Incidence and clearance of anal human papillomavirus infection in 16 164 individuals, according to HIV status, sex, and male sexuality: a collaborative pooled analysis of 34 longitudinal studies

Authors: Feixue Wei (PhD)[1], Marc T Goodman (PhD)[2], Ningshao Xia[3], Jun Zhang (MSc)[3], Anna R Giuliano (PhD)[4], Gypsyamber D'Souza(PhD)[5], Nancy A Hessol (MSPH)[6], Maarten F Schim van der Loeff (PhD)[7], Jianghong Dai (PhD)[8], Karin Neukam (PhD)[9], Alexandra de Pokomandy (MDCM)[10], I Mary Poynten (PhD)[11], Ronald B Geskus (PhD)[12,13], Joaquin Burgos (PhD)[14], Isabelle Etienney (MD)[15], Anna-Barbara Moscicki (MD)[16], Maria Gabriella Donà (PhD)[17], Maura L Gillison (PhD)[18], Alan G Nyitray (PhD)[19], Rebecca G Nowak (PhD)[20], Evy Yunihastuti (PhD)[21], Huachun Zou (PhD)[22,23], Carmen Hidalgo-Tenorio (PhD)[24], Nittaya Phanuphak (MD)[25], Jean-Michel Molina[26], Alice M Schofield (MD)[27], Stephen Kerr (PhD)[28], Song Fan (PhD)[29], Yong Lu (PhD)[30], Jason J Ong (PhD)[31], Admire T Chikandiwa (PhD)[32], Sirinya Teeraananchai (PhD)[33], Nicola Squillace (MD)[34], Dorothy J Wiley (PhD)[35], Joel Palefsky (PhD)[36], Damien Georges (MSc)[1], Catharina J Alberts (PhD)[1], Gary M Clifford (PhD)[1*]

Author affiliations:

[1]Early Detection, Prevention and Infections Branch, International Agency for Research on Cancer (IARC/WHO), Lyon, France;

[2]Cancer Prevention and Control Program, Cedars Cancer, Cedars-Sinai Medical Center, Los Angeles, CA, USA;

[3]State Key Laboratory of Molecular Vaccinology and Molecular Diagnostics, National Institute of Diagnostics and Vaccine Development in Infectious Diseases, School of Public Health, Xiamen University, Xiamen, Fujian, China;

[4]Center for Immunization and Infection Research in Cancer (CIIRC), Moffitt Cancer Center, Tampa, FL, USA;

[5]Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA;

[6]Department of Clinical Pharmacy, University of California San Francisco, CA, USA;

[7]Department of Infectious Diseases, GGD Amsterdam, Amsterdm, Netherlands;

[8]School of Public Health, Xinjiang Medical University, Xinjiang, Urumqi, China;

[9]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;

[10]Chronic Viral Illness Service, McGill University Health Centre and Department of Family Medicine, McGill University, Montreal, Quebec, Canada;

[11]The Kirby Institute, University of New South Wales, Kensington, Sydney, New South Wales, Australia;

[12]Oxford University Clinical Research Unit, Ho Chi Minh City, Vietnam;

[13]Centre for Tropical Medicine and Global Health, University of Oxford, Oxford, UK;

[14]Infectious Diseases Department, Hospital Universitari Vall d'Hebron, Vall d'Hebron Institut de Recerca (VHIR), Universitat Autónoma de Barcelona, Barcelona, Spain;

[15]Proctology, Diaconesses-Croix Saint Simon Hospital, Paris, France;

[16]Department of Pediatrics, University of California, Los Angeles, CA, USA;

[17]Sexually Transmitted Infections (STI)/HIV Unit, San Gallicano Dermatological Institute IRCCS, Rome, Italy;

[18]Thoracic Head and Neck Medical Oncology Department, University of Texas MD Anderson Cancer Center, Houston, TX, USA;

[19]Center for AIDS Intervention Research and Clinical Cancer Center, Medical College of Wisconsin, Milwaukee, WI, USA;

[20]Institute of Human Virology, University of Maryland School of Medicine, Baltimore, MD, USA;

[21]Faculty of Medicine Universitas Indonesia/Cipto Mangunkusumo Hospital, Jakarta, Indonesia;

[22]School of Public Health (Shenzhen), Sun Yat-sen University, Shenzhen, China;

[23]Kirby Institute, University of New South Wales, Sydney, Australia;

[24]Early Clinical Trial Unit. Biosanitary Institute (IBS.Granada). Infectious Diseases Unit. University Hospital Virgen de las Nieves, Granada, Spain;

[25]Institute of HIV Research and Innovation, Bangkok, Thailand;

[26]University of Paris Cité, Department of Infectious diseases, St-Louis hospital, Paris, France;

[27]Institute of Cancer Sciences, The University of Manchester, Manchester, UK;

[28]HIV-NAT, Thai Red Cross AIDS Research Centre, and Research Affairs, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand;

[29]School of Public Health, Southwest Medical University, Luzhou, China;

[30]School of Public Health, the Key Laboratory of Environmental Pollution Monitoring and Disease Control, Ministry of Education, Guizhou Medical University, Guiyang, China;

[31]Central Clinical School, Monash University, Melbourne, Australia;

[32]Wits RHI, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa;

[33]Department of Statistics, Faculty of Science, Kasetsart University, Bangkok, Thailand;

[34]Infectious Diseases Unit ASST-Monza, San Gerardo Hospital-University of Milano-Bicocca, Monza, Italy;

[35]School of Nursing, University of California, Los Angeles, CA, USA;

[36]Department of Medicine, University of California, San Francisco, CA, USA.

[*]**Corresponding author:** Dr. Gary M Clifford, Early Detection, Prevention and Infections Branch, International Agency for Research on Cancer (IARC/WHO), 150 cours Albert Thomas, 69372 Lyon Cedex 08, France. Tel.: +33-472738425; E-mail: cliffordg@iarc.fr

Short title: Anal HPV incidence and clearance by sex, HIV status, and male sexuality

Main text word count (3500 max): 3497

Abstract word count (250 max): 250

Number of references (30 max): 30

Tables: 1; **Figures:** 4

Appendix: Search strategy: 1; Model description: 1; Appendix tables: 3; Appendix figures: 6

Abbreviations:

ASCC, anal squamous cell carcinomas; CTMM, continuous-time Markov model; HPV, human papillomavirus; hrHPV, high-risk human papillomavirus; HR, hazard ratio; HSIL, high-grade squamous intraepithelial lesion; MSM, men who have sex with men; MSMLWH, MSM living with HIV; MSW, men who have sex with women; MSWLWH, MSW living with HIV; PLWH, people living with HIV; WLWH, women living with HIV.

E-mails (authors):

Feixue Wei: WeiF@iarc.fr

Marc T Goodman: marc.goodman@cshs.org

Ningshao Xia: nsxia@xmu.edu.cn

Jun Zhang: zhangj@xmu.edu.cn

Anna R Giuliano: anna.giuliano@moffitt.org

Gypsyamber D'Souza: gdsouza2@jhu.edu

Nancy A Hessol: nancy.hessol@ucsf.edu

Maarten F Schim van der Loeff: mschim@ggd.amsterdam.nl

Jianghong Dai: epi102@sina.com

Karin Neukam: karin.neukam@gmail.com

Alexandra de Pokomandy: alexandra.depokomandy@mcgill.ca

I Mary Poynten: mpoynten@kirby.unsw.edu.au

Ronald B Geskus: rgeskus@oucru.org

Joaquin Burgos: jburgos@vhebron.net

Isabelle Etienney: ietienney@hopital-dcss.org

Anna-Barbara Moscicki: amoscicki@mednet.ucla.edu

Maria Gabriella Donà: mariagabriella.dona@ifo.it

Maura L Gillison: MGillison@mdanderson.org

Alan G Nyitray: anyitray@mcw.edu

Rebecca G Nowak: rnowak@ihv.umaryland.edu

Evy Yunihastuti: evy.yunihastuti@gmail.com

Huachun Zou: zouhuachun@mail.sysu.edu.cn

Carmen Hidalgo-Tenorio: chidalgo72@gmail.com

Nittaya Phanuphak: nittaya.p@ihri.org

Jean-Michel Molina: jean-michel.molina@aphp.fr

Alice M Schofield: alice.schofield12@nhs.net

Stephen Kerr: skerr@kirby.unsw.edu.au

Song Fan: fansong@swmu.edu.cn

Yong Lu: luyong@gmc.edu.cn

Jason J Ong: doctorjasonong@gmail.com

Admire T Chikandiwa: achikandiwa@gmail.com

Sirinya Teeraananchai: sirinya.te@ku.th

Nicola Squillace: n.squillace@asst-monza.it

Dorothy J Wiley: dwiley@sonnet.ucla.edu

Joel Palefsky: joel.palefsky@ucsf.edu

Damien Georges: georgesd@iarc.fr

Catharina J Alberts: albertsc@iarc.fr

Research in context

Evidence before this study

We searched MEDLINE and Embase for studies on anal human papillomavirus (HPV) infection or anal cancer from 1, January, 1986 to 31, January, 2022. A recent meta-analysis describing anal cancer incidence showed that the key determinants of anal cancer at the population level were HIV status, sex, and male sexuality. Another meta-analysis showed HPV positivity to increase with severity of anal cytopathological diagnosis, especially for HPV16, which was the most carcinogenic HPV type in the anus. A subsequent collaborative pooled analyses using cross-sectional individual-level data indicated that anal HPV16 prevalence varies greatly by risk group, ranging from 2% in HIV-negative men who have sex with women (MSW) to 30% in men who have sex with men (MSM) living with HIV (LWH) [MSMLWH]. Prior longitudinal studies have described the incidence and clearance rates of anal HPV infection. However, these studies tended to focus on specific risk groups (e.g., MSM, people LWH) and used different study designs (e.g. duration and frequency of follow-up intervals) and statistical approaches, which hamper the direct comparison of anal HPV incidence and clearance rates within and between risk groups from different studies.

Added value of this study

We performed a collaborative re-analysis of individual-level longitudinal data from 34 different studies with 16 164 individuals and 56 048 visits, analysed by a two-state continuous-time Markov model developed to allow the standard analysis of studies of different duration and follow-up frequency. This analysis provides, for the first time, a unified picture of incidence and clearance of type-specific anal high-risk HPV (hrHPV) infection across six different risk groups: MSMLWH, HIV-negative MSM, women LWH (WLWH), HIV-negative women, MSWLWH, and HIV-negative MSW. Compared to other hrHPV, HPV16 tends to have the highest incidence:clearance ratio across six risk groups, supporting its unique carcinogenic potential at the anus. The groups at risk of anal HPV16 incidence were, in decreasing order, MSMLWH, HIV-negative MSM, WLWH, HIV-negative women, MSWLWH, and HIV-negative MSW. The reverse order of risk group was found when

comparing anal HPV16 clearance. The association between anal sex behaviour (i.e., ever having receptive anal sex, number of anal sexual partners) with anal HPV16 incidence was observed among MSM, but not among women, highlighting the important differences in modes of anal HPV acquisition in these two population groups. In each risk group, clearance of incident anal hrHPV infection was higher than that of prevalent HPV infection. Furthermore, age-specific differences in anal hrHPV clearance were observed in MSM. The fact that these differences were found for prevalent, but not incident, infection suggests that age-specific differences are likely driven by the prior duration of HPV infection rather than the age of the infected individuals.

Implications of all the available evidence

Robust estimates of absolute and relative measures of anal hrHPV incidence and clearance inform the understanding of the natural history of anal hrHPV infection across different risk groups. These data are key to the development of anal cancer prevention strategies and prediction of the impact of these strategies, particularly in high-risk groups such as MSM and people LWH. Our findings provide essential input to inform the population-level impact of primary anal cancer prevention (HPV vaccination) as well as facilitate the evaluation of secondary prevention (HPV-based screening). Of note, this work suggests that the carcinogenic potential of longstanding prevalent anal hrHPV infection is higher than that of more recent incident infection.

7

Abstract

Background Understanding the natural history of anal high-risk human papillomavirus (hrHPV) infection is key for designing anal cancer prevention programmes but has not been systematically characterised.

Methods We reanalysed data from 34 studies with 16 164 individuals in six risk groups defined by HIV status, sex, and male sexuality: men who have sex with men (MSM) living with HIV (LWH) [MSMLWH], HIV-negative MSM, women LWH (WLWH), HIV-negative women, men who have sex with women (MSW) LWH (MSWLWH), and HIV-negative MSW. We used Markov models to estimate incidence and clearance of 13 hrHPV types and their determinants.

Findings HPV16 had the highest incidence:clearance ratio of the hrHPV types. MSMLWH had highest hrHPV incidence (e.g. 15·5% newly HPV16-infected within two years), followed by HIV-negative MSM (7·5%), WLWH (6·6%), HIV-negative women (2·9%), MSWLWH (1·7%), and HIV-negative MSW (0·7%). Determinants of HPV16 incidence included HIV status and number of sexual partners for MSM, women, and MSW, and anal sex behaviour for MSM only. HPV16 clearance was lower for people LWH (PLWH), and lower for prevalent than incident infection. Among MSM, increasing age was associated with lower clearance of prevalent, but not incident, HPV16 infection.

Interpretation This robust and unifying pooled analysis of anal hrHPV natural history is essential to designing and predicting the impact of HPV vaccination and HPV-based screening programmes on anal cancer prevention, particularly in MSM and PLWH. Importantly, it suggests the higher carcinogenic potential of longstanding prevalent hrHPV infection than more recent incident infection.

Funding International Agency for Research on Cancer.

Keywords: HPV; HIV; anus; incidence; clearance

Introduction

Of 29 000 high-risk human papillomavirus (hrHPV)-attributable anal squamous cell carcinomas (ASCC) estimated to be diagnosed worldwide each year, 10 000 occur in men and 19 000 in women.[1] ASCC risk is low in the general population (1-2 cases per 100 000 person-years), but is known to be elevated in certain sub-groups, such as HIV-negative men who have sex with men (MSM) (~20), women living with HIV (LWH) [WLWH) (~30), men who have sex with women (MSW) LWH [MSWLWH] (~30), and most notably MSMLWH (~100).[2]

Anal hrHPV infection is the etiologic agent for ASCC and HPV16 is the most carcinogenic type among both HIV-negative people and people LWH (PLWH).[3] Differences in ASCC incidence by risk group are likely driven by variations in the underlying natural history of anal hrHPV(16) infection, through increased anal hrHPV(16) incidence, known to be heavily influenced by sexual behaviour,[4] or decreased anal hrHPV(16) clearance, known to be worsened by immune dysfunction related to HIV infection.[5]

Robust estimates of type-specific anal hrHPV incidence and clearance by risk group are essential to designing and predicting the population-wide impact of HPV-based ASCC prevention programmes targeted to high-risk groups. These programmes include primary prevention through HPV vaccination, as well as secondary prevention through, for example, HPV(16)-based screening algorithms, somewhat analogous to cervical cancer screening.

Many longitudinal studies have reported the natural history of anal HPV infection, focussing on specific risk groups (appendix pp 5-6). However, heterogeneity in study design, such as duration and follow-up intervals, differences in analytic definitions of incidence and clearance,[6] as well as relatively small sample sizes and number of events, hamper comparisons within and across risk groups, limiting their applicability to inform risk-targeted anal cancer prevention interventions.

Thus, we aimed to provide a robust, unified estimate of incidence and clearance of anal hrHPV infection within and across risk groups stratified by HIV status, sex, and male sexuality. We performed a collaborative-pooled re-analysis of individual-level longitudinal data, underpinned by a

9

statistical methodology allowing the pooling of data across studies of different duration and follow-up intervals.

Methods

Data collection

We conducted a systematic literature review on studies reporting on the incidence or clearance of anal HPV infection, by searching MEDLINE and Embase for studies published between 1 January, 1986 and 31 January, 2022, using the following terms: ("papillomaviridae" OR "papillomavirus" OR "HPV") AND ("anal canal" OR "anus" OR "anal") AND ("inciden*" OR "acqui*" OR "clear*" OR "persist*") (appendix p 2). Studies were eligible if they used polymerase chain reaction-based assays to detect type-specific HPV DNA (at least for HPV16) from anal samples collected from men or women at multiple time points.

Authors of eligible studies were invited to share de-identified individual-level data on the following variables: 1) HIV status, 2) sex, 3) male sexuality (MSW or MSM), 4) age; and for each eligible study visit: 5) date and 6) type-specific anal HPV result. Additional variables were also shared, if available, either from study entry (anal cytological diagnosis, anal histological diagnosis, lifetime number of sexual partners, ever having receptive anal sex, current smoking) or from each visit (recent number of sexual partners, recent number of anal sexual partners, HPV vaccination status, current CD4+ count, and current HIV viral load).

Data analysis

A two-state (HPV-negative and HPV-positive) continuous-time Markov model (CTMM) was used to estimate the pooled incidence rate (defined as the transmission rate from HPV-negative to HPV-positive) and clearance rate (defined as the transmission rate from HPV-positive to HPV-negative) of anal HPV infection. This model was well-suited for the current pooled analysis since it allows individuals to switch between the two states at any point in time, not only at the time of the visit when HPV was tested. Estimating the constant transmission rate addresses three issues: i) the nature of interval-censored data on HPV status, namely the time of the visit does not capture the exact time of

incidence or clearance of an infection; ii) the variability in HPV visit intervals for individuals within studies, and iii) the variability in visit interval protocols across studies. Importantly, clearance rates were estimated separately for infection that was detected at baseline (prevalent infection) or at follow-up visit (incident infection), by generating a co-variable 'infection type'. For more details on the CTMM and assumptions refer to appendix pp 3-4.

We ran separate CTMMs for 13 individual hrHPV type (HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68) (Group 1/2A, IARC),[7] by using HIV status (negative and positive), population (MSM, women, and MSW), age group (<25, 25–34, 35–44, 45–54, and ≥55 years) and infection type (prevalent and incident) as co-variables. This allowed post-estimation of type-specific incidence and clearance rates, expressed as events per 1000 person-months, in six risk groups (MSMLWH, HIV-negative MSM, WLWH, HIV-negative women, MSWLWH, and HIV-negative MSW), as well as incidence:clearance ratio and mean infection duration for the 13 hrHPV types.

Other outputs were also estimated using CTMM, with a focus on HPV16. First, hazard ratios of risk factors of HPV16 incidence and clearance were evaluated, with adjustment for HIV status, age group, and (for HPV clearance only) infection type. Individuals with missing data for a given risk factor were excluded from analyses for that risk factor. Second, the cumulative probability of HPV16 incidence and clearance up to two years was estimated by six risk groups and, for MSM and women, stratified by HIV status and age group. Last, we estimated the prevalence of HPV16 among MSM and women at two years post-baseline, according to HIV status, infection type (as a surrogate for infection duration: prevalent infection equate to ≥2 years duration and incident infection to <2 years) and, for MSM only, age group.

R (version 4.0.3, http://www.r-project.org, R Core Team 2021) was used for all analyses and CTMM was fitted by using the multi-state modelling package.[8]

Results

The systematic review identified 48 eligible longitudinal studies with 25 238 individuals, of which 34 studies with 21 069 individuals (83·5%) contributed data to the pooled individual-level dataset

(appendix p 10). Among the 21 069 individuals, 16 164 (76·7%) had at least two valid anal HPV results (contributing a total of 56 048 eligible visits), and were included in analyses, of which 29·4% were MSMLWH (n=4745), 24·0% HIV-negative women (n=3877), 21·4% HIV-negative MSM (n=3459), 16·6% HIV-negative MSW (n=2691), 6·6% WLWH (n=1062), and 2·0% MSWLWH (n=330) (appendix pp 5-8). The median number of visits per individual was 3·0 (interquartile range: 2·0-4·0). Median follow-up time was 1·4 (interquartile range: 1·0-2·5) years. Characteristics of included studies and individuals are shown in appendix pp 5-8.

Anal HPV16 incidence was highest in MSMLWH (14·8 per 1000 person-months, 95%CI 13·5–16·1), followed by HIV-negative MSM (9·1, 8·2–10·1), WLWH (7·9, 6·9–9·1), HIV-negative women (4·9, 4·3–5·6), MSWLWH (3·2, 2·1–5·0), and HIV-negative MSW (2·0, 1·3–3·1) (figure 1A). For anal HPV16 clearance, the same ranking by risk group was observed, being lowest in MSMLWH (61·5 per 1000 person-months, 95%CI 55·6–67·9), then HIV-negative MSM (95·5, 86·0–106·0), WLWH (96·2, 84·7–109·3), HIV-negative women (149·5, 130·7–170·9), MSWLWH (170·4, 125·2–231·8), and HIV-negative MSW (264·6, 193·9–361·0) (figure 1B). Similar patterns by risk group tended to be observed for incidence and clearance of all other hrHPV types.

Incidence:clearance ratios are shown for all hrHPV types by risk group in figure 2. HPV16 tended to have the highest incidence:clearance ratio of all hrHPV types, a pattern which was most evident among MSMLWH, HIV-negative MSM, WLWH, and HIV-negative women.

Of the 16 750 hrHPV infections observed during the study period, a greater proportion were prevalent (n=11 356) than incident (n=5394) infection, both overall and in each risk group (appendix p 11). The mean duration of prevalent infection was longer than incident infection (appendix p 12). For HPV16, for example, mean durations for prevalent and incident infection were 3·8 (3·5–4·1) versus 1·2 (1·1–1·4) years in MSMLWH; 2·2 (1·9–2·4) versus 0·8 (0·7–1·0) in HIV-negative MSM; 2·5 (2·0–3·1) versus 0·7 (0·6–0·8) in WLWH; and 0·8 (0·6–0·9) versus 0·5 (0·4–0·6) in HIV-negative women. Infections were too few to allow this type of analysis for MSW (appendix p 11).

The influence of risk factors on HPV16 incidence and clearance for MSM, women, and MSW is described in table 1. HPV16 incidence was significantly higher in younger people, HIV-positivity,

and high (lifetime and recent) number of sexual partners among the three populations, and in current smokers among MSM and women. Ever having receptive anal sex and high (lifetime and recent) number of anal sexual partners were significantly associated with higher HPV16 incidence in MSM, but not in women. Lower CD4 and higher HIV viral load were associated with HPV16 incidence among MSMLWH and WLWH, although differences were not always statistically significant.

Among the three populations, HPV16 clearance was significantly lower in PLWH than in HIV-negative people (table 1). For both MSM and women, clearance of HPV16 incident infection was significantly higher than that of prevalent infection. Older age and presence of anal HSIL at baseline were associated with lower clearance in MSM. HIV viral load was significantly associated with lower clearance in MSMLWH, and a consistent non-significant association was observed in WLWH.

Two-year cumulative HPV16 incidence in MSMLWH was 15·5% (14·6%–16·6%), in HIV-negative MSM 7·5% (6·9%–8·3%), WLWH 6·6% (5·8%–7·4%), HIV-negative women 2·9% (2·5%–3·3%), MSWLWH 1·7% (1·2%–2·4%), and HIV-negative MSW 0·7% (0·5%–1·0%) (figure 3A). Cumulative HPV16 incidence was higher in youngest MSMLWH (figure 3D) and HIV-negative women (appendix p 13), but the age effect was less clear for HIV-negative MSM (figure 3G) and WLWH (appendix p 13).

After 2 years, HPV16 prevalent infection persisted in 58·6% MSMLWH, in WLWH (42·7%), HIV-negative MSM (35·7%), HIV-negative women (19·4%), MSWLWH (15·3%), and in HIV-negative MSW (2·7%) (figure 3B). For each of these risk groups, respective 2-year persistence for incident infection was lower, namely 30·6%, 10·2%, 15·4%, 3·6%, 4·6%, and 1·2% (figure 3C). There was a strong relationship between age and persistence of HPV16 prevalent infection, both for MSMLWH and HIV-negative MSM (figure 3E and 3H), but not for incident infection (figure 3F and 3I). There were no differences in clearance of prevalent or incident HPV16 infection by age in WLWH or HIV-negative women (appendix p 13).

Figure 4 describes HPV16 prevalence as estimated by CTMM at 2 years after baseline, stratified by duration of infection. Among MSMLWH, HPV16 prevalence peaked at 25-34 years and

decreased with age (figure 4A). Age-specific HPV16 prevalence in HIV-negative MSM was lower than in MSMLWH and increased with age (figure 4B). Of note, the relative proportion of HPV16 infection with a duration ≥2 years (i.e. already prevalent at baseline) increased from 38% at age <25 years to 69% at age ≥55 years in MSMLWH (figure 4D), and from 13% (<25 years) to 68% (≥55 years) in HIV-negative MSM (figure 4E). Among women (for whom we observed no apparent age effect), the estimated HPV16 prevalence was higher in WLWH than in HIV-negative women (figure 4C), and the relative proportion of HPV16 infection with a duration ≥2 years was higher in WLWH (46%) than in HIV-negative women (11%) (figure 4F).

Discussion

This pooled re-analysis of individual-level longitudinal anal hrHPV data from 34 studies including 16 164 individuals built a robust, unified picture of the natural history of anal hrHPV infection across six ASCC risk groups. The current work overcame the issue of incidence and clearance rates not being directly comparable between previous reports due to inconsistencies in design and analytical approaches. We confirmed that HIV status, sex, and male sexuality are important population-level determinants of both anal hrHPV incidence and clearance. We clarified the important differences in mode of anal hrHPV acquisition for men versus women. In all risk groups, clearance of incident anal hrHPV infection was higher than that of prevalent infection. Age-specific differences in hrHPV clearance in MSM were predominantly observed for prevalent not incident infection, suggesting that age-specific differences are more likely linked to duration of HPV infection rather than age of the infected individuals.

Compared to other hrHPV types, HPV16 had the highest incidence:clearance ratio and longest infection duration, at least in MSM and women, as previously reported.[4,9,10] This finding could explain why HPV16 was the most prevalent type detected at the anus, both at baseline in our pooled dataset (appendix p 14), as well as in other studies,[11,12] and support the uniquely high potential of anal HPV16 infection to progress to ASCC in comparison to other hrHPV types.[3] Of note, HPV18

incidence:clearance ratio was no different from many other hrHPV types, corroborating evidence that the carcinogenicity of HPV18 in the anus is not as apparent as in the cervix.[1]

Most previous individual reports on anal hrHPV natural history have not been powered to separate clearance of prevalent infection from incident infection. Furthermore, prevalent hrHPV infection is not homogeneous, but is rather a mixture of antecedent natural histories. Prevalent infection may be recently acquired, like incident infection, or be longstanding and likely to have greater oncogenic potential. Indeed, using a similar CTMM approach, Plummer et al found that the longer a cervical hrHPV infection had persisted, the greater the probability that it would further persist.[13] In current study, we were able to provide robust evidence of the same tendency in the anus. First, incident anal HPV infection was shown to clear significantly faster than prevalent infection, consistently for all hrHPV types and across different risk groups, as previously reported.[9,14] Further, in MSM, irrespective of HIV status, prevalent HPV16 infection was more likely to clear in the young than at older ages. This finding is consistent with the higher cervical HPV infection clearance observed in young women,[15] and is expected to be related to differences in prior duration of infection by age. Indeed, our CTMM approach demonstrated that prevalent infection in older MSM is disproportionately represented by longstanding infection. The absence of an age effect on clearance of incident HPV16 infection also suggests that differences are driven by the duration of the infection rather than by age. On a similar note, the observation of a lower clearance of prevalent HPV16 infection in MSM than in women or MSW (even after adjustment for HIV status and age, appendix p 9) suggests that prevalent infection in MSM is more likely to represent longstanding persistent infection, and hence to have greater oncogenic potential than that detected in women and MSW of a similar age.

HIV-positivity was confirmed as an important risk factor for anal HPV16 incidence and clearance among all three populations, consistent with the evidence that PLWH have higher HPV prevalence and ASCC risk than their HIV-uninfected counterparts.[2,11] Additional evidence for the role of HIV-related immunosuppression on the natural history of anal HPV infection in this study comes

from the observation that CD4 and HIV viral load were determinants of anal HPV16 incidence and clearance in PLWH.

Having anal HSIL at baseline was a strong risk factor for lower HPV16 clearance in MSM, highlighting the strong causal link between HPV16 and anal HSIL.[3,16] Indeed, presence of underlying HSIL may even partially contribute to the lower HPV16 clearance observed in older MSM. Current smoking, on the other hand, was significantly associated with higher anal HPV16 incidence, likely reflecting confounding by sexual behaviour, but corroborating evidence that anal cancer is elevated among smokers.[17]

This pooled analysis highlighted important differences in anal HPV16 acquisition through sex. Generic number of sexual partners, whether lifetime or recent, was confirmed as a strong determinant of anal HPV16 incidence in both MSM and women. Number of anal sexual partners, on the other hand, was strongly associated with HPV16 incidence only in MSM, with no evidence of such associations in women, despite adequate sample sizes. This suggests that anal HPV16 incidence is similar in women having anal sexual intercourse or not, and supports other lines of evidence that anal HPV is frequently acquired from the cervix/external genital region via auto- or partner-assisted inoculation. These include strong correlations in type-specific HPV detection between genitals and anus among women[18] (and MSW[19]), as well as the associations between front-to-back post-toilet wiping or anal touching with female anal HPV infection.[20,21] Furthermore, a majority of women with ASCC report no history of anal sex.[17]

HPV clearance, defined as a single positive result followed by a single negative result, offers a real-life picture of repeat anal HPV testing in different risk groups (see below). Nevertheless, contamination with HPV, HPV intra-visit clearance, or HPV re-infection events, driven by recent sexual activity, can mimic lack of clearance. Thus, HPV clearance rate may remain under-estimated, particularly in highly exposed groups, and this may partly explain why incident infection is observed to clear less often in MSM than in women and MSW, even after adjustment for HIV status and age (appendix p 9). Of note, the CTMM developed for this analysis allows for individuals to switch HPV status between visits and so better addresses this issue than the more standard person-time approach

16

based only on observed events. Indeed, absolute estimates of incidence and clearance, as well as differences in these measures between risk groups, were much lower from a standard person-time approach than from our CTMM approach (appendix p 15), as shown previously.[9]

Our incidence and clearance rates were generally consistent with previous individual studies using CTMM for MSM.[9,10,22] Other generic strengths of CTMM, in addition to those mentioned above, include the avoidance of separating follow-up into two discrete datasets for incidence and clearance, as well as the ability to combine study designs with variable study visit intervals. However, combining studies with different visit intervals precluded us from investigating stricter criteria for incidence or clearance (e.g. a requirement for two subsequent positive, or negative, visits, respectively) or analysing groups of HPV types (e.g. any hrHPV). Other limitations of this pooled analysis, beyond the statistical model, should also be noted. First, our CTMM approach cannot overcome any lack of representativeness in the original study population. Most notably, previous evidence suggests that HIV-negative MSM recruited into HPV research studies are of higher-than-average HPV infection risk compared with the wider HIV-negative MSM population.[11,12] Second, while sample sizes were sufficient for MSM and women, irrespective of HIV status, small numbers of MSWLWH and few HPV infections in HIV-negative MSW hampered the robustness of estimates and strength of comparison for MSW, particularly with respect to non-HPV16 types. Furthermore, most individuals were from the USA, Europe, or Asia, with under-representation of Africa, even for PLWH.

Widespread gender-neutral HPV vaccination of children prior to sexual debut is expected to be the long-term solution for ASCC prevention in all risk groups, including MSM.[23] However, MSM will not receive protection from female-only HPV vaccination.[24] This, together with evidence of vaccine effectiveness on reducing incident anal HPV infection in clinical trials of MSM and women aged ≤26 years,[25,26] has led certain countries (e.g. USA, Australia, Canada, Belgium, Luxembourg, Ireland, France, New Zealand, UK) to recommend targeted vaccination at older ages for MSM (e.g., up to 45 years in the UK and Ireland), and other populations at high ASCC risk such as PLWH.[27] When predicting the relative public health benefits of age-targeted MSM versus gender-neutral HPV

17

vaccination programmes, however, it is important to consider that: a) incident infection tends to be shorter-lived, and b) the fraction of prevalent infection that represents longstanding persistent infection increases with age. Thus, in cohorts of increasing age, an increasingly important proportion of future ASCC can be expected to arise from existing prevalent HPV infection and will not be prevented by HPV vaccination. Of relevance, two clinical trials in MSMLWH and WLWH aged ≥27 years old were not able to demonstrate vaccine efficacy against anal HPV infection and lesions.[28,29]

Populations at highest risk of ASCC, that were not eligible for childhood HPV vaccination, could benefit from anal cancer screening,[30] analogous to HPV-based cervical cancer screening, but with a particular focus on HPV16 given its unique anal carcinogenicity.[3] However, up to 30% of MSMLWH, and 15% of HIV-negative MSM and WLWH are HPV16 positive at any one time,[12] and may not all be at sufficient ASCC risk to warrant referral for high-resolution anoscopy, an invasive technique with limited available clinical expertise.[12] Referral only of persistent HPV infections, known to be a necessary requirement for ASCC development, may thus improve risk stratification. This study provides the indicators to make predictions about including different HPV types in anal screening programmes based upon persistent anal HPV detection. For example, re-testing HPV16-positive MSM and PLWLH after one year avoids referral of about a quarter of those with HPV16 detected at their first screening visit, or half after 2 years, depending on their age.

In conclusion, robust estimates of absolute, and relative, measures of anal HPV incidence and clearance inform anal HPV natural history by risk group. They are key to designing and predicting the impact of ASCC prevention algorithms in different risk groups, including primary (HPV vaccination) and secondary (HPV-based screening) prevention modalities for targeted high-risk populations. Most notably, our study suggests that the carcinogenic potential of longstanding prevalent anal hrHPV infection is higher than that of more recent incident infection.

Contributors

GMC initiated and coordinated the study. FW and CJA selected the literature. FW collected the data. FW, DG, and CJA analysed the data. All other authors generated the data from the 34 original studies

18

and have contributed to the interpretation of the analysis. FW and GMC have accessed and verified all reported data. FW, DG, CJA and GMC wrote the first draft of the manuscript. All authors gave input to and have approved the final manuscript and had final responsibility for the decision to submit for publication.

Declaration of interests

MFSVDL has served on a Merck & Co advisory board. MLG has received research funding from Genocea Biosciences, Inc; Bristol-Myers Squibb; Genentech; Kura; Cullinan Labs; Agenus; DSBM; SQZBiotech; BioMimetix and Kura. She has served as a consultant for Istari Oncology Inc; LLX Solutions LLC; Kura Oncology; Mirati Therapeutics; BioNtech AG; Shattucks Labs, Inc; Bristol-Myers Squibb; Bicara Therapeutics; Bayer Healthcare Pharmaceutics; Genocea Biosciences, Inc., and Coherus. She has served a speaker/preceptorship role for OncLive and Roche Scientific. She has served on advisory committees for Seagen and Sensei Biotherapeutics, Inc. J-MM has received research grants from Gilead and has served on advisory boards for Gilead, Merck & Co, and ViiV. All other authors have no competing interests to declare.

Data Sharing

The data used for this analysis cannot be shared publicly because of legal and ethical requirements regarding re-sharing data from contributed studies. Researchers may request access to the summarized data from the corresponding author.

Acknowledgements

We thank Dr. Ashish A Deshmukh for his comments on the manuscript, Susan Gamon for her help on text editing, and the other colleagues involved in original studies: Ting Wu, Shoujie Huang, and Yingying Su (Ref #27 in the appendix); Luis F López Cortés, César Sotomayor de la Piedra, and Pompeyo Viciana (Ref #22 in the appendix); Cristina González, Montserrat Torres, Jorge Del Romero, Pompeyo Viciana, Mar Masiá, José R Blanco, Mauricio Iribarren, Silvia De Sanjosé, Beatriz

Hernández-Novoa, Marta Ortiz, Julia Del Amo (Ref #12 in the appendix); Alessandra Latini, Francesca Rollo, Maria Benevolo, Massimo Giuliani, and Amalia Giglio (Refs #11 and #33 in the appendix); Nipat Teeratakulpisarn, Tuti Parwati Merati, I Ketut Agus Somia, Iskandar Azwa, Ilias A Yee, Wifanto Saditya Jeo, and Hanny Nilasari (Ref #28 in the appendix); Isabelle Charrreau, Laurence Meyer, David Veyer, Laurent Cotte, Constance Delaugerre, and Catherine Capitant (Ref #29 in the appendix); and Davide Bernasconi (Ref #32 in the appendix). The authors alone are responsible for the views expressed in this paper and they do not necessarily represent the views, decisions, or policies of the institutions with which they are affiliated.

Role of the funding source

The sponsors 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 data in the study and had final responsibility for the decision to submit for publication.

References

1. de Martel C, Georges D, Bray F, Ferlay J, Clifford GM. Global burden of cancer attributable to infections in 2018: a worldwide incidence analysis. *Lancet Glob Health* 2020; **8**(2): e180-e90.

2. Clifford GM, Georges D, Shiels MS, et al. A meta-analysis of anal cancer incidence by risk group: Toward a unified anal cancer risk scale. *Int J Cancer* 2021; **148**(1): 38-47.

3. Lin C, Franceschi S, Clifford GM. Human papillomavirus types from infection to cancer in the anus, according to sex and HIV status: a systematic review and meta-analysis. *Lancet Infect Dis* 2018; **18**(2): 198-206.

4. Marra E, Kovaleva A, Bruisten SM, Vermeulen W, Boyd A, Schim van der Loeff MF. Incidence and Clearance of Anal High-risk Human Papillomavirus Infections and Their Determinants Over 5 Years Among Human Immunodeficiency Virus-negative Men Who Have Sex With Men. *Clin Infect Dis* 2019; **68**(9): 1556-65.

20

5. Mooij SH, van Santen DK, Geskus RB, et al. The effect of HIV infection on anal and penile human papillomavirus incidence and clearance: a cohort study among MSM. *AIDS* 2016; **30**(1): 121-32.

6. Jongen VW, van Santen DK, Alberts CJ, Schim van der Loeff MF. Estimating incidence rates of grouped HPV types: A systematic review and comparison of the impact of different epidemiological assumptions. *Papillomavirus Res* 2019; **8**: 100187.

7. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Biological agents. Volume 100B. A review of human carcinogens. IARC Monogr Eval Carcinog Risks Hum 2012; 100: 1–475.

8. Jackson C. Multi-state modelling with R: the msm package. 2021. https://cran.r-project.org/web/packages/msm/vignettes/msm-manual.pdf.

9. Geskus RB, Gonzalez C, Torres M, et al. Incidence and clearance of anal high-risk human papillomavirus in HIV-positive men who have sex with men: estimates and risk factors. *AIDS* 2016; **30**(1): 37-44.

10. Dona MG, Vescio MF, Latini A, et al. Anal human papillomavirus in HIV-uninfected men who have sex with men: incidence and clearance rates, duration of infection, and risk factors. *Clin Microbiol Infect* 2016; **22**(12): 1004 e1- e7.

11. Marra E, Lin C, Clifford GM. Type-Specific Anal Human Papillomavirus Prevalence Among Men, According to Sexual Preference and HIV Status: A Systematic Literature Review and Meta-Analysis. *J Infect Dis* 2019; **219**(4): 590-8.

12. Wei F, Gaisa MM, D'Souza G, et al. 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. *Lancet HIV* 2021; **8**(9): e531-e43.

13. Plummer M, Schiffman M, Castle PE, Maucort-Boulch D, Wheeler CM, Group A. A 2-year prospective study of human papillomavirus persistence among women with a cytological diagnosis of atypical squamous cells of undetermined significance or low-grade squamous intraepithelial lesion. *J Infect Dis* 2007; **195**(11): 1582-9.

14. Alberts CJ, Heard I, Canestri A, et al. Incidence and Clearance of Anal Human Papillomavirus (HPV)-16 and HPV-18 Infection, and Their Determinants, Among Human Immunodeficiency Virus-Infected Men Who Have Sex With Men in France. *J Infect Dis* 2020; **221**(9): 1488-93.

15. Maucort-Boulch D, Plummer M, Castle PE, et al. Predictors of human papillomavirus persistence among women with equivocal or mildly abnormal cytology. *Int J Cancer* 2010; **126**(3): 684-91.

16. Poynten IM, Jin F, Roberts JM, et al. The Natural History of Anal High-grade Squamous Intraepithelial Lesions in Gay and Bisexual Men. *Clin Infect Dis* 2021; **72**(5): 853-61.

17. Daling JR, Madeleine MM, Johnson LG, et al. Human papillomavirus, smoking, and sexual practices in the etiology of anal cancer. *Cancer* 2004; **101**(2): 270-80.

18. Wei F, Su Y, Cui X, et al. Sequential Acquisition of Human Papillomavirus Infection at Genital and Anal Sites, Liuzhou, China. *Emerg Infect Dis* 2020; **26**(10): 2387-93.

19. Pamnani SJ, Nyitray AG, Abrahamsen M, et al. Sequential Acquisition of Anal Human Papillomavirus (HPV) Infection Following Genital Infection Among Men Who Have Sex With Women: The HPV Infection in Men (HIM) Study. *J Infect Dis* 2016; **214**(8): 1180-7.

20. Simpson S, Jr., Blomfield P, Cornall A, Tabrizi SN, Blizzard L, Turner R. Front-to-back & dabbing wiping behaviour post-toilet associated with anal neoplasia & HR-HPV carriage in women with previous HPV-mediated gynaecological neoplasia. *Cancer Epidemiol* 2016; **42**: 124-32.

21. Moscicki AB, Ma Y, Farhat S, et al. Natural history of anal human papillomavirus infection in heterosexual women and risks associated with persistence. *Clin Infect Dis* 2014; **58**(6): 804-11.

22. Dona MG, Giuliani M, Rollo F, et al. Incidence and clearance of anal high-risk Human Papillomavirus infection and their risk factors in men who have sex with men living with HIV. *Sci Rep* 2022; **12**(1): 184.

23. Chow EPF, Tabrizi SN, Fairley CK, et al. Prevalence of human papillomavirus in young men who have sex with men after the implementation of gender-neutral HPV vaccination: a repeated cross-sectional study. *Lancet Infect Dis* 2021; **21**(10): 1448-57.

24. Brisson M, Benard E, Drolet M, et al. Population-level impact, herd immunity, and elimination after human papillomavirus vaccination: a systematic review and meta-analysis of predictions from transmission-dynamic models. *Lancet Public Health* 2016; **1**(1): e8-e17.

25. Palefsky JM, Giuliano AR, Goldstone S, et al. HPV vaccine against anal HPV infection and anal intraepithelial neoplasia. *N Engl J Med* 2011; **365**(17): 1576-85.

26. Kreimer AR, Gonzalez P, Katki HA, et al. Efficacy of a bivalent HPV 16/18 vaccine against anal HPV 16/18 infection among young women: a nested analysis within the Costa Rica Vaccine Trial. *Lancet Oncol* 2011; **12**(9): 862-70.

27. Nguyen-Huu NH, Thilly N, Derrough T, et al. Human papillomavirus vaccination coverage, policies, and practical implementation across Europe. *Vaccine* 2020; **38**(6): 1315-31.

28. Hidalgo-Tenorio C, Pasquau J, Omar-Mohamed M, et al. Effectiveness of the Quadrivalent HPV Vaccine in Preventing Anal ≥HSILs in a Spanish Population of HIV+ MSM Aged > 26 Years. *Viruses* 2021; **13**(2): 144.

29. Wilkin TJ, Chen H, Cespedes MS, et al. A Randomized, Placebo-Controlled Trial of the Quadrivalent Human Papillomavirus Vaccine in Human Immunodeficiency Virus-Infected Adults Aged 27 Years or Older: AIDS Clinical Trials Group Protocol A5298. *Clin Infect Dis* 2018; **67**(9): 1339-46.

30. Goldstone SE. ANCHOR Trial Results Are In: So Where Do We Go From Here? *Dis Colon Rectum* 2022; **65**(1): 1-3.

23

590 ***Table:*** **Risk factors for incidence and clearance of anal HPV16 infection in MSM, women, and MSW**

	Incidence			Clearance		
	MSM (aHR, 95%CI)	**Women (aHR, 95%CI)**	**MSW (aHR, 95%CI)**	**MSM (aHR, 95%CI)**	**Women (aHR, 95%CI)**	**MSW (aHR, 95%CI)**
Among all individuals						
Age group (years)						
<25	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
25–34	0·84 (0·65–1·09)	0·83 (0·61–1·13)	0·49 (0·15–1·61)	**0·74 (0·58–0·94)**	0·90 (0·68–1·20)	0·68 (0·22–2·05)
35–44	**0·73 (0·56–0·94)**	0·96 (0·69–1·34)	0·50 (0·17–1·50)	**0·63 (0·50–0·80)**	1·14 (0·80–1·61)	0·79 (0·31–2·01)
45–54	**0·55 (0·42–0·72)**	**0·38 (0·24–0·61)**	0·32 (0·10–1·05)	**0·51 (0·40–0·65)**	1·15 (0·76–1·73)	0·64 (0·22–1·85)
≥55	**0·31 (0·23–0·42)**	0·79 (0·41–1·52)	0·25 (0·03–2·21)	**0·42 (0·32–0·55)**	1·29 (0·72–2·31)	0·66 (0·20–2·16)
Age (per 10 years)	**0·77 (0·72–0·81)**	**0·85 (0·76–0·94)**	**0·72 (0·52–0·99)**	**0·81 (0·77–0·85)**	1·07 (0·95–1·19)	0·91 (0·71–1·17)
HIV status						
Negative	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Positive	**1·42 (1·22–1·64)**	**1·90 (1·47–2·46)**	**3·33 (1·46–7·64)**	**0·68 (0·60–0·77)**	**0·47 (0·36–0·62)**	**0·37 (0·18–0·75)**
Lifetime number of sexual partners*						
Low	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
High	**1·22 (1·01–1·47)**	**2·58 (1·86–3·57)**	**4·79 (1·38–16·7)**	0·90 (0·76–1·06)	1·00 (0·75–1·35)	0·61 (0·21–1·75)
Recent number of sexual partners†						
Low	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
High	**1·76 (1·38–2·23)**	**1·67 (1·12–2·47)**	1·90 (0·52–6·91)	1·14 (0·91–1·44)	1·09 (0·76–1·57)	1·70 (0·44–6·56)
Ever having receptive anal sex						
No	Ref.	Ref.	..	Ref.	Ref.	..
Yes	**1·43 (1·11–1·85)**	0·79 (0·60–1·04)	..	1·18 (0·92–1·51)	0·78 (0·61–1·01)	..
Lifetime number of anal sexual partners‡						
Low	Ref.	Ref.	..	Ref.	Ref.	..
High	**1·58 (1·18–2·13)**	0·79 (0·60–1·04)	..	1·24 (0·95–1·61)	0·78 (0·61–1·01)	..
Recent number of anal sexual partners§						
Low	Ref.	Ref.	..	Ref.	Ref.	..
High	**1·45 (1·17–1·8)**	0·80 (0·48–1·34)	..	1·04 (0·86–1·26)	0·97 (0·63–1·47)	..

24

	Incidence			Clearance		
	MSM (aHR, 95%CI)	**Women (aHR, 95%CI)**	**MSW (aHR, 95%CI)**	**MSM (aHR, 95%CI)**	**Women (aHR, 95%CI)**	**MSW (aHR, 95%CI)**
Current smoking						
No	Ref.	Ref.	..	Ref.	Ref.	..
Yes	**1·21 (1·03–1·43)**	**1·58 (1·14–2·18)**	..	0·94 (0·81–1·09)	0·98 (0·73–1·31)	..
Presence of anal HSIL at baseline						
No	Ref.	..	..	Ref.	..	..
Yes	1·13 (0·89–1·42)	..	..	**0·66 (0·54–0·79)**	..	..
Infection type						
Prevalent infection	..	..	..	Ref.	Ref.	..
Incident infection	..	..	..	**2·44 (2·16–2·74)**	**2·24 (1·81–2·78)**	..
Among individuals living with HIV only						
Current CD4 count (cells per µl)						
>500	Ref.	Ref.	..	Ref.	Ref.	..
350–500	**1·26 (1·02–1·55)**	0·99 (0·59–1·66)	..	1·16 (0·97–1·39)	0·94 (0·59–1·49)	..
<350	1·12 (0·89–1·42)	**1·65 (1·09–2·48)**	..	1·00 (0·82–1·23)	0·91 (0·63–1·32)	..
Current HIV viral load (copies per ml)						
<50	Ref.	Ref.	..	Ref.	Ref.	..
50–10 000	1·06 (0·81–1·39)	**2·47 (1·55–3·92)**	..	0·91 (0·72–1·14)	0·97 (0·66–1·43)	..
>10 000	1·14 (0·92–1·40)	**1·94 (1·18–3·19)**	..	**0·76 (0·63–0·92)**	0·68 (0·44–1·05)	..

Hazard ratios (aHR) were estimated from separate models for each variable, adjusted by age group and HIV status for incidence and clearance analyses, and also by infection type for clearance analyses, as appropriate. Significant aHRs relative to the reference group are shown in bold. MSM=men who have sex with men. MSW=men who have sex with women. HPV=human papillomavirus. HSIL=high-grade squamous intraepithelial lesions. The categories of (lifetime or recent) number of (anal) sexual partners were defined by the combination of median value for each population and the availability of categorical variables from contributed studies.

*MSM (low: ≤200; high: >200), women (low: ≤3; high: >3). †MSM (low: ≤5; high: >5), women (low: ≤1; high: >1). ‡MSM (low: ≤50; high: >50), women (low: 0; high: >0). §MSM (low: ≤3; high: >3), women (low: 0; high: >0).

25

Figure legends:

Figure 1: **Incidence and clearance of anal type-specific high-risk HPV infection in six risk groups**

Error bar=95% CI. HPV=human papillomavirus. HIV+=living with HIV. HIV-=HIV negative. MSM=men who have sex with men. MSW=men who have sex with women.

Figure 2: **Incidence:clearance ratio of anal type-specific high-risk HPV infection in six risk groups**

Error bar=95% CI. HPV=human papillomavirus. HIV+=living with HIV. HIV-=HIV negative. MSM=men who have sex with men. MSW=men who have sex with women.

Figure 3: **Cumulative incidence and clearance of anal HPV16 infection by risk group, as well as in MSMLWH and HIV-negative MSM by age group**

Error bar=95% CI. HPV=human papillomavirus. HIV+=living with HIV. HIV-=HIV negative. MSM=men who have sex with men. MSMLWH=MSM living with HIV. MSW=men who have sex with women.

Figure 4: **HPV16 prevalence in MSM and women according to prior duration of infection**

HPV=human papillomavirus. HIV+=living with HIV. HIV-=HIV negative. MSM=men who have sex with men.

Figure 1: **Incidence and clearance of anal type-specific high-risk HPV infection in six risk groups**

Error bar=95% CI. HPV=human papillomavirus. HIV+=living with HIV. HIV-=HIV negative. MSM=men who have sex with men. MSW=men who have sex with women.

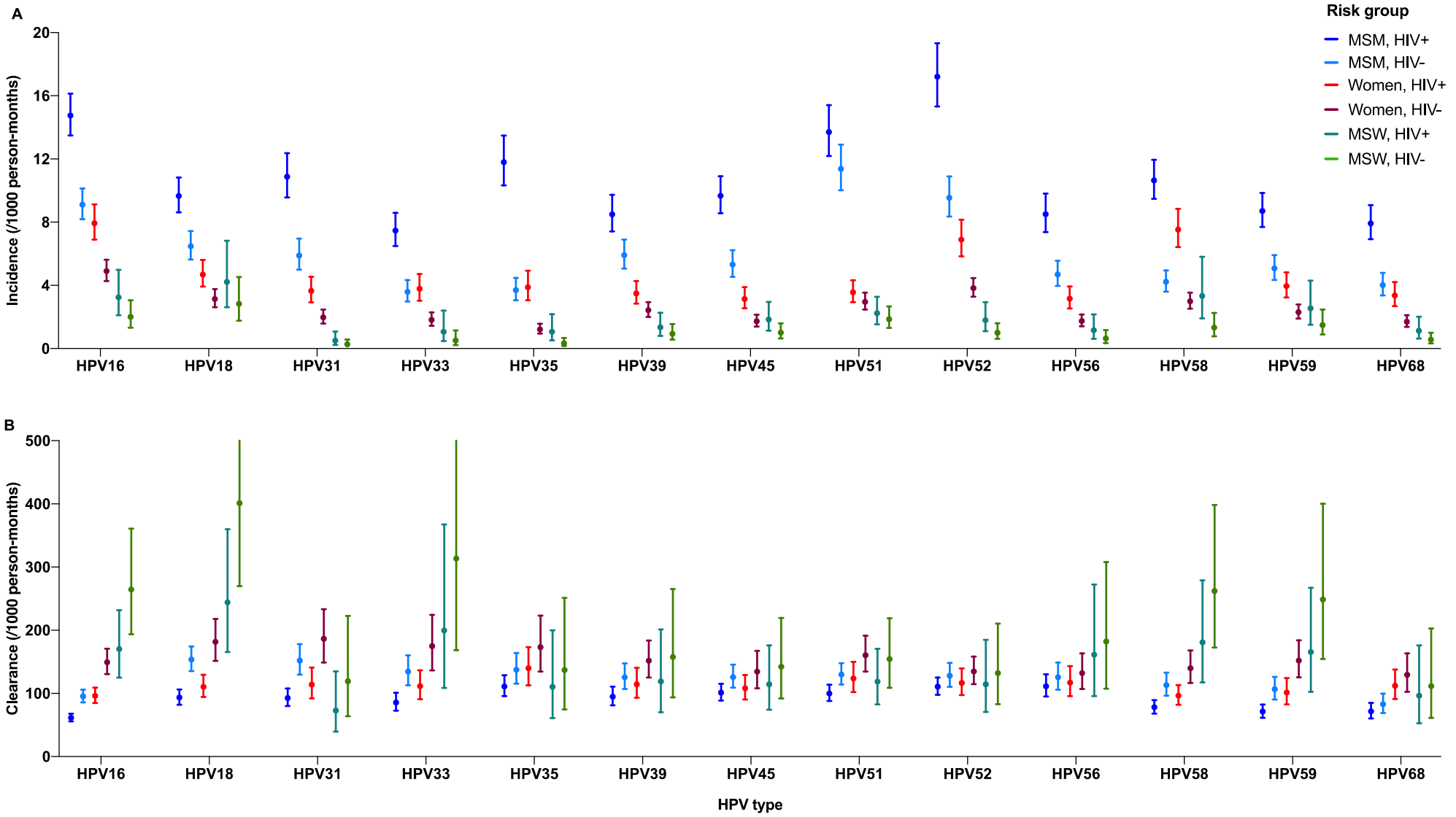


Figure 2: **Incidence:clearance ratio of anal type-specific high-risk HPV infection in six risk groups**

Error bar=95% CI. HPV=human papillomavirus. HIV+=living with HIV. HIV-=HIV negative. MSM=men who have sex with men. MSW=men who have sex with women.

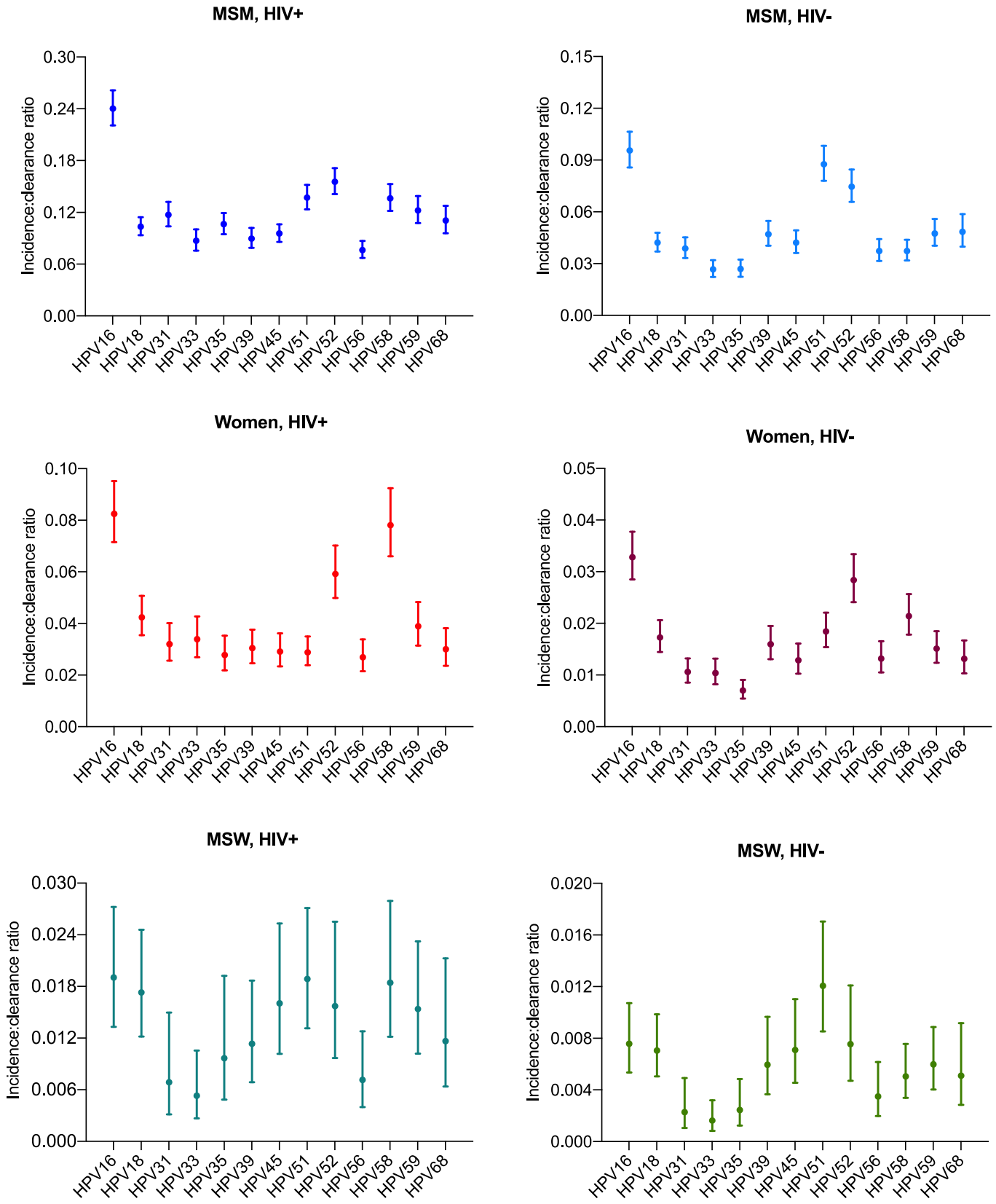
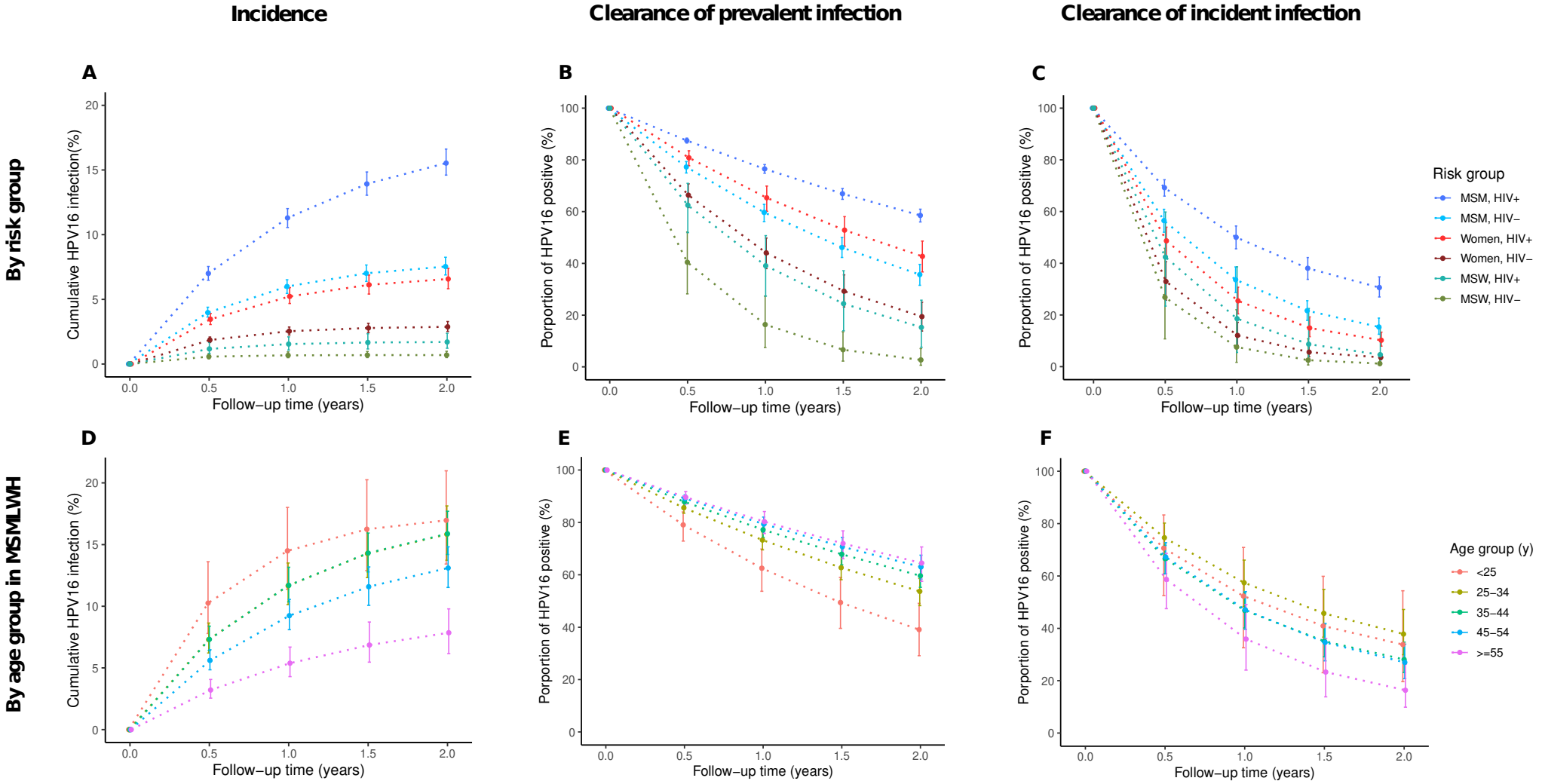
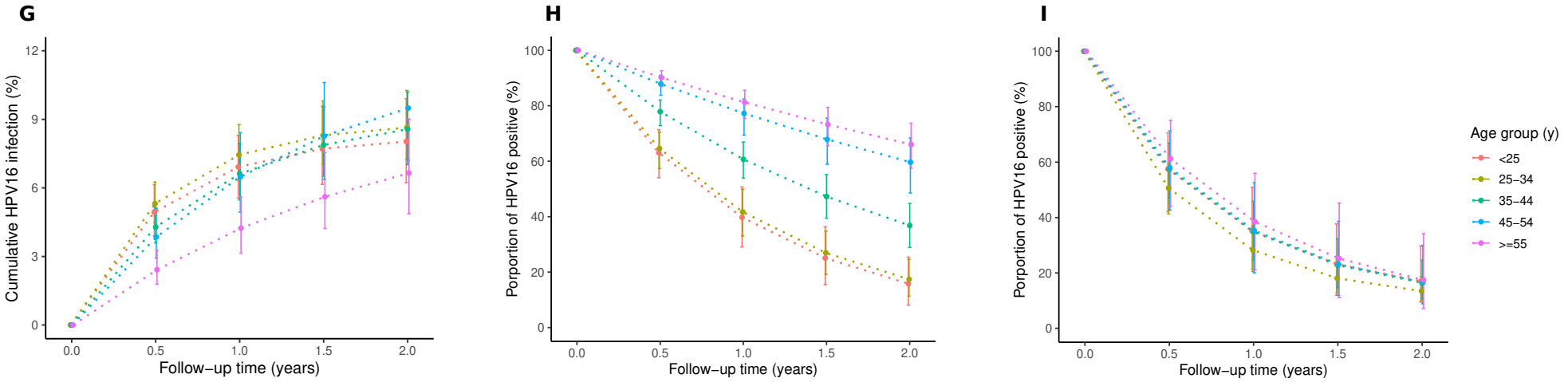


Figure 3: **Cumulative incidence and clearance of anal HPV16 infection by risk group, as well as in MSMLWH and HIV-negative MSM by age group**

Error bar=95% CI. HPV=human papillomavirus. HIV+=living with HIV. HIV-=HIV negative. MSM=men who have sex with men. MSMLWH=MSM living with HIV. MSW=men who have sex with women.



By age group in HIV-negative MSM



631

Figure 4: **HPV16 prevalence in MSM and women according to prior duration of infection**

HPV=human papillomavirus. HIV+=living with HIV. HIV-=HIV negative. MSM=men who have sex with men.

