadrivalent HPV vaccine by women younger than 27 years, striking reductions in cervical high-grade precancerous lesions in young women have been reported, in addition to a rapid decrease in the prevalence of genital warts.[10,1] A parallel, although lesser, decrease in genital warts in young heterosexual men[10] suggests that vaccination of women and girls will lead to a reduction in HPV-related morbidity in heterosexual men through herd immunity. Unfortunately, MSM will not benefit from such herd immunity, so other approaches are needed to reduce HPV-related morbidity in this population. Universal vaccination of adolescent boys (before sexual debut) has

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enormous potential to prevent HPV-related morbidity in the future,[12] but before such potential is realised, alternative approaches such as screening are needed.

Cervical screening based on detection of cytological abnormalities has existed for 60 years.[13] Since the discovery of HPV, many observational studies have described the natural history of cervical HPV infection and of cytological abnormalities.[14] Although many studies have estimated the prevalence and incidence of anal HPV infection, anal cytological abnormalities, and AIN in MSM, the natural history of progression of anal HPV infection to anal cancer in MSM is unclear. There is no consensus as to how widespread anal high-risk HPV infection is; the prevalence and significance of AIN; and the rate of progression of AIN to anal cancer.

This systematic review and meta-analysis presents a summary of all published estimates of data for anal HPV detection, cytological and histological abnormalities, and anal cancer in HIV-positive and HIV-negative MSM.

Methods

Search strategy and selection criteria

We did a systematic review without language restrictions for all peer-reviewed, published studies of the prevalence and incidence of anal HPV infection and anal cytological and histological neoplastic abnormalities, and the incidence of anal cancer in MSM published before Nov 1, 2011. We searched PubMed, OVID Medline, and Embase using the following combined heading search strategy: "anal intraepithelial neoplasia" OR "AIN" AND "men who have sex with men" OR "MSM" OR "homosexual men". For the review of HPV prevalence and incidence, we searched for studies using the combined heading search strategy "human papillomavirus" OR "HPV" AND "men who have sex with men" OR "MSM"OR "homosexual men". For the review of anal cancer incidence, we used the combined heading search strategy "anal cancer" AND "men who have sex with men" OR "MSM" OR "homosexual men". We also reviewed reference lists of retrieved articles to identify other relevant studies. We did not include data from abstracts or unpublished studies.

Studies were reviewed by DAM and MP. Studies were included in the review if they had quantitative estimates of the variables of interest and were undertaken for populations that included HIV-positive or HIV-negative men who were described as homosexual, bisexual, or MSM. In those studies in which data were not stratified by sexual orientation or HIV status, data were requested from the corresponding author via email, and a follow-up email was sent within 3–4 weeks of initial contact. In case of no response to the second email, the study was excluded from the meta-analysis. Additional data were obtained from six of 17 authors contacted.

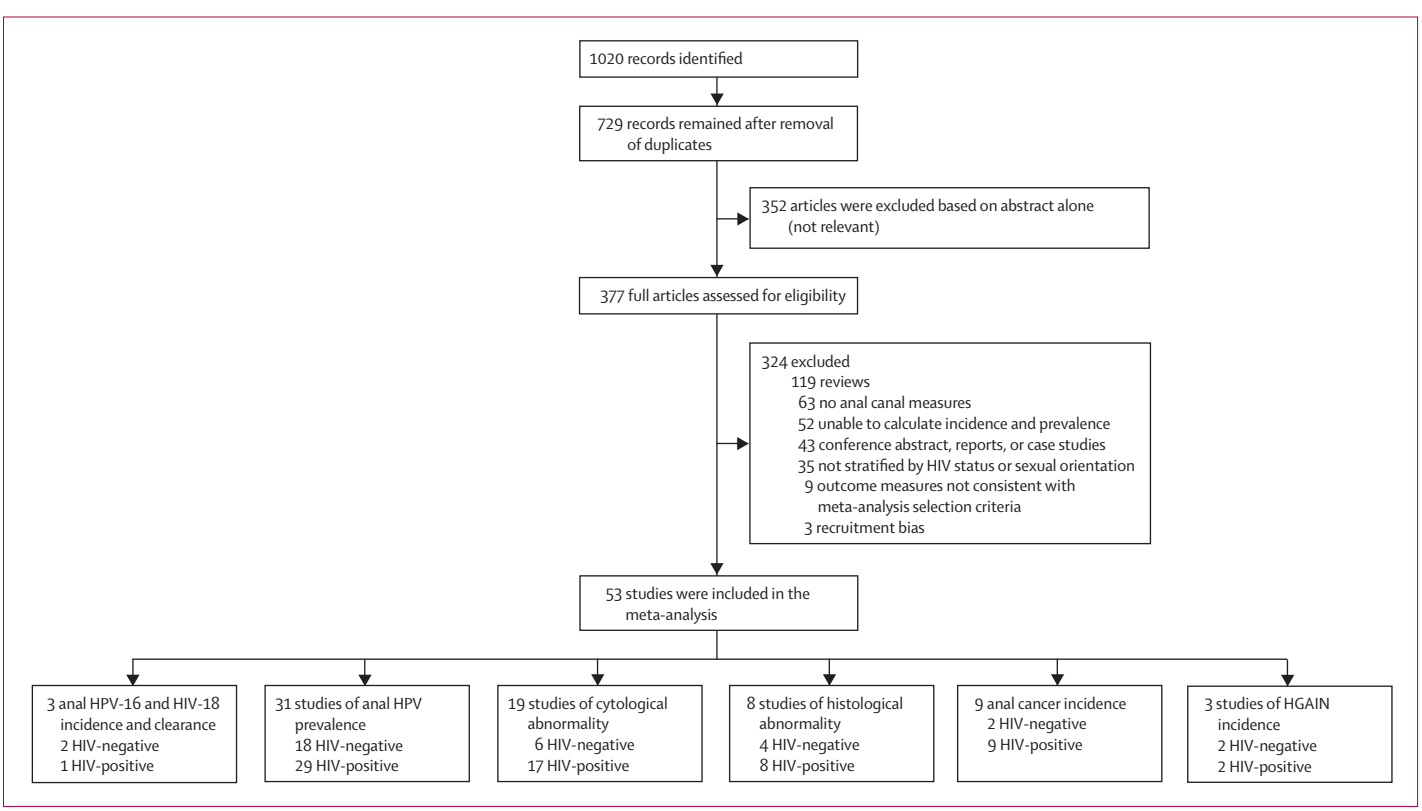


Figure 1: **Articles identified and screened for eligibility**
HGAIN=high-grade intraepithelial neoplasia. HPV=human papillomavirus.

We excluded studies that sampled in a way that would clearly over-represent or under-represent the prevalence of anal HPV-related disorders. We included studies reporting anal HPV infection if they measured anal canal HPV DNA by PCR-based technologies (including commercial and in-house assays) or by Hybrid Capture and Hybrid Capture 2. Studies that used older non-amplification methods such as in-situ or dot-blot hybridisation assays were also included, but were analysed separately because of their restricted sensitivity for HPV DNA detection.[15] We included studies if they reported anal cytological or histological findings in all participants. Studies in which high-resolution anoscopy examination was done only on participants with abnormal cytology were excluded from the meta-analysis. We excluded such studies because anal cytology is substantially less than 100% sensitive in the detection of anal histological abnormalities, and thus such studies are likely to underestimate the true prevalence of AIN.[16] We did not include studies that presented only a composite anal diagnosis comprising the most severe of the cytological and histological results.

Data extraction

For every study, data for first author, publication date, source of recruitment, study location, sample size, participant age range, and HIV status were recorded. For anal HPV prevalence studies, information about sample collection and detection methods were also recorded. Studies were stratified by HIV status, source of participants (community-based or clinic-based recruitment), and method of diagnosis of disease endpoints (cytology or histology).

Data for anal HPV prevalence were extracted for any HPV type, any low-risk HPV types, any high-risk HPV type, HPV-16, and HPV-18. If more than one type of assay was used to detect the presence of HPV, and the results of both were reported (eg, studies reporting HPV results with a PCR-based assay and Hybrid Capture), both results were recorded separately. Studies were stratified by HIV status and source of participants. Prevalence of anal HPV was expressed as a percentage of all participants tested for anal HPV. For PCR-based detection, results from samples negative for β globin, which were regarded as inadequate for analysis, were excluded.

We extracted cytological data if results were reported according to either the 1988 or the 2001 Bethesda System terminology with the following categories: negative; atypical squamous cells of undetermined significance; low-grade squamous intraepithelial lesions; and high-grade squamous intraepithelial lesions.[17] The 2001 Bethesda system also includes the category atypical squamous cells—cannot exclude high-grade squamous intraepithelial lesions. Cells in this category are likely to predict histological high-grade disease more often than atypical squamous cells of undetermined significance.[18] Cytological predictions were expressed as a percentage of the total samples tested after exclusion of samples that were inadequate for cytology.

	Number of studies or estimates	Total sample size
HIV-positive men who have sex with men		
Studies of anal HPV prevalence	29[23-31, 33-52]	4868
Any HPV type	27 (32)[23,24*,25-28,29*,30,31*,33-43,44*,46*,47,48,49*,50,51]	4624
Any high-risk HPV type	15 (16)[24*,25,26,28,29*,30,31*,34,37,40,42,43*,44,51†,52]	2448
Any low-risk HPV type only	2 (2)[24,39]	53
HPV-16	14 (14)[23,24,25,27,30,31,35,37,39,40,43-46]	1371
HPV-18	12 (12)[23-25,27,31,35,37,39,40,43,44,46]	1328
Incidence of anal HPV infection (HPV-16/HPV-18)	1[23]	316 person-years/416 person-years
Clearance of anal HPV infection (HPV-16/HPV-18)	1[23]	191 person-years/115 person-years
Studies of ASIL prevalence all studies	17[29,30,37,38,46,48,53,54,25,26,52,56-61,]	2791
Any abnormality	17 (2/15)[29,30,37,38,46,48,53,54,25,26,52,56-61,]	440/2351
LSIL	15 (2/13)[29,30,37,46,48,53,54,25,26,52,56-58,60,61]	440/2229
HSIL	15 (2/13)[29,30,37,46,48,53,54,25,26,52,56-58,60,61]	440/2229
Prevalence of AIN with HRA on all	8[19,29,30,34,38,53,54,62]	1494
Any abnormality	8 (3/5)[19,29,30,34,38,53,54,62]	479/1015
Low-grade AIN	7 (3/4)[19,29,30,34,53,54,62]	479/963
High-grade AIN	7 (3/4)[19,29,30,34,53,54,62]	479/963
Incidence of histologically confirmed high-grade AIN (progression from normal/lesser/AIN1)	2[53,63]	1480 person-years
Regression of histologically confirmed AIN2–3	0	..
Incidence of anal cancer	9[7,64-71]	956 095
HIV-negative men who have sex with men		
Studies of anal HPV prevalence	18[24,27,28,30,33,34,39,41–45,47–50,55,72]	4487
Any HPV type	17 (21)[24*,27,28,30,33,34,39,41-43,44*,47,48,49*,50,55,72]	4320
Any high-risk HPV type	9 (11)[24*,28,30,34,42,43*,44,55,72]	2618
Any low-risk HPV type only	3 (3)[24,39,55]	510
HPV-16	9 (9)[24,27,30,39,43–45,55,72]	2687
HPV-18	6 (6)[24,27,39,43,44,55]	1283
Incidence of anal HPV infection (HPV-16/HPV-18)	2[12,73]	686 person-years/730 person-years
Clearance of anal HPV infection (HPV-16/HPV-18)	1[73]	NA
Studies of ASIL prevalence (all studies)	6[30,45,48,58,54,74]	1827
Any abnormality	6 (3/3)[30,45,48,58,54,74]	1596/231
LSIL	6 (3/3)[30,45,48,58,54,74]	1596/231
HSIL	6 (3/3)[30,45,48,58,54,74]	1596/231
Prevalence of AIN with HRA on all	4[54,30,34,62]	449
Any abnormality	4 (3/1)[54,30,34,62]	423/26
Low-grade AIN	4 (3/1)[54,30,34,62]	423/26
High-grade AIN	4 (3/1)[54,30,34,62]	423/26
Incidence of histologically confirmed high-grade AIN (progression from normal/lesser/AIN1)	2[12,63]	1539 person-years
Regression of histologically confirmed high-grade	0	..
Incidence of anal cancer	2[7,71]	48 881

Data are number of studies (number of estimates) or number of studies (community/clinic). AIN=anal intraepithelial neoplasia. ASIL=any squamous intraepithelial lesions. HPV=human papillomavirus. HRA=high-resolution anoscopy. HSIL=high-grade squamous intraepithelial lesions. LSIL=low-grade squamous intraepithelial lesions. NA=not applicable. *Studies that had more than one estimate of HPV prevalnce. †This study was not included in the meta-analysis because non-amplification methods were used to estimate the prevalence of high-risk HPV.

Table: **Summary of identified studies**

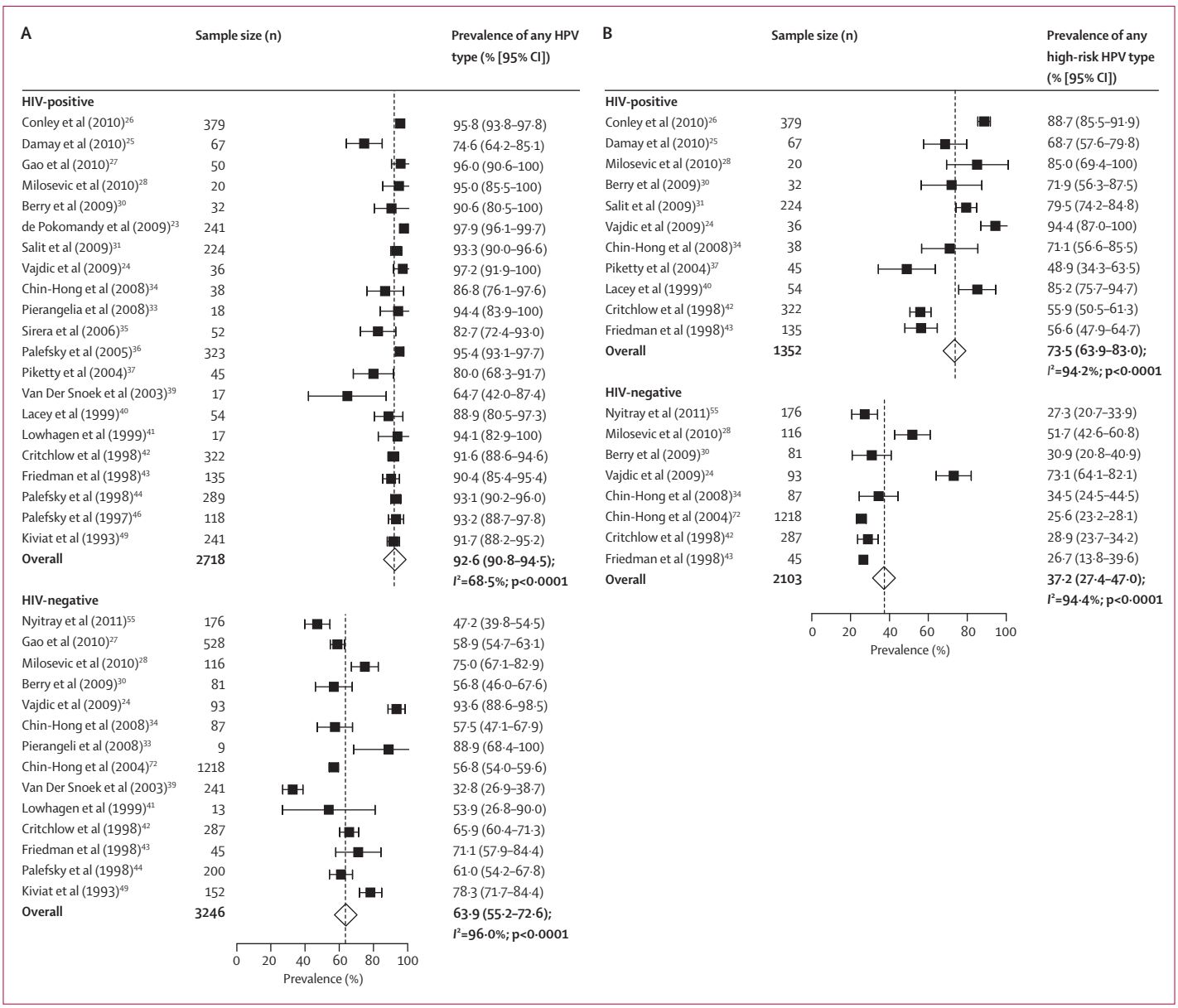


***Figure 2*: Prevalence of PCR-detected anal canal human papillomavirus (HPV) infection in men who have sex with men, by HIV status**
Prevalence of any anal canal HPV type (A) and high-risk anal canal HPV type (B).

Histological data were reported as low-grade AIN (or AIN1) and high-grade AIN (AIN2–3). AIN prevalence by histological diagnosis was expressed as a percentage of the total number of high-resolution anoscopy examinations done.

For anal cancer incidence studies, the recorded number of patients with cancer and the person-years of follow-up were extracted. When not presented, we calculated the number of person-years by dividing the number of recorded cases by the reported incidence rate. The diagnosis of invasive anal cancer was made with International Classification of Disease (ICD) codes, ICD9 before 1997 and ICD10 thereafter.[2] Carcinoma in situ was not included when presenting estimates of anal cancer incidence.

Incidence and regression of high-grade AIN and anal HPV-16 and HPV-18 infection were reported as percentage per year, whereas anal cancer incidence was reported per 100 000 person-years. We calculated a theoretical rate of progression from high-grade AIN to anal cancer, on the basis of the assumption that all anal cancer arises in a person with previous high-grade AIN, by dividing the prevalence of high-grade AIN by the incidence of invasive anal cancer.

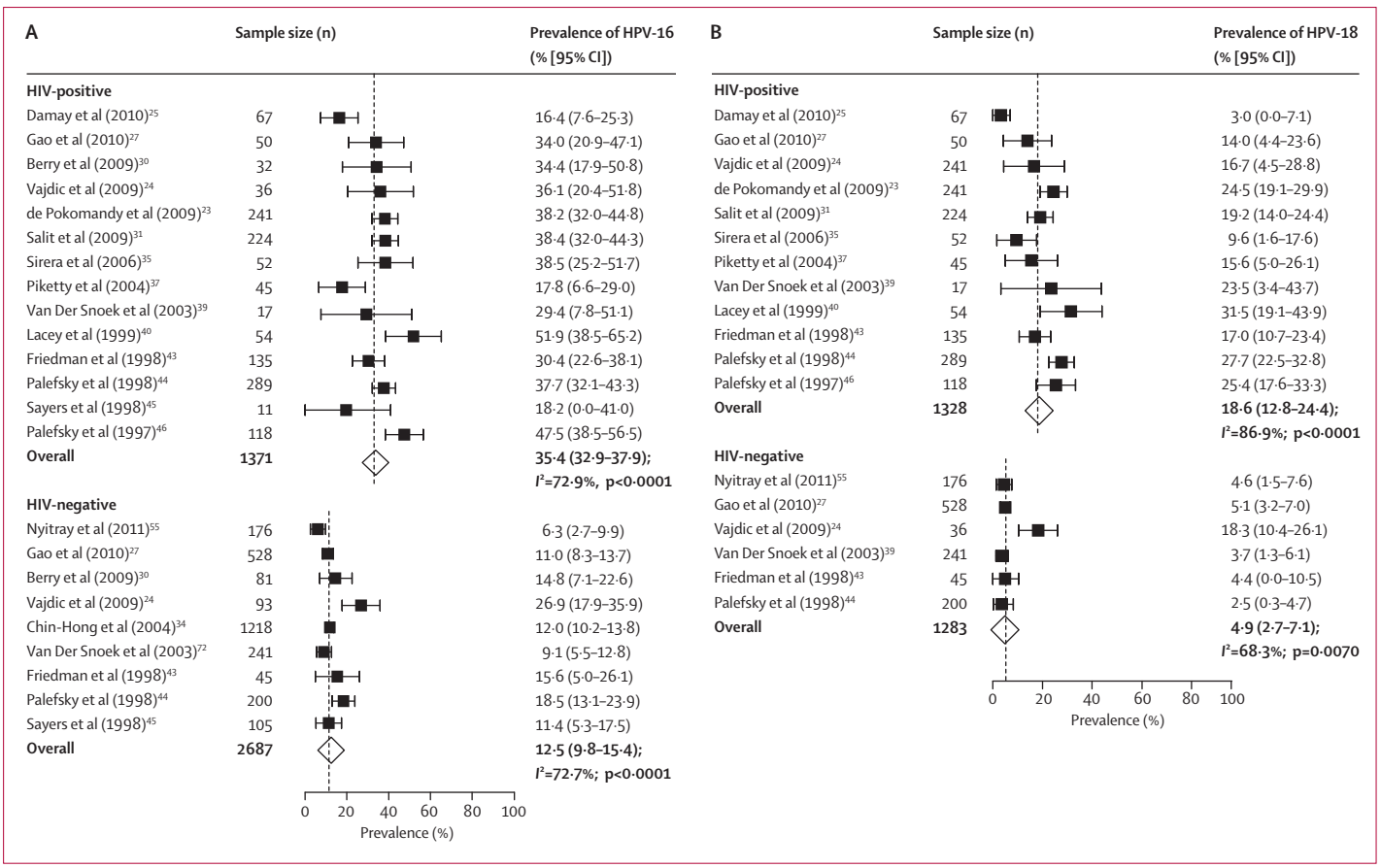


Figure 3: **Prevalence of PCR-detected anal canal human papillomavirus (HPV)-16 (A) and HPV-18 (B) in men who have sex with men, by HIV status**

Statistical analysis

Because of the expected heterogeneity in populations sampled, screening technique, and study method, we calculated pooled estimates and 95% CI using random-effects models.[20] Heterogeneity was measured with the I^2 statistic (values of <25%, 25–75%, and >75% representing low, medium, and high heterogeneity, respectively).[21] We did meta regression and subgroup analysis to investigate potential sources of heterogeneity, and calculated p values for linear trend using random effects meta regression.[20] The effect of individual studies on the meta-analysis pooled estimates was assessed by re-estimating the overall effect after omitting each study. We assessed the potential presence of publication bias using funnel plots and did statistical tests for asymmetry by regressing the estimate by the sample size, weighted by the reciprocal of the standard error (1/SE).[20,22] We used Stata (version 12) for all statistical analyses.

Role of the funding source

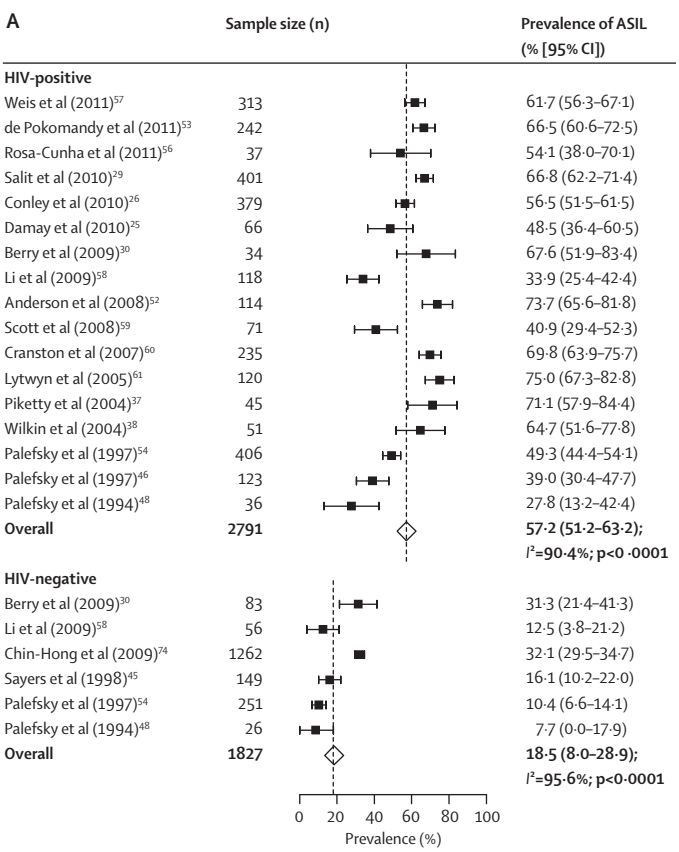
The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

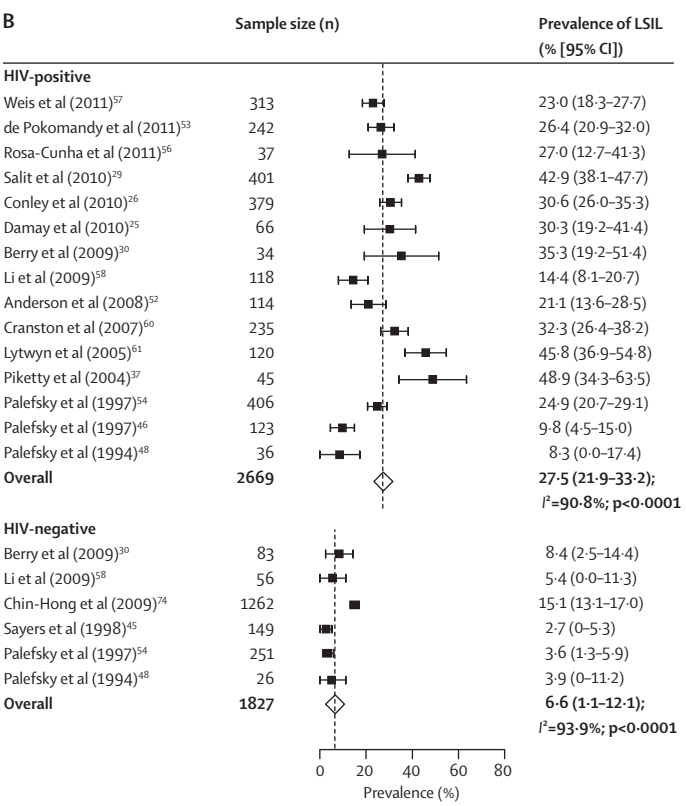
Results

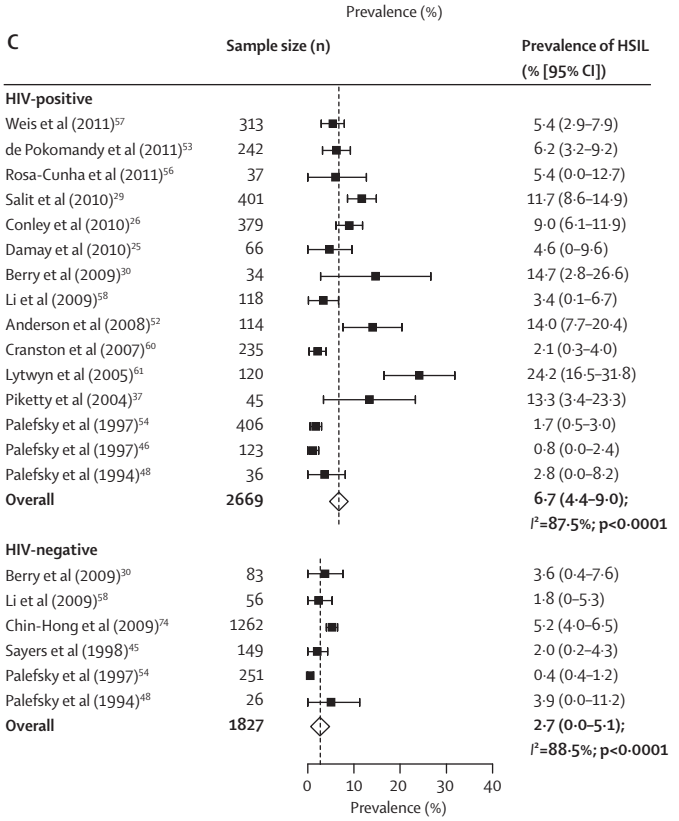
We identified 729 studies, of which 53 were included in our meta-analysis (figure 1 and table). Three studies were excluded from the analysis of anal HPV prevalence because their recruitment strategies resulted in non-representative samples (appendix p 9). One of these studies was restricted to MSM with fewer than five lifetime sexual partners, and two clinic-based studies recruited only patients with evidence of HPV-associated anal lesions. Three studies in which high-resolution anoscopy was done on only men with abnormal cytology were excluded from the histology meta-analysis (appendix p 9).

See Online for appendix

Most studies identified were cross-sectional studies and the vast majority were done in North America. For the detection of anal HPV, 86% and 64% of the sample size came from North America in HIV-positive and HIV-negative men, respectively. For cytological abnormalities, slightly fewer than 90% of the total sample size came from North America for both HIV-positive and HIV-negative men. For histologically confirmed abnormalities, 79% of the sample size in HIV-positive MSM, and 94% of


A
Sample size (n)
Prevalence of ASIL (% [95% CI])
HIV-positive
Weis et al (2011)[57] 313 61·7 (56·3–67·1)
de Pokomandy et al (2011)[53] 242 66·5 (60·6–72·5)
Rosa-Cunha et al (2011)[56] 37 54·1 (38·0–70·1)
Salit et al (2010)[29] 401 66·8 (62·2–71·4)
Conley et al (2010)[26] 379 56·5 (51·5–61·5)
Damay et al (2010)[25] 66 48·5 (36·4–60·5)
Berry et al (2009)[30] 34 67·6 (51·9–83·4)
Li et al (2009)[58] 118 33·9 (25·4–42·4)
Anderson et al (2008)[52] 114 73·7 (65·6–81·8)
Scott et al (2008)[59] 71 40·9 (29·4–52·3)
Cranston et al (2007)[60] 235 69·8 (63·9–75·7)
Lytwyn et al (2005)[61] 120 75·0 (67·3–82·8)
Piketty et al (2004)[37] 45 71·1 (57·9–84·4)
Wilkin et al (2004)[38] 51 64·7 (51·6–77·8)
Palefsky et al (1997)[54] 406 49·3 (44·4–54·1)
Palefsky et al (1997)[46] 123 39·0 (30·4–47·7)
Palefsky et al (1994)[48] 36 27·8 (13·2–42·4)
Overall 2791 57·2 (51·2–63·2); I²=90·4%; p<0·0001
HIV-negative
Berry et al (2009)[30] 83 31·3 (21·4–41·3)
Li et al (2009)[58] 56 12·5 (3·8–21·2)
Chin-Hong et al (2009)[74] 1262 32·1 (29·5–34·7)
Sayers et al (1998)[45] 149 16·1 (10·2–22·0)
Palefsky et al (1997)[54] 251 10·4 (6·6–14·1)
Palefsky et al (1994)[48] 26 7·7 (0·0–17·9)
Overall 1827 18·5 (8·0–28·9); I²=95·6%; p<0·0001
0 20 40 60 80 100
Prevalence (%)


B
Sample size (n)
Prevalence of LSIL (% [95% CI])
HIV-positive
Weis et al (2011)[57] 313 23·0 (18·3–27·7)
de Pokomandy et al (2011)[53] 242 26·4 (20·9–32·0)
Rosa-Cunha et al (2011)[56] 37 27·0 (12·7–41·3)
Salit et al (2010)[29] 401 42·9 (38·1–47·7)
Conley et al (2010)[26] 379 30·6 (26·0–35·3)
Damay et al (2010)[25] 66 30·3 (19·2–41·4)
Berry et al (2009)[30] 34 35·3 (19·2–51·4)
Li et al (2009)[58] 118 14·4 (8·1–20·7)
Anderson et al (2008)[52] 114 21·1 (13·6–28·5)
Cranston et al (2007)[60] 235 32·3 (26·4–38·2)
Lytwyn et al (2005)[61] 120 45·8 (36·9–54·8)
Piketty et al (2004)[37] 45 48·9 (34·3–63·5)
Palefsky et al (1997)[54] 406 24·9 (20·7–29·1)
Palefsky et al (1997)[46] 123 9·8 (4·5–15·0)
Palefsky et al (1994)[48] 36 8·3 (0·0–17·4)
Overall 2669 27·5 (21·9–33·2); I²=90·8%; p<0·0001
HIV-negative
Berry et al (2009)[30] 83 8·4 (2·5–14·4)
Li et al (2009)[58] 56 5·4 (0·0–11·3)
Chin-Hong et al (2009)[74] 1262 15·1 (13·1–17·0)
Sayers et al (1998)[45] 149 2·7 (0–5·3)
Palefsky et al (1997)[54] 251 3·6 (1·3–5·9)
Palefsky et al (1994)[48] 26 3·9 (0–11·2)
Overall 1827 6·6 (1·1–12·1); I²=93·9%; p<0·0001
0 20 40 60 80
Prevalence (%)


C
Sample size (n)
Prevalence of HSIL (% [95% CI])
HIV-positive
Weis et al (2011)[57] 313 5·4 (2·9–7·9)
de Pokomandy et al (2011)[53] 242 6·2 (3·2–9·2)
Rosa-Cunha et al (2011)[56] 37 5·4 (0·0–12·7)
Salit et al (2010)[29] 401 11·7 (8·6–14·9)
Conley et al (2010)[26] 379 9·0 (6·1–11·9)
Damay et al (2010)[25] 66 4·6 (0–9·6)
Berry et al (2009)[30] 34 14·7 (2·8–26·6)
Li et al (2009)[58] 118 3·4 (0·1–6·7)
Anderson et al (2008)[52] 114 14·0 (7·7–20·4)
Cranston et al (2007)[60] 235 2·1 (0·3–4·0)
Lytwyn et al (2005)[61] 120 24·2 (16·5–31·8)
Piketty et al (2004)[37] 45 13·3 (3·4–23·3)
Palefsky et al (1997)[54] 406 1·7 (0·5–3·0)
Palefsky et al (1997)[46] 123 0·8 (0·0–2·4)
Palefsky et al (1994)[48] 36 2·8 (0·0–8·2)
Overall 2669 6·7 (4·4–9·0); I²=87·5%; p<0·0001
HIV-negative
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Sayers et al (1998)[45] 149 2·0 (0·2–4·3)
Palefsky et al (1997)[54] 251 0·4 (0·4–1·2)
Palefsky et al (1994)[48] 26 3·9 (0·0–11·2)
Overall 1827 2·7 (0·0–5·1); I²=88·5%; p<0·0001
0 10 20 30 40
Prevalence (%)

the sample size in HIV-negative MSM, came from North America. We identified only six reports from four longitudinal cohort studies of incident HPV infection or high-grade AIN.[12,23,53,63,73] Information specific to individual studies included in the meta-analysis are summarised in the table and the appendix (pp 2–8).

31 studies were included in the meta-analysis of anal HPV. HPV prevalence was described in 29 studies for HIV-positive MSM (4868 samples) and 18 studies for HIV-negative MSM (4487 samples). Most HIV-positive men were recruited from clinics (68%) and most HIV-negative men were recruited from the community (68%).

The pooled prevalence of any anal HPV was substantially higher in HIV-positive men than it was in HIV-negative men (p=0·005; figure 2). We recorded no association between reported HPV prevalence and year of publication, number of HPV types detected, or the source of recruitment (data not shown). For any high-risk HPV type, the pooled prevalence of HPV was substantially higher in HIV-positive men than it was in HIV-negative men (p=0·010; figure 2). Studies published in more recent years reported higher prevalences of high-risk HPV types than did earlier studies, after accounting for the number of HPV types detected, in both HIV-positive (p=0·012) and HIV-negative (p=0·054) men. We recorded no association between source of recruitment and reported high-risk HPV prevalence (data not shown).

When Hybrid Capture or Hybrid Capture 2 was used for detection, the pooled prevalence of any HPV type and any high-risk HPV type varied slightly from PCR but remained higher in HIV-positive men than in HIV-negative men for any HPV type (89·0%, [95% CI 84·7–93·3] *vs* 53·6% [21·6–80·6]; p=0·047) and for any high-risk type (79·1% [70·0–88·2] *vs* 31·5% [7·2–55·8]; p=0·034). The pooled prevalence for any HPV type detected with other non-amplification methods was much lower than for PCR and Hybrid Capture or Hybrid Capture 2, however the statistically higher HPV prevalence in HIV-positive men than in HIV-negative men was still seen (54·2% [50·9–57·5] *vs* 21·6% [16·8–26·6]; p<0·0001; appendix p 11).

The prevalences of HPV-16 and HPV-18 were much higher in HIV-positive men than they were in HIV-negative men (p=0·0005 and p=0·019, respectively; figure 3). We recorded no association between year of publication or source of recruitment with either HPV-16 or HPV-18 detection (data not shown).

We identified three studies of anal HPV incidence and clearance; one in HIV-positive men after introduction of highly active antiretroviral therapy (HAART; from 1996 onwards)[23] and two in HIV-negative MSM (appendix p 4).[12,73] In HIV-positive men, the incidence HPV-16 was 13·0% per year (9·6–17·6; 316·2 person-years) and of HPV-18 was 5·3% per year (3·5–8·0; 415·8 person-years); the clearance rate of HPV-16 was 14·6% per year (10·2–21·2; 190·5 person-years) and of HPV-18 was 24·5% per year (16·9–35·4; 114·6 person-years). In HIV-negative men, annual HPV-16 incidence in the two studies was 11·8% (9·2–14·9; 599·9 person-years)[12] and 5·8% (1·9–13·5; 86·5 person-years),[73] and the annual incidence of HPV-18 was 6·1% (4·3–8·3; 641·3 person-years)[12] and 4·5% (1·2–11·6; 88·3 person-years).[73] Clearance rates were not presented, but in one study[73] with only 6 months follow-up, clearance of HPV-16 and HPV-18 occurred in 27% (three of 11 individuals) and 62·5% (five of eight individuals), respectively.

19 studies reporting the prevalence of anal cytological abnormalities were included in the meta-analysis, comprising 17 studies in HIV-positive men, and six studies in HIV-negative men (figure 4, appendix p 5). Most HIV-positive men were recruited from clinics (84%) and most HIV-negative men were recruited from the community (87%). About 70% of HIV-negative men analysed came from one community-based study in USA.[74]

The prevalence of any anal cytological abnormality was higher in HIV-positive MSM than it was in HIV-negative MSM (p=0·0051), as was the prevalence of low-grade anal lesions (p=0·010); we did not record a statistically significant difference between the prevalence of high-grade anal lesions in the two populations (p=0·11; figure 4). In meta-regression, neither the year of study publication nor the source of recruitment was related to the prevalence of cytological abnormalities.

Data from eight studies in which high-resolution anoscopy was done on all study participants irrespective of their cytology findings were included in the meta-analysis. Most HIV-positive men were recruited from clinics (88%) and most HIV-negative men were recruited from the community (94%; figure 5, appendix p 6). The pooled prevalence of histological abnormalities was non-significantly higher in HIV-positive men than it was in HIV-negative men (p=0·12 for any anal histological abnormality, p=0·029 for low-grade anal lesions, and p=0·48 for any high-grade anal lesions; figure 5). In meta-regression, studies published in more recent years reported higher prevalence of histological abnormalities than did earlier studies, in both HIV-positive men (p=0·010) and HIV-negative (p=0·025) men. In view of this association we excluded the two oldest studies,[19,54] which had substantially lower estimates, from our final meta-analytic estimate. The removal of these studies reduced some of the heterogeneity from the pooled estimates of AIN prevalence. After this exclusion, the pooled prevalence estimate for any abnormality was higher in HIV-positive men than it was in HIV-negative men (p=0·022; figure 5). The pooled prevalences of low-grade anal lesions and any high-grade anal lesions were both non-significantly higher in HIV-positive men than they were

Figure 4: **Prevalence of anal canal cytological abnormalities (A), low-grade cytological lesions (B), and high-grade cytological lesions (C) in men who have sex with men, by HIV status**

ASIL=any squamous intraepithelial lesions. HSIL=high-grade squamous intraepithelial lesions. LSIL=low-grade squamous intraepithelial lesions.

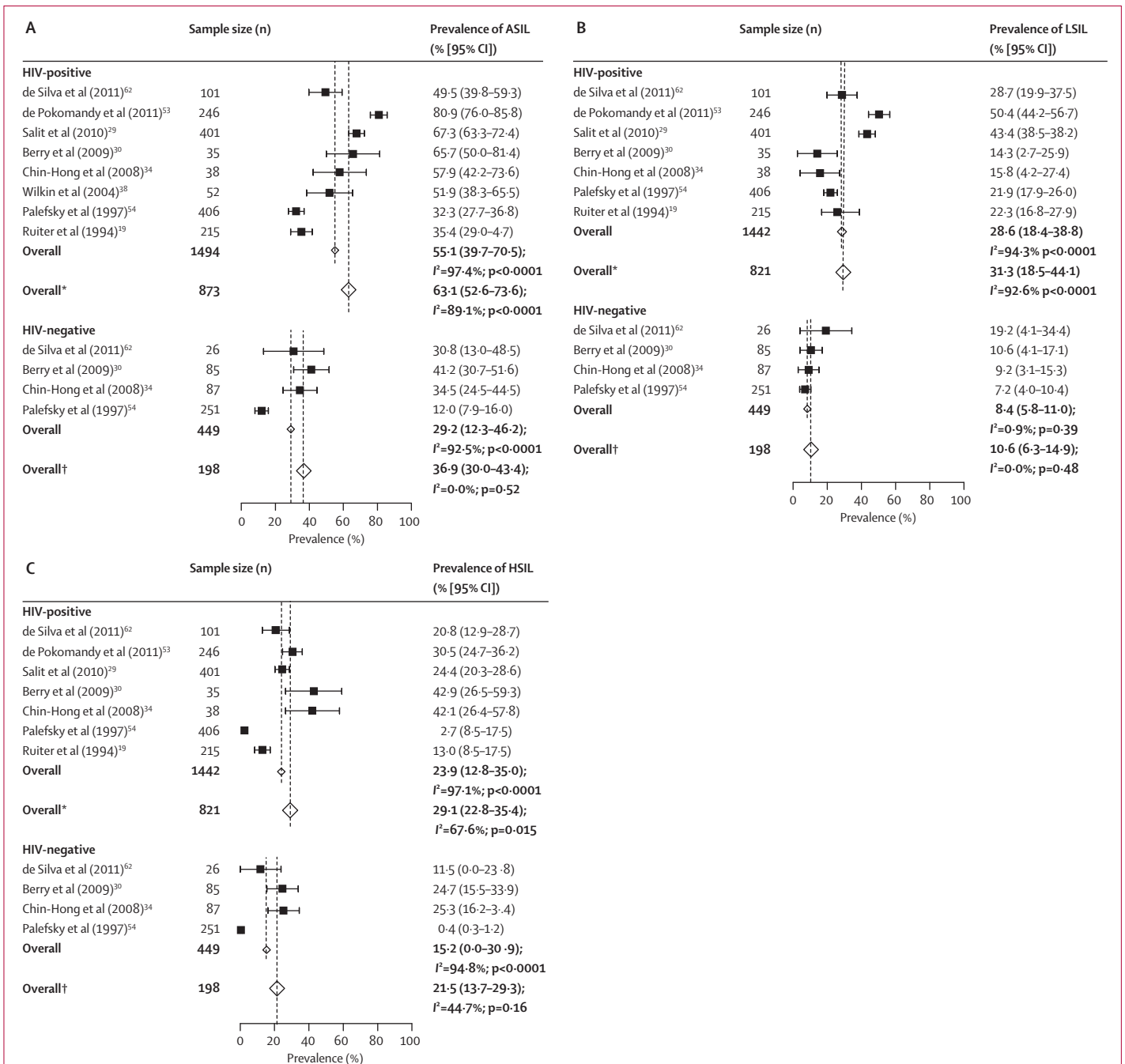

Figure 5: **Prevalence of anal canal histological abnormalities (A), low-grade histological lesions (B), and high-grade histological lesions (C) in men who have sex with men, by HIV status**
ASIL=any squamous intraepithelial lesions. HSIL=high-grade squamous intraepithelial lesions. LSIL=low-grade squamous intraepithelial lesions. *After exclusion of Palefsky et al (1997)[54] and de Ruiter et al (1994).[19] †After exclusion of Palefsky et al (1997).[54]

in HIV-negative men (p=0·056 and p=0·26, respectively; figure 5).

We identified two longitudinal studies that did baseline and follow-up anal cytology and high-resolution anoscopy examination, and that had data for histologically confirmed incidence of high-grade AIN for all participants. Both reported estimates of high-grade AIN incidence in HIV-positive men,[53,63] and one[63] reported an estimate in HIV-negative men (appendix p 7). In HIV-positive men the annual estimated incidence of high-grade AIN (progression from a lesser diagnosis) ranged from 8·5% (95% CI 6·9–10·4; based on 1108·0 person-years) to

15·4% (11·8–19·8; based on 372·3 person-years). The incidence of high-grade AIN was lower in HIV-negative men than it was in HIV-positive men, with one study[63] reporting a rate of 3·3% (2·2–4·7) per year (based on 884·0 person-years). In a second study of HIV-negative men,[12] in which high-resolution anoscopy was done only in those with abnormal cytology, incidence of high-grade AIN occurred in 6·0% (4·2–8·1) of men per year (based on 655·2 person-years). There were no published estimates of high-grade AIN regression rates for either HIV-positive or HIV-negative men.

Nine studies reporting anal cancer incidence in MSM were included in the meta-analysis. Six[64,65,67–69,70] were linkage studies based on data obtained from HIV/AIDS and cancer registries, and three[7,66,71] were observational cohort studies. All nine studies reported on cancer incidence in HIV-positive men (452 cases), and two[7,71] reported incidence in HIV-negative men (three cases; figure 6, appendix p 8). The incidence of anal cancer was higher in HIV-positive men than it was in HIV-negative men (p=0·011; figure 6). In HIV-positive men, the incidence of anal cancer was higher from 1996 onwards (after introduction HAART) than it was before 1996 (p=0·013; figure 6).

There were no direct estimates of the progression rate from high-grade AIN to anal cancer. From the available data, we calculated a theoretical progression rate from high-grade AIN to anal cancer of one in 633 patients (one in 377 in the HAART era) per year in HIV-positive men, and one in 4196 patients per year in HIV-negative men.

There was much heterogeneity in most of the meta-analytic results. For detection of any HPV and any high-risk HPV, restricting the analysis to studies that used the most common HPV detection methods removed much of the heterogeneity (appendix p 10). Assessment of funnel plots suggested substantial publication bias for prevalence of low-grade squamous intraepithelial lesions in HIV-negative men (p=0·032; appendix p 12), but the smaller studies tended to report lower prevalence.

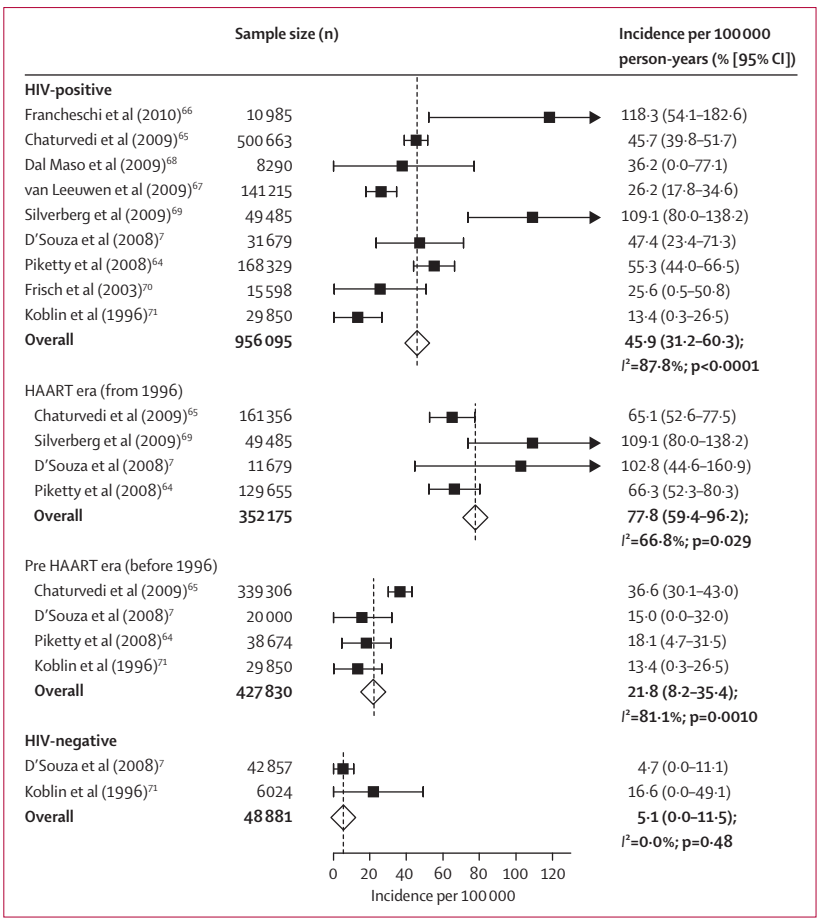

Figure 6: **Incidence of anal cancer in men who have sex with men, by HIV status**

Discussion

In the studies of MSM we reviewed, most men had detectable anal canal HPV, and histologically proven high-grade AIN was present in 20–30% of all men. HIV-positive MSM were consistently more affected by HPV and HPV-related abnormalities than were HIV-negative MSM, and they had a worryingly high incidence of anal cancer. These anal cancer rates are similar to the incidence of cervical cancer in the general female population before the introduction of national cervical screening programmes,[76] and, in HIV-positive men in the post-HAART era, incidence rates of anal cancer were even higher. Longitudinal data were very scarce, but those available suggested a very high annual incidence of high-grade AIN in HIV-positive men (about 10% or more) and roughly 3% in HIV-negative men. These incidence rates seem to be higher than our estimate of the prevalence of high-grade AIN (29% in HIV-positive MSM and 21% in HIV-negative MSM), unless many of these high-grade lesions regress. Unfortunately, although regression of high-grade AIN has been described,[77] there were no published prospective estimates of high-grade AIN regression rates from natural history studies to confirm this finding. There were also no published prospective estimates of high-grade AIN progression rates. We calculated a theoretical progression rate of high-grade AIN to anal cancer of about one in 600 per year in HIV-positive MSM, and roughly one in 4000 per year in HIV-negative MSM. This calculated rate of progression of high-grade AIN to anal cancer is substantially lower than that reported for cervical intraepithelial neoplasia (CIN) grade 3 to cervical cancer, which is estimated to be about one in 80 per year.[78]

A global review[11] of invasive anal cancer concluded that 84% of cases contain HPV DNA. Most individuals (87% of those who were HPV-positive) were positive for HPV-16, and many fewer (6%) were positive for HPV-18.[11] In our meta-analysis, anal canal HPV was very common, and the causative agent of most anal cancer, HPV-16, was detectable in about a third (35%) of the HIV-positive men

but only about one in eight (13%) HIV-negative men. There was moderate to high heterogeneity for all of these measures, which was not explained by the source of participant recruitment. For high-risk HPV only, prevalence increased in more recent publications, which might be explained by an increased sensitivity of testing for high-risk HPV types.[15] Differences in the age of study populations are unlikely to explain the heterogeneity. In MSM, anal HPV infection is common at all ages, irrespective of HIV status, and no evidence exists of a decrease with age.[24,72]

The findings from our meta-analysis show a higher prevalence of anal cytological abnormalities in HIV-positive men than in HIV-negative men. There were far fewer estimates of histologically confirmed diagnoses, particularly for HIV-negative men, in whom results were available for fewer than 500 men. The small number of cases in published studies might be because of the fact that high-resolution anoscopy is an invasive procedure, resulting in a reluctance to do high-resolution anoscopy on all participants, in the absence of cytological and clinical abnormalities. On the basis of the findings of these few studies, the prevalence of all histologically confirmed lesions was higher in HIV-positive men than it was in HIV-negative men. However, the excess in HIV-positive men was smallest for high-grade AIN, and was not statistically significant. Random error is one possible explanation. An alternate explanation is that some of the excess of low-grade AIN in HIV-positive MSM might be attributable to their higher risk behaviour compared with HIV-negative MSM,[79] with consequent higher rates of transient HPV infection that do not lead to high-grade AIN. In this study, HIV-positive men had substantially higher rates of HPV infection than did HIV-negative men. Those studies that reported age-specific prevalence reported that neoplastic lesions did not vary in prevalence by age.[80]

The prevalence of high-grade AIN was strikingly lower when based on a cytological diagnosis than it was when based on histology. This finding almost certainly represents underdiagnosis of high-grade AIN by cytology, because this technique has been shown to have restricted sensitivity to detect histologically proven high-grade AIN.[16] This is probably because the large and involuted surface area of the anal canal is much more technically difficult to sample with blind swabbing than is the cervix.[16,81]

Our meta-analytic estimate of anal cancer incidence was much higher in HIV-positive men (46 per 100 000 per year) than in it was HIV-negative men (five per 100 000 per year). Since the mid 1980s, estimates of anal cancer incidence in HIV-positive MSM have been made possible through the existence of HIV/AIDS registries, which contain basic information on risk behaviour. The existence of these registries might explain the greater number of studies (nine) with estimates of anal cancer incidence in HIV-positive men, compared with only two studies (with only three incident cases of anal cancer) in HIV-negative MSM. In a population-based, case-control study done in the early 1980s the odds ratio for anal cancer in MSM compared with that in heterosexual men was reported to be 33 (95% CI 4·0–272·1),[82] but the odds ratio for anal cancer in confirmed HIV-negative MSM has not been reported. In view of the fact that the general-population anal cancer incidence in men is about one or two per 100 000,[83] our incidence estimate of only five per 100 000 in HIV-negative MSM, based on two small studies, might be an underestimate. Further direct estimates of anal cancer incidence in HIV-negative men are needed, but such studies are hampered by the absence of any denominator and numerator data for homosexuality outside of dedicated cohort studies. For HIV-positive men, the reported yearly incidence of anal cancer in the HAART era was much higher (78 per 100 000) than it was in in the pre-HAART era (22 per 100 000). Because these incidence rates are not age-adjusted, some of the increase might be because of the ageing of the HIV-positive population. However, Piketty and colleagues[64] have reported that the average age of men diagnosed with anal cancer did not differ substantially between the pre-HAART and HAART era. The reason for the increase in anal cancer rates in HIV-positive men is unclear. The immune restoration related to HAART might not be sufficient to clear persistent long-standing HPV infection, and the improved survival associated with HAART might allow for sufficient time for men with chronic HPV infection to develop invasive anal cancer.[7,65] Increases in screening are highly unlikely to explain trends in anal cancer incidence because screening is not routinely recommended, and is not widespread outside of a few clinics in San Francisco and New York City.

Proposals for anal cancer screening in MSM are based largely on the model of cervical cancer screening, which is likely to be reasonable only if the natural history of HPV infection and the characteristics of treatment of precursors diagnosed by screening are similar at the two sites in the two populations. With regards to natural history, prospective studies in young women done shortly after sexual debut have shown that about half of new cervical HPV infections clear within 6–12 months, and more than 90% clear within a few years.[14] HPV prevalence in women peaks in individuals younger than 25 years and decreases rapidly in women of older ages.[14] For the 5% of HPV infections that persist for several years, the absolute risk of CIN3 diagnosis increases greatly, to more than 40% for long-standing HPV-16 infection.[14] CIN3 is strongly associated with age,with a peak about 10 years later than that of HPV detection, and cervical cancer typically emerges from CIN3 over several decades.[14] This meta-analysis shows that a strong foundation of natural history data, akin to that of cervical cancer, is absent for anal cancer precursors. We have shown that some important differences seem to exist between the natural history of the two disorders in the two populations. With

regards to treatment, the absence of data from randomised trials showing that treatment of high-grade AIN removes the lesion, or reduces the incidence of anal cancer, and the morbidity associated with high-grade AIN treatment[8] are additional factors suggesting that approaches to cervical cancer prevention cannot be simply extrapolated to anal cancer prevention.

The prevalence of anal HPV and anal dysplasia in MSM greatly exceeds that in the cervix. Furthermore, by contrast with the pattern in women, the prevalence of anal HPV and anal dysplasia in MSM seems not to decrease with increasing age.[24,72,80] These differences in overall and age-specific prevalence are probably explained by differences in sexual behaviour. In a population-based survey in Australia, 38% of MSM but only 1% of heterosexual women reported more than 50 lifetime sexual partners.[84,85] In heterosexual women, the reporting of multiple partners is common only in teenage years, and decreases rapidly after the age of 20 years,[84] whereas a substantial proportion of MSM aged 50–60 years continue to report multiple sexual partners.[86] Another potential explanation for higher HPV prevalence at older ages is that anal HPV clearance occurs more slowly than does cervical HPV clearance, leading to a longer duration of HPV infection. This explanation seems unlikely, because in women anal HPV clears more rapidly than does cervical HPV.[87] On the basis of our data, another seemingly important difference is that progression rates to cancer might also be substantially lower in the anus compared to the cervix. Few prospective data exist for rates of CIN2–3 regression and invasion in women because ablative treatment is given to all. A retrospective analysis of women with CIN3 who had treatment withheld recorded a crude incidence rate of progression to cervical cancer of 823 per 100 000 women-years.[78] Our calculated estimates of progression to invasion from high-grade AIN are clearly much lower than this in both HIV-positive and HIV-negative MSM. However, our estimates were based on a cross-sectional comparison of high-grade AIN prevalence and anal cancer incidence, and were not based on prospective follow-up. One potential explanation for a lower progression rate is that high-grade AIN might regress more often than CIN3. Another is that high-grade AIN includes both AIN2 and AIN3. The AIN2 category, although generally included in high-grade AIN, is probably a mixture of low-grade and high-grade disease, which is the case for CIN2.[88] Furthermore, evidence exists that CIN2 progresses to invasion less often than does CIN3.[89] Unfortunately, only two studies presented data for prevalence of AIN2 and AIN3 separately. In these two studies, about 60% of high-grade AIN was AIN2.[19,53]

This meta-analysis had several limitations. Obtaining a representative sample of MSM is challenging in view of the absence of a population register, which would inform the sampling frame. Nevertheless, we excluded studies that had a clearly biased sampling scheme, and we recorded no difference in the prevalence of outcomes between community-based and clinic-based samples. The excess of HPV-related lesions in HIV-positive men compared with HIV-negative men was present both in community-recruited and clinic-recruited men. In general, data for potentially important covariates such as age, anal signs and symptoms, risk behaviour, CD4 cell count, or HIV-related treatment were inconsistently collected. For this reason we did not identify predictors of prevalence beyond year of publication and whether the participants were sourced from clinics or the community. Most studies were cross-sectional and most of the data were from North America for all the study endpoints. The scarcity of longitudinal data, and the lack of geographical diversity limits the potential for drawing conclusions on the natural history of anal HPV and dysplasia in all MSM. Data were especially scarce for histologically proven disease and anal cancer incidence in HIV-negative MSM. For anal HPV detection, PCR results might not represent active or persistent HPV infection. However, the meta-analytic estimates for HPV detection by Hybrid Capture, which detects clinically relevant (active) infection,[15] were only slightly lower than those for PCR, indicating that true anal HPV infection was probably not greatly overestimated.

We recorded much heterogeneity in most of the meta-analytic estimates. A likely source of variation lies in the different laboratory detection methodologies used.[15] Insufficient data existed to allow for grouping of anal HPV prevalence results by individual PCR primer type, which, although extensively validated, have variable sensitivity for individual HPV genotypes.[15] For high-risk HPV, different studies included different numbers of HPV probes. Differences in cytology reporting systems (Bethesda 1988 and 2001[17]) might explain some variation in cytology reporting rates. Variation in technique and standards of obtaining, processing, or analysing smears and biopsies are likely to have contributed to the heterogeneity. In view of the very limited availability of clinical and pathology (cytology and histology) personnel who are trained in the detection and diagnosis of anal cancer precursors, such variation is not surprising, and is shown in widely varying estimates of the sensitivity and specificity of cytology to detect high-grade AIN (42–98% and 8–96%, respectively).[16] High-resolution anoscopy is a more technically difficult examination to do than cervical colposcopy,[16] and variations in the ability to biopsy-appropriate lesions at anoscopy will be shown in different histological prevalence rates.[81] The increasing prevalence of histologically confirmed abnormalties in HIV-positive and HIV-negative MSM in more recently published studies suggests improvements in the screening procedure with time. Evidence suggests that inexperienced anoscopists might be insufficiently skilled to correctly target lesions for biopsy,[16] leading to impaired sensitivty. On the basis of this observation, some have called for a composite endpoint of a positive cytological or histological diagnosis as a more sensitive measure of true disease.[81] Research in this area would greatly benefit

from standardised criteria for the reporting of incidence and regression of AIN.

Our findings show that the design of anal cancer screening programmes is challenging. Data for the natural history of anal HPV infection in MSM were restricted in number and heterogeneous. The prevalence of anal HPV infection and associated lesions was very high. Prospective data were so few as to make interpretation of data for the incidence of anal HPV infection, dysplasia, and cancer very difficult. A comparison of the prevalence of high-grade AIN with anal cancer incidence suggests that most high-grade AIN will never progress to anal cancer, and that progression might occur less often than it does for CIN3. However, the scarcity of data that separated AIN2 from AIN3 makes a direct comparison with data from the cervix impossible. The identification of biomarkers to establish which men with high-grade AIN are at highest risk of progression to anal cancer, and which are likely to regress, should be a research priority. The probable low progression rates of high-grade AIN to anal cancer that this review identifies provides an ethical justification for prospective studies of high-grade AIN with frequent follow-up to identify which men are likely to have persistent disease, and which are likely to regress. In such studies, men with persistent AIN3 over multiple visits would be offered treatment. The substantial differences in the natural history of anal HPV infection to those of cervical HPV infection that this review has identified suggests that we cannot simply transfer cervical cancer screening strategies to anal cancer screening. Large, good-quality prospective natural history studies, coupled with randomised trials of treatment options, are needed to inform the development of anal cancer screening guidelines in MSM. Until evidence from these studies is available, screening for anal cancer and treatment of high-grade AIN should be done in only a research setting.

Contributors

DAM co-designed the study, did the systematic search, the statistical analysis, and drafted the paper. MP and FJ participated in the conception and design of the study, assisted in the systematic search, and revised the paper for intellectual content. AEG co-designed the study and assisted in the drafting and revising of the paper for intellectual content. JR, KP AF, SNT, DJT, CKF, SMG, and RJH revised the paper for intellectual content.

Conflicts of interest

AEG has received honoraria and research funding from CSL Biotherapies, honoraria and travel funding from Merck, and sits on the Australian advisory board for the Gardasil. CKF has received honoraria, travel funding, and research funding from CSL Biotherapies and MSD, sits on the Australian advisory board for Gardasil HPV vaccine, and owns shares in CSL Biotherapies. SMG has received advisory board fees and grant support from CSL Biotherapies and GlaxoSmithKline, and lecture fees from Merck, GlaxoSmithKline, and Sanofi Pasteur; she has received funding through her institution to do HPV vaccine studies for MSD and GlaxoSmithKline and is a member of the Merck Global Advisory Board and the Merck Scientific Advisory Committee for HPV. RJH has received support from CSL Biotherapies and MSD. All other authors declare that they have no conflicts of interest.

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