Association of antiretroviral therapy with anal high-risk human papillomavirus, anal intraepithelial neoplasia, and anal cancer in people living with HIV: a systematic review and meta-analysis

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Summary

Background The effect of antiretroviral therapy (ART) on the natural history of anal high-risk HPV and anal lesion progression is not well established. We reviewed the association of ART and other HIV-related factors on anal HPV infection, anal intraepithelial neoplasia (AIN), and anal cancer among people living with HIV.

Methods For this systematic review and meta-analysis, we searched MEDLINE and EMBASE for studies published between Jan 1, 1996, and Oct 30, 2019, that reported the association of HIV-related exposures (ART or highly active ART [HAART], HIV-RNA plasma viral load [PVL], and nadir or current CD4 cell count) with outcomes of anal high-risk HPV prevalence, incidence, and persistence; prevalence, incidence, progression, or regression of anal histological and cytological abnormalities; and anal cancer incidence. Effect estimates were extracted whenever available; otherwise, they were calculated from raw data. We assessed the risk of bias of included studies using the Newcastle-Ottawa scale, and random-effects meta-analyses were done to examine heterogeneity using the I^2 statistic. This study is registered on the PROSPERO database, CRD42018007271.

Findings We identified 6777 studies, of which 5377 were excluded before full-text review. 122 studies providing estimates for 130 distinct populations matched the inclusion criteria. The populations comprised 417 006 people living with HIV (women, men who have sex with men, and men who have sex with women). 41 (32%) population estimates were not stratified by sex or sexual orientation. People living with HIV receiving ART had 35% lower high-risk HPV prevalence than ART-naive people (crude odds ratio [OR] 0·65, 95% CI 0·54–0·79; I^2 12·1%, p=0·31) in 18 studies, and prolonged ART use was associated with a 10% reduction per year in high-risk HPV prevalence in two studies (adjusted OR 0·90, 0·85–0·95; I^2 0%, p=0·88). People living with HIV with undetectable PVL had lower HSIL-AIN2+ prevalence than those with detectable PVL (crude OR 0·84, 0·72–0·98; I^2 0%, p=0·80) in 16 studies, particularly if sustained for more than 1 year (crude OR 0·62, 0·47–0·81; I^2 0%, p=0·51). ART was not associated with anal cancer incidence when adjusted for years living with HIV in three studies (adjusted hazard ratio [HR] 1·11, 95% CI 0·68–1·80; I^2 0%, p=0·57), but ART users with sustained undetectable HIV PVL had 44% lower risk of anal cancer than those without (adjusted HR 0·56, 0·44–0·70; I^2 0%, p=0·94) and for each increase in nadir CD4 cell counts of 100 cells per µL, there was a 40% decrease in anal cancer incidence (crude HR 0·60, 0·46–0·78; I^2 21·7%, p=0·26).

Interpretation Effective ART use and early initiation at high nadir CD4 counts might reduce anal high-risk HPV infection and anal cancer risk. Although most studies were cross-sectional in design and few adjusted for potential confounders, this analysis provides comprehensive estimates of the effect of ART and HIV-related factors on the natural history of anal HPV-related disease in people living with HIV.

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Introduction

People living with HIV are at increased risk of high-risk human papillomavirus (HPV) infection and persistence,[1] anal high-grade squamous intraepithelial lesions (HSIL) or high-grade anal intraepithelial neoplasia (AIN) 2, and incidence of anal cancer.[2,3] Anal cancer is the fourth most common cancer in men who have sex with men (MSM) living with HIV,[4] and evidence suggests increased incidence of anal cancer in women living with HIV and men who have sex with women (MSW) living with HIV compared with their HIV-negative counterparts.[3,5–7]

As antiretroviral therapy (ART) is scaled-up, increased survival times in people living with HIV might be associated with an increase in the incidence of anal and other cancers. A 2015 meta-analysis of observational studies evaluating the incidence of malignancies before and after the introduction of highly active antiretroviral therapy (HAART) reported that the risk of anal cancer was four times higher in the post-HAART period than in the

Research in context

Evidence before this study

We searched MEDLINE and EMBASE for all available publications in English from Jan 1, 1996, to Oct 30, 2019, using search terms for HPV, squamous intraepithelial lesions (SIL), anal intraepithelial lesions (AIN), anal cancer, antiretroviral therapy (ART and highly active ART [HAART]), and HIV. Studies were eligible if they reported the effect of ART on the prevalence, incidence, and persistence of high-risk HPV infections identified in the anal canal, the prevalence and incidence of anal pre-cancerous lesions, and the incidence of anal cancer. We were able to evaluate the association of ART, HIV plasma viral load, and markers of immune response such as CD4 cell counts (the lowest recorded [nadir] and the current, or CD4 counts measured at the same time as the outcome) with the different outcomes explored. However, most studies were cross-sectional in design, restricting our understanding of the effect of ART duration; few studies had rigorous histological verification for outcomes of low-grade and high-grade anal lesions; few studies adjusted for potential confounders including the history or frequency of receptive anal intercourse; and finally, few studies were done in population groups other than men who have sex with men in high-income settings.

Added value of this study

To our knowledge, this is the first meta-analysis investigating the association of ART use, HIV plasma viral load, and CD4 cell count with the outcomes of anal high-risk HPV infection, cytology-confirmed and histology-confirmed anal lesions, and anal cancer incidence in people living with HIV. Our findings suggest that current rather than historical immunosuppression could be effective in clearing high-risk HPV infection, whereas measures of past immunosuppression could be more predictive of anal cancer risk. A potential differential effect of HPV genotypes could not be explored.

Implications of all the available evidence

This study has practical implications for the management of people living with HIV and control of anal cancer worldwide. Given the high prevalence of anal lesions in high-risk populations such as people living with HIV and the challenges in diagnosis and effective management of anal lesions, our study highlights the need to emphasise early diagnosis of HIV infection and rapidly initiate and maintain effective ART in populations at increased risk of anal cancer.

pre-HAART period.[8] Given the limitations in anal cancer screening,[9,10] high rates of recurrence following management of anal lesions,[11] and low access to HPV vaccination in people living with HIV,[12] evidence of the effect of ART on the prevalence and incidence of anal high-risk HPV infection, anal lesions, and anal cancer is needed.

In a previous meta-analysis,[13] we reported that despite wide variability in the degree of immune deficiency of included participants, effective ART (evidenced by early initiation; sustained adherence consistent with undetectable HIV RNA plasma viral load [PVL] and sustained high CD4 cell count) was associated with reductions in the prevalence of cervical high-risk HPV infection, incidence or progression of cervical intraepithelial neoplasia (CIN), and incidence of invasive cervical cancer.

The aims of this study were to systematically review and summarise the literature on the association of ART and HIV-related factors, including HIV PVL and nadir and current CD4 cell count, with anal high-risk HPV prevalence; prevalence, incidence, progression, and regression of atypical squamous cells of undetermined significance or anal intraepithelial neoplasia, grade 1 or greater (ASCUS-AIN1+), or high-grade squamous intraepithelial lesions or anal intraepithelial neoplasia, grade 2 or greater (HSIL-AIN2+); and anal cancer incidence.

Methods

Search strategy and selection criteria

For this systematic review and meta-analysis, we searched MEDLINE and EMBASE for publications in English between Jan 1, 1996 (when HAART was introduced), and Oct 30, 2019, using search terms for HPV, SIL, AIN lesions, anal cancer and antiretroviral therapy (ART, HAART), and HIV (appendix pp 1–4). Reference lists of reviews and all original articles identified in the systematic search were checked. All abstracts were screened by one author (HK). Full-text copies of relevant publications were obtained and assessed for eligibility by one author (HK) and 20% verified by a second author (AC). Consensus was reached on potential relevance following detailed discussion between the data extractors.

See Online for appendix

Studies were eligible if they reported, in people living with HIV, the association of combined use of ART or HAART (analysis 1), HIV PVL (analysis 2), and nadir and current or contemporary (at time of outcome measure) CD4 cell count (analysis 3) with the following outcomes: anal high-risk HPV prevalence, incidence, and persistence; cytology-confirmed or histology-confirmed anal SIL or AIN lesion prevalence, incidence, progression, or regression; and anal cancer incidence. Studies were also considered eligible if they provided raw data to calculate an unadjusted effect estimate. Studies were included if they enrolled participants after HAART was introduced (ie, from 1996 onwards), with the exception of studies reporting anal cancer incidence, in which follow-up of people living with HIV was more commonly reported over a longer duration from 1980 onwards. There was no restriction on study design.

Various cutoffs for defining HIV viral detection were considered depending on the assays used. To maximise the number of studies included in analysis 2, we

considered undetectable HIV to have PVL of up to 400 copies per mL. For prospective studies, sustained viral suppression was defined as PVL lower than 1000 copies per mL at a minimum of two timepoints over an established period. Duration with undetectable HIV PVL was defined as PVL lower than 40 copies per mL at a minimum of two timepoints over an established period. Nadir CD4 cell counts with a cutoff of 200 cells per µL and current CD4 count with a cutoff of 500 cells per µL were used in the meta-analysis (analysis 3), as these measures were the most frequently reported.

For HPV outcomes, studies reporting prevalence, incidence or persistence of anal high-risk HPV or any HPV were included were included. There were no exclusions on the basis of HPV test methods (appendix pp 12–18). For the anal lesion outcomes, included studies reported on: associations of ART, HIV PVL, and nadir or current CD4 count with the incidence, progression, and regression of any AIN lesion grade diagnosed by histology or high-resolution anoscopy or any SIL grade diagnosed by cytology (including atypical squamous cells of undetermined significance [ASCUS], as well as HSIL and low-grade squamous intraepithelial lesions [LSIL]), or a combination of any of the three methods (ie, composite endpoint as previously described[14]).

For publications that reported results from the same cohort but at different follow-up visits, the publication that gave the most detailed description of the cohort and study design and the most complete set of results was included. There was no restriction on sex, age, or geographical location.

Data analysis

From the consensus list, data were extracted by one author (HK) and a random sample of 25% was independently verified by a second (AC). For studies reporting prevalence of high-risk HPV or anal lesions, odds ratios (ORs) were extracted. For studies reporting anal lesion incidence, progression, or regression, hazard ratios (HRs), rate ratios (RRs), or ORs were extracted. Adjusted effect estimates were extracted where available. For the cross-sectional studies, in which adjusted effect estimates were not reported but raw data were provided, crude ORs were calculated (HK) and independently verified (AC). For anal cancer incidence, estimates restricted to participants recruited after 1996 were extracted where available. In studies that provided estimates irrespective of recruitment year together with estimates for patients recruited after 1996, only the latter estimates were extracted to avoid data duplication.

For the **study dataset** see https://data.mendeley.com/datasets/vxbt7rc27j/1

We adapted the Newcastle-Ottawa scale[15] to assess the methodological quality of studies (criteria established by HK and PM; appendix pp 5–9), and assessment was done by one author (HK). Studies were assessed on: representativeness of participants (ie, proportion of ART users with undetectable HIV PVL); adjustment for HIV-related factors (including any of current and nadir CD4 cell count, HIV plasma viral detection or suppression, duration on ART or years living with HIV) and history of receptive anal intercourse; and ascertainment of outcome (HPV test used and method for diagnosis of cytology-confirmed and histology-confirmed lesions and anal cancer). Studies evaluating ASCUS-AIN1+ and HSIL-AIN2+ were assessed on the basis of their verification methods (high-resolution anoscopy alone, cytology alone, cytology combined with high-resolution anoscopy, histology alone, or in combination), biopsy indication and proportion of participants undergoing biopsy, and whether there was independent verification of final diagnosis (appendix pp 8, 9).

We did meta-analyses for the discrete outcomes of high-risk HPV prevalence, incidence, and persistence; prevalence, incidence, progression, and regression of low-grade lesions (ASCUS-AIN1+ verified by cytology or histology) and high-grade lesions (HSIL-AIN2+ by cytology or histology); and incidence of anal cancer. Individual meta-analyses were done for association of each of the outcomes with the following exposures: ART use, undetectable HIV viral load or duration of undetectable HIV PVL, nadir CD4 count (≥200 vs <200 cells per µL), and current CD4 count, irrespective of ART use (≥500 vs <500 cells per µL).

We used random-effects meta-analysis to estimate pooled effects to account for between-study heterogeneity.[16] We examined heterogeneity using the I^2 statistic and publication bias (defined as $p<0·05$) using funnel plots and Begg's test for correlation between the effect estimate and their variances.[17,18] Subgroup analyses by sex, sexual orientation, geographical region, and study design were done to compare pooled effects and heterogeneity. Studies that adjusted for HIV-related factors and receptive anal intercourse were considered separately in sensitivity analyses, as were studies that scored highly on the Newcastle-Ottawa adapted scale.

We also did a random-effects meta-analysis to derive pooled prevalence of ART use, undetectable HIV PVL, reported receptive anal intercourse, and prevalence of high-risk HPV, ASCUS-AIN1+, and HSIL-AIN2+, stratified by sex, sexual orientation, and geographical region.

Data were analysed using Stata (version 16). This Article was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[19] and the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines.[20] This study is registered on the PROSPERO database at the Centre of Reviews and Dissemination (University of York, York, UK), CRD42018007271. The study dataset is available on the Mendeley online repository.

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

Results

We identified 6777 publications through MEDLINE and EMBASE searches, of which 1975 duplicates were removed and then 3402 excluded after abstract review, leaving 1400 articles for full-text review. 118 articles matched the inclusion criteria and four additional publications[21–24] were identified through cross-referencing (figure 1), providing estimates from 130 discrete populations from 122 studies with data on 417 006 people living with HIV. There were 25 (19%) separate effect estimates for women (n=5221), 57 (44%) for MSM (n=33 888), and seven (5%) for MSW (including male users of injectable drugs; n=1084). 16 (12%) effect estimates included men only but were not stratified by sexual orientation (n=82 164 men) and 25 (19%) effect estimates included women and men but were not stratified by sex or sexual orientation (n=294 649 people living with HIV). Two studies included both MSM and MSW (or male users of injectable drugs), but presented separate effect estimates for each group,[25,26] and three studies included women, MSM, and MSW, but presented separate effect estimates for each group.[27–29]

Most studies were cross-sectional and prospective cohort studies. The rest were retrospective cohort or chart reviews, case-control or convenience studies, randomised control trials, and record or registry linkage studies (appendix p 10). Most studies were done in North America (n=53) and Europe (n=41), followed by Asia (n=20), Latin America (n=10), Africa (n=4), and Australia (n=2).

The pooled prevalence of ART use was 77·9% (95% CI 72·6–83·2) in women, 74·7% (70·4–78·9) in MSM, and 79·7% (71·8–87·5) in MSW (appendix p 11), and of undetectable HIV PVL was 71·2% (63·0–79·4), 67·0% (60·1–73·9), and 62·5% (47·0–77·9), respectively. Most studies reported HIV viral detection in all enrolled participants, and not in ART users alone. Of 40 studies with available data for distinct populations of women, MSM, and MSW, 3192 of 5888 of women and 42 of 660 of MSW reported ever practicing receptive anal intercourse, corresponding to a pooled prevalence of 34·6% for women and 6·8% for MSW (appendix p 11). 4338 of 8099 MSM (pooled prevalence 60·4%) reported recent (≤12 months) receptive anal intercourse. In women, the pooled prevalence of anal high-risk HPV was 43·8%, 18·3% for ASCUS-AIN1+, and 13·7% HSIL-AIN2+ (appendix p 11). In MSW, these estimates were 28·6%, 23·6%, and 4·1%; for MSM, they were 69·0%, 38·0%, and 30·5%.

100 populations were included in the meta-analysis evaluating any exposure (ART, undetectable HIV PVL, nadir or current CD4 count) and any of the outcomes of high-risk HPV prevalence, ASCUS-AIN1+ prevalence, HSIL-AIN2+ prevalence, and anal cancer incidence; six studies reported more than one outcome (table 1).[30–35] The remaining 30 populations evaluated any HIV-related factor and outcomes including any HPV prevalence, HPV16 prevalence, high-risk HPV incidence, high-risk HPV persistence, ASCUS-AIN1+ incidence, HSIL-AIN2+ incidence, HSIL-AIN2+ clearance following treatment, HSIL-AIN2+ recurrence following treatment, and spontaneous regression of HSIL-AIN2+. Individual study characteristics are summarised in the appendix (pp 12–18).

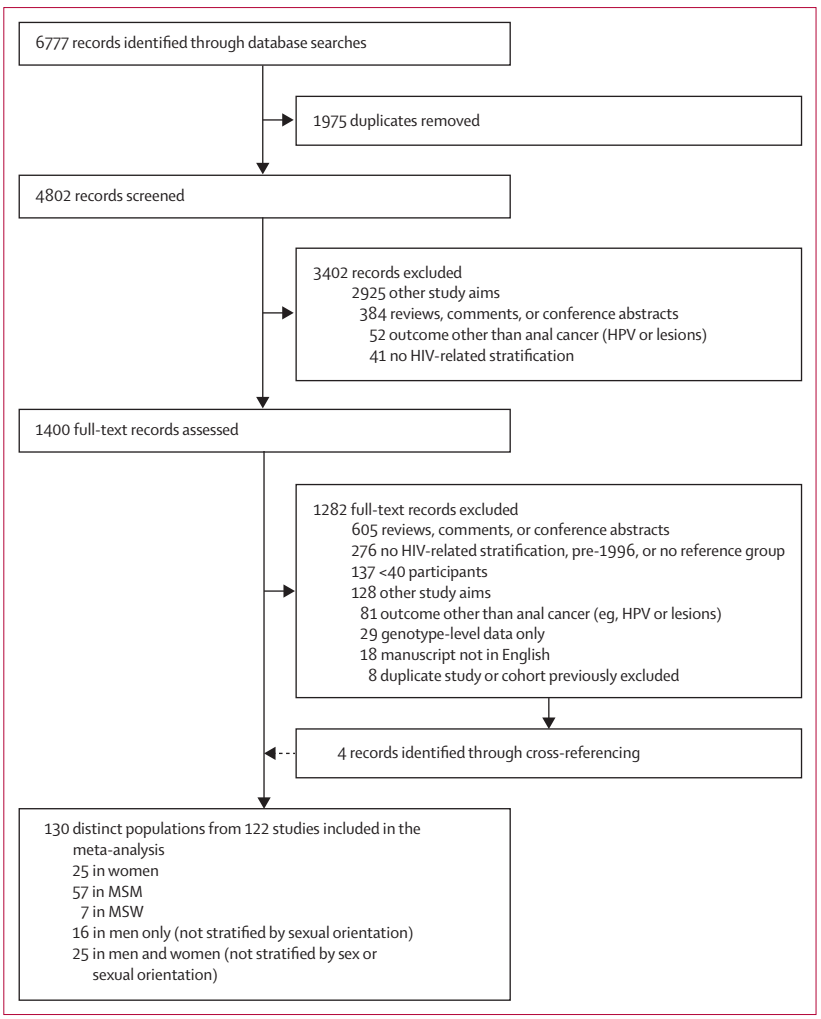

Figure 1: **Study selection for outcomes of anal high-risk HPV, anal lesions, and anal cancer**
MSM=men who have sex with men. MSW=men who have sex with women.

In the meta-analysis of the association of ART and anal high-risk HPV prevalence from 18 studies, people living with HIV and receiving ART had a 35% lower risk of anal high-risk HPV prevalence than ART-naive individuals (crude OR 0·65, 95% CI 0·54–0·79; adjusted OR 0·45, 0·19–1·07, for any nadir or current CD4 count, HIV PVL, or history of receptive anal intercourse), with a low degree of heterogeneity between studies (I^2 24·7% for adjusted estimate, p value for heterogeneity 0·27; table 2, figure 2). In two studies,[30,36] there was a 10% reduction in high-risk HPV prevalence per additional

	All populations	ART *vs* ART-naive	Undetectable *vs* detectable HIV PVL	Nadir CD4 count ≥200 cells per μL *vs* <200 cells per μL	Current CD4 count ≥500 cells per μL *vs* <500 cells per μL	Other*
All studies						
Populations	130	79	68	29	40	27
People living with HIV	417 006	161 982	45 912	26 001	17 390	257 771
HR-HPV prevalence[22,23,30-32,34-57]†						
Populations	29	18	17	6	8	4
People living with HIV	7750	5311	4487	1107	2505	1745
ASCUS-AIN1+ prevalence[26-28,32-35,58-82]						
Populations	37	28	20	10	11	2
People living with HIV	8790	6782	5342	1720	2198	351
HSIL-AIN2+ prevalence[30,31,83-103]						
Populations	23	15	16	6	5	7
People living with HIV	8400	6114	6412	3056	2614	3264
Anal cancer incidence[3,21,104-118]						
Populations	17	9	3	3	0	10
People living with HIV	380 231	141 877	20 862	19 775	..	251 580
Any HPV prevalence[25,33,65,119-127]‡						
Populations	13	5	5	0	5	1
People living with HIV	2968	559	1232	..	1098	404
HPV16 prevalence[23,32,37-39,47,53,119,120]						
Populations	9	7	6	2	4	0
People living with HIV	2539	1907	1848	354	1283	-
HR-HPV incidence[36,128]						
Populations	2	2	0	0	0	0
People living with HIV	1345	1345	..	..	..	..
HR-HPV persistence[24,128-130]						
Populations	4	4	0	0	0	1
People living with HIV	1444	1444	..	..	..	123
ASCUS-AIN1+ incidence[29,35,131]						
Populations	5	4	3	3	4	1
People living with HIV	562	514	243	243	329	233
HSIL-AIN2+ incidence[132-135]						
Populations	5	1	2	0	3	2
People living with HIV	898	310	299	..	623	270
HSIL-AIN2+ clearance following treatment[136-138]						
Populations	3	1	2	0	3	1
People living with HIV	7487	120	7331	..	7487	156
HSIL-AIN2+ recurrence following treatment[139]						
Populations	1	1	1	1	1	0
People living with HIV	100	100	100	100	100	..
HSIL-AIN2+ spontaneous regression[134,140]						
Populations	2	0	2	0	0	0
People living with HIV	261	..	261	..	..	..

ART=antiretroviral therapy. ASCUS-AIN1+=atypical squamous cells of undetermined significance or anal intraepithelial neoplasia, grade 1 or greater. HR-HPV=high-risk papillomavirus. HSIL-AIN2+=high-grade squamous intraepithelial lesions or anal intraepithelial neoplasia, grade 2 or greater. PVL=plasma viral load. *Includes associations of ART duration, HIV PVL, and nadir and current CD4 counts at thresholds other than those defined here. All results are given in the appendix (p 24). †Includes any of the following confirmed, probable, and possible carcinogenic types: HPV16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 67, 68, 70, 73, 82. ‡Includes any high-risk and low-risk HPV types.

Table 1: **Summary of studies included in the meta-analyses by outcome**

year of ART (table 2). Compared with detectable HIV PVL, undetectable HIV PVL was associated with a 33% reduction in high-risk HPV prevalence in 17 studies (table 2) and 36% reduction in HPV16 prevalence in four studies[37,38,119,120] (crude OR 0·64, 0·43–0·97; I^2 17·9%, p=0·30; appendix p 24).

	Crude analysis					Adjusted analysis				
	Studies (n)	Effect estimate (95%CI)	I^2	p for heterogeneity	Begg's p value	Studies (n)	Effect estimate (95% CI)	I^2	p for heterogeneity	Begg's p value
HR-HPV prevalence										
ART *vs* ART naive[22,23,31,32,34–37,39,41,42,44,47,48,50,52,53,57]	18	0·65 (0·54–0·79)	12·1%	0·31	0·622	3	0·45 (0·19–1·07)	24·7%	0·27	..
Per year of ART[30,36]	..	..	..	..	..	2	0·90 (0·85–0·95)	0%	0·88	..
Undetectable *vs* detectable HIV PVL[22,30,31,36–38,40–43,45,46,51–54,57]	17	0·67 (0·57–0·78)	4·0%	0·41	0·621	2	0·75 (0·52–1·09)	0%	0·41	..
Nadir CD4 count ≥200 cells per μL *vs* <200 cells per μL[22,38–40,54,57]	6	0·68 (0·40–1·14)	58·9%	0·033	..	1	0·27 (0·08–0·95)	..	..	..
Nadir CD4 count per increase of 100 cells per μL[30,35]	2	1·02 (0·76–1·36)	73·1%	0·054	..	..	..	..	..	..
Current CD4 count ≥500 cells per μL *vs* <500 cells per μL[23,37,38,41,44,46,49,56]	8	0·72 (0·60–0·87)	5·1%	0·39	..	..	..	..	..	..
Current CD4 count per increase of 100 cells per μL[30,35]	..	..	..	..	..	2	0·89 (0·81–0·97)	0%	0·58	..
ASCUS-AIN1+ prevalence										
ART *vs* ART naive[26,27,32–35,58–60,63–68,72–78,80–82]	28	0·96 (0·74–1·25)	55·4%	<0·0001	0·782	2	0·52 (0·08–3·47)	79·4%	0·027	..
Undetectable *vs* detectable HIV PVL[26,27,32,33,58,59,61–64,67,73,76–78,80,81]	20	0·73 (0·64–0·83)	0%	0·50	0·011	1	0·70 (0·57–0·86)	..	..	..
Nadir CD4 count ≥200 cells per μL *vs* <200 cells per μL[27,58,61,62,64,67,80,81]	10	0·52 (0·40–0·67)	0%	0·53	0·325	..	..	..	..	..
Current CD4 count ≥500 cells per μL *vs* <500 cells per μL[28,61,69–71,74,77,79,82]	11	0·65 (0·48–0·88)	38·1%	0·095	0·815	1	0·59 (0·37–0·92)	..	..	..
Current CD4 count per increase of 100 cells per μL[35,72]	2	0·92 (0·80–1·07)	0%	0·89	..	1	0·91 (0·68–1·14)	..	..	..
HSIL-AIN2+ prevalence										
ART *vs* ART naive[31,83–89,91,92,94,97,99,100,102]	15	1·18 (0·81–1·73)	48·0%	0·020	0·347	4	1·95 (0·80–4·77)	63·8%	0·040	..
Undetectable *vs* detectable HIV PVL[30,31,84–86,88,89,91–94,96,98–100]	16	0·84 (0·72–0·98)	0%	0·80	0·528	..	..	..	..	..
Sustained undetectable HIV PVL[83–86]	4	0·62 (0·47–0·81)	0%	0·51	..	1	0·61 (0·42–0·88)	..	..	..
Nadir CD4 count ≥200 cells per μL *vs* <200 cells per μL[83,84,86,91,92,103]	6	0·60 (0·41–0·89)	67·6%	0·009	..	1	0·29 (0·12–0·67)	..	..	..
Nadir CD4 count per increase of 100 cells per μL[30,86]	2	0·99 (0·92–1·08)	0%	0·64	..	1	1·00 (0·92–1·09)	..	..	..
Current CD4 count ≥500 cells per μL *vs* <500 cells per μL[31,86,90,91,99,101]	5	0·72 (0·46–1·13)	79·2%	0·001	..	..	..	..	..	..
Current CD4 count per increase of 100 cells per μL[30,95,100]	3	0·90 (0·78–1·04)	52·2%	0·12	..	2	0·97 (0·85–1·12)	5·0%	0·31	..
Anal cancer incidence										
ART *vs* ART naive[21,105,108,110,111,113,114,116,117]	9	1·34 (0·99–1·81)	0%	0·88	..	3	1·11 (0·68–1·80)	0%	0·57	..
Per year of ART[104,105]	2	1·06 (1·01–1·11)	0%	0·80	..	1	1·04 (0·91–1·20)	..	..	..
Undetectable *vs* detectable HIV PVL[112–114]*	3	0·84 (0·56–1·27)	0%	0·59	..	2	0·90 (0·57–1·42)	0%	0·44	..
Sustained undetectable HIV PVL[106,107]	..	..	..	..	..	2	0·56 (0·44–0·70)	0%	0·94	..
Nadir CD4 count ≥200 cells per μL *vs* <200 cells per μL[21,108,109]	3	0·33 (0·18–0·60)	0%	0·79	..	2	0·34 (0·16–0·71)	0%	0·51	..
Nadir CD4 count per increase of 100 cells per μL[109,110]	2	0·60 (0·46–0·78)	21·7%	0·26	..	1	0·65 (0·50–0·85)	..	..	..
Current CD4 count per increase of 100 cells per μL[3]	..	..	..	..	..	1	0·89 (0·71–1·10)	..	..	..

The crude analysis includes studies with no adjustment and studies that adjust for sociodemographic factors only, but not for HIV-related factors or history of receptive anal intercourse. The adjusted analysis was done according to at least one of the following factors: duration of ART, HIV PVL, current CD4 cell counts, nadir CD4 cell counts, years living with HIV, and receptive anal intercourse. Odds ratios were used for prevalent outcomes, and hazard ratios or rate ratios were used for prospective outcomes. Begg's p value is not reported when the number of studies included in the meta-analysis was fewer than ten. For studies evaluating HSIL-AIN2+ prevalence, sustained undetectable HIV PVL or sustained viral suppression was defined as: undetectable HIV PVL of fewer than 50 copies per mL for more than 2 years compared with detectable HIV or undetectable HIV of shorter duration;[83] 1–5 years versus less than 1 year living with viral suppression (ie, having a viral load of fewer than 200 copies per mL in tests made from Aug 1, 1999, onwards allowing for a onetime deviation in viral load of 200–400 copies per mL);[86] undetectable HIV PVL versus detectable for the preceding 2 years;[84] or viral suppression for 3 years or more compared with fewer than 3 years.[85] For studies evaluating anal cancer incidence, sustained HIV viral detection or suppression defined in ART users as percent undetectable HIV PVL of 80% or more versus up to 20% of the time[106] or versus 40% or less of the time under follow-up.[107] The possibility that these analyses have been done in the same individuals cannot be excluded (data from the US Veterans Administration HIV Clinical Case Registry[106,107] but published separately). ART=antiretroviral therapy. ASCUS-AIN1+=atypical squamous cells of undetermined significance or anal intraepithelial neoplasia, grade 1 or greater. HR-HPV=high-risk papillomavirus. HSIL-AIN2+=high-grade squamous intraepithelial lesions or anal intraepithelial neoplasia, grade 2 or greater. PVL=plasma viral load. *A cut-off of fewer than 400 copies per mL used by Cachey and colleagues,[113] fewer than 500 copies per mL by Barnell and colleagues,[112] and fewer than 1000 copies per mL by Crum-Cianflone and colleagues.[114]

Table 2: **Meta-analysis of anal HPV and HPV-related disease outcomes according to HIV-related factors**

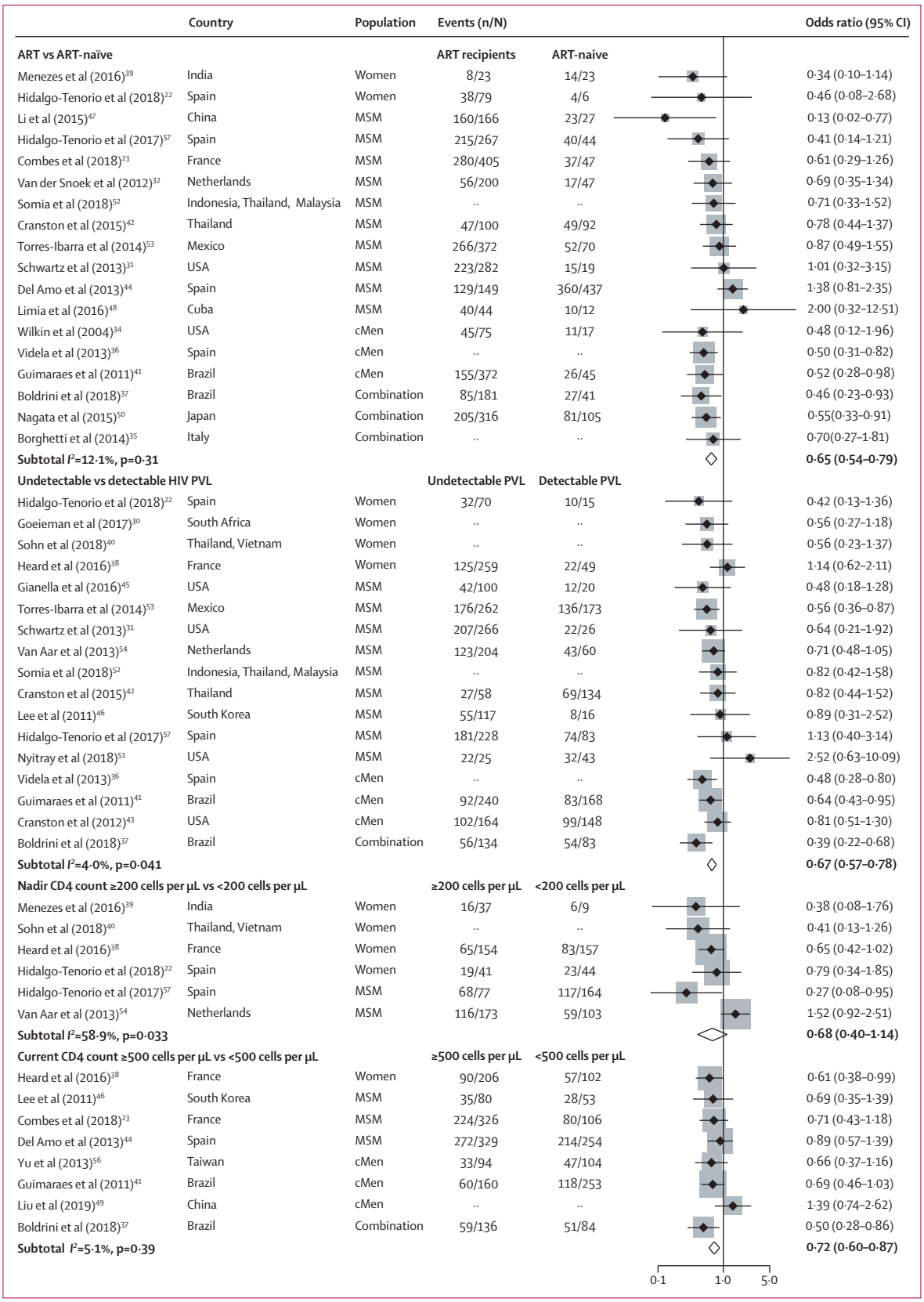

Figure 2: **Meta-analysis of HIV-related factors and anal high-risk HPV prevalence**
Individuals in the undetectable versus detectable HIV PVL analysis were included irrespective of their ART use. One study[40] compared nadir CD4 counts of 500 cells per μL or more to counts of fewer than 200 cells per μL. One study[32] used data for outcomes on high-risk HPV prevalence only (ie, no co-infection with non-high-risk types). One study[35] compared individuals receiving a ritonavir-boosted protease inhibitor regimen with ART-naïve individuals. Weights are from the random-effects analysis. cMen=combination of men for whom sexual orientation is not defined or effect estimate not given according to sexual orientation. Combination=combination of women and men for whom sexual orientation is not defined or effect estimate not given according to sex or sexual orientation. HPV=human papillomavirus. MSM=men who have sex with men. MSW=men who have sex with women. PVL=plasma viral load.

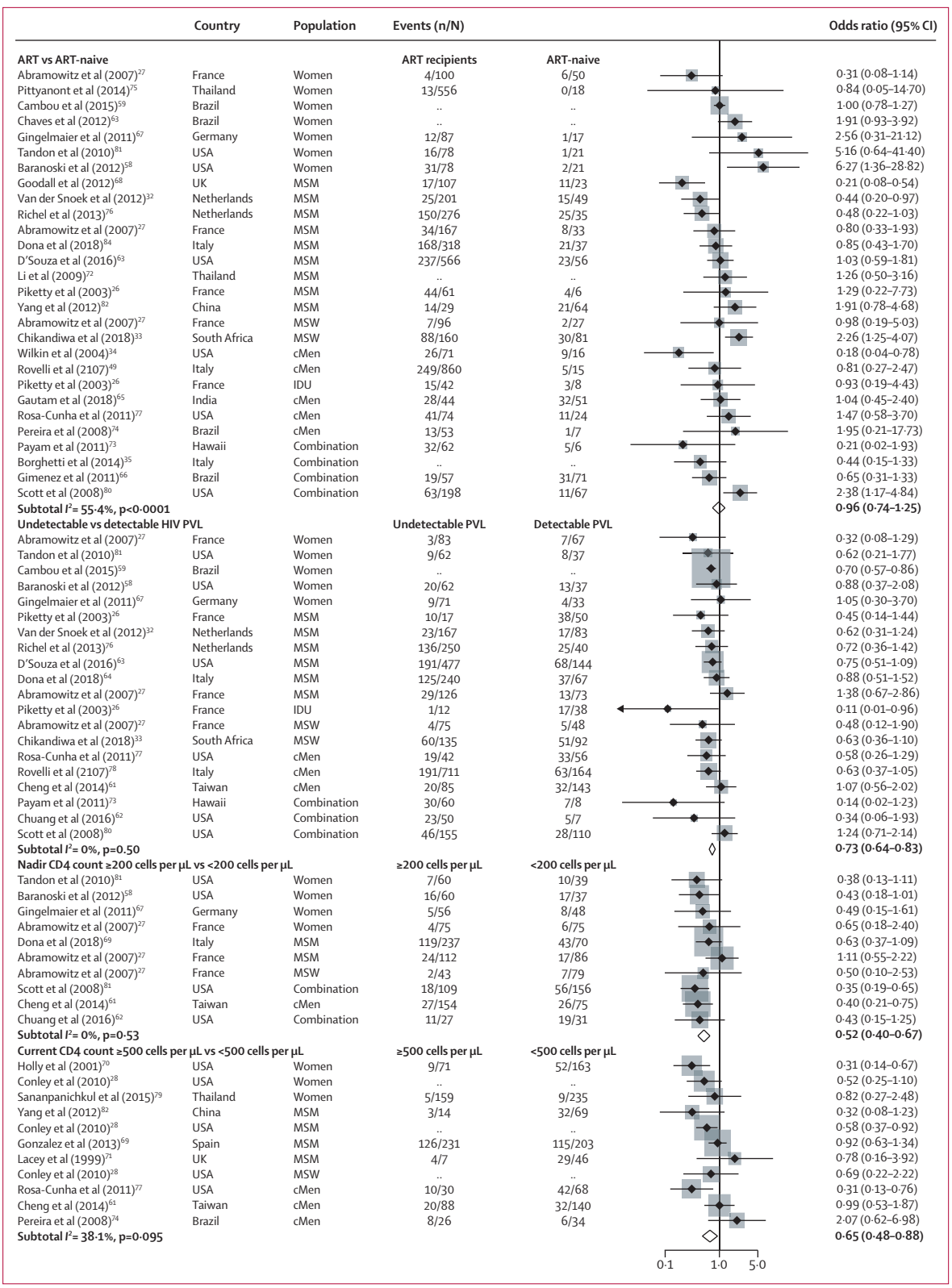

Figure 3: **Meta-analysis of HIV-related factors and ASCUS-AIN1+ prevalence**
Weights are from the random-effects analysis. ASCUS-AIN1+=atypical squamous cells of undetermined significance or anal intraepithelial neoplasia, grade 1 or greater. One study[35] compared individuals receiving a ritonavir-boosted protease inhibitor regimen with ART-naive individuals. cMen=combination of men for whom sexual orientation is not defined or effect estimate not given according to sexual orientation. Combination=combination of women and men for whom sexual orientation is not defined or effect estimate not given according to gender or sexual orientation. IDU=users of injectable drugs. MSM=men who have sex with men. MSW=men who have sex with women. PVL=plasma viral load.

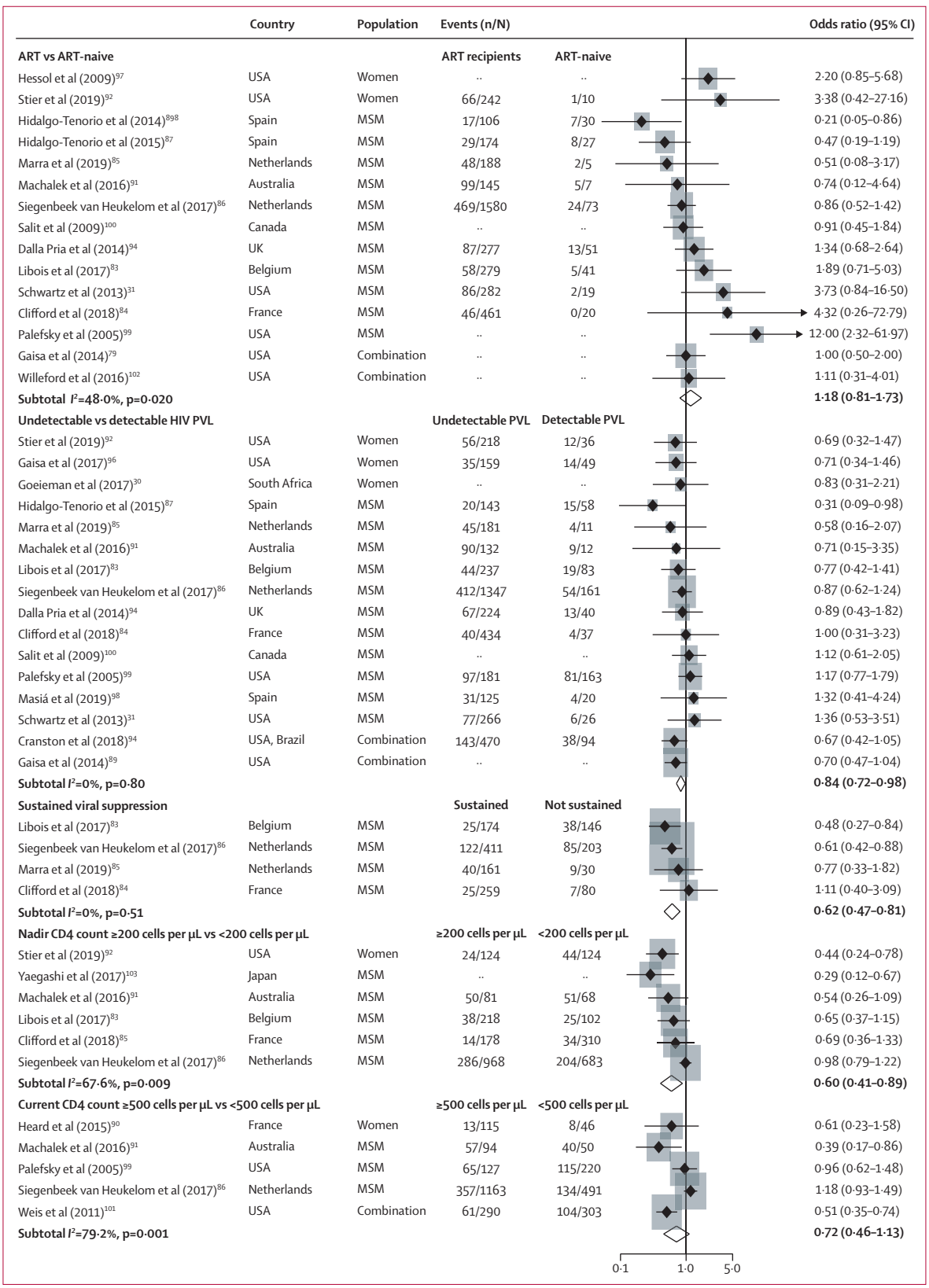

Figure 4: **Meta-analysis of HIV-related factors and HSIL-AIN2+ prevalence**

In the analysis of current CD4 cell counts, one study[101] reported the association of current CD4 counts of 400 cells per µL or more versus fewer than 400 cells per µL and HSIL-AIN2+ prevalence. cMen=combination of men for whom sexual orientation is not defined or effect estimate not given according to sexual orientation. Combination=combination of women and men for whom sexual orientation is not defined or effect estimate not given according to sex or sexual orientation. HSIL-AIN2+=high-grade squamous intraepithelial lesions or anal intraepithelial neoplasia, grade 2 or greater. MSM=men who have sex with men. MSW=men who have sex with women. PVL=plasma viral load.

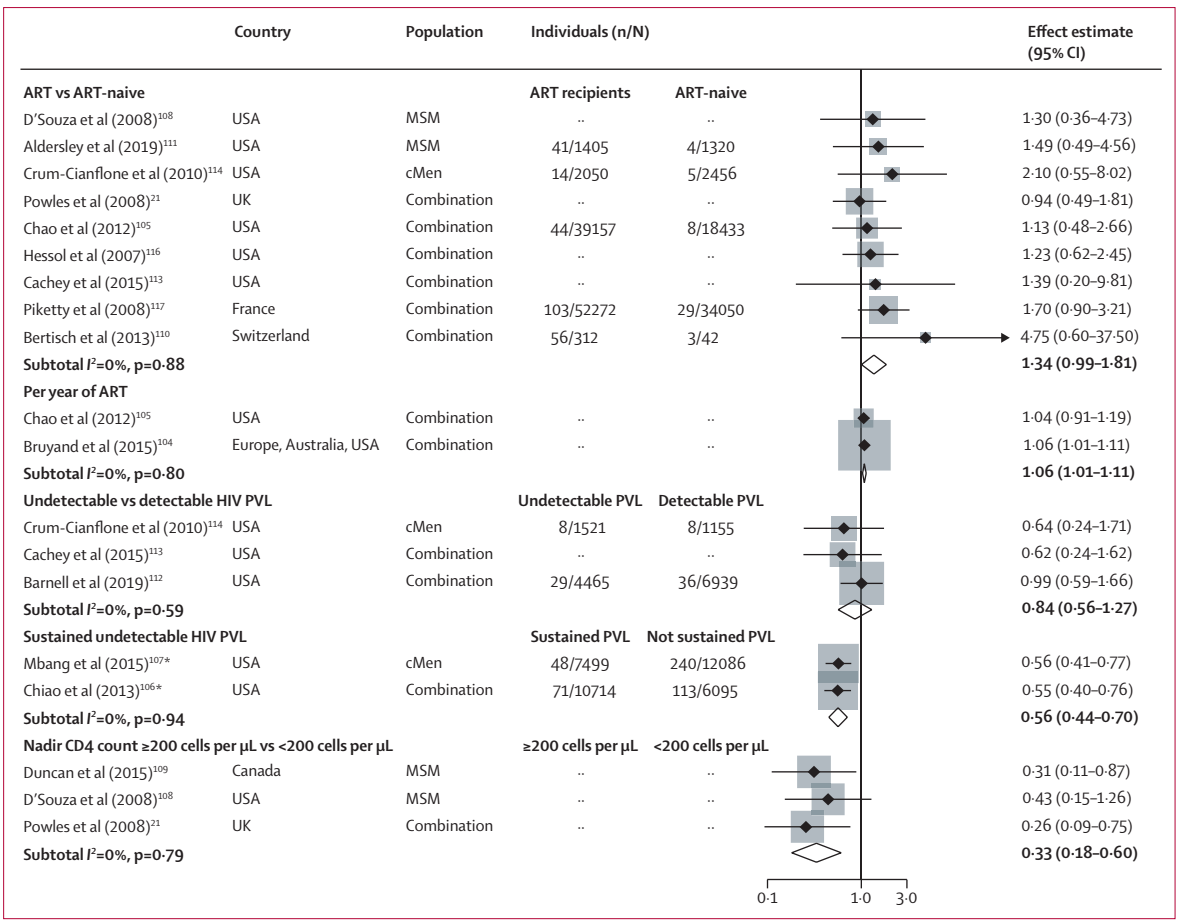

Figure 5: **Meta-analysis of HIV-related factors and anal cancer incidence**
Effect estimates are odds ratios, rate ratios, or hazard ratios (95% CIs). Hazard ratios are reported for nine studies;[21,106–109,113,114,116,117] incidence rate ratio reported by two studies;[111,112] rate ratio reported by two studies;[104,105] odds ratio reported by one study.[110] The number of individuals is used as denominator for all studies except one study[105] for which person-years (per 100 000 person-years) is the denominator. The estimate used for D'Souza and colleagues[108] is restricted to the period 1996–2007. The estimate for Piketty and colleagues[117] is restricted to the period 1998–2004. *Sustained HIV viral detection or suppression defined as percent undetectable HIV PVL (≥80% *vs* ≤20% of the follow-up time)[106] and undetectable HIV PVL (≥80% *vs* <40% of the follow-up time) in ART users.[107] The possibility that these analyses have been done in the same individuals cannot be excluded (data from the US Veterans Administration HIV Clinical Case Registry[106,107] but published separately). cMen=combination of men for whom sexual orientation is not defined or effect estimate not given according to sexual orientation. Combination=combination of women and men for whom sexual orientation is not defined or effect estimate not given according to sexor sexual orientation. MSM=men who have sex with men. MSW=men who have sex with women. PVL=plasma viral load.

In four studies,[22,38–40] high nadir CD4 cell counts were associated with lower prevalence of anal high-risk HPV than low nadir CD4 cell counts in women only (≥200 *vs* <200 cells per µL; crude OR 0·62, 0·43–0·90; I^2 0%, p=0·74; appendix p 19). Increased current CD4 counts (≥500 *vs* <500 cells per µL at the time of outcome measurement) were associated with a 28% reduction in high-risk HPV prevalence (table 2) and for each 100 cells per µL increase of current CD4, there was an 11% reduction in high-risk HPV prevalence (table 2) but no association was observed with HPV16 prevalence (appendix p 24).

There was no evidence to suggest publication bias for the association of any of the HIV-related factors and high-risk HPV prevalence (table 2, appendix p 20). Many studies, however, included people living with HIV with poor HIV control (ie, low proportion of ART users with detectable PVL or low median current CD4 count) and few studies provided estimates adjusted for potential confounders (appendix pp 21, 22). Restricting analysis to four studies[23,34,35,41] considered high-quality (Newcastle-Ottawa score ≥5), ART use was associated with an increased reduction in high-risk HPV prevalence (crude OR 0·57, 0·38–0·86; I^2 0%, p=0·95; appendix p 23).

Of the studies evaluating association of HIV-related factors and ASCUS-AIN1+ prevalence, people living with HIV with undetectable HIV PVL had 27% lower risk of ASCUS-AIN1+ than those with detectable HIV PVL (table 2, figure 3). The prevalence of ASCUS-AIN1+ was decreased by 48% in people living with HIV with nadir CD4 count of 200 cells per µL or more, and 35% decreased in people living with HIV current CD4 of 500 cells per µL or more (table 2, figure 3).

There was a 16% reduction in HSIL-AIN2+ prevalence in people living with HIV with undetectable HIV PVL (table 2) in 16 studies, especially if sustained over a long period (≥1 year; table 2, figure 4), as shown in four studies.[83–86] The prevalence of HSIL-AIN2+ was also decreased in people living with HIV with high nadir CD4 counts (table 2) but not in people with high current CD4 counts.

For the outcomes of ASCUS-AIN1+ and HSIL-AIN2+, the main risk of bias was linked to outcome ascertainment. Just over half of the studies evaluating ASCUS-AIN1+ prevalence (21 [57%] of 37) used cytology alone to diagnose ASCUS+ (appendix pp 28, 29). Seven (19%) ASCUS-AIN1+ studies did high-resolution anoscopy-directed biopsy of visible lesions, eight (22%) did high-resolution anoscopy of individuals with abnormal cytology with biopsies taken from visible lesions, and one (3%) study took biopsies from individuals with both abnormal and normal findings on high-resolution anoscopy; few studies used any independent verification of the final diagnosis (appendix pp 28, 29). Of two studies[32,34] that were considered high-quality, ART was associated with a 65% reduction in ASCUS-AIN1+ prevalence (appendix p 23). Of 23 studies evaluating HSIL-AIN2+, one (4%) used cytology alone to diagnose HSIL, 11 (48%) did high-resolution anoscopy-directed biopsy on visible lesions, eight (35%) did high-resolution anoscopy of individuals with abnormal cytology with biopsies taken from visible lesions, and three (13%) studies took biopsies from individuals with both abnormal and normal findings on high-resolution anoscopy. The highest scoring studies (≥5 on Newcastle-Ottawa scale, n=11)[30,84–93] included random biopsies of normal quadrants or an independent verification of histology (appendix pp 32, 33). Restricting analyses to these studies did not change the estimates, although there was weak evidence that ART was associated with lower risk of HSIL-AIN2+ (appendix p 23).

In nine studies of 141 877 people living with HIV, ART use was associated with a 34% increase in anal cancer incidence compared with no ART use, but this association did not persist when restricted to studies that adjusted for either nadir CD4 cell count, duration of ART use, previous AIDS event, or years living with HIV (adjusted HR 1·11, 95% CI 0·68–1·80; I^2 0%, p=0·57; table 2, figure 5). Two studies[104,105] reported a 6% increased risk of anal cancer per year in patients receiving ART, but associations were not significant in the analysis adjusted for pre-ART CD4 count and HIV RNA concentration.[105] In two studies of 56 190 people living with HIV receiving ART in the USA, individuals with sustained undetectable HIV PVL (defined as percent follow-up time with undetectable HIV PVL ≥80% *vs* ≤20% of the time[106] and percent follow-up time with undetectable HIV PVL ≥80% *vs* <40% of the time[107]) had a 44% decreased risk of anal cancer incidence (adjusted HR 0·56, 0·44–0·70; I^2 0%, p=0·94; table 2, figure 5). A high nadir CD4 cell count of 200 cells per µL or more was associated with 67% decreased risk of anal cancer incidence in three studies of 19 775 people living with HIV.[21,108,109] For each increase of nadir CD4 count of 100 cells per µL, there was a 40% reduction in anal cancer incidence (crude HR 0·60, 0·46–0·78; I^2 21·7%, p=0·26; table 2, figure 5).[109,110]

Most studies evaluating anal cancer were considered high-quality, and sensitivity analyses of the highest-quality papers did not change any of the estimates (appendix p 23). There was no evidence of publication bias for the studies included in the anal cancer meta-analyses.

Of studies evaluating longitudinal measures of high-risk HPV and HSIL-AIN2+, there was some evidence that ART users had an 18% decreased risk of high-risk HPV persistence compared with ART-naive people in two studies (appendix pp 24, 25).[128,129] There was a 61% reduction in HSIL-AIN2+ incidence in MSM receiving ART compared with ART-naive MSM,[134] and a 70% reduction in MSM with prolonged ART use (≥4 years) compared with MSM with short-term ART use (<4 years).[133] For each additional year of ART, there was a 7% increased likelihood of HSIL-AIN2+ clearance following lesion management (appendix pp 24, 25).[136]

Discussion

To our knowledge, this is the first meta-analysis investigating the association of ART use, HIV plasma viral load, and CD4 cell count with the outcomes of anal high-risk HPV, cytology-confirmed and histology-confirmed anal SIL, and anal cancer incidence in people living with HIV. The results indicate that people living with HIV who receive ART have a decreased prevalence of high-risk HPV, and those with undetectable HIV viral load have decreased risk of high-grade lesion (HSIL-AIN2+) prevalence. Overall, ART was not found to be associated with anal cancer risk, but the subgroup of ART users with sustained undetectable HIV viral load had a 44% reduced risk of anal cancer. Furthermore, an increase in nadir CD4 cell counts of 100 cells per µL was associated with a 40% reduction in anal cancer incidence.

A binary measure of ART use might not be a true measure of ART effectiveness and might dilute the positive effect of ART because of the heterogeneity in the history of immunodeficiency of ART users, as indicated by the variation in nadir CD4 cell counts. This effect is especially true of individuals who might have started HIV therapy before combination ART was introduced (a boosted protease inhibitor or non-nucleoside analogue with two reverse transcriptase inhibitors) or according to older guidelines when combination ART was started at low CD4 counts. Of the nine studies evaluating the association of ART and anal cancer, five included participants in the early years of the HIV epidemic (1983 onwards). A prolonged cumulative period of immunodeficiency or high viral replication might allow accumulation of genetic changes in patients with HIV that are important for anal cancer development.

It is also possible that ART-naive participants included in these studies might have been more recently infected with HIV, with a correspondingly shorter time to experience the effect of anal high-risk HPV infection and lesion development.[141] Because of this heterogeneity in past immunosuppression in ART users, some studies evaluated the association of high nadir CD4 cell counts and HIV viral control with anal cancer incidence, as a proxy measure for effective ART use. These studies found that ART use, when started early and with HIV viral control achieved over a prolonged period, was effective at lowering anal cancer risk. Large randomised controlled trials[142–144] have shown the clinical benefit of early ART initiation, including the reduction of infection-related cancers,[145] and current guidelines indicate that ART should be administered to all people living with HIV irrespective of their CD4 counts.[146] Consequently, contemporary cohorts of people living with HIV are unlikely to experience prolonged periods of immunosuppression, or none at all, which, coupled with sustained undetectable HIV PVL, could lead to a decrease in anal cancer incidence. However, the feasibility of universal ART access in low-income and middle-income settings with respect to financing, burden on health-care facilities, adherence, and potential risk of drug resistance is uncertain.[147] Future prospective studies are needed to monitor anal cancer incidence in people living with HIV globally in the era of universal and early ART.

Contrasting with observations for anal cancer incidence, contemporary measures of ART use (irrespective of duration), and high and increasing current, but not nadir CD4 cell counts, were associated with a reduction in high-risk HPV prevalence, suggesting that current rather than historical immunosuppression could be effective at clearing high-risk HPV infection. Although we observed no association between ART use and high-risk HPV persistence, there were too few studies reporting on this outcome. Further, prolonged ART use, accompanied by sustained undetectable HIV PVL, was associated with a decreased risk of HSIL-AIN2+ prevalence and incidence, and promoted lesion regression following management.[136]

We encountered several limitations in this study. First, most publications were cross-sectional studies, and many used a binary category of ART users versus ART-naive individuals. A more informative analysis would be to measure the effect of prolonged duration of ART use or effective ART, as measured by viral suppression or undetectable HIV PVL, which have been shown to decrease the risk of cervical high-risk HPV, cervical intraepithelial neoplasia, and cervical cancer.[13] There were also few prospective studies evaluating lesion progression and regression of anal lesions. The paucity of studies evaluating anal lesion regression and progression might be because, once detected, HSIL-AIN2+ might be immediately treated. Only two studies in our study evaluated spontaneous regression.[134,140]

Second, there was potential for misclassification bias of anal lesion outcomes. Contrary to observations in studies evaluating association of ART and cervical intraepithelial neoplasia,[13] few studies in our study had histological verification but were based on directed biopsy indicated by cytology or high-resolution anoscopy. Although there are few formal guidelines for anal cancer screening for high-risk groups, including people living with HIV,[148–150] cytology and high-resolution anoscopy are frequently used to detect anal lesions but these procedures might underestimate their severity compared with histological assessment.[9,151] Although high-resolution anoscopy is similar to cervical colposcopy, it requires extensive training and observer experience.[153] Nevertheless, the addition of random biopsy of quadrants with normal appearance has been reported to increase the number of HSIL identified when observers have little experience.[153] Few studies had independent verification of either cytology or histology, which has been shown to improve the accuracy of diagnosis.[155–157] As few of the included studies had such quality control measures, we cannot rule out the possibility of underdiagnosed high-grade disease contributing to the lack of associations observed. However, measures of high-risk HPV infection and anal cancer incidence are not very observer-dependent and associations found with these outcomes are likely to be robust.

There is also the possibility of unmeasured confounding, and few studies provided estimates adjusted for history or frequency of receptive anal intercourse. Most included studies were of MSM in Europe, USA, and Canada, and the prevalence of high-risk HPV, HSIL-AIN2+, and anal cancer incidence in this group is consistent with an earlier review.[2] Conversely, there were few studies in women and MSW, and studies done in Africa, making it difficult to assess if trends for ART, undetectable HIV PVL, and CD4 cell counts were similar by sex or sexual orientation group and geographical region. Notably, there was high prevalence of anal high-risk HPV, accompanied with high prevalence of HSIL-AIN2+, in these populations. For women and MSW, there could be a difference in risk of anal lesions if infected through auto-inoculation or passive migration,[157] and for women via sexual transmission. A small proportion of MSW reported ever practicing receptive anal intercourse, although we also cannot rule out the possibility that studies in MSW might have misreported or underreported the history of receptive anal intercourse. Individual patient-level data meta-analysis would allow for harmonisation of outcome and exposure definitions and adjustments that would provide a more precise and robust estimate of the association of ART and high-risk HPV with anal lesion outcomes than that reported here.

This study has practical implications for the management of people living with HIV and anal cancer control worldwide. The current recommendations of encouraging earlier ART initiation, coupled with a focus on

rapid virological control and sustained adherence, are likely to lead to an earlier and possibly more functionally complete mucosal immune reconstitution, in turn leading to clearance of anal high-risk HPV and control of associated anal lesion development. Although this Article included many studies, few evaluated the effect of ART prospectively on anal lesion progression, regression, or recurrence, and further prospective studies are needed. Given the high prevalence of anal lesions in high-risk populations such as people living with HIV and the challenges in diagnosis and effective management of anal lesions, this study points to yet one more reason to emphasise early diagnosis of HIV infection and immediate initiation of effective ART in populations at increased risk of anal cancer.

Contributors

HK, SdS, and PM conceptualised the study and developed the research protocol. HK and AC identified articles for full-text review. HK and AC extracted data from studies that matched inclusion criteria. HK did the statistical analyses. HK, AC, LAV, JMP, SdS, and PM contributed to the writing of the manuscript.

Declaration of interests

JP reports grants and non-financial support from Merck, stock options from Virion Therapeutics, non-financial support from Ubiome, personal fees from Vaccitech and Janssen Pharmaceuticals, grants, personal fees, and non-financial support from Vir Biotechnologies, and grants and travel support from Antiva Biociences, outside the submitted work. All other authors declare no competing interests.

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