Cervical determinants of anal HPV infection and high-grade anal lesions in women: a collaborative pooled analysis

Chunqing Lin, Jiri Slama, Paula Gonzalez, Marc T Goodman, Ningshao Xia, Aimée R Kreimer, Ting Wu, Nancy A Hessol, Yurii Shvetsov, Ana P Ortiz, Beatriz Grinsztejn, Anna-Barbara Moscicki, Isabelle Heard, María del Refugio González Losa, Erna M Kojic, Maarten F Schim van der Loeff, Feixue Wei, Adhemar Longatto-Filho, Zizipho A Mbulawa, Joel M Palefsky, Annette H Sohn, Brenda Y Hernandez, Katina Robison, Steve Simpson Jr, Lois J Conley, Alexandra de Pokomandy, Marianne A B van der Sande, Racheal S Dube Mandishora, Lays P B Volpini, Alessandra Pierangeli, Byron Romero, Timothy Wilkin, Silvia Franceschi, Carmen Hidalgo-Tenorio, Reshmie A Ramautarsing, Ina U Park, Fernanda K Tso, Sheela Godbole, Kathleen W M D'Hauwers, Borek Sehnal, Lynette J Menezes, Sandra A Heráclio, Gary M Clifford

Summary

Background Cervical cancer screening might contribute to the prevention of anal cancer in women. We aimed to investigate if routine cervical cancer screening results—namely high-risk human papillomavirus (HPV) infection and cytohistopathology—predict anal HPV16 infection, anal high-grade squamous intraepithelial lesions (HSIL) and, hence, anal cancer.

Methods We did a systematic review of MEDLINE, Embase, and the Cochrane library for studies of cervical determinants of anal HPV and HSIL published up to Aug 31, 2018. We centrally reanalysed individual-level data from 13 427 women with paired cervical and anal samples from 36 studies. We compared anal high-risk HPV prevalence by HIV status, cervical high-risk HPV, cervical cytohistopathology, age, and their combinations, using prevalence ratios (PR) and 95% CIs. Among 3255 women with anal cytohistopathology results, PRs were similarly calculated for all anal HSIL and HPV16-positive anal HSIL.

Findings Cervical and anal HPV infections were highly correlated. In HIV-negative women, anal HPV16 prevalence was 41% (447/1097) in cervical HPV16-positive versus 2% (214/8663) in cervical HPV16-negative women (PR 16·5, 95% CI 14·2–19·2, p<0·0001); these values were 46% (125/273) versus 11% (272/2588) in HIV-positive women (4·4, 3·7–5·3, p<0·0001). Anal HPV16 was also associated with cervical cytohistopathology, with a prevalence of 44% [101/228] for cervical cancer in HIV-negative women (PR *vs* normal cytology 14·1, 11·1–17·9, p<0·0001). Anal HSIL was associated with cervical high-risk HPV, both in HIV-negative women (from 2% [11/527] in cervical high-risk HPV-negative women up to 24% [33/138] in cervical HPV16-positive women; PR 12·9, 95% CI 6·7–24·8, p<0·0001) and HIV-positive women (from 8% [84/1094] to 17% [31/186]; 2·3, 1·6–3·4, p<0·0001). Anal HSIL was also associated with cervical cytohistopathology, both in HIV-negative women (from 1% [5/498] in normal cytology up to 22% [59/273] in cervical HSIL; PR 23·1, 9·4–57·0, p<0·0001) and HIV-positive women (from 7% [105/1421] to 25% [25/101]; 3·6, 2·5–5·3, p<0·0001). Prevalence of HPV16-positive anal HSIL was 23–25% in cervical HPV16-positive women older than 45 years (5/20 in HIV-negative women, 12/52 in HIV-positive women).

Interpretation HPV-based cervical cancer screening programmes might help to stratify anal cancer risk, irrespective of HIV status. For targeted secondary anal cancer prevention in high-risk groups, HIV-negative women with cervical HPV16, especially those older than 45 years, have a similar anal cancer risk profile to that of HIV-positive women.

Funding International Agency for Research on Cancer.

Copyright Copyright © 2019 International Agency for Research on Cancer; licensee Elsevier. This is an Open Access article published under the CC BY-NC-ND 3.0 IGO license which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. In any use of this article, there should be no suggestion that IARC endorses any specific organisation, products or services. The use of the IARC logo is not permitted. This notice should be preserved along with the article's original URL.

Lancet Infect Dis 2019

Published Online June 13, 2019 http://dx.doi.org/10.1016/S1473-3099(19)30164-1

See Online/Comment http://dx.doi.org/10.1016/S1473-3099(19)30296-8

International Agency for Research on Cancer, Lyon, France (C Lin PhD, G M Clifford PhD); **National Cancer Center, National Clinical Research Center for Cancer, and Cancer Hospital Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China** (C Lin); **Department of Gynecology and Obstetrics, General University Hospital and First Faculty of Medicine, Charles University, Prague, Czech Republic** (J Slama PhD, B Sehnal PhD); **Proyecto Epidemiológico Guanacaste, Fundación INCIENSA, San José, Costa Rica** (P Gonzalez MD, B Romero MD); **Samuel Oschin Comprehensive Cancer Institute, Cedars Sinai Medical Center, Los Angeles, CA, USA** (M T Goodman PhD); **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** (N Xia, T Wu PhD, F Wei PhD); **National Cancer Institute, National Institutes of Health, Bethesda, MD, USA** (A R Kreimer PhD); **University of California, San Francisco, CA, USA** (N A Hessol MSPH, J M Palefsky MD); **University of Hawaii Cancer Center, Honolulu, Hawaii, USA** (Y Shvetsov PhD, B Y Hernandez MD); **University of Puerto Rico Comprehensive Cancer Center, Department of**

Introduction

Compared with knowledge of how cervical high-risk human papillomavirus (HPV) infection and cervical cytohistopathological results are related to cervical cancer, less is known about how cervical screening results might predict anal cancer. A better understanding would help to prioritise women at greatest risk of anal cancer for secondary prevention measures in new HPV-based cervical cancer screening programmes.

Annually, about 18 000 women are diagnosed with anal cancer worldwide[1] and, although rare at a population level, anal cancer is more frequent in women than in men.[2] Furthermore, anal cancer incidence rates are increasing,[2] probably owing to changes in sexual risk

Biostatistics and Epidemiology, Graduate School of Public Health, UPR, San Juan, Puerto Rico (A P Ortiz PhD); Instituto Nacional de Infectologia Evandro Chagas-Fiocruz, Rio de Janeiro, Brazil (B Grinsztejn MD); David Geffen School of Medicine, University of California, Los Angeles, CA, USA (A-B Moscicki MD); Department of Endocrinology and Reproductive Medicine, IE3M, Groupe Hospitalier Pitié-Salpêtrière, Assistance Publique, Hôpitaux de Paris, Paris, France (I Heard PhD); Dr Hideyo Noguchy Center of Regional Investigations, Autonomous University of Yucatán, Mérida, Yucatán, México (M del Refugio González Losa MD); Mount Sinai West and St Luke's Hospitals, New York, NY, USA (E M Kojic MD); Department of Infectious Diseases, Infectious Diseases Research & Prevention, GGD Amsterdam, Netherlands (M F Schim van der Loeff PhD); Research Institute of Life and Health Sciences, School of Medicine, University of Minho, Braga, Portugal (A Longatto-Filho PhD); 3B's (Biomaterials, Biodegradables and Biomimetics) Research Group, Portugal Government Associate Laboratory, Braga, Portugal (A Longatto-Filho); Laboratory of Medical Investigation 14, Department of Pathology, Faculty of Medicine, University of São Paulo, São Paulo, Brazil (A Longatto-Filho); Teaching and Research Institute, Molecular Oncology Research Center, Barretos Cancer Hospital–Pio XII Foundation, Barretos, Brazil (A Longatto-Filho); Institute of Infectious Disease and Molecular Medicine, University of Cape Town, Cape Town, South Africa; Department of Pathology, Division of Medical Virology, University of Cape Town, Cape Town, South Africa (Z A Mbulawa PhD); Centre for HIV and STIs, National Institute for Communicable Diseases, National Health Laboratory Service, Johannesburg, South Africa (Z A Mbulawa); South African Medical Research Council Gynaecological Cancer Research Centre, University of Cape Town, Cape Town, South Africa (Z A Mbulawa);

Research in context

Evidence before this study

We searched MEDLINE, Embase, and the Cochrane Library for studies published between database inception and Aug 31, 2018, using the search terms ("papillomaviridae" OR "papillomavirus" OR "HPV") AND ("anal" OR "anus" OR "anal canal"), without language restrictions. A large systematic review and meta-analysis has shown the predominant role of HPV16 in the pathogenesis of anal high grade squamous intraepithelial lesion (HSIL) and cancer, both in men and women, and according to HIV status. Various studies, predominantly from high-income settings, have also shown that anal cancer incidence is higher in women than in men, is increasing over time and, among women, is particularly elevated in those with cervical precancer or cancer, or living with HIV. However, there has been no systematic appraisal of how routinely available information from cervical cancer screening—ie, cervical HPV infection and cytohistopathology—is predictive of risk of anal cancer or its surrogates.

Added value of this study

This collaborative pooled analysis is the first systematic effort to address how routinely available information from modern cervical cancer screening programmes—cervical HPV and cytohistopathology results—can predict anal HPV16, anal HSIL, or HPV16-positive anal HSIL, as best surrogates of anal cancer risk in women. We showed that cervical HPV infection, cervical cytohistopathological diagnosis, HIV status, and their combinations, are all associated with anal HPV16, anal HSIL, or HPV16-positive anal HSIL. The strongest determinants of these outcomes were the presence of cervical HPV16 infection or a diagnosis of cervical cancer, irrespective of HIV status. The degree of HIV-related immunodeficiency was also weakly associated.

Implications of all the available evidence

Women with cervical HPV16 infection or cervical cancer are at highest risk of anal HPV16, anal HSIL, or HPV16-positive anal HSIL. HPV-based cervical screening programmes might help to stratify anal cancer risk in women, irrespective of their HIV status.

factors for HPV transmission.[3] Persistent anal HPV infection is the major cause of anal cancer,[4] for which the most severe precursor is anal high-grade squamous intraepithelial lesion (HSIL).[5] In particular, HPV16 is detectable in over 90% of HPV-related anal cancers and 80% of HPV-related anal HSIL[5], a substantially higher attributable fraction than in the cervix. Anal cancer risk is also elevated in women infected with HIV,[6–8] although HIV does not account for a substantial proportion of anal cancer in women at a population level.[9,10] Women with a history of cervical cancer[9,11,12] and cervical intraepithelial neoplasia grade 3 (CIN3)[13–15] are also at increased risk for anal cancer.

To assess the association between cervical screening findings and surrogates of anal cancer risk, we did a collaborative pooled analysis of high-risk HPV and related lesions in paired anal and cervical samples. We hypothesised that it would be possible, based on HIV status and cervical screening results, to robustly identify subgroups of women with high prevalence of anal HPV16, anal HSIL, or HPV16-positive anal HSIL for the purpose of targeting anal cancer screening and early diagnosis.

Methods

Data collection

We previously did a systematic literature review for a meta-analysis of anal HPV prevalence according to anal cytohistopathology, sex, and HIV status. We searched MEDLINE, Embase, and the Cochrane Library for studies published between Jan 1, 1986, and July 31, 2017, using the terms ("papillomaviridae" OR "papillomavirus" OR "HPV") AND ("anal canal" OR "anus" OR "anal").[5] The same search strategy was extended to Aug 31, 2018 and identified 49 studies eligible for a pooled analysis of cervical determinants of anal HPV and HSIL (appendix p 2). Minimum eligibility criteria were paired anal and cervical samples (swabs or biopsies, or both) taken at the same study visit; in anal samples, type-specific HPV DNA detected by a PCR-based assay; and, in cervical samples, type-specific HPV DNA detected by a PCR-based assay, cytohistopathology results, or both. Authors of eligible studies were invited to share individual-level data on age, anal and cervical HPV genotyping, cervical cytohistopathology, and HIV status (including unknown HIV status), of which 36 accepted (appendix p 2). Anal cytohistopathology results from the same study visit were also extracted, if available, as were current and nadir CD4 cell count and HIV-1 viral load for HIV-positive women.

Statistical analysis

Type-specific HPV prevalence in the anus and cervix is reported for 13 high-risk HPV types judged to be carcinogenic or probably carcinogenic (HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68),[4] and is estimated only in studies that tested for the given high-risk HPV type, thus denominators vary by type, as in previous similar meta-analyses.[5,16] Anal HPV16 prevalence was available in all studies.

Anal and cervical cytohistopathological diagnoses were classified into four categories, as done previously:[5,16] normal, including normal cytology only; low grade, including atypical squamous cells of undetermined significance, low-grade squamous intraepithelial lesion, and intraepithelial neoplasia grade 1; high grade, including HSIL, atypical squamous cells for which HSIL cannot be excluded, intraepithelial neoplasia grade 2–3; and invasive cancer. We calculated prevalence ratios (PRs) from generalised linear models, with adjustment for age (<30 years, 30–44 years, and >45 years). Age-adjusted PRs and corresponding 95% CIs were used to compare prevalence of type-specific anal HPV (most notably HPV16), anal high-grade lesions (ie, HSIL),[17] and HPV16-positive anal HSIL, according to cervical high-risk HPV status, cervical cytohistopathology, age (<30 years, 30–44 years, and >45 years), and HIV status (negative or unknown *vs* positive). Among HIV-positive women, PRs were also calculated according to current CD4 cell count (<350 cells per µL, 350–499 cells per µL, or >500 cells per µL; defined as rough tertiles of available data), nadir CD4 count (<200 cells per µL or >200 cells per µL), and HIV viral load (<200 copies per mL or >200 copies per mL). All statistical analyses were two-sided and done in Stata (version 14).

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. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

Results

We included 36 studies contributing individual-level data on 13 427 women, representing 87% of 15 521 eligible women identified by our literature review (appendix p 2). 3352 women were HIV-positive, 3607 were HIV-negative, and 6468 had an unknown HIV status. Study characteristics are shown in table 1.[18–53] Most women with an unknown HIV status (5972 [92%] of 6468) came from three population-based studies in China, the USA, and Costa Rica (table 1). Furthermore, a preliminary analysis of women with normal cytology showed equivalent cervical and anal HPV prevalence in HIV-negative women and women with unknown HIV status (appendix p 3). Hence, participants with unknown HIV status are hereafter assumed to be HIV-negative.

	Country	HIV status	n	HPV genotyping		Cytohistopathology		HIV-positive women		
				Anal	Cervical	Anal	Cervical	Current CD4 cell count	Nadir CD4 cell count	HIV-1 viral load
Sohn et al (2018)[18]	Thailand and Vietnam	Negative	98	Yes	Yes	No	Yes	..	..	..
Sohn et al (2018)[18]	Thailand and Vietnam	Positive	93	Yes	Yes	No	Yes	Yes	No	Yes
Cranston et al (2018)[19]	USA	Positive	103	Yes	Yes	Yes	Yes	Yes	Yes	Yes
de Pokomandy et al (2017)[20]	Canada	Positive	151	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Wei et al (2018)[21]	China	Unknown	2283	Yes	Yes	No	No	..	..	..
Volpini et al (2017)[22]	Brazil	Positive	126	Yes	Yes	No	Yes	Yes	No	Yes
Marra et al (2018)[23]	Netherlands	Unknown	1	Yes	No	No	No	..	..	..
Marra et al (2018)[23]	Netherlands	Negative	285	Yes	Yes	No	No	..	..	..
Marra et al (2018)[23]	Netherlands	Positive	2	Yes	Yes	No	No	No	No	No
Hidalgo-Tenorio et al (2018)[24]	Spain	Positive	101	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Gonzalez-Losa et al (2018)[25]	Mexico	Unknown	305	Yes	Yes	No	Yes	..	..	..
Goeieman et al (2017)[26]	South Africa	Positive	200	Yes	No	Yes	Yes	Yes	Yes	Yes
Dube Mandishora et al (2017)[27]	Zimbabwe	Negative	74	Yes	Yes	No	Yes	..	..	..
Dube Mandishora et al (2017)[27]	Zimbabwe	Positive	70	Yes	Yes	No	Yes	No	No	No
Simpson et al (2016)[28]	Australia	Negative	163	Yes	Yes	Yes	Yes	..	..	..
Ortiz et al (2016)[29]	Puerto Rico	Negative	536	Yes	Yes	No	No	..	..	..
Menezes et al (2016)[30]	India	Positive	46	Yes	Yes	No	No	Yes	Yes	Yes
Heard et al (2016)[31]	France	Positive	311	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Veo et al (2015)[32]	Brazil	Negative	220	Yes	Yes	No	Yes	..	..	..
Tso et al (2015)[33]	Brazil	Negative	56	Yes	Yes	Yes	Yes	..	..	..
Tso et al (2015)[33]	Brazil	Positive	42	Yes	Yes	Yes	Yes	Yes	No	No
Slama et al (2015)[34]	Czech Republic	Negative	1085	Yes	Yes	No	Yes	..	..	..
Robison et al (2015)[35]	USA	Negative	174	Yes	Yes	Yes	Yes	..	..	..
Ramautarsing et al (2015)[36]	Thailand	Positive	101	Yes	Yes	Yes	Yes	Yes	No	Yes
Cambou et al (2015)[37]	Brazil	Positive	478	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Kojic et al (2014)[38]	USA, Brazil, South Africa	Positive	300	Yes	Yes	No	No	Yes	Yes	Yes
Godbole et al (2014)[39]	India	Positive	98	Yes	Yes	No	Yes	Yes	No	No

(Table 1 continues on next page)

TREAT Asia/amfAR–Foundation for AIDS Research, Thai Red Cross AIDS Research Centre, Bangkok, Thailand (A H Sohn MD); **Obstetrics & Gynecology and Medicine, The Warren Alpert Medical School of Brown University, Providence, RI, USA** (K Robison MD); **Menzies Institute for Medical Research, University of Tasmania, Hobart, Tasmania, Australia** (S Simpson Jr PhD); **Division of HIV/AIDS Prevention, Epidemiology Research Team, Centers for Disease Control and Prevention, Atlanta, GA, USA** (L J Conley MPH); **Chronic Viral Illness Service, McGill University Health Centre and Department of Family Medicine, McGill University, Montreal, QC, Canada** (A de Pokomandy MDCM); **Public Health Epidemiology, Head Department Public Health, Institute of Tropical Medicine, Antwerp, Belgium** (M A B van der Sande PhD); **Department of Medical Microbiology, University of Zimbabwe College of Health Sciences, Parirenyatwa Hospital premises, Harare, Zimbabwe** (R S Dube Mandishora PhD); **Health Sciences Center, Federal University of Espírito Santo, Vitória, Brazil** (L P B Volpini MSc); **Department of Molecular Medicine, Sapienza University of Rome, Rome, Italy** (A Pierangeli PhD); **Weill Cornell Medicine, New York, NY, USA** (T Wilkin MD); **Aviano Cancer Center, Aviano, Italy** (S Franceschi MD); **Infectious Diseases Service, University Hospital Virgen de las Nieves, Granada, Spain** (C Hidalgo-Tenorio PhD); **Thai Red Cross AIDS Research Centre, Bangkok, Thailand** (R A Ramautarsing PhD); **Department of Family and Community Medicine, University of California San Francisco School of Medicine, San Francisco, CA, USA** (I U Park MD); **Department of Gynecology of the Federal University of São Paulo, São Paulo, Brazil** (F K Tso PhD); **Division of Epidemiology and Biostatistics, ICMR-National AIDS Research Institute, Indian Council of Medical Research, Pune, India** (S Godbole MD); **Radboud University Nijmegen,**

Medical Centre, Department of Urology, Nijmegen, Netherlands (K W M D'Hauwers PhD); **Division of Infectious Disease, University of South Florida, Tampa, FL, USA** (L J Menezes PhD); **Women's Healthcare Center, Instituto de Medicina Integral Professor Fernando Figueira, Recife, PE, Brazil** (S A Heráclio PhD); **and Cytopathology Division, Public Health Laboratory of the State of Pernambuco, Recife, PE, Brazil** (S A Heráclio)

Correspondence to: Dr Gary M Clifford, International Agency for Research on Cancer, Lyon, France
cliffordg@iarc.fr

See Online for appendix

	Country	HIV status	n	HPV genotyping		Cytohistopathology		HIV-positive women		
				Anal	Cervical	Anal	Cervical	Current CD4 cell count	Nadir CD4 cell count	HIV-1 viral load
(Continued from previous page)										
Vriend et al (2013)[40]	Netherlands	Unknown	2	Yes	Yes	No	No	..	..	..
Vriend et al (2013)[40]	Netherlands	Negative	142	Yes	Yes	No	No	..	..	..
Vriend et al (2013)[40]	Netherlands	Positive	1	Yes	Yes	No	No	No	No	No
Ortiz et al (2013)[41]	Puerto Rico	Negative	99	Yes	Yes	No	Yes	..	..	..
Hessol et al (2013)[42]	USA	Negative	176	Yes	Yes	Yes	Yes	..	..	..
Hessol et al (2013)[42]	USA	Positive	457	Yes	Yes	Yes	Yes	Yes	No	Yes
Hernandez et al (2013)[43]	USA	Unknown	188	Yes	Yes	No	Yes	..	..	..
Pierangeli et al (2012)[44]	Italy	Negative	108	Yes	Yes	Yes	Yes	..	..	..
Pierangeli et al (2012)[44]	Italy	Positive	15	Yes	Yes	Yes	Yes	No	No	No
D'Hauwers et al (2012)[45]	Belgium	Negative	93	Yes	Yes	Yes	Yes	..	..	..
Castro et al (2012)[46]	Costa Rica	Unknown	2107	Yes	Yes	No	Yes	..	..	..
Kojic et al (2011)[47]	USA	Positive	152	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Heraclio et al (2011)[48]	Brazil	Negative	37	Yes	Yes	Yes	Yes	..	..	..
Park et al (2009)[49]	USA	Negative	101	Yes	No	Yes	Yes	..	..	..
Goncalves et al (2008)[50]	Brazil	Positive	102	Yes	Yes	No	No	Yes	No	No
Hernandez et al (2005)[51]	USA	Unknown	1582	Yes	Yes	No	Yes	..	..	..
Moscicki et al (2003)[52]	USA	Negative	128	Yes	Yes	Yes	Yes	..	..	..
Moscicki et al (2003)[52]	USA	Positive	238	Yes	Yes	Yes	Yes	Yes	No	Yes
Palefsky et al (2001)[53]	USA	Negative	32	Yes	Yes	Yes	Yes	..	..	..
Palefsky et al (2001)[53]	USA	Positive	165	Yes	Yes	Yes	Yes	Yes	No	Yes
Overall	..	..	13 427	..	..	..	..	..	..	..

HPV=human papillomavirus.

Table 1: **Principal characteristics of 36 included studies**

Cervical high-risk HPV positivity was associated with anal high-risk HPV prevalence (table 2). In HIV-negative women, anal high-risk HPV prevalence was 43% (1160/2693) in cervical high-risk HPV-positive women versus 9% (563/6543) in cervical high-risk HPV-negative women (PR 4·9, 95% CI 4·4–5·3, p<0·0001). In HIV-positive women, these proportions were 62% (678/1091) for HPV-positive women and 33% (579/1770) for HPV-negative women (1·9, 1·7–2·1, p<0·0001). Associations for individual high-risk HPV types were much stronger than for high-risk HPV overall (table 2). For example, for HIV-negative women, anal HPV16 prevalence was 41% (447/1097) in cervical HPV16-positive versus 2% (214/8663) in cervical HPV16-negative women (16·5, 14·2–19·2, p<0·0001; table 2). Equivalent proportions were 46% (125/273) and 11% (272/2588) in HIV-positive women (4·4, 3·7–5·3, p<0·0001).

For each high-risk HPV type, the association between cervical and anal positivity was weaker among HIV-positive than HIV-negative women (table 2). In cervical HPV16-negative women, anal HPV16 prevalence was 11% in HIV-positive women versus 2% in HIV-negative women (PR 3·9, 95% CI 3·3–4·7, p<0·0001); whereas, in HPV16-positive women, anal HPV16 prevalence was 46% in HIV-positive women versus 41% in HIV-negative women (1·1, 1·0–1·3, p=0·1501). Anal HPV16 prevalence was higher in cervical high-risk HPV-positive women than in cervical high-risk HPV-negative, regardless of HIV status (PR 9·2, 95% CI 7·5–11·2, p<0·0001 for HIV-negative women *vs* 2·4, 2·0–2·9, p<0·0001 for HIV-positive women; figure 1). Anal HPV16 prevalence was highest among cervical HPV16-positive women (table 2), but was also significantly higher in women infected with cervical non-HPV16 high-risk HPV than in women without high-risk HPV (2·1, 1·5–2·8, p<0·0001 for HIV-negative; 1·5, 1·2–1·9, p=0·0003 for HIV-positive women).

Cervical cytohistopathology was strongly associated with anal HPV16, particularly in HIV-negative women, among whom it increased from 4% (155/4358) in women with normal cytology to 22% (251/1131) in those with HSIL (PR 6·5, 95% CI 5·4–7·9, p<0·0001) and to 44% (101/228) in those with cervical cancer (14·1, 11·1–17·9, p<0·0001; figure 1A). Associations were also significant, albeit lower, in HIV-positive women (13% [230/1821] for normal cytology up to 23% [29/127] for HSIL; 1·9, 1·3–2·6, p=0·0004). Age was not a strong determinant of anal HPV16 prevalence, regardless of HIV status. Cervical cancer cases in HIV-positive women were too few (n=3) to be analysed separately.

Among cervical HPV16-positive women, anal HPV16 prevalence reached 66% [90/136] in cervical cancer (figure 1B). However, neither cytohistopathology, nor age, offered much discrimination of anal HPV16 prevalence, neither for HIV-negative nor HIV-positive women. Anal HPV16 prevalence according to other strata of cervical high-risk HPV status (cervical high-risk HPV-negative, cervical high-risk HPV-positive, and cervical non-HPV16 high-risk HPV-positive only) is shown in the appendix (p 4).

HIV status was a determinant of anal HPV16 prevalence within almost all strata of cervical cytohistopathology and age (figure 1A), but not in any stratum of cervical HPV16-positive women (figure 1B).

A subset of studies had data on anal cytohistopathology (1003 HIV-negative women from ten studies and 2252 HIV-positive women from 13 studies, table 1). Anal HSIL was associated with cervical high-risk HPV, both in HIV-negative women (from 2% [11/527] in cervical high-risk HPV-negative women up to 24% [33/138] in cervical HPV16-positive women; PR 12·9, 95% CI 6·7–24·8, p<0·0001) and HIV-positive women (from 8% [84/1094] to 17% [31/186]; 2·3, 1·6–3·4, p<0·0001). Cervical high-risk HPV-positive women had higher anal HSIL prevalence than did cervical high-risk HPV-negative women, regardless of HIV status (PR 10·4, 95% CI 5·5–19·5, p<0·0001 for HIV-negative women; 1·7, 1·3–2·2, p=0·0001 for HIV-positive women; figure 2A). For cervical HPV16-positive women, PRs versus cervical high-risk HPV-negative women reached 12·9 (95% CI 6·7–24·8, p<0·0001) and 2·3 (1·6–3·4, p<0·0001), for HIV-positive and HIV-negative women, respectively. Anal HSIL was also more common among women with cervical HPV16 than among women with cervical non-16 high-risk HPV, both in HIV-negative women (1·5, 1·0–2·5, p=0·0666) and HIV-positive women (1·6, 1·1–2·3, p=0·0227). Anal HSIL was associated with cervical cytohistopathology, particularly with cervical HSIL (PR *vs* normal cytology 23·1, 9·4–57·0, p<0·0001 in HIV-negative women, 3·6, 2·5–5·3, p<0·0001 in HIV-positive women) and cervical cancer (15·0, 4·3–52·3, p<0·0001 in HIV-negative women; figure 2A). Anal HSIL prevalence increased with age, but was significantly different only in HIV-positive women (2·5, 1·6–4·1, p=0·0001; figure 2A).

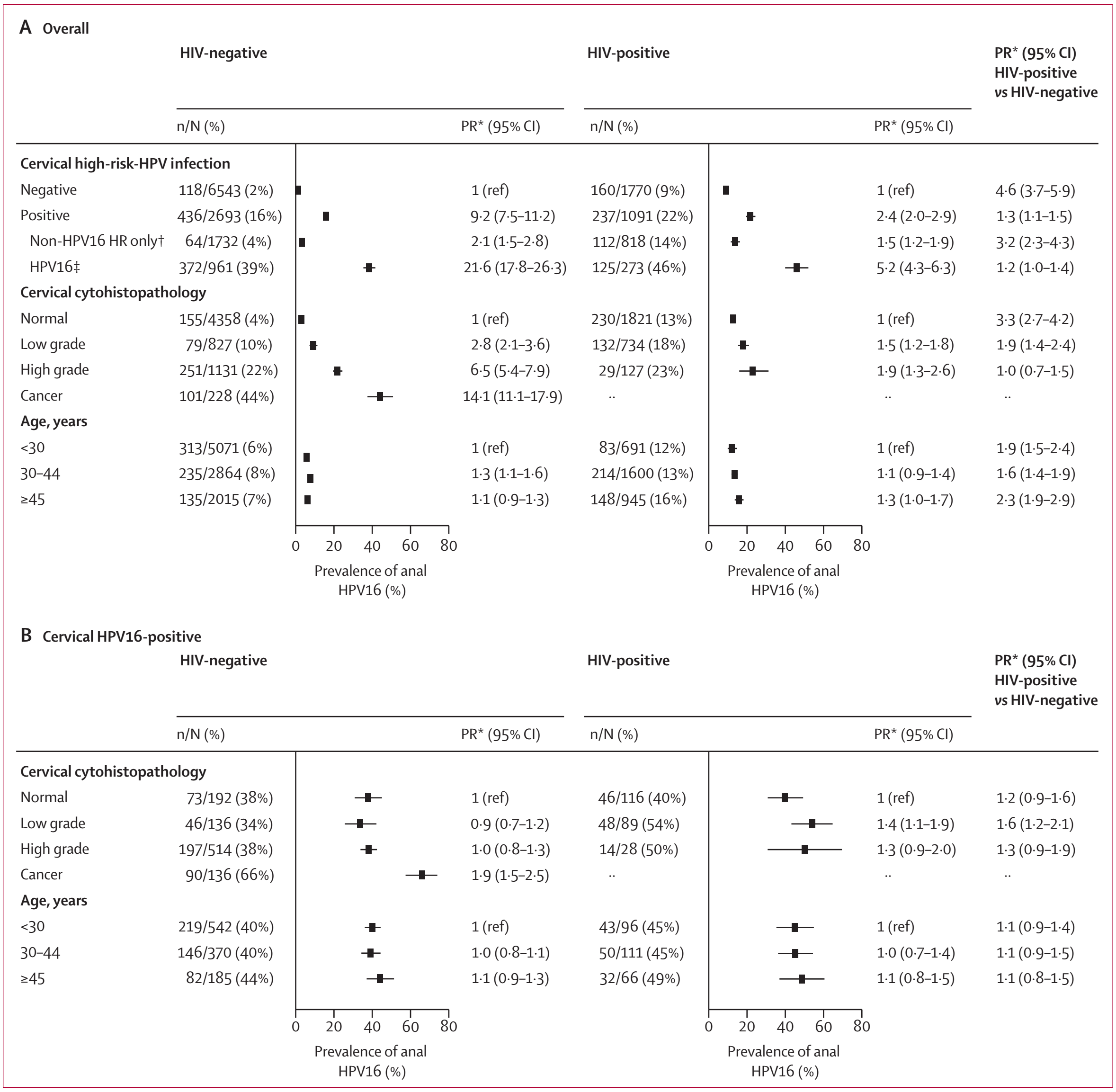
Among cervical HPV16-positive women, anal HSIL prevalence increased with advancing age (figure 2B). In HIV-negative women, HSIL prevalence was 38% (8/21) in those older than 45 years versus 17% (9/52) in those younger than 30 years (PR 2·2, 95% CI 1·0–4·9, p=0·0552); these values were 26% (14/53) versus 5% (3/58) in HIV-positive women (5·1, 1·6–16·8, p=0·0072; figure 2B). Anal HSIL prevalence is shown for other strata of cervical high-risk HPV status in the appendix (p 5).

HIV status was a significant determinant of anal HSIL for women in lower risk strata—for example, cervical high-risk HPV-negative women (PR 3·5, 95% CI 1·9–6·5, p=0·0001; figure 2A) and women with normal cervical cytology (PR 6·9, 2·8–16·9, p<0·0001; figure 2A)—but was not a significant determinant

	HIV-negative women		HIV-positive women		PR* (95% CI) (HIV-positive *vs* HIV-negative)
	n/N (%)	PR* (95% CI)	n/N (%)	PR* (95% CI)	
HPV16					
Negative	214/8663 (2%)	1 (ref)	272/2588 (11%)	1 (ref)	3·9 (3·3–4·7)
Positive	447/1097 (41%)	16·5 (14·2–19·2)	125/273 (46%)	4·4 (3·7–5·3)	1·1 (1·0–1·3)
HPV18					
Negative	115/9448 (1%)	1 (ref)	153/2716 (6%)	1 (ref)	4·4 (3·4–5·6)
Positive	93/312 (30%)	24·1 (18·8–30·9)	58/145 (40%)	7·1 (5·5–9·1)	1·4 (1·1–1·9)
HPV31					
Negative	95/8850 (1%)	1 (ref)	110/2542 (4%)	1 (ref)	3·9 (2·9–5·2)
Positive	79/280 (28%)	24·2 (18·3–31·9)	43/121 (36%)	7·7 (5·7–10·4)	1·4 (1·0–2·0)
HPV33					
Negative	47/8968 (1%)	1 (ref)	78/2571 (3%)	1 (ref)	5·0 (3·4–7·3)
Positive	37/162 (23%)	43·5 (29·1–65·1)	38/92 (41%)	13·8 (10·0–19·0)	1·9 (1·3–2·7)
HPV35					
Negative	51/9000 (1%)	1 (ref)	88/2580 (3%)	1 (ref)	6·1 (4·3–8·8)
Positive	29/130 (22%)	36·4 (23·9–55·6)	22/83 (27%)	7·9 (5·2–11·9)	1·9 (1·1–3·1)
HPV39					
Negative	105/9006 (1%)	1 (ref)	92/2791 (3%)	1 (ref)	2·9 (2·2–3·8)
Positive	66/230 (29%)	22·4 (16·8–29·8)	24/70 (34%)	10·6 (7·3–15·4)	1·2 (0·8–1·8)
HPV45					
Negative	71/9369 (1%)	1 (ref)	128/2759 (5%)	1 (ref)	5·8 (4·3–7·8)
Positive	45/172 (26%)	33·9 (24·1–47·7)	39/102 (38%)	8·0 (5·9–10·8)	1·5 (1·0–2·1)
HPV51					
Negative	180/8899 (2%)	1 (ref)	157/2728 (6%)	1 (ref)	2·9 (2·3–3·6)
Positive	117/337 (35%)	15·1 (12·2–18·6)	48/133 (36%)	5·8 (4·4–7·7)	1·1 (0·8–1·5)
HPV52					
Negative	132/8756 (2%)	1 (ref)	138/2686 (5%)	1 (ref)	3·5 (2·7–4·4)
Positive	147/480 (31%)	18·8 (15·2–23·4)	54/175 (31%)	6·4 (4·9–8·4)	1·0 (0·8–1·3)
HPV56					
Negative	74/9051 (1%)	1 (ref)	99/2736 (4%)	1 (ref)	4·3 (3·2–5·9)
Positive	62/185 (34%)	35·9 (26·2–49·1)	36/125 (29%)	7·8 (5·6–10·9)	0·9 (0·6–1·4)
HPV58					
Negative	118/9269 (1%)	1 (ref)	178/2622 (7%)	1 (ref)	4·8 (3·8–6·1)
Positive	74/272 (27%)	21·3 (16·3–27·7)	75/239 (31%)	4·6 (3·6–5·8)	1·2 (0·9–1·6)
HPV59					
Negative	52/8974 (1%)	1 (ref)	87/2559 (3%)	1 (ref)	5·7 (4·0–8·2)
Positive	48/156 (31%)	49·2 (34·1–70·9)	36/104 (35%)	10·2 (7·3–14·2)	1·3 (0·9–2·0)
HPV68					
Negative	52/6932 (1%)	1 (ref)	127/2582 (5%)	1 (ref)	6·1 (4·4–8·5)
Positive	30/91 (33%)	42·4 (28·2–63·7)	36/81 (44%)	8·9 (6·6–12·0)	1·5 (1·0–2·2)
HR-HPV (any)					
Negative	563/6543 (9%)	1 (ref)	579/1770 (33%)	1 (ref)	3·8 (3·4–4·2)
Positive	1160/2693 (43%)	4·9 (4·4–5·3)	678/1091 (62%)	1·9 (1·7–2·1)	1·4 (1·4–1·5)

HR-HPV=high-risk human papillomavirus. *Adjusted by age groups.

Table 2: **Anal high-risk HPV prevalence and corresponding prevalence ratios, according to the absence or presence of the same type in the cervix, by HIV status**



A Overall

	HIV-negative n/N (%)	HIV-negative PR* (95% CI)	HIV-positive n/N (%)	HIV-positive PR* (95% CI)	PR* (95% CI) HIV-positive *vs* HIV-negative
Cervical high-risk-HPV infection					
Negative	118/6543 (2%)	1 (ref)	160/1770 (9%)	1 (ref)	4·6 (3·7–5·9)
Positive	436/2693 (16%)	9·2 (7·5–11·2)	237/1091 (22%)	2·4 (2·0–2·9)	1·3 (1·1–1·5)
Non-HPV16 HR only†	64/1732 (4%)	2·1 (1·5–2·8)	112/818 (14%)	1·5 (1·2–1·9)	3·2 (2·3–4·3)
HPV16‡	372/961 (39%)	21·6 (17·8–26·3)	125/273 (46%)	5·2 (4·3–6·3)	1·2 (1·0–1·4)
Cervical cytohistopathology					
Normal	155/4358 (4%)	1 (ref)	230/1821 (13%)	1 (ref)	3·3 (2·7–4·2)
Low grade	79/827 (10%)	2·8 (2·1–3·6)	132/734 (18%)	1·5 (1·2–1·8)	1·9 (1·4–2·4)
High grade	251/1131 (22%)	6·5 (5·4–7·9)	29/127 (23%)	1·9 (1·3–2·6)	1·0 (0·7–1·5)
Cancer	101/228 (44%)	14·1 (11·1–17·9)	..	..	..
Age, years					
<30	313/5071 (6%)	1 (ref)	83/691 (12%)	1 (ref)	1·9 (1·5–2·4)
30–44	235/2864 (8%)	1·3 (1·1–1·6)	214/1600 (13%)	1·1 (0·9–1·4)	1·6 (1·4–1·9)
≥45	135/2015 (7%)	1·1 (0·9–1·3)	148/945 (16%)	1·3 (1·0–1·7)	2·3 (1·9–2·9)

B Cervical HPV16-positive

	HIV-negative n/N (%)	HIV-negative PR* (95% CI)	HIV-positive n/N (%)	HIV-positive PR* (95% CI)	PR* (95% CI) HIV-positive *vs* HIV-negative
Cervical cytohistopathology					
Normal	73/192 (38%)	1 (ref)	46/116 (40%)	1 (ref)	1·2 (0·9–1·6)
Low grade	46/136 (34%)	0·9 (0·7–1·2)	48/89 (54%)	1·4 (1·1–1·9)	1·6 (1·2–2·1)
High grade	197/514 (38%)	1·0 (0·8–1·3)	14/28 (50%)	1·3 (0·9–2·0)	1·3 (0·9–1·9)
Cancer	90/136 (66%)	1·9 (1·5–2·5)	..	..	..
Age, years					
<30	219/542 (40%)	1 (ref)	43/96 (45%)	1 (ref)	1·1 (0·9–1·4)
30–44	146/370 (40%)	1·0 (0·8–1·1)	50/111 (45%)	1·0 (0·7–1·4)	1·1 (0·9–1·5)
≥45	82/185 (44%)	1·1 (0·9–1·3)	32/66 (49%)	1·1 (0·8–1·5)	1·1 (0·8–1·5)

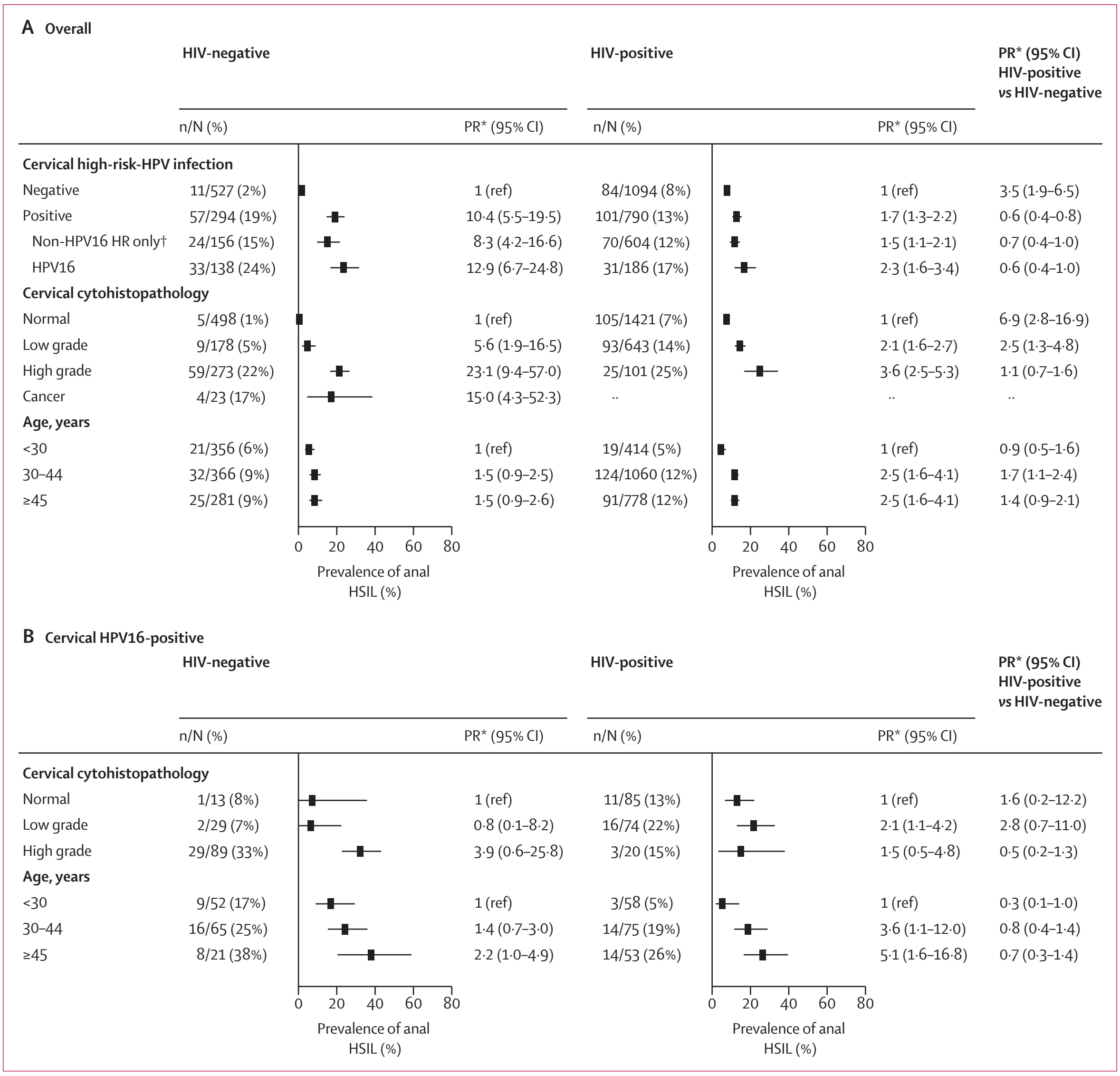
Figure 1: **Prevalence of anal HPV16 infection, by cervical high-risk HPV infection, cervical cytohistopathology, age, and HIV status**
Data are for all women (A) and cervical HPV16-positive women only (B). HPV16=human papillomavirus 16. PR=prevalence ratio. *Adjusted by age. †Coinfections of non-HPV16 high-risk HPV types and HPV16 are not included. ‡The denominator for HPV16 is different from that in table 2 because one study was excluded for reporting HPV16 prevalence, but not high-risk HPV prevalence.

in any stratum of cervical HPV16-positive women (figure 2B).

Prevalence of HPV16-positive anal HSIL was substantially higher in cervical high-risk HPV-positive women than in high-risk HPV-negative women (PR 14·8, 95% CI 3·3–66·3, p=0·0004 for HIV-negative and 3·0, 1·8–4·8, p<0·0001 for HIV-positive women; figure 3A), largely due to the strong association with cervical HPV16-positivity (24·9, 5·5–112·7, p<0·0001 for HIV-negative women and 6·2, 3·6–10·6 p<0·0001 for HIV-positive women; figure 3A). There were also significant associations with cervical cytohistopathology, most clearly with cervical HSIL versus normal cytology (PR not defined, 95% CI 2·6–∞ in HIV-negative women and PR 4·3, 2·4–7·8, p<0·0001 in HIV-positive women), but not with age (figure 3A).

In cervical HPV16-positive women, there was a strong association between HPV16-positive anal HSIL and age (figure 3B). In HIV-negative women, HPV16-positive anal HSIL prevalence was 25% (5/20) in women older than 45 years versus 4% (2/46) in women younger than 30 years (PR 5·8, 1·2–27·2, p=0·0273); in HIV-positive women, these values were 23% (12/52) versus 2% (1/55; 12·7, 1·7–94·2, p=0·0130). HPV16-positive anal HSIL prevalence is shown for other strata of cervical high-risk HPV status in the appendix (p 6).

www.thelancet.com/infection **Published online June 13, 2019** **http://dx.doi.org/10.1016/S1473-3099(19)30164-1**



A Overall

	HIV-negative n/N (%)	HIV-negative PR* (95% CI)	HIV-positive n/N (%)	HIV-positive PR* (95% CI)	PR* (95% CI) HIV-positive *vs* HIV-negative
Cervical high-risk-HPV infection					
Negative	11/527 (2%)	1 (ref)	84/1094 (8%)	1 (ref)	3·5 (1·9–6·5)
Positive	57/294 (19%)	10·4 (5·5–19·5)	101/790 (13%)	1·7 (1·3–2·2)	0·6 (0·4–0·8)
Non-HPV16 HR only†	24/156 (15%)	8·3 (4·2–16·6)	70/604 (12%)	1·5 (1·1–2·1)	0·7 (0·4–1·0)
HPV16	33/138 (24%)	12·9 (6·7–24·8)	31/186 (17%)	2·3 (1·6–3·4)	0·6 (0·4–1·0)
Cervical cytohistopathology					
Normal	5/498 (1%)	1 (ref)	105/1421 (7%)	1 (ref)	6·9 (2·8–16·9)
Low grade	9/178 (5%)	5·6 (1·9–16·5)	93/643 (14%)	2·1 (1·6–2·7)	2·5 (1·3–4·8)
High grade	59/273 (22%)	23·1 (9·4–57·0)	25/101 (25%)	3·6 (2·5–5·3)	1·1 (0·7–1·6)
Cancer	4/23 (17%)	15·0 (4·3–52·3)	..	..	..
Age, years					
<30	21/356 (6%)	1 (ref)	19/414 (5%)	1 (ref)	0·9 (0·5–1·6)
30–44	32/366 (9%)	1·5 (0·9–2·5)	124/1060 (12%)	2·5 (1·6–4·1)	1·7 (1·1–2·4)
≥45	25/281 (9%)	1·5 (0·9–2·6)	91/778 (12%)	2·5 (1·6–4·1)	1·4 (0·9–2·1)

B Cervical HPV16-positive

	HIV-negative n/N (%)	HIV-negative PR* (95% CI)	HIV-positive n/N (%)	HIV-positive PR* (95% CI)	PR* (95% CI) HIV-positive *vs* HIV-negative
Cervical cytohistopathology					
Normal	1/13 (8%)	1 (ref)	11/85 (13%)	1 (ref)	1·6 (0·2–12·2)
Low grade	2/29 (7%)	0·8 (0·1–8·2)	16/74 (22%)	2·1 (1·1–4·2)	2·8 (0·7–11·0)
High grade	29/89 (33%)	3·9 (0·6–25·8)	3/20 (15%)	1·5 (0·5–4·8)	0·5 (0·2–1·3)
Age, years					
<30	9/52 (17%)	1 (ref)	3/58 (5%)	1 (ref)	0·3 (0·1–1·0)
30–44	16/65 (25%)	1·4 (0·7–3·0)	14/75 (19%)	3·6 (1·1–12·0)	0·8 (0·4–1·4)
≥45	8/21 (38%)	2·2 (1·0–4·9)	14/53 (26%)	5·1 (1·6–16·8)	0·7 (0·3–1·4)

Figure 2: **Prevalence of anal HSIL, by cervical high-risk HPV infection, cervical cytohistopathology, age, and HIV status**
Data are for all women (A) and cervical HPV16-positive women only (B). HSIL=high-grade squamous intraepithelial lesions. HPV16=human papillomavirus 16. PR=prevalence ratio. *Adjusted by age. †Coinfections of non-HPV16 HR HPV types and HPV16 are not included.

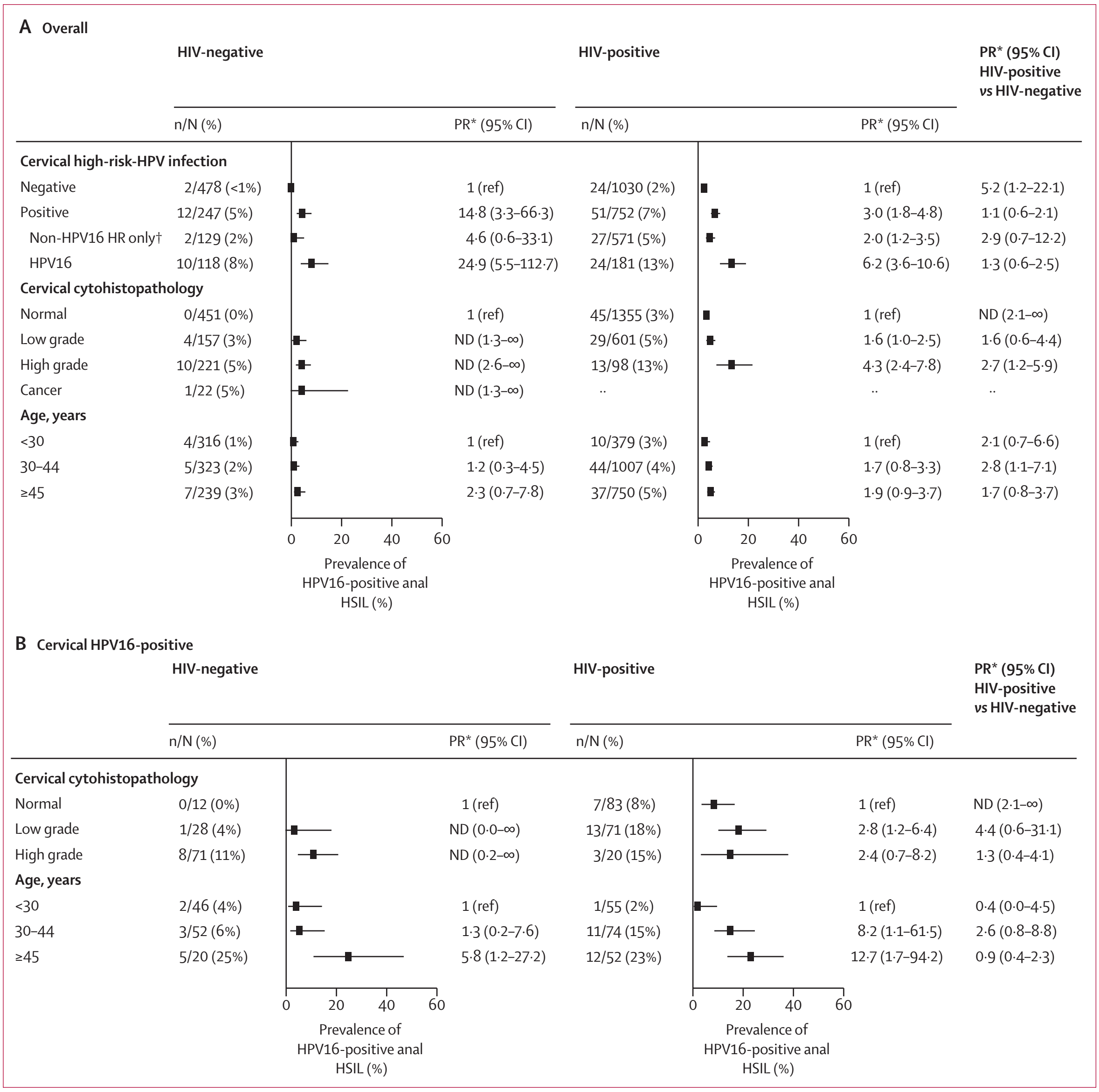
HIV status was a significant determinant of HPV16-positive anal HSIL in cervical high-risk HPV-negative women (PR 5·2, 95% CI 1·2–22·1, p=0·0242; figure 3A), women with normal cervical cytology (PR not defined, 2·1–∞, p<0·0001), and with cervical HSIL (2·7, 1·2–5·9, p=0·0142), but not in any stratum of cervical HPV16-positive women (figure 3B).

In HIV-positive women (appendix p 7), current CD4 cell count was significantly, albeit weakly, associated with anal HPV16 (for <350 cells per µL *vs* >500 cells per µL; PR 1·6, 95% CI 1·3–1·9, p<0·0001), anal HSIL (1·7, 1·3–2·2, p=0·0003), and HPV16-positive anal HSIL (1·6, 1·0–2·6, p=0·0365). Similar findings were seen for nadir CD4 cell count (appendix p 7). HIV viral load was positively associated with anal HPV16, but not with anal HSIL or HPV16-positive anal HSIL (appendix p 7).

Among HIV-positive women with cervical HPV16 infection (appendix p 7), anal HPV16 prevalence was highest in cervical HPV16-positive women with a current CD4 cell count of less than 350 cells per µL. No associations were seen for cervical HPV16-positive women in terms of HIV-related immunosuppression and anal HSIL nor HPV16-positive anal HSIL (appendix p 7).

Discussion

This collaborative pooled analysis is, to our knowledge, the first systematic effort to address how routine information from modern cervical cancer screening programmes



A Overall

	HIV-negative n/N (%)	HIV-negative PR* (95% CI)	HIV-positive n/N (%)	HIV-positive PR* (95% CI)	PR* (95% CI) HIV-positive *vs* HIV-negative
Cervical high-risk-HPV infection					
Negative	2/478 (<1%)	1 (ref)	24/1030 (2%)	1 (ref)	5·2 (1·2–22·1)
Positive	12/247 (5%)	14·8 (3·3–66·3)	51/752 (7%)	3·0 (1·8–4·8)	1·1 (0·6–2·1)
Non-HPV16 HR only†	2/129 (2%)	4·6 (0·6–33·1)	27/571 (5%)	2·0 (1·2–3·5)	2·9 (0·7–12·2)
HPV16	10/118 (8%)	24·9 (5·5–112·7)	24/181 (13%)	6·2 (3·6–10·6)	1·3 (0·6–2·5)
Cervical cytohistopathology					
Normal	0/451 (0%)	1 (ref)	45/1355 (3%)	1 (ref)	ND (2·1–∞)
Low grade	4/157 (3%)	ND (1·3–∞)	29/601 (5%)	1·6 (1·0–2·5)	1·6 (0·6–4·4)
High grade	10/221 (5%)	ND (2·6–∞)	13/98 (13%)	4·3 (2·4–7·8)	2·7 (1·2–5·9)
Cancer	1/22 (5%)	ND (1·3–∞)	..	..	..
Age, years					
<30	4/316 (1%)	1 (ref)	10/379 (3%)	1 (ref)	2·1 (0·7–6·6)
30–44	5/323 (2%)	1·2 (0·3–4·5)	44/1007 (4%)	1·7 (0·8–3·3)	2·8 (1·1–7·1)
≥45	7/239 (3%)	2·3 (0·7–7·8)	37/750 (5%)	1·9 (0·9–3·7)	1·7 (0·8–3·7)

B Cervical HPV16-positive

	HIV-negative n/N (%)	HIV-negative PR* (95% CI)	HIV-positive n/N (%)	HIV-positive PR* (95% CI)	PR* (95% CI) HIV-positive *vs* HIV-negative
Cervical cytohistopathology					
Normal	0/12 (0%)	1 (ref)	7/83 (8%)	1 (ref)	ND (2·1–∞)
Low grade	1/28 (4%)	ND (0·0–∞)	13/71 (18%)	2·8 (1·2–6·4)	4·4 (0·6–31·1)
High grade	8/71 (11%)	ND (0·2–∞)	3/20 (15%)	2·4 (0·7–8·2)	1·3 (0·4–4·1)
Age, years					
<30	2/46 (4%)	1 (ref)	1/55 (2%)	1 (ref)	0·4 (0·0–4·5)
30–44	3/52 (6%)	1·3 (0·2–7·6)	11/74 (15%)	8·2 (1·1–61·5)	2·6 (0·8–8·8)
≥45	5/20 (25%)	5·8 (1·2–27·2)	12/52 (23%)	12·7 (1·7–94·2)	0·9 (0·4–2·3)

Figure 3: **Prevalence of HPV16-positive anal HSIL, by cervical high-risk HPV infection, cervical cytohistopathology, age, and HIV status**
Data are for all women (A) and cervical HPV16-positive women only (B). HPV16=human papillomavirus 16. HSIL=high-grade squamous intraepithelial lesions. PR=prevalence ratio. ND=not defined *Adjusted by age. †Coinfections of non-HPV16 HR HPV types and HPV16 are not included.

might help to determine anal cancer risk. The findings show that cervical high-risk HPV infection, cervical cytohistopathological diagnosis, HIV status, and their combinations are all important determinants of a woman's anal cancer risk profile. The strongest determinants are a diagnosis of cervical cancer and cervical HPV16 positivity. HIV infection and severity of immunodeficiency are also strong determinants, but they offer little additional risk discrimination over status of cervical HPV genotype and cytohistopathology. Findings were broadly similar whether using anal HPV16 infection or anal HSIL as an outcome, and were consistent when restricted to a combined outcome of HPV16-positive anal HSIL, which highlighted age as a strong determinant of risk in cervical HPV16-positive women.

A strong association between the presence of high-risk HPV in cervical and anal specimens was confirmed.[46,51] However, the pooled analysis showed an even stronger association at the HPV type-specific level, suggesting shared exposure routes, with the cervix serving as a reservoir for HPV cross-infection of the anus or vice versa.[54] Given that studies in women have reported associations between anal sexual intercourse and anal HPV to be either non-significant,[47] or less important than number of sexual partners per se,[46,51] it is likely that HPV exposure is predominantly from cervix to anus. This

 Published online June 13, 2019 http://dx.doi.org/10.1016/S1473-3099(19)30164-1

exposure could be assisted by a sexual partner or, given the close anatomical proximity, non-sexual autoinoculation. These findings highlight notable differences from anal HPV transmission in men.[55]

Given the unique anal carcinogenicity of HPV16,[5] our primary objective was to measure female determinants of anal HPV16 prevalence as a surrogate of anal cancer risk. The prevalence of anal HPV16 is about 30% in HIV-positive men who have sex with men (MSM),[55] a population widely considered to be at a clinically relevant elevated risk of anal cancer, and the focus of numerous anal cancer prevention recommendations.[56–58] Using this benchmark, female subpopulations with clinically relevant elevated anal HPV16 prevalence included women with cervical cancer (44%), corroborating the excess anal cancer risk found in cancer registry-based studies,[11–13] followed by those with cervical HPV16 infection (39% in HIV-negative women, 46% in HIV-positive women), for which no studies of anal cancer outcomes exist.

In the absence of cervical genotyping for HPV16 or a history of cervical cancer, some discrimination of anal HPV16 prevalence can also be offered by cervical high-risk HPV, cervical cytopathology, and HIV status. For example, anal HPV16 prevalence is relatively high in HIV-positive women with cervical high-risk HPV infection (22%) or cervical HSIL (23%). In general, HIV-positive women had higher anal HPV16 prevalence than did HIV-negative women, supporting their known excess risk of anal cancer.[6–8] Severity of immunosuppression, although a risk factor for anal cancer,[8,59] was a relatively weak determinant of anal HPV16 prevalence (and anal HSIL) in HIV-positive women, which is consistent with findings in HIV-positive MSM.[60,61] Given that the non-HPV16 high-risk HPV fraction of anal cancer is somewhat larger in HIV-positive than in HIV-negative women,[5] anal HPV16 prevalence is arguably a less-specific surrogate of anal cancer risk in HIV-positive women. However, no other non-HPV16 high-risk HPV type clearly stands out as being associated with an increased risk of anal cancer;[5] not even HPV18, which does for cervical cancer. Therefore, we postulate that anal HPV16 still remains the most-specific virological surrogate of anal cancer risk, even in HIV-positive women.

As a complement to anal HPV16 as a surrogate for anal cancer risk, we also evaluated anal HSIL. Whereas anal HPV16 prevalence was standardly reported and measured by PCR-based assay in all studies, anal cytohistopathology was available only for about 24% of the study population. Furthermore, anal HSIL represents lesions reported according to cytology or histology (or both), the results of which were inextricably entwined (especially given the move towards harmonisation of cytology or histology nomenclature),[17] and might also be influenced by differing expertise in high-resolution anoscopy to detect biopsy-directed histological HSIL.[62] Despite these caveats, patterns of anal HSIL were broadly similar to those found for anal HPV16, with positivity for cervical HPV16 infection (24% prevalence of anal HSIL in HIV-negative women) or history of cervical cancer (17% prevalence of anal HSIL) being strong determinants of anal HSIL risk. These values compare to 24% prevalence of histological HSIL estimated in a large meta-analysis of HIV-positive MSM.[63]

22 (36%) of the 61 HIV-negative women with anal HSIL and 11 (5%) of the 217 HIV-positive women with anal HSIL were anal HPV-negative. HPV16 accounted for 41% (for HIV-negative women) and 42% (for HIV-positive women) of HPV-positive anal HSIL, which compares to 56% (for HIV-negative women) and 36% (for HIV-positive women), estimated in a wider meta-analysis of anal HSIL.[5] However, the meta-analysis showed further enrichment in HPV16 from anal HSIL to anal cancer,[5] irrespective of HIV status, suggesting that HPV16-positive anal HSIL is the most specific anal cancer surrogate. Although this outcome suffers from the same limitations of ascertainment as anal HSIL does, HPV16-positive anal HSIL showed strongest risk discrimination (ie, highest PRs) by cervical determinants, most notably by cervical HPV16 infection, cervical HSIL, and age group. Older age offered significant additional discrimination of HPV16-positive anal HSIL risk in cervical HPV16-positive women.

With respect to population representativeness, we did not present outcomes for HIV-negative women overall, given that many studies biased recruitment towards HIV-negative women with cervical lesions. For example, whereas anal HPV16 prevalence in HIV-negative women was 7% overall, it was only 3% in four large population-based studies totalling 6508 women.[21,29,46,51] Strata by cervical HPV and cytohistopathology, however, are expected to be representative of these subpopulations of HIV-negative women. HIV-positive women are also likely to be representative, because studies tended to recruit all patients in HIV clinics in a given time frame, without other selection criteria.

Our study has some limitations. First, the small numbers in certain important strata, most notably cervical HPV16-positive women with respect to the outcome of HPV16-positive anal HSIL. Second, the included studies lacked data on anal outcomes related to three areas: in HIV-positive women with cervical cancer, presumably due to their relative rarity at a population level (although we assume that they would show an anal cancer risk profile at least as bad as HIV-negative women with cervical cancer); according to the use of combined antiretroviral therapy (we addressed the issue of immune reconstitution through CD4 cell counts and HIV viral load); and by HPV vaccination status, although study years, country, and the age group of women suggest that most women were ineligible for HPV vaccination.

The rarity of anal cancer at a population level, combined with a scarcity of medical expertise and capacity—whether in digital anal rectal examination for early cancer diagnosis, or anal cytology in combination with high-resolution anoscopy for the detection and treatment of dysplastic anal lesions—means that any secondary anal cancer prevention programme needs to target the groups at highest risk. Although the effectiveness of such programmes is still to be established,[64] when such activities do exist, they should at least prioritise individuals according to an approach of equal management for equal risk. To date, secondary prevention in women has focused on HIV-positive populations and certain guidelines for HIV management make specific recommendations.[56–58] For example, the European AIDS Clinical Society advises digital rectal examination (with or without anal cytology) every 1–3 years for women with cervical dysplasia;[56] similarly, France recommends digital rectal examination and anoscopy for women with cervical dysplasia, with the option of expanding this approach to all HIV-positive women if local capacity allows.[57] New York State (USA) recommends digital rectal examination for all HIV-positive women, and annual cytology for those with cervical HSIL.[58] Thus, when recommendations for HIV-positive women exist, they tend to focus on women with cervical lesions and tend also to mirror those for HIV-positive MSM in the same setting.[56–58] The elevated anal cancer risk profile for HIV-positive women with cervical HSIL in the present work supports prioritisation over other HIV-positive women for secondary anal cancer prevention. However, in an era of shifting towards HPV-based cervical screening, the finding that HIV-positive women with cervical HPV16 infection (about 10% of HIV-positive women in this pooled analysis) have an at least similar anal cancer risk profile suggests they deserve similar prioritisation.

Expanding secondary anal cancer prevention beyond HIV-positive women would pose substantial problems of upscaling and require appropriate weighting of benefit versus risk. Nevertheless, HIV-negative women with cervical HPV16 had an anal cancer risk profile similar to that of HIV-positive women (and HIV-positive MSM) and arguably deserve equivalent anal cancer prevention management. Indeed, in high-income settings, the population burden of female anal cancer is largely unaffected by HIV[9,10] and so requires intervention in the HIV-negative population. As HPV-based cervical screening becomes more widespread, our findings advocate for further research into anal disease burden and prevention among HIV-negative cervical HPV16-positive women. There should be a particular focus on older generations of women who have missed out on the opportunity of prevention through HPV vaccination and in whom cervical HPV16 infection is rarer and more likely to represent long-standing persistent infection. Although numbers were small, half of all cervical HPV16-positive women aged older than 45 years harboured anal HPV16, and one quarter had HPV16-positive anal HSIL. Population-based anal cancer incidence begins to rise only in the fifth decade of life,[10] 10 years later than that for cervical cancer, so secondary prevention might also begin about 10 years later.

In summary, the prevalence of anal HPV16 infection, anal HSIL, or HPV16-positive HSIL can be used as surrogates to classify female subpopulations with different anal cancer risk. Such an approach is validated by identification of established high-risk groups—namely, women diagnosed with cervical precancer or cancer, or living with HIV. With respect to identifying the highest risk populations for targeted secondary prevention, HIV-negative women with cervical HPV16 infection, particularly those older than 45 years, had an anal cancer risk profile, based on these surrogate measures, that was similar to that of HIV-positive women.

Contributors

GMC initiated and coordinated the study. CL collected and analysed the data. CL and GMC wrote the first draft of the manuscript. All other authors generated the data from the 36 original studies. All authors interpreted the analysis and had input into the final manuscript.

Declaration of interests

AHS reports grants from US National Institutes of Health (NIH), during the conduct of the study, and grants and travel expenses from ViiV Healthcare, outside the submitted work. NAH reports grants from the US National Cancer Institute and NIH, during the conduct of the study. RAR reports grants from National Research University, Thailand and the Ratchadaphiseksomphot Endowment Fund, during the conduct of the study. JMP reports grants and personal fees from Antiva Biosciences; personal fees from Agenovir, Novan, Janssen Pharmaceuticals, and Vaccitech; grants and non-financial support from Merck; non-financial support from Hologic; and stock options from Virion Therapeutics and Ubiome, outside the submitted work. MFSvdL reports grants from Sanofi Pasteur, MSD, and Janssen Infectious Diseases and Vaccines; support for an investigator-initiated study from Merck; and non-financial support from Stichting Pathologie Onderzoek en Ontwikkeling, outside the submitted work. TW reports grants and personal fees from GlaxoSmithKline and ViiV Healthcare and grants from Gilead, outside the submitted work. All other authors declare no competing interests. The content of this publication is solely the responsibility of the authors and does not necessarily represent the official views of any of the institutions mentioned.

References

1 de Martel C, Plummer M, Vignat J, Franceschi S. Worldwide burden of cancer attributable to HPV by site, country and HPV type. *Int J Cancer* 2017; **141:** 664–70.

2 Islami F, Ferlay J, Lortet-Tieulent J, Bray F, Jemal A. International trends in anal cancer incidence rates. *Int J Epidemiol* 2017; **46:** 924–38.

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

4 IARC. Biological agents. Volume 100B. A review of human carcinogens. https://monographs.iarc.fr/wp-content/uploads/2018/06/mono100B.pdf (accessed Aug 22, 2018).

5 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:** 198–206.

6 Chaturvedi AK, Madeleine MM, Biggar RJ, Engels EA. Risk of human papillomavirus-associated cancers among persons with AIDS. *J Natl Cancer Inst* 2009; **101:** 1120–30.

7 Clifford GM, Polesel J, Rickenbach M, et al. Cancer risk in the Swiss HIV Cohort Study: associations with immunodeficiency, smoking, and highly active antiretroviral therapy. *J Natl Cancer Inst* 2005; **97:** 425–32.

8 Silverberg MJ, Lau B, Justice AC, et al. Risk of anal cancer in HIV-infected and HIV-uninfected individuals in North America. *Clin Infect Dis* 2012; **54:** 1026–34.

9 Tomassi MJ, Abbas MA, Klaristenfeld DD. Expectant management surveillance for patients at risk for invasive squamous cell carcinoma of the anus: a large US healthcare system experience. *Int J Colorectal Dis* 2019; **34:** 47–54.

10 Shiels MS, Pfeiffer RM, Chaturvedi AK, Kreimer AR, Engels EA. Impact of the HIV epidemic on the incidence rates of anal cancer in the United States. *J Natl Cancer Inst* 2012; **104:** 1591–98.

11 Acevedo-Fontanez AI, Suarez E, Torres Cintron CR, Ortiz AP. Risk of anal cancer in women with a human papillomavirus-related gynecological neoplasm: Puerto Rico 1987–2013. *J Low Genit Tract Dis* 2018; **22:** 225–30.

12 Teng CJ, Huon LK, Hu YW, et al. Secondary primary malignancy risk in patients with cervical cancer in Taiwan: a nationwide population-based study. *Medicine* 2015; **94:** e1803.

13 Hemminki K, Dong C, Vaittinen P. Second primary cancer after in situ and invasive cervical cancer. *Epidemiology* 2000; **11:** 457–61.

14 Ebisch RMF, Rutten DWE, IntHout J, et al. Long-lasting increased risk of human papillomavirus-related carcinomas and premalignancies after cervical intraepithelial neoplasia grade 3: a population-based cohort study. *J Clin Oncol* 2017; **35:** 2542–50.

15 Edgren G, Sparen P. Risk of anogenital cancer after diagnosis of cervical intraepithelial neoplasia: a prospective population-based study. *Lancet Oncol* 2007; **8:** 311–16.

16 Guan P, Howell-Jones R, Li N, et al. Human papillomavirus types in 115789 HPV-positive women: a meta-analysis from cervical infection to cancer. *Int J Cancer* 2012; **131:** 2349–59.

17 Darragh TM, Colgan TJ, Thomas Cox J, et al. The Lower Anogenital Squamous Terminology Standardization project for HPV-associated lesions: background and consensus recommendations from the College of American Pathologists and the American Society for Colposcopy and Cervical Pathology. *Int J Gynecol Pathol* 2013; **32:** 76–115.

18 Sohn AH, Kerr SJ, Hansudewechakul R, et al. Risk factors for human papillomavirus infection and abnormal cervical cytology among perinatally human immunodeficiency virus-infected and uninfected Asian youth. *Clin Infect Dis* 2018; **67:** 606–13.

19 Cranston RD, Cespedes MS, Paczuski P, et al. High baseline anal human papillomavirus and abnormal anal cytology in a phase 3 trial of the quadrivalent human papillomavirus vaccine in human immunodeficiency virus-infected individuals older than 26 years: ACTG 5298. *Sex Transm Dis* 2018; **45:** 266–71.

20 de Pokomandy A, Kaufman E, de Castro C, et al. The EVVA Cohort Study: anal and cervical type-specific human papillomavirus prevalence, persistence, and cytologic findings in women living with HIV. *J Infect Dis* 2017; **216:** 447–56.

21 Wei F, Li M, Wu X, et al. The prevalence and concordance of human papillomavirus infection in different anogenital sites among men and women in Liuzhou, China: a population-based study. *Int J Cancer* 2018; **142:** 1244–51.

22 Volpini LPB, Boldrini NAT, de Freitas LB, Miranda AE, Spano LC. The high prevalence of HPV and HPV16 European variants in cervical and anal samples of HIV-seropositive women with normal Pap test results. *PLoS One* 2017; **12:** e0176422.

23 Marra E, Kroone N, Freriks E, et al. Vaginal and anal human papillomavirus infection and seropositivity among female sex workers in Amsterdam, the Netherlands: prevalence, concordance and risk factors. *J Infection* 2018; **76:** 393–405.

24 Hidalgo-Tenorio C, de Jesus SE, Esquivias J, Pasquau J. High prevalence and incidence of HPV-related anal cancer precursor lesions in HIV-positive women in the late HAART era. *Enferm Infecc Microbiol Clin* 2018; **36:** 555–62.

25 Gonzalez-Losa MDR, Puerto-Solis M, Ayora-Talavera G, et al. Prevalence of anal infection due to high-risk human papillomavirus and analysis of E2 gene integrity among women with cervical abnormalities. *Enferm Infecc Microbiol Clin* 2018; **36:** 209–13.

26 Goeieman BJ, Firnhaber CS, Jong E, et al. Prevalence of anal HPV and anal dysplasia in HIV-infected women from Johannesburg, South Africa. *J Acquir Immune Defic Syndr* 2017; **75:** e59–64.

27 Dube Mandishora RS, Christiansen IK, Chin'ombe N, et al. Genotypic diversity of anogenital human papillomavirus in women attending cervical cancer screening in Harare, Zimbabwe. *J Med Virol* 2017; **89:** 1671–77.

28 Simpson S, 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.

29 Ortiz AP, Romaguera J, Perez CM, et al. Prevalence, genotyping, and correlates of anogenital HPV infection in a population-based sample of women in Puerto Rico. *Papillomavirus Res* 2016; **2:** 89–96.

30 Menezes LJ, Poongulali S, Tommasino M, et al. Prevalence and concordance of human papillomavirus infection at multiple anatomic sites among HIV-infected women from Chennai, India. *Int J STD AIDS* 2016; **27:** 543–53.

31 Heard I, Poizot-Martin I, Potard V, et al. Prevalence of and risk factors for anal oncogenic human papillomavirus infection among HIV-infected women in France in the combination antiretroviral therapy era. *J Infect Dis* 2016; **213:** 1455–61.

32 Veo CA, Saad SS, Fregnani JH, et al. Clinical characteristics of women diagnosed with carcinoma who tested positive for cervical and anal high-risk human papillomavirus DNA and E6 RNA. *Tumour Biol* 2015; **36:** 5399–405.

33 Tso FK, Rodrigues CL, Levi JE, Mattosinho de Castro Ferraz MG, Speck NM, Ribalta JC. HPV infection-associated anogenital cyto-colpo-histological findings and molecular typing in HIV-positive women. *Genet Mol Res* 2015; **14:** 17630–40.

34 Slama J, Sehnal B, Dusek L, Zima T, Cibula D. Impact of risk factors on prevalence of anal HPV infection in women with simultaneous cervical lesion. *Neoplasma* 2015; **62:** 308–14.

35 Robison K, Cronin B, Bregar A, et al. Anal cytology and human papillomavirus genotyping in women with a history of lower genital tract neoplasia compared with low-risk women. *Obstet Gynecol* 2015; **126:** 1294–300.

36 Ramautarsing RA, Phanuphak N, Chaithongwongwatthana S, et al. Cervical and anal HPV infection: cytological and histological abnormalities in HIV-infected women in Thailand. *J Virus Erad* 2015; **1:** 96–102.

37 Cambou MC, Luz PM, Lake JE, et al. Anal human papillomavirus (HPV) prevalences and factors associated with abnormal anal cytology in HIV-infected women in an urban cohort from Rio de Janeiro, Brazil. *AIDS Patient Care STDS* 2015; **29:** 4–12.

38 Kojic EM, Kang M, Cespedes MS, et al. Immunogenicity and safety of the quadrivalent human papillomavirus vaccine in HIV-1-infected women. *Clin Infect Dis* 2014; **59:** 127–35.

39 Godbole SV, Mane AK, Chidrawar SR, et al. Prevalence of anal human papillomavirus infection among HIV-infected women from India. *J Acquir Immune Defic Syndr* 2014; **67:** e111–14.

40 Vriend HJ, Bogaards JA, van der Klis FR, et al. Patterns of human papillomavirus DNA and antibody positivity in young males and females, suggesting a site-specific natural course of infection. *PLoS One* 2013; **8:** e60696.

41 Ortiz AP, Romaguera J, Perez CM, et al. Human papillomavirus infection in women in Puerto Rico: agreement between physician-collected and self-collected anogenital specimens. *J Low Genit Tract Dis* 2013; **17:** 210–17.

42 Hessol NA, Holly EA, Efird JT, et al. Concomitant anal and cervical human papillomavirusV infections and intraepithelial neoplasia in HIV-infected and uninfected women. *AIDS* 2013; **27:** 1743–51.

43 Hernandez BY, Ka'opua LS, Scanlan L, et al. Cervical and anal human papillomavirus infection in adult women in American Samoa. *Asia Pac J Public Health* 2013; **25:** 19–31.

44 Pierangeli A, Scagnolari C, Selvaggi C, et al. High detection rate of human papillomavirus in anal brushings from women attending a proctology clinic. *J Infect* 2012; **65:** 255–61.

45 D'Hauwers KW, Cornelissen T, Depuydt CE, et al. Anal human papillomavirus DNA in women at a colposcopy clinic. *Eur J Obstet Gynecol Reprod Biol* 2012; **164:** 69–73.

46 Castro FA, Quint W, Gonzalez P, et al. Prevalence of and risk factors for anal human papillomavirus infection among young healthy women in Costa Rica. *J Infect Dis* 2012; **206:** 1103–10.

47 Kojic EM, Cu-Uvin S, Conley L, et al. Human papillomavirus infection and cytologic abnormalities of the anus and cervix among HIV-infected women in the study to understand the natural history of HIV/AIDS in the era of effective therapy (the SUN study). *Sex Transm Dis* 2011; **38:** 253–59.

48 Heraclio Sde A, Souza AS, Pinto FR, Amorim MM, Oliveira Mde L, Souza PR. Agreement between methods for diagnosing HPV-induced anal lesions in women with cervical neoplasia. *Acta Cytol* 2011; **55:** 218–24.

49 Park IU, Ogilvie JW Jr, Anderson KE, et al. Anal human papillomavirus infection and abnormal anal cytology in women with genital neoplasia. *Gynecol Oncol* 2009; **114:** 399–403.

50 Goncalves MA, Randi G, Arslan A, et al. HPV type infection in different anogenital sites among HIV-positive Brazilian women. *Infect Agent Cancer* 2008; **3:** 5.

51 Hernandez BY, McDuffie K, Zhu X, et al. Anal human papillomavirus infection in women and its relationship with cervical infection. *Cancer Epidemiol Biomarkers Prev* 2005; **14:** 2550–56.

52 Moscicki AB, Durako SJ, Houser J, et al. Human papillomavirus infection and abnormal cytology of the anus in HIV-infected and uninfected adolescents. *AIDS* 2003; **17:** 311–20.

53 Palefsky JM, Holly EA, Ralston ML, Da Costa M, Greenblatt RM. Prevalence and risk factors for anal human papillomavirus infection in human immunodeficiency virus (HIV)-positive and high-risk HIV-negative women. *J Infect Dis* 2001; **183:** 383–91.

54 Goodman MT, Shvetsov YB, McDuffie K, et al. Sequential acquisition of human papillomavirus (HPV) infection of the anus and cervix: the Hawaii HPV Cohort Study. *J Infect Dis* 2010; **201:** 1331–39.

55 Marra E, Lin C, Clifford GM. Type-specific anal human papillomavirus prevalence among men, according to sexual preference and hiv status: a systematic literature review and meta-analysis. *J Infect Dis* 2019; **219:** 590–98.

56 European AIDS Clinical Society. EACS guidelines version 9.1. 2018. http://www.eacsociety.org/files/2018_guidelines-9.1-english.pdf (accessed Nov 17, 2018).

57 Morlat P. Prise en charge médicale des personnes vivant avec le VIH. Recommandations du groupe d'expert. Cancers. Conseil national du sida et des hépatites virales/Agence nationale de recherches sur le sida et les hépatites virales. 2017. https://cns.sante.fr/wp-content/uploads/2017/10/experts-vih_cancers.pdf (accessed Aug 22, 2018).

58 National AIDS Treatment Advocacy Project. NYS guidelines recommendations on anal pap smears. http://www.natap.org/2010/HIV/032510_01.htm (accessed Aug 22, 2018).

59 Bertisch B, Franceschi S, Lise M, et al. Risk factors for anal cancer in persons infected with HIV: a nested case-control study in the Swiss HIV Cohort Study. *Am J Epidemiol* 2013; **178:** 877–84.

60 Combes JD, Heard I, Poizot-Martin I, et al. Prevalence and risk factors for anal human papillomavirus infection in human immunodeficiency virus-positive men who have sex with men. *J Infect Dis* 2018; **217:** 1535–43.

61 de Pokomandy A, Rouleau D, Ghattas G, et al. HAART and progression to high-grade anal intraepithelial neoplasia in men who have sex with men and are infected with HIV. *Clin Infect Dis* 2011; **52:** 1174–81.

62 Clifford GM, Siproudhis L, Piroth L, et al. Determinants of high-grade anal intraepithelial lesions in HIV-positive men having sex with men. *AIDS* 2018; **32:** 2363–71.

63 Machalek DA, Poynten M, Jin F, et al. Anal human papillomavirus infection and associated neoplastic lesions in men who have sex with men: a systematic review and meta-analysis. *Lancet Oncol* 2012; **13:** 487–500.

64 Stewart DB, Gaertner WB, Glasgow SC, et al. The American Society of Colon and Rectal Surgeons clinical practice guidelines for anal squamous cell cancers (revised 2018). *Dis Colon Rectum* 2018; **61:** 755–74.