Epidemiology of anal human papillomavirus infection and high-grade squamous intraepithelial lesions in 29 900 men according to HIV status, sexuality, and age: a collaborative pooled analysis of 64 studies

Feixue Wei, Michael M Gaisa, Gypsyamber D'Souza, Ningshao Xia, Anna R Giuliano, Stephen E Hawes, Lei Gao, Shu-Hsing Cheng, Maria Gabriella Donà, Stephen E Goldstone, Maarten F Schim van der Loeff, Karin Neukam, Elissa Meites, I Mary Poynten, Jianghong Dai, Jean-Damien Combes, Ulrike Wieland, Joaquin Burgos, Timothy J Wilkin, Alexandra L Hernandez, Mauricio Iribarren Díaz, Carmen Hidalgo-Tenorio, Marleny Valencia Arredondo, Alan G Nyitray, Nicolas Wentzensen, Eric PF Chow, Vitaly Smelov, Rebecca G Nowak, Nittaya Phanuphak, Yin Ling Woo, Yoojin Choi, Yifei Hu, Alice M Schofield, Petra J Woestenberg, Admire T Chikandiwa, Andrew C Hickey, Alexandra de Pokomandy, Gad Murenzi, Hélène Péré, Marta del Pino, Ana P Ortiz, Angella Charnot-Katsikas, Xing Liu, Suwat Chariyalertsak, Carol Strong, Jason J Ong, Evy Yunihastuti, Isabelle Etienney, Valentine M Ferré, Huachun Zou, Michel Segondy, Simbarashe Chinyowa, Catharina J Alberts, Gary M Clifford

Summary

Background Robust age-specific estimates of anal human papillomavirus (HPV) and high-grade squamous intraepithelial lesions (HSIL) in men can inform anal cancer prevention efforts. We aimed to evaluate the age-specific prevalence of anal HPV, HSIL, and their combination, in men, stratified by HIV status and sexuality.

Methods We did a systematic review for studies on anal HPV infection in men and a pooled analysis of individual-level data from eligible studies across four groups: HIV-positive men who have sex with men (MSM), HIV-negative MSM, HIV-positive men who have sex with women (MSW), and HIV-negative MSW. Studies were required to inform on type-specific HPV infection (at least HPV16), detected by use of a PCR-based test from anal swabs, HIV status, sexuality (MSM, including those who have sex with men only or also with women, or MSW), and age. Authors of eligible studies with a sample size of 200 participants or more were invited to share deidentified individual-level data on the above four variables. Authors of studies including 40 or more HIV-positive MSW or 40 or more men from Africa (irrespective of HIV status and sexuality) were also invited to share these data. Pooled estimates of anal high-risk HPV (HR-HPV, including HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68), and HSIL or worse (HSIL+), were compared by use of adjusted prevalence ratios (aPRs) from generalised linear models.

Findings The systematic review identified 93 eligible studies, of which 64 contributed data on 29 900 men to the pooled analysis. Among HIV-negative MSW anal HPV16 prevalence was 1·8% (91 of 5190) and HR-HPV prevalence was 6·9% (345 of 5003); among HIV-positive MSW the prevalences were 8·7% (59 of 682) and 26·9% (179 of 666); among HIV-negative MSM they were 13·7% (1455 of 10 617) and 41·2% (3798 of 9215), and among HIV-positive MSM 28·5% (3819 of 13 411) and 74·3% (8765 of 11 803). In HIV-positive MSM, HPV16 prevalence was 5·6% (two of 36) among those age 15–18 years and 28·8% (141 of 490) among those age 23–24 years (p_{trend}=0·0091); prevalence was 31·7% (1057 of 3337) among those age 25–34 years and 22·8% (451 of 1979) among those age 55 and older (p_{trend}<0·0001). HPV16 prevalence in HIV-negative MSM was 6·7% (15 of 223) among those age 15–18 and 13·9% (166 of 1192) among those age 23–24 years (p_{trend}=0·0076); the prevalence plateaued thereafter (p_{trend}=0·72). Similar age-specific patterns were observed for HR-HPV. No significant differences for HPV16 or HR-HPV were found by age for either HIV-positive or HIV-negative MSW. HSIL+ detection ranged from 7·5% (12 of 160) to 54·5% (61 of 112) in HIV-positive MSM; after adjustment for heterogeneity, HIV was a significant predictor of HSIL+ (aPR 1·54, 95% CI 1·36–1·73), HPV16-positive HSIL+ (1·66, 1·36–2·03), and HSIL+ in HPV16-positive MSM (1·19, 1·04–1·37). Among HPV16-positive MSM, HSIL+ prevalence increased with age.

Interpretation High anal HPV prevalence among young HIV-positive and HIV-negative MSM highlights the benefits of gender-neutral HPV vaccination before sexual activity over catch-up vaccination. HIV-positive MSM are a priority for anal cancer screening research and initiatives targeting HPV16-positive HSIL+.

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Pathogen Biology, and Center
for Tuberculosis Research,
Chinese Academy of Medical
Sciences and Peking Union
Medical College, Beijing, China
(Prof L Gao PhD); **Department
of Infectious Diseases, Taoyuan
General Hospital, Ministry of
Health and Welfare, Taoyuan,
Taiwan** (S-H Cheng PhD); **School
of Public Health, Taipei Medical
University, Taipei, Taiwan**
(S-H Cheng); **Sexually
Transmitted Infections/HIV
Unit, San Gallicano
Dermatological Institute,
IRCCS, Rome, Italy**
(M G Donà PhD); **Department of
Infectious Diseases, Public
Health Service of Amsterdam,
Amsterdam, Netherlands**
(Prof M F Schim van der Loeff
MD); **Department of Internal
Medicine, Amsterdam institute
for Infection and Immunity,
Amsterdam UMC, University of
Amsterdam, Amsterdam,
Netherlands**
(Prof M F Schim van der Loeff);
**Unidad Clínica de
Enfermedades Infecciosas y
Medicina Preventiva, UCEIMP,
Instituto de Biomedicina de
Sevilla, CSIC, Universidad de
Sevilla, Hospital Universitario
Virgen del Rocío, Seville, Spain**
(K Neukam PhD); **Division of
Viral Diseases, Centers for
Disease Control and
Prevention, Atlanta, GA, USA**
(E Meites MD); **Kirby Institute,
University of New South Wales,
Sydney, NSW, Australia**
(I M Poynten PhD,
Prof H Zou PhD); **School of
Public Health, Xinjiang Medical
University, Xinjiang, Urumqi,
China** (Prof J Dai PhD); **Institute
of Virology, University of
Cologne, National Reference
Center for Papilloma and
Polyomaviruses, Cologne,
Germany** (U Wieland MD);
**Department of infectious
Diseases, Vall d'Hebron
University Hospital, Barcelona,
Spain** (J Burgos MD); **Division of
Infectious Diseases, Weill
Cornell Medicine, New York,
NY, USA** (T J Wilkin MD);
**Department of Medicine,
University of California,
San Francisco, CA, USA**
(A L Hernandez PhD); **Public
Health Program, College of
Education and Health Sciences,
Touro University, Vallejo, CA,
USA** (A L Hernandez);
**Department of Surgery,
Complexo Hospitalario
Universitario de Vigo-Hospital**

Research in context

Evidence before this study

We searched MEDLINE, Embase, and the Cochrane Library on March 12, 2021, using the terms ("papillomaviridae" OR "papillomavirus" OR "HPV") AND ("anal canal" OR "anus" OR "anal"). We searched for primary research on anal human papillomavirus (HPV) infection in men published between Jan 1, 1986, and Feb 28, 2021, with no language restrictions. Persistent anal high-risk HPV (HR-HPV, including HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68), particularly HPV16, is the established cause of anal cancer, for which anal high-grade squamous intraepithelial lesion (HSIL) is the assumed precursor. Several systematic reviews and relevant meta-analyses exist on the topic, one of which (published in 2012) focused on men who have sex with men (MSM). Other meta-analyses have since established HIV status and sexuality as important predictors of anal HPV prevalence and anal cancer incidence in men, as well as degree of immunosuppression and antiretroviral therapy in men living with HIV. However, these meta-analyses of summary-level data did not allow the analysis of patterns of anal HR-HPV and HSIL in risk groups by age and degree of HIV-related immunosuppression, nor combinations of anal HPV and HSIL, which require individual-level data and sample sizes larger than those available from any single study.

Added value of this study

To our knowledge, this is the first systematic reanalysis of the age-specific epidemiology of anal HPV in men, which offers a comprehensive picture of anal HPV infection in men before HPV vaccination. Our results show rapid increases in the prevalence of anal HPV16 in HIV-positive and HIV-negative MSM aged 15–24 years, and consistently high HPV16

prevalence in all MSM aged 25 years or older. We also provide evidence for the amplifying effect of HIV infection and HIV-related immunosuppression on anal HPV16 infection in men who have sex with women and MSM. The additional novelty of this collaborative reanalysis is the description of the epidemiology of HSIL in MSM by HIV status, including in combination with HPV16 data. This approach revealed important heterogeneity in HSIL detection, even across studies that used similar diagnostic strategies (eg, both cytology and high-resolution anoscopy). Despite this heterogeneity, HIV infection and degree of HIV immunosuppression were shown to be significant predictors of anal HSIL and HPV16-positive anal HSIL in MSM, as well as of anal HSIL among HPV16-positive MSM. Furthermore, the prevalence of anal HSIL slightly increased with age in HPV16-positive MSM.

Implications of all the available evidence

These data can inform the development of various anal cancer prevention efforts, both through primary prevention (ie, vaccination against HPV or prevention and control of HIV infection) and secondary prevention (eg, the potential screening of high-risk populations, such as people living with HIV), with the aim of detecting and managing HSIL, especially HPV16-positive HSIL. Of note, the rapid increase in anal HPV infection among young MSM highlights the benefits of gender-neutral HPV vaccination before sexual debut over catch-up HPV vaccination, regardless of HIV status. Our findings indicate that the prevalence of HPV16-positive anal HSIL in the HIV-positive MSM population is high, and that anal cancer screening research and initiatives should be prioritised in this group.

Introduction

Of 35 000 human papillomavirus (HPV)-related anal cancers diagnosed worldwide each year, 17 000 (48·6%) occur in men.[1] Anal cancer is rare in the general male population (about one case per 100 000 person-years), but its incidence is elevated in HIV-negative men who have sex with men (MSM; about 20 cases per 100 000 person-years) and HIV-positive men who have sex with women (MSW; about 30 cases per 100 000 person-years), and can exceed 100 cases per 100 000 person-years in HIV-positive MSM due to increased anal HPV exposure and HIV-related immunosuppression.[2] Indeed, the incidence of anal cancer is increasing in high-income countries,[3] and a substantial proportion of this increase among men can be attributed to HIV.[4]

Persistent anal HPV infection is the major cause of anal cancer.[5,6] Although 13 high-risk HPV (HR-HPV; HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68) types are classified as human carcinogens (on the basis of evidence from cervical cancer),[6] HPV16 is the most carcinogenic type in the anus.[5] HPV16 is more frequently identified in HPV-related anal cancer than in

cervical cancer,[1,5] albeit in a larger majority of anal cancers in HIV-negative individuals than in HIV-positive individuals.[5] HPV16 is also the dominant type in high-grade squamous intraepithelial lesions (HSIL), which is the precursor of anal cancer.[5]

Potential modalities for anal cancer prevention can be separated into those relevant to primary prevention (eg, vaccination against HPV[7] and the prevention and control of HIV infection), and those relevant to secondary prevention (eg, screening of high-risk populations), which aim to detect and manage HSIL. Although there are parallels with modalities established for cervical cancer prevention, many differences exist, particularly for men.[8] Thus, robust age-specific epidemiological data of anal HPV infection and HSIL in target populations can inform anal cancer prevention programmes for men and predict their potential effect.

To this end, we initiated a collaborative, individual-level, pooled analysis of anal HPV and HSIL in men according to HIV status, sexuality, and age. This analysis is complementary to a similar, previously published, collaborative, pooled analysis done in women according

to HIV status.[9] Our aim was to evaluate age-specific prevalence of HPV16, HSIL, and their combination, across the risk strata of HIV-positive MSM, HIV-negative MSM, HIV-positive MSW, and HIV-negative MSW.

Methods

Data collection

We did a systematic literature review for studies on anal HPV infection in men, by updating the strategy used in two previous meta-analyses.[5,10] We searched MEDLINE, Embase, and the Cochrane Library for primary research published between Jan 1, 1986, and Feb 28, 2021, using the search terms ("papillomaviridae" OR "papillomavirus" OR "HPV") AND ("anal canal" OR "anus" OR "anal"), with no language restrictions (appendix p 2).

To be eligible, studies were required to report type-specific HPV infection (for at least HPV16), detected by use of a PCR-based test of anal swabs; HIV status; sexuality (MSM, including those who have sex with men only or also with women, or MSW); and age. Authors of eligible studies with sample sizes of 200 individuals or more were invited to share deidentified individual-level data on the above four variables. Due to sparse data, authors of studies including 40 or more HIV-positive MSW, 40 or more men from Africa (irrespective of HIV status and sexuality), or both, were also invited to share deidentified individual-level data.

Although not strict inclusion requirements, other data were included when available on anal cytology or histology results collected at the same visit as (or within 6 months of) HPV sample collection and, for HIV positive men, on current and nadir CD4 cell counts and most recent HIV viral loads. The only exclusion criteria at the individual level were age younger than 15 years and having had one or more dose of HPV vaccine.

FW and CJA performed the literature search and possible conflicts were resolved by discussion with GMC.

Data analysis

Pooled anal HPV prevalence estimates were calculated for 13 individual HR-HPV types (HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68), as well as for four groups of HPV types (HPV16 and 18; HPV6, 11, 16, and 18; HPV6, 11, 16, 18, 31, 33, 45, 52, and 58; and any 13 HR-HPV types). Not all studies tested for all HPV types, thus denominators vary by type or groups of types. Only studies testing for all 13 individual HR-HPV types contributed to analyses of prevalence for any or multiple HR-HPV types.

Studies with cytopathology were classified into four groups according to diagnostic strategy: high-resolution anoscopy for all participants; high-resolution anoscopy for participants with abnormal cytology only; anoscopy for all participants; and cytology only. Only men with a cytology result were included in analyses of HSIL or worse (HSIL+), defined as either (1) cytological diagnosis of atypical squamous cells, cannot exclude HSIL, HSIL, or anal cancer, or (2) histological diagnosis
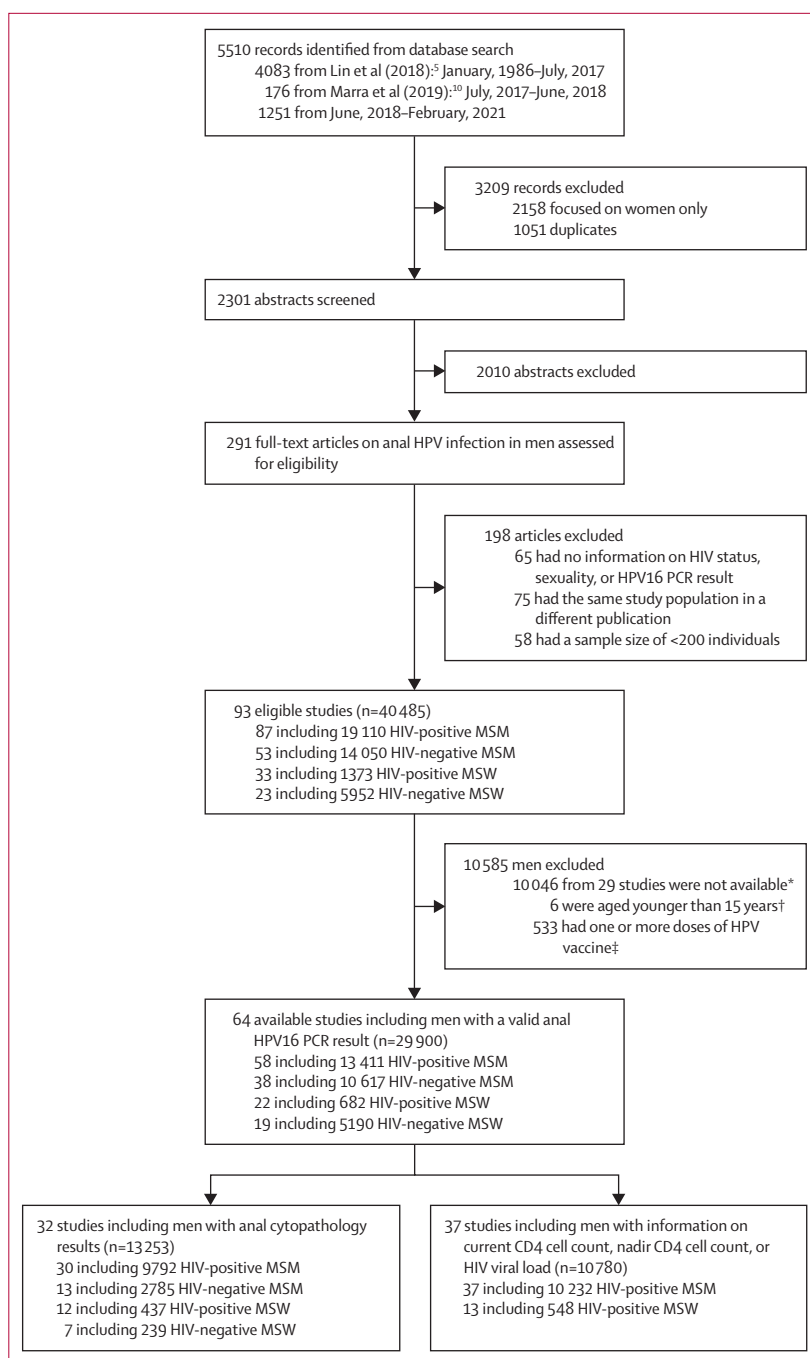
Figure 1: Study selection
All studies included in this pooled analysis were mutually exclusive. HPV=human papillomavirus. MSM=men who have sex with men. MSW=men who have sex with women. *The authors of these studies did not share individual-level data. †Included five HIV-positive MSM and one HIV-positive MSW. ‡Included 247 HIV-positive MSM, 278 HIV-negative MSM, one HIV-positive MSW, and seven HIV-negative MSW.

of grade 2 or 3 anal intraepithelial neoplasia or anal cancer. Prevalence estimates were also calculated for having HSIL+ and HPV16-positive anal swabs simultaneously (hereafter referred to as HPV16-positive anal HSIL+) in all MSM, and HSIL+ in HPV16-positive MSM. Sensitivity

Álvaro Cunqueiro, Vigo, Spain (M Iribarren Díaz MD); **Infectious Disease Unit, Biosanitary Research Institute Granada, University Hospital Virgen de las Nieves, Granada, Spain**
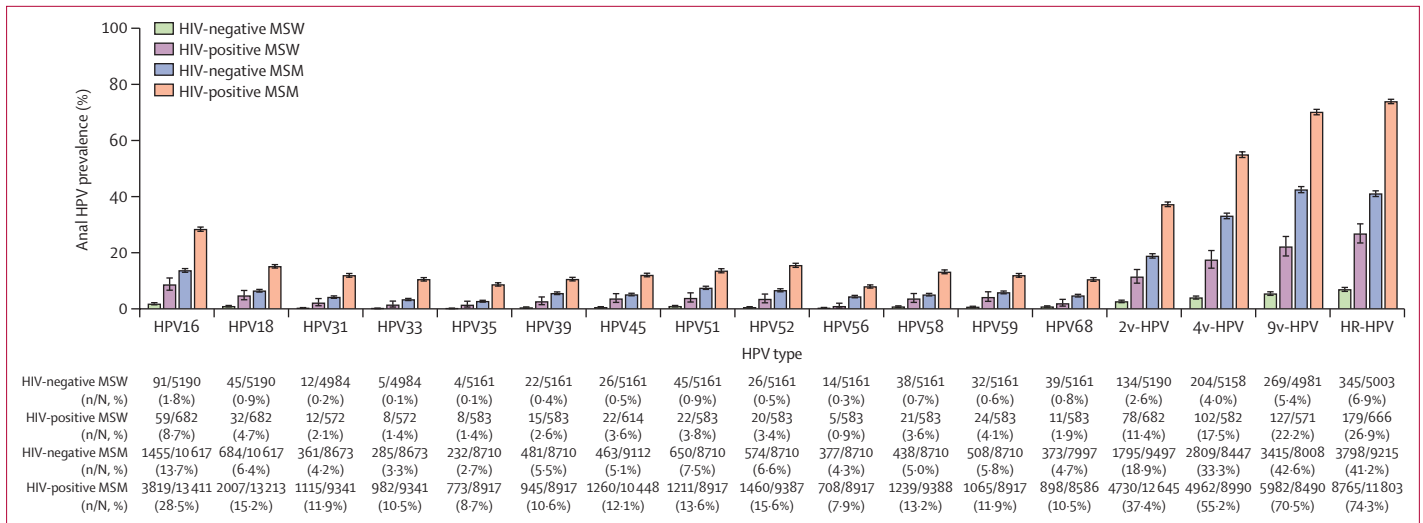
Figure 2: Prevalence of type-specific and grouped type HPV infection in four male risk groups

HR-HPV includes HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68. Error bars show 95% CIs. HPV=human papillomavirus. 2v-HPV=HPV16 and 18. 4v-HPV=HPV6, 11, 16, and 18. 9v-HPV=HPV6, 11, 16, 18, 31, 33, 45, 52, and 58. HR-HPV=high-risk HPV. MSW=men who have sex with women. MSM=men who have sex with men.

(C Hidalgo-Tenorio MD);
Universidad de Antioquia,
Escuela de Microbiología,
Grupo de investigación Salud
Sexual y Cáncer, Medellín,
Antioquia, Colombia (Prof M
Valencia Arredondo PhD);
Clinical Cancer Center and
Center for AIDS Intervention
Research, Medical College of
Wisconsin, Milwaukee, WI, USA
(A G Nyitray PhD); Division of
Cancer Epidemiology and
Genetics, National Cancer
Institute, Bethesda, MD, USA
(N Wentzensen MD); Melbourne
Sexual Health Centre,
The Alfred Hospital,
Melbourne, VIC, Australia
(E P F Chow PhD); Central
Clinical School, Monash
University, Melbourne, VIC,
Australia (E P F Chow,
J J Ong PhD); Melbourne School
of Population and Global
Health, The University of
Melbourne, Melbourne, VIC,
Australia (E P F Chow); Division
of Country Health
Programmes, WHO Regional
Office for Europe, Copenhagen,
Denmark (V Smelov); Institute
of Human Virology, University
of Maryland School of
Medicine, Baltimore, MD, USA
(R G Nowak PhD); Institute of
HIV Research and Innovation,
Bangkok, Thailand
(N Phanuphak MD); Center of
Excellence in Transgender
Health, Chulalongkorn
University, Bangkok, Thailand
(N Phanuphak); Faculty of

analyses of HSIL+ outcomes were done, in which studies were restricted to those that enrolled both HIV-positive and HIV-negative MSM and did high-resolution anoscopy for all participants. A random-effects meta-analysis and I^2 were used to measure heterogeneity by study.

In HIV-positive men, estimates of HPV16 infection, HSIL+, and their combination, were stratified by current and nadir CD4 count (<200 cells per μL, 200–499 cells per μL, and ≥500 cells per μL), and HIV viral load (<200 copies per mL and ≥200 copies per mL).

The prevalence of HPV infection, HSIL+, and their combination, were stratified by risk group (HIV-positive MSM, HIV-negative MSM, HIV-positive MSW, and HIV-negative MSW) and age group. We estimated prevalence ratios (PRs) with corresponding 95% CIs by use of generalised linear models with a log-link function. To account for heterogeneity between studies, all PRs were adjusted by study (used as a fixed effect in the model), and by HIV and age group (used as covariables) in specific analyses, as appropriate. p values of age-specific trends in HPV prevalence were calculated with age group as a continuous variable. Stata (version 14) was used for statistical analyses, which were all two-sided.

Role of the funding source
The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results
The systematic review identified 93 eligible studies (including 40 485 men), of which 64 (73·9%) contributed data on 29 900 men to the pooled analysis of HPV infection (figure 1). 44·9% (n=13 411) of all included

men were HIV-positive MSM, 35·5% (n=10 617) HIV-negative MSM, 2·3% (n=682) HIV-positive MSW, and 17·4% (n=5190) HIV-negative MSW. 9877 men (33·0%) were from North America, 8028 (26·8%) from Asia, and 7524 (25·2%) from Europe (appendix pp 4–6); other regions were less well represented, but men from Africa contributed 46·2% of all HIV-positive MSW (315 of 682).

For all individual and groups of HPV types, anal HPV prevalence was lowest in HIV-negative MSW, followed by HIV-positive MSW and HIV-negative MSM, and was highest in HIV-positive MSM (figure 2). When comparing age-specific prevalence of HPV16 and HR-HPV, similar ranking among the four risk groups was consistently observed within each age group (figure 3). In HIV-positive MSM, the age-specific anal HPV16 prevalence increased from 5·6% at 15–18 years to 28·8% at 23–24 years (p_{trend}=0·0091), then decreased significantly with increasing age from 31·7% at 25–34 years to 22·8% at 55 years and older (adjusted PR [aPR] for ≥55 years vs 25–34 years 0·71, 95% CI 0·64–0·79; p_{trend}<0·0001; figure 3A). A similar age-specific pattern was observed for HR-HPV prevalence in HIV-positive MSM, increasing from 58·3% at 15–18 years to 74·4% at 23–24 years (p_{trend}=0·038), then decreasing significantly from 78·6% at 25–34 years to 67·3% at 55 years and older (aPR for ≥55 years vs 25–34 years 0·83, 95% CI 0·80–0·87, p_{trend}<0·0001; figure 3B). Similar increases in HPV16 (p_{trend}=0·0076) and HR-HPV (p_{trend}=0·011) prevalence from 15–18 years to 23–24 years were observed in HIV-negative MSM, but with no significant differences thereafter (from 25–34 years to ≥55 years HPV16 p_{trend}=0·72 and HR-HPV p_{trend}=0·73; figure 3). HIV-positive MSW were underrepresented in younger age groups, but prevalence of HPV16 increased from 6·1% at 25–34 years to 13·4% at 55 years and older (figure 3A), and prevalence of HR-HPV increased from
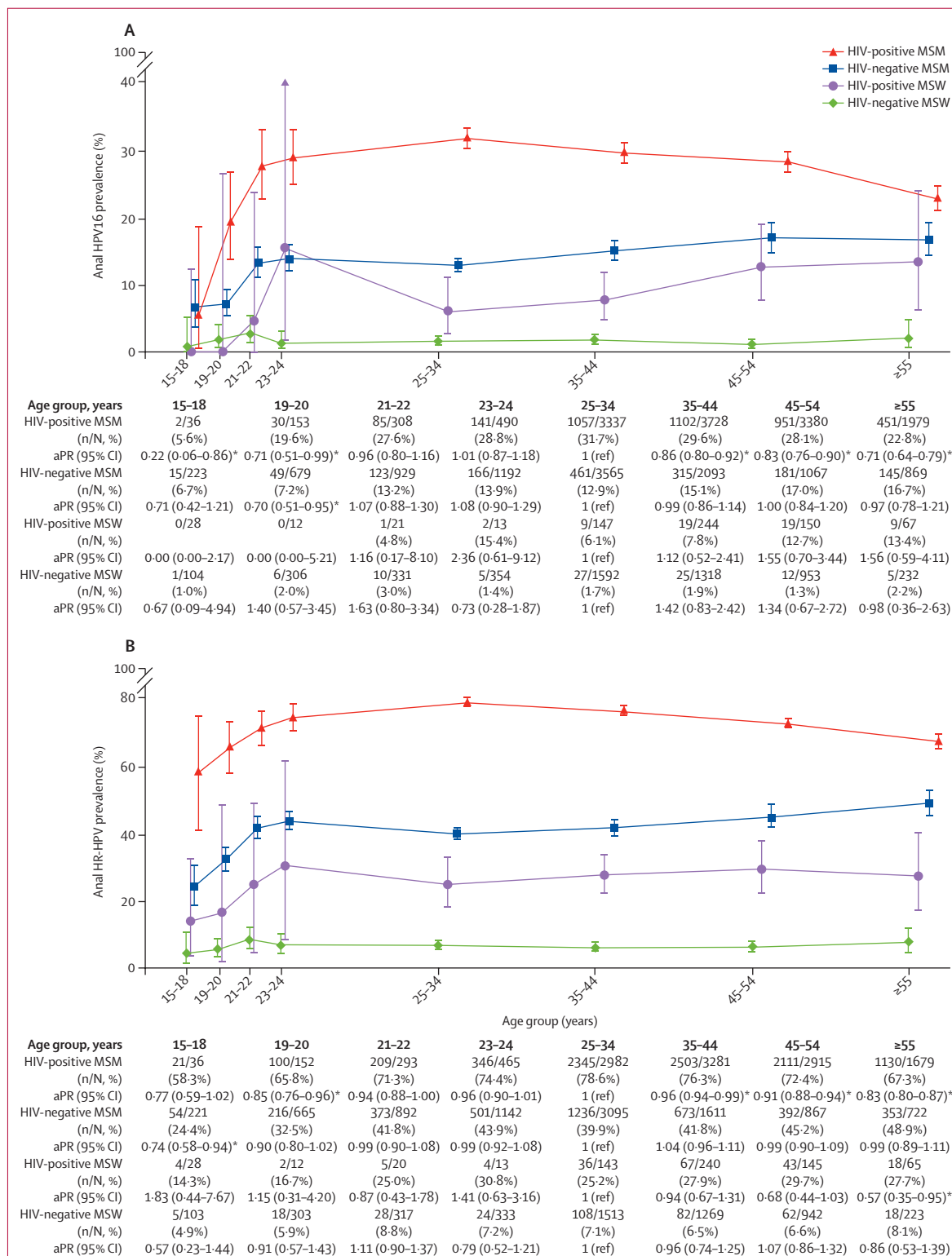
Figure 3: Age-specific prevalence of HPV16 (A) and HR-HPV (B) infection in four male risk groups
Error bars show 95% CIs. PRs were adjusted for study. HR-HPV includes HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68. HPV=human papillomavirus. HR-HPV=high-risk HPV. MSM=men who have sex with men. MSW=men who have sex with women. aPR=adjusted prevalence ratio. *Significant aPRs relative to the reference group.

Medicine, University of Malaya, Kuala Lumpur, Malaysia (Y L Woo PhD); **Department of Immunology, University of Toronto, Toronto, ON, Canada** (Y Choi PhD); **Department of Child and Adolescent Health and Maternal Care, School of Public Health, Capital Medical University, Beijing, China** (Prof Y Hu PhD); **Institute of Cancer Sciences, University of Manchester, Manchester, UK** (A M Schofield MD); **Center for Infectious Disease Control, National Institute for Public Health and the Environment, Bilthoven, Netherlands** (P J Woestenberg PhD); **Wits RHI, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa** (A T Chikandiwa PhD); **Division of HIV/AIDS Prevention, Centers for Disease Control and Prevention, Nonthaburi, Thailand** (A C Hickey PhD); **Chronic Viral Illness Service, McGill University Health Centre and Department of Family Medicine, McGill University, Montreal, QC, Canada** (A de Pokomandy MDCM); **Rwanda Military Hospital and Research for Development Rwanda, Kigali, Rwanda** (G Murenzi MD); **Assistance Publique Hôpitaux de Paris-Centre, Service de Microbiologie (Unité de virologie), Hôpital Européen Georges Pompidou, Paris, France** (H Péré PhD); **Centre de Recherche des Cordeliers, Sorbonne Université, Inserm, Université de Paris, Functional Genomics of Solid Tumors Laboratory, Equipe Labellisée Ligue Nationale contre le Cancer, Labex OncoImmunology, Paris, France** (H Péré); **Institute Clinic of Gynecology, Obstetrics, and Neonatology, Gynecology Oncology Unit, Hospital Clínic, Barcelona, Spain** (M del Pino MD); **Institut d'Investigacions Biomèdiques August Pi i Sunyer, Barcelona, Spain** (M del Pino); **Medicine Faculty, Barcelona University, Barcelona, Spain** (M del Pino); **Cancer Control and Population Sciences Program, University of Puerto Rico Comprehensive Cancer Center, San Juan, PR, USA** (A P Ortiz PhD); **Graduate School of Public Health, University of Puerto Rico,**
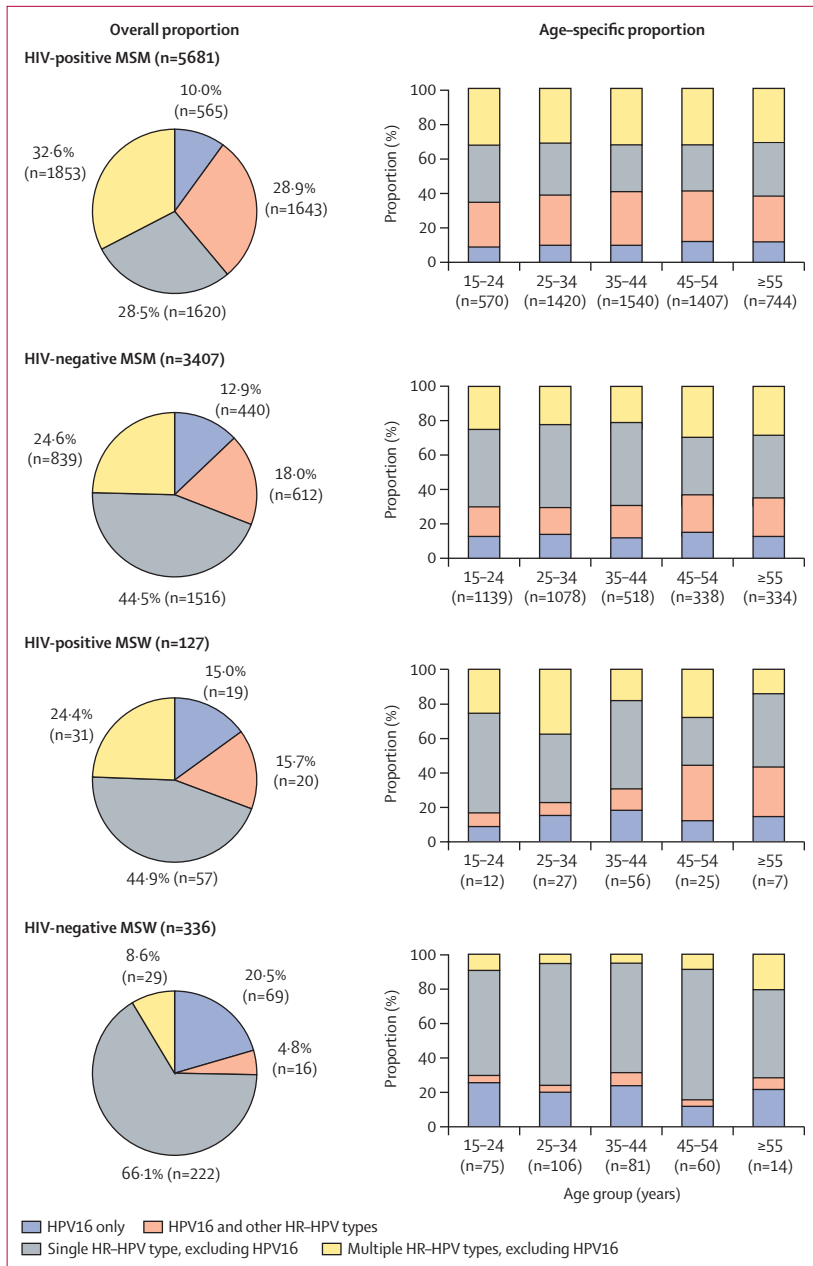
Figure 4: Overall and age-specific proportion of men infected with HPV16 and other HR-HPV types
HR-HPV includes HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68. HPV=human papillomavirus. HR-HPV=high-risk HPV. MSM=men who have sex with men. MSW=men who have sex with women.

San Juan, PR, USA (A P Ortiz);

Department of Pathology, The University of Chicago, Chicago, IL, USA (A Charnot-Katsikas MD); MolDx Program, Palmetto GBA, Columbia, SC, USA (A Charnot-Katsikas); Department of Epidemiology, School of Public Health, and the Key Laboratory of Public Health Safety of Ministry of

25·2% at 25–34 years to 27·7% at 55 years and older (figure 3B), albeit non-significantly. HPV16 and HR-HPV prevalence did not vary by age in HIV-negative MSW. Age-specific prevalence of individual HR-HPV excluding HPV16 and groups of HPV types by risk group are shown in the appendix (pp 9–14, 15–17).

Among HR-HPV-positive men, infection with multiple HR-HPV types was observed in 61·5% HIV-positive MSM (28·9% including HPV16; 32·6% not including HPV16), 42·6% HIV-negative MSM (18·0%; 24·6%),
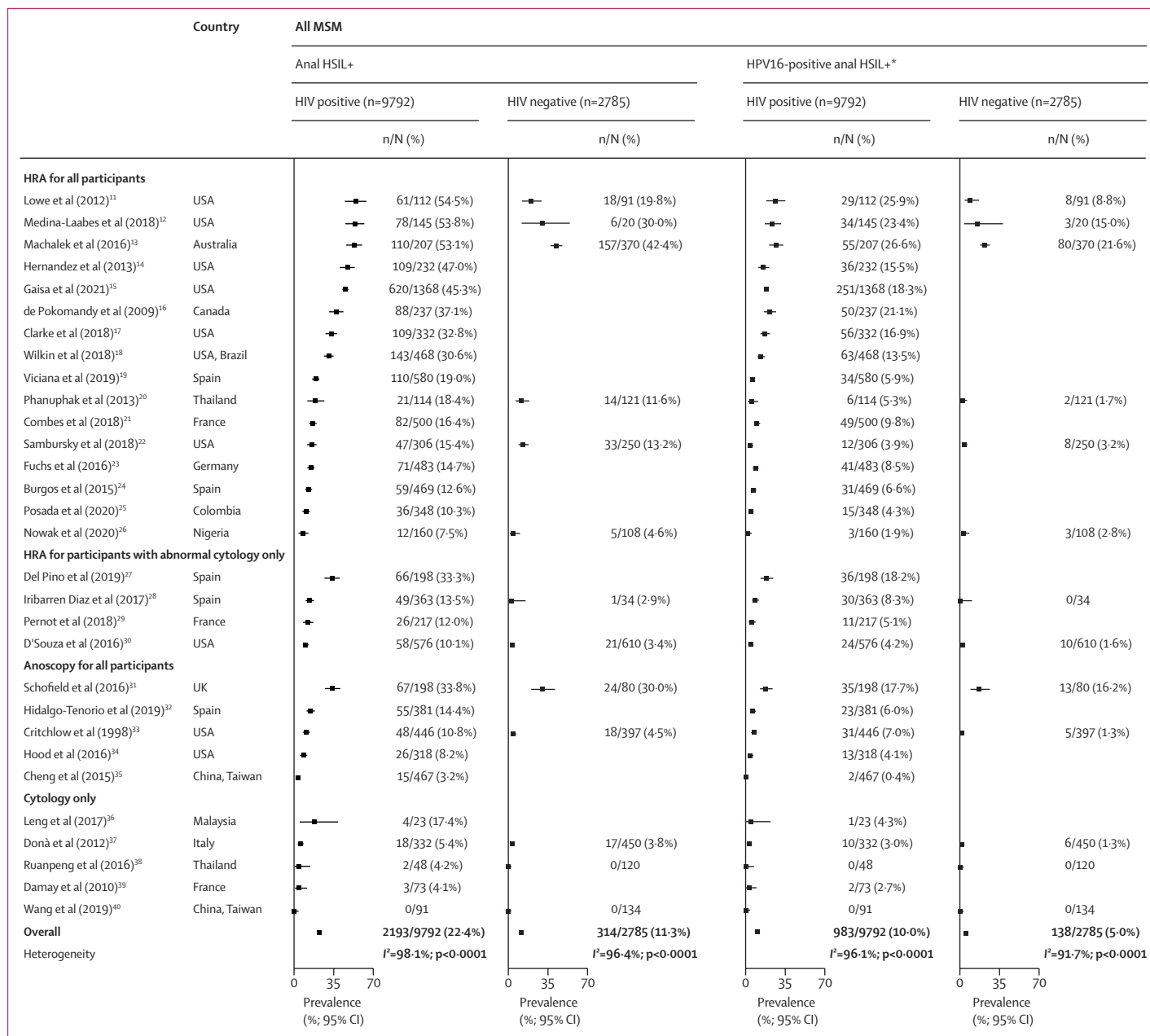
40·1% HIV-positive MSW (15·7%; 24·4%), and 13·4% HIV-negative MSW (4·8%; 8·6%), with no differences in the proportion of those with multiple HPV infections by age group (figure 4). Further details on the distribution of infection with different numbers of HR-HPV types in the four male risk groups, overall and by age group, are described in the appendix (p 18).

In total, 32 studies (including 13 253 men) contributed data on cytopathology. 73·9% (n=9792) of men with cytopathology data were HIV-positive MSM, 21·0% (n=2785) were HIV-negative MSM, 3·3% (n=437) HIV-positive MSW, and 1·8% (n=239) HIV-negative MSW (figure 1; appendix pp 4–6). Prevalence of HPV16 and HR-HPV was lower in men without cytopathological data than in those with cytopathological data, in all risk groups (appendix p 19), especially for HIV-negative MSM aged 35 years and older (appendix p 20).

Because of small number of MSW, HSIL+ analyses were restricted to 30 studies including 12 577 MSM. With respect to diagnostic strategy, in addition to cytology, 16 studies, with 55·8% of all 12 577 MSM did high-resolution anoscopy in all participants; four, with 15·9%, did high-resolution anoscopy in participants with abnormal cytology only; five, with 18·2%, did anoscopy in all participants; and five, with 10·1%, did cytology only (figure 5). The pooled prevalence of anal HSIL+ was 22·4% in HIV-positive MSM, and 11·3% in HIV-negative MSM, with high study heterogeneity. The corresponding prevalence of HPV16-positive anal HSIL+ was 10·0% in HIV-positive MSM and 5·0% in HIV-negative MSM. When restricting the analysis to HPV16-positive MSM, HSIL+ prevalence was 34·0% in HIV-positive MSM and 26·8% in HIV-negative MSM. The high heterogeneity between studies for anal HSIL+ prevalence remained even when the analysis was restricted to studies in which HSIL+ was histologically confirmed by high-resolution anoscopy in all participants (appendix p 21).

HIV positivity was a significant risk factor for HSIL+ (aPR 1·54, 95% CI 1·36–1·73), HPV16-positive HSIL+ (1·66, 1·36–2·03), and HSIL+ in HPV16-positive MSM (1·19, 1·04–1·37; table). The prevalence of HSIL+ decreased significantly with age in all MSM (aPR 0·96 per 10 years increase in age, 95% CI 0·94–0·99), but increased significantly with age in HPV16-positive MSM (1·05, 1·01–1·09). The effects of HIV status and age on HSIL+ measures were materially unchanged in two sensitivity analyses (appendix pp 7–8).

37 studies (including 10 780 HIV-positive men) provided data on current CD4 cell counts, nadir CD4 cell counts, or HIV viral load; most of which were from MSM (94·9%; figure 1; appendix pp 4–6). Low current CD4 count was significantly associated with HPV16 infection, HSIL+, and HPV16-positive HSIL+ in all HIV-positive MSM, and with HSIL+ in HPV16-positive, HIV-positive MSM (figure 6). After stratifying by age, the effects of low current CD4 count on HPV16 infection, anal HSIL+, and HPV16-positive anal HSIL+ were most clearly observed in the 25–54 years age

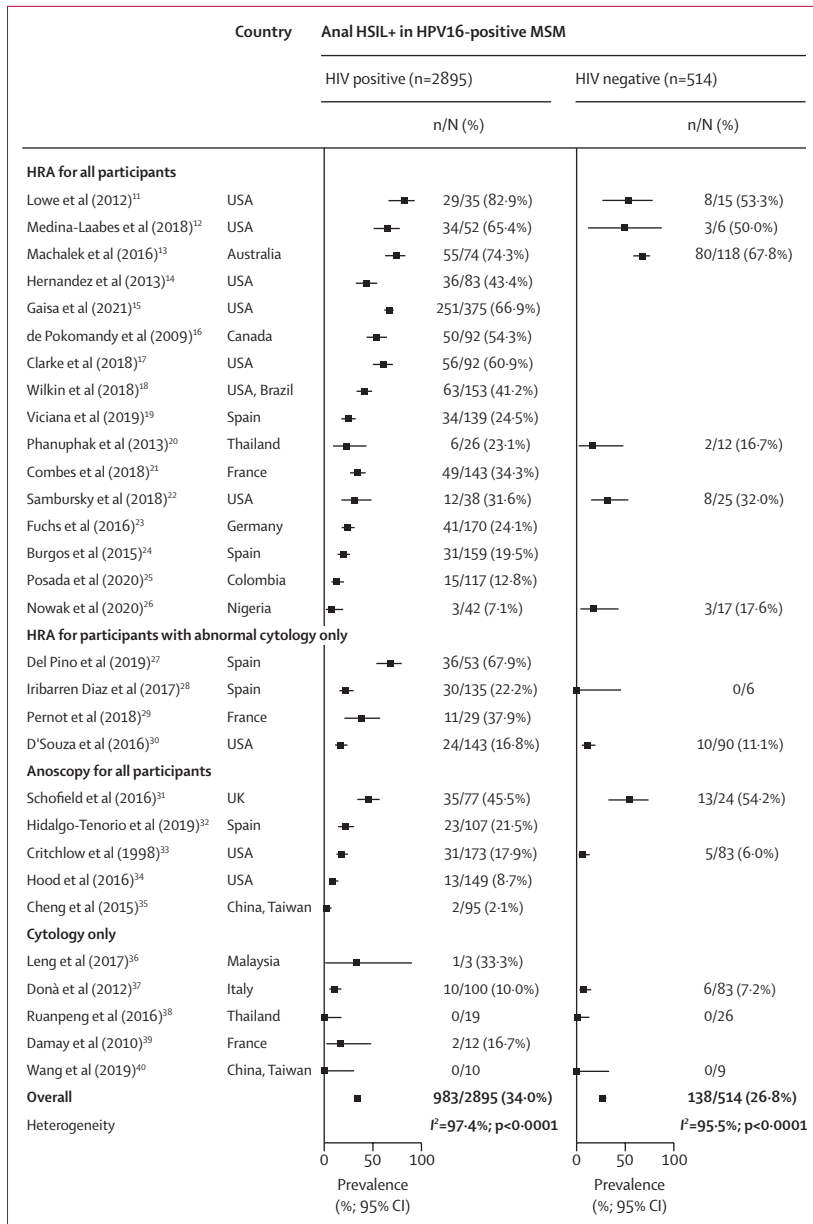|	Country	All MSM			
		Anal HSIL+		**HPV16-positive anal HSIL+***	
		HIV positive (n=9792)	HIV negative (n=2785)	HIV positive (n=9792)	HIV negative (n=2785)
		n/N (%)	n/N (%)	n/N (%)	n/N (%)
HRA for all participants					
Lowe et al (2012)[11]	USA	61/112 (54·5%)	18/91 (19·8%)	29/112 (25·9%)	8/91 (8·8%)
Medina-Laabes et al (2018)[12]	USA	78/145 (53·8%)	6/20 (30·0%)	34/145 (23·4%)	3/20 (15·0%)
Machalek et al (2016)[13]	Australia	110/207 (53·1%)	157/370 (42·4%)	55/207 (26·6%)	80/370 (21·6%)
Hernandez et al (2013)[14]	USA	109/232 (47·0%)		36/232 (15·5%)	
Gaisa et al (2021)[15]	USA	620/1368 (45·3%)		251/1368 (18·3%)	
de Pokomandy et al (2009)[16]	Canada	88/237 (37·1%)		50/237 (21·1%)	
Clarke et al (2018)[17]	USA	109/332 (32·8%)		56/332 (16·9%)	
Wilkin et al (2018)[18]	USA, Brazil	143/468 (30·6%)		63/468 (13·5%)	
Viciana et al (2019)[19]	Spain	110/580 (19·0%)		34/580 (5·9%)	
Phanuphak et al (2013)[20]	Thailand	21/114 (18·4%)	14/121 (11·6%)	6/114 (5·3%)	2/121 (1·7%)
Combes et al (2018)[21]	France	82/500 (16·4%)		49/500 (9·8%)	
Sambursky et al (2018)[22]	USA	47/306 (15·4%)	33/250 (13·2%)	12/306 (3·9%)	8/250 (3·2%)
Fuchs et al (2016)[23]	Germany	71/483 (14·7%)		41/483 (8·5%)	
Burgos et al (2015)[24]	Spain	59/469 (12·6%)		31/469 (6·6%)	
Posada et al (2020)[25]	Colombia	36/348 (10·3%)		15/348 (4·3%)	
Nowak et al (2020)[26]	Nigeria	12/160 (7·5%)	5/108 (4·6%)	3/160 (1·9%)	3/108 (2·8%)
HRA for participants with abnormal cytology only					
Del Pino et al (2019)[27]	Spain	66/198 (33·3%)		36/198 (18·2%)	
Iribarren Diaz et al (2017)[28]	Spain	49/363 (13·5%)	1/34 (2·9%)	30/363 (8·3%)	0/34
Pernot et al (2018)[29]	France	26/217 (12·0%)		11/217 (5·1%)	
D'Souza et al (2016)[30]	USA	58/576 (10·1%)	21/610 (3·4%)	24/576 (4·2%)	10/610 (1·6%)
Anoscopy for all participants					
Schofield et al (2016)[31]	UK	67/198 (33·8%)	24/80 (30·0%)	35/198 (17·7%)	13/80 (16·2%)
Hidalgo-Tenorio et al (2019)[32]	Spain	55/381 (14·4%)		23/381 (6·0%)	
Critchlow et al (1998)[33]	USA	48/446 (10·8%)	18/397 (4·5%)	31/446 (7·0%)	5/397 (1·3%)
Hood et al (2016)[34]	USA	26/318 (8·2%)		13/318 (4·1%)	
Cheng et al (2015)[35]	China, Taiwan	15/467 (3·2%)		2/467 (0·4%)	
Cytology only					
Leng et al (2017)[36]	Malaysia	4/23 (17·4%)		1/23 (4·3%)	
Donà et al (2012)[37]	Italy	18/332 (5·4%)	17/450 (3·8%)	10/332 (3·0%)	6/450 (1·3%)
Ruanpeng et al (2016)[38]	Thailand	2/48 (4·2%)	0/120	0/48	0/120
Damay et al (2010)[39]	France	3/73 (4·1%)		2/73 (2·7%)	
Wang et al (2019)[40]	China, Taiwan	0/91	0/134	0/91	0/134
Overall		2193/9792 (22·4%)	314/2785 (11·3%)	983/9792 (10·0%)	138/2785 (5·0%)
Heterogeneity		I^2=98·1%; p<0·0001	I^2=96·4%; p<0·0001	I^2=96·1%; p<0·0001	I^2=91·7%; p<0·0001

Prevalence (%; 95% CI)

(Figure 5 continues on next page)

group (appendix p 22). However, there were no associations between nadir CD4 cell count and HPV16 or HSIL+ outcomes (figure 6). HPV16 prevalence was higher in HIV-positive MSM with HIV viral loads of 200 copies per mL or higher than in those with lower viral loads, but HIV viral load was not significantly associated with HSIL+ outcomes. In HIV-positive MSW, prevalence of HPV16 was higher in men with CD4 counts of less than 200 cells per µL than in those with CD4 counts of 500 cells per µL or more (aPR 2·10, 0·98–4·49), although this difference was not significant (appendix p 23).

Discussion

Pooling of individual-level data for 29 900 men provides a comprehensive picture of age-specific epidemiology of anal HPV infection in HIV-positive and HIV-negative men before HPV vaccination. Consistent with previous research,[10] patterns of anal HR-HPV prevalence, most notably for HPV16, showed HIV status and sexuality to be important population-level determinants of anal HPV infection in men. Anal HPV data were particularly abundant for both HIV-negative and HIV-positive MSM, allowing robust estimates of age-specific changes in

Education, Fudan University, Shanghai, China (X Liu PhD); Faculty of Public Health, Chiang Mai University and Research Institute for Health Sciences, Chiang Mai University, Chiang Mai, Thailand (S Chariyalertsak DrPH); Department of Public Health, National Cheng Kung University Hospital, College of Medicine, National Cheng

	Country	Anal HSIL+ in HPV16-positive MSM	
		HIV positive (n=2895)	HIV negative (n=514)
		n/N (%)	n/N (%)
HRA for all participants			
Lowe et al (2012)[11]	USA	29/35 (82·9%)	8/15 (53·3%)
Medina-Laabes et al (2018)[12]	USA	34/52 (65·4%)	3/6 (50·0%)
Machalek et al (2016)[13]	Australia	55/74 (74·3%)	80/118 (67·8%)
Hernandez et al (2013)[14]	USA	36/83 (43·4%)	
Gaisa et al (2021)[15]	USA	251/375 (66·9%)	
de Pokomandy et al (2009)[16]	Canada	50/92 (54·3%)	
Clarke et al (2018)[17]	USA	56/92 (60·9%)	
Wilkin et al (2018)[18]	USA, Brazil	63/153 (41·2%)	
Viciana et al (2019)[19]	Spain	34/139 (24·5%)	
Phanuphak et al (2013)[20]	Thailand	6/26 (23·1%)	2/12 (16·7%)
Combes et al (2018)[21]	France	49/143 (34·3%)	
Sambursky et al (2018)[22]	USA	12/38 (31·6%)	8/25 (32·0%)
Fuchs et al (2016)[23]	Germany	41/170 (24·1%)	
Burgos et al (2015)[24]	Spain	31/159 (19·5%)	
Posada et al (2020)[25]	Colombia	15/117 (12·8%)	
Nowak et al (2020)[26]	Nigeria	3/42 (7·1%)	3/17 (17·6%)
HRA for participants with abnormal cytology only			
Del Pino et al (2019)[27]	Spain	36/53 (67·9%)	
Iribarren Diaz et al (2017)[28]	Spain	30/135 (22·2%)	0/6
Pernot et al (2018)[29]	France	11/29 (37·9%)	
D'Souza et al (2016)[30]	USA	24/143 (16·8%)	10/90 (11·1%)
Anoscopy for all participants			
Schofield et al (2016)[31]	UK	35/77 (45·5%)	13/24 (54·2%)
Hidalgo-Tenorio et al (2019)[32]	Spain	23/107 (21·5%)	
Critchlow et al (1998)[33]	USA	31/173 (17·9%)	5/83 (6·0%)
Hood et al (2016)[34]	USA	13/149 (8·7%)	
Cheng et al (2015)[35]	China, Taiwan	2/95 (2·1%)	
Cytology only			
Leng et al (2017)[36]	Malaysia	1/3 (33·3%)	
Donà et al (2012)[37]	Italy	10/100 (10·0%)	6/83 (7·2%)
Ruanpeng et al (2016)[38]	Thailand	0/19	0/26
Damay et al (2010)[39]	France	2/12 (16·7%)	0/9
Wang et al (2019)[40]	China, Taiwan	0/10	
Overall		983/2895 (34·0%)	138/514 (26·8%)
Heterogeneity		I^2=97·4%; p<0·0001	I^2=95·5%; p<0·0001

Prevalence (%; 95% CI) | Prevalence (%; 95% CI)

Figure 5: **Prevalence of anal HSIL+**
All men included in this analysis had anal cytology results. Studies are ranked in descending order of anal HSIL+ prevalence among HIV-positive MSM, stratified by diagnostic strategy. HPV=human papillomavirus. HRA=high-resolution anoscopy. HSIL+=high-grade squamous intraepithelial lesions or worse. MSM=men who have sex with men. *Only includes participants with HSIL+ plus HPV16-positive swabs.

Kung University, Tainan, Taiwan (C Strong PhD); Department of Internal Medicine, University of Indonesia, Jakarta, Indonesia (E Yunihastuti PhD); Proctology, Diaconesses-Croix Saint Simon Hospital, Paris, France (I Etienney MD); Université de Paris, Assistance Publique–Hôpitaux de Paris, Service de Virologie, Hôpital Bichat, Paris,

HPV infection, which notably indicated a rapid increase in prevalence from the age of 15 years to 24 years.

For HIV-negative MSW, HR-HPV prevalence was low relative to all other risk groups, but nonetheless present (including HPV16) across all age groups. To our knowledge, these data provide the most robust evidence to date on the prevalence of HPV infection in men without established risk factors, highlighting background transmission in the absence of anal sexual intercourse (as observed in women).[41] This is an important concept, given that, because

of population size, HIV-negative MSW still contribute a substantial proportion of anal cancer burden in men at a population level,[42] despite having a low risk at the individual level. HPV vaccination is the only, albeit long-term, solution to anal cancer prevention in HIV-negative MSW. Although gender-neutral vaccination before sexual activity offers maximum protection, girls-only vaccination programmes provide substantial indirect protection (ie, herd immunity) in this low-risk group.[43]

HIV-positive MSW were the least represented risk group in our analysis, particularly those aged younger than 25 years. Nevertheless, for each age group, HPV prevalence was elevated multiple-fold in HIV-positive MSW versus that in HIV-negative MSW, consistent with a worsening effect of HIV on the natural history of HPV (as established in MSM),[8] and resulting increased anal cancer risk.[2] Indeed, HPV infection was associated with low current CD4 cell counts in this study. Of note, half of HIV-positive MSW in this analysis (but none of HIV-negative MSW) were from sub-Saharan Africa, the global epicentre of heterosexual HIV transmission. In HIV endemic settings, the long-term solution to anal cancer prevention in MSW remains direct and indirect protection from HPV vaccination. Nevertheless, our data also high-light how preventing HIV transmission could affect the future burden of male anal cancer in these settings.

Since establishment of the link between anal sexual intercourse and anal cancer risk,[44] MSM have been the focus of anal HPV studies, and all age groups were well represented in this study. For every age category, pooled HPV prevalence was higher in HIV-negative MSM than in HIV-negative MSW, confirming the association with sexuality in immunocompetent men.[45] High HPV exposure was already evident in young HIV-negative MSM, with approximately a quarter of those aged 15–18 years infected with HR-HPV. HPV prevalence increased rapidly with age, reaching a maximum by 23–24 years and remaining constant across older age groups. This pattern contrasts that observed for cervical HPV infection in immunocompetent women, which is characterised by a peak in young women (ie, those aged around 25 years) and a subsequent decline with increasing age.[46] This difference could reflect biological factors (eg, impaired clearance of anal HPV compared with cervical HPV) or behavioural factors (eg, more new partners in older age groups in MSM than in women).[47,48]

Anal HPV prevalence was consistently higher in HIV-positive MSM than in HIV-negative MSM, and this difference was already evident in the youngest men, with approximately half of HIV-positive MSM aged 15–18 years having been infected with HR-HPV. The prevalence of HPV increased rapidly with age, reaching a peak by 25 years. Although a significant decrease in prevalence was subsequently observed at older ages, it remained higher in HIV-positive MSM than in all other risk groups. Additional evidence for the role of HIV-related immuno-suppression on HPV prevalence in MSM from this

	Anal HSIL+ in all MSM (n=12 577)		HPV16-positive anal HSIL+* in all MSM (n=12 577)		Anal HSIL+ in HPV16-positive MSM (n=3409)	
	n/N (%)	aPR (95% CI)	n/N (%)	aPR (95% CI)	n/N (%)	aPR (95% CI)
Age group, years						
15–24	72/794 (9·1%)	0·98 (0·78–1·22)	23/794 (2·9%)	0·76 (0·50–1·17)	23/183 (12·6%)	0·89 (0·62–1·29)
25–34	452/2847 (15·9%)	1 (ref)	200/2847 (7·0%)	1 (ref)	200/847 (23·6%)	1 (ref)
35–44	725/3307 (21·9%)	1·00 (0·91–1·10)	334/3307 (10·1%)	0·99 (0·84–1·17)	334/965 (34·6%)	1·13 (0·99–1·28)
45–54	778/3278 (23·7%)	0·95 (0·86–1·05)	343/3278 (10·5%)	0·90 (0·76–1·07)	343/903 (38·0%)	1·09 (0·95–1·24)
≥55	480/2351 (20·4%)	0·89 (0·79–0·99)†	221/2351 (9·4%)	0·91 (0·75–1·10)	221/511 (43·2%)	1·19 (1·03–1·36)†
Age, per 10 years	··	0·96 (0·94–0·99)†	··	0·97 (0·92–1·02)	··	1·05 (1·01–1·09)†
HIV status						
Negative	314/2785 (11·3%)	1 (ref)	138/2785 (5·0%)	1 (ref)	138/514 (26·8%)	1 (ref)
Positive	2193/9792 (22·4%)	1·54 (1·36–1·73)†	983/9792 (10·0%)	1·66 (1·36–2·03)†	983/2895 (34·0%)	1·19 (1·04–1·37)†

PRs were adjusted for study, age group, and HIV status, as appropriate. aPR=adjusted prevalence ratio. HPV=human papillomavirus. HSIL+=high-grade squamous intraepithelial lesions or worse. MSM=men who have sex with men. *Only includes participants with HSIL+ plus HPV16-positive swabs. †Significant aPRs relative to the reference group.

Table: Prevalence of anal HSIL+ in MSM

Figure 6: Prevalence of anal HPV16 infection and anal HSIL+
PRs were adjusted for age group and study. Error bars show 95% CIs. aPR=adjusted prevalence ratio. HPV=human papillomavirus. HSIL+=high-grade squamous intraepithelial lesions or worse. MSM=men who have sex with men. *Significant aPRs relative to the reference group. †Only includes participants with HSIL+ plus HPV16-positive swabs.

France (V M Ferré PharmD);
Decision Science in Infectious Disease Prevention, Control and Care, INSERM, Université de Paris, Paris, France (V M Ferré); School of Public Health (Shenzhen), Sun Yat-sen University, Shenzhen, China (Prof H Zou); School of Public Health, Shanghai Jiao Tong University, Shanghai, China (Prof H Zou); Melbourne Sexual Health Centre, Sydney, NSW, Australia (Prof H Zou); Pathogenesis and Control of Chronic Infections, INSERM, CHU, University of Montpellier, Montpellier, France (M Segondy PhD); Department of Surgery, College of Health Sciences University of Zimbabwe, Harare, Zimbabwe (S Chinyowa PhD)

Correspondence to:
Dr Gary M Clifford, Early Detection, Prevention and Infections Branch, International Agency for Research on Cancer (IARC/WHO), Lyon 69372, France
cliffordg@iarc.fr

See Online for appendix

analysis, is the significantly higher prevalence of HPV16 in MSM with low versus high current CD4 cell counts and in those with high versus low HIV viral loads.[49]

In recognition of their elevated anal cancer risk and possible absence of herd immunity from girls-only vaccination programmes, some countries recommend

targeted HPV vaccination of MSM. Nevertheless, given the absence of vaccine efficacy against previous HPV infection, the cost-benefit ratio of vaccination in this heavily exposed population decreases with age. For example, as HPV16 reaches peak prevalence by the age of 22–24 years, the incremental benefit of HPV vaccination might be expected to be minimal at older ages. Indeed, a clinical trial published in 2018, did not find effectiveness of HPV vaccine against anal HPV infection in HIV-infected adults aged 27 years or older.[50] The potential limitation of a targeted approach for MSM is further highlighted by the high rate of current HPV detection, even in the youngest men who identify as homosexual, and in whom cumulative exposure (ie, including cleared and current infections) is expected to be even higher.[51] Indeed, a large proportion of future anal cancers among young MSM are expected to occur among those with prevalent HPV16 infection. Hence, gender-neutral vaccination before sexual activity, rather than a targeted approach, is the long-term solution to anal cancer prevention for future generations of MSM, irrespective of HIV status.[52]

Current generations of MSM and HIV-positive men remain at high risk of anal cancer and could benefit from secondary prevention measures. In this report, we describe the epidemiology of anal HSIL in studies with concurrent assessment of cytology or histology, which, given the greater clinical imperative, tend to focus on HIV-positive MSM. Notably, however, even in this high-risk group with ubiquitously high HR-HPV infection, we observed wide variation in HSIL prevalence. Some of this heterogeneity could be explained by differences in the diagnostic strategy used between studies, with the lowest prevalence of anal HSIL+ observed between studies that used cytology only, consistent with reports of lower sensitivity for cytology versus high-resolution anoscopy-directed biopsy to diagnose HSIL.[53] However, study-specific heterogeneity remained even in those that used high-resolution anoscopy in all participants, highlighting variability in the performance of this technique. Indeed, high-resolution anoscopy is a difficult technique characterised by a long learning period,[54,55] for which international standards were published only relatively recently, in 2016.[56] Further support for differences in HSIL ascertainment, rather than underlying differences in risk, came from the observations that study-specific differences in HSIL were closely mirrored in HIV-negative MSM, and also when restricted to HPV16-positive MSM only (a homogeneously high-risk group of MSM).

We chose to study patient-level determinants (eg, HIV status and age) of HSIL+ outcomes in MSM, with a focus on relative, rather than absolute risk, and with adjustment by study. These analyses support HIV infection as a risk factor for HSIL in MSM.[8] Further evidence for the worsening effect of HIV-related immunosuppression on HSIL came from the association between HSIL prevalence and low current CD4 cell counts. This finding highlights the potential effect of wider and earlier use of combined antiretroviral therapy (ART) to reduce risk of HSIL in HIV-positive populations.[49]

Recognising the unique anal carcinogenicity of HPV16, the novelty and power of our approach was to combine HSIL outcomes with concurrent HPV16 data. This combined analysis showed that HIV infection was associated with an increased risk of HPV16-positive HSIL, the most severe known anal cancer precursor that has a higher potential for persistence and for progression to cancer than HSIL with other HR-HPV types.[5,57] Even when restricted to HPV16-positive MSM, HIV infection (and low CD4 cell counts in HIV-positive MSM) conferred a significantly higher risk for HSIL compared with those who were HIV negative. Conversely, we found no evidence that nadir CD4 cell count affected the risk of HPV16-positive HSIL, and only a weak association between HPV16-positive HSIL risk with increasing age was observed. This result somewhat contrasts that for anal cancer risk, which is significantly associated with nadir CD4 cell count and increases significantly with age,[2,49] suggesting that not all prevalent HSIL (not even all HPV16-positive HSIL) are equally likely to progress to anal cancer, consistent with the report of increased spontaneous regression of HSIL observed in young MSM (those aged ≤35 years).[58]

Limitations of our analysis should be noted. We focused on characteristics associated with robust evidence on anal cancer risk that are pragmatic targets for public health programmes (ie, HIV status, sexuality, and age). Detailed sexual practices, for which data are less easily obtainable than for the included characteristics, were beyond the scope of our study. Nevertheless, studies of HIV-negative MSM could include important remaining heterogeneity, in terms of sexual behaviour, because of the over-representation of HIV-negative MSM recruited from sexual health clinics who are at higher risk of anal HPV infection than the whole HIV-negative MSM population.[10] Indeed, the higher prevalence of HR-HPV in HIV-negative MSM from studies with cytopathology compared with those without cytopathology supports such selection bias, which could partly explain why age-specific anal HR-HPV prevalence was higher in HIV-negative MSM than in HIV-positive MSW, whereas relative anal cancer incidence appears to show an opposite pattern.[2] External representativeness and internal consistency is expected to be better for HIV-positive MSM (who have a ubiquitously high risk and are recruited mainly from HIV treatment clinics) and HIV-negative MSW (who are predominantly recruited using community-based approaches). Time-dependent variables of duration of ART and immunosuppression, which are not typically available in studies, nor for pragmatic clinical decisions, were also beyond the scope of our study. For studies with HPV vaccination data,[11,15,22,30,59] we excluded the few vaccinated men. Furthermore, combinations of age and country or calendar year of study

recruitment preclude widespread HPV vaccination in other studies; therefore, we consider this analysis to represent HR-HPV prevalence in the absence of HPV vaccination. There were also insufficient data to allow robust comparison of age-specific prevalence within risk groups by region or other study-specific variables.

We addressed the major limitation of variability in HSIL ascertainment by adjusting relative risk estimates at an individual study level. We also did sensitivity analyses, which did not materially change the findings for MSM. By contrast, this problem did preclude the interpretation of HSIL outcomes by HIV status in MSW, for which data were too scarce to allow appropriate adjustment. Finally, we relied on a pragmatic definition of HPV16-positive HSIL, combining HPV16 obtained from anal swabs with the presence of composite HSIL, as detected from anal swabs or biopsies. Hence, we cannot establish true causality of HPV16 to HSIL, which, given the widespread multiplicity of HR-HPV highlighted by our analysis, would require laser capture microdissection of biopsies.[60] For these reasons, we did not report on HSIL positive for non-HPV16 HR-HPV types, for which the causal links to anal cancer are less well established.[5]

Finally, findings from this pooled analysis can inform future anal screening efforts that involve HPV testing. Firstly, the results highlight the paucity of useful clinical stratification offered by testing 13 HR-HPV types defined as carcinogenic in the cervix; three quarters of HIV-positive MSM and half of HIV-negative MSM would test positive and require follow-up, despite the absence of strong evidence for anal carcinogenicity of non-HPV16 HR-HPV types. In a more specific approach of screening for HPV16 only, 20–30% of adult HIV-positive MSM and 10–15% of HIV-negative MSM would be positive at a single timepoint. If these men were referred for high-resolution anoscopy, our findings suggest that more than half could have HSIL, irrespective of HIV status, even if not all cases of HSIL would progress to cancer. Further improvements to risk stratification in high-risk men are therefore necessary, of which the most promising approaches include assessment of persistent, rather than prevalent, anal HPV16 infection[57] or host methylation markers, which could have additional potential to prevent the few anal cancers caused by non-HPV16 HR-HPV types.[61,62]

Contributors
GMC initiated and coordinated the study. FW and CJA collected and analysed the data. All other authors generated the data from the 62 original studies and contributed to the interpretation of the analysis. FW and GMC had full access to and verified all the data in the study. FW and GMC wrote the first draft of the manuscript. All authors provided input, approved the final manuscript, and had final responsibility for the decision to submit for publication.

Declaration of interests

Data sharing
The data used for this analysis cannot be shared publicly because of legal and ethical requirements regarding the resharing of data from included studies. Researchers can request access to the summarised data from the corresponding author.

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